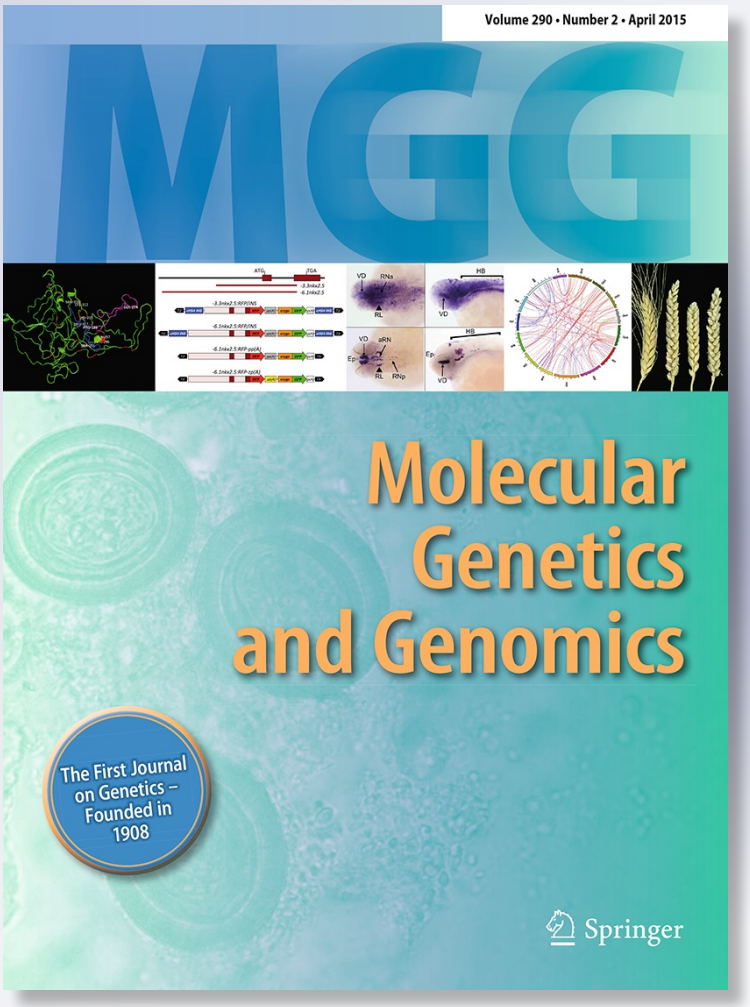
Common variants of the PINK1 *and* PARL *genes do not confer genetic susceptibility to schizophrenia in Han Chinese*

Xiao Li, Wen Zhang, Chen Zhang, Zhenghui Yi, Deng-Feng Zhang, Wei Gong, Jinsong Tang, Dong Wang, Weihong Lu, Xiaogang Chen, et al.

Molecular Genetics and Genomics

ISSN 1617-4615
Volume 290
Number 2

Mol Genet Genomics (2015)
290:585-592
DOI 10.1007/s00438-014-0942-1



Springer

Mol Genet Genomics (2015) 290:585–592
DOI 10.1007/s00438-014-0942-1

ORIGINAL PAPER

Common variants of the *PINK1* and *PARL* genes do not confer genetic susceptibility to schizophrenia in Han Chinese

Xiao Li · Wen Zhang · Chen Zhang · Zhenghui Yi · Deng-Feng Zhang · Wei Gong · Jinsong Tang · Dong Wang · Weihong Lu · Xiaogang Chen · Yiru Fang · Yong-Gang Yao

Received: 6 September 2014 / Accepted: 16 October 2014 / Published online: 30 October 2014

Abstract Schizophrenia is a prevalent psychiatric disorder with a complex etiology. Mitochondrial dysfunction has been frequently reported in schizophrenia. Phosphatase and tension homologue-induced kinase 1 (PINK1) and presenilin-associated rhomboid-like protease (PARL) are mitochondrial proteins, and genetic variants of these two genes may confer genetic susceptibility to schizophrenia by influencing mitochondrial function. In this study, we conducted a two-stage genetic association study to test this hypothesis. We genotyped 4 *PINK1* and 5 *PARL* genetic variants and evaluated the potential association of the 9 SNPs with schizophrenia in two independent case–control cohorts of 2510 Han Chinese individuals. No positive association of common genetic variants of the *PINK1* and *PARL* genes with schizophrenia was identified in our samples after Bonferroni correction. Re-analysis of the newly updated Psychiatric Genetics Consortium (PGC) data sets confirmed our negative result. Intriguingly, one *PINK1* SNP (rs10916832), which showed a marginally significant association in only Hunan samples ($P = 0.032$), is associated with the expression of a schizophrenia susceptible gene *KIF17* according to the expression quantitative trait locus (eQTL) analysis. Our study indicated that common genetic variants of the *PINK1* and *PARL* genes are unlikely to be involved in schizophrenia. Further studies are essential to characterize the role of the *PINK1* and *PARL* genes in schizophrenia.

Keywords PINK1 · PARL · Mitochondria · Schizophrenia · Association

Introduction

Schizophrenia (SCZ) is a complex psychiatric disorder affected by both genetic and environmental factors

Communicated by S. Hohmann.

Electronic supplementary material The online version of this article (doi:10.1007/s00438-014-0942-1) contains supplementary material, which is available to authorized users.

X. Li · W. Zhang · D.-F. Zhang · W. Gong · D. Wang · Y.-G. Yao (✉)
Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences and Yunnan Province, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming 650223, Yunnan, China
e-mail: yaoyg@mail.kiz.ac.cn

X. Li · D.-F. Zhang
Kunming College of Life Science, University of Chinese Academy of Sciences, Kunming 650201, Yunnan, China

C. Zhang · Z. Yi · W. Lu · Y. Fang
Schizophrenia Program, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

W. Gong
School of Life Sciences, University of Science and Technology of China, Hefei 230026, Anhui, China

J. Tang · X. Chen
Institute of Mental Health, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

(Harrison and Weinberger 2005; Brown 2011). A large amount of genetic studies have devoted to explore the genetic factor of SCZ susceptibility (Allen et al. 2008), but these findings can only explain a small portion of the heritability of SCZ. The genetic etiology of SCZ is still far from clear. Human brain is a large energy consumer, and brain mitochondria consumed more than 90 % of the oxygen in the brain to generate ATP through oxidative phosphorylation (Amar et al. 2007). Abnormal energy metabolism caused by mitochondrial dysfunction may lead to alterations of neuronal function, plasticity and brain circuitry and thus resulting in cognitive and behavioral abnormalities of SCZ (Amar et al. 2007; Shao et al. 2008). In accordance with the potential role of mitochondria in the aberrant energy utilization of SCZ, there are increasing lines of evidence which suggested that mitochondrial alterations were involved in SCZ (Prabakaran et al. 2004; Rosenfeld et al. 2011). Hitherto, more studies shall be carried out to define the relationship between mitochondrial function and schizophrenia. Phosphatase and tension homologue-induced kinase 1 (PINK1) and presenilin-associated rhomboid-like protease (PARL) are proteins that can localize to mitochondria and play a crucial role in mitochondrial function (Cipolat et al. 2006; Lin and Kang 2008; Hill and Pellegrini 2010; McLelland et al. 2014). Whether genetic variants of these two mitochondrial-related genes (*PINK1* and *PARL*) confer susceptibility to schizophrenia is an interesting yet unanswered question.

PINK1 functions in the regulation of mitochondrial quality control. *PINK1* and *Parkin*, two genes associated with Parkinson's disease, have been implicated in the degradation of depolarized mitochondria via autophagy (McLelland et al. 2014). Loss-of-function mutants of *Drosophila PINK1* caused mitochondrial dysfunction and led to flight muscle and dopaminergic neuronal degeneration (Park et al. 2006). PINK1 knockout mice exhibited impaired mitochondrial respiration and increased sensitivity to oxidative stress (Gautier et al. 2008). Mutations in the *PINK1* gene are frequently associated with psychiatric symptoms. Heterozygous carriers of *PINK1* mutations were reported showing affective and SCZ spectrum disorders (Steinlechner et al. 2007). Limbic and frontal gray matter alterations in *PINK1* mutation carriers could explain various psychiatric symptoms in a large German family (Reetz et al. 2008).

PARL is a member of the mitochondrial rhomboid family of proteases and is a key regulator of mitochondrial integrity and function (Hill and Pellegrini 2010). Many recent studies have recognized the key role of PARL in maintaining mitochondrial integrity, mitochondrial morphology and apoptosis (McQuibban et al. 2003; Curran et al. 2010). Functional alterations of PARL could contribute to mitochondrial dysregulation (Shi et al. 2011). PARL affected the proteolytic processing of PINK1 (Deas et al. 2011; Shi et al. 2011). Interaction between mitochondria and PINK1 and PARL has also been reported (Jin et al. 2010).

Given the important role of the *PINK1* and *PARL* genes in mitochondrial function, we tested whether genetic variants of these two mitochondrial-related genes confer susceptibility to SCZ in Han Chinese in this study. In total, we screened 9 tag SNPs (4 in *PINK1* and 5 in *PARL*) which were selected according to the linkage disequilibrium (LD) pattern of HapMap CHB population (http://www.hapmap.ncbi.nlm.nih.gov/) in two independent sample sets involving 2510 Han Chinese individuals. We also checked the newly updated Psychiatric Genetics Consortium (PGC) dataset of the 9 SNPs to further validate our association result in Han Chinese. However, we identified no association between the *PINK1* or *PRAL* genetic polymorphisms and SCZ.

Materials and methods

Subjects

Two cohorts of SCZ cases and controls were analyzed. The discovery cohort was composed of 504 Han Chinese with SCZ and 480 controls collected from Hunan Province; the replication cohort was composed of 624 Han Chinese with SCZ and 902 controls from Shanghai. Most of these case and control samples were previously analyzed for other genetic variants (Ma et al. 2013, 2014; Zhang et al. 2014; Li et al. 2014). Demographical data such as age, sex and education year of those participants were collected. The patients were independently diagnosed by two psychiatrists according to the Diagnostic and Statistical Manual, the Fourth Version (DSM-IV) for SCZ. The control subjects were composed of adult individuals who visited the hospital for physical examinations. The control samples were geographically and ethnically matched with the patients and were clinically diagnosed having no psychiatric disorders. Written informed consent was obtained from all participants of this study. This study complies with the ethical standards recommended by the Helsinki Declaration and was approved by the institutional review board of Kunming Institute of Zoology.

SNP selection and genotyping

Nine SNPs (4 in *PINK1* and 5 in *PARL*) were selected for genotyping according to the following criteria: (1) SNPs with a high capability of tagging other SNPs based on the linkage disequilibrium (LD) pattern of the *PINK1* and *PARL* genes in HapMap CHB data set (http://www.hapmap.ncbi.nlm.nih.gov); (2) SNPs with a

minor allele frequency (MAF) >5 % in Hap Map CHB data set and dbSNP (http://www.ncbi.nlm.nih.gov/SNP/). The information of each SNP is shown in Table S1.

Genomic DNA of all participants was extracted from peripheral blood using the AxyPrep™ Blood Genomic DNA Miniprep Kit according to the manufacturer's instruction. The 9 SNPs were detected by the SNaPshot assay following the procedure described in our previous study (Li et al. 2014; Bi et al. 2014).

Statistical analysis

We estimated deviation from the Hardy–Weinberg equilibrium (HWE), individual SNP association and haplotype analysis using PLINK (Purcell et al. 2007). Quanto software was used to estimate the statistical power (Gauderman 2002). Haploview 4.2 (Barrett et al. 2005) was used to construct the linkage disequilibrium (LD) plots for our samples.

Re-analysis of Psychiatric Genetics Consortium data

Publicly available database was used to further analyze the potential association of the nine SNPs with SCZ. The newly updated Psychiatric Genetics Consortium (PGC, http://www.broadinstitute.org/mpg/ricopili/) data of the *PINK1* and *PARL* genes were retrieved to determine the association between the 9 SNPs and psychiatric disorders (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Genevar (http://www.sanger.ac.uk/resources/software/genevar/) (Yang et al. 2010) and eQTL Browser (http://www.eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/) (Pickrell et al. 2010) were used to obtain the expression quantitative trait locus (eQTL) information of the 9 SNPs.

Results

In total, we genotyped 4 *PINK1* and 5 *PARL* SNPs in two independent Han Chinese sample sets from South Central China (480 SCZ cases and 504 normal individuals) and East China (624 SCZ cases and 902 normal controls). With false positive rate being controlled as 0.05, for MAF ranging from 0.1 to 0.5, the statistical power to detect the odds ratio (OR) value as 1.5 for risk allele was above 82 % in our discovery cohort and 90 % in the replication cohort under the log additive model.

Genotype and allele frequencies of the 9 SNPs and haplotype frequencies of the two genes were compared between case and control samples. None of these SNPs showed a positive association with SCZ considering genotype and allele frequencies in the discovery cohort (Table 1). Note that rs10916832 was marginally significant in the allele comparison in the discovery sample from Hunan Province, China ($P = 0.032$, Table 1), but the significance did not survive after Bonferroni correction for multiple testing. There were two haplotypes of the *PINK1* gene showing significant associations with SCZ in the discovery cohort ($P = 0.009$, OR = 1.950 for CGAC; $P = 0.008$, OR = 0.771 for TGAC; Table 2), however, this positive result was not verified in the replication cohort ($P = 0.362$, OR = 0.818 for CGAC; $P = 0.095$, OR = 1.142 for TGAC; Table 2), suggesting that the association observed in the discovery cohort may not be true and/or caused by population stratification. When the two cohorts were combined together (1,128 SCZ patients and 1,382 controls), we found no significant association. LD analysis showed similar LD patterns of both genes in the case and control cohorts (Fig. 1).

We further analyzed the association between the 9 SNPs and SCZ, bipolar disorder and major depression using the newly updated PGC data sets (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). No association was observed between the 9 SNPs and bipolar disorder or major depression. Three SNPs, rs1061593, rs2305666 and rs10937153 of the *PARL* gene, were marginally significant with SCZ (Table S2). Similarly, the association did not survive Bonferroni correction for multiple testing.

Intriguingly, eQTL analysis showed that the *PINK1* SNP rs10916832, which showed a suggestive association with SCZ only in Hunan sample, is associated with the expression of a reported SCZ susceptibility gene *KIF17* (Tarabeux et al. 2010), suggesting that rs10916832 may be involved in SCZ through affecting other gene(s). Other SNPs showed signals as eQTL for several genes that may not be involved in SCZ (Valente et al. 2004; Dimas et al. 2009; Phasukkijwatana et al. 2010; Kishi et al. 2011; Nica et al. 2011; Guintivano et al. 2014) (Table 3).

Discussion

PINK1 is a protein that can localize to mitochondria and PARL is an inner mitochondrial membrane rhomboid (Cipolat et al. 2006; Lin and Kang 2008). Genetic variations of the *PINK1* and *PARL* genes have been reported to influence mitochondrial function (Park et al. 2006; Curran et al. 2010). In PINK1 knock down cells, membrane potential, oxygen consumption and mitochondrial mass are all decreased (Park et al. 2006; Corona et al. 2014). One

Table 1 Comparison of genotype and allele frequencies of 4 *PINK1* and 5 *PARL* SNPs in 504 schizophrenia patients and 480 healthy controls from Hunan Province, and in 624 schizophrenia cases and 902 healthy controls from Shanghai

SNP ID	Populations	Allele	Number of samples		*P* value[a]	Genotype	Number of samples		*P* value[a]	Adjusted *P* value[b]	HWE *P* value[c]
			Case	Control			Case	Control			
PINK1 gene											
rs10916832	Hunan	C/T	359/649	298/662	0.032	CC/CT/TT	70/219/215	49/200/231	0.102	0.115	0.594
	Shanghai		411/837	623/1,181	0.358		60/291/273	104/415/383	0.489	0.368	0.659
	Combined		770/1,486	921/1,843	0.546		130/510/488	153/615/614	0.829	0.950	1.000
rs10916840	Hunan	A/G	293/715	259/701	0.303	AA/AG/GG	46/201/257	34/191/255	0.478	0.467	0.908
	Shanghai		309/935	463/1,339	0.594		42/225/355	51/361/489	0.261	0.306	0.162
	Combined		602/1,650	722/2,040	0.637		88/426/612	85/552/744	0.199	0.231	0.210
rs1043424	Hunan	C/A	363/645	335/625	0.605	CC/AC/AA	71/221/212	53/229/198	0.266	0.236	0.315
	Shanghai		474/774	718/1,086	0.311		86/302/236	140/438/324	0.572	0.515	0.728
	Combined		837/1,419	1,053/1,711	0.469		157/523/448	193/667/522	0.583	0.551	0.425
rs4704	Hunan	T/C	396/612	363/597	0.502	TT/CT/CC	85/226/193	70/223/187	0.612	0.588	0.772
	Shanghai		457/791	675/1,129	0.654		90/277/257	117/441/344	0.220	0.167	0.201
	Combined		853/1,403	1,038/1,726	0.852		175/503/450	187/664/531	0.163	0.142	0.390
PARL gene											
rs1061593	Hunan	A/G	488/520	482/478	0.426	AA/AG/GG	120/248/136	106/270/104	0.064	0.070	0.008
	Shanghai		604/644	837/967	0.276		145/314/165	203/431/268	0.375	0.317	0.255
	Combined		1,092/1,164	1,319/1,445	0.630		265/562/301	309/701/372	0.794	0.880	0.554
rs2305666	Hunan	C/A	428/580	408/552	0.986	CC/AC/AA	87/254/163	87/234/159	0.868	0.917	1.000
	Shanghai		490/756	705/1,099	0.891		93/304/226	143/419/340	0.660	0.625	0.484
	Combined		918/1,336	1,113/1,651	0.741		180/558/389	230/653/499	0.529	0.499	0.503
rs10937153	Hunan	G/A	468/540	449/511	0.879	GG/AG/AA	109/250/145	108/233/139	0.930	0.941	0.583
	Shanghai		639/607	907/897	0.585		166/307/150	231/445/226	0.863	0.893	0.690
	Combined		1,107/1,147	1,356/1,408	0.970		275/557/295	339/678/365	0.983	0.973	0.485
rs12631031	Hunan	A/G	266/742	258/702	0.807	AA/AG/GG	33/200/271	29/200/251	0.803	0.821	0.204
	Shanghai		310/938	467/1,337	0.514		39/232/353	60/347/495	0.801	0.813	1.000
	Combined		576/1,680	725/2,039	0.574		72/432/624	89/547/746	0.791	0.641	0.444
rs7653061	Hunan	G/T	456/552	426/534	0.700	GG/GT/TT	104/248/152	92/242/146	0.842	0.827	0.712
	Shanghai		524/724	759/1,045	0.962		108/308/208	163/433/306	0.861	0.659	0.682
	Combined		980/1,276	1,185/1,579	0.687		212/556/360	255/675/452	0.912	0.910	0.913

[a] *P* values were calculated by the Chi-square test

[b] Binary logistic regression analysis was performed to assess the association of *PINK1* and *PARL* SNPs with schizophrenia with an adjustment for sex and age

[c] *P* values were calculated in the control groups

Table 2 Haplotype frequencies of 4 SNPs of the *PINK1* gene and 5 SNPs of the *PARL* gene in 504 schizophrenia patients and 480 healthy controls from Hunan Province, and in 624 schizophrenia cases and 902 healthy controls from Shanghai

Haplotype[a]	Hunan				Shanghai				Combined			
	Case no.	Control no.	*P* value	OR (95 % CI)	Case no.	Control no.	*P* value	OR (95 % CI)	Case no.	Control no.	*P* value	OR (95 % CI)
PINK1												
TGCT	76	80	0.519	0.898 (0.647–1.246)	121	182	0.721	0.957 (0.751–1.219)	197	262	0.361	0.914 (0.753–1.109)
TAAT	291	260	0.370	1.094 (0.899–1.333)	308	461	0.584	0.955 (0.808–1.128)	599	721	0.709	1.024 (0.903–1.162)
CGAT	25	22	0.782	1.085 (0.608–1.938)	24	25	0.245	1.395 (0.793–2.455)	49	47	0.224	1.283 (0.857–1.923)
CGCC	287	253	0.286	1.114 (0.914–1.358)	355	541	0.357	0.928 (0.792–1.088)	642	794	0.834	0.987 (0.873–1.116)
CGAC	47	23	0.009	1.950 (1.173–3.243)	33	58	0.362	0.818 (0.530–1.261)	80	81	0.218	1.218 (0.890–1.667)
TGAC	282	322	0.008	0.771 (0.636–0.934)	407	537	0.095	1.142 (0.977–1.334)	689	859	0.682	0.975 (0.864–1.100)
PARL												
ACAAG	133	136	0.542	0.923 (0.714–1.194)	163	233	0.913	1.012 (0.817–1.254)	296	369	0.811	0.980 (0.832–1.155)
GCAAG	17	13	0.664	1.177 (0.563–2.461)	14	30	0.217	0.670 (0.354–1.269)	31	43	0.595	0.882 (0.554–1.404)
GAAAG	118	108	0.739	1.048 (0.794–1.383)	131	206	0.420	0.909 (0.721–1.146)	249	314	0.718	0.968 (0.811–1.155)
ACAGG	151	137	0.643	1.061 (0.826–1.363)	172	221	0.217	1.144 (0.924–1.417)	323	358	0.160	1.123 (0.955–1.320)
GCAGG	36	29	0.489	1.192 (0.725–1.959)	36	56	0.823	0.953 (0.625–1.453)	72	85	0.814	1.039 (0.755–1.429)
ACGGT	11	13	0.599	0.805 (0.359–1.807)	27	40	0.918	0.974 (0.595–1.596)	38	53	0.538	0.876 (0.576–1.334)
AAGGT	118	116	0.809	0.967 (0.736–1.270)	166	219	0.346	1.109 (0.894–1.377)	284	335	0.616	1.044 (0.882–1.236)
GAGGT	344	325	0.911	1.011 (0.839–1.218)	456	664	0.867	0.987 (0.850–1.147)	800	989	0.814	0.986 (0.878–1.108)
ACAGT	80	83	0.577	0.913 (0.662–1.258)	83	135	0.377	0.880 (0.663–1.168)	163	218	0.378	0.910 (0.737–1.123)

[a] The order of 4 *PINK1* SNPs in each haplotype is rs10916832–rs10916840–rs1043424–rs4704; the order of 5 *PARL* SNPs in each haplotype is rs1061593–rs2305666–rs10937153–rs12631031–rs7653061

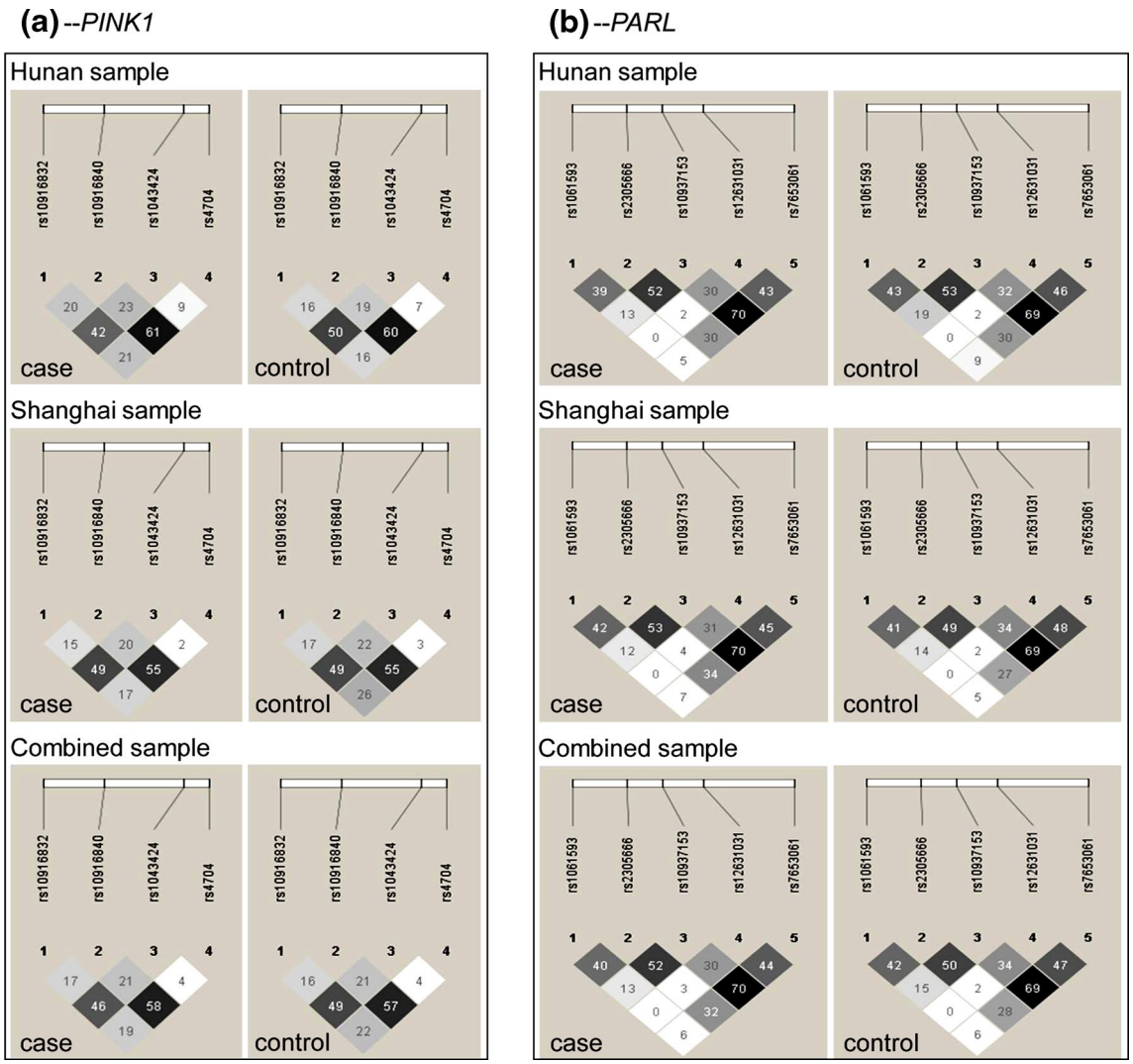


Fig. 1 The linkage disequilibrium (LD) structures of the *PINK1* and *PARL* genes in Han Chinese with and without schizophrenia. The value in each square refers to $r^2 \times 100$ for each SNP pair. The *blacker square* represented the higher LD. LD pattern of the 4 *PINK1* SNPs (**a**) and 5 *PARL* SNPs (**b**) was constructed in schizophrenia patients and controls from Hunan, Shanghai and the combined samples

Table 3 eQTL information of *PINK1* and *PARL* SNPs analyzed in this study

SNP	Gene	Population/tissue	Associated disease
rs10916832	*KIF17*[a]	CHB	Schizophrenia (Tarabeux et al. 2010)
	HP1BP3[b]	Twin1-A[e]	Postpartum depression (Guintivano et al. 2014)
rs1043424	*PINK1*[c]	Gencord-F[f]	Parkinson's disease (Valente et al. 2004)
rs4704	*HTR6*[b]	Twin2-A[e]	Methamphetamine-induced psychosis (Kishi et al. 2011)
rs2305666	*PARL*[d]	European	Leber hereditary optic neuropathy (Phasukkijwatana et al. 2010)
rs10937153	*PARL*[d]	European	Leber hereditary optic neuropathy (Phasukkijwatana et al. 2010)

[a] Data source: Genevar (http://www.sanger.ac.uk/resources/software/genevar/), HapMap3

[b] Data source: Genevar MuTHER Pilot

[c] Data source: Genevar Geneva GenCord

[d] Data source: eQTL Browser (http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/)

[e] A, Adipose (Nica et al. 2011)

[f] F, Fibroblast (Dimas et al. 2009)

promoter variant of *PARL*, T-191C, can significantly affect mitochondrial content levels (Curran et al. 2010). Mitochondrial dysfunction has been recognized to be prevalent in neuropsychiatric diseases, especially in SCZ (Shao et al. 2008). Therefore, we speculated that genetic polymorphisms of the *PINK1* and *PARL* genes may confer susceptibility to SCZ.

In this study, we analyzed the association between 4 *PINK1* and 5 *PARL* SNPs and SCZ in two independent Han Chinese sample sets and the newly released PGC data sets. We observed inconsistent patterns regarding the association of *PINK1* and *PARL* SNPs with SCZ in different populations. For instance, rs10916832 of the *PINK1* gene (at the genotypic level) and two *PINK1* haplotypes showed significant associations with SCZ in our discovery sample from Hunan Province, but this result was not validated in the validation sample from Shanghai and the PGC sample. None of the 5 *PARL* SNPs were associated with SCZ in Han Chinese analyzed in this study, but we observed 3 SNPs (rs1061593, rs2305666 and rs10937153) showing marginally significant associations with SCZ in the PGC sample (Table S2). These inconsistent results suggested that the observed positive association should be received with caution.

The current study has some limitations. First, the relatively small sample size of this study limited us to get a high power to make a firm conclusion. This may account for the inconsistent patterns of association between the two independent case and control samples analyzed in this study. Second, we did not perform analysis for potential association between specific psychiatric phenotypes and *PINK1* and *PARL* SNPs, as we lacked the detailed clinical information for these patients. There is a possibility that variants in the *PINK1* and/or *PARL* gene(s) may be associated with certain subtype(s) or symptom(s) of SCZ, or antipsychotic medication. Third, we could not exclude the possibility for an active role of rare variants in these two genes in SCZ.

In summary, we found no association of common genetic variants of the *PINK1* and *PARL* genes with SCZ in Han Chinese and the PGC dataset. Other factors, such as rare variants, SNP–SNP interactions and gene–gene interactions might have crucial roles in SCZ and account for the missing heritability (Manolio et al. 2009). Our current data provide helpful information and reference data for future studies focused on the *PINK1* and *PARL* genes in neuropsychiatric disorders. Further validation and functional study may help to explore the potential relationship between the two mitochondrial-related genes and SCZ.

Acknowledgments This study was supported by the Strategic Priority Research Program (B) of the Chinese Academy of Sciences (XDB02020000) and the West Light Foundation of the Chinese Academy of Sciences.

Conflict of interest The authors declare that they have no conflicts of interest concerning this article.

References

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

Amar S, Shamir A, Ovadia O, Blanaru M, Reshef A, Kremer I, Rietschel M, Schulze TG, Maier W, Belmaker RH, Ebstein RP, Agam G, Mishmar D (2007) Mitochondrial DNA HV lineage increases the susceptibility to schizophrenia among Israeli Arabs. Schizophr Res 94:354–358

Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265

Bi R, Zhao L, Zhang C, Lu W, Feng JQ, Wang Y, Ni J, Zhang J, Li GD, Hu QX, Wang D, Yao YG, Li T (2014) No association of the LRRK2 genetic variants with Alzheimer's disease in Han Chinese individuals. Neurobiol Aging 35(2):444.e5–444.e9

Brown AS (2011) The environment and susceptibility to schizophrenia. Prog Neurobiol 93:23–58

Cipolat S, Rudka T, Hartmann D, Costa V, Serneels L, Craessaerts K, Metzger K, Frezza C, Annaert W, D'Adamio L, Derks C, Dejaegere T, Pellegrini L, D'Hooge R, Scorrano L, De Strooper B (2006) Mitochondrial rhomboid PARL regulates cytochrome c release during apoptosis via OPA1-dependent cristae remodeling. Cell 126:163–175

Corona JC, de Souza SC, Duchen MR (2014) PPARgamma activation rescues mitochondrial function from inhibition of complex I and loss of PINK1. Exp Neurol 253:16–27

Curran JE, Jowett JB, Abraham LJ, Diepeveen LA, Elliott KS, Dyer TD, Kerr-Bayles LJ, Johnson MP, Comuzzie AG, Moses EK, Walder KR, Collier GR, Blangero J, Kissebah AH (2010) Genetic variation in PARL influences mitochondrial content. Hum Genet 127:183–190

Deas E, Plun-Favreau H, Gandhi S, Desmond H, Kjaer S, Loh SH, Renton AE, Harvey RJ, Whitworth AJ, Martins LM, Abramov AY, Wood NW (2011) PINK1 cleavage at position A103 by the mitochondrial protease PARL. Hum Mol Genet 20:867–879

Dimas AS, Deutsch S, Stranger BE, Montgomery SB, Borel C, Attar-Cohen H, Ingle C, Beazley C, Gutierrez Arcelus M, Sekowska M, Gagnebin M, Nisbett J, Deloukas P, Dermitzakis ET, Antonarakis SE (2009) Common regulatory variation impacts gene expression in a cell type-dependent manner. Science 325:1246–1250

Gauderman WJ (2002) Sample size requirements for matched case-control studies of gene-environment interaction. Stat Med 21:35–50

Gautier CA, Kitada T, Shen J (2008) Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci USA 105:11364–11369

Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA (2014) Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. Mol Psychiatry 19:560–567

Harrison PJ, Weinberger DR (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 10:40–68

Hill RB, Pellegrini L (2010) The PARL family of mitochondrial rhomboid proteases. Semin Cell Dev Biol 21:582–592

Jin SM, Lazarou M, Wang C, Kane LA, Narendra DP, Youle RJ (2010) Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. J Cell Biol 191:933–942

Kishi T, Fukuo Y, Okochi T, Kitajima T, Kawashima K, Naitoh H, Ujike H, Inada T, Yamada M, Uchimura N, Sora I, Iyo M, Ozaki N, Iwata N (2011) Serotonin 6 receptor gene is associated with methamphetamine-induced psychosis in a Japanese population. Drug Alcohol Depend 113:1–7

Li X, Zhang W, Zhang C, Gong W, Tang J, Yi Z, Wang D, Lu W, Fang Y, Chen X, Yao YG (2014) No association between genetic variants of the LRRK2 gene and schizophrenia in Han Chinese. Neurosci Lett 566:210–215

Lin W, Kang UJ (2008) Characterization of PINK1 processing, stability, and subcellular localization. J Neurochem 106:464–474

Ma L, Tang J, Wang D, Zhang W, Liu W, Wang D, Liu XH, Gong W, Yao YG, Chen X (2013) Evaluating risk loci for schizophrenia distilled from genome-wide association studies in Han Chinese from Central China. Mol Psychiatry 18:638–639

Ma L, Wu DD, Ma SL, Tan L, Chen X, Tang NL, Yao YG (2014) Molecular evolution in the CREB1 signal pathway and a rare haplotype in CREB1 with genetic predisposition to schizophrenia. J Psychiatr Res 57:84–89

Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium (2013) A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 18:497–511

Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TF, McCarroll SA, Visscher PM (2009) Finding the missing heritability of complex diseases. Nature 461:747–753

McLelland GL, Soubannier V, Chen CX, McBride HM, Fon EA (2014) Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. EMBO J 33:282–295

McQuibban GA, Saurya S, Freeman M (2003) Mitochondrial membrane remodelling regulated by a conserved rhomboid protease. Nature 423:537–541

Nica AC, Parts L, Glass D, Nisbet J, Barrett A, Sekowska M, Travers M, Potter S, Grundberg E, Small K, Hedman AK, Bataille V, Tzenova Bell J, Surdulescu G, Dimas AS, Ingle C, Nestle FO, di Meglio P, Min JL, Wilk A, Hammond CJ, Hassanali N, Yang TP, Montgomery SB, O'Rahilly S, Lindgren CM, Zondervan KT, Soranzo N, Barroso I, Durbin R, Ahmadi K, Deloukas P, McCarthy MI, Dermitzakis ET, Spector TD, Mu TC (2011) The architecture of gene regulatory variation across multiple human tissues: the MuTHER study. PLoS Genet 7:e1002003

Park J, Lee SB, Lee S, Kim Y, Song S, Kim S, Bae E, Kim J, Shong M, Kim JM, Chung J (2006) Mitochondrial dysfunction in *Drosophila* PINK1 mutants is complemented by parkin. Nature 441:1157–1161

Phasukkijwatana N, Kunhapan B, Stankovich J, Chuenkongkaew WL, Thomson R, Thornton T, Bahlo M, Mushiroda T, Nakamura Y, Mahasirimongkol S, Tun AW, Srisawat C, Limwongse C, Peerapittayamongkol C, Sura T, Suthammarak W, Lertrit P (2010) Genome-wide linkage scan and association study of PARL to the expression of LHON families in Thailand. Hum Genet 128:39–49

Pickrell JK, Marioni JC, Pai AA, Degner JF, Engelhardt BE, Nkadori E, Veyrieras JB, Stephens M, Gilad Y, Pritchard JK (2010) Understanding mechanisms underlying human gene expression variation with RNA sequencing. Nature 464:768–772

Prabakaran S, Swatton JE, Ryan MM, Huffaker SJ, Huang JT, Griffin JL, Wayland M, Freeman T, Dudbridge F, Lilley KS, Karp NA, Hester S, Tkachev D, Mimmack ML, Yolken RH, Webster MJ, Torrey EF, Bahn S (2004) Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. Mol Psychiatry 9:684–697

Psychiatric GWAS Consortium Bipolar Disorder Working Group (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet 43:977–983

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

Reetz K, Lencer R, Steinlechner S, Gaser C, Hagenah J, Buchel C, Petersen D, Kock N, Djarmati A, Siebner HR, Klein C, Binkofski F (2008) Limbic and frontal cortical degeneration is associated with psychiatric symptoms in PINK1 mutation carriers. Biol Psychiatry 64:241–247

Rosenfeld M, Brenner-Lavie H, Ari SG, Kavushansky A, Ben-Shachar D (2011) Perturbation in mitochondrial network dynamics and in complex I dependent cellular respiration in schizophrenia. Biol Psychiatry 69:980–988

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

Shao L, Martin MV, Watson SJ, Schatzberg A, Akil H, Myers RM, Jones EG, Bunney WE, Vawter MP (2008) Mitochondrial involvement in psychiatric disorders. Ann Med 40:281–295

Shi G, Lee JR, Grimes DA, Racacho L, Ye D, Yang H, Ross OA, Farrer M, McQuibban GA, Bulman DE (2011) Functional alteration of PARL contributes to mitochondrial dysregulation in Parkinson's disease. Hum Mol Genet 20:1966–1974

Steinlechner S, Stahlberg J, Volkel B, Djarmati A, Hagenah J, Hiller A, Hedrich K, Konig I, Klein C, Lencer R (2007) Co-occurrence of affective and schizophrenia spectrum disorders with PINK1 mutations. J Neurol Neurosurg Psychiatry 78:532–535

Tarabeux J, Champagne N, Brustein E, Hamdan FF, Gauthier J, Lapointe M, Maios C, Piton A, Spiegelman D, Henrion E, Synapse to Disease Team, Millet B, Rapoport JL, Delisi LE, Joober R, Fathalli F, Fombonne E, Mottron L, Forget-Dubois N, Boivin M, Michaud JL, Lafreniere RG, Drapeau P, Krebs MO, Rouleau GA (2010) De novo truncating mutation in Kinesin 17 associated with schizophrenia. Biol Psychiatry 68:649–656

Valente EM, Abou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio AR, Healy DG, Albanese A, Nussbaum R, Gonzalez-Maldonado R, Deller T, Salvi S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G, Wood NW (2004) Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 304:1158–1160

Yang TP, Beazley C, Montgomery SB, Dimas AS, Gutierrez-Arcelus M, Stranger BE, Deloukas P, Dermitzakis ET (2010) Genevar: a database and Java application for the analysis and visualization of SNP-gene associations in eQTL studies. Bioinformatics 26:2474–2476

Zhang W, Tang J, Zhang AM, Peng MS, Xie HB, Tan L, Xu L, Zhang YP, Chen X, Yao YG (2014) A matrilineal genetic legacy from the last glacial maximum confers susceptibility to schizophrenia in Han Chinese. J Genet Genomics 41:397–407

Common variants of the *PINK1* and *PARL* genes do not confer genetic susceptibility to schizophrenia in Han Chinese

Xiao Li · Wen Zhang · Chen Zhang · Zhenghui Yi · Deng-Feng Zhang · Wei Gong · Jinsong Tang · Dong Wang · Weihong Lu · Xiaogang Chen · Yiru Fang · Yong-Gang Yao

X. Li · W. Zhang · D.-F. Zhang · W. Gong · D. Wang · Y.-G. Yao
Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences & Yunnan Province, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan, China

C. Zhang · Z. Yi · W. Lu · Y. Fang
Schizophrenia Program, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

J. Tang · X. Chen
Institute of Mental Health, the Second Xiangya Hospital, Central South University, Changsha, Hunan, China

X. Li · D.-F. Zhang
Kunming College of Life Science, University of Chinese Academy of Sciences, Kunming, Yunnan, 650201, China

W. Gong
School of Life Sciences, University of Science and Technology of China, Hefei, Anhui, 230026, China
Correspondence to Dr. Yong-Gang Yao, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming 650223, China. Tel/Fax: 86-871-65180085; E-mail: ygyaozh@gmail.com or yaoyg@mail.kiz.ac.cn

Table S1 Primers for genotyping 4 *PINK1* and 5 *PARL* SNPs by using SNaPshot assay

SNP ID	Location and function	Relevant gene	Primer (5'-3') [a]
rs10916832	3'UTR of *CDA* gene	*CDA-PINK1*	F: TGGGCTGGACCTAACTGC
	Tag SNP		R: AGTAGCTACTGAGAAAACCCTTTGT
			E: act$(gact)_2$ TAACCATCCTAGAGTGTGTTTTTGTCTCAT
rs10916840	5'UTR	*PINK1*	F: TGCGTGTGTGTGTTCTGTG
	Tag SNP		R: TTTTGAAGACCCCAAGACAA
			E: $(gact)_1$ CTATGCCATTAAACAAACGGTGTGGCTTTG
rs1043424	Exon 8	*PINK1*	F: AAATGTGCTTCATCTAAGCCTC
	Tag SNP		R: AACACTTCTCTGTGAGCCTGTT
			E: GGTGAACATATTCTAGCCCTGAAGA
rs4704	exon 3 of *DDOST*	*PINK1-DDOST*	F: TTGGAGGCAACATCAACG
	Tag SNP		R: ACTCACCAATGTCGGAGCT
			E: t$(gact)_5$ CGTGGAGACCATCAGTGCCTTTATTGACGG
rs1061593	3'UTR of *MAP6D1*	*MAP6D1-PARL*	F: ACGGGCTTCCACTTCACA
	Tag SNP		R: TAAATGTGAGTCATTCAATCCCA
			E: ct$(gact)_8$ ACAGACCTCCTTATGGCCAAGATGAGCCTC
rs2305666	intron 7	*PARL*	F: TCTAAAGAGCAGCACATTTTCTAG
	Tag SNP		R: ACCTATTATTGGGGACATAAGTAACT
			E: t$(gact)_7$ AGTTTACATGCTGCACATTTCTAGGTGAGC
rs10937153	intron 4	*PARL*	F: AGGTATTCCTCTACTTGTTGAATTAAAA
	Tag SNP		R: TTATTGAAATCAGTCCTTATTGGC
			E: t$(gact)_6$ ATTCCTCCAGTCTCTGTAGGCAACAGGCAA
rs12631031	intron 1	*PARL*	F: TATTCTTTGATACATGAAGTGGATTT
	Tag SNP		R: TTATCCTCATTTCTCAGATGGG

			E: (gact) $_{11}$ ATTCCCGAATCCACCCAGTTCTAGCTGTGT
rs7653061	5'UTR	*PARL*	F: ACCTCTTCCAGGAGGCCT
	Tag SNP		R: TTGCAGAGATAAGCATAAAGCG
			E: act(gact) $_{9}$ CCTTTCCCAGACCTCCACTCCAATTTAGAT

[a] In the "$(gact)_n$", n means repeats of "gact". F: forward primer; R: reverse primer; E: extension primer.

Table S2 PGC data of the 9 SNPs for schizophrenia, bipolar disorder and major depressive disorder

SNP ID	Data sets	*P* value	Allele	FRQ(HM)	OR
rs10916832	PGC_SCZ52_may13	0.748	T/C	0.817	1.006
	PGC Bipolar GWAS	0.195	C/T	0.107	1.058
	PGC MDD GWAS	0.614	T/C	0.932	1.020
rs10916840	PGC_SCZ52_may13	0.550	A/G	0.382	0.994
	PGC Bipolar GWAS	-	-	-	-
	PGC MDD GWAS	0.278	A/G	0.403	0.977
rs1043424	PGC_SCZ52_may13	0.966	A/C	0.718	1.001
	PGC Bipolar GWAS	0.808	A/C	0.648	0.994
	PGC MDD GWAS	0.281	A/C	0.714	0.975
rs4704	PGC_SCZ52_may13	0.499	A/G	0.600	0.993
	PGC Bipolar GWAS	0.347	A/G	0.607	0.978
	PGC MDD GWAS	0.865	A/G	0.621	1.004
rs1061593	PGC_SCZ52_may13	**0.045**	T/C	0.564	1.021
	PGC Bipolar GWAS	0.258	C/T	0.467	1.027
	PGC MDD GWAS	0.381	T/C	0.507	0.982
rs2305666	PGC_SCZ52_may13	**0.013**	A/C	0.753	0.966
	PGC Bipolar GWAS	0.221	A/C	0.828	0.962
	PGC MDD GWAS	0.248	A/C	0.816	0.967
rs10937153	PGC_SCZ52_may13	**0.049**	A/G	0.329	1.024
	PGC Bipolar GWAS	0.521	A/G	0.230	1.018
	PGC MDD GWAS	0.430	A/G	0.250	1.020
rs12631031	PGC_SCZ52_may13	0.983	A/G	0.152	1.000
	PGC Bipolar GWAS	0.991	A/G	0.074	1.000
	PGC MDD GWAS	0.844	A/G	0.102	0.994
rs7653061	PGC_SCZ52_may13	0.893	T/G	0.803	0.998
	PGC Bipolar GWAS	0.997	G/T	0.090	1.000
	PGC MDD GWAS	0.739	T/G	0.893	1.011

Sources of the data sets: PGC_SCZ52_may13 (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), PGC Bipolar GWAS (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011), PGC MDD GWAS (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium 2013).

Supplementary references

Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium (2013) A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 18:497-511

Psychiatric GWAS Consortium Bipolar Disorder Working Group (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet 43:977-983

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421-427