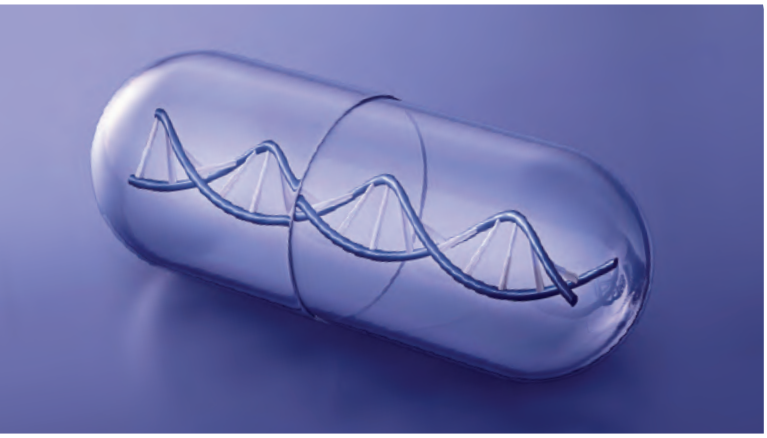
GENOMIND®

PROFESSIONAL PGx™

(Formally known as the Genecept Assay®)



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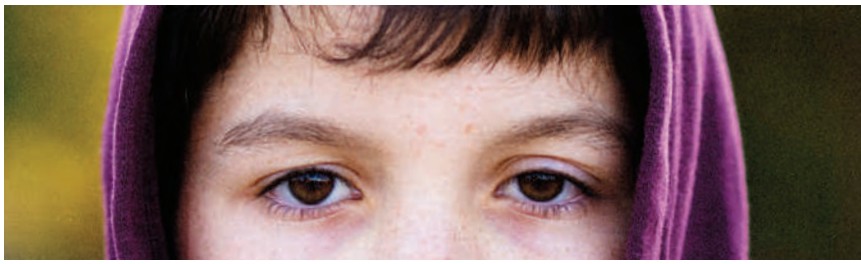

Summary of Literature and Clinical Impact

May 2019

The following is a summary of the key published literature relevant to a variety of genetic variations. The purpose of this document is to summarize the information available. Prescribing health care professionals must use their independent medical judgment and are solely responsible for determining the most appropriate medication for their patients. The clinican must consider other relevant clinical factors in determining which is the most appropriate medication. The understanding of the relationship between genetics, pharmacokinetics and pharmacodynamics changes periodically. The information in this summary is current at the time of publication.

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Introduction

Genomind, a unique personalized medicine platform that brings innovation to healthcare around the world, is pleased to present this summary of the genes behind Genomind Professional PGx® (formerly The Genecept Assay), a genetic test that analyzes both pharmacokinetic and pharmacodynamic genes. The current test includes the analysis of 15 pharmacodynamic genes and 9 pharmacokinetic genes.

Genomind Professional PGx® is used to assist clinical decision-making when prescribing medication for psychiatric conditions. It is a simple, non-invasive buccal test (cheek swab) that can be administered quickly in a clinician's office. The comprehensive results report provides clear data that can inform clinical decisions. A complimentary consultation with experts in the field of psychopharmacogenetics is available to the clinician along with each patient report.

Background on Genomind Professional PGx

Psychiatric practice is uniquely challenging because of the variability in treatment response. Even with the application of treatment guidelines, this leads many clinicians to utilize a trial-and-error approach during treatment planning. Moreover, it is difficult to determine in advance whether a patient will respond positively to a medication or experience adverse events that may force discontinuation.

It is well known that differences in patient response patterns may be partially explained by underlying genetic and biochemical disparities. Utilizing this information may provide an important tool in diminishing the trial-and-error process. Genomind Professional PGx is designed for this purpose. Genomind Professional PGx is a genetic test developed by Genomind to assess variations in deoxyribonucleic acid (DNA) that may alter gene function and response to psychotropic therapies. It sheds light on any differences to help the clinician arrive at informed and personalized therapeutic decisions.

Genomind Professional PGx analyzes 24 selected genes that have been shown in numerous clinical studies to have implications for response to treatments used for depression, anxiety, OCD, ADHD, bipolar disorder, PTSD, autism, schizophrenia, chronic pain and substance abuse. The genes assessed target major hepatic enzymes and key neurotransmitter pathways including serotonin, dopamine, norepinephrine and glutamate. These genes can be further categorized as follows:

- **Pharmacodynamic**: Genes that relate to the effect of the drug on the body, including interactions with receptors, transporters and neurotransmitters

- **Pharmacokinetic**: Genes that relate to the effect of the body on the drug, including drug metabolism and absorption.

Using Genetic Information to Inform Treatment Planning

Genetic testing results provide additional evidence for the heterogeneity observed in medication response. They offer information about the likelihood that a patient will respond to a medication therapy and/or experience adverse events or drug interactions. Pharmacodynamic results, though not diagnostic, describe the underlying biochemistry of presenting symptoms and adverse events, while pharmacokinetic results guide dosing decisions to optimize response. The genes analyzed by Genomind Professional PGx are associated with a wide range of psychotropic medications and the results can help inform treatment plans for patients with a variety of conditions.

Evidence Supporting Use of Genomind Professional PGx in Clinical Practice

Treatment of psychiatric patients guided by Genomind Professional PGx
https://www.ncbi.nlm.nih.gov/pubmed/?term=26445691 [1]

"This was a naturalistic, unblinded, prospective analysis of psychiatric patients and clinicians who utilized (Genomind Professional PGx) between April and October of 2013… Data from 685 patients were collected. Approximately 70% and 29% of patients had primary diagnoses of either a mood or anxiety disorder, respectively. Clinician-reported data, as measured by the Clinical Global Impressions-Improvement scale, indicated that 87% of patients showed clinically measurable improvement (rated as very much improved, much improved, or minimally improved), with 62% demonstrating clinically significant improvement. When analysis was restricted to the 69% of individuals with ≥ 2 prior treatment failures, 91% showed clinically measurable improvement. Patients also reported significant decreases in depression (P < .001), anxiety (P < .001), and medication side effects (P < .001) and increases in quality of life (P<.001)."[1]

Treatment guided by Genomind Professional PGx reduces health care utilization and costs
https://www.ncbi.nlm.nih.gov/pubmed/29734486 [2]

A propensity-score matched case-control analysis of longitudinal health claims data from a large US insurer was performed. Individuals with a mood or anxiety disorder diagnosis (N = 817) whose physician received Genomind Professional PGx were matched to 2,745 individuals who did not receive such testing. Outcomes included number of outpatient visits, inpatient hospitalizations, emergency room visits, and prescriptions, as well as associated costs over 6 months. On average, individuals who underwent testing experienced 40% fewer all-cause emergency room visits (mean difference 0.13 visits; P < 0.0001) and 58% fewer inpatient all-cause hospitalizations (mean difference 0.10 visits; P < 0.0001) than individuals in the control group. The Genomind Professional PGx users consumed an estimated $1948.00 less in health care resources than controls in the six-month period after testing. The two groups did not differ significantly in number of psychotropic medications prescribed or mood-disorder related hospitalizations.[2]

Increased Medication Adherence and Reduced Health Care Costs with Assay-guided Therapy
https://www.ncbi.nlm.nih.gov/pubmed/25326929 [3]

Individuals for whom pharmacogenetic testing was ordered (cases) were contrasted with those who did not undergo such testing (controls). Cases and controls were propensity score matched in order to minimize risk of confounding in this nonrandomized study. An initial analysis of 111 cases and 222 controls examined both adherence and healthcare costs. A replication study of 116 cases and 232 controls examined adherence alone, as cost data was not available for this latter cohort. Overall, **individuals with assay-guided treatment were significantly more medication adherent** (P = 1.56 3 10–3; Cohen's d = 0.511) than patients with standard treatment and demonstrated a relative cost savings of 9.5% in outpatient costs over a 4-month follow-up period, or $562 in total savings.[3]

Pharmacotherapy Concordant with Genomind Professional PGx Result in Greater Clinical Improvement
https://www.personalizedmedpsych.com/article/S2468-1717(17)30027-3/fulltext [4]

Researchers evaluated the use of Genomind Professional PGx testing in an open-label trial of 468 patients. After 8 weeks of treatment, patients with either a risk MTHFR or SLC6A4 genotype that were treated with assay-guided treatment regimens—as compared to those that were not—demonstrated significantly greater reduction in symptoms of depression and anxiety, and significantly increased quality of life.[4]

Review of Current Evidence Supports Pharmacogenetic Testing in Psychiatric Clinical Care
https://www.ncbi.nlm.nih.gov/pubmed/?term=28990639 [5]

Approximately one in five individuals in the United States experiences mental health issues in any given year, and these disorders are consistently among the leading causes of years lived with disability. Unfortunately, many mental illnesses are lifelong conditions that require medication and therapy to improve quality of life, yet clinical trial data show that many patients fail to achieve remission or require several pharmacological interventions prior to remission. One approach that may help explain patient variability in response to medication is pharmacogenetic testing. The current review shows the clinical use of pharmacogenetic testing in a small subset of gene variants and how they pertain to psychiatric illness and treatment. **Recent evidence suggests that genetic testing for psychiatric illness can improve patient outcomes in addition to decreasing health care costs.[5]**

Case Report: Patient with Intermittent Explosive Disorder
https://www.ncbi.nlm.nih.gov/pubmed/?term=24441311 [6]

An 18-year-old male presented to the outpatient psychiatric practice for medication evaluation and psychotherapy due to recurrent, violent outbursts with no identifiable precipitant or psychosocial stressor. The patient described “blacking out” and had “no recollection” of the events surrounding these episodes. The outbursts had become increasingly frequent and violent over the last 6 months and ranged from extreme verbal aggression to physically assaulting family members. The patient had significant medication trials in his history, including multiple psychostimulant agents, which caused intolerable agitation and late-day “rebound” insomnia. Trials of clonidine and guanfacine produced sedation and daytime drowsiness. The mood-stabilizing antiepileptic drugs valproic acid and carbamazepine had no apparent effect, and the patient was uncooperative with lab studies and blood draws to monitor drug levels. SSRIs had produced restlessness and diarrhea, while antipsychotics caused irritability and weight gain. Given the lack of symptom stabilization, despite the various psychotropic medication trials, Genomind Professional PGx was ordered to personalize treatment options. The results indicated that the patient may not respond well to atypical antipsychotics and SSRIs, which is supported by his previous treatment failure and intolerability with these agents. In accordance with these results, a trial of lithium was started. Upon achieving a therapeutic level of 1.0 on lithium 600 mg twice daily, this young man’s symptoms markedly decreased. He and his family reported that over the 3 months since initiation of the new psychopharmacologic therapies based on the results of the Genecept Assay, he experienced only two brief episodes of anger, both of which were less severe in both duration and intensity. [6]

Case Report: Complete Remission of Depression with Genomind Professional PGx Guided Treatment

https://www.omicsonline.org/open-access/patient-with-major-depressive-disorder-responds-to-lmethylfolate-postgenetic-testing-2167-1044-3-156.php?aid=24982 [7]

The case describes a 69-year-old Caucasian male with a long history of untreated depressive symptoms. At age 68, the patient was started on a treatment regime for depression, but remission was not achieved. Genetic testing was performed to determine if this patient’s genetic background could help explain his resistance and suggest a more effective treatment strategy. The results of the genetic test showed variations in four pharmacodynamic-related genes. Addition of adjunctive therapy as indicated by these results led to complete remission of depression symptoms.[7]

Case Report: Improvement in depression, agitation, and panic attacks after genetic testing was used to inform treatment

https://www.ncbi.nlm.nih.gov/pubmed/?term=24744941 [8]

“This case describes a 31-year-old female Caucasian patient with complaints of ongoing depression, agitation, and severe panic attacks. The patient was untreated until a recent unsuccessful trial of citalopram followed by venlafaxine which produced a partial response. Genetic testing was performed to assist in treatment decisions and revealed the patient to be heterozygous for polymorphisms in 5HT2C, ANK3, and MTHFR and homozygous for a polymorphism in SLC6A4 and the low activity (Met/Met) COMT allele. In response to genetic results and clinical presentation, venlafaxine was maintained and lamotrigine was added leading to remission of agitation and depression.”[8]

Case Report: Improved Function in a Patient with Atypical Psychosis and Depression with Long-standing Attentional Difficulty

https://www.ncbi.nlm.nih.gov/pubmed/?term=25916515 [9]

This case highlights the potential of pharmacogenomics to inform medical decision-making in a male with atypical psychosis and depression with longer-standing attentional difficulties. Likely because of his specific COMT polymorphism and intermediate metabolizing liver enzymes, when the patient's stimulant medications were titrated to affect for attentional needs, he became psychotic secondary to a hyperdopaminergic state. Past prescriptions of dopaminergic antidepressant agents (e.g., bupropion) likely would have exacerbated the problem. The patient's serotonin transporter polymorphism also potentially was associated with SSRI inefficacy and increased side effects. Knowledge of the patient's genetically influenced departure from average response allowed for personalization of pharmacology with clinical improvement across measures of functioning.[9]

Pharmacodynamic Genes

5HT2C, Serotonin Receptor 2C

The serotonin receptor (5HT2C) is a site of action of various neuroleptic medications. Serotonin acting at this receptor is involved in the regulation of appetite, and is one mechanism utilized to signal satiety. [10] Inhibition of this signaling pathway via 5HT2C antagonism has been shown in clinical studies to lead to increased food intake. [11, 12]

In patients taking second generation antipsychotics, the *5HT2C* **C/C** genotype confers standard risk for weight gain, while the **T** allele demonstrates a protective effect. [13-21] Greater clinical vigilance related to weight gain and metabolic syndrome, including assessment of blood lipids and sugar, may be indicated for individuals carrying the **C/C** genotype when taking second generation antipsychotics. [12, 19]

Medications that have been shown to decrease antipsychotic-induced weight gain include metformin, which is traditionally used in type II diabetes and other metabolic disorders.[22-24]

Literature Summary: Serotonin Receptor 2C (5HT2C)

The 5-HT2C receptor and antipsychotic induced weight gain – mechanisms and genetics.
http://www.ncbi.nlm.nih.gov/pubmed/16785265 [10]

> "We have been studying pharmacogenetic correlates and find that common 5-HT_{2C} receptor promoter region polymorphisms demonstrate strong associations with weight gain in two first episode psychotic samples. In both series, we have found further association of antipsychotic drug-induced weight gain with a common and functional polymorphism of the gene for leptin. Along with initial BMI, these two pharmacogenetic factors account for almost 30% of the variance in drug-induced weight gain. Interestingly, the 5-HT_{2C} polymorphism appears to determine levels of circulating leptin, providing a potential mechanism underlying the genetic association of the 5-HT_{2C} receptor with weight gain. We have undertaken functional studies of haplotypes of the 5-HT_{2C} promoter region and find the allele associated with protection from weight gain results in reduced promoter activity." [10]

Association of 5HT2C variant with antipsychotic-induced weight gain.
http://www.ncbi.nlm.nih.gov/pubmed/15741483 [13]
https://www.ncbi.nlm.nih.gov/pubmed/27414739 [14]
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [15]
http://www.ncbi.nlm.nih.gov/pubmed/15635667 [16]
http://www.ncbi.nlm.nih.gov/pubmed/23431082 [17]

Polymorphisms of the HTR2C gene and antipsychotic-induced weight gain: an update and meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/21121776 [18]

> "An updated meta-analysis of nine previous studies plus our current sample suggest that the -759C allele is associated with antipsychotic-induced weight gain… Numerous studies have confirmed that the 5HT2C polymorphism is associated with increased weight gain in response to atypical antipsychotic medication regimens. The data suggest that the polymorphism results in an under-expression of this receptor, which has been associated with satiety signaling in the hypothalamus. Therefore, reduction in neural satiety signaling is the putative mechanism behind the increased weight gain." [17, 18]

Pharmacogenetics of second-generation antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [20]
http://www.ncbi.nlm.nih.gov/pubmed/25138234 [21]

> "Antipsychotic-induced weight gain (AIWG) is a prevalent side effect of antipsychotic treatment, particularly with second generation antipsychotics, such as clozapine and olanzapine. At this point, there is virtually nothing that can be done to predict who will be affected by AIWG. However, hope for the future of prediction lies with genetic risk factors…Although there are significant findings in many other genes, the most consistently replicated findings are in the melanocortin 4 receptor (MC4R), the

serotonin 2C receptor (HTR2C), the leptin, the neuropeptide Y (NPY) and the cannabinoid receptor 1 (CNR1) genes." [21]

Metformin treatment of antipsychotic-induced dyslipidemia.
https://www.ncbi.nlm.nih.gov/pubmed/?term=26809842 [22]
https://www.ncbi.nlm.nih.gov/pubmed/20336059 [23]
https://www.ncbi.nlm.nih.gov/pubmed/30238318 [24]

ADRA2A, Alpha-2A Adrenergic Receptor

ADRA2A encodes a subtype of alpha 2 adrenergic receptors. Norepinephrine (NE) is the main catecholamine which signals via adrenergic receptors, and ADRA2A is the major receptor subtype found in the brain, particularly the prefrontal cortex (PFC). NE and the PFC are both critical for working memory and executive function measures, such as regulating attention, controlling impulses and inhibiting inappropriate behavior.[25] NE stimulates ADRA2A to improve PFC function, including attention regulation and working memory. [26, 27] Studies have shown that ADRA2A dysregulation is associated with impaired PFC function and ADHD.[25-27]

Children and adolescents being treated for ADHD symptoms are likely to have an increased response to stimulants if they are carriers of a **G** allele variant in *ADRA2A.* [28-33] For example, two studies have shown that methylphenidate (MPH) improved inattentive symptoms in **G** allele carriers based on the Swanson, Nolan, and Pelham Scale version IV (SNAP-IV) rating scale. [32, 33]

MPH increases synaptic levels of dopamine and NE and increased NE may bind and stimulate ADRA2A to improve PFC function. The exact mechanism of this drug-gene effect of MPH and ADRA2A has not been fully elucidated. However, an animal study demonstrated that MPH activity was inhibited when co-administered with an ADRA2A blocker, suggesting ADRA2A is involved in the mechanism of action of MPH.[26]

Literature Summary: Alpha-2A Adrenergic Receptor (ADRA2A)

Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD
https://www.ncbi.nlm.nih.gov/pubmed/?term=29230023 [28]

Using meta-analysis, researchers sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine 36 studies were identified (3647 children) linking the effectiveness of methylphenidate treatment with DNA variants. Pooled-data revealed a statistically significant association between single nucleotide polymorphisms (SNPs) rs1800544 ADRA2A (odds ratio: 1.69; confidence interval: 1.12-2.55), with response rate, whereas the following variants were not statistically significant: rs1947274 LPHN3 (odds ratio: 0.95; confidence interval: 0.71-1.26), rs5661665 LPHN3 (odds ratio: 1.07; confidence interval: 0.84-1.37) and VNTR 7 DRD4 (odds ratio: 0.68; confidence interval: 0.47-1.00). These findings have major implications for advancing our therapeutic approach to childhood ADHD treatment.[28]

Regional differences in cerebral perfusion associated with the alpha-2A-adrenergic receptor genotypes in attention deficit hyperactivity disorder.
http://www.ncbi.nlm.nih.gov/pubmed/20731965 [29]

"Our findings suggest that regional differences in cerebral perfusion in the orbitofrontal cortex represent an intermediate neuroimaging phenotype associated with the ADRA2A polymorphism; these data support the validity of the noradrenergic hypothesis regarding the pathophysiology of ADHD." [29]

Norepinephrine genes predict response time variability and methylphenidate-induced changes in neuropsychological function in attention deficit hyperactivity disorder.
http://www.ncbi.nlm.nih.gov/pubmed/23609393 [31]

"The aim of this study was to examine the relationship between polymorphisms in the α-2A-adrenergic receptor (ADRA2A) and norepinephrine transporter (SLC6A2) genes and attentional performance in ADHD children before and after pharmacological treatment…After medication,

increasing possession of a G allele at the MspI polymorphism of the ADRA2A gene was associated with increased MPH-related change in response time variability in the flanker task (P = 1.0 × 10). Our study suggested an association between norepinephrine gene variants and response time variability measured at baseline and after MPH treatment in children with ADHD." [31]

Adrenergic alpha2A receptor gene and response to methylphenidate in attention-deficit/hyperactivity disorder-predominantly inattentive type.

http://www.ncbi.nlm.nih.gov/pubmed/18200436 [32]

"In this naturalistic pharmacogenetic study, 59 subjects with ADHD-I from a non-referred sample were treated with short-acting methylphenidate and genotyped for ADRA2A -1291 C > G polymorphism. The primary outcome measure was the inattentive subscale of the SNAP-IV applied by a child psychiatrist blinded to genotype at baseline and first month of treatment. Children and adolescents with the G allele showed significantly lower inattentive scores with MPH treatment at the first month of treatment than subjects without the G allele (n = 59; F = 6.14; p = 0.016). We extended to ADHD-I previous findings suggesting the influence of the G allele at the ADRA2A -1291 C > G polymorphism on the improvement of inattentive symptoms with methylphenidate in children with all ADHD subtypes." [32]

Association of the adrenergic alpha2A receptor gene with methylphenidate improvement of inattentive symptoms in children and adolescents with attention-deficit/hyperactivity disorder.

http://www.ncbi.nlm.nih.gov/pubmed/17283289 [33]

"Objective: To evaluate the association between the ADRA2A -1291 C>G polymorphism and the clinical response to methylphenidate treatment in children and adolescents with ADHD…A significant interaction effect between the presence of the G allele and treatment with methylphenidate over time on inattentive scores was detected during the 3 months of treatment (n = 106; F (2,198) = 4.30; P = .02)…We documented the effect of the G allele at the ADRA2A -1291 C>G polymorphism on the improvement of inattentive symptoms with methylphenidate treatment in children and adolescents with ADHD. Our findings provide clinical evidence for the involvement of the noradrenergic system in the modulation of methylphenidate action." [33]

ANK3, Sodium Channel Component, Ankyrin G

ANK3 belongs to a family of scaffolding proteins known as the ankyrins and plays a role in the maintenance of sodium ion channels. A variation in this gene, the **T** allele, can potentially lead to abnormal clustering of sodium channels and dysfunction in action potential firing.[34-36] Genome-wide association studies (GWAS) have shown a correlation between this variant and disorders characterized by mood instability and lability.[36-42] Many studies indicate that this variant is associated with changes in anatomical connections that may be related to cognitive and affective symptoms. More specifically, this variation has been associated with anhedonia, altered novelty seeking, impaired threat/stress signal processing, poorer cognition and reduced integrity of white matter tracts.[43-46] As with the variant in *CACNA1C*, the therapeutic implications of this variation are not yet fully understood. Where clinically appropriate, traditional mood stabilizers or Omega-3 FA may be used to reduce excess excitatory signaling by sodium channels. Various meta-analyses have validated the utility of Omega-3 FA for bipolar depression (but not mania).[47-52] These studies suggest that antidepressant effects of Omega-3 FA may be largely dependent on the fatty acid eicosapentaenoic acid (EPA). While the antidepressant efficacy of Omega-3 FA is not fully understood, it may be related to stabilization of calcium and/or sodium channels.[53-55]

Literature Summary: Sodium Channel Component, Ankyrin G (ANK3)

Ankyrin-G regulates inactivation gating of the neuronal SODIUM CHANNEL, Nav1.6.

http://www.ncbi.nlm.nih.gov/pubmed/16775201 [35]

"Ankyrin-G, a modular protein, plays a critical role in clustering voltage-gated sodium channels (Nav channels) in nodes of Ranvier and initial segments of mammalian neurons…These results suggest that ankyrin-G regulates neuronal excitability not only through clustering Nav channels but also by directly modifying their channel gating." [35]

CACNA1C and ANK3 are among the most widely shared subset of genes linked to multiple psychiatric disorders

https://www.ncbi.nlm.nih.gov/pubmed/?term=25414627 [37]

In the current article researchers systematically tested the degree of genetic commonality across six major neuropsychiatric disorders-attention deficit hyperactivity disorder (ADHD), anxiety disorders (Anx), autistic spectrum disorders (ASD), bipolar disorder (BD), major depressive disorder (MDD), and

schizophrenia (SCZ). We curated a well-vetted list of genes based on large-scale human genetic studies based on the NHGRI catalog of published genome-wide association studies (GWAS). A total of 180 genes were accepted into the analysis on the basis of low but liberal GWAS p-values (<10(-5)). 22% of genes overlapped two or more disorders. The most widely shared subset of genes-common to five of six disorders included ANK3, AS3MT, CACNA1C, CACNB2, CNNM2, CSMD1, DPCR1, ITIH3, NT5C2, PPP1R11, SYNE1, TCF4, TENM4, TRIM26, and ZNRD1. Using a suite of neuroinformatic resources, we showed that many of the shared genes are implicated in the postsynaptic density (PSD), expressed in immune tissues and co-expressed in developing human brain.[37]

Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder.

http://www.ncbi.nlm.nih.gov/pubmed/18711365 [38]

Evidence for single nucleotide polymorphisms and their association with bipolar disorder.

http://www.ncbi.nlm.nih.gov/pubmed/24143106 [39]

Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder.

http://www.ncbi.nlm.nih.gov/pubmed/19088739 [40]

ANK3 as a risk gene for schizophrenia: new data in Han Chinese and meta analysis.

http://www.ncbi.nlm.nih.gov/pubmed/23109352 [41]

Ankyrin 3: genetic association with bipolar disorder and relevance to disease pathophysiology.

http://www.ncbi.nlm.nih.gov/pubmed/23025490 [36]

Analogous to CACNA1C, a number of GWAS have implicated a polymorphism in the ANK3 gene as a risk factor for the development of bipolar disorder. A study of 4,387 cases and 6,209 controls linked the ANK3 SNP with bipolar risk ($p = 9.1 \times 10^{-9}$) [36, 38-41]

Genetic analysis of SNPs in CACNA1C and ANK3 gene with schizophrenia: A comprehensive meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/26227746 [42]

"Recently, genome-wide association studies (GWAS), meta-analyses, and replication studies focusing on bipolar disorder (BD) have implicated the α-1C subunit of the L-type voltage-dependent calcium channel (CACNA1C) and ankyrin 3 (ANK3) genes in BD. Based on the hypothesis that both schizophrenia (SZ) and BD may share some common genetic risk factors, we investigated the association of CACNA1C and ANK3 with SZ using meta-analytic techniques, combining all published data up to April 2015… In summary, our study provides further evidence for the positive association of CACNA1C and ANK3 with SZ. These results support the hypothesis that both SZ and BD share common genetic risk factors. Further research is needed to examine the functions of CACNA1C and ANK3, and their interacting partners in the molecular, developmental, and pathophysiological processes in SZ." [42]

What is the impact of genome-wide supported risk variants for schizophrenia and bipolar disorder on brain structure and function? A systematic review.

http://www.ncbi.nlm.nih.gov/pubmed/25858580 [56]

"The powerful genome-wide association studies (GWAS) revealed common mutations that increase susceptibility for schizophrenia (SZ) and bipolar disorder (BD), but the vast majority were not known to be functional or associated with these illnesses. To help fill this gap, their impact on human brain structure and function has been examined. We systematically discuss this output to facilitate its timely integration in the psychosis research field; and encourage reflection for future research." [56]

Genome-wide supported risk variant for bipolar disorder alters anatomical connectivity in the human brain.

http://www.ncbi.nlm.nih.gov/pubmed/22079454 [43]

"A meta-analysis of genome-wide association studies as well as independent replications showed ankyrin 3 (ANK3) to be one of the best-supported risk genes for bipolar disorder. Using an imaging genetics approach employing diffusion tensor imaging in 88 healthy volunteers, we show decreased white matter integrity, indicated by lower fractional anisotropy and longitudinal diffusivity, in healthy carriers of the ANK3 rs10994336 risk genotype in the anterior limb of the internal capsule. We are also able to show that the resulting alterations of cortical-striatal-thalamic circuits are related to impaired set-shifting and increased risk-taking." [43]

The effect of ANK3 bipolar-risk polymorphisms on the working memory circuitry differs between loci and according to risk-status for bipolar disorder.

http://www.ncbi.nlm.nih.gov/pubmed/25711502 [44]

"We examined the effect of BD-risk polymorphisms at rs10994336 and rs9804190 on the working memory (WM) circuit using functional magnetic resonance imaging (fMRI) data obtained from euthymic patients with BD (n = 41), their psychiatrically healthy first-degree relatives (n = 25) and unrelated individuals without personal or family history of psychiatric disorders (n = 46) while performing the N-back task… This study provides new insights on the neurogenetic correlates of allelic variation at different genome-wide supported BD-risk associated ANK3 loci that support their involvement in BD and highlight the modulatory influence of increased background genetic risk for BD." [44]

Genetic modulation of working memory deficits by ankyrin 3 gene in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/24361380 [45]

"Neuropsychological endophenotype approach is an emerging strategy in schizophrenia research to understand and identify the functional importance of genetically transmitted, brain-based deficits present in this disorder. Accumulating evidence indicated that working memory deficit is a core neuropsychological dysfunction in schizophrenia and a primary endophenotype indexing the liability to develop schizophrenia…Our results indicated that genetic variation within ANK3 may exert gene-specific modulating effects on working memory deficits in schizophrenia." [45]

The cognitive impact of the ANK3 risk variant for bipolar disorder: initial evidence of selectivity to signal detection during sustained attention.

http://www.ncbi.nlm.nih.gov/pubmed/21304963 [46]

"Abnormalities in cognition have been reported in patients with Bipolar Disorder (BD) and their first degree relatives, suggesting that susceptibility genes for BD may impact on cognitive processes. The risk allele T was associated with reduced sensitivity in target detection (p = 0.0004) and increased errors of commission (p = 0.0018) during sustained attention regardless of diagnosis. Our results suggest that allelic variation in ANK3 impacts cognitive processes associated with signal detection and this mechanism may relate to risk for BD." [46]

The ANK3 bipolar disorder gene regulates psychiatric-related behaviors that are modulated by lithium and stress.

http://www.ncbi.nlm.nih.gov/pubmed/23237312 [57]

"Ankyrin 3 (ANK3) has been strongly implicated as a risk gene for bipolar disorder (BD) by recent genome-wide association studies of patient populations. RNA interference of Ank3 in hippocampus dentate gyrus induced a highly specific and consistent phenotype marked by decreased anxiety-related behaviors and increased activity during the light phase, which were attenuated by chronic treatment with the mood stabilizer lithium." [57]

Efficacy of omega-3 fatty acids in mood disorders.

http://www.ncbi.nlm.nih.gov/pubmed/21903025 [48]
http://www.ncbi.nlm.nih.gov/pubmed/19752840 [49]
http://www.ncbi.nlm.nih.gov/pubmed/20452573 [50]
http://www.ncbi.nlm.nih.gov/pubmed/24083675 [51]

"The findings of 5 pooled datasets (n = 291) on the outcome of bipolar depression revealed a significant effect in favor of omega-3 (p = .029), with a moderate effect size of 0.34. The meta-analytic findings provide strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, does not support its adjunctive use in attenuating mania." [48-51]

https://www.ncbi.nlm.nih.gov/pubmed/?term=30646157 [52]

A random-effects model meta-analysis was performed and this study was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. In total, 1203 participants with omega-3 PUFA treatment (mean age, 43.7 years; mean female proportion, 55.0%; mean omega-3 PUFA dosage, 1605.7 mg/d) and 1037 participants without omega-3 PUFA treatment (mean age, 40.6 years; mean female proportion, 55.0%) showed an association between clinical anxiety symptoms among participants with omega-3 PUFA treatment compared with control arms (Hedges g, 0.374; 95% CI, 0.081-0.666; P = .01). Subgroup analysis showed that the association of treatment with reduced anxiety symptoms was significantly greater in subgroups with specific clinical diagnoses than in subgroups without clinical conditions. The anxiolytic effect of omega-3 PUFAs was significantly better than that of controls only in subgroups with a higher dosage (at least 2000 mg/d) and not in subgroups with a lower dosage (<2000 mg/d).[52]

BDNF, Brain-derived Neurotrophic Factor

BDNF plays a role in regulating the growth, development and survival of neurons as well as the release of neurotransmitters.[58] *BDNF* may serve as a candidate gene for depression and PTSD. A variation in this gene, the **Met** allele, is associated with reduced BDNF secretion, impaired working memory, altered stress reactivity, and depression.[59-67] Studies have suggested that Caucasian **Met** carriers have poorer response to SSRIs compared with **Val/Val** patients, but these data are preliminary and await replication.[68, 69] Additionally, this association was not found in Asian patients.[70] In fact, an opposite association was found in Asians, such that Met carriers were associated with an improved response to SSRIs. [71-73] Several studies indicate that physical activity may improve cognition and working memory in **Met** carriers by directly upregulating BDNF activity.[74-77] Physical activity may also mitigate PTSD symptoms in **Met** allele carriers, as shown in a recent study of 1,895 U.S. military veterans.[78]

Literature Summary: Brain-derived Neurotrophic Factor (BDNF)

Genetic and epigenetic regulation of the brain-derived neurotrophic factor in the central nervous system.
http://www.ncbi.nlm.nih.gov/pubmed/24910563 [58]

> "BDNF is required for the development and proper function of the central nervous system, where it is involved in a variety of neural and molecular events relevant to cognition, learning, and memory processes… The present essay aims to summarize the published information on the matter, emphasizing their possible implications in health and disease or in the treatment of different neurologic and psychiatric disorders." [58]

The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: progress and controversy.
http://www.ncbi.nlm.nih.gov/pubmed/25824305 [59]

> "A single-nucleotide polymorphism of BDNF, termed the Val66Met polymorphism, results in deficient subcellular translocation and activity-dependent secretion of BDNF, and has been associated with impaired neurocognitive function in healthy adults and in the incidence and clinical features of several psychiatric disorders… Here we comprehensively review the role and relevance of the Val66Met polymorphism in psychiatric disorders, with emphasis on suicidal behavior and anxiety, eating, mood and psychotic disorders." [59]

Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity.
http://www.ncbi.nlm.nih.gov/pubmed/18852698 [60]

Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/24433458 [61]

> Several meta-analyses have demonstrated the BDNF polymorphism Val66Met (rs6265) is associated with major depression and mood-related phenotypes. Results have demonstrated that there may be differential impact of the polymorphism between the sexes and across ethnicities; however, these associations need to be confirmed in future studies. BDNF has been shown to moderate the relationship between life stress and depression. Results have also shown that Met carriers have an increased risk for geriatric depression compared to Val/Val homozygotes. These meta-analyses demonstrate the importance of BDNF polymorphisms in depression and treatment response. [60, 61]

The brain-derived neurotrophic-factor (BDNF) val66met polymorphism is associated with geriatric depression: a meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/22610920 [62]

> "Genetic association studies of the BDNF Val66Met polymorphism (rs6265) in geriatric depression have produced inconsistent results. A meta-analysis of studies was conducted to compare the frequency of the BDNF Val66Met variant between cases with geriatric depression and age-matched controls. A total of five studies involving 523 cases with geriatric depression and 1,220 psychiatrically healthy controls was included. Met allele carriers had an increased risk for geriatric depression when compared to Val/Val homozygotes (P = 0.004, OR = 1.48, 95% CI = 1.13-1.93). Our findings suggest the BDNF Met allele may confer increased risk for depression as individual age." [62]

BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents.

http://www.ncbi.nlm.nih.gov/pubmed/19931400 [63]

"The current study investigated the association between BDNF genotype and amygdala-hippocampal responses to emotional stimuli in adolescents with anxiety disorders and/or major depressive disorder (MDD) and in healthy adolescents…Greater activations in patients than healthy adolescents were found. Critically, these hyper activations were modulated by BDNF genotype: Met-carriers showed greater neural responses of emotional faces than Val/Val homozygotes in patients only. These data are first to demonstrate the contribution of BDNF gene variants to the neural correlates of adolescent anxiety and depression. Early "gene-brain" linkages may lay the foundation for longer-term patterns of neural dysfunction in affective disorders." [63]

Impact of genetic variant BDNF (Val66Met) on brain structure and function.

http://www.ncbi.nlm.nih.gov/pubmed/18497103 [64]

"…We generated a variant BDNF mouse (BDNF (Met/Met)) that reproduces the phenotypic hallmarks in humans with the variant allele. Variant BDNF (Met) was expressed in brain at normal levels, but its secretion from neurons was defective… When placed in conflict settings, BDNF (Met/Met) mice display increased anxiety-related behaviors that were not normalized by the antidepressant, fluoxetine. A genetic variant BDNF may thus play a key role in genetic predispositions to anxiety and depressive disorders." [64]

Predicting change in symptoms of depression during the transition to university: the roles of BDNF and working memory capacity.

http://www.ncbi.nlm.nih.gov/pubmed/24920443 [65]

"The present study has provided the first examination of whether working memory capacity, the BDNF Val66Met polymorphism, and their interaction predict changes in symptoms of depression during the transition to university… The BDNF Val66Met polymorphism, however, moderated the association between working memory capacity and symptom change. Among met carriers, lower working memory capacity in the presence of negative—but not neutral—distractors was associated with increased symptoms of depression over the semester. For the Val/Val group, working memory capacity did not predict symptom change. These findings contribute directly to biological and cognitive models of depression and highlight the importance of examining Gene × Cognition interactions when investigating risk for depression." [65]

Valence-specific effects of BDNF Val66Met polymorphism on dopaminergic stress and reward processing in humans.

http://www.ncbi.nlm.nih.gov/pubmed/24760847 [67]

"Neuroimaging results revealed a significant effect of BDNF (Met (66) carriers > Val/Val) on brain responses during the anticipation of monetary losses, baseline D2/3 receptor availability, and pain-stress-induced DA release in the Nucleus Accumbens. Conversely, BDNF Met (66) carriers showed no activation in response to monetary gains and a blunted DA response to the analgesic placebo in the nucleus accumbens. These results provide initial human evidence regarding the effect of the BDNF Val (66) Met polymorphism on DA-mediated responses to stress, its cognitive regulation by positive expectations, and the anticipatory responses to monetary gains and losses in the VTA-NAc pathway. Our results are of relevance to the neurobiology of stress and reward interactions and the pathophysiology of stress-related disorders." [67]

BDNF Met allele associated with response and remission with non-SSRI antidepressants in Caucasian patients.

http://www.ncbi.nlm.nih.gov/pubmed/23619509 [69]

http://www.ncbi.nlm.nih.gov/pubmed/25658497 [68]

"We assessed the impact of Val66Met polymorphism on antidepressant response and remission depending on antidepressant classes…With SSRI, Val/Val patients had a higher response rate 3 months post-treatment than Met patients (68.1% versus 44%; adjusted-OR: 3.04, IC95% [1.05; 9.37], p=0.04). With SNRI/TCA, Val/Val patients had a lower remission rate 6 months post-treatment than Met patients (33.3% versus 60.9%, adjusted-OR: 0.27, IC95% [0.09; 0.76], p=0.02)…This study argues for a personalized prescription of antidepressants in Caucasian patients with major depressive disorder, based on the BDNF Val66Met polymorphism: SSRI should be preferred for Val/Val patients and SNRI/TCA for Met patients. Further studies are required to confirm these data." [68]

BDNF Met allele associated with improved response to SSRIs in Asian patients.

http://www.ncbi.nlm.nih.gov/pubmed/21253406 [70]
https://www.ncbi.nlm.nih.gov/pubmed/23733030 [71]
http://www.ncbi.nlm.nih.gov/pubmed/20167454 [72]

"The aim of our meta-analysis was to assess the association between BDNF Val66Met polymorphism and treatment response in patients with MDD…a significant association of Val/Met genotype and increased response rate was found in comparison to Val/Val in overall population (OR=1.66, 95%CI=1.07-2.57, P=0.02). In the subgroup analysis, similar result was shown in Asian population (OR=1.83, 95%CI=1.03-3.26, P=0.04), but not in Caucasian population. We didn't observe a significant association of BDNF Val66Met polymorphism with remission rate. This meta-analysis demonstrates the association between BDNF Val66Met polymorphism and treatment response in patients with MDD, and Val66Met heterozygous patients have a better response rate in comparison to Val/Val homozygote patients, especially in Asian population." [72]

[73]

"We searched MEDLINE, PubMed, EMBASE, and Chinese Databases (Biomedical Literature Database, National Knowledge Infrastructure, Weipu, and WanFang) up to March 2013 for relevant studies (584 retrieved, 16 met inclusion criteria). We conducted six comparisons for both response and remission rates for three genotypes in Caucasians and Asians (4 weeks or ≥6 weeks; selective serotonin reuptake inhibitors [SSRIs], serotonin-noradrenaline reuptake inhibitors, or mixed antidepressants). Met carriers had a better response rate than Val/Val. In Asians, the Met carrier was positively associated with response rate (odds ratio; 95% confidence interval: 1.48; 1.02-2.14) in the SSRI group (1.81; 1.10-2.97) and with treatments ≥6 weeks. Met/Val showed a positive association with the response rate versus homozygotes (1.60; 1.20-2.13) and for ≥6 weeks (mixed antidepressant, 1.36; 1.04-1.77; SSRI, 1.55; 1.11-2.17). There was a weak effect of Met/Val versus Val/Val in response to SSRIs (mixed time, 2.07; 1.48-2.89; ≥6 weeks, 2.25; 1.53-3.32). For remission, Met/Val was better than the homozygotes (1.71; 1.09-2.68, Asians, SSRIs only)."[73]

The brain-derived neurotrophic factor Val66Met polymorphism moderates an effect of physical activity on working memory performance.

http://www.ncbi.nlm.nih.gov/pubmed/23907543 [74]

"…carriers of the methionine-specifying (Met) allele of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism have reduced secretion of BDNF and poorer memory, yet physical activity increases BDNF levels…we evaluated participants' performance on a battery of tests assessing memory, learning, and executive processes, and evaluated their physical activity with the Paffenbarger Physical Activity Questionnaire. BDNF genotype interacted robustly with physical activity to affect working memory, but not other areas of cognitive functioning. In particular, greater levels of physical activity offset a deleterious effect of the Met allele on working memory performance. These findings suggest that physical activity can modulate domain-specific genetic (BDNF) effects on cognition." [74]

The effect of acute exercise on blood concentrations of BDNF in healthy adults: a meta-analysis.

https://www.ncbi.nlm.nih.gov/pubmed/?term=28493624 [77]
This meta-analysis sought to determine the effect of a single exercise session on concentrations of BDNF in peripheral blood, in order to evaluate the potential role of BDNF in mediating the beneficial effects of exercise on brain health. In 55 studies that met inclusion criteria, concentrations of peripheral blood BDNF were higher after exercise (SMD = 0.59, 95% CI: 0.46-0.72, P < 0.001). In meta-regression analysis, greater duration of exercise was associated with greater increases in BDNF.[77]

BDNF Val66Met polymorphism and PTSD in U.S. military veterans: Protective effect of physical exercise.

https://www.ncbi.nlm.nih.gov/pubmed/30388593 [78]

"In this study, we examined the relationship between the BDNF Val66Met polymorphism and PTSD symptoms in two nationally representative samples of European American U.S. military veterans (main sample, n = 1386; replication sample, n = 509). Results revealed that, relative to Val/Val homozygotes, Met allele carriers reported greater severity of lifetime and current PTSD symptoms, specifically re-experiencing symptoms. Met allele carriers with high trauma burden also reported greater severity of lifetime and past-month PTSD symptoms. Greater engagement in physical exercise moderated this gene-by-environment interaction. Specifically, among veterans with high lifetime trauma burden, Met allele carriers who exercised had significantly lower severity of PTSD symptoms compared to those who did not exercise. These findings

suggest that interventions designed to bolster engagement in physical exercise may help mitigate PTSD symptoms in veterans who are Met allele carriers and highly exposed to trauma."

CACNA1C, Calcium Channel, L-type Voltage-gated, Alpha 1C Subunit

CACNA1C is important in the regulation of calcium signaling. Several genome-wide association studies (GWAS) have identified a variant in this gene, the **A** allele, which is associated with conditions related to mood instability and lability[37-39, 42, 79-84]. Variations in this gene may lead to ion channel dysfunction, resulting in a prolongation of the period during which the pore remains open, leading to increased excitatory signaling. It has also been reported that this variant is associated with changes in amygdala volume, frontal-hippocampal function, and disruptions in cognition in both schizophrenic and bipolar patients[34, 85-93]. This variant also has been hypothesized to be related to glutamate signaling[94]. The implications for treatment are not fully understood; however, if clinically relevant, traditional mood stabilizers, second generation antipsychotic medications, or omega-3 fatty acids (ώ-3 FA) may be used to reduce the excess excitatory calcium signaling resulting from this variation[53-55]. Various meta-analyses have validated the utility of ώ-3 FA for major depression, bipolar depression (but not mania), and anxiety[47-52]. These studies suggest that antidepressant effects of ώ-3 FA may be largely dependent on the fatty acid eicosapentaenoic acid (EPA), whereas anxiolytic effects may be less reliant on EPA.

Literature Summary: Calcium Channel, L-type Voltage-gated, Alpha 1C Subunit (CACNA1C)

Common variants in CACNA1C and MDD susceptibility: A comprehensive meta-analysis.
https://www.ncbi.nlm.nih.gov/pubmed/27260792 [82]

"Major depressive disorder (MDD) is one of the most common psychiatric disorders with a relatively high heritability (35-40%). Though rs1006737 in the CACNA1C gene showed significant association with MDD in a British large-scale candidate association study, most of the replication analyses with relatively small sample size reported negative association… Rs1006737 showed significant association with MDD in the fixed-effect model (Z = 2.56, P = 0.011, OR = 1.08, 95%CI = 1.04-1.12) and the association remained after reanalyzing the data according to ethnicity. We additionally analyzed other 25 SNPs, genotyped in only one replication study, across the CACNA1C locus, and found that two SNPs, rs4765905 (P = 0.041, OR = 1.05, 95%CI 1.00-1.09) and rs4765937 (P = 0.025, OR = 1.05, 95%CI 1.01-1.09) showed nominal association with MDD, while rs2239073 (P = 0.002, OR = 1.07, 95%CI 1.02-1.11) exhibited significant association with MDD, which survived from multiple corrections. Our study provides support for positive association between CACNA1C and MDD; however, the current data suggest the necessity of replication analyses in a larger-scale sample." [82]

Identification of pathways for bipolar disorder: a meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/24718920 [83]

"Among 966 genes, 226 were empirically significant (P < .05). Seventeen pathways were overrepresented in analyses of the initial data set. Six of the 17 pathways were associated with BP in both the initial and replication samples: corticotropin-releasing hormone signaling, cardiac β-adrenergic signaling, phospholipase C signaling, glutamate receptor signaling, endothelin 1 signaling, and cardiac hypertrophy signaling. Among the 226 genes, 9 differed in expression in the dorsolateral prefrontal cortex in patients with BP: CACNA1C, DTNA, FOXP1, GNG2, ITPR2, LSAMP, NPAS3, NCOA2, and NTRK3." [83]

Evaluating the association between CACNA1C rs1006737 and schizophrenia risk: A meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/25588813 [84]

Many GWAS have been conducted examining the relationship of CACNA1C rs1006737 to bipolar disorder and schizophrenia. Recently, two extensive meta-analyses have reviewed these studies and supported the association of rs1006737 as a risk for schizophrenia in a wide range of ethnicities. One study concluded, "a significant difference was identified between patients and controls for the A-allele of rs1006737 in combined studies (Z = 6.02, P = 1.74E-09), in European studies (Z = 4.08, P = 4.50E-05), and in Asian studies (Z = 4.60, P = 4.22E-06)." [80] The other study demonstrated similar findings, "Our results revealed a significant association between rs1006737 and schizophrenia (allelic model, P = 4.39 × 10(-6), pooled odds ratio [OR] = 1.20), and the results were much strengthened when the

European and East Asian samples were combined together (P = 2.40 × 10(-17), pooled OR = 1.12)." [42, 84, 95]

Molecular neurobiological clues implicating CACNA1C A allele in psychopathology: Altered neuronal signaling

http://www.ncbi.nlm.nih.gov/pubmed/26210959 [34]

"Bipolar disorder is a serious psychiatric disorder, with a high heritability and unknown pathogenesis. Recent genome-wide association studies have identified the first loci, implicating genes such as CACNA1C and ANK3. The genes highlight several pathways, notably calcium signalling, as being of importance. Molecular studies suggest that the risk variants impact on gene regulation and expression."[34]

CACNA1C risk variant and amygdala activity in bipolar disorder, schizophrenia and healthy controls.

https://www.ncbi.nlm.nih.gov/pubmed/23437284 [91]

"Several genetic studies have implicated the CACNA1C SNP rs1006737 in bipolar disorder (BD) and schizophrenia (SZ) pathology. This polymorphism was recently found associated with increased amygdala activity in healthy controls and patients with BD. We performed a functional Magnetic Resonance Imaging (fMRI) study in a sample of BD and SZ cases and healthy controls to test for altered amygdala activity in carriers of the rs1006737 risk allele (AA/AG), and to investigate if there were differences across the diagnostic groups… These results indicate that CACNA1C SNP rs1006737 affects amygdala activity during emotional processing across all diagnostic groups. The current findings add to the growing body of knowledge of the pleiotropic effect of this polymorphism, and further support that ion channel dysregulation is involved in the underlying mechanisms of BD and SZ." [91]

Association of rs1006737 in CACNA1C with alterations in prefrontal activation and fronto-hippocampal connectivity.

http://www.ncbi.nlm.nih.gov/pubmed/23404764 [92]

"Genome-wide association studies have identified the rs1006737 single nucleotide polymorphism (SNP) in the CACNA1C gene as a susceptibility locus for schizophrenia and bipolar disorder. The homozygous A (risk) group showed decreased activation compared to G-allele carriers. Further, the functional connectivity analysis revealed a positive association of fronto-hippocampal connectivity with rs1006737 A alleles." [92]

The effects of the CACNA1C rs1006737 A/G on affective startle modulation in healthy males.

http://www.ncbi.nlm.nih.gov/pubmed/25841664 [93]

"Here we studied the impact of the risk A allele on affective startle modulation…The results taken together suggest that healthy homozygous individuals for the risk A allele for major depression and bipolar disorder are sensitive to contextual aversion which leads to a reactivity pattern akin to a mixed anxious/depressed phenotype. This phenotype reflects the non-specific anxiety/depression psychopathology that often precedes the formal clinical disorders associated with this gene variant… Our findings provide phenotypic detail of the CACNA1C AA genotype in non-symptomatic individuals, which suggest primary effects in emotional circuitry, consistent with previously documented alterations in hippocampal/amygdala processing." [93]

Effects of the CACNA1C risk allele on neurocognition and executive function.

http://www.ncbi.nlm.nih.gov/pubmed/22957138 [96]
http://www.ncbi.nlm.nih.gov/pubmed/23406546 [97]

Efficacy of omega-3 fatty acids in mood disorders.

http://www.ncbi.nlm.nih.gov/pubmed/21903025 [48]
http://www.ncbi.nlm.nih.gov/pubmed/19752840 [49]
http://www.ncbi.nlm.nih.gov/pubmed/20452573 [50]
http://www.ncbi.nlm.nih.gov/pubmed/24083675 [51]

"The findings of 5 pooled datasets (n = 291) on the outcome of bipolar depression revealed a significant effect in favor of omega-3 (p = .029), with a moderate effect size of 0.34. The meta-analytic findings provide strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, does not support its adjunctive use in attenuating mania." [48-51]

Meta-analysis: Use Omega-3 fatty acids associated with reduction of clinical symptoms of anxiety

https://www.ncbi.nlm.nih.gov/pubmed/?term=30646157 [52]

A random-effects model meta-analysis was performed and this study was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. In total, 1203 participants with omega-3 PUFA treatment (mean age, 43.7 years; mean female proportion, 55.0%; mean omega-3 PUFA dosage, 1605.7 mg/d) and 1037 participants without omega-3 PUFA treatment (mean age, 40.6 years; mean female proportion, 55.0%) showed an association between clinical anxiety symptoms among participants with omega-3 PUFA treatment compared with control arms (Hedges g, 0.374; 95% CI, 0.081-0.666; P = .01). Subgroup analysis showed that the association of treatment with reduced anxiety symptoms was significantly greater in subgroups with specific clinical diagnoses than in subgroups without clinical conditions. The anxiolytic effect of omega-3 PUFAs was significantly better than that of controls only in subgroups with a higher dosage (at least 2000 mg/d) and not in subgroups with a lower dosage (<2000 mg/d).[52]

COMT, Catechol-O-Methyltransferase

COMT is an enzyme responsible for breakdown of dopamine in the frontal lobes of the brain. Dopamine levels here are critical for memory, attention, judgment and other executive functions.[98, 99] A valine (**Val**) to methionine (**Met**) variation results in reduced capacity of the enzyme to degrade dopamine, which results in increased dopamine activity.[100] Patients who have normal levels of dopamine degradation possess one increased and one decreased function allele (**Val/Met**). Patients with the **Val/Val** genotype display elevated enzyme activity and increased dopamine degradation; conversely, patients who are **Met/Met** have reduced enzyme activity and reduced dopamine degradation.[100-103] Clinical studies have shown that the **Val/Val** genotype may have behavioral consequences regarding cognitive function, memory, attention, motivation and judgment.[103, 104]

In **Val/Val** (high-activity) patients, dopaminergic agents have been shown to improve executive function and working memory in both animal and human studies. However, these agents may produce a deleterious effect on cognition in **Met/Met** (low-activity) patients. [105-108] Another class of drugs known as COMT inhibitors have also been shown to produce this biphasic effect on cognition in **Val/Val** versus **Met/Met** individuals, and may be clinically useful in patients with impaired executive function. [109-116]

Recent clinical studies investigating the effects of antipsychotic medications on cognitive function in schizophrenia and bipolar disorder found that patients with the **Met/Met** genotype had improved scores on measures of executive function (as well as positive symptoms of schizophrenia) when compared with their **Val/Met** and **Val/Val** counterparts. [117-122] In addition to stimulant and antipsychotic response, COMT genotype impacts sensitivity to opioids, with COMT **Val/Val** individuals requiring higher doses and COMT **Met/Met** individuals requiring lower doses for analgesia.[123]

Alternative antidepressant therapeutic strategies include electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) for **Val/Val** patients. Studies have associated the COMT **Val/Val** genotype with greater sensitivity to ECT and improvements in depressive scores.[124, 125] As stated previously, the increased activity of the **Val/Val** genotype can result in a hypo-dopaminergic state. Studies in rats have shown that TMS can increase dopamine outflow compared with sham stimulation.[126] Additionally, studies in humans have demonstrated TMS can be beneficial for patients suffering from depression, potentially by increasing dopamine levels in the prefrontal cortex.[127-131] Based on these studies it is thought that ECT or TMS may be an effective strategy in patients who are COMT **Val/Val** via stimulation of dopamine release.

Literature Summary: Catechol-O-Methyltransferase (COMT)

Effect of COMT val158met genotype on memory, attention, judgment and other executive functions.

http://www.ncbi.nlm.nih.gov/pubmed/26255563 [101]
http://www.ncbi.nlm.nih.gov/pubmed/20631684 [102]
http://www.ncbi.nlm.nih.gov/pubmed/18755576 [100]

"The gene encoding catechol-O-methyltransferase (COMT), an enzyme which regulates prefrontal cortex dopamine, contains a common functional single nucleotide polymorphism (val158met, rs4680G/A), which accounts for part of the interindividual variance in performance during working memory tasks and also predicts personality traits. We examined the relationship between the val158met polymorphism and cognitive function as well as personality traits in 522 healthy individuals (mean age: 24.75 years, SD=5.84, mean years of education: 15.59, SD=2.65). COMT val158met genotype was related in allele dosage fashion to performance in an executive function test, with the Met/Met carriers scoring highest." [100]

http://www.ncbi.nlm.nih.gov/pubmed/17325717 [103]

"The catechol-O-methyltransferase (COMT) Val (158) Met polymorphism is hypothesized to affect executive function in patient and control populations. Twelve studies met inclusion criteria (total n=1910) providing 10 samples each of patients and controls. In healthy controls, individuals with the Met/Met genotype performed better than those with the Val/Val genotype (d=0.29; 95% confidence interval (CI) 0.02-0.55; P=0.03)." [103]

http://www.ncbi.nlm.nih.gov/pubmed/26999687 [104]

"Impaired cognitive functioning is a core feature of schizophrenia. Cognitive impairment in schizophrenia has been associated with white-matter (WM) abnormalities and degenerative changes of cortical myelin in the cerebral cortex. Furthermore, findings suggested a role of the COMT gene in affecting both WM and neuropsychological performances. We thus hypothesized that the COMT Val/ Met genotype would affect the association between cognitive functions and WM microstructure in a sample of schizophrenic patients….Analysis indicated an association between cognitive functions and WM microstructure in the Val/Val group, but not in the Met carriers group. WM tracts include the corpus callosum, thalamic radiations, corona radiata, forceps major and minor, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and cingulum." [104]

Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine.

http://www.ncbi.nlm.nih.gov/pubmed/20414144 [105]

"The results of this study extend earlier findings with the COMT genotypes to additional measures of cognition, and suggest that the presence of the Val allele is associated with poorer performance and greater improvement with a stimulant drug." [105]

COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review.

http://www.ncbi.nlm.nih.gov/pubmed/27241058 [106]

"The relationship between dopamine (DA) tone in the prefrontal cortex (PFC) and PFC-dependent cognitive functions (for example, working memory, selective attention, executive function) may be described by an inverted-U-shaped function, in which both excessively high and low DA is associated with impairment. In the PFC, the COMT val158met single nucleotide polymorphism (rs4680) confers differences in catechol-O-methyltransferase (COMT) efficacy and DA tone, and individuals homozygous for the Val allele display significantly reduced cortical DA. Many studies have investigated whether val158met genotype moderates the effects of dopaminergic drugs on PFC-dependent cognitive functions. A review of 25 such studies suggests evidence for this pharmacogenetic effect is mixed for stimulants and COMT inhibitors, which have greater effects on D1 receptors, and strong for antipsychotics, which have greater effects on D2 receptors. Overall, COMT val158met genotype represents an enticing target for identifying individuals who are more likely to respond positively to dopaminergic drugs." [106]

COMT val158met impact on methylphenidate response

https://www.ncbi.nlm.nih.gov/pubmed/29230023 [28]

Pooled-data revealed a statistically significant association between single nucleotide polymorphisms (SNPs) rs1800544 ADRA2A (odds ratio: 1.69; confidence interval: 1.12–2.55), rs4680 COMT (odds ratio (OR): 1.40; confidence interval: 1.04–1.87), rs5569 SLC6A2 (odds ratio: 1.73; confidence interval: 1.26–2.37) and rs28386840 SLC6A2 (odds ratio: 2.93; confidence interval: 1.76–4.90), and, repeat variants variable number tandem repeat (VNTR) 4 DRD4 (odds ratio: 1.66; confidence interval: 1.16–2.37) and VNTR 10 SLC6A3 (odds ratio: 0.74; confidence interval: 0.60–0.90). [28]

COMT Val66Met determines the direction of cognitive effects produced by COMT inhibition.

http://www.ncbi.nlm.nih.gov/pubmed/17063156 [110]
"We found significant drug effects on measures of executive function and verbal episodic memory…individuals with Val/Val genotypes improved, whereas individuals with Met/Met genotypes worsened on tolcapone." [110]

https://www.ncbi.nlm.nih.gov/pubmed/18536698 [113]
"Recent evidence suggests that prepulse inhibition (PPI) levels relate to executive function possibly by a prefrontal cortex (PFC) dopamine (DA) link. We explored the effects of enhanced PFC DA signaling by the nonstimulant catechol-O-methyltransferase (COMT) inhibitor tolcapone, on PPI and working

memory of subjects homozygous for the Val (low PFC DA) and the Met (high PFC DA) alleles of the COMT Val158Met polymorphism…These results suggest that early information processing and working memory may both depend on PFC DA signaling, and that they may both relate to PFC DA levels according to an inverted U-shaped curve function." [113]

https://www.ncbi.nlm.nih.gov/pubmed/22364739 [114]
"Catechol-O-methyltransferase (COMT) metabolizes dopamine. The COMT Val (158) Met polymorphism influences its activity, and multiple neural correlates of this genotype on dopaminergic phenotypes, especially working memory, have been reported. COMT activity can also be regulated pharmacologically by COMT inhibitors. The inverted-U relationship between cortical dopamine signaling and working memory predicts that the effects of COMT inhibition will differ according to COMT genotype…Depending on genotype, COMT inhibition can enhance or impair working memory and increase or decrease risky decision making. To our knowledge, the data are the clearest demonstration to date that the direction of effect of a drug can be influenced by a polymorphism in its target gene. The results support the inverted-U model of dopamine function. The findings are of translational relevance, because COMT inhibitors are used in the adjunctive treatment of Parkinson's disease and are under evaluation in schizophrenia and other disorders." [114]

https://www.ncbi.nlm.nih.gov/pubmed/21521027 [116]

"It is widely accepted that abnormal prefrontal cortex biology resulting in deficient cognition is a primary problem in schizophrenia and that all currently available antipsychotics fail to improve cognitive and negative symptoms originating from this deficit. Evidence from basic science has revealed the importance of prefrontal dopamine signaling for optimal prefrontal function. This article describes succinctly the progress made so far, taking into account the mechanisms involved in catechol-O-methyltransferase (COMT)-induced modulation of prefrontal dopamine signaling, the impact of COMT on cognitive function and the role of COMT gene polymorphisms. The potential role of the COMT inhibitor tolcapone to improve cognitive function in health and disease is also presented here. It will soon be understood if tolcapone represents one of the first hypothesis-driven, biology-based, genotype-specific, targeted treatments of cognitive and negative symptoms of schizophrenia." [116]

COMT Val158Met Polymorphism and Clinical Response to Antipsychotic Treatment in Schizophrenia and Schizo-Affective Disorder Patients: a Meta-Analysis.
http://www.ncbi.nlm.nih.gov/pubmed/26745992 [117]

"Ten studies met inclusion criteria for the meta-analysis. Five additional antipsychotic-treated samples were analyzed for Val158Met and response and included in the meta-analysis (total=1416). Met/Met individuals were significantly more likely to respond than Val-carriers (P=.039, OR Met/Met=1.37, 95% CI: 1.02-1.85). Met/Met patients also experienced significantly greater improvement in positive symptoms relative to Val-carriers (P=.030, SMD=0.24, 95% CI: 0.024-0.46). Posthoc analyses on patients treated with atypical antipsychotics (n=1207) showed that Met/Met patients were significantly more likely to respond relative to Val-carriers (P=.0098, OR Met/Met=1.54, 95% CI: 1.11-2.14), while no difference was observed for typical-antipsychotic-treated patients (n=155) (P=.65)." [117]

[COMT genetic variation and clinical response to antipsychotic drug treatment: A Meta-analysis].
https://www.ncbi.nlm.nih.gov/pubmed/26164511 [118]

Nine studies included 868 participants who met inclusion criteria. Significant association was found between the COMT Val108/158Met gene polymorphism and antipsychotic drug efficacy. Evaluating the therapeutic efficacy through general symptoms: Met vs Val, RR=1.18, 95% CI: 1.04-1.35, P=0.013; Met/Met vs Val/Val, RR=1.40, 95% CI: 1.08-1.82, P=0.010. Evaluating the therapeutic efficacy through negative symptoms: Met vs Val, RR=1.24, 95% CI: 1.05-1.46, P=0.013; Met/Met vs Val/Val, RR=1.60, 95% CI: 1.04-2.46, P=0.031.COMT Val108/158Met gene polymorphism is significantly associated with antipsychotic drug efficacy, and Met gene is a dominant gene which displays a better response to antipsychotic drugs. [118]

COMT (Val(158/108) Met) genotype moderates the impact of antipsychotic medication on verbal IQ in twins with schizophrenia.
https://www.ncbi.nlm.nih.gov/pubmed/21233783 [119]

"In this study, we aimed to assess the moderating effects of the catechol-O-methyl transferase (COMT) (Val (158/108) Met) genotype on antipsychotic medication-induced changes in the cognitive performance of patients with chronic schizophrenia. The sample consisted of 85 monozygotic and 53

dizygotic twin pairs, of varying concordance for schizophrenia, and healthy control twins. Cognitive ability was measured using the Wechsler Adult Intelligence Scale-third edition. We used structural equation modelling to estimate main and interaction effects of the COMT status and antipsychotic medication dose on verbal intelligence quotient (VIQ) and performance intelligence quotient scores…Our results show that the verbal abilities of Val homozygotes of the COMT gene are cognitively impaired by higher doses of antipsychotic medication. This association is reversed in Met carriers. These data are consistent with an earlier study that found evidence of moderating effects of antipsychotic medication on N-back and verbal fluency tasks." [119]

Antipsychotic medications and cognitive functioning in bipolar disorder: moderating effects of COMT Val108/158 Met genotype.

https://www.ncbi.nlm.nih.gov/pubmed/23421957 [120]

"There is a negative association between the use of antipsychotics and cognitive functioning in bipolar patients, which may be mediated by altered dopamine signaling in selected brain areas, and moderation thereof by genetic sequence variation such as COMT Val108/158Met. The interaction between antipsychotic drug use and the COMT Val108/158Met genotype on two-year cognitive functioning in bipolar patients was examined…The negative effects of antipsychotics on cognitive functioning in bipolar disorder may be moderated by the COMT Val 108/158 Met genotype, with a negative effect of Val allele load. If replicated, the results may be indicative of pharmacogenetic interactions in bipolar disorder." [120]

COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia.

https://www.ncbi.nlm.nih.gov/pubmed/17123785 [121]

"Preliminary evidence suggests that a single nucleotide polymorphism (SNP), the val108/158met SNP, within the gene that codes for catechol-O-methyltransferase (COMT), a key enzyme involved in regulating dopamine (DA) transmission within the prefrontal cortex (PFC), is related to cognitive function in schizophrenia and cognitive improvement with atypical antipsychotic drugs (APDs)... Consistent with several previous studies, an association between COMT genotype and tests of executive function and working memory was identified at baseline. In addition, a novel interaction between genotype and improvement on tests of attention and verbal fluency was identified. Specifically, met homozygous and Val/ Met heterozygous patients demonstrated significantly greater improvement than Val homozygous patients following 6 months of treatment with clozapine. The results are discussed in relation to previous cross-sectional studies and prospective investigations of the associations between COMT genotype, cognition, and cognitive improvement with atypical APDs in schizophrenia." [121]

Catechol-O-methyltransferase val108/158met genotype predicts working memory response to antipsychotic medications.

https://www.ncbi.nlm.nih.gov/pubmed/15522252 [122]

"The gene encoding catechol-O-methyltransferase (COMT), an enzyme that regulates prefrontal cortex dopamine, contains a common functional polymorphism (Val (108/158) Met) that influences prefrontal cortex function in an allelic dose-dependent manner. A recent study reported that the COMT Val (108/158) Met polymorphism influences cognitive- and physiologic-related prefrontal cortex responses to antipsychotic treatment. The present study tested the effects of several COMT polymorphisms on the cognitive response to antipsychotic medication in patients with schizophrenia…These results support other data suggesting that the COMT Val (108/158) Met polymorphism might be an important factor in the cognitive response to antipsychotic medication." [122]

Pain polymorphisms and opioids: An evidence based review.

https://www.ncbi.nlm.nih.gov/pubmed/30592275 [123]

"It has been shown that the Val158Met polymorphism, a common genetic variant in Caucasian populations, influences the activity of the COMT enzyme. This enzyme, which metabolizes dopamine, adrenaline and noradrenaline, is an important modulator of dopaminergic and noradrenergic neurotransmission, known to play a role in pain… In human studies, COMT genotype affects the efficacy of opioids in acute and chronic pain in different settings (e.g. migraines, fibromyalgia, musculoskeletal pain and cancer pain). Low COMT activity increases opioid receptors and enhances opioid analgesia and adverse effects in cancer pains."[123]

Influence of Val108/158Met COMT Gene Polymorphism on the Efficacy of Modified Electroconvulsive Therapy in Patients with Treatment Resistant Depression.
https://www.ncbi.nlm.nih.gov/pubmed/?term=25388840 [124]

"In this double-blinded control study, we tested the efficacy of modified electroconvulsive therapy (MECT) in patients with treatment resistant depression (TRD) using the Hamilton Depression Rating Scale for Depression (HAMD). The total scores of HAMD were found to be significantly decreased after the treatment. The genotyping of catechol-O-methyltransferase (COMT) was carried out with polymerase chain reaction-based testing. Our results demonstrated that frequency of mutant COMT alleles in TRD patients was significantly higher than that of the controls indicating a correlation of the enzyme genotype to the occurrence of TRD. Moreover, the patients homozygous for wild-type COMT gene (G/G) were evidenced to be more sensitive to MECT treatment than those with an heterozygous mutant genotype (A/G)."[124]

Catechol-O-methyltransferase (COMT) polymorphisms predict treatment response in electroconvulsive therapy.
https://www.ncbi.nlm.nih.gov/pubmed/17700596 [125]

"Several lines of evidence suggest that catechol-O-methyltransferase (COMT) may be associated with treatment response in depression. We conducted a study on 119 patients with treatment-refractory depression admitted consecutively for electroconvulsive therapy (ECT). The COMT high/high genotype leads to a higher enzyme activity and thus lowers dopaminergic activity in the prefrontal cortex. In the present sample, those homozygous to high-active allele of COMT responded significantly more frequently to ECT." [125]

DRD2, Dopamine 2 Receptor

DRD2 is involved in movement and perception. Most neuroleptics act through antagonism of the D2 receptor to inhibit dopamine signaling. The deletion (**DEL**) variant reduces gene expression in vitro, resulting in altered D2 receptor density,[132, 133] and increased risk for poor response and adverse events (predominately weight gain) with antipsychotic medications.[134-137] Assessment of antipsychotic alternatives should be considered if clinically appropriate. One example of clinical utility could be in the treatment of bipolar disorders where mood stabilizers or antipsychotics are often first line agents. The presence of the **DEL** allele could be taken into consideration when deciding between drug classes.

The deletion (**DEL**) allele is also associated with increased risk for opioid dependence in Asians, with homozygotes at even greater risk.[138]

Literature Summary: Dopamine 2 Receptor (DRD2)

Pharmacogenetics and antipsychotic treatment response.
http://www.ncbi.nlm.nih.gov/pubmed/26076775 [134]

"Antipsychotic drugs are widely used in the treatment of schizophrenia and psychotic disorder. The lack of antipsychotic response and treatment-induced side-effects, such as neuroleptic syndrome, polydipsia, metabolic syndrome, weight gain, extrapyramidal symptoms, tardive dyskinesia or prolactin increase, are the two main reasons for non-compliance and increased morbidity in schizophrenic patients. During the past decades intensive research has been done in order to determine the influence of genetic variations on antipsychotics dosage, treatment efficacy and safety. The present work reviews the molecular basis of treatment response of schizophrenia." [134]

DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/20664489 [135]

"We… examined the relationship between -141C Ins/Del (rs1799732), a functional promoter region polymorphism in DRD2, and antipsychotic-induced weight gain in 58 first episode schizophrenia patients enrolled in a randomized trial of risperidone versus olanzapine. Carriers of the deletion allele (n=29) were compared with Ins/Ins homozygotes (noncarriers, n=29) in a mixed model encompassing 10 weight measurements over 16 weeks. Deletion allele carriers showed significantly more weight gain after 6 weeks of treatment regardless of assigned medication." [135]

D2 receptor genetic variation and clinical response to antipsychotic drug treatment: A meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/20194480 [136]

"There was a significant difference in response rate between the Del carrier vs. Ins/Ins genotypes (pooled OR = 0.65, 95% CI = 0.43 ~ 0.97, p = 0.03), indicating that Del carriers tend to have less favorable antipsychotic drug responses than patients with the Ins/Ins genotype." [136]

Association between polymorphisms of DRD2 and DRD4 and opioid dependence: evidence from the current studies.
https://www.ncbi.nlm.nih.gov/pubmed/21714067 [138]

"Several studies have assessed the association between genetic polymorphisms of DRD2 and DRD4 genes and opioid dependence risk, while the results were inconsistent. We performed a meta-analysis, including 6,846 opioid dependence cases and 4,187 controls from 22 individual studies, to evaluate the roles of four variants (DRD2 -141ins/del C, rs1799732; DRD2 311 Ser > Cys, rs1801028; DRD2-related Taq1 A, rs1800497 and DRD4 exon III VNTR) in opioid dependence for the first time… In conclusion, our results suggested that DRD2 -141ins/del C, DRD2-related TaqI A and DRD4 exon III VNTR polymorphisms might play important roles in the development of opioid dependence." [138]

GRIK1, Glutamate Receptor Kainate 1

Topiramate is a promising anticonvulsant medication used to treat alcohol dependence. However, response to topiramate varies. Topiramate blocks highly selective glutamate receptors, most notably receptors within the GRIK1 subunit. GRIK1 helps to assemble these excitatory glutamate receptors, which are involved in various neurological processes. Polymorphisms in this gene have been shown to predict response to topiramate. A polymorphism in *GRIK1*, specifically **C/C** homozygosity, has been associated with improved topiramate response for alcohol abuse. [139-143] However, the exact mechanism by which this genotype moderates the effect remains undetermined. Topiramate may be used for alcohol dependence/abuse in patients with the **C/C** genotype where clinically indicated.[139]

Literature Summary: Glutamate Receptor Kainate 1 (GRIK1)

GRIK1 C/C Genotype is associated with improved response to topiramate in reducing heavy drinking
https://www.ncbi.nlm.nih.gov/pubmed/26891181 [139]

The number needed to treat (NNT) "…for topiramate was 5.29, the NNT for patients with moderate adverse events was 7.52, and the NNT for patients with severe adverse events was 6.12. Among European Americans with the rs2832407*CC genotype, the NNT was 2.28, the NNT for patients with moderate adverse events was 2.63, and the NNT for patients with severe adverse events was 2.56. In contrast, for rs2832407*A-allele carriers, the NNT was 180.00, the NNT for patients with moderate adverse events was 322.16, and the NNT for patients with severe adverse events was 217.45…In this sample of heavy drinkers, topiramate had a clinically important treatment effect that was most evident in European Americans with the rs2832407*CC genotype. In that group, in particular, it had a robust treatment effect, even when adjusted for adverse events." [139]

Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism.

http://www.ncbi.nlm.nih.gov/pubmed/24525690 [140]

"Topiramate has been shown to reduce drinking and heavy drinking in individuals with alcohol dependence whose goal was to stop drinking. The authors evaluated the efficacy and tolerability of topiramate in heavy drinkers whose treatment goal was to reduce drinking to safe levels... Topiramate treatment significantly reduced heavy drinking days and increased abstinent days relative to placebo. In a European American subsample (N=122), topiramate's effect on heavy drinking days was significantly greater than that for placebo only in rs2832407 C-allele homozygotes. These findings support the use of topiramate at a daily dose of 200 mg to reduce heavy drinking in problem drinkers. The moderator effect of rs2832407, if validated, would facilitate the identification of heavy drinkers who are likely to respond well to topiramate treatment and provide an important personalized treatment option. The

pharmacogenetic findings also implicate the kainate receptor in the mechanism of topiramate's effects on heavy drinking." [140]

Posttreatment effects of topiramate treatment for heavy drinking.
http://www.ncbi.nlm.nih.gov/pubmed/25581656 [141]

"We examined whether the effects of topiramate and a single nucleotide polymorphism (rs2832407) in GRIK1, which encodes a kainate receptor subunit, persisted following a 12-week, placebo-controlled trial in 138 heavy drinkers with a treatment goal of reduced drinking. During treatment, topiramate 200 mg/d significantly reduced heavy drinking days and increased the frequency of abstinent days (Am J Psychiatry, 2014, 171:445). In the European-American (EA) subsample (n = 122), rs2832407 moderated the treatment effect on heavy drinking…In the full sample, the lower PHDD and higher PDA seen with topiramate treatment were no longer significant during follow-up. Nonetheless, the topiramate-treated patients had lower alcohol-related problem scores during treatment and both follow-up periods. Further, in the EA subsample, the greater reduction in PHDD seen with topiramate treatment in rs2832407*C-allele homozygotes persisted throughout follow-up, with no significant effects in A-allele carriers. A reduction in GGTP concentration was consistent with the reduction in heavy drinking, but did not reach statistical significance." [141]

GRIK1 genotype moderates topiramate's effects on daily drinking level, expectations of alcohol's positive effects and desire to drink.
http://www.ncbi.nlm.nih.gov/pubmed/24786948 [142]

"We found that rs2832407*C allele homozygotes treated with topiramate drank less overall during treatment than those receiving placebo, validating our earlier findings for heavy drinking days There was also a study day × medication group × genotype group interaction that predicted both positive alcohol expectancies and desire to drink, with rs2832407 C-allele homozygotes treated with topiramate showing the largest decreases in these outcomes during the study period. Changes in positive alcohol expectancies or desire to drink did not mediate the effects on drinking. These findings validate and extend our previous pharmacogenetic findings with topiramate." [142]

Self-efficacy mediates the effects of topiramate and GRIK1 genotype on drinking.
http://www.ncbi.nlm.nih.gov/pubmed/25496338 [143]

"In a 12-week, placebo-controlled trial of topiramate, we used daily interactive voice response technology to measure self-efficacy (i.e. confidence in avoiding heavy drinking later in the day) and drinking behavior in 122 European-American heavy drinkers. Topiramate's effects on both self-efficacy and drinking level were moderated by rs2832407. C-allele homozygotes treated with topiramate showed higher levels of self-efficacy and lower levels of nighttime drinking across the 12-week trial. Further, the interactive effect of topiramate and genotype on mean nighttime drinking levels was mediated by mean levels of self-efficacy. By modeling topiramate's effects on nighttime drinking across multiple levels of analysis, we found that self-efficacy, a key psychologic construct, mediated the effect of topiramate, which was moderated by rs2832407 genotype. Thus, it may be possible to use an individualized assessment (i.e. genotype) to select treatment to optimize the reduction in heavy drinking and thereby provide a personalized treatment approach." [143]

HLA-A & HLA-B, Human Leukocyte Antigen, Class I, A & B

The HLA-1 class of genes includes HLA-A, HLA-B, and HLA-C and encodes the heavy chains of class I antigen-presenting molecules that are expressed on most nucleated cells. These genes are highly polymorphic and code for proteins that bind and present antigens to immune cells.[144] Specific polymorphisms in this gene have been associated with adverse response to the anti-epileptic carbamazepine as well as oxcarbazepine, phenytoin/fosphenytoin, and possibly lamotrigine and other aromatic anticonvulsants (eslicarbazepine, phenobarbital). The variants HLA-A*31:01 and HLA-B*15:02 are associated with risk of developing Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), predominately in patients of Asian descent when taking carbamazepine. HLA-A*31:01 has been strongly associated with only carbamazepine-induced SJS and TEN,[145-149] while HLA-B*15:02 increases risk for these disorders with carbamazepine, oxcarbazepine, phenytoin and possibly other aromatic anticonvulsants.[146, 147, 150-154] SJS and TEN are life-threatening conditions characterized by widespread lesions on the epidermis. Due to the severity of carbamazepine-induced SJS/TEN, the FDA has made label changes to this drug, in addition to suggesting genetic screening for patients of Asian ancestry before initiation of carbamazepine therapy.[155] The Clinical Pharmacogenetics Implementation

Consortium (CPIC) also has prescribing guidelines for both HLA-B*15:02 and HLA-A*31:01, which includes carbamazepine, oxcarbazepine and other aromatic anticonvulsants.[147]

Literature Summary: HLA-A; *31:01 allele

Association of the HLA-A*31:01 Screening With the Incidence of Carbamazepine-Induced Cutaneous Adverse Reactions in a Japanese Population.

https://www.ncbi.nlm.nih.gov/pubmed/29610831 [145]

"Neuropsychiatrists were asked to prescribe carbamazepine for patients who tested negative for HLA-A*31:01 and alternative drugs for those who tested positive for HLA-A*31:01…Of the 1130 included patients who were prescribed carbamazepine or alternative drugs, the mean (range) age was 37.4 (0-95) years, 614 (54.3%) were men, and 198 (17.5%) were positive for HLA-A*31:01. Expert dermatologists identified 23 patients (2.0%) who had carbamazepine-induced cADRs, of which 4 patients required hospitalization. Drug-induced hypersensitivity syndrome was observed for 3 patients, maculopapular eruption for 9 patients, erythema multiforme for 5 patients, and an undetermined type of cADR for 6 patients. No patient developed Stevens-Johnson syndrome or toxic epidermal necrolysis. Compared with historical controls, the incidence of carbamazepine-induced cADRs was significantly decreased (for BioBank Japan data: incidence, 3.4%; odds ratio, 0.60; 95% CI, 0.36-1.00; P = .048; for the Japan Medical Data Centre claims database: incidence, 5.1%; odds ratio, 0.39; 95% CI, 0.26-0.59; P < .001)." [145]

Association between *HLA* gene polymorphism and cutaneous adverse reactions caused by antiepileptic drugs.

https://www.ncbi.nlm.nih.gov/pubmed/29545861 [146]

"Through the case-control study, 30 child patients with AED-induced cADRs (cADRs group), 60 AED-tolerant child patients (AED-tolerant group) and 60 normal children not taking AEDs (normal group) were collected. The HLA-B*15:02 and HLA-A*31:01 genotypes were detected using the polymerase chain reaction-sequence-specific oligonucleotide (PCR-SSO) probe method, and the correlation of *HLA-B*15:02* and *HLA-A*31:01* genes with the incidence of cADRs was analyzed. The positive rate of *HLA-B*15:02* gene was 83.33% in the cADRs group, which was significantly increased compared with that in the AED-tolerant and normal groups (P<0.01). The positive rate of *HLA-A*31:01* gene was 63.33% in the cADRs group, which was obviously increased compared with that in the AED-tolerant and normal groups (P<0.01). There were no significant differences in HLA-B*15:02 and HLA-A*31:01 genotypes between the AED-tolerant and normal groups (P>0.05). The results showed that HLA-B*15:02 and HLA-A*31:01 are significantly associated with cADRs in a Chinese Han population in Shanghai, suggesting that HLA-B*15:02 and HLA-A*31:01 genotypes should be detected in the application of AEDs." [146]

Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients.

https://www.ncbi.nlm.nih.gov/pubmed/29288229 [148]

"HLA-A*31:01 was the most strongly associated marker with carbamazepine-induced MPE in Europeans in this study. Forty-three of the 95 cases studied here were also included in the discovery publication,8 but the effect of the allele remains significant when we restrict to new cases only (p = 4 × 10−7), thus providing an additional independent replication of the initial finding." [148]

HLA-A*31:01 and carbamazepine-induced DRESS syndrome in a sample of North African population.

https://www.ncbi.nlm.nih.gov/pubmed/29125944 [149]

"The HLA-A*31:01 allele, which has a prevalence of 1% in Tunisian population, was significantly associated with DRESS syndrome. It was detected in 57.14% of cases (4/7) and only 4% of controls subjects (1/25). Thus, the carrier frequency of HLA-A*31:01 allele in the cases group was also significantly higher than in the controls group (57, 14% vs 4% P = 0,004). Odds ratio is estimated 32 (OR = 32 [2.6; 389.2])… Similarly to other ethnicities, the presence of the HLA-A*31:01 allele was associated with carbamazepine-DRESS syndrome in a sample of North African population. Future study must be conducted on a larger sample in order to confirm these results." [149]

Clinical Pharmacogenetics Implemtation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update.

https://www.ncbi.nlm.nih.gov/pubmed/29392710 [147]

"The variant allele HLA-A*31:01 is associated with greater risk of maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms, and SJS/TEN in patients treated with

carbamazepine. We summarize evidence from the published literature supporting these associations and provide recommendations for carbamazepine and oxcarbazepine use based on HLA genotypes." [147]

Literature Summary: HLA-B; *15:02 allele

Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations.

https://www.ncbi.nlm.nih.gov/pubmed/?term=18855540 [155]

"Current recommendations for genotyping all Asian patients are based on a strong correlation between HLA-B*1502 and carbamazepine-SJS/TEN in Han Chinese. Importantly, there is a wide access to high-resolution HLA typing within the USA and other developed countries. The relative lack of information regarding the correlation in both Asian population groups who have a high frequency of HLA-B*1502 should prompt further investigation. Given the availability of other effective medications for similar indications, it is likely prudent to avoid carbamazepine when patients have tested positive, despite the low estimated positive predictive value of the test."[155]

HLA-B*15:02 can be predicted by rs144012689 with >95% sensitivity and specificity in Hong Kong Han Chinese

https://www.ncbi.nlm.nih.gov/pubmed/?term=28398356 [156]

Using 184 epilepsy patients with both genome-wide SNP array and HLA-A/B candidate gene sequencing data, we sought tagging SNPs that completely represent sixHLA risk alleles; in addition, a Hong Kong population-specific reference panel was constructed for SNP-based HLA imputation. The performance of our new panel was compared to a recent Han Chinese panel. Finally, genetic associations of HLA variants with mild skin rash were performed on the combined sample of 408 patients. Common SNPs rs2571375 and rs144295468 were found to successfully tag HLA risk alleles A*31:01 and B*13:01, respectively. HLA-B*15:02 can be predicted by rs144012689 with >95% sensitivity and specificity.[156]

The HLA-B*15:02 polymorphism and Tegretol®-induced serious cutaneous reactions in epilepsy: An updated systematic review and meta-analysis.

https://www.ncbi.nlm.nih.gov/pubmed/29685430 [150]

"Out of 807 articles, nine were included in the present meta-analysis to assess the association between human leukocyte antigen (HLA)-B*15:02 polymorphisms and CBZ-induced serious cutaneous reactions (SCRs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in epilepsy. It was found that HLA-B*15:02 polymorphisms were significantly associated with CBZ SCR risk (OR: 27.325, 95% CI: 9.933-51.166), while subgroup analyses by ethnicity showed that the association was significant in Han Chinese (OR: 42.059, 95% CI: 9.587-184.514). The HLA-B*15:02 polymorphism was also strongly associated with the CBZ-SJS subgroup (OR: 152.089, 95% CI: 34.737-665.901) and significantly associated with the CBZ-SJS/TEN subgroup (OR: 13.993, 95% CI: 7.291-26.856). Also, the allele was overrepresented in the Han Chinese population (OR: 17.886, 95% CI: 8.411-38.034) within the CBZ-SJS/TEN subgroup. Although the number of studies available in other Asian ethnicities was insufficient for determining publication bias, it nevertheless showed a relationship between the HLA-B*15:02 polymorphism and SCRs. In addition, despite the small number of included studies, the results reveal strong evidence that the HLA-B*15:02 polymorphism can induce SCRs among Asian CBZ users. These findings should prompt physicians to individualize CBZ therapy for patients with epilepsy." [150]

Association between HLA-B*15:02 and oxcarbazepine-induced cutaneous adverse reaction: a meta-analysis.

https://www.ncbi.nlm.nih.gov/pubmed/29629814 [151]

In the tolerant control group, an association was found between HLA-B*15:02 genotype and OXC [oxcarbazepine]-induced sCAR [severe cutaneous adverse reaction] (odds ratio [OR]: 18.13; 95% CI: 6.77-48.56), but not in mcADR [mild cutaneous adverse reaction] (OR: 1.43; 95% CI: 0.56-3.64). In population control group, an association was found between HLA-B*15:02 genotype and OXC-induced sCAR, (OR: 8.22; 95% CI: 3.03-22.34), but not in mcADR (OR: 2.06; 95% CI: 0.91-4.67). Our study demonstrates that the genetic risk factor HLA-B*15:02 may be a factor in OXC-induced sCAR. [151]

Association between HLA-B Alleles and Carbamazepine-Induced Maculopapular Exanthema and Severe Cutaneous Reactions in Thai Patients.

https://www.ncbi.nlm.nih.gov/pubmed/29546073 [152]

"The aim of the present study was to carry out an analysis of the involvement of *HLA-B* alleles in carbamazepine-induced cutaneous adverse drug reactions (cADRs) in the Thai population. A case-control study was performed by genotyping the *HLA-B* alleles of Thai carbamazepine-induced hypersensitivity reaction patients (17 MPE, 16 SJS/TEN, and 5 DRESS) and 271 carbamazepine-tolerant controls. We also recruited 470 healthy Thai candidate subjects who had not taken carbamazepine. *HLA-B∗15:02* showed a significant association with carbamazepine-induced MPE (P = 0.0022, odds ratio (OR) (95% confidence interval [CI]) = 7.27 (2.04-25.97)) and carbamazepine-induced SJS/TEN (P = 4.46 × 10-13; OR (95% CI) = 70.91(19.67-255.65)) when compared with carbamazepine-tolerant controls." [152]

Association between *HLA* gene polymorphism and cutaneous adverse reactions caused by antiepileptic drugs.

https://www.ncbi.nlm.nih.gov/pubmed/29545861 [146]

"Through the case-control study, 30 child patients with AED-induced cADRs (cADRs group), 60 AED-tolerant child patients (AED-tolerant group) and 60 normal children not taking AEDs (normal group) were collected. The HLA-B*15:02 and HLA-A*31:01 genotypes were detected using the polymerase chain reaction-sequence-specific oligonucleotide (PCR-SSO) probe method, and the correlation of HLA-B*15:02 and HLA-A*31:01 genes with the incidence of cADRs was analyzed. The positive rate of HLA-B*15:02 gene was 83.33% in the cADRs group, which was significantly increased compared with that in the AED-tolerant and normal groups (P<0.01). The positive rate of HLA-A*31:01 gene was 63.33% in the cADRs group, which was obviously increased compared with that in the AED-tolerant and normal groups (P<0.01). There were no significant differences in HLA-B*15:02 and HLA-A*31:01 genotypes between the AED-tolerant and normal groups (P>0.05). The results showed that HLA-B*15:02 and HLA-A*31:01 are significantly associated with cADRs in a Chinese Han population in Shanghai, suggesting that HLA-B*15:02 and HLA-A*31:01 genotypes should be detected in the application of AEDs." [146]

Clinical Pharmacogenetics Implemtation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update.

https://www.ncbi.nlm.nih.gov/pubmed/29392710 [147]

"The variant allele HLA-B*15:02 is strongly associated with greater risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients treated with carbamazepine or oxcarbazepine... We summarize evidence from the published literature supporting these associations and provide recommendations for carbamazepine and oxcarbazepine use based on HLA genotypes." [147]

Association of *HLA-A* and *HLA-B* Alleles with Lamotrigine-Induced Cutaneous Adverse Drug Reactions in the Thai Population.

https://www.ncbi.nlm.nih.gov/pubmed/29238301 [153]

The proportion of *HLA-A∗02:07* and *HLA-B∗15:02* allele carriers were significantly higher in the LTG-induced CADR [cutaneous adverse reactions] group than in the tolerant controls [odds ratio (OR): 7.83; 95% confidence interval (CI): 1.60-38.25; P = 0.013, and OR: 4.89; 95% CI: 1.28-18.67; P = 0.014]. In addition, subjects with *HLA-A∗33:03, HLA-B∗15:02*, and *HLA-B∗44:03* were significantly higher in the LTG-induced MPE [maculopapular exanthema] group than in the tolerant controls (OR: 8.27; 95% CI: 1.83-37.41; P = 0.005, OR: 7.33; 95% CI: 1.63-33.02; P = 0.005; and OR: 10.29; 95% CI: 1.45-72.81; P = 0.029). In contrast to the LTG-induced MPE group, there were no significant differences between *HLA* alleles and LTG-induced SCAR [severe cutaneous adverse reactions] group. [153]

Association of the HLA-B alleles with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in the Javanese and Sudanese population of Indonesia: the important role of the HLA-B75 serotype.

https://www.ncbi.nlm.nih.gov/pubmed/29053440 [154]

"Nine unrelated patients with CBZ-induced SJS/TEN and 236 healthy Javanese and Sudanese controls were genotyped for HLA-B and their allele frequencies were compared. The HLA-B*15:02 allele was found in 66.7% of the patients with CBZ-induced SJS/TEN, but only in 29.4% of tolerant control (p = 0.029; odds ratio [OR]: 6.5; 95% CI: 1.2-33.57) and 22.9% of healthy controls (p = 0.0021; OR: 6.78; 95% CI: 1.96-23.38)." [154]

HLA-B 15:13 associated with phenytoin related Stevens-Johnson syndrome and toxic epidermal necrolysis

https://www.ncbi.nlm.nih.gov/pubmed/26927288 [157]

"Phenytoin (PHT) is a common cause of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Although HLA-B*15:02 is associated with PHT-induced SJS/TEN (PHT-SJS/TEN) in Han Chinese and Thais, the genetic basis for susceptibility to PHT-induced SCARs (PHT-SCAR) in other populations remains unclear. We performed a case-control association study by genotyping the human leukocyte antigen (HLA)-B alleles of 16 Malay PHT-SCAR patients (13 SJS/TEN and 3 DRESS), 32 PHT-tolerant controls and 300 healthy ethnicity-matched controls. A novel genetic biomarker, HLA-B*15:13, showed significant association with PHT-SJS/TEN (53.8%, 7/13 cases) (odds ratio (OR) 11.28, P=0.003) and PHT-DRESS (100%, 3/3 cases) (OR 59.00, P=0.003) when compared with PHT-tolerant controls (9.4%, 3/32 controls). We also confirmed HLA-B*15:02 association with PHT-SJS/TEN (61.5%, 8/13 cases vs 21.9%, 7/32 controls; OR 5.71, P=0.016) when compared with PHT-tolerant controls. These alleles may serve as markers to predict PHT-SCAR in Malays."

HTR2A, Serotonin Receptor 2A

The single nucleotide polymorphism rs7997012 was originally identified as a marker of citalopram response in the seminal Sequenced Treatment Alternatives for Depression (STAR*D) study. Two studies using STAR*D data found an association between the **A/A** genotype and citalopram response,[158, 159] but this effect was not replicated in other SSRIs (selective serotonin reuptake inhibitors).[160, 161] Studies also found an increased odds of response to non-SSRI and mixed class antidepressants in patients carrying a **G** allele at this position.[71, 162] Limited evidence exists for the relationship between rs7997012 and side effects. Two studies found that patients with the **A/A** genotype suffered from significantly more side effects compared to **G** allele carriers when investigating both selective and non-selective SRIs (serotonin reuptake inhibitors), as well as olanzapine.[163, 164]

Literature Summary: Serotonin Receptor 2A (HTR2A)

HTR2A A/A genotype associated with improved response to citalopram, but not other SSRIs

https://www.ncbi.nlm.nih.gov/pubmed/19365399 [160]
https://www.ncbi.nlm.nih.gov/pubmed/?term=19590397 [161]
https://www.ncbi.nlm.nih.gov/pubmed/?term=19077664 [159]
https://www.ncbi.nlm.nih.gov/pubmed/16642436 [158]

We searched for genetic predictors of treatment outcome in 1,953 patients with major depressive disorder who were treated with the antidepressant citalopram in the Sequenced Treatment Alternatives for Depression (STAR*D) study and were prospectively assessed. We detected significant and reproducible association between treatment outcome and a marker in HTR2A (P range 1 x 10(-6) to 3.7 x 10(-5) in the total sample). Participants who were homozygous for the A allele had an 18% reduction in absolute risk of having no response to treatment, compared with those homozygous for the other allele.[158]

HTR2A G-allele associated with improved response to venlafaxine in generalized anxiety disorder

https://www.ncbi.nlm.nih.gov/pubmed/?term=22006095 [162]

Treatment response was assessed in 156 patients that participated in a 6-month open-label clinical trial of venlafaxine XR for GAD. Primary analysis included Hamilton Anxiety Scale (HAM-A) reduction at 6 months. Secondary outcome measure was the Clinical Global Impression of Improvement (CGI-I) score at 6 months. The frequency of the G-allele differed significantly between responders (70%) and nonresponders (56%) at 6 months (P=0.05) using the HAM-A scale as outcome measure. Similarly, using the CGI-I as outcome, the G-allele was significantly associated with improvement (P=0.01). Assuming a dominant effect of the G-allele, improvement differed significantly between groups (P=0.001, odds ratio=4.72).[162]

HTR2A G-allele associated with improved response to non-SSRI antidepressants in major depressive disorder.

https://www.ncbi.nlm.nih.gov/pubmed/?term=23733030 [71]

"We performed a comprehensive meta-analysis of published candidate gene studies focused on AD efficacy in MD to evaluate the cumulative evidence. A random-effect model was applied to study the polymorphisms with genotypic counts available from at least three independent studies…. Regarding rs7997012, 3 studies and the STAR*D data including a total of 2195 subjects, and 5 studies and the

STAR*D data including a total of 2704 subjects were analyzed for response and remission phenotypes, respectively… In non-SSRIs/mixed ADs subgroup… associations with remission were found in the pooling G/G and G/A versus A/A (OR = 3.19, 95%CI: 1.57–6.46, p = 0.001; Supplementary Fig. 5.1), and in the pooling G/G versus A/A (OR = 3.40, 95%CI: 1.69–6.85, p=0.0006; Supplementary Fig. 5.2), with null-to-low heterogeneity across studies (I^2 within 0 and 9%)."[71]

HTR2A A/A genotype associated with increased adverse effect reports with serotonin reuptake inhibitors
https://www.ncbi.nlm.nih.gov/pubmed/?term=24192302 [163]

"We studied the influence of the [several genetic variants previously associated with antidepressant response] with regard to response and side effects in 273 psychiatric inpatients... 5-HTR2A intron 2 polymorphisms were associated significantly with adverse effects in patients with selective and nonselective SRI (rs7997012 [A/A]: n = 50, p = 0.020, side effects rates: 43% vs. 11%). No impact of the polymorphisms on mirtazapine treatment was found. Our study confirms the influence of serotonergic polymorphisms at the receptor and transporter level on SSRI response and side effects, supporting previous reports based on various study designs. The effects were strong enough to be noticed clinically in this naturalistic setting." [163]

HTR2A A/A genotype associated with adverse effect reports with olanzapine
https://www.ncbi.nlm.nih.gov/pubmed/?term=19636338 [164]

"We investigated the influence of… serotonergic polymorphisms on olanzapine serum concentrations and clinical outcome in a naturalistic clinical setting. Included were 124 Caucasian psychiatric inpatients treated with olanzapine for at least 4 weeks with steady-state serum concentrations available for 73 patients… No relationship between serum concentrations and the side effects (DOTES) score was detected. However, patients with the 5-HTR2A intron 2 (rs7997012) AA genotype suffered from more pronounced side effects compared to carriers of the GA or GG genotype (P=0.018 and P=0.002)." [164]

MC4R, Melanocortin 4 Receptor

MC4R is expressed in various sites of the brain, including the hypothalamus, and has a central role in the regulation of satiety, body weight and energy balance. Over 70 variations in *MC4R* have been identified, and about half of these variants result in partial or total loss of function, which may lead to hyperphagia, hyperinsulinemia, binge eating, food-seeking behavior and excessive hunger.[21, 165, 166] Moreover, studies have shown that a particular variation in this gene, the **A/A** genotype, is associated with increased risk of weight gain and adverse changes in metabolic indices among individuals receiving second generation antipsychotics.[167, 168] Clinicians should use caution when prescribing second generation antipsychotics to individuals with the homozygote risk genotype. In general, those drugs that pose the highest risk for weight gain are clozapine and olanzapine, while aripiprazole, iloperidone, paliperidone, quetiapine and risperidone are medium-risk medications, and asenapine, brexpiprazole, cariprazine, lurasidone and ziprasidone tend to be lower-risk medications.[23, 169-171]

Literature Summary: Melanocortin 4 Receptor (MC4R)

MC4R rs489693: a clinical risk factor for second generation antipsychotic-related weight gain
http://www.ncbi.nlm.nih.gov/pubmed/23920449 [167]

"The rs489693 polymorphism near the MC4R gene was associated with SGA-related weight gain in a genome-wide association study. We tried to replicate these results in our independent naturalistic study population. From 341 Caucasian inpatients receiving at least one SGA drug (olanzapine, clozapine, risperidone, paliperidone, quetiapine or amisulpride), carriers homozygous for the rs489693 A-allele (n = 35) showed a 2.2 times higher weight increase (+2.2 kg) than carriers of the CC-genotype (+1 kg) after 4 wk of treatment (analysis of covariance, p = 0.039). We revealed an even stronger effect in a subpopulation without weight gain inducing co-medication (factor 3.1, +2.8 kg, p = 0.044, (n = 16 of 169)) and in first episode patients (factor 2.7, +2.7 kg, p = 0.017, (n = 13 of 86)). Our results confirm the rs489693 A-allele as a possible risk factor for SGA-related weight gain." [167]

Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain.

http://www.ncbi.nlm.nih.gov/pubmed/22566560 [168]

"Our genome-wide association study yielded 20 single-nucleotide polymorphisms at a single locus exceeding a statistical threshold of P<10(-5). This locus, near the melanocortin 4 receptor (MC4R) gene, overlaps a region previously identified by large-scale genome-wide association studies of obesity in the general population. Effects were recessive, with minor allele homozygotes gaining extreme amounts of weight during the 12-week trial. These results were replicated in 3 additional cohorts, with rs489693 demonstrating consistent recessive effects; meta-analysis revealed a genome-wide significant effect (P=5.59 X 10 (-12). Moreover, we observed consistent effects on related metabolic indices, including triglyceride, leptin, and insulin levels…These data implicate MC4R in extreme SGA-induced weight gain and related metabolic disturbances. A priori identification of high-risk subjects could lead to alternative treatment strategies in this population." [168]

Antipsychotic drugs and obesity.

http://www.ncbi.nlm.nih.gov/pubmed/21185230 [172]

"Mechanisms underlying antipsychotic cardiometabolic adverse effects are incompletely understood. This hampers the identification of high-risk patients, low-risk antipsychotics and preventive/ameliorative treatments. Recent clinical, molecular and genetic data suggest that: (i) antipsychotic-naïve samples provide the greatest power for mechanistic studies; (ii) weight and metabolic effects can be discordant, pointing to overlapping and distinct mechanisms; (iii) antipsychotics affect satiety and energy homeostasis signaling; (iv) the specific peptides mediating these effects are unknown but probably overlap with those involved in idiopathic obesity; and (v) single nucleotide polymorphisms in genes encoding known neurotransmitter receptors and metabolic proteins are promising pharmacogenomic targets for countering adverse effects. However, sophisticated molecular studies and genome-wide association studies, ideally in antipsychotic-naïve/first episode samples, are needed to further advance the field." [172]

Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review.

http://www.ncbi.nlm.nih.gov/pubmed/15998156 [169]

"Increasing numbers of reports concerning diabetes, ketoacidosis, hyperglycemia and lipid dysregulation in patients treated with second-generation (or atypical) antipsychotics have raised concerns about a possible association between these metabolic effects and treatment with these medications. This comprehensive literature review considers the evidence for and against an association between glucose or lipid dysregulation and eight separate second-generation antipsychotics currently available in the US and/or Europe, specifically clozapine, olanzapine, risperidone, quetiapine, zotepine, amisulpride, ziprasidone and aripiprazole." [169]

Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/27217270 [170]

"Altogether, 72 articles reporting on 46 non-duplicated samples (n = 6700, mean follow-up = 25.1wk) with 38 SNPs from 20 genes/genomic regions were meta-analyzed (for each meta-analysis, studies = 2-20, n = 81-2082). Eleven SNPs from 8 genes were significantly associated with weight or BMI change, and 4 SNPs from 2 genes were significantly associated with categorical weight or BMI increase. Combined, 13 SNPs from 9 genes (Adrenoceptor Alpha-2A [ADRA2A], Adrenoceptor Beta 3 [ADRB3], Brain-Derived Neurotrophic Factor [BDNF], Dopamine Receptor D2 [DRD2], Guanine Nucleotide Binding Protein [GNB3], 5-Hydroxytryptamine (Serotonin) Receptor 2C [HTR2C], Insulin-induced gene 2 [INSIG2], Melanocortin-4 Receptor [MC4R], and Synaptosomal-associated protein, 25kDa [SNAP25]) were significantly associated with antipsychotic-related weight gain (P-values < .05-.001). SNPs in ADRA2A, DRD2, HTR2C, and MC4R had the largest effect sizes (Hedges' g's = 0.30-0.80, ORs = 1.47-1.96). Less prior antipsychotic exposure (pediatric or first episode patients) and short follow-up (1-2 months) were associated with larger effect sizes. Individual antipsychotics did not significantly moderate effect sizes." [170]

Management of antipsychotic-related weight gain.

https://www.ncbi.nlm.nih.gov/pubmed/20586697 [171]

"Despite variations across individuals and agents, antipsychotics are associated with clearly documented weight gain and adverse metabolic effects. Although increased appetite/caloric intake and various receptors, hormones and peptides have been implicated, biological mechanisms contributing to the increase in weight and glucose and lipid abnormalities with antipsychotics are largely unknown. This

has hampered the creation of antipsychotics that are free of cardiometabolic effects, even in antipsychotic-naive/early-phase patients, as well as the development of strategies that can prevent or drastically diminish the adverse cardiometabolic effects. In general, three strategies can reduce the cardiometabolic risk of antipsychotics: switching to a less orexigenic/metabolically adverse antipsychotic; adjunctive behavioral treatments; and adjunctive pharmacologic interventions. However, each of these strategies has only been shown to be modestly effective. Among different behavioral interventions (N = 14, n = 746), group and individual treatment, dietary counseling and cognitive-behavioral therapy seem to be similarly effective. Among 15 different pharmacologic strategies (N = 35, n = 1629), only metformin, fenfluramine, sibutramine, topiramate and reboxetine were more effective than placebo, with the most evidence being available for metformin, and no head-to-head trials comparing individual pharmacologic interventions. However, even in the most successful trials the risk reduction was modest. Weight was not decreased to a pretreatment level, and despite superiority compared with placebo, weight gain still often occurred, particularly in antipsychotic-naive patients and when interventions were 'preventively' coinitiated with antipsychotics. Future research should focus on combining treatment modalities or agents and on exploring novel mechanism-based interventions." [171]

MTHFR, Methylenetetrahydrofolate Reductase

MTHFR is an enzyme responsible for catalyzing the conversion of folic acid to methylfolate. Methylfolate is the active form of folic acid, a vital cofactor for the synthesis of norepinephrine, dopamine and serotonin.[173, 174] Two variations are tested within this gene. The **T** allele of C677T and the **C** allele of A1298C lead to reduced enzymatic activity of MTHFR, resulting in inefficient folic acid metabolism and production of methylfolate. [175] Several studies have shown these variations are associated with depression, bipolar disorder and schizophrenia.[176-178] Studies in psychiatric patients analyzing the therapeutic efficacy of L-methylfolate found superior outcomes when SSRI/SNRI treatment was supplemented with L-methylfolate compared with SSRIs/SNRIs alone.[179-182] A 2016 study with a methylfolate B-vitamin complex showed depression remission rates of 42% as monotherapy when *MTHFR* genotype was taken into consideration. [183] Preliminary data also suggest that biomarkers related to L-methylfolate synthesis and/or metabolism may identify patients who would benefit from supplementation with L-methylfolate. [184]

Literature Summary: Methylenetetrahydrofolate Reductase (MTHFR)

Vitamins, Monoamines, and Depression.

http://primarypsychiatry.com/vitamins-monoamines-and-depression/ [174]

Synthesis of the three monoamine neurotransmitters, serotonin, dopamine, and norpepinephrine, is regulated by L-methylfolate. "There are several mechanisms by which folate may affect central nervous system (CNS) pathways implicated in the depressive disorders. Biopterin, which is dependent on L-methylfolate for synthesis, serves as an essential co-factor for converting phenylalanine to tyrosine, and for hydroxylation of tyrosine and tryptophan to yield dopamine, norepinephrine, and serotonin." [174]

Association between MTHFR C677T polymorphism and depression: An updated meta-analysis of 26 studies.

http://www.ncbi.nlm.nih.gov/pubmed/23831680 [175]

"Previous studies concerning the association between the 5, 10-methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism and depression have provided inconclusive findings…This meta-analysis recruited 26 published studies which were selected by a search of electronic databases up to January 2013, including 4992 depression cases and 17,082 controls. Meta-analyses results suggested that MTHFR C677T polymorphism contributed to the increased depression risk in overall populations (for T vs. C: OR=1.19, 95%CI=1.07-1.32; for TT+CT vs. CC: OR=1.15, 95%CI=1.01-1.31; for TT vs. CC: OR=1.42, 95%CI=1.16-1.75; for TT vs. CT+CC: OR=1.38, 95%CI=1.16-1.63)." [175]

Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review.

http://www.ncbi.nlm.nih.gov/pubmed/17074966 [176]

"The authors performed a meta-analysis of studies examining the association between polymorphisms in the 5, 10-methylenetetrahydrofolate reductase (MTHFR) gene, including MTHFR C677T and A1298C, and common psychiatric disorders, including unipolar depression, anxiety disorders, bipolar

disorder, and schizophrenia. The primary comparison was between homozygote variants and the wild type for MTHFR C677T and A1298C... This meta-analysis demonstrates an association between the MTHFR C677T variant and depression, schizophrenia, and bipolar disorder, raising the possibility of the use of folate in treatment and prevention." [176]

Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: evidence for a common genetic vulnerability?

http://www.ncbi.nlm.nih.gov/pubmed/21185933 [177]

"We conducted a meta-analysis of all published case-control studies investigating associations between two common MTHFR single nucleotide polymorphisms (SNPs), MTHFR C677T (sample size 29,502) and A1298C (sample size 7934), and the major psychiatric disorders (i) schizophrenia (SZ), (ii) bipolar disorder (BPD), and (iii) unipolar depressive disorder (UDD)… MTHFR C677T was significantly associated with all of the combined psychiatric disorders (SZ, BPD and UDD); random effects odds ratio (OR) =1.26 for TT versus CC genotype carriers; confidence interval (CI) 1.09-1.46); meta-regression did not suggest moderating effects of psychiatric diagnosis, sex, ethnic group or year of publication. Although MTHFR A1298C was not significantly associated with the combination of major psychiatric disorders, nor with SZ, there was evidence for diagnostic moderation indicating a significant association with BPD (random effects OR=2.03 for AA versus CC genotype carriers, CI: 1.07-3.86). Meta-analysis on UDD was not possible due to the small number of studies available. This study provides evidence for shared genetic vulnerability for SZ, BPD and UDD mediated by MTHFR 677TT genotype, which is in line with epigenetic involvement in the pathophysiology of these psychiatric disorders." [177]

Role of MTHFR C677T gene polymorphism in the susceptibility of schizophrenia: An updated meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/27025471 [178]

"Total 38 studies with 10,069 cases and 13,372 controls were included in the present meta-analysis. Results of meta-analysis showed significant associated between C677T polymorphism and risk of schizophrenia (OR T vs C=1.18, 95%CI=1.10-1.27, p=<0.001; OR CT vs CC=1.10, 95%CI=1.04-1.17, p=<0.001; OR TT vs CC=1.40, 95%CI=1.20-1.64, p=<0.001; OR TT + CT vs CC=1.19, 95%CI=1.09-1.30, p=<0.001). We also performed subgroup and sensitivity analyses. Subgroup analysis was done according to ethnicity and significant association was found between C677T polymorphism and risk of schizophrenia in all three ethnic populations-African (OR=2.51; 95%CI=1.86-3.40; p=<0.001), Asian (OR=1.21; 95%CI=1.10-1.33; p=<0.001) and Caucasian (OR=1.07; 95%CI=1.01-1.14; p=0.01). In conclusion the results of the present meta-analysis suggested that the MTHFR C677T polymorphism is a risk factor for schizophrenia." [178]

L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials.

http://www.ncbi.nlm.nih.gov/pubmed/23212058 [179]

L-methylfolate Plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036555/ [180]

Several studies have demonstrated l-methylfolate as an effective augmentation strategy with SSRI/SNRIs. [179, 180]

Comparative assessment of adherence measures and resource use in SSRI/SNRI-treated patients with depression using second-generation antipsychotics or L-methylfolate as adjunctive therapy.

http://www.ncbi.nlm.nih.gov/pubmed/24372461 [181]

"Patients who augmented SSRI/SNRI therapy with [second-generation atypical antipsychotics] (SGA) or L-methylfolate achieved [modified application of the HEDIS] (mHEDIS) acute medication management (AMM) acute phase and continuation phase adherence scores of 69%-79% and 50%-62%, respectively. These modified scores exceeded the 2012 national median benchmarks for unmodified HEDIS AMM measures for commercial health plans. In this study, augmentation with L-methylfolate was associated with significantly higher adherence measures compared with augmentation with SGA. In addition, health care utilization and total health care costs, as well as depression-related costs, were significantly lower in the L-methylfolate augmentation group compared with augmentation with SGA." [181]

Effect of adjunctive L-methylfolate 15 mg among inadequate responders to SSRIs in depressed patients who were stratified by biomarker levels and genotype: results from a randomized clinical trial.

http://www.ncbi.nlm.nih.gov/pubmed/24813065 [182]

"The objective of the current post hoc analysis was to evaluate the effect of specific biological and genetic markers on the antidepressant efficacy of adjunctive L-methylfolate 15 mg versus placebo from a trial of inadequate responders to selective serotonin reuptake inhibitors (SSRIs)… Biomarkers associated with inflammation or metabolism and genomic markers associated with L-methylfolate synthesis and metabolism may identify patients with SSRI-resistant depression who are responsive to adjunctive therapy with L-methylfolate 15 mg. Confirmatory studies are needed." [182]

Correlation of clinical response with homocysteine reduction during therapy with reduced B vitamins in patients with MDD who are positive for MTHFR C677T or A1298C polymorphism: a randomized, double-blind, placebo-controlled study.

http://www.ncbi.nlm.nih.gov/pubmed/27035272 [183]

"159 of 170 vitamin-treated patients and 123 of 160 placebo-treated patients were completers. Of the active treatment group, 131 (82.4%) showed a reduction in homocysteine (for a mean in this subgroup of 25%, $p < .001$), while 28 (17.6%) showed no significant change. Placebo patients demonstrated a small elevation in homocysteine. Active-treatment patients demonstrated, on average, a 12-point reduction on the MADRS by week 8, and 42% achieved full remission ($p < .001$). No side effect was significantly different between groups. No patients experienced mania." [183]

Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases.

http://www.ncbi.nlm.nih.gov/pubmed/25449138 [184]

"The Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with various diseases (vascular, cancers, neurology, diabetes, psoriasis, etc.) with the epidemiology of the polymorphism of the C677T that varies dependent on the geography and ethnicity. The 5, 10-Methylenetetrahydrofolate reductase (MTHFR) locus is mapped on chromosome 1 at the end of the short arm (1p36.6). This enzyme is important for the folate metabolism which is an integral process for cell metabolism in the DNA, RNA and protein methylation. The mutation of the MTHFR gene which causes the C677T polymorphism is located at exon 4 which results in the conversion of valine to alanine at codon 222, a common polymorphism that reduces the activity of this enzyme. The homozygous mutated subjects have higher homocysteine levels while the heterozygous mutated subjects have mildly raised homocysteine levels compared with the normal, non-mutated controls. Hyperhomocysteinemia is an emerging risk factor for various cardiovascular diseases and with the increasing significance of this polymorphism in view of the morbidity and mortality impact on the patients, further prevention strategies and nutritional recommendations with the supplementation of vitamin B12 and folic acid which reduces plasma homocysteine level would be necessary as part of future health education. This literature review therefore focuses on the recent evidence-based reports on the associations of the MTHFR C677T polymorphism and the various diseases globally." [184]

Methylfolate meta-analysis for depression

https://www.ncbi.nlm.nih.gov/pubmed/29442609 [185]

No trials report on folate or methylfolate versus placebo as a monotherapeutic option. Only when the evidence was restricted to folate at a dose of <5 mg/day or methylfolate at a dose of 15 mg once daily as an adjunct to selective serotonin reuptake inhibitor therapy was there a significant benefit compared with placebo. [185]

OPRM1, μ Opioid Receptor

Mu-opioid receptors are located throughout brain circuits that are involved in processing rewards, analgesia and stress response. OPRM1 is the main target for many natural and synthetic compounds including opioid medications. A variation in this gene, the **G** allele, has been linked to reduced expression of OPRM1. Clinically, this variation has been linked to higher pain intensity and slower recovery from certain injuries such as a herniated disc.[186, 187] Studies have also found that patients with the **G** allele may need higher doses of opioids to achieve similar analgesia, compared to **A/A** controls. [188-192] Non-opioid analgesics may be a therapeutic option for these patients if clinically indicated. Clinical data also suggest that *OPRM1* **G** allele carriers may be less likely to relapse with naltrexone for the treatment of alcohol use disorders.[193-197]

Literature Summary: Mu Opioid Receptor (OPRM1)

Pharmacogenetics of OPRM1.

http://www.ncbi.nlm.nih.gov/pubmed/24201053/ [188]

"The OPRM1 gene has been a target of interest in a large number of pharmacogenetic studies due to its genetic and structural variation, as well as the role of opioid receptors in a variety of disorders. The mu-opioid receptor (MOR), encoded by OPRM1, naturally regulates the analgesic response to pain and also controls the rewarding effects of many drugs of abuse, including opioids, nicotine, and alcohol. Genetic variants in OPRM1, particularly the non-synonymous polymorphism A118G, have been repeatedly associated with the efficacy of treatments for pain and various types of dependence. This review focuses on the current understanding of the pharmacogenetic impact of OPRM1, primarily with regard to the treatment of pain and addiction." [188]

The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: a systematic review and meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/25794200 [189]

"This study sought to clarify the impact of distinct genetic variations on pain, opioid consumption, and opioid side effects in patients with postoperative pain…The results showed that human μ-opioid receptor gene (OPRM1) 118G allele variant carriers consumed more opioids for analgesia (SMD = -0.17, 95% CI = [-0.25, -0.10], P < 0.00001), but reported higher pain scores (MD = -0.11, 95% CI = [-0.17, -0.04], P = 0.002) and less nausea and vomiting (odds ratio = 1.30, 95% CI = [1.08, 1.55], P = 0.005) than the homozygous 118AA patients during the first 24 hour but not the 48 hour postoperative period… The A118G allele variant of OPRM1 has the most potent influence on pain management of postoperative patients. Opioid receptor gene information may provide valuable information for clinicians to properly manage the analgesic use of opioids individually for better pain management." [189]

Genotyping test with clinical factors: better management of acute postoperative pain?

http://www.ncbi.nlm.nih.gov/pubmed/25809606 [190]

"The aim of this study is to investigate the influence of genetic and non-genetic factors on the variability of response to morphine in acute postoperative pain…OPRM1 and ABCB1 polymorphisms were significantly associated with administered dose of morphine (p = 0.038 and 0.012 respectively). Patients with at least one G allele for c.118A>G OPRM1 polymorphism (AG/GG) needed 4 times the dose of morphine of AA patients…Our preliminary results support the evidence that OPRM1/ABCB1 genotypes along with age, weight and duration of operation have an impact on morphine consumption for acute postoperative pain treatment." [190]

The Influence of Genotype Polymorphism on Morphine Analgesic Effect for Postoperative Pain in Children.

http://www.ncbi.nlm.nih.gov/pubmed/26839669 [191]

"Children with at least one G allele for OPRM1 (AG/GG) had higher postoperative pain scores compared with those with the AA genotype at the time of discharge from the post-anesthesia care unit (P = 0.025). Other recovery profiles were not significantly different between the two groups. There was no significant relationship between genotypes and postoperative pain scores in analysis of ABCB1 and COMT polymorphisms…Genetic polymorphism at OPRM1 A118G, but not at ABCB1 C3435T and COMT Val158Met, influences the analgesic effect of morphine for immediate acute postoperative pain in children." [191]

The pharmacogenetics of opioid therapy in the management of postpartum pain: a systematic review.

http://www.ncbi.nlm.nih.gov/pubmed/26652709 [192]

"Among the 2082 papers retrieved from the search, 17 were included in the review. These 17 papers consisted of various study designs, opioids, polymorphisms and patient outcomes. This systematic review reveals that CYP2D6, OPRM1 A118G, UGT2B7 C802T and ABCB1 G2677AT may contribute to postpartum analgesia or adverse events." [192]

Variation in Mu-Opioid Receptor Gene (*OPRM1*) as a Moderator of Naltrexone Treatment to Reduce Heavy Drinking in a High Functioning Cohort.

https://www.ncbi.nlm.nih.gov/pubmed/24729984 [193]

"It is well known that naltrexone, an FDA-approved medication for treatment of alcohol dependence, is effective for only a subset of individuals. Recent studies have examined the utility of a functional A118G single nucleotide polymorphism (SNP) of the mu-opioid receptor gene (*OPRM1*) as a predictor of naltrexone treatment response. Although the findings to date have generally been consistent with a moderating effect of the SNP, further evaluation of this hypothesis is warranted…Naltrexone-treated

subjects with one or two 118G alleles had a significantly greater percentage of non-hazardous drinking (NoH) ($p < 0.01$) than those treated with placebo or A118 homozygotes in either medication group. These results are consistent with a modest moderating effect of the OPRM1 118G allele on the reduction of heavy drinking by naltrexone treatment." [193]

Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment.

https://www.ncbi.nlm.nih.gov/pubmed/22784013 [194]

"To evaluate the role of the functional Asn40Asp polymorphism in the mu-opioid receptor gene on drinking behavior and naltrexone's ability to attenuate drinking, we used a daily diary method in a 12-week, randomized clinical trial of naltrexone to reduce drinking. Participants (n = 158 problem drinkers) were assigned to receive either daily or targeted naltrexone 50 mg (n = 81) or matching placebo (n = 77)… In summary, when the evening level of desire to drink was relatively high, Asp40 allele carriers were at greater risk than Asn40 homozygotes to drink more, which was attenuated by naltrexone. Although average measures across the study were not informative, daily reports helped to demonstrate the moderating effects of genetic variation on the relation between desire to drink and alcohol consumption and the effects of naltrexone on that phenotype." [194]

Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis.

https://www.ncbi.nlm.nih.gov/pubmed/22515274 [195]

"Previous studies have suggested that the effect of naltrexone in patients with alcohol dependence may be moderated by genetic factors. In particular, the possession of the G allele of the A118G polymorphism of the micro-opioid receptor gene (OPRM1) has been associated with a better response to naltrexone, although controversial results have been reported. The aim of this paper is to combine previous findings by means of a systematic review and a meta-analysis. We retrieved studies on the relationship between A118G polymorphism in OPRM1 gene and response to treatment with naltrexone in patients with alcohol dependence by means of electronic database search. A meta-analysis was conducted using a random-effects model. Calculations of odds ratio (OR) and their confidence intervals (CI) and tests for heterogeneity of the results have been performed. Six previous studies have analyzed the role of A118G polymorphism in response to naltrexone for alcohol dependence. After meta-analysis, we found that naltrexone-treated patients carrying the G allele had lower relapse rates than those who were homozygous for the A allele (OR: 2.02, 95% CI 1.26-3.22; P = 0.003). There were no differences in abstinence rates. Our results support the fact that the G allele of A118G polymorphism of OPRM1 moderates the effect of naltrexone in patients with alcohol dependence. This genetic marker may therefore identify a subgroup of individuals more likely to respond to this treatment." [195]

A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans.

https://www.ncbi.nlm.nih.gov/pubmed/15608594 [196]

"Recent research has implicated the endogenous opioid system in the development of alcohol use disorders. The A118G polymorphism of the OPRM1 gene has been shown to confer functional differences to mu-opioid receptors, such that the G variant binds beta-endorphin three times more strongly than the A variant. The goal of this study was to test whether the A118G polymorphism is associated with sensitivity to the effects of alcohol…These findings may help to explain previous research suggesting that naltrexone is more effective among individuals with the G allele. A medication that reduces feelings of euphoria after alcohol consumption may be more successful among individuals with a genetic predisposition to greater feelings of euphoria after consuming alcohol." [196]

An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study.

https://www.ncbi.nlm.nih.gov/pubmed/18250251 [197]

"Naltrexone hydrochloride treatment for alcohol dependence works for some individuals but not for everyone. Asn40Asp, a functional polymorphism of the mu-opioid receptor gene (OPRM1), might predict naltrexone response. To evaluate whether individuals with alcoholism who are heterozygous (Asp40/Asn40) or homozygous (Asp40/Asp40) for the OPRM1 Asp40 allele respond better to naltrexone…These results confirm and extend the observation that the functionally significant OPRM1 Asp40 allele predicts naltrexone treatment response in alcoholic individuals. This relationship might be

obscured, however, by other efficacious treatments. OPRM1 genotyping in alcoholic individuals might be useful to assist in selecting treatment options." [197]

SLC6A4, Serotonin Transporter

SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake. Antidepressant activity of SSRI medications is achieved through inhibition of this protein. Two variations in *SLC6A4* are tested within the serotonin-transporter-linked polymorphic region (5-HTTLPR).

- 5-HTTLPR is a 43 or 44-base-pair deletion of DNA in *SLC6A4*. Patients who have a deletion of this section are termed "short" or **S** patients. Patients who do not have this deletion are termed "long" or **L** patients. Studies have repeatedly shown that the short variant is associated with a reduction in the expression of the serotonin transporter.

In addition to the long/short variation, Genomind Professional PGx also tests for a single nucleotide polymorphism (SNP) within the long (L) gene, which causes impaired expression similar to the short variant. This variation is represented by either an **L(A)** or an **L(G)**, and patients who possess the **L(G)** allele have poorer expression of the serotonin transporter.

Individuals with these variations may have reduced reuptake of synaptic serotonin, and several studies have shown that individuals who are homozygous for the L(A) allele demonstrate improved response to SSRIs and lower likelihood of side effects. Retrospective studies have also shown that Caucasian individuals with risk variations [**S or L(G)**] may be more likely to have a poor response, slow response, or increased risk for adverse events during treatment with SSRI medications, as compared to individuals who do not possess these variants. [163, 198-204] More specifically, individuals who carry only a single risk variant [**S or L(G)** alone] appear to be at increased risk of adverse reactions, particularly gastrointestinal side effects, whereas the **S/S, S/L(G)** and **L(G)/L(G)** homozygotes are at a greater risk of non-response and adverse effects. These homozygous risk allele carriers have also been shown to have an increased risk for abnormal cortisol release in response to stressors.[205-212] Among Caucasians with risk alleles, one should carefully assess SSRI medications, including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Alternative interventions, such as SNRIs or non-SSRI antidepressants that do not singularly target the serotonin transporter protein, may be relevant in these patients.

Literature Summary: Serotonin Transporter (SLC6A4)

Meta-analysis Confirm SLC6A4 variants (5-HTTLPR) are associated with SSRI response and adverse effects.

http://www.ncbi.nlm.nih.gov/pubmed/18982004 [198]
http://www.ncbi.nlm.nih.gov/pubmed/17146470 [199]
http://www.ncbi.nlm.nih.gov/pubmed/22137564 [200]

"…we systematically reviewed literature, selecting 33 studies for an exploratory analysis without any a priori hypothesis. Then we analyzed separately 19 studies performed on Caucasians and 11 on Asians. We tested two phenotypes--remission and response rates--and three genotype comparisons--ll versus ls/ss, ss versus ll/ls and ll versus ss - using the Cochrane review manager. Evaluations were performed separately for SSRIs and mixed/other drugs. Possible clinical modulators were investigated. In the exploratory analysis, we found an association between l allele and l/l genotype and remission. When the analysis was split for ethnic group, in Caucasians we found an association between l allele and both response (OR = 1.58, C.I. 1.16-2.16, p = 0.004), and remission (OR = 1.53, C.I. 1.14-2.04, p = 0.004) in the SSRI group. Only a marginal association between l allele and remission (OR = 1.41, C.I. 1.02-1.95, p = 0.04) survived pooling together mixed antidepressant treatments. In Asians, a small effect of 5-HTTLPR on remission for mixed antidepressants was detected (OR = 2.10, C.I. 1.15-3.84, p = 0.02)." [200]

Variants of SLC6A4 Influence the Outcome of Antidepressant Therapy in Psychiatric Inpatients.

http://www.ncbi.nlm.nih.gov/pubmed/17617292 [201]
http://www.ncbi.nlm.nih.gov/pubmed/25980509 [202]
http://www.ncbi.nlm.nih.gov/pubmed/23973251 [203]
http://www.ncbi.nlm.nih.gov/pubmed/24192302 [163]

http://www.ncbi.nlm.nih.gov/pubmed/24558768 [204]

"This paper gives an overview of 35 studies investigating the efficacy of SSRI antidepressants in dependence of 5-HTTLPR polymorphism… Briefly, the great majority of studies conducted have shown that L-allele carriers have a faster and better response to SSRI antidepressants, if they are Caucasians…Pharmacogenetic analysis of 5-HTTLPR polymorphism has proven to be economically cost-effective considering the recurrent course of the disease. It would appear that the response to SSRI antidepressants and the development of adverse reactions are associated with 5-HTTLPR polymorphism in Caucasians and this pharmacogenetic analysis could be one of the first in future clinical practice." [204]

Serotonin transporter 5-HTTLPR genotype moderates the effects of childhood adversity on posttraumatic stress disorder risk: a replication study.

http://www.ncbi.nlm.nih.gov/pubmed/22693124 [205]

"We reported that the 5-HTTLPR polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) moderates the effect of childhood adversity on posttraumatic stress disorder (PTSD) risk. In the present study, we considered 5,178 subjects (a group with generally high substance dependence comorbidity, as for our previous study) using similar methodology to replicate our previous results. We found that, as reported in our previous study, in individuals with childhood adversity, the presence of one or two copies of the S allele of 5-HTTLPR increased the risk to develop PTSD. This gene-environment interaction effect was present in European Americans (EAs), but not in African Americans (AAs; EAs, OR = 1.49, 95% CI = 1.07-2.08, P = 0.019; AAs, OR = 0.90, 95% CI = 0.60-1.35, P = 0.62)." [205]

An examination of the association between 5-HTTLPR, combat exposure, and PTSD diagnosis among U.S. veterans.

http://www.ncbi.nlm.nih.gov/pubmed/25793742 [206]

Objective was to, "…examine the association between the 5-HTTLPR polymorphism of the serotonin transporter (SLC6A4) gene, combat exposure, and posttraumatic stress disorder (PTSD) diagnosis and among two samples of combat-exposed veterans…The first sample included 550 non-Hispanic Black (NHB) combat-exposed veterans. The second sample included 555 non-Hispanic White (NHW) combat-exposed veterans…Within the NHB sample, a significant additive effect was observed for 5-HTTLPR (OR = 1.502, p = .0025), such that the odds of having a current diagnosis of PTSD increased by 1.502 for each additional S' allele. No evidence for an association between 5-HTTLPR and PTSD was observed in the NHW sample…The present study suggests that there may be an association between 5-HTTLPR genotype and PTSD diagnosis among NHB veterans; however, no evidence for the hypothesized 5-HTTLPR x combat interaction was found." [206]

Interaction between SLC6A4 promoter variants and childhood trauma on the age at onset of bipolar disorders.

http://www.ncbi.nlm.nih.gov/pubmed/26542422 [213]

"Age at onset (AAO) of bipolar disorders (BD) could be influenced both by a repeat length polymorphism (5HTTLPR) in the promoter region of the serotonin transporter gene (SLC6A4) and exposure to childhood trauma. We assessed 308 euthymic patients with BD for the AAO of their first mood episode and childhood trauma. Patients were genotyped for the 5HTTLPR (long/short variant) and the rs25531. Genotypes were classified on functional significance (LL, LS, and SS)…These results remained significant after correction using FDR. Regression models suggested an interaction between emotional neglect and 'SS' genotype on the AAO (p = 0.009) and no further interaction with other trauma subtypes. Partial replication was obtained in the Brazilian sample, showing an interaction between emotional abuse and 'LS' genotype on the AAO (p = 0.02). In conclusion, an effect of childhood trauma on AAO of BD was observed only in patients who carry a specific stress responsiveness-related SLC6A4 promoter genotype." [213]

SLC6A4 variants are associated with cortisol response to psychosocial stress.

https://www.ncbi.nlm.nih.gov/pubmed/20006325 [207]
http://www.ncbi.nlm.nih.gov/pubmed/26464328 [208]
https://www.ncbi.nlm.nih.gov/pubmed/17353910 [209]
https://www.ncbi.nlm.nih.gov/pubmed/24821403 [210]
https://www.ncbi.nlm.nih.gov/pubmed/18005940 [211]

"Recent evidence indicates that individuals who are homozygous for the short (s) allele in the promoter region of the serotonin transporter gene have higher rates of depression and other psychiatric disorders as a function of exposure to increasing levels of stressful life events than do individuals who have one or two copies of the long (l) allele. Despite the reliability of this association, the mechanism by which this polymorphism confers risk for psychopathology in the presence of stress is not understood. This study was designed to examine the formulation that individuals who are homozygous for the s allele are characterized by a greater biological reactivity to stress than are their counterparts who have one or two copies of the l allele…Girls at high (n = 25) and low (n = 42) risk for depression by virtue of the presence or absence of a family history of this disorder were genotyped and exposed to a standardized laboratory stress task. Cortisol levels were assessed before the stressor, after the stressor, and during an extended recovery period. Girls who were homozygous for the s allele produced higher and more prolonged levels of cortisol in response to the stressor than did girls with an l allele. These findings indicate that the 5-HTTLPR polymorphism is associated with biological stress reactivity, which may increase susceptibility to depression in the face of stressful life events." [211]

https://www.ncbi.nlm.nih.gov/pubmed/26136163 [212]
"The serotonin transporter genetic variant 5HTTLPR influences activation and feedback control of the hypothalamic-pituitary-adrenal axis, and has been shown to influence the effect of stressful life events on behavioral health…Distinct and interactive effects of 5HTTLPR long allele carriage [L] versus homozygous short allele carriage [SS]) and prior trauma exposure (low versus high) were evaluated, after which a priori group comparisons were performed between hypothesized high resilience (L/low) and low resilience (SS/high) groups. For sNGF, L/low produced the greatest sNGF throughout stress exposure while SS/high demonstrated the smallest; L/high and SS/low bisected these two extremes and were nearly identical to each other (i.e., SS/high < SS/low = L/high < L/low). Thus, 5HTTLPR and prior trauma exposure demonstrated counterbalancing (additive) forces." [212]

SLC6A4 S/S genotype is Associated with Violent Suicide in Male Citalopram Users

https://www.ncbi.nlm.nih.gov/pubmed/?term=28608626 [214]

In this study, researchers tested the hypothesis that the genetic variants associated with decreased citalopram efficiency, 5HTTLPR/rs25531… is more frequent among citalopram users committing suicide than among the citalopram users in general. The study population comprised 349 suicide victims (184 males and 165 females). Based on the suicide method used, cases were divided into two groups; violent (88 males and 49 females) and non-violent (96 males and 116 females). The control group (284; 159 males and 125 females) consisted of citalopram users who died of causes other than suicide. Researchers found that male citalopram users with low functioning s/s genotype of 5HTTLPR/rs25531 were at increased risk to commit violent suicide (OR 2.50, 95%CI 1.15-5.42, p = 0.020).[214]

Pharmacokinetic Genes

ABCB1, ATP Binding Cassette Subfamily B Member 1

P-glycoprotein (P-gp), encoded by the **ABCB1** gene, is an efflux pump responsible for transport of a number of drugs and exogenous compounds out of the cell. Depending on the tissue, these pumps can affect drug absorption (e.g., intestinal lining), distribution (e.g., blood–brain barrier), and excretion (e.g., proximal tubules of the kidney).[215] In the context of psychiatric medications, particular variants can increase the intestinal absorption and brain permeability of certain drugs. [215-219] This gene has >120 polymorphisms, but only a handful have shown any predictive validity for response to antidepressant agents. A recent review by Brückl and Uhr (2016) identified two candidate SNPs (**rs2032583 and rs1045642**) that were more consistently associated with either clinical efficacy or risk for side effects to some antidepressants, antipsychotics, or opioids.[219] Some common antidepressants affected by the **ABCB1** gene include citalopram, escitalopram, fluvoxamine, paroxetine, desvenlafaxine, venlafaxine, vilazodone, amitriptyline and nortriptyline.[220-223] Most opioids seem susceptible to increased brain permeability in the presence of certain ABCB1 variants.[216, 224-228] Several of the second-generation antipsychotics are sensitive to p-glycoprotein and have been associated with higher rates of side effects with this gene. [220, 229-233] These data suggest that genetic variants of ABCB1, which impact drug absorption and brain penetration, may play a role in patient response to medications that are substrates of this protein.

Literature Summary: ATP Binding Cassette Subfamily B Member 1 (ABCB1)

Variants of the ABCB1 gene alter increase absorption and brain permeability of certain drugs

https://www.ncbi.nlm.nih.gov/pubmed/?term=24086514 [216]
https://www.ncbi.nlm.nih.gov/pubmed/?term=17192767 [217]
https://www.ncbi.nlm.nih.gov/pubmed/?term=26664259 [218]
https://www.ncbi.nlm.nih.gov/pubmed/27918249 [219]
https://www.ncbi.nlm.nih.gov/pubmed/?term=20216335 [215]

"P-gp is expressed… in the plasma membrane of cells in barrier and elimination organs, where it has protective and excretory functions. It plays an important role in first-pass elimination of orally administered drugs to limit their bioavailability by effluxing drugs from the lumen-facing epithelia of the small intestine and colon, and from the bile-facing canaliculi of the liver… It restricts the permeability of drugs into 'sanctuary' organs from the apical or serosal side of blood-tissue barriers (e.g. blood-brain, blood-cerebral spinal fluid, blood-placenta, blood-testis barriers) … A great number of studies have been carried out to establish the role of ABCB1 genetics in various phenotypes such as P-gp expression, function, drug response, and disease susceptibility." [215]

ABCA7 C3435T is associated with nortriptyline-induced postural hypotension in patients treated for major depression.

https://www.ncbi.nlm.nih.gov/pubmed/?term=12082591 [220]

"A single nucleotide polymorphism (SNP) of ABCB1 (3435C>T) was recently correlated with expression levels and in vivo function of P-gp. We examined this SNP in patients with major depression enrolled in a randomized antidepressant treatment trial of nortriptyline and fluoxetine, and observed a significant association between nortriptyline-induced postural hypotension and 3435C>T (chi(2) = 6.78, df = 2, P = 0.034). Our results suggest that homozygosity for 3435T alleles of ABCB1 is a risk factor for occurrence of nortriptyline-induced postural hypotension (OR = 1.37, P = 0.042, 95% CI 1.01-1.86)."[220]

ABCB1 rs2032583 influences response to SSRIs.

https://www.ncbi.nlm.nih.gov/pubmed/?term=22641028 [221]
https://www.ncbi.nlm.nih.gov/pubmed/27918249 [219]
https://www.ncbi.nlm.nih.gov/pubmed/?term=26704739 [222]
https://www.ncbi.nlm.nih.gov/pubmed/?term=25847751 [223]

"In this meta-analysis, we systematically summarized 16 pharmacogenetic studies focused on the association of ABCB1 variants and antidepressant treatment outcome in patients with MD (overall n = 2695). We investigated the association of treatment outcome and six ABCB1 single nucleotide polymorphisms (SNPs)….SNP rs2032583 showed a nominally significant association across all studies (P = 0.035, SNP was studied in a total of 2,037 patients) and a significant Bonferroni-corrected association among inpatients (P = 1.5 × 10(-05), n = 485)."[223]

Single-nucleotide polymorphism C3435T in the ABCB1 gene is associated with opioid consumption in postoperative pain.

https://www.ncbi.nlm.nih.gov/pubmed/24034787 [224]

"Based on a mixed linear model, the ABCB1 three genotypes showed a statistically significant effect on opioid consumption (F = 4.20, P = 0.017). There was a statistically significant difference in opioid consumption among the ABCB1 three genotypes in the 0-6 hours (P = 0.031, 95% confidence interval [CI] CC 14.7-24.8 mg and TT 5.2-14.6 mg) and 6-12 hours (P = 0.009, 95% CI CC 5.6-13.8 mg and TT 1.2 mg-5.1 mg) postoperative period. There were no significant statistical differences in opioid consumption among the ABCB1 three genotypes in the 12-24 hours (P = 0.302) and 24-48 hours (P = 0.763) postoperative period. The TT genotype had significantly lower levels of cumulative opioid consumption compared with the CC genotype in first 24 hours after surgery (P = 0.029). [224]

Gene polymorphisms of OPRM1 A118G and ABCB1 C3435T may influence opioid requirements in Chinese patients with cancer pain.

https://www.ncbi.nlm.nih.gov/pubmed/23803057 [225]

"Significant higher 24h-opioid doses were observed in patients with GG (P=0.0004) and AG + GG (P=0.005) genotypes than the AA carriers. The dominant mutant 118G allele tended to be associated with progressively increasing 24h-opioid doses (P=0.001). Compared with CC/CT, patients with ABCB1 TT genotype received higher 24h- and weight-surface area-adjusted-24h- opioids doses (P=0.057 and 0.028, respectively)." [225]

Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers.

https://www.ncbi.nlm.nih.gov/pubmed/19514130 [226]

"In a multicenter study conducted in tertiary care outpatient pain centers, 352 patients (156 men and 196 women, aged 58.5+/- 14.6 years) treated for 1-600 months (63.4 +/- 92.4 months) with various opioids for pain of various origins were included. Genotyping was performed for all the variants reportedly modulating pain in well-defined cohorts. Association analyses focused on opioid dosing, the actual 24-h pain score on a 0-10 rating scale and the occurrence of side effects… Daily opioid doses ranged from 4 to 1750 mg oral morphine equivalents (133.4 +/- 203.2 mg) and significantly decreased in a gene dose-dependent manner with the P-glycoprotein variant ABCB1 3435C>T." [226]

Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief.

https://www.ncbi.nlm.nih.gov/pubmed/17898703 [227]

"…univariate analysis with a recessive model allowed us to detect a significant difference in morphine response between the two genotype groups: patients sharing C/C and C/T alleles proved to be moderate responders (ΔNRS = 2.73), whereas T/T carriers were good responders (ΔNRS = 4.39). The biological plausibility of such an association relies on the assumption that a function membrane transporter determines an effect drug flux from the cell, reducing morphine absorption, permeability of the blood-brain barrier, and thus bioavailability of morphine for brain receptors. Therefore, these findings lead to the conclusion that the *ABCB1*/*MDR1* gene may play a relevant role in morphine pharmacokinetics as well." [227]

Pharmacokinetic modelling of morphine, morphine-3-glucuronide and morphine-6-glucuronide in plasma and cerebrospinal fluid of neurosurgical patient after short-term infusion of morphine.

https://www.ncbi.nlm.nih.gov/pubmed/12492606 [228]

"The homozygous mutant genotype (TT) coincided with the highest maximum CSF concentrations of [morphine] ($P<0.001$, nonparametric rank test), which is consistent with previously published data indicating that the TT genotype is associated with lower expression of P-glycoprotein. This would be compatible with high CSF concentrations due to decreased efflux of [morphine] across the blood-brain barrier." [228]

Associations of ABCB1 gene polymorphisms with aripiprazole-induced autonomic nervous system dysfunction in schizophrenia.

https://www.ncbi.nlm.nih.gov/pubmed/29191720 [229]

"Our study revealed that the T allele of rs1045642, C allele of rs2235048, and T-C-T-A haplotype (rs1045642-rs2235048-rs1128503-rs2032582) are associated with decreased sympathetic activity in patients with schizophrenia treated with aripiprazole. Previous studies have reported that the rs1045642 T variant was associated with a lower level of intestinal MDR1 expression and affected the plasma aripiprazole levels." [229]

Genetic risk factors for clozapine-induced neutropenia and agranulocytosis in a Dutch psychiatric population.

https://www.ncbi.nlm.nih.gov/pubmed/27168101 [230]

"When comparing neutropenia patients with controls, again the risk of having neutropenia was about threefold higher in patients with the ABCB1 3435TT genotype; the ABCB1 3435TT genotype was more frequent in neutropenia patients (34% versus 20% in controls) and the wild-type ABCB1 3435CC genotype was more frequent in controls (31% versus 18% in neutropenia patients; $P=0.05$)." [230]

Association study of MDR1 and 5-HT2C genetic polymorphisms and antipsychotic-induced metabolic disturbances in female patients with schizophrenia.

https://www.ncbi.nlm.nih.gov/pubmed/20195292 [231]

"…among olanzapine-treated patients, statistically significant glucose level increase was obtained in association with C3435T genotype as well, with the greatest increase among patients without the C3435 allele (mean±s.d. baseline C vs no C: 4.70±0.47 vs 5.09±0.72 increased to 5.07±0.79 vs 5.80± 2.26, $F=5.062$, d.f.=1, $P=0.028$" [231]

The influence of 5-HT(2C) and MDR1 genetic polymorphisms on antipsychotic-induced weight gain in female schizophrenic patients.

https://www.ncbi.nlm.nih.gov/pubmed/18718676 [232]

"Haplotype-based analysis of two MDR1 loci, exon 21 G2677T and exon 26 C3435T, revealed a slightly lower representation of the G2677/C3435 haplotype in the >or=7% group [patients gaining more than 7% of their initial weight]. In the subgroup of patients treated with risperidone, we found borderline overrepresentation of 2677T, significant overrepresentation of 3435T variant and borderline overrepresentation of 2677T/3435T haplotype the >or=7% group, whereas G2677/C3435 haplotype was found to be less represented in the >or=7% group. Our data indicate a nonsignificant role of 759C/T 5-HT(2C) in SDA-induced weight gain, and a stronger influence of the MDR1 G2677T and C3435T polymorphisms on risperidone-induced weight gain in female schizophrenic patients. 3435T and 2677T MDR1 variants, both associated with lower P-gp function, might predispose to higher risperidone accessibility to the brain that would lead to stronger effects, including weight gain." [232]

Antipsychotic drug dosage and therapeutic response in schizophrenia is influenced by ABCB1 genotypes.

https://www.ncbi.nlm.nih.gov/pubmed/?term=22909202 [233]

"A strong allelic, genotypic and haplotypic association, was observed, which was predictive of good response to antipsychotics. Individuals carrying the favorable homozygous genotypes of rs1045642 and rs2032582 displayed better response with increased dosage while those carrying risk genotype manifested refractoriness on increased dosage." [233]

UGT1A4 & UGT2B15: UDP Glucuronosyltransferase Genes

Uridine 5'-diphospho-glucuronosyltransferase **(UGT)** is an enzyme responsible for transferring the glucuronic acid component of UDP-glucuronic acid to a drug, in order to increase water solubility and aid in drug excretion.[234] It is an important part of phase II drug metabolism and mutations in the UGT genes, similar to mutations in CYP450 enzymes, can produce changes in drug exposure. Two UGT enzymes have been shown to have a clinically significant impact on drug exposure for anxiolytics, mood stabilizers, and antipsychotics.

UGT1A4*3 is a variant of UGT1A4 in which a single SNP substitution may result in ultra-rapid metabolizer **(UM)** status and decreased serum levels of lamotrigine.[235-237] Olanzapine metabolism may also be affected by this mutation, though there is some conflicting evidence between in vivo studies, and this impact appears to be relatively minor.[238]

UGT2B15*2, a variant of another family of UGT enzymes, may result in intermediate metabolizer **(IM)** status and subsequent increased serum levels of some benzodiazepines. Both in vitro and in vivo studies observed an impact of this polymorphism on oxazepam and lorazepam drug exposure.[238-241] As oxazepam is an active metabolite of several other benzodiazepines (e.g., chlordiazepoxide, clorazapate, diazepam, and temazepam), drug exposure of these compounds may be affected as well.

Literature Summary: UGT1A4

Systematic review of UGT polymorphisms for drug dosing

https://www.ncbi.nlm.nih.gov/pubmed/24076267 [238]

"… compared to other drug metabolizing enzymes much less systematic research has been conducted on the polymorphisms of UGT enzymes. However, there is evidence of the existence of large monogenetic functional polymorphisms affecting pharmacokinetics and suggesting a potential use of UGT polymorphisms for the individualization of drug therapy." [238]

Correlation of the UGT1A4 gene polymorphism with serum concentration and therapeutic effiacy of lamotrigine in Han Chinese of Northern China.

https://www.ncbi.nlm.nih.gov/pubmed/24820767 [235]

"The study cohort comprised 106 Han Chinese patients with epilepsy who were receiving LTG monotherapy. Blood samples were taken and LTG levels measured. The presence of UGT1A4 (70C > A) and UGT1A4 (142 T > G) was determined. The therapeutic efficacy of LTG at the 1-year time-point was assessed. All patients were homozygous for the CC genotype of UGT1A4 (70C > A), while the distribution of UGT1A4 (142 T > G) varied among patients. Two patients had a single nucleotide deletion at position 127 (UGT1A4 127delA). To evaluate the effect of the UGT1A4 (142 T > G) polymorphism on LTG pharmacokinetics, patients were divided into two groups. Group A included patients with the 142TG or 142GG polymorphism and Group B patients had the 142TT polymorphism. The normalized

blood concentration and the efficacy of LTG were higher in Group B patients than in Group A patients ($P < 0.05$). The two patients with UGT1A4 127delA genotype had extremely high blood levels of LTG, and treatment was discontinued in one of these patients due to a severe LTG-associated rash. Patients with the UGT1A4 142TT polymorphism had a higher blood LTG concentration and better therapeutic efficacy, suggesting that this polymorphism influences LTG activity." [235]

Factors that influence the pharmacokinetics of lamotrigine in Japanese patients with epilepsy.
https://www.ncbi.nlm.nih.gov/pubmed/26790665 [236]

"We derived a formula to predict LTG concentrations that considers the daily dose of LTG, body weight, valproic acid concentration, phenytoin co-administration, and the co-administration of phenobarbital and/or carbamazepine as well as UGT1A4 142T>G and UGT2B7 -161C>T polymorphisms (adjusted coefficients of determination R (2) = 0.734). Furthermore, we used this formula to reveal a strong positive correlation between measured and predicted LTG concentrations ($r^2 = 0.76$, $p < 0.001$)." [236]

UGT1A4*3 encodes significantly increased glucuronidation of olanzapine in patients on maintenance treatment and in recombinant systems.
https://www.ncbi.nlm.nih.gov/pubmed/22713701 [237]

"Olanzapine, a world leader in antipsychotic drugs, is used in the treatment of schizophrenia and bipolar disorder. There is considerable interpatient variability in its hepatic clearance. Polymorphic glucuronidation of olanzapine by uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4) was investigated retrospectively in patient samples taken for routine therapeutic drug monitoring (TDM) and in recombinant metabolic systems in vitro. Multivariate analyses revealed that patients who were heterozygous as well as those who were homozygous for the UGT1A4*3 allelic variant had significantly higher concentrations of the major metabolite olanzapine 10-N-glucuronide in serum (+38% ($P = 0.011$) and +246% ($P < 0.001$), respectively). This finding was in line with the significant increases in glucuronidation activity of olanzapine observed with recombinant UGT1A4.3 (Val-48) as compared with UGT1A4.1 (Leu-48) (1.3-fold difference, $P < 0.001$). By contrast, serum concentrations of the parent drug were not significantly influenced by UGT1A4 genotype. Our findings therefore indicate that UGT1A4-mediated metabolism is not a major contributor to interpatient variability in olanzapine levels. However, with respect to other drugs for which UGT1A4 has a dominant role in clearance, increased glucuronidation encoded by UGT1A4*3 might impact the risk for subtherapeutic drug exposure." [237]

Literature Summary: UGT2B15

Systematic review of UGT polymorphisms for drug dosing
https://www.ncbi.nlm.nih.gov/pubmed/24076267 [238]

In conclusion, compared to other drug metabolizing enzymes much less systematic research has been conducted on the polymorphisms of UGT enzymes. However, there is evidence of the existence of large monogenetic functional polymorphisms affecting pharmacokinetics and suggesting a potential use of UGT polymorphisms for the individualization of drug therapy. [238]

Evidence for oxazepam as an in vivo probe of UGT2B15: oxazepam clearance is reduced by UGT2B15 D85Y polymorphism but unaffected by UGT2B17 deletion.
https://www.ncbi.nlm.nih.gov/pubmed/19916996 [239]

"Median oxazepam apparent oral clearance was significantly lower in 85YY subjects (1.62 ml min(-1) kg(-1)) compared with 85DD subjects (3.35 ml min(-1) kg(-1); P= 0.003, Student-Newman-Keuls test), whereas 85DY subjects were intermediate (2.34 ml min(-1) kg(-1); P= 0.018 vs. 85DD, P= 0.034 vs. 85YY). Regression analysis indicated that UGT2B15 D85Y genotype accounted for 34% of interindividual variability." [239]

Effect of the UGT2B15 genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers.
https://www.ncbi.nlm.nih.gov/pubmed/15961980 [240]

"The UGT2B15*2/*2 group showed 0.58-fold (95% confidence interval, 0.43-0.72; $P < .0001$) lower systemic clearance during the basal state and 1.37-fold (95% confidence interval, 1.05-1.88; $P = .037$) higher area under the visual analog scale-time curve during the induced state compared with the UGT2B15*1/*1 group. The mean systemic clearance of lorazepam decreased by 20% in the inhibited state and increased by 140% in the induced state. During the inhibited or induced state, absolute values of clearance were consistently lower in the *2/*2 group, but the percent changes from baseline did not differ significantly by genotype…Our results suggest that the UGT2B15*2 polymorphism is a major

determinant of interindividual variability with respect to the pharmacokinetics and pharmacodynamics of lorazepam." [240]

UDP-glucuronosyltransferase (UGT) 2B15 pharmacogenetics: UGT2B15 D85Y genotype and gender are major determinants of oxazepam glucuronidation by human liver.

https://www.ncbi.nlm.nih.gov/pubmed/15044558 [241]

"Phenotype-genotype studies were conducted using microsomes and DNA prepared from the same set of 54 human livers. Sequencing of the UGT2B15 gene revealed three nonsynonymous polymorphisms, D85Y, T352I, and K523T, with variant allele frequencies of 0.56, 0.02, and 0.40, respectively. D85Y genotype showed a significant effect (p = 0.012) on S-oxazepam glucuronidation with lower median activities in 85Y/Y livers (49 pmol/min/mg protein) compared with 85D/D livers (131 pmol/min/mg), whereas 85D/Y livers were intermediate in activity (65 pmol/min/mg)… In conclusion, gender and D85Y genotype are identified as major determinants of S-oxazepam glucuronidation by human liver and may explain in part polymorphic oxazepam glucuronidation by human subjects." [241]

Cytochrome P450 (CYP450) Genes

CYP450s constitute a family of hepatic enzymes that catalyze the breakdown of various substances. **CYP1A2**, **CYP2B6**, **CYP2C9**, **CYP2C19**, **CYP2D6** and **CYP3A4/5** are responsible for the degradation of a large number of psychotropic medications, and variations in the genes encoding for these enzymes can alter their activity, resulting in unexpected drug serum levels, altered efficacy and adverse events. Furthermore, various medications, including but not limited to many psychotropic drugs, can inhibit or induce these enzymes, altering their phenotypic expression.

For **CYP1A2**, **CYP2B6**, **CYP2C9**, **CYP2C19**, and **CYP2D6**, patients with normal rates of drug metabolism are termed extensive metabolizers (**EM**). Patients exhibiting the intermediate metabolizer (**IM**) or poor metabolizer (**PM**) phenotype (intermediate or low activity) have reduced enzyme activity, resulting in increased risk for elevated drug serum levels, drug-drug interactions and/or reduced production of active metabolites. Reduced doses of medications metabolized by these systems may be clinically appropriate.[242-246] The ultra-rapid metabolizer (**UM**) phenotype (high/fast activity) may lead to elevated enzyme activity, resulting in increased risk for subtherapeutic drug serum levels, poor efficacy and adverse events associated with metabolite buildup. Increased doses of medications in patients with this phenotype may be clinically appropriate. [247-251] [252-257]

CYP1A2 activity can result in the same metabolizer phenotypes as the previously mentioned CYPs; **PM** or **IM** indicating reduced metabolism, or **EM** indicating normal metabolism. [20, 247-250][252, 258]

Additionally, **CYP1A2** may also be greatly affected by the presence of inducers, leading to increased metabolism. A common variation in this gene, ***1F**, affects how potently inducers may increase **CYP1A2** activity. [164, 259-273] [274, 275] [276-281] The presence of this variant may increase the metabolism of a drug **in the presence of inducers** such as marijuana/tobacco smoke, coffee or other medications[164, 259, 265, 267, 269-271, 277].

Lastly, the combinatorial effects of CYP3A enzymes, including **CYP3A4** and **CYP3A5**, are responsible for the overall metabolism of CYP3A substrates. Variations in ***CYP3A4*** and ***CYP3A5*** can affect the rate of metabolism for CYP3A substrates, and the combined phenotype is reported as **slow**, **normal** or **fast** activity. Patients who have fast **CYP3A4/5** activity may display increased metabolism, which may lead to a risk for subtherapeutic drug serum levels, poor efficacy and adverse events associated with metabolite buildup. Increased doses of medications metabolized by this system may be clinically appropriate. Patients who are slow metabolizers for **CYP3A4/5** may have reduced enzyme activity, resulting in increased risk for elevated drug serum levels, drug-drug interactions and/or reduced production of active metabolites. [15, 251] [20, 247-250, 252, 258, 261, 273, 274, 282-285]

Literature Summary: Cytochrome P450 1A2: (CYP1A2)

Pharmacogenetics of second-generation antipsychotics.

http://www.ncbi.nlm.nih.gov/pubmed/24897292 [20]

Pharmacogene Variation Consortium

https://www.pharmvar.org/

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [248]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [249]

Meta-analysis of genetic polymorphisms on CYP1A2 activity
https://www.ncbi.nlm.nih.gov/pubmed/29282363 [286]

Single nucleotide polymorphisms and haplotypes of CYP1A2 in a Japanese population.
https://www.ncbi.nlm.nih.gov/pubmed/15770072 [287]

"In order to identify genetic polymorphisms and haplotype frequencies of CYP1A2 in a Japanese population, the enhancer and promoter regions, all the exons with their surrounding introns, and intron 1 were sequenced from genomic DNA from 250 Japanese subjects. Thirty-three polymorphisms were found, including 13 novel ones: 2 in the enhancer region, 5 in the exons, and 6 in the introns. The most common single nucleotide polymorphism (SNP) was -163C>A (CYP1A2*1F allele) with a 0.628 frequency. In addition to six previously reported non-synonymous SNPs, three novel ones, 125C>G (P42R, CYP1A2*15 allele, MPJ6_1A2032), 1130G>A (R377Q, *16 allele, MPJ6_1A2033), and 1367G>A (R456H, *8 allele, MPJ6_1A2019), were found with frequencies of 0.002, 0.002, and 0.004, respectively. No polymorphism was found in the known nuclear transcriptional factor-binding sites in the enhancer region. Based on linkage disequilibrium analysis, the CYP1A2 gene was analyzed as one haplotype block. Using the 33 detected polymorphisms, 14 haplotypes were unambiguously identified, and 17 haplotypes were inferred by aid of an expectation-maximization-based program. Among them, the second major haplotype CYP1A2*1L is composed of -3860G>A (*1C allele), -2467delT (*1D allele), and -163C>A (*1F allele). Network analysis suggested that relatively rare haplotypes were derived from three major haplotypes, *1A, *1M, and *1N in most cases. Our findings provide fundamental and useful information for genotyping CYP1A2 in the Japanese, and probably Asian populations."[287]

Influence of genetic polymorphisms, smoking, gender and age on CYP1A2 activity in a Turkish population.
https://www.ncbi.nlm.nih.gov/pubmed/15770072[281]

"The 17X:137X ratios were increased in smokers ($p < 0.0001$) and tended to be higher in men both among nonsmokers ($p = 0.051$) and smokers ($p = 0.064$). Age-related differences were observed only among nonsmoking women ($p = 0.024$). The -163C>A polymorphism correlated with 17X:137X ratios only in smokers ($p = 0.006$). Furthermore, increased 17X:137X ratios were observed in CYP1A2 haplotype H4 (-3860G, -3113G, -2467del, -739T, -729C, -163A and 5347T) carriers in the overall study population ($p = 0.026$). Multiple regression analyses including smoking, gender, -163C>A genotype and age revealed a significant influence of smoking ($p < 0.0001$) and gender ($p = 0.002$) in the overall study population. However, in nonsmokers only the influence of gender remained significant ($p = 0.021$), while in smokers the influence of the -163C>A genotype held the statistical significance ($p = 0.019$). The influence of haplotype H4 remained significant ($p = 0.028$) in the overall study population in similar analyses."[281]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [250]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP1A2, which may affect this variability. There are several articles, which review the relevant clinical implications of altered CYP1A2 metabolism. [20, 247-250]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [252]

"To this end, we genotyped, expression-profiled, and measured P450 activities of 466 human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-

regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [252]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence.
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [258]

"CYP2D6, CYP1A2, and CYP3A4/5 are major enzymes in the metabolism of antipsychotics and polymorphisms of alleles for these proteins are associated with altered plasma levels… Numerous studies have shown a significant association between genotype and adverse effects, such as CYP2D6 polymorphisms and tardive dyskinesia. This review summarizes evidence for the role of CYP450 genetic variants in the response to antipsychotic medications and the clinical implications of pharmacogenetics in the management of patients with schizophrenia." [258]

Insights into the substrate specificity, inhibitors, regulation, and polymorphisms and the clinical impact of human cytochrome P450 1A2.

http://www.ncbi.nlm.nih.gov/pubmed/19590965 [259]

"To date, more than 15 variant alleles and a series of sub-variants of the CYP1A2 gene have been identified and some of them have been associated with altered drug clearance and response to drug therapy. For example, lack of response to clozapine therapy due to low plasma drug levels has been reported in smokers harboring the -163A/A genotype; there is an association between CYP1A2*1F (-163C>A) allele and the risk for leflunomide-induced host toxicity. The *1F allele is associated with increased enzyme induction whereas *1C causes reduced induction. Further studies are warranted to explore the clinical and toxicological significance of altered CYP1A2 expression and activity caused by genetic, epigenetic, and environmental factors." [259]

CYP1A2 is more variable than previously thought: a genomic biography of the gene behind the human drug-metabolizing enzyme.
http://www.ncbi.nlm.nih.gov/pubmed/20881513 [260]

"As human genetic diversity has been reported to decrease with distance from Ethiopia, we resequenced CYP1A2 in five Ethiopian ethnic groups representing a rough northeast to southwest transect across… We found 49 different variable sites (30 of which are novel), nine nonsynonymous changes (seven of which are novel), one synonymous change and 55 different haplotypes, only three of which are previously reported." [260]

The dosing of atypical antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [261]

"Dosage alterations of …quetiapine, dependent on cytochrome P450 3A (CYP3A), may be necessary when used with other drugs that inhibit or induce their metabolic enzymes. Genetic variations of cytochrome P450 2D6 (CYP2D6) and drug-drug interactions causing inhibition (CYP2D6 and/or CYP3A) or induction (CYP3A) may be important for risperidone, and perhaps for aripiprazole, dosing. Adding inhibitors may cause side effects more easily in drugs with a narrow therapeutic window, such as clozapine or risperidone, than in those with a wide therapeutic window, such as olanzapine or aripiprazole. Adding inducers may be associated with a gradual development of lost efficacy." [261]

Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms.

http://www.ncbi.nlm.nih.gov/pubmed/18466106 [262]

"CYP1A2 is involved in the metabolism of several widely used drugs and endogenous compounds, and in the activation of pro-carcinogens. Both genetic and environmental factors influence the activity of this enzyme. The current knowledge regarding factors influencing the activity of CYP1A2 is summarized in this review…The functional significance and clinical importance of CYP1A2 gene polymorphisms are reviewed and interethnic differences in the distribution of CYP1A2 variant alleles and haplotypes are summarized. Finally, future perspectives for the possible clinical applications of CYP1A2 genotyping are discussed." [262]

A theoretical study on the mechanism of a superficial mutation inhibiting the enzymatic activity of CYP1A2.
http://www.ncbi.nlm.nih.gov/pubmed/24464701 [263]

"CYP1A2, one of the major members of cytochrome P450 in human liver, participates in the metabolism of various drugs. While most harmful mutations are located near the catalytic core of CYP1A2, a recently found loss-of-function mutation, F186L, is on the surface… Based on these findings, a detailed

mechanism of how F186 regulates the functions of CYP1A2 was proposed, and it may shed light on the diverse effects of SNPs and the personalized drug design." [263]

Six novel nonsynonymous CYP1A2 gene polymorphisms: catalytic activities of the naturally occurring variant enzymes.

http://www.ncbi.nlm.nih.gov/pubmed/14563787 [264]

"Six novel nonsynonymous nucleotide alterations were found in the cytochrome P450 1A2 gene in a Japanese population, which resulted in the following amino acid substitutions: T83M, E168Q, F186L, S212C, G299A, and T438I… Kinetic analyses performed for the ethoxyresorufin O-deethylation revealed that the Vmax of the F186L (*11) variant was approximately 5% of that of the CYP1A2 wild type, despite a 5-fold lower Km value of the variant, the consequence of which was reduced enzymatic activity toward the substrate. Thus, for the first time, phenylalanine at residue 186 is suggested to be a critical amino acid for catalytic activity." [264]

Association between CYP1A2 polymorphisms and clozapine-induced adverse reaction in patients with schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/22901441 [265]

"CYP1A2 *1F contains a 163 C4A transition in intron 1, which influences the gene's induction affecting the magnitude of increase of caffeine metabolism after smoking…CYP1A2 alleles *1C, *1D and *1F are all due to mutations in the regulatory regions of the gene and at least for CYP1A2 *1C and *1F, the functional effects associated with their presence have been adequately characterized. CYP1A2 *1C contains a 3860 G>A transition in the flanking region of the gene, causing a decrease in induction. CYP1A2 *1F contains a 163 C>A transition in intron 1, which influences gene induction affecting the magnitude of increase of caffeine metabolism after smoking…Patients with ADRs had a higher frequency of CYP1A2 low activity allele combinations (8/12; 67%) and lower CYP1A2-mRNA levels than patients without ADRs (6/22; 27%, $P = 0.019$)." [265]

Impact of CYP1A2 and CYP2D6 polymorphisms on drug metabolism and on insulin and lipid elevations and insulin resistance in clozapine-treated patients.

http://www.ncbi.nlm.nih.gov/pubmed/17503978 [266]

"Clozapine and N-desmethylclozapine concentration-to-dose (C/D) ratios were significantly higher in patients carrying 2 CYP1A2 single nucleotide polymorphisms (SNPs), previously suggested to cause low enzyme activity, compared to those with no such SNPs ($p < .05$)… CYP1A2 variants *1C and *1D seem to be associated with higher serum clozapine concentrations and an increased risk of developing insulin and lipid elevations and insulin resistance on a given dose of clozapine." [266]

Influence of the genetic polymorphism in the 5'-noncoding region of the CYP1A2 gene on CYP1A2 phenotype and urinary mutagenicity in smokers.

http://www.ncbi.nlm.nih.gov/pubmed/16188490 [267]

"The functional significance of genetic polymorphisms on tobacco smoke-induced CYP1A2 activity was examined…Heavy smokers (n=48, with urinary nicotine plus its metabolites>or=0.69 mg/mmol creatinine) with variant allele -2467delT or -163A had significantly increased urinary mutagenicity ($p<0.01$ and <0.05). CYP1A2 genetic polymorphisms are shown to influence the CYP1A2 phenotype in smokers, -2467 T-->Del T having the main effect. This information is of interest for future studies assessing the possible role of tobacco smoke-inducible CYP1A2 genotypes as individual susceptibility factors in exposure to carcinogens." [267]

CYP1A2 genetic polymorphisms are associated with early antidepressant escitalopram metabolism and adverse reactions.

http://www.ncbi.nlm.nih.gov/pubmed/23859573 [268]

"The liver CYP1A2 enzyme may metabolize antidepressant escitalopram (S-CIT) to S-desmethylcitalopram (S-DCIT) and S-didesmethylcitalopram (S-DDCIT). This study tested whether genetic polymorphisms in the CYP1A2 gene are associated with the treatment responses to S-CIT…CYP1A2 SNPs rs2069521, rs2069526, rs4646425 and rs4646427 are significantly associated with the metabolic ratios of S-DDCIT/S-DCIT ($p = 0.002$, 0.018, 0.008 and 0.004, respectively) at week 2 of treatment. Carriers of the allele types associated with higher S-DDCIT/S-DCIT ratios had more severe side effects…These results suggest that genetic variants in CYP1A2 may be indicators for S-CIT metabolism and that the fast metabolizers may experience more severe adverse reactions in the early stages of S-CIT treatment." [268]

Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome.

http://www.ncbi.nlm.nih.gov/pubmed/19636338 [164]

"In our study population, CYP1A2*1F/*1F genotype alone resulted in a 22% reduction of dose-/body weight-normalized olanzapine serum concentrations compared to homo- and heterozygote carriers of CYP1A2*1A (both groups without inducers). This effect was independent of the well-known effect of inducing agents (here tobacco smoke and carbamazepine which led to on average 28% lower concentrations in CYP1A2*1A carriers and 26% lower concentrations in CYP1A2*1F/*1F carriers). Consistently, patients with the CYP1A2*1F/*1F genotype taking inducers had 22% lower concentrations compared to CYP1A2*1A carriers taking inducers. The influence of genotype alone remained significant after Bonferroni's post hoc test." [164]

Genetics of caffeine consumption and responses to caffeine.

http://www.ncbi.nlm.nih.gov/pubmed/20532872 [269]

"Modeling based on twin studies reveals that genetics plays a role in individual variability in caffeine consumption and in the direct effects of caffeine. Both pharmacodynamic and pharmacokinetic polymorphisms have been linked to variation in response to caffeine… A single nucleotide C→A polymorphism at position 734 within intron 1 (rs762551) is correlated with high induction of the P-450 1A2 enzyme in Caucasian subjects. Smoking subjects with A/A genotype metabolize caffeine at 1.6 times the rate of the other genotypes, while no significant differences are found for nonsmoking subjects. The genetic polymorphism therefore modifies environmental impact on enzyme activity." [269]

Inducibility of CYP1A2 by omeprazole in vivo related to the genetic polymorphism of CYP1A2.

http://www.ncbi.nlm.nih.gov/pubmed/12445035 [270]

"Mutations of CYP2C19 and CYP1A2 were identified by PCR-RFLP. Omeprazole, 120 mg day-1, was given to 12 extensive metabolizers (EM) with respect to CYP2C19 (six CYP1A2*1F/CYP1A2*1F and six CYP1A2*1C/CYP1A2*1F of CYP1A2) for 7 days. CYP1A2 activity was determined on three occasions, namely on day 1, day 9 and day 16 using the caffeine plasma index (the ratio of the concentrations of paraxanthine to caffeine), 6 h after oral administration of 200 mg caffeine… There was a significant difference ($P = 0.002$) between the caffeine ratios for CYP1A2*1F/CYP1A2*1F and CYP1A2*1C/CYP1A2*1F genotypes on day 9, but not on day 1 or day 16 ($P > 0.05$). The changes in the ratios from day 9 to day 1 (48% +/- 20%vs 19% +/- 20%) and from day 9 to day 16 (50% +/- 31%vs 15% +/- 22%) were significantly different ($P < 0.05$) between the CYP1A2*1F/CYP1A2*1F and CYP1A2*1C/CYP1A2*1F genotypes… The CYP1A2*1C and CYP1A2*1F genetic polymorphisms influenced the induction of CYP1A2 activity in vivo by omeprazole." [270]

CYP1A2, GSTM1, and GSTT1 polymorphisms and diet effects on CYP1A2 activity in a crossover feeding trial.

http://www.ncbi.nlm.nih.gov/pubmed/19843669 [271]

"Using a randomized, crossover feeding trial in humans, we investigated the dose effects of cruciferous vegetables and the effects of any interaction between cruciferous and apiaceous vegetables on CYP1A2 activity. We also investigated whether response varied by CYP1A2*1F, GSTM1, and GSTT1 genotypes (glutathione S-transferases that metabolize crucifer constituents) and whether CYP1A2 activity rebounds after apiaceous vegetables are removed from the diet… These results suggest complex interactions among dietary patterns, genetic variation, and modulation of biotransformation that may not be apparent in observational studies." [271]

Duloxetine: clinical pharmacokinetics and drug interactions.

http://www.ncbi.nlm.nih.gov/pubmed/21366359 [272]

"Patient demographic characteristics found to influence the pharmacokinetics of duloxetine include sex, smoking status, age, ethnicity, cytochrome P450 (CYP) 2D6 genotype, hepatic function and renal function… Pharmacokinetic results from drug interaction studies show that activated charcoal decreases duloxetine exposure, and that CYP1A2 inhibition increases duloxetine exposure to a clinically significant degree… Specifically, following oral administration in the presence of fluvoxamine, the area under the plasma concentration-time curve and C(max) of duloxetine significantly increased by 460% (90% CI 359, 584) and 141% (90% CI 93, 200), respectively. In addition, smoking is associated with a 30% decrease in duloxetine concentration. The exposure of duloxetine with CYP2D6 inhibitors or in CYP2D6 poor metabolizers is increased to a lesser extent than that observed with CYP1A2 inhibition and does not require a dose adjustment." [272]

Genomics and pharmacogenomics of schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/20718829 [273]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [273]

Pharmacogenomics can improve antipsychotic treatment in schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/23606027 [274]

"Schizophrenia is a widespread mental disease with a prevalence of about 1% in the world population, and heritability of up to 80%. Drug therapy is an important approach to treating the disease. However, the curative effect of antipsychotic is far from satisfactory in terms of tolerability and side effects. Many studies have indicated that nearly 30% of patients exhibit little or no improvements associated with antipsychotics. The response of individual patients who are given the same dose of the same drug varies considerably. In addition, antipsychotic drugs are often accompanied by adverse drug reactions (ADRs), which can cause considerable financial loss in addition to the obvious societal harm… In this review, we will focus on the latest research on polymorphisms of candidate genes that code for drug metabolic enzymes (CYP2D6, CYP1A2, CYP3A4, etc.), drug transporters (mainly ABCB1) and neurotransmitter receptors (dopamine receptors and serotonin receptors, etc.). We also discuss the genome-wide pharmacogenomic study of schizophrenia and review the current state of knowledge on epigenetics and potential clinical applications." [274]

The CYP1A2 -163C>A polymorphism is associated with clozapine-induced generalized tonic-clonic seizures in Brazilian schizophrenia patients.
http://www.ncbi.nlm.nih.gov/pubmed/23601795 [275]

"We evaluated two polymorphisms at CYP1A2 (*1C and *1F) in a sample of 108 European-derived patients with schizophrenia and their influence on the pro-convulsive effect of clozapine. We found the *1F/*1F genotype to be significantly associated with seizures, and no relationship was observed with combinations of *1F and *1C alleles." [275]

Clinically significant drug interactions with atypical antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/24170642 [276]

"Atypical antipsychotics [also known as second-generation antipsychotics (SGAs)] have become a mainstay therapeutic treatment intervention for patients with schizophrenia, bipolar disorders and other psychotic conditions. … Smoking is very common among psychiatric patients and can induce CYP1A2 enzymes, thereby lowering expected plasma levels of certain SGAs. It is recommended that ziprasidone and lurasidone are taken with food to promote drug absorption, otherwise their bioavailability can be reduced. Clinicians must be aware of the variety of factors that can increase the likelihood of clinically significant drug interactions with SGAs, and must carefully monitor patients to maximize treatment efficacy while minimizing adverse events." [276]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.
http://www.ncbi.nlm.nih.gov/pubmed/25987241 [288]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-

effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [288]

Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review.

https://www.ncbi.nlm.nih.gov/pubmed/24160757 [277]

"Exogenous cannabinoids are structurally and pharmacologically diverse compounds that are widely used. The purpose of this systematic review is to summarize the data characterizing the potential for these compounds to act as substrates, inhibitors, or inducers of human drug metabolizing enzymes, with the aim of clarifying the significance of these properties in clinical care and drug interactions… However, the absence of interaction between CBD from oromucosal cannabis extract with omeprazole suggests a less significant role of CYP2C19 in CBD metabolism. Studies of THC, CBD, and CBN inhibition and induction of major human CYP-450 isoforms generally reflect a low risk of clinically significant drug interactions with most use, but specific human data are lacking. Smoked cannabis herb (marijuana) likely induces CYP1A2 mediated theophylline metabolism, although the role of cannabinoids specifically in eliciting this effect is questionable." [277]

Cruciferous vegetable consumption alters the metabolism of the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP) in humans.

https://www.ncbi.nlm.nih.gov/pubmed/15073045 [278]

"Consumption of red meat is associated with an increased risk of colorectal cancer, whereas cruciferous vegetable consumption reduces cancer risk. While the mechanisms remain to be determined, cruciferous vegetables may act by altering the metabolism of carcinogens present in cooked food, such as the heterocyclic amine 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP). The aim of this study was to evaluate the effect of cruciferous vegetable consumption on the metabolism of PhIP in 20 non-smoking Caucasian male subjects…While the urinary excretion of both PhIP metabolites accounted for approximately 39% of the PhIP dose in phases 1 and 3, they accounted for approximately 49% of the dose in phase 2. This study demonstrates that cruciferous vegetable consumption can induce both the phase I and II metabolism of PhIP in humans." [278]

Genetic polymorphism analysis of the drug-metabolizing enzyme CYP1A2 in a Uyghur Chinese population: a pilot study.

https://www.ncbi.nlm.nih.gov/pubmed/26383175 [279]

"CYP1A2 is a highly polymorphic gene and CYP1A2 enzyme results in broad inter-individual variability in response to certain pharmacotherapies, while little is known about the genetic variation of CYP1A2 in Uyghur Chinese population. The aim of the present study was to screen Uyghur volunteers for CYP1A2 genetic polymorphisms. 2. We used DNA sequencing to investigate promoter, exons, introns, and 3' UTR of the CYP1A2 gene in 96 unrelated healthy Uyghur individuals. We also used SIFT (Sorting Intolerant from Tolerant) and PolyPhen-2 (Polymorphism Phenotyping v2) to predict the protein function of the novel non-synonymous mutation in CYP1A2 coding regions. 3. We identified 20 different CYP1A2 polymorphisms in the Uyghur Chinese population, including two novel variants (119A > G and 2410G > A). Variant 119A > G was predicted to be probably damaging on protein function by PolyPhen-2, by contrast, 2410G > A was identified as benign. The allele frequencies of CYP1A2*1A, *1B, *1F, *1G, *1J, *1M, *4, and *9 were 23.4%, 53.1%, 3.7%, 2.6%, 2.6%, 13.5%, 0.5%, and 0.5%, respectively. The frequency of *1F, a highly inducible allele, was higher in our sample population compared with that in the Caucasian population ($p < 0.05$). The most common genotype combinations were *1A/*1B (46.9%) and *1B/*1M (27.1%). 4. Our results provide basic information on CYP1A2 polymorphisms in Uyghur individuals and suggest that the enzymatic activities of CYP1A2 may differ among the diverse ethnic populations of the world." [279]

Pharmacogenetics of CYP1A2 activity and inducibility in smokers and exsmokers.

https://www.ncbi.nlm.nih.gov/pubmed/23492909 [280]

"There is a high interindividual variability in cytochrome P4501A2 (CYP1A2) activity and in its inducibility by smoking, only poorly explained by known CYP1A2 polymorphisms. We aimed to study the contribution of other regulatory pathways, including transcription factors and nuclear receptors, toward this variability. CYP1A2 activity was determined by the paraxanthine/caffeine ratio in 184 smokers and in 113 of them who were abstinent for 4 weeks. Participants were genotyped for 22 polymorphisms in

12 genes. A significant influence on CYP1A2 inducibility was observed for the NR1I3 rs2502815 (P=0.0026), rs4073054 (P=0.029), NR2B1 rs3818740 (P=0.0045), rs3132297 (P=0.036), AhR rs2282885 (P=0.040), rs2066853 (P=0.019), NR1I1 rs2228570 (P=0.037), and NR1I2 rs1523130 (P=0.044) polymorphisms. Among these, the NR1I3 rs2502815 (P=0.0045), rs4073054 (P=0.048), and NR2B1 rs3818740 (P=0.031) also influenced CYP1A2 basal activity. This is the first in-vivo demonstration of the influence of genes involved in CYP1A2 regulatory pathways on its basal activity and inducibility by smoking. These results need to be confirmed by other studies." [280]

Influence of genetic polymorphisms, smoking, gender and age on CYP1A2 activity in a Turkish population.
https://www.ncbi.nlm.nih.gov/pubmed/19450128 [281]

"Smoking has the strongest impact on CYP1A2 activity, while gender and haplotype H4 showed marginal effects. The influence of the -163C>A polymorphism on CYP1A2 activity in smokers suggests an effect on the inducibility of the enzyme." [281]

Literature Summary: Cytochrome P450 2B6: (CYP2B6)

Pharmacogene Variation Consortium
https://www.pharmvar.org/

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [248]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [249]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [250]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [251]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP2B6, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP2B6 metabolism. [247-249, 251]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [252]

"…we genotyped, expression-profiled, and measured P450 activities of 466 human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [252]

Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance.
http://www.ncbi.nlm.nih.gov/pubmed/23467454 [289]

CYP2B6: new insights into a historically overlooked cytochrome P450 isozyme.
http://www.ncbi.nlm.nih.gov/pubmed/18781911 [290]

CYP2B6 is responsible for the metabolism of several medications including bupropion and methadone. This gene is also displays highly variable expression between individuals due to genetic variation, environmental contributions, and inhibition and induction effects of other co-administered medications and food products. Resent advances in the understanding of this enzyme have made it a potential therapeutic target. [289, 290]

Prevalence of poor and rapid metabolizers of drugs metabolized by CYP2B6 in North Indian population residing in Indian national capital territory.
http://www.ncbi.nlm.nih.gov/pubmed/23961363 [291]

"Identification of poor and rapid metabolizers for the category of drugs metabolized by cytochrome P450 2B6 (CYP2B6) is important for understanding the differences in clinical responses of drugs metabolized by this enzyme... Results indicate that 20.56% individuals in the target population were poor metabolizers for the category of drugs metabolized by CYP2B6. The baseline information would be clinically useful before administering the drugs metabolized by this isoform." [291]

Polymorphic variants of cytochrome P450 2B6 (CYP2B6.4–CYP2B6.9) exhibit altered rates of metabolism for bupropion and efavirenz: a charge-reversal mutation in the K139E variant (CYP2B6.8) impairs formation of a functional cytochrome p450-reductase complex.
http://www.ncbi.nlm.nih.gov/pubmed/21659470 [292]

"In this study, metabolism of bupropion, efavirenz, and 7-ethoxy-4-trifluoromethylcoumarin (7-EFC) by CYP2B6 wild type (CYP2B6.1) and six polymorphic variants (CYP2B6.4 to CYP2B6.9) was investigated in a reconstituted system to gain a better understanding of the effects of the mutations on the catalytic properties of these naturally occurring variants… In this work, we have characterized the catalytic properties of six polymorphic variants of CYP2B6 (CYP2B6.4 to CYP2B6.9) in a reconstituted system to gain a better understanding of the mechanism by which these genetic mutations affect the catalytic activities of CYP2B6… Results from this work provide further insights to better understand the genotype-phenotype correlation regarding CYP2B6 polymorphisms and drug metabolism." [292]

Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/11470993 [293]

"In this study, we present the first systematic investigation of genetic polymorphism in the CYP2B6 gene on chromosome 19… A total of nine novel point mutations were identified, of which five result in amino acid substitutions in exon 1 (C64T, Arg22Cys), exon 4 (G516T, Gln172His), exon 5 (C777A, Ser259Arg and A785G, Lys262Arg) and exon 9 (C1459T, Arg487Cys) and four are silent mutations (C78T, G216C, G714A and C732T)… By screening a population of 215 subjects the C64T, G516T, C777A, A785G and C1459T mutations were found at frequencies of 5.3%, 28.6%, 0.5%, 32.6% and 14.0%, respectively. Haplotype analysis revealed six different mutant alleles termed CYP2B6*2 (C64T), *3 (C777A), *4 (A785G), *5 (C1459T), *6 (G516T and A785G) and *7 (G516T, A785G and C1459T). By analyzing a large number of human liver samples, significantly reduced CYP2B6 protein expression and S-mephenytoin N-demethylase activity were found in carriers of the C1459T (R487C) mutation (alleles *5 and *7). These data demonstrate that the extensive interindividual variability of CYP2B6 expression and function is not only due to regulatory phenomena, but also caused by a common genetic polymorphism." [293]

Aberrant splicing caused by single nucleotide polymorphism c.516G>T [Q172H], a marker of CYP2B6*6, is responsible for decreased expression and activity of CYP2B6 in liver.
http://www.ncbi.nlm.nih.gov/pubmed/18171905 [294]

"The common allele CYP2B6*6 [c. 516G>T, Q172H, and c.785A>G, K262R] has previously been associated with lower expression in human liver and with increased plasma levels of efavirenz in human immunodeficiency virus patients, but the molecular mechanism has remained unclear. We present novel data showing that hepatic CYP2B6 mRNA levels are reduced in *6 carriers, suggesting a pretranslational mechanism resulting in decreased expression." [294]

Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro.
http://www.ncbi.nlm.nih.gov/pubmed/17559344 [295]

"We have shown that CYP2B6 genetic polymorphism markedly influences the metabolism of efavirenz in human liver microsomes. Importantly, the CYP2B6*6 allele harboring the SNPs c.516G>T [Q172H] and c.785A>G [K262R] was significantly associated with a pronounced decrease in CYP2B6 expression and activity, as well as a low rate of efavirenz 8-hydroxylation. These results represent a first step towards elucidating the mechanism by which this allele identifies patients exhibiting very high efavirenz plasma concentrations." [295]

CYP2B6 SNPs are associated with methadone dose required for effective treatment of opioid addiction.
http://www.ncbi.nlm.nih.gov/pubmed/21790905 [296]

"Adequate methadone dosing in methadone maintenance treatment (MMT) for opioid addiction is critical for therapeutic success. One of the challenges in dose determination is the inter-individual variability in dose-response. Methadone metabolism is attributed primarily to cytochrome P450 enzymes CYP3A4, CYP2B6 and CYP2D6. The CYP2B6*6 allele [single nucleotide polymorphisms (SNPs) 785A>G (rs2279343) and 516G>T (rs3745274)] was associated with slow methadone metabolism… The results remain significant after controlling for age, sex and the ABCB1 SNP 1236C>T (rs1128503), which was previously shown to be associated with high methadone dose requirement in this population (P=0.006, 0.030, respectively). An additional 77 CYP2B6, CYP3A4 and CYP2D6 SNPs were genotyped. Of these, 24 SNPs were polymorphic and none showed significant association with methadone dose. Further studies are necessary to replicate these preliminary findings in additional subjects and other populations." [296]

Genomics and pharmacogenomics of schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/20718829 [273]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [273]

Pharmacogenomics study in a Taiwan methadone maintenance cohort.

http://www.ncbi.nlm.nih.gov/pubmed/25278738 [284]

"Pharmacogenomics is research to study the drug treatment responses in subgroups of patients according to their genetic variants or genetic expression information. Methadone maintenance treatment, which is usually prescribed for patients with heroin dependence, was launched in Taiwan by the government in 2006. In this study, 366 patients who had taken methadone continually in the previous 7 days were examined. Data from administration of the Treatment Outcomes Profile (TOP), Severity of Dependence Scale (SDS), Clinical Opioid Withdrawal Scale (COWS), and Treatment Emergent Symptoms Scale (TESS) were obtained from patients' report records. Genes encoding the liver cytochrome P-450 (CYP) enzymes that are involved with the metabolism of methadone (CYP2B6, 3A4 and 2C19) were selected and genotyped in this cohort. We found that the SNPs on CYP2B6 were associated with plasma S-methadone concentration; SNPs on CYP3A4 were associated with withdrawal symptoms and side effects; and SNPs on CYP2C19 were associated with methadone dose. SNPs in the genes encoding the morphine phase II metabolic enzyme, UGT2B7, were associated with withdrawal symptom scores. In pharmacodynamic genes, the SNPs on OPRM1 were associated with insomnia and change in libido side effects. We conclude that SNP markers may be useful for future methadone dosage adjustment and to reduce adverse reactions." [284]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.

http://www.ncbi.nlm.nih.gov/pubmed/25987241 [288]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [288]

CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion.
https://www.ncbi.nlm.nih.gov/pubmed/23149928 [297]

"Bupropion is indicated to promote smoking cessation. Animal studies suggest that the pharmacologic activity of bupropion can be mediated by its major metabolite, hydroxybupropion. We measured plasma bupropion and its metabolite levels in a double-blind, placebo controlled, randomized smoking-cessation trial…These findings suggest that dosing of bupropion to achieve a hydroxybupropion level of 0.7 µg/ml or increasing bupropion dose for CYP2B6 slow metabolizers could improve bupropion's cessation outcomes." [297]

Serum concentrations of hydroxybupropion for dose optimization of depressed patients treated with bupropion.
https://www.ncbi.nlm.nih.gov/pubmed/24452068 [298]

"Bupropion is a dopamine and norepinephrine reuptake inhibitor approved for the treatment of depression and smoking cessation. According to the recently published reviews, it is a candidate for therapeutic drug monitoring (TDM) to improve therapeutic outcomes and reduce risks of intolerability or intoxication. In practice, however, the use of TDM is limited due to the chemical instability of bupropion. This investigation sought to determine if the major, active, and chemically stable metabolite 4-hydroxybupropion is a suitable measure to guide antidepressant drug therapy with bupropion…Despite multiple limitations of this naturalistic study, evidence could be given that the measurement of 4-hydroxybupropion in serum is suitable to perform TDM for bupropion. Blood levels should be above 860 ng/mL to attain therapeutic improvement. Potential sex differences in bupropion pharmacokinetics, probably due to differential activities of CYP2B6, should be taken into account when the drug is prescribed." [298]

A simple and sensitive LC-ESI-MS (ion trap) method for the determination of bupropion and its major metabolite, hydroxybupropion in rat plasma and brain microdialysates.
https://www.ncbi.nlm.nih.gov/pubmed/21315892 [299]

"A specific and highly sensitive liquid chromatography-electrospray mass spectrometry (LC-ESI-MS) method for the direct determination of bupropion (BUP) and its main metabolite hydroxybupropion (HBUP) in rat plasma and brain microdialysate has been developed and validated. The analysis was performed on a Bonus RP C18 (100 mm × 2.1mm i.d., 3.5 µm particles) column using gradient elution with the mobile phase consisting of acetonitrile and ammonium formate buffer (10mM, pH 4)…The method was validated in both plasma and microdialysate samples, and the obtained lower limit of quantification (LLOQ) was 1.5 ng mL (-1) for BUP and HBUP in both matrices. The intra- and inter-day assay variability was less than 15% for both analytes. This LC-ESI-MS method provided simple sampling, rapid clean-up and short analysis time (<9 min), applicable to the routine therapeutic monitoring and pharmacokinetic studies of BUP and HBUP." [299]

Effect of CYP2B6*6 on Steady-State Serum Concentrations of Bupropion and Hydroxybupropion in Psychiatric Patients: A Study Based on Therapeutic Drug Monitoring Data.
https://www.ncbi.nlm.nih.gov/pubmed/25565674 [300]

"The clinical effect of bupropion is mediated by its active metabolite hydroxybupropion. Previous studies have reported conflicting impact of the CYP2B6*6 variant allele on the formation of hydroxybupropion from bupropion. The aim of this study was to clarify the effect of CYP2B6*6 and secondarily CYP2D6 genotype on steady-state serum concentrations of bupropion and hydroxybupropion in a large population of psychiatric patients…This study shows that the CYP2B6*6 variant allele is associated with significantly reduced formation of the active bupropion metabolite in psychiatric patients. Our findings suggest that dose-adjusted serum concentrations of hydroxybupropion at steady state is approximately halved in homozygous CYP2B6*6 carriers, which might imply risk of reduced clinical response in this patient subgroup. The CYP2D6 genotype does not affect hydroxybupropion concentrations and is therefore unlikely to impact bupropion treatment." [300]

Human cytochrome P450 2B6 genetic variability in Botswana: a case of haplotype diversity and convergent phenotypes.
https://www.ncbi.nlm.nih.gov/pubmed/?term=29559695 [301]

"A total of 570 subjects were analyzed for CYP2B6 polymorphisms at position 516 G > T (rs3745274), 785 A > G (rs2279343) and 983 T > C (rs28399499). Samples were collected in three districts of

Botswana where the population belongs to Bantu (Serowe/Palapye and Chobe) and San-related (Ghanzi) ethnicity. The three districts showed different haplotype composition according to the ethnic background but similar metabolic inferred phenotypes, with 59.12%, 34.56%, 2.10% and 4.21% of the subjects having, respectively, an extensive, intermediate, slow and rapid metabolic profile. The results hint at the possibility of a convergent adaptation of detoxifying metabolic phenotypes despite a different haplotype structure due to the different genetic background. The main implication is that, while there is substantial homogeneity of metabolic inferred phenotypes among the country, the response to drugs metabolized via CYP2B6 could be individually associated to an increased risk of treatment failure and toxicity. These are important facts since Botswana is facing malaria elimination and a very high HIV prevalence."[301]

Determinants of the rate of nicotine metabolism and effects on smoking behavior

https://www.ncbi.nlm.nih.gov/pubmed/?term=17015050 [302]

"We investigated determinants of the rate of nicotine metabolism and effects on smoking behavior in a United Kingdom cohort who participated in a placebo-controlled trial of smoking cessation via nicotine replacement therapy. Those who continued to smoke cigarettes at the 8-year follow-up formed our study group (N = 545). The ratio of the nicotine metabolite trans-3'-hydroxycotinine to cotinine in plasma was used as an index of CYP2A6 activity and thus as a marker of the rate of nicotine metabolism. The nicotine metabolite ratio was associated with sex (P < .0001), CYP2A6 genotype (*1B, *2, *4, *9, and *12) (P < .0001), CYP2B6 haplotype (*4-dominant) (P = .02), plasma nicotine concentration (P < .0001), and age (P = .02) but was not associated with dependence score (P > .20). The ratio also predicted the number of cigarettes smoked at will per day, although the association was weak (F(1, 492) = 4.05, P = .04)."[302]

Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance, and Metabolism.

https://www.ncbi.nlm.nih.gov/pubmed/?term=26389554 [303]

"Healthy volunteers in genotype cohorts CYP2B6*1/*1 (n = 21), CYP2B6*1/*6 (n = 20), and CYP2B6*6/*6 (n = 17), and also CYP2B6*1/*4 (n = 1), CYP2B6*4/*6 (n = 3), and CYP2B6*5/*5 (n = 2) subjects, received single doses of IV and oral methadone. Plasma and urine methadone and metabolite concentrations were determined by tandem mass spectrometry… R- and S-methadone apparent oral clearance was threefold and fourfold greater in CYP2B6*4 carriers. IV and oral R- and S-methadone metabolism was significantly lower in CYP2B6*6 carriers compared with that of CYP2B6*1 homozygotes and greater in CYP2B6*4 carriers."[303]

Multicenter study on the clinical effectiveness, pharmacokinetics, and pharmacogenetics of mirtazapine in depression.

https://www.ncbi.nlm.nih.gov/pubmed/?term=22926595 [304]

"Inpatients and outpatients (n = 45; mean age, 51 years; range, 19-79 years) with major depressive episode received mirtazapine (MIR) for 8 weeks (30 mg/d on days 1-14 and 30-45 mg/d on days 15-56)… Only in nonsmokers, plasma levels of S(+)-enantiomer of MIR and metabolites depended on the CYP2D6 genotype. Therefore, high CYP1A2 activity seen in smokers seems to mask the influence of the CYP2D6 genotype. In patients presenting the CYP2B6 *6/*6 genotype (n = 8), S-OH-MIR concentrations were higher those in the other patients (n = 37)."[304]

CYP2B6 Genotype Guided Dosing of Propofol Anesthesia in the Elderly based on Nonparametric Population Pharmacokinetic Modeling and Simulations.

https://www.ncbi.nlm.nih.gov/pubmed/?term=28154789 [305]

"A total of 51 patients were included in the final PK analysis. A two-compartment gamma multiplicative error model adequately described the propofol concentration-time data. The precision of the goodness-of-fit plots resulted in an R2 of 0.927 and an R2 of 0.992 for the population prediction and individual predictions, respectively. Neither the UGT1A9 nor the CYP2B6 G516T gene variants resulted in statistically significant PK parameter differences while the CYP2B6 A785G gene variants resulted in statistically significant differences for the elimination rate. Model-based dosing-simulations comparing patients with the CYP2B6 AA & AG genotypes to both GG genotypes and patients from a multicenter trial suggest a 50% decrease in propofol infusion dose, to 25mg/kg/min, be made to result in approximately equivalent drug exposures."[305]

Literature Summary: Cytochrome P450 2C9: (CYP2C9)

Pharmacogene Variation Consortium
https://www.pharmvar.org/
PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [248]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [249]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [250]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [251]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP2C9, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP2C9 metabolism. [247-251]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [252]

"…we genotyped, expression-profiled, and measured P450 activities of 466 human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [252]

The dosing of atypical antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [261]

"Dosage alterations of …quetiapine, dependent on cytochrome P450 3A (CYP3A), may be necessary when used with other drugs that inhibit or induce their metabolic enzymes. Genetic variations of cytochrome P450 2D6 (CYP2D6) and drug-drug interactions causing inhibition (CYP2D6 and/or CYP3A) or induction (CYP3A) may be important for risperidone, and perhaps for aripiprazole, dosing. Adding inhibitors may cause side effects more easily in drugs with a narrow therapeutic window, such as clozapine or risperidone, than in those with a wide therapeutic window, such as olanzapine or aripiprazole. Adding inducers may be associated with a gradual development of lost efficacy." [261]

Cytochrome P450 2C9-CYP2C9.
http://www.ncbi.nlm.nih.gov/pubmed/20150829 [253]

"CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds… CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds." [253]

Pharmacogenetics: from bench to byte— an update of guidelines.
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [306]

"Currently, there are very few guidelines linking the results of pharmacogenetic tests to specific therapeutic recommendations... After systematic review of the literature, recommendations were developed for 53 drugs associated with genes coding for CYP2D6, CYP2C19, CYP2C9, thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), vitamin K epoxide reductase (VKORC1), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (FVL)." [306]

Characterization of 107 genomic DNA reference materials for CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1: a GeT-RM and Association for Molecular Pathology collaborative project.
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [254]

"…the Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program, in collaboration with members of the pharmacogenetics testing community and the Coriell Cell

Repositories, have characterized a panel of 107 genomic DNA reference materials for five loci (CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1) that are commonly included in pharmacogenetic testing panels and proficiency testing surveys. Genomic DNA from publicly available cell lines was sent to volunteer laboratories for genotyping. Each sample was tested in three to six laboratories using a variety of commercially available or laboratory-developed platforms. The results were consistent among laboratories, with differences in allele assignments largely related to the manufacturer's assay design and variable nomenclature, especially for CYP2D6. The alleles included in the assay platforms varied, but most were identified in the set of 107 DNA samples." [254]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance.

http://www.ncbi.nlm.nih.gov/pubmed/21906384 [255]

"Regarding drug metabolism, specific polymorphisms to the cytochrome (CYP) P450 enzyme family are linked to phenotypes that describe reaction rates as "ultra", "intermediate", and "poor," as referenced to "extensive" metabolizers that are assigned to wildtype individuals. Activity scores is an alternate designation that provides more genotype-to-phenotype resolution. Understanding the relative change in enzyme activities or rate of clearance of specific drugs relative to an individual's genotypes is an important component in the interpretation of pharmacogenomic data for personalized medicine." [255]

Polymorphisms of human cytochrome P450 2C9 and the functional relevance.

http://www.ncbi.nlm.nih.gov/pubmed/19715737 [256]

"Human cytochrome P450 2C9 (CYP2C9) accounts for ~20% of hepatic total CYP content and metabolizes ~15% clinical drugs such as phenytoin, S-warfarin, tolbutamide, losartan, and many nonsteroidal anti-inflammatory agents (NSAIDs). CYP2C9 is highly polymorphic, with at least 33 variants of CYP2C9 (*1B through *34) being identified so far… The CYP2C9 polymorphisms are relevant for the efficacy and adverse effects of numerous NSAIDs, sulfonylurea antidiabetic drugs and, most critically, oral anticoagulants belonging to the class of vitamin K epoxide reductase inhibitors… Genetic testing of CYP2C9 is expected to play a role in predicting drug clearance and conducting individualized pharmacotherapy." [256]

CYP2C9*3 Loss-of-Function Allele Is Associated With Acute Upper Gastrointestinal Bleeding Related to the Use of NSAIDs Other Than Aspirin.

http://www.ncbi.nlm.nih.gov/pubmed/20445534 [257]

"Nonsteroidal anti-inflammatory drugs (NSAIDs), other than aspirin, are to some extent metabolized by cytochrome P450 2C9 (CYP2C9). The CYP2C9 359Leu (CYP2C9*3) loss-of-function allele could be a risk factor for acute upper gastrointestinal bleeding (AUGIB) related to the use of NSAIDs other than aspirin. To test this hypothesis, we performed a prospective, multicenter, case-case study in patients hospitalized for AUGIB related to the use of NSAIDs… the results of the study support the hypothesis that the CYP2C9 359Leu allele is a robust risk factor for AUGIB related to the use of NSAIDs other than aspirin." [257]

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing.

http://www.ncbi.nlm.nih.gov/pubmed/21900891 [307]

"Warfarin is a widely used anticoagulant with a narrow therapeutic index and large interpatient variability in the dose required to achieve target anticoagulation. Common genetic variants in the cytochrome P450-2C9 (CYP2C9) and vitamin K-epoxide reductase complex (VKORC1) enzymes, in addition to known non-genetic factors, account for ~50% of warfarin dose variability." [307]

Genetically based impairment in CYP2C8- and CYP2C9-dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: is a combination of pharmacogenomics and metabolomics required to improve personalized medicine?

http://www.ncbi.nlm.nih.gov/pubmed/19422321 [308]

"Polymorphisms in CYP2C8 and CYP2C9 are common in all the human populations and many CYP2C8 and CYP2C9 gene variations cause decreased enzyme activity towards the NSAIDs aceclofenac, celecoxib, diclofenac, ibuprofen, indomethazine, lornoxicam, meloxicam, naproxen, piroxicam, tenoxicam and valdecoxib… Individuals carrying the gene variants CYP2C8*3 (rs11572080; rs10509681), CYP2C9*2 (rs1799853) or CYP2C9*3 (rs1057910) show increased risk of developing

acute gastrointestinal bleeding during the use of NSAID that are CYP2C8 or CYP2C9 substrates… We present an overview of the current knowledge of relevant polymorphisms of CYP2C8 and CYP2C9 genes, their association with NSAID metabolism and pharmacokinetics and a meta-analysis that confirms the clinical significance of these gene variations with regard to gastrointestinal bleeding." [308]

Decreased warfarin clearance associated with the CYP2C9 R150H (*8) polymorphism.
http://www.ncbi.nlm.nih.gov/pubmed/22378156 [309]

"The cytochrome P450 (CYP) 2C9 R150H (*8) allele occurs commonly in African Americans and is associated with lower warfarin dose requirements… We observed a 30% reduction in the unbound oral clearance of S-warfarin and a 25% lower R- to S-warfarin plasma concentration ratio in patients with the CYP2C9*8 allele (n = 12) as compared to CYP2C9*1 homozygotes (n = 26). Consistent with these findings, the in vitro intrinsic clearance of S-warfarin was 30% lower with the cDNA-expressed R150H protein as compared to the wild-type protein. These data show that the R150H variant protein expressed by the CYP2C9*8 allele is associated with lower S-warfarin clearance." [309]

Role of CYP2C9 and its variants (CYP2C9*3 and CYP2C9*13) in the metabolism of lornoxicam in humans.
http://www.ncbi.nlm.nih.gov/pubmed/15764711 [310]

"CYP2C9 is an important member of the cytochrome P450 enzyme superfamily with some 12 CYP2C9 alleles (*1-*12) being previously reported… Mean values of Km and Vmax for CYP2C9*1, *3, and *13 were 1.24, 1.61, and 2.79 microM and 0.83, 0.28, and 0.22 pmol/min/pmol, respectively. Intrinsic clearance values (Vmax/Km) for variant CYP2C9*3 and CYP2C9*13 on the basis of CYP2C9 protein levels were separately decreased to 28% and 12% compared with wild type. In a subsequent clinical study, the AUC of lornoxicam was increased by 1.9-fold and its oral clearance (CL/F) decreased by 44% in three CYP2C9*1/*13 subjects, compared with CYP2C9*1/*1 individuals. This suggests that the CYP2C9*13 allele is associated with decreased enzymatic activity both in vitro and in vivo." [310]

Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options.
http://www.ncbi.nlm.nih.gov/pubmed/24523097 [311]

"Advancements in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Understanding how and when to use this technology to guide pharmacotherapy used to treat psychiatric and neurological (neuropsychiatric) conditions remains a challenge for many clinicians. Currently, guidelines exist to assist clinicians in the use of existing genetic information for drug selection and/or dosing for the tricyclic antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for determining the starting and target doses, as well as drug interaction potential, for a number of other drugs. In this review, we outline the current status of pharmacogenomic testing for neuropsychiatric drugs as it pertains to information contained in drug labeling, consensus guidelines, and test panels, as well as considerations related to obtaining tests for patients." [311]

Role of cytochrome P450 genotype in the steps toward personalized drug therapy.
http://www.ncbi.nlm.nih.gov/pubmed/23226058 [312]

"Genetic polymorphism for cytochrome 450 (P450) enzymes leads to interindividual variability in the plasma concentrations of many drugs. In some cases, P450 genotype results in decreased enzyme activity and an increased risk for adverse drug effects…The CYP2C9, CYP2C19, and CYP2D6 genes are the P450 genes most often cited. To date, integration of P450 genetic information into clinical decision making is limited. However, some institutions are beginning to embrace routine P450 genotyping to assist in the treatment of their patients. Genotyping for P450 variants may carry less risk for discrimination compared with genotyping for disease-associated variants. As such, P450 genotyping is likely to lead the way in the clinical implementation of pharmacogenomics. This review discusses variability in the CYP2C9, CYP2C19, and CYP2D6 genes and the implications of this for drug efficacy and safety." [312]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.
http://www.ncbi.nlm.nih.gov/pubmed/25987241 [288]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and

estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [288]

Literature Summary: Cytochrome P450 2C19: (CYP2C19)

Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy.
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [15]

Pharmacogene Variation Consortium
https://www.pharmvar.org/

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [248]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [249]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [250]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [251]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP2C19, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP2C19 metabolism and also review practice guidelines based upon patients' altered 2C19 metabolic capacity. [15, 247-251]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [252]

"…we genotyped, expression-profiled, and measured P450 activities of 466 human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [252]

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors.
http://www.ncbi.nlm.nih.gov/pubmed/25974703 [244]

"Selective serotonin reuptake inhibitors (SSRIs) are primary treatment options for major depressive and anxiety disorders. CYP2D6 and CYP2C19 polymorphisms can influence the metabolism of SSRIs, thereby affecting drug efficacy and safety. We summarize evidence from the published literature supporting these associations and provide dosing recommendations for fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline based on CYP2D6 and/or CYP2C19 genotype (updates at www.pharmgkb.org)." [244]

Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.
http://www.ncbi.nlm.nih.gov/pubmed/23486447 [313]

"Polymorphisms in CYP2D6 and CYP2C19 affect the efficacy and safety of tricyclics, with some drugs being affected by CYP2D6 only, and others by both polymorphic enzymes. Amitriptyline, clomipramine, doxepin, imipramine, and trimipramine are demethylated by CYP2C19 to pharmacologically active

metabolites. These drugs and their metabolites, along with desipramine and nortriptyline, undergo hydroxylation by CYP2D6 to less active metabolites. Evidence from published literature is presented for CYP2D6 and CYP2C19 genotype-directed dosing of tricyclic antidepressants." [313]

Pharmacogenetics: from bench to byte— an update of guidelines.
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [306]

"Currently, there are very few guidelines linking the results of pharmacogenetic tests to specific therapeutic recommendations... After systematic review of the literature, recommendations were developed for 53 drugs associated with genes coding for CYP2D6, CYP2C19, CYP2C9, thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), vitamin K epoxide reductase (VKORC1), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (FVL)." [306]

Characterization of 107 Genomic DNA Reference Materials for CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1.
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [254]

"…the Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program, in collaboration with members of the pharmacogenetics testing community and the Coriell Cell Repositories, have characterized a panel of 107 genomic DNA reference materials for five loci (CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1) that are commonly included in pharmacogenetic testing panels and proficiency testing surveys. Genomic DNA from publicly available cell lines was sent to volunteer laboratories for genotyping. Each sample was tested in three to six laboratories using a variety of commercially available or laboratory-developed platforms. The results were consistent among laboratories, with differences in allele assignments largely related to the manufacturer's assay design and variable nomenclature, especially for CYP2D6. The alleles included in the assay platforms varied, but most were identified in the set of 107 DNA samples." [254]

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http://www.ncbi.nlm.nih.gov/pubmed/21906384 [255]

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Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype.
http://www.ncbi.nlm.nih.gov/pubmed/16044105 [314]

"The relationships between the observed metabolic ratios and CYP2D6 and/or CYP2C19 genotype were characterized using nonparametric statistical analysis… According to these data, correlations exist between the log (MR) of venlafaxine, amitriptyline, and risperidone and the genotype of the CYP enzymes involved in their metabolism. From the ranges of log (MR) defined here, a high percentage of aberrant metabolizers can be detected even when patients are not routinely genotyped. Thus, the metabolic ratio may serve as an indication of when genotyping should be considered." [314]

CYP2C19 variation and citalopram response.
http://www.ncbi.nlm.nih.gov/pubmed/21192344 [315]

"CYP2C19 and CYP3A4 play a primary role in citalopram metabolism, whereas CYP2D6 plays a secondary role… Generally, patients who had CYP2C19 genotypes associated with decreased metabolism were less likely to tolerate citalopram than those with increased metabolism, although this difference was not statistically significant (P = 0.06). However, patients with the inactive 2C19*2 allele had significantly lower odds of tolerance (P = 0.02)… this study showed that variations in CYP2C19 were associated with tolerance and remission in a large sample of White non-Hispanic patients treated with citalopram." [315]

Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients.
http://www.ncbi.nlm.nih.gov/pubmed/17625515 [316]

The CYP2C19*17 genotype is associated with lower imipramine plasma concentrations in a large group of depressed patients.
http://www.ncbi.nlm.nih.gov/pubmed/19884907 [317]

CYP2C19*17 affects R-warfarin plasma clearance and warfarin INR/dose ratio in patients on stable warfarin maintenance therapy.
http://www.ncbi.nlm.nih.gov/pubmed/25652102 [318]

Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement.
http://www.ncbi.nlm.nih.gov/pubmed/20083681 [242]

A recently explored CYP2C19*17 allelic variant has been linked to increased transcriptional activity, resulting in increased metabolism of CYP2C19 substrates. The *17 allele leads to ultra rapid metabolism of CYP2C19 substrates, producing lower plasma levels of drugs and probable decreases in efficacy. [242, 316-318]

Influence of CYP2D6 and CYP2C19 genotypes on venlafaxine metabolic ratios and stereo selective metabolism in forensic autopsy cases.
http://www.ncbi.nlm.nih.gov/pubmed/25245581 [319]

"We investigated whether polymorphisms in the CYP2D6 and CYP2C19 genes influence the metabolic ratios and enantiomeric S/R ratios of venlafaxine (VEN) and its metabolites O-desmethylvenlafaxine (ODV), N-desmethylvenlafaxine (NDV) and N, O-didesmethylvenlafaxine (DDV) in blood from forensic autopsy cases…Our results show that the CYP2D6 genotype influences the O-demethylation whereas CYP2C19 influences the N-demethylation of VEN and its metabolites. In addition, we show a stereoselective metabolism where CYP2D6 favors the R-enantiomer whereas CYP2C19 favors the S-enantiomer." [319]

Functional characterization of 21 CYP2C19 allelic variants for clopidogrel 2-oxidation.
http://www.ncbi.nlm.nih.gov/pubmed/25001882 [320]

"Genetic variations in cytochrome P450 2C19 (CYP2C19) contribute to interindividual variability in the metabolism of therapeutic agents such as clopidogrel… This study evaluated the in vitro oxidation of clopidogrel by 21 CYP2C19 variants harboring amino acid substitutions… Among the 21 CYP2C19 variants, 12 (that is, CYP2C19.5A, CYP2C19.5B, CYP2C19.6, CYP2C19.8, CYP2C19.9, CYP2C19.10, CYP2C19.14, CYP2C19.16, CYP2C19.19, CYP2C19.22, CYP2C19.24 and CYP2C19.25) showed no or markedly low activity compared with the wild-type protein CYP2C19.1B. This comprehensive in vitro assessment provided insights into the specific metabolic activities of CYP2C19 proteins encoded by variant alleles, and this may to be valuable when interpreting the results of in vivo studies." [320]

Evaluation of the effects of 20 nonsynonymous single nucleotide polymorphisms of CYP2C19 on S-mephenytoin 4'-hydroxylation and omeprazole 5'-hydroxylation.
http://www.ncbi.nlm.nih.gov/pubmed/21325430 [321]

"CYP2C19 is a highly polymorphic enzyme that affects the metabolism of a wide range of therapeutic drugs…The objective of this study was to functionally characterize 20 nsSNPs of CYP2C19, distributed throughout the entire coding region, most of which have not been thoroughly characterized… CYP2C19.5B, CYP2C19.6, and CYP2C19.8 were found to be catalytically inactive…CYP2C19.9, CYP2C19.10, CYP2C19.16, CYP2C19.18, CYP2C19.19, A161P, W212C, and D360N were substantially altered in catalytic properties in comparison with the WT, with each of these variants exhibiting either dramatically decreased catalytic activities or higher K(m) values." [321]

Genomics and pharmacogenomics of schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/20718829 [273]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the

positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [273]

Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options.

http://www.ncbi.nlm.nih.gov/pubmed/24523097 [311]

"Advancements in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Understanding how and when to use this technology to guide pharmacotherapy used to treat psychiatric and neurological (neuropsychiatric) conditions remains a challenge for many clinicians. Currently, guidelines exist to assist clinicians in the use of existing genetic information for drug selection and/or dosing for the tricyclic antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for determining the starting and target doses, as well as drug interaction potential, for a number of other drugs. In this review, we outline the current status of pharmacogenomic testing for neuropsychiatric drugs as it pertains to information contained in drug labeling, consensus guidelines, and test panels, as well as considerations related to obtaining tests for patients." [311]

Role of cytochrome P450 genotype in the steps toward personalized drug therapy.

http://www.ncbi.nlm.nih.gov/pubmed/23226058 [312]

"Genetic polymorphism for cytochrome 450 (P450) enzymes leads to interindividual variability in the plasma concentrations of many drugs. In some cases, P450 genotype results in decreased enzyme activity and an increased risk for adverse drug effects. For example, individuals with the CYP2D6 loss-of-function genotype are at increased risk for ventricular arrhythmia if treated with usual doses of thioridazine. In other cases, P450 genotype may influence the dose of a drug required to achieve a desired effect. This is the case with warfarin, with lower doses often necessary in carriers of a variant CYP2C9*2 or *3 allele to avoid supra-therapeutic anticoagulation. When a prodrug, such as clopidogrel or codeine, must undergo hepatic biotransformation to its active form, a loss-of-function P450 genotype leads to reduced concentrations of the active drug and decreased drug efficacy. In contrast, patients with multiple CYP2D6 gene copies are at risk for opioid-related toxicity if treated with usual doses of codeine-containing analgesics. At least 25 drugs contain information in their US Food and Drug Administration-approved labeling regarding P450 genotype. The CYP2C9, CYP2C19, and CYP2D6 genes are the P450 genes most often cited. To date, integration of P450 genetic information into clinical decision making is limited. However, some institutions are beginning to embrace routine P450 genotyping to assist in the treatment of their patients. Genotyping for P450 variants may carry less risk for discrimination compared with genotyping for disease-associated variants. As such, P450 genotyping is likely to lead the way in the clinical implementation of pharmacogenomics. This review discusses variability in the CYP2C9, CYP2C19, and CYP2D6 genes and the implications of this for drug efficacy and safety." [312]

Pharmacogenomics study in a Taiwan methadone maintenance cohort.

http://www.ncbi.nlm.nih.gov/pubmed/25278738 [284]

"Pharmacogenomics is research to study the drug treatment responses in subgroups of patients according to their genetic variants or genetic expression information. Methadone maintenance treatment, which is usually prescribed for patients with heroin dependence, was launched in Taiwan by the government in 2006. In this study, 366 patients who had taken methadone continually in the previous 7 days were examined. Data from administration of the Treatment Outcomes Profile (TOP), Severity of Dependence Scale (SDS), Clinical Opioid Withdrawal Scale (COWS), and Treatment Emergent Symptoms Scale (TESS) were obtained from patients' report records. Genes encoding the liver cytochrome P-450 (CYP) enzymes that are involved with the metabolism of methadone (CYP2B6, 3A4 and 2C19) were selected and genotyped in this cohort. We found that the SNPs on CYP2B6 were associated with plasma S-methadone concentration; SNPs on CYP3A4 were associated with withdrawal symptoms and side effects; and SNPs on CYP2C19 were associated with methadone dose. SNPs in the genes encoding the morphine phase II metabolic enzyme, UGT2B7, were associated with

withdrawal symptom scores. In pharmacodynamic genes, the SNPs on OPRM1 were associated with insomnia and change in libido side effects. We conclude that SNP markers may be useful for future methadone dosage adjustment and to reduce adverse reactions." [284]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.

http://www.ncbi.nlm.nih.gov/pubmed/25987241 [288]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [288]

Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine.

http://www.ncbi.nlm.nih.gov/pubmed/27289413 [322]

"Antidepressants are commonly prescribed medications in the United States, and there is increasing interest in individualizing treatment selection for more than 20 US Food and Drug Administration-approved treatments for major depressive disorder. Providing greater precision to pharmacotherapeutic recommendations for individual patients beyond the large-scale clinical trials evidence base can potentially reduce adverse effect toxicity profiles and increase response rates and overall effectiveness. It is increasingly recognized that genetic variation may contribute to this differential risk to benefit ratio and thus provides a unique opportunity to develop pharmacogenetic guidelines for psychiatry. Key studies and concepts that review the rationale for cytochrome P450 2D6 (CYP2D6) and cytochrome P450 2C19 (CYP2C19) genetic testing can be delineated by serum levels, adverse events, and clinical outcome measures (e.g, antidepressant response). In this article, we report the evidence that contributed to the implementation of pharmacokinetic pharmacogenetic guidelines for antidepressants primarily metabolized by CYP2D6 and CYP2C19." [322]

The CYP2C19 Intron 2 Branch Point SNP is the Ancestral Polymorphism Contributing to the Poor Metabolizer Phenotype in Livers with CYP2C19*35 and CYP2C19*2 Alleles.

https://www.ncbi.nlm.nih.gov/pubmed/26021325 [323]

"CYP2C19 rs12769205 alters an intron 2 branch point adenine leading to an alternative mRNA in human liver with complete inclusion of intron 2 (exon 2B). rs12769205 changes the mRNA reading frame, introduces 87 amino acids, and leads to a premature stop codon. The 1000 Genomes project indicated rs12769205 is in linkage disequilibrium with rs4244285 on CYP2C19*2, but found alone on CYP2C19*35 in Blacks. Minigenes containing rs12769205 transfected into HepG2 cells demonstrated this single nucleotide polymorphism (SNP) alone leads to exon 2B and decreases CYP2C19 canonical mRNA. A residual amount of CYP2C19 protein was detectable by quantitative proteomics with tandem mass spectrometry in CYP2C19*2/*2 and *1/*35 liver microsomes with an exon 2 probe. However, an exon 4 probe, downstream from rs12769205, but upstream of rs4244285, failed to detect CYP2C19 protein in livers homozygous for rs12769205, demonstrating rs12769205 alone can lead to complete loss of CYP2C19 protein. CYP2C19 genotypes and mephenytoin phenotype were compared in 104 Ethiopians. Poor metabolism of mephenytoin was seen in persons homozygous for both rs12769205 and rs4244285 (CYP2C19*2/*2), but with little effect on mephenytoin disposition of CYP2C19*1/*2, CYP2C19*1/*3, or CYP2C19*1/*35 heterozygous alleles." [323]

Literature Summary: Cytochrome P450 2D6: (CYP2D6)

Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy.

http://www.ncbi.nlm.nih.gov/pubmed/24151799 [15]

Pharmacogenetics of second-generation antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [20]

Pharmacogene Variation Consortium
https://www.pharmvar.org/

PharmGKB The Pharmacogenomics Knowledgebase.
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Applications of CYP450 testing in the clinical setting.
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Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I.
http://www.ncbi.nlm.nih.gov/pubmed/19817501 [324]

Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part II.
http://www.ncbi.nlm.nih.gov/pubmed/19902987 [325]

Recent examples on the clinical relevance of the CYP2D6 polymorphism and endogenous functionality of CYP2D6.
http://www.ncbi.nlm.nih.gov/pubmed/24088607 [326]

Pharmacokinetics of venlafaxine extended release 75 mg and desvenlafaxine 50 mg in healthy CYP2D6 extensive and poor metabolizers: a randomized, open-label, two-period, parallel-group, crossover study.
http://www.ncbi.nlm.nih.gov/pubmed/21288052 [327]

The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation.
http://www.ncbi.nlm.nih.gov/pubmed/15669884 [328]

There are numerous studies which support the fact that CYP2D6 metabolizer status can lead to altered drug clearance and levels of active metabolites of psychiatric medications. These changes may lead to increased risk for side effects or treatment inefficacy. For example, CYP2D6 poor metabolizer genotype is associated with increased risk for side effects and medication discontinuation. [15, 20, 247-251, 324-328]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [252]

"…we genotyped, expression-profiled, and measured P450 activities of 466 human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [252]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence.
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [258]

"CYP2D6, CYP1A2, and CYP3A4/5 are major enzymes in the metabolism of antipsychotics and polymorphisms of alleles for these proteins are associated with altered plasma levels… Numerous studies have shown a significant association between genotype and adverse effects, such as CYP2D6 polymorphisms and tardive dyskinesia. This review summarizes evidence for the role of CYP450 genetic variants in the response to antipsychotic medications and the clinical implications of pharmacogenetics in the management of patients with schizophrenia." [258]

The Dosing of Atypical Antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [261]

"Drug-drug interactions or genetic variability may require using doses different from those recommended for atypical antipsychotics… Genetic variations of cytochrome P450 2D6 (CYP2D6) and drug-drug interactions causing inhibition (CYP2D6 and/or CYP3A) or induction (CYP3A) may be important for risperidone, and perhaps for aripiprazole, dosing. Adding inhibitors may cause side effects more easily in drugs with a narrow therapeutic window, such as clozapine or risperidone, than in those with a wide therapeutic window, such as olanzapine or aripiprazole. Adding inducers may be associated with a gradual development of lost efficacy." [261]

Pharmacogenetics: from bench to byte— an update of guidelines.
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [306]

"…the Royal Dutch Association for the Advancement of Pharmacy established the Pharmacogenetics Working Group with the objective of developing pharmacogenetics-based therapeutic (dose) recommendations. After systematic review of the literature, recommendations were developed for 53 drugs associated with genes coding for CYP2D6, CYP2C19, CYP2C9, thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), vitamin K epoxide reductase (VKORC1), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (FVL)." [306]

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype.
http://www.ncbi.nlm.nih.gov/pubmed/22205192 [245]

"Codeine is bioactivated to morphine, a strong opioid agonist, by the hepatic cytochrome P450 2D6 (CYP2D6); hence, the efficacy and safety of codeine as an analgesic are governed by CYP2D6 polymorphisms. Codeine has little therapeutic effect in patients who are CYP2D6 poor metabolizers, whereas the risk of morphine toxicity is higher in ultra rapid metabolizers. The purpose of this guideline (periodically updated at http://www.pharmgkb.org) is to provide information relating to the interpretation of CYP2D6 genotype test results to guide the dosing of codeine." [245]

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors.
http://www.ncbi.nlm.nih.gov/pubmed/25974703 [244]

"Selective serotonin reuptake inhibitors (SSRIs) are primary treatment options for major depressive and anxiety disorders. CYP2D6 and CYP2C19 polymorphisms can influence the metabolism of SSRIs, thereby affecting drug efficacy and safety. We summarize evidence from the published literature supporting these associations and provide dosing recommendations for fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline based on CYP2D6 and/or CYP2C19 genotype (updates at www.pharmgkb.org)." [244]

Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.
http://www.ncbi.nlm.nih.gov/pubmed/23486447 [313]

"Polymorphisms in CYP2D6 and CYP2C19 affect the efficacy and safety of tricyclics, with some drugs being affected by CYP2D6 only, and others by both polymorphic enzymes. Amitriptyline, clomipramine, doxepin, imipramine, and trimipramine are demethylated by CYP2C19 to pharmacologically active metabolites. These drugs and their metabolites, along with desipramine and nortriptyline, undergo hydroxylation by CYP2D6 to less active metabolites. Evidence from published literature is presented for CYP2D6 and CYP2C19 genotype-directed dosing of tricyclic antidepressants." [313]

Characterization of 107 Genomic DNA Reference Materials for CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1: a GeT-RM and Association for Molecular Pathology collaborative project.
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [254]

"…the Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program, in collaboration with members of the pharmacogenetics testing community and the Coriell Cell Repositories, have characterized a panel of 107 genomic DNA reference materials for five loci (CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1) that are commonly included in

pharmacogenetic testing panels and proficiency testing surveys. Genomic DNA from publicly available cell lines was sent to volunteer laboratories for genotyping. Each sample was tested in three to six laboratories using a variety of commercially available or laboratory-developed platforms. The results were consistent among laboratories, with differences in allele assignments largely related to the manufacturer's assay design and variable nomenclature, especially for *CYP2D6*. The alleles included in the assay platforms varied, but most were identified in the set of 107 DNA samples." [254]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance.

http://www.ncbi.nlm.nih.gov/pubmed/21906384 [255]

"Regarding drug metabolism, specific polymorphisms to the cytochrome (CYP) P450 enzyme family are linked to phenotypes that describe reaction rates as "ultra", "intermediate", and "poor," as referenced to "extensive" metabolizers that are assigned to wildtype individuals. Activity scores is an alternate designation that provides more genotype-to-phenotype resolution. Understanding the relative change in enzyme activities or rate of clearance of specific drugs relative to an individual's genotypes is an important component in the interpretation of pharmacogenomic data for personalized medicine." [255]

Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype.

http://www.ncbi.nlm.nih.gov/pubmed/16044105 [314]

"The relationships between the observed metabolic ratios and CYP2D6 and/or CYP2C19 genotype were characterized using nonparametric statistical analysis. A clear correlation was observed between the CYP2D6 genotype and the metabolic ratio of venlafaxine." [314]

CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure.

http://www.ncbi.nlm.nih.gov/pubmed/17301689 [329]

"Our study shows that (i) CYP2D6 diversity is far greater within than between populations and groups thereof, (ii) null or low-activity variants occur at high frequencies in various areas of the world, (iii) linkage disequilibrium is lowest in Africa and highest in the Americas. Patterns of variation, within and among populations, are similar to those observed for other autosomal markers (e.g. microsatellites and protein polymorphisms), suggesting that the diversity observed at the CYP2D6 locus reflects the same factors affecting variation at random genome markers." [329]

CYP2D6 genotype information to guide pimozide treatment in adult and pediatric patients: basis for the U.S. Food and Drug Administration's new dosing recommendations.

http://www.ncbi.nlm.nih.gov/pubmed/23059146 [330]

"The occurrence of pimozide-induced arrhythmias is concentration dependent. Hence, it is important for prescribers to consider causes of increased pimozide exposure. This article summarizes the U.S. Food and Drug Administration's (FDA's) review of drug interaction and pharmacogenomic studies and discusses pharmacokinetic simulations we performed to develop new cytochrome P450 2D6 (CYP2D6) genotype-guided dosing recommendations for pimozide." [330]

Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder.

http://www.ncbi.nlm.nih.gov/pubmed/20441720 [331]

"Compared with PMs, EMs had significantly greater mean changes from baseline on 4 of 5 depression rating scales (all 4 comparisons, $P \leq .020$). A significantly greater percentage of EMs achieved response or remission by most measures compared with PMs (4 of 5 comparisons, $P \leq .015$). Rates of discontinuation and AEs did not differ significantly between EMs and PMs." [331]

Clinical pharmacokinetics of atomoxetine.

http://www.ncbi.nlm.nih.gov/pubmed/15910008 [332]

Effects of the CYP2D6*10 allele on the pharmacokinetics of atomoxetine and its metabolites.

http://www.ncbi.nlm.nih.gov/pubmed/26254792 [333]

CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial.

http://www.ncbi.nlm.nih.gov/pubmed/25919121 [334]

Several studies have shown that CYP2D6 polymorphism can lead to altered atomoxetine metabolism and varied blood levels, as well as increased risk of side effects. The mean exposure to active moieties of atomoxetine was markedly higher in subjects with the CYP2D6*10/*10 genotype compared to that in those with the CYP2D6* WT/*WT genotype. Poor metabolizers had higher frequencies of dry mouth, erectile dysfunction, hyperhidrosis, insomnia, and urinary retention compared with the other metabolizer groups. [332-334]

Cytochrome P450 2D6 genotype affects the pharmacokinetics of controlled-release paroxetine in healthy Chinese subjects: comparison of traditional phenotype and activity score systems.

http://www.ncbi.nlm.nih.gov/pubmed/25967538 [335]

"…the pharmacokinetics of controlled-release paroxetine after a single administration was affected by CYP2D6 polymorphisms. Both the traditional phenotype and the activity score systems performed well and distinguished subjects with different drug exposures. The activity score system provided a more detailed classification for the subjects." [335]

Genetics-Based Population Pharmacokinetics and Pharmacodynamics of Risperidone in a Psychiatric Cohort.

http://www.ncbi.nlm.nih.gov/pubmed/26129906 [336]

"High interindividual variability in plasma concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, may lead to suboptimal drug concentration… Genetic polymorphisms of CYP2D6 play an important role in risperidone, 9-hydroxyrisperidone and active moiety plasma concentration variability, which were associated with common side effects. These results highlight the importance of a personalized dosage adjustment during risperidone treatment." [336]

Impact of multiple inhibitors or substrates of cytochrome P450 2D6 on plasma risperidone levels in patients on polypharmacy.

http://www.ncbi.nlm.nih.gov/pubmed/18728628 [337]

"CYP2D6 catalyzes the conversion of risperidone to the active metabolite 9-OH-risperidone… Concentration-to-dose (C: D) ratios of risperidone and 9-OH-risperidone in 218 patients were associated with the number of concomitantly used substrates or inhibitors of CYP2D6. The C: D ratios of risperidone in patients with 0, 1, and >1 numbers of CYP2D6 inhibitors were 2.6, 8.5, and 17 nmol L^{-1} mg^{-1}, respectively. Differences between the groups were highly significant ($p < 0.001$). All patients with >1 CYP2D6 inhibitors were administered at least 1 potent CYP2D6 inhibitor, that is fluoxetine, paroxetine, thioridazine, and/or levomepromazine. The C:D ratios of the active moiety (risperidone + 9-OH-risperidone) in patients with 0, 1, and >1 numbers of concomitant CYP2D6 inhibitors were 17, 24, and 30 nmol L^{-1} mg^{-1}, respectively ($p = 0.001$), which was explained by higher levels of risperidone without any change in the levels of 9-OH-risperidone… An indication for risperidone drug monitoring should therefore include concomitant medication with established CYP inhibitors." [337]

CYP2D6 genetic polymorphisms and their relevance for poisoning due to amphetamines, opioid analgesics and antidepressants.

http://www.ncbi.nlm.nih.gov/pubmed/25998998 [338]

"This review will focus specifically on CYP2D6 genetic polymorphisms and their relevance for poisoning due to amphetamines, opioid analgesics and antidepressants in humans…Either poor or extensive/ultra-rapid CYP2D6 metabolizers may be exposed to toxic effects of amphetamines, opioid analgesics and antidepressants. In these three categories, the level of evidence is substance dependent, with differences within the same pharmacological class." [338]

Opioid metabolism.

http://www.ncbi.nlm.nih.gov/pubmed/19567715 [339]

"Clinicians understand that individual patients differ in their response to specific opioid analgesics and that patients may require trials of several opioids before finding an agent that provides effective analgesia with acceptable tolerability… This review describes the basics of opioid metabolism as well as the factors influencing it and provides recommendations for addressing metabolic issues that may compromise effective pain management." [339]

CYP2D6 phenotype-specific codeine population pharmacokinetics.

http://www.ncbi.nlm.nih.gov/pubmed/25562725 [340]

"We aimed to develop a codeine pharmacokinetic pathway model for codeine and its metabolites that incorporates the effects of genetic polymorphisms… The population model indicated that about 10% of a codeine dose was converted to morphine in poor-metabolizer phenotype subjects. The model also showed that about 40% of a codeine dose was converted to morphine in EM subjects, and about 51% was converted to morphine in ultra rapid-metabolizers… Our study suggests that pharmacogenetics for personalized dosing might be most effectively advanced by studying the interplay between pharmacogenetics, population pharmacokinetics, and clinical pharmacokinetics." [340]

Individualized Hydrocodone Therapy Based on Phenotype, Pharmacogenetics, and Pharmacokinetic Dosing.

http://www.ncbi.nlm.nih.gov/pubmed/25621429 [341]

"Our results demonstrate that pharmacogenetics afford clinicians an opportunity to individualize [hydrocodone] HC dosing, while adding enhanced opportunity to account for its conversion to HM in the body." [341]

Genomics and pharmacogenomics of schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/20718829 [273]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [273]

Pharmacogenomics can improve antipsychotic treatment in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/23606027 [274]

"Schizophrenia is a widespread mental disease with a prevalence of about 1% in the world population, and heritability of up to 80%. Drug therapy is an important approach to treating the disease. However, the curative effect of antipsychotic is far from satisfactory in terms of tolerability and side effects. Many studies have indicated that nearly 30% of patients exhibit little or no improvements associated with antipsychotics. The response of individual patients who are given the same dose of the same drug varies considerably. In addition, antipsychotic drugs are often accompanied by adverse drug reactions (ADRs), which can cause considerable financial loss in addition to the obvious societal harm. So, it is strongly recommended that personalized medicine should be implemented both to improve drug efficacy and to minimize adverse events and toxicity. There is therefore a need for pharmacogenomic studies into the factors affecting response of schizophrenia patients to antipsychotic drugs to provide informed guidance for clinicians. Individual differences in drug response is due to a combination of many complex factors including ADEM (absorption, distribution, metabolism, excretion) process, transporting, binding with receptor and intracellular signal transduction. Pharmacogenetic and pharmacogenomic studies have successfully identified genetic variants that contribute to this interindividual variability in antipsychotics response. In addition, epigenetic factors such as methylation of DNA and regulation by miRNA have also been reported to play an important role in the complex interactions between the multiple genes and environmental factors which influence individual drug response phenotypes in patients. In this review, we will focus on the latest research on polymorphisms of candidate genes that code for drug metabolic enzymes (CYP2D6, CYP1A2, CYP3A4, etc.), drug transporters (mainly ABCB1) and neurotransmitter receptors (dopamine receptors and serotonin receptors, etc.). We also discuss the genome-wide pharmacogenomic study of schizophrenia and review the current state of knowledge on epigenetics and potential clinical applications." [274]

Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options.

http://www.ncbi.nlm.nih.gov/pubmed/24523097 [311]

"Advancements in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Understanding how and when to use this technology to guide pharmacotherapy used to treat psychiatric and neurological (neuropsychiatric) conditions remains a challenge for many clinicians. Currently, guidelines exist to assist clinicians in the use of existing genetic information for drug selection and/or dosing for the tricyclic antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for determining the starting and target doses, as well as drug interaction potential, for a number of other drugs. In this review, we outline the current status of pharmacogenomic testing for neuropsychiatric drugs as it pertains to information contained in drug labeling, consensus guidelines, and test panels, as well as considerations related to obtaining tests for patients." [311]

Role of cytochrome P450 genotype in the steps toward personalized drug therapy.

http://www.ncbi.nlm.nih.gov/pubmed/23226058 [312]

"Genetic polymorphism for cytochrome 450 (P450) enzymes leads to interindividual variability in the plasma concentrations of many drugs. In some cases, P450 genotype results in decreased enzyme activity and an increased risk for adverse drug effects. For example, individuals with the CYP2D6 loss-of-function genotype are at increased risk for ventricular arrhythmia if treated with usual doses of thioridazine. In other cases, P450 genotype may influence the dose of a drug required to achieve a desired effect. This is the case with warfarin, with lower doses often necessary in carriers of a variant CYP2C9*2 or *3 allele to avoid supra-therapeutic anticoagulation. When a prodrug, such as clopidogrel or codeine, must undergo hepatic biotransformation to its active form, a loss-of-function P450 genotype leads to reduced concentrations of the active drug and decreased drug efficacy. In contrast, patients with multiple CYP2D6 gene copies are at risk for opioid-related toxicity if treated with usual doses of codeine-containing analgesics. At least 25 drugs contain information in their US Food and Drug Administration-approved labeling regarding P450 genotype. The CYP2C9, CYP2C19, and CYP2D6 genes are the P450 genes most often cited. To date, integration of P450 genetic information into clinical decision making is limited. However, some institutions are beginning to embrace routine P450 genotyping to assist in the treatment of their patients. Genotyping for P450 variants may carry less risk for discrimination compared with genotyping for disease-associated variants. As such, P450 genotyping is likely to lead the way in the clinical implementation of pharmacogenomics. This review discusses variability in the CYP2C9, CYP2C19, and CYP2D6 genes and the implications of this for drug efficacy and safety." [312]

Copy number variations' effect on drug response still overlooked.

http://www.ncbi.nlm.nih.gov/pubmed/25742449 [342]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.

http://www.ncbi.nlm.nih.gov/pubmed/25987241 [288]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [288]

Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine.

http://www.ncbi.nlm.nih.gov/pubmed/27289413 [322]

"Antidepressants are commonly prescribed medications in the United States, and there is increasing interest in individualizing treatment selection for more than 20 US Food and Drug Administration-approved treatments for major depressive disorder. Providing greater precision to pharmacotherapeutic recommendations for individual patients beyond the large-scale clinical trials evidence base can potentially reduce adverse effect toxicity profiles and increase response rates and overall effectiveness. It is increasingly recognized that genetic variation may contribute to this differential risk to benefit ratio and thus provides a unique opportunity to develop pharmacogenetic guidelines for psychiatry. Key studies and concepts that review the rationale for cytochrome P450 2D6 (CYP2D6) and cytochrome P450 2C19

(CYP2C19) genetic testing can be delineated by serum levels, adverse events, and clinical outcome measures (e.g, antidepressant response). In this article, we report the evidence that contributed to the implementation of pharmacokinetic pharmacogenetic guidelines for antidepressants primarily metabolized by CYP2D6 and CYP2C19." [322]

Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol.
http://www.ncbi.nlm.nih.gov/pubmed/26514968 [343]

"Overall, 6.1 % UM (n = 5), 25.6 % EM-f (n = 21), 46.3 % EM-s (n = 38), 1.2 % EM-s/EM-f (n = 1), 6.1 % IM (n = 5), and 14.6 % PM (n = 12) were found, taking co-administration of strong and moderate CYP2D6 inhibitors into account (pheno-conversion). It was demonstrated that CYP2D6 polymorphisms affect the serum concentrations of aripiprazole (n = 18), haloperidol (n = 11), risperidone (n = 20), and zuclopenthixol (n = 6), while no influence was seen on the paliperidone serum concentrations (n = 31)." [343]

Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease.
http://www.ncbi.nlm.nih.gov/pubmed/27335380 [344]

"Here we describe the implementation of pharmacogenetics-based codeine prescribing that accounts for CYP2D6 metabolizer status. Clinical decision support was implemented within the electronic health record to guide prescribing of codeine with the goal of preventing its use after tonsillectomy or adenoidectomy and in CYP2D6 ultra-rapid and poor metabolizer (high-risk) genotypes. As of June 2015, CYP2D6 genotype results had been reported for 2468 unique patients. Of the 830 patients with sickle cell disease, 621 (75%) had a CYP2D6 genotype result; 7.1% were ultra-rapid or possible ultra-rapid metabolizers, and 1.4% were poor metabolizers. Interruptive alerts recommended against codeine for patients with high-risk CYP2D6 status. None of the patients with an ultra-rapid or poor metabolizer genotype were prescribed codeine. Using genetics to tailor analgesic prescribing retained an important therapeutic option by limiting codeine use to patients who could safely receive and benefit from it. Our efforts represent an evidence-based, innovative medication safety strategy to prevent adverse drug events, which is a model for the use of pharmacogenetics to optimize drug therapy in specialized pediatric populations." [344]

Literature Summary: Cytochrome P450 3A4/5: (CYP3A4/5)

Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy.
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [15]

Pharmacogenetics of second-generation antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [20]

Pharmacogene Variation Consortium
https://www.pharmvar.org/

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [248]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [249]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [250]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [251]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP3A4/5, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP3A4/5 metabolism. [15, 20, 247-251]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [252]

"…we genotyped, expression-profiled, and measured P450 activities of 466 human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [252]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence.
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [258]

"CYP2D6, CYP1A2, and CYP3A4/5 are major enzymes in the metabolism of antipsychotics and polymorphisms of alleles for these proteins are associated with altered plasma levels… Numerous studies have shown a significant association between genotype and adverse effects, such as CYP2D6 polymorphisms and tardive dyskinesia. This review summarizes evidence for the role of CYP450 genetic variants in the response to antipsychotic medications and the clinical implications of pharmacogenetics in the management of patients with schizophrenia." [258]

The dosing of atypical antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [261]

"Dosage alterations of …quetiapine, dependent on cytochrome P450 3A (CYP3A), may be necessary when used with other drugs that inhibit or induce their metabolic enzymes. Genetic variations of cytochrome P450 2D6 (CYP2D6) and drug-drug interactions causing inhibition (CYP2D6 and/or CYP3A) or induction (CYP3A) may be important for risperidone, and perhaps for aripiprazole, dosing. Adding inhibitors may cause side effects more easily in drugs with a narrow therapeutic window, such as clozapine or risperidone, than in those with a wide therapeutic window, such as olanzapine or aripiprazole. Adding inducers may be associated with a gradual development of lost efficacy." [261]

CYP3A5 genetic polymorphisms in different ethnic populations.
http://www.ncbi.nlm.nih.gov/pubmed/15833928 [282]

"Cyp3A5 activity varies within any given ethnic population, suggesting that genetic variation within the Cyp3A5 gene may be the most important contributor to interindividual and interracial differences in Cyp3A-dependent drug clearance and response. …Significant differences were observed in the distribution of Cyp3A5*3, Cyp3A5*6, and Cyp3A5*7 alleles among white and African populations. The frequency of Cyp3A5*3 allele in white Canadians (93%) is higher than in Zimbabweans (77.6%) ($p < 0.001$). In contrast, Cyp3A5*6 and Cyp3A5*7 alleles are relatively frequent in African subjects (10–22%) but absent in white subjects ($p < 0.001$). These differences may reflect evolutionary pressures generated by environmental factors in geographically distinct regions. However, the genetic polymorphism of Cyp3A5alone does not explain the interindividual differences in Cyp3A mediated metabolism." [282]

Lurasidone drug-drug interaction studies: a comprehensive review.
http://www.ncbi.nlm.nih.gov/pubmed/24825095 [283]

"Lurasidone PK is altered by strong cytochrome P450 (CYP) 3A4 inhibitors or inducers, and co-administration is contraindicated; whereas moderate CYP3A4 inhibitors have less effect, and lurasidone dosage restrictions are recommended." [283]

Genomics and pharmacogenomics of schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/20718829 [273]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and

95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [273]

Pharmacogenomics can improve antipsychotic treatment in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/23606027 [274]

"Schizophrenia is a widespread mental disease with a prevalence of about 1% in the world population, and heritability of up to 80%. Drug therapy is an important approach to treating the disease. However, the curative effect of antipsychotic is far from satisfactory in terms of tolerability and side effects. Many studies have indicated that nearly 30% of patients exhibit little or no improvements associated with antipsychotics. The response of individual patients who are given the same dose of the same drug varies considerably. In addition, antipsychotic drugs are often accompanied by adverse drug reactions (ADRs), which can cause considerable financial loss in addition to the obvious societal harm. So, it is strongly recommended that personalized medicine should be implemented both to improve drug efficacy and to minimize adverse events and toxicity. There is therefore a need for pharmacogenomic studies into the factors affecting response of schizophrenia patients to antipsychotic drugs to provide informed guidance for clinicians. Individual differences in drug response is due to a combination of many complex factors including ADEM (absorption, distribution, metabolism, excretion) process, transporting, binding with receptor and intracellular signal transduction. Pharmacogenetic and pharmacogenomic studies have successfully identified genetic variants that contribute to this interindividual variability in antipsychotics response. In addition, epigenetic factors such as methylation of DNA and regulation by miRNA have also been reported to play an important role in the complex interactions between the multiple genes and environmental factors which influence individual drug response phenotypes in patients. In this review, we will focus on the latest research on polymorphisms of candidate genes that code for drug metabolic enzymes (CYP2D6, CYP1A2, CYP3A4, etc.), drug transporters (mainly ABCB1) and neurotransmitter receptors (dopamine receptors and serotonin receptors, etc.). We also discuss the genome-wide pharmacogenomic study of schizophrenia and review the current state of knowledge on epigenetics and potential clinical applications." [274]

Pharmacogenomics study in a Taiwan methadone maintenance cohort.

http://www.ncbi.nlm.nih.gov/pubmed/25278738 [284]

"Pharmacogenomics is research to study the drug treatment responses in subgroups of patients according to their genetic variants or genetic expression information. Methadone maintenance treatment, which is usually prescribed for patients with heroin dependence, was launched in Taiwan by the government in 2006. In this study, 366 patients who had taken methadone continually in the previous 7 days were examined. Data from administration of the Treatment Outcomes Profile (TOP), Severity of Dependence Scale (SDS), Clinical Opioid Withdrawal Scale (COWS), and Treatment Emergent Symptoms Scale (TESS) were obtained from patients' report records. Genes encoding the liver cytochrome P-450 (CYP) enzymes that are involved with the metabolism of methadone (CYP2B6, 3A4 and 2C19) were selected and genotyped in this cohort. We found that the SNPs on CYP2B6 were associated with plasma S-methadone concentration; SNPs on CYP3A4 were associated with withdrawal symptoms and side effects; and SNPs on CYP2C19 were associated with methadone dose. SNPs in the genes encoding the morphine phase II metabolic enzyme, UGT2B7, were associated with withdrawal symptom scores. In pharmacodynamic genes, the SNPs on OPRM1 were associated with insomnia and change in libido side effects. We conclude that SNP markers may be useful for future methadone dosage adjustment and to reduce adverse reactions." [284]

The Absence of CYP3A5*3 Is a Protective Factor to Anticonvulsants Hypersensitivity Reactions: A Case-Control Study in Brazilian Subjects.

http://www.ncbi.nlm.nih.gov/pubmed/26291084 [285]

"Although aromatic anticonvulsants are usually well tolerated, they can cause cutaneous adverse drug reactions in up to 10% of patients. The clinical manifestations of the antiepileptic-induced hypersensitivity reactions (AHR) vary from mild skin rashes to severe cutaneous drug adverse reactions which are related to high mortality and significant morbidity. Genetic polymorphisms in cytochrome P450 genes are associated with altered enzymatic activity and may contribute to the risk of AHR. Here we present a case-control study in which we genotyped SNPs of CYP2C19, 2C9 and 3A5 of 55 individuals

with varying severities of AHR, 83 tolerant, and 366 healthy control subjects from São Paulo, Brazil. Clinical characterization was based on standardized scoring systems and drug patch test. All in vivo investigation followed the ENDA (European Network of Drug Allergy) recommendations. Genotype was determined by real time PCR using peripheral blood DNA as a template. Of all 504 subjects, 65% were females, 45% self-identified as Afro-American, 38% as Caucasian and 17% as having non-African mixed ascendancy. Amongst 55 subjects with AHR, 44 had severe cutaneous drug adverse reactions. Of the 46 drug patch tests performed, 29 (63%) were positive. We found a strong association between the absence of CYP3A5*3 and tolerant subjects when compared to AHR (p = 0.0002, OR = 5.28 [CI95% 2.09-14.84]). None of our groups presented positive association with CYP2C19 and 2C9 polymorphisms, however, both SNPs contributed to separation of cases and tolerants in a Classification and Regression Tree. Our findings indicate that drug metabolism genes can contribute in the tolerability of antiepileptics. CYP3A5*3 is the most prevalent CYP3A5 allele associated with reduced enzymatic function. The current study provides evidence that normal CYP3A5 activity might be a protective factor to aromatic antiepileptics-induced hypersensitivity reactions in Brazilian subjects." [285]

PharmGKB Annotations

The Pharmacogenomics Knowledgebase (PharmGKB) is an NIH-funded resource that provides information about how human genetic variation affects response to medications. PharmGKB collects, curates and disseminates knowledge about clinically actionable gene-drug associations and genotype-phenotype relationships. More information about PharmGKB can be found at https://www.pharmgkb.org/

PharmGKB Strength of Evidence Scores

Level 1A: Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.

Level 1B: Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.

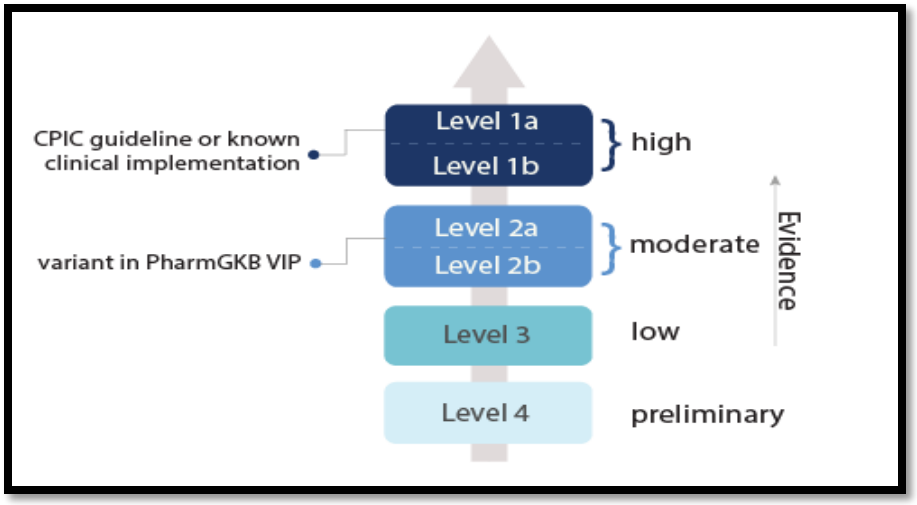
Level 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

Level 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Level 3: Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.

Level 4: Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.

For more information about clinical annotations and levels of evidence, please refer to *Pharmacogenomics knowledge for personalized medicine.* Clinical pharmacology and therapeutics. 2012. Whirl-Carrillo M, McDonagh E M, Hebert J M, Gong L, Sangkuhl K, Thorn C F, Altman R B, Klein T E. https://www.ncbi.nlm.nih.gov/pubmed/22992668



PharmGKB drug-gene annotations pertinent to Genomind Professional PGx

https://www.pharmgkb.org/

Gene	PharmGKB Score	Drug(s)	Gene		PharmGKB score	Drug(s)
ABCB1	2B	opioids	DRD2		3	antipsychotics, bupropion
ADRA2A	3	methylphenidate	GRIK1		3	topiramate
ANK3	Unranked	null	HLA-A		1A	carbamazepine
BDNF	3	citalopram, paroxetine, olanzapine, (assorted antidepressants and antipsychotics)	HLA-B		1A	carbamazepine, oxcarbazepine, phenytoin
CACNA1C	4	citalopram	MTHFR		3	clozapine, olanzapine, folate
COMT	2B	opioids	MC4R		2B	antipsychotics
CYP1A2	3	olanzapine, clozapine (assorted antipsychotics)	OPRM1		2B	naloxone, opioids
CYP2B6	2A	methadone	SLC6A4		2A	escitalopram, citalopram
CYP2C9	1A	phenytoin, celecoxib, (assorted NSAIDS)	5HT2A		2B	citalopram and assorted antidepressants
CYP2C19	1A	citalopram, escitalopram, sertraline, tricyclic antidepressants	5HT2C		2B	antipsychotics
CYP2D6	1A/2A	paroxetine, fluvoxamine, tricyclic antidepressants, codeine//tramadol, venlafaxine, oxycodone, mirtazapine, risperidone, atomoxetine	UGT1A4		2B	lamotrigine
CYP3A4/5	3	midazolam, risperidone	UGT2B15		2B	lorazepam, oxazepam

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