REVIEW

Clinical significance of pharmacogenomic studies in tardive dyskinesia associated with patients with psychiatric disorders

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Abstract: Pharmacogenomics is the study of the effects of genetic polymorphisms on medication pharmacokinetics and pharmacodynamics. It offers advantages in predicting drug efficacy and/or toxicity and has already changed clinical practice in many fields of medicine. Tardive dyskinesia (TD) is a movement disorder that rarely remits and poses significant social stigma and physical discomfort for the patient. Pharmacokinetic studies show an association between cytochrome P450 enzyme-determined poor metabolizer status and elevated serum antipsychotic and metabolite levels. However, few prospective studies have shown this to correlate with the occurrence of TD. Many retrospective, case-control and cross-sectional studies have examined the association of cytochrome P450 enzyme, dopamine (receptor, metabolizer and transporter), serotonin (receptor and transporter), and oxidative stress enzyme gene polymorphisms with the occurrence and severity of TD. These studies have produced conflicting and confusing results secondary to heterogeneous inclusion criteria and other patient characteristics that also act as confounding factors. This paper aims to review and summarize the pharmacogenetic findings in antipsychotic-associated TD and assess its clinical significance for psychiatry patients. In addition, we hope to provide insight into areas that need further research.

Keywords: pharmacogenomics, tardive dyskinesia, cytochrome P450, pharmacogenetic, schizophrenia

Introduction

Pharmacogenomics is the study of the effect of genetic polymorphisms on medication pharmacokinetics and pharmacodynamics. This has predictive implications on the medication efficacy, toxicity or side effect profile for the individual. It was first described in 1999 by Evans et al[1] who proposed a prediction of medication response can be made from an individual's genetic constitution. Genetic polymorphisms of drug metabolizing enzymes, drug transporter and drug target receptor genes have each been implicated. Pharmacogenomics has been used in numerous medical specialties. For example, testing for thiopurine methyltransferase metabolizer status prior to azathioprine commencement can predict and avoid life-threatening myelosuppression.[2] Pharmacogenomics offers an advantage in predicting drug efficacy and/or toxicity, hence provides cost-effectiveness, and has already changed clinical practice in the field of oncology, hematology, and immunology.

Tardive dyskinesia (TD) is a movement disorder that rarely remits[3] and poses significant social stigma and physical discomfort for the patient. It occurs following the initiation, administration or withdrawal of a dopaminergic antagonist or indirect dopaminergic inhibitor such as a selective serotonergic reuptake inhibitor.[4]

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TD comprises of non-rhythmic, repetitive stereotyped tongue protrusion, lip smacking, chewing and smacking movements, and may also involve the limbs and trunk.[5] The prevalence of TD is between 9.3%–39.7% of patients on dopamine antagonists.[6–8] The estimated incidence is 2.9% and 5%–7.7% per year for second-generation (atypical) and first-generation (typical) antipsychotics, respectively.[9] Several studies found varying prevalence between different ethnicities.[10,11] African ethnicity is associated with higher risk of TD and less likelihood of improvement in a number of studies, even after correcting for antipsychotic dose.[12,13] Familial TD has been reported,[14,15] even with correction for antipsychotic dose and patient age,[16] further implicating genetic contribution to this condition. This has led to investigations into the contribution of genetic polymorphism in patients with TD following antipsychotic exposure.

The exact pathophysiology of TD to date is unclear. A number of hypotheses have been proposed over the decades. Genetic predisposition is suggested by reports of familial TD. However, environmental influence and increased susceptibility due to the effects of aging such as accumulated oxidative stress could explain the increased prevalence of TD with older age. In the 1990s, various studies found polymorphisms associated with poor metabolizer status for the cytochrome 2D6 (CYP2D6) gene are associated with TD.[17] This enzyme metabolizes all the first-generation (typical) antipsychotics as well as second-generation antipsychotics such as aripiprazole, risperidone and paliperidone.[18] However, more recent studies and meta-analysis have found no association between TD and CYP2D6 polymorphisms. Other case-control and longitudinal studies examined the role of dopamine receptor D2 and D3 subtypes in TD and found it is associated with TD in Caucasian, Chinese and Jewish populations.[19–21] Studies examining dopamine receptor subtypes from animal models and human observations of TD, showing dopamine receptor hypersensitivity following prolonged dopaminergic antagonist exposure, are another hypothesis for TD. However this hypothesis does not explain the persistence of TD despite cessation of the dopaminergic antagonist. An alternative hypothesis of neuronal toxicity through oxidative stress was proposed in the 1990s. In vitro studies that supported this theory found haloperidol produced oxidative stress, with subsequent neuronal death in vitro.[22,23] These neurons are rescued by the addition of vitamin E[24] and this led to a clinical study which found vitamin E reduces TD.[25] Subsequent pharmacogenomic studies examined the various genes involved in oxidative stress for their role in TD. Genes that encode the oxidative stress pathway enzymes and antioxidants may alter the production of free radicals. Some examples of oxidative pathway enzymes examined for their role in TD are glutathione-S-transferase, manganese superoxide dismutase, nitric oxide synthase, and quinone oxidoreductase.

In the last 14 years, novel genetic polymorphisms in the alpha-1A adrenergic receptor (ADRA1A),[26] G-protein signaling regulator (RGS9),[27] solute family carrier 18 (SLC18A2),[28] nitric oxide synthase 3 (NOS3),[29] cannabinoid receptor (CNR1),[30] and beta-arrestin (ARRB2),[31] have been associated with TD in single studies. Other genes have polymorphisms associated with reduced risk of TD. These are: manganese superoxide dismutase gene (MnSOD),[32] NOS3,[33] CYP3A5, serotonin receptor 2A (5-HT2A) and dopamine receptor 4 (DRD4). Recent observational studies investigating the role of dopamine receptor subtypes, serotonin receptor subtypes, CYP2D6, and CYP1A2 in TD, have yielded conflicting results. This may be explained by confounding factors such as a small sample size, retrospective study design, heterogeneous ethnic cohort, heterogeneous antipsychotic use, age, smoking status, and concurrent medication or alcohol use.[34] Further complicating the matter, meta-analysis and genome-wide association studies have found conflicting results for dopamine receptor and serotonergic receptor gene polymorphisms. Although many pharmacokinetic studies have demonstrated elevated serum antipsychotic levels in patients who are poor metabolizers according to cytochrome enzyme status, they did not find a correlation between TD and serum antipsychotic levels. This paper aims to review and summarize the pharmacogenetic findings in antipsychotic-associated TD and assess its clinical significance for psychiatry patients. In addition, we hope to provide insight into areas that need further research.

Method

The literature search was performed through PubMed and OVID by entering the following keywords: "(pharmacogenetic) OR (cytochrome P*) AND (tardive dyskinesiaTD)". Searches were limited to English language articles and publications published before March 2014.

Results
CYP2D6

CYP2D6 is the main cytochrome enzyme responsible for the metabolism of all the typical and many atypical antipsychotic medications such as aripiprazole, risperidone and paliperidone[18] (Table 1). The prevalence of poor metabolizer status varies across different ethnicities (Table 2). CYP2D6 poor metabolizer status is found in 8% of Caucasian and

Table 1 Effect of cytochrome enzyme metabolism state on serum antipsychotic level and its association with tardive dyskinesia

Cytochrome enzyme	Antipsychotic	Serum antipsychotic level PM compared to EM	Serum antipsychotic level UM compared to EM	Metabolizer group associated with TD
CYP2D6	Aripiprazole	60% higher serum level[46], 1.6 fold increase in active metabolite[46,47]		NSD
	Clozapine	No difference[47,156–158]	No difference[157,158]	NSD
	Haloperidol	Increased serum haloperidol and metabolite levels[38–42,44,45,159]		No association with TD[44]
	Risperidone	Increased serum risperidone[42,48]		No association with TD[58,59]
	Zuclopenthixol	1.6–2 fold increased serum level[49–52]		Conflicting results. PM associated with TD in one study,[51] another found no association with TD[58,59]
	Perphenazine	2.9–4 fold increased serum level[54,160]		No association with TD[58,59]
	Thioridazine	1.8–4.5 fold increased serum level[55–57]		NSD
	Olanzapine	No difference[161]		No association with TD[58,59]
CYP1A2	Olanzapine	No difference[161]		No association with TD[58,59]
CYP3A4	Thioridazine	1.8–4.5 fold increase serum level[55–57]		NSD
	Aripiprazole	1.5–1.8 fold increase in serum level, 1.6 fold increase in active metabolite[46]		NSD
	Ziprasidone	NSD		NSD
	Olanzapine	NSD	Subtherapeutic serum olanzapine level[162]	NSD

Abbreviations: PM, poor metabolizer; EM, extensive metabolizer; UM, ultrafast metabolizer; TD, tardive dyskinesia; NSD, no studies done.

African cohorts, 6%–10% of Asian cohorts, but is relatively rare in Japanese and Korean cohorts.[35–38]

CYP2D6 poor metabolizers have a 1.5- to 2-fold increase in serum levels of haloperidol and its metabolite,[39–47] aripiprazole[48] and its active metabolite,[48,49] risperidone,[44,50] and zuclopenthixol.[51–54] Serum perphenazine and thioridazine levels are increased 2- to 4-fold in poor metabolizers compared to extensive metabolizers.[55–59] However, pharmacokinetic studies have not found higher incidences of TD in poor metabolizers for other antipsychotics.[46,60,61] One study found zuclopenthixol-poor metabolizers are more likely to develop TD (odds ratio [OR] =1.7; 95% confidence interval [CI] =0.5–4.9) and Parkinsonism[53] than extensive metabolizers. However, the OR did not reach significance. In addition, a randomized, blinded prospective study in Caucasian and African American cohorts did not find such an association.[60] No pharmacokinetic studies have examined if TD is more common in poor metabolizers, or associated with higher serum antipsychotic levels in aripiprazole or thioridazine users. Small retrospective case-control studies have found a significant association between TD and CYP2D6 poor metabolizer alleles in both Japanese and Caucasian cohorts.[17,62] However, only two small case-control studies, one cross-sectional and one longitudinal study, replicated this in both Caucasian and Chinese cohorts.[63–66] Larger case-control studies did not find an association between TD and CYP2D6 polymorphisms in Korean,[67] Japanese,[47] Chinese,[68] Caucasian,[69–72] and Indian cohorts.[73] These results were confirmed in a meta-analysis but no studies have examined the prospective use of CYP2D6 genotype test in clinical practice. Finally, a genome-wide association study on a longitudinal cohort of 710 subjects, of mixed ethnicity, found no correlation between TD and CYP2D6 polymorphisms.[74]

CYP1A2

CYP1A2 is the primary metabolizer for olanzapine and clozapine. CYP1A2 and CYP2D6 are the primary

Table 2 Ethnicity and cytochrome enzyme metabolic action

Ethnicity	CYP2D6		CYP3A4		CYP1A2	
	PM	UM	PM	UM	PM	UM
Caucasian	8%[33,34]	1%–10%[163]	2%–9.6%[164]	14%[162]	NSD	NSD
African	3%–8%[33,34]	2%–29%[165]	26%–67%[164]	67%[162]	NSD	NSD
Asian	6%–10%[33,34]	0%–2%	0%–22%[164]	NSD	5%[166]	NSD
Japanese	0.39%[35]	NSD	NSD	NSD	14%[166]	NSD
Korean	0.22%[36]	NSD	NSD	NSD	NSD	NSD
Australian	NSD	NSD	NSD	NSD	5%[7]	NSD

Abbreviations: PM, poor metabolizers; UM, ultrafast metabolizers; NSD, no study done.

metabolizers for thioridazine and perphenazine.[59,75] A case-control study on 335 Indians found an association between CYP1A2*1C and 1545 T>C polymorphisms and TD[29]. Fu et al found CYP1A2 −163 C/A T and C allele were associated with TD in a Chinese cohort of 182 patients.[68] However, this was not replicated by a larger study of 291 Chinese subjects, which found no association between CYP1A2 polymorphisms and TD.[76] Similarly, two case-control studies on a Turkish and a Caucasian cohort found no association between TD and CYP1A2 polymorphisms.[77,78]

Other cytochrome P450 enzymes

CYP3A4 is the primary metabolizer for quetiapine and together with CYP2D6 acts as the primary metabolizer for haloperidol and loxapine.[79] CYP3A4 and CYP3A5 share sequence homology and substrate specificity[80] and are capable of metabolizing a large number of substrates. A case-control study did not find an association between TD and CYP3A4*1B polymorphism in an Indian cohort.[73] The presence of CYP3A5 was associated with TD in a subgroup of Caucasian males, although it did not reach significance for the entire cohort.[61]

Dopamine receptor and its subtypes

Dopamine receptor is upregulated in the post-synaptic membrane of the basal ganglia following chronic antipsychotic exposure in animal models.[81] Subsequent hypersensitivity of the dopaminergic system is thought to be responsible for TD.[82] Positron emission tomography found increased D2 receptor binding potential in subjects on chronic antipsychotic drugs compared to control subjects.[83] While striatal D2 receptor density is not associated with TD, the severity of orofacial TD seems to depend on its relative density.[84] Only one case-control study examined and found no association between the D1 dopamine receptor and TD.[85] In contrast, D2 receptor TaqA A2, C957T and C939T polymorphisms were found to be associated with TD. Two case-control studies on Chinese cohorts and two meta-analyses on mixed ethnic cohorts found the D2 dopamine receptor TaqA A2 allele was associated with TD[19,32,86,87] (OR =1.80, 95% CI =1.03–1.65; P=0.03). In contrast, one longitudinal cohort study in Caucasian subjects[88] and four case-control studies in Indian, Chinese, Japanese, and Korean cohorts did not find such an association.[85,89–91] There was no association between D2 receptor gene Ser311Cys or −141C Ins/del polymorphisms with TD in three studies.[89–91] One case-control study on a Caucasian and African American cohort (n=232) found D2 receptor gene functional C957T polymorphism was

associated with TD (P=0.013) and higher abnormal involuntary movement scale score (AIMS) (P=0.0087).[92] The C957T haplotype was also associated with TD in the African American subcohort (P=0.047).[92] The same study found an adjacent C939T polymorphism was also associated with TD and a higher AIMS.

The association between the D3 receptor gene Ser9Gly polymorphism and TD seems to depend on ethnicity. A number of retrospective studies across Jewish, Russian and Asian cohorts have found an association between D3 receptor Ser9Gly Gly allele and Gly/Gly genotype with TD.[21,61,89,93–95] However, two longitudinal cohort studies on Caucasian cohorts and one genome-wide association study found no such association.[20,88,96] A meta-analysis found the Ser9Gly Gly/Gly genotype was highly associated with TD in a large Caucasian cohort,[97] (OR =1.52, 95% CI =1.08–1.68, P<0.0001) whereas a meta-analysis on the same polymorphism in an East Asian cohort (n=1,291) did not replicate such finding (OR =0.94; 95% CI =0.78–1.12.)[98] The Ser9Gly polymorphism was also not associated with TD in Indian and African-Caribbean cohorts.[85,99] Before routine testing for D3 receptor Ser9Gly polymorphisms can be recommended in schizophrenia patients, more evidence for its association would be required through large prospective pharmacogenomic studies.[100]

While D1, D2 and D3 dopamine receptor polymorphisms were not associated with TD in an Indian cohort of 335 patients, this study found that homozygosity for a 120 base pair duplication of the D4 dopamine receptor gene was associated with a reduced risk of TD[85] (OR =0.52, 95% CI =0.31–0.86, P=0.009). Four tag polymorphisms (rs3758653, rs916457, rs762502, rs11246226) of the D4 receptor gene were associated with TD in males in a Caucasian cohort.[101] However, another case-control study in Caucasian, Jewish, and Korean cohorts did not find an association between D4 receptor gene polymorphisms and TD.[102–104]

Dopamine transporter gene

The dopamine transporter (DAT1) mediates the reuptake of dopamine from the synapse and plays a role in dopaminergic transmission. Individuals with TD were found to have lower dopamine transporter density than those without TD.[105] The two case-control studies (Jewish and Indian cohorts) did not find an association between DAT1 gene polymorphism and TD.[85,103]

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is capable of controlling D3 dopamine receptor (DRD3) expression in

animal studies, promoting behavioral sensitization through overexpression of DRD3 in the striatum of hemiparkinsonian rats.[106] It also has an influence on the survival, differentiation and function of dopaminergic neurons.[107,108] As studies on the association between DRD3 and TD are conflicting, one case-control study on a Chinese cohort (n=216) examined whether DRD3 ser9gly and brain-derived neurotrophic factor (BDNF) val66met genetic polymorphisms were associated with TD.[109] They found patients with the BDNF Val66Met polymorphism had significantly higher AIMS than Val66Val or Met66Met homozygotes combined. However, this association was not replicated in a Caucasian cohort of 171 patients, nor was there an association between other BDNF polymorphisms and TD.[110] Both glycogen synthase kinase (GSK)-3beta and BDNF are important in neuronal survival, and its regulation is hypothesized to play a role in susceptibility for TD.[111] A study on a Korean cohort found GSK-3beta with C/C genotype and BDNF Val allele were associated with a decreased risk of TD (OR =0.1, 95% CI =0.02–0.48, P=0.001).[112]

Glutathione S-transferase

Glutathione S-transferase (GST) is a group of phase II detoxifying enzymes that conjugate glutathione to a range of compounds. A deletion of GST genes may lead to a build-up of toxic intermediates in the basal ganglia from increased dopamine turnover secondary to long-standing dopamine antagonist use.[113] Neuronal toxicity through oxidative stress has been hypothesized as the pathophysiology of TD. One of the classes of glutathione, GSTM1, if deleted, is associated with schizophrenia. However, GSTM1 is not associated with TD nor correlated with higher AIMS.[114,115] In contrast, one large Caucasian case-control study (n=516) found an association between GSTM1 deletion and TD, particularly in the female subpopulation (OR =1.7, 95% CI =1.2–2.4, P=0.007).[61] Similarly, studies examining the GSTP1 enzyme found conflicting results. One cross-sectional study found GSTP1 was associated with a reduced risk of TD and lower AIMS,[116] while another case control study found no such association in a mixed ethnic cohort.[117] To confirm the association between TD and GSTM1 or GSTP1 deletion, it needs to be replicated in future association studies.

Glutathione peroxidase

Glutathione peroxidase 1 (GPX1) is an antioxidant enzyme that reduces organic hydroperoxides and hydrogen peroxide. Pro197Leu is a functional polymorphism of GPX1, with the Leu allele being less responsive to stimulation of GPX1

enzyme activity,[118] and potentially more at risk of oxidative stress. Both a cross-sectional study on a Russian cohort and case-control study on a Caucasian cohort did not find any association between Pro197Leu polymorphism and TD.[116,119]

Manganese dependent superoxide dismutase-2

Manganese dependent superoxide dismutase-2 (MnSOD) is a mitochondrial enzyme that scavenges the largest amount of superoxide anions produced in the mitochondria.[120] Neuronal toxicity through oxidative stress has been hypothesized as the pathophysiology of TD. Three case-control studies in Asian cohorts and one genome-wide association study found the Ala9Val polymorphism of MnSOD is not associated with TD.[74,121–123] Whereas a cross-sectional study on a Russian cohort found the Val allele of Ala9Val polymorphism was associated with orofacial TD.[116] This is in contrast with the finding from a meta-analysis, where Val allele of Ala9Val polymorphism was found to be protective against TD. The discrepancy in the results of these studies may be explained by the relative high Ala allele carriers in the Russian cohort (70%), compared to the Asian cohort where 70% were Val/Val genotype, 30% were Val/Ala genotype and 0% had Ala/Ala genotype. If Val allele truly offers a protective effect against TD, then this may explain the lack of association in the Asian cohort study. However, it would not explain the association between TD and Val allele of Ala9Val polymorphism in the Russian study.

Catechol-O-methyltransferase and monoamine oxidase

Catechol-O-methyltransferase (COMT) is a dopamine-metabolizing enzyme. Functional excess of dopamine in the postsynaptic cleft of the central nervous system has been hypothesized as a contributing factor to TD. Researchers have examined the possibility of COMT genetic polymorphism and its association with TD. The Val158Met is a functional polymorphism, where Met/Met genotype confers a 3- to 4-fold reduction in COMT enzyme activity, compared to Val/Val genotype.[124] One large case-control study on Indian cohorts found the Val/Val genotype had a reduced risk of TD (OR =0.24, 95% CI =0.11–0.55),[85] whereas a study on a Korean cohort found the Val/Val genotype had significantly higher incidence of TD than heterozygotes.[125] However, three case-control studies on Chinese, Japanese and Turkish cohorts found no association between Val158Met polymorphism and TD.[126–128] A meta-analysis of five studies found

that Met carriers and Val-Met heterozygotes for Val158Met polymorphism of this enzyme, offered a protective effect against TD (OR =0.66, 95% CI =0.49–0.88, P=0.005 and OR =0.64, 95% CI =0.46–0.86, P=0.004, respectively).[32] It is difficult to draw a conclusion about the role of COMT in TD based on these studies and future prospective studies are needed for clarification.

Monoamine oxidase A (MAOA) and monoamine oxidase B (MAOB) both degrade dopamine and are thought to implicate susceptibility to TD. Functional polymorphism of MAOA such as 30 base pair (bp) repeat is thought to mediate transcriptional activity of this enzyme[129] and intron 13 polymorphism of the MAOB gene is associated with MAOB enzyme activity in human platelets.[130] Two case-control studies on Japanese and Caucasian cohorts did not find an association between MAOA 30 bp repeat polymorphism or MAOB polymorphism with TD.[128,131]

Serotonin receptor gene (5HT)

Increased sensitivity of the striatal dopaminergic system after chronic dopamine antagonist use is proposed as the pathophysiological mechanism of TD.[82] Serotonergic projections from the dorsal raphe lead to tonic inhibition of the nigrostriatal dopaminergic system[132] and selective serotonin reuptake inhibitors have been associated with TD.[4] Typical and atypical antipsychotic drugs have variable effects on the serotonergic system. Therefore investigators postulate that the serotonin receptor gene may play a role in the pathophysiology of TD. 5-HT2A receptor gene T102C polymorphism is a silent mutation,[133] but interestingly has been reported to predict clozapine response in schizophrenia.[134] A case-control study on a Jewish cohort[135] and a longitudinal cohort study found the T102C polymorphism C/C genotype is associated with TD.[88] However, other case-control studies and genome-wide association studies have not confirmed such an association because age is an additional risk factor in TD.[74,126,136] The mean age of participants in the negative studies was between 33 and 40 years, compared with 52 years in the positive study.[135] A meta-analysis combining the subjects from these studies by Lerer et al confirmed the T102C polymorphism conferred a small risk towards TD (OR =1.64, 95% CI =1.17–2.32, P=0.002),[137] whereas the T/C genotype or T allele is associated with non-TD group in Chinese cohorts.[138,139] The −1438G/A polymorphism is associated with TD in two case-control studies,[77,135] but this may be explained by its complete linkage equilibrium with T102C polymorphism.[135] In studies on Indian, Russian, and African-Caribbean cohorts, no association between 5-HT2A

receptor gene polymorphisms and TD has been found.[34,95,99] Two case control studies did not find His452Tyr polymorphism conferring an increased risk towards TD.[135,136]

The role of the 5-HT2C receptor gene has been examined in several case-control studies. An 5-HT2C antagonist reduces cataplexy secondary to haloperidol[140] and an injection of 5-HT2C agonist in rats induces orofacial dyskinesia,[141] therefore investigators postulate it may play a role in the pathophysiology of TD. The −697G/C polymorphism, located in the promoter region of the 5-HT2C gene, has been associated with TD in a case study on a Chinese male cohort (OR =2.80, 95% CI =1.08–7.27, P=0.03).[142] In Jewish cohorts, the Cys23Ser polymorphism Ser allele is associated with higher orofacial dyskinesia AIMS (P=0.0007) after controlling for age at antipsychotic initiation.[143,144] In an African-Caribbean cohort, the combination of 23Ser allele and 9Ser carriership (DRD3 receptor gene polymorphism) or −1438A/G (5-HT2A gene) polymorphisms in male patients was associated with a higher AIMS and TD, respectively.[99] Whereas in a Russian cohort, the Ser allele of the Cys23Ser polymorphism was associated with a lower limb-trunk TD AIMS (OR =0.7, 95% CI not published, P=0.034).[95] Interestingly, in the Indian cohort, there was no association between TD and 5-HT2C gene polymorphism.[34] The 5HT6 receptor is upregulated in the extrapyramidal regions of the brain in animal studies, hence implicated in the pathophysiology of TD.[145] 5HT6 receptor 267T/C polymorphism has not been found to be associated with TD in a case-control study.[146] Similarly, no association between serotonin transporter gene polymorphism and TD has been found.[126,139,147]

Nitric oxide synthase

The nitric oxide synthase (NOS) enzyme produces nitric oxide, which is involved in oxidative stress. Animal studies implicated the likelihood of neural nitric oxide synthase (NOS1) and endothelial nitric oxide synthase (NOS3) in the pathophysiology of TD.[148] Two studies examined the NOS1 gene and its C276T polymorphism and found no association with TD.[149] A case-control study of 251 Chinese subjects did not find an association between AIMS and C276T genotypes.[150] Liou et al found no association between single nucleotide polymorphisms such as 27-bp VNTR, Glu289Asp and −786T/C with TD in a Chinese cohort. However, they found the T-4b-Glu haplotype was associated with the non-TD group after correcting for duration of antipsychotic use and mean antipsychotic dose (OR =0.648, 95% CI =0.432–0.973, P=0.021).[33] In an Indian cohort, the 27-bp VNTR polymorphism was not associated with TD per

se, but influences its severity, as 27-bp duplication correlates with a higher AIMS.[151]

Quinone oxidoreductase

Quinone oxidoreductase (NQO1) is a reductase enzyme located in the human substantia nigra. It is both an antioxidant and pro-oxidant. Its main function is to counteract the toxic dopamine semiquinone. Functional polymorphism of NQO1 with T allele is associated with reduced function, thus a potential mechanism for cellular damage and TD. Studies examining the 609 C>T polymorphism found the T allele is associated with a higher risk of TD and higher AIMS in a Korean cohort (OR =2.25, 95% CI =1.23–4.13, P=0.004),[152] but not in a Chinese cohort.[33] This may be due to differences in allelic frequency within different ethnic groups and the exclusion of subjects on atypical antipsychotic drug in the negative study.

Other gene polymorphisms

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in dopamine synthesis. Val81Met polymorphism is a marker for dopamine susceptibility traits in the TH gene. A case-control study on a Korean cohort found no association between TD genotype and allele frequency for Val81Met polymorphism.[153]

The N-methyl-D-aspartate (NMDA) receptor has been implicated in TD pathogenesis through the glutamatergic neurotoxicity hypothesis. The 2B subunit of NMDA receptor gene was investigated in a case-control study of 273 Chinese subjects. They found no association between genotype, allele frequency and TD occurrence, nor a significant difference between AIMS in the three genotypes.[154]

Regulators of G-protein signaling (RGS) are involved in signal termination of the G-protein coupled D2 dopamine receptor. D2 receptor hypersensitivity occurs following chronic dopamine antagonist use and is hypothesized as the pathophysiology of TD. A Korean case-control study examining the G-protein beta3 subunit gene found no association between the C825T polymorphism and TD.[155] In contrast, a case-control study found the AGG haplotype is significantly associated with TD phenotype (P=0.007).[27] To date, the function of this haplotype is unknown and this result is yet to be replicated.

The cannabinoid receptor 1 (CNR1) activator inhibits movement and this effect is blocked by a cannabinoid receptor antagonist in animal models.[156] Tiwari et al found rs806374 polymorphism C/C genotype is associated with TD (P=0.036) and higher AIMS after correction for age and sex.[30] When comparing haplotype across groups with or without TD, none was significant for TD.

Vesicular monoamine transporter 2 (VMAT2) is encoded by the SLC18A2 gene. It is responsible for the release of neurotransmitters implicated in TD, such as dopamine, serotonin and gamma-aminobutyric acid. VMAT2 is also the target for tetrabenazine, a drug used in TD. Zai et al found a number of single nucleotide polymorphisms associated with TD occurrence and higher AIMS. This rs363224 marker interacts with functional D2 receptor C957T polymorphism.[28]

The alpha-1A adrenergic receptor (ARRB2) is an important target for atypical antipsychotic drugs and linked to the potential extrapyramidal side effect of these drugs.[157,158] A case-control study on a Chinese cohort found polymorphism rs1045280 (Ser280ser) in the ARRB2 gene is associated with TD compared to the non-TD group.[31] In contrast, Saiz et al examined the effect of three single nucleotide polymorphisms, −563C/T, −4155C/G and −4884A/G, and their effect on TD on 427 Caucasian subjects who were on typical and atypical antipsychotics. Apart from the −4155 C/C genotype whose association with severe TD trended towards significance, they found the other genotypes were not associated with TD after controlling for age and multiple factors.[26] Future replicable studies for VMAT2, CNR1 and ARRB2 receptor gene polymorphism and TD are needed.

Akt1 is a protein kinase that provides downstream signal transduction for the D2 receptor.[159] Akt1 has an important influence on regulation of neuronal plasticity through receptor phosphorylation and upregulation.[160] Therefore Akt1 may play a role in dopaminergic association conditions such as TD. However a case-control study on a mixed ethnic population found no significant association between the Akt1 gene haplotypes and TD. The same study found a significant interaction between the Akt1 rs3730358 haplotype and DRD2 rs6275 haplotype.[161] It is not known how these haplotypes may cause TD and interaction analysis with larger sample studies is needed.

Conclusion

There is a lack of prospective pharmacogenomic studies investigating the clinical utility and cost-effectiveness of genetic polymorphisms in predicting TD in psychiatric patients. Further studies are needed before there is enough evidence to recommend routine genotyping with predictive information for counselling and/or prevention. To date, meta-analysis of retrospective studies suggests that the D3 dopamine receptor Ser9Gly polymorphism and D2 dopamine receptor TaqA polymorphism are potential targets for prospective pharmacogenomic studies. Conflicting results for CYP2D6, CYP1A2,

COMT and 5-HT2A T102C polymorphisms may also benefit from prospective well-designed studies, gene polymorphism interaction studies and studies into the epigenetics of receptor polymorphisms. More association studies are required for D4 receptor, BDNF, GSK3-beta, GSTM, GSTP, MnSOD, 5-HT2C, NOS3, NQO1, RGS9, CRN1, VMAT2 and ARRB2 genetic polymorphism. To date, studies have shown no association between CYP3A4 and CYP3A5, DAT, GPX1, MAOA, MAOB, 5-HTT, NOS1, TH, and NMDA 2B genetic polymorphisms with TD.

Disclosure
The authors report no conflict of interest in this work.

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