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Genetic associations with schizophrenia: Meta-analyses of 12 candidate genes

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Abstract

Genetic association studies on schizophrenia (SZ) have been repeatedly performed over the last two decades, resulting in a consensus that results are generally inconsistent. This consensus has begun to change as a result of meta-analyses (*e.g.*, (Glatt and Jonsson, 2006)). The SchizophreniaGene database (http://www.schizophreniaforum.org/res/sczgene/default.asp) has been a leader in meta-analyses of SZ association data, by dynamically and comprehensively cataloging all public genetic association studies, and preparing meta-analyses of case-control data. There are 19 "top" candidate genes from these analyses (access on December 20, 2007), showing the highest effect sizes and nominally significant associations of at least one variant in the meta-analyses of all ethnic samples or of samples of Caucasian ancestry. We selected 40 polymorphisms in 12 selected "top" genes for additional meta-analyses, which had at least one familial association data. We found gene-wide (correction for the number of meta-analyses for each gene) significant allelic association evidence for seven genes in the combined samples. The odds ratios (ORs) of the associated minor risk alleles range from 1.072 to 1.121, for *DRD4*, *MTHFR*, *PPP3CC* and *TP53*. For protective allele associations, the ORs are between 0.842 and 0.886, for *DAO*, *IL1B*, and *SLC6A4*. In population based sub-analyses, we found significant results in four genes in Asians (ORs between 1.084 and 1.309 for *DRD4*, *GABRB2*, *PPP3CC*, and *TP53*), and one gene in European (OR of 0.888 for *SLC6A4*). However, none of these associations survive experiment-wide correction for multiple testing. No significant heterogeneity between case-control and family-based study designs was detected in 35 out of 40 polymorphisms. Our results suggest eight potential SZ candidate genes and suggest that family data can reasonably be included in the meta-analysis of genetic associations.

Keywords

meta-analysis; schizophrenia; genetics; single nucleotide polymorphism; variable number tandem repeats

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1. Introduction

Schizophrenia (SZ) is a genetically complex and heterogeneous psychiatric disorder. Genetic association studies on SZ have been repeatedly performed over the last two decades. There are more than 1,200 published reports in the PubMed database of the National Center for Biotechnology Information (NCBI), which are cataloged in the SchizophreniaGene (SZGene) database of the Schizophrenia Research Forum (http://www.schizophreniaforum.org/res/sczgene/default.asp). It would appear that very few consistent replications have been observed in these association studies. Clinical and genetic heterogeneity might account for the apparent inconsistency. Another possible cause is the very limited sample size in most individual studies, which thus have relatively low statistical power. Meta-analysis is a quantitative approach to systematically combing existing results from multiple individual studies and generating an overall conclusion; it has been shown as an effective method to estimate the genetic effects on common diseases with increased power (Ioannidis et al., 2007; Levinson, 2005; Munafo and Flint, 2004; Munafo, 2006).

SZGene has become the leading source of meta-analyses in SZ, by dynamically and comprehensively cataloging all known genetic association studies, and preparing meta-analyses of polymorphisms in candidate genes that have been examined in four or more sample sets (http://www.schizophreniaforum.org/res/sczgene/default.asp). There are 19 “top” candidate genes from these analyses (access on December 20, 2007), showing the highest effect sizes and nominally significant associations of at least one variant in the meta-analyses of all ethnic samples or of samples of Caucasian ancestry. However, these meta-analyses do not include family-based association studies at this time, and summary results in Asians are not presented either. This paper aims to maximize the number of individuals included, and to test for separate allelic associations in the two major population groups that have been studied, Asians and Europeans. We also investigated the influence of family-based data on meta-analysis of genetic association studies on SZ, by performing a testing of heterogeneity between case-control and family-based study designs. Of the 19 “top” SZ candidate genes, 13 had at least one family data set suitable for meta-analysis. Since we previously published a meta-analysis of *G72*/*G30* (also known as D-amino acid oxidase activator, *DAOA*) in SZ and bipolar disorder (Shi et al., 2008), here we report our meta-analyses of 12 other genes, including *AKT1* (v-akt murine thymoma viral oncogene homolog 1), *COMT* (catechol-O-methyltransferase, *DAO* (D-amino acid oxidase), *DRD2* (dopamine receptor D2), *DRD4* (dopamine receptor D4), *DTNBP1* (dystrobrevin binding protein 1), *GABRB2* (gamma-aminobutyric acid A receptor, beta), *IL1B* (interleukin1, beta proprotein), *MTHFR* (5,10-methylenetetrahydrofolate reductase), *PPP3CC* (protein phosphatase 3 [formerly 2B], catalytic), *SLC6A4* (solute carrier family 6 member 4, also known as 5-hydroxytryptamine transporter, 5-HTT), and *TP53* (tumor protein p53).

2. Methods

2.1. Literature searches

First, the association studies were extracted from the SZGene database (http://www.schizophreniaforum.org/res/sczgene/default.asp). Then, the literature was further retrieved by searching the PubMed database using the keywords “schizophrenia”, “gene” and symbols of the 12 genes or their full name. All association studies published in English before March 1, 2008 were analyzed. Additionally, all references cited in articles on association studies, reviews and/or meta-analyses (Supplementary 1 summarizes previous meta-analyses of genes *COMT*, *DRD2*, *DRD4*, *DTNBP1*, *MTHFR*, and *SLC6A4*) were examined to identify potential additional studies that might not be collected in SZGene or PubMed.

2.2. Inclusion Criteria

Polymorphisms (single nucleotide polymorphisms [SNPs] and variable number tandem repeats [VNTRs]) with meta-analyses in the SZGene database were re-analyzed. Studies included in our meta-analyses were based on the following criteria: (1) published in a peer-reviewed journal in English; (2) detailed description of the samples tested (including sample size, ancestry of samples, diagnostic criteria for schizophrenia); (3) data published or furnished by correspondence before March 2008. These data had to contain genetic polymorphism information (standard polymorphism name or position on chromosome), minor allele frequency in case and control groups in population-based studies or numbers of transmitted and un-transmitted minor alleles from heterozygous parents to affected offspring in family-based studies; (4) sample not duplicative of other reports. We used the data from the larger sample set if studies had overlapping subjects; (5) at least one family-based association data set available; and (6) genotypic distribution in the controls of population-based studies not inconsistent with Hardy-Weinberg Equilibrium (HWE).

2.3. Statistical Analyses

The term “data set” here refers to one polymorphism, studied in one case-control or family-based association sample. A single report could be considered as containing separate association data sets, when it included unrelated case-control and family-based data, or if it separately examined distinct samples such as German and Japanese. We integrated population-based and family-based association data set(s) into a single meta-analysis using a method recently developed independently by several groups (Cho et al., 2005; Kazeem and Farrall, 2005; Lohmueller et al., 2003). Briefly, counts of minor alleles in case and control groups in population-based studies were summarized in two-by-two tables. The minor alleles of each polymorphism are annotated in the SZGene database. For family-based studies, the number of each transmitted minor allele from heterozygous parents to affected offspring were treated as the number of occurrence of that “risk” or “protective” minor allele in cases. The controls were assumed from a very large population with equal numbers of each allele (to reflect the expected 50:50 transmission ratio from parents to offspring (Lohmueller et al., 2003)). The transmitted and un-transmitted minor alleles were summarized in two-by-one tables. For each table, the natural logarithms of odds ratios (Ln(ORs)) and standard errors (SEs) were calculated based on the allelic data (Kazeem and Farrall, 2005).

We tested heterogeneity between studies using Cochran’s chi-square-based Q-statistic and estimated the degree of heterogeneity with I^2 ($I^2 = ((Q-(k-1))/Q)\times 100\%$, where k indicates number of studies). I^2 ranges from 0% to 100%. It indicates the proportion of between-study variability in point estimates that was due to heterogeneity rather than sampling error (Higgins and Thompson, 2002; Huedo-Medina et al., 2006). An overall OR and 95% confidence interval (CI) was estimated under the Mantel-Haenszel’s fixed-effects model (MANTEL and HAENSZEL, 1959) if there was no evidence for heterogeneity ($I^2 < 50\%$), otherwise ($I^2 = 50\%$) under the DerSimonian-Laird random-effects model (DerSimonian and Laird, 1986). Significance of overall OR was examined using a *Z*-test. The nominally significant *P* values were adjusted using two Bonferroni corrections: 1) for each individual gene (to test gene-wide significance) when two or more polymorphisms in one gene were meta-analyzed or subgroup analyses were performed according to sample ancestry (Europeans and Asians), 2) for the whole experiment (40 meta-analyses for all populations and 120 for subpopulations were reviewed). Sensitivity analysis was analyzed by dropping one study in turn, recalculating the overall OR of the remaining studies, and testing its significance. This approach can determine whether a finding in the meta-analysis is due to the contribution of a single study. However, this type of analysis is largely influenced by the total number of studies included in the meta-analysis. Evidence for publication bias was assessed using Egger’s regression asymmetry test with a funnel plot of Ln(OR) against inverse SE in each study (Egger et al., 1997).

To detect potential effects of study design types (case-control versus family-based) or different populations (Europeans versus Asians), overall ORs and SEs were obtained for each subgroup, then heterogeneity of overall ORs between study designs or different populations were evaluated by means of a chi-square test with one degree of freedom, as described in detail elsewhere (Kazeem and Farrall, 2005). Meta-analyses were also carried out after excluding family-based association studies to visually evaluate the effects of such data. The statistical analyses were performed using the program Meta-analysis with Interactive eXplanations (MIX, version 1.61) (Bax et al., 2006). A significance level was set at $P = 0.05$ for all tests with exception of $P = 0.1$ for Egger's test for publication bias.

Power was estimated using the Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/) (Purcell et al., 2003), under the assumption of a dominant model, with a disease prevalence of 1%, D' of 0.8 between risk allele and marker allele, and the real data from the meta-analyses (significance level adjusted by Bonferroni correction for each gene).

3. Results

3.1. Description of Studies

The procedure to retrieve studies for further meta-analysis is described in Supplementary Figure 1. In total, for 12 of the 19 "top" SZ candidate genes, we found 185 reports with 488 separate association data sets on 40 polymorphisms, which met our criteria for inclusion here (Supplementary Table 2). The number of published family-based association report(s) that have available data suitable for meta-analysis ranged from 1 (78–693 families) to 5 (1242 families). Seven hundred and seventeen data sets on 386 polymorphisms in these 12 genes were excluded from our analyses based on the study selection criteria (Supplementary Table 3). We did not include studies on *DAOA*, as we have recently published a meta-analysis on this gene using similar methods (Shi et al., 2008).

3.2. Meta-analyses

Table 1 shows the results of meta-analyses of 12 SZ candidate gene association studies. When we included all population sources in one analysis, with Bonferroni correction of each *P* value for the number of meta-analyzed polymorphisms in that gene, we found seven significant allelic associations (*DAO*, *DRD4*, *IL1B*, *MTHFR*, *PPP3CC*, *SLC6A4*, and *TP53*) (Table 1 and Supplementary Table 4). In population-based analyses, we found significant results in four genes in Asians (*DRD4*, *GABRB2*, *PPP3CC*, and *TP53*), and one gene in Europeans (*SLC6A4*) (Table 1 and Supplementary Table 4). The Forest plots of these significant meta-analyses are shown in Figure 1. However, none of the associations reached experiment-wide association, after correction for all the meta-analyses performed (Supplementary Table 4). For polymorphisms that revealed gene-wide significant results, there was evidence for significant heterogeneity between Asians and Europeans at rs1816072 in *GABRB2* ($P = 0.0009$) and between case-control and family-based association studies at rs16944 in *IL1B* ($P = 0.023$) (Supplementary Table 5). Egger's regression test did not detect significant publication bias (data not shown), except for the studies on the *DTNP1* gene (rs2619539, $P = 0.028$; rs2619528, $P = 0.049$; rs760761, $P = 0.026$; rs1018381, $P = 0.070$).

When family association data was removed, rs1816072 and rs1816071in *GABRB2* and rs16944 in *IL1B* showed gene-wide significant disease associations in Europeans, while significant associations of 10 tandem repeats in *SLC6A4* (allele 10) disappeared either in all combined populations or in Europeans (underlined results in Table 1). Whereas at significance level of $P = 0.05$, nominal associations in five polymorphisms were detected, three associations disappeared, and 17 remain in meta-analyses with case-control data (Table 1).

When meta-analyses were performed combing data sets from all the populations, sensitivity analysis indentified that the significant association with *DAO* was ascribed to a Japanese study with 570 cases and 570 controls (Yamada et al., 2005) (adjusted $P = 0.132$), and that the association with *DRD4* was ascribed to a Japanese study with 252 cases and 269 controls (Okuyama et al., 1999) (adjusted $P = 0.081$). In population-based sub-analyses, sensitivity analysis found that the association with *DRD4* was ascribed to a Japanese study with 252 cases and 269 controls (Okuyama et al., 1999) (adjusted $P = 0.102$), and that the association with *SLC6A4* was ascribed to a study with 129 cases and 187 controls (Collier et al., 1996) (adjusted $P = 0.192$). Interestingly, when removing the data from a large study with 1870 cases and 2002 controls in European Americans (Sanders et al., 2008), we could detect four additional gene-wide significant associations (all populations: rs165599 in *COMT* and rs1801028 in *DRD2*; Europeans: rs1801028 in *DRD2* and rs1011313 in *DTNBP1*, Supplementary Table 6).

3.3 Power estimation

The combined sample in our meta-analyses has generally low power to detect small genetic effects with OR less than 1.3 (data not shown). For example, a sample of approximately 1500 cases and 1500 controls has only 8% power to detect the highest OR of 1.2 for the SNP with MAF of 0.3 in the *DAO* gene in all populations at the experiment-wide significance level ($P < 0.00125$ for Bonferroni correction for 40 polymorphisms); a sample of 1000 cases has 5% power to detect OR of 0.4 in Asians at $P < 0.00042$ (Bonferroni correction for 120 tests based on 40 polymorphisms and sub-populations). To achieve 80% power, 7627 and 5400 cases and comparable controls are needed to detect above effect sizes, respectively.

4. Discussion

Our meta-analyses combing population- and family-based association studies identified significant association evidence across populations for genes *DAO*, *DRD4*, *IL1B*, *MTHFR*, *PPP3CC*, *SLC6A4*, and *TP53*. Where separate population analyses could be performed, we found that genes *DRD4*, *GABRB2*, *PPP3CC*, and *TP53* had SNPs that were uniquely associated with disease risk in Asians and *SLC6A4* in Europeans.

Empirical evidence from an analysis of 93 association studies has shown no significant heterogeneity between case-control and family-based study designs (Evangelou et al., 2006). Consistent with that evidence, we have not found significant heterogeneity between study designs for 35 out of 40 polymorphisms (Supplementary Table 5). The differences in the five polymorphisms may result from relatively small sample sizes of the family studies (numbers of families range from 78 to 267), or the limited power of the heterogeneity test of modest genetic effects itself. Therefore, it is reasonable to combine case-control and family association data for meta-analysis (Kazeem and Farrall, 2005; Evangelou et al., 2006).

Our results further suggest eight potential candidate genes that are involved in known biological pathways implicated in the pathophysiology of SZ. The *DRD4* gene is in the dopaminergic signaling pathway, where abnormal dopamine transmission has been a prominent hypothesis for schizophrenia over the past half century (Carlsson and LINDQVIST, 1963; Carlsson, 1988; Carlsson and Carlsson, 2006; Toda and bi-Dargham, 2007; Winterer, 2006). SLC6A4, a serotonin transporter, plays a key role in serotonin neurotransmission, which has also implicated in the pathophysiology and antipsychotic treatment of schizophrenia (Breier, 1995; Iqbal and van Praag, 1995; Meltzer, 1989; Meltzer et al., 2003). GABRB2 is one of the most abundant GABA receptor subunits, which mediate inhibitory neurotransmission. GABAergic dysfunction in prefrontal cortex has been linked to the pathophysiology of SZ (Blum and Mann, 2002; Costa et al., 2004; Coyle, 2004; Guidotti et al., 2005). D-amino acid oxidase (DAO) modulates NMDA-receptor mediated signaling. Recently a NMDA receptor-mediated glutamate hypothesis of SZ has received accumulating evidence (Coyle, 1996; Coyle

et al., 2003; Coyle, 2006; Lindsley et al., 2006; Moghaddam, 2003). PPP3CC may play a role in the downstream regulation of dopaminergic signal transduction (Greengard, 2001), as well as in the NMDA receptor-dependent synaptic plasticity (Groth et al., 2003). SZ has long been hypothesized as a neurodevelopmental disorder (Arnold et al., 2005; Weinberger, 1987). TP53 has shown a direct role in neurodevelopment (Culmsee and Mattson, 2005; Jacobs et al., 2006). MTHFR participates in the metabolism of folate and DNA methylation, thus may influence neurodevelopment (Greenblatt et al., 1994). IL1B also plays a role in neurodevelopment (Ashdown et al., 2006).

Our results should be interpreted with certain cautions. First, the genetic effects of associated alleles were modest or small (average allelic OR of 1.14 for “risk” genes and 0.87 for “protective” genes). Therefore, the power to detect such small genetic effects are relatively low, even the combined sample for several polymorphism has more than 20,000 individuals (data not shown). Second, most case-control studies we analyzed did not address population stratification using genomic control (Devlin and Roeder, 1999; Reich and Goldstein, 2001), structured association (Pritchard and Rosenberg, 1999; Pritchard et al., 2000), principal components analysis (Price et al., 2006), or other approaches with sub-structure/population informative loci, which would be an issue for the population-specific findings here (Cardon and Palmer, 2003; Freedman et al., 2004). Third, although no evidence for publication bias was detected for all the gene-wide significant associations, the power of the Egger’s regression test is generally low (Macaskill et al., 2001), and this method is further limited for some genes that were meta-analyzed with small numbers of studies (Egger et al., 1997). Fourth, none of the associations could survive correction for multiple testing for all the meta-analyses performed. However, experiment-wide Bonferroni correction may be overly conservative when tests are correlated (e.g., due to linkage disequilibrium of polymorphisms or gene-gene interaction), and there is no consensus on correction for multiple testing in a meta-analysis simultaneously testing a number of genes and polymorphisms (Bertram et al., 2007; Levinson, 2005; Lopez-Leon et al., 2007). Finally, we excluded association studies published in other languages other than in English, which may introduce publication bias in our meta-analyses.

We excluded studies with controls not in HWE, based on several reasons. First, violation of HWE in genetic association studies indicates genotyping errors, population stratification, or selection bias (Cardon and Palmer, 2003; Freedman et al., 2004; Hosking et al., 2004; Xu et al., 2002; Schaid and Jacobsen, 1999). Secondly, lack of HWE in a population implies continued selection, migration, mutation, and assorted mating (Salanti et al., 2005). Thirdly, studies departure from HWE have been proposed to be a potential source of heterogeneity across studies in meta-analysis (Attia et al., 2003; Salanti et al., 2005). However, recent empirical data suggest studies violating HWE may be included in meta-analysis except that the quality of those studies is highly doubtable (Attia et al., 2003; Minelli et al., 2007; Salanti et al., 2007). Family-based association studies were included in meta-analyses except that significant departure from HWE was reported. However, the type I error for classical chi-square goodness-of-fit HWE test in founders (parents) may be over inflated, because founders are not from a random sample from the general population due to typically ascertained families through the affected probands and/or due to potential disease association of the tested marker (Bourgain et al., 2004; Li and Li, 2008). Therefore, HWE assessing should be performed using all the family genotype data conditional on relatedness of the individuals, which can differentiate HWE departure caused by disease association from departure caused by other reasons such as genotyping errors (Bourgain et al., 2004; Li and Li, 2008).

In conclusion, our results further suggest eight susceptibility genes to schizophrenia with modest or small effects, and suggest that family data can reasonably be included in the meta-analysis of genetic associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Arnold SE, Talbot K, Hahn CG. Neurodevelopment, neuroplasticity, and new genes for schizophrenia. Prog Brain Res 2005;147:319–345. [PubMed: 15581715]

Ashdown H, Dumont Y, Ng M, Poole S, Boksa P, Luheshi GN. The role of cytokines in mediating effects of prenatal infection on the fetus: implications for schizophrenia. Mol Psychiatry 2006;11:47–55. [PubMed: 16189509]

Attia J, Thakkinstian A, D'Este C. Meta-analyses of molecular association studies: methodologic lessons for genetic epidemiology. J Clin Epidemiol 2003;56:297–303. [PubMed: 12767405]

Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KG. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. BMC Med Res Methodol 2006;6:50. [PubMed: 17038197]

Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet 2007;39:17–23. [PubMed: 17192785]

Blum BP, Mann JJ. The GABAergic system in schizophrenia. Int J Neuropsychopharmacol 2002;5:159–179. [PubMed: 12135541]

Bourgain C, Abney M, Schneider D, Ober C, McPeek MS. Testing for Hardy-Weinberg equilibrium in samples with related individuals. Genetics 2004;168:2349–2361. [PubMed: 15371359]

Breier A. Serotonin, schizophrenia and antipsychotic drug action. Schizophr Res 1995;14:187–202. [PubMed: 7539288]

Cardon LR, Palmer LJ. Population stratification and spurious allelic association. Lancet 2003;361:598–604. [PubMed: 12598158]

Carlsson A. The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1988;1:179–186. [PubMed: 3075131]

Carlsson A, Carlsson ML. A dopaminergic deficit hypothesis of schizophrenia: the path to discovery. Dialogues Clin Neurosci 2006;8:137–142. [PubMed: 16640125]

Carlsson A, LINDQVIST M. Effect of chlopromazine or haploperidol on formation of 3 methoxytyramine and normetanephrine in mouce brain. Acta Pharmacol Toxicol (Copenh) 1963;20:140–144. [PubMed: 14060771]

Cho HJ, Meira-Lima I, Cordeiro Q, Michelon L, Sham P, Vallada H, Collier DA. Population-based and family-based studies on the serotonin transporter gene polymorphisms and bipolar disorder: a systematic review and meta-analysis. Mol Psychiatry 2005;10:771–781. [PubMed: 15824745]

Collier DA, Arranz MJ, Sham P, Battersby S, Vallada H, Gill P, Aitchison KJ, Sodhi M, Li T, Roberts GW, Smith B, Morton J, Murray RM, Smith D, Kirov G. The serotonin transporter is a potential

susceptibility factor for bipolar affective disorder. Neuroreport 1996;7:1675–1679. [PubMed: 8904780]

Costa E, Davis JM, Dong E, Grayson DR, Guidotti A, Tremolizzo L, Veldic M. A GABAergic cortical deficit dominates schizophrenia pathophysiology. Crit Rev Neurobiol 2004;16:1–23. [PubMed: 15581395]

Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. Harv Rev Psychiatry 1996;3:241–253. [PubMed: 9384954]

Coyle JT. The GABA-glutamate connection in schizophrenia: which is the proximate cause? Biochem Pharmacol 2004;68:1507–1514. [PubMed: 15451393]

Coyle JT. Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol 2006;26:365–384. [PubMed: 16773445]

Coyle JT, Tsai G, Goff D. Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. Ann N Y Acad Sci 2003;1003:318–327. [PubMed: 14684455]

Culmsee C, Mattson MP. p53 in neuronal apoptosis. Biochem Biophys Res Commun 2005;331:761–777. [PubMed: 15865932]

DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188. [PubMed: 3802833]

Devlin B, Roeder K. Genomic control for association studies. Biometrics 1999;55:997–1004. [PubMed: 11315092]

Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634. [PubMed: 9310563]

Evangelou E, Trikalinos TA, Salanti G, Ioannidis JP. Family-based versus unrelated case-control designs for genetic associations. PLoS Genet 2006;2:e123. [PubMed: 16895437]

Freedman ML, Reich D, Penney KL, McDonald GJ, Mignault AA, Patterson N, Gabriel SB, Topol EJ, Smoller JW, Pato CN, Pato MT, Petryshen TL, Kolonel LN, Lander ES, Sklar P, Henderson B, Hirschhorn JN, Altshuler D. Assessing the impact of population stratification on genetic association studies. Nat Genet 2004;36:388–393. [PubMed: 15052270]

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;141:149–154. [PubMed: 16402354]

Greenblatt JM, Huffman LC, Reiss AL. Folic acid in neurodevelopment and child psychiatry. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:647–660. [PubMed: 7938557]

Greengard P. The neurobiology of slow synaptic transmission. Science 2001;294:1024–1030. [PubMed: 11691979]

Groth RD, Dunbar RL, Mermelstein PG. Calcineurin regulation of neuronal plasticity. Biochem Biophys Res Commun 2003;311:1159–1171. [PubMed: 14623302]

Guidotti A, Auta J, Davis JM, Dong E, Grayson DR, Veldic M, Zhang X, Costa E. GABAergic dysfunction in schizophrenia: new treatment strategies on the horizon. Psychopharmacology (Berl) 2005;180:191–205. [PubMed: 15864560]

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558. [PubMed: 12111919]

Hosking L, Lumsden S, Lewis K, Yeo A, McCarthy L, Bansal A, Riley J, Purvis I, Xu CF. Detection of genotyping errors by Hardy-Weinberg equilibrium testing. Eur J Hum Genet 2004;12:395–399. [PubMed: 14872201]

Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193–206. [PubMed: 16784338]

Ioannidis JP, Patsopoulos NA, Evangelou E. Heterogeneity in meta-analyses of genome-wide association investigations. PLoS ONE 2007;2:e841. [PubMed: 17786212]

Iqbal N, van Praag HM. The role of serotonin in schizophrenia. Eur Neuropsychopharmacol 1995;5 (Suppl):11–23. [PubMed: 8775754]

Jacobs WB, Kaplan DR, Miller FD. The p53 family in nervous system development and disease. J Neurochem 2006;97:1571–1584. [PubMed: 16805769]

Kazeem GR, Farrall M. Integrating case-control and TDT studies. Ann Hum Genet 2005;69:329–335. [PubMed: 15845037]

Levinson DF. Meta-analysis in psychiatric genetics. Curr Psychiatry Rep 2005;7:143–151. [PubMed: 15802092]

Li M, Li C. Assessing departure from Hardy-Weinberg equilibrium in the presence of disease association. Genet Epidemiol. 2008

Lindsley CW, Shipe WD, Wolkenberg SE, Theberge CR, Williams DL Jr, Sur C, Kinney GG. Progress towards validating the NMDA receptor hypofunction hypothesis of schizophrenia. Curr Top Med Chem 2006;6:771–785. [PubMed: 16719816]

Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet 2003;33:177–182. [PubMed: 12524541]

Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM, Del-Favero J, Claes SJ, Oostra BA, van Duijn CM. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry. 2007

Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med 2001;20:641–654. [PubMed: 11223905]

MANTEL N, HAENSZEL W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–748. [PubMed: 13655060]

Meltzer HY. Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. Psychopharmacology (Berl) 1989;99(Suppl):S18–S27. [PubMed: 2682729]

Meltzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1159–1172. [PubMed: 14642974]

Minelli C, Thompson JR, Abrams KR, Thakkinstian A, Attia J. How should we use information about HWE in the meta-analyses of genetic association studies? Int J Epidemiol. 2007

Moghaddam B. Bringing order to the glutamate chaos in schizophrenia. Neuron 2003;40:881–884. [PubMed: 14659087]

Munafo MR. Candidate gene studies in the 21st century: meta-analysis, mediation, moderation. Genes Brain Behav 2006;5(Suppl 1):3–8. [PubMed: 16417611]

Munafo MR, Flint J. Meta-analysis of genetic association studies. Trends Genet 2004;20:439–444. [PubMed: 15313553]

Okuyama Y, Ishiguro H, Toru M, Arinami T. A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia. Biochem Biophys Res Commun 1999;258:292–295. [PubMed: 10329380]

Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 2006;38:904–909. [PubMed: 16862161]

Pritchard JK, Rosenberg NA. Use of unlinked genetic markers to detect population stratification in association studies. Am J Hum Genet 1999;65:220–228. [PubMed: 10364535]

Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. Genetics 2000;155:945–959. [PubMed: 10835412]

Purcell S, Cherny SS, Sham PC. Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. Bioinformatics 2003;19:149–150. [PubMed: 12499305]

Reich DE, Goldstein DB. Detecting association in a case-control study while correcting for population stratification. Genet Epidemiol 2001;20:4–16. [PubMed: 11119293]

Salanti G, Higgins JP, Trikalinos TA, Ioannidis JP. Bayesian meta-analysis and meta-regression for gene-disease associations and deviations from Hardy-Weinberg equilibrium. Stat Med 2007;26:553–567. [PubMed: 16685693]

Salanti G, Sanderson S, Higgins JP. Obstacles and opportunities in meta-analysis of genetic association studies. Genet Med 2005;7:13–20. [PubMed: 15654223]

Sanders AR, Duan J, Levinson DF, Shi J, He D, Hou C, Burrell GJ, Rice JP, Nertney DA, Olincy A, Rozic P, Vinogradov S, Buccola NG, Mowry BJ, Freedman R, Amin F, Black DW, Silverman JM, Byerley WF, Crowe RR, Cloninger CR, Martinez M, Gejman PV. No significant association of 14

candidate genes with schizophrenia in a large European ancestry sample: implications for psychiatric genetics. Am J Psychiatry 2008;165:497–506. [PubMed: 18198266]

Schaid DJ, Jacobsen SJ. Biased tests of association: comparisons of allele frequencies when departing from Hardy-Weinberg proportions. Am J Epidemiol 1999;149:706–711. [PubMed: 10206619]

Shi J, Badner JA, Gershon ES, Liu C. Allelic association of G72/G30 with schizophrenia and bipolar disorder: A comprehensive meta-analysis. Schizophr Res 2008;98:89–97. [PubMed: 18023149]

Toda M, bi-Dargham A. Dopamine hypothesis of schizophrenia: making sense of it all. Curr Psychiatry Rep 2007;9:329–336. [PubMed: 17880866]

Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44:660–669. [PubMed: 3606332]

Winterer G. Cortical microcircuits in schizophrenia--the dopamine hypothesis revisited. Pharmacopsychiatry 2006;39(Suppl 1):S68–S71. [PubMed: 16508900]

Xu J, Turner A, Little J, Bleecker ER, Meyers DA. Positive results in association studies are associated with departure from Hardy-Weinberg equilibrium: hint for genotyping error? Hum Genet 2002;111:573–574. [PubMed: 12516594]

Yamada K, Ohnishi T, Hashimoto K, Ohba H, Iwayama-Shigeno Y, Toyoshima M, Okuno A, Takao H, Toyota T, Minabe Y, Nakamura K, Shimizu E, Itokawa M, Mori N, Iyo M, Yoshikawa T. Identification of multiple serine racemase (SRR) mRNA isoforms and genetic analyses of SRR and DAO in schizophrenia and D-serine levels. Biol Psychiatry 2005;57:1493–1503. [PubMed: 15953485]

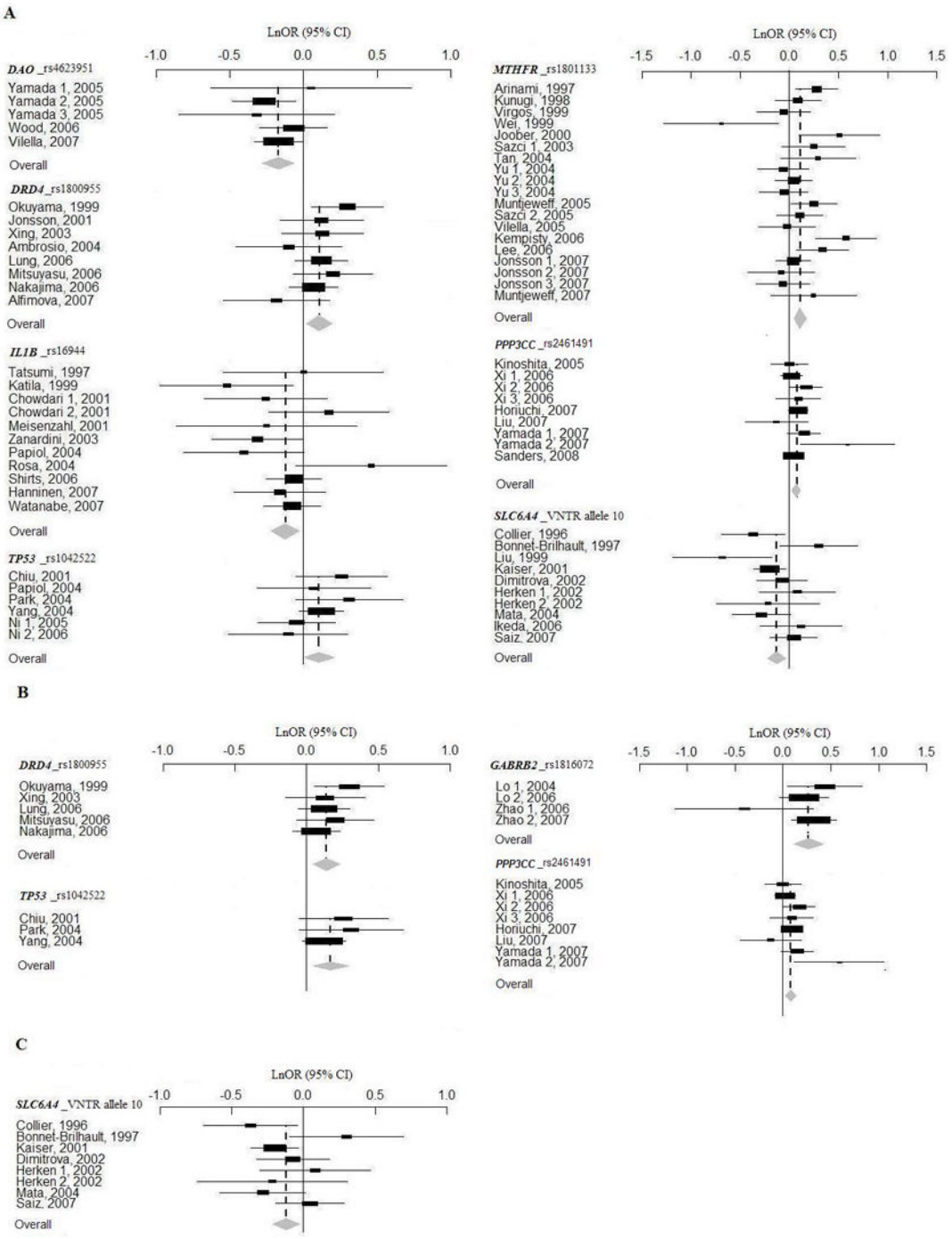

Figure 1.

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Table 1

Meta-analyses of allelic association studies for 12 schizophrenia candidate genes

Gene	Polymorphism/ minor allele[a]	Population[b]	Studies[c]		Minor allele frequency[d]		Family-based studies included			Family-based studies excluded		
			Fam	CC	Cases	Controls	I^2 (%)[e]	OR (95% CI)[f]	*P*(Z)[g]	I^2 (%)[e]	OR (95% CI)[f]	*P*(Z)[g]
AKT1	rs2494732/G	All	4 (683)	6	0.445 (4195)	0.433 (4416)	36	1.065 (1.005–1.130)	**0.035**	38	1.064 (0.999–1.131)	0.050
		European	2 (344)	2	0.434 (2458)	0.431 (2665)	49	1.017 (0.943–1.097)	0.660	NA	NA	NA
		Asian	2 (339)	4	0.461 (1737)	0.435 (1706)	0	1.144 (1.041–1.256)	**0.005**	30	1.150 (1.040–1.271)	**0.006**
AKT1	rs2498799/A	All	2 (389)	5	0.403 (2291)	0.402 (2403)	0	0.991 (0.912–1.078)	0.838	0	0.977 (0.896–1.065)	0.591
		European	1 (265)	1	0.225 (592)	0.245 (659)	NA	NA	NA	NA	NA	NA
		Asian	1 (124)	4	0.466 (1699)	0.460 (1744)	0	1.020 (0.927–1.121)	0.689	0	1.006 (0.912–1.109)	0.907
AKT1	rs3730358/T	All	2 (389)	6	0.133 (4205)	0.137 (4249)	0	0.987 (0.904–1.077)	0.760	0	0.978 (0.895–1.069)	0.630
		European	1 (265)	2	0.149 (2478)	0.156 (2531)	0	0.951 (0.854–1.060)	0.363	NA	NA	NA
		Asian	1 (124)	4	0.111 (1727)	0.109 (1718)	0	1.058 (0.912–1.228)	0.455	0	1.046 (0.898–1.218)	0.565
AKT1	rs1130214/T	All	2 (389)	6	0.293 (4190)	0.297 (4417)	0	0.991 (0.926–1.061)	0.796	0	0.989 (0.922–1.060)	0.751
		European	1 (265)	2	0.300 (2456)	0.301 (2662)	0	0.998 (0.918–1.084)	0.960	NA	NA	NA
		Asian	1 (124)	4	0.283 (1734)	0.290 (1755)	4	0.977 (0.867–1.101)	0.703	25	0.972 (0.860–1.099)	0.650
AKT1	rs3803300/A	All	1 (124)	5	0.352 (2389)	0.353 (2447)	51	0.965 (0.841–1.107)	0.607	0	0.978 (0.864–1.109)	0.732
		European	0	1	0.095 (660)	0.086 (707)	NA	NA	NA	NA	NA	NA
		Asian	1 (124)	4	0.451 (1729)	0.461 (1740)	54	0.940 (0.808–1.094)	0.422	62	0.922 (0.782–1.088)	0.337
COMT	rs737865/C	All	1 (267)	8	0.312 (5020)	0.332 (7747)	40	1.040 (0.983–1.100)	0.173	36	1.044 (0.987–1.104)	0.136
		European	1 (267)	5	0.318 (4060)	0.340 (6638)	61	1.035 (0.925–1.159)	0.551	54	1.050 (0.944–1.169)	0.368
		Asian	0	3	0.287 (960)	0.286 (1109)	NA	NA	NA	0	1.004 (0.877–1.150)	0.196
COMT	rs4680/A	All	4 (1153)	40	0.418 (9762)	0.428 (11607)	11	1.006 (0.968–1.045)	0.779	17	1.006 (0.966–1.047)	0.777
		European	2 (755)	24	0.494 (5940)	0.493 (7270)	8	1.011 (0.964–1.061)	0.646	11	1.017 (0.967–1.069)	0.511
		Asian	2 (398)	15	0.298 (3760)	0.317 (4284)	8	1.003 (0.939–1.071)	0.931	16	0.994 (0.927–1.065)	0.862
COMT	rs165599/G	All	1 (267)	8	0.359 (4810)	0.362 (9709)	54	1.058 (0.967–1.158)	0.218	55	1.067 (0.977–1.167)	**0.035**
		European	1 (267)	6	0.339 (4171)	0.353 (8979)	65	1.045 (0.935–1.169)	0.437	67	1.059 (0.947–1.184)	0.314
		Asian	0	2	0.493 (639)	0.469 (730)	NA	NA	NA	NA	NA	NA
DAO	rs4623951/C	All	1 (124)	4	0.296 (1509)	0.334 (1461)	0	0.842 (0.754–0.940)	**0.002**[h]	0	0.846 (0.758–0.948)	**0.004**[h]
		European	0	2	0.378 (900)	0.409 (905)	NA	NA	NA	NA	NA	NA
		Asian	1 (124)	2	0.175 (609)	0.212 (556)	0	0.779 (0.643–0.944)	**0.011**	NA	NA	NA
DAO	rs2111902/C	All	1 (113)	8	0.391 (2517)	0.368 (2960)	72	1.055 (0.896–1.241)	0.52	75	1.069 (0.902–1.267)	0.444
		European	0	5	0.305 (1364)	0.304 (1812)	NA	NA	NA	85	1.061 (0.792–1.422)	0.692
		Asian	1 (113)	3	0.493 (1153)	0.470 (1148)	0	1.085 (0.969–1.216)	0.157	0	1.096 (0.977–1.231)	0.119
DAO	rs3918346/T	All	1 (113)	8	0.351 (2521)	0.330 (2966)	78	1.037 (0.856–1.256)	0.711	81	1.046 (0.855–1.281)	0.661
		European	0	5	0.237 (1365)	0.238 (1814)	NA	NA	NA	89	1.058 (0.734–1.523)	0.763
		Asian	1 (113)	3	0.486 (1156)	0.474 (1152)	0	1.046 (0.934–1.172)	0.44	0	1.051 (0.936–1.180)	0.398
DAO	rs3741775/G	All	1 (113)	8	0.420 (2514)	0.445 (2959)	79	0.910 (0.758–1.091)	0.307	82	0.923 (0.763–1.117)	0.411
		European	0	5	0.469 (1363)	0.465 (1812)	NA	NA	NA	78	0.985 (0.788–1.232)	0.895
		Asian	1 (113)	3	0.363 (1151)	0.413 (1147)	76	0.806 (0.600–1.083)	0.152	84	0.824 (0.580–1.170)	0.279
DRD2	rs1800497/T	All	1 (90)	10	0.216 (1124)	0.223 (1218)	86	0.833 (0.587–1.184)	0.309	87	0.821 (0.553–1.219)	0.328
		European	1 (90)	9	0.197 (912)	0.199 (1024)	73	0.908 (0.673–1.224)	0.525	76	0.899 (0.630–1.281)	0.555
		mixed	0	1	0.300 (212)	0.348 (194)	NA	NA	NA	NA	NA	NA
DRD2	rs1801028/G	All	1 (90)	28	0.031 (5647)	0.024 (7392)	17	1.189 (1.014–1.395)	**0.033**	19	1.184 (1.008–1.389)	**0.039**
		European	1 (90)	15	0.025 (3887)	0.020 (5499)	39	1.158 (0.935–1.433)	0.179	43	1.148 (0.925–1.423)	0.210
		Asian	0	11	0.037 (1443)	0.029 (1585)	NA	NA	NA	0	1.325 (0.992–1.771)	0.057
DRD2	rs1799732/Del	All	1 (78)	15	0.122 (4509)	0.116 (4466)	77	0.882 (0.707–1.100)	0.267	76	0.924 (0.745–1.146)	0.471
		European	1 (78)	9	0.109 (3203)	0.098 (3434)	79	0.904 (0.657–1.244)	0.534	77	0.990 (0.73–1.345)	0.951
		Asian	0	6	0.154 (1306)	0.175 (1032)	NA	NA	NA	66	0.843 (0.637–1.115)	0.232
DRD4	rs1800955/C	All	1 (90)	7	0.420 (2128)	0.398 (2206)	0	1.113 (1.022–1.211)	**0.014**[h]	0	1.126 (1.032–1.230)	**0.008**[h]
		European	1 (90)	2	0.442 (258)	0.436 (498)	0	0.977 (0.809–1.180)	0.811	NA	NA	NA
		Asian	0	5	0.417 (1870)	0.387 (1708)	NA	NA	NA	0	1.150 (1.046–1.265)	**0.004**[h]
DTNBP1	rs760666/T	All	2 (177)	6	0.240 (1959)	0.240 (2057)	11	0.968 (0.877–1.069)	0.521	0	0.995 (0.898–1.102)	0.917
		European	1 (41)	6	0.240 (1959)	0.240 (2057)	0	0.988 (0.893–1.094)	0.818	0	0.995 (0.898–1.102)	0.917
		Mixed	1 (136)	0	NA	NA	NA	NA	NA	NA	NA	NA

Gene	Polymorphism/ minor allele[a]	Population[b]	Studies[c]		Minor allele frequency[d]		Family-based studies included			Family-based studies excluded		
			Fam	CC	Cases	Controls	I^2 (%)[e]	OR (95% CI)[f]	*P(Z)*[g]	I^2 (%)[e]	OR (95% CI)[f]	*P(Z)*[g]
DTNBP1	rs2619539/G	All	3 (870)	15	0.496 (6212)	0.504 (6553)	0	0.955 (0.911–1.001)	0.057	0	0.960 (0.913–1.010)	0.115
		European	1 (41)	10	0.452 (5085)	0.463 (5401)	0	0.945 (0.893–1.001)	0.051	0	0.946 (0.894–1.002)	0.057
		Asian	1 (693)	3	0.692 (1127)	0.697 (1152)	0	0.971 (0.879–1.073)	0.563	0	0.992 (0.874–1.127)	0.901
DTNBP1	rs3213207/G	All	2 (177)	17	0.100 (6889)	0.108 (7098)	29	0.915 (0.847–0.989)	**0.025**	36	0.918 (0.848–0.993)	**0.034**
		European	1 (41)	13	0.110 (5663)	0.122 (5913)	0	0.896 (0.826–0.972)	**0.008**	0	0.895 (0.824–0.971)	**0.008**
		Asian	0	2	0.029 (156)	0.040 (272)	NA	NA	NA	NA	NA	NA
DTNBP1	rs1011313/T	All	2 (177)	17	0.107 (6681)	0.100 (6596)	10	1.084 (1.002–1.174)	**0.046**	15	1.075 (0.992–1.165)	0.080
		European	1 (41)	13	0.101 (5439)	0.092 (5593)	0	1.105 (1.009–1.210)	**0.031**	5	1.103 (1.007–1.208)	**0.035**
		Asian	0	2	0.152 (982)	0.156 (898)	NA	NA	NA	NA	NA	NA
DTNBP1	rs2619528/A	All	5 (1242)	11	0.206 (4076)	0.200 (4572)	54	1.067 (0.939–1.213)	0.320	66	1.103 (0.937–1.299)	0.239
		European	3 (413)	8	0.206 (3549)	0.204 (4172)	63	1.116 (0.946–1.316)	0.194	72	1.120 (0.929–1.350)	0.234
		Asian	1 (693)	1	0.082 (267)	0.097 (295)	NA	NA	NA	NA	NA	NA
DTNBP1	rs2005976/A	All	1 (693)	9	0.197 (4675)	0.205 (4672)	21	0.947 (0.883–1.015)	0.125	21	0.947 (0.883–1.015)	0.157
		European	0	9	0.197 (4675)	0.205 (4672)	NA	NA	NA	21	0.947 (0.883–1.015)	0.157
		Asian	1 (693)	0	NA	NA	NA	NA	NA	NA	NA	NA
DTNBP1	rs760761/T	All	1 (136)	16	0.194 (5940)	0.191 (6198)	41	1.001 (0.938–1.068)	0.982	44	0.997 (0.933–1.065)	0.925
		European	0	11	0.211 (4525)	0.215 (4844)	NA	NA	NA	36	0.972 (0.905–1.043)	0.429
		Asian	0	3	0.096 (1155)	0.090 (1249)	NA	NA	NA	43	1.132 (0.927–1.382)	0.225
DTNBP1	rs2619522/C	All	3 (870)	14	0.185 (5679)	0.179 (5941)	47	1.008 (0.945–1.076)	0.802	57	1.064 (0.941–1.203)	0.321
		European	1 (41)	9	0.200 (4279)	0.200 (4642)	49	0.990 (0.920–1.066)	0.794	55	1.036 (0.908–1.182)	0.599
		Asian	1 (693)	3	0.095 (1141)	0.088 (1194)	39	1.069 (0.905–1.261)	0.434	46	1.142 (0.931–1.401)	0.202
DTNBP1	rs1018381/T	All	3 (870)	13	0.096 (4933)	0.088 (4937)	5	1.041 (0.949–1.142)	0.395	16	1.064 (0.963–1.174)	0.224
		European	1 (41)	11	0.089 (4439)	0.086 (4553)	23	1.065 (0.959–1.182)	0.240	28	1.069 (0.962–1.187)	0.217
		Asian	1 (693)	1	0.074 (310)	0.068 (310)	NA	NA	NA	NA	NA	NA
DTNBP1	rs909706/G	All	3 (870)	7	0.339 (3535)	0.323 (3733)	0	0.988 (0.928–1.052)	0.712	0	1.006 (0.937–1.080)	0.865
		European	1 (41)	6	0.356 (3350)	0.353 (3383)	0	1.009 (0.941–1.083)	0.801	0	1.008 (0.939–1.082)	0.827
		Asian	1 (693)	1	0.024 (185)	0.030 (350)	NA	NA	NA	NA	NA	NA
DTNBP1	rs2619538/T	All	1 (136)	10	0.372 (4817)	0.363 (5172)	40	1.036 (0.975–1.101)	0.259	30	1.025 (0.964–1.090)	0.437
		European	0	6	0.440 (3562)	0.437 (3909)	NA	NA	NA	5	1.006 (0.942–1.074)	0.858
		Asian	0	2	0.037 (855)	0.026 (938)	NA	NA	NA	NA	NA	NA
GABRB2	rs187269/C	All	2 (349)	7	0.292 (1480)	0.280 (1526)	73	1.093 (0.890–1.342)	0.399	78	1.057 (0.814–1.372)	0.680
		European	2 (349)	3	0.328 (806)	0.361 (758)	44	0.955 (0.843–1.083)	0.474	0	0.866 (0.746–1.004)	0.057
		Asian	0	4	0.249 (674)	0.200 (768)	NA	NA	NA	75	1.296 (0.883–1.903)	0.186
GABRB2	rs252944/C	All	2 (349)	8	0.159 (1790)	0.167 (1631)	63	1.058 (0.862–1.299)	0.589	64	0.989 (0.788–1.242)	0.926
		European	2 (349)	4	0.129 (1135)	0.150 (992)	54	0.961 (0.763–1.210)	0.733	0	0.843 (0.707–1.005)	0.056
		Asian	0	4	0.212 (655)	0.193 (639)	NA	NA	NA	70	1.250 (0.837–1.866)	0.276
GABRB2	rs194072/C	All	2 (349)	8	0.170 (1808)	0.181 (1613)	65	1.060 (0.858–1.310)	0.587	67	0.991 (0.782–1.257)	0.942
		European	2 (349)	4	0.131 (1137)	0.153 (991)	58	0.955 (0.752–1.212)	0.704	7	0.835 (0.702–0.994)	**0.042**
		Asian	0	4	0.236 (671)	0.224 (622)	NA	NA	NA	70	1.276 (0.850–1.915)	0.241
GABRB2	rs1816072/C	All	2 (349)	8	0.414 (1863)	0.420 (1614)	69	1.012 (0.854–1.198)	0.892	75	0.981 (0.801–1.203)	0.856
		European	2 (349)	4	0.360 (1129)	0.407 (995)	39	0.881 (0.789–0.984)	**0.024**	0	0.819 (0.723–0.928)	**0.0016**[h]
		Asian	0	4	0.498 (734)	0.441 (619)	NA	NA	NA	32	1.309 (1.022–1.527)	**0.0006**[h]
GABRB2	rs1816071/G	All	2 (349)	8	0.359 (1847)	0.375 (1619)	67	1.001 (0.849–1.180)	0.989	72	0.970 (0.797–1.181)	0.764
		European	2 (349)	4	0.361 (1133)	0.408 (993)	35	0.886 (0.794–0.988)	**0.029**	0	0.821 (0.725–0.930)	**0.002**[h]
		Asian	0	4	0.356 (714)	0.323 (626)	NA	NA	NA	67	1.227 (0.895–1.683)	0.203
GABRB2	rs6556547/T	All	2 (349)	8	0.123 (1788)	0.121 (1581)	75	1.081 (0.878–1.331)	0.465	80	1.023 (0.807–1.298)	0.851
		European	2 (349)	3	0.058 (794)	0.078 (672)	80	0.924 (0.669–1.276)	0.630	0	0.722 (0.539–0.967)	**0.029**
		Asian	0	5	0.175 (994)	0.152 (909)	NA	NA	NA	80	1.220 (0.948–1.571)	0.122
IL1B	rs1143634/T	All	1 (132)	4	0.162 (1207)	0.180 (1435)	0	0.939 (0.810–1.089)	0.406	0	0.946 (0.814–1.099)	0.465
		European	0	3	0.231 (791)	0.245 (995)	NA	NA	NA	0	0.945 (0.808–1.106)	0.481
		Asian	1 (132)	1	0.032 (416)	0.034 (440)	NA	NA	NA	NA	NA	NA
IL1B	rs16944/T	All	1 (89)	10	0.372 (1583)	0.401 (2373)	32	0.886 (0.805–0.974)	**0.013**[h]	5	0.867 (0.787–0.956)	**0.004**[h]
		European	1 (89)	6	0.332 (932)	0.384 (1695)	47	0.852 (0.754–0.962)	**0.01**	8	0.820 (0.724–0.930)	**0.002**[h]

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Gene	Polymorphism/ minor allele[a]	Population[b]	Studies[c]		Minor allele frequency[d]		Family-based studies included			Family-based studies excluded		
			Fam	CC	Cases	Controls	I^2 (%)[e]	OR (95% CI)[f]	*P*(Z)[g]	I^2 (%)[e]	OR (95% CI)[f]	*P*(Z)[g]
		Asian	0	4	0.430 (651)	0.445 (678)	NA	NA	NA	0	0.942 (0.808–1.098)	0.444
MTHFR	rs1801131/C	All	1 (267)	10	0.308 (2428)	0.297 (3690)	38	1.065 (0.986–1.150)	0.11	25	1.090 (1.007–1.181)	**0.034**
		European	0	8	0.329 (1963)	0.309 (3203)	NA	NA	NA	0	1.106 (1.014–1.205)	**0.022**
		Asian	1 (267)	2	0.223 (465)	0.224 (487)	66	0.922 (0.689–1.234)	0.587	NA	NA	NA
MTHFR	rs1801133/T	All	3 (416)	16	0.348 (3874)	0.317 (5210)	52	1.121 (1.022–1.229)	**0.015**[h]	47	1.135 (1.065–1.210)	**0.0001**[h]
		European	2 (149)	11	0.329 (2533)	0.304 (3927)	57	1.107 (0.980–1.250)	0.102	52	1.127 (1.005–1.264)	**0.041**
		Asian	1 (267)	5	0.385 (1341)	0.360 (1283)	46	1.146 (1.033–1.272)	**0.010**	38	1.195 (1.065–1.340)	**0.002**[h]
PPP3CC	rs2461491/A	All	3 (694)	6	0.447 (6558)	0.434 (6527)	23	1.072 (1.022–1.239)	**0.004**[h]	0	1.070 (1.018–1.124)	**0.007**[h]
		European	0	1	0.549 (1870)	0.539 (2002)	NA	NA	NA	NA	NA	NA
		Asian	3 (694)	5	0.406 (4688)	0.388 (4525)	28	1.084 (1.025–1.146)	**0.005**[h]	0	1.083 (1.021–1.149)	**0.008**[h]
SLC6A4	5-NTR/allele 10	All	1 (266)	9	0.279 (2043)	0.302 (2336)	49	0.882 (0.804–0.967)	**0.007**[h]	54	0.883 (0.751–1.038)	0.133
		European	1 (266)	7	0.357 (1496)	0.388 (1687)	40	0.888 (0.807–0.978)	**0.016**[h]	48	0.882 (0.795–0.978)	**0.018**
		Asian	0	2	0.067 (547)	0.080 (649)	NA	NA	NA	NA	NA	NA
TP53	rs1042522/C	All	1 (163)	5	0.399 (1418)	0.369 (1410)	0	1.112 (1.001–1.236)	**0.048**[h]	0	1.130 (1.013–1.260)	**0.029**[h]
		European	1 (163)	2	0.278 (383)	0.281 (443)	0	0.969 (0.800–1.174)	0.749	NA	NA	NA
		Asian	0	3	0.443 (1035)	0.409 (967)	NA	NA	NA	0	1.181 (1.041–1.340)	**0.010**[h]

[a] Polymorphsims and their minor alleles were annotated on the SchizophreniaGene of the Schizophrenia Research Forum (http://www.schizophreniaforum.org/res/sczgene/default.asp).

[b] Meta-analyses were performed for samples from all populations, Europeans, and Asians, respectively.

[c] Numbers of Family-based (Fam, numbers of families are shown in the parentheses) and Case-Control (CC) association studies included in the meta-analyses.

[d] Minor allele frequencies based on case-control association data, numbers of cases and controls are shown in the parentheses.

[e] I^2 was employed to assess between-study heterogeneity. $I^2 > 50\%$ indicates evidence for significant between-study heterogeneity.

[f] Overall Odds Ratios (OR) and their 95% Confidence Intervals (CI) were based on the random-effects model if $I^2 = 50\%$, otherwise based on the fix-effects model ($I^2 < 50\%$).

[g] P(Z), *Z* test was used to detect the significance of the overall OR. *P*-values < 0.05 are shown in bold type.

[h] Associations remain significant after correction for the number of meta-analyses for each gene. Underlined are obvious different results (significant gene-wide associations appear or disappear) of meta-analyses including or excluding family-based association data in Caucasian and all populations. The results excluding family data are similar to those of "all excluding HWE deviations" in the Schizophrenia Research Forum. Note that meta-analyses were performed for polymorphisms with at least one family-based association study, except for those in the *DAOA* gene, which have been reported recently (Shi et al., Schizophr. Res. 2008; 98: 89–97). NA: not applicable.