PharmGKB summary: dopamine receptor D2

Huaiyu Mi[a], **Paul D. Thomas**[a], **Huijun Z. Ring**[a], **Ruhong Jiang**[a], **Katrin Sangkuhl**[b], **Teri E. Klein**[b], and **Russ B. Altman**[b,c]

[a]Evolutionary Systems Biology, Artificial Intelligence Center, SRI International, Menlo Park, Stanford, California, USA

[b]Department of Genetics, Stanford University, Stanford, California, USA

[c]Department of Bioengineering, Stanford University, Stanford, California, USA

Keywords

Overview

Dopamine is a catecholamine neurotransmitter and controls a variety of functions including cognition, emotion, locomotor activity, food intake, and endocrine system regulation in the central nervous system [1]. In the periphery, dopamine modulates cardiovascular and renal functions, hormone secretion, and gastrointestinal motility [1]. Several pathological conditions, such as Parkinson's disease (PD), schizophrenia, restless leg syndrome, and endocrine tumors, for example, pituitary adenomas have been linked to dysregulation of dopaminergic signal transmission [1,2]. The dopamine D_2 receptor (DRD2) is one of the five different dopamine receptors that have been identified in humans, and shows high expression in both the pituitary gland and the central nervous system [3]. The dopamine receptors belong to the family of G protein coupled receptors. They are grouped into D_1-like receptors, including DRD1 and DRD5, generally associated with stimulatory functions, and D_2-like receptors, including DRD2, DRD3, and DRD4, generally associated with inhibitory functions [1]. The distinct subfamily of G protein coupled receptors, to which DRD2, DRD3, and DRD4 belong, was derived likely from gene duplication before the vertebrate expansion; these receptors are also known to share similar pharmacological profiles [4,5].

In 1989, Grandy *et al.* [6] cloned and mapped the *DRD2* gene to the 11q22–q23 junction by in-situ hybridization [7]. The gene is interrupted by six introns [6]. Alternative splicing of this gene results in short (D2S) and long (D2L) isoforms [8]. The short isoform is also known as D2(415), whereas the long isoform is known as D2(444). The difference between the long and short isoforms is the inclusion of an alternatively spliced exon that accounts for the 29 extra amino acids found in third cytoplasmic loop in the protein structure of the long isoform [9]. D2L is primarily located postsynaptically, whereas D2S functions as a presynaptic autoreceptor [10]. The two isoforms have similar pharmacological characteristics [1,11]. The length modification of the third cytoplasmatic loop suggests that there may be downstream signaling differences between the two isoforms. Differences in Gi protein subtype preferences and in regulation of receptor internalization were found for D2S and D2L [10,12–16]. A third longer isoform was reported in brains from patients who died

Correspondence to Teri E. Klein, PhD, Department of Genetics, Medical Center, Stanford University, 300 Pasteur Dr Lane L301, Mail Code: 5120, Stanford, CA 94305-5120, USA Tel: + 1 650 725 0659; fax: + 1 650 725 3863; feedback@pharmgkb.org.

with psychosis, but this isoform has not been fully characterized [17]. A study, which investigated regulatory polymorphisms in *DRD2* gene, showed that the T allele of two highly linked single nucleotide polymorphisms (SNPs) in intron 5, rs2283265 (G > T) and intron 6, rs1076560 (G > T) shift splicing from D2S to D2L [18].

Many dopamine receptor agonists that bind to the D_2-like family of dopamine receptors are used as antiparkinsonian medications, such as apomorphine, bromocriptine, cabergoline, dihydroergocryptine, lisuride, pergolide, piribedil, pramipexole, ropinirole, and rotigotine [19,20]. Most antipsychotics antagonize the DRD2 as part of their pharmacological profile but also act at a number of other neurotransmitter receptors including other dopamine receptor subtypes, serotonin and histamine receptors [21–23]. First generation or typical antipsychotic drugs such as chlorpromazine and haloperidol cause both antipsychotic actions and many side effects, which are contributed to their high affinity DRD2 antagonism [24]. Side effects of antipsychotics include risk of tardive dyskinesia (TD), extrapyramidal side effects, and hyper-prolactinemia [24]. Olanzapine, quetiapine, and ziprasi-done are second generation or atypical antipsychotics that have a more pronounced serotonin antagonism than dopamine antagonism but still antagonize DRD2 [24]. Risperidone, another second generation antipsychotic, has a more balanced serotonin–dopamine antagonism profile [25]. Aripiprazole [26] and bifeprunox [27] are the newest atypical antipsychotic drugs [28]. Unlike other antipsychotics, aripiprazole and bifeprunox act as partial DRD2 agonists. Aplindore, another partial DRD2 agonist, was originally developed as an antipsychotic and is currently being studied as a potential treatment for PD [28,29]. Kapur and Seeman [30] also postulated a fast dissociation hypothesis based on a study of clozapine and quetiapine toward D2 receptor, and suggested that it is the possible explanation for the low extrapyramidal side effects induced by these two drugs as compared with other atypical and typical antipsychotics.

More than 200 polymorphisms have been identified in the DNA encompassing the genomic sequence of this gene; most are in the introns and the downstream flanking region [7,15,31–36], but some are in the coding [37] and the upstream promoter regions [38]. Allele frequencies of a number of these polymorphisms have been determined in different populations (http://alfred.med.yale.edu/alfred/recordinfo.asp?condition=loci.locus_uid=`LO000168P). Variants of the *DRD2* gene have been associated with alcoholism and other addictive disorders such as cocaine, nicotine and opioid dependence, mood disorders, schizophrenia, and movement disorders, reviewed in [39]. *DRD2* variants are not only relevant to disease susceptibility but also have been associated with the pharmacogenetics of several antipsychotics [40]. In addition, *DRD2* is among the several candidate genes that have been reported to be associated with the efficacy of bupropion and nicotine replacement therapy (NRT) for smoking cessation [41]. The four SNPs, discussed in more detail in the important variant section below, are the most commonly investigated SNPs in the *DRD2* gene.

Online content for the DRD2 gene (PA27478) and very important pharmacogene summary information is available at *http://www.pharmgkb.org/search/annotatedGene/drd2*.

Important variants:

DRD2: −141C Insertion/Deletion (Ins/Del); rs1799732

DRD2: Taq1A; rs1800497

DRD2: 957C > T; rs6277

DRD2: Ser311Cys; rs1801028

Rs1799732; –141C Ins/Del

The –141C Ins/Del polymorphism of *DRD2* has been reported to influence the outcome of both antipsychotic [40] and addiction treatments [42,43]. The –141C Ins/ Del polymorphism is located in the promoter region of the DRD2 gene (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=rs1799732) and is found at an allele frequency of approximately 22% of the Japanese population. This allele is less common among Chinese and Caucasian populations (9%) [44]. Allele frequencies are known for a number of different populations, and of these, the deletion polymorphism is the most common allele in only the Yoruban sample set (see Alfred; http://alfred.med.yale.edu/alfred/mvograph.asp?siteuid=SI000135J). A number of studies have shown that the –141C Ins/Del polymorphism of *DRD2* seems to have a role in determining the response to antipsychotic drugs in schizophrenic patients, in which the Ins allele is associated with favorable treatment outcome (see Table 1). But there are contrary results also which report no association (Table 1). A recent meta-analysis examined the relationship of *DRD2* genetic variation and clinical response to antipsychotic treatment (risperidone, olanzapine, chlorpromazine, clozapine, and aripiprazole) [40]. This analysis included six studies, which met the inclusion criteria for reported results on the –141C Ins/ Del polymorphism, with a total sample size of 687 patients [40]. The investigators showed that the group of Del allele carrier was significantly associated with poorer antipsychotic drug response relative to the Ins/Ins genotype [40].

The –141C Ins/Del variant has also been investigated in the context of substance addiction and treatments. Li *et al.* [42] found a positive association between nasal inhaled but not injected heroin use and the –141C Ins/Del *DRD2* polymorphism in Chinese patients. Lerman *et al.* [43] suggested that the –141C Ins/Del polymorphism may influence whether bupropion or NRT would be more effective for tobacco dependence treatment. The investigators found that bupropion was more effective for patients who were homozygous for the Ins allele, whereas NRT seemed to be more helpful for patients who were homozygous for the Del allele [43].

Rs1800497, Taq1A (32806C > T) (now associated with ANKK1)

The Taq1A polymorphism is the most studied polymorphism in association with the *DRD2* gene. It is not clear whether it is associated with effects of antipsychotic drugs, although some reports support such a conclusion. It is, however, quite clear that it is associated with nicotine dependency and treatment. The frequency of the minor T allele differs among ethnic populations. It occurs in approximately 22% of the European Caucasian population but is more frequent in Asian and African populations (42%) (HapMap data set, dbSNP http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1800497). The Taq1A site is a SNP in a *Taq*1 restriction site located 10 kb downstream of the *DRD2* gene [7]. Neville *et al.* [54] showed that the variation is an amino acid changing polymorphism (Glu713Lys) within the 11th ankyrin repeat of *ANKK1* gene. Neville *et al.* [54] showed low level expression of ANKK1 in placenta and whole spinal cord RNA, whereas Hoenicka *et al.* [55] showed that ANKK1 mRNA and protein were expressed in the adult central nervous system in human and rodents, exclusively in astrocytes. In contrast, this variation is also associated with the *DRD2* gene. Zhang *et al.* [18] found that the Taq1A A1 allele was in linkage disequilibrium with the minor allele of the intronic SNPs rs2283265 (G > T) and rs1076560 (G > T). Both the intronic SNPs were involved in splicing modification of the *DRD2* gene and affected working memory [18]. Taq1A was also part of *DRD2* haplotypes associated with vulnerability to heroin dependence [56], risk of opiate addiction [57], alcohol dependence [58], and clozapine treatment response [50]. In addition, this variation was associated with reduced *DRD2* gene expression and lower glucose metabolic rate in dopaminergic regions in

the human brain [59–61]. In this overview we refer to the *DRD2* gene for consistency with the majority of the existing literature.

Taq1A variation was associated with clinical response to antipsychotic drug treatment and adverse effects. Individual studies have shown that after short-term treatment, the effects of antipsychotic drugs (haloperidol [62], nemonapride [63], ripiprazole [53], risperidone [64]) on positive psychotic symptoms are better in patients with the A1 allele than in patients homozygous for A2/A2. In contrast, a meta-analysis focusing on the relationship of *DRD2* variants and antipsychotic drug response was not able to detect an association between clinical response and the Taq1A variant [40]. The analysis included eight studies, which assessed the Taq1A polymorphism and antipsychotic response (risperidone, haloperidol, chlorpromazine, clozapine, nemonapride, bromperidol, and aripiprazole), with a total sample size of 748 patients [40].

Antipsychotic agents have been associated with hyperprolactinemia, or elevated prolactin levels. This effect is particularly frequent with first generation antipsychotics and with the second generation antipsychotic risperidone and paliperidone [65]. A study of 25 Japanese schizophrenic inpatients suggested that female patients with the A1 allele showed a greater prolactin response to nemonapride. These patients may be at high risk for adverse effects associated with neuroleptic-induced hyperprolactinemia [66]. Another study including several antipsychotics also showed that patients carrying the A1 allele had higher prolactin levels and were overrepresented among those with hyperprolactinaemia [67]. Calarge *et al.* [68] also concluded that the Taq1A and –241A > G (rs1799978) variants of the *DRD2* gene could be useful in predicting the emergence of hyperprolactinemia. The study determined that the Taq1A A1 and the –241G alleles were associated with higher prolactin concentration in children and adolescents in long-term treatment with risperidone [68]. Alenius *et al.* [69] found that patients with one or two A1 alleles had a greater risk of significant side effects. (This study did not report the specific side effects observed.) TD is a movement disorder often caused by a history of neuroleptic use. Thelma *et al.* [70] reviewed the possible pharmacogenetic influences on TD in association with antipsychotics. A meta-analysis indicated an association of the A2 with TD by showing that TD-positive patients have a higher A2 allele frequency [71]. Another meta-analysis suggests multiple genetic influences on TD, including the *DRD2* Taq1A SNP with A2 as the risk-increasing allele [72].

Different *DRD2* variants have been reported to be associated with nicotine dependence and the efficacy of bupropion and NRT. Several studies found no evidence for an association of Taq1A with smoking behavior [73] or nicotine dependence [74,75]. The *DRD2* Taq1A was implicated in association with response to bupropin and NRT. Johnstone *et al.* [76] found that in the first week of use, smokers with the T variant allele (A1) showed the greatest benefit from the nicotine transdermal patch. Results of a NRT randomized trial did not support the association of the T allele with improved response to NRT [77]. However, Swan *et al.* [78] reported that the *DRD2* gene Taq1A polymorphism was associated with 12-month smoking cessation outcomes after treatment with a combination of bupropion SR and behavioral counseling in women. In this study women carrying at least one A1 allele were more likely to report that they stopped taking bupropion because of the side effects of the medication [78]. An analysis of pooled data from two clinical trials also found that smokers carrying the A2/A2 genotype using bupropion were more than three times as likely, relative to placebo, to be abstinent at the end of the treatment [79]. David and Munafo [41] reviewed the association of variation in the dopamine pathway with smoking cessation and concluded that there is some degree of replication regarding the association of the rs1800497 CC genotype with improved response to bupropion.

An association of Taq1A with alcoholism was first identified by Blum *et al.* [80] with an even more robust association of the A1 allele in case of severe alcoholism [81]. A recent meta-analysis by Smith *et al.* [82] which included 44 studies with 9382 participants, found only a small but significant association of the Taq1A polymorphism with alcohol dependency. The investigators point out that the relatively small effect for this association indicates a multigene causality [82]. Another meta-analysis regarding the association of Taq1A with alcoholism is part of a recent review by Le Foll *et al.* [83], which concludes a significant association. The investigators also summarize studies related to *DRD2* variants and nicotine, opiates, and psychostimulants [83]. Doehring *et al.* [57] showed that opiate addicts had a higher frequency of the T allele, and a number of other minor alleles of *DRD2* (e.g. rs1076560G > T SNP or the ATCT haplotype of DRD2 rs1799978A > G, rs1076560G > T, rs6277C > T, and ANKK1 rs1800497C > T) relative to controls.

Dopamine agonists are part of the pharmacotherapeutic management of patients with PD. Paus *et al.* [84] concluded that TaqIA polymorphism alone had no effect on interindividual variability of dopaminergic requirement in PD. A study exploring the effect of several *DRD2* variants for the discontinuation of nonergoline dopamine agonists ropinirole and pramipexole found no association with Taq1A or –141C Ins/Del polymorphism [85]. The study identified the $15 \times DRD2$ CA repeat allele as genetic determinants for the discontinuation [85]. Liu *et al.* [86] found no impact of the TaqIA SNP on the efficacy of pramipexole in treating patients with PD.

Rs6277, 957C > T

It has been reported that the 957C > T polymorphism of DRD2 is associated with both schizophrenia susceptibility substance addiction and treatment. This variant is a synonymous coding SNP located in exon 7. The minor allele (T) frequency varies among geographic groups ranging from 3 to 8% in African and Asian populations to over 50% in Caucasian populations (see dbSNP http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=6277). Lawford *et al.* [87] conducted a study that examined the effect of the 957C > T polymorphism on mRNA levels of DRD2. The investigators found that the T allele led to a decrease in mRNA levels and stability whereas the C allele was not found to be associated with any mRNA changes, which led to a relative increase in the expression of DRD2 in carriers of the C allele [87]. Results of an invivo study with [^{11}C] raclopride indicated that the variant increased binding potential by decreasing DRD2 K_D (C/C > C/T > T/T), whereas B_{max} was not significantly altered [88].

The 957C > T polymorphism is implicated in schizophrenia susceptibility. Several studies have postulated a protective role against schizophrenia for the minor T allele [89–92]. Shen *et al.* [53] studied the effect of *DRD2* variation (–141C Ins/Del, Ser311Cys, 957C > T, and Taq1A) on aripiprazole response in schizophrenic patients with the use of the positive and negative syndrome scale for assessment of drug efficacy. The effect of 957C > T polymorphism on positive and negative syndrome scale performance was an association of poor aripiprazole response with C/C genotype compared with T/T genotype for excitement symptoms [53]. The 957C > T SNP was also investigated in association with substance addiction and treatment. Lerman *et al.* [43] reported that smokers homozygous for the 957C > T T allele exhibited a better response to NRT. Carriers of the wild-type C allele had a higher likelihood of not responding to methadone substitution therapy [93]. Recent studies also found that the 957C > T polymorphism in *DRD2* was related to learning differences associated with the risk of developing psychiatric disorders in individuals that are carriers of the homozygous CC genotype [94].

Rs1801028, Ser311Cys

It is not clear whether the Ser311Cys polymorphism is associated with schizophrenia. There have been reports supporting and refuting such results. This variant is a C > G SNP in exon 7 that alters the codon 311 from the more common Ser to the less common Cys. The Cys311 variant has decreased affinity for dopamine [95]. The minor allele frequency (G allele) is 0.02 based on the 102 individuals of self-described heritage (African/African–American, $n = 24$; Caucasian, $n = 31$; Hispanic, $n = 23$; and Pacific Rim, $n = 24$) (see dbSNP http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801028). From the same data set, the frequency of the G allele is higher in a self-described Pacific Rim population (0.043) than that in a Caucasian population (0.016). There is published evidence both supporting [96–101] and refuting [102] the association between Ser311Cys polymorphism of the *DRD2* gene and schizophrenia. A possible link between the Cys allele of 311 Ser > Cys in *DRD2* and schizophrenia was first reported in the mid 1990s [96–98], although Goldman *et al.* [102] found no correlation between carriers of Cys 311 and schizophrenia in a Native American population. Jonsson *et al.* [100] examined the possible association of Ser311Cys and schizophrenia in control and schizophrenic populations, both of Swedish origin. The schizophrenic patient population ($n = 173$) showed a higher allele frequency of Cys 311 than the control population ($n = 236$) [100]. Interestingly, this association was detected only in male patients [100]. In a more recent study by Glatt and Jonsson [101], an analysis was conducted of several different studies, which contained a total of 3707 schizophrenia patients and 5363 control individuals. The investigators found that the Cys 311 allele had a significant effect [101]. In the same study, the investigators reported that Cys/Ser heterozygotes were at increased risk for schizophrenia as compared with the Ser/Ser homozygotes, but there was no increased risk detected for Cys/Cys homozygotes [101].

Acknowledgments

References

1. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. Physiol Rev. 1998; 78:189–225. [PubMed: 9457173]

2. Filopanti M, Lania AG, Spada A. Pharmacogenetics of D2 dopamine receptor gene in prolactin-secreting pituitary adenomas. Expert Opin Drug Metab Toxicol. 2010; 6:43–53. [PubMed: 19929252]

3. Kidd KK, Morar B, Castiglione CM, Zhao H, Pakstis AJ, Speed WC, et al. A global survey of haplotype frequencies and linkage disequilibrium at the DRD2 locus. Hum Genet. 1998; 103:211–227. [PubMed: 9760208]

4. Le Crom S, Kapsimali M, Barome PO, Vernier P. Dopamine receptors for every species: gene duplications and functional diversification in Craniates. J Struct Funct Genomics. 2003; 3:161–176. [PubMed: 12836695]

5. Callier S, Snapyan M, Le Crom S, Prou D, Vincent JD, Vernier P. Evolution and cell biology of dopamine receptors in vertebrates. Biol Cell. 2003; 95:489–502. [PubMed: 14597267]

6. Grandy DK, Marchionni MA, Makam H, Stofko RE, Alfano M, Frothingham L, et al. Cloning of the cDNA and gene for a human D2 dopamine receptor. Proc Natl Acad Sci U S A. 1989; 86:9762–9766. [PubMed: 2532362]

7. Grandy DK, Litt M, Allen L, Bunzow JR, Marchionni M, Makam H, et al. The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. Am J Hum Genet. 1989; 45:778–785. [PubMed: 2573278]

8. Giros B, Sokoloff P, Martres MP, Riou JF, Emorine LJ, Schwartz JC. Alternative splicing directs the expression of two D2 dopamine receptor isoforms. Nature. 1989; 342:923–926. [PubMed: 2531847]

9. Vallone D, Picetti R, Borrelli E. Structure and function of dopamine receptors. Neurosci Biobehav Rev. 2000; 24:125–132. [PubMed: 10654668]

10. Usiello A, Baik JH, Rouge-Pont F, Picetti R, Dierich A, LeMeur M, et al. Distinct functions of the two isoforms of dopamine D2 receptors. Nature. 2000; 408:199–203. [PubMed: 11089973]

11. Pivonello R, Ferone D, Lombardi G, Colao A, Lamberts SW, Hofland LJ. Novel insights in dopamine receptor physiology. Eur J Endocrinol. 2007; 156(Suppl 1):S13–S21. [PubMed: 17413183]

12. Liu LX, Monsma FJ Jr, Sibley DR, Chiodo LA. D2L, D2S, and D3 dopamine receptors stably transfected into NG108-15 cells couple to a voltage-dependent potassium current via distinct G protein mechanisms. Synapse. 1996; 24:156–164. [PubMed: 8890457]

13. Dal Toso R, Sommer B, Ewert M, Herb A, Pritchett DB, Bach A, et al. The dopamine D2 receptor: two molecular forms generated by alternative splicing. EMBO J. 1989; 8:4025–4034. [PubMed: 2531656]

14. Guiramand J, Montmayeur JP, Ceraline J, Bhatia M, Borrelli E. Alternative splicing of the dopamine D2 receptor directs specificity of coupling to G-proteins. J Biol Chem. 1995; 270:7354–7358. [PubMed: 7706278]

15. Senogles SE. The D2 dopamine receptor isoforms signal through distinct Gi alpha proteins to inhibit adenylyl cyclase. A study with site-directed mutant Gi alpha proteins. J Biol Chem. 1994; 269:23120–23127. [PubMed: 7916015]

16. Kim SJ, Kim MY, Lee EJ, Ahn YS, Baik JH. Distinct regulation of internalization and mitogen-activated protein kinase activation by two isoforms of the dopamine D2 receptor. Mol Endocrinol. 2004; 18:640–652. [PubMed: 14684845]

17. Seeman P, Nam D, Ulpian C, Liu IS, Tallerico T. New dopamine receptor, D2(Longer), with unique TG splice site, in human brain. Brain Res Mol Brain Res. 2000; 76:132–141. [PubMed: 10719223]

18. Zhang Y, Bertolino A, Fazio L, Blasi G, Rampino A, Romano R, et al. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. Proc Natl Acad Sci U S A. 2007; 104:20552–20557. [PubMed: 18077373]

19. Nyholm D. Pharmacokinetic optimisation in the treatment of Parkinson's disease: an update. Clin Pharmacokinet. 2006; 45:109–136. [PubMed: 16485914]

20. Rascol O, Slaoui T, Regragui W, Ory-Magne F, Brefel-Courbon C, Montastruc JL. Dopamine agonists. Hand Clin Neurol. 2007; 84:73–92.

21. Mailman RB. GPCR functional selectivity has therapeutic impact. Trends Pharmacol Sci. 2007; 28:390–396. [PubMed: 17629962]

22. Cummings DF, Ericksen SS, Schetz JA. Three amino acids in the D2 dopamine receptor regulate selective ligand function and affinity. J Neurochem. 2009; 110:45–57. [PubMed: 19486266]

23. Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. Curr Pharm Des. 2009; 15:2550–2559. [PubMed: 19689327]

24. Mailman RB, Murthy V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? Curr Pharm Des. 2010; 16:488–501. [PubMed: 19909227]

25. Leysen JE, Janssen PM, Megens AA, Schotte A. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. J Clin Psychiatry. 1994; 55(Suppl):5–12. [PubMed: 7520908]

26. Lawler CP, Prioleau C, Lewis MM, Mak C, Jiang D, Schetz JA, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. Neuropsychopharmacology. 1999; 20:612–627. [PubMed: 10327430]

27. Biedermann F, Fleischhacker WW. Antipsychotics in the early stage of development. Curr Opin Psychiatry. 2009; 22:326–330. [PubMed: 19346948]

28. Mailman RB, Murthy V. Ligand functional selectivity advances our understanding of drug mechanisms and drug discovery. Neuropsychopharmacology. 2010; 35:345–346. [PubMed: 20010712]

29. Klivenyi P, Vecsei L. Novel therapeutic strategies in Parkinson's disease. Eur J Clin Pharmacol. 2010; 66:119–125. [PubMed: 19834698]

30. Kapur S, Seeman P. Does fast dissociation from the dopamine D(2) receptor explain the action of atypical antipsychotics?: a new hypothesis. Am J Psychiatry. 2001; 158:360–369. [PubMed: 11229973]

31. Bolos AM, Dean M, Lucas-Derse S, Ramsburg M, Brown GL, Goldman D. Population and pedigree studies reveal a lack of association between the dopamine D2 receptor gene and alcoholism. JAMA. 1990; 264:3156–3160. [PubMed: 1979357]

32. Hauge XY, Grandy DK, Eubanks JH, Evans GA, Civelli O, Litt M. Detection and characterization of additional DNA polymorphisms in the dopamine D2 receptor gene. Genomics. 1991; 10:527–530. [PubMed: 1679742]

33. Sarkar G, Kapelner S, Grandy DK, Marchionni M, Civelli O, Sobell J, et al. Direct sequencing of the dopamine D2 receptor (DRD2) in schizophrenics reveals three polymorphisms but no structural change in the receptor. Genomics. 1991; 11:8–14. [PubMed: 1837284]

34. Parsian A, Fisher L, O'Malley KL, Todd RD. A new TaqI RFLP within intron 2 of human dopamine D2 receptor gene (DRD2). Nucleic Acids Res. 1991; 19:6977. [PubMed: 1684859]

35. Seeman P, Ohara K, Ulpian C, Seeman MV, Jellinger K, Van Tol HH, Niznik HB. Schizophrenia: normal sequence in the dopamine D2 receptor region that couples to G-proteins. DNA polymorphisms in D2. Neuropsychopharmacology. 1993; 8:137–142. [PubMed: 8471125]

36. Castiglione CM, Deinard AS, Speed WC, Sirugo G, Rosenbaum HC, Zhang Y, et al. Evolution of haplotypes at the DRD2 locus. Am J Hum Genet. 1995; 57:1445–1456. [PubMed: 8533775]

37. Gejman PV, Ram A, Gelernter J, Friedman E, Cao Q, Pickar D, et al. No structural mutation in the dopamine D2 receptor gene in alcoholism or schizophrenia. Analysis using denaturing gradient gel electrophoresis. JAMA. 1994; 271:204–208. [PubMed: 8277546]

38. Arinami T, Gao M, Hamaguchi H, Toru M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum Mol Genet. 1997; 6:577–582. [PubMed: 9097961]

39. Noble EP. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet B Neuropsychiatr Genet. 2003; 116B:103–125. [PubMed: 12497624]

40. Zhang JP, Lencz T, Malhotra AK. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. Am J Psychiatry. 2010; 167:763–772. [PubMed: 20194480]

41. David SP, Munafo MR. Genetic variation in the dopamine pathway and smoking cessation. Pharmacogenomics. 2008; 9:1307–1321. [PubMed: 18781857]

42. Li T, Liu X, Zhao J, Hu X, Ball DM, Loh el W, et al. Allelic association analysis of the dopamine D2, D3, 5-HT2A, and GABA(A)gamma2 receptors and serotonin transporter genes with heroin abuse in Chinese subjects. Am J Med Genet. 2002; 114:329–335. [PubMed: 11920858]

43. Lerman C, Jepson C, Wileyto EP, Epstein LH, Rukstalis M, Patterson F, et al. Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. Neuropsychopharmacology. 2006; 31:231–242. [PubMed: 16123753]

44. Li T, Arranz M, Aitchison KJ, Bryant C, Liu X, Kerwin RW, et al. Case-control, haplotype relative risk and transmission disequilibrium analysis of a dopamine D2 receptor functional promoter polymorphism in schizophrenia. Schizophr Res. 1998; 32:87–92. [PubMed: 9713903]

45. Arranz MJ, Li T, Munro J, Liu X, Murray R, Collier DA, Kerwin RW. Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. Pharmacogenetics. 1998; 8:481–484. [PubMed: 9918131]

46. Ohara K, Nagai M, Tani K, Nakamura Y, Ino A, Ohara K. Functional polymorphism of -141C Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. Psychiatry Res. 1998; 81:117–123. [PubMed: 9858029]

47. Suzuki A, Kondo T, Mihara K, Yasui-Furukori N, Ishida M, Furukori H, et al. The -141C Ins/Del polymorphism in the dopamine D2 receptor gene promoter region is associated with anxiolytic and antidepressive effects during treatment with dopamine antagonists in schizophrenic patients. Pharmacogenetics. 2001; 11:545–550. [PubMed: 11505224]

48. Yamanouchi Y, Iwata N, Suzuki T, Kitajima T, Ikeda M, Ozaki N. Effect of DRD2, 5-HT2A, and COMT genes on antipsychotic response to risperidone. Pharmacogenomics J. 2003; 3:356–361. [PubMed: 14610521]

49. Wu S, Xing Q, Gao R, Li X, Gu N, Feng G, He L. Response to chlorpromazine treatment may be associated with polymorphisms of the DRD2 gene in Chinese schizophrenic patients. Neurosci Lett. 2005; 376:1–4. [PubMed: 15694263]

50. Hwang R, Shinkai T, De Luca V, Muller DJ, Ni X, Macciardi F, et al. Association study of 12 polymorphisms spanning the dopamine D(2) receptor gene and clozapine treatment response in two treatment refractory/intolerant populations. Psychopharmacology (Berl). 2005; 181:179–187. [PubMed: 15830237]

51. Lencz T, Robinson DG, Xu K, Ekholm J, Sevy S, Gunduz-Bruce H, et al. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. Am J Psychiatry. 2006; 163:529–531. [PubMed: 16513877]

52. Xing Q, Qian X, Li H, Wong S, Wu S, Feng G, et al. The relationship between the therapeutic response to risperidone and the dopamine D2 receptor polymorphism in Chinese schizophrenia patients. Int J Neuropsychopharmacol. 2007; 10:631–637. [PubMed: 17105675]

53. Shen YC, Chen SF, Chen CH, Lin CC, Chen SJ, Chen YJ, Luu SU. Effects of DRD2/ANKK1 gene variations and clinical factors on aripiprazole efficacy in schizophrenic patients. J Psychiatr Res. 2009; 43:600–606. [PubMed: 18926547]

54. Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat. 2004; 23:540–545. [PubMed: 15146457]

55. Hoenicka J, Quinones-Lombrana A, Espana-Serrano L, Alvira-Botero X, Kremer L, Perez-Gonzalez R, et al. The ANKK1 gene associated with addictions is expressed in astroglial cells and upregulated by apomorphine. Biol Psychiatry. 2010; 67:3–11. [PubMed: 19853839]

56. Xu K, Lichtermann D, Lipsky RH, Franke P, Liu X, Hu Y, et al. Association of specific haplotypes of D2 dopamine receptor gene with vulnerability to heroin dependence in 2 distinct populations. Arch Gen Psychiatry. 2004; 61:597–606. [PubMed: 15184239]

57. Doehring A, Hentig N, Graff J, Salamat S, Schmidt M, Geisslinger G, et al. Genetic variants altering dopamine D2 receptor expression or function modulate the risk of opiate addiction and the dosage requirements of methadone substitution. Pharmacogenet Genomics. 2009; 19:407–414. [PubMed: 19373123]

58. Kraschewski A, Reese J, Anghelescu I, Winterer G, Schmidt LG, Gallinat J, et al. Association of the dopamine D2 receptor gene with alcohol dependence: haplotypes and subgroups of alcoholics as key factors for understanding receptor function. Pharmacogenet Genomics. 2009; 19:513–527. [PubMed: 19603545]

59. Ritchie T, Noble EP. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. Neurochem Res. 2003; 28:73–82. [PubMed: 12587665]

60. Pohjalainen T, Rinne JO, Nagren K, Lehikoinen P, Anttila K, Syvalahti EK, Hietala J. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol Psychiatry. 1998; 3:256–260. [PubMed: 9672901]

61. Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, Sedvall GC. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry. 1999; 4:290–296. [PubMed: 10395223]

62. Schafer M, Rujescu D, Giegling I, Guntermann A, Erfurth A, Bondy B, Moller HJ. Association of short-term response to haloperidol treatment with a polymorphism in the dopamine D(2) receptor gene. Am J Psychiatry. 2001; 158:802–804. [PubMed: 11329406]

63. Suzuki A, Mihara K, Kondo T, Tanaka O, Nagashima U, Otani K, Kaneko S. The relationship between dopamine D2 receptor polymorphism at the Taq1 A locus and therapeutic response to nemonapride, a selective dopamine antagonist, in schizophrenic patients. Pharmacogenetics. 2000; 10:335–341. [PubMed: 10862524]

64. Ikeda M, Yamanouchi Y, Kinoshita Y, Kitajima T, Yoshimura R, Hashimoto S, et al. Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. Pharmacogenomics. 2008; 9:1437–1443. [PubMed: 18855532]

65. Monteleone P, Martiadis V, Maj M. Management of schizophrenia with obesity, metabolic, and endocrinological disorders. Psychiatr Clin North Am. 2009; 32:775–794. [PubMed: 19944883]

66. Mihara K, Kondo T, Suzuki A, Yasui N, Nagashima U, Ono S, et al. Prolactin response to nemonapride, a selective antagonist for D2 like dopamine receptors, in schizophrenic patients in relation to Taq1A polymorphism of DRD2 gene. Psychopharmacology (Berl). 2000; 149:246–250. [PubMed: 10823405]

67. Young RM, Lawford BR, Barnes M, Burton SC, Ritchie T, Ward WK, Noble EP. Prolactin levels in antipsychotic treatment of patients with schizophrenia carrying the DRD2*A1 allele. Br J Psychiatry. 2004; 185:147–151. [PubMed: 15286066]

68. Calarge CA, Ellingrod VL, Acion L, Miller DD, Moline J, Tansey MJ, Schlechte JA. Variants of the dopamine D2 receptor gene and risperidone-induced hyperprolactinemia in children and adolescents. Pharmacogenet Genomics. 2009; 19:373–382. [PubMed: 19339912]

69. Alenius M, Wadelius M, Dahl ML, Hartvig P, Lindstrom L, Hammarlund-Udenaes M. Gene polymorphism influencing treatment response in psychotic patients in a naturalistic setting. J Psychiatr Res. 2008; 42:884–893. [PubMed: 18086475]

70. Thelma B, Srivastava V, Tiwari AK. Genetic underpinnings of tardive dyskinesia: passing the baton to pharmacogenetics. Pharmacogenomics. 2008; 9:1285–1306. [PubMed: 18781856]

71. Zai CC, De Luca V, Hwang RW, Voineskos A, Muller DJ, Remington G, Kennedy JL. Meta-analysis of two dopamine D2 receptor gene polymorphisms with tardive dyskinesia in schizophrenia patients. Mol Psychiatry. 2007; 12:794–795. [PubMed: 17767146]

72. Bakker PR, Van Harten PN, Van Os J. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. Mol Psychiatry. 2008; 13:544–556. [PubMed: 18180754]

73. Munafo MR, Timpson NJ, David SP, Ebrahim S, Lawlor DA. Association of the DRD2 gene Taq1A polymorphism and smoking behavior: a meta-analysis and new data. Nicotine Tob Res. 2009; 11:64–76. [PubMed: 19246443]

74. Huang W, Payne TJ, Ma JZ, Beuten J, Dupont RT, Inohara N, Li MD. Significant association of ANKK1 and detection of a functional polymorphism with nicotine dependence in an African-American sample. Neuropsychopharmacology. 2009; 34:319–330. [PubMed: 18354387]

75. Bergen AW, Conti DV, Van Den Berg D, Lee W, Liu J, Li D, et al. Dopamine genes and nicotine dependence in treatment-seeking and community smokers. Neuropsychopharmacology. 2009; 34:2252–2264. [PubMed: 19494806]

76. Johnstone EC, Yudkin PL, Hey K, Roberts SJ, Welch SJ, Murphy MF, et al. Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. Pharmacogenetics. 2004; 14:83–90. [PubMed: 15077009]

77. Munafo MR, Johnstone EC, Murphy MF, Aveyard P. Lack of association of DRD2 rs1800497 (Taq1A) polymorphism with smoking cessation in a nicotine replacement therapy randomized trial. Nicotine Tob Res. 2009; 11:404–407. [PubMed: 19273465]

78. Swan GE, Valdes AM, Ring HZ, Khroyan TV, Jack LM, Ton CC, et al. Dopamine receptor DRD2 genotype and smoking cessation outcome following treatment with bupropion SR. Pharmacogenomics J. 2005; 5:21–29. [PubMed: 15492764]

79. David SP, Strong DR, Munafo MR, Brown RA, Lloyd-Richardson EE, Wileyto PE, et al. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. Nicotine Tob Res. 2007; 9:1251–1257. [PubMed: 18058343]

80. Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, et al. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA. 1990; 263:2055–2060. [PubMed: 1969501]

81. Blum K, Noble EP, Sheridan PJ, Finley O, Montgomery A, Ritchie T, et al. Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. Alcohol. 1991; 8:409–416. [PubMed: 1839129]

82. Smith L, Watson M, Gates S, Ball D, Foxcroft D. Meta-analysis of the association of the Taq1A polymorphism with the risk of alcohol dependency: a HuGE gene-disease association review. Am J Epidemiol. 2008; 167:125–138. [PubMed: 17989061]

83. Le Foll B, Gallo A, Le Strat Y, Lu L, Gorwood P. Genetics of dopamine receptors and drug addiction: a comprehensive review. Behav Pharmacol. 2009; 20:1–17. [PubMed: 19179847]

84. Paus S, Grünewald A, Klein C, Knapp M, Zimprich A, Janetzky B, et al. The DRD2 TaqIA polymorphism and demand of dopaminergic medication in Parkinson's disease. Mov Disord. 2008; 23:599–602. [PubMed: 18175338]

85. Arbouw ME, Movig KL, Egberts TC, Poels PJ, Van Vugt JP, Wessels JA, et al. Clinical and pharmacogenetic determinants for the discontinuation of non-ergoline dopamine agonists in Parkinson's disease. Eur J Clin Pharmacol. 2009 [Epub ahead of print].

86. Liu YZ, Tang BS, Yan XX, Liu J, Ouyang DS, Nie LN, et al. Association of the DRD2 and DRD3 polymorphisms with response to pramipexole in Parkinson's disease patients. Eur J Clin Pharmacol. 2009; 65:679–683. [PubMed: 19396436]

87. Lawford BR, Young RM, Swagell CD, Barnes M, Burton SC, Ward WK, et al. The C/C genotype of the C957T polymorphism of the dopamine D2 receptor is associated with schizophrenia. Schizophr Res. 2005; 73:31–37. [PubMed: 15567074]

88. Hirvonen MM, Laakso A, Nagren K, Rinne JO, Pohjalainen T, Hietala J. C957T polymorphism of dopamine D2 receptor gene affects striatal DRD2 in-vivo availability by changing the receptor affinity. Synapse. 2009; 63:907–912. [PubMed: 19582781]

89. Hanninen K, Katila H, Kampman O, Anttila S, Illi A, Rontu R, et al. Association between the C957T polymorphism of the dopamine D2 receptor gene and schizophrenia. Neurosci Lett. 2006; 407:195–198. [PubMed: 16973280]

90. Hoenicka J, Aragues M, Rodriguez-Jimenez R, Ponce G, Martinez I, Rubio G, et al. C957T DRD2 polymorphism is associated with schizophrenia in Spanish patients. Acta Psychiatr Scand. 2006; 114:435–438. [PubMed: 17087792]

91. Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. Nat Genet. 2008; 40:827–834. [PubMed: 18583979]

92. Betcheva ET, Mushiroda T, Takahashi A, Kubo M, Karachanak SK, Zaharieva IT, et al. Case-control association study of 59 candidate genes reveals the DRD2 SNP rs6277 (C957T) as the only susceptibility factor for schizophrenia in the Bulgarian population. J Hum Genet. 2009; 54:98–107. [PubMed: 19158809]

93. Crettol S, Besson J, Croquette-Krokar M, Hammig R, Gothuey I, Monnat M, et al. Association of dopamine and opioid receptor genetic polymorphisms with response to methadone maintenance treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32:1722–1727. [PubMed: 18687376]

94. Huertas E, Ponce G, Koeneke MA, Poch C, Espana-Serrano L, Palomo T, et al. The D2 dopamine receptor gene variant C957T affects human fear conditioning and aversive priming. Genes Brain Behav. 2010; 9:103–109. [PubMed: 19900188]

95. Cravchik A, Sibley DR, Gejman PV. Functional analysis of the human D2 dopamine receptor missense variants. J Biol Chem. 1996; 271:26013–26017. [PubMed: 8824240]

96. Arinami T, Itokawa M, Enguchi H, Tagaya H, Yano S, Shimizu H, et al. Association of dopamine D2 receptor molecular variant with schizophrenia. Lancet. 1994; 343:703–704. [PubMed: 7907680]

97. Shaikh S, Collier D, Arranz M, Ball D, Gill M, Kerwin R. DRD2 Ser311/Cys311 polymorphism in schizophrenia. Lancet. 1994; 343:1045–1046. [PubMed: 7909081]

98. Arinami T, Itokawa M, Aoki J, Shibuya H, Ookubo Y, Iwawaki A, et al. Further association study on dopamine D2 receptor variant S311C in schizophrenia and affective disorders. Am J Med Genet. 1996; 67:133–138. [PubMed: 8723039]

99. Fitzgerald MA. To the test: assessment skills. Adv Nurse Pract. 2000; 8:29. [PubMed: 11011590]

100. Jonsson EG, Sillen A, Vares M, Ekholm B, Terenius L, Sedvall GC. Dopamine D2 receptor gene Ser311Cys variant and schizophrenia: association study and meta-analysis. Am J Med Genet B Neuropsychiatr Genet. 2003; 119B:28–34. [PubMed: 12707934]

101. Glatt SJ, Jonsson EG. The Cys allele of the DRD2 Ser311Cys polymorphism has a dominant effect on risk for schizophrenia: evidence from fixed- and random-effects meta-analyses. Am J Med Genet B Neuropsychiatr Genet. 2006; 141B:149–154. [PubMed: 16402354]

102. Goldman D, Urbanek M, Guenther D, Robin R, Long JC. A functionally deficient DRD2 variant [Ser311Cys] is not linked to alcoholism and substance abuse. Alcohol. 1998; 16:47–52. [PubMed: 9650635]

Table 1

Effect of the −141C Ins/Del polymorphism on antipsychotics response in schizophrenic patients based on studies investigating association between DRD2 variants and response to antipsychotic drugs

Patients (population)	Antipsychotic drug	Treatment duration (weeks)	Response measurement	Genotyped DRD2 polymorphisms	−141C Ins/Del effect	References
151 schizophrenics; 95 controls (Caucasian)	Clozapine	–	GAS	−141C Ins/Del	No association	[45]
170 schizophrenics; 121 controls (Japanese)	Antipsychotic drugs not specified	–	PANSS	−141C Ins/Del	No association	[46]
49 schizophrenic inpatients (Japanese)	Bromperidol or nemonapride	3	BPRS	−141C Ins/Del	Ins allele associated with greater improvement (only for anxiety–depression symptoms)	[47]
73 schizophrenic patients (Japanese)	Risperidone	8	PANSS	−141C Ins/Del, Taq1A	Ins-A2/Del-A1 diplotype associated with better response	[48]
135 schizophrenic inpatients (Chinese)	Chlorpromazine	8	BPRS		Del (−) genotype associated with higher degree of improvement	[49]
DSM-III-R or DSM-IV schizophrenics (183 Caucasian; 49 African–American)	Clozapine	6	BPRS	−141C Ins/Del, Taq1A, Taq1B, and rs1125394	No association	[50]
61 first-episode schizophrenia patients (41% African–American; 28% Caucasian; 18% Hispanic; 5% Asian; 8% other)	Olanzapine or risperidone	16	CGIIS	−141C Ins/Del, −241A>G	−141C Del allele showed significantly longer time to respond relative to Ins/Ins homozygotes	[51]
125 schizophrenia patients (Chinese)	Risperidone	8	BPRS	−141C Ins/Del, Taq1B, rs1076562, Taq1A	No association	[52]
128 schizophrenic inpatients (Han Chinese)	Aripiprazole	4	PANSS	−141C Ins/Del, Taq1A, C957T, Ser311Cys	No significant effect	[53]

−141C Ins/Del (rs1799732); Taq1A (rs1800497); Taq1B (rs1079597); −241A>G (rs1799978); 957C>T (rs6277); Ser311Cys (rs1801028).

BPRS, brief psychiatric rating scale; CGIIS, clinical global impression improvement scale; DRD2, dopamine receptor D2; DSM-IV; Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-III-R, revision of DSM-III; GAS, global assessment scale; PANSS, positive and negative symptom scale.