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Evaluating the Dopamine Hypothesis of Schizophrenia in a Large-Scale Genome-Wide Association Study

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Abstract

Background—The dopamine hypothesis, which posits that dysregulation of the dopaminergic system is etiologic for schizophrenia, is among the most enduring biological theories in psychiatry. Although variation within genes related to dopaminergic functioning has been associated with schizophrenia, an aggregate test of variation, using the largest publicly available schizophrenia dataset, has not previously been conducted.

Methods—We first identified a core set of 11 genes involved in the synthesis, metabolism, and neurotransmission of dopamine. We then extracted summary statistics of markers falling within, or flanking, these genes from the Psychiatric Genomics Consortium's most recent schizophrenia mega-analysis results. We conducted aggregate tests for enrichment of dopamine-related pathways for association with schizophrenia.

Results—We did not detect significant enrichment of signals across the core set of dopamine-related genes. However, we did observe modest to strong enrichment of genetic signals within the *DRD2* locus.

Conclusions—Within the limits of available power, common sequence variation within core genes of the dopaminergic system is not related to risk of schizophrenia. This does not preclude a role of dopamine, or dopamine-related genes, in the clinical presentation of schizophrenia or in treatment response. However, it does suggest that the genetic risk for schizophrenia is not substantially affected by common variation in those genes which, collectively, critically impact dopaminergic functioning.

Keywords

genetic risk; statistical enrichment; dopamine hypothesis of schizophrenia

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1. Introduction

The first widely cited articulation of the dopamine (DA) hypothesis of schizophrenia (DHS) was by Matthysse in 1973 (Kendler and Schaffner, 2011a; Matthysse, 1973) when he suggested that schizophrenia might result from an "over-activity of dopaminergic transmission." (Matthysse, 1973) For several decades in the late 20th century, the DHS was the leading etiologic theory in psychiatry and generated an immense amount of both basic and clinical research.

Two prominent themes emerge from an analysis of the history of the DHS (Kendler and Schaffner, 2011a, b). First, the empirical track-record of the theory has been spotty, with a failure to verify robustly most—albeit probably not all—of its key empirical predictions. Second, its persistence over four decades is probably related to the protean nature of the theory undergoing a number of substantial revisions and re-interpretations. For example, Davis and colleagues proposed, in 1991, a major revision of the theory suggesting that "… schizophrenia can be characterized by hypodopaminergia in mesocortical and hyperdopaminergia in mesolimbic dopamine neurons …" (Davis et al., 1991) More recently, Howes and Kapur proposed another substantial modification of the DHS focusing on DA striatal dysfunction as a "final common pathway" for the etiopathogenesis of schizophrenia (Howes and Kapur, 2009). In addition, a review by Howes et al. (2015) described the extent of evidence implicating the dopaminergic system, ranging from antipsychotic efficacy to in vivo imaging. Furthermore, the authors elaborated on the interplay among glutamatergic and dopaminergic systems and their impact of schizophrenia etiology, demonstrating that the effects of dopamine do not act in isolation.

Given the central role of genetic factors in the etiology of schizophrenia, demonstrated both by classical genetic-epidemiologic methods (Sullivan et al., 2003) and by newer analytic methods applied to molecular data (Cross-Disorder Group of the Psychiatric Genomics et al., 2013), a plausible prediction of the DHS would be that variation in at least some genes critical to DA function would impact on risk for schizophrenia. Indeed, a large and inconclusive candidate gene literature emerged in the last several decades years examining DA receptor genes and genes involved in the uptake, synthesis and metabolism of DA (Kendler and Schaffner, 2011a). As depicted in Table 1, quite large numbers of individual association studies have been reported for most of the core DA related genes. The percentage of positive reports for a number of them substantially exceed the 5% expected under the null hypothesis although meta-analyses have not provided consistent positive evidence for association for any gene with the possible exception of *DRD4*. It is now clear from recent advances in complex disease genetics, as we have clarified the typical effect size of variants impacting multifactorial biomedical disorders, that these earlier candidate gene studies were unpowered which might explain the variability and inconsistency in findings. Furthermore, the potential for publication bias cannot be excluded, raising the possibility that more null results exist than are in the extant literature.

Advances in the field of schizophrenia genetics have now provided us with a much more powerful way to test the genetic predictions of the DHS. As a result of massive efforts, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) have

collected and made publically available GWAS results on 34,241 cases of schizophrenia and 45,604 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The PGC recently reported strong evidence of an association between variation in *DRD2* and schizophrenia case-control status. In addition, they found signal enrichment in KEGG's dopaminergic synapse gene set. However, that category consists of >100 genes (Kanehisa et al., 2016) whose functions are quite diverse and in many cases only indirectly related to dopamine function. Thus, in some ways the category reflects the diffuse nature of the DHS itself and may not represent a valid test of the core underlying theory.

In this paper, we selected, a priori, 11 genes directly related to DA function which have all been subject to prior candidate gene studies motivated by the DHS (Table 1). We ask a single, simple question: do common molecular variants in these genes, examined as a group, differ significantly in their frequency in cases and controls? A positive response to this question would provide confirmatory evidence for the DHS. By contrast, a negative response – in which the distributions of these variants in the two groups were consistent with chance effects – would provide evidence, although far from conclusive, against the importance of the etiologic role of DA dysfunction in schizophrenia.

2. Materials and Methods

2.1 Gene selection

We selected 11 genes that are directly involved in the synthesis, metabolism, or neurotransmission of dopamine: *catechol-o-methyltransferase* (*COMT*), *dopamine beta-hydroxylase* (*DBH*), the five dopamine receptors (*DRD1-DRD5*), *dopa-decarboxylase* (*DDC*), *tyrosine hydroxylase* (*TH*), *monoamine oxidase A* (*MAOA*), and the dopamine transporter (*solute carrier member 6 carrier 3*, known as *SLC6A3* or *DAT*). Using positions from genome build hg37, we selected markers in the PGC's most recently publicly available schizophrenia dataset (PGC2) that mapped to within or near genes of interest. We considered two ranges: the first was selected for consistency with a previous PGC publication (The Network Pathway Analysis Subgroup of the Psychiatric Genomics Consortium and International Inflammatory Bowel Disease Genetics Consortium, 2015), which selected markers within 35kb upstream (5′) or 10kb downstream (3′) as being relevant to the gene. The second range was selected to allow for the possibility of broader regulatory regions, and included 50kb upstream and downstream; this 50kb window was previously used for pathway analyses in the largest schizophrenia mega-analysis to date (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Though this range allows for more distal signals to be considered, it is potentially more conservative due to the larger number of potentially irrelevant SNPs included in the test.

2.2 Addressing linkage disequilibrium

We used publicly available 1000 Genomes (The 1000 Genomes Project Consortium et al., 2010) Phase 1 Version 3 data to establish linkage disequilibrium within the range of our SNPs of interest. For each chromosome on which a target gene was located, we used the --ld-window-kb option in Plink (Purcell et al., 2007) to calculate pairwise LD within a 10,000kb range of the target markers.

2.3 Tests of significance

Similar to Bacanu and colleagues (Bacanu et al., 2014), to test competitive enrichment of association signals in the hypothesized gene sets, we employed the Simes and sum of squares tests (SST) (see Supplementary Methods). The choice of the two tests is due to the intuition that the Simes test would be especially useful for detecting enrichment in SNP sets harboring a few strong signals, whereas the SST would be better for detecting enrichment in SNP sets having many signals of small magnitude. To guard against violation of distributional assumptions, the statistical significance of SST was assessed via 50,000 simulations based on the LD patterns of the 396 Europeans sequenced by the 1000 Genomes Project Phase 1 Version 3.

3. Results

3.1 Simes tests

Using the Simes test, we first tested for evidence of enrichment (relative to background) in the form of a few signals of at least moderate effect size within or near DA-related genes (Table 2). For both ranges tested, we observed no significant enrichment of signals within the 11 genes tested. Given the strong signal mapping to near and within *DRD2* in the PGC2 results, we further tested for enrichment near that locus versus among all non-*DRD2* SNPs (Table 2). For both ranges tested, we observed modest but significant enrichment at the DRD2 locus only, but no evidence of enrichment when that locus was excluded.

3.2 Sum of squares tests (SST)

We next used SST to test for evidence of enrichment (relative to background) in the form of more numerous signals of modest effect size, within or near DA-related genes. We observed no evidence of enrichment for either range when the complete set of SNPs was tested (Table 2). However, we observed strong enrichment when only the *DRD2* locus was considered. When excluding SNPs mapping to *DRD2*, we observed no evidence of enrichment.

4. Discussion

In this study, we empirically tested whether core dopamine-related genes were enriched for signals associated with schizophrenia using the largest currently available dataset (PGC2). Our results indicate that, despite strong signal(s) within/near the *DRD2* locus, overall there is no enrichment of signals within this core group of genes involved in the synthesis, metabolism, and primary neurotransmission of dopamine.

Given the strong evidence that the etiology of schizophrenia has a substantial genetic basis, it is reasonable to hypothesize that if the DHS were true, then variation within core DA genes would influence the liability to schizophrenia. As outlined in Table 1, previous efforts to validate this implicit prediction of the DHS have been inconsistent (Farrell et al., 2015; Kendler and Schaffner, 2011a). However, many prior genetic studies have been statistically underpowered, raising the possibility that support for the DHS could be identified in an adequately powered sample.

The recent PGC mega-analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) has made such an investigation possible. Indeed, in that analysis, the "KEGG_DOPAMINERGIC_SYNAPSE" category was ranked 3rd. However, as noted previously, the functions of genes within that category are quite broad, mitigating the assertion that these results provide strong empirical support for the DHS. In addition, a later network/pathway analysis that employed a wider array of analytic methods did not replicate the link between the dopaminergic synapse and schizophrenia; rather, the top-ranking pathway was "postsynaptic density" (The Network Pathway Analysis Subgroup of the Psychiatric Genomics Consortium and International Inflammatory Bowel Disease Genetics Consortium, 2015), which is, of course, not specific to the dopaminergic system.

Our analyses, which included flanking regions comparable to the previous studies, were designed to more specifically target genes of direct relevance to the DHS: although most if not all of the 10 genes included in the analysis have roles outside of dopaminergic functioning, they constitute the cellular machinery essential to DA synthesis, metabolism, and neurotransmission. Therefore, this limited set of genes constitutes a more focused test of the genetic component of the DHS than had heretofore been conducted. Our results are clear: using the largest dataset currently available, there is no empirical support for enrichment of genetic effects arising from variation in core DA genes on risk for schizophrenia.

The scientific value of disconfirmatory evidence for any hypothesis is directly related to the quality of the test. One of the difficulties in testing the DHS is its non-specificity. Which dopamine systems, where in the brain and at which developmental periods are actually disordered in schizophrenia? As reviewed previously (Kendler and Schaffner, 2011a), these questions fall under the rubric of specific versus more general aspects of the DHS: we provided here a global test for a global theory. Critically, the current report has delineated a hypothesis—sequence variation in core DA genes is related to schizophrenia liability—that could be unambiguously falsified due in part to its relatively narrow scope. However, as discussed below, our negative results do not preclude other interpretations of the DHS, genomic or otherwise. This is in contrast to general hypotheses such as "dysfunction of the dopaminergic system in the brain contributes to schizophrenia liability" which is far more difficult to test definitively.

Indeed, if we modified our test to examine whether **any one** DA-related gene was associated with schizophrenia our results might differ. In confirmation of the results of the recent PGC mega-analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), we found evidence that variants in *DRD2* were significantly associated with risk for schizophrenia. However, when the *DRD2* gene was analyzed along with the other core dopamine genes, the aggregate results no longer differed from null expectations. Importantly, our findings do not address the potential for other manifestations of genomic variation within dopamine genes – e.g., transcript variation, rare variants or epigenetic changes – to impact schizophrenia risk. Nor do they preclude a role for these genes, or the dopaminergic system more generally, in the heterogeneity of clinical presentation or treatment response. Indeed, neuroleptic medications target the dopamine system and can be effective in the treatment of schizophrenia (Furukawa et al., 2015). Regardless, the results

suggest that novel models of the etiopathogenesis of schizophrenia are needed, as the DHS is insufficient in explaining risk, at least from the perspective of common genetic variation.

Our results appear inconsistent with the prior candidate gene literature outlined in Table 1 where for many of the key dopamine genes (i.e., *COMT*, *DRD2*, *DRD3*, *DRD5*, *SLC6A3* and *TH*) the proportion of positive association studies, often based on quite modest sample sizes, far exceeded the 5% expected under the null hypothesis. While a number of factors might be involved, publication bias, in which positive reports are much more likely than negative reports to be submitted and accepted, is the most likely explanation. A prior detailed study of the SZGene database noted evidence for publication bias but only in a modest percentage of the meta-analyses (Allen et al., 2008).

These results should be interpreted in the context of at least four potential methodological limitations. First, we used publicly available data from the most recently published PGC2 schizophrenia mega-analysis, which was limited to common variants (minor allele frequency ≥ 1%) and is derived from samples of predominantly (~92%) European descent. Thus, our results do not necessarily generalize to non-European samples.

Second, we elected to focus on a narrow set of 11 dopamine-related genes. As described above, previous studies have reported evidence of enrichment for pathways or networks that include these genes (e.g., KEGG's “dopaminergic synapse”) but which are far broader than our selection in terms of gene membership and functionality. It is therefore possible that, had we delineated a more inclusive list of dopamine-related genes, our results might have differed. However, we contend that departure from this central, limited gene set maps poorly onto the DHS and instead addresses issues related to neurotransmission more generally.

Third, our approach differs from many previous analyses in a potentially critical way: we included all markers within the genes of interest for which the PGC reported results, rather than one or a few markers as most prior candidate gene studies have done. This enables us to test whether variation anywhere within the core DA genes is related to schizophrenia risk beyond chance expectation. The approach increases the likelihood of identifying signals across linkage disequilibrium blocks, but also introduces the possibility that a true signal will be diluted by its inclusion with markers in large “null blocks.” It is possible that a test including only the limited set of previously interrogated markers across all 11 genes would have yielded a different result. We employed the current approach to pool the information across blocks. Thus, these results represent tests based on quantitatively more information that is qualitatively different from many candidate gene studies, and should be interpreted accordingly.

Finally, while limiting our analysis to only 11 core genes of interest was the most appropriate approach for testing our hypothesis, this might introduce power issues. Gene set enrichment tests are sensitive to the size of the set, and although it is common to include sets of modest size in such analyses, we cannot exclude the possibility that our null results are due to type II error. However, given the very large number of signals and sample size of PGC2, this would imply that the dopamine pathway would explain at most a minor fraction of the heritability of schizophrenia. We conducted post hoc analyses and found that the

h^2_{SNP} for markers used in our analyses was 0.0019 (SE=0.0022; n.s.) using the more restricted flanking regions and 0.0025 (SE=0.0026; n.s.) using the broader flanking region. We interpret this as further evidence that common variation in core dopaminergic genes has at most a minor impact on the overall schizophrenia genetic liability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The summary statistics for PGC2 schizophrenia results were obtained from https://pgc.unc.edu/Sharing.php#SharingOpp; we are grateful to the investigators who produced and analyzed these datasets.

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References

Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ, Tanzi RE, Bertram L. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. Nat Genet. 2008; 40(7):827–834. [PubMed: 18583979]

Bacanu SA, Chen J, Sun J, Richardson K, Lai CQ, Zhao Z, O'Donovan MC, Kendler KS, Chen X. Functional SNPs are enriched for schizophrenia association signals. Mol Psychiatry. 2014; 19(3): 276–277. [PubMed: 23546170]

Costas J, Sanjuan J, Ramos-Rios R, Paz E, Agra S, Ivorra JL, Paramo M, Brenlla J, Arrojo M. Heterozygosity at catechol-O-methyltransferase Val158Met and schizophrenia: new data and meta-analysis. J Psychiatr Res. 2011; 45(1):7–14. [PubMed: 20488458]

Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A, Bauer M, Bayes M, Bellivier F, Bergen SE, Berrettini W, Betancur C, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DH, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M, Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook EH, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Degenhardt F, Djurovic S, Donohoe GJ, Doyle AE, Duan J, Dudbridge F, Duketis E, Ebstein RP, Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A, Farmer AE, Ferrier IN, Flickinger M, Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag CM, Friedl M, Frisen L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind DH, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan W, Gurling H, De Haan L, Haines JL, Hakonarson H, Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Tzeng JY, Kahler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirov GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landen M, Langstrom N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Ledbetter DH, Lee PH, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu C, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, MacIntyre DJ, Madden PA, Maestrini E, Magnusson PK, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingsdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H,

Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Muhleisen TW, Muir WJ, Muller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nievergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nothen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Olincy A, Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Quested DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri S, Rehnstrom K, Reif A, Ribases M, Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo SL, Sergeant JA, Schachar R, Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ, Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi J, Shilling PD, Shyn SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJ, St Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS, Sutcliffe JS, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Van Os J, Vicente AM, Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman MM, Werge T, Wienker TF, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zollner S, International Inflammatory Bowel Disease Genetics, C. Devlin B, Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW, Kendler KS, Wray NR. Cross-Disorder Group of the Psychiatric Genomics, C. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013; 45(9):984–994. [PubMed: 23933821]

Dai D, Wang Y, Yuan J, Zhou X, Jiang D, Li J, Zhang Y, Yin H, Duan S. Meta-analyses of 10 polymorphisms associated with the risk of schizophrenia. Biomed Rep. 2014; 2(5):729–736. [PubMed: 25054019]

Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: A review and reconceptualization. Am J Psychiatry. 1991; 148(11):1474–1486. [PubMed: 1681750]

Dubertret C, Gorwood P, Ades J, Feingold J, Schwartz JC, Sokoloff P. Meta-analysis of DRD3 gene and schizophrenia: ethnic heterogeneity and significant association in Caucasians. Am J Med Genet. 1998; 81(4):318–322. [PubMed: 9674978]

Farrell MS, Werge T, Sklar P, Owen MJ, Ophoff RA, O'Donovan MC, Corvin A, Cichon S, Sullivan PF. Evaluating historical candidate genes for schizophrenia. Mol Psychiatry. 2015

Furukawa TA, Levine SZ, Tanaka S, Goldberg Y, Samara M, Davis JM, Cipriani A, Leucht S. Initial severity of schizophrenia and efficacy of antipsychotics: participant-level meta-analysis of 6 placebo-controlled studies. JAMA Psychiatry. 2015; 72(1):14–21. [PubMed: 25372935]

Gamma F, Faraone SV, Glatt SJ, Yeh YC, Tsuang MT. Meta-analysis shows schizophrenia is not associated with the 40-base-pair repeat polymorphism of the dopamine transporter gene. Schizophr Res. 2005; 73(1):55–58. [PubMed: 15567077]

Glatt SJ, Faraone SV, Tsuang MT. Schizophrenia is not associated with DRD448-base-pair-repeat length or individual alleles: results of a meta-analysis. Biol Psychiatry. 2003; 54(6):629–635. [PubMed: 13129658]

Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. J Psychopharmacol. 2015; 29(2):97–115. [PubMed: 25586400]

Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull. 2009; 35(3):549–562. [PubMed: 19325164]

Jonsson EG, Kaiser R, Brockmoller J, Nimgaonkar VL, Crocq MA. Meta-analysis of the dopamine D3 receptor gene (DRD3) Ser9Gly variant and schizophrenia. Psychiatr Genet. 2004; 14(1):9–12. [PubMed: 15091310]

Jonsson EG, Sedvall GC, Nothen MM, Cichon S. Dopamine D4 receptor gene (DRD4) variants and schizophrenia: meta-analyses. Schizophr Res. 2003; 61(1):111–119. [PubMed: 12648742]

Kanehisa M, Sato Y, Kawashima M, Furumichi M, Tanabe M. KEGG as a reference resource for gene and protein annotation. Nucleic Acids Res. 2016; 44(D1):D457–462. [PubMed: 26476454]

Kendler KS, Schaffner KF. The Dopamine Hypothesis of Schizophrenia: An Historical and Philosophical Analysis. Philosophy, Psychiatry, & Psychology. 2011a; 18(1):41–63.

Kendler KS, Schaffner KF. Further thoughts on the dopamine hypothesis of schizophrenia. Philosophy, Psychiatry, and Psychology. 2011b; 18(1):73–75.

Li D, He L. Meta-analysis shows association between the tryptophan hydroxylase (TPH) gene and schizophrenia. Hum Genet. 2006; 120(1):22–30. [PubMed: 16741719]

Li D, He L. Meta-study on association between the monoamine oxidase A gene (MAOA) and schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2008; 147B(2):174–178. [PubMed: 17894408]

Matthysse S. Antipsychotic drug actions: a clue to the neuropathology of schizophrenia? Fed Proc. 1973; 32(2):200–205. [PubMed: 4348519]

Munafo MR, Bowes L, Clark TG, Flint J. Lack of association of the COMT (Val158/108 Met) gene and schizophrenia: a meta-analysis of case-control studies. Mol Psychiatry. 2005; 10(8):765–770. [PubMed: 15824744]

Nunokawa A, Watanabe Y, Kaneko N, Sugai T, Yazaki S, Arinami T, Ujike H, Inada T, Iwata N, Kunugi H, Sasaki T, Itokawa M, Ozaki N, Hashimoto R, Someya T. The dopamine D3 receptor (DRD3) gene and risk of schizophrenia: case-control studies and an updated meta-analysis. Schizophr Res. 2010; 116(1):61–67. [PubMed: 19897343]

Okochi T, Ikeda M, Kishi T, Kawashima K, Kinoshita Y, Kitajima T, Yamanouchi Y, Tomita M, Inada T, Ozaki N, Iwata N. Meta-analysis of association between genetic variants in COMT and schizophrenia: an update. Schizophr Res. 2009; 110(1-3):140–148. [PubMed: 19329282]

Pan Y, Yao J, Wang B. Association of dopamine D1 receptor gene polymorphism with schizophrenia: a meta-analysis. Neuropsychiatr Dis Treat. 2014; 10:1133–1139. [PubMed: 25018632]

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81(3):559–575. [PubMed: 17701901]

Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511(7510):421–427. [PubMed: 25056061]

Shi J, Gershon ES, Liu C. Genetic associations with schizophrenia: meta-analyses of 12 candidate genes. Schizophr Res. 2008; 104(1-3):96–107. [PubMed: 18715757]

Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003; 60(12):1187–1192. [PubMed: 14662550]

Talkowski ME, Bamne M, Mansour H, Nimgaonkar VL. Dopamine genes and schizophrenia: case closed or evidence pending? Schizophr Bull. 2007; 33(5):1071–1081. [PubMed: 17630406]

Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. The 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. Nature. 2010; 467(7319):1061–1073. [PubMed: 20981092]

The Network Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, International Inflammatory Bowel Disease Genetics Consortium. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. Nat Neurosci. 2015

Utsunomiya K, Shinkai T, De Luca V, Hwang R, Sakata S, Fukunaka Y, Chen HI, Ohmori O, Nakamura J. Genetic association between the dopamine D3 gene polymorphism (Ser9Gly) and schizophrenia in Japanese populations: evidence from a case-control study and meta-analysis. Neurosci Lett. 2008; 444(2):161–165. [PubMed: 18703116]

Williams J, Spurlock G, Holmans P, Mant R, Murphy K, Jones L, Cardno A, Asherson P, Blackwood D, Muir W, Meszaros K, Aschauer H, Mallet J, Laurent C, Pekkarinen P, Seppala J, Stefanis CN, Papadimitriou GN, Macciardi F, Verga M, Pato C, Azevedo H, Crocq MA, Gurling H, Owen MJ, et al. A meta-analysis and transmission disequilibrium study of association between the dopamine D3 receptor gene and schizophrenia. Mol Psychiatry. 1998; 3(2):141–149. [PubMed: 9577838]

Zhang B, Jia Y, Yuan Y, Yu X, Xu Q, Shen Y, Shen Y. No association between polymorphisms in the DDC gene and paranoid schizophrenia in a northern Chinese population. Psychiatr Genet. 2004; 14(3):161–163. [PubMed: 15318031]

Table 1

Overview of findings listed on www.szgene.org and results of recent meta-analyses on 11 core dopamine-related genes.

Gene	SZgene.org Summary: Total # case-control studies[1] (% positive[2])	SZgene.org Summary: Total # family-based studies[1] (% positive[2])	Summary of prior published meta-analytic results[3]
COMT	63 (23.8)	15 (26.7)	Conflicting results from meta-analyses: three suggested that variants in *COMT* are unlikely to contribute to schizophrenia risk (Munafo et al., 2005; Okochi et al., 2009; Shi et al., 2008), while another reported some support for multiple variants (Allen et al., 2008). A fourth reported a protective effect of heterozygosity at rs4680 (Costas et al., 2011).
DBH	11 (9.1)	3 (0)	No support for an association between a common insertion/deletion in *DBH* and schizophrenia (Dai et al., 2014).
DDC	5 (0)	1 (0)	No meta-analytic results available. No evidence for association between *DDC* and paranoid schizophrenia (Zhang et al., 2004).
DRD1	10 (10.0)	2 (0)	Meta-analytic results provided support for an association between one *DRD1* variant and schizophrenia (rs5326) but not another (rs4532) (Pan et al., 2014). A separate meta-analysis reported weak support for rs4532 (Allen et al., 2008).
DRD2	46 (34.8)	8 (25.0)	One prior meta-analysis reported an association at this locus (Allen et al., 2008), but another found no support for an association (Shi et al., 2008).
DRD3	66 (36.4)	8 (12.5)	Multiple meta-analysis have reported no evidence of association (Jonsson et al., 2004; Nunokawa et al., 2010; Utsunomiya et al., 2008), though earlier meta-analyses did report an association (Dubertret et al., 1998; Williams et al., 1998).
DRD4	23 (8.7)	5 (0)	Two meta-analyses reported modest support for association between variants in *DRD4* and schizophrenia (Allen et al., 2008; Shi et al., 2008), but another earlier meta-analysis found no evidence of association (Glatt et al., 2003). The meta-analysis by Jonsson et al. (2003) reported mixed evidence across variants.
DRD5	7 (42.9)	2 (0)	No meta-analytic results are available.
MAOA	19 (5.3)	0 (0)	A meta-analysis found no overall support for an association between two common polymorphisms and schizophrenia (Li and He, 2008).
SLC6A3	16 (25.0)	5 (60.0)	The only meta-analysis available found no association between a common VNTR and schizophrenia (Gamma et al., 2005).
TH	10 (40.0)	1 (0)	Only one meta-analysis was found, and it reported no association between *TH* and schizophrenia (Li and He, 2006).

[1] Because the current analyses are based on summary statistics from samples of predominantly European descent, we report here only the studies of Caucasian subjects in SZgene.org. Some studies included overlapping samples; this non-independence has not been accounted for in here.

[2] "Positive" in this context means at least one marker tested had $p<0.05$.

[3] A more comprehensive review of four of these genes, not limited to meta-analyses, is available from Talkowski et al. (2007).

Table 2

Results from Simes and SST analyses of enrichment.

SNP Set	N SNPs with LD	*p*-value Simes test	*p*-value SST
35-10[1] *all*	3829	0.1831	0.3426
35-10 DRD2 only	326	0.0158	>0.0001
35-10 excluding DRD2	3503	0.9997	0.9999
50-50[2] *all*	6205	0.2849	0.9157
50-50 DRD2 only	487	0.0224	>0.0001
50-50 excluding DRD2	5718	0.9996	0.9999

SST – Sum of Squares Test; SNP – single nucleotide polymorphism; LD – linkage disequilibrium; DRD2 – dopamine receptor D2

[1]Includes SNPs mapping to within -35kb upstream or +10kb downstream from genes of interest.

[2]Includes SNPs mapping to within -50kb upstream or +50kb downstream from genes of interest.