Pharmacology & Therapeutics 194 (2019) 22–43

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Genetic variants in major depressive disorder: From pathophysiology to therapy

Xenia Gonda [a,b,c,*,1], Peter Petschner [c,d,1], Nora Eszlari [b,d], Daniel Baksa [d,e], Andrea Edes [d,e], Peter Antal [f], Gabriella Juhasz [d,e,g], Gyorgy Bagdy [b,c,d,**]

[a] Department of Psychiatry and Psychotherapy, Kutvolgyi Clinical Centre, Semmelweis University, Budapest, Hungary
[b] NAP-2-SE New Antidepressant Target Research Group, Hungarian Brain Research Program, Semmelweis University, Budapest, Hungary
[c] MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary
[d] Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary
[e] SE-NAP 2 Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Hungarian Brain Research Program, Semmelweis University, Budapest, Hungary
[f] Department of Measurement and Information Systems, Budapest University of Technology and Economics, Budapest, Hungary
[g] Neuroscience and Psychiatry Unit, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, UK

ARTICLE INFO

Available online 4 September 2018

Keywords:
Antidepressant drug
Depression
Genetics
Genomics
Pharmacogenetics
Pharmacogenomics

ABSTRACT

In spite of promising preclinical results there is a decreasing number of new registered medications in major depression. The main reason behind this fact is the lack of confirmation in clinical studies for the assumed, and in animals confirmed, therapeutic results. This suggests low predictive value of animal studies for central nervous system disorders. One solution for identifying new possible targets is the application of genetics and genomics, which may pinpoint new targets based on the effect of genetic variants in humans. The present review summarizes such research focusing on depression and its therapy. The inconsistency between most genetic studies in depression suggests, first of all, a significant role of environmental stress. Furthermore, effect of individual genes and polymorphisms is weak, therefore gene x gene interactions or complete biochemical pathways should be analyzed. Even genes encoding target proteins of currently used antidepressants remain non-significant in genome-wide case control investigations suggesting no main effect in depression, but rather an interaction with stress. The few significant genes in GWASs are related to neurogenesis, neuronal synapse, cell contact and DNA transcription and as being nonspecific for depression are difficult to harvest pharmacologically. Most candidate genes in replicable gene x environment interactions, on the other hand, are connected to the regulation of stress and the HPA axis and thus could serve as drug targets for depression subgroups characterized by stress-sensitivity and anxiety while other risk polymorphisms such as those related to prominent cognitive symptoms in depression may help to identify additional subgroups and their distinct treatment. Until these new targets find

Abbreviations: *5HTTLPR*, Repeat length polymorphism in promoter region of serotonin transporter gene; *ABCB1*, ATP Binding Cassette Subfamily B Member 1; *AD*, antidepressant; *CACNA1E*, Calcium voltage-gated channel subunit alpha1 E; *CACNA2D1*, Calcium voltage-gated channel auxiliary subunit alpha2delta 1; *CEP350*, Centrosomal protein 350; *CNR1*, Cannabinoid receptor 1; CNV, Copy number variation; *COMT*, Cathecol-o-methyltransferase; *CREB*, cAMP responsive element binding protein; *CRHR1*, Corticotropin releasing hormone receptor 1; CYP, Cytochrome P450; *DCC*, Dcc netrin 1 receptor; *DRD2*, Dopamine receptor D2; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ExE, Environment-environment interaction; *FAAH*, Fatty acid amide hydrolase; *FKBP5*, FK506 binding protein 5; *GABRA6*, Gamma-aminobutyric acid type A receptor alpha6 subunit; GAL, Galanin; *GALR1*, Galanin receptor 1; *GALR2*, Galanin receptor 2; *GALR3*, Galanin receptor 3; *GC*, Glucocorticoid receptor; GENDEP, Genome-wide Pharmacogenetics of Antidepressant Response; GenRED, Genetics of Recurrent Early-Onset Depression; GERA, Genetic Epidemiology Research on Adult Health and Aging; *GRIK4*, Ionotropic glutamate kainate 4 receptor; *GRIK5*, Glutamate ionotropic receptor kainate type subunit 5; *GRM5*, Glutamate metabotropic receptor 5; GWAS, Genome-wide association study; GWS, Genome-wide significant; GxE, Gene-environment interaction; GxG, Gene-gene interaction; HPA, Hypothalamus-pituitary-adrenal cortex; *HTR1A*, Serotonin transporter 1A receptor; *HTR1B*, Serotonin transporter 1B receptor; *IL1B*, Interleukine 1 beta; *IL-6*, Interleukine 6; *KSR2*, Kinase suppressor of ras 2; *LHPP*, Phospholysine phosphohistidine inorganic pyrophosphate phosphatase; *LRFN5*, Leucine rich repeat and fibronectin type III domain containing 5; MAF, Minimal allele frequency; MAOI, Monoamine oxidase inhibitor; *MAOA*, Monoamine oxidase A; MDD, Major depressive disorder; *MEF2C*, Myocyte enhancer factor 2C; *MEIS2*, Meis homeobox 2; MESA, Multi-Ethnic Study of Atherosclerosis; *MTHFR*, Methyl-tetrahydrofolate reductase; *MUC13*, Mucin 13, cell surface associated; NaSSA, Noradrenergic and selective serotonergic antidepressant; NDRI, Noradrenaline dopamine reuptake inhibitor; *NEGR1*, Neuronal growth regulator 1; *NOS1*, Nitric oxide synthase 1; NRI, Noradrenaline reuptake inhibitor; *OLFM4*, Olfactomedin 4; *PCDH9*, Protocadherin 9; *PCLO*, Piccolo presynaptic cytomatrix protein; PGC, Psychiatric Genomics Consortium; *PHF21B*, PHD finger protein 21B; *RBFOX1*, RNA binding protein fox-1 homolog 1; rG, Genetic correlation; *RGS10*, Regulators of G-protein signaling 10; SARI, Serotonin antagonist and reuptake inhibitor; *SIRT1*, Sirtuin 1; *SLC6A2*, Solute carrier family 6 member 2; SLE, Stressful life events; SNP, Single nucleotide polymorphism; SNRI, Serotonin noradrenaline reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TCA, Tricyclic antidepressant; *TMCO5A*, Transmembrane and coiled-coil domains 5A; *TMEM161B*, Transmembrane protein 161B; *TPH*, Tryptophan hydroxylase; VNTR, Variable number tandem repeats.

* Correspondence to: X. Gonda, Department of Psychiatry and Psychotherapy, Semmelweis University, 1125 Budapest, Kútvölgyi út 4., Hungary.
** Correspondence to: G. Bagdy, Department of Pharmacodynamics, Semmelweis University, 1089 Budapest, Nagyvárad tér 4., Hungary.
E-mail addresses: gonda.xenia@med.semmelweis-univ.hu (X. Gonda), bag13638@iif.hu (G. Bagdy).
[1] These authors contributed equally to the manuscript.

https://doi.org/10.1016/j.pharmthera.2018.09.002

their way into therapy, the optimization of current medications can be approached by pharmacogenomics, where metabolizing enzyme polymorphisms remain prominent determinants of therapeutic success.

Contents

1. Introduction

Depression is a widely known diagnosis both for the general public and in the medical community, yet its severity and complexity is not sufficiently understood and acknowledged. Many equate depression simply with bad mood. Depression, however, is a severe and debilitating disease characterized by a wide variety of symptoms, including at least one of the two core criteria referring to depressed mood and loss of interest, motivation or pleasure accompanied by at least four of several additional symptoms related to the physical axis (appetite, sleep, pain, lack of energy), psychomotor symptoms, and symptoms related to cognitive functions (inability to plan or decide, slowed thinking, memory problems, attention problems) or the content of cognitions (thoughts of death or dying, suicide, guilt) (Fig. 1). These symptoms affect patients and society alike through significantly reduced functioning, interference with normal activity in the academic/work sphere, social and family domains, and cause significant suffering and distress. Depression affects more than 300 million people worldwide with one in 20 people reporting a depressive episode within one year and the disease is currently the leading cause of disability worldwide (WHO, 2017).

In spite of the high prevalence, the huge burden, the extensive research dating back nearly half a century, and the increasing number of antidepressant medications available, we are still far away from being able to treat depression sufficiently. There are severe unmet needs concerning the efficacy of antidepressant medications, including 1) the low response and remission rates to the first chosen antidepressant, 2) the failure to treat the full spectrum of symptoms, 3) the lack of efficacy for a given antidepressant for all subtypes and symptoms, 4) the significant residual symptoms, 5) the lack of effective long-term relapse prevention, and 6) the relatively high prevalence of resistance to antidepressant treatment (Crisafulli et al., 2011; Rush et al., 2006; Trivedi et al., 2006). These concerns indicate that currently available antidepressive medications targeting the monoaminergic system are far from adequate in therapeutic settings. Whether the lack of efficacy results from our neurochemical shortcomings in focusing on monoamines or the heterogeneity of depression is yet to be understood.

1.1. Endogenous or reactive? Etiopathological factors in the background of depression

In previous decades depression was alternatingly attributed to internal biological/genetic and external environmental factors best reflected by the concepts of endogenous depression and reactive depression proposed by Gillespie in 1929 (Gillespie, 1929). The advent of high throughput genetic methods reformed the field of mental disorders and the search for genetic variants responsible for the disease truly resulted in the identification of causal variants in many disorders. This suggested that there are underlying biological/genetic determinants of all mental disorders, among them depression, and this idea of endogenous depression at least partially can be tracked in the ever-larger genetic and genomic investigations. However, these studies including both candidate gene approaches and genome-wide association studies (GWASs), although confirmed the overall role of genetic factors in depression e.g. through sharpening/refined SNP-heritability estimates, could yield only few replicable, directly associated genetic hits refuting the existence of a common, comprehensive genetic architecture with few independent factors and, thus, pure endogenous depression.

One obvious explanation is reflected in the current mainstream conceptualization of depression as a stress-related disorder with the etiological role of environmental influences in its development and manifestation. While numerous environmental stressors are consistently proven to be directly involved in the etiology of depression, it is unlikely that these alone could be responsible for the development of the disease given the relatively high heritability of this disorder, which leads to the rejection of the idea of a common, pure reactive depression too. Rather, effects of both genes and environment are important and they interact, with different relative weights in different manifestations and even in different depression cases. In support of this, patients with contributing stressors in their anamnesis also show a family history for the disease, implicating that investigation of gene-environment interactions (GxE) seems more feasible to find etiopathological variants. While GxE interaction effects presented additional novel candidates in depression pathophysiology, most of these studies also remained heterogeneous. Less well-explored factors, such as gene x gene interactions (GxG), environment x environment (ExE) interactions, rare variants, copy number variations (CNVs) and epigenetic changes may mask effects. However, a prime candidate to account for these inconsistencies remains the heterogeneity of depression itself.

1.2. One disease with a thousand faces: symptoms and subtypes of depression

Depression may manifest with a wide spectrum of symptoms, with differing severity and temporal characteristics, and most clinicians and researchers agree that major depressive disorder is an umbrella term. This heterogeneity can be grasped from multiple angles and at least two major approaches may exist, neither of them being perfect. From one point of view, different depression subtypes may result from

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation.)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition

Note: Criteria A-C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the contest of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance induced or are attributable to the physiological effects of another medical condition.

Fig. 1. DSM-5 criteria for major depressive disorder (American Psychiatric Association., 2013).

different combinations of cognitive characteristics, personality traits and temperaments that coexist and interact in a temporal fashion with environmental influences within a person. These may have biological background, thus their genetic basis can be and has been, indeed, examined in association analyses of genetic main effect (e.g. genetic variants associated with rumination scores) or in GxE interaction analyses. Consistent results in these investigations may represent another subset of genes that could be tested in the search for novel antidepressants. From another perspective depression can also be decomposed based on its symptoms. Different clusters of symptoms may represent subtypes of the disease and may be investigated separately for their genetic backgrounds. Even having only one of the two core symptoms, either marked loss of interest/pleasure or persistent sadness and low mood, represents different etiologies, the former being a lack of positive emotions, while the latter the appearance of negative emotions. Some propose different pathophysiological backgrounds for these two types of symptoms. Still, two patients manifesting each and only one of the core symptoms would both receive the same diagnosis of depression. Even more obvious differences exist between such symptoms of depression as insomnia and hypersomnia, decreased or increased appetite, psychomotor agitation or retardation. Furthermore, symptoms associated with depression may cluster based on a common etiological background and these clusters may lead to distinct clinical manifestations (Drevets, Price, & Furey, 2008). These different symptom-sets could also be investigated from a genetic angle, again ideally with the inclusion of GxE interactions (or even additional masking factors, like GxG or CNVs) resulting in another subset of genes for testing in preclinical models.

None of these methods, however, is impeccable: 1) direct genetic variant-depression relationship is inconsistent, and so is GxE; 2) GxG, CNVs or rare variants lack current methodology or (usually) data for genome-scale investigations; 3) psychological traits and temperaments associate with many other diseases; 4) cognitive symptoms are characteristic of other severe disorders; and 5) symptom clusters do not necessarily represent true biological background. Still, these can be directions capable of revealing novel candidate genes/targets (and even compounds) that are desperately needed. Desperately needed, because almost all antidepressants still act on the monoaminergic systems

that were proposed to be involved in depression by Coppen and Schildkraut in the 1960's (Coppen, 1967; Schildkraut, 1965) and because results from animal depression models could not be translated into clinical success. As we will discuss, clinical trials failed to provide convincing results with substances aiming at new targets. Therefore, we believe progress in the field can only be achieved by the better, finer understanding of underlying pathophysiology. This means that until then pharmacogenetic approaches are left to the optimization of current therapies. Consequently, in the last third of this review we provide an overview of pharmacogenetic studies aimed to unravel therapy failures and improve outcomes with currently applied agents. In these investigations the consideration of interacting genetic and environmental effects is similarly crucial in understanding treatment, as it seems that depression may respond differentially to treatment depending on whether there has been an environmental factor in the etiology (Keers & Uher, 2012). In addition, we propose another helpful approximation, which may bind current therapeutic effects and genetic variations in the form of different brain region activations demonstrated by imaging methods. We believe, as in the case of symptom clusters/temperaments for pathophysiology, this may represent an intermediate layer, where important results could be obtained, but this time for the optimization of already existing therapeutic approaches.

In summary, we attempt to review the current state of the inherently complex field of depression and antidepressant genetics/genomics utilizing the complex, systems-based framework for pathophysiology shown in Fig. 2. We do not aim for completeness, but besides providing a brief introduction we try to present evidence, raise problems and solutions for the different aspects from this unified point of view. While all of these reviewed approaches can be criticized as heterogeneous, fragmented and because they neglect certain aspects of the disease, clinical, biological or psychological relationships, we believe that only such a complex view on pathophysiology can decode depression and lead to efficient pharmacotherapy.

2. Genetic background of depression

2.1. Genes with a main effect in depression

Genetic variation explains a significant portion of the variance in depression. A large U.S. family-based study estimated the heritability of depression at 52% (Wang, Gaitsch, Poon, Cox, & Rzhetsky, 2017) and generally, estimates are in the range of 35-45% for general population samples which provides a profound evidence for a genetic basis (Kendler, Gatz, Gardner, & Pedersen, 2006). Another estimate after detaching contextual effects such as shared environment and household report a smaller but still substantial heritability of 25% from a large U.K. population (Munoz et al., 2016). Single nucleotide polymorphism (SNP)-based heritability estimates (h^2SNP) for depression were reported close to 10% (Cross-Disorder Group of the Psychiatric Genomics et al., 2013). However, the genetic contribution appears to be severity-dependent with 48-72% in hospital samples and 72% for severe, recurrent depression patients indicating that in certain subtypes of depression genetic contribution plays a more marked role (Sullivan, Daly, & O'Donovan, 2012; Uher, 2014). Besides major depressive disorder (MDD) heritability, and especially the SNP-based heritability estimates, further indirect evidence for the pronounced genetic effects in depression has been provided by the significant gene and pathway-level results by enrichment methods (Network and Pathway Analysis Subgroup of Psychiatric Genomics, 2015), shared genetic factors (Purves et al., 2017), genetic correlations (rG), polygenic risk scores, genetic sub-classification of depression (Yu, Baune, Licinio, & Wong, 2017), multivariate prediction of treatment success (Kautzky et al., 2015), and the shared genetics and epidemiological multimorbidity with other diseases (Marx et al., 2017).

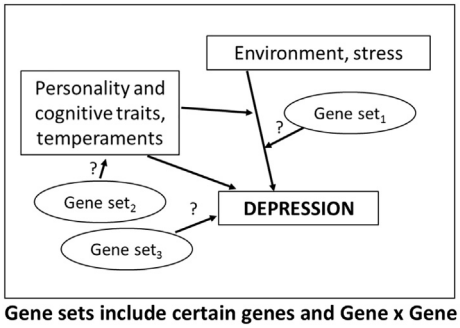

Fig. 2. Proposed mechanism for the development of depression (Bagdy, Juhasz, & Gonda, 2012). The figure depicts possible interrelations that may shape depression. Genes that may influence the disease directly (Gene set_3) are rare and are usually involved in basic functions thus are unfeasible as therapeutic targets. Gene set_2 contains genes that contribute to personality traits, whose different combination in different individuals may results in the disease and can represent a subset of therapeutic targets in the future. The personality traits, temperaments and cognitive functions act together with environmental stress, for which individuals are sensitized through a different set of genes (Gene set_1) in shaping depression.

These heritability estimates and the ever-lower genotyping costs accelerated research that tried to unravel the implied genetic underpinnings of depression. In the last three decades research concerning the genetic background of depression has seen a vast increase, at first, with a large number of association studies focusing on identifying candidate genetic variants. The assumptions behind the genes tested for simple pairwise statistical associations stemmed from our presumed knowledge of the neurobiology and neural systems involved in depression. During the initial years, research focused on testing main effects of variants in major depression, which means that certain alleles or genotypes are more likely associated with the disease.

A meta-analysis in 2008 reported that 393 genetic polymorphisms have been investigated in depression, with results published in 183 papers (Lopez-Leon et al., 2008). However, while replication is crucial in genetic studies, only 22 of the above 393 variants have been examined in at least three different studies, and could, therefore, be included in a meta-analysis. This meta-analysis supported a significantly elevated odds ratio for depression in case of *APOE, GNB3* (C825T), *MTHFR* (C677T), *SLC6A4* (40 bp VNTR, serotonin-transporter-linked polymorphic region (*5HTTLPR*)), and *SLC6A3* (44 bp Ins/Del), while found no significant effects in case of several other variants of genes repeatedly implicated in depression (*HTR1A, HTR1B, HTR2A, HTR2C, TPH1, MAOA, COMT, BDNF, SLC6A2, DRD3, GABRA3 and ACE*) (Lopez-Leon et al., 2008). Separately, some of these findings were supported, others debated by subsequent meta-analyses. For example, positive or partially positive associations were demonstrated for *5HTTLPR* (Clarke, Flint, Attwood, & Munafo, 2010; Kiyohara & Yoshimasu, 2010), *MTHFR* C677T (Wu et al., 2013), while negative results were obtained for *BDNF* Val66Met (Gyekis et al., 2013), *SLC6A2* T-182C and G1287A (Zhao et al., 2013; Zhou, Su, Song, Guo, & Sun, 2014), *HTR2A* rs6311 (Jin, Xu, Yuan, Wang, & Cheng, 2013) and *CLOCK* polymorphisms (though the latter in the Japanese population; (Kishi et al., 2011)).

It was also demonstrated that these genes are non-specific to depression, with 1) the *SLC6A4* polymorphism *5HTTLPR* conferring risk for anxiety disorders, bipolar disorder, and depression, 2) *SLC6A3* 10-repeat variant (40bp VNTR) elevating chance for both ADHD and depression, and 3) *MTHFR* C677T polymorphism shared between schizophrenia, bipolar disorder and depression. Only *GNB3* TT homozygote and *APOE3* status showed elevated odds ratio specific for depression (Gatt, Burton, Williams, & Schofield, 2015). Most of the studies involving the above genetic variants, furthermore, had low sample sizes and faced replication issues. Analyses recruiting larger samples could not provide genetic validation for the candidate gene approach (Bosker et al., 2011; Wray et al., 2012) and indicated that most found associations were probably chance (false positive) findings (Flint & Kendler, 2014). While it cannot be excluded that some purely genetic factors, like e.g. those that may trigger mitochondrial dysfunctions can

influence the development of the disease, these are non-specific for depression and rather mediate fundamental processes in mood regulation, cognition, etc. (Petschner et al., 2018). The dead-end of the candidate gene approach in revealing causal variants fostered the accumulation of more reliable genotypic information and larger clinical samples sparking the genome-wide association study (GWAS) and computational era of depression.

2.2. Results of genome-wide association studies in depression

To solve the problems of candidate gene association studies, GWASs tried to exceed their limitations. With large samples collected already, statistically significant genetic hits were rapidly accumulating for a wide range of psychiatric diseases but no replicable GWAS results were reported for depression as of 2014 (Flint & Kendler, 2014). Dunn et al (Dunn et al., 2015) systematically reviewed 15 GWASes published before October 2013 conducted in major depressive disorder, depressive symptoms, or age at onset of depression. Popular candidate genes did not show any association, even though they were significant candidate genes in meta-analyses. Therefore, in accordance with Flint and Kendler (Flint & Kendler, 2014), it seemed ever less compelling that these genes would play substantial, generalizable roles. Furthermore, the only genome-wide significant (GWS) hit in these 15 studies was the association of rs1545843 within *SLC6A15* (Kohli et al., 2011). Despite its plausible action in depression as a neutral amino acid transporter, the association could only be replicated at a nominally significant level and in four of the five replication samples (Kohli et al., 2011). With these unconvincing results the authors remark that GWASs for depression lack environmental exposure as a variable and large enough samples (Dunn et al., 2015).

Somewhat paradoxically, this relative lack of GWAS results combined with *a priori* (stemming from candidate gene approaches) information already implicated an essential insight into the genetic background of depression, namely, an upper bound for the genetic main effect strengths and consequently a polygenic architecture involving common variants with high population occurrence (minor allele frequencies or MAFs over 10%) and weak individual effects (odds ratios below 1.3) (Flint & Kendler, 2014). Remarkably, based on this polygenic model, depression genetics suggested a rather continuous risk for any person through the coincidental settings of myriads of common variants, just like blood pressure in hypertension risking stroke, with the only difference that sadness cannot be measured accurately (Sullivan, 2015). Another surprising, practical consequence, also recently receiving explicit confirmation (Mullins & Lewis, 2017) was that a significant proportion of the genetic background is stable behind depression subclasses, e.g. lifetime vs. severe forms or clinically established vs. self-reported, which could be used to achieve very large sample sizes, e.g. beyond 1 million, where sample size trumps accuracy (Major Depressive Disorder Working Group of the PGC. et al., 2017). A further stunning consequence of this model is that 20% of the 18,000 genes expressed in the brain should be involved in the genetic architecture of major depression (Flint & Kendler, 2014). This substantial genetic contribution is independent of further specialties of depression with respect to other psychiatric diseases, such as the relatively high prevalence, high heterogeneity and high environmental dependency of depression, however, these depression specificities may give further explanations for the lack of results below a critical GWAS sample size (Levinson et al., 2014).

Equipped with this knowledge, after reaching critical study designs in GWASs, this much expected voluminous set of weak factors recently started to become statistically visible, providing at least testable hits (Cai et al., 2015; Major Depressive Disorder Working Group of the PGC. et al., 2017; Mullins et al., 2016). Several GWAS studies have been published with large sample sizes and on various measurements of the depression phenotype. Table 1 provides an overview of these recent findings within each study, and the discovery and replication samples, also underscoring the overlap in them.

Besides internal replications from the above results only three replicated between different studies (Table 2). The presynaptic cytomatrix protein piccolo (*PCLO*) gene proposed originally (but remained non-significant) by Sullivan in 2009 (Sullivan et al., 2009) became a GWS hit in the work of Mbarek et al. and could be replicated by Wray et al. (but only with gene-based analysis, not on variant level) (Mbarek et al., 2017; Wray et al., 2012). The polymorphism rs12552 of olfactomedin 4 (*OLFM4*) seems to be the only SNP currently replicated in two separate GWASs (with overlapping populations) and different SNPs showed genome-wide significant (GWS) hits in neuronal growth factor regulator 1 (*NEGR1*) in the Hyde- and Wray-studies.

In summary, despite enormous sample sizes, replicability of GWS findings in independent samples could not be reliably achieved and even large-scale GWASs fail to replicate each other's findings in addition to the unsuccessful internal replications. These problems, thus, still leave a considerable gap in our understanding of the genetic contributions that can be related to the unique feature of depression among psychiatric diseases: to the well-known, strong influence of environmental factors.

3. The role of environment in the development of depression

Besides genetic factors depression heavily depends on environmental influence. A recent study in more than 2 million offsprings from the Swedish Extended Adoption Study has proven that genetic factors and rearing experiences contribute equally to depression risk in parent-offspring transmission (Kendler, Ohlsson, Sundquist, & Sundquist, 2018) providing strong evidence for a significant, large role of environmental stressors. In further support, antecedent chronic and acute stressors were associated significantly with depression in women, stressors were 2.5 times more likely in depressed subjects than in controls and around 80% of depression cases had relevant negative life events in the anamnesis (Hammen, 2005; Hammen, Kim, Eberhart, & Brennan, 2009). Diverse environmental factors have been connected through evidence to depression and in Table 3 we collected the most important findings according to reviews from the past few years categorizing them into life stages (Schmitt, Malchow, Hasan, & Falkai, 2014).

Before concluding that environment-driven depression is a common phenomenon, it is worth to note the marked difference between stressors and depression: whereas the total prevalence of the heterogeneous stressors is common, e.g. frequency of severe life events is estimated to be one in every 3–4 years, depression is triggered in only about 20% of those with acute stress exposure (Brown, Bifulco, & Harris, 1987). In addition, we would like to point out again the already discussed study showing aggregation of family cases in those exposed to environmental stress, where the authors hint that vulnerability towards stress and environmental influences may be dependent on the genetic background (Kendler & Karkowski-Shuman, 1997). All these results suggest complex interactions of the genetic background with these stress factors and their synergistic or interaction effects in depression (Lopizzo et al., 2015).

3.1. Concept of gene-environment interaction studies and evidence for their role in depression

The seminal GxE study on depression was published in 2003 showing that the short (S) allele of the *5HTTLPR* polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*) interacts with stressful life events and childhood maltreatment to affect depression (Caspi et al., 2003). This study generated interest in the field and many researchers conducted replication studies resulting in large enough populations for meta-analyses that showed mixed results. Three meta-analyses could demonstrate positive interactions (Bleys, Luyten, Soenens, & Claes, 2018; Karg, Burmeister, Shedden, & Sen, 2011; Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014), while

Table 1
Genome-wide significant findings for depression phenotypes in main genetic effect models, since 2013

Reference	Discovery sample	Findings in the discovery sample	Replication sample	Replicated findings
Mbarek et al., 2017	NESDA, NTR (European)	*PCLO*	-	-
Power et al., 2017	9 studies of PGC (European) (including NESDA / NTR)	intergenic rs7647854	TwinGene; PsyCoLaus; SHIP-LEGEND; GenRED2/DepGenesNetworks; University of Münster; combined Danish sample; deCODE; Generation Scotland (all of these: European); CONVERGE (Chinese)	Nominal association of intergenic rs7647854
Wray et al, 2017	PGC; deCODE; Generation Scotland; GERA; iPSYCH; UK Biobank; 23andMe (all of these: European)	44 independent loci; the most remarkable genes, or SNPs in genes: *OLFM4*; *NEGR1*; *RBFOX1*; *LRFN5; CACNA1E; CACNA2D1; DRD2; GRIK5; GRM5; PCLO*	-	-
Xiao et al., 2018	23andMe; PGC; (both: European) CONVERGE (Chinese)	rs9540720 in *PCDH9*	independent 23andMe replication sample (European); a Chinese MDD sample	Nominal association of rs9540720 in *PCDH9*
Huo et al., 2016	PGC (European); CONVERGE (Chinese)	-	-	-
Hyde et al., 2016	23andMe; PGC (both: European)	SNPs in *OLFM4*; *TMEM161B-MEF2C*; *MEIS2-TMCO5A*; *NEGR1*	independent 23andMe replication sample (European)	Nominal associations: *TMEM161B-MEF2C*; *NEGR1*
Okbay et al., 2016	PGC; UK Biobank; GERA (all of these: European)	rs7973260 in *KSR2*; rs62100776 in *DCC*	23andMe (European)	Nominal associations of rs7973260 in *KSR2* and rs62100776 in *DCC*
CONVERGE, 2015 (Cai et al., 2015; Ware et al., 2015)	CONVERGE (Chinese)	rs12415800 in *SIRT1*; rs35936514 in *LHPP*	independent Chinese MDD sample	Nominal associations of rs12415800 in *SIRT1* and rs35936514 in *LHPP*
Ware et al., 2015	MESA (European, African, Chinese and Hispanic Americans)	rs1127233 in *MUC13* in Hispanic Americans	joint analyses with HRS in African and European Americans	-

CACNA1E: calcium voltage-gated channel subunit alpha1 E; *CACNA2D1*: calcium voltage-gated channel auxiliary subunit alpha2delta 1; CONVERGE: China Oxford and VCU Experimental Research on Genetic Epidemiology; *DCC*: DCC netrin 1 receptor; *DRD2*: dopamine receptor D2; GenRED: Genetics of Recurrent Early-Onset Depression; GERA: Genetic Epidemiology Research on Adult Health and Aging; *GRIK5*: glutamate ionotropic receptor kainate type subunit 5; *GRM5*: glutamate metabotropic receptor 5; HRS: Health and Retirement Study; *KSR2*: kinase suppressor of ras 2; *LHPP*: phospholysine phosphohistidine inorganic pyrophosphate phosphatase; *LRFN5*: leucine rich repeat and fibronectin type III domain containing 5; MDD: major depressive disorder; *MEF2C*: myocyte enhancer factor 2C; *MEIS2*: meis homeobox 2; MESA: Multi-Ethnic Study of Atherosclerosis; *MUC13*: mucin 13, cell surface associated; *NEGR1*: neuronal growth factor regulator 1; NESDA: the Netherlands Study of Depression and Anxiety; NTR: the Netherlands Twin Registry; *OLFM4*: olfactomedin 4; *PCDH9*: protocadherin 9; *PCLO*: presynaptic cytomatrix protein piccolo; PGC: Psychiatric Genomics Consortium; *RBFOX1*: RNA binding protein fox-1 homolog 1; SHIP-LEGEND: Study of Health in Pomerania–Life-Events and Gene-Environment Interaction in Depression; *SIRT1*: sirtuin 1; SNP: single nucleotide polymorphism; *TMCO5A*: transmembrane and coiled-coil domains 5A; *TMEM161B*: transmembrane protein 161B.

other three could not replicate original findings (Culverhouse et al., 2018; Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009) (Table 4). It is important to use deep-phenotyped samples in GxE studies, because particular and often neglected factors can further strongly affect findings. For example a study demonstrated an interaction between *5HTTLPR* and financial difficulties but not other types of stress on depression (Gonda et al., 2016).

Brain-derived neurotrophic factor *(BDNF)* is another example often investigated in a GxE setup. Two meta-analyses confirmed the significant GxE effect in depression between *BDNF* Val66Met polymorphism and life stress (Hosang, Shiles, Tansey, McGuffin, & Uher, 2014; Zhao et al., 2017), one of them highlighting that results were stronger in the case of stressful life events, but only a statistical trend was found with childhood adversity (Hosang et al., 2014). Besides *5HTTLPR*, other monoaminergic genes have frequently been tested. Polymorphisms in *MAOA* encoding monoamine-oxidase A playing a role in serotonin, noradrenaline and dopamine catabolism interacted with childhood maltreatment and maternity difficulty affecting depression (Mandelli & Serretti, 2013; Naoi, Maruyama, & Shamoto-Nagai, 2018; Uher, 2014), although at least four studies presented negative results (Mandelli & Serretti, 2013), therefore, the role of *MAOA* in GxE studies of depression remains, at best, questionable. *COMT* encoding catechol-O-methyltransferase involved in the metabolism of noradrenalin and dopamine interacted with several forms of stressors showing a more consistent role in modulating environmental effect on depression (Mandelli & Serretti, 2013). *SLC6A2* encoding noradrenaline transporter which reuptakes noradrenalin from synaptic clefts showed an interaction effect with severe stressful life events and rural living among women in depression (Mandelli & Serretti, 2013). Some variants of HPA axis genes have also been investigated in GxE interactions for depression. *FKBP5* interacted with childhood trauma and stressful life events; and corticotropin-releasing hormone receptor 1, *CRHR1* with childhood maltreatment predicting depression, although the latter gene showed mixed results in subsequent studies (Mandelli & Serretti,

Table 2
Variants within genes or genes replicated in the different GWAS studies investigating depression after 2015.

Gene	First study and sample	Hit of the first study	Second study and sample	Hit of the second study
PCLO	Mbarek et al., 2017 (NESDA, NTR)	rs2715157 + **gene-based test**	Wray et al, 2017 (PGC; deCODE; Generation Scotland; GERA; iPSYCH; UK Biobank; 23andMe)	**gene-based test**
OLFM4	Hyde et al., 2016 (23andMe; PGC)	rs2806933; **rs12552**	Wray et al, 2017 (PGC; deCODE; Generation Scotland; GERA; iPSYCH; UK Biobank; 23andMe)	**rs12552**
NEGR1	Hyde et al., 2016 (23andMe; PGC)	rs11209948; rs2422321 not investigating rs1432639	Wray et al, 2017 (PGC; deCODE; Generation Scotland; GERA; iPSYCH; UK Biobank; 23andMe)	rs1432639; rs12129573 (statistically independent)

PCLO: Piccolo Presynaptic Cytomatrix Protein; *OLFM4*: Olfactomedin 4; *NEGR1*: Neuronal Growth Regulator 1

Table 3
Environmental risk factors of depression

Environmental risk factors	
Risk factor	*Articles*
Pre- or perinatal	
Season of birth	Uher, 2014
Inadequate nutrition	Lopizzo et al., 2015; Uher, 2014
Prenatal stress	Schmitt et al., 2014; Uher, 2014
In utero exposure to Infection	Lopizzo et al., 2015
Preterm birth	Schmitt et al., 2014; Uher, 2014,
Perinatal complications	Lopizzo et al., 2015
Childhood	
Maltreatment, abuse	Dunn et al., 2015; Juhasz et al., 2015; Lopizzo et al., 2015; Schmitt et al., 2014; Smoller, 2016; Uher, 2014
Loss of a parent	Lopizzo et al., 2015; Uher, 2014
Parental divorce	Dunn et al., 2015; Smoller, 2016
Negative family relationships	Dunn et al., 2015; Lopizzo et al., 2015; Mandelli & Serretti, 2013; Smoller, 2016
Social disadvantage, poverty	Dunn et al., 2015; Lopizzo et al., 2015; Smoller, 2016; Uher, 2014
Bullying	Lopizzo et al., 2015; Uher, 2014
Urban upbringing	Lopizzo et al., 2015
Adolescence	
Cannabis use	Lopizzo et al., 2015; Uher, 2014
Adulthood	
Stressful life events	Dunn et al., 2015; Lopizzo et al., 2015; Risch et al., 2009; Smoller, 2016; Uher, 2014
Occupational stress, unemployment	Mandelli & Serretti, 2013
Poor social contacts/support	Mandelli & Serretti, 2013
Separation	Mandelli & Serretti, 2013
Interpersonal problems	Mandelli & Serretti, 2013
Ethnic minority status	Lopizzo et al., 2015

2013). A novel study (Gonda et al., 2017) identified an interaction between *GABRA6* and stressful life events in depression.

Inflammation as a result of chronic stress has also been proposed in depression etiology (for a review see (Kiecolt-Glaser, Derry, & Fagundes, 2015). Such a connection was supported by some GxE studies – for example *IL-1B* and *IL-6* interacted with several stress factors (stressful life events, childhood maltreatment, chronic interpersonal stress) in the background of depression (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Kovacs et al., 2016a; Kovacs et al., 2016b; Tartter, Hammen, Bower, Brennan, & Cole, 2015). Genes of the galanin (a stress-inducible neuropeptide) system have also been proposed as important mediators of stress effects in depression (Juhasz et al., 2014) suggesting that *GALR1* and *GALR3* possibly exert their modulating effect through childhood maltreatment, while *GALR2* through recent stressful life events. Another interesting target in GxE studies of depression is the endocannabinoid system due to its role in recovery from stress (Lazary et al., 2009). *CNR1* (cannabinoid receptor 1 gene) showed interaction with stressful life events and physical abuse (Juhasz et al., 2009; Mandelli & Serretti, 2013), although further proof is needed to elucidate its role in the pathogenesis of depression. A study also identified an interaction between *FAAH* (encoding fatty acid amide hydrolase which is responsible for anandamide degradation) and childhood maltreatment to associate with depression (Lazary, Eszlari, Juhasz, & Bagdy, 2016). Multiple other genes have been tested with highly mixed or negative results in GxE studies of depression. Instead of elaborating these we focused here on main findings from such investigations and also on other lesser known variants or interactional findings with multiple environmental factors.

3.2. Interaction with stress in depression GWAS studies

To date, two studies have assessed GxE effects on a genome-wide scale (genome-wide gene-environment interaction study, GWEIS) with childhood trauma in depression. In one of them (Van der Auwera et al., 2018), to test these GxE effects in depression in 3944 European subjects, the GWEIS approach was combined with a candidate gene analysis to obtain a proper power, choosing candidate genes based on two reviews and former GWAS results. No GWS hits emerged, and the authors also did not find consistency between the different analytic approaches leading them to suggest the need for larger samples (Van der Auwera et al., 2018). The other study conducted a GWAS on depression in 203 patients and 193 controls from a Mexican American cohort, both groups having significant hyperactivation of the HPA axis related to distress and acculturation issues (Wong et al., 2017a). Their results revealed 44 common and rare functional variants in the Mexican American sample, but only the rare variant analysis came to a successful replication in a European cohort: it replicated the association of *PHF21B* (PHD finger protein 21B) gene.

Further two GWEIS studies have been performed on CES-D (Center for Epidemiological Studies-Depression) depression scale, seeking the interaction of genetic variants with stressful life events within the previous one year. Dunn et al. investigated this interaction in 7179 African American and 3138 Hispanic American postmenopausal women from the WHI (Women's Health Initiative). They found one GWS GxE signal in African Americans, rs4652467 near *CEP350* (centrosomal protein 350) gene, but it could not be replicated in 1231 African American women from the HRS (Health and Retirement Study) and 2010 African American women from the Grady Trauma Project (using the Beck Depression Inventory to measure depression) (Dunn et al, 2016). The other study on recent life stress and CES-D (Otowa et al., 2016) was conducted in 320 Japanese subjects and found only a marginally significant GxE finding, the rs10510057 near *RGS10* (regulators of G-protein signaling 10) gene.

3.3. Summary of GxE investigations in depression

While GxE studies provide the opportunity to have a better characterization (and additional evidence) of genes with previously identified roles in a disease, and also to identify new genes with (only) environment-dependent effects, they also make it possible to determine the type of risk environments that may facilitate disease development, and also to find protective effects (Mandelli & Serretti, 2013). Although candidate GxE studies have a better replicability record, results remain inconclusive, which can be understood by the larger expected sample size corresponding to potential environmental context-specific GxE interactions and the high variability of the distributions of environmental stressors in different populations. Only the stratification for these potential environmental factors without their explicit inclusion in the analysis could hypothetically decrease the variability of the results and improve replicability. However, measuring all these environmental factors, which have substantially different distributions in the population (for example childhood maltreatment/abuse being intuitively rarer than recent life events that are experienced by all individuals) poses a significant problem (see Table 3 that listed some of the environmental risk factors for depression.).

Despite the problems the field faces, GxE investigations in depression are important exploratory tools in the search for novel candidates. In fact, they already provided some of the testable markers awaiting confirmation and replication. Unfortunately, the studies (especially candidate gene studies) often use very small sample sizes that are inadequate to draw decisive conclusions. As a final remark, we have to note that in addition to GxE interactions, other candidates to provide novel targets are abundant and include CNVs (Flint & Kendler, 2014; Levinson et al., 2014), rare variants, GxG and ExE interactions.

4. Other directions: rare variants, CNVs, GxG, ExE and higher-order interaction combinations in association with depression

Rare variants (with MAF<0.01) remained unfeasible to investigate, especially because of the common variant-common disease hypothesis,

Table 4
Gene-environment interaction studies in depression.

GxE interactions			
Gene	*Environmental factor*	*Articles*	*Gene function*
5HTTLPR	x stressful life events x childhood maltreatment x financial difficulties	Caspi et al., 2003 Gonda et al., 2016	Repeat length polymorphism in the promoter region of serotonin transporter gene (*SLC6A4*) which encodes a protein involved in serotonin transportation.
Meta-analyses	- - + (only in Caucasians) + - +	Risch et al., 2009 Munafo et al., 2009 Karg et al., 2011 Sharpley et al., 2014 Culverhouse et al., 2018 Bleys et al., 2018	
BDNF Val66Met	x childhood adversity x recent stressful events x childhood sexual abuse	Hosang et al., 2014; Lopizzo et al., 2015; Mandelli & Serretti, 2013; Sharma, Powers, Bradley, & Ressler, 2016; Uher, 2014; Zhao et al., 2017 Lopizzo et al., 2015; Mandelli & Serretti, 2013	Encodes a nerve growth factor protein. *BDNF* is widely expressed in the central nervous system (including regions of mood regulation). Carrying Val66Met influences the activity of the coded protein.
MAOA	x childhood maltreatment x maternity difficulty (postpartum depression) (but other four studies did not find interaction)	Mandelli & Serretti, 2013; Naoi et al., 2018; Uher, 2014	Encodes monoamine oxidase A, which catabolizes monoamines (serotonin, norepinephrine, dopamine).
COMT	x stress exposure x family stress (adolescent) x maternity stressors (postpartum depression) x early environmental risk (in men)	Mandelli & Serretti, 2013	Involved in metabolism of noradrenalin and dopamine.
FKBP5	x childhood trauma x stressful life events (1 out of 2 studies) x traumatic life events	Dunn et al., 2015; Lopizzo et al., 2015; Mandelli & Serretti, 2013; Sharma et al., 2016; Smoller, 2016 Lopizzo et al., 2015	Regulation of stress-response via HPA axis.
CRHR1	x childhood maltreatment (although mixed results – *Mandelli et al, 2013*)	Dunn et al., 2015; Smoller, 2016; Uher, 2014	Regulation of stress-response via HPA axis.
SLC6A2	x severe stressful life events x women living in a rural area (2 studies)	Mandelli & Serretti, 2013	Encodes noradrenaline transporter reuptaking neurotransmission of noradrenalin and dopamine beta-hydroxylase.
CNR1	x stressful life events x physical abuse (2 studies)	Juhasz et al., 2009; Mandelli & Serretti, 2013	Human cannabinoid receptor 1 gene.
GABRA6	x stressful life events	Gonda et al., 2017	Encodes gamma-aminobutyric acid receptor subunit alpha-6 protein.
GAL, GALR1	x stressful life events x childhood maltreatment	Juhasz et al., 2014	Galanin (a stress-inducible neuropeptide) gene and its receptor.
GALR2	x stressful life events (not with childhood maltreatment)	Juhasz et al., 2014	Galanin receptor gene.
GALR3	x childhood maltreatment (not with stressful life events)	Juhasz et al., 2014	Galanin receptor gene.
IL1B	x stressful life events x childhood maltreatment x chronic interpersonal stress	Kovacs et al., 2016a; Tartter et al., 2015	*IL-1B* encodes interleukin-1β, a proinflammatory cytokine.
IL-6	x stressful life events x childhood maltreatment x chronic interpersonal stress	Baumeister et al., 2016; Kovacs et al., 2016b; Tartter et al., 2015	*IL-6* encodes interleukin-6, a modulator of pain processing.
FAAH	x childhood maltreatment	Lazary et al., 2016	Encodes fatty acid amide hydrolase enzyme which is responsible for anandamide degradation.
HTR1A	x stressful life events (but one negative finding)	Bukh et al., 2009; Mekli et al., 2011	Serotonin receptor gene 1A .
HTR1B	x stressful life events	Mekli et al., 2011	Serotonin receptor gene 1B.
NOS1	x financial hardship	Sarginson et al., 2014	Encodes neuronal nitric oxide synthase 1 with multiple roles (for example synaptic signaling, regulation of serotonin pathway and HPA-axis).

BDNF Val66Met: Brain derived neurotrophic factor 66 valine-methionine polymorphism; *MAOA*: Monoamino-oxidase A; *COMT*: Cathecol-o-methyltransferase; *FKBP5*: FK506 binding protein 5; *CRHR1*: Corticotropin releasing hormone receptor 1; *SLC6A2*: solute carrier family 6 member 2; *CNR1*: Cannabinoid receptor 1; *GABRA6*: Gamma-Aminobutyric Acid Type A Receptor Alpha6 Subunit; *GAL*: Galanin; *GALR1*: galanin receptor 1; *GALR2*: galanin receptor 2; *GALR3*: galanin receptor 3; *IL-1B*: interleukin 1 beta; *IL-6*: interleukine 6; *FAAH*: Fatty acid amide hydrolase; *HTR1A*: serotonin transporter 1A receptor; *HTR1B*: Serotonin transporter 1B receptor; *NOS1*: Nitric oxide synthase 1
+ indicates confirmatory while – indicates negative metaanalyses

although a few studies yielded results. Altogether 11 rare (MAF<0.01 in the control population) variants were associated with depression in the already mentioned GWAS study of Wong et al. in a Mexican-American cohort, although it must be noted that participants were also exposed to environmental stress (Wong et al., 2017a, 2017b). A GWS missense mutation was demonstrated in the *LIPG* gene on chromosome 18 in an investigation for depressive symptoms in an elderly sample (Amin et al., 2017), and variants in *LHPP* and *CPXM2* genes were also suggested to be risk factors for depression in Mexican-Americans (Knowles et al., 2016). A gene set including *STXBP5, RIMS1, CTNNB1, DMXL2, SYN1, YWHAB, YWHAH* genes was found to be significantly enriched in European-American early-onset depression cases in a rare variant analysis (Pirooznia et al., 2016), while both F528C in *SLC6A2* and R219L in *HTR1A* showed associations with depression in a German sample (Haenisch et al., 2009). Other approaches also yielded some results. Rare diseases, like Huntington's disease, acute intermittent porphyria, Wolfram syndrome or mitochondrial disorders are often accompanied by depression or depressive symptoms mostly in addition to severe other impairments (Berrios et al., 2002; Perlis et al., 2010; Petschner et al., 2018; Smoller, 2016). In case of diseases with cognitive involvement, like Huntington's disease, mood disorders can precede the onset of the primary disease by decades. However, the possibility of rare variants causing exclusively depressive symptoms with no manifestation of Huntington's disease was also raised for the CAG repeats in the huntingtin gene (Perlis, Smoller, et al., 2010). Such possibilities are hard to exclude, because investigations into major depressive disorder enroll younger patients and follow-up is often limited and restrict determination of disease manifestation with later onset.

A GWAS, applying another approach, examined structural CNVs in relation to depression. Duplication of a sequence near *SLIT3* has been identified by Glessner et al. (Glessner et al., 2010) which found partial confirmation in another family-based study that identified mutations in the *SLIT3* among patients of autism spectrum disorders showing depressive symptoms (Cukier et al., 2014). In recurrent depression copy number deletions were also detected but remained unsupported by a re-analysis (Rucker et al., 2013; Rucker et al., 2016). In summary, while depression cases without rare disease comorbidity are probably not substantially influenced by rare variants, rare and structural variations may mask some patient populations and interfere with GWAS and GWEIS results, especially because these variants are often excluded in initial quality control steps (see e.g. protocol of (Coleman et al., 2016)), but in fact, regardless of exclusion they may be causal in phenotype variation and distribution in the background. Their inclusion into the analysis, therefore, would be more than welcome. Even better would be to filter healthy individuals carrying known mutations, thus, more homogeneous genetic samples were to be analyzed. On the other side, even Mendelian diseases not necessarily manifest in carriers of penetrant mutations (Chen et al., 2016), which leads us to another well-known phenomenon, GxG interactions.

GxG interactions are equally promising candidates as GxE interactions (Gage, Davey Smith, Ware, Flint, & Munafo, 2016; Taylor & Ehrenreich, 2015) and analyses were mostly performed on candidate genes. Linkage analysis pointed to a possible interaction of *5HTTLPR* with an unknown gene on chromosome 4 (Neff et al., 2010). *MTHFR* A1298C polymorphism was shown to interact with *COMT* Val158Met with homozygous CC carriers and *COMT* Met carriers having elevated risk, especially in women according to two studies (Nielsen et al., 2015). Polymorphisms interacting within the *CRHR1* and *AVPR1b* genes may also underlie depression susceptibility (Szczepankiewicz et al., 2013) but could not be replicated for depression after suicide attempts (Ben-Efraim, Wasserman, Wasserman, & Sokolowski, 2013), while by investigating other polymorphisms in *CRHR1* an interaction was also demonstrated with *BDNF* Val66Met polymorphism in a Chinese sample (Xiao et al., 2011). Less obvious candidates were also investigated. In a small, heterogeneous sample depression diagnosis was influenced by polymorphisms in matrix-metalloproteinase (*MMP*) genes, but the effect depended on the carrier status of the polymorphisms examined (Bobinska, Szemraj, Czarny, & Galecki, 2016). *BCL1* rs41423247 and *CHRNA4* rs1044396 were also shown to interact on current depression scores in a nonclinical sample of 800 (Reuter, Markett, Melchers, & Montag, 2012) and *TAAR6* and *HSP-70* could also influence each other's effect in a Korean sample for both depression and bipolar disorder, though small sample size may have distorted results (Pae, Drago, Forlani, Patkar, & Serretti, 2010).

However, as in the case of main effect analyses, the only large study conducted to our knowledge could not confirm candidate GxG findings in 4,824 cases and 36,162 controls and 978 cases and 2,992 controls as replication. While no GWS hits (in this case p-value<10^{-12}) were demonstrated for pairwise GxG interactions in logistic regressions, nominally significant interactions were found between 1) rs16912862 (*ZNF169*) and rs4769180, 2) rs7587468 and rs13120959 (*PRSS12*), 3) rs2651975 (*TMCC3*) and rs9940287 and 4) rs6414384 (*KCNAB1*) and rs10843021, according to the two applied methods and with 2) and 4) replicated (Murk & DeWan, 2016). Thus, like in the case of main effect analyses, candidate gene approaches and large, genome-wide approaches yield no overlapping results, even if we consider the found results valid, which is often debated due to sample sizes. Additionally, we already cited research demonstrating that genes without any main effect may also contribute to GxG interactions (Culverhouse, Suarez, Lin, & Reich, 2002) and also discussed the concept of GxE interactions that may also contribute to different interpretation of GxG interactions expanding the possibilities.

While interaction between genes seems to be plausible, less well explored are ExE interactions. To briefly discuss the concept of ExE interactions we only bring one example. Evidence suggests that experienced stress in adolescence may mediate the connection between early adversities and onset of depression (Shapero et al., 2014). In our European non-clinical sample of more than 2000, those exposed to both childhood abuse and lifetime negative life events had a disproportionately higher likelihood ratio for lifetime depression than having only one of the stress factors in their life (unpublished data). Three-way interactions are also possible. GxGxE interactions were demonstrated especially after a combined *BDNF* Val66Met and *5HTTLPR* influence on amygdala and subgenual portion of anterior cingulate connectivity was proven in 2008 (Pezawas et al., 2008). The S carrier status was a risk factor in the presence of Val/Val genotype after childhood abuse (Grabe et al., 2012) but elevated risk for depression was found in *5HTTLPR* S and *BDNF* Val66Met Met carriers and family environment in a longitudinal youth sample (Dalton, Hammen, Najman, & Brennan, 2014). Authors reviewing evidence on the topic concluded that the interaction between *BDNF* Val66Met and *5HTTLPR* may involve epigenetic regulating mechanisms triggered by environmental stress (Ignacio, Reus, Abelaira, & Quevedo, 2014). *BDNF* Val66Met polymorphism was the center of another GxGxE investigation yielding positive results with *GSK3B* and recent life events in a Chinese sample (Yang et al., 2010). ExExG interactions are also plausible opportunities, as demonstrated for the dependency of *5HTTLPR* effects on both recent life event and childhood abuse exposure on a multivariate phenotype including lifetime depression, depression and anxiety scores in young (Juhasz et al., 2015).

Even higher order interactions may be possible, as in the case of the *BDNF* Val66Met polymorphism showing significant 5-way interactions with four different polymorphisms, though all from within the *NTRK2* gene in a geriatric clinical sample (Lin et al., 2009). From a genome-wide perspective higher order (but even GxG) investigations require new methods coping with interaction that can be scaled-up both statistically and computationally. Unfortunately, currently available tools handling two-way, but especially higher-order interactions cannot be easily (or at all) scaled-up to the genome-wide level (see e.g. (Moore et al., 2017; Musani et al., 2007; Wright, Ziegler, & Konig, 2016)). A promising direction is the incorporation of background knowledge into machine learning methods

Table 5
Summary of genes implicated in depression: association with diagnosis and biological involvement.

	Depression diagnosis or sum of symptom scores			Biological involvement according to GeneCard's summaries				
Gene	G	GxE	GxG	Mono-amines	Glu/GABA	Neurogenesis/ neuronal projection/synapse/cell-cell contact	Immune functions	Other/not-known
APOE	+ #							+ (lipid metabolism)
GNB3	+ #							+ (G-protein coupled signaling)
MTHFR	+ #		+ by COMT					+ (folate cycle)
SLC6A4 (*5-HTTLPR*)	+/- #	+/- by stressful life events and by childhood maltreatment; (+) by financial difficulties	(+) by unknown gene on chromosome 4	+ (5HT)				
SLC6A3	+ #			+ (DA)				
HTR1A	-	(+/-) by stressful life events		+ (5HT)				
HTR1B	-			+ (5HT)				
HTR2A	-			+ (5HT)				
HTR2C	-			+ (5HT)				
TPH1	-			+ (5HT)				
MAOA	-	+/- by childhood maltreatment; (+) by maternity difficulty		+ (5HT, DA, NA)				
COMT	-	(+/-) by stressful life events; (+) by family stress; (+) by maternity stress; (+) by early environmental risk	+ by MTHFR	+ (DA, A, NA)				
BDNF	-	+ by stressful life events and by childhood maltreatment	(+) by *CRHR1*			+ (neuronal survival)		
SLC6A2	-	(+) by stressful life events; (+) by living in rural areas		+ (NA)				
DRD3	-			+ (DA)				
GABRA3	-				+ (GABA)			
ACE	-							+ (RAS)
CLOCK	-							+ (circadian rhythm)
DRD4	+ #			+ (DA)				
SLC6A15	**							+ (neutral amino acid transport)
PCLO	**					+ (synaptic zone cytomatrix)		
OLFM4	**					+ (cell adhesion)		
NEGR1	**					+ (axon growth)		
PCDH9	**					+ (cell adhesion in neural tissues)		
TMEM161B-MEF2C	**							+ (DNA binding)
KSR2	**							(+ kinase regulation)
DCC	**					+ (axon guidance)		
SIRT1	**							unknown
LHPP	**							+ (phosphatase)
RBFOX1	*							+ (alternative splicing regulation)
LRFN5	*					+ (neurite outgrowth, cell adhesion)		
CACNA1E	*							+ (calcium channel, skeletal muscle contraction)
CACNA2D1	*							+ (calcium channel)
DRD2	*			+ (DA)				
GRIK5	*				+ (Glu)			
GRM5	*				+ (Glu)			
MEIS2-TMCO5A	*							+ (MEIS2 – transcriptional regulator; TMCO5A - unknown)
MUC13	*							+ (epithelial mucin)
CNR1	(+)	(+) by stressful life events; (+) by childhood maltreatment						+ (endocannabinoid)
GABRA6	(-)	+ by stressful life events			+ (GABA)			
GAL	(+)	(+) by stressful life events and by						+ (galanin signaling)

(continued on next page)

Table 5 (*continued*)

Gene	Depression diagnosis or sum of symptom scores			Biological involvement according to GeneCard's summaries				
	G	GxE	GxG	Mono-amines	Glu/GABA	Neurogenesis/ neuronal projection/synapse/cell-cell contact	Immune functions	Other/not-known
		childhood maltreatment						
GALR1	(-)	(+) by stressful life events and by childhood maltreatment						+ (galanin signaling)
GALR2	(-)	(+) by stressful life events; (-) by childhood maltreatment						+ (galanin signaling)
GALR3	(-)	(-) by stressful life events (+) by childhood maltreatment						+ (galanin signaling)
IL1B	-	(+) by stressful life events and by childhood maltreatment; (+) by chronic interpersonal stress					+ (proinflammatory interleukin)	
IL-6	-	(+) by stressful life events + childhood maltreatment; (+) by chronic interpersonal stress					+ (proinflammatory interleukin)	
FAAH	(-)	(+) by childhood maltreatment						+ (endocannabinoid signaling)
NOS1	(-)	(+) by financial hardship						+ (nitric oxide synthase)
MMP-9	(+)		(+) by *MMP-2*; (+) by *MMP-7*; (+) by *TIMP-2*					+ (extracellular matrix breakdown)
TIMP-2	(+)		(+) by *MMP-2*; (+) by *MMP-7*; (+) by *MMP-9*					+ (extracellular matrix breakdown)
MMP-7	(+) on middle-age depression		(+) by *MMP-2*; (+) by *MMP-9*; (+) by *TIMP-2*					+ (extracellular matrix breakdown)
MMP-2	(-)		(+) by *MMP-7*; (+) by *MMP-9*; (+) by *TIMP-2*					+ (extracellular matrix breakdown)
BCL1	(-)		(+) by *CHRNA4*					+ (cell cycle regulation)
CHRNA4	(-)		(+) by *BCL1*					+ (cholinergic neurotransmission)
HTR2B				+ (5HT)				
GRIA3					+ (Glu)			
GRIK2					+ (Glu)			
5HT2A				+ (5HT)				
ZNF169	(-)		(+/-) by rs4769180					+ (unknown, probably transcription regulation)
rs4769180	(-)		(+/-) by *ZNF169*					+ (no associated gene)
PRSS12	(-)		+ by rs7587468			+ (excitatory synapse protease)		
rs7587468	(-)		+ by *PRSS12*					+ (no associated gene)
TMCC3	(-)		(+/-) by rs9940287					+ (unknown)
rs9940287	(-)		(+/-) by *TMCC3*					+ (no associated gene)
KCNAB1	(-)		+ by rs10843021					+ (potassium channel)
rs10843021	(-)		+ by *KCNAB1*					+ (no associated gene)
PHF21B		+ (in populations exposed to stress)						+ (unknown)
CEP350		* (stress of the previous one year)						+ (centrosome and nuclear hormone receptor regulation)
RGS10		* (stress of the previous one year)						+ (regulator of G-protein signaling)
TAAR6			(+) by *HSPA1A*					+ (putative trace amine receptor
HSPA1A			(+) by *TAAR6*					+ (stress protection)
XKR6								+ (unknown)
MSRA								+ (methionine sulfoxide reduction, repair of oxidized proteins)
LINGO2								+ (unknown, possibly involved in negative regulation of axonal regeneration)
AGBL2								+ (degluatmylation)

CELF4							+ (mRNA editing and translation)
ZC3H7B							+ (unknown)
BAIAP2					+ (neurite growth, adapter protein)		
GNL3							+ (stem cell regulation)
FAM120AOS							+ (unknown)
ANKK1							+ (gene itself not known, but closely linked to DRD2)
RPS6KL1							+ (unknown)
ZNF646							+ (transcription regulation)
CRHR1	+ /(-)	+ / (-) by childhood maltreatment	(+/-) by AVPR1b; (+) by *BDNF*			+ (corticotropin releasing hormone receptor)	
SPPL2C							+ (signal peptide cleaving)
MAPT					+ (axon maintenance)		
L3MBTL2/CHADL							+ (L3MBTL2 – transcriptional regulator; CHADL – chondrocyte differentiation)
LINC00461							+ (unknown)
GBE1							+ (glycogen solubility and accumulation)
MTMR9							+ (unknown)
PCDH15					+ (cell-cell adhesion)		
WSCD2							+ (unknown)
GRIK3				+ (Glu)			
ENAH/SRP9					+ (ENAH -axon guidance)		+ (SRP9 – secretory protein guiding)
PVRL3					+ (synapse maintenance)		
TMEM192/KLHL2/MSMO1						+ (KLHL2 – antigen processing)	+ (unknown – TMEM192; KLHL2 – olygodendrocyte projection development; MSMO1 – cholesterol biosynthesis)
PTPRD					+ (neuron differentiation)		
ELAVL2							+ (neuronal specific RNA binding)
MAGI1					+ (cell-cell junction)		
KATNAL2					+ (microtubule reorganization)		
AVPR1b	(-)		(+/-) by *CRHR1*				+ (arginine vasopressin receptor)
TPH2				+ (5HT)			
CREB1							+ (circadian rhythmicity and transcriptional regulation)
KCNJ6							+ (potassium channel)
FKBP5	-	+ by childhood trauma; (+/-) by stressful life events				+ (glucocorticoid receptor regulation, steroid hormone receptor regulation)	
MTHFD1L							+ (tetrahydrofolate synthesis)
NR3C2							+ (mineralocortocoid receptor)
OXTR							+ (oxytocin receptor)
GSK3β					+ (neuronal polarity and neurite outgrowth)		+ (glycogen homeostasis)
PPARD							+ (myelinizaton, transcriptional regulator)
ARNTL							+ (circadian rhythm regulation)
hTIM							+ (circadian rhythm regulation)
PER3							+ (circadian rhythm regulation)

The table summarizes the results of genetic studies mentioned and referenced in the main text to provide an overview about the ethiopathological genetic variants in depression. Please, note that empty cells mean that the effect was not discussed in the present review. Gene functions were manually searched in GeneCards (retrieved on 23th of March, 2018). See references for individual studies in the text.
(+): evidence of association in a single study, without replication.
(-): investigated with a negative association result in a single study, without replication.
+: evidence of association in meta-analysis / meta-analyses or otherwise replicated studies.
-: investigated with a negative association result in meta-analysis / meta-analyses or other replication studies.
5HT: serotonin; NA: noradrenaline; DA: dopamine; A: adrenaline; Glu: glutamate.
* significant at a genome-wide level.
# insignificant at a genome-wide level.
** significant at a genome-wide level, and replicated either in a replication sample within the same study, or in another GWAS with also a genome-wide significance.

exploring interactions in the future (Ritchie et al., 2017). In light of the results, it may seem tempting to conclude that endless possibilities exist and that even higher-order interactions may represent the future in the genetic research of depression. While they may be, indeed, an interesting opportunity, all the above candidate gene studies can best be regarded as pilot investigations, because of their highly limited sample sizes. Especially higher-order interaction analyses lose rapidly on power, on one hand, because considering the already discussed ExE interaction, very few individuals will be included in a given group of patients. However, because of similar considerations, in case of true non-random distribution of alleles, results may be highly inflated. Additional investigations are required with adequate sample sizes to secure the place for such interactions in the genetic analyses for depression.

5. Unmet needs of currently available antidepressive medications: pharmacogenomics approaches

Contrary to the huge variability of genes with possible pathophysiological roles (see Table 5), all current antidepressant medications influence the monoaminergic systems. This mechanism of action comprises reuptake inhibition, a decrease in monoamine metabolism and manipulation of pre- or postsynaptic receptors. The oldest classes of antidepressants were the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). As a results of their relatively abundant side effects, more selective substances, including selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline/dopamine reuptake inhibitors (NDRIs), noradrenaline reuptake inhibitors (NRIs), in addition to noradrenergic and selective serotonergic antidepressants (NaSSAs) and serotonin antagonist and reuptake inhibitors (SARIs) were developed. While these are more selective towards their molecular targets than TCAs, this selectivity manifests only in better side effect profiles, not better efficacy. And efficacy remains sobering. Only one third of patients experience attenuation of depression symptoms after first treatment and only two thirds of patients show remission after four treatment trials, while altogether 10% of patients do not react to any of the available treatments even after multiple attempts (Crisafulli et al., 2011; Rush et al., 2006; Trivedi et al., 2006). Consequently, quality life years and huge costs go wasted, thus, the need for better therapies, including drugs with novel mechanisms of action and the optimization of current therapeutic approaches, remains enormous.

However, according to completed clinical trials, substances with novel mechanisms of action, like those with ketamine-like NR2B antagonistic, tramadol-like opioidergic, p38 mitogen-activated protein kinase inhibitor or CRHR1 antagonistic properties consistently failed to show long-term therapeutic antidepressant effects in adults (Ibrahim et al., 2012; Richards et al., 2016) (Clinical trials: www.clinicaltrials.gov; NCT00472576; NCT00986479; NCT01482221; NCT02014363). These results suggest that investigators are rather left to optimize current therapeutic approaches than obtaining novel ones in the near future.

One obvious choice for such optimization was the field of pharmacogenetics or the broader field of pharmacogenomics. The term pharmacogenetics marks 'clinically important hereditary variation in response to drugs' as defined by Vogel in 1959 (Vogel, 1959), while pharmacogenomics is the extension of this concept into a genome-scale scope. Variations in medication response may be divided into two main areas. First, inherited variation in the resorption, distribution, metabolism and excretion of drugs called comprehensively pharmacokinetics results in altered drug concentrations at the site of action. Second, variation in the molecules directly implicated in the effects antidepressants may cause altered direct response to these medications and is referred to as inherited variation in the pharmacodynamics of antidepressants. The foremost aim of precision and personalized medicine is the identification of genes involved behind pharmacokinetic and pharmacodynamic variation of treatment response to antidepressants and by selectively matching patients and appropriate therapies based on this information, to improve outcomes.

5.1. Pharmacogenetic studies of pharmacokinetic variation of antidepressants

Among the distribution, metabolism and excretion of antidepressants (ADs) two processes deserve distinguished attention: distribution and metabolism. Distribution is special because antidepressants act in the brain and have to penetrate the blood-brain barrier (BBB). Evidence supports the notion that genetic polymorphisms in the *ABCB1* transporter gene (P-glycoprotein, MDR1), a member of the ATP-binding cassette superfamily of membrane transport proteins (Schinkel et al., 1994), may influence therapeutic efficacy through efflux transport in the BBB and, thereby, lower concentrations of antidepressants in the brain (Peters et al., 2009). Studies have shown influence of single nucleotide polymorphism carrier status on therapeutic outcomes after antidepressant treatment with substrates of the ABCB1 (Breitenstein, Scheuer, & Holsboer, 2014), while such effects with non-substrates of ABCB1 were lacking suggesting true influence (Laika, Leucht, & Steimer, 2006; Mihaljevic Peles, Bozina, Sagud, Rojnic Kuzman, & Lovric, 2008; O'Brien, Clarke, Dinan, Cryan, & Griffin, 2013; Perlis, Fijal, Dharia, Heinloth, & Houston, 2010; Peters et al., 2008). However, some contradictory findings also emerged and point to the need for further studies (Fukui et al., 2007; Gex-Fabry et al., 2008). In summary, *ABCB1* polymorphisms seem to be able to affect therapeutic outcomes of antidepressants.

The cytochrome P450 (CYP) enzymes are hepatic hemeproteins responsible for first phase drug metabolism. Several lipophilic substances, including antidepressants, are metabolized by CYPs. The genes encoding these enzymes are highly polymorphic and in the population people have different metabolizing capabilities, and altered metabolism rates can result in altered drug plasma concentrations (Wolf & Smith, 1999). The metabolism of antidepressants occurs mainly through CYP2D6, CYP2C9, CYP2C19, CYP3A4 and CYP1A2 isoenzymes (Crisafulli et al., 2011; Spina, Santoro, & D'Arrigo, 2008). CYP2D6 metabolizer status can be poor, intermediate, extensive and ultrarapid (PM, IM, EM, UM, respectively) and similar classification is also common for other CYP enzymes. From a pharmacokinetic perspective, drug plasma levels were associated consistently with metabolizer status with PMs and IMs showing higher levels of antidepressants and UMs having lower plasma levels for substrates of CYP2D6, CYP2C9 and CYP2C19 (Altar et al., 2013). However, association with treatment response was less clear cut. Only four from ten studies that investigated antidepressant response in association with CYP2D6 metabolizer status showed significant association while CYP2C19 and CYP2C9 metabolizer status and therapeutic response remained uninvestigated by the review of Altar and colleagues (Altar et al., 2013). Indecisive results were obtained by Müller and colleagues providing mixed results for the association of metabolizer status and treatment response with various antidepressants in their review (Muller, Kekin, Kao, & Brandl, 2013). To specify, a study has shown that paroxetine was less effective in CYP2D6 EMs (Gex-Fabry et al., 2008), while escitalopram and citalopram were more effective in IMs for CYP2D6 and CYP2C19 (Mrazek et al., 2011; Tsai et al., 2010). In summary of the two reviews, overall 62.5% of studies showed association between metabolizer status and antidepressant adverse events in Altar et al. and a modest association between adverse events and metabolizer status of various CYP enzymes was also supported by Müller et al. (Altar et al., 2013; Muller et al., 2013). At the same time, Crisafulli and colleagues conclude that data regarding the importance of CYP genotypes in AD effects remain inconclusive with both positive and negative results (Crisafulli et al., 2011).

The discrepancies may be explained in light of the complexity of the metabolic pathways. Most of the metabolic routes of a given drug are redundant and in case of lower activity of a given CYP enzyme (which may

be through an inherited PM status), other enzymes may contribute more intensively. Therefore, one might argue, a more complex approach that considers all possibly relevant CYP polymorphisms may reveal composite phenotypes in which these polymorphisms could influence therapeutic efficacy. However, even these approaches failed to be consistent. An approach creating a composite phenotype using 44 alleles in *CYP2D6, CYP2C19, CYP1A2, SLC6A4*, and *HTR2A* (the latter two belonging to pharmacodynamics) genes showed an association with clinical response but not with remission rates in a combined population of 258 patients (Altar et al., 2015). Another study indicated that the inclusion of pharmacogenetics based on CYP genes (*CYP2D6, CYP2C9, CYP2C19* and *CYP3A4/5*) could have a positive impact on therapeutic response to antidepressants (Torrellas, Carril, & Cacabelos, 2017). Another systematic review included 2 randomized clinical trials, 5 cohort studies and 6 modelling studies and found that *ABCB1* genotyping and CNSDose based genotyping (based on *ABCB1, ABCC1, CYP2C19, CYP2D6, UGT1A1* genes) could also improve response (Breitenstein et al., 2016; Peterson et al., 2017; Singh, 2015; Winner, Carhart, Altar, Allen, & Dechairo, 2013). At the same time routine screening for these genotypes is not recommended by the authors (Peterson et al., 2017). Despite the separated plasma concentrations and therapeutic efficacies most articles conclude that CYP metabolizer and *ABCB1* status can be an important influencing factor of antidepressant efficacy (Torrellas et al., 2017). Such genotyping, however, is rather valid in case of side effects, where more conclusive results are found, though not without contradictions (Altar et al., 2013; Crisafulli et al., 2011; Horstmann & Binder, 2009). As a summary, while *ABCB1* polymorphisms seem to consistently influence antidepressant efficacy, CYP enzymes and metabolizer statuses require more complex approaches and their roles remain unconvincing.

5.2. Pharmacogenetics of antidepressant pharmacodynamics

Most pharmacogenetics studies on antidepressant treatment response investigated monoaminergic candidate genes with the highest attention to the serotoninergic system as a result of the proven mechanism of action of antidepressants. Among serotonergic genes, *SLC6A4* is one of the most widely studied candidate genes of antidepressant treatment response. *5HTTLPR* besides having two (short and long) alleles (Heils et al., 1996), can also be regarded as a triallelic polymorphism due to the presence of SNP rs25531 in the region (Praschak-Rieder et al., 2007), with possible impact on treatment outcome via increased gene expression in A allele carriers (Manoharan, Shewade, Rajkumar, & Adithan, 2016). Meta-analyses showed better antidepressant treatment response and remission rates in L and L(A) carriers (Porcelli, Fabbri, & Serretti, 2012; Serretti, Kato, De Ronchi, & Kinoshita, 2007). However, findings are divergent with one meta-analysis and several previous studies showing no association between *5HTTLPR* and treatment response (Andre et al., 2015; Dogan et al., 2008; Perlis, Fijal, et al., 2010; Poland et al., 2013; Taylor, Sen, & Bhagwagar, 2010). Another polymorphism, a variable number tandem repeat (VNTR) in intron 2 of *SLC6A4* implicates enhanced expression in individuals with longer repeats (Murphy & Moya, 2011) and meta-analyses also confirmed better response to antidepressant treatment mostly in Asian patients with the 12/12 genotype (Kato & Serretti, 2010; Niitsu, Fabbri, Bentini, & Serretti, 2013). However, reported results are puzzling as a number of studies reported contradictory results (Dogan et al., 2008; Ito et al., 2002; Smits et al., 2008; Weinshilboum, 2009; Wilkie et al., 2008).

Besides *5HTTLPR*, serotonin receptor-encoding genes were also extensively studied, especially *HTR1A* and *HTR2A*. Although a promoter polymorphism in *HTR1A* gene has been associated initially with antidepressant treatment response (Hong, Chen, Yu, & Tsai, 2006; Villafuerte et al., 2009; Yu, Tsai, Liou, Hong, & Chen, 2006), recent studies contradict these findings (Antypa et al., 2013; Basu, Chadda, Sood, Kaur, & Kukreti, 2015; Dong et al., 2016; Kato et al., 2009; Serretti et al., 2013; Zhao et al., 2012). Moreover, three meta-analyses found no significant effect on antidepressant side effects or treatment response (Kato & Serretti, 2010; Niitsu et al., 2013; Zhao et al., 2012). Concerning other less widely studied polymorphisms in the *HTR1A* gene findings are similarly less decisive (Chang et al., 2014; Kato et al., 2009; Yu et al., 2006). The A allele of the intronic polymorphism rs7997012 in *HTR2A* has been associated with better outcome during antidepressant treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (McMahon et al., 2006). Consequently, the gene has been widely investigated but, again, with heterogeneous results. Despite some supporting evidence (Kishi et al., 2010; Peters, Reus, & Hamilton, 2009), a number of studies reported an inverse allelic association (Antypa et al., 2013; Lucae et al., 2010) or no association (Hong et al., 2006; Illi et al., 2009; Perlis et al., 2009; Rhee-Hun, Myoung-Jin, Jong-Woo, Sang-Woo, & Min-Soo, 2007; Sato et al., 2002; Serretti et al., 2013; Staeker, Leucht, Laika, & Steimer, 2014; Zhi et al., 2011) with treatment response, whereas meta-analyses reported mixed results (Lin, Jiang, Kan, & Chu, 2014; Niitsu et al., 2013). Other polymorphisms in *HTR2A*, including rs6311 (Choi, Kang, Ham, Jeong, & Lee, 2005; Kato et al., 2006; Kishi et al., 2010) and rs6313 (Kautzky et al., 2015; Kishi et al., 2010; Noordam et al., 2015) were also associated with antidepressant response, but meta-analyses (Kato & Serretti, 2010; Lin et al., 2014; Niitsu et al., 2013) and a plethora of previous studies (Basu et al., 2015; Dong et al., 2016; Hong et al., 2006; Illi et al., 2009; Qesseveur et al., 2016; Rhee-Hun et al., 2007; Zhi et al., 2011) showed mixed or contradictory results. The influence of other variants within the gene remains similarly controversial through the lack of wide-scale replications (Kishi et al., 2010; Lucae et al., 2010; Qesseveur et al., 2016; Tiwari et al., 2013; Uher et al., 2009).

Three metabolic enzymes, MAOA, COMT, and TPH were investigated for their roles in antidepressant response. The VNTR in the promoter region of *MAOA* has been associated with better treatment outcome in individuals carrying the short form (Tzeng, Chien, Lung, & Yang, 2009) but results were mostly restricted to female patients (Domschke et al., 2008; Yu et al., 2005). Regarding other variants within the *MAOA* gene, including rs1465108, rs6323 and rs1799835, findings are not clear since studies reported either no association (Leuchter, McCracken, Hunter, Cook, & Alpert, 2009; Peters, Reus, & Hamilton, 2009) or associations only in females (Tadic et al., 2007). The *COMT* rs4680 polymorphism has been suggested to influence antidepressant treatment response but there is a big discrepancy regarding which genotype is more advantageous. First studies reported the Val allele to be associated with better outcome (Arias et al., 2006; Szegedi et al., 2005), later, however, various studies reported opposite allelic association (Baune et al., 2007; Benedetti et al., 2010; Benedetti, Colombo, Pirovano, Marino, & Smeraldi, 2009; Spronk, Arns, Barnett, Cooper, & Gordon, 2011; Tsai et al., 2009; Yoshida et al., 2008), or even no significant association with treatment response (Kautzky et al., 2015; Kocabas et al., 2010; Leuchter et al., 2009; Serretti et al., 2013; Taranu et al., 2017), with a meta-analysis also failing to confirm any impact (Niitsu et al., 2013). From the two isoforms of TPH, attention focused on a polymorphism within *TPH1* (Ham et al., 2007; Viikki et al., 2010). Nevertheless, most studies on rs1800532 could not confirm the role of this polymorphism in antidepressant efficacy (Ham et al., 2005; Illi et al., 2009; Kato et al., 2007; Kim, Chang, Won, Ham, & Lee, 2014; Uher et al., 2009; Wang et al., 2011) and meta-analyses again failed to provide decisive conclusions (Kato & Serretti, 2010; Niitsu et al., 2013; Zhao, Huang, Li, Han, & Kan, 2015).

Genes influencing glutamatergic neurotransmission have also been implicated in therapeutic response to antidepressants. An association between rs1954787 in ionotropic glutamate kainate 4 receptor (*GRIK4*) gene and citalopram response have been reported in the STAR*D study (Paddock et al., 2007). Despite some negative findings (Horstmann et al., 2010; Perlis, Fijal, et al., 2010; Serretti et al., 2012), subsequent meta-analysis confirmed the relevance of rs1954787 in antidepressant treatment outcome (Kawaguchi & Glatt, 2014), furthermore, some studies showed associations with other *GRIK4* polymorphisms too

(Horstmann et al., 2010; Milanesi et al., 2015), but further studies are still needed.

The most investigated polymorphism of *BDNF* (brain derived neurotrophic factor), involved in neuroplasticity and showing lower levels in depressed patients and an increase following antidepressive or electroconvulsive therapy (Brunoni, Lopes, & Fregni, 2008), is rs6265 (Val66Met). Meta-analyses showed the involvement of rs6265 in antidepressant treatment response and remission (Kato & Serretti, 2010; Niitsu et al., 2013; Yan et al., 2014) and some recent studies supported these results (Colle et al., 2015; Murphy Jr. et al., 2013). Despite these promising findings, numerous studies reported again no association (Katsuki et al., 2012; Li et al., 2013; Matsumoto et al., 2014; Musil et al., 2013; Yoshimura et al., 2011). One study found another SNP within the *BDNF* gene to be associated with treatment response, however, this result could not be replicated in other samples (Domschke et al., 2010).

In the gene encoding the FK506-Binding Protein 51 (*FKBP5*), involved in the modulation of glucocorticoid receptor (GC) sensitivity and considered as a regulator of stress response (Binder, 2009), three polymorphisms, rs1360780, rs3800373 and rs4713916 have so far been associated with antidepressant treatment response (Binder et al., 2004) and findings are confirmed by meta-analyses (Niitsu et al., 2013; Zou et al., 2010). Still, unequivocal conclusions are again lacking because various studies found no association (Perlis et al., 2009; Sarginson, Lazzeroni, Ryan, Schatzberg, & Murphy Jr., 2010; Uher et al., 2009). All these results provide an evidence for the complexity and contradictions in the field.

5.3. Pharmacogenomics of antidepressants: moving from candidate gene studies to GWASs

Since candidate gene studies remain heterogeneous, the recent surge in available genotyping data and methodological development fostered the extension of association studies from individual genes to the genome-wide level also in the field of efficacy of antidepressants. Genome-wide association studies (GWASs) associating single nucleotide polymorphisms in the whole genome with antidepressant treatment response represent a hypothesis-free approach to the problem and could theoretically reveal polymorphisms which were ignored so far because of lack of evidence.

In line with pharmacokinetic results from candidate gene studies, Ji et al. provided evidence for association of escitalopram plasma levels with an SNP in or near the *CYP2C19* gene and a metabolite (S-didesmethylcitalopram) level with SNPs near the *CYP2D6* locus (Ji et al., 2014). From a pharmacodynamics perspective a recent GWAS study using rare variants could demonstrate a genome-wide significant hit in the *integrin α9* gene that replicated in one but not the other replication control using GENDEP and STAR*D populations (Fabbri et al., 2018). In the 23andMe cohort, another SNP in an intergenic region between the *GPRIN3* and *SNCA* genes was demonstrated to be significantly associated with treatment response after bupropion treatment, however, no genome-wide association could be demonstrated for treatment resistant vs non-treatment resistant depression, citalopram or SSRI response (Li, Tian, Seabrook, Drevets, & Narayan, 2016). Antidepressant response was associated with the *CTNNA3* gene without genome-wide significant individual SNP hits in a small Korean sample (Cocchi et al., 2016), while in another Korean sample SSRI response was associated with two polymorphisms in the intergenic region of the *AUTS2* gene (Myung et al., 2015). Gupta et al. demonstrated associations with an indirect measure of citalopram/escitalopram efficacy, serotonin plasma concentrations, in *TSPAN5* and *ERICH3* gene polymorphisms in a small sample, in the only functionally validated study, where altered *TSPAN5* expression caused changes in serotonergic gene expression in cell lines (Gupta et al., 2016). The international SSRI Pharmacogenomics Consortium could identify an *NRG1* polymorphism influencing SSRI response (Biernacka et al., 2015), which, however, remained non-significant after the necessary correction for multiple hypothesis testing. A small sample of Mexican Americans showed exome-wide association with remission after desipramine or fluoxetine treatment in a SNP harboring an epigenetic methylation site in the vicinity of *TBX18*, *NT5E*, and *SNX14* genes (Wong et al., 2014). A SNP near the *NEDD4L* gene was demonstrated to be associated with antidepressant response using the STAR*D population, but in Caucasians results became unconvincing (Antypa, Drago, & Serretti, 2014). No SNP reached GWS in an investigation of sustained vs non-sustained response, but KEGG pathway long-term potentiation remained significant after correction (Hunter et al., 2013). Another study also failed to demonstrate significantly associated SNPs with SSRI or NRI treatment response (Tansey et al., 2012). Citalopram response or remission was similarly not associated with genome-wide significance, while below the genome-wide significance threshold the most suggestive SNPs were in *UBE3C*, *BMP7*, and *RORA* genes (Garriock et al., 2010). In the GENDEP project, outcome after nortriptyline and escitalopram treatment was associated with SNPs in the *uronyl 2-sulphotransferase* gene and *IL-11*, respectively (Uher et al., 2010). Genes *CDH17, EPHB1, AK090788* and *PDE10A* were also suggested to be involved in response to antidepressants, but even selected multilocus analysis failed to demonstrate consistent results in the same study (Ising et al., 2009). And finally, the meta-analysis of the largest genetic databases on antidepressant response (STAR*D, GENDEP, MARS) could not provide results despite the larger sample sizes (Gendep Investigators. et al., 2013).

GWAS investigation of side-effects also provided heterogeneous results. Citalopram-induced side effects were associated with two SNPs: one in the *EMID2* gene with vision/hearing loss, the other in a region without genes with the overall side effect burden (Adkins et al., 2012). SNPs in the *MDGA2* gene showed relevance in SSRI or SNRI-induced sexual dysfunction in a small Japanese sample (Kurose et al., 2012), while bupropion-induced sexual dysfunction was associated with SNPs in the *SACM1L* gene in the STAR*D population, however, with non-convincing significance (Clark et al., 2012). Antidepressant-emergent suicidal ideation showed the most significant association with a SNP in *ANXA2* gene, which, however, could not reach GWS in a sample of 397 (Menke et al., 2012), while in the GENDEP project a SNP in *GDA* was associated with suicidal ideation after medication with different antidepressants and two, one within *KCNIP4* and one near *ELP3* was associated after citalopram treatment (Perroud et al., 2012). Roles for polymorphisms of *PAPLN* and *IL28RA* genes were also suggested in citalopram-induced suicidal ideation (Laje et al., 2009). Despite lack of reliable results, genes and environmental effects which play a role in the pathogenesis of depression may play a role also in differences of response during treatment (Keers & Uher, 2012), and if the impact of such genetic variants in depression is a function of exposure to environmental influences then treatment may also be influenced by GxE interactions.

5.4. GxE interactions in the pharmacotherapy of depression

Previous studies have reported that environmental factors may predict response to antidepressant treatment (Keers & Uher, 2012). Earlier results from family studies suggested that there is a GxE interaction influencing response to antidepressants (Mandelli et al., 2009). However, except for a few positive results there is a remarkable lack of research concerning this topic. Depression developing following serious environmental stress events was reported to respond better to psychotherapy or placebo, while depression developing rather independently of environmental triggers to antidepressants or electroconvulsive therapy, and better to TCAs than SSRIs (Andersen et al., 1990). Results of the GENDEP study have demonstrated that the effect of life events on antidepressant treatment efficacy varies by medication, with exposure to recent stressors predicting better escitalopram response, but no effect on nortriptyline response (Keers et al., 2010). Furthermore, considering GxE effects, in *5HTTLPR* SS carriers a worse response was detected to fluoxetine and escitalopram but only after stress exposure, and no such

interaction effect was observable for nortriptyline (Keers et al., 2011; Mandelli et al., 2009). Altogether, while only a handful of genetic variants, mainly *5HTTLPR, BDNF, CRHR1, FKBP5* or *NR3C1* have been implicated to influence response to antidepressant pharmacotherapy (Keers & Uher, 2012), and the effect of these variants could not be supported in meta-analyses or in the STAR*D study (Mandelli et al., 2009), studies focusing on the pharmacogenetics of these polymorphisms have not considered the effects of life events, stressors or environmental influences. Generally, besides *5HTTLPR*, only in case of *CRHR1* and *FKBP5* have there been significant GxE interactions reported concerning efficacy of antidepressant treatment (Keers & Uher, 2012).

5.5. Imaging genetics of antidepressant efficacy

Considering the lack of significant genetic associations of antidepressant efficacy, and the above problems, instead of a direct application of genetics onto therapeutic response, the use of "surrogate markers", at least, until the etiopathology of depression and causal carriers of antidepressant response are found, can be pursued. For the problem that we also lack biomarkers, imaging genetics can be a decent candidate solution. Imaging depression genetics can be defined as applying neuroimaging methods to explore intermediate phenotypes between genetic variations and disease through which we may be able to explore the connection between genetic variants and depression at a neural level (Hariri & Weinberger, 2003). These intermediate phenotypes in depression are represented by functional and structural alterations in emotional processing-related brain regions including amygdala hyperreactivity, decreased functional connectivity between the amygdala and anterior cingulate cortex, and structural changes in the hippocampus and anterior cingulate cortex (Scharinger, Rabl, Pezawas, & Kasper, 2011). Previous meta-analyses showed that antidepressant treatment tends to normalize altered activations in these regions (Delaveau et al., 2011; Fitzgerald, 2013).

Two meta-analyses showed an association between *5HTTLPR* and amygdala activation to negative emotional stimuli (Munafò, Brown, & Hariri, 2008; Murphy & Moya, 2011). Regarding antidepressant treatment, Ramasubbu and colleagues have recently shown that brain activation changes to negative emotional faces after antidepressant therapy are related to *5HTTLPR* genotype (Ramasubbu et al., 2016). L-allele homozygotes showed decreased amygdala activation after one week and increased activation after eight weeks of citalopram therapy compared to baseline. In addition, quetiapine treatment led to decreased amygdala activation at week 1 and week 2 in S/L carriers. In a single-photon emission-computed tomography (SPECT) study, a positive relationship was observed in depressed patients with L/L genotype between reduction of Hamilton Depression Rating Scale (HDRS)-17 score and serotonin transporter occupancy in the midbrain after 6 weeks of paroxetine treatment (Ruhe et al., 2009). Three studies investigating the effect of a single dose of citalopram and *5HTTLPR* genotypes on brain activation and functional connectivity in healthy subjects reported that amygdala connectivity (Outhred et al., 2016) and activation (Outhred et al., 2014) during emotion processing correlated with the number of L alleles, while increased amygdala responsiveness to fearful faces was found in L/L carriers (Ma et al., 2015). Besides the widely investigated *5HTTLPR*, other polymorphisms including variants of *IL-1B* (Baune et al., 2010), *NPY* (Domschke et al., 2010) and *CNR1* (Domschke et al., 2008) genes were also associated with remission and brain activation during face processing in depression. In addition, studies aiming to explore genetic variants-related anatomical changes to predict treatment response in depression reported that genetic polymorphisms including *5HTTLPR* (Tatham, Hall, Clark, Foster, & Ramasubbu, 2017), *BDNF* (Tatham et al., 2017) and *FKBP5* (Cardoner et al., 2013; Zobel et al., 2010) may influence brain structures-associated treatment outcome.

Imaging genetics is a promising new method to explore the complex link between genes and clinical phenotypes such as depression or antidepressant efficacy. Findings showed that even with small sample sizes the impact of genetic polymorphisms on brain structure and function related to treatment response may be more significant than on treatment response itself (Lett, Walter, & Brandl, 2016). However, in spite of some consistent results concerning *5HTTLPR*, it is hard to draw a conclusion. Multiple studies employed region of interest analysis instead of whole brain analysis. Moreover, every study used different designs and statistical analysis methods and thresholds. In order to make imaging genetics findings more comparable and to be able to draw clear conclusions from such studies more uniform study designs are required.

5.6. Summary of the pharmacogenetics and pharmacogenomics of antidepressants

The above results provide an overview about the problems in the pharmacogenetics and pharmacogenomics of antidepressants. There exist, maybe with the exception of *ABCB1* functional polymorphisms, no unequivocal results about which polymorphisms in which genes influence response to antidepressants or their side effects.

Among the pharmacokinetic genetic differences, polymorphisms within the *ABCB1* seem to consistently influence antidepressants that are transported by the protein. While CYP enzyme-based metabolizer status shows a well-established connection with plasma levels of antidepressants, this does not manifest in a clear influence on side effects and, even less so, on therapeutic efficacy. Pharmacogenetic studies on pharmacodynamic markers are even less consistent. Most of the investigated genes belong to the serotonergic system, despite the fact that most current antidepressants may also have other mechanisms of action and that they may differ substantially from each other as demonstrated in e.g. expression studies (Petschner et al., 2016; Tamasi et al., 2014). Apart from serotonergic studies, however, *BDNF* and *FKBP5* seem to be the most plausible candidates according to recent theories for depression pathophysiology, however, they also fail to replicate, which suggests that polymorphisms within these genes do not consistently contribute to antidepressant efficacy. The failure of candidate gene studies in the field fostered research on the genome-wide scale with GWASs, to find novel candidates in the background. But these studies failed to provide targets that could be replicated in functional studies or which could be bound to the known pathophysiology of depression, except for citalopram and *TSPAN5,* and a demonstration of an association between *CYP2D6* and *CYP2C19* and plasma levels, a result already known from candidate gene studies.

All these contradictory results possibly reflect that mechanisms of ADs still remain unclear and that we simply lack a unifying concept about how depression, its correlates and subtypes evolve and develop in an individual. The failure of novel drugs to exert effects on depression reflects exactly that. We can most probably develop novel therapeutics after we have solved at least most, if not all of the problems raised in the present review. That supports the notion that basic research in depression cannot be substituted by applied research and we cannot jump straight into therapeutic development without risking failures and huge costs.

6. A foreboding paradigm shift in the understanding of the etiopathogenetics of depression and approaching its treatment?

As we have seen so far, the past several decades of research concerning depression, its etiopathogenetic background, as well as its treatment revealed more about what we don't understand than about the complex architecture in the background of this highly prevalent and debilitating disorder and its therapy. By discovering how the majority of genes underpinning depression does not exert a main effect but may have a varying impact in interaction with different types, severity and timing of stressors we had to make yet another step towards conceptualizing depression as a stress-related disorder. It also appears

that depression is a much more heterogeneous disorder than how we previously saw it simply based on the wide range of different symptomatic manifestations. The role that different types of previous stress plays in the manifestation of depression should probably be one of the possible bases for differentiating its main distinct subtypes, with the mediating role of different genetic and neurobiological pathways in more and less stress-related forms of depression. This may give rise to the need to develop a whole new conceptual framework, approach and reclassification of depressive disorders and its subtypes, building more on the differences of these subtypes rather than the similarities between them.

Similarly, a paradigm shift seems necessary and even likely in the approach to, development of and also clinical study of new and already existing antidepressive medications. As genetics and environmental influences and neurochemical modulation appear to be different in more and less stress-related forms of depression, a better distinction between such depressive subtypes would be needed in clinical trials to avoid masking of the existing efficacy of antidepressants due to heterogeneous samples. Furthermore, stress and environmental influences should be considered not only as etiological factors of depression, but through interacting with genes involved in treatment efficacy and side effects, the influence of such stressors should also be considered during antidepressant trials and development. Thus giving more emphasis to stress and gene x environment interactions both in the development of and response to treatment in depression, we will likely have to reformulate how we think about the development and treatment of this illness.

7. Concluding remarks

From all the above study results and considerations regarding the genetic background of depression and antidepressant therapy four major conclusions could be drawn, which are relevant in two translational directions, namely new drug targets and personalized therapy (patient group identification for selection of specific treatments).

First of all, when considering the major biological pathways of GWS genes implicated in depression or its pharmacotherapy (according to GeneCards), these, with a few exceptions, belong to neurogenesis, neuronal projection or synapse, cell contact (e.g., *OLFM4, NEGR1, PCLO, DCC, PCDH9*), Ca^{2+} channels (*CACNA1E, CACNA2D1*), DNA binding or transcription (*TMEM161B-MEF2C, MEIS2-TMCO5A*), meaning that their effects are probably several steps away from the development of the disorder, probably not specific for depression, and will be difficult to use as real drug targets. Lack of specificity in the therapeutic effect and possible serious side effects could thus be the most important factors. Surprises, however, are possible, such as in the case of kinase inhibitors in oncology, where actual side-effects were not as strong as previously predicted, and thus drug development became possible. Since polymorphism of the kinase regulator gene *KSR2* has been identified as a GWS finding, certain kinase related developments could be possible.

Second, genes of target proteins of currently used antidepressants (e.g., those of the serotonin or noradrenaline transporter, or *MAOA*) do not show up in GWAS studies, thus, based on genomic studies no main effect of these proteins on depression could be expected. Rather, their effect could be therapeutic in stress-induced depression. Such clinical evidence is, however, lacking, suggesting that either genes emerging in GxE studies could be relevant targets in general and not only for reactive depression, or the negative bias and increased stress reaction in depression could, indeed, fade the border between endogenous and reactive depression when it comes to the question of effective antidepressant drug target proteins.

Third, most candidate genes that came up and were proven in GxE interactions in depression (e.g., *CRHR1, FKBP5, SLC6A4, SLC6A2, CNR1, GABRA6, IL1B, IL-6, FAAH, HTR1A*) could be connected directly to the activity of the HPA-axis. Thus, these risk alleles and their combinations could help to identify groups with altered stress sensitivity and anxiety-related phenotypes. Furthermore, they may point to possible new drug targets.

Finally, nuclear gene variations affecting mitochondrial functions can contribute to attenuated cognitive performance, and secondarily, to depression. It has been shown that if mitochondrial processes are affected, cognitive symptoms are more prominent in depression. These cognitive symptoms (e.g., rumination) in mood disorders remain often overlooked, despite the fact that they impose a serious burden on patients significantly compromising quality of life and impairing daily function in all domains. Risk polymorphisms may help to identify this subgroup of depression. Furthermore, they may point to possible new target proteins for antidepressant development in this specific group. Their effect is not dependent on stress exposure, therefore, patients with these risk alleles and altered mitochondrial functions are more frequently present among patients without any serious stress preceding the development of the disorder.

Conflict of interest statement

The authors report no conflict of interest in relation to the current paper.

Acknowledgement

This work was supported by NEWMOOD (LSHM-CT-2004-503474); TAMOP-4.2.1.B-09/1/KMR-2010-0001; KTIA_13_NAP-A-II/14 and 2017-1.2.1-NKP-2017-00002 (Hungarian Brain Research Program), KTIA_NAP_13-1-2013-0001 (National Development Agency); KTIA_NAP_13-2-2015-0001 (MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group: Hungarian Academy of Sciences, Hungarian National Development Agency, Semmelweis University and the Hungarian Brain Research Program); MTA-SE Neuropsychopharmacology and Neurochemistry Research Group (Hungarian Academy of Sciences); OTKA 119866; the ÚNKP-16-3, ÚNKP-17-3-III-SE-2, ÚNKP-17-3-IV-SE-3 and ÚNKP-17-4-I-SE-8 by the New National Excellence Program of the Ministry of Human Capacities; and by the BME-Biotechnology FIKP grant of EMMI (BME FIKP-BIO). Xenia Gonda is recipient of the Janos Bolyai Research Fellowship of the Hungarian Academy of Sciences.

References

Adkins, D.E., Clark, S.L., Aberg, K., Hettema, J.M., Bukszar, J., McClay, J.L., et al. (2012). Genome-wide pharmacogenomic study of citalopram-induced side effects in STAR*D. *Transl Psychiatry 2*, e129.

Altar, C.A., Hornberger, J., Shewade, A., Cruz, V., Garrison, J., & Mrazek, D. (2013). Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. *Int Rev Psychiatry 25*, 509–533.

Altar, C.A., Carhart, J., Allen, J.D., Hall-Flavin, D., Winner, J., & Dechairo, B. (2015). Clinical Utility of Combinatorial Pharmacogenomics-Guided Antidepressant Therapy: Evidence from Three Clinical Studies. *Mol Neuropsychiatry 1*, 145–155.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders : DSM-5* (5th ed.). Washington, D.C.: American Psychiatric Association.

Amin, N., Jovanova, O., Adams, H.H., Dehghan, A., Kavousi, M., Vernooij, M.W., et al. (2017). Exome-sequencing in a large population-based study reveals a rare Asn396Ser variant in the LIPG gene associated with depressive symptoms. *Mol Psychiatry 22*, 537–543.

Andersen, B., Brosen, K., Christensen, P., Lolk, A., Kragh-Sorensen, P., Nielsen, S., et al. (1990). Paroxetine - a Selective Serotonin Reuptake Inhibitor Showing Better Tolerance, but Weaker Antidepressant Effect Than Clomipramine in a Controlled Multicenter Study. *J Affect Disord 18*, 289–299.

Andre, K., Kampman, O., Illi, A., Viikki, M., Setala-Soikkeli, E., Mononen, N., et al. (2015). SERT and NET polymorphisms, temperament and antidepressant response. *Nordic Journal of Psychiatry 69*, 531–538.

Antypa, N., Calati, R., Souery, D., Pellegrini, S., Sentissi, O., Amital, D., et al. (2013). Variation in the HTR1A and HTR2A genes and social adjustment in depressed patients. *Journal of Affective Disorders 150*, 649–652.

Antypa, N., Drago, A., & Serretti, A. (2014). Genomewide interaction and enrichment analysis on antidepressant response. *Psychol Med 44*, 753–765.

Arias, B., Serretti, A., Lorenzi, C., Gastó, C., Catalán, R., & Fañanás, L. (2006). Analysis of COMT gene (Val 158 Met polymorphism) in the clinical response to SSRIs in depressive patients of European origin. *Journal of Affective Disorders 90*, 251–256.

Bagdy, G., Juhasz, G., & Gonda, X. (2012). A new clinical evidence-based gene-environment interaction model of depression. *Neuropsychopharmacol Hung 14*, 213–220.

Basu, A., Chadda, R.K., Sood, M., Kaur, H., & Kukreti, R. (2015). Association of serotonin transporter (SLC6A4) & receptor (5HTR1A, 5HTR2A) polymorphisms with response to treatment with escitalopram in patients with major depressive disorder: A preliminary study. *The Indian Journal of Medical Research 142*, 40–45.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol Psychiatry 21*, 642–649.

Baune, B.T., Hohoff, C., Berger, K., Neumann, A., Mortensen, S., Roehrs, T., et al. (2007). Association of the COMT val158met Variant with Antidepressant Treatment Response in Major Depression. *Neuropsychopharmacology 33*, 924.

Baune, B.T., Dannlowski, U., Domschke, K., Janssen, D.G.A., Jordan, M.A., Ohrmann, P., et al. (2010). The Interleukin 1 Beta (IL1B) Gene Is Associated with Failure to Achieve Remission and Impaired Emotion Processing in Major Depression. *Biol Psychiatry 67*, 543–549.

Benedetti, F., Colombo, C., Pirovano, A., Marino, E., & Smeraldi, E. (2009). The catechol-O-methyltransferase Val(108/158)Met polymorphism affects antidepressant response to paroxetine in a naturalistic setting. *Psychopharmacology (Berl) 203*, 155–160.

Benedetti, F., Dallaspezia, S., Colombo, C., Lorenzi, C., Pirovano, A., & Smeraldi, E. (2010). Effect of catechol-O-methyltransferase Val(108/158)Met polymorphism on antidepressant efficacy of fluvoxamine. *European Psychiatry 25*, 476–478.

Ben-Efraim, Y.J., Wasserman, D., Wasserman, J., & Sokolowski, M. (2013). Family-based study of AVPR1B association and interaction with stressful life events on depression and anxiety in suicide attempts. *Neuropsychopharmacology 38*, 1504–1511.

Berrios, G.E., Wagle, A.C., Markova, I.S., Wagle, S.A., Rosser, A., & Hodges, J.R. (2002). Psychiatric symptoms in neurologically asymptomatic Huntington's disease gene carriers: a comparison with gene negative at risk subjects. *Acta Psychiatr Scand 105*, 224–230.

Biernacka, J.M., Sangkuhl, K., Jenkins, G., Whaley, R.M., Barman, P., Batzler, A., et al. (2015). The International SSRI Pharmacogenomics Consortium (ISPC): a genome-wide association study of antidepressant treatment response. *Transl Psychiatry 5*, e553.

Binder, E.B. (2009). The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology 34*, S186–S195.

Binder, E.B., Salyakina, D., Lichtner, P., Wochnik, G.M., Ising, M., Pütz, B., et al. (2004). Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet 36*, 1319.

Bleys, D., Luyten, P., Soenens, B., & Claes, S. (2018). Gene-environment interactions between stress and 5-HTTLPR in depression: A meta-analytic update. *Journal of Affective Disorders 226*, 339–345.

Bobinska, K., Szemraj, J., Czarny, P., & Galecki, P. (2016). Role of MMP-2, MMP-7, MMP-9 and TIMP-2 in the development of recurrent depressive disorder. *J Affect Disord 205*, 119–129.

Bosker, F.J., Hartman, C.A., Nolte, I.M., Prins, B.P., Terpstra, P., Posthuma, D., et al. (2011). Poor replication of candidate genes for major depressive disorder using genome-wide association data. *Mol Psychiatry 16*, 516–532.

Breitenstein, B., Scheuer, S., & Holsboer, F. (2014). Are there meaningful biomarkers of treatment response for depression? *Drug Discov Today 19*, 539–561.

Breitenstein, B., Scheuer, S., Bruckl, T.M., Meyer, J., Ising, M., Uhr, M., et al. (2016). Association of ABCB1 gene variants, plasma antidepressant concentration, and treatment response: Results from a randomized clinical study. *J Psychiatr Res 73*, 86–95.

Brown, G.W., Bifulco, A., & Harris, T.O. (1987). Life events, vulnerability and onset of depression: some refinements. *Br J Psychiatry 150*, 30–42.

Brunoni, A.R., Lopes, M., & Fregni, F. (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *The international journal of neuropsychopharmacology 11*, 1169–1180.

Bukh, J.D., Bock, C., Vinberg, M., Werge, T., Gether, U., & Vedel Kessing, L. (2009). Interaction between genetic polymorphisms and stressful life events in first episode depression. *J Affect Disord 119*, 107–115.

Cai, N., Bigdeli, T.B., Kretzschmar, W., Li, Y.H., Liang, J.Q., Song, L., et al. (2015). Sparse whole-genome sequencing identifies two loci for major depressive disorder. *Nature 523* 588-+.

Cardoner, N., Soria, V., Gratacòs, M., Hernández-Ribas, R., Pujol, J., López-Solà, M., et al. (2013). VAL66MET BDNF genotypes in melancholic depression: effects on brain structure and treatment outcome. *Depression and Anxiety 30*, 225–233.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., et al. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science 301*, 386–389.

Chang, H.S., Lee, H.Y., Cha, J.H., Won, E.S., Ham, B.J., Kim, B., et al. (2014). Interaction of 5-HTT and HTR1A gene polymorphisms in treatment responses to mirtazapine in patients with major depressive disorder. *Journal of clinical psychopharmacology 34*, 446–454.

Chen, R., Shi, L., Hakenberg, J., Naughton, B., Sklar, P., Zhang, J., et al. (2016). Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. *Nat Biotechnol 34*, 531–538.

Choi, M.J., Kang, R.H., Ham, B.J., Jeong, H.Y., & Lee, M.S. (2005). Serotonin Receptor 2A Gene Polymorphism (–1438A/G) and Short-Term Treatment Response to Citalopram. *Neuropsychobiology 52*, 155–162.

Clark, S.L., Adkins, D.E., Aberg, K., Hettema, J.M., McClay, J.L., Souza, R.P., et al. (2012). Pharmacogenomic study of side-effects for antidepressant treatment options in STAR*D. *Psychol Med 42*, 1151–1162.

Clarke, H., Flint, J., Attwood, A.S., & Munafo, M.R. (2010). Association of the 5- HTTLPR genotype and unipolar depression: a meta-analysis. *Psychol Med 40*, 1767–1778.

Cocchi, E., Fabbri, C., Han, C., Lee, S.J., Patkar, A.A., Masand, P.S., et al. (2016). Genome-wide association study of antidepressant response: involvement of the inorganic cation transmembrane transporter activity pathway. *BMC Psychiatry 16*, 106.

Coleman, J.R., Euesden, J., Patel, H., Folarin, A.A., Newhouse, S., & Breen, G. (2016). Quality control, imputation and analysis of genome-wide genotyping data from the Illumina HumanCoreExome microarray. *Brief Funct Genomics 15*, 298–304.

Colle, R., Gressier, F., Verstuyft, C., Deflesselle, E., Lépine, J. -P., Ferreri, F., et al. (2015). Brain-derived neurotrophic factor Val66Met polymorphism and 6-month antidepressant remission in depressed Caucasian patients. *Journal of Affective Disorders 175*, 233–240.

Coppen, A. (1967). The biochemistry of affective disorders. *Br J Psychiatry 113*, 1237–1264.

Crisafulli, C., Fabbri, C., Porcelli, S., Drago, A., Spina, E., De Ronchi, D., et al. (2011). Pharmacogenetics of antidepressants. *Front Pharmacol 2*, 6.

Cross-Disorder Group of the Psychiatric Genomics, Lee, C., Ripke, S.H., Neale, S., Faraone, B. M., Purcell, S.V., et al. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet 45*, 984–994.

Cukier, H.N., Dueker, N.D., Slifer, S.H., Lee, J.M., Whitehead, P.L., Lalanne, E., et al. (2014). Exome sequencing of extended families with autism reveals genes shared across neurodevelopmental and neuropsychiatric disorders. *Mol Autism 5*, 1.

Culverhouse, R., Suarez, B.K., Lin, J., & Reich, T. (2002). A perspective on epistasis: limits of models displaying no main effect. *Am J Hum Genet 70*, 461–471.

Culverhouse, R.C., Saccone, N.L., Horton, A.C., Ma, Y., Anstey, K.J., Banaschewski, T., et al. (2018). Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. *Molecular Psychiatry 23*, 133–142.

Dalton, E.D., Hammen, C.L., Najman, J.M., & Brennan, P.A. (2014). Genetic susceptibility to family environment: BDNF Val66met and 5-HTTLPR influence depressive symptoms. *J Fam Psychol 28*, 947–956.

Delaveau, P., Jabourian, M., Lemogne, C., Guionnet, S., Bergouignan, L., & Fossati, P. (2011). Brain effects of antidepressants in major depression: A meta-analysis of emotional processing studies. *Journal of Affective Disorders 130*, 66–74.

Dogan, O., Yuksel, N., Ergun, M.A., Yilmaz, A., Ilhan, M.N., Karslioglu, H.E., et al. (2008). Serotonin transporter gene polymorphisms and sertraline response in major depression patients. *Genetic testing 12*, 225–231.

Domschke, K., Dannlowski, U., Ohrmann, P., Lawford, B., Bauer, J., Kugel, H., et al. (2008). Cannabinoid receptor 1 (CNR1) gene: Impact on antidepressant treatment response and emotion processing in Major Depression. *European Neuropsychopharmacology 18*, 751–759.

Domschke, K., Hohoff, C., Mortensen, L.S., Roehrs, T., Deckert, J., Arolt, V., et al. (2008). Monoamine oxidase A variant influences antidepressant treatment response in female patients with Major Depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry 32*, 224–228.

Domschke, K., Dannlowski, U., Hohoff, C., Ohrmann, P., Bauer, J., Kugel, H., et al. (2010). Neuropeptide Y (NPY) gene: Impact on emotional processing and treatment response in anxious depression. *European Neuropsychopharmacology 20*, 301–309.

Domschke, K., Lawford, B., Laje, G., Berger, K., Young, R., Morris, P., et al. (2010). Brain-derived neurotrophic factor (BDNF) gene: no major impact on antidepressant treatment response. *International Journal of Neuropsychopharmacology 13*, 93–101.

Dong, Z. -Q., Li, X. -R., He, L., He, G., Yu, T., & Sun, X. -L. (2016). 5-HTR1A and 5-HTR2A genetic polymorphisms and SSRI antidepressant response in depressive Chinese patients. *Neuropsychiatric Disease and Treatment 12*, 1623–1629.

Drevets, W.C., Price, J.L., & Furey, M.L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct 213*, 93–118.

Dunn, E.C., Brown, R.C., Dai, Y., Rosand, J., Nugent, N.R., Amstadter, A.B., et al. (2015). Genetic Determinants of Depression: Recent Findings and Future Directions. *Harvard Review of Psychiatry 23*, 1–18.

Dunn, E. C., Wiste, A., Radmanesh, F., Almli, L. M., Gogarten, S. M., Sofer, T., Faul, J. D., Kardia, S. L., Smith, J. A., Weir, D. R., Zhao, W., Soare, T. W., Mirza, S. S., Hek, K., Tiemeier, H., Goveas, J. S., Sarto, G. E., Snively, B. M., Cornelis, M., Koenen, K. C., Kraft, P., Purcell, S. , Ressler, K. J., Rosand, J., Wassertheil-Smoller, S., & Smoller, J. W. (2016). Genome-wide association study (gwas) and genome-wide by environment interaction study (gweis) of depressive symptoms in african american and hispanic/latina women. *Depress Anxiety. 33*(4), 265–280. https://doi.org/10.1002/da.22484.

Fabbri, C., Tansey, K.E., Perlis, R.H., Hauser, J., Henigsberg, N., Maier, W., et al. (2018). New insights into the pharmacogenomics of antidepressant response from the GENDEP and STAR*D studies: rare variant analysis and high-density imputation. *Pharmacogenomics J. 18*(3), 413–421.

Fitzgerald, P.J. (2013). Gray colored glasses: is major depression partially a sensory perceptual disorder? *J Affect Disord 151*, 418–422.

Flint, J., & Kendler, K.S. (2014). The genetics of major depression. *Neuron 81*, 484–503.

Fukui, N., Suzuki, Y., Sawamura, K., Sugai, T., Watanabe, J., Inoue, Y., et al. (2007). Dose-dependent effects of the 3435 C>T genotype of ABCB1 gene on the steady-state plasma concentration of fluvoxamine in psychiatric patients. *Ther Drug Monit 29*, 185–189.

Gage, S.H., Davey Smith, G., Ware, J.J., Flint, J., & Munafo, M.R. (2016). G = E: What GWAS Can Tell Us about the Environment. *PLoS Genet 12*, e1005765.

Garriock, H.A., Kraft, J.B., Shyn, S.I., Peters, E.J., Yokoyama, J.S., Jenkins, G.D., et al. (2010). A genomewide association study of citalopram response in major depressive disorder. *Biol Psychiatry 67*, 133–138.

Gatt, J.M., Burton, K.L., Williams, L.M., & Schofield, P.R. (2015). Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. *Journal of Psychiatric Research 60*, 1–13.

Gendep Investigators., Mars Investigators., & Star D* Investigators (2013). Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetic studies. *American Journal of Psychiatry 170*, 207–217.

Gex-Fabry, M., Eap, C.B., Oneda, B., Gervasoni, N., Aubry, J.M., Bondolfi, G., et al. (2008). CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. *Ther Drug Monit 30*, 474–482.

Gillespie, R.D. (1929). The clinical differentiation of types of depression. *Guy's Hospital Reports 79*, 306–344.
Glessner, J.T., Wang, K., Sleiman, P.M., Zhang, H., Kim, C.E., Flory, J.H., et al. (2010). Duplication of the SLIT3 locus on 5q35.1 predisposes to major depressive disorder. *PLoS One 5*, e15463.
Gonda, X., Eszlari, N., Kovacs, D., Anderson, I.M., Deakin, J.F., Juhasz, G., et al. (2016). Financial difficulties but not other types of recent negative life events show strong interactions with 5-HTTLPR genotype in the development of depressive symptoms. *Translational Psychiatry 6*, e798.
Gonda, X., Sarginson, J., Eszlari, N., Petschner, P., Toth, Z.G., Baksa, D., et al. (2017). A new stress sensor and risk factor for suicide: the T allele of the functional genetic variant in the GABRA6 gene. *Sci Rep 7*, 12887.
Grabe, H.J., Schwahn, C., Mahler, J., Appel, K., Schulz, A., Spitzer, C., et al. (2012). Genetic epistasis between the brain-derived neurotrophic factor Val66Met polymorphism and the 5-HTT promoter polymorphism moderates the susceptibility to depressive disorders after childhood abuse. *Prog Neuropsychopharmacol Biol Psychiatry 36*, 264–270.
Gupta, M., Neavin, D., Liu, D., Biernacka, J., Hall-Flavin, D., Bobo, W.V., et al. (2016). TSPAN5, ERICH3 and selective serotonin reuptake inhibitors in major depressive disorder: pharmacometabolomics-informed pharmacogenomics. *Mol Psychiatry 21*, 1717–1725.
Gyekis, J.P., Yu, W., Dong, S., Wang, H., Qian, J., Kota, P., et al. (2013). No association of genetic variants in BDNF with major depression: a meta- and gene-based analysis. *Am J Med Genet B Neuropsychiatr Genet 162B*, 61–70.
Haenisch, B., Linsel, K., Bruss, M., Gilsbach, R., Propping, P., Nothen, M.M., et al. (2009). Association of major depression with rare functional variants in norepinephrine transporter and serotonin1A receptor genes. *Am J Med Genet B Neuropsychiatr Genet 150B*, 1013–1016.
Ham, B.J., Lee, M.S., Lee, H.J., Kang, R.H., Han, C.S., Choi, M.J., et al. (2005). No association between the tryptophan hydroxylase gene polymorphism and major depressive disorders and antidepressant response in a Korean population. *Psychiatr Genet 15*, 299–301.
Ham, B. -J., Lee, B. -C., Paik, J. -W., Kang, R. -H., Choi, M. -J., Choi, I. -G., et al. (2007). Association between the tryptophan hydroxylase-1 gene A218C polymorphism and citalopram antidepressant response in a Korean population. *Progress in Neuro-Psychopharmacology and Biological Psychiatry 31*, 104–107.
Hammen, C. (2005). Stress and depression. *Annu Rev Clin Psychol 1*, 293–319.
Hammen, C., Kim, E.Y., Eberhart, N.K., & Brennan, P.A. (2009). Chronic and acute stress and the prediction of major depression in women. *Depress Anxiety 26*, 718–723.
Hariri, A.R., & Weinberger, D.R. (2003). Imaging genomics. *British Medical Bulletin 65*, 259–270.
Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., et al. (1996). Allelic variation of human serotonin transporter gene expression. *J Neurochem 66*, 2621–2624.
Hong, C.J., Chen, T.J., Yu, Y.W., & Tsai, S.J. (2006). Response to fluoxetine and serotonin 1A receptor (C-1019G) polymorphism in Taiwan Chinese major depressive disorder. *Pharmacogenomics J 6*, 27–33.
Horstmann, S., & Binder, E.B. (2009). Pharmacogenomics of antidepressant drugs. *Pharmacol Ther 124*, 57–73.
Horstmann, S., Lucae, S., Menke, A., Hennings, J.M., Ising, M., Roeske, D., et al. (2010). Polymorphisms in GRIK4, HTR2A, and FKBP5 Show Interactive Effects in Predicting Remission to Antidepressant Treatment. *Neuropsychopharmacology 35*, 727–740.
Hosang, G.M., Shiles, C., Tansey, K.E., McGuffin, P., & Uher, R. (2014). Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. *BMC Med 12*, 7.
Hunter, A.M., Leuchter, A.F., Power, R.A., Muthen, B., McGrath, P.J., Lewis, C.M., et al. (2013). A genome-wide association study of a sustained pattern of antidepressant response. *J Psychiatr Res 47*, 1157–1165.
Huo, Y.X., Huang, L., Zhang, D.F., Yao, Y.G., Fang, Y.R., Zhang, C., et al. (2016). Identification of SLC25A37 as a major depressive disorder risk gene. *Journal of Psychiatric Research 83*, 168–175.
Hyde, C.L., Nagle, M.W., Tian, C., Chen, X., Paciga, S.A., Wendland, J.R., et al. (2016). Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nat Genet 48*, 1031–1036.
Ibrahim, L., Diaz Granados, N., Jolkovsky, L., Brutsche, N., Luckenbaugh, D.A., Herring, W.J., et al. (2012). A Randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. *J Clin Psychopharmacol 32*, 551–557.
Ignacio, Z.M., Reus, G.Z., Abelaira, H.M., & Quevedo, J. (2014). Epigenetic and epistatic interactions between serotonin transporter and brain-derived neurotrophic factor genetic polymorphism: insights in depression. *Neuroscience 275*, 455–468.
Illi, A., Setala-Soikkeli, E., Viikki, M., Poutanen, O., Huhtala, H., Mononen, N., et al. (2009). 5-HTR1A, 5-HTR2A, 5-HTR6, TPH1 and TPH2 polymorphisms and major depression. *Neuroreport 20*, 1125–1128.
Ising, M., Lucae, S., Binder, E.B., Bettecken, T., Uhr, M., Ripke, S., et al. (2009). A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. *Arch Gen Psychiatry 66*, 966–975.
Ito, K., Yoshida, K., Sato, K., Takahashi, H., Kamata, M., Higuchi, H., et al. (2002). A variable number of tandem repeats in the serotonin transporter gene does not affect the antidepressant response to fluvoxamine. *Psychiatry Research 111*, 235–239.
Ji, Y., Schaid, D.J., Desta, Z., Kubo, M., Batzler, A.J., Snyder, K., et al. (2014). Citalopram and escitalopram plasma drug and metabolite concentrations: genome-wide associations. *Br J Clin Pharmacol 78*, 373–383.
Jin, C., Xu, W., Yuan, J., Wang, G., & Cheng, Z. (2013). Meta-analysis of association between the -1438A/G (rs6311) polymorphism of the serotonin 2A receptor gene and major depressive disorder. *Neurol Res 35*, 7–14.
Juhasz, G., Chase, D., Pegg, E., Downey, D., Toth, Z.G., Stones, K., et al. (2009). CNR1 Gene is Associated with High Neuroticism and Low Agreeableness and Interacts with Recent Negative Life Events to Predict Current Depressive Symptoms. *Neuropsychopharmacology 34*, 2019–2027.
Juhasz, G., Hullam, G., Eszlari, N., Gonda, X., Antal, P., Anderson, I.M., et al. (2014). Brain galanin system genes interact with life stresses in depression-related phenotypes. *Proc Natl Acad Sci U S A 111*, E1666–E1673.
Juhasz, G., Gonda, X., Hullam, G., Eszlari, N., Kovacs, D., Lazary, J., et al. (2015). Variability in the effect of 5-HTTLPR on depression in a large European population: the role of age, symptom profile, type and intensity of life stressors. *PLoS One 10*, e0116316.
Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Arch Gen Psychiatry 68*, 444–454.
Kato, M., & Serretti, A. (2010). Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry 15*, 473–500.
Kato, M., Fukuda, T., Wakeno, M., Fukuda, K., Okugawa, G., Ikenaga, Y., et al. (2006). Effects of the Serotonin Type 2A, 3A and 3B Receptor and the Serotonin Transporter Genes on Paroxetine and Fluvoxamine Efficacy and Adverse Drug Reactions in Depressed Japanese Patients. *Neuropsychobiology 53*, 186–195.
Kato, M., Wakeno, M., Okugawa, G., Fukuda, T., Azuma, J., Kinoshita, T., et al. (2007). No Association of TPH1 218A/C Polymorphism with Treatment Response and Intolerance to SSRIs in Japanese Patients with Major Depression. *Neuropsychobiology 56*, 167–171.
Kato, M., Fukuda, T., Wakeno, M., Okugawa, G., Takekita, Y., Watanabe, S., et al. (2009). Effect of 5-HT1A Gene Polymorphisms on Antidepressant Response in Major Depressive Disorder. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics 150b*, 115–123.
Katsuki, A., Yoshimura, R., Kishi, T., Hori, H., Umene-Nakano, W., Ikenouchi-Sugita, A., et al. (2012). Serum levels of brain-derived neurotrophic factor (BDNF), BDNF gene Val66Met polymorphism, or plasma catecholamine metabolites, and response to mirtazapine in Japanese patients with major depressive disorder (MDD). *CNS Spectrums 17*, 155–163.
Kautzky, A., Baldinger, P., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., et al. (2015). The combined effect of genetic polymorphisms and clinical parameters on treatment outcome in treatment-resistant depression. *Eur Neuropsychopharmacol 25*, 441–453.
Kawaguchi, D.M., & Glatt, S.J. (2014). GRIK4 polymorphism and its association with antidepressant response in depressed patients: a meta-analysis. *Pharmacogenomics 15*, 1451–1459.
Keers, R., & Uher, R. (2012). Gene-Environment Interaction in Major Depression and Antidepressant Treatment Response. *Current Psychiatry Reports 14*, 129–137.
Keers, R., Uher, R., Gupta, B., Rietschel, M., Schulze, T.G., Hauser, J., et al. (2010). Stressful life events, cognitive symptoms of depression and response to antidepressants in GENDEP. *J Affect Disord 127*, 337–342.
Keers, R., Uher, R., Huezo-Diaz, P., Smith, R., Jaffee, S., Rietschel, M., et al. (2011). Interaction between serotonin transporter gene variants and life events predicts response to antidepressants in the GENDEP project. *Pharmacogenomics Journal 11*, 138–145.
Kendler, K.S., & Karkowski-Shuman, L. (1997). Stressful life events and genetic liability to major depression: genetic control of exposure to the environment? *Psychol Med 27*, 539–547.
Kendler, K.S., Gatz, M., Gardner, C.O., & Pedersen, N.L. (2006). A Swedish national twin study of lifetime major depression. *Am J Psychiatry 163*, 109–114.
Kendler, K.S., Ohlsson, H., Sundquist, K., & Sundquist, J. (2018). Sources of parent-offspring resemblance for major depression in a national swedish extended adoption study. *JAMA Psychiatry 75*(2), 194–200.
Kiecolt-Glaser, J.K., Derry, H.M., & Fagundes, C.P. (2015). Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry 172*, 1075–1091.
Kim, Y.G., Chang, H.S., Won, E.S., Ham, B.J., & Lee, M.S. (2014). Serotonin-Related Polymorphisms in TPH1 and HTR5A Genes Are Not Associated with Escitalopram Treatment Response in Korean Patients with Major Depression. *Neuropsychobiology 69*, 210–219.
Kishi, T., Yoshimura, R., Kitajima, T., Okochi, T., Okumura, T., Tsunoka, T., et al. (2010). HTR2A is Associated with SSRI Response in Major Depressive Disorder in a Japanese Cohort. *NeuroMolecular Medicine 12*, 237–242.
Kishi, T., Yoshimura, R., Fukuo, Y., Kitajima, T., Okochi, T., Matsunaga, S., et al. (2011). The CLOCK gene and mood disorders: a case-control study and meta-analysis. *Chronobiol Int 28*, 825–833.
Kiyohara, C., & Yoshimasu, K. (2010). Association between major depressive disorder and a functional polymorphism of the 5-hydroxytryptamine (serotonin) transporter gene: a meta-analysis. *Psychiatr Genet 20*, 49–58.
Knowles, E.E., Kent, J.W., Jr., McKay, D.R., Sprooten, E., Mathias, S.R., Curran, J.E., et al. (2016). Genome-wide linkage on chromosome 10q26 for a dimensional scale of major depression. *J Affect Disord 191*, 123–131.
Kocabas, N.A., Faghel, C., Barreto, M., Kasper, S., Linotte, S., Mendlewicz, J., et al. (2010). The impact of catechol-O-methyltransferase SNPs and haplotypes on treatment response phenotypes in major depressive disorder: a case-control association study. *Int Clin Psychopharmacol 25*, 218–227.
Kohli, M.A., Lucae, S., Saemann, P.G., Schmidt, M.V., Demirkan, A., Hek, K., et al. (2011). The Neuronal Transporter Gene SLC6A15 Confers Risk to Major Depression. *Neuron 70*, 252–265.
Kovacs, D., Eszlari, N., Petschner, P., Pap, D., Vas, S., Kovacs, P., et al. (2016a). Effects of IL1B single nucleotide polymorphisms on depressive and anxiety symptoms are determined by severity and type of life stress. *Brain Behav Immun 56*, 96–104.
Kovacs, D., Eszlari, N., Petschner, P., Pap, D., Vas, S., Kovacs, P., et al. (2016b). Interleukin-6 promoter polymorphism interacts with pain and life stress influencing depression phenotypes. *J Neural Transm (Vienna) 123*, 541–548.
Kurose, K., Hiratsuka, K., Ishiwata, K., Nishikawa, J., Nonen, S., Azuma, J., et al. (2012). Genome-wide association study of SSRI/SNRI-induced sexual dysfunction in a Japanese cohort with major depression. *Psychiatry Res 198*, 424–429.

Laika, B., Leucht, S., & Steimer, W. (2006). ABCB1 (P-glycoprotein/MDR1) gene G2677T/a sequence variation (polymorphism): lack of association with side effects and therapeutic response in depressed inpatients treated with amitriptyline. *Clin Chem 52*, 893–895.

Laje, G., Allen, A.S., Akula, N., Manji, H., John Rush, A., & McMahon, F.J. (2009). Genome-wide association study of suicidal ideation emerging during citalopram treatment of depressed outpatients. *Pharmacogenet Genomics 19*, 666–674.

Lazary, J., Lazary, A., Gonda, X., Benko, A., Molnar, E., Hunyady, L., et al. (2009). Promoter variants of the cannabinoid receptor 1 gene (CNR1) in interaction with 5-HTTLPR affect the anxious phenotype. *Am J Med Genet B Neuropsychiatr Genet 150B*, 1118–1127.

Lazary, J., Eszlari, N., Juhasz, G., & Bagdy, G. (2016). Genetically reduced FAAH activity may be a risk for the development of anxiety and depression in persons with repetitive childhood trauma. *Eur Neuropsychopharmacol 26*, 1020–1028.

Lett, T.A., Walter, H., & Brandl, E.J. (2016). Pharmacogenetics and Imaging–Pharmacogenetics of Antidepressant Response: Towards Translational Strategies. *Cns Drugs 30*, 1169–1189.

Leuchter, A.F., McCracken, J.T., Hunter, A.M., Cook, I.A., & Alpert, J.E. (2009). Monoamine oxidase a and catechol-o-methyltransferase functional polymorphisms and the placebo response in major depressive disorder. *Journal of Clinical Psychopharmacology 29*, 372–377.

Levinson, D.F., Mostafavi, S., Milaneschi, Y., Rivera, M., Ripke, S., Wray, N.R., et al. (2014). Genetic studies of major depressive disorder: why are there no genome-wide association study findings and what can we do about it? *Biol Psychiatry 76*, 510–512.

Li, Z., Zhang, Y., Wang, Z., Chen, J., Fan, J., Guan, Y., et al. (2013). The role of BDNF, NTRK2 gene and their interaction in development of treatment-resistant depression: Data from multicenter, prospective, longitudinal clinic practice. *Journal of Psychiatric Research 47*, 8–14.

Li, Q.S., Tian, C., Seabrook, G.R., Drevets, W.C., & Narayan, V.A. (2016). Analysis of 23andMe antidepressant efficacy survey data: implication of circadian rhythm and neuroplasticity in bupropion response. *Transl Psychiatry 6*, e889.

Lin, E., Hong, C.J., Hwang, J.P., Liou, Y.J., Yang, C.H., Cheng, D., et al. (2009). Gene-gene interactions of the brain-derived neurotrophic-factor and neurotrophic tyrosine kinase receptor 2 genes in geriatric depression. *Rejuvenation Res 12*, 387–393.

Lin, J. -Y., Jiang, M. -Y., Kan, Z. -M., & Chu, Y. (2014). Influence of 5-HTR2A genetic polymorphisms on the efficacy of antidepressants in the treatment of major depressive disorder: A meta-analysis. *Journal of Affective Disorders 168*, 430–438.

Lopez-Leon, S., Janssens, A.C., Gonzalez-Zuloeta Ladd, A.M., Del-Favero, J., Claes, S.J., Oostra, B.A., et al. (2008). Meta-analyses of genetic studies on major depressive disorder. *Mol Psychiatry 13*, 772–785.

Lopizzo, N., Bocchio Chiavetto, L., Cattane, N., Plazzotta, G., Tarazi, F.I., Pariante, C.M., et al. (2015). Gene-environment interaction in major depression: focus on experience-dependent biological systems. *Front Psychiatry 6*, 68.

Lucae, S., Ising, M., Horstmann, S., Baune, B.T., Arolt, V., Müller-Myhsok, B., et al. (2010). HTR2A gene variation is involved in antidepressant treatment response. *European Neuropsychopharmacology 20*, 65–68.

Ma, Y., Li, B., Wang, C., Zhang, W., Rao, Y., & Han, S. (2015). Allelic variation in 5-HTTLPR and the effects of citalopram on the emotional neural network. *The British Journal of Psychiatry 206*, 385–392.

Major Depressive Disorder Working Group of the PGC, Wray, N. R., & Sullivan, P. F. (2017). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *bioRxiv*, 167577. https://doi.org/10.1101/167577.

Mandelli, L., & Serretti, A. (2013). Gene environment interaction studies in depression and suicidal behavior: An update. *Neurosci Biobehav Rev 37*, 2375–2397.

Mandelli, L., Marino, E., Pirovano, A., Calati, R., Zanardi, R., Colombo, C., et al. (2009). Interaction between SERTPR and stressful life events on response to antidepressant treatment. *European Neuropsychopharmacology 19*, 64–67.

Manoharan, A., Shewade, D.G., Rajkumar, R.P., & Adithan, S. (2016). Serotonin transporter gene (SLC6A4) polymorphisms are associated with response to fluoxetine in south Indian major depressive disorder patients. *European Journal of Clinical Pharmacology 72*, 1215–1220.

Marx, P., Antal, P., Bolgar, B., Bagdy, G., Deakin, B., & Juhasz, G. (2017). Comorbidities in the diseasome are more apparent than real: What Bayesian filtering reveals about the comorbidities of depression. *PLoS Comput Biol 13*, e1005487.

Matsumoto, Y., Fabbri, C., Pellegrini, S., Porcelli, S., Politi, P., Bellino, S., et al. (2014). Serotonin Transporter Gene: A New Polymorphism May Affect Response to Antidepressant Treatments in Major Depressive Disorder. *Molecular Diagnosis & Therapy 18*, 567–577.

Mbarek, H., Milaneschi, Y., Hottenga, J.J., Ligthart, L., de Geus, E.J.C., Ehli, E.A., et al. (2017). Genome-Wide Significance for PCLO as a Gene for Major Depressive Disorder. *Twin Research and Human Genetics 20*, 267–270.

McMahon, F.J., Buervenich, S., Charney, D., Lipsky, R., Rush, A.J., Wilson, A.F., et al. (2006). Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet 78*, 804–814.

Mekli, K., Payton, A., Miyajima, F., Platt, H., Thomas, E., Downey, D., et al. (2011). The HTR1A and HTR1B receptor genes influence stress-related information processing. *Eur Neuropsychopharmacol 21*, 129–139.

Menke, A., Domschke, K., Czamara, D., Klengel, T., Hennings, J., Lucae, S., et al. (2012). Genome-wide association study of antidepressant treatment-emergent suicidal ideation. *Neuropsychopharmacology 37*, 797–807.

Mihaljevic Peles, A., Bozina, N., Sagud, M., Rojnic Kuzman, M., & Lovric, M. (2008). MDR1 gene polymorphism: therapeutic response to paroxetine among patients with major depression. *Prog Neuropsychopharmacol Biol Psychiatry 32*, 1439–1444.

Milanesi, E., Bonvicini, C., Congiu, C., Bortolomasi, M., Gainelli, G., Gennarelli, M., et al. (2015). The role of GRIK4 gene in treatment-resistant depression. *Genetics Research 97*.

Moore, J.H., Andrews, P.C., Olson, R.S., Carlson, S.E., Larock, C.R., Bulhoes, M.J., et al. (2017). Grid-based stochastic search for hierarchical gene-gene interactions in population-based genetic studies of common human diseases. *BioData Min 10*, 19.

Mrazek, D.A., Biernacka, J.M., O'Kane, D.J., Black, J.L., Cunningham, J.M., Drews, M.S., et al. (2011). CYP2C19 variation and citalopram response. *Pharmacogenet Genomics 21*, 1–9.

Muller, D.J., Kekin, I., Kao, A.C., & Brandl, E.J. (2013). Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. *Int Rev Psychiatry 25*, 554–571.

Mullins, N., & Lewis, C.M. (2017). Genetics of Depression: Progress at Last. *Curr Psychiatry Rep 19*, 43.

Mullins, N., Power, R.A., Fisher, H.L., Hanscombe, K.B., Euesden, J., Iniesta, R., et al. (2016). Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. *Psychol Med 46*, 759–770.

Munafò, M.R., Brown, S.M., & Hariri, A.R. (2008). Serotonin Transporter (5-HTTLPR) Genotype and Amygdala Activation: A Meta-Analysis. *Biol Psychiatry 63*, 852–857.

Munafo, M.R., Durrant, C., Lewis, G., & Flint, J. (2009). Gene x Environment Interactions at the Serotonin Transporter Locus. *Biol Psychiatry 65*, 211–219.

Munoz, M., Pong-Wong, R., Canela-Xandri, O., Rawlik, K., Haley, C.S., & Tenesa, A. (2016). Evaluating the contribution of genetics and familial shared environment to common disease using the UK Biobank. *Nat Genet 48*, 980–983.

Murk, W., & DeWan, A.T. (2016). Exhaustive Genome-Wide Search for SNP-SNP Interactions Across 10 Human Diseases. *G3 (Bethesda) 6*, 2043–2050.

Murphy, G.M., Jr., Sarginson, J.E., Ryan, H.S., O'Hara, R., Schatzberg, A.F., & Lazzeroni, L.C. (2013). BDNF and CREB1 genetic variants interact to affect antidepressant treatment outcomes in geriatric depression. *Pharmacogenetics and Genomics 23*, 301–313.

Murphy, D.L., & Moya, P.R. (2011). Human Serotonin Transporter Gene (SLC6A4) Variants: Their contributions to understanding pharmacogenomic and other functional G x G and G x E differences in health and disease. *Current Opinion in Pharmacology 11*, 3–10.

Musani, S.K., Shriner, D., Liu, N., Feng, R., Coffey, C.S., Yi, N., et al. (2007). Detection of gene x gene interactions in genome-wide association studies of human population data. *Hum Hered 63*, 67–84.

Musil, R., Zill, P., Seemuller, F., Bondy, B., Obermeier, M., Spellmann, I., et al. (2013). No influence of brain-derived neurotrophic factor (BDNF) polymorphisms on treatment response in a naturalistic sample of patients with major depression. *European Archives of Psychiatry and Clinical Neuroscience 263*, 405–412.

Myung, W., Kim, J., Lim, S.W., Shim, S., Won, H.H., Kim, S., et al. (2015). A genome-wide association study of antidepressant response in Koreans. *Transl Psychiatry 5*, e633.

Naoi, M., Maruyama, W., & Shamoto-Nagai, M. (2018). Type A monoamine oxidase and serotonin are coordinately involved in depressive disorders: from neurotransmitter imbalance to impaired neurogenesis. *J Neural Transm (Vienna) 125*(1), 53–66.

Neff, C.D., Abkevich, V., Potter, J., Riley, R., Shattuck, D., & Katz, D.A. (2010). Evidence for epistasis between SLC6A4 and a chromosome 4 gene as risk factors in major depression. *Am J Med Genet B Neuropsychiatr Genet 153B*, 321–322.

Network, & Pathway Analysis Subgroup of Psychiatric Genomics, C (2015). Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci 18*, 199–209.

Nielsen, M.G., Congiu, C., Bortolomasi, M., Bonvicini, C., Bignotti, S., Abate, M., et al. (2015). MTHFR: Genetic variants, expression analysis and COMT interaction in major depressive disorder. *Journal of Affective Disorders 183*, 179–186.

Niitsu, T., Fabbri, C., Bentini, F., & Serretti, A. (2013). Pharmacogenetics in major depression: A comprehensive meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry 45*, 183–194.

Noordam, R., Direk, N., Sitlani, C.M., Aarts, N., Tiemeier, H., Hofman, A., et al. (2015). Identifying genetic loci associated with antidepressant drug response with drug–gene interaction models in a population-based study. *Journal of Psychiatric Research 62*, 31–37.

O'Brien, F.E., Clarke, G., Dinan, T.G., Cryan, J.F., & Griffin, B.T. (2013). Human P-glycoprotein differentially affects antidepressant drug transport: relevance to blood-brain barrier permeability. *Int J Neuropsychopharmacol 16*, 2259–2272.

Okbay, A., Baselmans, B.M.L., De Neve, J.E., Turley, P., Nivard, M.G., Fontana, M.A., et al. (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses (vol 48, pg 624, 2016). *Nature Genetics 48*, 1591.

Otowa, T., Kawamura, Y., Tsutsumi, A., Kawakami, N., Kan, C., Shimada, T., et al. (2016). The first pilot genome-wide gene-environment study of depression in the Japanese population. *PLoS One 11*.

Outhred, T., Das, P., Dobson-Stone, C., Felmingham, K.L., Bryant, R.A., Nathan, P.J., et al. (2014). The impact of 5-HTTLPR on acute serotonin transporter blockade by escitalopram on emotion processing: Preliminary findings from a randomised, crossover fMRI study. *Australian & New Zealand Journal of Psychiatry 48*, 1115–1125.

Outhred, T., Das, P., Dobson-Stone, C., Felmingham, K.L., Bryant, R.A., Nathan, P.J., et al. (2016). Impact of 5-HTTLPR on SSRI serotonin transporter blockade during emotion regulation: A preliminary fMRI study. *Journal of Affective Disorders 196*, 11–19.

Paddock, S., Laje, G., Charney, D., Rush, A.J., Wilson, A.F., Sorant, A.J., et al. (2007). Association of GRIK4 with outcome of antidepressant treatment in the STAR*D cohort. *American Journal of Psychiatry 164*, 1181–1188.

Pae, C.U., Drago, A., Forlani, M., Patkar, A.A., & Serretti, A. (2010). Investigation of an epistastic effect between a set of TAAR6 and HSP-70 genes variations and major mood disorders. *Am J Med Genet B Neuropsychiatr Genet 153B*, 680–683.

Perlis, R.H., Fijal, B., Adams, D.H., Sutton, V.K., Trivedi, M.H., & Houston, J.P. (2009). Variation in Catechol-O-methyltransferase is associated with duloxetine response in a clinical trial for major depressive disorder. *Biol Psychiatry 65*, 785–791.

Perlis, R.H., Fijal, B., Dharia, S., Heinloth, A.N., & Houston, J.P. (2010). Failure to replicate genetic associations with antidepressant treatment response in duloxetine-treated patients. *Biol Psychiatry 67*, 1110–1113.

Perlis, R.H., Smoller, J.W., Mysore, J., Sun, M., Gillis, T., Purcell, S., et al. (2010). Prevalence of incompletely penetrant Huntington's disease alleles among individuals with major depressive disorder. *Am J Psychiatry 167*, 574–579.
Perroud, N., Uher, R., Ng, M.Y., Guipponi, M., Hauser, J., Henigsberg, N., et al. (2012). Genome-wide association study of increasing suicidal ideation during antidepressant treatment in the GENDEP project. *Pharmacogenomics J 12*, 68–77.
Peters, E.J., Slager, S.L., Kraft, J.B., Jenkins, G.D., Reinalda, M.S., McGrath, P.J., et al. (2008). Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. *PLoS One 3*, e1872.
Peters, E.J., Reus, V., & Hamilton, S.P. (2009). The ABCB1 transporter gene and antidepressant response. *F1000 Biol Rep 1*, 23.
Peters, E.J., Slager, S.L., Jenkins, G.D., Reinalda, M.S., Garriock, H.A., Shyn, S.I., et al. (2009). Resequencing of serotonin-related genes and association of tagging SNPs to citalopram response. *Pharmacogenetics and genomics 19*, 1–10.
Peterson, K., Dieperink, E., Anderson, J., Boundy, E., Ferguson, L., & Helfand, M. (2017). Rapid evidence review of the comparative effectiveness, harms, and cost-effectiveness of pharmacogenomics-guided antidepressant treatment versus usual care for major depressive disorder. *Psychopharmacology (Berl) 234*, 1649–1661.
Petschner, P., Juhasz, G., Tamasi, V., Adori, C., Tothfalusi, L., Hokfelt, T., et al. (2016). Chronic venlafaxine treatment fails to alter the levels of galanin system transcripts in normal rats. *Neuropeptides 57*, 65–70.
Petschner, P., Gonda, X., Baksa, D., Eszlari, N., Trivaks, M., Juhasz, G., et al. (2018). Genes linking mitochondrial function, cognitive impairment and depression are associated with endophenotypes serving precision medicine. *Neuroscience. 370*, 207–217.
Pezawas, L., Meyer-Lindenberg, A., Goldman, A.L., Verchinski, B.A., Chen, G., Kolachana, B. S., et al. (2008). Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. *Mol Psychiatry 13*, 709–716.
Pirooznia, M., Wang, T., Avramopoulos, D., Potash, J.B., Zandi, P.P., & Goes, F.S. (2016). High-throughput sequencing of the synaptome in major depressive disorder. *Mol Psychiatry 21*, 650–655.
Poland, R.E., Lesser, I.M., Wan, Y.J.Y., Gertsik, L., Yao, J., Raffel, L.J., et al. (2013). Response to citalopram is not associated with SLC6A4 genotype in and Caucasians with major depression. *Life Sciences 92*, 967–970.
Porcelli, S., Fabbri, C., & Serretti, A. (2012). Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *Eur Neuropsychopharmacol 22*, 239–258.
Power, R.A., Tansey, K.E., Buttenschon, H.N., Cohen-Woods, S., Bigdeli, T., Hall, L.S., et al. (2017). Genome-wide association for major depression through age at onset stratification: Major depressive disorder working group of the psychiatric genomics consortium. *Biological Psychiatry 81*, 325–335.
Praschak-Rieder, N., Kennedy, J., Wilson, A.A., Hussey, D., Boovariwala, A., Willeit, M., et al. (2007). Novel 5-HTTLPR allele associates with higher serotonin transporter binding in putamen: A [C-11] DASB positron emission tomography study. *Biol Psychiatry 62*, 327–331.
Purves, K.L., Coleman, J.R.I., Rayner, C., Hettema, J.M., Deckert, J., McIntosh, A.M., et al. (2017). The common genetic architecture of anxiety disorders. *bioRxiv*, 203844. https://doi.org/10.1101/203844.
Qesseveur, G., Petit, A.C., Nguyen, H.T., Dahan, L., Colle, R., Rotenberg, S., et al. (2016). Genetic dysfunction of serotonin 2A receptor hampers response to antidepressant drugs: A translational approach. *Neuropharmacology 105*, 142–153.
Ramasubbu, R., Burgess, A., Gaxiola-Valdez, I., Cortese, F., Clark, D., Kemp, A., et al. (2016). Amygdala responses to quetiapine XR and citalopram treatment in major depression: the role of 5-HTTLPR-S/Lg polymorphisms. *Human Psychopharmacology: Clinical and Experimental 31*, 144–155.
Reuter, M., Markett, S., Melchers, M., & Montag, C. (2012). Interaction of the cholinergic system and the hypothalamic-pituitary-adrenal axis as a risk factor for depression: evidence from a genetic association study. *Neuroreport 23*, 717–720.
Rhee-Hun, K., Myoung-Jin, C., Jong-Woo, P., Sang-Woo, H., & Min-Soo, L. (2007). Effect of serotonin receptor 2A gene polymorphism on mirtazapine response in major depression. *The International Journal of Psychiatry in Medicine 37*, 315–329.
Richards, E.M., Mathews, D.C., Luckenbaugh, D.A., Ionescu, D.F., Machado-Vieira, R., Niciu, M.J., et al. (2016). A randomized, placebo-controlled pilot trial of the delta opioid receptor agonist AZD2327 in anxious depression. *Psychopharmacology (Berl) 233*, 1119–1130.
Risch, N., Herrell, R., Lehner, T., Liang, K.Y., Eaves, L., Hoh, J., et al. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA 301*, 2462–2471.
Ritchie, M.D., Davis, J.R., Aschard, H., Battle, A., Conti, D., Du, M., et al. (2017). Incorporation of biological knowledge into the study of gene-environment interactions. *American Journal of Epidemiology 186*, 771–777.
Rucker, J.J., Breen, G., Pinto, D., Pedroso, I., Lewis, C.M., Cohen-Woods, S., et al. (2013). Genome-wide association analysis of copy number variation in recurrent depressive disorder. *Mol Psychiatry 18*, 183–189.
Rucker, J.J., Tansey, K.E., Rivera, M., Pinto, D., Cohen-Woods, S., Uher, R., et al. (2016). Phenotypic association analyses with copy number variation in recurrent depressive disorder. *Biol Psychiatry 79*, 329–336.
Ruhe, H.G., Ooteman, W., Booij, J., Michel, M.C., Moeton, M., Baas, F., et al. (2009). Serotonin transporter gene promoter polymorphisms modify the association between paroxetine serotonin transporter occupancy and clinical response in major depressive disorder. *Pharmacogenetics and Genomics 19*, 67–76.
Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., et al. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry 163*, 1905–1917.
Sarginson, J.E., Lazzeroni, L.C., Ryan, H.S., Schatzberg, A.F., & Murphy, G.M., Jr. (2010). FKBP5 polymorphisms and antidepressant response in geriatric depression. *Am J Med Genet B Neuropsychiatr Genet 153B*, 554–560.
Sarginson, J.E., Deakin, J.F., Anderson, I.M., Downey, D., Thomas, E., Elliott, R., et al. (2014). Neuronal nitric oxide synthase (NOS1) polymorphisms interact with financial hardship to affect depression risk. *Neuropsychopharmacology 39*, 2857–2866.
Sato, K., Yoshida, K., Takahashi, H., Ito, K., Kamata, M., Higuchi, H., et al. (2002). Association between -1438G/A Promoter Polymorphism in the 5-HT_{2A} Receptor Gene and Fluvoxamine Response in Japanese Patients with Major Depressive Disorder. *Neuropsychobiology 46*, 136–140.
Scharinger, C., Rabl, U., Pezawas, L., & Kasper, S. (2011). The genetic blueprint of major depressive disorder: Contributions of imaging genetics studies. *The World Journal of Biological Psychiatry 12*, 474–488.
Schildkraut, J.J. (1965). The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry 122*, 509–522.
Schinkel, A.H., Smit, J.J., van Tellingen, O., Beijnen, J.H., Wagenaar, E., van Deemter, L., et al. (1994). Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. *Cell 77*, 491–502.
Schmitt, A., Malchow, B., Hasan, A., & Falkai, P. (2014). The impact of environmental factors in severe psychiatric disorders. *Front Neurosci 8*, 19.
Serretti, A., Kato, M., De Ronchi, D., & Kinoshita, T. (2007). Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry 12*, 247–257.
Serretti, A., Chiesa, A., Crisafulli, C., Massat, I., Linotte, S., Calati, R., et al. (2012). Failure to replicate influence of GRIK4 and GNB3 polymorphisms on treatment outcome in major depression. *Neuropsychobiology 65*, 70–75.
Serretti, A., Fabbri, C., Pellegrini, S., Porcelli, S., Politi, P., Bellino, S., et al. (2013). No effect of serotoninergic gene variants on response to interpersonal counseling and antidepressants in major depression. *Psychiatry Investigation 10*, 180–189.
Shapero, B.G., Black, S.K., Liu, R.T., Klugman, J., Bender, R.E., Abramson, L.Y., et al. (2014). Stressful life events and depression symptoms: the effect of childhood emotional abuse on stress reactivity. *J Clin Psychol 70*, 209–223.
Sharma, S., Powers, A., Bradley, B., & Ressler, K.J. (2016). Gene x environment determinants of stress- and anxiety-related disorders. *Annu Rev Psychol 67*, 239–261.
Sharpley, C.F., Palanisamy, S.K., Glyde, N.S., Dillingham, P.W., & Agnew, L.L. (2014). An update on the interaction between the serotonin transporter promoter variant (5-HTTLPR), stress and depression, plus an exploration of non-confirming findings. *Behav Brain Res 273*, 89–105.
Singh, A.B. (2015). Improved antidepressant remission in major depression via a pharmacokinetic pathway polygene pharmacogenetic report. *Clin Psychopharmacol Neurosci 13*, 150–156.
Smits, K.M., Smits, L.J., Peeters, F.P., Schouten, J.S., Janssen, R.G., Smeets, H.J., et al. (2008). The influence of 5-HTTLPR and STin2 polymorphisms in the serotonin transporter gene on treatment effect of selective serotonin reuptake inhibitors in depressive patients. *Psychiatric Genetics 18*, 184–190.
Smoller, J.W. (2016). The genetics of stress-related disorders: ptsd, depression, and anxiety disorders. *Neuropsychopharmacology 41*, 297–319.
Spina, E., Santoro, V., & D'Arrigo, C. (2008). Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: an update. *Clin Ther 30*, 1206–1227.
Spronk, D., Arns, M., Barnett, K.J., Cooper, N.J., & Gordon, E. (2011). An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study. *Journal of Affective Disorders 128*, 41–48.
Staeker, J., Leucht, S., Laika, B., & Steimer, W. (2014). Polymorphisms in serotonergic pathways influence the outcome of antidepressant therapy in psychiatric inpatients. *Genetic testing and molecular biomarkers 18*, 20–31.
Sullivan, P.F. (2015). Genetics of disease: Associations with depression. *Nature 523*, 539–540.
Sullivan, P.F., de Geus, E.J., Willemsen, G., James, M.R., Smit, J.H., Zandbelt, T., et al. (2009). Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. *Mol Psychiatry 14*, 359–375.
Sullivan, P.F., Daly, M.J., & O'Donovan, M. (2012). DISEASE MECHANISMS Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature Reviews Genetics 13*, 537–551.
Szczepankiewicz, A., Leszczynska-Rodziewicz, A., Pawlak, J., Rajewska-Rager, A., Wilkosc, M., Zaremba, D., et al. (2013). Epistatic interaction between CRHR1 and AVPR1b variants as a predictor of major depressive disorder. *Psychiatr Genet 23*, 239–246.
Szegedi, A., Rujescu, D., Tadic, A., Muller, M.J., Kohnen, R., Stassen, H.H., et al. (2005). The catechol-O-methyltransferase Val108/158Met polymorphism affects short-term treatment response to mirtazapine, but not to paroxetine in major depression. *The Pharmacogenomics Journal 5*, 49–53.
Tadic, A., Muller, M.J., Rujescu, D., Kohnen, R., Stassen, H.H., Dahmen, N., et al. (2007). The MAOA T941G polymorphism and short-term treatment response to mirtazapine and paroxetine in major depression. *Am J Med Genet B Neuropsychiatr Genet 144B*, 325–331.
Tamasi, V., Petschner, P., Adori, C., Kirilly, E., Ando, R.D., Tothfalusi, L., et al. (2014). Transcriptional evidence for the role of chronic venlafaxine treatment in neurotrophic signaling and neuroplasticity including also Glutamatergic [corrected] - and insulin-mediated neuronal processes. *PLoS One 9*, e113662.
Tansey, K.E., Guipponi, M., Perroud, N., Bondolfi, G., Domenici, E., Evans, D., et al. (2012). Genetic predictors of response to serotonergic and noradrenergic antidepressants in major depressive disorder: a genome-wide analysis of individual-level data and a meta-analysis. *PLoS Med 9*, e1001326.
Taranu, A., Asmar, K.E., Colle, R., Ferreri, F., Polosan, M., David, D., et al. (2017). The Catechol-O-methyltransferase Val(108/158)Met genetic polymorphism cannot be recommended as a biomarker for the prediction of venlafaxine efficacy in patients treated in psychiatric settings. *Basic & Clinical Pharmacology & Toxicology 121*, 435–441.

Tartter, M., Hammen, C., Bower, J.E., Brennan, P.A., & Cole, S. (2015). Effects of chronic interpersonal stress exposure on depressive symptoms are moderated by genetic variation at IL6 and IL1beta in youth. *Brain Behav Immun 46*, 104–111.
Tatham, E.L., Hall, G.B.C., Clark, D., Foster, J., & Ramasubbu, R. (2017). The 5-HTTLPR and BDNF polymorphisms moderate the association between uncinate fasciculus connectivity and antidepressants treatment response in major depression. *European Archives of Psychiatry and Clinical Neuroscience 267*, 135–147.
Taylor, M.B., & Ehrenreich, I.M. (2015). Higher-order genetic interactions and their contribution to complex traits. *Trends Genet 31*, 34–40.
Taylor, M.J., Sen, S., & Bhagwagar, Z. (2010). Antidepressant response and the serotonin transporter gene-linked polymorphic region. *Biol Psychiatry 68*, 536–543.
Tiwari, A.K., Zai, C.C., Sajeev, G., Arenovich, T., Müller, D.J., & Kennedy, J.L. (2013). Analysis of 34 candidate genes in bupropion and placebo remission. *International Journal of Neuropsychopharmacology 16*, 771–781.
Torrellas, C., Carril, J.C., & Cacabelos, R. (2017). Optimization of Antidepressant use with Pharmacogenetic Strategies. *Curr Genomics 18*, 442–449.
Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., et al. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry 163*, 28–40.
Tsai, S. -J., Gau, Y. -T.A., Hong, C. -J., Liou, Y. -J., Yu, Y.W.Y., & Chen, T. -J. (2009). Sexually dimorphic effect of catechol-O-methyltransferase val158met polymorphism on clinical response to fluoxetine in major depressive patients. *Journal of Affective Disorders 113*, 183–187.
Tsai, M.H., Lin, K.M., Hsiao, M.C., Shen, W.W., Lu, M.L., Tang, H.S., et al. (2010). Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. *Pharmacogenomics 11*, 537–546.
Tzeng, D.S., Chien, C.C., Lung, F.W., & Yang, C.Y. (2009). MAOA gene polymorphisms and response to mirtazapine in major depression. *Human psychopharmacology 24*, 293–300.
Uher, R. (2014). Gene-environment interactions in severe mental illness. *Front Psychiatry 5*, 48.
Uher, R., Huezo-Diaz, P., Perroud, N., Smith, R., Rietschel, M., Mors, O., et al. (2009). Genetic predictors of response to antidepressants in the GENDEP project. *The Pharmacogenomics Journal 9*, 225.
Uher, R., Perroud, N., Ng, M.Y., Hauser, J., Henigsberg, N., Maier, W., et al. (2010). Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. *Am J Psychiatry 167*, 555–564.
Van der Auwera, S., Peyrot, W.J., Milaneschi, Y., Hertel, J., Baune, B., Breen, G., et al. (2018). Genome-wide gene-environment interaction in depression: A systematic evaluation of candidate genes: The childhood trauma working-group of PGC-MDD. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics 177*, 40–49.
Viikki, M., Kampman, O., Illi, A., Setälä-Soikkeli, E., Anttila, S., Huuhka, M., et al. (2010). TPH1 218A/C polymorphism is associated with major depressive disorder and its treatment response. *Neurosci Lett 468*, 80–84.
Villafuerte, S.M., Vallabhaneni, K., Sliwerska, E., McMahon, F.J., Young, E.A., & Burmeister, M. (2009). SSRI response in depression may be influenced by SNPs in HTR1B and HTR1A. *Psychiatric Genetics 19*, 281–291.
Vogel, F. (1959). Moderne Probleme der Humangenetik. In L. Heilmeyer, R. Schoen, & B. de Rudder (Eds.), *Ergebnisse der Inneren Medizin und Kinderheilkunde* (pp. 52–125). Berlin, Heidelberg: Springer Berlin Heidelberg.
Wang, H. -C., Yeh, T.L., Chang, H.H., Gean, P.W., Chi, M.H., Yang, Y.K., et al. (2011). TPH1 is associated with major depressive disorder but not with SSRI/SNRI response in Taiwanese patients. *Psychopharmacology (Berl) 213*, 773–779.
Wang, K., Gaitsch, H., Poon, H., Cox, N.J., & Rzhetsky, A. (2017). Classification of common human diseases derived from shared genetic and environmental determinants. *Nat Genet 49*, 1319–1325.
Ware, E.B., Mukherjee, B., Sun, Y.V., Diez-Roux, A.V., Kardia, S.L.R., & Smith, J.A. (2015). Comparative genome-wide association studies of a depressive symptom phenotype in a repeated measures setting by race/ethnicity in the multi-ethnic study of atherosclerosis. *Bmc Genetics*, 16.
Weinshilboum, R.M. (2009). SLC6A4 Variation and Citalopram Response. *Am J Med Genet B Neuropsychiatr Genet 150B*, 341–351.
WHO (2017). *Depression and Other Common Mental Disorders. In.* Geneva, Switzerland: WHO.
Wilkie, M.J.V., Smith, G., Day, R.K., Matthews, K., Smith, D., Blackwood, D., et al. (2008). Polymorphisms in the SLC6A4 and HTR2A genes influence treatment outcome following antidepressant therapy. *The Pharmacogenomics Journal 9*, 61.
Winner, J.G., Carhart, J.M., Altar, C.A., Allen, J.D., & Dechairo, B.M. (2013). A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discov Med 16*, 219–227.
Wolf, C.R., & Smith, G. (1999). Pharmacogenetics. *Br Med Bull 55*, 366–386.
Wong, M.L., Dong, C., Flores, D.L., Ehrhart-Bornstein, M., Bornstein, S., Arcos-Burgos, M., et al. (2014). Clinical outcomes and genome-wide association for a brain methylation site in an antidepressant pharmacogenetics study in Mexican Americans. *Am J Psychiatry 171*, 1297–1309.
Wong, M.L., Arcos-Burgos, M., Liu, S., Velez, J.I., Yu, C., Baune, B.T., et al. (2017a). The PHF21B gene is associated with major depression and modulates the stress response. *Molecular Psychiatry 22*, 1015–1025.
Wong, M.L., Arcos-Burgos, M., Liu, S., Velez, J.I., Yu, C., Baune, B.T., et al. (2017b). The PHF21B gene is associated with major depression and modulates the stress response. *Mol Psychiatry 22*, 1015–1025.
Wray, N.R., Pergadia, M.L., Blackwood, D.H., Penninx, B.W., Gordon, S.D., Nyholt, D.R., et al. (2012). Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. *Mol Psychiatry 17*, 36–48.
Wright, M.N., Ziegler, A., & Konig, I.R. (2016). Do little interactions 0get lost in dark random forests? *BMC Bioinformatics 17*, 145.
Wu, Y.L., Ding, X.X., Sun, Y.H., Yang, H.Y., Chen, J., Zhao, X., et al. (2013). Association between MTHFR C677T polymorphism and depression: An updated meta-analysis of 26 studies. *Prog Neuropsychopharmacol Biol Psychiatry 46*, 78–85.
Xiao, Z., Liu, W., Gao, K., Wan, Q., Yang, C., Wang, H., et al. (2011). Interaction between CRHR1 and BDNF genes increases the risk of recurrent major depressive disorder in Chinese population. *PLoS One 6*, e28733.
Xiao, X., Zheng, F., Chang, H., Ma, Y., Yao, Y.G., Luo, X.J., et al. (2018). The gene encoding protocadherin 9 (PCDH9), a novel risk factor for major depressive disorder. *Neuropsychopharmacology. 43*(5), 1128–1137.
Yan, T., Wang, L., Kuang, W., Xu, J., Li, S., Chen, J., et al. (2014). Brain-derived neurotrophic factor Val66Met polymorphism association with antidepressant efficacy: a systematic review and meta-analysis. *Asia-Pacific psychiatry: Official Journal of the Pacific Rim College of Psychiatrists 6*, 241–251.
Yang, C., Xu, Y., Sun, N., Ren, Y., Liu, Z., Cao, X., et al. (2010). The combined effects of the BDNF and GSK3B genes modulate the relationship between negative life events and major depressive disorder. *Brain Res 1355*, 1–6.
Yoshida, K., Higuchi, H., Takahashi, H., Kamata, M., Sato, K., Inoue, K., et al. (2008). Influence of the tyrosine hydroxylase val81met polymorphism and catechol-O-methyltransferase val158met polymorphism on the antidepressant effect of milnacipran. *Human Psychopharmacology: Clinical and Experimental 23*, 121–128.
Yoshimura, R., Kishi, T., Suzuki, A., Umene-Nakano, W., Ikenouchi-Sugita, A., Hori, H., et al. (2011). The brain-derived neurotrophic factor (BDNF) polymorphism Val66Met is associated with neither serum BDNF level nor response to selective serotonin reuptake inhibitors in depressed Japanese patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry 35*, 1022–1025.
Yu, Y.W.Y., Tsai, S. -J., Hong, C. -J., Chen, T. -J., Chen, M. -C., & Yang, C. -W. (2005). Association study of a monoamine oxidase A gene promoter polymorphism with major depressive disorder and antidepressant response. *Neuropsychopharmacology 30*, 1719.
Yu, Y.W., Tsai, S.J., Liou, Y.J., Hong, C.J., & Chen, T.J. (2006). Association study of two serotonin 1A receptor gene polymorphisms and fluoxetine treatment response in Chinese major depressive disorders. *Eur Neuropsychopharmacol 16*, 498–503.
Yu, C., Baune, B.T., Licinio, J., & Wong, M.L. (2017). A novel strategy for clustering major depression individuals using whole-genome sequencing variant data. *Sci Rep 7*, 44389.
Zhao, X.F., Huang, Y.L., Li, J.Y., Ma, H., Jin, Q., Wang, Y., et al. (2012). Association between the 5-HT1A receptor gene polymorphism (rs6295) and antidepressants: a meta-analysis. *International Clinical Psychopharmacology 27*, 314–320.
Zhao, X.F., Jin, Q., Wu, L.J., Huang, Y.L., Li, J., & Zhu, G. (2012). Sertraline (Zoloft) response in major depressive disorder is not associated with three 5-HT1A receptor gene polymorphisms (rs6295, rs10042486, or rs1364043) in Chinese-Han patients. *Psychiatric Genetics 22*, 261–262.
Zhao, X., Huang, Y., Ma, H., Jin, Q., Wang, Y., & Zhu, G. (2013). Association between major depressive disorder and the norepinephrine transporter polymorphisms T-182C and G1287A: a meta-analysis. *J Affect Disord 150*, 23–28.
Zhao, X., Huang, Y., Li, D., Han, C., & Kan, Q. (2015). Association between the TPH1 A218C polymorphism and antidepressant response: evidence from an updated ethnicity, antidepressant-specific, and ethnicity-antidepressant interaction meta-analysis. *Psychiatr Genet 25*, 1–8.
Zhao, M., Chen, L., Yang, J., Han, D., Fang, D., Qiu, X., et al. (2017). BDNF Val66Met polymorphism, life stress and depression: A meta-analysis of gene-environment interaction. *J Affect Disord 227*, 226–235.
Zhi, X., Zhijun, Z., Yanyan, S., Mengjia, P., Yonggui, Y., Xiangrong, Z., et al. (2011). Influence and interaction of genetic polymorphisms in the serotonin system and life stress on antidepressant drug response. *Journal of Psychopharmacology 26*, 349–359.
Zhou, Y., Su, H., Song, J., Guo, L., & Sun, Y. (2014). Association between norepinephrine transporter T-182C polymorphism and major depressive disorder: a meta-analysis. *Neurosci Lett 561*, 64–68.
Zobel, A., Schuhmacher, A., Jessen, F., Höfels, S., von Widdern, O., Metten, M., et al. (2010). DNA sequence variants of the FKBP5 gene are associated with unipolar depression. *International Journal of Neuropsychopharmacology 13*, 649–660.
Zou, Y. -F., Wang, F., Feng, X. -L., Li, W. -F., Tao, J. -H., Pan, F. -M., et al. (2010). Meta-analysis of FKBP5 gene polymorphisms association with treatment response in patients with mood disorders. *Neurosci Lett 484*, 56–61.