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In Review

From Pharmacogenetics to Pharmacogenomics: The Way Toward the Personalization of Antidepressant Treatment

Chiara Fabbri, MD[1]; Stefano Porcelli, MD[1]; Alessandro Serretti, MD, PhD[2]

[1]Researcher, Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy.

[2]Professor, Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy.
Correspondence: Institute of Psychiatry, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy; alessandro.serretti@unibo.it.

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Objective: Major depressive disorder is the most common psychiatric disorder, worldwide, yet response and remission rates are still unsatisfactory. The identification of genetic predictors of antidepressant (AD) response could provide a promising opportunity to improve current AD efficacy through the personalization of treatment. The major steps and findings along this path are reviewed together with their clinical implications and limitations.

Method: We systematically reviewed the literature through MEDLINE and Embase database searches, using any word combination of "antidepressant," "gene," "polymorphism," "pharmacogenetics," "genome-wide association study," "GWAS," "response," and "adverse drug reactions." Experimental works and reviews published until March 2012 were collected and compared.

Results: Numerous genes pertaining to several functional systems were associated with AD response. The more robust findings were found for the following genes: solute carrier family 6 (neurotransmitter transporter), member 4; serotonin receptor 1A and 2A; brain-derived neurotrophic factor; and catechol-*O*-methyltransferase. Genome-wide association studies (GWASs) provided many top markers, even if none of them reached genome-wide significance.

Conclusions: AD pharmacogenetics have not produced any knowledge applicable to routine clinical practice yet, as results were mainly inconsistent across studies. Despite this, the rising awareness about methodological deficits of past studies could allow for the identication of more suitable strategies, such as the integration of the GWAS approach with the candidate gene approach, and innovative methodologies, such as pathway analysis and study of depressive endophenotypes.

De la pharmacogénétique à la pharmacogénomique : la voie vers la personnalisation du traitement par antidépresseur

Objectif : Le trouble dépressif majeur est le trouble psychiatrique le plus commun dans le monde entier, et pourtant, les taux de réponse et de rémission sont toujours insatisfaisants. L'identification des prédicteurs génétiques de la réponse aux antidépresseurs (AD) pourrait présenter une occasion prometteuse d'améliorer l'efficacité actuelle des AD par la personnalisation du traitement. Les étapes et les résultats majeurs de cette démarche sont examinés conjointement avec leurs implications cliniques et leurs limitations.

Méthode : Nous avons effectué une revue systématique de la littérature dans les bases de données MEDLINE et Embase, à l'aide de toute combinaison des mots « antidépresseur », « gène », « polymorphisme », « pharmacogénétique », « étude d'association pangénomique », « GWAS ou EAPG », « réponse », et « réactions indésirables aux médicaments ». Les travaux expérimentaux et les revues publiés jusqu'en mars 2012 ont été retenus et comparés.

Résultats : De nombreux gènes liés à plusieurs systèmes fonctionnels ont été associés à la réponse aux AD. Les résultats les plus solides ont été trouvés pour les gènes suivants : famille du transport des composants 6 (neurotransmetteur transporteur), membre 4; récepteurs de sérotonine 1A et 2A; facteur neurotrophique dérivé du cerveau; et catéchol-*O*-méthyltransférase. Les études d'association pangénomique (EAPG) ont produit nombre de principaux marqueurs, même si aucun d'eux n'était pangénomiquement significatif.

Conclusions : La pharmacogénétique des AD n'a encore produit aucune connaissance applicable à la pratique clinique régulière, car les résultats étaient principalement inconsistants entre les études. Malgré cela, la prise de conscience grandissante des déficiences méthodologiques d'études antérieures pourrait permettre l'identification de stratégies plus appropriées, comme l'intégration de l'approche des EAPG avec l'approche de gènes candidats, et de méthodologies innovatrices, comme l'analyse des trajectoires et l'étude des endophénotypes dépressifs.

The hypothesis of a genetic component in AD response arose from the observation that mood disorders and treatment response often show a familiar clustering.[1] Subsequent studies have suggested that genetic polymorphisms contribute about 50% or more to AD response,[2] allowing the spread of rising optimism about the possibility to dramatically improve MDD prognosis. Since the birth of AD pharmacogenetics in the 1990s, studies have been based on the candidate gene approach, that is, the analysis of genetic variants selected a priori on the base of preclinical evidence (molecular biology and animal models). Although this method allowed for the identification of the most replicated predictor of AD response thus far (the 5-HTTLPR polymorphism[3]), it produced mainly inconsistent findings. Indeed, candidate gene studies show a fundamental limitation: the multiple loci with small effect size involved in treatment response are not detectable by this approach in real-world sample sizes. In the last years, GWASs have been an attempt to overcome this issue. Indeed, GWASs can provide unbiased information about outcome-associated variation in almost all genes in the genome, opening the way toward pharmacogenomics. Nonetheless, as we underline further on, GWASs also show some limitations, and that initial promises were not kept. Regardless, strategies to solve the limitations of past pharmacogenetic studies could be carried out, as we later discuss.

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
5-HTTLPR	serotonin-transporter-linked polymorphic region
AD	antidepressant
BDNF	brain-derived neurotrophic factor
COMT	catechol-*O*-methyltransferase
CRH	corticotropin releasing hormone
CRHR	CRH receptor
CYP	cytochrome P450
CYP2D6	CYP, family 2, subfamily D, polypeptide 6
CYP2C19	CYP, family 2, subfamily C, polypeptide 19
DRD2	dopamine receptor D2
FKBP5	FK506 binding protein 5
GNB3	guanine nucleotide binding protein (G protein), beta polypeptide 3
GR	glucocorticoid receptor
GRIK4	glutamate receptor, ionotropic, kainate 4
GWAS	genome-wide association study
HPA	hypothalamic–pituitary–adrenal
HTR1A	5-HT receptor 1A, G protein-coupled
HTR2A	5-HT receptor 2A, G protein-coupled
l	long
MAOA	monoamine oxidase A
MDD	major depressive disorder
NR3C1	nuclear receptor subfamily 3, group C, member 1 (GR)
P-gp	permeability glycoprotein
rs	reference SNP
s	short
SLC6A4	solute carrier family 6 (neurotransmitter transporter), member 4
SNP	single-nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TCA	tricyclic AD
TPH	tryptophan hydroxylase
VNTR	variable number tandem repeat

Methods

In our review, we aimed to trace the growth of AD pharmacogenetics, underlying major findings and limits, the clinical implications, and possible future perspectives. To reach this objective, both reviews and experimental works published until March 2012 were collected through MEDLINE and Embase database searches, using any word

Clinical Implications

- The spread of genotyping procedures in clinical practice could become a reality if specific cost-effectiveness indications could be provided.
- Genotyping prior to treatment beginning may provide tailored therapies.
- Ethical issues linked to genotyping procedures (genetic knowledge and deoxyribonucleic acid banking) should be considered.

Limitations

- AD pharmacogenetics have not produced any knowledge applicable to routine clinical practice yet, as results were mainly inconsistent across studies.
- Technical and methodological limitations are thought to be responsible for the inconsistency in results.
- The integration of complementary methodologies (GWAS, pathway analysis, candidate gene sequencing), and the investigation of endophenotypes, may help to disclose the supposed 40% to 50% of variance in response owing to genes.

Table 1a Most investigated polymorphisms regarding AD response and side effects (treatment-emergent suicidal ideation was not included): serotoninergic genes

Gene	Polymorphism	Drug class	Therapeutic effect	Study reference numbers	Side effects	Study reference numbers
			Serotoninergic system			
SLC6A4	5HTTLPR	SSRIs	+27, –9	12, 92–125	+4, –6	97, 106, 117, 119, 126–131
		Other or mixed	+6, –5	123, 132–141	+2, –3	133, 142–145
		Augmented	+2	127, 146	+1	127
	STin2 VNTR	SSRIs	+6, –3	104, 107, 110, 113, 118, 120, 122, 138, 147	+1, –1	126, 142
		Other or mixed	+3, –1	109, 120, 135, 138	–1	145
	rs25531	SSRIs	+1, –5	96, 105, 106, 110, 111, 148	+1	106
		Other or mixed	–2	12, 140		
HTR1A	rs6295 (–1019C/G)	SSRIs	+7, –5	16, 21, 104, 118, 149–156	–1	128
		Other or mixed	+1, –2	21, 157, 158		
	rs1800042 (Gly272Asp)	SSRIs	+1, –2	151, 155, 159		
HTR1B	rs6298	SSRIs	+1	153		
	rs6298 and rs6296	Other or mixed	+1	158		
	rs130058	SSRIs	+1, –1	153, 160		
HTR2A	rs6311 (1438G/A)	SSRIs	+2, –2	119, 154, 161, 162	+3, –2	119, 131, 163–165
		Other or mixed	–3	141, 158, 166	–1	145
	rs6313 (102T/C) (in LD with rs6311)	SSRIs	–3	118, 154, 167	–2	128, 130
		Other or mixed	+1	134	+1	168
	rs6314 (452His/Tyr)	SSRIs	+1, –1	135, 169	–1	128
	rs7997012	SSRIs	+3, –1	154, 169, 170		
		Other or mixed	+2, –1	58, 171, 172		
	rs1928040	SSRIs	+1	173		
		Other or mixed	+2, –1	58, 171, 172		
	rs9316233 and rs2224721	SSRIs	+1	174		
HTR3A	rs1062613 (178C/T)	SSRIs			+1, –4	119, 128, 130, 163, 175
	rs33940208, rs1176713	Other or mixed	–1	158		
HTR3B	rs1176744 (A27373G)	SSRIs			+1, –3	128, 130, 163, 175
HTR6	rs1805054 (C267T)	SSRIs	–2	154, 176		
		Other or mixed	+1, –2	135, 177, 178		
TPH1	rs1800532 (A218C)	SSRIs	+4, –7	103, 104, 118, 154, 179–185	–2	129, 185
		Other or mixed	–1	186	+1, –1	143, 145
TPH2	1463G/A	SSRIs	+2	24, 104		
		Other or mixed			–1	187
	rs7305115	Other or mixed	+1	158		
	rs7305115 and rs4290270	Fluoxetine or olanzapine in TRD	+1	188		

+ = studies that found a positive result; – = studies that did not detect any association; Asp = aspartic acid; Gly = glycine; His = histidine; LD = linkage disequilibrium; STin2 = second intron VNTR polymorphism; TRD = treatment-resistant depression; Tyr = tyrosine

Table 1b Most investigated polymorphisms regarding AD response and side effects (treatment-emergent suicidal ideation was not included): other genes

Gene	Polymorphism	Drug class	Therapeutic effect	Study reference numbers	Side effects	Study reference numbers
		Noradrenergic system				
COMT	rs4680 (Val108/158Met)	SSRIs	+3, –2	27, 189–192		
		Other or mixed	+3	193–195	+1	143
	rs4633, rs4818 and rs769224	Other or mixed	+1	196		
MAOA	VNTR 1.2 kbp upstream the coding sequence	SSRIs	+1, –4	104, 167, 184, 197, 198	+1	165
		Other or mixed	+2, –1	31, 199, 200	–1	145
	rs1137070 and rs6323	Other or mixed	+1	196		
SLC6A2	rs2242446 (T-182C)	Other or mixed	+1, –2	12, 138, 141	–1	145
	rs5569 (G1287A)	Other or mixed	+2, –1	120, 138, 141		
	rs36024	Fluoxetine or olanzapine in TRD	+1	188		
		Dopaminergic system				
SLC6A3	3′ UTR 40-bp VNTR	Other or mixed	+2	132, 201		
DRD4	3rd exon 48-bp VNTR	SSRIs	–1	202		
		Other or mixed	+1	203		
		HPA axis				
FKBP5	rs1360780	SSRIs	+2, –2	42, 48, 204, 205		
		Other or mixed	+2, –3	46, 47, 174, 205, 206		
		Other or mixed	+1, –3	46, 47, 172, 206		
NR3C1	rs1876828, rs242939, rs242941 haplotype	SSRIs	+1	41		
		Other or mixed	+1	40		
		Signal transduction pathways and growth factors				
BDNF	rs6265 (196G/A)	SSRIs	+5, –2	207–213	+1	212
		Other or mixed	+3, –4	50, 213–218		
GNB3	rs5443 (C825T)	SSRIs	+1, –2	118, 219, 220	–2	164, 220
		Other or mixed	+6, –1	21, 95, 216, 221–224	+1	223
OPRM1	rs540825	SSIRs	+1	225		
		Other or mixed	–1	226		
		Enzymes				
ACE	insertion or deletion	Other or mixed	+5, –1	227–231		
GSK3B	rs334558 (–50 T/C)	SSRIs	+1	232		
		Lithium augmented	+2	233, 234		
IDO2	rs2929115 and rs2929116	SSRIs	+1	235		
		Glutamatergic system				
GRIK4	rs1954787	SSRIs	+1	55		
		Other or mixed	+1, –2	56, 57, 226		
		Pharmacokinetics				
ABCB1	rs2032582 (G2677T/A)	SSRIs	+3, –3	62–64, 67, 68, 236	–1	67
		Other or mixed	–2	64, 66	–1	66
	rs1045642 (C3435T)	SSRIs	+1, –3	62, 67, 68, 236	–	67
		Other or mixed	–1	237	+1, –1	237, 238
	rs1882478, rs2235048, rs2235047, rs1045642, rs6949448 haplotype	SSRIs	+1	239		

+ = studies that found a positive result; – = studies that did not detect any association; *ABCB1* = ATP-binding cassette, subfamily B (multi-drug resistance/transporter associated with antigen processing), member 1 gene [encodes P-gp];
ACE = angiotensin I converting enzyme; bp = base pair; *DRD4* = dopamine receptor D4; *GSK3B* = glycogen synthase kinase 3 beta;
IDO2 = indoleamine 2,3-dioxygenase 2; kbp = kilo base pair; Met = methionine; *OPRM1* = opioid receptor, mu 1;
TRD = treatment-resistant depression; UTR = untranslated region

combination of "antidepressant," "gene," "polymorphism," "pharmacogenetics," "genome-wide association study," "GWAS," "response," and "adverse drug reactions." Only the main candidate genes and polymorphisms are discussed in the body of our text, while a more comprehensive view of the findings is given in Table 1 (1a and 1b) for candidate gene studies and in Table 2 for GWASs.

Pharmacogenetic Findings

Candidate Gene Studies

Monoaminergic System

The monoaminergic system was the first and more extensively investigated in AD pharmacogenetics, as the monoaminergic theory is the theoretical basis for most of the current AD pharmacological treatments.[4] As one of the main targets of AD drugs, the 5-HT transporter *SLC6A4* gene is a priori an excellent candidate. Interest in this gene particularly grew after an insertion–deletion polymorphism (5-HTTLPR) within the promoter was reported to affect the transcription level.[5] Indeed, the 5-HTTLPR l allele was associated with twice the basal expression, compared with the s allele, making this variant a potential modulator of the central serotoninergic neurotransmission. Despite preclinical evidence and association of the variant with several psychiatric disorders with affective symptomatology as well as with personality traits related to mood disorders,[6] pharmacogenetic studies did not provide univocal findings[2,3] (Table 1a). A possible explanation can be found in the very different 5-HTTLPR allelic frequencies across populations: indeed, the s allele is present in 42% of Caucasians, but in 79% of Asians.[7] Consistently, pharmacogenetic studies mainly suggested that the l allele was associated with better response in Caucasians, especially for SSRIs, while in Asians results were more contradictory.[2] Although 3 meta-analyses were focused on the 5-HTTLPR l/s variant,[3,8,9] the role of the polymorphism was not definitively clarified. Contrasting findings may also be due to other genetic variants within the *SLC6A4* gene or related genes, which could concur to gene expression regulation, such as the rs25531, 3 novel alleles identified within the promoter,[10] and a VNTR in the second intron of the gene.[11] Thus a more comprehensive knowledge of *SLC6A4* variants and their functional effect should be a good base for future pharmacogenetic studies. Recent studies tried to dissect other possible stratification factors, particularly those of a clinical nature. In other words, 5-HTTLPR may predict AD response only in groups of patients with MDD with particular clinical or behavioural features, as standard diagnostic criteria for MDD are not based on biological mechanism. For example, the s allele was associated with poor AD response only in patients with anxious depression.[12] Other authors reported an effect of 5-HTTLPR on some personality traits that may, in turn, modulate AD efficacy.[13] In this view, the detection of depressive endophenotypes may allow for identifying groups that shared higher genetic load related to a particular condition, such as AD response (refer also to Conclusion).

Among serotoninergic genes, 5-HT receptors were also widely investigated, especially 5-HT receptors 1A (*5-HTR1A*) and 2A (*5-HTR2A*). The *HTR1A* gene was labelled as a good candidate because several ADs desensitize raphe *5-HT1A* autoreceptors, leading to an enhancement of the serotonergic neurotransmission that could be associated with the AD effect. Moreover, the blocking of *HTR1A* autoreceptors may lead to faster AD action[14] and was the theoretical basis for the clinical use of *HTR1A* blockers such as pindolol. Within the *HTR1A* gene, rs6295 was the most investigated polymorphism because the G allele was associated with an upregulation of the receptor.[15] Thus the risk allele may lead to a higher number of inhibitory *HTR1A* autoreceptors and contrast with the efficacy of ADs. As well as for 5-HTTLPR, rs6295 may also only have a role in AD response in a group with particular clinical features, as reported for melancholic MDD.[16]

The hypothesis of a role of the *HTR2A* gene in AD effect arose from the observation that agonists of this receptor showed euphoriant effects.[17] Further, it has been hypothesized that the AD effect of paroxetine and nefazodone is due to a regulation of 5-HT2A receptors, at least partially.[18,19] Among the most studied 5-HTR2A polymorphisms, we found rs6313 and rs6311, 2 variants in high linkage disequilibrium.[20] It has been suggested that rs6311 may interact with other 5-HT-related genes, that is, *GNB3* (rs5443) and *SLC6A4* (rs25533), in determining short-term AD response.[21] An effect on drug-related adverse events was reported by more than one study (Table 1a).

Given that it codes for the enzyme catalyzing the rate-limiting step in 5-HT biosynthesis, the *TPH* gene has also been a relevant subject in pharmacogenetic research. *TPH* isoform 2 seems to be a more promising candidate gene than *TPH1*, as it is more selectively expressed in the brain.[22] Two interestingly functional polymorphisms have been identified within this gene: arginine441/proline447 and 1463G/A, which resulted in a reduction of 5-HT synthesis by about of 55% and 80%, respectively.[23,24] More recently, another functional polymorphism that needs further investigation was identified: rs7305115.[25]

From the perspective of the monoaminergic theory of MDD, key molecular components of the noradrenergic system have also been extensively investigated. Among them, the most investigated were the *COMT* and *MAOA* genes (which are clearly also involved in other systems, such as the dopaminergic one), which code for the main enzymes responsible for monoamine metabolism. Within the *COMT* gene, the attention was especially focused toward the functional rs4680 polymorphism,[26] which may affect SSRI response through the modulation of the dopamine bioavailability in the prefrontal cortex.[27] Several studies reported an association between rs4680 and AD response, even if it is still unclear as to what is the favourable genotype (Table 1b).

Within the *MAOA* gene, the most studied variant is a VNTR, located 1.2 kbp upstream of the gene coding sequence. This variant regulates the transcriptional level and was linked

to variations in the enzyme activity.[28] This was found to reflect the concentrations of 5-hydroxyindoleacetic acid (the main metabolite of 5-HT) in cerebrospinal fluid.[29] Despite promising preclinical findings, several pharmacogenetic results were negative, but 2 recent studies reported an association between this variant and mirtazapine response,[30,31] supporting the need for further investigation (Table 1b).

Finally, among the most studied noradrenergic genes, we underline the norepinephrine transporter solute carrier family 6 (neurotransmitter transporter), member 2 (*SLC6A2*) gene, which codes for one of the main targets of TCAs. Pharmacogenetic studies were focused on numerous polymorphisms within this gene reporting some evidence of association, but confirmatory findings are needed.

The dopaminergic system was less investigated, compared with the previous ones, although both preclinical[32] and clinical data[33] underlined its involvement in the pathogenesis of MDD. Particularly, a specific role for dopaminergic impairment in melancholic depression was proposed.[34] Intriguingly, it has also been suggested that an excessive dopaminergic stimulation could even be detrimental for depressed patients.[35]

Several studies support *DRD2* involvement in AD pharmacodynamics, leading to the hypothesis that the dopaminergic–mesolimbic pathway may represent a final common pathway in AD action.[36] Nevertheless, pharmacogenetic studies investigating the functional polymorphism rs1801028 (S311C) harboured by *DRD2* repeatedly reported negative findings. Conversely, promising results were reached for rs4245147,[37] although confirmations are still lacking.

HPA Axis

HPA axis dysfunction is one of the main neuroendocrine abnormalities found in MDD, as it was reported to affect up to 70% of depressed patients.[38] The pathogenesis, treatment, and course of MDD were hypothesized to be linked to HPA axis hyperactivity.[39] The main neuroendocrine regulator of the HPA axis is the CRH, and in the central nervous system *CRHR1* and *CRHR2* are the 2 fundamental types of CRH receptors. Several polymorphisms within the *CRHR1* gene were associated with AD response, particularly the rs242941 and 1 haplotype, including 2 other SNPs beyond rs242941 (rs1876828 and rs242939).[40,41] Interestingly, the association was more robust for a cluster of patients with anxious depression, although a further study failed to replicate the result.[42] Regarding the *CRHR2* gene, a positive correlation was reported for rs2270007.[42] Recently, confirmations for both these genes were provided, also with positive findings for the CRH-binding protein gene.[43]

On a lower level along the HPA axis, the GR (coded by the *NR3C1* gene) acts as a nuclear receptor to regulate the transcription rate of genes controlling the development, metabolism, and immune response. The inactive form of the GR is bound to various proteins, including the FKBP5 protein (FK506-binding protein 5),[44] which seems to modulate the GR sensitivity. Thus genetic variants within the *FKBP5* gene were hypothesized to be involved in the dysregulation of stress response duration.[45] Given their role within the glucocorticoid signalling pathway, both *NR3C1* and *FKBP5* are promising candidate genes. Concerning *FKBP5*, rs1360780, rs3800373, and rs4713916 were associated with AD response.[46–48] Nevertheless, negative findings exist as well, while *NR3C1* was less studied and results still need replication (Table 1b).

Signal Transduction Pathways and Growth Factors

Neuronal growth is regulated by an intricate and poorly decoded network of events in which neurotrophins play a key role. The *BDNF*, a member of the nerve growth factor superfamily, was found underexpressed during depressed states,[49] and it has been hypothesized that AD treatments may work through the reestablishing of such balance.

The most investigated genetic variant within the *BDNF* gene is rs6265 (196G/A), with an involvement in AD response that is supported by an increasing body of evidence, although it is still controversial whether allele or genotype has to be considered the risk factor.[11] This mismatch may be partially linked to different ethnicity in the examined samples,[50] as considerable *BDNF* allele and haplotype diversity among global populations was reported.[51] Other promising polymorphisms within the gene include rs11030104, which was found to interact with the temperamental trait harm avoidance in predicting AD response.[50] The neurotrophic tyrosine kinase, receptor, type 2 gene, which codes for the *BDNF* receptor, has recently received attention.[52]

Among signal transduction proteins, previous studies mainly focused on the *GNB3* gene, which codes for the beta polypeptide of guanine nucleotide binding protein (G protein). Owing to the great complexity generated by G proteins in the signal transduction cascade and their wide diffusion, they have been hypothesized to be involved in neuronal plasticity.[53] The most investigated variant within the *GNB3* gene is rs5443 (Table 1b), as it was associated with the occurrence of a splice variant that showed an altered activity.[54]

Finally, after the first association reported in the STAR*D between the *GRIK4* gene and citalopram response,[55] subsequent studies investigated the involvement of glutamatergic receptor genes in AD response,[56,57] treatment-emergent suicidal ideation (*GRIK2*, *GRIA3*),[58] and sexual dysfunction (*GRIK2*, *GRIA1*, *GRIA3*, and *GRIN3A*),[59] but inconsistent results were reported (Table 1b).

AD Pharmacokinetics

Genes coding for proteins involved in the transport and metabolism of ADs were considered possible modulators of drug–plasma level and concentration at target sites. P-gp, coded by adenosine triphosphate-binding cassette, subfamily B (multi-drug resistance/transporter associated with antigen processing), member 1 gene (*ABCB1*), and the CYP superfamily were the main subjects of research, as the former regulates drug efflux across endothelial cells, including the blood–brain barrier,[60] and the latter includes the major enzymes responsible for AD phase I oxidative

reactions.[11] Another source of interest came from the discovery of functional variants within these genes. Both rs2032582 and rs1045642 were associated with alteration of P-gp expression and (or) function,[61] and they were repeatedly associated with AD efficacy,[62–65] even if negative findings exist as well.[66–68]

The high polymorphic nature of the genes coding for CYP enzymes made them one of the main subjects in AD pharmacogenetics. The known alleles show normal, reduced and (or) absent, or increased activity, allowing to distinguish different theoretical metabolic classes.[69] Pharmacogenetic studies were mainly focused on *CYP2D6* and *CYP2C19* genes, as they code for the main isoforms involved in AD metabolism. Quite consistent evidence suggest that *CYP2D6* and *CYP2C19* genotypes can predict plasma levels of target ADs, but a direct correlation between drug–plasma concentrations and clinical outcomes was not found for most ADs.[69] Despite no definitive knowledge, *CYP2D6* poor metabolizers appear to have lower tolerance to TCAs as well as to venlafaxine, whereas they have an average tolerance to other ADs.[70] Dose adjustments for different metabolizing groups were calculated, even if prospective validations should be performed before a routine application in clinical practice.[71] Nevertheless, the available evidence about CYP genes' impact on drug metabolism was consistent enough for the approval of the AmpliChip test by the Food and Drug Administration. It is a genotyping test that enables classification of people for their *CYP2D6* and *CY2C19* phenotype[72] and made the actual application of genotyping to psychiatric clinical practice nearer. Nevertheless, given the lack of evidence linking this test to clinical outcomes and cost-effectiveness studies, guidelines do not yet recommend its use in clinical practice.[73] The overcoming of methodological deficits of previous pharmacogenetic studies on CYP genes (for example, evaluations performed after a single or a limited number of drug doses with no data about the steady state, a lack of homogeneity in AD treatment and population studied, and that fail to consider that the deficit of one enzyme can be balanced by other isoforms) could plug these gaps in knowledge.

From Pharmacogenetics to Pharmacogenomics: GWASs

In recent years, the shift from the study of single genes to GWASs has progressively become a need, as increasing evidence suggested that the candidate gene approach was not enough to disclose the genetic complexity of mood disorders and AD response. GWASs overcome the need for an a priori hypothesis, a major limitation of candidate gene studies, as AD mechanisms of action are not fully understood.[36] Conversely, biological plausibility is not needed for a convincing statistical association, as there are many examples of previously unsuspected candidate genes showing highly compelling associations.[74] The usefulness of this new approach in genetic studies was demonstrated in several fields of medicine,[75] with evidence that the GWAS is a powerful method for the identification of genes involved in common multifactorial diseases.

Currently, 3 large trials implemented the GWAS approach to detect genetic variants associated with AD response: the STAR*D study ($n = 1953$),[76] the Genome-based Therapeutic Drugs for Depression (also known as GENDEP) project ($n = 706$),[77] and the Munich Antidepressant Response Signature (also known as MARS) project ($n = 339$).[78] None of these studies reported results that achieved genome-wide significance; however, they found top markers (Table 2) that should be further investigated to clarify their role. There may be several reasons for the lack of genome-wide significant results and for the nonreplication of previous findings. First, the inadequate sample size, as our current knowledge suggests that future GWASs will need samples of tens of thousands rather than the thousands traditionally used.[79] This issue may be overcome by the use of large replication samples, as made possible thanks to the growth of controlled-access data repositories.[80] Another issue is placed on a technical level. Indeed, reliable genotyping should be extended to polymorphisms present in less than 5% of the population and also rare variants (less than 1% of the population), which cannot be detected through current GWAS technology. Moreover, the available genotyping platforms are able to provide only a relatively narrow genomic coverage (for example, less than 50% in the STAR*D).[81] A third relevant issue pertains to phenotype definition. In fact, mood disorders show a wide range of clinical presentations and standard diagnostic criteria could not completely reflect them, also because these standard criteria are not based on biological evidence. Thus the effect of numerous stratification factors may be a source of bias.[82] Finally, we underline that the GWAS only allows for the detectection of genetic regions of interest. Therefore, for a better underpinning of the role of each genetic variant within a region identified by a GWAS, a re-sequencing of the region is likely needed, as well as the further study of the variants identified through the candidate gene approach. And last but not least, GWASs focus on individual SNPs of interest, while probably the focus should be moved to pathways of interest, where an average significant association is observed across many variants within the same pathway.[83]

Conclusion

Despite the identification of several genetic variants associated with AD response, a clinical impact for pharmacogenetics is still lacking. Nevertheless, clinical applications of pharmacogenetic research have already produced relevant effects in other fields of medicine, especially oncology,[84,85] allowing for careful optimism in psychiatry.

Results achieved so far suggest that a more comprehensive and suitable strategy to cover the complexity of the AD effect should not only be based on a wide analysis of genetic predictors but also should consider the interaction among them (Gene × Gene) as well as their interaction with clinical and environmental modulators (Gene × Environment).

Table 2 Top genome-wide association markers found within the STAR*D study, the GENDEP project, and the MARS project

Study	Diagnosis	Sample size and ethnicity	AD	Top markers (Chr, gene)	Outcome: phenotypic value	Pathway analysis
Garriock et al[76] (STAR*D study)	MDD	*N* = 1491 for RE and *N* = 1351 for RM Non-Hispanic Caucasian: *n* = 1067 (71.5%) African Americans: *n* = 241 (16.2%) Hispanic Caucasians: *n* = 183 (12.3%)	Citalopram	rs6966038 (7, *UBE3C*) rs6127921 (20, *BMP7*) rs809736 (15, *RORA*)	RE, compared with NRE: 4.65E-07 RM, compared with NRM: 3.63E-07 RE, compared with NRE: 3.45E-06 RM, compared with NRM: 1.07E-06 RE, compared with NRE: 8.19E-06 RM, compared with NRM: 7.64E-05	—
Uher et al[77] (GENDEP project)	MDD	*N* = 706 Caucasian (European)	Escitalopram (*N* = 394) or nortriptyline (*N* = 312)	rs1126757 (6, *IL11*) rs2500535 (6, *UST*)	% change in MADRS during escitalopram treatment: 2.83E-06 % change in MADRS during nortriptyline treatment: 3.56E-08	—
Ising et al[78] (MARS project)	MDD, BP	MARS sample[a]: *n* = 339 Caucasian (European) German replication sample: *n* = 361 STAR*D: *n* = 832 white subjects	Mixed	rs6989467 (8, *CDH17*)[a] rs1502174 (3, *EPHB1*)[a]	Early partial RE: 7.60E-07 Early partial RE: RE, RM: 8.50E-05	3 clusters: 1. *FN1* 2. *ADAMTSL1* 3. *EDN1*

[a] Discovery sample

ADAMTSL1 = ADAMTS-like 1; *BMP7* = bone morphogenetic protein 7; BP = bipolar disorder; *CDH17* = cadherin 17, LI cadherin (liver-intestine); Chr = chromosome; E = environmental deviation; *EDN1* = endothelin 1; *EPHB1* = EPH receptor B1; *FN1* = fibronectin 1; GENDEP = Genome-based Therapeutic Drugs for Depression; *IL11* = interleukin 11; MADRS = Montgomery–Åsberg Depression Rating Scale; MARS = Munich Antidepressant Response Signature; NRE = nonresponse; NRM = nonremission; RE = response; RM = remission; *RORA* = RAR-related orphan receptor A; *UBE3C* = ubiquitin protein ligase E3C; *UST* = uronyl-2-sulfotransferase

Indeed, the so-called flip-flop phenomenon, that is, the interaction of multiple loci and environmental effects in determining susceptibility to complex diseases, may lead to ambiguous results.[86] To overcome this phenomenon, the analysis of multiple variant interactions is needed. One of the most promising approaches to reach the objective is pathway analysis, that is, the analysis of genetic variants within genes involved in the same biological pathway.[78,83] Pathway analysis may yield more insights into disease biology because it overcomes the genetic heterogeneity bias (for example, owing to population stratification, differential rates of genotyping error between subjects and control subjects). Indeed, if the genes in question are members of the same biological pathway, then considering the pathway as the unit of analysis may increase power to detect association and to replicate findings across studies.[87] Conversely, clinical, environmental, and neurobiological modulators may increase the specificity of genotyping. Therefore, the detection of more homogeneous groups of MDD patients (the so-called endophenotypes) may increase the power to detect specific predictors of AD outcome. Nevertheless, no single MDD feature is able to define an endophenotype, but the endophenotype is characterized by specific properties, in particular:

1) the endophenotype is heritable;
2) the endophenotype is primarily state-independent (manifests in an individual whether or not illness is active);
3) within families, endophenotype and illness cosegregate; and
4) the endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population.[88]

Thus endophenotypes are measureable characteristics that fill "the gap between available descriptors and between the gene and the elusive disease process."[89, p 1766] Currently, behavioural and neural factors and biomarkers were tested for their meaningfulness in defining MDD endophenotypes.[90] The results suggested that particular

neuroimaging markers, such as diencephalon volume, may be useful in identifying MDD endophenotypes based on the endophenotype ranking value (commonly referred to as ERV), an index for measuring the strength of association with genetics of endophenotypes.[91] Conversely, the use of behavioural factors for defying endophenotypes may be more difficult, as they are state-dependent. This suggests that the integration of genetics with neuroscience and molecular biology may be a promising strategy for application in future studies.

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