Review

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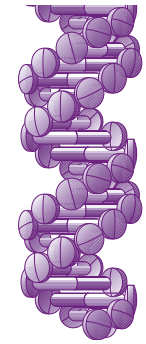
Pharmacogenomics



Pharmacogenomics of autism spectrum disorder

Autism spectrum disorder (ASD) is characterized by persistent deficits in social communication and interactions as well as restricted, repetitive behaviors and interests. Pharmacologic interventions are often needed to manage irritability, aggressive behaviors and hyperactivity. Pharmacogenomic studies have investigated genetic associations with treatment response and side effects in an attempt to better understand drug mechanisms in hopes of optimizing the balance of symptom improvement versus side effects. The majority of pharmacogenomic studies to date have focused on antipsychotics, antidepressants and stimulants that are the most commonly utilized medication classes for ASD. This review is a comprehensive examination of the existing pharmacogenomic studies in ASD highlighting the current state of knowledge regarding genetic variation influencing pharmacokinetics and pharmacodynamics, and associated clinical outcomes.

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Autism spectrum disorder (ASD) is often identified early in development and characterized by persistent deficits in social communication/interactions, as well as restricted, repetitive behaviors and interests [1]. The currently estimated prevalence of ASD is reported to be one in 68 children [2], with a greater prevalence in males than females at a ratio of approximately 4.5:1 [3]. Symptom presentation and response to interventions are highly variable which has resulted in a number of studies examining the genetic underpinnings of disease risk as well as treatment response. The purpose of this comprehensive review is to examine the literature regarding pharmacogenomic investigations in ASD and describe the clinical implications of this work.

The multifactorial etiology of ASD includes considerable variation in clinical presentation with evidence to suggest strong genetic and environmental components underlying disease risk [4,5]. ASD is strongly linked with other genetic diseases, which account for approximately 3–10% of cases (i.e., Fragile X syndrome, Rett syndrome, among others). Family studies including mono- and dizygotic twin studies have also shown a very high concordance for ASD in monozygotic twins (~90% in social impairment), while lower in dizygotic twins or siblings (~20% concordance) [6,7]. Disease–risk investigations estimate that hundreds of genes or rare variants may contribute to ASD susceptibility within a given individual [8]. Genome-wide association studies have identified potential regions associated with disease, including between *CDH10* and *CDH9* [9] genes as well as within the *MACROD2* gene [10], although at the time of this publication these have not yet been replicated. Common variants have been shown to account for approximately 15–40% of the inherited risk for ASD [11–13]. As noted in a recent review [5], it is likely that

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the development of ASD is due to a large number of variants in multiple genes and a minority of *de novo* single nucleotide variants (SNVs) and copy number variant cases. In addition to support of a genetic contribution to etiology, twin studies have provided evidence as high as 55% for shared environmental factors [14].

Primary treatments of ASD include nonpharmacologic interventions, such as specialized educational approaches to improve symptoms, quality of life and promote independence [15]. The use of psychotropic medications in individuals with ASD serve in an adjunct manner to manage comorbid conditions (i.e., anxiety and mood disorders) as well as symptoms of aggression, irritability, hyperactivity and self-injurious behaviors that may be detrimental and/or prohibitive to the patient's behavioral therapy or quality of life [15]. Over a third of patients with ASD are prescribed psychotropic medications to assist with symptom management. The most commonly utilized medications are antipsychotics (most notably risperidone and aripiprazole), selective serotonin reuptake inhibitors (SSRIs) and stimulants [16]. Additionally, approximately 10% of patients report the use of three or more medications in these major drug classes [16]. Other commonly used medications include α-2 agonists and anticonvulsant/mood stabilizers.

Pharmacogenomics is generally defined as how an individual's genetics contribute to response to medications. Pharmacogenomic studies can help us better understand the variability in treatment response and tolerability with clinical implications for optimizing drug selection and dosing strategies based on genetic information. In the context of neuropsychiatric disorders, these studies generally describe how differences in metabolism can impact serum levels of medications, or how polymorphisms in specific pharmacodynamic targets (e.g., receptors, transporters, among others) result in altered binding affinity or expression. Variation in either example (i.e., pharmacokinetic and/or pharmacodynamics) may result in differences related to clinical response and the frequency of adverse effects. This is especially true for neuropsychiatric disorders, where the medications commonly prescribed can have considerable variability in their metabolism (i.e., through mutations in the *CYP2D6* and *CYP2C19* genes) and formation of metabolites, as well as the target receptors (i.e., dopamine receptors, transporters, among others).

This variation in response is seen in several medications prescribed to patients with ASD. Antipsychotic agents, such as aripiprazole [17–19] and risperidone [20] have indications for the treatment of irritability symptoms in children and adolescents with ASD. Trials suggest that the proportion of participants improved or very much improved ranges from 50 to 67% as compared with 16–35% of placebo control groups [17,18]. The benefits of these two agents are limited by the risk of weight gain, movement disorders and prolactin elevation that are commonly observed in patients [21]. Antidepressants, while not indicated for ASD, are used in 13–25% [16,22] of patients with global improvement response rates in randomized clinical trials of SSRIs ranging from 33 to 43% [23]. The caveat to the more recent and larger SSRI evaluations [24] is the substantial placebo response observed in some studies [25]. Additionally, dose-related sensitivities to SSRI-associated irritability and aggression are commonly observed. As an example, 23–38% of participants in the largest SSRI study to date reported adverse effects of this nature [24]. The clear clinical benefits to some (but not all patients) along with risks for potentially severe side effects, advocate for evaluations of how to best use these agents and who is most likely to benefit [25]. These issues may often be ameliorated with conservative dose titrations in order to avoid excessive side effects. Numerous genes involved in the metabolism (i.e., *CYP2D6* and *CYP2C19*) and pharmacodynamic aspects of these medications (i.e., dopamine and serotonin system genes) have been implicated in the safety and efficacy of antipsychotic and antidepressant medications, with some consistencies as well as some differences across diagnoses (i.e., psychosis, mood disorders and ASD).

Individuals with ASD face unique challenges in today's healthcare system, specifically in transitioning from adolescence to adulthood. Recently, Hall *et al.* highlighted the challenges faced by young adults with ASD [26], including difficulties in navigating the current healthcare system, appointment logistics (i.e., waiting rooms), and difficulties in understanding and communicating with providers. Pharmacogenomics offers the potential to alleviate some of these issues by identifying individuals most likely to respond to specific medications (as well as which medications might be avoided) and aid in dose selection and titration strategies of some of the commonly utilized psychotropic medications. The current state of the science and clinical implications of ASD pharmacogenomics is reviewed herein.

Methods

To identify relevant studies, we conducted a comprehensive search of the electronic database PubMed using various combinations of keywords including 'autism', 'ASD', 'pharmacogenetics', 'pharmacogenomics', 'polymorphism', 'ASD', 'α agonist', 'antipsychotic', 'aripiprazole', 'atomoxetine', 'citalopram', 'clonidine', 'escitalopram', 'fluoxetine', 'fluvoxamine', 'guanfacine', 'methylphenidate', 'mood stabilizer', 'paroxetine', 'sertraline', 'SSRI', 'stimulant', 'risperidone' and 'valproate'. Articles were also identified through cited references in

other papers. All articles identified as examining the impact of pharmacogenomics in ASD populations were included within the review. These included pharmacogenomic studies, antipsychotic, antidepressant, and stimulant medications. While clinical studies of other medications (e.g., mood stabilizers, atomoxetine, among others) were identified, to date there are not published pharmacogenomic studies of these drugs in the context of treating ASD.

Antipsychotics

Risperidone and aripiprazole are both indicated for the treatment of irritability in ASD, and have been shown to provide benefit in regard to irritability and aggression [18,20,27]; however, use of these medications is often limited by weight gain, extrapyramidal symptoms and increase in serum prolactin levels (in the case of risperidone). The majority of research thus far related to antipsychotic pharmacogenomics in ASD pertains to clinical response and adverse effects (predominantly weight gain and the increase of serum prolactin levels) in regard to risperidone.

Drug metabolism

Risperidone is primarily metabolized by the drug-metabolizing enzyme CYP2D6 to the active metabolite 9-hydroxyrisperidone (now marketed as paliperidone) [28]. With over 100 SNV and a common copy number variant resulting in whole gene deletion or duplication [29], CYP2D6 activity can range from no activity (i.e., poor metabolizers [PMs]) to individuals with one or more functional allele duplications (i.e., ultra-rapid metabolizers) resulting in higher than normal expression levels and metabolic capacity [30]. Thus, PMs will experience much higher concentrations of risperidone at standard dosing as compared with ultra-rapid metabolizers, who will have much higher levels of 9-hydroxyrisperidone [31,32]. Although the ratio of risperidone/9-hydroxyrisperidone varies considerably between poor and ultra-rapid metabolizers, the combined steady-state concentrations of risperidone and 9-hydroxyrisperidone are not significantly different across *CYP2D6* genotypes. The maximum concentration of the parent drug (risperidone) is approximately 80% higher in poor as compared with extensive metabolizers (8.99 ± 4.2 vs 5.01 ± 2.14 ng/ml, respectively), and the AUC of PMs is approximately 33% higher than extensive metabolizers when considering combined risperidone plus 9-OH-risperidone concentrations [33]. Little pharmacokinetic data are available for ultra-rapid metabolizers, although increased CYP2D6 metabolism would be hypothesized to decrease parent drug half-life and lower maximum concentrations. Notably, aripiprazole is also a substrate for CYP2D6 with dosing recommendations based on *CYP2D6* genotype within the package insert [34]. Aripiprazole, like risperidone, has an active metabolite (dehydroaripiprazole), which adds complexity to the consequences of genetically altered CYP2D6 metabolism. While there is a dearth of literature regarding its pharmacogenomics as it relates to ASD, the influences of genetic effects on pharmacokinetic parameters may be of use for dosing [35]. Dose/concentration ratios of aripiprazole to dehydroaripiprazole appear to be increased in CYP2D6 PMs 30–66% [36,37].

Symptom response

Correia *et al.* examined 15 variants across eight genes in 45 autistic children/young adults 3–21 years of age (average of 8.7 years) being seen in a Portuguese hospital who were taking risperidone alone for up to 1 year (Table 1) [38]. Specifically, this study examined treatment response relationships with genes involving drug metabolism (*CYP2D6*), drug transport (*ABCB1*), dopamine signaling (*DRD2*, *DRD3*) and serotonin signaling (*HTR2A*, *HTR6*, *HTR2C*). Safety and efficacy was determined utilizing the Autism Treatment Evaluation Checklist (ATEC) at 1, 3, 6 and 12 months after the start of risperidone. The ATEC is a validated instrument that can be completed by parents, teachers or caretakers and assesses aspects of communication, social interactions, cognitive awareness and physical behavior. On an average, ATEC scores in all participants taking risperidone were significantly reduced (improved) over the course of 1 year. Participants with the AA or AG genotype of the -1438G>A (rs6311) SNV in the promoter region of the *HTR2A* gene (conferring increased expression) [39] experienced 2% lower ATEC scores (better response) than those with the GG genotype, while those with the TT or CT genotype of the 1236C>T (rs1128503) SNV in the *ABCB1* gene had 4.7% lower ATEC scores than those with the CC genotype. Conversely, participants with the TT (encoding for the serine amino acid shown to have less dopamine affinity as compared with C/glycine carriers; rs6280) [40] genotype of the *DRD3* gene scored 3.9% higher overall on ATEC scores as compared with those with the CT or CC genotypes. The *HTR2A* and *DRD3* findings in relation to symptom improvement are consistent with trends observed in adult psychosis patient populations treated with antipsychotics [41,42]; however, it is important to note that these are relatively small clinical differences.

Youngster *et al.* [43] evaluated clinical response as determined by parents and the treating neurologist as a function of *CYP2D6* genotypes (testing up to 34 alleles and allele duplications) in an observational cohort of 40 Israeli children (34 males; 3–18 years of age) with

Table 1. Pharmacogenomic studies in individuals with autism spectrum disorder.

Medications	Genes		Main findings		Ref.
Antipsychotics					
Risperidone	*CYP2D6*	PK	Drug metabolism	Significantly higher RIS levels and RIS to 9-OH-RIS ratio in PMs compared with EMs (RIS levels: ninefold higher in PMs than in EMs/IMs)	[31,43]
				No significant differences in 9-OH-RIS or total active moiety plasma levels across the *CYP2D6* genotypes or CYP2D6 activity score.	[31,32,43]
			Symptom response	2 out of 2 PMs responded to treatment, but 2 out of 2 UMs had no response to treatment	[43]
			Weight gain	Significantly lower increase in BMI (kg/m^2) and waist circumference in UMs compared with homozygous EMs (BMI: 4.8% lower increase in UMs than in EMs)	[38]
			Prolactin elevation: conflicting results	Higher prolactin level in PMs compare to other metabolizer status, but no statistical analyses were done due to the small sample size (Prolactin levels: 2.5-fold higher in PMs than in EMs)	[44]
				No significant differences in prolactin levels among the *CYP2D6* genotypes and predicted phenotypes	[45]
	ABCB1	PD	Symptom response	*ABCB1* c. 1236C>T (rs1128503) polymorphism was significantly associated with clinical improvement from risperidone therapy (ATEC scores: 4.7% higher in CC than in TT or CT genotype)	[38]
	DRD2	PD	Prolactin elevation: conflicting results	Significant differences in prolactin levels across the *DRD2* Taq1A (rs1800497) genotype groups (Prolactin levels: 1.4-fold higher in A2A2 or A1A2 than in A1A1 genotype)	[45]
				No statistically significant *DRD2* Taq1A (rs1800497), -141C Ins/Del (rs1799732), and C957T (rs6277) genotype effects on risperidone-induced prolactin elevation	[44,46]
	DRD3	PD	Symptom response	*DRD3* Ser9Gly (rs6280) polymorphism was significantly associated with clinical improvement from risperidone therapy (ATEC scores: 3.9% higher in TT than in CT or CC genotype)	[38]
	HTR2A	PD	Symptom response	*HTR2A* c.1438G>A (rs6311) polymorphism was significantly associated with clinical improvement from risperidone therapy (ATEC scores: 2% higher in GG than in AA or AG genotype)	[38]
	HTR2C	PD	Weight gain	Protective effect of the variant T allele of the *HTR2C* -759C>T (rs3813929) against risperidone-induced weight gain (Weight gain: 1.8-fold increase in CC than in TT or TC genotype)	[47]

5-HTTLPR: Serotonin-transporter-linked polymorphic region; 9-OH-RIS: 9-hydroxyrisperidone; ATEC: Autism treatment evaluation checklist; COMT: Catechol-*O*-methyltransferase.; EM: Extensive metabolizer; IM: Intermediate metabolizer; LEP: Leptin; MC4R: Melanocortin receptor 4; Misc: Miscellaneous; PD: Pharmacodynamic; PK: Pharmacokinetic; PM: Poor metabolizer; RIS: Risperidone; UM: Ultra-rapid metabolizer; VNTR: Variable number tandem repeat.

Table 1. Pharmacogenomic studies in individuals with autism spectrum disorder (cont.).

Medications	Genes		Main findings		Ref.
Antipsychotics (cont.)					
Risperidone (cont.)	Energy balance genes: *FTO*, *MC4R*, *LEP*, *CNR1*, *FAAH*	Misc	Weight gain	Polymorphisms found to be significantly associated with antipsychotic-induced weight gain: *CNR1* (rs806378 and rs1049353), *LEP* (rs7799039)	[48]
	Peripheral blood gene expression	Misc	Symptom response	Expression of exons within 5 genes was correlated with the behavioral response to risperidone treatment: *GBP6*, *RABL5*, *RNF213*, *NFKBID*, and *RNF40*	[49]
SSRIs					
Fluvoxamine	5-HTTLPR (*SLC6A4*)	PD	Symptom response	Significantly better response to fluvoxamine treatment in patients with L/L or L/S genotype compared with S/S genotype	[50]
Escitalopram	*CYP2C19*	PK	Symptom response	No statistically significant differences in symptom improvement and final daily dose across CYP2C19 metabolizer groups	[51]
	5-HTTLPR (*SLC6A4*)	PD	Symptom response: conflicting results	The smallest improvement in patients who had S/S genotype without the intron 1 TT/TT diplotype (low expression group) compared with intermediate or high expression group	[52]
				No statistically significant differences in the rate of symptom improvement over time and dosing trajectory across 5-HTTLPR genotype groups	[53]
Stimulants					
Methylphenidate	*DRD1–DRD5*, *ADRA2A*, *SLC6A3*, *SLC6A4*, *MAOA*, *MAOB*, *COMT*	PD	Symptom response	Polymorphisms found to be significantly associated with response: *DRD1* (rs5326 & rs4867798), *DRD3* (rs6280), *DRD4* (rs11246226), *ADRA2A* (rs1800544), *SLC6A3* (VNTR), *SLC6A4* STin2 (VNTR), and *COMT* (rs4680)	[54]
			Tolerability	Polymorphisms found to be significantly associated with tolerability: *DRD2* (rs6275) and *DRD3* (rs6280)	[54]

5-HTTLPR: Serotonin-transporter-linked polymorphic region; 9-OH-RIS: 9-hydroxyrisperidone; ATEC: Autism treatment evaluation checklist; COMT: Catechol-*O*-methyltransferase.; EM: Extensive metabolizer; IM: Intermediate metabolizer; LEP: Leptin; MC4R: Melanocortin receptor 4; Misc: Miscellaneous; PD: Pharmacodynamic; PK: Pharmacokinetic; PM: Poor metabolizer; RIS: Risperidone; UM: Ultra-rapid metabolizer; VNTR: Variable number tandem repeat.

ASD taking risperidone. Their results are limited due to the limited numbers of poor (n = 2) and ultra-rapid (n = 2) metabolizers, although they describe both of the PMs as having desirable symptom improvements, but with accompanying side effects and conversely neither of the ultra-rapid metabolizers were noted to have a clinical response [43].

Finally, Lit *et al.* [49] investigated whether or not gene expression levels from peripheral blood samples prior to risperidone treatment predicted responders via the Aberrant Behavior Checklist Irritability subscale (ABC-Irr) in 42 children (79% male, 57% Caucasian) with ASD around 9 years of age. Risperidone dose was titrated up, starting at 0.5 mg at bedtime for 4 days, increased to 1 mg at bedtime for 4 days, and if tolerated up to 1.5 mg/day for 8 weeks. After participants were subgrouped into high and low responders, peripheral blood expression of five genes were significantly associated with percent change in ABC-Irr, including *GBP6*, *RABL5*, *RNF213*, *NFKBID* and *RNF40* [49].

Weight gain

Weight gain is a common adverse effect of second-generation antipsychotics, leading to an increased risk of cardiovascular disease and metabolic syndrome in patients taking them [55]. Variation in specific pharmacogenes (i.e., *HTR2C*, *LEP*, *PER*) has been shown to either increase or decrease the extent of an individual's risk of weight gain when taking a second-generation antipsychotic for other psychiatric conditions [56]. There appear to be some differences identified in the patterns of weight gain across antipsychotic

agents in younger patients as compared with adults [57] underscoring the importance of investigating genetic associations with this phenotype across the lifespan.

Nurmi *et al.* [48] examined weight gain in 184 predominantly Caucasian male children with ASD taking risperidone over 8 weeks with several genes involved in energy balance pathways. Of note, two SNV in the cannabinoid receptor gene (*CNR1*; rs806378 and rs1049353) and one SNV in the leptin gene (*LEP*; rs7799039) were shown to have significantly greater increases in BMI. Regarding the *CNR1* gene, the rs806378 SNV showed an increase in BMIs of 1.85 in the TT genotypes, 1.57 in the TC genotypes and 1.34 for the CC genotype group, while for the rs1049353, SNV increases in BMI were 1.25 for the GG genotypes as compared with 1.49 for those with the AG or GG genotypes. The rs779039 SNV in *LEP* showed BMI increases of 1.37 and 1.43 in the GG and AG genotypes, and just 1.07 in the AA genotype group. Interestingly, the authors also describe that change in weight increases when the previously described SNV are found in combination, suggesting an additive effect with increasing risk alleles [48].

Hoekstra *et al.* [47] reported on 32 children (28 males) from 5 to 16 years of age with a diagnosis of pervasive developmental disorder taking risperidone [47]. Consistent with results seen in adults [58,59], children with the -759C>T SNV (rs3813929; 22% of the cohort) in the *HTR2C* promoter region experienced less increase in BMI-standardized z-scores (z = 0.64 ± 0.35 or 3.23 ± 1.47kg noncarriers vs z = 0.043 ± 0.017 or 1.84 ± 1.51 kg in carriers) over 8 weeks, inferring that having the T allele may have a protective effect against weight gain with risperidone use. Younger age and higher doses of risperidone also contributed to weight gain, while gender and concomitant use of methylphenidate were not associated with change in BMI [47]. Of note, these results are in concordance with a recent meta-analysis that also found SNV of the *HTR2C* gene to be associated with antipsychotic-induced weight gain in individuals with schizophrenia [60].

Last, in regard to weight gain, eight participants identified as ultra-rapid metabolizers (i.e., those with duplications of one or more functional allele) of *CYP2D6* by Correia *et al.* had a 4.8% lower BMI increase and 5.8% lower increase in waist circumference as compared with extensive metabolizers [38].

Prolactin elevation

Medications with dopamine receptor blocking properties, such as risperidone, have been well established to increase prolactin levels in both adults and children [61]. This is associated with several clinical outcomes, including galactorrhea, libido loss and amenorrhea in females, as well as gynecomastia, impotence and hypospermatogenesis in males [62,63]. Dopamine signaling through D2 receptors on the anterior pituitary regulates prolactin release, and D2 blockade from some antipsychotic medications disinhibits this negative feedback resulting in prolactin elevation [64]. While prolactin elevation is common in patients taking risperidone, the degree of elevation and the severity of clinical sequelae often vary. Polymorphisms in or near the *DRD2* gene are known to impact receptor expression or binding [65,66], and thus may contribute to the pharmacodynamic effects of high-affinity D2 receptor antagonists, such as risperidone have on prolactin levels.

Anderson *et al.* [46] examined the impact of risperidone on prolactin levels in children (81% male; 66% white) from 5 to 17 years of age with autism. Mean prolactin levels increased significantly between baseline (9.3 ± 7.6 ng/ml in placebo group vs 9.3 ± 7.5 ng/ml in risperidone group) and after 8 weeks of therapy (10.1 ± 8.8 ng/ml in placebo group vs 39 ± 19.2 ng/ml in risperidone group), with an average risperidone dose of 1.80 mg/day. Participants were genotyped for the following polymorphisms that have been shown to decrease expression of the *DRD2* gene: Taq1A (rs1800497), -141C ins/del (rs1799732) and C957T (rs6277) [45]. Similar to what was seen in an adult population [67], serum prolactin levels in the different *DRD2* genotype groups were not observed to be statistically significant following 8 weeks of risperidone therapy.

In a retrospective cross-sectional study, Sukasem *et al.* [45] compared prolactin levels in Thai children (86% male; mean age: 9.5 years) receiving risperidone for a minimum of 4 weeks. Participants were genotyped for the *DRD2* Taq1A polymorphism in addition to *CYP2D6 *4*, **10*, **41* and **5* alleles. Participants were divided into those with and without hyperprolactinemia, with hyperprolactinemia defined as a prolactin level greater than the 97.5th percentile based on sex and age. Serum prolactin levels were compared between the different genotype groups, with no significant differences in serum prolactin between individuals with different *CYP2D6* alleles and genotypes [45]. In contrast to the Anderson *et al.* study [46], they reported significant differences of serum prolactin in the lower D2 expression *DRD2* Taq1A variant, where individuals with the A2/A2 (17.8 ng/ml) and A1/A2 (17.1 ng/ml) genotypes had significantly higher prolactin levels than those with the A1/A1 (12.7 ng/ml) genotype. Serum prolactin levels were also considerably higher in the Anderson *et al.* study, which may have been due in part to a higher average risperidone dose (1.80 vs 0.93 mg/day).

Roke *et al.* [44] also examined the impact of *CYP2D6* alleles **3*, **4*, **5*, **6* and *DRD2* Taq1A on prolac-

tin levels in 47 males (98% Caucasian; average age: 14.7 years) with autism taking risperidone. The mean risperidone dose and duration was 1.6 mg/day for 4.4 years. Higher risperidone doses and subsequently higher risperidone levels, were significantly associated with higher serum prolactin levels. Individuals with at least one Taq1A/A1 allele showed no difference in prolactin levels to those without. *CYP2D6* poor metabolizers (n = 2) had a mean prolactin level of 48.6 ng/ml as compared with 18.4 ng/ml for *CYP2D6* intermediate metabolizers (n = 17), 19.8 ng/ml for *CYP2D6* extensive metabolizers (n = 25) and 6.8 ng/ml for *CYP2D6* ultra-rapid metabolizers (n = 2); however, results are limited in that there were only two individuals in each of the poor and ultra-rapid metabolizer groups [44].

Ngamsamut *et al.* [68] performed a retrospective study comparing risperidone and 9-hydroxyrisperidone levels in a cohort of 103 Thai children with ASD (87% male; average age of 9.7 years) with their serum prolactin levels. This study found a positive correlation between plasma 9-hydroxyrisperidone levels and serum prolactin levels [68]. These findings are consistent to the limited results described by Roke *et al.* [44], where individuals with lower CYP2D6 activity and thus higher expected levels of risperidone as compared with 9-hydroxyrisperidone experienced higher prolactin levels. They also noted significant differences in median 9-hydroxyrisperidone concentrations in participants with hyperprolactinemia (7.59 ng/ml) as compared with those without hyperprolactinemia (5.18 ng/ml) [68].

The pharmacogenomics of risperidone represents by far the most studied medication utilized for reducing symptoms in ASD patients, focusing primarily on CYP2D6 and genes involved in dopamine and serotonin regulation. Current studies looking for genetic associations in regard to risperidone response and severity of adverse effects have focused exclusively on children and have to this point yielded largely negative or conflicting results. Studies examining differences in risperidone metabolism have been limited by small sample sizes at the two extremes (and thus most likely to show response/adverse effect differences) of CYP2D6 expression (i.e., poor/ultra-rapid metabolizers). Additionally, these studies have also included children around the age of puberty, where metabolism differences may exist. However, the pharmacokinetic consequences of *CYP2D6* variation seem consistent with some trends observed in cases of response/nonresponse as well as dose-related findings with prolactin elevation. Notably, some identified associations (i.e., *HTR2C* and antipsychotic induced weight gain) are consistent with those found in other diseases (i.e., schizophrenia) and adults, suggesting that some associations provide similar response/adverse effect profiles between children and adults. Prolactin elevation phenotypes may be associated with genetic variables influencing dose or exposure more than pharmacodynamic genes. Prolactin-related side effects, particularly galactorrhea (females and males) and gynecomastia, can be quite distressing. With some forms of severe gynecomastia in males irreversible if left untreated, a better understanding of sensitivities to this side effect is important. Of note, we did not identify studies investigating genetic associations with movement disorder side effects. Although severe antipsychotic-associated dyskinesias are rare at lower doses, both risperidone and aripiprazole are known to cause akathisia in some patients that can be a barrier to optimal dosing and treatment. The considerable variability observed in these studies warrants further investigation in order to parse out genetic associations in individuals with ASD taking risperidone. In the meantime, all patients should be closely monitored for these serious and potentially irreversible adverse events.

Selective serotonin reuptake inhibitors

SSRIs do not currently have the US FDA approved indications for the treatment of symptoms related to ASD in the absence of comorbid conditions, such as mood and anxiety disorders, and obsessive-compulsive disorders; however, they are commonly used to manage symptoms related to significant repetitive behaviors, obsessive-compulsive behaviors, and in some cases irritability [23]. Clinical trials examining SSRIs for the treatment of core symptoms for ASD have had mixed results, resulting in a Cochrane review from 2013 concluding there is limited evidence of their effectiveness in children on repetitive behaviors and evidence of adverse events [23]. Studies targeting ABC-defined irritability factor (which also includes features of anxiety) have been more consistently positive and this factor was significantly improved after citalopram treatment in the largest negative trial for effectiveness of repetitive behavior [25]. For example, it may be argued that the primary contribution of serotonergic agents to 'core' symptoms of ASD is that the compulsions often accompanying comorbid obsessive compulsive disorder (OCD) register on scales assessing restricted and repetitive behaviors [25]. The notable heterogeneous responses observed across patients as well as observed differences in side effect sensitivities (particularly to the exacerbation of irritability and/or hyperactivity) have led to pharmacogenomic studies in this patient population. Studies to date have largely focused on the genetics of drug metabolism and pharmacodynamic genes related to serotonin signaling.

The *5-HTTLPR* is a widely studied polymorphism in the promoter region of the serotonin transporter

gene (*SLC6A4*) resulting in either a short or long allele. Initial reports described the short allele resulting in decreased expression [69]; however, additional subtypes of this polymorphism have been described and utilized to group patients within pharmacogenetic studies. Notably, the SNV (rs25531) identified within this repetitive region is described as occurring predominantly within the long allele [70]. This has resulted in further categorization of individuals [71] with specific haplotypes described herein.

Fluvoxamine

In one of the first pharmacogenetic studies in patients with autism, Sugie *et al.* [50] enrolled 20 Japanese participants (18 of which completed the study; 15 males and four females; average age of 5 years and 4 months) in a double-blind crossover trial of fluvoxamine and placebo to see if variation in the 5-HT transporter (*SLC6A4*) gene affected clinical outcomes. The *SLC6A4* associations were focused on the long and short variations in the promoter locus of the gene (5-HTTLPR). While on fluvoxamine, participants were started on 1 mg/kg/day for 2 weeks, followed by 2 mg/kg/day for 4 weeks and 3 mg/kg/day for 6 weeks. Participants with at least one allele containing the long variant responded better to fluvoxamine as determined by Clinical Global Impression scores as compared with those homozygous for the short allele; however, individuals homozygous for the short allele showed significant improvement regarding delayed, peculiar or inappropriate speech as per the Behavioral Assessment Scale [50].

Escitalopram

Owley *et al.* [52] examined the impact of the serotonin transporter polymorphism 5-HTTPLR in a forced-titration candidate gene study in 58 participants from 4 to 14 years of age over the course of 10 weeks. Participants were started on escitalopram monotherapy at 2.5 mg/day and titrated up to 20 mg or a tolerable dose over a 5-week period, with change in ABC – Community Version Irr (ABC-CV-Irr) as the primary outcome. Genotype groups were defined by high, intermediate or low expression transporter status based on 5-HTTLPR promoter (long/short with rs25531 subtypes and rs2020936–rs2020937 haplotypes). Individuals identified as low expressors improved the least over the first 4 weeks of treatment, while a secondary analysis also showed the low expressors having the least improvement based on ABC-CV-Irr scores [52].

Similar to Owley *et al.* [52], Najjar *et al.* [53] recruited 44 participants with ASD including autism, Asperger disorder or pervasive developmental disorder not otherwise specified prescribed escitalopram and genotyped for variation in the *SLC6A4* and *HTR2A* genes. Through the same escitalopram dose titration schedule, they primarily looked at insistence on sameness through the Repetitive Behavior Scale-Revised Compulsive Behavior Subscale and Ritualistic/Sameness Behavior Subscale Scores to escitalopram based on variation in the aforementioned genes. While symptoms on an average significantly improved throughout the trial, no differences were seen across genotype groups [53].

In a further examination of participants from the aforementioned Najjar [53] and Owley [52] studies, Bishop *et al.* [51] studied *CYP2C19* variants with symptoms, tolerability and dosing outcomes in 84 individuals (4–45 years of age) with ASD taking escitalopram. Overall change in clinical symptoms was measured utilizing the ABC-CV, while irritability was assessed via the ABC-CV-Irr. While there was no difference in ABC-CV scores between *CYP2C19* genotypes, the average final daily dose was highest in the *CYP2C19* reduced metabolizers (16.7 ± 5.8 mg) as compared with extensive (15.4 ± 6.4 mg) and ultra-rapid (12.5 ± 7.8 mg) metabolizers, although these differences were not statistically significant. When looking at titration trajectories, unexpectedly the *CYP2C19* ultra-rapid metabolizers (i.e., patients expected to have reduced levels of escitalopram and thus requiring increased doses) experienced a significantly reduced tolerance to the dose escalation schedule as compared with the reduced function metabolizers. The authors of this study hypothesized that the observed reduced tolerability may be due to the differences in metabolite formation of escitalopram or altered pharmacokinetic parameters resulting in differential sensitivities to the study titration schemes [51]. Regarding the altered pharmacokinetic properties, rapid metabolism is also noted to decrease half-life of a medication. A somewhat counterintuitive consequence of this is that steady state concentrations are reached sooner (albeit presumably at lower concentrations) than those with unaltered metabolism. Given known sensitivities to faster SSRI titration schemes in some anxiety disorders, it was postulated that the rate of increased exposure may be a contributing factor in some scenarios and that perhaps this warrants further exploration in ASD given these findings.

Studies of SSRI pharmacogenomics are notable for a few interesting trends. First of all, the published studies to date are small and represent secondary analyses of open-label or uncontrolled studies. Variants examined include many of the serotonergic or drug metabolism genes also investigated in pharmacogenomic studies of antidepressant response and tolerability in the treatment of major depressive disorder. Two of the three studies examining the serotonin transporter in relation to treatment response, identified some similar trends as prior studies in depression, most notably the

5-HTTLPR 'long' or higher expressing alleles generally associated with a more favorable response to treatment. The only examination of drug metabolism pharmacogenomics to date suggested some dose sensitivity in ultra-rapid metabolizers, which is different than what has been observed in similar studies in depressed populations. While these findings require further validation, they bring up questions of the generalizability of pharmacogenomic findings across different conditions that may all benefit from SSRI treatment, but perhaps for different consequences of serotonin dysregulation. As previously mentioned, better identification of the underlying source of symptoms being targeted with antidepressant therapies (anxiety, OCD, among others) may be helpful in clarifying who may benefit most as well as assist pharmacogenetic evaluations of treatment.

Stimulants

Stimulants, such as methylphenidate are often used to treat comorbid attention deficit-hyperactivity disorder (ADHD) symptoms in ASD. Methylphenidate is the most commonly utilized medication to treat individuals with ADHD, and response is regulated in part by variation in genes related to dopamine, norepinephrine and serotonin. McCracken *et al.* [54] performed a 4-week, placebo-controlled, double-blind crossover study to assess efficacy and variation in several genes thought to play a role in methylphenidate response in a cohort of 66 children (mean age of 6.9 years, ~75% Caucasian and 88% male) with autistic disorder, Asperger disorder or pervasive developmental disorder not otherwise specified. Clinical responses were defined by the Clinical Global Impression scale and the ABC hyperactivity subscale. Variations in seven of the ten candidate genes were noted to be significantly different between those categorized as responders as compared with nonresponders in regard to response and tolerability, including *DRD1* (rs5326, rs4867798), *DRD3* (rs6280), *DRD4* (rs11246226), *ADRA2A* (rs1800544), *SLC6A3* (VNTR), *SLC6A4* STin2 (VNTR) and *COMT* (rs4680), with the strongest associations found in the dopamine transporter and receptor [54].

Based on the use of methylphenidate, mixed amphetamine salts and nonstimulants medications (i.e., atomoxetine, guanfacine, clonidine) used to alleviate ADHD symptoms in ASD patients, ample opportunity exists to expand upon the currently limited literature. Notably, the previously described study of methylphenidate is the only ADHD medication with pharmacogenetic research in an ASD population. While atomoxetine has been studied in children with ASD [72], and its metabolism shown to be significantly impacted by CYP2D6 [73], the impact of this variation has not been described in individuals with ASD.

Conclusion & Future perspective

Numerous psychiatric medications used to treat the array of symptoms present in patients with ASD are impacted by variability in genes involved in metabolism (i.e., pharmacokinetics) and response (i.e., pharmacodynamics). In spite of this, very few studies have examined the pharmacogenomic impact of these medications in patients with ASD. This dearth of literature presents a clear opportunity to potentially improve upon the medication and dose selection in ASD patients. Having a better understanding of which individuals are likely to respond to a medication while reducing their risk of adverse effects would greatly improve the clinical care and behavioral therapies in these patients.

From the relatively small number of studies conducted at the time of this review, a couple of important themes have arisen. First, most studies have relatively limited sample sizes and have used a variety of study designs, which creates challenges in comparing results across studies as well as elucidating the effects of rare but potentially impactful gene variants (e.g., CYP2D6 poor/ultra-rapid metabolizers). Second, a more comprehensive and combinatorial approach to the selection of which genes to investigate could provide useful information to which are most clinically relevant for specific drugs or medication classes.

Pharmacogenomic test panels are now commercially available for many of the medications used to treat ASD; however, the information for these recommendations is primarily based on studies in other diagnoses, such as depression or psychosis, with recommendations that are not always generalizable. As illustrated herein, some pharmacogenomic associations appear consistent with those observed in other diagnostic categories, while others have disparate findings. This underscores the importance of the need to better understand the diagnostic specificity of these relationships (as opposed to generalizing) with supporting evidence. Further studying the pharmacogenomic impact on these medications would serve to identify any potential differences in how patients with ASD may have differences in response.

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Executive summary

- Autism spectrum disorder (ASD) is a complex disease with a highly variable presentation of symptoms.
- Hundreds of genes are currently thought to contribute to an individual's risk of ASD.
- Several medications (i.e., risperidone, aripiprazole, methylphenidate, escitalopram and atomoxetine) with known variation in pharmacokinetic and pharmacodynamic genes are commonly utilized in patients with ASD to alleviate symptoms; however, pharmacogenomic studies of these medications are limited in the ASD population.
- The majority of studies to date have examined pharmacogenomic associations with response and tolerability to risperidone as well as selected selective serotonin reuptake inhibitors.
- There is evidence that some pharmacogenomic relationships in ASD may be consistent with those observed in other disease states (i.e., HTR2C and antipsychotic induced weight gain) while others may be unique.
- Many opportunities exist to better describe response and side effects with respect to the pharmacogenomics of medications used in ASD.

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