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A two-method meta-analysis of Neuregulin 1(*NRG1*) association and heterogeneity in schizophrenia

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ABSTRACT

NRG1 is one of the most researched genes associated with schizophrenia. Although three meta-analyses in this area have been published, the results have been inconclusive and even conflicting. Family based studies can be problematical due to the difficulty of synthesizing them with case-control studies. Heterogeneity is another persistently difficult problem which tends to be side-stepped in genetic studies. To deal with these points, we performed a meta-analysis of 26 published case-control and family-based association studies up to September 2008 covering 8049 cases, 8869 controls and 1515 families. The matrix of coancestry coefficient was also calculated using population genetics. Across these studies, the conclusions are as follows: Firstly, only SNP8NRG221132, 420M9-1395(0) and 478B14-848(0) showed significant association in the relatively small sample size. Secondly, we applied both Kazeem's and Lohmueller's methods for synthesizing family and case control studies and there was no statistically significant difference between the results from the two methods, suggesting that either method can be used. In addition, the association analysis of case-control studies was statistically consistent with that of family studies. Finally, the matrix of coancestry coefficient suggested obvious population stratification. The study reveals that one SNP of the *NRG1* gene does not contribute significantly to schizophrenia and that population stratification is evident. In future genetic association analysis on complex psychic diseases, haplotype blocks and population structure should be given greater consideration.

1. Introduction

Schizophrenia is a severe psychiatric disease which exhibits a complicated interplay between receptors, kinases, proteins and hormones. Five main hypotheses of the causes of the disease have been reported: the neurodevelopmental hypothesis, the dopamine hypothesis, the glutamatergic hypothesis, the GABAergic hypothesis and the immune hypothesis (Lang et al., 2007). Recently, Neuregulin 1(*NRG1*) has received special attention as a key mediator in glutamatergic hypothesis. It has multiple physiological functions in both the peripheral and central nervous systems. Studies have shown that genetic deficits in *NRG1*, or its postsynaptic receptor ErbB4, lead to impaired activity-driven glutamatergic synapse development and thus glutamatergic hypofunction (Xie et al., 2007). *NRG1* has also been shown to regulate cell adhesion via the ErbB2/Phosphoinositide-3 Kinase/Akt dependent pathway and thus is potentially implicated in schizophrenia and cancer (Christopher et al., 2007).

The linkage disequilibrium of *NRG1* with schizophrenia was first reported by Stefansson et al. (Stefansson et al., 2002). A number of association studies have tried to replicate those results and have found the haplotype blocks of Hap_{ICE} to be

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present in several large populations, namely $Hap_{China\ 1}$, $Hap_{China\ 2}$ and HapChina 3 in the Chinese population (Li et al., 2004), and HapIre in the Irish population, in particular Hap_{ICE} which was constructed from five or seven markers (Corvin et al., 2004). Our own laboratory carried out a meta-analysis of the genetic association of *NRG1*, based on studies up to November 2005 and reached a strong positive conclusion (Li et al., 2006). Two other studies (Munafo et al., 2006; Marcus et al., 2008), analyzed only SNP8NRG221533 of the *NRG1* gene. They dealt only with case-control studies, omitting family based studies, and these produced a negative result.

In fact, family based studies are more important than case-control studies in genetic association analysis and it is very difficult to synthesize these two different types of studies. Lohmueller KE (Lohmueller et al., 2003) and Kazeem GR (Kazeem and Farrall, 2005) have reported their respective statistical methods for achieving integration. It is not obvious which of the methods is better and so far there has been no published comparison. In addition, in genetic association studies, heterogeneity is a pervasive and difficult problem. *NRG1* has been studied in so many populations that it would be useful to show the extent to which population stratification contributes to heterogeneity.

2. Materials and methods

2.1. Data sources

The literature included in the current analysis was selected using PubMed and focusing on the keywords "schizophrenia", "neuregulin 1", and the abbreviation of the gene "*NRG1*". All references cited in these studies and published reviews were reviewed to identify additional work not indexed by MEDLINE. Some raw data, unavailable in articles, were obtained from the authors. The analyzed data covered those from all English-language publications up to September 2008. The studies analyzed included 8049 cases, 8869 controls and 1515 families (Table 1).

2.2. Data extraction

All the reported SNPs and microsatellites featuring in more than 3 studies were extracted and the effect size was calculated by 2 authors. We examined the seven constituents of Hap_{ICE}. Then, based on the frequency of SNP8NRG221533 and SNP8NRG243177, the matrix of coancestry coefficient was calculated using population genetics.

2.3. Data synthesis

Data from each case-control study was used to construct two-by-two tables and data from each transmission/disequilibrium test (TDT) study to construct one-by-two tables in which subjects were classified by diagnostic category and type of allele. The Cochran's χ^2-based Q statistic test was performed to assess heterogeneity and thus to ensure that each group of studies was suitable for the appropriate meta-analysis model. If heterogeneity was found, the random effects model, which yields wider CIs, was adopted; otherwise, the fixed effects model was deemed suitable.

For the synthesis of TDT and case-control studies, two different methods were used. One method was that of Kazeem GR et al. (Kazeem and Farrall, 2005) (which we have named Kazeem's method). After obtaining the estimates of the

Table 1
Characteristics of included samples of schizophrenia.

Study	Year	Case/control(family)	Ancestry	Method	Criteria
Stefansson	2002	478/394	Iceland	Case-control	DSM-III-R
Stefansson	2003	609/618	Scottish	Case-control	DSM-III-R
Yang	2003	246	Chinese	Family	ICD-10
Williams	2003	573/618	UK	Case-control	DSM-IV
Iwata	2004	607/515	Japanese	Case-control	DSM-IV
Bakker	2004	282/585	Dutch	Case-control	DSM-IV
Hong	2004	228/269	Chinese	Case-control	DSM-IV
Corvin	2004	243/222	Ireland	Case-control	DSM-IV
Li	2004	298/336	Chinese	Case-control	DSM-IV
Kampman	2004	94/395	Finnish	Case-control	DSM-IV
Zhao	2004	369/299	Chinese	Case-control	DSM-III-R
Zhao	2004	352	Chinese	Family	DSM-III-R
Petryshen	2005	321/242	Portuguese	Case-control	DSM-IV
Petryshen	2005	111	Portuguese	Family	DSM-IV
Fukui	2006	349/424	Japanese	Case-control	DSM-IV
Ingason	2006	325/353	Danis	Case-control	ICD-10
Kim	2006	242/242	korean	Case-control	DSM-IV
Lachman	2006	141/142	African	Case-control	DSM-IV
Lachman	2006	573/618	UK	Case-control	DSM-IV
Hanninen	2008	113/393	Finland	Case-control	DSM-IV
Rosa	2007	151	Spanish	Family	DSM-IV
Hall	2007	103/89	Swedish	Case-control	DSM-IV
Thomson	2007	386/478	Scotland	Case-control	DSM-IV
Vilella	2008	589/615	Spanish	Case-control	DSM-IV
Ikeda	2008	1126/1022	Japanese	Case-control	DSM-IV
Georgieva	2008	655	Bulgarian	Family	DSM-IV

ICD-10, International Statistical Classification of Diseases, 10th Revision; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.

logarithm of the odds ratios φ_i and there associated standard errors σ_i in case-control and TDT study designs, the estimate of the combined odds ratio Ψ and its associated SE can be obtained using a weighted analysis method (Hedges and Olkin, 1985), $\Psi = \sum_{i=1}^{2} w_i\varphi_i / \sum_{i=1}^{2} w_i, Var(\Psi) = 1 / \sum_{i=1}^{2} w_i (w_i = 1/\sigma_i^2)$, The significance of the combined odds ratio estimate and its homogeneity can then be examined using the test statistic, following a chi-square distribution with 1 degree of freedom under the null hypothesis of no association $X_W^2 = \frac{(\Psi-\Psi_0)^2}{Var(\Psi)}$, $X_H^2 = \sum_{i=1}^{2} w_i(\varphi_i, \Psi)^2 \approx \chi_1^2$ (i.e. $\Psi_0 = 0$). The "Catmap" software (Nicodemus, 2008) for this method was downloaded from the comprehensive *R* archive network http://www.r-project.org. The level for type I errors was set at 0.05. The other method was that of Lohmueller KE et al. (Lohmueller et al., 2003) (which we have named Lohmueller's method), which uses a very large population as the controls and a 50:50 transmission ratio, implying that the risk allele is transmitted evenly in controls. The data format of the software "Comprehensive meta-analysis version 2.0" was used to apply this method. We then calculated a combined estimate of disease association including the logarithm of the Odds Ratios, heterogeneity *Q* test, associated *p* values and forest plot using fixed and random effects methods. The 95% CIs were calculated using Woolf's method. For the sensitivity analysis, each study was removed in turn and the remaining studies were reanalyzed. Comparatively, the theory behind Kazeem's method is more complex and stringent than that underlying Lohmueller's method.

We assessed publication bias using an ancillary procedure originated by Egger et al. (Egger et al., 1997) which takes a linear regression approach to measuring funnel plot asymmetry on the natural logarithm of the OR. The larger the deviation from the funnel curve of each study, the more pronounced the asymmetry. The results from small studies tend to scatter widely at the bottom of the graph, with the spread narrowing among larger studies. The significance of the intercept was evaluated using the *t*-test.

A paired sampled *t*-test was used to compare the effect of the two methods of integrating case-control and TDT studies on the OR value, and an independent sample *t*-test was used to compare the effect on the OR value of whole studies and case-control studies. The frequency of markers (SNPs or microsatellites) was calculated using population genetics software "arlequin3" (http://cmpg.unibe.ch/software/arlequin3).

3. Results

3.1. Association

The markers of *NRG1* featuring in more than 3 studies are listed in Fig. 1. They were calculated using both Kazeem's and Lohmueller's methods (Table 2). If $p(Q) > 0.05$, the fixed model was chosen and the value of the Inverse Variance Fixed-Effects OR was used as the OR item. Otherwise, the random model was used, and the DerSimonian & Laird Random-Effects OR was employed. SNP8NRG221132, 420M9-1395(0), 478B14-848(0) showed significant association with schizophrenia under both methods ($p < 0.05$). However, the others, including SNP8NRG221533, SNP8NRG241930, SNP8NRG243177, SNP8NRG433E1006, 420M9-1395(2), presented no association ($p > 0.05$). The heterogeneity of the SNP8NRG221533 showed positive results across all the markers.

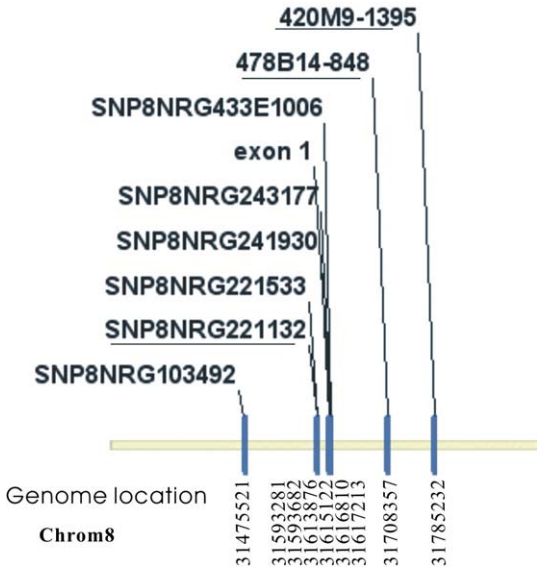

Fig. 1. The location of SNPs of *NRG1* included in the present study. The SNPs of positive association are underlined.

3.2. Comparison of the two methods

There was no significant difference in either the OR or the $p(Z)$ value between Kazeem's and Lohmueller's Methods ($p = 0.110$) using the paired samples *t*-test. For each marker, the OR and $p(Z)$ values in the synthesis of both family and case-control studies were consistent with that in the case-control studies ($p = 0.628$) using the independent sample *t*-test (Table 2).

3.3. Sensitivity, retrospection and publication bias analysis

As the association of SNP8NRG221533 has been most widely analyzed, although with conflicting results, we took this marker as an example. The cumulative forest plots and sensitivity plots of the SNP8NRG221533 analysis are presented in Fig. 2 and supplement Fig. 1 respectively. The remaining sensitivity and forest plots of other markers are all available on request. The Funnel plot of the SNP8NRG221533 (supplement Fig. 2), which was highly symmetrical and spread narrowly on either side of the *Y* axis, indicated little publication bias. The funnel plots of all the other markers showed similar results.

3.4. Population stratification

The matrix of coancestry coefficient of SNP8NRG221533 is shown in Table 3. The twenty populations involved were classified as Asian (Japanese A, Japanese B, Japanese C, Chinese A, Chinese B, Korean), European (Scottish, Icelandic, Danish, Spanish, Dutch, Finnish A, Finnish B, Portuguese, Swedish, Irish, UK, American), and African. According to the minor allele frequency of SNP8NRG221533, the coancestry coefficients suggested evident population stratification (Table 3). When

Table 2
Association and heterogeneity analysis of markers of NRG1 gene under the two methods.

SNP/microsatellites marker	No.	Kazeem 's method			Lohmueller 's method	
		OR (95% CI)	$p(Z)$	$p(Q)$	OR (95% CI)	$p(Z)$
478B14-848(0)	6	1.14(1.01–1.28)	**0.023**	0.77	1.14(1.02–1.28)	**0.023**
478B14-848(0)(case)	5	1.16(1.03–1.30)	**0.018**	0.72	1.16(1.03–1.30)	**0.013**
478B14-848(4)	6	1.00(0.88–1.15)	0.94	0.17	1.04(0.9–1.19)	0.6
478B14-848(4)(case)	4	0.96(0.81–1.15)	0.69	0.39	0.97(0.81–1.15)	0.67
478B14-848(6)	3	1.26(0.97–1.64)	0.08	0.34	1.26(0.97–1.64)	0.08
478B14-848(6)(case)	2	1.23(0.91–1.65)	0.18	0.16	1.23(0.91–1.65)	0.18
420M9-1395(2)	3	1.1(0.93–1.31)	0.26	0.31	1.09(0.93–1.27)	0.29
420M9-1395(2)(case)	2	0.99(0.79–1.24)	0.92	0.48	1.0(0.82–1.22)	0.97
420M9-1395(0)	4	1.18(1.03–1.35)	**0.017**	0.26	1.18(1.03–1.35)	**0.017**
SNP8NRG221132	6	1.23(1.01–1.50)	**0.04**	0.87	1.27(1.04–1.55)	**0.021**
SNP8NRG221132(case)	5	1.19(0.96–1.46)	0.11	0.95	1.22(0.99–1.51)	0.07
SNP8NRG241930	14	1.06(0.98–1.15)	0.12	0.35	1.06(0.98–1.15)	0.13
SNP8NRG241930(case)	11	1.06(0.96–1.16)	0.26	0.30	1.06(0.96–1.16)	0.26
SNP8NRG243177	13	1.03(0.97–1.10)	0.33	0.35	1.03(0.97–1.10)	0.34
SNP8NRG243177(case)	10	1.02(0.95–1.10)	0.54	0.16	1.02(0.95–1.10)	0.54
SNP8NRG433E1006	6	0.93(0.76–1.16)	0.56	0.105	0.93(0.76–1.16)	0.56
SNP8NRG433E1006(case)	4	0.85(0.66–1.08)	0.19	0.09	0.85(0.66–1.08)	0.19
SNP8NRG103492	3	0.90(0.7–1.15)	0.40	0.45	0.90(0.70–1.15)	0.41
SNP8NRG103492(case)	1	1.01(0.65–1.57)	0.95	–	1.01(0.65–1.57)	0.95
SNP8NRG221533	24	1.02(0.92–1.11)	0.76	**0.0007**	1.01(0.96–1.05)	0.79
SNP8NRG221533(case)	20	1.01(0.94–1.09)	0.8	**0.03**	1.0(0.95–1.06)	0.87
SNP8NRG221533asian	8	1.02(0.95–1.1)	0.5	0.07	1.02(0.95–1.10)	0.51
SNP8NRG221533asian(case)	6	0.98(0.91–1.06)	0.61	0.62	0.98(0.91–1.06)	0.61
SNP8NRG221533europ	16	0.99(0.89–1.1)	0.91	**0.002**	0.99(0.93–1.06)	0.82
SNP8NRG221533europ(case)	14	1.01(0.9–1.14)	0.82	**0.01**	1.02(0.95–1.09)	0.51

$p(Z)$: Z-test used to determine the significance of the overall OR. p-values<0.05 are indicated in boldfaces. $p(Q)$: Cochran's X^2-based Q statistic test used to assess the heterogeneity. "Case" in bracket means only case/control study included. Otherwise study number was the sum of the case/control study and family study. "–" means its heterogeneity does not exist because of only one case.

the Asian and European populations were separately meta-analyzed, the significance of the heterogeneity ($p(Q)$) tended to be weaker (Table 2).

4. Discussion

Many genetic association studies for *NRG1* and schizophrenia have been reported, but the results have been conflicting. In the present meta-analysis, SNP8NRG221132, 420M9-1395(0) and 478B14-848(0) (all members of Hap_{ICE} block) were found to be significantly associated with schizophrenia, but the sample sizes were comparatively smaller than that of the other markers. On the other hand, none of the other markers showed association but they involved larger sample sizes. In a retrospective analysis of SNP8NRG221533 (Fig. 2), from 2002 to 2008, it was evident that the cumulative OR values became progressively closer to 1.0. This suggests that, as the number of studies increased, the results tended to become stable. It can be presumed that the association of SNP8NRG221132, 420M9-1395(0) and 478B14-848(0) will similarly change with the increases in sample size. This phenomenon may partly explain the reported positive association (Li et al., 2006) and, consequently, the "no association" findings in our analysis appear more convincing.

Integrating family based and case-control based studies is an important aspect of genetic analysis. Kazeem's and Lohmueller's methods offer two different approaches to achieving this integration. In our analysis, there was no obvious difference in OR and $p(Z)$ values between the two methods ($p>0.05$,Table 2). On the other hand, when the family based studies were removed, the OR and $p(Z)$ values still showed no significant differences also ($p>0.05$). This confirms the statistical consistency of the case-control studies with the family studies. When family based studies are included, statistical power is much enhanced with the enlargement of sample size. Family based studies should therefore be considered as an important element in genetic association analysis.

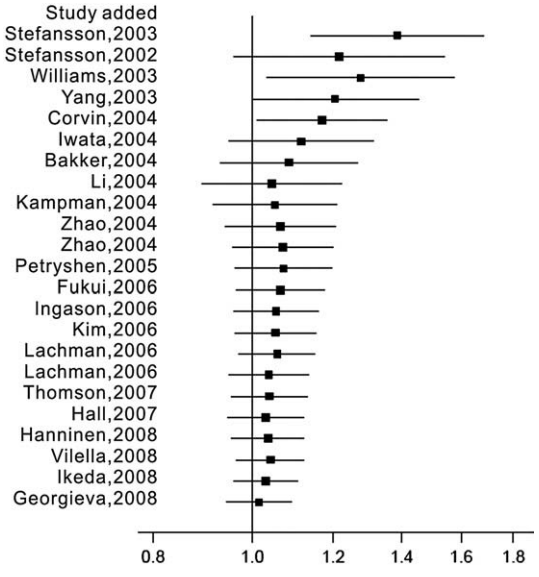

Fig. 2. The cumulative forest plots of ln(OR) with 95%CIs for the SNP8NRG221533 of the *NRG1* gene for schizophrenia using the random model.

Table 3
Matrix of coancestry coefficients of SNP8NRG221533 of *NRG1* gene.

Population	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	0.000																			
2	0.000	0.000																		
3	0.000	0.000	0.000																	
4	0.000	0.000	0.000	0.000																
5	0.009	0.014	0.011	0.009	0.000															
6	0.003	0.000	0.001	0.003	0.029	0.000														
7	0.043	0.055	0.048	0.044	0.011	0.081	0.000													
8	0.051	0.064	0.057	0.052	0.015	0.093	0.000	0.000												
9	0.053	0.066	0.059	0.054	0.016	0.095	0.000	0.000	0.000											
10	0.063	0.078	0.070	0.064	0.022	0.109	0.000	0.000	0.000	0.000										
11	0.057	0.090	0.064	0.058	0.019	0.101	0.000	0.000	0.000	0.000	0.000									
12	0.074	0.082	0.082	0.075	0.029	0.124	0.001	0.000	0.000	0.000	0.000	0.000								
13	0.050	0.063	0.056	0.051	0.014	0.091	0.000	0.000	0.000	0.000	0.000	0.000	0.000							
14	0.059	0.073	0.065	0.060	0.019	0.102	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000						
15	0.221	0.261	0.240	0.221	0.134	0.317	0.075	0.066	0.064	0.054	0.059	0.043	0.067	0.057	0					
16	0.002	0.000	0.000	0.002	0.030	0.000	0.084	0.097	0.100	0.115	0.105	0.130	0.095	0.107	0.347	0				
17	0.014	0.021	0.017	0.015	0.000	0.04	0.003	0.006	0.007	0.012	0.009	0.017	0.006	0.010	0.132	0.042	0			
18	0.085	0.103	0.093	0.086	0.035	0.137	0.005	0.002	0.001	0.000	0.001	0.000	0.002	0.001	0.038	0.144	0.024	0.000		
19	0.009	0.015	0.011	0.010	0.000	0.031	0.008	0.012	0.013	0.019	0.016	0.026	0.0123	0.017	0.143	0.032	0.000	0.033	0.000	
20	0.26	0.310	0.285	0.261	0.164	0.372	0.103	0.094	0.092	0.019	0.084	0.071	0.094	0.080	0.000	0.413	0.170	0.059	0.18	0.000

Project information:NbSamples = 20, DataType = Frequency, GenotypicData = 0.
Population pairwise Fst values: compute pairwise differences; compute relative population sizes; distance matrix: compute *F*-statistics on haplotype frequencies only. Genetic structure analysis: Computing conventional *F*-statistics from haplotype frequencies; matrix of coancestry coefficients as $t/M = -\ln(1\text{-FST})$ Weir and Cockerham, 1984; Reynold et al., 1983.
Comparisons of pairs of population samples: 1: Japanese A 2: Chinese A 3: Chinese B 4: Japanese B 5: Japanese C 6: Korean 7: Scottish A 8: Scottish B 9: Iceland 10: Danish 11: Spanish 12:Dutch 13: Ireland 14: UK 15: Swedish 16: Finnish A 17: Finnish B 18: Portuguese 19: American 20: African.

Heterogeneity is a pervasive and difficult problem, but has tended to be neglected in population genetics research into association between *NRG1* and schizophrenia. In our study, the matrix of coancestry coefficient was calculated based on the minor allele frequency of SNP8NRG221533. It showed evident population stratification (Table 3). When the Asian or the European population was analyzed independently, the heterogeneity ($p(Q)$) of the population tended to be weaker (Table 2). Since each population has its own characteristic risk allele frequency, the haplotype blocks constituted by these allelotypes were also different from each other. Again, when selecting another marker (the ($p(Q)$ value being insignificant) for analysis, such as SNP8NRG243177, the matrix of coancestry coefficients produced the same phenomenon of obvious population stratification (supplement Table 1). Therefore, for the markers of the *NRG1* gene, population stratification is universal and is one of the major reasons for heterogeneity. This also suggests the need to consider population stratification in future meta-analyses of *NRG1* or other genes.

4.1. Limitations and implications

Although the current study detected statistical primary evidence in international populations, several problems, including the possible effects of variables such as age, ethnicity and gender, need to be investigated in future meta-analyses. Again, more accurate phenotype definition, strict selection of patients, and much larger samples will be required. As for optimum sample size, because it depends on the degree of association, LD, accuracy of phenotypic data, and heterogeneity of allelic frequencies, it is difficult to define. Moreover, the establishment and use of standardized criteria for sample collection methods, DNA marker sets, assessment protocol, and application of demographic statistical methods would also be beneficial. This would enhance the comparability between study outcomes, simplify collaboration among investigators, and allow the pooling of data in future multi-sided projects or meta-analyses.

4.2. Electronic-database information

Accession numbers and URLs for data in this article are as follows:

- deCODE genetics http://www.decode.com/nrg1/markers for SNPs and microsatellite markers in the *NRG1* locus sequence;
- GenBank, http://www.ncbi.nlm.nih.gov/Genbank/for *NRG1* (AF491780);
- Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for *NRG1* (MIM 142445), SCZD (MIM 181500) and SCZD6 (MIM 603013));
- Third Party Annotation, DDBJ/EMBL/GenBank databases for *NRG1* (TPA: BK000383).

Role of the funding source
No.

Contributors
Lin He and Yunguo Gong designed the study and wrote the protocol. Yunguo Gong Chaoneng Wu and Qinghe XING managed the literature searches and analyses. Xingzhi Zhao and Jun Zhu undertook the statistical analysis, and Yunguo Gong wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
The authors declare no financial conflicts.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2009.03.017.

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