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Prospects for personalization of depression treatment with genome sequencing

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The effectiveness of antidepressants in the treatment of major depressive disorder varies considerably between patients. With these interindividual differences and a number of antidepressants to choose from, the first choice of treatment often fails to produce improvement in the patient's condition. A substantial part of the variation in response to antidepressants can be explained by genetic factors. Accordingly, variants related to drug metabolism in two pharmacogenes, *CYP2D6* and *CYP2C19*, have already been translated into guidelines for antidepressant prescriptions. The role of variants in other genes that influence antidepressant responses is not yet understood. Furthermore, rare and individual variants account for a substantial part of genetic differences in antidepressant efficacy. Recent years have brought a tremendous increase in the accessibility of genome sequencing in terms of data availability and its clinical use. In this review, we summarize recent developments and current issues in the personalization of major depressive disorder treatment through pharmacogenomics.

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1 | COSTS, SYMPTOMS AND THE AETIOLOGY OF MAJOR DEPRESSIVE DISORDER

The World Health Organization (WHO, 2017) estimates that 4.4% of the world's population currently suffers from major depressive disorder. The COVID-19 pandemic is expected to further increase the prevalence of mood disorders (Ettman et al., 2020). Major depressive disorder already costs humanity approximately 80 million disability-adjusted life years (DALYs) each year, predominantly in low- and middle-income countries, and depressive disorders are the single largest contributor to health loss (WHO, 2017).

The heritability of major depressive disorder is estimated to be between 40% and 50% based on familial and twin studies (Sullivan et al., 2000). Accordingly, major depressive disorder is considered to have a major genetic component. Variants at multiple loci have been associated with major depressive disorder in genome-wide association studies (GWASs) (Sullivan et al., 2000, 2012). Similar to other psychiatric disorders of complex aetiology, successful depression-related GWASs included cohorts in the range of hundreds of thousands. Although variants significantly associated with the disease were found

Abbreviations: MAF, minor allele frequency; SNP, single-nucleotide polymorphism; SNRI, serotonin (5-HT)–noradrenaline reuptake inhibitor; SSRI, selective serotonin (5-HT) reuptake inhibitor; WES, whole-exome sequencing; WGS, whole-genome sequencing.

in genes involved in neurotransmission (***DRD2*** and ***GRM5***) and other neuronal functions (e.g. *ATXN10*, *ANKS1B*, *CABP1* and *TENM2*) (Howard et al., 2018), the exact aetiology of major depressive disorder remains poorly understood.

The most influential hypothesis for the aetiology of major depressive disorder is the monoamine theory, which posits that the disease is caused by a decrease in the levels of monoamine neurotransmitters **(5-hydroxytryptamine (5-HT; serotonin)**, **noradrenaline** and **dopamine)** (Coppen, 1967). Although the theory offers a plausible explanation for the efficacy of most commonly used antidepressants, it does not readily explain the delay in the onset of antidepressant effects (Liu et al., 2017). Furthermore, it remains unclear which brain areas are primarily involved in the development of major depressive disorder. Analysis of depressive patients with focal brain damage has not identified a single area where damage leads to development of an affective disorder, though some evidence points at a connected brain circuit centred on the left dorsolateral prefrontal cortex (Padmanabhan et al., 2019). Accordingly, a neural-circuit model of major depressive disorder has been proposed in which dysfunctions within and between brain structures such as the medial prefrontal cortex, amygdala, hippocampus and ventromedial parts of the basal ganglia may drive major depressive disorder symptoms (Drevets et al., 2008). Finally, it should be noted that environmental factors, such as stressful life events or childhood abuse, as well as socio-economic status and medical conditions such as cancer or chronic pain, also contribute to development of the disease (Saveanu & Nemeroff, 2012).

2 | POTENTIAL FOR TREATMENT IMPROVEMENT IN THE PHARMACOTHERAPY OF DEPRESSION

The criteria for selection of antidepressant therapy are usually arbitrary (Trivedi & Kleiber, 2001; Zeier et al., 2018). Available antidepressant medications are divided into subclasses based on their effect on the reuptake or metabolism of monoamines, primarily 5-HT (serotonin), noradrenaline, dopamine, **histamine** and **melatonin**. Some antidepressants additionally directly interact with **5-HT receptors** and other mechanisms may contribute to antidepressant action (Artigas et al., 2002).

Most guidelines recommend a selective serotonin (5-HT) reuptake inhibitor (SSRI) as the initial treatment, usually at a maximum tolerated dose (Bayes & Parker, 2018). Approximately one third of patients respond favourably to the first selected treatment, and a similar proportion experience significant improvement with the second choice (Figure 1.1). Further changes in therapy are occasionally able to achieve the expected therapeutic effect; however, a considerable fraction of patients do not experience satisfactory improvement in their condition (Fabbri et al., 2016; Souery et al., 2006, 2011). The trial and error approach has the major caveat that patients are more likely to discontinue treatment if they have to try more than one drug (Rush et al., 2009).

The development of more efficient drugs could potentially improve the success rate of antidepressant treatment. Unfortunately, in recent decades, few antidepressive agents have successfully entered the market (Hillhouse & Porter, 2015; van Westrhenen et al., 2020). One notable exception is **ketamine**, a known anaesthetic and recreational drug that has recently been approved for treatment-resistant major depressive disorder (Elliott & Chan, 2019). Nevertheless, the long-term effects of ketamine intake on major depressive disorder have not been rigorously studied in large clinical trials (Short et al., 2018).

Accordingly, a major avenue for improving antidepressant treatment outcomes is the personalization of therapy. The basic premise is that by taking into consideration the individual characteristics of the patient (rather than a general guideline), the odds of the first selected treatment being effective could be improved dramatically. The potential of this approach is well illustrated by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial that examined the

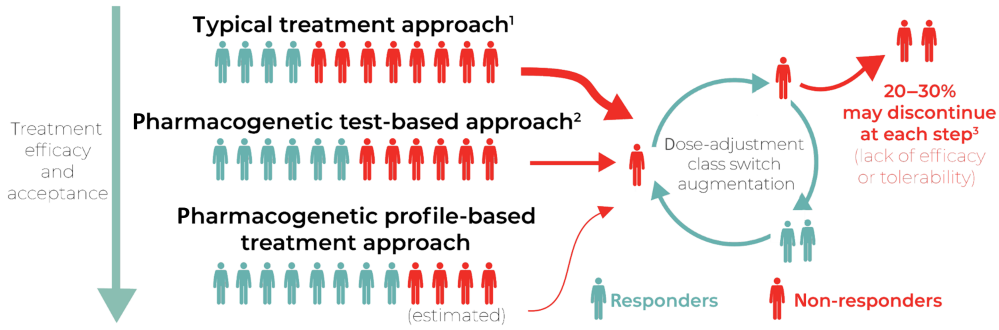

FIGURE 1 With better individualization, the number of non-responders to the first drug and thus the number of patients entering the dose/medication-switch cycle can be substantially decreased. Response to treatment is defined as at least a 50% reduction in points on a depression rating scale (e.g., Hamilton Rating Scale of Depression). (1) Typical treatment approach refers to an approach where medication is prescribed according to other than genetic criteria (Rush et al., 2009). (2) Pharmacogenetic test-based approach: antidepressant selection with guidance from currently available genetic tests (Bradley et al., 2018; Bush et al., 2016; Pérez et al., 2017). (3) Pharmacogenetic profile-based approach: a potential approach where rare and common genetic variants are collected for each patient and the complete information is used to select the most appropriate therapy. Estimation based on the STAR*D trial results (Rush et al., 2009)

potential for improvement in remission rates when optimal treatment is prescribed for each patient (Rush et al., 2009; Warden et al., 2007). A total of 4000 participants were recruited in the trial, with 2876 individuals receiving a maximally tolerated dose of citalopram as the first treatment. Approximately 33% of them showed improvement in their condition; 1439 patients for whom citalopram did not alleviate symptoms continued into Part 2 of the trial and were divided into augmentation or medicine-switch groups (Rush et al., 2009). Augmentation of **citalopram** therapy with **bupropion** or **buspirone** was successful in 36% of the remaining patients. Switching to another SSRI (**sertraline**), a serotonin–noradrenaline reuptake inhibitor (SNRI, **venlafaxine**) or an antidepressant with a different mechanism of action (bupropion) resulted in remission in approximately 26% of patients, regardless of the drug. Participants who did not enter remission were offered more treatment switches and a further expanded set of therapy options. Overall, 67% of all patients participating in the study achieved remission. This percentage is considerably more than the one third of patients who typically improve with the first drug. It should be noted, however, that over 20% of the patients dropped out from the trial after each step. Sociodemographic disadvantages, lower symptom improvement and greater symptom severity were associated with increased risk of treatment discontinuation (Warden et al., 2009). Furthermore, at Step 2, over one third of patients who were still symptomatic did not want to switch to another drug and preferred to continue with their current medication. The results of this trial illustrate that each medication switch is a possible point of resignation from therapy and that many patients become discouraged after taking two distinct antidepressants, lowering the possible chance of successful therapy. Thus, one conclusion from the STAR*D trial was that improving in the efficacy of the first choice of antidepressant could dramatically increase the fraction of patients experiencing remission (Figure 1).

3 | THE CURRENT STATE OF PHARMACOGENETICS OF DEPRESSION TREATMENT

Pharmacogenetics is a science that focuses on the associations between genetic variants and drug responses. For antidepressants, genetic variation explains a substantial part of the variability in treatment outcomes; thus, it is especially relevant to study their pharmacogenetics (Tansey et al., 2013). Drug properties may be described from a pharmacokinetic or pharmacodynamic perspective, related to drug metabolism or effects, respectively. Pharmacokinetics focuses mainly on the hepatic metabolism of drugs that neutralize or produce active forms of compounds (Preskorn, 2019). Genes encoding proteins involved in absorption, distribution, metabolism, excretion and transport of drugs (absorption, distribution, metabolism, excretion and transport genes) have relatively frequent loss-of-function (LoF) mutations (Bush et al., 2016; Fujikura et al., 2015; Ingelman-Sundberg et al., 2018). A study of more than 16,000 participants recruited by the Estonian Biobank showed that 32.5% of people carried at least one loss of function variant in an absorption, distribution, metabolism, excretion and transport pharmacogene; thus, a large proportion of individuals may exhibit significantly different drug responses (Tasa et al., 2019). Notably, several of the identified variants corresponded to genes associated with the pharmacokinetics of antidepressant responses (i.e. ***ABCB1***, ***CYP1A2***, ***CYP2B6***, ***CYP2C19*** and ***CYP2CC8***) (Barbarino et al., 2018). The high level of genetic polymorphism of pharmacogenes may arise from adaptive evolutionary processes, as selection pressure favours a broader range of responses to potentially toxic external substances both within and between individuals (Fuselli, 2019).

Among the genes encoding enzymes metabolizing antidepressants, ***CYP2D6*** and *CYP2C19* genotypes have been consistently shown to impact the outcome of antidepressant treatment. Both belong to the class of P450 cytochromes and are primarily active in the liver. Patients carrying *CYP2C19* variants that lead to poor metaboliser status due to reduced enzymatic activity are more sensitive to **escitalopram** and sertraline, are more likely to experience side effects and discontinue treatment when prescribed with escitalopram (Fabbri, Tansey, Perlis, Hauser, Henigsberg, Maier, Mors, Placentino, Rietschel, Souery, Breen, Curtis, Lee, et al., 2018; Jukić et al., 2018). ***CYP2D6***–poor metabolisers have lower remission rates when receiving treatment with venlafaxine than normal metabolizers (Lobello et al., 2010). Based on existing evidence, the Clinical Pharmacogenetics Implementation Consortium (CPIC) offers guidelines for the selection and dosage of tricyclic antidepressants (TCAs) and SSRIs based on *CYP2D6* and *CYP2C19* genotypes (Hicks et al., 2015, 2017). These recommendations include lower starting doses or alternative treatments for poor metaboliser phenotypes for drugs such as citalopram and sertraline and higher doses for ultrarapid metabolizer phenotypes for drugs such as venlafaxine and TCAs. When these guidelines are applied, the fraction of favourable responses to the first choice of antidepressant treatment may increase to approximately 50% (Bradley et al., 2018; Pérez et al., 2017). However, it should be noted that several additional genes play a role in regulating antidepressant treatment responses. For example, antidepressants are often metabolized by more than one CYP2 protein, and CYP2D6, CYP2C19, CYP2C9, **CYP3A4** and **CYP3A5** all take part in biotransformations of fluoxetine (Margolis et al., 2000). The list of genes implicated in the variance of individual responses to antidepressant treatment is not limited to P450 cytochromes. It also includes genes involved in drug pharmacodynamics, such as the serotonin (5-HT) transporter, **SERT (SCL6A4)** and the neurotrophic factor (***BDNF***) genes (Kato & Serretti, 2010). Other pathways not directly related to neurotransmitters also include potentially relevant genes. Point mutations in ***FKBP5***, which is involved in regulation of the hormonal response to stress, have been associated with antidepressant treatment response. This observation indicates a promising candidate gene, although not all of the reported results are conclusive (Binder et al., 2004; Lekman et al., 2008). Nevertheless, the associations between polymorphisms in genes that putatively influence antidepressant responses and treatment outcomes remain uncertain (Porcelli, Drago, et al., 2011; Porcelli, Fabbri, et al., 2011; van Westrhenen et al., 2020). This is particularly curious,

as some of the variants have been very extensively investigated. For instance, the association of the repeat length polymorphism (serotonin (5-HT)-transporter-linked polymorphic region; 5-HTTLPR) in the *SLC6A4* gene with major depressive disorder severity and outcomes has been investigated in more than a thousand studies, and the results remain ambiguous (Culverhouse et al., 2018). Some of the reasons behind the difficulty in providing clear pharmacogenetic guidelines based on genes that are a target for psychiatric drugs may include the lack of understanding of the precise molecular mechanisms of drug action or the inclusion of only relatively common variants in most studies. However, if a better interpretation of both common and rare genotypes in these genes becomes available, it could aid in therapy personalization.

Even though current knowledge is limited, commercial antidepressant pharmacogenetic tests are already offered. Their efficacy seems to be based mostly on *CYP2D6* and *CYP2C19* genotypes, as other genes genotyped by them have only preliminary or limited supporting evidence (Bousman & Hopwood, 2016). This pharmacogenetic test approach to antidepressant personalisation is based on currently available genotyping tests and pharmacogenetic decision support tools (DSTs) that provide medication recommendations (Arandjelovic et al., 2019) (Figure 1.2). These tools support known and thus mostly common variants. Studies have shown that the use of common genotypes in known pharmacogenes when selecting antidepressant treatment already significantly improves remission (from 13% to 35%) and response rate (from 28–36% to 51–55%) (Bradley et al., 2018; Pérez et al., 2017). Moreover, in a meta-analysis of randomized controlled trials (RCTs) of DSTs (total $n = 1737$) participants were 1.7 times more likely to achieve remission (Bousman et al., 2019). It should be stressed though that the evidence in favour of genetic testing is not conclusive. In the recent 'Genomics Used to Improve DEpression Decisions' (GUIDED) trial, a commercially available pharmacogenomic test improved remission but failed to affect the mean symptom improvement (Greden et al., 2019). Moreover, there is only a partial consensus between commercial DSTs: when four different tools were tested, the agreement in medication recommendation for antidepressants was 56% (Bousman & Dunlop, 2018). Published trials were also criticized for not being transparent enough, and the need for more RCTs has been highlighted (Solomon et al., 2019; Suthers & Polasek, 2019). Overall, there is considerable evidence that adequate use of currently available pharmacogenetic tests may improve remission rates, but there are discrepancies among the tests, and more precise DSTs need to be developed. Today, next-generation sequencing data may already be included in pharmacogenetic testing, for example, in the form of targeted sequencing, where sequencing data of known pharmacogenes are translated into STAR genotypes (Ji et al., 2016). A possible pharmacogenetic profile approach would include incorporation of the most complete information from next-generation sequencing data and is yet to be implemented in the clinic (Figure 1.3). The implementation of this approach depends on two aspects: better knowledge about the underlying genetics and adjustment of current clinical guidelines. The main disadvantage of using next-generation sequencing data in the clinic today is the lack of established interpretation algorithms and the difficulties in haplotype calling of genetic regions with large structural variation (i.e., the *CYP2D6* locus) (Ji et al., 2018). Nevertheless, if the most effective treatment was assigned to each patient, a 67% remission rate, as based on the data from the STAR*D trial, is potentially achievable. Below, we discuss the current state of knowledge on antidepressant pharmacogenetics, the challenges and the opportunities of successful incorporation of next-generation sequencing data into the antidepressant pharmacogenetics.

4 | GENOME-WIDE ASSOCIATION STUDIES OF ANTIDEPRESSANT RESPONSES

GWASs allow for the analysis of millions of single-nucleotide polymorphisms (SNPs) spread across the whole human genome. The findings described in the previous section were derived from studies using the candidate gene approach, which starts with the identification of proteins that are involved in either the pharmacokinetics or pharmacodynamics of a given drug. Candidate genes are then investigated, relevant genotypes are described and their association with corresponding features of drug response are analysed. This approach is plagued by failures in replication of the reported associations, and with its inherent limit of only being able to confirm an a priori hypotheses, it is thus unable to reveal unpredicted effects (Duncan et al., 2019). GWASs offer a way to overcome these limitations. Among the few comprehensive GWASs focused on antidepressant response published are the analyses of the GENDEP and STAR*D trials as well as recent studies on population-based cohorts. Multiple SNPs that affect the antidepressant response have been identified in these analyses; however, similar to candidate gene studies, there is no general consensus among them. One STAR*D GWAS focused on drug response and remission rate found two significant SNPs associated with citalopram response (rs6966038, 51 kb from *UBE3C* and 77 kb from *MNX1*) (Garriock et al., 2010). Another study on the same data found that variants in *PAPLN* and *IL28RA* are associated with suicidal ideation, an adverse effect of citalopram treatment (Laje et al., 2009). A joint GENDEP and STAR*D GWAS analysis identified SNPs in **ITGA9 (integrin, alpha 9 subunit gene)** and *NRXN3* (neurexin-3-alpha gene) as associated with symptom improvement during citalopram/escitalopram treatment, but only one of these associations (*ITGA9* SNP) was replicated in one of the two additional datasets used for validation (Fabbri, Tansey, Perlis, Hauser, Henigsberg, Maier, Mors, Placentino, Rietschel, Souery, Breen, Curtis, Sang-Hyuk, et al., 2018). Genotyping data from the Generation Scotland Biobank meta-analysed with GENDEP data did not identify any significant loci, genes or haplotypes associated with antidepressant treatment resistance or stages of resistance (Wigmore et al., 2020). Other large GWAS studies to assess responses to particular drugs have been conducted. Notably, ConLiGen, a study that included 2563 participants, found a locus on chromosome 21 that contains two

long non-coding RNAs: *AL157359.3* and *AL157359.4* significantly associated with response to lithium (Hou et al., 2016). This observation is of particular interest for major depressive disorder treatment as lithium is often offered as a therapy augmentation for treatment-resistant depression (Bschor, 2014). A study that used the data from the 23andMe antidepressant efficacy survey found one significant SNP (rs1908557) associated with response to bupropion. The variant identified in this GWAS was located within the intron of human spliced expressed sequence tags on chromosome 4 (Li et al., 2016). A more detailed study of 23andMe data investigated responses to distinct antidepressant classes and found the rs4884091 in the *RNF219-AS1* genomic region to be associated with SSRI response (Li et al., 2020). The CO-MED trial that investigated escitalopram monotherapy, escitalopram augmented with bupropion and venlafaxine with mirtazapine therapy identified a potentially regulatory SNP rs10769025 in the *ALX4*, homeobox protein aristaless-like 4 gene, with a strong association with response to escitalopram monotherapy in Caucasians (Gadad et al., 2018). A drug-level analysis of the GENDEP study showed that response to escitalopram is best predicted by a marker in the **IL-11** (*IL11*) gene (Uher et al., 2010). This marker (rs1126757) has been later shown to be associated with the methylation pattern of *IL11*. This result indicates that chromatin landscape may also be considered a factor in antidepressant response and offers a path for future studies (Powell et al., 2013).

In summary, current GWASs of antidepressant pharmacogenetics do not replicate well and continue to be inconclusive. Nevertheless, when only a subset of genes were analysed in the GWAS data, significant associations for some previously reported genes were confirmed. Although *CYP2* genotypes do not appear in the top associations in GWAS, they show results when preselected for analysis (Fabbri, Tansey, Perlis, Hauser, Henigsberg, Maier, Mors, Placentino, Rietschel, Souery, Breen, Curtis, Lee, et al., 2018; Fabbri, Tansey, Perlis, Hauser, Henigsberg, Maier, Mors, Placentino, Rietschel, Souery, Breen, Curtis, Sang-Hyuk, et al., 2018). Similarly, when STAR*D GWAS results were analysed only for a subset of proposed genes, some of the candidate gene findings were replicated, for example, *FKBP5* (Laje et al., 2009).

Although GWASs reveal novel genetic associations, they are not without caveats. Their power to identify associations appears weaker compared with, for instance, the identification of genes relevant to drug-related adverse immune effects (Daly, 2012). The primary difference is that high-impact variants in CNS genes tend to be rarer than in the case of genes expressed in other tissues. For example, dopamine receptor D2 gene (*DRD2*) has only two loss of function alleles reported among the 75,000 individuals included in the GnomAD database (Karczewski et al., 2020). GWAS SNPs are typically relatively common variants, and even the largest GWASs exclude variants of minor allele frequency (MAF) smaller than 0.5% (Howard et al., 2019). As common variants likely have minor effects on antidepressant response, even significant findings may be hard to replicate (Figure 2). These difficulties in replication could be overcome with better powered studies that include tens to hundreds of thousands of individuals (Duncan et al., 2019). However, such large studies have not yet been completed for antidepressant response.

In summary, there has been considerable progress in the translation of genotypes that affect antidepressant hepatic metabolism into actionable clinical guidelines. Conversely, there has been little success in understanding the role of variants in other genes that affect antidepressant response with either the candidate gene approach or GWAS analyses. Thus, there are still many possibilities to improve the efficacy and acceptability of existing antidepressants, and more research is needed on the pharmacogenetics of antidepressant-related pharmacodynamic genes to reach conclusions that could eventually be translated into clinical guidelines.

5 | THE RATIONALE FOR USING GENOME SEQUENCING IN PHARMACOGENETICS

It is uncertain how the highly polygenic and heterogeneous background of major depressive disorder relates to variation in treatment responses. Some knowledge may be transferred from what is already known about genes involved in responses to other drugs. Accumulated evidence indicates that at least a part of an individual response to drugs may be explained by an oligogenic mechanism (Pirmohamed & Park, 2001). However, there is a known issue in regard to variant discovery: the more common a variant is, the smaller impact it usually has (Tennessen et al., 2012) (Figure 2). Exceptions include highly variable genes with common variants of high impact, such as many pharmacogenes (Bush et al., 2016; Fujikura et al., 2015). This observation explains the success of research regarding some of the *CYP2* genotypes that are common variants that lead to loss of function. The *CYP2D6*4* allele, which involves a frameshift variant that results in a poor metaboliser phenotype of the CYP2D6 protein, occurs in 15.5% of the European population. Consequently, carriers of two *CYP2D6*4* alleles have recommendations for reduced doses of multiple antidepressants (Barbarino et al., 2018). Other canonical examples of successful implementation of pharmacogenetic testing in other disciplines are based on variants relatively common in specific populations that are associated with severe side effects, such as Stevens–Johnson syndrome caused by carbamazepine (Ferrell & McLeod, 2008). For many other genes, including genes involved in antidepressant pharmacodynamics, rare variants with substantial influence on drug response are expected to exist (Duncan et al., 2019). Incorporation of very rare variants may significantly improve the predictive value of pharmacogenomics, as rare variants explain up to 40% of inter-individual variability in drug response. This information is based on the percentage of functional variability in key pharmacogenes, including *CYP* genes and transporters, attributed to rare variants and estimates of rare-variant contribution to pharmacokinetics and toxicity of a range of drugs, including **warfarin** and **irinotecan** (Ingelman-Sundberg et al., 2018; Kozyra et al., 2017).

In a study of 208 pharmacogenes in more than 60,000 individuals, it was estimated that for more than half of the pharmacogenes, rare

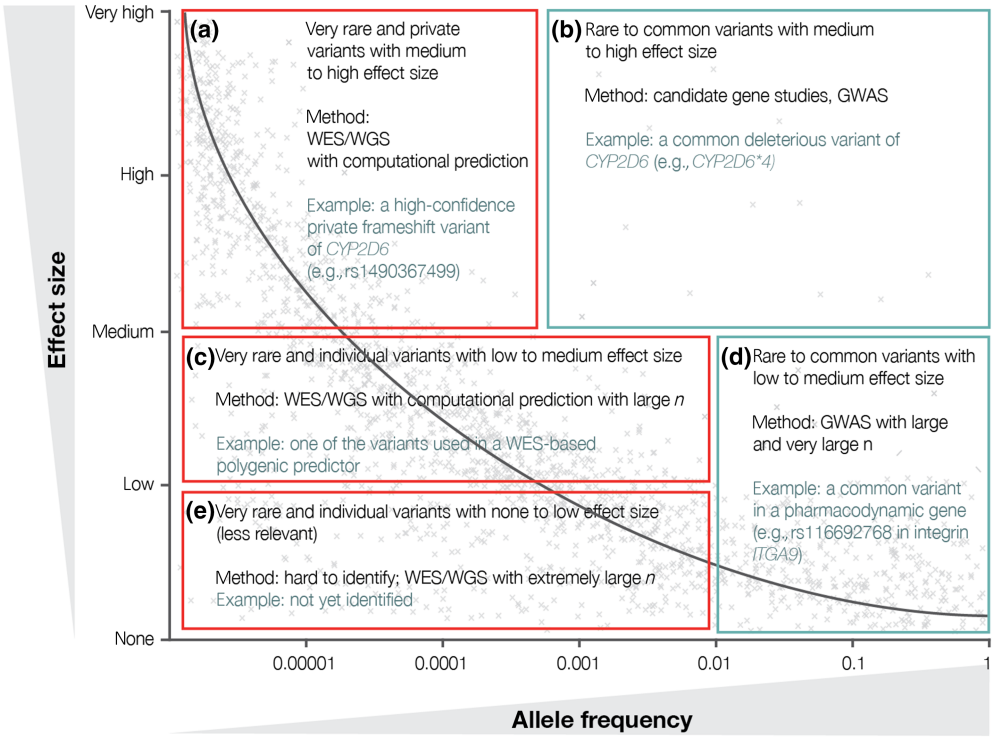

FIGURE 2 The genetic landscape of variants underlying antidepressant (AD) responses. Schematic representation of the relationship between genetic variant frequency (*X* axis, distances between values are log10 scaled) and effect size related to AD responses (*Y* axis). Grey points are a graphical representation of schematically represented individual variants, and the dark line represents regression curve. (a) The results from rare-variant analyses show that typically approximately 50% of variants in major pharmacogenes (e.g., *CYP2* genes) are singletons (found in only one individual). Some of these variants may be highly deleterious (e.g., frameshift variants). For such variants, the whole-exome sequencing (WES)/whole-genome sequencing (WGS) approaches with computational prediction could be translated into pharmacogenetic guidelines (Ingelman-Sundberg et al., 2018; Karczewski et al., 2020). (b) In pharmacogenetics, unlike in other polygenic traits, highly impactful common variants exist due to the specific evolutionary pressure on genes involved in detoxification. These variants are typically discoverable with genotyping of common variants in candidate genes (e.g., genes from the CYP2 family). (c) Research on rare variants with low to medium impact requires sequenced and phenotyped cohorts future years will bring advances in this area. A recent study of a polygenic WES-based predictor of AD responses included such variants (Fabbri, Kasper, et al., 2020). (d) Variants with minor allele frequency (MAF) >0.01 may be successfully discovered with genome-wide association studies (GWASs), and the example variant was discovered and replicated in GWASs with *n*s in the range of thousands and has an MAF of approximately 0.05 (Fabbri, Tansey, Perlis, Hauser, Henigsberg, Maier, Mors, Placentino, Rietschel, Souery, Breen, Curtis, Lee, et al., 2018; Fabbri, Tansey, Perlis, Hauser, Henigsberg, Maier, Mors, Placentino, Rietschel, Souery, Breen, Curtis, Sang-Hyuk, et al., 2018). (e) Rare variants with low impact contribute the least to drug responses, and their discovery would require sequenced cohorts in the ranges of hundreds of thousands of individuals. Such variants remain to be discovered

variants (MAF < 0.01) account for the entire genetic variability that has a functional impact (Ingelman-Sundberg et al., 2018). This list included two pharmacogenes implicated in antidepressant response:- *UTG2B7* and *UTG2B4* (Barbarino et al., 2018). In another study that investigated more than 200,000 exonic single-nucleotide variants in the genes encoding solute carrier transporter superfamily (SLC) proteins, 99.8% were present in less than 1% of analysed alleles, and more than half of all variants were singletons (found only once) (Schaller & Lauschke, 2019). Other analyses revealed that as much as 90% or more of the overall genetic variability in pharmacogenes can be attributed to rare variants (Bush et al., 2016; Fujikura et al., 2015; Gordon et al., 2014; Kozyra et al., 2017). The rare-variant contribution is gene and drug specific. In the case of warfarin, an anticoagulant, the contribution of rare variants to impaired metabolism was estimated to be approximately 10% (Ingelman-Sundberg et al., 2018). Such estimates have not yet been performed for antidepressants; nevertheless, it can be assumed that rare-variant contribution is also significant in the case of antidepressants.

A better functional understanding must be achieved to incorporate rare-variant analysis into clinical practice for psychiatric drugs (van Westrhenen et al., 2020). This has, until recently, been impossible due to the unavailability of sufficiently large cohorts of sequenced patients needed for rare-variant discovery. The largest resource of this type is the UK Biobank (UKB), which combines data from 500,000 participants and provides exome sequences for 250,000 participants (Sudlow et al., 2015). A recent analysis of 49,702 UKB participants that included both genotyping and whole-exome sequencing (WES) data discovered 244 novel deleterious variants across eight pharmacogenes that have not been observed previously in gnomAD (McInnes et al., 2020). In clinical practice in some areas of medicine, techniques that allow for rare-variant analysis are already more cost-effective than more traditional approaches (Monroe et al., 2016).

Next-generation sequencing is typically performed as either whole-genome sequencing (WGS) or WES. WES is often advised in the clinical setting, as it is less costly, and mutations in non-coding regions are often difficult to interpret (for more WES-related information, see Adams & Eng, 2018). An advantage of WGS is that it allows for discovery of novel non-coding variants of high impact, that is, mutations that affect the chromatin accessibility. As described in this chapter, sequencing approaches are undoubtedly beneficial for pharmacogenetic variant discovery, and future years will most likely bring many publications with WES/WGS approaches applied to antidepressant pharmacogenetics.

6 | CHALLENGES OF AN NEXT-GENERATION SEQUENCING-BASED APPROACH TO PHARMACOGENETICS

The technical aspects of sequencing methodologies give rise to particular challenges in the context of pharmacogenomics. From a technical standpoint, genetic variants can be assigned to two groups: one includes SNPs and short indels (insertions or deletions), and the other encompasses larger structural variants. The latter include large deletions, inversions and copy number variants, including duplications (Chiang et al., 2017). Many of the known genotypes of important pharmacogenes include structural variants. As an example, *CYP2D6* has multiple genotypes where it is multiplicated either in its reference or mutated form. In the US population, 13% of individuals carry haplotypes that include an structural variant of *CYP2D6* (Del Tredici et al., 2018). Moreover, the region containing *CYP2* genes contains multiple similar sequences and several duplications, including the *CYP2D7* pseudogene, a non-functional *CYP2D6* paralogue (Jukic et al., 2018). Most next-generation sequencing technologies involve alignment of short reads (typically approximately 150 bp) to the reference genome. This limits the ability to precisely call variants that are longer than the reads and to accurately align reads in regions with many similar or identical sequences present. The use of long-read sequencing technologies and bioinformatics software that includes structural variant analysis from next-generation sequencing data mitigates these challenges (Amarasinghe et al., 2013; Liau et al., 2019; Plagnol et al., 2012). Although long-read sequencing remains more expensive and is associated with additional technical difficulties, it can be used to develop new tools for short-read sequencing analysis.

Pharmacogenetic variants are usually reported and annotated in STAR nomenclature, where each allele represents a set of variants inherited together (a haplotype) (Barbarino et al., 2018). This system, developed for genotyping studies, is not well suited to the research of very rare or de novo variants, as each variant combination would require a new STAR allele. Some tools for translation of sequencing data into STAR alleles have already been developed (Table 1), but a more next-generation sequencing-centred variant annotation scheme is still necessary (Klein & Ritchie, 2018; Krebs & Milani, 2019).

As discussed, most variants in sequencing datasets are rare and frequently occur only once (Ingelman-Sundberg et al., 2018; Schaller & Lauschke, 2019). Currently, especially in the area of psychiatric drugs, there is a lack of understanding of the effects of these variants on drug response (van Westrhenen et al., 2020). One of the ways this could be improved is the use of computational prediction of variant effects. Prediction algorithms are widely used in the genomics field, but special considerations must be taken before applying them to pharmacogenes. Namely, absorption, distribution, metabolism, excretion and transport genes are often more tolerant to damaging mutations than other genes and exhibit greater variability, which causes many of the variant prediction algorithms to underperform (Zhou et al., 2018). Thus, variant prediction algorithms should be created specifically for pharmacogenes. However, even existing tools, when combined in an optimal way, are successful in predicting the impact of known pharmacogenetic variants (Zhou et al., 2019).

The improvement offered by rare and individual variant analysis depends on the gene characteristics (Figure 3). As described throughout this review, absorption, distribution, metabolism, excretion and transport genes are relatively well studied and often exhibit high loss of function frequency. Thus, for absorption, distribution, metabolism,

TABLE 1 Overview of bioinformatic tools for pharmacogenetic variant calling and nomenclature translation from next-generation sequencing data

Tool	Data	Usage	Reference
PharmCat	WES/WGS vcf files	STAR allele calling with an actionable report generated based on CPIC guidelines	Sangkuhl et al. (2020)
Astrolabe (formerly Constellation)	WGS vcf and bam files	Translation of WGS results into STAR nomenclature and phenotypic assignment	Twist et al. (2016)
Stargazer	WGS vcf and GDF[a] files or vcf files	STAR allele calling of 51 pharmacogenes including structural alleles	Lee et al. (2019)
Aldy	WES/WGS bam files	Allele decomposition from aligned reads, including novel and structural alleles	Numanagić et al. (2018)
PGxPOP	Multisample WES/WGS vcf files	STAR allele calling based on PharmCat for population-based samples	McInnes et al. (2020)

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; WES, whole-exome sequencing; WGS, whole-genome sequencing.
[a]GATK-DepthOfCoverage format file generated from bam file.

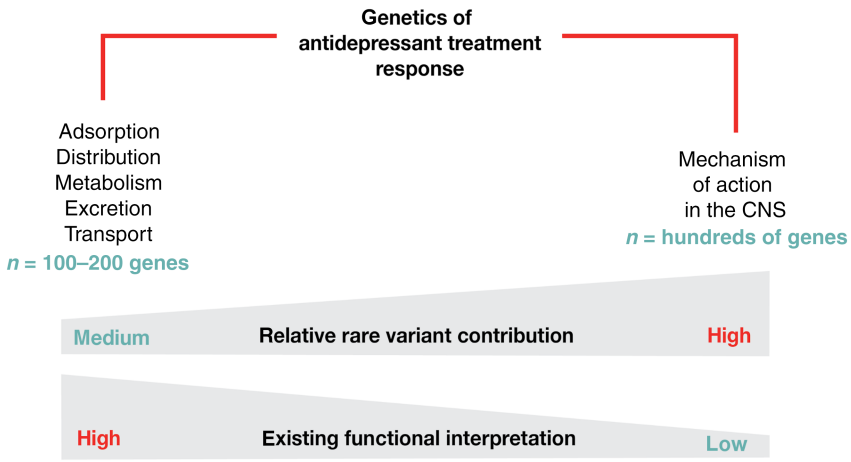

FIGURE 3 Next-generation sequencing offers improvement of depression treatment personalization by incorporating rare-variant information. Genetics of antidepressant (AD) response can be roughly divided into pharmacokinetic (left side of the figure) and pharmacodynamic (right side of the figure) areas. The impact of pharmacogenetic variants in absorption, distribution, metabolism, excretion and transport (ADMET) genes (i.e., *CYP2D6* and *CYP2C19*) is largely known, and as these genes often have common variants with large effect sizes (i.e., duplications or deletions), the relative contribution of rare variants to AD responses is lower for these genes than for typical pharmacodynamic genes. On the other hand, typical CNS genes (i.e. *BDNF*, *FKBP5* and *DRD2*) have low frequencies of deleterious variants; thus, the relative contribution of rare genetic variants in these genes is high. As described in this review, the precise interpretation of the effects of variants in CNS genes on AD treatment responses remains unclear. Whole-exome sequencing (WES)/whole-genome sequencing (WGS) approaches to pharmacogenetic studies provide a better understanding of the role of particular genes in AD treatment responses

excretion and transport genes, even if only the effects of alleles that are common are known, the predictive value of genotyping remains higher compared with other genes. However, even for a thoroughly investigated gene—*CYP2D6*, many rare (<0.01 MAF) impactful variants remain unknown; thus, there is still potential for improvement of genotype interpretation for absorption, distribution, metabolism, excretion and transport genes (Kiss et al., 2018). As genes that are involved in the pharmacodynamics of antidepressants in the CNS are often highly conserved, rare-variant genotyping and interpretation offers the only way to incorporate them into pharmacogenetic testing. Overall, despite the challenges in data analysis and interpretation, as more knowledge is acquired, WES/WGS information could improve current pharmacogenetic guidelines by integrating the variability determined by rare variants.

7 | POSSIBILITIES FOR PERSONALIZED ANTIDEPRESSANT TREATMENT USING GENOME SEQUENCES

Current research and possible development directions described above show that integration of common, rare and individual variants detected using genome sequencing could further improve the possibilities for personalized antidepressant treatment. This development can be done through advancements in two areas of antidepressant pharmacogenetics: basic research and creation of new pharmacogenetic guidelines.

State-of-the-art pharmacogenetics of antidepressant are based on candidate gene and GWAS approaches, although the influence of the latter is still relatively limited. Data from WES/WGS cohorts may be used to discover new genes with a role in antidepressant response and crucial variants in known genes. Recently, a targeted-exome sequencing study conducted in Han Chinese individuals ($n = 929$) found that structural variant burden and polymorphisms in the ***IL1A***, *GNA15*, *PPP2CB*, *PLA2G4C* and *GBA* genes were associated with antidepressant response (Xu et al., 2020). A small exome sequencing study in Mexican–Americans identified 35 genes with rare (MAF < 0.01) variants associated with antidepressant response (Wong et al., 2021). In another study, researchers used WES data to build a successful polygenic predictor of treatment-resistant major depressive disorder ($n = 1209$) (Fabbri, Kasper, et al., 2020). Studies with larger cohorts will both aid with replication of existing GWAS findings and contribute more basic knowledge to the field. Recently, a novel approach has gained momentum, namely, the use of population-based cohorts, such as the UKB. In these large databases, it is possible to infer antidepressant efficacy and tolerability from healthcare data, including diagnoses, self-reported events and prescriptions (Fabbri, Hagenaars, et al., 2020; Wigmore et al., 2020). Incorporation of WES/WGS approaches should greatly increase the value of studies on these large cohorts and provide new discoveries in terms of variants and genes important for antidepressant pharmacogenetics. Additionally, pharmacogenetic studies can be used to search for novel uses of existing drugs. In a recent study, a list of 1542 genes that form a polygenic predictor for treatment-resistant major depressive disorder was compared with a database of gene targets of available drugs. Researchers found a range of compounds enriched for tested genes, including lithium and ketamine, drugs already used for treatment-resistant depression (Fabbri et al., 2021). This study illustrates that pharmacogenetic studies with WES/WGS can also be used to screen for drugs targeting discovered genes. Nevertheless, next-generation sequencing-based approaches

to antidepressant pharmacogenetics have not yet been tested in RCTs, and further replication studies are necessary. Another promising avenue for pharmacogenetics is its integration with the developing fields of epigenetics, pharmacotranscriptomics and pharmacoproteomics, especially with the rise of high-throughput techniques in these fields (Athreya et al., 2018; D'Adamo et al., 2021).

8 | SUMMARY

In this review, we first described rationale for the search of better therapy individualisation with existing antidepressants. Then the current state of the art and the opportunities offered by incorporation of next-generation sequencing data into pharmacogenetics of antidepressants were described. In summary, only next-generation sequencing data offer incorporation of rare and individual variants into antidepressant response prediction. Major challenges in implementation of this approach include technical difficulties, such as those posed by structural variant calling, and the requirement of large cohorts. In an ideal scenario, incorporation of genome sequencing would lead to the creation of individual pharmacogenetic profiles containing information about all possibly actionable pharmacogenetic variants in a patient's genome. To include these individual variants, the pharmacogenetic guidelines would have to be revised, as it is not possible to include all the identified rare variants in recommendations. Rather, broader definitions of variants could be used together with optimized variant effect predictors. For such recommendations to become part of the daily practice of psychiatric care, more research on the genetics of drug responses is needed. Furthermore, the prediction of variant effects needs to be optimized and validated. Nevertheless, computational predictors can currently be used to more closely monitor antidepressant responses in patients with putatively damaging variants in key pharmacogenes such as frameshift and stop-gain variants that have not been described. Thus, even today, WES/WGS data may be implemented into guidelines for clinicians. In summary, genome sequencing undoubtedly offers progress in terms of major depressive disorder treatment personalization, but sequencing-based pharmacogenetics of antidepressants is still a field in its early development.

8.1 | NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

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AUTHOR CONTRIBUTIONS

M.B. drafted the manuscript. M.P., J.R.P. and M.K. provided conceptual input and essential revisions and assisted in writing of the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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