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Understanding the genetic aspects of resistance to antidepressants treatment

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Abstract. **Major depression disorder (MDD) is an extremely prevalent disorder and is expected to be the second leading cause of disease burden by 2020 according to the World Health Organisation (WHO). Moreover, this disease burden is predicted to rise in the next 20 years. Antidepressant medications are vital in the therapy of major depression. However, approximately 30-60% of patients treated with current antidepressant drugs fail to attain remission of depressive symptoms leading to drug resistance. Such patients account for a disproportionately great burden of disease, as supported by cost, augmented disability, and suicidal incidents. Antidepressants resistance remains to challenge mental health care professionals, and more relevant research relating newer medications is necessitated to enhance the quality of life of patients with depression. Enhancement in response rates continues the major challenge in antidepressant research, thus a wealth of potentials still exists concerning the antidepressant resistance for the management of major depression. However, the mechanisms causing resistance to antidepressant treatment remain unknown. Hence, clinical and basic research in understanding the fundamental mechanism of antidepressant resistance should remain a key priority. One potential source accounting for these differences in treatment outcome is genetic variations. The pharmacological mechanisms behind antidepressant response are only partly known but genetic factors play a significant role. Future research of risk factors should assist to advance the understanding of the mechanisms underlying drug resistance in mood disorders and contribute to progress their therapeutic management. Thus, psychiatrists could rely on more effective approaches to treat depressive episodes, reducing the incidence of further drug resistance. This review critically summarises the author's view on many aspects of treatment resistance, specific genetic biomarkers, potential strategies and clinical relevance from both clinical and preclinical studies in drug resistance to antidepressant therapies. Finally, this will allow us to suggest possible recommendations and innovative treatment strategies to improve therapeutic outcomes in managing antidepressant resistance.**

Key Words:
Major depression disorder, Antidepressants, Response rate, Treatment resistance, Candidate genes, Polymorphisms.

Abbreviations

WHO: World Health Organization; MDD: Major Depression Disorder; SSRIs: Selective Serotonin Reuptake Inhibitors; STAR*D: Sequenced Treatment Alternatives to Relieve Depression; AD- Antidepressants; TPH2- Tryptophan Hydroxylase 2; mRNA- messenger RNA; BBB - blood–brain barrier; ABCB1-ATP Binding Cassette Subfamily B Member-1; SNPs - Single nucleotide polymorphisms; 5-HT: 5-Hydroxytryptamine; HTR1A:5-Hydroxytryptamine Receptor 1A; KCNK2: Potassium Two Pore Domain Channel Subfamily K Member-2; TREK1: TWIK-related K+ Channel-1; TRD: Treatment-resistant depression; HPA: Hypothalamic-Pituitary-Adrenal Axis; cyclic GMP: Cyclic guanosine monophosphate; cyclic AMP: Cyclic adenosine; monophosphate; PDE11A: Phosphodiesterase-11A; SLC6A4: Solute Carrier Family 6 Member 4; HTTLPR: Serotonin-Transporter-Linked Polymorphic Region; SERT/5-HTT: Serotonin Transporter; GENDEP: Genome Based Therapeutic Drugs for Depression; CREB: Cyclic Adenosine Monophosphate Response Element-Binding; P2X7: P2X purinoceptor 7; Bcl-2-B-cell lymphoma 2; GRIK- Glutamate Ionotropic Receptor Kainate; FasL: Fas receptor-Fas ligand; BDNF: Brain-Derived Neurotrophic Factor; miRNA: microRNA; IL1β: Interleukin-1 beta; FZD7: Frizzled Class Receptor 7; WNT2B: Wnt Family Member-2B; KO mice- Knock Out mice; TNF: Tumor Necrosis Factor; WT: Wild Type.

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Introduction

Depression is amongst the major public health concerns globally, causing considerable disability and disease burden[1]. It is a debilitating and potentially a chronic illness with substantial morbidity, and a high rate of recurrence and relapse. The MDD has multifactorial aetiology and its heritability is expected to be nearly 35%. It is the third cause for burden worldwide according to the World Health Organization (WHO). The standard treatment approach for major depression is pharmacotherapy. Antidepressant medications are the first-line treatment for major depression, with more than 30 varieties of drugs available[2]. Despite antidepressant, their therapeutic efficiencies are repeatedly not permanent. Most extensively, it is estimated that approximately about 30-60% of patients with a major depressive episode unsuccessful to achieve remission with primary antidepressant (AD) medications[3].

The serendipitous invention of mono-aminergic antidepressants revolutionized the area of mental health. First-line therapy of major depression consists prescription of selective serotonin reuptake inhibitors (SSRIs), nevertheless, several clinical studies suggest that remission rates after two trials of an SSRI are below 50%[4]. Antidepressant medications were discovered and found to be valuable in the treatment of major depression, but, in current years, we must be aware that we are extending their original indications[5]. Their clinical use has been expanded and stretched to the maintenance and prevention of relapse, anxiety disorders and others. Although antidepressant therapies are valuable to numerous patients, existing treatments for depression remain suboptimal due to their drug resistance[6]. Hence, antidepressant resistance in treating major depression patients represents a dilemma for mental health care professionals. This drug resistance issue is currently neglected, but it is noteworthy of research consideration.

Now, there is substantial confusion about the term "drug-resistance" in mood disorders. Lieb and Balter[7] explained the resistance of various patients to antidepressant medications that had earlier been successful. They defined this "drug-resistance" as tachyphylaxis (the increased tolerance to a drug that causes following repeated use). The change to a different antidepressant drug produced appropriate clinical effects, but was followed by refractoriness as well. A century later, a similar phenomenon was explained and associated with long-term low-dose antidepressant drugs[8]. Currently, antidepressant drug resistance is generally defined as an inadequate clinical effect, including non-response, subsequent at least two trials of the suitably prescribed antidepressant drug among patients suffering from major depression[9]. Depression patients who respond to the reinstitution of similar antidepressant medication may exhibit a subsequent loss of clinical effect[10]. This implies that resistance and loss of therapeutic effects may be associated and share a common phenomenon. Another symptomatic associate of treatment resistance is the universal severity of major depression. Further, breakthrough episodes can also occur among patients partially or fully recovered that may lead to the treatment resistance. Besides, misdiagnosis of disease also contributes to treatment-resistant. It includes failure to diagnosis the actual subtype of depression, such as psychotic, atypical, melancholic or bipolar depression, that has a great impact on therapy choice selection and clinical outcome. Hence, it is a major source at both the societal and individual levels, especially when resistance to antidepressants[11,12]. Antidepressants treatment resistance is usually defined as an insufficient clinical response, including non-response, following at least two trials of suitably prescribed anti-depressants among patients suffering from major depression[9]. Resistance to antidepressants is not only general but also leads to deteriorated outcomes, together with further hospitalisations and even elevated mortality rates[13,14]. Furthermore, patients who experience a poor response to general antidepressant medication have augmented disease advancement and larger associated economic costs compared with those experiencing an appropriate response[15,16]. This increases the pressing question of which mechanism triggers this phenomenon. The nature and fundamental reasons for drug resistance can be very diverse. Moreover, the pharmacology of the model and the mechanisms responsible for the drug resistance are not completely understood. Also, advances are still needed in terms of addressing the greater percentage of patients who continue treatment-resistant.

When a depressed patient is unsuccessful in response or only does so partly to an adequate trial of single antidepressant treatment, a variety of new approaches have been proposed as considers what to do further. Unfortunately, the greater parts of these recommendations are unsupported by clinical evidence-based research. Several new approaches can be employed for patients with inad-

equate antidepressant response. Numerous systematic reviews have gone further in their investigation of a broad range of drug therapy options in patients with major depression and an inadequate response to first-line drugs[17,18]. However, most clinical approaches to treating drug-resistant have focused on the following main strategies: the switching, augmentation (dose of medication increased), combination and augment with atypical antipsychotics[19]. Nevertheless, numerous patients remain insensitive to such combination approaches. Besides, it is still preliminary in the clinical development of such combination stratagems and much essential evidence on clinical records concerning efficiency, as well as safety and tolerability, is intensely presumed. The dilemma of antidepressant resistance in major depression is of such magnitude that the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, to establish the subsequent treatment approaches[3]. To identify such combination approaches with more certainty, the large scale of samples or collective analyses will be needed. Many other investigators have previously sought to explore predictors of resistance to different antidepressant treatments and have focused on the guidance of genetic, nutritional, clinical and sociodemographic causes on the advancement of antidepressants resistance. One probable source responsible for these differences in the therapeutic outcome is genetic variations. These diverse groups of patients might, however, be very different in their response nature to presently used antidepressants. Until now, biological markers identifying such significant sub-populations have not been validated yet, so that all pharmacogenetic studies so far use patient characterizations that might not reveal a biologically homogeneous patient population[20-22]. Prediction of the clinical response of an individual patient to a specific antidepressant is not achievable yet and selection of drug treatment is still ruled by the doctor's experience. The ability to predict whether a patient is more likely to show resistance to a specific antidepressant treatment approach would have grander advantages in the management of the major depressive disorder and should be considered among the vital aims of future antidepressants resistance research.

The antidepressant response can be considered to be a multifaceted phenotype, with individual unpredictability ensuing from the interaction between clinical factors and biological pathways, as well as gene x environment interactions[23]. However, up to date, no suitable socio-demographic or clinical biomarkers have developed successfully for the prediction of antidepressant response[24]. Moreover, antidepressant therapy is related to a high rate of poor response, and thus, early biomarker development is vital to manage the treatment resistance. As a result, biomarkers that exhibit high accuracy in predicting antidepressant response would be highly valuable. Major depression has become increasingly clear that it is a heterogeneous disorder, and that antidepressant response, while currently unpredictable is not an arbitrary outcome. Managing patients with treatment resistance with suitable therapy may be greatly assisted by early indicators of poor therapy response. The identification of precise markers and the development of quantifiable methods to evaluate behavioural features related to treatment resistance in depression could support in recommending optimal clinical care, focusing specific vulnerable subgroups and making short-and long-term of treatment approaches. Identification of such risk factors of resistance may be useful to improve early recognition as well as treatment selection and prediction of an outcome in patients with depression. Moreover, the optimization of a treatment response needs an appropriate knowledge of the variables related to resistance to antidepressant medications. Several investigations thus support the use of multi-marker sets in the prediction of antidepressants response. The ultimate goal of our ongoing research is to find genetic variations that are associated with susceptibility to depression/antidepressant drug response and to use this information to identify genetic markers. Besides, patients respond differently to various treatments; some of these variations are attributed to genetic differences. Genes associated with treatment outcome may help expose the pathophysiology of MDD and lead to better treatments. There are very little shreds of evidence may support the primary mechanisms of response to antidepressants treatment, and limited biomarkers are exist than can predict response to pharmacological approach. Recent studies have identified associations of polymorphisms in several target genes with antidepressant treatment response of serotonin reuptake inhibitors and a tricyclic antidepressant. This review article is based on searching the literature indexed in PubMed and the search was performed using keywords 'antidepressants', 'mechanisms of resistance', 'treatment response' genetic variations and polymorphisms. Association results for the polymorphism of various candidate genes (genetic predictors) with p-values are shown in Table I.

Table I. Key genetic polymorphisms of treatment-resistant depression and the results from the current literature.

Chromosome	SNP	Gene	p-value	Reference
7q21.12	rs2032583 rs2235040	ABCB1	p=0.000065 p<0.05	Uhr et al[77] Sarginson et al[78]
18q21.33	rs2279115	Bcl-2	p=0.048	Zhang et al[67]
2q33.3	rs2253206	CREB1	p<0.05	Dong et al[79]
11q23.3	rs1954787	GRIK4	p=0.076	Horstmann et al[80]
5q12.3	rs6295 rs1364043	HTR1A	p=0.033 p=0.045	Villafuerte et al[81]
2q31–q32	rs1880916 rs1549870	PDE1A	p<0.05	Wong et al[50]
12q24.31	rs2230912 rs208294	P2RX7	Not significant association	Viikki et al[63]
17q11.1–q12	rs25531	SLC6A4	p<0.0001	Mrazek et al[82]
12q21.1	rs2171363	TPH2	p<0.042	Zill et al[26]
1q41	rs6686529	TREK1	p=0.00052	Liou et al[83]

Tryptophan Hydroxylase-2 (TPH2)

TPH2 is the rate-limiting enzyme in the synthetic pathway for brain serotonin and is considered a key factor for maintaining normal serotonin transmission in the central neuron system. Several studies suggested that TPH2 is expressed in several brain regions and the greatest expression of TPH2 mRNA is located in the raphe nucleus. A systematic meta-analysis from Gao et al[25] found strong epidemiologic credibility for rs4570625 and significant evidence but weaker credibility for rs17110747 in TPH2. In 2004, Zill et al[26] found two SNPs in TPH2 that were associated with MDD in Caucasians. However, the important biological function of TPH2 attracted many researchers to explore a wider range of SNPs covering exons and introns that might identify genetic risk variants that are associated with MDD[27]. In treatment-resistant patients with major depressive disorder, the AA genotype of the TPH2 rs1386494 polymorphism is associated with severity of depression. This genetic polymorphism might be related to the intensity of treatment-resistant depression.

ABCB1 (MDR1) and P-gp

P-glycoprotein (P-gp) is a transmembrane protein located at the luminal membrane of the endothelial cells that form the BBB. P-gp efflux participates a central role in the BBB transport of several antidepressant drugs. It is encoded by the ABCB1 gene is located on chromosome 7q21. Besides, a growing body of support from clinical and preclinical research has revealed a potentially significant role for P-gp in the brain distribution, and therefore efficacy, of several antidepressant drugs[28]. High P-gp expression is hypothesized to lead to lower and often insufficient brain concentrations of P-gp substrate antidepressants. Interestingly, P-gp function is reported to be elevated in medicated depressed patients' implication that P-gp efflux may be of particular importance in this population[29]. Recent animal studies[30] explained that promoting the brain delivery of antidepressant drugs by P-gp modulation may result in amplified antidepressant effect. These animal studies, which have shown that P-gp knockout or inhibition results elevated brain concentrations of antidepressants. Further research in P-gp knockout mice has also exhibited that P-gp restricts the brain distribution of several antidepressant drugs[31]. Nikisch et al[32] has investigated the relation of ABCB1 gene variants, plasma levels of citalopram and treatment outcome. A few pharmacogenetic studies found an association of ABCB1 and antidepressant treatment outcome[33]. Uhr et al[34] were the first to show that in patients with MDD, specific sequence variants of the ABCB1 gene significantly influenced the treatment success with antidepressants that are substrates of the P-gp, overall, ABCB1 polymorphisms predicted antidepressant drug response. Minor allele carriers of SNPs rs2032583 and rs2235015 had higher remission rates than major allele homozygotes[35]. Finally, the results from numerous clinical investigations proposed that the polymorphism of ABCB1 influenced the short-term antidepressant response in MDD patients.

HTR1A

It is well known that SSRIs rapidly inhibit the serotonin (5-hydroxytryptamine [5-HT]) transporters, within hours, and yet begin to exert an antidepressant response well after they achieve a steady-state level in the human brain. 5-HT1A receptor was identified as mediating initial decrease of the firing of 5-HT neurons[36]. The common polymorphism rs6295 of the serotonin-1A receptor gene (HTR1A) is affecting the transcriptional regulation of the 5-HT_{1A} receptor and has been closely linked to MDD A functional HTR1A C-1019G polymorphism (rs6295) in the promoter region was found to be associated with antidepressant pharmacogenetics in different populations[37]. However, inconsistent and inconclusive results have been obtained. One explanation could be the presence of the C(−1019)G 5-HT1A promoter polymorphism that prevents gene repression of the 5-HT1A autoreceptor[38]. Additionally, it would be important to determine how 5-HT1A agonists affect the expression and activity of key transcriptional regulators of the 5-HT1A receptor gene. Currently used 5-HT1A selective ligands are well known to induce desensitization of 5-HT1A receptors, but should be tested for their ability to alter 5-HT1A gene transcription replication in larger samples of MDD patients is necessary to substantiate these findings.

TREK1

Another remarkable candidate that has newly emerged is KCNK2 (also referred to as TREK1) which encodes a neuronal potassium channel. KCNK2 is a neuronal background potassium channel that is widely expressed in the brain[39]. TREK1 is blocked by SSRIs, and mice deficient the TREK1 gene reveal a depression-resistant phenotype. More recently, TREK1 has also been linked with clinical resistance to antidepressants[40]. Several SNPs within the KCNK2 gene were found to be predictors of non-remission after first and second-line treatments, suggesting that the gene plays a role in TRD. Preclinical studies on animal models have proved that KCNK2 is a downstream target of SSRIs[41]. It was further confirmed the involvement of KCNK2 in treatment resistance showing 12SNPs associated with the outcome[42]. One of the most reliable findings in major depression is of changes in the hypothalamic-pituitary-adrenal (HPA) axis[43]. A subgroup of depressed patients with changes in the HPA axis may be less likely to respond to therapy with antidepressants. One way to conclude this is that very old patients have both elevated cortisol levels and poor response rates to antidepressant drugs[44,45]. Researches using basal HPA evaluation are well-advised to use non-invasive HPA markers whenever possible. This may support the final goal of categorizing patients that are at risk of not responding to primary antidepressants and might need adjuvant or alternative treatments. Additional evidence from various investigations endorses that depressed patients with comorbid anxiety are more likely to be associated with a poor response to antidepressant treatment than those without anxiety[46]. Additionally, depressed patients with co-morbid behaviour diseases are also more resistant to antidepressant medications when paralleled to those without personality diseases[47]. In another investigation, up to 80% of cases of unipolar treatment-resistant depression truly suffered from bipolar spectrum disorders[48]. Nevertheless, these data probably mean that distinctive regions in the kcnk2 gene contribute to particular clinical responses to the first or sequential AD treatment. The KCNK2 gene represents a compelling candidate for influencing antidepressant treatment response based on data from animal models.

PDE11A

PDE11A is an enzyme uniquely enriched in the hippocampus that breaks down cyclic AMP and cyclic GMP equally well. Some studies[49,50] show that phosphodiesterase genes are strongly linked with vulnerability to antidepressant treatment response and major depression disorder. PDE11A KO mice also exhibit significantly higher levels of the pro-inflammatory cytokine IL-6 relative to BALB/cJ and WT mice, respectively. PDE11A gene is associated with major depression and is predictive of antidepressant responses. However, data from Luo et al[51] suggest that the PDE11A global haplotype is associated with both MDD and antidepressant drug response. Remission on antidepressants (fluoxetine or desipramine) was shown to be significantly associated with variations within PDE1A (rs1549870) and PDE11A (rs1880916). Teranishi et al[52], which also used the STAR*D sample, reached a similar conclusion about the involvement of PDE11A in MDD. A more focused study of functions related to the haplotypes in the PDE11A gene will improve our understanding of how genetic factors might contribute to individual susceptibility for major depression and antidepressant drug response.

SLC6A4

The 5-HTT is encoded by the 'solute carrier family 6' (neurotransmitter transporter) member 4 (SLC6A4) gene, at locus 17q11.2. Genetic polymorphism of SLC6A4 (serotonin transporter gene) have been associated in modifying antidepressant drug response to SSRIs, and this linkage is influenced by various ethnicities. SLC6A4 is another noticeable genetic applicant as the serotonin transporter (SERT) is the major site of SSRI action[53]. Genetic studies confirmed the involvement of 5-HT-related targets in the outcome of 5-HT therapy. Several functional polymorphisms have been found in the SLC6A4 gene. Increased transcription of the SLC6A4 gene results in a higher probability of poor antidepressant response. Therefore, SLC6A4 was the prime candidate for a response to the SSRI escitalopram and the first gene to be genotyped and tested in the Genome Based Therapeutic Drugs for Depression (GENDEP) project. For example, different studies indicated a polymorphism in the human gene encoding SERT (SLC6A4*)* as a predictor of response to AD. The majority of published studies suggest that subjects with genotypes that lead to the expression of fewer 5-HTT proteins have an associated greater risk of developing a major depressive disorder. A polymorphism of SLC6A4 has been associated with an increased response to ADs[54]. However, these findings have not been consistently replicated. Many studies investigated the SLC6A4 gene locus role in the SSRI treatment response of MDD and their findings are still a theme of debate. The insertion/deletion functional polymorphism (5-HTTLPR) of the SLC6A4 gene (Long allele) was linked with a greater transcription of the gene and superior antidepressant treatment response paralleled with the S (short) allele in the Caucasian population[54]. However, the lack of association of HTTLPR does not completely rule out the role of SLC6A4 in SSRI response and remission.

CREB1

The transcription factor cyclic adenosine monophosphate response element-binding (CREB) protein has been frequently implicated in the neuronal plasticity, cognition, long-term memory, and pathophysiology, as well as pharmacotherapy of major depression[55,56]. It has also been found to be linked with antidepressant response in patients suffering from depression[57]. Recent research generally proposes that genetic variants in CREB1 could play a key role in both the development of major depression, as well as in the response to antidepressant drugs. The major finding of these studies was an important relation between some genetic variants within CREB1 and the status of antidepressants resistance[58]. In humans, alterations in CREB have been associated with the pathophysiology of depression, as well as the mechanism of antidepressant action and response[59]. Hence, it could be hypothesized that specific genetic variations within CREB might be related to a lower likelihood of recovery from MDD, possibly through differential modulations of gene expression and activation. Indeed, subjects carrying rs2253206, rs4675690 and rs7569963, have been found to have an increased risk of developing TRD[60]. RNA, epigenetic and proteomic biomarkers of antidepressant response define a promising area for the development of new biological tools in psychiatry, both in hypothesis-driven and hypothesis-free approaches.

P2RX7

There has been significant interest in the role of the P2X7 receptor and it has been suggested as a possible drug target in major depression. Single nucleotide polymorphisms in the human P2X7 gene have been associated with MDD. It is a major regulator of proinflammatory cytokines family on microglia. The P2X7 receptor is an ATP-gated non-specific cation-permeable ionotropic receptor selectively expressed in neurons. Previous scholars[61] revealed that P2X7 receptors played an important role in the processing and secretion of mature pro-inflammatory cytokines. Further, in animal models of depression, P2X7 KO mice displayed antidepressant-like profiles in comparison with WT controls[62]. Two functional single-nucleotide polymorphisms located within the P2X7 gene appear to associate with a familial mood disorder, but primary data have not demonstrated any linkage between these SNPs and the risk of TRD or treatment (SSRI) response[63]. Genetic variations in the P2X7R gene have been recently reported in populations suffering from the major depressive disorder, thus providing the P2X7R as a new potential tool to target depression[64]. Overall P2X7 antagonists reduced disease symptoms in a rodent model of depression.

BCL2

The anti-apoptotic protein B-cell/lymphoma 2 (Bcl-2) seems to act as a major regulator of neural plasticity and cellular resilience[65]. Neurotrophins activate the expression of Bcl-2 protein, which protect cells from death and counteract the effects of pathogenic processes damaging brain structure. Recent findings demonstrate that stressful experiences can rapidly increase Bcl-xL protein expression in the cell bodies of 5-HT neurons. Liu et al[66] revealed that untreated MDD patients had lower levels of Bcl-2 mRNA expression than healthy controls. Many findings collectively support the potential role of Bcl-2 in the aetiology of MDD and antidepressant treatment outcome. Acute antidepressant treatment can increase the mRNA expression of Bcl-2 only in non-treatment-resistant depression (NTRD) patients, but not among those with TRD. The key finding of Zhang et al[67] analysis was a significant association between rs2279115C allele and TRD among male patients. These initial findings strengthen the hypothesis that BCL2 may play an important role in mediating the outcome of antidepressant treatment.

GRIK4

GRIK4 gene, which codes for the kainic acid-type glutamate receptor KA1, a type of neurotransmitter receptor subunit helps to form a glutamate receptor. There is a strong association between impaired regulation of glutamatergic signaling and behavioral disorders. Genetic variants in the glutamate receptor gene GRIK4, which encodes the glutamate kainate receptor subunit GluK4 is expressed in the hippocampus and exerts a modulatory effect on synaptic plasticity, clearly alter the susceptibility for major depressive disorder and other mood disorders[68]. Association of the newly identified GRIK4 marker rs1954787 also remained significant. STAR*D trial identified an association of treatment response with polymorphisms in the GRIK4, GRIN2A and GRIK1 genes, each of which encodes proteins contributing to glutamatergic signaling. Milanesi et al[69] observed the involvement of GRIK4 in TRD and in the risk of developing psychotic symptoms during depressive episodes. There is considerable uncertainty regarding the putative relationships between all genes (including GRIK4) and antidepressant treatment response. Milanesi et al[70] suggests that several independent associations were detected and that common variation in the GRIK4 gene is associated with treatment-resistant depression. The role of the GRIK4 gene coding for glutamate receptors need to be investigated, could be a possible modulator of TRD.

Fas/FasL System

Fas, a cell surface receptor, interacts with its natural ligand FasL (CD95L) to initiate a death signaling cascade, leading to apoptosis. It is relevant to neurogenesis and neuroplasticity *via* death-receptor mediated cell signaling systems[71]. Taking in consideration the link between neurogenesis and the mechanism of action of antidepressant drugs, and the recently recognized function of Fas/FasL system in neurogenesis and neuritogenesis, it may be hypothesized that the variability of AD therapeutic effect may be influenced by differential expression of Fas/FasL system. Santos et al[72] suggest an association of FAS-670A4G genetic polymorphism with resistance to antidepressant treatment and poor prognosis in depressed patients.

Other Potential Genes

The induction of neurogenesis is associated with improved neuroplasticity, which in turn, leads to a normalization of the depressed brain function[73]. The neurotrophic hypothesis of depression guides a linkage between effects on neuroplasticity and clinical response to antidepressants therapy. Also, the decreased levels of BDNF and lower methylation rates at CpG sites within the BDNF promoter have been most frequently associated with antidepressant response[74]. Recently, the investigation of miRNA in major depression has been increasing rapidly and numerous researchers have identified associations between miRNA and major depression or antidepressant response[75]. Current results suggest that IL1β mRNA concentrations are an important predictive and mediator biomarker. Belzeaux et al[76] established that the level of expression of the pro-inflammatory cytokine tumor necrosis factor (TNF) was also a good predictor of antidepressant response. More recently, gene expression study of the candidate gene panel discovered and confirmed the influence of the candidate genes ABCB1, FZD7 and WNT2B on antidepressant drug resistance. The significance of these genes as possible biomarkers for antidepressant drug

resistance was further confirmed. Nevertheless, more investigations are warranted to better measure the truth of these biomarkers and to replicate all these results in an independent cohort.

Discussion

Resistance to antidepressant treatment continues to challenge mental health care professionals, and more significant research relating to newer drugs is warranted to advance the quality of life of patients with major depression. Novel biomarker-based new antidepressant medications are on the horizon to deal further with the multiple complex issues of treatment-resistance. It is important to note that to date negligible research has focused on discovering animal models of antidepressant resistance, although there is promising interest in this field. Well-designed clinical trials offer strong evidence-based results for antidepressant therapy for treatment-resistance, but there are several complexities in interpreting their results. Moreover, the study of individual genetic linkages with antidepressant therapy response has been challenging, with no genome-wide studies discovering replicated signals for the association. Modern accomplishments in discovering the genetic components of psychiatric disorders are supporting, but progress in identifying the genetic component to treatment response or resistance remains slower. Extended cohorts study will be needed to discover the genetic association of antidepressant response or resistance, a crucial step if defined medication in major depression is to become achievable. Given the concern related to medication failure and the lack of suitable pretreatment factors for non-response, clinicians have attempted to discover early predictors of clinical effect to implement antidepressant approaches before their usually admitted onset of action. Hence, psychiatrists could rely on further effective clinical strategies to treat depressive episodes, decreasing the occurrence of further resistance. There is a requisite for additional high-quality investigation regarding the use of add-on therapy in major depressed patients and clinical resistance to antidepressant treatment. It is vital to avoid pessimism. In STAR*D clinical study, the collective remission rate after four trials of antidepressant therapy was 67%. Further investigations of antidepressant resistance to maintain an initial treatment response are needed. Hopefully, this review provides recent information on antidepressant drug resistance, opens new research developments on treatment resistance depression at preclinical levels and makes clinician's choice easier at clinical levels.

Limitations

This article aims to review the most current literature on antidepressant treatment response, resistance and associated genetic predictors. We did our best to retrieve all the relevant published literature associated with the genetic variations contribute to antidepressant resistance to summarize all the crucial candidate genes. However, there are a lot of limitations related to this review that, understanding the basics involved in the antidepressant treatment resistance is a multifaceted subject, with countless definitions are existing in the available literature, and is beyond the scope of our article. Only key literature related to treatment resistance and their potential candidate genes is referred to and quoted in this article.

Conclusions

The practice of evidence-based pharmacological treatment approaches is primarily recommended for the treatment of MDD. However, a substantial proportion of MDD patients do not respond to initial AD therapy. AD resistance significantly contributes to the disability and costs related to the management of MDD. Results gained from these data; numerous genetic biomarkers are now allowed to predict an elevated risk of poor response to AD treatment. The pharmacogenetic markers include the polymorphism of TPH2, ABCB1, Pgp, HTR1A, TREK1, PDEIIA, SL6A4, CREB1, P2RX7, BCL2, GRIK4, Fas/FasL system, BDNF and many other candidate genes. Comprehensively, these results suggest that identifying appropriate candidate genes may further highlight the potential importance of treatment resistance to AD in humans. These potential approaches make research on treatment-resistance high importance for new AD research advances at both the preclinical and clinical levels.

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Conflict of Interests

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