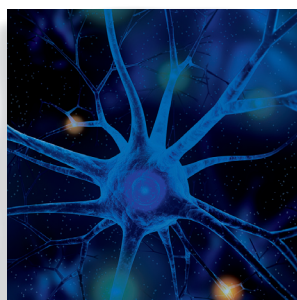


## *The role of genetics and genomics in clinical psychiatry*

*Margret R. Hoehe, MD, PhD; Deborah J. Morris-Rosendahl, PhD*



*The enormous successes in the genetics and genomics of many diseases have provided the basis for the advancement of precision medicine. Thus, the detection of genetic variants associated with neuropsychiatric disorders, as well as treatment outcome, has raised growing expectations that these findings could soon be translated into the clinic to improve diagnosis, the prediction of disease risk and individual response to drug therapy. In this article, we will provide an introduction to the search for genes involved in psychiatric illness and summarize the present findings in major psychiatric disorders. We will review the genetic variants in genes encoding drug metabolizing enzymes and specific drug targets which were found to be associated with variable drug response and severe side effects. We will evaluate the clinical translatability of these findings, whether there is currently any role for genetic testing and in this context, make valuable sources of information available to the clinician seeking guidance and advice in this rapidly developing field of psychiatric genetics.*

© 2018, AICH – Servier Group

*Dialogues Clin Neurosci.* 2018;20:169-177.

### The search for genes underlying psychiatric illness

**F**or decades, researchers have intensively sought to identify the underlying molecular causes of psychiatric illness. Understanding the biology of the disease, they believed, would enable valid clinical diagnosis and risk prediction, as well as a better treatment of the individual. So from the 1960s, the biological hypotheses for psychiatric diseases were focused primarily on the catecholamine and indoleamine neurotransmitter systems, which were tested by use of indirect strategies, such as neuroendocrinological challenges, as “windows to the brain.” From the mid-1980s, family, twin, and adoption studies have provided consistent evidence for aggregate genetic effects for psychiatric disorders, demonstrating the substantial role of genetic factors in the etiology of mental illness.<sup>1</sup> The heritability estimates for most psychiatric disorders were found to be high, between 0.4 and 0.8.<sup>2</sup> These results motivated efforts to search for molecular genetic variants predisposing to psychiatric

**Keywords:** *genetics; genetic testing; genomics; pharmacogenomics; psychiatric disorder*

**Author affiliations:** Max-Planck Institute for Molecular Genetics, Berlin, Germany (Margret R. Hoehe); Clinical Genetics and Genomics, Royal Brompton and Harefield NHS Foundation Trust, London, UK, NHLI, Imperial College London, UK (Deborah J. Morris-Rosendahl)

**Address for correspondence:** Dr. M.R. Hoehe, Max-Planck Institute for Molecular Genetics, 14195 Berlin-Dahlem, Germany (email: hoehe@molgen.mpg.de)

---

## Selected abbreviations and acronyms

<b>CNV</b>	<i>Copy number variant</i>
<b>OMIM</b>	<i>Online Inheritance in Man</i>
<b>SNP</b>	<i>Single nucleotide polymorphism</i>
<b>SNV</b>	<i>Single nucleotide variant</i>
<b>WES</b>	<i>Whole exome sequencing</i>
<b>WGS</b>	<i>Whole genome sequencing</i>

---

disease. The first-generation molecular genetic studies were, however, largely unsuccessful. Genetic linkage studies of psychiatric disease, pre-assuming existence of single major loci or few large-effect genes, produced mostly negative or irreproducible results. Candidate gene association studies primarily focusing on synaptic, degradative, and receptor components of neurotransmitter systems proved controversial.<sup>1,3</sup>

The release of a working draft of human genome sequence in 2000 marked the beginning of a new era, with enormous progress in the development of increasingly more efficient sequencing and genotyping technologies allowing the assessment of human genetic variation genome-wide, systematically, and much more completely. Exome- and genome-wide analysis in substantial numbers of individuals became feasible. Genome-wide association studies (GWAS) evolved as a key tool to identify genetic risk variants related to complex disease. This “reverse genetics” approach facilitated the identification of potentially pathogenic variants never previously conceived of, without prior pathophysiological hypothesis. Moreover, statistical methods were developed that allowed assessment of the aggregate effects of genome-wide DNA variation captured by GWAS,<sup>1</sup> for instance by calculating the joint contribution of common variants as a “polygene score.”<sup>4</sup> Finally, progress in psychiatric genetics would have been impossible without the international community combining data sets across multiple GWAS studies to maximize sample size (projecting for instance 100 000 cases for schizophrenia by 2019) and statistical power.<sup>5</sup> So from 2011, replicated common SNPs began to emerge from the GWAS of major psychiatric disorders, beginning with schizophrenia<sup>6</sup> and bipolar disorder.<sup>7</sup> By far the strongest GWAS signal was the association between schizophrenia and genetic markers across the Major Histocompatibility Complex (MHC) locus on chromosome 6. Through very careful molecular dissection of this complex locus, the signal on chromosome 6 was traced to the C4 gene.<sup>8</sup>

It has been suggested that increased C4 activity in the brain of people with schizophrenia causes excessive synaptic pruning during postnatal brain development.<sup>8</sup> If this is supported by further work, it is one of very few times that the underlying biological process has been revealed from a GWAS signal.

Mostly facilitated by data from high density genomic arrays used in GWAS, large de novo and rare chromosomal deletions and duplications, so-called copy number variants (CNVs), began to be identified, that substantially increase risk for psychiatric disorders, especially autism spectrum disorder<sup>9,10</sup> and schizophrenia<sup>11,12</sup> but also other conditions such as attention-deficit hyperactivity disorder (ADHD).<sup>13</sup> Whole-exome sequencing (WES), the high throughput sequencing of all coding exons in the human genome, resulted in first (replicated) discoveries of de novo (gene-disrupting) coding mutations in autism spectrum disorder<sup>14-17</sup> and schizophrenia.<sup>18-20</sup>

Taken together, the emerging architecture of psychiatric disease was found to be highly polygenic, with hundreds or even thousands of common variants of small effect size (with 1.1% to 1.2% absolute risk of illness compared with a ~1.0% population risk), accounting collectively for about one third to one half of the heritability between 0.4 and 0.8.<sup>2</sup> Such a polygenic picture is typical for most complex traits. In addition, rare and de novo CNVs with large effect size (odds ratio ~2 to >20) as well as rare and de novo (disrupting) variants can significantly contribute to risk for major psychiatric disorders. The overall contribution of these types of variants is, however, less well understood.

There is increasing evidence for an etiological overlap between major psychiatric disorders, which would in many, though not all, instances have been predicted from their clinical presentation.<sup>2</sup> Major psychiatric disorders have been found to share common genetic variation,<sup>5,21,22</sup> with the first GWAS meta-analyses implicating neuronal/synaptic, immune and histone pathways.<sup>23</sup> Similarly, an overlap has been observed for rare and de novo CNVs<sup>24</sup> and other coding mutations.<sup>19,20</sup> The substantial overlap of genetic risk between the disorders reinforces evidence for comorbidity from earlier genetic epidemiological studies, as exemplified by an increased risk for different psychiatric disorders in relatives of a patient.<sup>5</sup> A recent, elegant study<sup>25</sup> using transcriptomic profiling in the cerebral cortex across autism, schizophrenia, bipolar disorder, depression and

alcoholism, revealed patterns of shared and distinct gene-expression perturbations across these disorders. Their data suggested that common polygenic variation underlies a substantial proportion of cross-disorder expression overlap. These results underscore that psychiatric disorders as “clinical-historical constructs”<sup>1</sup> do not correspond to distinct definable pathophysiological entities<sup>1</sup> and question the value of clinical diagnostic stratification and classification.

### Translating genetic findings to clinical practice

The enormous successes in genomic medicine, with the dramatic increase in the number of established gene-disease relationships for Mendelian disorders and the distinction of individual molecular tumor profiles in cancer allowing individualized diagnosis and treatment, have motivated efforts to advance precision medicine. These developments have been spurred mainly by the dramatic technological advances of the past 7 years with the implementation of next-generation sequencing (NGS) and all that it has enabled. Whereas genetic testing prior to NGS was performed primarily for very rare, single gene disorders, many of which had recurrent mutations, the advent of NGS has allowed the simultaneous interrogation of many genes and all their variants, using either targeted gene panels, WES, or whole genome sequencing (WGS). The detection of replicated genetic variants associated with neuropsychiatric disorders and treatment outcome has raised growing expectations that these results could be translated into the clinic, to improve individual diagnosis and the prediction of individual risk and treatment response, as well as predict the risk for other family members. Comprehensive genetic tests have become available, and are also commercially provided to doctors and individuals, not least by “direct-to-consumers” (DTC) testing. Thus, it is time to address the potential clinical relevance of genetic testing in psychiatry.

Prerequisites for genetic testing are analytic validity (does the test accurately detect whether a specific genetic variant is present or absent), and clinical validity (is there adequate scientific evidence to support the correlation between the genetic variant and a specific disease phenotype or risks?). Replication is critical for clinical validity. Clinical utility refers to whether the test can “provide information about diagnosis, treat-

ment, management, or prevention of a disease that is likely to improve patient outcomes” (<https://ispg.net/genetic-testing-statement/>; <http://www.cdc.gov/genomics/gtesting/ACCE/index.htm>). The essential prerequisite is knowledge of the genetic causes of the disorder and robust genotype-phenotype correlations, to enable for instance predictive testing for later onset disorders for family members of affected patients.

As outlined above, major adult psychiatric disorders are generally not caused by a single gene or variant, nor do they have a rare Mendelian subform as many other complex disorders do, eg, the adult-onset neurodegenerative disorders such as Alzheimer disease. On the contrary, they are complex, highly polygenic disorders involving numerous genes and variants that have only a modest impact on risk and are neither necessary nor sufficient to cause disease. This makes a clinical interpretation of the present findings at the individual level extremely difficult, if not impossible. Thus, despite tremendous progress in recent years, psychiatric genetics has, with few exceptions, not yet sufficiently advanced to be able to deduce concrete recommendations, or even clinical guidelines, for the use of genetic testing for diagnostic purposes and risk prediction. This applies in particular to major psychiatric disorders which typically begin in adult life, such as depression, bipolar disorder, substance dependence, and schizophrenia (see also <https://ispg.net/genetic-testing-statement/>; the ‘Genetic Testing Statement’ of the International Society of Psychiatric Genetics (ISPG) is being periodically updated as research progresses).

There are, however, a few circumstances where genetic testing may be useful in various clinical settings. These pertain to the analysis of variants of strong effect, such as rare or de novo CNVs and disrupting mutations, prevalent in individuals with autism spectrum disorders (ASD), schizophrenia, or other psychiatric disorders, especially when accompanied by intellectual disability. ASD not only has shared phenotypic overlap with many syndromic forms, such as Down syndrome, Prader-Willi/Angelman syndrome and Fragile X-linked intellectual disability (about 4% to 5% of ASD),<sup>26</sup> but is also one of the disorders for which rare variants have been demonstrated to have strong effect. The potential detection of such rare variants has made it amenable to genetic testing in one form or another. Microdeletion 22q11.1 syndrome is typically caused by a recurrent 3 MB deletion of 40 genes, including *TBX1*. Twenty to

# 20th anniversary issue

50% of patients with this deletion develop ASD,<sup>27</sup> but the deletion is also found in approximately 1% of people with schizophrenia and also in patients with bipolar disorder and idiopathic Parkinson disease.<sup>28,29</sup> Current microarrays detect an ASD-associated CNV in 7% to 10% of cases.<sup>30</sup> There are now more than 50 ASD-associated CNVs and at least 61 ASD-risk genes, 18 of which have recently been identified in a comprehensive study using WGS of trios.<sup>31</sup> Of the 61 ASD-associated genes, 36 (59%) are associated with known syndromes/phenotypes in OMIM (Online Mendelian Inheritance in Man, [www.omim.org](http://www.omim.org)), with *CHD8*, *SHANK2*, and *NLGN3* associated only with ASD. Many of the identified ASD-risk genes converge into shared biological pathways and networks, including synaptic and neuronal adhesion (*SHANK3*, *SCN2A*, *GRIN2B*, *SYNGAP1*, *ANK2*), axonal guidance, transcriptional regulation (eg, *NFI*, *PTEN* and *SYNGAP1*) and chromatin remodeling (eg, *MECP2*, *MBD5*, *CHD8*, *ADNP*, *ARID1B* and *TBRI*).<sup>31,32</sup> Sixteen genes contain subdomains that could be targeted by pharmaceutical interventions and specific drug-gene interactions are known for seven genes.<sup>31</sup> For example, individuals with pathogenic variants in *SCN2A* are potential candidates for drug trials involving allosteric modulators of GABA receptors.<sup>33</sup>

Multiple, rare CNVs have been associated with schizophrenia, all of which encompass many genes and are also common to other psychiatric and neurological disorders.<sup>34</sup> Approximately 2.5% of schizophrenia patients will carry one of the associated CNVs, and many more genes may be associated through more powerful sequencing studies in the near future.<sup>35</sup> The use of patient-parent trios to identify potentially harmful “de novo” variants has been applied to schizophrenia in a number of studies.<sup>18-20,36</sup> Each of these studies demonstrated an excess of damaging de novo variants in schizophrenia, particularly in glutamatergic postsynaptic proteins and proteins whose messenger RNAs are targets of the Fragile X-linked mental retardation protein, FMRP. A subsequent, combined whole-exome sequencing case-control analysis in 4264 patients, 9343 controls and 1077 trios from previous studies revealed a significant excess of very rare, gene-disrupting variants in the *SETD1A* gene in patients (0.19%). This was the first statistically significant association between schizophrenia and a single candidate gene,<sup>37</sup> although pathogenic *SETD1A* variants are also found in patients with more severe developmental and physical abnormalities.

*SETD1A* is involved in histone methylation, substantiating the report that common risk variants for psychiatric disorders may aggregate on histone methylation pathways.<sup>23</sup>

Although individually rare, the net effects of CNVs across psychiatric disorders are substantial. Specifically, the net effects of the more frequent CNVs on a broad range of psychiatric and intellectual disability syndromes have already been sufficiently well-assessed by Malhotra et al<sup>38</sup> and Gershon and Alliey-Rodriguez.<sup>39</sup> A recent review of CNVs in schizophrenia in over 41 000 subjects by Marshall et al<sup>34</sup> largely confirmed previous reports of CNV associations in schizophrenia, adding suggestive evidence for six novel CNVs and providing analyses of the genes involved and of the net effects of these CNVs on schizophrenia. Although the majority of adult patients would not be expected to carry a large CNV and such CNVs mostly lack diagnostic specificity, the identification of an inherited or de novo CNV in a known high-risk region for one of the major psychiatric disorders in such patients, may help diagnose a rare condition that has important medical and psychiatric implications for the patient and their family. Patients who carry such CNVs may find it easier to accept their diagnosis and adhere to treatment when presented with an objective “laboratory test.”<sup>39</sup> Siblings and offspring could be offered genetic testing and might be reassured if they do not carry the same CNV as their mentally ill relative;<sup>39</sup> (<https://ispg.net/genetic-testing-statement/>). The identification of de novo CNVs could be useful in the management of severe psychiatric disorders, especially those that present atypically or in the context of intellectual disability or certain medical syndromes (<https://ispg.net/genetic-testing-statement/>).

## The analysis of genes involved in variable drug response

The pharmacological treatment of psychiatric disorders has been severely hampered by a large inter-individual variation in drug response and/or severe side effects, often leading to painful, frustrating and inefficient trial-and-error-based changes of treatment regimens. This variation is to a large extent due to genetic factors, with an estimated heritability  $h^2$  of  $\sim 0.6 - 0.8$ .<sup>40</sup> Thus, numerous studies attempted to detect gene variants associated with individually different drug responsiveness or serious side effects. Their motivation was to iden-

tify pharmacogenetic biomarkers for drug efficacy and safety, which would allow prediction of an individual's response to drug therapy and facilitate individually tailored treatment. These studies focused primarily on the analysis of candidate genes including (i) genes involved in drug metabolism (pharmacokinetics); (ii) genes encoding the specific target molecules mediating drug action (pharmacodynamics); and (iii) genes mediating severe side effects. Typically, a few up to hundreds of SNPs within these genes were genotyped in cases and controls. Furthermore, GWAS were applied to scan the genome for variants predisposing to differential drug response "hypothesis-free," allowing detection of yet unknown genes or biological mechanisms. In view of the immense literature, we will prioritize those results which proved to be most consistent and therefore merit further consideration for potential translation in the clinic. We will focus on the pharmacogenomics of antidepressants and antipsychotics. The results essentially refer to drug-gene relationships.

Two genes of central importance in the metabolism of antidepressants and antipsychotics are those encoding cytochrome P450 (CYP) monooxygenase system enzymes, *CYP2D6* and *CYP2C19*.<sup>41,42</sup> Variants in these genes can cause different pharmacokinetic phenotypes in individuals treated with the same dose of a drug: "ultrarapid metabolizers" (UM), characterized by significantly reduced drug concentrations, hence decreased drug effect or non-response; "extensive metabolizers" (EM) representing the "normal" phenotype; "intermediate metabolizers" (IM), characterized by drug concentrations that are higher compared to EM; and "poor metabolizers" (PM) having the highest drug concentrations at all, resulting potentially in drug-related toxicity due to overdosing.<sup>41</sup> Thus, UM and PM appear to represent the clinically most relevant phenotypes/genotypes. In effect, comprehensive systematic literature reviews have substantiated evidence for lower plasma levels and an increased risk for non-response to tricyclic antidepressant treatment in UM as well as an increased risk for severe side effects in PM.<sup>43-45</sup> The same applied to antidepressant treatment with selective serotonin reuptake inhibitors (SSRI).<sup>43,46</sup> Regarding treatment with antipsychotics, the studies show a significantly increased risk for tardive dyskinesias in particular for *CYP2D6*-PM, while *CYP2D6*-UM overall does not appear to have a significant influence on antipsychotic drug response. Furthermore, a potential influence of

*CYP1A2* and *CYP3A4* variants, other pharmacokinetic candidates of importance, on antipsychotic response has remained inconclusive.<sup>40,42,43,45</sup> Importantly, the altered activity *CYP2D6* variants have been reported to exhibit substantial population differences in comprehensive global surveys.<sup>47-49</sup> Based on the first global data,<sup>48</sup> Europeans showed the highest fraction of *CYP2D6*-PM (8%) and ~3% *CYP2D6*-UM, while for instance 40% of the population were *CYP2D6*-UM in North Africa. Thus, knowledge of ethnic background is of critical clinical relevance for the development of personalized pharmacological treatment strategies. The classification of pharmacokinetic phenotypes described above is subject to constant efforts towards further standardization. Although well-established, it does not yet represent the entirety of genetic variation, or allelic combinations. A meta-analysis of population scale sequencing projects integrating whole-genome and exome NGS data from 56 945 individuals of five major populations, demonstrated that the previous pharmacokinetic phenotype predictions from genotype data may have underestimated the prevalence of *CYP2D6*-PM and -IM subjects substantially.<sup>49</sup> Between 25.3% and 70.3% of analyzed CYP alleles contained variant combinations with no or reduced functional activity. This trend was further substantiated in a comprehensive literature review.<sup>47</sup> Another gene of potential importance for the pharmacokinetics of many antidepressants and some antipsychotics encodes the ATP Binding Cassette (ABC) Subfamily B Member 1 (*ABCB1*); this ABC transporter gene is expressed at blood-brain barrier (BBB) sites. Its membrane-associated gene product, P Glycoprotein, also known as Multidrug-Resistance Protein 1, transports various substances across the BBB out of the brain. Meta-analyses have shown associations of two (out of several) SNPs with antidepressant response.<sup>50,51</sup> Overall, however, the role of genetic variation in *ABCB1* in variable antidepressant response has remained controversial and will require further examination.

Concerning the analysis of pharmacodynamic candidate genes involved in antidepressant response, a large number of studies have addressed the gene encoding the serotonin transporter (*SCL6A4*), a direct target for most prescribed antidepressants. The functional insertion-deletion polymorphism located in the promoter region, 5-HTTLPR, possibly was the most studied variant in relation to antidepressant response at all. Significant associations between this polymorphism and antidepressant

# 20th anniversary issue

response and remission rates were described in major meta-analyses.<sup>52,53</sup> Particularly, a higher probability of response and remission to SSRI treatment was observed in Caucasian carriers of the long (“l”) allele, although its influence on SSRI efficacy was of modest effect.<sup>52</sup> Inversely, Caucasian patients with the short (“s”) allele were found to have difficulties to achieve remission and showed a reduced response to SSRI<sup>52,53</sup> as well as an increased risk for side effects.<sup>54</sup> Overall, however, the results are still inconsistent, precluding the use of 5-HTTLPR as a predictor of antidepressant response at present.<sup>42</sup> Condensing other candidate gene data of note, a comprehensive meta-analysis by<sup>51</sup> has suggested a significant association of variants in the serotonin 2A receptor gene (*HTR2A*) with antidepressant response; the same was true for variants in the gene encoding the FK506-binding protein 5 (*FKBP5*), which is involved in the regulation of stress hormones. Furthermore, this meta-analysis substantiated evidence that heterozygous carriers of the rs6265 polymorphism (Val66Met) in the brain-derived neurotrophic factor gene (*BDNF*) respond best to SSRI, particularly Asian patients.<sup>51</sup> Numerous other plausible candidate genes have been investigated, with controversial results and modest effect sizes overall.<sup>42</sup>

Concerning pharmacodynamic candidate genes involved in antipsychotic treatment response, the most consistent results have been obtained for genes of the dopaminergic and serotonergic systems.<sup>40,42</sup> Thus, an insertion deletion (Ins/Del) polymorphism of the dopamine D2 receptor gene (*DRD2*) was found significantly associated with antipsychotic drug response, Del allele carriers exhibiting a poorer response rate than patients with the Ins/Ins genotype.<sup>55</sup> Moreover, a Ser9Gly polymorphism of the dopamine D3 receptor gene (*DRD3*) showed a consistent, though not significant trend for the Ser-allele and reduced clozapine response.<sup>56</sup> Also, two polymorphisms in the *HTR2A* gene (His452Tyr and T102C) were found associated with clozapine response.<sup>57</sup> Another receptor gene of the serotonergic system (*HTR2C*) contained a C759T polymorphism, the C-allele of which conferred a significantly increased risk for antipsychotic-induced weight gain, one of the most consistent associations observed in antipsychotics pharmacogenetics.<sup>58,59</sup> Strong candidates known to be involved in the genetics of obesity, the melanocortin 4 receptor (*MC4R*) and leptin genes, were also suggested to be prominent risk factors predisposing to this serious adverse effect of antipsychotics.<sup>58,59</sup> Finally,

several polymorphisms of the HLA-system, specifically of HLA-B38, DR4 and DQw3<sup>60</sup> and HLA-DQB1 and HLA-B<sup>61</sup> were found associated with clozapine-induced agranulocytosis, another serious side effect of antipsychotics. For a detailed summary of the genetics of common antipsychotic-induced adverse effects see also MacNeil and Müller.<sup>62</sup> Numerous studies were performed with candidate genes potentially involved in lithium response, which all were inconclusive, in part also due to its unresolved underlying biology.<sup>42</sup>

## Translating pharmacogenomics to clinical practice

Pharmacogenomic studies aimed to improve individual psychiatric drug treatment through pre-emptive genotyping, which would allow adjustment of dosages to reduce the risk of overdosing and serious side effects, or a change of drug. In sum, the scientific evidence to support the clinical validity of pharmacogenetic testing is still insufficient for most gene-drug pairs. Moreover, the clinical utility of specific gene-drug pairs has not yet been clearly demonstrated in adequately powered, double-blind clinical trials, which need to be conducted to clarify whether patients benefit substantially from genotype-guided treatment compared to “treatment as usual.” Also other factors that influence treatment response such as co-medication, age, gender, disease symptoms/comorbidity, smoking and diet and, importantly, ethnic background, need to be taken into account and studied further. Despite these limitations, *CYP2D6* and *CYP2C19* testing has already been recommended for clinical use,<sup>63</sup> and guidelines for using and generating genetic information have been outlined.<sup>64</sup> First implementation studies using *CYP2D6* and *CYP2C19* genotype information in clinical practice indicated that pharmacogenetic testing was very well accepted by both physicians and patients, could particularly be beneficial for non-extensive metabolizing patients, and hold great potential for optimization of drug treatment in psychiatry.<sup>45,65</sup> Recently, the Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT) study was launched to demonstrate the feasibility and utility of pharmacogenetic testing on a large scale and facilitate implementation of this testing in routine health care practice.<sup>66</sup>

The implementation of pharmacogenomics in the clinic is supported by the establishment of comprehen-

sive resources such as the Pharmacogenomic Knowledge Base (PharmGKB) (<https://www.pharmgkb.org>), and international expert groups that enable objective and transparent assessment of existing pharmacogenetic studies to derive clinical recommendations, such as the Clinical Pharmacogenomics Implementation Consortium (CPIC). Accordingly, CPIC performs a systematic review/evaluation of the comprehensive literature curated in PharmGKB to develop peer-reviewed gene–drug guidelines that are published and updated periodically (for further information on pharmacogenomics resources see Pouget et al<sup>40</sup> and Müller et al).<sup>42</sup> Thus, CPIC guidelines for *CYP2D6* and *CYP2C19* genotype-directed dosing of tricyclic antidepressants as well as SSRIs<sup>44,46</sup> have been published. These guidelines provide concrete information for the interpretation of genetic tests, that is, a list of existing genotypes with their “likely (pharmacokinetic) phenotypes” assigned and corresponding dosing recommendations or alternative therapeutic recommendations (suggesting selection of a drug not primarily metabolized by *CYP2D6*). The expert groups’ recommendations are further translated by national or cross-national regulatory agencies. Thus, the US Food and Drug Administration (FDA) and other agencies distinguish for instance four categories, “required,” “recommended,” “actionable,” and “informative,” this classification of gene–drug pairs often varying between agencies and countries.

In sum, there is very good consensus concerning the pharmacogenetic testing of *CYP2D6*, which is “recommended” for therapy with tricyclic antidepressants with particular reference to the increased risk for serious side effects in patients with PM-status. Also the testing of *CYP2C19* is considered “particularly clinically relevant.” Beyond avoiding harm, testing both CYPs is considered to improve therapy through selection of alternative drugs and provide useful information for many other diseases. Agencies such as the FDA have begun to include pharmacogenomics information in drug labeling and recommend genetic testing for now 25 psychiatric drugs.<sup>42</sup> As emphasized in the Genetic Testing Statement released by the ISPG, clinicians are encouraged to consider such recommendations in their treatment decisions and to “stay current on changes to drug labeling and adverse event reports” (<https://ispg.net/genetic-testing-statement/>). The FDA and other agencies “require” genetic testing in patients of Asian ancestry before carbamazepine treatment; carriers of

the major histocompatibility allele HLA-B\*15:02 are at highly increased risk to develop Stevens-Johnson syndrome (SJS), a potentially lethal skin disease. The only other “required” genetic test concerns children and adult patients who receive pimozone, an antipsychotic, to prevent side effects in *CYP2D6*-PM.

## Conclusions and outlook

Psychiatric genetics has generated very promising results in terms of risk variants associated with major psychiatric disorders and treatment outcome. Despite these successes, psychiatry still lags behind other fields in medicine in terms of translation of existing knowledge into diagnostic genetic tests that could facilitate early diagnosis and accurate classification of disorders. The nature of genotype-phenotype-relationships has remained largely elusive, and the “fundamental biology” of psychiatric disorders has yet to be revealed.<sup>1,5</sup> Significant progress can be expected from several lines of technological advancement/development. For example, there is reason to be excited about the prospect of WGS being increasingly implemented as the assay of choice for both gene discovery and diagnostic testing in highly heterogeneous disorders. Advantages of WGS include its comprehensiveness, with the analysis of coding and non-coding sequence, the improved coverage of sequences, and in fact, of whole genes that were previously not easily sequenced, as well as the detection of all types of genetic variation. This also promises to increase diagnostic yield. Moreover, it will allow establishment of a catalogue of non-coding variation, which is assumed to contribute substantially to the development of psychiatric disorders. One could envisage a comprehensive, genome-wide panel assay, where one assesses all known variants with proven associations to psychiatric disorders in an individual patient. Since these disorders, as well as individual drug response, are complex traits which can be influenced by multiple genes, further progress can be expected through assessment of gene-gene interactions, gene networks and the application of systems approaches.<sup>67</sup> Complex traits are also significantly influenced by environmental factors. Thus, the analysis of the epigenome as the interface between genome and environment is expected to contribute key insights into the development of psychiatric disorders.<sup>68,69</sup> True genome-wide assessments of epigenetic marks, such as

# 20th anniversary issue

DNA methylation, or chromatin modifications have become possible, mainly also through progress in second-generation DNA sequencing methods.<sup>69</sup> Furthermore, the inaccessibility of the human brain can now be overcome by stem cell approaches, which make it possible to study (pluripotent stem cell-derived) neurons from patients “in a dish.”<sup>70</sup> The generation of CNS organoids as model systems may open new avenues towards precision drug treatment. Beyond technological advancements, a reconsideration/rethinking of previous research concepts could critically move the field forward. As outlined by Kapur et al,<sup>71</sup> to achieve clinical

utility of diagnostic genetic testing may require a new approach. Rather than comparing prototypic patients to healthy controls, the field should focus on “identifying biologically homogeneous subtypes that cut across phenotypic diagnosis.” Validating such biomarker/genetically-defined subtypes will require longitudinal studies of individual patients, providing the “natural basis for a ‘stratified’ psychiatry that will improve clinical outcomes across conventional diagnostic boundaries,” ultimately more compatible with the major goal of precision medicine<sup>71</sup>—and the findings obtained to date. □

## REFERENCES

1. Kendler KS. What psychiatric genetics has taught us about the nature of psychiatric illness and what is left to learn. *Mol Psychiatry*. 2013;18(10):1058-1066.
2. Gratten J, Wray NR, Keller MC, Visscher PM. Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nat Neurosci*. 2014;17(6):782-790.
3. McCarroll SA, Feng G, Hyman SE. Genome-scale neurogenetics: methodology and meaning. *Nat Neurosci*. 2014;17(6): 756-763.
4. International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460(7256):748-752.
5. Sullivan PF, Agrawal A, Bulik CM, et al. Psychiatric genomics: an update and an agenda. *Am J Psychiatry*. 2018;175(1):15-27.
6. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet*. 2011;43(10): p. 969-976.
7. Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet*. 2011;43(10):977-983. doi: 10.1038/ng.943. Erratum in: *Nat Genet*. 2012;44(9):1072.
8. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530(7589):177-183.
9. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. *Science*. 2007; 316(5823):445-449.
10. Marshall CR, Noor A, Vincent JB, et al. Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet*. 2008;82(2):477-488.
11. Walsh T, McClellan JM, McCarthy SE, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science*. 2008;320(5875):539-543.
12. Stefansson H, Rujescu D, Cichon S, et al. Large recurrent microdeletions associated with schizophrenia. *Nature*. 2008; 455(7210):232-236.
13. Williams NM, Zaharieva I, Martin A, et al. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet*. 2010;376(9750):1401-1408.
14. Iossifov I, Ronemus M, Levy D, et al. De novo gene disruptions in children on the autistic spectrum. *Neuron*. 2012;74(2):285-299.
15. Sanders SJ, Murtha MT, Gupta AR, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature*. 2012;485(7397):237-241.
16. Neale BM, Kou Y, Liu L, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature*. 2012;485(7397):242-245.
17. O’Roak BJ, Vives L, Girirajan S, et al. Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature*. 2012;485(7397):246-250.

18. Xu B, Roos JL, Dexeimer P, et al. Exome sequencing supports a de novo mutational paradigm for schizophrenia. *Nat Genet*. 2011;43(9):864-868.
19. Fromer M, Pocklington AJ, Kavanagh DH, et al. De novo mutations in schizophrenia implicate synaptic networks. *Nature*. 2014;506(7487):179-184.
20. Purcell SM, Moran JL, Fromer M, et al. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*. 2014;506(7487):185-190.
21. Cross-Disorder Group of the Psychiatric Genomics Consortium, et al., Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45(9):984-94.
22. Cross-Disorder Group of the Psychiatric Genomics Consortium, et al. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*. 2013;381(9875):1371-1379.
23. Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci*. 2015;18(2):199-209.
24. Sebat J, DL Levy, McCarthy SE. Rare structural variants in schizophrenia: one disorder, multiple mutations; one mutation, multiple disorders. *Trends Genet*. 2009;25(12):528-535.
25. Gandal MJ, Haney JR, Parikshak NN, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science*. 2018;359(6376):693-697.
26. Tammimies K, Marshall CR, Walker S, et al. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. *JAMA*. 2015;314(9):895-903.
27. Vorstman JA, Morcus ME, Duijff SN, et al. The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. *J Am Acad Child Adolesc Psychiatry*. 2006;45(9):1104-1113.
28. Mok KY, Sheerin U, Simón-Sánchez J, et al. Deletions at 22q11.2 in idiopathic Parkinson’s disease: a combined analysis of genome-wide association data. *Lancet Neurol*. 2016;15(6):585-596.
29. Malhotra D, Sebat J. CNVs: harbingers of a rare variant revolution in psychiatric genetics. *Cell*. 2012;148(6):1223-1241.
30. Fernandez BA, Scherer SW. Syndromic autism spectrum disorders: moving from a clinically defined to a molecularly defined approach. *Dialogues Clin Neurosci*. 2017;19(4):353-371.
31. C Yuen RK, Merico D, Bookman M, et al. Whole genome sequencing resource identifies 18 new candidate genes for autism spectrum disorder. *Nat Neurosci*. 2017;20(4):602-611.
32. Pinto D, Delaby E, Merico D, et al. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *Am J Hum Genet*. 2014;94(5): 677-694.
33. Hadley D, Wu ZL, Kao C, et al. The impact of the metabotropic glutamate receptor and other gene family interaction networks on autism. *Nat Commun*. 2014;5:4074.



34. Marshall CR, Howrigan DP, Merico D, et al. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat Genet.* 2017;49(1):27-35.
35. Brand H, Pillalamarri V, Collins RL, et al. Cryptic and complex chromosomal aberrations in early-onset neuropsychiatric disorders. *Am J Hum Genet.* 2014;95(4):454-461.
36. Xu B, Ionita-Laza I, Roos JL, et al. De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia. *Nat Genet.* 2012;44(12):1365-1369.
37. Singh T, Kurki MI, Curtis D, et al. Rare loss-of-function variants in SET-D1A are associated with schizophrenia and developmental disorders. *Nat Neurosci.* 2016;19(4):571-577.
38. Malhotra D, McCarthy S, Michaelson JJ, et al. High frequencies of de novo CNVs in bipolar disorder and schizophrenia. *Neuron.* 2011;72(6):951-963.
39. Gershon ES, Alliey-Rodriguez N. New ethical issues for genetic counseling in common mental disorders. *Am J Psychiatry.* 2013;170(9):968-976.
40. Pouget JG, Shams TA, Tiwari AK, Müller DJ. Pharmacogenetics and outcome with antipsychotic drugs. *Dialogues Clin Neurosci.* 2014;16(4):555-566.
41. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther.* 2013;138(1):103-141.
42. Muller DJ, Brandl EJ, Degenhardt F, et al. Pharmacogenetics in psychiatry: state of the art. *Nervenarzt.* 2018;89(3):290-299.
43. Altar CA, Hornberger J, Shewade A, Cruz V, Garrison J, Mrazek D. Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. *Int Rev Psychiatry.* 2013;25(5):509-533.
44. Hicks JK, Swen JJ, Thorn CF, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther.* 2013;93(5):402-408.
45. Muller DJ, Kekin I, Kao AC, Brandl EJ. Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. *Int Rev Psychiatry.* 2013;25(5):554-571.
46. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther.* 2015; 98(2):127-134.
47. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder J. Prediction of CYP2D6 phenotype from genotype across world populations. *Genet Med.* 2017;19(1):69-76.
48. Sistonen J, Sajantila A, Lao O, Corander J, Barbuiani G, Fuselli S. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenet Genomics.* 2007; 17(2):93-101.
49. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of cytochrome P450 alleles: a meta-analysis of population-scale sequencing projects. *Clin Pharmacol Ther.* 2017;102(4):688-700.
50. Breitenstein B, Brückl TM, Ising M, Müller-Myhsok B, Holsboer F, Czamara D. ABCB1 gene variants and antidepressant treatment outcome: A meta-analysis. *Am J Med Genet B Neuropsychiatr Genet.* 2015;168B(4):274-283.
51. Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;45:183-194.
52. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *Eur Neuropsychopharmacol.* 2012;22(4):239-258.
53. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry.* 2007;12(3):247-257.
54. Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry.* 2010;15(5):473-500.
55. Zhang JP, Lencz T, Malhotra AK. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. *Am J Psychiatry.* 2010;167(7):763-772.
56. Hwang R, Zai C, Tiwari A, et al. Effect of dopamine D3 receptor gene polymorphisms and clozapine treatment response: exploratory analysis of nine polymorphisms and meta-analysis of the Ser9Gly variant. *Pharmacogenomics J.* 2010;10(3):200-218.
57. Gressier F, Porcelli S, Calati R, Serretti A. Pharmacogenetics of clozapine response and induced weight gain: A comprehensive review and meta-analysis. *Eur Neuropsychopharmacol.* 2016;26(2):163-185.
58. Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry.* 2012;17(3):242-266.
59. Zhang JP, Lencz T, Zhang RX, et al. Pharmacogenetic associations of antipsychotic drug-related weight gain: a systematic review and meta-analysis. *Schizophr Bull.* 2016;42(6):1418-1437.
60. Lieberman JA, Yunis J, Egea E, Canoso RT, Kane JM, Yunis EJ. HLA-B\*38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry.* 1990;47(10):945-948.
61. Goldstein JL, Jarskog LF, Hilliard C, et al. Clozapine-induced agranulocytosis is associated with rare HLA-DQB1 and HLA-B alleles. *Nat Commun.* 2014;5:4757.
62. MacNeil RR, Muller DJ. Genetics of common antipsychotic-induced adverse effects. *Mol Neuropsychiatry.* 2016;2(2):61-78.
63. Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry.* 2004;9(5):442-473.
64. Drozda K, Muller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy.* 2014;34(2):166-184.
65. Walden LM, Brandl EJ, Changasi A, et al. Physicians' opinions following pharmacogenetic testing for psychotropic medication. *Psychiatry Res.* 2015;229(3):913-918.
66. Herbert D, Neves-Pereira M, Baidya R, et al. Genetic testing as a supporting tool in prescribing psychiatric medication: Design and protocol of the IMPACT study. *J Psychiatr Res.* 2017. pii: S0022-3956(17)30288-1.
67. Demkow U, Wolanczyk T. Genetic tests in major psychiatric disorders-integrating molecular medicine with clinical psychiatry-why is it so difficult? *Transl Psychiatry.* 2017;7(6):e1151.
68. Ptak C, Petronis A. Epigenetic approaches to psychiatric disorders. *Dialogues Clin Neurosci.* 2010; 12(1):25-35.
69. Bell CG, Beck S. The epigenomic interface between genome and environment in common complex diseases. *Brief Funct Genomics.* 2010;9(5-6):477-485.
70. Dolmetsch R, Geschwind DH. The human brain in a dish: the promise of iPSC-derived neurons. *Cell.* 2011;145(6):831-834.
71. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry.* 2012;17(12):1174-1179.

### ***El papel de la genética y de la genómica en la psiquiatría clínica***

*Los enormes éxitos en la genética y la genómica de muchas enfermedades han proporcionado la base para el avance de la medicina de precisión. Por lo tanto, la detección de variantes genéticas asociadas con trastornos neuropsiquiátricos, así como el resultado del tratamiento, han aumentado las expectativas que estos hallazgos pronto podrían traducirse en la clínica para mejorar el diagnóstico, la predicción de riesgo de enfermar y la respuesta individual a la terapia farmacológica. En este artículo, se presentará una introducción sobre la búsqueda de genes implicados en enfermedades psiquiátricas y se resumirán los hallazgos actuales en los principales trastornos psiquiátricos. Se revisarán las variantes genéticas para genes que codifican enzimas metabolizadoras de fármacos y los blancos farmacológicos específicos que se encontraron asociados con una respuesta farmacológica variable y efectos secundarios graves. Se evaluará la traducción clínica de estos hallazgos, la posibilidad actual de algún papel para las pruebas genéticas y, en ese contexto, se pondrá a disposición del clínico que busca guía y consejo, valiosas fuentes de información para este campo de rápido desarrollo que es la psiquiatría genética.*

### ***Rôles de la génétique et de la génomique en psychiatrie clinique***

*Les énormes succès obtenus en génétique et génomique dans de nombreuses maladies ont fourni la base des avancées en médecine de précision. La détection de variants génétiques, associés à des troubles neuropsychiatriques comme à des résultats thérapeutiques, a donc soulevé une attente grandissante de voir traduire ces résultats en pratique clinique pour améliorer le diagnostic, la prédiction du risque d'avoir la maladie et la réponse individuelle au traitement médicamenteux. Nous introduisons dans cet article la recherche de gènes impliqués en pathologie psychiatrique et nous résumons les résultats actuels pour les principaux troubles psychiatriques. Nous analysons les variants génétiques des gènes codant pour les enzymes métabolisant les médicaments et les cibles médicamenteuses spécifiques ayant montré une association avec une réponse variable au médicament et des effets indésirables sévères. Nous évaluons la traduction de ces résultats en pratique clinique, la possibilité actuelle d'un rôle du dépistage génétique et, dans ce contexte, la mise à disposition du médecin en recherche d'aide et de conseils, de sources valables d'information dans ce domaine en rapide développement qu'est la psychiatrie génétique.*