ORIGINAL RESEARCH

## Associations between dopamine D2 receptor gene polymorphisms and schizophrenia risk: a PRISMA compliant meta-analysis

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**Objective:** To determine the relationships between dopamine D2 receptor gene polymorphisms and the risk of schizophrenia using meta-analysis.

**Method:** The PubMed, Embase, and China National Knowledge Infrastructure databases were searched to identify relevant literature published up to February 2016. The allele contrast model was used. Stata software was used for statistical analysis, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated to evaluate the associations between dopamine D2 receptor gene polymorphisms and the risk of schizophrenia. Meta-regression and publication bias, trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analyses were also performed.

**Results:** This meta-analysis included 81 studies. The rs1801028 and rs1799732 were associated with schizophrenia risk among Asians (P=0.04, OR =1.25, 95% CI =1.01–1.55; P<0.01, OR =0.76, 95% CI =0.63–0.92, respectively), while the rs6277 was associated with schizophrenia risk in Caucasians (P<0.01, OR=0.72, 95% CI =0.66–0.79). The rs1800497 was also associated with schizophrenia risk in population-based controls (P<0.01, OR =0.84, 95% CI =0.72–0.97). The rs6275, rs1079597, and rs1800498 were not associated with schizophrenia risk. In addition, meta-regression indicated that the controls may be sources of heterogeneity for the rs1801028 single-nucleotide polymorphism (SNP), while ethnicity may be sources of heterogeneity for the rs6277 SNP. Publication bias was significant for the rs1801028 SNP, and this result changed after the publication bias was adjusted using the trim-and-fill method.

**Conclusion:** This meta-analysis demonstrated that the rs1801028 may be a risk factor for susceptibility to schizophrenia among Asians, while the rs1799732 may be a protective factor for that population. Large-sample studies are necessary to verify the results of this meta-analysis. **Keywords:** dopamine D2 receptor, polymorphisms, schizophrenia

## Introduction

Schizophrenia is a severe mental disorder characterized by changes in its higher functions and deterioration of behavior, cognition, emotions, motivation, and perception, and is marked by socio-occupational dysfunction. Schizophrenia manifests with a wide variety of positive (auditory hallucinations and paranoid delusions), negative (affective flattening, anhedonia, and alogia), and cognitive (declined attention and memory) symptoms.<sup>1</sup> It is a complex multifactorial psychiatry disorder involving genetic and environmental factors, with a global lifetime prevalence of 0.5%–1%.<sup>2</sup>

Family, twin, and adoption studies have shown that genetic factors play a significant role in the pathogenesis of schizophrenia, with the heritability of schizophrenia being estimated at 70%–80%.<sup>3,4</sup> Additionally, Lee et al estimated that 23% of variation in

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 Commercial use of this work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution — Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nd/3.0). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php). liability to schizophrenia is captured by single-nucleotide polymorphisms (SNPs).<sup>5</sup> For schizophrenia, some genetic factors were shared with other psychiatric disorders (bipolar disorder, major depressive disorder, autism spectrum disorders, and attention-deficit/hyperactivity disorder),<sup>6</sup> and some genetic factors associated with its risk were overlapped with those associated with reproduction traits (eg, age at first birth).<sup>7</sup> In short, schizophrenia is highly polygenic.<sup>8</sup>

The dopamine hypothesis is one of the main ideas for explaining the etiology of schizophrenia.<sup>9</sup> There are several lines of evidence implicating dopamine D2 receptor (DRD2) as the main candidate gene for the risk of schizophrenia.<sup>10</sup> In humans, the DRD2 gene is located on chromosome 11 at q22-q23, extends over 270 kb, and has eight exons.<sup>11</sup> Associations between schizophrenia risk and four SNPs have been widely studied: rs1799732 (-141C Ins/Del), rs1801028 (311 Ser/Cys), rs1800497 (TaqIA), and rs6277 (C957T).<sup>12,13</sup> The rs1799732 SNP is located in the DRD2 promoter region and has been demonstrated to affect gene expression in vitro.14 The rs1801028 SNP is the missense variant 960C/G in exon 7 of the DRD2 gene<sup>15</sup> that can alter the physiology and function of the D2 receptor.12 The rs1800497 SNP was previously thought to be located in the DRD2 3'-untranslated region and was recently identified as being in exon 8 of the ankyrin repeat and kinase domain containing 1 (ANKK1) gene. This SNP has been considered to alter substrate-binding specificity.<sup>16</sup> The rs6277 SNP is located in exon 7 of the DRD2 gene and alters mRNA folding, leading to a decrease in mRNA stability and translation, and markedly changing dopamine-induced up-regulation of DRD2 expression.<sup>17</sup> In addition, associations between schizophrenia risk and the rs6275 (C939T), rs1079597 (TaqIB), and rs1800498 (TaqID) SNPs have been widely reported.18,19

While associations between *DRD2* gene polymorphisms and the risk of schizophrenia have been studied extensively, there are still some uncertainties about these associations. The present meta-analysis was therefore performed to further identify the associations between *DRD2* gene polymorphisms and schizophrenia risk. Meta-regression and publication bias, nonparametric trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analyses were also performed.

## Method

### Search strategy

The PubMed, Embase, and China National Knowledge Infrastructure databases were independently searched by two reviewers (He and Wu) to collect the literature related to associations between *DRD2* gene polymorphisms and schizophrenia risk. The last search update was performed in February 2016, and the following keywords were used in the literature search: "schizophrenia", "psychosis", "schizophrenic," "DRD2," "dopamine receptor 2," "dopamine receptor D2", "dopamine D2 receptor", "polymorphism", "variant", "variation", "allele", and "genotype". The species was limited to human. Moreover, the literature references in all of the included documents were searched to find more studies that were consistent with the eligibility criteria.

### Eligibility criteria

- 1. Studies that met the following inclusion criteria were included:
  - a) Research study with a case-control design.
  - b) Written in Chinese or English.
  - c) Investigation of the associations between *DRD2* gene polymorphisms and the risk of schizophrenia.
  - d) Providing sufficient allele or genotype distribution data of the included cases and controls.
- 2. Studies that met any of the following exclusion criteria were excluded:
  - a) Repetition of information in other literature.
  - b) A review, comment, or conference proceedings.
  - c) Results obtained in an animal model.
  - d) Series of reports or case reports.

### Research screening

The studies were first screened by browsing the titles and abstracts of the identified documents. Secondary screening was then performed by reading the full text of selected reports. Finally, data extraction and quality assessment were performed for the included studies.

### Data extraction

In our present study, two reviewers (He and Wu) independently extracted the following information from the included literature: first author, publication year, mean age of the cases and controls, country, ethnicity, source of controls, numbers of cases and controls, *DRD2* gene locus, diagnostic criteria of schizophrenia, genotyping method, and conformity with Hardy–Weinberg equilibrium (HWE) for the controls. If the allele or genotype distribution data of the cases and controls were not reported in the original articles, the corresponding author was contacted by mail to obtain this information.

### Quality assessment

Two authors (HH and HW) independently performed quality assessment using quality scoring criteria<sup>20</sup> based on criteria previously applied in observational studies for addressing genetic epidemiological issues, with the scores ranging from 0 points (worst) to 9 points (best) (Table S1). A study was classified as being of low quality when it scored <6 points. Sensitivity analysis was conducted by deleting these low-quality studies.

### Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strengths of the associations between *DRD2* gene polymorphisms and schizophrenia risk. Pooled effect sizes were calculated using the random-effects model. This model evaluated different underlying influences considering both within- and between-study variations, which provided the advantage of accommodating diversity between studies and yielding a more conservative estimate of the assessed effect.<sup>21</sup> The present study used an allele comparison model because this maximized the number of included studies.

Cochran's Q statistic was used to estimate the degree of heterogeneity in the included studies. Heterogeneity was considered to be high when the *P*-value was <0.1. The heterogeneity was also quantified using the  $l^2$  statistic and was considered high when  $l^2>50\%$ . Based on clinical knowledge, the ethnicity and source of controls were considered to be responsible for heterogeneity, and so these parameters were set as covariates in the meta-regression. A subgroup analysis was also conducted. Publication bias was analyzed using Begg's funnel plots. An asymmetrical funnel plot indicated the presence of significant publication bias. The symmetry of Begg's funnel plots was judged using Egger's linear regression, and a *P*-value of <0.05 was considered to indicate that the funnel plots were significantly asymmetrical. The trim-and-fill method was used to correct for publication bias and also to assess the impact of publication bias on the results.

Sensitivity analysis was used to assess both the potential impact of single studies on the pooled effect size and the impact of removing low-quality studies on the obtained results. Cumulative analysis by publication year was used to explore temporal trends in the results. Finally, the fail-safe number of negative studies that would be required to nullify (ie, make P>0.05) the effect size was calculated.

All of the statistical analyses were conducted using Stata software, version 12.0 (Stata Corporation, College Station, TX, USA).

### Results

### Study characteristics

A flow chart of the study selection procedure is shown in Figure 1. Briefly, 1,267 studies were identified after eliminating 304 duplications. After reviewing the abstracts or reading full texts carefully according to eligibility criteria,

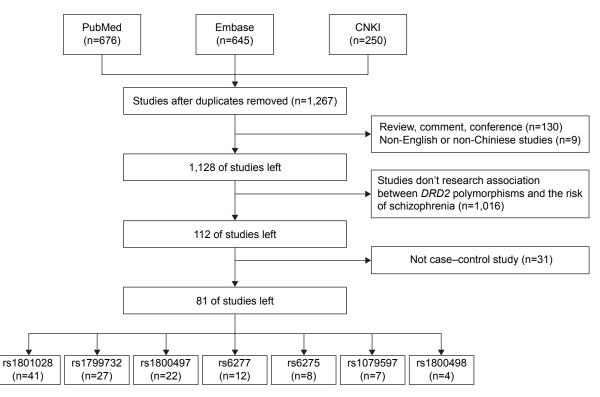


Figure I Flow diagram of the study selection process.

Abbreviations: CNKI, China National Knowledge Infrastructure; DRD2, dopamine D2 receptor.

a further 1,186 studies were excluded. Finally, 81 studies were identified for exploring the associations between *DRD2* gene polymorphisms and susceptibility to schizophrenia in a meta-analysis.

The main features of the included studies are listed in Table 1. The 81 studies comprised 45 studies focused on Caucasians, 34 on Asians, and 2 on mixed populations. The distributions of genotypes in the control groups deviated from HWE for the rs1801028, rs1800497, and rs1800498 SNPs in seven studies.<sup>11,22–27</sup> The quality assessment revealed that four studies were of low quality.<sup>26,28–30</sup>

# Association between the rs1801028 (311 Ser/Cys) and schizophrenia risk

A meta-analysis of 42 case–control studies (9,771 cases and 11,900 controls) revealed that the variant allele G (Cys) was associated with increased schizophrenia risk in all populations (P=0.009, OR =1.23, 95% CI=1.05–1.44; Figure 2A). The fail-safe number was 104.52, and there was moderate heterogeneity (P=35%). Meta-regression indicated that the source of controls may have been responsible for this heterogeneity (P<0.01). The subgroup analysis, whose results are presented in Table 2, revealed that the G allele was associated with increased susceptibility to schizophrenia in Asians (P=0.04, OR =1.25, 95% CI=1.01–1.55) and hospital-based controls (P<0.01, OR =1.91, 95% CI =1.39–2.61).

Sensitivity analysis indicated that no single study qualitatively changed the pooled ORs (Figure 3). Removing the low-quality studies<sup>26,29,30</sup> did not change the results. Four of the studies deviated from HWE,<sup>22,24,26,27</sup> but removing them from the analysis did not change the results. Cumulative analysis by publication year confirmed that pooled ORs and 95% CIs were stable and that there was a reliable temporal trend in the results from 1996<sup>31</sup> (Figure 4).

In terms of publication bias, Egger's linear regression showed that the funnel plots were asymmetrical (P=0.023). The trim-and-fill method suggested that eight studies were missing, and the results for the association between the rs1801028 SNP and schizophrenia changed after replacing the data for these eight studies (OR =1.063, 95% CI =0.892–1.266; Figure 5). This indicates that our analyses were not stable and that future research is very likely to produce different results.

# Association between the rs6277 (C957T) and schizophrenia risk

A meta-analysis of 12 case–control studies (2,919 cases and 3,600 controls) revealed that the variant allele T was associated with decreased schizophrenia risk (P=0.002, OR =0.80, 95% CI =0.69–0.92; Figure 2B). The failsafe number was 91.00, there was high heterogeneity ( $I^2$ =58.5%), and meta-regression indicated that ethnicity may have been responsible for this heterogeneity (P<0.01). A subgroup analysis based on ethnicity showed that the T allele was associated with decreased susceptibility to schizophrenia in Caucasians (P<0.01, OR =0.72, 95% CI =0.66–0.79).

Cumulative analysis by publication year did not show a reliable temporal trend. Sensitivity analysis showed that no single study qualitatively changed the pooled ORs. In terms of publication bias, Egger's linear regression showed that the funnel plots were symmetrical (P=0.119).

# Association between the rs1799732 (-141C Ins/Del) and schizophrenia risk

A meta-analysis of 27 case-control studies (6,770 cases and 7,347 controls) demonstrated that the rs1799732 SNP was not associated with schizophrenia risk (P=0.26, OR =0.91, 95% CI =0.78-1.07; Figure 2C). There was high heterogeneity ( $l^2=76\%$ ), and meta-regression indicated that neither ethnicity (P=0.119) nor the source of controls (P=0.452) was responsible for this heterogeneity. A subgroup analysis based on ethnicity showed that the variant type (-141C Del) was associated with decreased susceptibility to schizophrenia in Asians (P=0.004, OR =0.76, 95% CI =0.63–0.92). A subgroup analysis based on the source of controls found no significant association between the rs1799732 SNP and schizophrenia risk in population-based controls or hospital-based controls. In terms of publication bias, Egger's linear regression showed that the funnel plots were symmetrical (P=0.173).

# Association between the rs1800497 (TaqIA) and schizophrenia risk

A meta-analysis of 22 case–control studies (4,017 cases and 4,209 controls) demonstrated that the rs1800497 SNP was not associated with schizophrenia risk (P=0.06, OR =0.87, 95% CI =0.75–1.01; Figure 2D). There was high heterogeneity ( $l^2$ =72%), and meta-regression indicated that neither ethnicity (P=0.612) nor the source of controls (P=0.372) was responsible for this heterogeneity. A subgroup analysis based on the source of controls revealed that the variant allele A (A2) was associated with decreased schizophrenia risk in population-based controls (P<0.01, OR =0.84, 95% CI =0.72–0.97). A subgroup analysis based on ethnicity revealed that the rs1800497 SNP was also not associated with susceptibility to

Author	Year	Country	Ethnicity	No of	No of sample	Control	Mutation	Criteria	SNP	HWE	Quality
				Cases	Controls	sources	analysis method			(P-value)	score
Caprini et al <sup>28</sup>	2011	Scandinavia	Caucasians	837	1,471	PB	1	ICD-10 + DSM-III-R + DSM-IV	TaqID	Yes	S
Dollfus et al <sup>35</sup>	1996	France	Caucasians	62	161	PB	PCR-RFLP	DSM-III-R	TaqIA	Yes	8
Luo <sup>24</sup>	2008	China	Asians	211	201	PB	Direct sequencing	DSM-IV	-141C Ins/Del	Yes	9
Watanabe et al <sup>36</sup>	2012	Japan	Asians	648	664	PB	TaqMan	DSM-IV	Ser 311 Cys	Yes	7
Crawford et al <sup>31</sup>	1996	America	Caucasians	84	81	HB	Direct sequencing	DSM-III-R	Ser 311 Cys	Yes	9
Dubertret et al <sup>13</sup>	2010	France	Caucasians	50	50	PB	PCR	DSM-IV	TaqlB	I	I
									TaqlA	Yes	7
Himei et al <sup>37</sup>	2002	Japan	Asians	190	103	PB	PCR-RFLP	DSM-IV	Ser 311 Cys	Yes	7
									-141C Ins/Del	Yes	7
Jonsson et al <sup>87</sup>	1996	Sweden	Caucasians	118	78	PB	PCR	DSM-III-R	TaqIA	Yes	7
Kunii et al <sup>62</sup>	2014	Japan	Asians	12	12	PB	PCR-RFLP	DSM-IV	TaqIA	Yes	8
Srivastava et al <sup>4</sup>	2010	India	Caucasians (Indians)	233	224	PB	PCR-RFLP	DSM-IV	-141C Ins/Del	Yes	8
									TaqIA	Yes	8
									TaqlB	I	I
									Ser311Cys	Yes	8
Arinami et al <sup>47</sup>	1996	Japan	Asians	136	279	PB	PCR	ICD-10 + DSM-III-R	Ser 311 Cys	Yes	7
Arinami et al <sup>57</sup>	1 99 T	Japan	Asians	260	312	PB	PCR-RFLP	DSM-III-R	-141C Ins/Del	Yes	7
Aslan et al <sup>23</sup>	2010	Turkey	Caucasians	66	601	PB	PCR	DSM-IV	TaqIA	No	9
Behravan et al <sup>l l</sup>	2008	Iran	Caucasians	38	63	PB	PCR	DSM-IV	TaqlB	Yes	7
									TaqIA	No	6
Betcheva et al <sup>1</sup>	2009	Bulgaria	Caucasians	255	556	PB	PCR	DSM-IV	C957T	Yes	œ
									С939Т	Yes	8
Breen et al <sup>63</sup>	666 I	England	Caucasians	439	437	PB	PCR	DSM-III-R + DSM-IV	-141C Ins/Del	Yes	7
Chen et al <sup>38</sup>	1996	China	Asians	114	88	PB	PCR	DSM-III-R	Ser311Cys	Yes	9
Cordeiro et al <sup>14</sup>	2009	Brazil	Mixed	229	733	PB	I	DSM-IV	-141C Ins/Del	Yes	8
Cordeiro and Vallada <sup>16</sup>	2014	Brazil	Mixed	235	834	PB	PCR	DSM-IV	TaqIA	Yes	8
Dubertret et al <sup>15</sup>	2004	France	Caucasians	103	83	PB	PCR-RFLP	DSM-IV	-141C Ins/Del	Yes	7
									TaqIB	I	I
									TaqID	I	I
									Ser311Cys	Yes	7
									TaqIA	Yes	7
Dubertret et al <sup>13</sup>	2010	France	Caucasians	144	142	PB	TaqMan	DSM-IV	TaqlA	Yes	8
									C957T	I	I
									Ser311Cys	Yes	œ
									-141C Ins/Del	Yes	œ
									TaqID	I	I
									TaqlB	I	I
Fan et al <sup>39</sup>	2010	China	Asians	421	404	PB	PCR	DSM-IV	Ser 311 Cys	Yes	7
									C957T	Yes	7
									C939T	Yes	7
al <sup>40</sup>	2011	Russia	Caucasians	366	387	PB	PCR	ICD-10	Ser311Cys	Yes	œ
Gupta et al <sup>41</sup>	2009	India	Caucasians (Indians)	254	225	PB	PCR	DSM-IV	-141C Ins/Del	Yes	œ

Cates         Controls         sources         analysismethod           1         2006         Finland         Cancasiane         88         384         PS         PCR         DSH1V           1         2006         Finland         Cancasiane         13         314         PS         PCR         DSH1V           1         2006         Finland         Cancasiane         13         314         PS         PCR         DSH1V           1         2006         Finlan         Cancasiane         13         314         PS         PCR         DSH1V           2001         Spain         Adams         13         134         PS         PCR         DSH1V           2006         India         Cancasiane         13         134         PB         PCR         DSH1V           2001         Turleey         Cancasiane         131         184         PB         PCR         DSH1V           2003         Finland         Cancasiane         131         184         PB         PCR         DSH1V           2004         Finland         Cancasiane         131         134         PB         PCR         DSH1V           2005         Finland	Author	Year	Country	Ethnicity	No of	No of sample	Control	Mutation	Criteria	SNP	HWE	Quality
etal         300         Finand         Constant         18         344         PE         CCR         DSM-IV         CSPT           etal         300         Finand         Canciante         18         344         PE         CCR         DSM-IV         CSPT           etal         300         Finand         Canciante         18         344         PE         CCR         DSM-IV         Serial Constante         CSPT           etal         200         Finan         Canciante         13         346         PE         CCR         DSM-IV         Serial Constante         CSPT           etal         200         Finan         Canciante         13         346         PE         CCR         DSM-IV         Serial Constante         CSPT           etal         200         Financ         13         346         PE         CCR         DSM-IV         Serial Constante         CSPT           etal         2001         Turkey         Canciante         101         145         PE         CCR         DSM-IV         Serial Constante         CSPT           etal         2001         Turkey         Canciante         101         145         PE         DSM-IV         DSM-IV					Cases		sources	analysis method			(P-value)	score
eel <sup>1</sup> 200         Filment         283         File         C877           eel <sup>1</sup> 200         Spin         Auman         281         File         C877           eel <sup>1</sup> 200         Spin         Auman         281         284         C877           eel <sup>1</sup> 200         Spin         Auman         281         284         C877           eel <sup>1</sup> 200         Spin         Auman         21         284         C877         C937           eel <sup>1</sup> 200         Spin         Auman         21         264         DSH-M         SeiTIC           eel <sup>1</sup> 2005         Spin         Auman         21         264         PC         DSH-M         SeiTIC           eel <sup>1</sup> 2005         File         PC         DSH-M         DSH-M         SeiTIC         SeiTIC           eel <sup>1</sup> 2006         File         PC         DSH-M         DSH-M         SeiTIC           eel <sup>1</sup> 2006         File         PC         DSH-M         DSH-M         SeiTIC           eel <sup>1</sup> 2006         File         PC         DSH-M         DSH-M         SeiTIC           eel <sup>1</sup> </td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Ser311Cys</td> <td>Yes</td> <td>8</td>										Ser311Cys	Yes	8
etal         203         Final         Curation         28         34         PC         Constant         23         Constant         23         Constant         23         Constant         23										C957T	Yes	8
etal         2006         Final         Cuestant         18         384         18         PCR         DSM/V         C557           etal         2006         Span         Asins         21         20         Par         SSM/V         SM/V         SSM/V         SSM/V         SSM/V         SSM/V         SM/V										C939T	Yes	8
41         197         Ppin         Adams         70         101         HB         PCR         DSM-UIR         Se311Cys         Se311Cys </td <td>Hanninen et al<sup>64</sup></td> <td>2006</td> <td>Finland</td> <td>Caucasians</td> <td>188</td> <td>384</td> <td>PB</td> <td>PCR</td> <td>DSM-IV</td> <td>C957T</td> <td>Yes</td> <td>8</td>	Hanninen et al <sup>64</sup>	2006	Finland	Caucasians	188	384	PB	PCR	DSM-IV	C957T	Yes	8
etal <sup>6</sup> 2006         Spin         Curstants         13         34         PB         PCR         DSM/V         C577           1         2001         ppan         Adims         21         20         PB         PCR         DSM/V         S9311Cys           1         2001         ppan         Adims         51         13         24         201         PCR         DSM/V         S9311Cys           1         2003         ppan         Adims         51         13         26         PB         PCR         DSM/V         S9311Cys           1         2006         India         Carcians         73         20         PB         PCR         DSM/V         S9311Cys           1         2001         Turkuy         Carcians         21         14         PB         PCR         DSM/V         S9311Cys           1         2005         Australia         201         Turkuy         Carcians         213         14         PCR         DSM/V	Harano <sup>42</sup>	1997	Japan	Asians	70	101	HB	PCR	DSM-III-R	Ser311Cys	Yes	9
0         2001         Ippan         Asian         241         201         PB         PCR         DSH-IV         Sed11Cys           11         2003         Jppan         Asians         51         53         HB         PCR         DSH-IV         Sed311Cys           11         2003         Jppan         Asians         51         53         HB         PCR         DSH-IV         Sed311Cys           11         2005         India         Caucisation         101         145         PB         PCR         DSH-IV         Se311Cys           11         2006         India         Caucisation         101         145         PB         PCR         DSH-IV         Se311Cys           11         2006         India         Caucisation         101         145         PB         PCR         DSH-IV         Se311Cys           12         2011         Turkley         Caucisation         101         145         PB         PCR         DSH-IV         Se311Cys           12         2011         Turkley         Caucisation         121         PB         PCR         DSH-IV         Se311Cys           12         2014         PR         PCR         DSH-IV </td <td>Hoenicka et al<sup>65</sup></td> <td>2006</td> <td>Spain</td> <td>Caucasians</td> <td>131</td> <td>364</td> <td>PB</td> <td>PCR</td> <td>DSM-IV</td> <td>C957T</td> <td>Yes</td> <td>7</td>	Hoenicka et al <sup>65</sup>	2006	Spain	Caucasians	131	364	PB	PCR	DSM-IV	C957T	Yes	7
1         1	Hori et al <sup>43</sup>	2001	Japan	Asians	241	201	PB	PCR	DSM-IV	Ser311Cys	Yes	7
(H)         203         PID         PCR_RLP         DSM-IV         Secility										-141C Ins/Del	Yes	7
at         199         Swelen         Curcatans         123         149         PCR         DSM-III.R         s-141C include           at at         997         Jawa         Curcatans         73         126         HB         PCR         DSM-III.R         s-141C include           at at         997         Jawa         Curcatans         73         126         HB         PCR         DSM-III.R         s-141C include           at         2006         Inda         Curcatans         73         60         PB         PCR         DSM-III.R         s-141C include           at         2001         Turkey         Caucatans         73         60         PB         PCR         DSM-III.R         s-141C include           at         2003         Famic         Caucatans         13         146         PR         DSM-III.R         S-311C/5           at         1794         Famic         Caucatans         151         145         HB         PCR         DSM-III.R         S-311C/5           at         1796         Famic         Caucatans         151         145         HB         PCR         DSM-III.R         S-311C/5           at         170         145         F	lwata et al <sup>44</sup>	2003	Japan	Asians	51	63	PB	PCR-RFLP	DSM-IV	Ser311Cys	Yes	7
etal         203         Swelen         Cancains         173         236         HB         PCR         DSF-HIJR         Ser31(Cs           1         106         rigin         2037         78         112         78         FCR         DSF-HIJR         Ser31(Cs           1         201         Turkey         Cancasins         73         60         PB         PCR         DSF-HJV         Ser31(Cs           1         2011         Turkey         Cancasins         73         60         PB         PCR         DSF-HJV         C9377           1         208         Spain         Cancasins         113         184         PB         PCR         DSF-HJV         C9377           1         208         Karsnia         Cancasins         113         144         PB         -         143(Lins/Del           1         198         PCR         DSF-HJV         DSF-HJV         C9377         143(Lins/Del           1         198         PCR         DSF-HJV         DSF-HJV         C9377         146(Lins/Del           1         198         PCR         DSF-HJV         DSF-HJV         DSF-HJV         146(Lins/Del           1         198         PCR	Jonsson et al <sup>66</sup>	6661	Sweden	Caucasians	129	179	ΗB	PCR	DSM-III-R	-141C Ins/Del	Yes	9
a c aff         197         pan         Asans         78         112         PB         PCR         RDC - DSN-IV         Ser31Cps           e aff         2001         Turkey         Caucasines (indians)         101         145         PB         PCR         DSN-IV         Ser31         Ser31           e aff         2001         Turkey         Caucasines         73         60         PB         PCR         DSN-IV         Caucasine         C9337           e aff         2001         Turkey         Caucasine         113         184         PB          DSN-IV         C337         C337           e aff         199         France         Caucasine         131         184         PB          DSN-IV         Tadia           e aff         199         Rusia         Laucasine         131         344         PB         -         DSN-IV         DSN-IV         Tadia           e atf         199         Rusia         Caucasine         131         344         PB         PCR         DSN-IV	Jonsson et al <sup>45</sup>	2003	Sweden	Caucasians	173	236	ΕB	PCR	DSM-III-R	Ser 311 Cys	Yes	9
cal         2006         Inda         Carasians (Indians)         101         145         PB         PCR         DSM-IV         C9577           ecal <sup>al</sup> 2001         Turkey         Carasians         73         60         PB         PCR         DSM-IV         73         61         HB         PCR         DSM-IV         7461         C9577           ecal <sup>al</sup> 2008         Spain         Carasians         13         184         PB         PC         DSM-IV         7461         TagA           etal <sup>al</sup> 2008         Russia         Carasians         13         184         PB         PC         DSM-IV         141C Ins/De           etal <sup>al</sup> 2008         Russia         Carasians         13         148         PC         DSM-IV         141C Ins/De           etal <sup>al</sup> 2008         Russia         Carasians         13         148         PC         DSM-IV         141C Ins/De           etal <sup>al</sup> 1996         Enrope         Carasians         13         148         PCR         DSM-IV         141C Ins/De           a <sup>al</sup> 1996         Bpan         Asians         13         154         PB         PCR         DSM-IV	Kaneshima et al <sup>46</sup>	1997	Japan	Asians	78	112	PB	PCR	RDC + DSM-IV	Ser311Cys	Yes	7
n         2011         Turkey         Caucasins         73         60         PB         PCR.RELP         DSM-V         -141C ins/Del           cali         2008         Spain         Caucasins         73         60         PB         PCR         DSM-V         -141C ins/Del           cali         2008         Spain         Caucasins         113         184         PB         -         -141C ins/Del           cali         2005         Australia         Caucasins         151         145         HB         PCR         DSM-V         -141C ins/Del           vect ll*         2005         Australia         Caucasins         151         145         HB         PCR         DSM-V         -141C ins/Del           vect ll*         2005         Spain         Caucasins         151         145         HB         PCR         DSM-V         -141C ins/Del           alt         1996         Expent         Caucasins         121         PB         PCR         DSM-V         -141C ins/Del           alt         1998         PCR         DSM-V         DSM-V         DSM-V         -141C ins/Del           alt         1998         PCR         DSM-V         DSM-V         DSM-V	Kukreti et al²	2006	India	Caucasians (Indians)	101	145	PB	PCR	DSM-IV	C957T	Yes	8
0         2011         Turkey         Caucasians         23         60         PB         PCR.RFLP         DSN-IV         -14/C Ins/Del           etal <sup>#</sup> 2008         Spain         Caucasians         243         291         HB         PCR         DSN-IV         -14/C Ins/Del           etal <sup>#</sup> 1994         France         Caucasians         113         194         PB         -         -         -14/C Ins/Del           etal <sup>#</sup> 1998         Ergland         Caucasians         113         144         PB         PCR         DSN-IV         -14/C Ins/Del           etal <sup>#</sup> 1998         Ergland         Caucasians         151         145         HB         PCR         DSN-IV         -14/C Ins/Del           etal <sup>#</sup> 1998         Ergland         Caucasians         151         145         PR         PCR         DSN-IV         -14/C Ins/Del           etal <sup>#</sup> 1998         Ergen         Caucasians         170         121         PB         PCR         DSN-IV         -14/C Ins/Del           a <sup>17</sup> 1998         Ergen         Caucasians         137         2007         Spain         -44/C Ins/Del           a <sup>18</sup> 2007<										C939T	Yes	8
ec alle         2008         Spain         Curcaians         243         291         HB         PCR         DSN-IV         TadiA           tall         1934         France         Curcaians         113         184         PB          DSN-IIV         -141C ins/Del           et all         1936         Austrains         151         146         PB          DSN-IV         -141C ins/Del           et all         2008         Austrains         151         134         PB         PCR         DSN-IV         -141C ins/Del           vet all         2008         Russin         151         134         PB         PCR         DSN-IV         -141C ins/Del           all         1936         Jpan         Asians         151         121         PB         PCR         DSN-IV         -141C ins/Del           all         1936         Jpan         Asians         170         121         PB         PCR         DSN-IV         -141C ins/Del           all         1936         Jpan         Asians         170         121         PB         PCR         DSN-IV         -141C ins/Del           all         1936         Jpan         Caucasians         123 <td>Kurt et al<sup>67</sup></td> <td>2011</td> <td>Turkey</td> <td>Caucasians</td> <td>73</td> <td>60</td> <td>PB</td> <td>PCR-RFLP</td> <td>DSM-IV</td> <td>-141C Ins/Del</td> <td>Yes</td> <td>7</td>	Kurt et al <sup>67</sup>	2011	Turkey	Caucasians	73	60	PB	PCR-RFLP	DSM-IV	-141C Ins/Del	Yes	7
tat <sup>11</sup> 1994         France         Curcasians         113         184         PB          DSM-II-R         Sea311C/s           et allo         2005         Australia         Caucasians         13         144         PB          DSM-IV           vet allo         2005         Australia         Caucasians         13         14         PB          DSM-IV           vet allo         2008         Russia         Caucasians         13         14         PB         PCR         DSM-IV          141C Ins/Del           all         1936         Epgan         Caucasians         13         14         PB         PCR         DSM-IV          -141C Ins/Del           all         1938         Epan         Asins         170         121         PB         PCR         DSM-IV          -141C Ins/Del           all         1938         Epon         Caucasians         13         121         PB         PCR         DSM-IV          -141C Ins/Del           all         1938         Europe         Caucasians         137         235         PB         PCR.RELP         DSM-IV          -141C Ins/Del<	Lafuente et al <sup>68</sup>	2008	Spain	Caucasians	243	291	НВ	PCR	DSM-IV	TaqIB	Yes	7
tail         194         France         Caucasians         113         184         PB          141 ClasTole           1         198         France         Caucasians         151         145         HB         PC         DSM-III.R         55371           1         1998         England         Caucasians         151         145         HB         PCR         DSM-III.R         55371           vectal <sup>10</sup> 2008         Russia         Caucasians         151         145         PB         PCR         DSM-III.R         -141C Ins/Del           1         1998         Japan         Caucasians         151         145         PB         PCR         DSM-III.R         -141C Ins/Del           1         1998         Japan         Asians         151         121         PB         PCR         DSM-III.R         -141C Ins/Del           1         1998         Japan         Asians         151         121         PB         PCR         DSM-III.R         -141C Ins/Del           1         1998         Japan         Asians         137         230         231         23         231         23         231         23         231         23         231<										TagIA	Yes	7
cal <sup>8</sup> 1994         France         Caucasians         113         184         PB         -         DSN-IL         Ser31Cys           etal <sup>8</sup> 2005         Australia         Caucasians         134         148         PB         PCR         DSN-IL         Ser31Cys           vetal <sup>96</sup> 2008         Russia         Caucasians         131         345         HB         PCR         DSN-IL         DSN-IL         Ser31Cys           vetal <sup>96</sup> 2008         Russia         Caucasians         153         121         PB         PCR         DSN-IL         Cay577           al <sup>1</sup> 1996         Jpan         Asians         153         121         PB         PCR         DSN-IL         Cay577           al <sup>1</sup> 1996         Jpan         Asians         153         121         PB         PCR         DSN-IL         Cay577           al <sup>1</sup> 1996         Jpan         Asians         170         121         PB         PCR         DSN-IL         Cay17         Cay577           al <sup>1</sup> 1996         Jpan         Asians         170         121         PB         PCR         DSN-IL         Cay11         Cay13      <										-141C Ins/Del	Yes	7
eral <sup>10</sup> 2005         Australia         Carcasians         154         148         PB         PCR         DSN-IV         C957T         C957T           vetal <sup>10</sup> 2008         Kussia         Carcasians         151         145         HB         PCR         DSN-IV         DSN-IV         DSN-IV         C957T           vetal <sup>10</sup> 2008         Kussia         Carcasians         151         145         HB         PCR         DSN-IV         DSN-IV         C957T         C957T           a <sup>11</sup> 1996         Jpan         Asians         153         121         PB         PCR         DSN-IV         C957T         C957T           a <sup>11</sup> 1996         Jpan         Asians         153         121         PB         PCR         DSN-IV         C957T         C957T           a <sup>11</sup> 1996         Jpan         Asians         170         121         PB         PCR         DSN-IV         C957T         C957T           a <sup>11</sup> 2000         Spain         Carcasians         119         165         DSN-IV         DSN-IV         DSN-IV         C957T           a <sup>12</sup> 2000         Spain         Carcasians         119	Laurent et al <sup>48</sup>	1994	France	Caucasians	113	184	PB	I	DSM-III-R	Ser311Cys	Yes	9
198         Engand         Caucasians         151         145         HB         PCR         DSM-IV         DSM-IV         DSM-IV         DSM-IV         C937           vecal <sup>10</sup> 2008         Russia         Caucasians         311         344         PB         PCR         DSM-IV         C937         C937           a <sup>11</sup> 1996         Japan         Asians         153         121         PB         PCR         DSM-IV         C937         C9397           a <sup>11</sup> 1996         Japan         Asians         153         121         PB         PCR         DSM-IV         C937         C9397           a <sup>11</sup> 2007         Spain         Caucasians         119         165         PB         PCR         DSM-IV         -141C         Ins/Del           a <sup>11</sup> 2001         Spain         Caucasians         1870         2002         PB         PCR         DSM-IV         -141C         Ins/Del           a <sup>12</sup> 1996         Europe         Caucasians         237         255         HB         PCR         DSM-IV         -141C         Ins/Del           a <sup>12</sup> 1996         Europe         Caucasians         237         25	Lawford et al <sup>10</sup>	2005	Australia	Caucasians	154	I 48	PB	PCR	DSM-IV	C957T	Yes	7
vec al <sup>16</sup> 2008         Russia         Caucasians         311         364         PB         PCR         DSN-IV         C9571           al <sup>1</sup> 1996         Japan         Asians         153         121         PB         PCR         DSN-IV         C9371           al <sup>1</sup> 1996         Japan         Asians         153         121         PB         PCR         DSN-IV         C9371           al <sup>1</sup> 1996         Japan         Asians         153         121         PB         PCR         DSN-IV         C141C Ins/Del           2         2001         Spain         Caucasians         119         165         PB         PCR-RFLP         DSN-IV         -141C Ins/Del           2         2001         Spain         Caucasians         1370         2.002         PB         PCR-RFLP         DSN-IV         -141C Ins/Del           2         2010         Spain         Caucasians         2.002         PB         PCR         DSN-IV         -141C Ins/Del           2         2010         Spain         Caucasians         2.002         PB         PCR         DSN-IV         -141C Ins/Del           2         1996         Europe         Cauca	Li et al <sup>70</sup>	1998	England	Caucasians	151	I 45	HB	PCR	DSM-IV + DSM-III-R	-141C Ins/Del	Yes	9
196         Japan         Asians         153         121         PB         PCR         DSM-IV         C33311C/s           1988         Japan         Asians         170         121         PB         PCR         DSM-IV	Monakhov et al <sup>69</sup>	2008	Russia	Caucasians	311	364	PB	PCR	DSM-IV	C957T	Yes	7
196         Japan         Asians         153         121         PB         PCR         DSM-IV         TaqIA           2007         Spain         Asians         170         121         PB         PCR         DSM-IV         587-311Cys         587-311Cys           2007         Spain         Caucasians         119         165         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2010         Spain         Caucasians         288         4.21         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         2.88         4.21         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         2.3         2.55         HB         PCR-RFLP         DSM-IV         -141C Ins/Del           1996         Europe         Caucasians         273         255         HB         PCR         DSM-IV         -141C Ins/Del           1998         Europe         Caucasians         273         255         HB         PCR         DSM-IV         -141C Ins/Del           1998         German         Caucasians         260         290         PR         PCR										C939T	Yes	7
19%         Japan         Asians         153         121         PB         PCR         DSN-IV         Ser311Cys           1998         Japan         Asians         170         121         PB         PCR         DSN-IV         -141C Ins/Del           2007         Spain         Caucasians         119         165         PB         PCR-RFLP         DSN-IV         -141C Ins/Del           2010         Spain         Caucasians         288         4.21         PB         PCR-RFLP         DSN-IV         -141C Ins/Del           2010         Spain         Caucasians         288         4.21         PB         PCR-RFLP         DSN-IV         -141C Ins/Del           2010         Spain         Caucasians         233         213         255         HB         PCR         DSN-IV         -141C Ins/Del           1996         Europe         Caucasians         273         255         HB         PCR         DSN-III-R         Ser311Cys           1998         Europe         Caucasians         260         290         PB         PCR         DSN-III-R         Ser311Cys           1998         Fernoma         Caucasians         50         51         PB         PCR         DS										TaqIA	Yes	7
1998         Japan         Asians         170         121         PB         PCR         DSM-IV         -141C Ins/Del           2007         Spain         Caucasians         119         165         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2010         Spain         Caucasians         119         165         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2010         Spain         Caucasians         288         421         PB         PCR         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         233         235         HB         PCR         DSM-II         -141C Ins/Del           1996         Europe         Caucasians         273         235         HB         PCR         DSM-II         -141C Ins/Del           1998         Europe         Caucasians         260         290         PB         PCR         DSM-II         -141C Ins/Del           1998         Europe         Caucasians         260         290         PB         PCR         DSM-II         -141C Ins/Del           1999         America         Caucasians         260         290         PB         PCR         DSM-II	Ohara et al <sup>3</sup>	966	Japan	Asians	153	121	PB	PCR	DSM-IV	Ser311Cys	Yes	7
2007         Spain         Caucasians         119         165         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2010         Spain         Caucasians         288         421         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2010         Spain         Caucasians         288         421         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         1.870         2.002         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           1996         Europe         Caucasians         273         255         HB         PCR         DSM-III-R         Ser311Cys           1998         German         Caucasians         273         255         HB         PCR         DSM-III-R         Ser311Cys           1998         German         Caucasians         260         290         PB         PCR         DSM-III-R         Ser311Cys           1999         America         Caucasians         260         290         PB         PCR         DSM-III-R         Ser311Cys           1999         America         Caucasians         50         51         PB         PCR         D	Ohara et al <sup>71</sup>	1998	Japan	Asians	170	121	PB	PCR	DSM-IV	-141C Ins/Del	Yes	8
2010         Spain         Caucasians         288         4.21         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         1,870         2.002         PB         TaqMan         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         2,373         2,55         HB         PCR         DSM-IV         -141C Ins/Del           1996         Europe         Caucasians         273         255         HB         PCR         DSM-III-R         Ser311Cys           1998         Europe         Caucasians         260         290         PB         PCR         DSM-III-R         Ser311Cys           1999         America         Caucasians         260         290         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         106         106         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         103         97         PB         PCR         DSM-IV         -141C Ins/Del           1997         Japan         Asians         103         97         PB         PCR         DSM-IV         -141C Ins/Del	Parsons et al <sup>25</sup>	2007	Spain	Caucasians	611	165	PB	PCR-RFLP	DSM-IV	-141C Ins/Del	Yes	7
2010         Spain         Caucasians         288         4.21         PB         PCR-RFLP         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         1,870         2,002         PB         TaqMan         DSM-IV         -141C Ins/Del           2008         Europe         Caucasians         1,870         2,002         PB         TaqMan         DSM-IV         -141C Ins/Del           1996         Europe         Caucasians         273         255         HB         PCR         DSM-IILR         Ser311Cys           1998         Europe         Caucasians         273         255         HB         PCR         DSM-IILR         Ser311Cys           1999         America         Caucasians         260         290         PB         PCR         DSM-IILR         Ser311Cys           1995         Japan         Asians         106         106         PCR         DSM-IILR         Ser311Cys           2011         Japan         Asians         106         106         PCR         DSM-IILR         Ser311Cys           2011         Japan         Asians         106         106         PCR         DSM-IV         COB-100         I-141C Ins/Del										TaqIA	No	9
2008         Europe         Caucasians         1,870         2,002         PB         TaqMan         DSN-IV         Ser311Cys           1946         Europe         Caucasians         273         255         HB         PCR         DSN-III-R         Ser311Cys           1948         Europe         Caucasians         273         255         HB         PCR         DSN-III-R         Ser311Cys           1948         Europe         Caucasians         273         250         PB         PCR         DSN-III-R         Ser311Cys           1948         German         Caucasians         260         290         PB         PCR         DSN-III-R         Ser311Cys           1994         Japan         Asians         106         106         PB         PCR         DSN-III-R         Ser311Cys           2011         Japan         Asians         106         106         PB         PCR         DSN-III-R         Ser311Cys           2011         Japan         Asians         106         106         PR         PCR         DSN-IV         C9577           2011         Japan         Asians         52         26         PB         PCR         DSN-IV         C9577 <t< td=""><td>Saiz et al<sup>72</sup></td><td>2010</td><td>Spain</td><td>Caucasians</td><td>288</td><td>421</td><td>PB</td><td>PCR-RFLP</td><td>DSM-IV</td><td>-141C Ins/Del</td><td>Yes</td><td>6</td></t<>	Saiz et al <sup>72</sup>	2010	Spain	Caucasians	288	421	PB	PCR-RFLP	DSM-IV	-141C Ins/Del	Yes	6
1996       Europe       Caucasians       273       255       HB       PCR       DSM-III-R       5er311Cys         1998       Europe       Caucasians       373       413       PB       PCR       DSM-III-R       Ser311Cys         1998       German       Caucasians       373       413       PB       PCR       DSM-III-R       Ser311Cys         1999       America       Caucasians       50       51       PB       PCR       DSM-III-R       Ser311Cys         1994       Apan       Caucasians       50       51       PB       PCR       DSM-III-R       Ser311Cys         1996       Japan       Asians       106       106       PC       PCR       DSM-III-R       Ser311Cys         2011       Japan       Asians       106       106       PC       PCR       DSM-III-R       Ser311Cys         2011       Japan       Asians       106       106       PC       PCR       DSM-III-R       Ser311Cys         2011       Japan       Asians       52       26       PB       PCR       DSM-IV       C9577         2003       Finland       Caucasians       103       97       PB       PCR <t< td=""><td>Sanders et al<sup>49</sup></td><td>2008</td><td>Europe</td><td>Caucasians</td><td>1,870</td><td>2,002</td><td>PB</td><td>TaqMan</td><td>DSM-IV</td><td>Ser311Cys</td><td>Yes</td><td>8</td></t<>	Sanders et al <sup>49</sup>	2008	Europe	Caucasians	1,870	2,002	PB	TaqMan	DSM-IV	Ser311Cys	Yes	8
196         Europe         Caucasians         273         255         HB         PCR         DSM-III-R         Ser311Cys           1998         Europe         Caucasians         373         413         PB         PCR         DSM-III-R         Ser311Cys           1998         German         Caucasians         373         413         PB         PCR         DSM-III-R         Ser311Cys           1999         America         Caucasians         50         51         PB         PCR         DSM-III-R         Ser311Cys           1996         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         103         97         PB         PCR         DSM-II         C9577           2003         Finland         Caucasians         103         97         PB         PCR         DSM-IV         HCD-IO         Ser311Cy										-141C Ins/Del	Yes	8
1998         Europe         Caucasians         373         413         PB         PCR         DSM-III-R         Ser311Cys           1998         German         Caucasians         260         290         PB         PCR         DSM-III-R         Ser311Cys           1999         America         Caucasians         50         51         PB         PCR         DSM-III-R         Ser311Cys           1996         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         407         384         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         103         97         PB         PCR         DSM-IV         C9577           2003         Finland         Caucasians         103         97         PB         PCR         DSM-IV         Ser311Cys           2002         Japan         Asians         52         2.6         PB         PCR         DSM-IV         -141C Ins/Del	Sasaki et al <sup>26</sup>	966	Europe	Caucasians	273	255	HB	PCR	DSM-III-R	Ser 311 Cys	Yes	5
1998         German         Caucasians         260         290         PB         PCR         ICD-10        141C Ins/Del           1999         America         Caucasians         50         51         PB         PCR         DSM-III-R        141C Ins/Del           1996         Japan         Asians         106         106         PB         PCR         DSM-III-R        141C Ins/Del           1996         Japan         Asians         106         106         PB         PCR         DSM-III-R         -141C Ins/Del           2011         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2017         Italy         Caucasians         103         97         PB         PCR         DSM-III-R         Ser311Cys           1997         Japan         Asians         52         2.6         PB         PCR         DSM-II-R         Ser311Cys           2003         Finland         Caucasians         93         94         PB         PCR         DSM-IV         -141C Ins/Del           2002         Japan         Asians         213         196         PB         PCR         DSM-IV         -141C Col0	Spurlock et al <sup>50</sup>	1998	Europe	Caucasians	373	413	PB	PCR	DSM-III-R	Ser311Cys	Yes	7
1999         America         Caucasians         50         51         PB         PCR         DSM-III-R         -141C Ins/Del           1996         Japan         Asians         106         106         106         PB         PCR         DSM-III-R         -141C Ins/Del           2011         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         407         384         PB         PCR         DSM-III-R         Ser311Cys           1997         Italy         Caucasians         103         97         PB         PCR         DSM-III-R         Ser311Cys           1997         Japan         Asians         52         2.6         PB         PCR         DSM-III-R         Ser311Cys           2003         Finland         Caucasians         93         94         PB         PCR         DSM-IV         -141C Ins/Del           2002         Japan         Asians         213         196         PB         PCR         DSM-IV         -141C Ins/Del           2007         India         Caucasians (Indians)         213         196         PB         PCR         DSM-IV	Stöber et al <sup>73</sup>	1998	German	Caucasians	260	290	PB	PCR	ICD-10	-141C Ins/Del	Yes	7
1996         Japan         Asians         106         106         PB         PCR         DSM-III-R         Ser311Cys           2011         Japan         Asians         407         384         PB         PCR- RFLP         DSM-III-R         Ser311Cys           2011         Japan         Asians         407         384         PB         PCR- RFLP         DSM-IV         C957T           1997         Italy         Caucasians         103         97         PB         PCR         DSM-IV         C9571           1997         Japan         Asians         52         2.6         PB         PCR         DSM-IV + ICD-10         Ser311Cys           2003         Finland         Caucasians         9.3         9.4         PB         PCR         DSM-IV         -141C Ins/Del           2002         Japan         Asians         213         196         PB         PCR         DSM-IV         -161C-10         Ser311Cys           2007         India         Caucasians (Indians)         213         196         PB         PCR         DSM-IV         TaqlB	Tallerico et al <sup>74</sup>	666	America	Caucasians	50	51	PB	PCR	DSM-III-R	-141C Ins/Del	Yes	7
2011         Japan         Asians         407         384         PB         PCR-RFLP         DSM-IV         C957T           1997         taly         Caucasians         103         97         PB         PCR         DSM-IV         C957T           1997         taly         Caucasians         103         97         PB         PCR         DSM-III-R         Ser311Cys           1997         Japan         Asians         52         2.6         PB         PCR         DSM-IV         HCD-10         Ser311Cys           2003         Finland         Caucasians         9.3         9.4         PB         PCR         DSM-IV         -1.41C Ins/Del           2002         Japan         Asians         4.8         PB         PCR         DSM-IV         -1.41C Ins/Del           2007         India         Caucasians (Indians)         213         196         PB         PCR         DSM-IV         TaqlB	Tanaka et al <sup>51</sup>	1996	Japan	Asians	901	106	PB	PCR	DSM-III-R	Ser311Cys	Yes	7
197         Italy         Caucasians         103         97         PB         PCR         DSM-III-R         Ser311Cys           1997         Japan         Asians         52         26         PB         PCR         DSM-III-R         Ser311Cys           1997         Japan         Asians         52         26         PB         PCR         DSM-IV         HCD-10         Ser311Cys           2003         Finland         Caucasians         93         94         PB         PCR         DSM-IV         -141C Ins/Del           2002         Japan         Asians         48         PB         PCR         DSM-IV         -16D-10         Ser311Cys           2007         India         Caucasians (Indians)         213         196         PB         PCR         DSM-IV         TaqlB	Tsutsumi et al <sup>22</sup>	2011	Japan	Asians	407	384	PB	PCR-RFLP	DSM-IV	C957T	Yes	7
197         Italy         Caucasians         103         97         PB         PCR         DSM-III-R         Ser311Cys           1997         Japan         Asians         52         26         PB         PCR         DSM-IV         + ICD-10         Ser311Cys           2003         Finland         Caucasians         93         94         PB         PCR         DSM-IV         - I 41C         Ins/Del           2002         Japan         Asians         48         48         PB         PCR         DSM-IV         - I 41C         Ins/Del           2007         India         Caucasians (Indians)         213         196         PB         PCR         DSM-IV         TaqIB										Ser311Cys	No	9
197         Japan         Asians         52         26         PB         PCR         DSM-IV + ICD-10         Ser311Cys           2003         Finland         Caucasians         93         94         PB         PCR         DSM-IV         - 1         -1         -1         1         1         2003         Japan         Asians         48         PB         PCR         DSM-IV         - 1         -1         1         1         Caucasians         -1         48         PB         PCR         DSM-IV         + ICD-10         Ser311Cys         -1         2007         India         Caucasians (Indians)         213         196         PB         PCR         DSM-IV         TaqIB         TaqIB         -1         -	Verga et al <sup>52</sup>	1997	ltaly	Caucasians	103	97	PB	PCR	DSM-III-R	Ser311Cys	Yes	7
2003         Finland         Caucasians         93         94         PB         PCR         DSM-IV         -1141C Ins/Del           2002         Japan         Asians         48         48         PB         PCR         DSM-IV         +1CD-10         Ser311Cys           2007         India         Caucasians (Indians)         213         196         PB         PCR         DSM-IV         TagIB	Fujiwara et al <sup>s4</sup>	1997	Japan	Asians	52	26	PB	PCR	DSM-IV + ICD-I0	Ser311Cys	Yes	7
2002     Japan     Asians     48     48     PB     PCR     DSM-IV + ICD-10     Ser311Cys       2007     India     Caucasians (Indians)     213     196     PB     PCR     DSM-IV     TaqIB	Kampman et al <sup>75</sup>	2003	Finland	Caucasians	93	94	PB	PCR	DSM-IV	-141C Ins/Del	Yes	7
2007 India Caucasians (Indians) 213 196 PB PCR DSM-IV TagIB	Morimoto et al <sup>55</sup>	2002	lapan	Asians	48	48	PB	PCR	DSM-IV + ICD-I0	Ser311Cys	Yes	7
	Vijayan et al <sup>19</sup>	2007	India	Caucasians (Indians)	213	196	PB	PCR	DSM-IV	TaqIB	Yes	œ

							TaqlD C939T	Yes Yes	ω ω ά
2	Asians	120	001	PB	PCR	DSM-IV-TR	Ser311Cys —141C Ins/Del	Yes Yes	8 2
	Caucasians	87	69	면	PCR	DSM-III-R	TaglA	Yes	7
	Caucasians	55	51	PB	PCR-RFLP	DSM-III-R + RDC	TaqIA	Yes	80
	Caucasians	80	80	PB	PCR-RFLP	DSM-III-R	TaqIA	Yes	7
.00	Asians	50	011	PB	PCR-RFLP	DSM-III-R	Ser 311 Cys	Yes	7
					SSCP analysis				
	Caucasians	60	60	PB	PCR	DSM-III-R	TaqIA	Yes	7
.00	Asians	156	300	ЯB	PCR	DSM-III-R	Ser 311 Cys	Yes	9
	Caucasians	112	64	BB	PCR	DSM-III-R	Ser 311 Cys	Yes	9
	Caucasians	901	113	8 H	PCR-RFLP	DSM-III-R	Ser 311 Cys	Yes	7
.0	Asian	001	001	PB	PCR-RFLP	DSM-III-R	Ser 311 Cys	No	9
<u>.</u>	Asian	001	001	PB	PCR	DSM-III-R	Ser 311 Cys	Yes	9
n	Caucasians	179	138	PB	PCR	DSM-III-R	Ser 311 Cys	Yes	7
ă	Caucasians	147	001	ΗB	PCR	DSM-III-R	Ser 311 Cys	٥N	S
<sup>o</sup>	Caucasians	338	1,914	ΗB	I	I	Ser 311 Cys	Yes	S
Asian		234	94	PB	PCR	ICD-I0	-141C Ins/Del	Yes	80
ă	Caucasians	366	267	ΗB	I	I	Ser 311 Cys	Yes	I
Asian		156	300	ΒB	SSCP	DSM-III-R	Ser 311 Cys	Yes	7
		291	579		PCR				
Asian		915	421	РВ	PCR-AFLP	ICD-I0 + CCMD-II-R	TaqIA	Yes	7
					Sequenom Mass ADD AV				
,		L (	00				()	>	r
Asian		201 7 1 C	801	22 2	PCK		Ser311Cys	Yes	- r
Asian		317	310	8	PCK		I aqlA	Yes	<b>-</b> 1
Asian		128	124	BB	PCR-RFLP	CCMD-3	-141C Ins/Del	Yes	7
Asian		512	480	BB	PCR	DSM-IV	-141C Ins/Del	Yes	7
							Ser 311 Cys	No	9
							C957T	Yes	7
							C939T	Yes	7
							TaqlA	No	9
Asian		120	001	PB	PCR	DSM-IV	-141C Ins/Del	Yes	7
Asian		67	77	PB	PCR	CCMD-II-R	TaqIA	Yes	9
Asian		92	96	PB	PCR	1	C957T	Yes	9
							C939T	Yes	9
							Ser 311 Cys	Yes	9
<u>ם</u> .	Asian	101	105	PB	PCR	DSM-IV + CCMD-3	-141C Ins/Del	Yes	7

Α	Study	ID
~	Study	ıυ

Study ID	OR (95% CI)	% weight
Watanabe et al <sup>36</sup> (2012)	0.89 (0.59, 1.36)	5.19
Crawford et al <sup>31</sup> (1996)	2.30 (0.59, 9.07)	1.13
Himei et al <sup>37</sup> (2002)	1.75 (0.69, 4.46)	2.10
Srivastava et al <sup>4</sup> (2010)	0.90 (0.55, 1.47)	4.60
Arinami et al <sup>47</sup> (1996)	1.93 (0.87, 4.30)	2.63
Chen et al <sup>38</sup> (1996)	0.61 (0.16, 2.31)	1.19
Dubertret et al <sup>15</sup> (2004)	1.63 (0.40, 6.62)	1.08
Dubertret et al <sup>13</sup> (2010)	0.99 (0.28, 3.44)	1.32
Fan et al <sup>39</sup> (2010)	1.27 (0.75, 2.13)	4.33
Golimbet et al <sup>40</sup> (2011)	➡ 2.24 (1.20, 4.18)	3.57
Gupta et al41 (2009)	1.09 (0.71, 1.68)	5.07
Harano <sup>42</sup> (1997)	1.47 (0.54, 4.01)	1.88
Hori et al43 (2001)	1.24 (0.66, 2.33)	3.54
Iwata et al44 (2003)	0.13 (0.01, 2.50)	0.27
Jonsson et al <sup>45</sup> (2003)	4.93 (1.61, 15.12)	1.58
Kaneshima et al <sup>46</sup> (1997)	0.82 (0.23, 2.84)	1.33
Laurent et al <sup>48</sup> (1994)	<b>2.75 (0.65, 11.63)</b>	1.03
Ohara et al <sup>3</sup> (1996)	0.26 (0.03, 2.53)	0.45
Sanders et al <sup>49</sup> (2008)	0.73 (0.54, 0.98)	6.39
Sasaki et al <sup>26</sup> (1996)	— 1.02 (0.45, 2.33)	2.50
Spurlock et al <sup>50</sup> (1998)	- 0.91 (0.45, 1.86)	3.04
Tanaka et al <sup>51</sup> (1996)	1.13 (0.43, 2.99)	1.98
Tsutsumi et al <sup>22</sup> (2011)	0.75 (0.46, 1.22)	4.56
Verga et al <sup>52</sup> (1997)	◆ 2.13 (0.73, 6.25)	1.69
Fujiwara et al <sup>54</sup> (1997)	1.00 (0.09, 11.29)	0.40
Morimoto et al <sup>55</sup> (2002)	1.00 (0.31, 3.22)	1.47
Vijayan et al <sup>19</sup> (2007)	1.02 (0.65, 1.61)	4.91
Fan et al <sup>56</sup> (1996)	<ul> <li>1.73 (0.41, 7.34)</li> </ul>	1.03
Luo <sup>24</sup> (2008)	0.80 (0.46, 1.39)	4.05
Itokawa et al <sup>58</sup> (1993)	<ul> <li>1.79 (0.47, 6.82)</li> </ul>	1.18
Arinami et al <sup>9</sup> (1994)	<b>3.09</b> (1.43, 6.67)	2.75
Asherson et al <sup>59</sup> (1994)	1.14 (0.10, 12.74)	0.40
Gejman et al <sup>61</sup> (1994)	0.80 (0.18, 3.60)	0.95
Hattori et al <sup>27</sup> (1994)	- 0.87 (0.31, 2.45)	1.80
Nanko et al <sup>60</sup> (1994)	1.00 (0.34, 2.91)	1.71
Shaikh et al <sup>29</sup> (1994)	4.85 (0.59, 39.76)	0.52
Sobell et al <sup>30</sup> (1994)	- 1.01 (0.55, 1.89)	3.61
Itokawa et al <sup>53</sup> (2010)	<b>3.09</b> (1.43, 6.67)	2.75
Itokawa et al <sup>53</sup> (2010)	◆ 2.12 (1.19, 3.76)	3.92
Serretti et al <sup>81</sup> (2000)	◆ 1.84 (1.00, 3.39)	3.67
Zheng <sup>18</sup> (2012)	1.58 (0.44, 5.71)	1.26
Nothen et al <sup>34</sup> (1993)	0.61 (0.16, 2.30)	1.19
Overall ( <i>I</i> <sup>2</sup> =34.7%, <i>P</i> =0.016)	1.23 (1.05, 1.44)	100
0.00707 1	142	
	• •=	

_	Study ID	OR (95% CI)	% weight
	Lawford et al <sup>10</sup> (2005)	0.58 (0.42, 0.80)	8.69
	Kukreti et al <sup>2</sup> (2006)	0.84 (0.58, 1.21)	7.75
	Hanninen et al <sup>64</sup> (2006)	0.79 (0.62, 1.01)	10.58
	Hoenicka et al <sup>e5</sup> (2006)	0.67 (0.50, 0.89)	9.58
	Luo <sup>24</sup> (2008)	1.35 (0.88, 2.06)	6.60
	Monakhov et al <sup>69</sup> (2008)	0.68 (0.55, 0.84)	11.47
	Gupta et al41 (2009)	0.90 (0.69,1.17)	10.23
	Betcheva et al' (2009)	0.70 (0.57, 0.86)	11.58
	Fan et al <sup>39</sup> (2010)	1.58 (1.03, 2.43)	6.51
	Dubertret et al <sup>13</sup> (2010)	0.66 (0.47, 0.91)	8.51
	Tsutsumi et al <sup>22</sup> (2011)	0.80 (0.52, 1.23)	6.41
	Zheng <sup>18</sup> (2012)	0.94 (0.37, 2.36)	2.08
	Overall (P=58.5%, P=0.005)	0.80 (0.69, 0.92)	100
	0.372 1	2.69	

Figure 2 (Continued)

#### С

Study ID	OR (95% CI)	% weight
Arinami et al <sup>57</sup> (1997)	0.60 (0.44, 0.81)	1.49
Stöber et al <sup>73</sup> (1998)	1.15 (0.78, 1.71)	4.08
Ohara et al <sup>3</sup> (1996)	0.60 (0.36, 0.98)	3.57
Li et al <sup>70</sup> (1998)	1.39 (0.83, 2.32)	3.47
Breen et al <sup>63</sup> (1999)		1.64
Tallerico et al <sup>74</sup> (1999)		1.88
Jonsson et al <sup>66</sup> (1999)		3.01
Inada et al <sup>80</sup> (1999)		4.01
Hori et al <sup>43</sup> (2001)		4.28
Himei et al <sup>37</sup> (2002)	,	3.86
Dubertret et al <sup>15</sup> (2003) ← ●		1.51 3.24
Liang <sup>86</sup> (2005)		3.42
Parsons et al <sup>25</sup> (2007)		2.81
Luo <sup>24</sup> (2008)		3.85
Lafuente et al <sup>68</sup> (2008)	, , ,	3.89
Sanders et al <sup>49</sup> (2008)	• 1.13 (0.98, 1.32) §	5.17
Luo <sup>24</sup> (2008)	0.90 (0.66, 1.23)	1.49
Liu et al <sup>83</sup> (2009)	0.50 (0.33, 0.76)	3.92
Cordeiro <sup>14</sup> (2009)		1.48
Gupta et al <sup>41</sup> (2009)		3.99
Saiz et al <sup>72</sup> (2010)		1.58
Dubertret et al <sup>13</sup> (2010)	,	3.37
Srivastava et al <sup>4</sup> (2010)		1.20
Shen et al <sup>84</sup> (2011)		3.33 3.13
Xiao et al <sup>76</sup> (2013) $\rightarrow$		3.33
Overall ( <i>I</i> <sup>2</sup> =76.1%, <i>P</i> =0.000)		100
T T		
0.164 D	l l 1 6.11	
Study ID	OR (95%CI)	% weigh
Comings et al <sup>77</sup> (1991)	2.77 (1.31, 5.88)	2.56
Sanders et al <sup>78</sup> (1993)	0.91 (0.45, 1.87)	2.30
Nothen et al <sup>34</sup> (1993)	1.00 (0.55, 1.83)	3.34
Campion et al <sup>79</sup> (1994)	• 1.18 (067, 2.07)	3.62
Jonsson et al <sup>87</sup> (1996)	0.93 (0.53, 1.62)	3.67
Dollfus et al <sup>35</sup> (1996)	• 1.11 (0.65, 1.89)	3.78
Dubertret et al <sup>13</sup> (2010)	0.48 (0.24, 0.97)	2.79
Zhang et al <sup>85</sup> (2003)	- 0.72 (0.45, 1.15)	4.33
Dubertret et al <sup>15</sup> (2004)	0.31 (0.19, 0.50)	4.23
Parsons et al <sup>25</sup> (2007)	0.48 (0.30, 0.76)	4.37
Vijayan et al <sup>19</sup> (2007)	- 0.80 (0.60, 1.08)	5.82
Luo <sup>24</sup> (2008)	0.97 (0.80, 1.18)	6.71
Lafuente et al68 (2008)	0.91 (0.67, 1.23)	5.72
Monakhov et al69 (2008)	▲ 1.26 (0.97, 1.65)	6.10
Behravan et al <sup>11</sup> (2008)	1.38 (0.77, 2.47)	3.49
Aslan et al <sup>23</sup> (2010)	★ 1.10 (0.75, 1.62	5.01
Srivastava et al <sup>4</sup> (2010)	- 0.86 (0.65, 1.14)	5.92
Dubertret et al <sup>13</sup> (2010)	0.71 (0.48, 1.06)	4.91
Liu et al <sup>33</sup> (2012)	0.56 (0.44, 0.70)	6.41
		4.00

Figure 2 Calculated OR and 95% CI for the associations between DRD2 gene polymorphism and schizophrenia risk. Notes: (A) rs1801028; (B) rs6277; (C) rs1799732; (D) rs1800497. weights are from random effects analysis. Abbreviations: CI, confidence interval; DRD2, dopamine D2 receptor; OR, odds ratio.

0.86

schizophrenia. There were four studies of the rs1800497 SNP that included controls that did not conform with HWE, but they did not influence the results.<sup>11,23–25</sup> In terms of publication bias, Egger's linear regression showed that the funnel plots were symmetrical (P=0.861).

Kunii et al62 (2014)

Li<sup>82</sup> (2014)

Cordeiro and Vallada<sup>16</sup> (2014)

Overall (I2=71.6%, P=0.000)

## Association between the other SNPs and schizophrenia risk

3.00 (0.77, 11.63) 1.03

6.56

6.92

100

0.82 (0.66, 1.01)

1.00 (0.85, 1.18)

0.87 (0.75, 1.01)

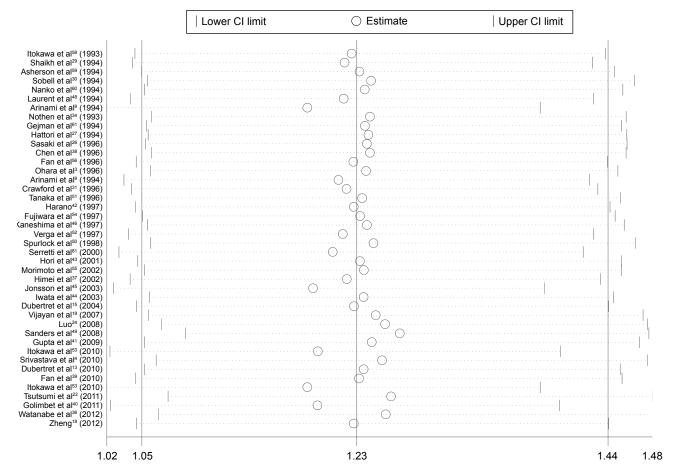
11.6

There was no evidence that the susceptibility to schizophrenia was associated with the rs6275 (T vs C, P=0.10, OR =0.92, 95% CI=0.83-1.02), rs1079597 (T vs C, P=0.12, OR =0.72, 95%

SNP	Subgroup type	Subgroup	N	P-value	OR	95% CI	l² (%)
rs1801028	Control sources	Population-based	31	0.99	1.00	0.88, 1.14	0
		Hospital-based	11	<0.01	1.91	1.39, 2.61	31
	Ethnicity	Caucasians	19	0.09	1.22	0.97, 1.54	41
		Asians	23	0.04	1.25	1.01, 1.55	31
rs6277	Ethnicity	Caucasians	8	<0.01	0.72	0.66, 0.79	0
		Asians	4	0.37	1.17	0.83, 1.64	46
rs   799732	Control sources	Population-based	24	0.36	0.92	0.78, 1.10	77
		Hospital-based	3	0.46	0.81	0.47, 1.41	71
	Ethnicity	Caucasians	15	0.33	1.11	0.90, 1.36	71
		Asians	11	0.004	0.76	0.63, 0.92	56
		Mixed	I	0.002	0.61	0.44, 0.83	-
rs   800497	Control sources	Population-based	20	0.02	0.84	0.72, 0.97	71
		Hospital-based	2	0.46	1.50	0.51, 4.47	86
	Ethnicity	Caucasians	16	0.24	0.88	0.72, 1.08	71
		Asians	5	0.29	0.85	0.63, 1.15	82
		Mixed	I	0.06	0.82	0.66, 1.01	-

Table 2 Subgroup analysis of case-control studies on DRD2 gene polymorphisms and schizophrenia risk

Abbreviations: CI, confidence intervals; DRD2, dopamine D2 receptor; OR, odds ratios; SNP, single-nucleotide polymorphisms.



#### Meta-analysis estimates, given named study is omitted

Figure 3 Sensitivity analysis via deletion of each individual study reflecting the relative influence of each individual dataset on the pooled ORs for the rs1801028. Abbreviations: Cl, confidence interval; OR, odds ratio.

Itokawa et al⁵ଃ (1993)		1.79 (0.47, 6.82
Shaikh et al²º (1994)		2.39 (0.77, 7.3)
Asherson et al <sup>59</sup> (1994)		2.09 (0.75, 5.8
Sobell et al <sup>30</sup> (1994)	<b>_</b>	1.23 (0.73, 2.09
Nanko et al <sup>60</sup> (1994)	<b>—   •</b>	1.18 (0.74, 1.90
Laurent et al <sup>48</sup> (1994)	_ <b>_</b>	1.28 (0.82, 2.0)
Arinami et alº (1994)	<b>│↓</b>	1.67 (1.05, 2.6
Nothen et al <sup>34</sup> (1993)	<b>↓</b> → →	1.52 (0.96, 2.4)
Gejman et al <sup>61</sup> (1994)	+	1.45 (0.94, 2.2
Hattori et al <sup>27</sup> (1994)	+	1.36 (0.92, 2.0
Sasaki et al² (1996)	+	1.31 (0.93, 1.8
Chen et al <sup>38</sup> (1996)	++	1.25 (0.90, 1.7
Fan et al <sup>56</sup> (1996)	+	1.27 (0.93, 1.7
Ohara et al³ (1996)	++	1.23 (0.89, 1.7
Arinami et alº (1994)	<b>├</b>	1.30 (0.96, 1.7
Crawford et al <sup>31</sup> (1996)	<b>├</b> →	1.33 (1.00, 1.7
Tanaka et al⁵¹ (1996)	<b>→</b>	1.32 (1.01, 1.7
Harano42 (1997)	<b> </b> →→	1.33 (1.03, 1.7
Fujiwara et al⁵⁴ (1997)	<b> </b> →→	1.32 (1.03, 1.7
Kaneshima et al <sup>46</sup> (1997)	<b>⊢</b> ←	1.30 (1.01, 1.6
/erga et al <sup>52</sup> (1997)	→	1.33 (1.04, 1.7
Spurlock et al⁵ (1998)	<b> </b> →→	1.28 (1.02, 1.6
Serretti et al <sup>81</sup> (2000)	<b> </b> →−	1.34 (1.08, 1.6
Hori et al <sup>43</sup> (2001)	<b> </b> →	1.33 (1.08, 1.6
Morimoto et al⁵⁵ (2002)	→	1.32 (1.08, 1.6
Himei et al <sup>37</sup> (2002)	→	1.33 (1.10, 1.6
Jonsson et al <sup>45</sup> (2003)		1.39 (1.14, 1.6
lwata et al <sup>44</sup> (2003)		1.37 (1.13, 1.6
Dubertret et al <sup>15</sup> (2004)		1.38 (1.14, 1.6
√ijayan et al¹ (2007)	<b> </b> →-	1.32 (1.10, 1.5
_uo <sup>24</sup> (2008)	<b> </b> →-	1.27 (1.06, 1.5
Sanders et al <sup>49</sup> (2008)	<b>→</b>	1.21 (1.00, 1.4
Gupta et al <sup>41</sup> (2009)	<b>↓</b>	1.19 (1.00, 1.4
ltokawa et al⁵³ (2010)	<b> </b> →-	1.24 (1.03, 1.4
Srivastava et al⁴ (2010)		1.21 (1.02, 1.4
Dubertret et al <sup>13</sup> (2010)		1.20 (1.02, 1.4
Fan et al <sup>39</sup> (2010)		1.20 (1.03, 1.4
tokawa et al⁵³ (2010)	-←-	1.25 (1.06, 1.4
Tsutsumi et al²² (2011)	<b> </b> →-	1.22 (1.04, 1.4
Golimbet et al40 (2011)	-←-	1.25 (1.06, 1.4
Watanabe et al <sup>36</sup> (2012)	-←-	1.23 (1.05, 1.4
Zheng <sup>18</sup> (2012)	<b> </b> →	1.23 (1.05, 1.4
<b>I</b> 0.136		<u> </u>

Figure 4 Cumulative meta-analyses according to publication year for the rs1801028.

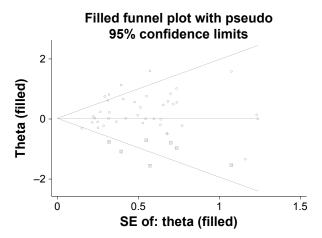


Figure 5 Trim-and-fill plot to correct publication bias for the rs1801028. Abbreviation: SE, standard error.

CI =0.47–1.10), or rs1800498 (T vs C, P=0.52, OR =1.03, 95% CI =0.93–1.15) SNP. Sensitivity analysis indicated that no single study of the rs1800498 SNP qualitatively changed the pooled ORs. Removing the low-quality study<sup>28</sup> did not change the result.

### Discussion

A comprehensive analysis about schizophrenia-associated genetic loci had been performed in a genome-wide association study.<sup>32</sup> Our meta-analysis results provide evidence that the rs1801028 and rs6277 SNPs are associated with the risk of schizophrenia. A subgroup analysis indicated that the rs1801028 SNP may increase the risk of schizophrenia in Asians and hospital-based controls, the rs6277 SNP may reduce the risk of schizophrenia in Caucasians, the rs1799732 SNP may reduce the risk of schizophrenia in Asians, and the rs1800497 SNP may reduce the risk of schizophrenia in population-based controls.

Yao et al performed a similar study of the associations between *DRD2* gene polymorphisms and schizophrenia risk.<sup>12</sup> That study used a genetic model, while our study used an allele contrast model since this made it possible to include the largest number of documents and the maximum sample sizes. Other advantages of the present study were 1) the inclusion of more published documents (including those written in Chinese), which increased the statistical power of our results, 2) more SNPs being investigated, and 3) the application of meta-regression and publication bias, nonparametric trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analysis also being performed.

The results of the present study show that the rs1801028 SNP may increase the risk of schizophrenia in Asians and hospital-based controls. Yao et al reported the same result under the dominant model.<sup>12</sup> Different results may be

obtained for different races due to differences in genetic backgrounds and living conditions.<sup>33</sup> Moreover, the results for the subgroup analysis based on hospital-based controls are not reliable because such controls may not be representative and samples of hospital-based controls are often too small, and so these results should be treated cautiously. The results for publication bias were significant, and these changed after being adjusted using the trim-and-fill method, which indicated that those results may not be very stable. This means that if new articles are published in the future, the results of a complete meta-analysis including all available data are very likely to change. The presence of significant publication bias was probably due to our meta-analysis including many small-sample studies. Yao et al found only slight publication bias, but this was not corrected using the trim-and-fill method.<sup>12</sup>

Twelve of the included documents related to the rs6277 SNP and the meta-analysis showed that this SNP may reduce the risk of schizophrenia in Caucasians; however, Yao et al did not study this SNP.<sup>12</sup> However, our included samples for this SNP were small and the cumulative analysis by publication year did not show a reliable trend. This means that the statistical power of the results may not have been high.

In our meta-analysis the rs1799732 SNP was not associated with schizophrenia risk, and Yao et al obtained the same result under the dominant model.<sup>12</sup> After performing subgroup analysis, the current meta-analysis indicated that the rs1799732 SNP might reduce the risk of schizophrenia in Asians. In contrast, Yao et al did not find any correlation between the rs1799732 SNP and schizophrenia risk in different races and different populations. The possible reasons for different conclusions being drawn based on the current and previous meta-analyses of the rs1799732 SNP are 1) more documents being included in the present study, especially the Chinese literature, because this is likely to have greatly increased the sample size for Asians, and 2) the use of different genetic models.

The previous meta-analyses did not explore the correlations between the rs1800497 SNP and schizophrenia risk in all populations. After performing subgroup analysis, the present study found that the rs1800497 SNP was associated with schizophrenia risk in population-based controls. In contrast, Yao et al found that the rs1800497 SNP may increase the risk of schizophrenia in Caucasians.<sup>12</sup> The possible reasons for the current and previous meta-analyses drawing different conclusions from their subgroup analyses of the rs1800497 SNP are 1) Yao et al applying the wrong allele or genotype distribution data of cases and controls regarding the study of Nothen et al;<sup>34</sup> 2) the smallness of the study sample of Yao et al; 3) that study not including Chinese studies; and 4) our use of different genetic models. These factors mean that the statistical power would have been higher for the present study.

It is important to note the limitations of our metaanalysis. 1) Meaningless or negative results might not be published, which would lead to some degree of publication bias. 2) Schizophrenia is a multifactorial disease, whereas the present study only considered the impact of the *DRD2* gene on schizophrenia risk, and also ignored the possible impacts of environmental factors, age, gender, lifestyle, and diagnosis standards.

In conclusion, this meta-analysis has shown that the rs1801028 SNP may be a risk factor for susceptibility to schizophrenia in Asians, the rs6277 SNP may be a protective factor for susceptibility to schizophrenia in Caucasians, and the rs1799732 SNP may be a protective factor for susceptibility to schizophrenia in Asians. However, the occurrence of schizophrenia represents the cumulative effect of multiple genes, and so only studying a single gene or single polymorphism is unlikely to be adequate. Future studies should pay more attention to the interactions within and between genes as well as within and between their polymorphisms in order to better explain the genetic mechanisms underlying mental illness.

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### **Author contributions**

HRH and HHW performed literature research, data extraction, statistical analysis, and data interpretation. XCM contributed to the study concept and study design. LHY and FG contributed to make figures and tables. YJF and JGF were responsible for the quality control of data and algorithms. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

### Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

 Table SI
 Scale for quality assessment

Criteria	Score
Representativeness of cases	
Consecutive/randomly selected form case population with clearly defined sampling frame	2
Consecutive/randomly selected form case population without clearly defined sampling frame or with extensive	I
Not described	0
Definition of the DR	
Population- or health-based	2
Hospital-bases	I
Not described	0
Hardy–Weinberg equilibrium in controls	
Hardy–Weinberg equilibrium	2
Hardy–Weinberg disequilibrium	I.
Genotyping examination	
Genotyping done under "blinded" condition	I.
Unblinded done or not mentioned	0
Association assessment	
Assess association between genotypes and head and neck cancer with appropriate statistics and adjustment for confounders	2
Assess association between genotypes and head and neck cancer with appropriate statistics and without adjustment for confounders	I.
Inappropriate statistics used	0

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