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Further evidence for an association of *G72/G30* with schizophrenia in Chinese

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Dear Editors

The *G72/G30* gene complex (*G72* also known as D-aminoacid oxidase activator, *DAOA*) is considered as one of the most promising candidate genes for both schizophrenia (SCZ) and bipolar disorder (Craddock et al., 2006). Our recent meta-analysis found that major alleles of two single nucleotide polymorphisms (SNPs) in the *G72/G30* gene region, M18/rs947267 and M22/rs778293, were significantly associated with SCZ in Asians (Shi et al., 2008). To replicate the association, we performed a family-based association analysis in a larger Han Chinese family sample, and an updated meta-analysis of association data in Asians.

Five hundred and sixty-one Han Chinese schizophrenic families with 2277 individuals from Taiwan (a collection for the Han Chinese Schizophrenia Linkage Study supported by the National Institute of Mental Health (http://nimhgenetics.org/)) were genotyped. A subset of this sample (124 families with 500 individuals) was analyzed for SCZ association by Liu *et al.* (2006). The informative members of the remaining 1777 samples from 437 families were statistically analyzed in this replication study. Methods for sample recruitment and assessments have been described elsewhere (Glatt et al., 2008; Hwu et al., 2005). Briefly, the sibling-pair families had at least two children that met the diagnostic criteria for SCZ, schizoaffective disorder (SA) or schizoaffective disorder depressed type (SADD) in the fourth edition of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (*DSM-IV*). All affected subjects were assessed with the Mandarin Chinese version of the Diagnostic Instrument for Genetic Studies (DIGS) and the Family Interview for Genetic Studies (FIGS) by a clinically trained professional. Subsequently, two psychiatrists made separate reviews of all available information including DIGS and FIGS data and medical records, and made a final diagnosis using a best-estimate procedure. Informed consent was obtained from all the participants and efforts in clinical assessment and biological sample collection were approved by the Institutional Review Boards of all project sites in Taiwan. All individuals were of Han Chinese ancestry. A statistical description of 1777 samples from 437 families is presented in Supplementary Table 1. Of 1116 siblings, 897 met *DSM-IV* criteria for SCZ, seven for SADD, and one for SA; 405 were females and 711 were males. We used SCZ as the disease trait for statistical analyses. Power calculation using PBAT (http://www.biostat.harvard.edu/~clange/default.htm) showed that, at $P < 0.05$, this sample

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Appendix A. Supplementary data
Supplementary data associated with this article is available in the online version, at the *Schizophrenia Research* website.

had 55% and 51% power to detect association with odds ratio (OR) of 1.25 for “risk” (minor) allele frequency of 0.4 of M18 and 0.3 of M22, respectively.

Genotyping of M18 and M22 was performed using TaqMan pre-designed SNP genotyping assays (Applied Biosystems Inc., Foster City, CA, USA). Samples that failed in the first round genotyping were re-genotyped. PedCheck1.1 (http://watson.hgen.pitt.edu/register/docs/pedcheck.html) was used to detect any Mendelian inconsistencies and Merlin (http://www.sph.umich.edu/csg/abecasis/Merlin/) was used to check any unlikely recombinants. After removing problematic genotypes due to the failure of genotyping or filtering by quality control (seven for M18 and three for M22), the genotyping success rates for 2277 samples were 99.7% and 99.9% for M18 and M22, respectively.

No departures from Hardy-Weinberg equilibrium were detected when the genotype data was made conditional on relatedness of the family samples (Bourgain et al., 2004). Transmission disequilibrium test (TDT) using FBAT (http://www.biostat.harvard.edu/~fbat/default.html) did not find allelic association with SCZ (M18, $P = 0.359$; M22, $P = 0.227$). However, the haplotype AG was nominally associated with disease ($P = 0.049$). To calculate OR for subsequent meta-analysis, only one affected offspring per sibling pairs was randomly selected to calculate transmitted and non-transmitted alleles from heterozygous parents (from complete “trio” families) to affected offspring. This step would yield more accurate OR than looking at all the affected siblings, because transmission to siblings is correlated in the presence of linkage.

For the updated meta-analysis of M18 and M22 in Asians, we used a similar statistical approach as previously described in detail (Shi et al., 2008). Combining family-based M22 association data (this study and data from *Liu et al.* (2006)) with two case-control studies in Han Chinese (Ma et al., 2006; Wang et al., 2004), we identified a significant association (two tailed $P = 0.0012$, Table 1 and Supplementary Figure 1). In contrast, combining new M18 data from Koreans (Shin et al., 2007) and our family study with previous Asian data (Hong et al., Liu et al., 2006; Yue et al., 2007), we could not detect a significant association anymore ($P = 0.255$, Table 1). However, M18 was significantly associated with SCZ in Chinese (fix-effect model: OR = 0.794, 95% CI = 0.703-0.897, $P_Z = 0.0002$) after removing the Korean study, showing significant genetic heterogeneity between Chinese and Koreans ($P_Q = 0.0002$). We did not detect significant publication bias, although such a test has certain limitations in terms of low power and few studies included.

In summary, our updated meta-analysis further supports a significant association of M22 with SCZ in Chinese. Independent studies with larger Han Chinese and/or other ethnic sample are warranted to confirm this finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Meta-analysis of association studies between *G72*/*G30* and schizophrenia in Asian

Study	Number of		M18/rs947267 ©		rs778293 (A)	
	Cases	Controls	OR	95% CI	OR	95% CI
Shin et al	388	367	1.277	1.028-1.587	—	—
Yue et al	359	359	0.724	0.582-0.902	—	—
Honget al	216 families		0.723	0.555-0.943	—	—
Yue et al	237 families		0.689	0.520-0.913	—	—
Liu et al	218 families[a]		1.105	0.713-1.714	0.774	0.454-1.319
This study	437 families		1.000	0.769-1.301	0.989	0.739-1.324
Wang et al	537	538	—	—	0.878	0.738-1.046
Ma et al	588	588	—	—	0.758	0.641-0.897
Pooled			0.889	0.709-1.112	0.835	0.748-0.931
Significance for pooled OR			Z[b] = 1.040	p_Z = 0.299	Z = 3.234	p_Z = **0.0012**
Heterogeneity test			Q[c] = 21.230	p_Q = **0.0007**	Q = 2.961	p_Q = 0.398

[a] Fianlly statistical analysis used data from 124 families.

[b] *Z* test was used to determine the significance of the overall odds ratio (OR); unadjusted $p_Z < 0.05$ is shown in bold type. Results under the fix-effects model are reported here if there is no evidence of between-study heterogeneity, otherwise under random-effects model.

[c] Cochran's Q test was used to assess the heterogeneity between samples; $p_Q < 0.1$ indicates significant between-study heterogeneity and are shown in bold type. Note that one affected offspring from each family was chosen to estimate OR, in avoid of potential bias.