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Pharmacogenomic Studies in Intellectual Disabilities and Autism Spectrum Disorder: A Systematic Review

Études Pharmacogénomiques en Déficiences Intellectuelles et Trouble du Spectre de L'autisme: Une Revue Systématique

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Abstract

Background: Individuals with intellectual disability (ID) and autism spectrum disorder (ASD) often receive psychotropic medications such as antipsychotics and antidepressants to treat aberrant behaviors and mood symptoms, frequently resulting in polypharmacy and drug-related adverse effects. Pharmacogenomic (PGx) studies with ASD and/or ID (ASD/ID) have been scarce despite the promise of optimizing treatment outcomes. We reviewed the literature on PGx studies with antipsychotics and antidepressants (e.g., treatment response and adverse effects) in ASD/ID.

Methods: We performed a systematic review using MEDLINE, Embase, and PsycINFO, including peer-reviewed original articles in English referring to PGx in the treatment of ASD/ID in any age groups (e.g., treatment response and adverse effects).

Results: A total of 28 PGx studies using mostly candidate gene approaches were identified across age groups. Notably, only 3 studies included adults with ASD/ID while the other 25 studies focused specifically on children/adolescents with ASD/ID. Twelve studies primarily investigated treatment response, of which 5 and 6 studies included patients treated with antipsychotics and antidepressants, respectively. Most interesting results for response were reported for 2 sets of candidate gene studies, namely: (1) The *DRD3 Ser9Gly* (rs6280) polymorphism was examined in patients treated with risperidone in 3 studies, 2 of which reported an association with risperidone treatment response and (2) the *SLC6A4* 5-HTTLPR polymorphism and treatment response to antidepressants which was investigated in 4 studies, 3 of which reported significant associations. In regard to side effects, 9 of 15 studies focused on hyperprolactinemia in patients treated with risperidone. Among them, 7 and 5 studies examined the impact of *CYP2D6* and *DRD2 Taq1A* polymorphisms, respectively, yielding mostly negative study findings.

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Conclusions: There is limited data available on PGx in individuals with ASD/ID and in particular in adults. Given the potential for PGx testing in improving treatment outcomes, additional PGx studies for psychotropic treatment in ASD/ID across age groups are warranted.

Abrégé

Contexte : Les personnes souffrant de déficience intellectuelle (DI) et du trouble du spectre de l'autisme (TSA) reçoivent souvent des médicaments psychotropes comme des antipsychotiques et des antidépresseurs pour traiter des comportements aberrants et des symptômes de l'humeur, ce qui se traduit fréquemment par des effets indésirables de polypharmacie et liés aux médicaments. Les études pharmacogénomiques (PGx) sur les TSA/DI se sont faites rares malgré la promesse d'optimiser les résultats des traitements. Nous avons examiné la littérature traitant des études PGx à l'égard des antipsychotiques et des antidépresseurs (p. ex., la réponse au traitement et les effets indésirables) dans les TSA/DI.

Méthodes : Nous avons mené une revue systématique à l'aide de MEDLINE, Embase, et PsycINFO, et avons inclus des articles originaux révisés par les pairs en anglais qui mentionnaient les PGx dans le traitement des TSA/DI pour tout groupe d'âge (p. ex., la réponse au traitement et les effets indésirables).

Résultats : Un total de 28 études PGx recourant surtout à des approches de gènes candidats ont été identifiées dans tous les groupes d'âge. Notablement, seulement trois études incluaient des adultes souffrant de TSA/DI alors que les 25 autres études se concentraient spécifiquement sur les enfants/adolescents souffrant de TSA/DI. Douze études investiguaient principalement la réponse au traitement, parmi lesquelles cinq et six études incluaient des patients traités par antipsychotiques et antidépresseurs, respectivement. Les résultats les plus intéressants pour la réponse au traitement étaient rapportés pour deux ensembles d'études de gènes candidats, notamment: 1) le polymorphisme *DRD3 Ser9Gly* (rs6280) était examiné chez les patients traités par rispéridone dans trois études, dont deux rapportaient une association avec la réponse au traitement par rispéridone; 2) le polymorphisme *SLC6A4* 5-HTTLPR et la réponse au traitement par antidépresseurs qui a été investiguée dans quatre études, dont trois rapportaient des associations significatives. En ce qui concerne les effets secondaires, neuf études sur 15 portaient sur l'hyperprolactinémie chez les patients traités par rispéridone. Parmi celles-ci, sept et cinq études examinaient l'impact des polymorphismes *CYP2D6* et *DRD2 Taq1A,* respectivement, aboutissant surtout à des résultats d'étude négatifs.

Conclusions : Les données disponibles sur les PGx sont limitées pour les personnes souffrant de TSA/DI et en particulier pour les adultes. Compte tenu du potentiel des tests de PGx pour améliorer les résultats des traitements, des études PGx additionnelles des traitements par psychotropes dans les TSA/DI dans tous les groupes d'âge sont justifiées.

Keywords

autism spectrum disorder, antidepressants, antipsychotics, intellectual disabilities, pharmacogenomics

Introduction

It is estimated that 1% to 2% of the population are affected by either intellectual disability (ID) or autism spectrum disorder (ASD),[1-3] which are neurodevelopmental disorders according to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*.[4] Children/adolescents with ASD and/or ID (i.e., ASD/ID for short) often present with problem behaviors including aggression toward others, self-injurious behavior, and disruptive behavior.[5,6] Such challenging behaviors often persist into adulthood.[7-9] In addition, individuals with ASD/ID have higher rates of comorbid psychiatric disorders than other individuals; approximately 30% of individuals with ID[10] and 70% with ASD have comorbid psychiatric disorders.[11,12]

High rates of use of psychotropic medications for children/adolescents and adults with ASD/ID have been reported in many countries.[13-21] Notably, psychotropic medication use increases with age[22,23] and is highest in individuals with both ASD and ID.[24] Furthermore, polypharmacy and excessive dosages are common in children/adolescents and adults with ASD/ID.[22,25,26] Polypharmacy is frequent in these populations, and rates among individuals with ID have been reported between 11% and 60%, depending on the study design and sample size.[22] Likewise, a recent systematic review reported that the rate of psychotropic polypharmacy in individuals with ASD was estimated between 5.4% and 54%.[25] In general, polypharmacy and high doses are commonly associated with increased adverse effects, medication nonadherence, functional decline, and cognitive impairment, in addition to increased health-care costs.[27] Furthermore, polypharmacy is associated with a highly increased risk for drug–drug interactions typically occurring at the pharmacokinetic level, that is, the Phase-I cytochrome P450 enzymes.[28] Individuals with ID have been reported to be more susceptible to movement side effects of antipsychotic medications than those without ID.[29]

Pharmacogenomics (PGx) enables us the opportunity to remedy these treatment inadequacies in individuals with

ASD/ID. In general, PGx represents a decision support tool based on well-established gene–drug interactions.[30] Such gene–drug interactions depend on interindividual variability in human DNA sequence, which can determine plasma levels of medications and metabolites and thereby tolerance and response to medications. For antidepressants and antipsychotics medications, which are predominantly metabolized by CYP2C19 and CYP2D6, assessing the genetic variation of these enzymes has enabled researchers and clinicians to estimate their activities; this strongly correlates with exposure to medications (i.e., parent compound and metabolites) and affects treatment outcome for depression and psychotic disorders, respectively.[31,32] For various nonpsychiatric medications, clinical utility of PGx testing compared to treatment as usual has been demonstrated resulting in a reduction of hospitalization rates, health-care costs, and polypharmacy.[33-35] In psychiatry, favorable treatment outcomes (e.g., higher remission rates) have also been observed in patients receiving PGx-guided antidepressant and antipsychotic treatments compared to those receiving treatment as usual.[36-41] Therefore, PGx testing is globally becoming increasingly implemented, which is further encouraged by expert recommendation guidelines for psychiatric medications.[31,42-44]

Taken together, in addition to avoiding polypharmacy, PGx testing could be extremely useful for optimizing pharmacological treatment in individuals with ASD/ID by optimizing likelihood for treatment response and minimizing risk for adverse events. However, to the best of our knowledge, no study has systematically reviewed the clinical utility of PGx testing in individuals with ASD or ID, and no reviews have focused specifically on particular in adults. While there is a literature review using only 1 search engine (i.e., PubMed) that focused on PGx studies in ASD, there was no discussion regarding the age of the participants.[45] We aimed to review the literature on PGx studies with psychotropic drugs including antipsychotics and antidepressants (e.g., treatment response and adverse effects) in individuals with ASD/ID across all age groups (i.e., adults and children/adolescents).

Methods

Literature Search

We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[46] The search was performed with MEDLINE, Embase, and PsycINFO until February 29, 2020. The following search terms were applied: (neuroleptic* OR antipsychotic* OR amisulpride OR aripiprazole OR chlorpromazine OR fluphenazine OR haloperidol OR olanzapine OR quetiapine OR risperidone OR thioridazine OR ziprasidone OR antidepressant* OR SNRI OR SSRI OR citalopram OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR mirtazapine OR paroxetine OR sertraline OR venlafaxine OR "alpha agonist" OR stimulant* OR atomoxetine OR clonidine OR guanfacine OR methylphenidate OR benzodiazepine* OR "mood stabilizer*" OR valproate) and (variant* OR polymorphism* OR gene OR genetic OR genetics OR pharmacogenetic OR pharmacogenetics OR pharmacogenomic OR pharmacogenomics) and (autism OR ASD OR "Intellectual* disab*" OR "Intellectual* impair*" OR "Intellectual* retard*" OR "Intellectual* handicap*" OR "Intellectual* subnormal*" OR "Intellectual* deficien*" OR "Learning disab*" OR "Learning impair*" OR "Learning retard*" OR "Learning handicap*" OR "Learning subnormal*" OR "Learning deficien*" OR "Mental* disab*" OR "Mental* impair*" OR "Mental* retard*" OR "Mental* handicap*" OR "Mental* subnormal*" OR "Mental* deficien*" OR "Developmental* disab*" OR "Developmental* impair*" OR "Developmental* retard*" OR "Developmental* handicap*" OR "Developmental* subnormal*" OR "Developmental* deficien*" OR "Neurodevelopmental* disab*" OR "Neurodevelopmental* impair*" OR "Neurodevelopmental* retard*" OR "Neurodevelopmental* handicap*" OR "Neurodevelopmental* subnormal*" OR "Neurodevelopmental* deficien*" OR "down syndrome" OR "Fragile X Syndrome" OR "Prader-Willi Syndrome" OR "Smith-Magenis Syndrome" OR "22q11.2 Deletion Syndrome" OR "15q13.3 Deletion Syndrome"). Limit was set for "English language" and "humans." References of relevant articles were manually searched and an additional hand search was performed using available citations by 2 authors (K.Y. and E.K.) independently. Candidate articles were independently screened and scrutinized by these authors. Discrepancies in study selection were resolved by discussion between them.

Inclusion Criteria

Studies were included if (1) they were peer-reviewed original articles; (2) they investigated the association between any gene variants and serum/plasma concentrations or dosages of any psychotropics, treatment response to any psychotropics, and adverse effects of any psychotropics; and (3) they were published in English until February 29, 2020. In addition, we included PGx studies meeting the inclusion criteria above across all age groups in order to perform the literature search as comprehensively as possible.

Data Extraction

The following data were extracted by the 2 authors (K.Y. and E.K.) independently for each study: author name, year of publication, diagnosis, age, presence/absence of ID, gene(s) and polymorphism(s), outcomes, study design, sample size, ethnicity or nationality, treatment duration, treatment medication, and main findings.

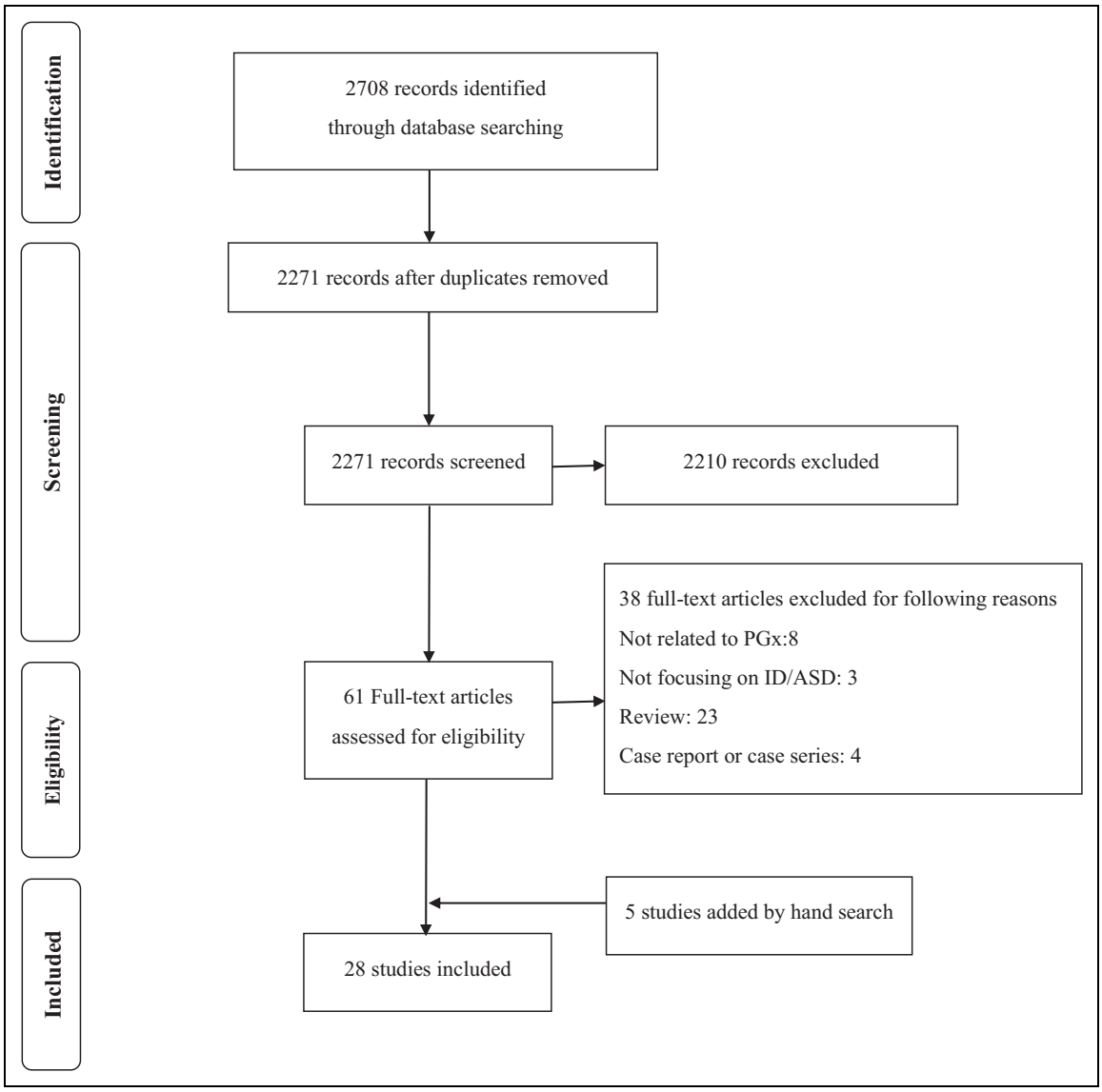

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for review eligibility and inclusion. *Note.* ASD = autism spectrum disorder; ID = intellectual disabilities; PGx = pharmacogenomics.

Results

Twenty-eight studies were identified through the literature search (Figure 1). Identified studies were summarized in Table 1. We summarized those studies based on age category (i.e., adults and children/adolescents) and treatment outcomes, respectively.

PGx Studies Based on Age Groups

PGx studies in adults with ASD/ID. There were no PGx studies exclusively focusing on adults with ASD/ID although 3 PGx studies included adults with ASD/ID in their analyses.[49,51,61] One PGx study by Bishop et al. examined the association between metabolizer status for the *CYP2C19* gene (i.e., ultrarapid metabolizer [UM; $n = 26$], extensive metabolizer [EM; $n = 40$], and poor [PM]/intermediate [IM] metabolizer; $n = 23$) and assessed treatment response to escitalopram using the Aberrant Behavior Checklist–Community Version (ABC-CV) in individuals with ASD.[49] Although adults were included, no breakdown by age was provided (mean $\pm$ standard deviation [SD] [range]: 136.7 $\pm$ 66.9 [54 to 532] months, $N = 89$), but this study included at least 1 adult patient (44.3 years old). A subgroup of individuals in this study had ID in addition to ASD, but no individuals were exclusively diagnosed with ID (nonverbal intelligence quotient [IQ]: 83.2 $\pm$ 31.7 [21 to 146], $N = 89$; verbal IQ: 76.7 $\pm$ 31.7 [11 to 141], $N = 79$). However, no information on response in adults versus children/adolescents or in those with or without concurrent ID was provided. Another study by Najjar et al. examined whether the *SLC6A4* (5-HTTLPR) and *HTR2A* (rs7997012) polymorphisms were associated with response to escitalopram,

Table 1. Association between Genetic Polymorphisms and Treatment Outcomes.

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
AlOlaby et al., 2017[47]	Fragile X syndrome (58.8% of the subjects had ASD)	46.1 ± 12.6 (range: 24.1 to 71.9) months	Patients with fragile X syndrome were included	SLC6A4 (5-HTTLPR, S or L alleles), BDNF (Val66Met [rs6265]), MAOA-VNTR (2, 3, 3.5, 4, 5 repeat alleles), CYP2C19 (*1, *2, *3, *17), CYP2D6 (*1, *2, *2, *4, *5, *6, *7, *8, *9, *10, *11, *15, * 17, *29, *35, *41)	Treatment response	DBRCT	51	Mainly Caucasian	6 Months	Sertraline	Significant association between the BDNF polymorphism and improvements for several measures, including CGI-I ($P = 0.008$) and the cognitive T score ($P = 0.017$) for those treated with sertraline compared to placebo. MAOA, CYP2C19 and CYP2D6, and 5-HTTLPR also significantly correlated with secondary measures.
Anderson et al., 2007[48]	Autism (DSM-IV and ADI)	8.4 ± 2.7 Years	Not reported (approximately 70% of patients treated with risperidone in the RUPP were with mild or more ID)	DRD2 Taq1A (rs1800497), -141C Ins/Del (rs1799732), and C957T (rs6277)	Adverse effect (hyperprolactinemia)	DBRCT (RUPP)	78	Various (mainly Caucasian)	8Weeks	Risperidone	No significant association of the DRD2 variants with increases in prolactin.
Bishop et al., 2015[49]	ASD (autism, Asperger disorder, or PDD-NOS; DSM-IV-TR)	136.7 ± 66.9 (range: 54 to 532) months	Mean ± SD (range)—nonverbal IQ ($n = 89$): 83.2 ± 31.7 (21 to 146), verbal IQ ($n = 79$): 76.7 ± 31.7 (11 to 141)	CYP2C19 (rs4244285, rs4986893, and rs12248560)	Treatment response	Prospective	89	Various (mainly Caucasian)	6 Weeks	Escitalopram	No significant difference in the rate of improvement among metabolizer groups (UM, EM, and PM/IM) for the ABC-CV Irritability subscale.
Calarge et al., 2009[50]	Various diagnoses including ADHD, disruptive behavior, tic disorder, and PDD (a combination of a review of the psychiatric record and the National Institute of Mental Health Diagnostic Interview Schedule for Children)	12.1 ± 2.8 Years	Not reported	DRD2 Taq1A (rs1800497), C957T (rs6277), -141C Ins/Del (rs1799732), and A-241G (rs1799978)	Adverse effect (hyperprolactinemia)	Cross-sectional	90	Non-Hispanic Caucasians	≥6 Months	Risperidone	After controlling for risperidone concentration and the dose of psychostimulants, a synergistic effect of the TaqIA and the A-241G variants was found on prolactin concentration, using multiple regression analysis ($P = 0.003$).

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Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Correia et al., 2010[51]	Patients who met the algorithm cutoff for the ADI-R and the ADOS	8.67 $\pm$ 4.30 (range: 3 to 21) years	Absent (IQ $\geq$ 70): 37.8%, mild (69 $\geq$ IQ $\geq$ 50): 31.1%, moderate (49 $\geq$ IQ $\geq$ 35): 24.4%, severe (IQ < 35): 6.7%	CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6 gene duplication, ABCB1 (rs1128503, rs1045642), HTR2A (rs6311), DRD2 (rs1800497), HTR2C (rs6318, rs3813928, rs3813929), BDNF (rs6265), HTR6 (rs9659997), DRD3 (rs6280)	Treatment response and adverse effect (AIWG and prolactin elevation)	Prospective	45	Various (mainly Caucasian)	Up to 1 year	Risperidone	The HTR2A rs6311 ($P = 0.019$), DRD3 rs6280 ($P = 0.012$), HTR2C rs3813928 ($P = 0.035$), and ABCB1 rs1128503 ($P = 0.002$) were significantly associated with the decline in the ATEC scores. The HTR2A rs6311 ($P = 0.018$), HTR2C rs6318 ($P = 0.006$), HTR6 rs9659997 ($P = 9.5 \times 10^{-5}$), and BDNF rs6265 ($P = 0.016$) significantly associated with prolactin elevation. The CYP2D6 and HTR2C rs6318 polymorphisms were significantly associated with increase in BMI or waist circumference ($P < 0.05$).
Cote et al., 2015[52]	Various diagnoses including anxiety disorder, mood disorder, ADHD, and PDD (DSM-IV-TR)	13.1 $\pm$ 3.0 Years	Not reported	COMT Val158Met (rs4680)	Adverse effects (blood pressure and other cardiovascular risk factors)	Cross-sectional	302	Various (mainly European)	Median = 7 months	SGAs	SGA-treated children with the Met allele showed higher systolic and diastolic blood pressure ($P = 0.014$ and $P = 0.034$, respectively) and higher fasting glucose concentrations ($P = 0.030$) than those who with the Val/Val genotype.

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Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
dos Santos Júnior et al., 2015[53]	Various diagnoses including mild or moderate mental retardation ($n = 36$, 30%) and PDD ($n = 26$, 21.7%; ICD)	13.0 ± 3.1 Years	Patients with mild or moderate ID were included	DRD2 (rs1799978 and rs6277), HTR2C (rs6318 and rs3813929), CYP2D6*10 (rs1065852), LEP (rs7799039), LEPR (rs1137101), MC4R (rs17782313), SCARB2 (rs3853188)	Adverse effect (hyperprolactinemia)	Cross-sectional	120	Various (mainly Caucasian)	23.4 ± 28.6 Months (cases with hyperprolactinemia) and 30.9 ± 23.9 months (controls without hyperprolactinemia)	Risperidone	Hyperprolactinemia occurred with higher frequency in patients with the C allele of the HTR2C rs6318 polymorphism ($P = 0.02$).
Firouzabadi et al., 2017[54]	ASD (DSM-V)	6.8 ± 1.3 (2.5 to 14) Years	Patients with severe ID were excluded	DRD3 Ser9Gly (rs6280)	Treatment response	Prospective	56	Persian	8 Weeks	Risperidone	Responder rates (i.e., a 50% or greater decrease from baseline in ABC score) were significantly higher in carriers of Gly allele as well as carriers of Gly/Gly and Ser/Gly genotypes compared with carriers of Ser allele and Ser/Ser genotype ($P = 0.027$ and 0.014, respectively).
Hoekstra et al., 2010[55]	PDD (ADI-R)	8.74 ± 2.83 (5 to 16) Years	Not reported	HTR2C (rs3813929 and rs1414334)	Adverse effect (AIWG)	Prospective	32	Dutch	8 weeks	Risperidone	Presence of rs3813929T allele was significantly associated with a smaller weight gain ($P < 0.001$).
Hongkaew et al., 2018[56]	ASD (DSM-IV)	Median: 8.96 (quartile 1 to 3: 7.44 to 10.98) years	Not reported	508 Drug-metabolizing enzymes and transporters SNPs	Adverse effect (hyperprolactinemia)	Observational-retrospective	84	Thai	Total sample duration: 43.57 months	Risperidone	Three UGT1A1 SNPs (UGT1A1*80 c.-364C > T [rs887829], UGT1A1*93 c.-3156G > A [rs10929302], and UGT1A1 c.-2950A > G [rs111741722]) showed a suggestive association with hyperprolactinemia ($P = 0.0014$).

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Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Lit et al., 2012[57]	ASD (DSM-IV and ADI-R)	112.7 ± 51.2 Months	Patients with nonverbal intelligence quotient < 55 were excluded	Exon expression levels in blood assessed using Affymetrix GeneChip Human Exon 1.0 ST Arrays	Gene expression and treatment response	Prospective	42	Caucasian ($n = 24$) and others ($n = 18$)	8 Weeks	Risperidone	Expression of exons within 5 genes (GBP6, RABL5, RNF213, NFKBID, and RNF40) was significantly correlated with change in ABC Irritability subscale scores (GBP6, $r = 0.78$; RABL5, $r = 0.72$; RNF213, $r = -0.73$; NFKBID, $r = 0.75$; and RNF40, $r = -0.74$; $P < 0.001$).
McCracken et al., 2010[58]	PDD (PDD-NOS, Asperger disorder, or autistic disorder) with clinically significant symptoms of ADHD	9.03 ± 3.14 Years	Not reported	MDR1 C3435T (rs1045642)	Treatment response	Prospective	25	Caucasian ($n = 18$), African American ($n = 6$), and Hispanic ($n = 1$)	8 Weeks	Guanfacine	Patients with either C/T or C/C genotypes showed a significant greater improvement than T/T MDR1 C3435T genotype in the ABC hyperactivity scores ($P < 0.03$) and a greater improvement in the Swanson, Nolan, and Pelham (SNAP) scores ($P = 0.05$).

(continued)

Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
McCracken et al., 2014[59]	ASD (DSM-IV and ADI-R)	6.90 ± 2.2 (range 5.0 to 13.0) years	Mean intelligence quotient: 65.0 ± 33.3 (range: 16 to 135)	DRD1 (rs4867798, rs5326, rs686), DRD2 (rs6277, rs6589377, rs4938019, rs7131056, rs1800498, rs2283265, rs6275, rs1800497), DRD3 (rs6280 [Ser9Gly], rs2134655, rs9880168, rs7633291, rs167771, rs3732790), DRD4 (rs11246226, rs3758653, Exon 3 VNTR), DRD5 (rs10033951), ADRA2A (rs1800544, rs12246561, rs3750625), SLC6A3 (3'UTR VNTR), SLC6A4 (rs12150214, rs4251417, rs11080121, 5HTT-LPR, STin2 VNTR), MAOA (rs1465108, rs3810709, rs3027399), MAOB (rs10521432, rs1799836), COMT (rs4680 [Val158Met])	Treatment response and tolerability determined by adherence	Random-order, placebo-controlled, double-blind crossover	58	Caucasian (75.9%)	4 Weeks	Methylphenidate	The DRD1 rs4867798 ($P = 0.042$), DRD1 rs5326 ($P = 0.006$), DRD3 rs6280 ($P = 0.044$), DRD4 rs11246226 ($P = 0.038$), SLC6A4 STin2 VNTR ($P = 0.049$), SLCA4 STin2 VNTR ($P = 0.041$), ADRA2A rs1800544 ($P = 0.015$), COMT rs4680 ($P = 0.049$) were significantly associated with responder status assessed using the CGI-I and ABC hyperactivity subscale. The DRD2 rs6275 ($P < 0.001$) and DRD3 rs6280 ($P = 0.031$) were significantly associated with tolerability.

(continued)

Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Medhasi et al., 2016[60]	ASD (DSM-IV)	8.8 (range: 3.4 to 18.6) years	Not reported	Exploratory analysis using Affymetrix DMET™ Plus Gene Chip microarray interrogating 1931 variants in 231 genes; 483 variants were included for final analysis	Plasma concentrations	Retrospective	102	Thai	Median duration of risperidone used: 41.62 months (range: 1.03 to 152.97)	Risperidone	ABCB11 (c.3084A>G, c.420A>G, c.368G>A, and c.236G>A) and ADH7 (c.690G>A and c.-5360G>A) were significantly associated with plasma concentrations of risperidone ($P < 0.01$). Two of the SCLO1B1 polymorphisms (c.-11187G>A and c.521T>C), SLCO1B3 (c.334G>T, c.699A>G, and c.1557G>A), and SLC7A5 c.438C>G were significantly associated with 9-hydroxyrisperidone and the total active-moiety levels ($P < 0.01$).
Najjar et al., 2015[61]	ASD (DSM-IV, Autism Diagnostic Interview–Revised, and Autism Diagnostic Observation Scale, second edition)	161 ± 86 (range:61 to 532) months	Mean ± *SD* (range)—nonverbal IQ ($n = 44$): 80 ± 25 (35 to 130), verbal IQ ($n = 38$): 78 ± 25 (30 to 120), full scale ($n = 38$): 80 ± 25 (33 to 130)	SLC6A4 (5-HTTLPR) and HTR2A (rs7997012)	Treatment response	Prospective	44	Various (mainly Caucasian)	6 Weeks	Escitalopram	No significant differences in the rate of symptom improvement assessed using the RBS-R CRS and the ABC-CV Irritability subscale scores over time across genotype groups.

(continued)

Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Nuntamool et al., 2017[62]	Autistic disorder (91.36%), PDD-NOS (6.17%), Rett disorder (1.23%), and Asperger disorder (1.23%; DSM-IV)	Median:11 (IQR: 9.00 to 14.00)	Not reported	DRD2 (TaqIA [rs1800497], -241A>G [rs1799978]); DRD3 (25T>C [rs6280]); HTR2A (-1438G>A [rs6311]); ABCB1 (3435C>T [rs1045642], 2677G>T/A [rs2032582], 1236C>T [rs1128503]); CYP2D6 polymorphisms	Treatment response as the primary outcome	Cross-sectional	82	Thai	Median duration of risperidone used: 67.90 months (IQR: 52.53 to 90.93)	Risperidone	The nonstable symptom group assessed using CGI-I score and a 4-point scale for each of aggression, overactivity, and repetitive behaviors had DRD2 Taq1A non-wild-type (TT and CT) higher frequencies than the stable group ($P = 0.048$). Other gene polymorphisms showed no significant association.
Nurmi et al., 2013[63]	ASD (autism, Asperger disorder, PDD-NOS; DSM-IV)	96.5 $\pm$ 32.3 Months	Not reported (approximately 70% and 40% of patients treated with risperidone in the RUPP and RUPP-PI were with mild or more ID)	FTO (rs1421085, rs6499640, rs1121980, rs17817449, rs8050136, rs9939609); MC4R (rs8087522, rs11872992, rs8093815, rs489693); LEP (rs7799039, rs10244329, rs12706832, rs2071045); CNR1 (rs806378, rs806377, rs1049353, rs806368); FAAH (rs324420)	Adverse effect (AIWG)	Data from 2 trials (RUPP: DBRCT, RUPP-PI: randomized, parallel-groups clinical trial)	181	Various (mainly Caucasian)	8 Weeks	Risperidone	Three gene variants (LEP rs7799039, CNR1 rs806378, and rs1049353) were significantly associated with AIWG ($P = 1.4 \times 10^{-4}$, 1.0×10^{-6}, and 9.6×10^{-5}, respectively).
Owley et al., 2010[64]	ASD (autism, Asperger disorder, PDD-NOS; ADI-R and ADOS-2)	117 $\pm$ 31 (range: 54 to 204) months	Mean $\pm$ SD (range); nonverbal IQ: 86 $\pm$ 34 (21 to 146), verbal IQ: 76 $\pm$ 35 (11 to 141)	SLC6A4 5-HTTLPR (S, LA, LG alleles, TT diplotype)	Treatment response	Prospective	58	Various (mainly Caucasian)	10 Weeks	Escitalopram	A significant interaction between genotype group and time on the ABC Irritability subscale (linear maximum marginal likelihood estimation $= -4.84$, $Z = -2.89$, $SE = 1.67$, $P = 0.004$).

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Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Prows et al., 2009[65]	Various diagnoses including mood disorders, disruptive behavior disorders, PDD (DSM-IV-TR)	12.7 ± 3.2 Years	Patients with severe ID were excluded	CYP2D6*1, *3, *4, *5 and CYP2C19*1, *2	Treatment response and adverse effects (the number of adverse effects)	Retrospective	279	Various (mainly Caucasian)	Not mentioned	Psychotropics including antidepressants and antipsychotics	Combined phenotype of CYP2D6 and CYP2C19 was significantly associated with the BIS ($P = 0.01$) and the number of adverse effects ($P = 0.03$).
Roke et al., 2013[66]	ASD or disruptive behavior disorder (no diagnostic tool was reported)	14.7 ± 2.1 (range: 10 to 19) years	Patients with IQ above 85 were included	DRD2 Taq1A (rs1800497), CYP2D6*3 del A (rs35742686), CYP2D6*4G>A (rs3892097), CYP2D6*6 del T (rs5030655), CYP2D6 gene deletion (CYP2D6*5), and the gene duplication (CYP2D6xN)	Adverse effect (hyperprolactinemia)	Cross-sectional	47	Caucasian (97%)	Mean 52 months (range: 16 to 126 months)	Risperidone	No significant correlations between prolactin level and the presence of at least 1 Taq1A A1 allele of the DRD2 gene, using multiple regression analysis ($P = 0.12$). No significant difference in prolactin level between the CYP2D6 reduced activity group and the normal activity group, using an independent sample t test ($P = 0.8$).
Sherwin et al., 2012[67]	Mainly ASD	9.6 ± 3.7 (3 to 18.3) Years	Some of the patients had ID (Aman et al., 2007[68])	CYP2D6 *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *40, *41, *42, deletion, and duplication	Relative clearance of risperidone CL/F (liters/hour)	Prospective in original studies	45	Caucasian (93.3%)	Not mentioned. All patients started risperidone treatment prior to age 18 to treat neuropsychiatric disorder	Risperidone	Clearance estimates in the mixture model were 9.38 L/h (PM), 29.2 L/h (IM), and 37.4 L/h (EM).
Sugie et al., 2005[69]	Autism (DSM-IV)	Mean: 5 years and 4 months ($n = 19$)	Not reported	SLC6A4 (5-HTTLPR (S or L alleles)	Treatment response as the primary outcome	Crossover double-blind, placebo-controlled study	19 (18 subjects were included in the analysis)	Japanese	12 Weeks	Fluvoxamine	Fluvoxamine was significantly more effective in the L allele variant than the S allele variant when CGI was used as an assessment scale ($P = 0.047$).

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Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Sukasem et al., 2016[70]	ASD (DSM: version was not reported)	9.52 Years (inclusion criteria: 3 to 19 years)	Not reported	CYP2D6*4 (1846G>A, [rs3892097]), CYP2D6*10 (100C>T [rs1065852]), CYP2D6*41 (2988G>A [rs28371725]), CYP2D6 gene deletion (CYP2D6*5), and DRD2 Taq1A (rs1800497)	Adverse effect (hyperprolactinemia)	Retrospective cross-sectional	147	Thai	46.06 Months	Risperidone	No significant correlation between the concentrations of prolactin among the CYP2D6 genotypes. There were statistically significant differences in prolactin level of patients among the DRD2 Taq1A A2A2, A1A2, and A1A1 groups ($P = 0.033$).
Sukasem et al., 2018[71]	ASD (DSM-IV)	Median: 10.00 (IQR: 8.90 to 13.40) years	Not reported	ABCB1 (2677G>T/A [rs2032582], 3435C>T [rs1045642]), DRD2 (Tag-SNP [T>C; rs4436578], TaqIA [C>T; [rs1800497]), BDNF (196G>A [rs6265]), LEP (-2548G>A [rs7799039]), GHRL (-604G>A [rs27647]), CYP2D6*4 (1846G>A [rs3892097]), CYP2D6*10 (100C>T [rs1065852]), and CYP2D6*41 (2988G>A [r s28371725]); CYP2D6*5 (gene deletion)	Adverse effect (insulin resistance)	Observational	89	Thai	63.92 (40.40 to 83.49) Months	Risperidone	A significant association between insulin resistance and BDNF 196 G>A, using multiple regression analysis ($P = 0.025$).

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Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Troost et al., 2007[72]	PDD (autistic disorder, Asperger disorder, or PDD-NOS; DSM-IV-TR)	8.6 ± 2.2 Years	Not reported	CYP2D6*3, *4, *5, *6, and *7	Adverse effect (prolactin elevation)	Prospective	25	Dutch	8 Weeks	Risperidone	Significant positive correlations of serum prolactin level with dose per kilogram ($r = 0.648$, $P < 0.001$), number of functional CYP2D6 genes ($J = 2.117$, $P = 0.034$), and serum 9-hydroxyrisperidone concentration ($r = 0.664$, $P = 0.001$) and a negative correlation with the risperidone/9-hydroxyrisperidone ratio ($r = 0.571$, $P = 0.004$).
Vanwong et al., 2016[73]	ASD (DSM-IV)	Median: 10.00 (IQR: 6.83 to 11.55) years	Not reported	CYP2D6*1, *2, *3, * 4, *5, *6, *7, *8, * 9, *10, *11, *15, *17, *29, *41, *35, and duplications	Plasma concentrations	Prospective	84	Thai	>4 Weeks	Risperidone	IMs showed significantly higher plasma concentration of risperidone than EMs ($P < 0.0001$) but not UMs ($P = 0.14$), and significantly higher plasma concentration of risperidone/ 9-hydroxyrisperidone ratio than EMs ($P < 0.0001$) and UMs ($P = 0.02$)
Vanwong et al., 2017[74]	ASD (DSM-IV)	Median: 10.00 (IQR: 7.00 to 12.15) years	Not reported	CYP2D6*4 (1846G>A [rs3892097]), CYP2D6*10 (100C>T [rs1065852]), CYP2D6*41 (2988G>A [rs28371725]), CYP2D6*5 (CYP2D6 gene deletion), and CYP2D6*1 (absence of SNPs)	Plasma concentrations	Prospective	97	Thai	>4 Weeks	Risperidone	A significant association between high plasma levels of risperidone and CYP2D6*5/*10 ($P = 0.02$), CYP2D6*10/*10 ($P = 0.04$), and CYP2D6*10/*41 ($P = 0.04$).

(continued)

Table 1. (continued)

Study (First Author, Years)	Diagnoses	Age	Presence/Absence of Intellectual Disabilities	Gene(s) and Polymorphism(s)	Outcomes	Study Design	Number of Subjects	Ethnicity or Nationality	Treatment Duration	Treatment Medication	Main Findings
Youngster et al., 2014[75]	ASD (autism, Asperger disorder, or PDD-NOS; DSM-IV, ADI-R, and Childhood Autism Rating Scale)	Median: 7 (range: 3 to 18) years	Not reported	CYP2D6*2, *3, *4, *5, *6, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *52, and a number of duplicated alleles	Treatment response and adverse effects (e.g., hyperprolactinemia, AIWG, and EPS)	Observational cohort study	40	Israeli	A median of 6 months (3 months minimum)	Risperidone	UMs ($n = 2$) were classified as nonresponders and had no adverse effects. In contrast, PMs ($n = 2$) were classified as responders and experienced adverse effects. PMs had significantly higher risperidone plasma levels ($P = 0.03$) and higher risperidone-to-9-OH-risperidone ratio ($P = 0.02$: as continuous variable, $P = 0.004$: as dichotomous with a cutoff ratio of 1)

Note. ABC = Aberrant Behavior Checklist; ABC-CV = ABC–Community Version; ADHD = attention deficit hyperactivity disorder; ADI-R = Autism Diagnostic Interview–Revised; AIWG = antipsychotic-induced weight gain; ADOS = Autism Diagnostic Observation Scale: ASD = autism spectrum disorder; ATEC = Autism Treatment Evaluation Checklist; BIS = Behavioral Intervention Score; BMI = body mass index; CGI-I = Clinical Global Impression Scale–Improvement; DBRCT = double-blind randomized controlled trial; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision; EM = extensive metabolizer; EPS = extrapyramidal symptom; ICD 10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision; ID = intellectual disability; IM = intermediate metabolizer; IQ = intelligence quotient; IQR = interquartile range; PDD = pervasive developmental disorder; PDD-NOS = pervasive developmental disorder not otherwise specified; PM = poor metabolizer; RBS-R CRS = Repetitive Behavior Scale–Revised, Compulsive Behavior and Ritualistic/Sameness Behavior subscales; RUPP = Research Units on Pediatric Psychopharmacology; RUPP-PI = RUPP–Psychosocial Intervention; SD = standard deviation; SGAs = second-generation antipsychotics; SNP = single nucleotide polymorphism; UM = ultrarapid metabolizer.

using the Repetitive Behavior Scale–Revised, Compulsive Behavior and Ritualistic/Sameness Behavior Subscales (RBS-R-CRS) and ABC-CV Irritability subscale (ABC-CV-IRR) scores ($N = 44$).[61] Similar to the previous study,[49] this study also included adults but did not provide a breakdown by age (mean $\pm$ SD [range]: 161 $\pm$ 86 [61 to 532] months) while this study included at least 1 adult patient aged 44 years.[61] A subgroup of individuals had ASD with ID, but no individuals were exclusively affected with ID (nonverbal IQ: 80 $\pm$ 25 [35 to 130], $N = 44$; verbal IQ: 78 $\pm$ 25 [30 to 120], $N = 38$). A study by Correia et al. examined the relationship between treatment response to risperidone, which was assessed by the Autism Treatment Evaluation Checklist (ATEC), and 15 variants across 8 genes in autistic children and young adults who were receiving risperidone up to 1 year ($N = 45$).[51] Similar to the other 2 studies,[49,61] this study also included at least 1 adult with an age of 21 years (mean $\pm$ SD [range]: 8.67 $\pm$ 4.30 [3 to 21]). It reported patients' IQ levels and included individuals with ID; however, it was not clear whether adults with ID were included or not (IQ $\geq$ 70, 37.8% of the patients; 69 $\geq$ IQ $\geq$ 50, 31.1%; 49 $\geq$ IQ $\geq$ 35, 24.4%; and IQ < 35, 6.7%).[51]

PGx studies in children/adolescents with ASD/ID. In contrast to the 3 studies that included adults and children/adolescents,[49,51,61] the other 25 studies focused specifically on children/adolescents with ASD/ID. Among them, 1 PGx study by AlOlaby et al. included only children/adolescents with fragile X syndrome which is the most common inherited cause of ID.[47] In addition, 6 additional studies were conducted in children/adolescents with ASD, some of whom also had ID.[48,53,59,63,64,67] Three of the 6 studies clearly described that they included ASD with ID.[53,59,64] For the other 3 studies,[48,63,67] it was likely that they also included children/adolescents with ASD and ID, given their inclusion criteria. More specifically, Nurmi et al. investigated the association of key energy balance genes (i.e., *FTO*, *MC4R*, *LEP*, *CNR1*, *FAAH*) with antipsychotic-induced weight gain (AIWG) in children/adolescents with ASD treated with risperidone in the 2 National Institute of Mental Health Research Units on Pediatric Psychopharmacology (RUPP) Autism Network trials.[63] It was reported that approximately 70% and 40% of patients in the 2 trials had intellectual disabilities.[68,76] Likewise, Anderson et al. included individuals with ASD treated with risperidone from the RUPP trial, in which approximately 70% of the individuals were affected with mild or more ID.[48] The study by Sherwin et al. investigated the effect of the *CYP2D6* phenotype on pharmacokinetic variability of risperidone in children and adolescents (majority of ASD; $N = 45$).[67] This study did not specify diagnoses but reported that the majority of individuals were affected by ASD. Forty-one of the 45 patients included in this study were from other studies, 1 of which included some individuals with ASD who had co-occurring ID.[68] Thus, it was possible that some individuals had ASD and possibly ID in this study.[67]

There were 18 studies of children/adolescents with ASD, which either did not describe whether any of the participants also had ID or specifically mentioned including only individuals without ID.[50,52,54-58,60,62,65,66,69,70-75] For example, Roke et al. listed IQ above 85 in their inclusion criteria.[66] Three other studies specified excluding children/adolescents with IQs below 55 but did not provide information indicating whether individuals with IQs ranging from 56 to 75 participated in the studies.[54,57,65] The other 14 studies did not report if they included children/adolescents with ASD who also had ID.

PGx Studies Based on Treatment Outcomes

Response to psychotropics. Among the 28 studies included, twelve studies primarily investigated the association between treatment response and specific gene polymorphisms.[47,49,51,54,58,59,61,62,64,65,69,75]

Response to antipsychotics. Five of the 12 studies focused on patients treated with antipsychotics.[51,54,62,65,75] Among them, 4 studies[51,54,62,75] included only patients treated with risperidone monotherapy and the other one used various antipsychotics.[65]

Pharmacokinetic Genes: Three studies investigated the *CYP* polymorphisms,[51,62,75] among which 1 study[75] suggested an association of CYP2D6 metabolizer status with treatment response to risperidone. More specifically, an observational cohort study of 40 Israeli children by Youngster et al. evaluated the association between *CYP2D6* genotypes (up to 34 *CYP2D6* alleles and allele duplications) and treatment response to risperidone determined by parents and the treating neurologist, using a simple 3-point scale (i.e., improvement in disruptive behaviors, no change, or worsening).[75] This study reported that PMs ($n = 2$) were classified as responders whereas UMs ($n = 2$) were classified as nonresponders, while no serum levels of risperidone were taken. However, other studies reported no association of the *CYP2D6* polymorphisms with treatment response.[51,62] Two studies examined the impact of the *ABCB1 1236C>T* polymorphism on treatment response to risperidone.[51,62] Correia et al. reported that the *ABCB1 1236C>T* (rs1128503) was significantly associated with clinical improvement assessed by the ATEC ($P = 0.002$; see also the "PGx Studies in Adults with ASD/ID" section)[51] whereas a cross-sectional study by Nuntamool et al.,[62] where 82 Thai children/adolescents treated with risperidone for more than 1 year were included, reported no significant association with treatment response determined by the Clinical Global Impression Scale–Improvement (CGI-I) score and a 4-point scale for each of aggression, overactivity, and repetitive behaviors.

Pharmacodynamic Genes: Among the 4 studies investigating gene variants associated with treatment response

to risperidone,[51,54,62,75] the *DRD3 Ser9Gly* (rs6280) polymorphism was examined in 3 studies,[51,54,62] 2 of which reported significant findings.[51,54] More specifically, Correia et al. reported carriers of Gly allele showed greater treatment response to risperidone than noncarriers of Gly allele (i.e., Ser/Ser genotype; see also the "PGx Studies in Adults with ASD/ID" section).[51] An 8-week prospective study by Firouzabadi et al. reported that responder rates (i.e., a 50% or greater decrease of the ABC scores from baseline) were significantly higher in carriers of Gly allele as well as carriers of Gly/Gly and Ser/Gly genotypes compared with carriers of Ser allele and Ser/Ser genotype in Iranian children ($N = 56$; $P = 0.027$ and 0.014, respectively).[54] In contrast, a cross-sectional study by Nuntamool et al.[62] reported no significant association of the *DRD3* rs6280 polymorphism with treatment response. The following other gene variants were also significantly associated with treatment response to risperidone in 1 study: the *HTR2A c.-1438G>A* (rs6311; $P = 0.019$),[51] *HTR2C c.995G>A* (rs3813928; $P = 0.035$),[51] and *DRD2* Taq1A (rs1800497; $P = 0.048$).[62]

Response to antidepressants. The association between response to antidepressants and gene variants was examined in 6 studies.[47,49,61,64,65,69] Among them, escitalopram was used in 3 studies (see also the "PGx Studies in Adults with ASD/ID" section),[49,61,64] sertraline in 1 study (see also the "Pharmacogenomic Studies in Children/Adolescents with ASD/ID" section),[47] fluvoxamine in 1 study,[69] and various antidepressants in 1 study.[65]

- Pharmacokinetic Genes: Bishop et al. found that there were no differences in the rate of improvement assessed using the ABC-CV across metabolizer groups for the *CYP2C19* gene (i.e., UM [$n = 26$], EM [$n = 40$], and PM/IM metabolizer [$n = 23$]) in individuals with ASD treated with escitalopram in 6 weeks ($P = 0.39$).[49] However, the UM group exhibited a slower rate of dosing change compared to other groups when looking at titration trajectories, contrary to expectations. On the other hand, AlOlaby et al. reported that subjects with the PM/IM genotypes for the *CYP2C19* gene showed a significant percentage in the very much improved/much improved CGI-I if they were treated with sertraline ($n = 6$) compared to those who were with placebo ($n = 5$) in patients with fragile X syndrome ($P = 0.007$).[47]
- Pharmacodynamic Genes: The association of the *SLC6A4* (5-HTTLPR) gene and treatment response to antidepressants was investigated in 4 studies.[47,61,64,69] AlOlaby et al. reported that sertraline was associated with a significantly different change (i.e., symptom improvement) from baseline in the social participation raw score on the active arm compared to placebo in those with the L/L genotype ($P = 0.005$) whereas no significant difference was observed for the S/L ($P = 0.422$) or S/S ($P = 0.997$) genotypes ($N = 51$).[47] Likewise, Sugie et al.[69] found that the L allele conferred better response to fluvoxamine than the S allele in a 12-week double-blind crossover trial of fluvoxamine and placebo, in which treatment response was determined by CGI scores in Japanese patients ($N = 18$; $P = 0.047$). In addition, Owley et al. reported a significant interaction between genotype group of the 5-HTTLPR and time on the ABC-CV-IRR in patients treated with escitalopram for 10 weeks ($N = 58$; $P = 0.004$).[64] In contrast, Najjar et al. reported no significant differences in the rate of symptom improvement assessed using the RBS-R-CRS and ABC-CV-IRR across genotype groups in ASD treated with escitalopram over the 6 weeks ($N = 44$; $P = 0.273$ for RBS-R-CRS and $P = 0.122$ for ABC-CV-IRR).[61] Other results were summarized in Table 1.

Response to other medications. An 8-week open-label trial examined the effect of the *MDR1* (*ABCB1*) C3435T polymorphism on treatment response to guanfacine in PDD patients with clinically significant symptoms of attention deficit hyperactivity disorder (ADHD; $N = 25$).[58] Patients with either C/T or C/C genotypes showed a significantly greater improvement than T/T genotype in the ABC Hyperactivity scores ($P < 0.03$) and Swanson, Nolan, and Pelham (SNAP) scores ($P = 0.05$). Another study reported a 4-week, placebo-controlled, double-blind crossover study with 58 children to evaluate the association between 36 variants across 10 genes and treatment response to methylphenidate defined by CGI and ABC hyperactivity subscale.[59] This study reported that the *DRD1* rs4867798 ($P = 0.042$) and rs5326 ($P = 0.006$), *DRD3* rs6280 ($P = 0.044$), *DRD4* rs11246226 ($P = 0.038$), *SLC6A3* VNTR ($P = 0.049$), *SLC6A4* STin2 VNTR ($P = 0.041$), *ADRA2A* rs1800544 ($P = 0.015$), and *COMT* rs4680 ($P = 0.049$) among 36 variants tested were significantly associated with responder status; however, this significance in each variant did not remain after correction for multiple testing.

Adverse effects. Fifteen studies primarily investigated the association of side effects with gene polymorphisms.[48,50-53,55,56,59,63,65,66,70-72,75] Among them, 9 studies focused on prolactin elevation or hyperprolactinemia as primary outcome in patients treated with risperidone.[48,50,51,53,56,66,70,72,75] Other adverse effects were also investigated in 8 studies (e.g., AIWG, blood pressure, and insulin resistance).[51,52,55,59,63,65,71,75]

Prolactin elevation or hyperprolactinemia. The most commonly investigated gene variant associated with prolactin elevation or hyperprolactinemia was CYP2D6 polymorphisms,[51,53,56,66,70,72,75] followed by the DRD2 Taq1A (rs1800497) polymorphism.[48,50,51,66,70]

Pharmacokinetic Genes. Seven studies examined the impact of *CYP2D6* polymorphisms on prolactin elevation or hyperprolactinemia.[51,53,56,66,70,72,75] Although 1 prospective study by Troost et al. reported a positive correlation of the number of functional *CYP2D6* genes and serum prolactin level in 8 weeks ($P = 0.034$),[72] other studies reported no significant association of *CYP2D6* polymorphisms, genotypes, or predicted phenotypes with prolactin elevation or hyperprolactinemia.[51,53,56,66,70,75]

Pharmacodynamic Genes. Five studies investigated the association of the *DRD2 Taq1A* (rs1800497) polymorphism with hyperprolactinemia in patients treated with risperidone,[48,50,51,66,70] and 3 of them reported nonsignificant findings[48,51,66] whereas the others reported a synergistic effect of the *DRD2 TaqIA* and *DRD2 A-241G* variants on prolactin concentration using multiple regression analysis ($P = 0.003$)[50] and significant differences in prolactin level of patients among the *DRD2 Taq1A* A2A2, A1A2, and A1A1 groups ($P = 0.033$).[70]

The presence of the C allele of *HTR2C* rs6318 polymorphism was significantly associated with prolactin elevation or hyperprolactinemia in 2 studies ($P = 0.006$ and 0.02, respectively).[51,53] Other results were summarized in Table 1.

Other adverse effects. Four studies investigated the association of gene variants with AIWG in patients treated with risperidone.[51,55,63,75] The *HTR2C* rs6318[51] and rs3813929,[55] *LEP* rs7799039,[63] and *CNR1* rs806378 and rs1049353 polymorphisms[63] were significantly associated with AIWG ($P < 0.05$) whereas the findings of the association between the *HTR2C* rs3813929 polymorphism and AIWG yielded opposite findings in 2 studies.[51,55] In addition, UMs of *CYP2D6* showed a 4.8% and 5.8% lower increase in body mass index and waist circumference compared to EMs.[51]

Drug concentrations. Four studies investigated the association of drug concentrations with gene polymorphisms in patients treated with risperidone.[60,67,73,74] PMs/IMs of CYP2D6 showed significantly higher plasma concentration of risperidone and risperidone/9-hydroxyrisperidone ratio than EMs in 2 studies focusing on Thai patients ($P < 0.05$).[73,74] Other results were summarized in Table 1.

Discussion

The aim of this systematic review was to identify and review publications investigating the association between selected gene variants and treatment outcomes (e.g., treatment response and adverse effects) in individuals with ASD/ID and to review the clinical validity and utility of PGx. To achieve this aim, we included each identifiable study of individuals with ASD/ID regardless of age in our research. We found that although there were several PGx studies in children/adolescents with ASD, there were only very limited studies reported in adults with ASD/ID while not a single study focused exclusively on adults.

Similar to a recent review on PGx studies in ASD by Brown,[45] several gene variants associated with treatment response, and adverse effects of antipsychotics and antidepressants were reported exclusively in children/adolescents with ASD/ID. However, the number of PGx studies in ASD/ID across age groups, especially in adults with ASD/ID, was still very few. Also, it should be kept in mind that identified studies had relatively limited sample sizes and a variety of ethnicities and study designs. Furthermore, almost all studies applied a classic "candidate gene" approach. No genome-wide association studies were reported while there were 1 study investigating exonic expression levels using Affymetrix GeneChip Human Exon 1.0 ST Arrays (Affymetrix, Santa Clara, CA)[57] and 2 studies investigating several genetic variants in drug-metabolizing enzyme and transporter (DMET) genes using Affymetrix DMET arrays (Affymetrix Inc., Santa Clara, CA).[56,60]

The majority of studies identified in this review have examined PGx associations with treatment response and/or adverse effects in patients treated with risperidone. The possible reasons for this finding are as follows: (1) Risperidone is one of the FDA-approved drugs for the treatment of challenging behavior in children/adolescents with ASD,[77] and (2) risperidone is similarly one of the most commonly studied medications for challenging behavior (i.e., repetitive, self-injurious, and aggressive behaviors) in adults with ASD/ID.[78] Although the *DRD3* rs6280 polymorphism was the most investigated gene variant in regard to treatment response to risperidone in the 3 studies,[51,54,62] the results were still inconclusive. This inconclusive finding is consistent with a recent systematic review on the association between dopamine receptor gene polymorphisms and treatment response to risperidone assessed using the Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale, or CGI in schizophrenia.[79] Likewise, the association between pharmacokinetic gene variants (e.g., *CYP* and *ABCB1* gene variants) and response to risperidone also remains controversial in ASD/ID, which is consistent with mixed findings in a recent review in patients with schizophrenia.[80]

In regard to adverse effects, prolactin elevation or hyperprolactinemia was the most investigated adverse effect as a primary outcome in patients treated with risperidone in 9 studies,[48,50,51,53,56,66,70,72,75] examining the impact of several gene variants (e.g., *CYP2D6* polymorphisms and *DRD2* rs1800497). Most of the studies examining the impact of *CYP2D6* polymorphisms on prolactin elevation or hyperprolactinemia reported negative findings. However, most of them were based on a cross-sectional or observational study design in relatively small sample sizes ($n = 40$ to 147). In regard to the *DRD2* rs1800497, a recent meta-analysis that included 772 patients with schizophrenia, ASD, or disruptive behavior disorder from 8 studies showed no significant difference between the *DRD2* Taq1A (rs1800497) A1 carriers and non-A1 carriers in risperidone-related prolactin level ($P = 0.423$);[81] this meta-analysis included 5 studies identified in our review.[48,50,51,66,70]

Similar to PGx studies on antipsychotics, published PGx studies using antidepressants (e.g., selective serotonin reuptake inhibitors [SSRI]) are still limited in individuals with ASD/ID across age groups. We identified only 6 studies with relatively small sample sizes ($n = 19$ to 279) for whom the majority of individuals were of European ancestry.[47,49,61,64,65,69] For instance, although 3 studies reported a significant association of the 5-HTTLPR with treatment response to antidepressants (escitalopram, sertraline, and fluvoxamine) assessed using the ABC-CV-IRR or CGI, the small sample size in each study is a major limitation in each study ($N = 58$, 51, and 18, respectively).[47,64,69] It is of interest that this finding in individuals with ASD/ID is consistent with a meta-analysis of the association between 5-HTTLPR and treatment response to SSRIs (i.e., remission and response rates) in patients with major depressive disorder (MDD) and bipolar disorder (28 studies and 3,866 subjects).[82] In line with the findings of this meta-analysis,[82] the associations between 5-HTTLPR and treatment response to SSRIs were reported in patients with anxiety disorder in several studies although the findings were mixed.[83] However, it should be kept in mind that treatment response is assessed by depression and anxiety scales but not the ABC or CGI in the studies in patients with mood disorders and anxiety disorder.[82,83] Likewise, the findings of the association between *CYP2C19* gene variants and response to antidepressants are mixed in ASD/ID, which is in line with previous studies showing inconsistent linking the *CYP2D6* and *CYP2C19* gene variants to antidepressant treatment response in patients with MDD.[84,85] Although antipsychotics are the most commonly prescribed medications in adults with ID in the United States,[24] a population-based study in UK ($N = 33{,}016$) reported the most common class of drugs to be prescribed was anxiolytics/hypnotics, followed by antidepressants in adults with ID between 1999 and 2013 and that the incidence rate of new antidepressants over the follow-up period was approximately 350 per 10,000 person years in 2013.[15] Nevertheless, the evidence for antidepressant use in individuals with ID across all age groups is sparse, and generally, low response rates and high rates of adverse events have been reported.[86] Although studies in ASD suggested that SSRIs might be better tolerated in adults than in children, most studies of SSRIs in individuals with ID included both adults and children/adolescents, and age-specific data were still limited.[86] Therefore, further investigation on PGx studies on antidepressants as well as antipsychotics is warranted.

While specific PGx guidelines have not been established for individuals with ASD/ID, several established PGx guidelines provided useful gene–drug information for medications used in ASD/ID across age groups.[87,88] For instance, the Clinical Pharmacogenetics Implementation Consortium Dosing Guidelines recommend SSRI dosing adjustment based on the metabolizer status of the *CYP2C19* for citalopram, escitalopram, and sertraline and the *CYP2D6* for fluvoxamine.[87] Likewise, the Royal Dutch Association for the Advancement of Pharmacy–Pharmacogenetics Working Group has also recommended the dosing adjustment of antipsychotics based on the *CYP2D6* genotypes for 6 antipsychotics: aripiprazole, brexpiprazole, clozapine, haloperidol, olanzapine, risperidone, and zuclopenthixol.[89] These guidelines are also well summarized on the Pharmacogenomics Knowledgebase website,[88] which also provides levels of evidence for gene–drug associations. Given that those gene–drug pairs should be also relevant in ASD/ID across all age groups as regardless of diagnoses, minimal or excessive serum/plasma levels of antipsychotics and antidepressants are likely to affect treatment response and side effects in this population.

To the best of our knowledge, this is the first systematic review of PGx studies with psychotropic drugs including antipsychotics and antidepressants (i.e., treatment response, adverse effects, and drug concentrations) in adults and children/adolescents with ASD/ID. Nevertheless, the results of our study must be interpreted with caution, given several limitations. First, on a systematic level, despite that articles were systematically investigated through MEDLINE, Embase, and PsycINFO, some references may still have been missed, nonsignificant findings might not have been published (i.e. "publication bias"), and only articles written in English were included in this review. Second, although we included some studies that might have partly included adults with ASD/ID, the actual number of the adults included in each study was unclear. Third, although several studies reported significant associations between several gene variants and treatment outcomes (e.g., treatment response to antipsychotics and antidepressants, and adverse effects) prior to multiple testing, there were few studies that reported gene variants surviving correction for multiple testing (e.g., Nurmi et al.[63]).

In conclusion, there is a limited number of PGx studies in individuals with ASD/ID in particular in adults. Given that psychotropic medication use increases with age,[22,23] accumulating evidence on PGx studies and further investigation focusing on the clinical validity and efficacy of PGx testing for psychotropic treatment in individuals with ASD/ID across age groups are warranted.

Author Contributions

These authors Pushpal Desarkar and Daniel J. Müller equally contributed to this work. Kazunari Yoshida and Emiko Koyama did the literature search, extracted the data, and wrote the first draft of the manuscript. All authors interpreted the data, wrote the report, and approved the final version of the manuscript.

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References

1. McKenzie K, Milton M, Smith G, Ouellette-Kuntz H. Systematic review of the prevalence and incidence of intellectual disabilities: current trends and issues. Curr Dev Disord Rep. 2016;3(2):104-115.
2. Christensen DL, Baio J, Van Naarden Braun K, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveill Summ. 2016;65(3):1-23.
3. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychol Med. 2015;45(3):601-613.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington (DC): American Psychiatric Publishing; 2013.
5. Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism: national survey of children's health. Arch Pediatr Adolesc Med. 2006;160(8):825-830.
6. Dekker MC, Koot HM, van der Ende J, Verhulst FC. Emotional and behavioral problems in children and adolescents with and without intellectual disability. J Child Psychol Psychiatry. 2002;43(8):1087-1098.
7. Tsakanikos E, Costello H, Holt G, Sturmey P, Bouras N. Behaviour management problems as predictors of psychotropic medication and use of psychiatric services in adults with autism. J Autism Dev Disord. 2007;37(6):1080-1085.
8. Cooper SA, Smiley E, Morrison J, Williamson A, Allan L. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. Br J Psychiatry. 2007;190(1):27-35.
9. Crocker AG, Mercier C, Lachapelle Y, Brunet A, Morin D, Roy ME. Prevalence and types of aggressive behaviour among adults with intellectual disabilities. J Intellect Disabil Res. 2006;50(Pt 9):652-661.
10. Mazza MG, Rossetti A, Crespi G, Clerici M. Prevalence of co-occurring psychiatric disorders in adults and adolescents with intellectual disability: a systematic review and meta-analysis. J Appl Res Intellect Disabil. 2020;33(2):126-138.
11. Abdallah MW, Greaves-Lord K, Grove J, Nørgaard-Pedersen B, Hougaard DM, Mortensen EL. Psychiatric comorbidities in autism spectrum disorders: findings from a Danish Historic Birth Cohort. Eur Child Adolesc Psychiatry. 2011;20(11–12):599-601.
12. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry. 2008;47(8):921-929.
13. Lunsky Y, Khuu W, Tadrous M, Vigod S, Cobigo V, Gomes T. Antipsychotic use with and without comorbid psychiatric diagnosis among adults with intellectual and developmental disabilities. Can J Psychiatry. 2018;63(6):361-369.
14. de Kuijper GM, Hoekstra PJ. Physicians' reasons not to discontinue long-term used off-label antipsychotic drugs in people with intellectual disability. J Intellect Disabil Res. 2017;61(10):899-908.
15. Sheehan R, Hassiotis A, Walters K, Osborn D, Strydom A, Horsfall L.Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study. BMJ. 2015;351:h4326.
16. Deb S, Unwin G, Deb T. Characteristics and the trajectory of psychotropic medication use in general and antipsychotics in particular among adults with an intellectual disability who exhibit aggressive behaviour. J Intellect Disabil Res. 2015;59(1):11-25.
17. Hsu SW, Chiang PH, Chang YC, Lin JD, Tung HJ, Chen CY. Trends in the use of psychotropic drugs in people with intellectual disability in Taiwan: a nationwide outpatient service study, 1997-2007. Res Dev Disabil. 2014;35(2):364-372.
18. Tsiouris JA, Kim SY, Brown WT, Pettinger J, Cohen IL. Prevalence of psychotropic drug use in adults with intellectual disability: positive and negative findings from a large scale study. J Autism Dev Disord. 2013;43(3):719-731.
19. Coury DL, Anagnostou E, Manning-Courtney P, et al. Use of psychotropic medication in children and adolescents with autism spectrum disorders. Pediatrics. 2012;130 (Suppl. 2):S69-S76.
20. Matson JL, Neal D. Psychotropic medication use for challenging behaviors in persons with intellectual disabilities: an overview. Res Dev Disabil. 2009;30(3):572-586.
21. Holden B, Gitlesen JP. Psychotropic medication in adults with mental retardation: prevalence, and prescription practices. Res Dev Disabil 2004;25(6):509-521.
22. Stortz JN, Lake JK, Cobigo V, Ouellette-Kuntz HM, Lunsky Y. Lessons learned from our elders: how to study polypharmacy in populations with intellectual and developmental disabilities. Intellect Dev Disabil. 2014;52(1):60-77.
23. Esbensen AJ, Greenberg JS, Seltzer MM, Aman MG. A longitudinal investigation of psychotropic and non-psychotropic medication use among adolescents and adults with autism

spectrum disorders. J Autism Dev Disord. 2009;39(9): 1339-1349.
24. Esler A, Hewitt A, Hall-Lande J, Pettingell SL, Houseworth J. Psychotropic medication use for adults with autism spectrum disorder who receive services and supports through adult developmental disability services in the United States. J Autism Dev Disord. 2019;49(6):2291-2303.
25. Jobski K, Höfer J, Hoffmann F, Bachmann C. Use of psychotropic drugs in patients with autism spectrum disorders: a systematic review. Acta Psychiatr Scand. 2017;135(1):8-28.
26. Spencer D, Marshall J, Post B, et al. Psychotropic medication use and polypharmacy in children with autism spectrum disorders. Pediatrics. 2013;132(5):833-840.
27. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1): 57-65.
28. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. Ann Pharmacother. 2013;47(3):324-332.
29. Sheehan R, Horsfall L, Strydom A, Osborn D, Walters K, Hassiotis A.Movement side effects of antipsychotic drugs in adults with and without intellectual disability: UK population-based cohort study. BMJ Open. 2017;7(8):e017406.
30. Bousman CA, Zierhut H, Müller DJ. Navigating the labyrinth of pharmacogenetic testing: a guide to test selection. Clin Pharmacol Ther. 2019;106(2):309-312.
31. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015; 98(2):127-134.
32. Cacabelos R, Hashimoto R, Takeda M. Pharmacogenomics of antipsychotics efficacy for schizophrenia. Psychiatry Clin Neurosci. 2011;65(1):3-19.
33. Kim K, Magness JW, Nelson R, Baron V, Brixner DI. Clinical utility of pharmacogenetic testing and a clinical decision support tool to enhance the identification of drug therapy problems through medication therapy management in polypharmacy patients. J Manag Care Spec Pharm. 2018;24(12):1250-1259.
34. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: a prospective pilot randomized controlled trial. PLoS One. 2017;12(2):e0170905.
35. Brixner D, Biltaji E, Bress A, et al. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. J Med Econ. 2016;19(3):213-228.
36. Arranz MJ, Gonzalez-Rodriguez A, Perez-Blanco J, et al. A pharmacogenetic intervention for the improvement of the safety profile of antipsychotic treatments. Transl Psychiatry. 2019;9(1):177.
37. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics. 2019;20(1):37-47.
38. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 2019;111:59-67.
39. Bousman C, Maruf AA, Müller DJ. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. Curr Opin Psychiatry. 2019;32(1):7-15.
40. Jukic MM, Smith RL, Haslemo T, Molden E, Ingelman-Sundberg M. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry. 2019;6(5):418-426.
41. Jukić MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. Am J Psychiatry. 2018;175(5):463-470.
42. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1): 37-44.
43. Hicks JK, Dunnenberger HM, Gumpper KF, Haidar CE, Hoffman JM. Integrating pharmacogenomics into electronic health records with clinical decision support. Am J Health Syst Pharm. 2016;73(23):1967-1976.
44. Leckband SG, Kelsoe JR, Dunnenberger HM, et al. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013;94(3):324-328.
45. Brown JT, Eum S, Cook EH, Bishop JR. Pharmacogenomics of autism spectrum disorder. Pharmacogenomics. 2017;18(4): 403-414.
46. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339(Jul 21 1): b2535-b2535.
47. AlOlaby RR, Sweha SR, Silva M, et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev. 2017;39(6):483-492.
48. Anderson GM, Scahill L, McCracken JT, et al. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. Biol Psychiatry. 2007;61(4):545-550.
49. Bishop JR, Najjar F, Rubin LH, et al. Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in autism spectrum disorder. Pharmacogenet Genomics. 2015;25(11):548-554.
50. Calarge CA, Ellingrod VL, Zimmerman B, Acion L, Sivitz WI, Schlechte JA. Leptin gene -2548G/A variants predict risperidone-associated weight gain in children and adolescents. Psychiatr Genet. 2009;19(6):320-327.
51. Correia CT, Almeida JP, Santos PE, et al. Pharmacogenetics of risperidone therapy in autism: association analysis of eight candidate genes with drug efficacy and adverse drug reactions. Pharmacogenomics J. 2010;10(5):418-430.

52. Cote AT, Panagiotopoulos C, Devlin AM. Interaction between the Val158Met catechol-O-methyltransferase gene variant and second-generation antipsychotic treatment on blood pressure in children. Pharmacogenomics J. 2015;15(1):95-100.
53. dos Santos Júnior A, Henriques TB, de Mello MP, et al. Hyperprolactinemia in children and adolescents with use of risperidone: clinical and molecular genetics aspects. J Child Adolesc Psychopharmacol. 2015;25(10):738-748.
54. Firouzabadi N, Nazariat A, Zomorrodian K. DRD3 Ser9Gly polymorphism and its influence on risperidone response in autistic children. J Pharm Pharm Sci. 2017;20(1):445-452.
55. Hoekstra PJ, Troost PW, Lahuis BE, et al. Risperidone-induced weight gain in referred children with autism spectrum disorders is associated with a common polymorphism in the 5-hydroxytryptamine 2C receptor gene. J Child Adolesc Psychopharmacol. 2010;20(6):473-477.
56. Hongkaew Y, Medhasi S, Pasomsub E, et al. UGT1A1 polymorphisms associated with prolactin response in risperidone-treated children and adolescents with autism spectrum disorder. Pharmacogenomics J. 2018;18(6):740-748.
57. Lit L, Sharp FR, Bertoglio K, et al. Gene expression in blood is associated with risperidone response in children with autism spectrum disorders. Pharmacogenomics J. 2012;12(5):368-371.
58. McCracken JT, Aman MG, McDougle CJ, et al. Possible influence of variant of the P-glycoprotein gene (MDR1/ABCB1) on clinical response to guanfacine in children with pervasive developmental disorders and hyperactivity. J Child Adolesc Psychopharmacol. 2010;20(1):1-5.
59. McCracken JT, Badashova KK, Posey DJ, et al. Positive effects of methylphenidate on hyperactivity are moderated by monoaminergic gene variants in children with autism spectrum disorders. Pharmacogenomics J. 2014;14(3):295-302.
60. Medhasi S, Pinthong D, Pasomsub E, et al. Pharmacogenomic study reveals new variants of drug metabolizing enzyme and transporter genes associated with steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone in Thai autism spectrum disorder patients. Front Pharmacol. 2016;7:475.
61. Najjar F, Owley T, Mosconi MW, et al. Pharmacogenetic study of serotonin transporter and 5HT2A genotypes in autism. J Child Adolesc Psychopharmacol. 2015;25(6):467-474.
62. Nuntamool N, Ngamsamut N, Vanwong N, et al. Pharmacogenomics and efficacy of risperidone long-term treatment in Thai autistic children and adolescents. Basic Clin Pharmacol Toxicol. 2017;121(4):316-324.
63. Nurmi EL, Spilman SL, Whelan F, et al. Moderation of antipsychotic-induced weight gain by energy balance gene variants in the RUPP autism network risperidone studies. Transl Psychiatry. 2013;3(6):e274.
64. Owley T, Brune CW, Salt J, et al. A pharmacogenetic study of escitalopram in autism spectrum disorders. Autism Res. 2010;3(1):1-7.
65. Prows CA, Nick TG, Saldaña SN, et al. Drug-metabolizing enzyme genotypes and aggressive behavior treatment response in hospitalized pediatric psychiatric patients. J Child Adolesc Psychopharmacol. 2009;19(4):385-394.
66. Roke Y, van Harten PN, Franke B, Galesloot TE, Boot AM, Buitelaar JK. The effect of the Taq1A variant in the dopamine D_2 receptor gene and common CYP2D6 alleles on prolactin levels in risperidone-treated boys. Pharmacogenet Genomics. 2013;23(9):487-493.
67. Sherwin CMT, Saldaña SN, Bies RR, Aman MG, Vinks AA. Population pharmacokinetic modeling of risperidone and 9-hydroxyrisperidone to estimate CYP2D6 subpopulations in children and adolescents. Ther Drug Monit. 2012;34(5):535-544.
68. Aman MG, Vinks AA, Remmerie B, et al. Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. Clin Ther. 2007;29(7):1476-1486.
69. Sugie Y, Sugie H, Fukuda T, et al. Clinical efficacy of fluvoxamine and functional polymorphism in a serotonin transporter gene on childhood autism. J Autism Dev Disord. 2005;35(3):377-385.
70. Sukasem C, Hongkaew Y, Ngamsamut N, et al. Impact of pharmacogenetic markers of CYP2D6 and DRD2 on prolactin response in risperidone-treated Thai children and adolescents with autism spectrum disorders. J Clin Psychopharmacol. 2016;36(2):141-146.
71. Sukasem C, Vanwong N, Srisawasdi P, et al. Pharmacogenetics of risperidone-induced insulin resistance in children and adolescents with autism spectrum disorder. Basic Clin Pharmacol Toxicol. 2018;123(1):42-50.
72. Troost PW, Lahuis BE, Hermans MH, et al. Prolactin release in children treated with risperidone: impact and role of CYP2D6 metabolism. J Clin Psychopharmacol. 2007;27(1):52-57.
73. Vanwong N, Ngamsamut N, Hongkaew Y, et al. Detection of CYP2D6 polymorphism using Luminex xTAG technology in autism spectrum disorder: CYP2D6 activity score and its association with risperidone levels. Drug Metab Pharmacokinet. 2016;31(2):156-162.
74. Vanwong N, Ngamsamut N, Medhasi S, et al. Impact of CYP2D6 polymorphism on steady-state plasma levels of risperidone and 9-hydroxyrisperidone in Thai children and adolescents with autism spectrum disorder. J Child Adolesc Psychopharmacol. 2017;27(2):185-191.
75. Youngster I, Zachor DA, Gabis LV, et al. CYP2D6 genotyping in paediatric patients with autism treated with risperidone: a preliminary cohort study. Dev Med Child Neurol. 2014;56(10):990-994.
76. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med. 2002;347(5):314-321.
77. Xiong W. Pediatric pharmacologic management of autism-associated behavioral dysregulation. Am J Psychiatry Resid J. 2017;12(9):3-5.
78. Sawyer A, Lake JK, Lunsky Y, Liu SK, Desarkar P. Psychopharmacological treatment of challenging behaviours in adults with autism and intellectual disabilities: a systematic review. Res Autism Spectr Disord. 2014;8(7):803-813.
79. Ma L, Zhang X, Xiang Q, et al. Association between dopamine receptor gene polymorphisms and effects of risperidone

treatment: a systematic review and meta-analysis. Basic Clin Pharmacol Toxicol. 2019;124(1):94-104.
80. Yoshida K, Müller DJ. Pharmacogenetics of antipsychotic drug treatment: update and clinical implications. Mol Neuropsychiatry. 2018;5(1):1-26.
81. Ma L, Xiang Q, Zhou S, et al. Association of dopamine D2 receptor gene polymorphisms with prolactin levels related to risperidone treatment: a systematic review and meta-analysis. J Clin Pharm Ther. 2019;44(4):543-552.
82. Lueken U, Zierhut KC, Hahn T, et al. Neurobiological markers predicting treatment response in anxiety disorders: a systematic review and implications for clinical application. Neurosci Biobehav Rev. 2016;66:143-162.
83. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol. 2012;22(4):239-258.
84. Solomon HV, Cates KW, Li KJ. Does obtaining CYP2D6 and CYP2C19 pharmacogenetic testing predict antidepressant response or adverse drug reactions? Psychiatry Res. 2019; 271:604-613.
85. Müller DJ, Kekin I, Kao ACC, Brandl EJ. Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. Int Rev Psychiatry. 2013;25(5): 554-571.
86. Ji NY, Findling RL. Pharmacotherapy for mental health problems in people with intellectual disability. Curr Opin Psychiatry. 2016;29(2):103-125.
87. Clinical Pharmacogenetics Implementation Consortium (CPIC). Genes-drugs. [accessed 2020 Mar 10]. https://cpicpgx.org/genes-drugs/
88. PharmGKB. [accessed 2020 Mar 10]. https://www.pharmgkb.org/
89. Royal Dutch association for the advancement of pharmacy–pharmacogenetics working group (DPWG). dosing guidelines. [accessed 2020 Mar 10]. https://www.pharmgkb.org/view/dosing-guidelines.do?source=DPWG#/