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Effect of the *SIRT1* gene on regional cortical grey matter density in the Han Chinese population

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Background

Our previous genome-wide association study (CONVERGE sample) identified significant association between single nucleotide polymorphisms (SNPs) near the *SIRT1* gene and major depressive disorder (MDD) in Chinese populations.

Aims

To investigate whether SNPs across the *SIRT1* gene locus affect regional grey matter density in the Han Chinese population.

Method

T1-weighted structural magnetic resonance imaging was conducted on 92 healthy participants from Eastern China. Grey matter was segmented from the image, which consisted of voxel-wise grey matter density. The effect of *SIRT1* SNPs on grey matter density was determined by a multiple linear regression framework.

Results

SNP rs4746720 was significantly associated with grey matter density in two brain cortical regions: the orbital part of the right inferior frontal gyrus and the orbital part of the left inferior frontal gyrus (family-wise error-corrected $P < 0.05$; voxel-wise $P < 0.001$). Also, rs4746720 exceeded genome-wide significance in association with MDD in our CONVERGE sample ($P = 3.32 \times 10^{-08}$, odds ratio 1.161).

Conclusions

Our results provided evidence for a potential role of the *SIRT1* gene in the brain, implying a possible pathophysiological mechanism underlying susceptibility to MDD.

Declaration of interest

None.

Keywords

SIRT1; sMRI; grey matter density.

Copyright and usage

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Major depressive disorder (MDD) is a chronic psychiatric illness and remains one of the most important contributors to morbidity and mortality.[1] The development of novel interventions has been hampered by a deficient understanding of the underlying neurobiology. Despite convincing evidence for a genetic contribution to disease susceptibility (estimated heritability of 37%), there has been a dearth of substantive genetic findings of MDD, with the lack of success attributed to the phenotypic and aetiologic heterogeneity.[2,3] In our previous study, we performed whole-genome sequencing of 5303 Chinese women with recurrent MDD selected to reduce phenotypic heterogeneity and 5337 controls (CONVERGE sample), and revealed the *SIRT1* gene, located on chromosome 10q21.3, as one of the first two genes successfully linked to MDD.[4]

SIRT1 is characterised as a class-III histone deacetylase, which can deacetylate numerous substrates of histones and non-histone proteins and thereby influence gene expression and cellular physiology.[5] Supportive of the genetic observation in the CONVERGE sample, results from several independent studies have suggested the involvement of *SIRT1* in MDD. First, *SIRT1* expression is markedly downregulated in the peripheral of people with MDD when compared with healthy individuals and those with remitted MDD cases.[6,7] Second, inhibition of hippocampal *SIRT1* function by either pharmacologic or genetic treatment led to an elevation in depression-like behaviours, whereas *SIRT1* activation could block both the development of depression-related phenotypes and abnormal dendritic structures.[8] Similarly, increased expression of *SIRT1* in the nucleus accumbens was observed in depressed mice. Pharmacologic or genetic activation of *SIRT1* in the nucleus accumbens increased both depression- and anxiety-like behaviours and, conversely, inhibition of *SIRT1* reduced these behaviours.[9] Third, it has been shown that resveratrol-triggered *SIRT1* activation increased neurogenesis in the hippocampus of aged rats and prevented ageing-associated memory loss and mood dysfunction.[10] These above lines of evidence partially revealed the mechanisms of *SIRT1* in the pathogenesis of MDD, especially the involved brain regions. However, direct evidence as to whether genetic variants across the *SIRT1* gene locus can affect brain structure is lacking. In this study, we performed imaging genetics to assess whether the *SIRT1* variants affect brain structure using high-resolution magnetic resonance imaging (MRI) data of 92 healthy individuals from Eastern China.

Method

This study was approved by the Medical Research Ethics Committee of Wuxi Mental Health Center, China (no. WXMHCIRB2013LLKY001). Written informed consent was obtained from each person before participation in this study.

Participants

A total of 92 healthy individuals (41 males and 51 females, aged 40.3 ± 14.9 years) were enrolled from the Wuxi Mental Health Center, Nanjing Medical University, China. All controls were assessed using the Chinese version of the Modified Structured Clinical Interview for DSM-IV-TR Axis-I Disorders Non-patient Edition (SCID-I/NP). Individuals with a history of major psychiatric disorders or suicidal behaviour were excluded. Individuals who had a first-degree relative with a history of severe mental disorder or suicidal behaviour were also excluded. All participants were of Chinese Han origin, and none of belonged to extended family.

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Table 1 The *SIRT1* single nucleotide polymorphisms from this study and their association with major depressive disorder from the CONVERGE samples

SNP						Frequency			The CONVERGE sample			Linkage disequilibrium (r^2)
Chromosome	Position	RSID	Location	Ref.	Alt.	EAS	EUR	AFR	Odds ratio	s.e.	*P*-value	
10	69676830	rs4746720	3′ near gene	A	G	0.400	0.008	N/A	1.161	0.028	3.32×10^{-08}	0.839
10	69670816	rs10823112	Intron	A	G	0.312	0.076	0.020	0.942	0.032	0.042	0.332
10	69643342	rs3758391	5′ near gene	T	C	0.158	0.667	0.646	0.876	0.038	0.001	0.098
10	69624180	rs12415800	5′ near gene	G	A	0.401	0.023	0.002	1.164	0.028	1.92×10^{-08}	1.000

The first six columns give the chromosome (Chr.), genomic position (Pos.), SNP identifier (RSID), location in the gene locus (Location), reference allele (Ref.) on National Center for Biotechnology Information Build GRCh37 and alternative allele (Alt.) called in 10 640 CONVERGE samples (5303 cases, 5337 controls). The next three columns show the alternative allele frequency (Freq.) in three superpopulations according to the 1000 Genome Project.[18] The final four columns present the results of association testing with major depressive disorder in CONVERGE samples: odds ratio of association with major depressive disorder with respect to the alternative allele and standard error in the odds ratio were obtained from a logistic regression model, *P*-values of association were obtained from a linear-mixed model with a genetic relatedness matrix containing all samples and linkage disequilibrium of each SNP with the index SNP rs12415800 from the original manuscript in EAS populations. SNP, single nucleotide polymorphism; EAS, East Asian; EUR, European; AFR, African.

MRI

T1-weighted structural MRIs (sMRIs) were conducted on a 3.0-T scanner (Siemens MAGNETOM Trio with Tim, syngo MR B17 software, Erlangen, Germany) using a three-dimensional volumetric sequence (repetition time/echo time/inversion time 2530/3.44/900 ms, flip angle 7°, field of view 256 mm^2, voxel size $1 \times 1 \times 1$ mm^3, pixel bandwidth 190 Hz, total scan time 6.6 min).

Voxel-wise morphometric MRI data processing

The T1-weighted sMRI data were preprocessed with the Statistical Parametric Mapping 12 (SPM12, www.fil.ion.ucl.ac.uk/spm/software) by using unified segmentation in which image registration, bias correction and tissue classification are performed using a single integrated algorithm.[11] In this way, brains were segmented into grey matter, white matter and cerebrospinal fluid and non-linearly transformed into the standard Montreal Neurological Institute space.[12] Unmodulated normalised parameters were used to segment the brain into probabilistic maps of grey matter, white matter and cerebrospinal fluid. The resulting grey matter images consisting of voxel-wise grey matter density were resliced to $3 \times 3 \times 3$ mm^3, resulting in $53 \times 63 \times 46$ voxels, which was then smoothed with an 8-mm full width at half-maximum Gaussian kernel. A mask was then generated to include only the segmented grey matter voxels inside the brain, as described in our previous study.[13] Finally, voxels in the grey matter maps of each participant were collapsed into a one-dimensional vector and stacked, forming a population matrix (number of participants [$N_{participant}$] × number of voxels [N_{voxel}]).

Genotyping

Genomic DNA was extracted from peripheral blood cells according to the standard phenol–chloroform method. Genotyping of the *SIRT1* gene locus was performed on the human Illumina PsychArray-24 (Illumina, USA), strictly according to the manufacturer's instructions. The single nucleotide polymorphism (SNP) data were subjected to a series of standard quality control procedures by using PLINK (Massachusetts General Hospital, Boston, USA; http://pngu.mgh.harvard.edu/puurcell/plink), which included checking for missing data, gender mismatch relatedness, Hard–Weinberg equilibrium and minor allele frequency as described elsewhere.[14,15]

Statistical analysis

For each SNP, we divided the participants into three categories: AA (assigned as '0'), Aa (assigned as '1') and aa (assigned as '2'). 'A' and 'a' indicated the major and minor allele, respectively. The additive dosage value was regressed against the voxel-wise grey matter density by using a multiple linear regression framework controlling for age, gender and diagnosis (when applicable). To correct for multiple comparisons, a Monte Carlo cluster simulation was performed to identify any cluster that shows significant correlation between SNPs and grey matter density.[16] The algorithm of cluster-wise correction for multiple comparisons by a Monte Carlo cluster simulation was implemented in the framework of AFNI software,[17] and 1000 iterations were performed in the simulation procedure. Significance was thresholded at the uncorrected voxel-wise *P*-value of 0.001, followed by the family-wise error-corrected cluster-wise *P*-value of 0.05. To compare the grey matter density between any two groups, a *post hoc* test was performed by using the two-tailed *t*-test, with a statistical significance level set at $P < 0.05$.

Results

After genotyping and quality control, three SNPs – rs4746720, rs10823112 and rs3758391 – across the *SIRT1* locus were finally analysed (Table 1). As shown in Fig. 1a, significant association between rs4746720 and grey matter density was observed in two brain regions: the orbital part of the right inferior frontal gyrus (cluster size 76 voxels) and the orbital part of the left inferior frontal gyrus (cluster size 104 voxels) (family-wise, error-corrected $P < 0.05$; voxel-wise $P < 0.001$). The sMRI images for all the slices can be found in the Supplementary materials available at https://doi.org/10.1192/bjp.2018.270. *Post hoc* comparisons between different genotypes of rs4746720 revealed that the carriers of the risk allele (G) predicted higher mean grey matter density than the carriers of the non-risk allele (Fig. 1b). No significant sMRI–SNP association was observed for either rs10823112 or rs3758391 after correcting for multiple comparisons (both family-wise, error-corrected $P > 0.05$).

We next investigated whether these SNPs are associated with MDD in the CONVERGE sample. Supporting the imaging genetic results, genome-wide significant association with MDD was only observed for rs4746720 ($P = 3.32 \times 10^{-08}$, odds ratio 1.161), but not for either rs10823112 ($P = 0.042$) or rs3758391 ($P = 0.001$) (Table 1). Given that rs12415800, the top-risk SNP close to the *SIRT1* locus from the CONVERGE sample, was not successfully genotyped in the current study,[4] we next investigated whether rs4746720 was in linkage disequilibrium with rs12415800. Interestingly, strong linkage disequilibrium between rs4746720 and rs12415800 was observed in East Asian populations from the 1000 Genomes Project pilot study ($r^2 = 0.839$; Fig. 2), strongly suggesting that the sMRI–SNP association might not be generated by chance.

Discussion

Neuroimaging has been widely applied to identify the key brain regions implicated in the pathophysiology of MDD, and imaging

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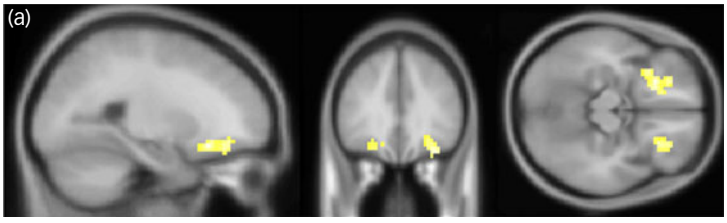

(b)

Cluster size (voxels)	Peak MNI coordinate	Peak MNI *t*-value	Peak MNI region
Cluster 1			
76	(33, 36, –21)	4.20	Frontal_Inf_Orb_R
Cluster 2			
104	(–24, 24 –15)	3.97	Frontal_Inf_Orb_L

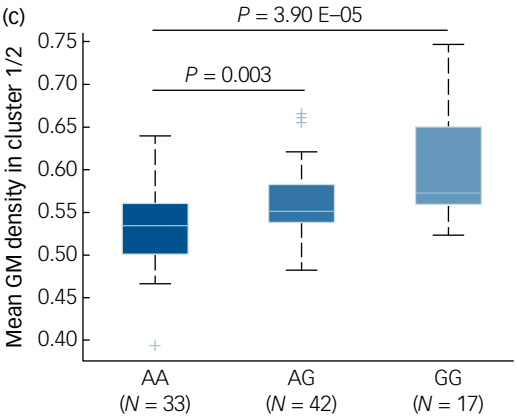

Fig. 1 Significant association of the *SIRT1* rs4746720 with cortical grey matter density in two clusters. (a) Spatial map of the two clusters where the *SIRT1* rs4746720 genotypes had an effect on grey matter density. A multiple regression model and voxel-wise *t*-test was applied to test the correlation between rs4746720 and grey matter density. The colour bar specified the statistics of the *t*-test. Significance was thresholded at the uncorrected voxel-wise *P*-value of 0.001 and the family-wise, error-corrected cluster-wise *P*-value of 0.05. (b) Detailed summary of the two clusters. Coordinates referred to the Montreal Neurological Institute (MNI) space in mm. (c) The rs4746720 risk-allele (G) carriers exhibited higher mean grey matter density in the two clusters compared with non-risk allele carriers (two-tailed *t*-test). Frontal_Inf_Orb_L, orbital part of the left inferior frontal gyrus; Frontal_Inf_Orb_R, orbital part of the right inferior frontal gyrus; GM, grey matter.

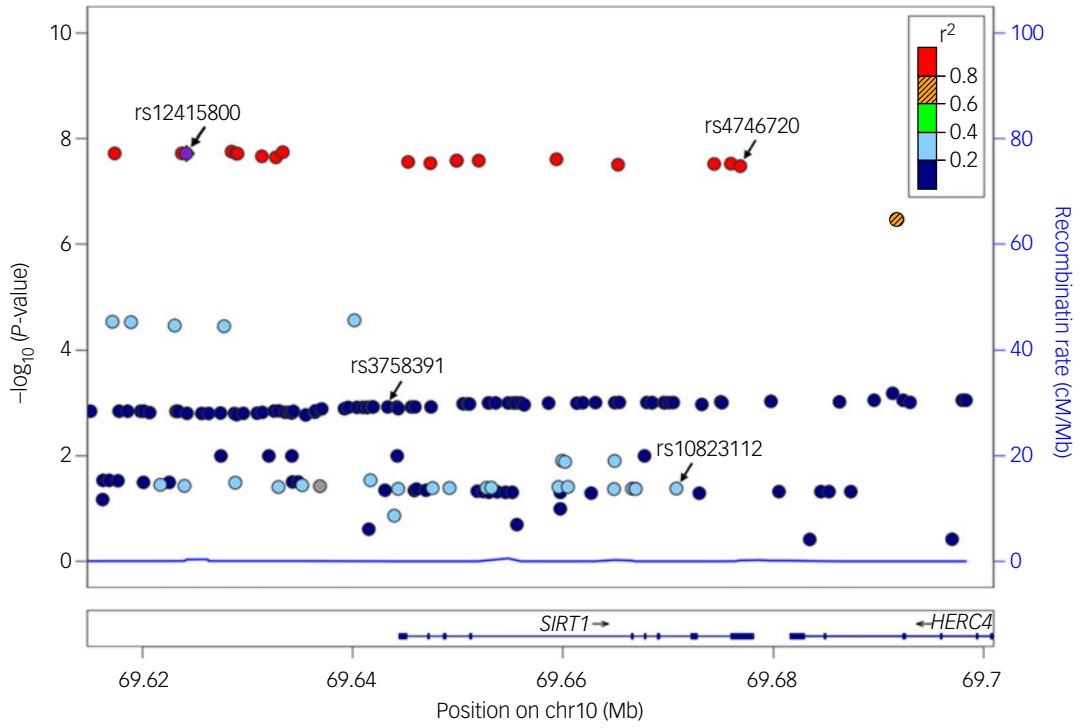

Fig. 2 Linkage disequilibrium plots between rs12415800 and adjacent single nucleotide polymorphisms (SNPs) across the *SIRT1* gene locus in Asian populations and their association with major depressive disorder in the CONVERGE sample. Statistical results of association with major depressive disorder were extracted from the CONVERGE samples. A physical map of the region is given and depicts known genes within the region. The recombination rates expressed in centimorgans (cM) per megabase (Mb) (National Center for Biotechnology Information Build GRCh37; light blue lines) are shown on the right *y*-axis. Position in Mb is on the *x*-axis. Linkage disequilibrium of each SNP, with the top SNP rs12415800 displayed as a purple diamond, is indicated by its colour (data from the 1000 Genomes Project, pilot 1, Asian panel). The plots were drawn using LocusZoom. Chr10, chromosome 10.

Please refer to this figure online to view the original colours in the key and plot points more clearly.

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genetic methods have also been applied to investigate the functions of specific MDD-risk SNPs in previous studies.[20,21] In contrast to white matter, which shows linear increase in volume, previous studies have suggested a pattern of rapid neurogenesis and related volume increase of grey matter from early childhood to the adolescent period, followed by a process of selective elimination and myelination which leads to volume loss and thinning.[22] Associations of cortical and subcortical volume with people with MDD have been extensively reported. For instance, based on data from 8927 participants using an individual participant data-based meta-analysis approach, the MDD working group within the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) reported subcortical volume differences, which were greatest in the hippocampus, between people with MDD and healthy controls.[23] Again, the same group collected brain MRI data from >10 000 people and found significant differences in cortical thickness in 13 out of 68 regions examined, encompassing the medial prefrontal cortex, rostral anterior and posterior cingulated cortex, insula and fusiform gyrus.[24] More importantly, the development of cortical and subcortical grey matter regions is largely influenced by genetic factors, suggesting a neurobiological basis underlying the risk variants identified in MDD genetic studies.[25,26]

In the current study, we found significant association between rs4746720, a genome-wide significant SNP located within the *SIRT1* locus, and grey matter density in the inferior frontal cortex, with the risk allele-G carriers predicting higher mean grey matter than the non-risk allele carriers. In support of the result observed in our study, accumulating evidence from sMRI studies have suggested the involvement of neuroanatomical changes in the frontal lobe in mood disorders, including both MDD and bipolar disorder.[27,28] For example, abnormalities of both grey matter and cortical thickness have been reported in the inferior frontal gyrus in patients with MDD.[27,29] Furthermore, through systematic meta-analysis, Kempton *et al*[30] found that, compared with the structure of a healthy brain, MDD was associated with smaller volumes of the frontal lobe and several other brain regions. More importantly, people with MDD showed increased rates of subcortical grey matter hyperintensities compared with healthy controls.[30]

We next moved from the imaging genetic finding to the putative mechanisms for the inferior frontal gyrus. It has been reported that the inferior frontal gyrus is involved in a number of cognitive processes of potential relevance to MDD, including response inhibition, set switching, socioemotional learning and sustained attention.[31] Moreover, the patients with MDD showed dysfunction of language processing and cognitive performance, possibly due to impairment of the network of the 'theory of mind', which includes inferior frontal gyrus.[32] These studies strongly suggest the possibility that loss of the functional integrity of the inferior frontal gyrus may underlie trait dysfunction in MDD.

Notwithstanding its significant strengths, our study has some inherent shortcomings due to its design. First, we employed healthy participants but not people with MDD. Although the use of healthy controls for imaging genetics at the level of brain function avoids potential confounders related to chronic illness and medical treatment, it is unclear whether grey matter density in the inferior frontal cortex was correlated with the symptoms of depression. Second, the sample size ($N = 92$) recruited in our study was relatively small when compared with other neuroimaging studies,[23,24] which may obscure other true correlations. Third, we performed the whole brain-wide correction for each association test, however, whole brain-wide correction might preclude some positive associations of moderate association. We acknowledge that brain regions other than the inferior frontal cortex might also be involved in the pathogenesis of depression. Third, it is worth noting that only Han Chinese women with severe MDD were recruited in our CONVERGE MDD genome-wide association study.[4] On one hand, this could definitely have minimised the phenotypic and aetiologic heterogeneity, allowing for the discovery of the risk variants; but on the other hand, this could have precluded some promising risk variants.

In sum, our results provide evidence for a potential role of the *SIRT1* gene in the brain, implying a possible pathophysiological mechanism underlying susceptibility to major depression. However, additional investigation of the underlying molecular pathways within affected brain regions is warranted.

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Supplementary material

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EXTRA CONTENT ONLINE

100 words

100 words on transgenderism in the Indian sacred text *Ramayana*

Jessy Fenn

The earliest documented account of transgender people is in the *Ramayana*: a sacred Indian text written around 5 BCE. When King Rama left for his 14-year exile to the forest, he told his subjects who followed him not to mourn and asked all men and women to go back. On his return, after 14 years, he found transgender people where he had left them as he had asked only 'men and women' to return. Impressed by their devotion, he granted them the boon to bless people. To this day, transgender people in India sing, dance and offer blessings on auspicious occasions.

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