Accepted Manuscript

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PII: S0163-7258(18)30156-6
DOI: doi:10.1016/j.pharmthera.2018.09.002
Reference: JPT 7273

To appear in: *Pharmacology and Therapeutics*

Please cite this article as: Xenia Gonda, Peter Petschner, Nora Eszlari, Daniel Baksa, Andrea Edes, Peter Antal, Gabriella Juhasz, Gyorgy Bagdy , Genetic variants in major depressive disorder: From pathophysiology to therapy. Jpt (2018), doi:10.1016/j.pharmthera.2018.09.002

P&T 23274

Genetic variants in major depressive disorder: From pathophysiology to therapy

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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 GxE interactions, on the other hand, are connected to the regulation of stress and the HPA axis and thus could serve as drug targets for a 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 their way in the therapy, the optimization of current medications can be approached by pharmacogenomics, where metabolizing enzyme polymorphisms remain prominent determinants of therapeutic success.

Keywords: Antidepressant drug, Depression, Genetics, Genomics, Pharmacogenetics, Pharmacogenomics

Abbreviations

5HTTLPR Repeat length polymorphism in promoter region of serotonin transporter gene

ABCB1 ATP Binding Cassette Subfamily B Member 1

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 Monoaminoxidase inhibitor

MAOA Monoaminoxidase 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

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 2 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) (Figure 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-gene interactions (GxG), environment x environment (ExE) interactions, rare variants, copy number variations (CNVs) and epigenetic changes may mask effects. However, a prime candidate 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 also 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 be results of different combinations of cognitive characteristics, personality traits and temperaments that coexist and interact in a temporal fashion in an individual with the environmental influences. These may have biological background, thus their genetic basis can be and has been, indeed, examined in association analysis 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 symptoms. Different clusters of

symptoms may represent subtypes of the disease and may be investigated separately for 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 et al., 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, are 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 candidates 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 and 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 Figure 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 et al., 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 et al., 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 et al., 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 et al., 2017), multivariate prediction of treatment success (Kautzky et al., 2015), and the shared genetics and epidemiological multimorbidity with other diseases (Marx et al., 2017).

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 initial years, research focused on testing main effects of variants in major depression, which means that carriers of 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 et al., 2010; Kiyohara and 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 et al., 2014), *HTR2A* rs6311 (Jin et al., 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 et al., 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 and 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., 2017). 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 and Kendler, 2014). Dunn et al (Dunn et al., 2015) systematically reviewed 15 GWASes published before October 2013 conducted on 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 and 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 and 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 and 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 and 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 offspring from the Swedish Extended Adoption Study has proven that genetic factors and rearing experiences contribute equally to depression risk in parent-offspring transmission (Kendler et al., 2017) providing strong evidence for a significant, large role of environmental stressors. In further support, antecedent chronic and acute stressors associated significantly with depression in women, stressors were 2.5 times more likely in depressed than controls and around 80% of depression cases had life events in anamnesis (Hammen, 2005; Hammen et al., 2009). Diverse environmental factors have been connected through evidences 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 et al., 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 et al., 1987). In addition, we would like to point out again to 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 and Karkowski-Shuman, 1997). All these results suggest complex interactions of the genetic background with these stress factors and their synergistic or interaction effects on 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 *5HTTLPR* polymorphism in the promoter region of 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 et al., 2018; Karg et al., 2011; Sharpley et al., 2014), while other three could not replicate original findings (Culverhouse et al., 2018; Munafo et al., 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 on depression between

BDNF Val66Met polymorphism and life stress (Hosang et al., 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 and Serretti, 2013; Naoi et al., 2017; Uher, 2014), although at least four studies presented negative results (Mandelli and 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 and 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 on depression (Mandelli and 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 and Serretti, 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 et al., 2015). Such a connection was supported by some GxE studies – for example *IL1B* and *IL-6* interacted with several stress factors (stressful life events, childhood maltreatment, chronic interpersonal stress) in the background of

depression (Baumeister et al., 2016; Kovacs et al., 2016a; Kovacs et al., 2016b; Tartter et al., 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 and 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 et al., 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 effect on a genome-wide scale (genome-wide gene-environment interaction study, GWEIS) with childhood trauma on depression. In one of them (Van der Auwera et al., 2018), to test these GxE effects on 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 and 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 and 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, 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., 2010b; Petschner et al., 2017; Smoller, 2016). In case of diseases with cognitive involvement, like Huntington's disease, mood disorders can precede the onset of the primary disease with 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 et al., 2010b). 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 with 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., 2016; Rucker et al., 2013). 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 GWASs and GWEISs 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 lead us to another well-known phenomenon, GxG interactions.

GxG interactions are equally promising candidates as GxE interactions (Gage et al., 2016; Taylor and Ehrenreich, 2015) and 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 et al., 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 effect depended on the carrier

status of polymorphisms examined (Bobinska et al., 2016). BCL1 rs41423247 and the CHRNA4 rs1044396 were also shown to interact on current depression scores in a nonclinical sample of 800 (Reuter et al., 2012) and TAAR6 and HSP-70 also could influence each other's effect on a Korean sample for both depression and bipolar disorder, though small sample size may have distorted results (Pae et al., 2010).

However, as in the case of main effect analyses, the only large study conducted to our knowledge could not confirm candidate GxG findings on 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 and 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 et al., 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 et al., 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 et al., 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 et al., 2016)). A promising direction is the incorporation

of background knowledge into machine learning methods 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

On the contrary of the huge variability of genes with possible pathophysiological roles (see Table 5), all current antidepressant medications influence 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 monoaminoxidase inhibitors (MAOIs). As a results of their relatively abundant side effects, more selective substances, like 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. Just 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, like 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 CHRH1 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 of 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 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 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 E. J. 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 et al., 2014), while such effects with non-substrates of ABCB1 were lacking suggesting true influence (Laika et al., 2006; Mihaljevic Peles et al., 2008; O'Brien et al., 2013; Perlis et al., 2010a; 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 and Smith, 1999). The metabolism of antidepressants occurs mainly through CYP2D6, CYP2C9, CYP2C19, CYP3A4 and CYP1A2 isoenzymes (Crisafulli et al., 2011; Spina et al., 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 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 et al., 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 sum of the two reviews, overall 62.5% of studies showed association with metabolizer status and antidepressant adverse events in by 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 remains 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 could prove an association in a combined population of 258 patients for clinical response, but not for remission rates (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 et al., 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 et al., 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 and 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 alleles (Heils et al., 1996), through SNP rs25531 can also be regarded as a triallelic polymorphism (Praschak-Rieder et al., 2007) with possible impact on treatment outcome via increased gene expression in A allele carriers at the latter (Manoharan et al., 2016). Meta-analyses showed better antidepressant treatment response and remission rates with the L and L(A) carriers (Porcelli et al., 2012; Serretti et al., 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 et al., 2010a; Poland et al., 2013; Taylor et al., 2010). Another polymorphism, a variable number tandem repeat (VNTR) in the intron2 of *SLC6A4* implicates enhanced expression in individuals with longer repeats (Murphy and Moya, 2011) and meta-analysis also confirmed better response to antidepressant treatment expressed mostly in Asian patients with the 12/12 genotype (Kato and Serretti, 2010; Niitsu et al., 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 et al., 2006; Villafuerte et al., 2009; Yu et al., 2006), recent studies contradict these findings (Antypa et al., 2013; Basu

et al., 2015; Dong et al., 2016; Kato et al., 2009; Serretti et al., 2013; Zhao et al., 2012a). Moreover, three meta-analyses found no significant effect on antidepressant side effects or treatment response (Kato and Serretti, 2010; Niitsu et al., 2013; Zhao et al., 2012b). 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 in rs7997012 *HTR2A* has been associated with better outcome to 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 Eric J. et al., 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 et al., 2007; Sato et al., 2002; Serretti et al., 2013; Staeker et al., 2014; Zhi et al., 2011) with treatment response, whereas meta-analyses reported mixed results (Lin et al., 2014; Niitsu et al., 2013). Other polymorphisms in *HTR2A*, like rs6311 (Choi et al., 2005; Kato et al., 2006; Kishi et al., 2010) and rs6313 (Kautzky et al., 2015; Kishi et al., 2010; Noordam et al., 2015) also associated with antidepressant response but meta-analyses (Kato and 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 et al., 2009), but results were mostly restricted to female patients (Domschke et al., 2008a; 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 et al., 2009; Peters Eric J. et al., 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, various studies reported opposite allelic association (Baune et al., 2007; Benedetti et al., 2009; Benedetti et al., 2010; Spronk et al., 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). However, 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 et al., 2014; Uher et al., 2009; Wang et al., 2011) and meta-analyses again failed to provide decisive conclusions (Kato and Serretti, 2010; Niitsu et al., 2013; Zhao et al., 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 et al., 2010a; Serretti et al., 2012), subsequent meta-analysis confirmed the relevance of rs1954787 in antidepressant treatment outcome (Kawaguchi and 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 et al., 2008), is rs6265 (Val66Met). Meta-analyses showed the involvement of rs6265 in antidepressant treatment response and remission (Kato and Serretti, 2010; Niitsu et al., 2013; Yan et al., 2014) and some recent studies supported these results (Colle et al., 2015; Murphy 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., 2010a).

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 et al., 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 onto the genome-wide level also in the field of efficacy of antidepressants. Genome-wide association studies (GWASs) associating single-nucleotide polymorphisms on the whole genome to antidepressant response represent a hypothesis-free approach to the problem and theoretically, could reveal polymorphisms which were left out 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 in the other replication control using GENDEP and STAR*D populations (Fabbri et al., 2017). In the 23andME cohort, another SNP in an intergenic region between the *GPRIN3* and *SNCA* gene 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 SSRIs (Li et al., 2016). Antidepressant response 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 administration 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 associate with antidepressant response using the STAR*D population, but in Caucasians results became unconvincing (Antypa et al., 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 associating SNPs with SSRI or NRI treatment response (Tansey et al., 2012). Citalopram response or remission could similarly not associate with genome-wide significance, while below genome-wide significance threshold the most suggestive SNPs were in *UBE3C*, *BMP7*, *RORA* genes (Garriock et al., 2010). In the GENDEP project, outcome after nortriptyline and escitalopram treatment 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 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 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 an SNP in *ANXA2* gene, which, however, could not reach genome-wide significance in a sample of 397 (Menke et al., 2012), while in the GENDEP project a SNP in *GDA* associated with suicidal ideation after medication with different antidepressants and two, one within *KCNIP4* and one near *ELP3* associated after citalopram treatment (Perroud et al., 2012). Roles for polymorphisms of *PAPLN* and *IL28RA* genes were also raised 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 and 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 and Uher, 2012). Earlier results from family studies suggested that there is a GxE interaction in 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 and Uher, 2012), and the effect of these variants could not be supported in metaanalyses or in the STAR*D study (Mandelli et al., 2009), the studies focusing on the pharmacogenetics of these polymorphism have not considered the effects of life events, stressors or environmental influences. Generally, besides *5HTTLPR*, only in case of *CHRH1* and *FKBP5* have there been significant GxE interactions reported concerning efficacy of antidepressant treatment (Keers and 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. 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 and 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 et al., 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 et al., 2008; Murphy and Moya, 2011). Regarding antidepressant treatment, Ramasubbu and colleges 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 that in individuals 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 in depressed patients (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

IL1B (Baune et al., 2010), *NPY* (Domschke et al., 2010b) and *CNR1* (Domschke et al., 2008b) 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 et al., 2017), *BDNF* (Tatham et al., 2017) and *FKPB5* (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 et al., 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 equivocal 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, in 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* seemed to be the most plausible candidates according to recent theories for depression pathophysiology, however, they also fail to replicate, which suggest 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 remained indebted for providing targets that could be replicated in functional studies or that could be bound to the known pathophysiology of depression, except for citalopram and *TSPAN5* and a demonstration of an association between *CYP2D6* and *CYP2C19* with plasma levels, a result already known from candidate gene studies.

All these contradictory results possibly reflect that mechanisms of ADs remain still 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 end environmental influences in drug development and trials should be considered not only as

etiological factors, but through interacting with genes involved in treatment efficacy and side effects, the influence of such stressors should also be considered during antidepressant trials. Thus giving more emphasis to stress and gene x environment interactions both in the development 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*), Ca2+ 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, KTIA_NAP_13-1-2013-0001; KTIA_NAP_13-2-2015-0001 (MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group: Hungarian Academy of Sciences, Semmelweis University and the Hungarian Brain Research Program); 2017-1.2.1- NKP-2017- 00002; MTA-SE Neuropsychopharmacology and Neurochemistry Research Group; 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. Xenia Gonda is recipient of the Janos Bolyai Research Fellowship of the Hungarian Academy of Sciences.

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

Figure 2. Proposed mechanism for the development of depression (Bagdy et al., 2012)

The figure depicts possible interrelations that may shape depression. Genes that may influence the disease directly (Gene set3) 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 set1) in shaping depression.

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

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.

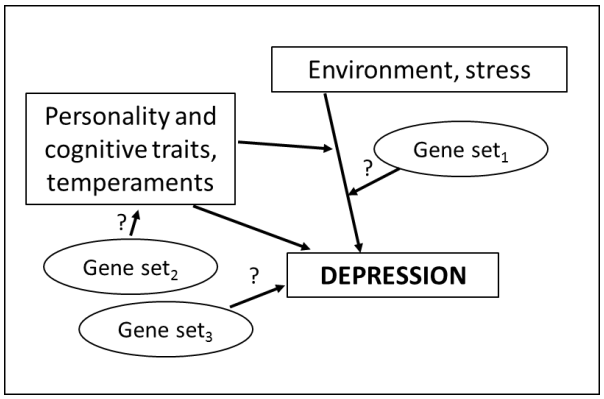
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble 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.

Figure 2. Proposed mechanism for the development of depression (Bagdy et al., 2012)



Gene sets include certain genes and Gene x Gene interactions

The figure depicts possible interrelations that may shape depression. Genes that may influence the disease directly (Gene set3) 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 set1) in shaping depression.

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

Reference	**Discovery sample**	**Findings in the discovery sample**	**Replication sample**	**Replicated findings**
Mbarek et al, 2017 (Mbarek et al., 2017)	NESDA, NTR (European)	*PCLO*	-	-
Power et al, 2017 (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;	44 independent loci; the most remarkable genes, or	-	-

	UK Biobank; 23andMe (all of these: European)	SNPs in genes: *OLFM4*; *NEGR1*; *RBFOX1*; *LRFN5;* *CACNA1E;* *CACNA2D1 ; DRD2;* *GRIK5;* *GRM5;* *PCLO*		
Xiao et al, 2017 (Xiao et al., 2017)	23andMe; PGC; (both: European) CONVERG E (Chinese)	rs9540720 in *PCDH9*	independent 23andMe replication sample (European); a Chinese MDD sample	nominal association of rs9540720 in *PCDH9*
Huo et al, 2016 (Huo et al., 2016)	PGC (European); CONVERG E (Chinese)	-	-	-
Hyde et al, 2016 (Hyde et al., 2016)	23andMe; PGC (both: European)	SNPs in *OLFM4*; *TMEM161B*	independent 23andMe replication sample (European)	nominal associations: *TMEM161B*

		-MEF2C; *MEIS2-TMCO5A*; *NEGR1*		*-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.

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 and 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 and Serretti, 2013)
poor social contacts/support	(Mandelli and Serretti, 2013)
separation	(Mandelli and Serretti, 2013)
interpersonal problems	(Mandelli and Serretti, 2013)
ethnic minority status	(Lopizzo et al., 2015)

Table 4. Gene-environment interaction studies in depression

GxE interactions			
Gene	***Environmental factor***	***Articles***	***Gene function***
5HTTLPR	x stressful life events	(Caspi et al., 2003)	Repeat length

	x childhood maltreatment		polymorphism in the promoter region of serotonin transporter gene (*SLC6A4*) which encodes a protein involved in serotonin transportation.
	x financial difficulties	(Gonda et al., 2016)	
Meta-analyses	-	(Risch et al., 2009)	
	-	(Munafo et al., 2009)	
	+ (only in Caucasians)	(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	(Hosang et al., 2014; Lopizzo et al., 2015; Mandelli and Serretti, 2013; Sharma et al., 2016; Uher, 2014; Zhao et al., 2017)	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.
	x childhood sexual abuse	(Lopizzo et al., 2015; Mandelli and Serretti, 2013)	
MAOA	x childhood maltreatment x maternity difficulty	(Mandelli and Serretti, 2013; Naoi et al.,	Encodes monoamine oxidase A, which catabolizes

	(postpartum depression) (but other four studies did not find interaction)	2017; Uher, 2014)	monoamines (serotonin, norepinephrine, dopamine).
COMT	x stress exposure x family stress (adolescent) x maternity stressors (postpartum depression) x early environmental risk (in men)	(Mandelli and Serretti, 2013)	Involved in metabolism of noradrenalin and dopamine.
FKBP5	x childhood trauma x stressful life events (1 out of 2 studies)	(Dunn et al., 2015; Lopizzo et al., 2015; Mandelli and Serretti, 2013; Sharma et al., 2016; Smoller, 2016)	Regulation of stress-response via HPA axis.
	x traumatic life events	(Lopizzo et al., 2015)	
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 and 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 and 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)	*IL1b* 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; IL1B: 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

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

	Depression diagnosis or sum of symptom scores			**Psychological endophenotypes**			**Symptom clusters**			**Biological involvement according to GeneCard's summaries**				
Gene	**G**	**GxE**	**GxG**	**G**	**GxE**	**GxG**	**G**	**GxE**	**GxG**	**Mono-a**	**Glu/GAB**	**Neurogenesis/neu**	**Immune functions**	**Other/not-known**

										mines	**A**	**ronal projection/ synapse /cell-cell contact**		
APOE	+ #													+ (lipid metabolism)
GNB3	+ #							(+) oncore, psychic anxiety and						+ (G-protein coupled signaling)

							delusion symptoms							
MTHFR	+ #		+ by COMT	(-) on rumination										+ (folate cycle)
SLC6A4 (*5-HTTLPR*)	+/- #	+/- by stressful life events and by childhood malt	(+) by unknown gene on chromosome 4	+/- on neuroticism; - on harm avoidance; - on impulsivity; - on	(+) on impulsivity by childhood trauma; + on rum	(+) on impulsivity by *MAOA*; (+) on impul	(+) on somatization; (+) on dysphoria			+ (5HT)				

		reatment; (+) by financial difficulties		rumination; (+/-) on either depressive, hyperthymic, irritable or anxious temperament; (+)/- on cyclothymic	ination by various types of stress	sivity by *HTR2A*; (+) on impulsivity by *TPH2*; (-) on impulsivity by either								

				temperament		*HTR1A* or *HTR1B*; (-) on rumination by *BDNF*; (-) on TEMPS-A by *DR*								

						D4								
SLC6A3	+ #			(+) on impulsivity						+ (DA)				
HTR1A	-	(+/-) by stressful life events		(-) on impulsivity	(-) on impulsivity by childhood trauma	(-) on impulsivity by either *TPH2*, *5-HTTLPR*, *MAOA*,	(-) on suicidality in depression			+ (5HT)				

						HTR1B or *HTR2A*								
HTR1B	-			(+/-) on impulsivity	(-) on impulsivity by childhood trauma	(+) on impulsivity by *HTR2A*; (-) on impulsivity by eit				+ (5HT)				

						her *TPH2*, *5-HTTLPR*, *MAOA* or *HTR1A*								
HTR2A	-			+/(-) on impulsivity	(-) on impulsivity by childhood trau	(+) on impulsivity by *5-HTTL*	(+) on somatization; (-) on suicidality			+ (5HT)				

					ma	*PR*; (+) on im pul siv ity by *HT R1 B*; (-) on im pul siv ity by eit her *TP H2*, *M*	in dep ress ion							

						AOA or *HTR1A*								
HTR2C	-									+ (5HT)				
TPH1	-							(+) on middle insomnia; (+) on somatic anxiety; (-)			+ (5HT)			

							on MADRS symptom clusters							
MAOA	-	+/- by childhood maltreatment; (+) by maternity difficult			(-) on impulsivity by childhood trauma	(+) on impulsivity by *5-HTTLPR*; (-) on impul	(-) on MDD subgroups			+ (5HT, DA, NA)				

		y				siv ity by eit her *TP H2* , *HT R1 A*, *HT R1 B* or *HT R2 A*								
COMT	-	(+/-) by stre ssfu l life eve	+ by MT HF R	- on impu lsivit y; (+)/- on rumi			(+) on som atiz atio n			+ (D A , A ,				

		nts; (+) by family stress; (+) by maternity stress; (+) by early environmental risk		nation						NA)				
BDNF	-	+ by stre	(+) by	+/- on	(+) on	(-) on						+ (neu		

		ssful life events and by childhood maltreatment	*CRHR1*	rumination; (-) on either depressive, cyclothymic, hyperthymic, irritable or anxious temperament	rumination by adverse events	rumination by *5-HTTLPR*						ronal survival)		
SLC6A2	-	(+) by stre					(+) on som			+ (N				

		ssful life events; (+) by living in rural areas					atization			A)				
DRD3	-									+(DA)				
GABRA3	-										+(GABA)			
ACE	-													+

														(RAS)
CLOCK	-													+ (circadian rhythm)
DRD4	+ #			(-) on impulsivity; (+/-) on either cyclothymic or irritable temperament; (-) on eithe		(+) on impulsivity by *ANKK1*; (-) on TEMPS-A by *5*-				+ (DA)				

				r depressive, hyperthymic or anxious temperament		*HTTLPR*								
SLC6A15	**													+ (neutral amino acid transport)
PCLO	**												+ (synaptic zone	

												cyto matrix)		
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	*			* on extra version										+ (alternative splicing

														regulation)
LRFN5	*											+ (neurite outgrowth, cell adhesion)		
CACNA1E	*			** on neuroticism										+ (calcium channel, skeletal muscle contraction)
CACNA	*													+

2D1														(calcium channel)
DRD2	*			(+/-) on rumination						+ (DA)				
GRIK5	*										+ (Glu)			
GRM5	*										+ (Glu)			
MEIS2-TMCO5A	*													+ (MEIS2 – transcriptional regulator;

														TMCO5A - unknown)
MUC13	*													+ (epithelial mucin)
CNR1	(+)	(+) by stressful life events; (+) by childhood maltreat												+ (endocannabinoid)

		ment												
GABRA 6	(-)	+ by stressful life events									+ (GABA)			
GAL	(+)	(+) by stressful life events and by childhood maltreatment												+ (galanin signaling)

		t												
GALR1	(-)	(+) by stressful life events and by childhood maltreatment												+ (galanin signaling)
GALR2	(-)	(+) by stressful life eve												+ (galanin signaling)

		nts; (-) by childhood maltreatment												
GALR3	(-)	(-) by stressful life events (+) by childhood malt												+ (galanin signaling)

		reatmen t												
IL1B	-	(+) by stressful life events and by childhood maltreatment; (+) by chronic inte											+ (proinflammatory interleukin)	

		rperson al stress												
IL-6	-	(+) by stressful life events + childhood maltreatment; (+) by chronic											+ (proinflammatory interleukin)	

		interpersonal stress												
FAAH	(-)	(+) by childhood maltreatment												+ (endocannabinoid signaling)
NOS1	(-)	(+) by financial hardship												+ (nitric oxide synthase)
MMP-9	(+)		(+) by *M*											+ (extracellul

			MP-2; (+) by *MMP-7*; (+) by *TIMP-2*											ar matrix breakdown)
TIMP-2	(+)		(+) by *MMP-2*; (+) by *MMP-7*; (+) by *M*											+ (extracellular matrix breakdown)

			MP-9											
MMP-7	(+) on middle-age depression		(+) by *MMP-2*; (+) by *MMP-9*; (+) by *TIMP-2*											+ (extracellular matrix breakdown)
MMP-2	(-)		(+) by *MMP-7*; (+) by *M*											+ (extracellular matrix breakdown

			MP-9; (+) by *TIMP-2*											)
BCL1	(-)		(+) by *CHRNA4*											+ (cell cycle regulation)
CHRNA4	(-)		(+) by *BCL1*											+ (cholinergic neurotransmission)
HTR2B				(+) on impulsivity						+ (5HT)				

GRIA3							(+) on guilt (in female only)				+ (Glu)			
GRIK2							(+) on somatic anxiety				+ (Glu)			
5HT2A							(+) on vegetative symptoms			+ (5HT)				
ZNF169	(-)		(+/-) by rs4											+ (unknown,

			769180											probably transcription regulation)
rs4769180	(-)		(+/-) by *ZNF169*											+ (no associated gene)
PRSS12	(-)		+ by rs7587468									+ (excitatory synapse protease)		
rs7587468	(-)		+ by *PRSS1*											+ (no associated gene)

			2											
TMCC3	(-)		(+/-) by rs9940287											+ (unknown)
rs9940287	(-)		(+/-) by *TMCC3*											+ (no associated gene)
KCNAB1	(-)		+ by rs1084302 1											+ (potassium channel)
rs10843021	(-)		+ by *KCNAB1*											+ (no associated gene)
PHF21B		+ (in												+ (unkn

		populations exposed to stress)												own)
CEP350		* (stress of the previous one year)												+ (centrosome and nuclear hormone receptor regulation)
RGS10		* (stress of the												+ (regulator of G-protei

		previous one year)												n signaling)
TAAR6			(+) by *HSPA1A*											+ (putative trace amine recep tor
HSPA1A			(+) by *TAAR6*											+ (stress prote ction)
XKR6				** on neuroticism										+ (unknown)
MSRA				** on neur										+ (meth

				oticism										ionine sulfoxide reduction, repair of oxidized proteins)
LINGO2				** on neuroticism										+ (unknown, possibly involved in negative regulation of

														axonal regeneration)
AGBL2				** on neuroticism										+ (deglutamylation)
CELF4				** on neuroticism										+ (mRNA editing and translation)
ZC3H7B				** on neuroticism										+ (unknown)
BAIAP2				** on neuroticism								+ (neurite gro		

												wth, adapter protein)		
GNL3				* on neuroticism										+ (stem cell regulation)
FAM120AOS				* on neuroticism										+ (unknown)
ANKK1				* on neuroticism; + on impulsivity	(-) on impulsivity by psychosocial stre	(+) on impulsivity by *DRD4*								+ (gene itself not known, but closely linked to DRD

					ss									2)
RPS6KL1				* on neuroticism										+ (unknown)
ZNF646				* on neuroticism										+ (transcription regulation)
CRHR1	+ /(-)	+ / (-) by childhood maltreatment	(+/-) by AVPR1b; (+) by *BDNF*	* on neuroticism									+ (corticotropin releasing hormone receptor)	
SPPL2C				* on neuroticism										+ (signal pepti

														de cleaving)
MAPT				* on neuroticism								+ (axon maintenance)		
L3MBTL2/CHADL				** on neuroticism										+ (L3MBTL2 – transcriptional regulator; CHADL – chondrocyte differ

														entiation)
LINC00461				* on consciousness										+ (unknown)
GBE1				* on extraversion										+ (glycogen solubility and accumulation)
MTMR9				** on extraversion										+ (unknown)
PCDH15				** on extraversion								+ (cell-cell adhesion		

												)		
WSCD2				** on extra versi on										+ (unkn own)
GRIK3				* on neur oticis m							+ (G lu)			
ENAH/S RP9				* on neur oticis m								+ (EN AH - axo n guid ance)		+ (SRP 9 – secret ory protei n guidi ng)
PVRL3				* on neur oticis m								+ (syn apse mai nten ance)		

TMEM192/KLHL2/MSMO1				* on neuroticism									+ (KLHL2 – antigen processing)	+ (unknown – TMEM192; KLHL2 – oligodendrocyte projection development; MSMO1 – cholesterol biosynthesis)
PTPRD				* on								+		

				neuroticism								(neuron differentiation)		
ELAVL2				* on neuroticism										+ (neuronal specific RNA binding)
MAGI1				* on neuroticism								+ (cell-cell junction)		
KATNAL2				* on conscientiousness								+ (microtubule reorgani		

												zation)		
AVPR1b	(-)		(+/-) by *CRHR1*											+ (arginine vasopressin receptor)
TPH2				(-) on impulsivity	(-) on impulsivity by childhood trauma	(+) on impulsivity by *5-HTTLPR*; (-) on im	(+) on suicidality in depression; (+) on suicidal attempt			+ (5HT)				

						pulsivity by either *MAOA*, *HTR1A*, *HTR1B* or *HTR2A*	s							
CREB1				(+) on rumination		+ on rumination								+ (circadian rhythmicity and

						by *KCNJ6*								transcriptional regulation)
KCNJ6						+ on rumination by *CREB1*								+ (potassium channel)
FKBP5	-	+ by childhood trauma; (+/-) by stressfu		- on rumination	+ on rumination by childhood eve								+ (glucocorticoid receptor regulation, steroi	

		l life eve nts			nts							d horm one recep tor regul ation)	
MTHFD 1L				+ on rumi natio n									+ (tetra hydro folate synth esis)
NR3C2				(+/-) on rumi natio n									+ (mine raloc ortoc oid recep tor)
OXTR				(+) on depre ssive									+ (oxyt ocin recep

				temperament; (-) on either cyclothymic, hyperthymic, irritable and anxious temperament										tor)
GSK3β				(-) on either depressive,								+ (neuronal pola		+ (glycogen homeostasi

				cyclothymic, hyperthymic, irritable or anxious temperament								rity and neurite outgrowth)		s)
PPARD				(-) on either depressive, cyclothymic, hyperthymic,										+ (myelinization, transcriptional regulator)

				irritable or anxious temperament										
ARNTL				(+) on cyclothymic temperament; (-) on either depressive, hyperthymic, irrita										+ (circadian rhythm regulation)

				ble or anxious temperament										
hTIM				(+) on hyperthymic temperament; (-) on either depressive, cyclothymic, irritable										+ (circadian rhythm regulation)

				or anxious temperament										
PER3				(-) on either depressive, cyclothymic, hyperthymic, irritable or anxious temperament										+ (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).

(+): 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

*: 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

5HT: serotonin; NA: noradrenaline; DA: dopamine; A: adrenaline; Glu: glutamate