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An Interleukin-1 beta (*IL1B*) haplotype linked with psychosis transition is associated with *IL1B* gene expression and brain structure

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ABSTRACT

We investigated *IL1B* genetic variation previously associated with risk for transition to psychosis for its association with gene expression in human post-mortem dorsolateral prefrontal cortex (DLPFC) from 74 (37 schizophrenia, 37 control) individuals and brain structure in 92 (44 schizophrenia, 48 control) living individuals. The *IL1B* A-G-T 'risk for psychosis transition' haplotype (rs16944|rs4848306|rs12621220) was associated with upregulation of *IL1B* mRNA expression in the DLPFC as well as reduced total grey matter and left middle frontal volumes and enlarged left lateral ventricular volume. Our results suggest *IL1B* genetic variation may confer psychosis risk via elevated mRNA expression and/or brain structure abnormalities.

1. Introduction

Genotype and haplotype variation within the interleukin-1 beta (*IL1B*) gene was recently shown to predict transition to psychosis among individuals at ultra-high risk (Bousman et al. 2018). However, the intermediary by whom this *IL1B* genetic variation confers this risk is not clear. Several genetic studies have linked *IL1B* genetic variants with schizophrenia (Papiol et al. 2004; Xu and He 2010; Yoshida et al. 2012) as well as dorsolateral prefrontal cortex (DLPFC) activity (Papiol et al. 2007) and frontal grey matter deficits (Meisenzahl et al. 2001). Furthermore, elevated blood (Fillman et al. 2016) and brain *IL1B* mRNA expression (Fillman et al. 2013; Zhang et al. 2016) have been reported in schizophrenia and are correlated with reduced Broca's area volume (Fillman et al. 2016) and decreased cortical grey matter volumes (Zhang et al. 2016). However, the impact, if any, that *IL1B* genetic variation has on gene expression and brain structure remains to be elucidated in schizophrenia. As such, we investigated the effects of *IL1B* genotype and haplotype variation on gene expression and brain structure among individuals with schizophrenia and healthy controls, with particular focus on the DLPFC given previous evidence suggesting neuroinflammation in this region (Fillman et al. 2013; Volk et al. 2015).

2. Methods

2.1. Participants

Two independent cohorts were examined; a human DLPFC post-mortem brain cohort comprising 37 individuals with schizophrenia and 37 healthy controls and a clinical cohort consisting of 44 individuals

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Table 1
Demographic data and clinical characteristics of participants.

Characteristic	Clinical cohort			Post-mortem cohort		
	Treatment-resistant schizophrenia (n = 44)	Controls (n = 48)	*p* Value	Schizophrenia (n = 37)	Controls (n = 37)	*p* Value
Age, mean (sd) years	40 (10.5)	40 (10.8)	0.99[a]	51.3 (14.1)	51.1 (14.6)	0.96[a]
Gender, n (%) males	34 (77.3)	30 (62.5)	0.13[b]	24 (64.9)	30 (81.1)	0.12[b]
RNA integrity number, mean (sd)	8.36 (1.1)	8.82 (0.3)	**0.009**[a]	7.27 (0.6)	7.30 (0.6)	0.81[a]
Ancestry, n (%) CEU	37 (88.1)	43 (89.6)	0.98[b]	36 (97.3)	36 (97.3)	1.0[b]
PMI (hours)	–	–	–	28.8 (13.8)	24.8 (10.9)	0.52[a]
Tissue pH	–	–		6.61 (0.3)	6.66 (0.3)	0.21[a]
Clozapine plasma level, mean (sd) μg/L	412.61 (253.16)	–	–	–	–	–
Chlorpromazine equivalent (excluding clozapine) dosage mean (sd) mg/day	141.10 (318.70)	–	–	691.5 (502.2)[c]	–	–
Age of onset, mean (sd) years	22.16 (6.02)	–	–	23.7 (6.1)	–	–
Duration of illness, mean (sd) years	16.98 (9.03)	–	–	27.6 (13.8)	–	–
Substance use in past three months, n (%)					–	–
Tobacco (smoked)	21 (47.7)	11 (22.9)	**0.01**[b]	–	–	–
Alcohol	39 (88.6)	46 (95.8)	0.20[b]	–	–	–
Cannabis	7 (16.3)	7 (14.6)	0.82[b]	–	–	–
Amphetamine	4 (9.8)	2 (4.3)	0.31[b]	–	–	–
Cocaine	0 (0)	2 (4.3)	0.17[b]	–	–	–
Opiates	1 (2.5)	1 (2.1)	0.90[b]	–	–	–

$p < 0.05$ values are made bold.
RIN = RNA integrity number; mg = milligram.
[a] Independent samples *t*-test.
[b] Chi-square (χ^2) test.
[c] Chlorpromazine equivalent neuroleptic dose (mg).

with schizophrenia and 48 healthy controls. In the clinical cohort, all the schizophrenia patients were of Caucasian ancestry and taking clozapine. While in the post-mortem cohort, controls were matched with cases on the following factors: brain pH (±1), age at death (within 10 years), PMI (within 10 h), hemisphere, gender, time in freezer, agonal state. Table 1 details the demographics and clinical characteristics of the participants. Details of patient recruitment, inclusion/exclusion criteria, and assessment for both cohorts are described elsewhere (Mostaid et al. 2017a; Weickert et al. 2010). All participants or their next of kin provided written informed consent prior to participation. The study was conducted in accordance with the declaration of Helsinki (World Medical Association, 2013) and approved by the Melbourne Health Human Research Ethics Committee (MHREC ID 2012.069) and Human Research Ethics Committee at the University of New South Wales (HREC #07261).

2.2. Genotyping and gene expression

Six single nucleotide polymorphisms (SNPs) spanning the *IL1B* gene were genotyped (Supplementary Table S1) in both the clinical and post-mortem cohort by Sequenom MassARRAY MALDI-TOF genotyping system. These SNPs were chosen based on our previous study where we showed genotype and haplotype variations within the *IL1B* gene predict transition to psychosis among individuals at ultra-high risk (Bousman et al. 2018). Details of genotyping are described elsewhere (Mostaid et al. 2017a). *IL1B* SNPs were mapped using the human genome research assembly (GRCh38/hg38). Haploview was used to examine linkage disequilibrium between SNPs and haplotype blocks were determined using the solid spine method (Barrett et al. 2005). For each individual, haplotypes were determined based on the best posterior probability procedure implemented in PLINK 1.07 (Purcell et al. 2007). For comparison, we also examined the haplotype structure of the six selected *IL1B* SNPs using the 1000Genomes CEU population data.

The probes for *IL1B* and the reference genes (*UBC, ACTB, GAPDH*, and *TBP*) are given in Supplementary Table S2. Tissue collection, RNA isolation, cDNA preparation and qPCR experiments from both the post-mortem and clinical cohorts were performed as described previously (Fillman et al. 2013; Mostaid et al. 2017a, 2017b; Weickert et al. 2010).

2.3. Structural brain imaging

Participants from the clinical cohort were scanned using a 3.0 Tesla MRI-scanner to obtain high-resolution structural (T1-weighted) MRI images. The images were coded to make sure investigator blindness to diagnosis and identity of the participants. MRI image processing was performed using FreeSurfer software, version 5.3.0 (http://surfer.nmr.mgh.harvard.edu), to automatically parcellate each cortical hemisphere corresponding to the Desikan-Kilinary Atlas (Desikan et al. 2006). A brief summary of the FreeSurfer method is described elsewhere (Van Rheenen et al. 2018). The cortical and subcortical segmentation was checked manually for major topological inconsistencies and corrected whenever necessary by vertex edits or control points blinded to the diagnosis by trained raters. The process was repeated to produce final volume estimates (Fischl et al. 2002), including total grey matter volume, cortical white matter volume, left and right lateral ventricle volume, and cerebrospinal fluid volume. In addition, left and right middle frontal volumes were obtained as this region corresponds to the DLPFC, approximating the post-mortem region we examined.

2.4. Statistical analysis

Two-tailed tests were used for all statistical analyses. The Shapiro-Wilk test and quantile-quantile (Q-Q) plots (Supplementary Fig. S1 and S2) were used to assess normality of variable distributions. Group differences in categorical and continuous data were analysed with chi-squared and student's *t*-tests, respectively. Prior to analysis, linear regression models were used to obtained standardised residuals accounting for the effect of age and intracranial volume on each of the brain measurements (total grey matter volume, cortical white matter volume, left and right lateral ventricle volume, and cerebrospinal fluid volume) and *IL1B* mRNA expression. General linear models (GLM) were then used to examine the effects of *IL1B* SNPs and haplotypes on the standardised residuals each of the brain indices as well as *IL1B* mRNA expression adjusting for appropriate covariates (gender, RIN, smoking, alcohol, illicit drug use). Each GLM included genotype/haplotype, case status, genotype/haplotype x case status. Significant genotype/haplotype x case status interactions were analysed post hoc by case status

stratification analyses. A secondary analysis was undertaken to examine the effects of *IL1B* variants and haplotypes on left and right middle frontal volumes, corresponding to the DLPFC in the post-mortem analysis. All *p*-values were calculated using a standard 1000 permutation bootstrap procedure implemented in IBM® SPSS® 24 and the alpha threshold was set at 0.027 based on the Benjamini-Yekutieli multiple comparisons correction method (Benjamini and Yekutieli 2001).

3. Results

All examined SNPs were in Hardy-Weinberg equilibrium. Haplotype analysis in both the post-mortem and clinical cohorts revealed two haplotype blocks (Fig. 1a and Supplementary Fig. S3a). The first block contained two SNPs (rs1143643|rs1143633) and the second block comprised three SNPs (rs16944|rs4848306|rs12621220). The identical haplotype blocks were detected from the 1000Genomes CEU data (Supplementary Fig. S3b). Across both cohorts, neither genotype nor haplotype frequencies differed between schizophrenia and control subjects (Supplementary Table S3).

Within the post-mortem cohort, the previously identified A-G-T 'psychosis transition risk' haplotype had trend level associations with mRNA expression in the DLPFC. Individuals (both schizophrenia and controls) with one or two copies of the risk haplotype showed 14.3% ($p_{perm} = 0.035$) and 25.7% ($p_{perm} = 0.093$) higher *IL1B* mRNA compared to individuals with zero copies of the risk haplotype (Fig. 1b and Supplementary Table S4). Individual SNP analyses did not show any significant eQTL with brain *IL1B* mRNA expression. Among individuals with schizophrenia, *IL1B* mRNA expression in the DLPFC was positively correlated with duration of illness (Spearman's rho = 0.341, $p_{perm} = 0.045$) but not with age of illness onset or daily chlorpromazine equivalent mean dose (Fig. 1c and Supplementary Table S5).

In the clinical cohort, individuals (both schizophrenia and controls) with two copies of the A-G-T 'risk' haplotype had significantly lower total grey matter volume compared to those with zero or one copy of the risk haplotype ($p_{perm} = 0.002$ and $p_{perm} = 0.001$, respectively) (Fig. 1d and Supplementary Table S7). Moreover, individuals with two copies of the A-G-T 'risk' haplotype also showed a near significant association with left lateral ventricle volume ($p_{perm} = 0.030$) relative to those who were non-carriers (Fig. 1e). Individual SNP analyses echoed the haplotype analysis (Supplementary Fig. 4a/b and Supplementary Table S6), apart from rs16944. Among the schizophrenia group only, as the number of rs16944 A-alleles present increased so did cerebrospinal fluid volume (Supplementary Fig. 4c).

Our secondary analysis of the left and right middle frontal volume showed that individuals with two copies of the risk (A-G-T) haplotype had lower left middle frontal volume compared to those with one copy of the risk haplotype ($p_{perm} = 0.002$) (Fig. 1f), regardless of case status. However, this finding did not remain significant after adjustment for total grey matter volume ($p_{perm} = 0.07$).

4. Discussion

We found that the *IL1B* A-G-T haplotype, which was recently reported as a putative marker of psychosis transition (Bousman et al. 2018), was associated with an increase in *IL1B* mRNA in human post-mortem DLPFC and was positively correlated with duration of illness.

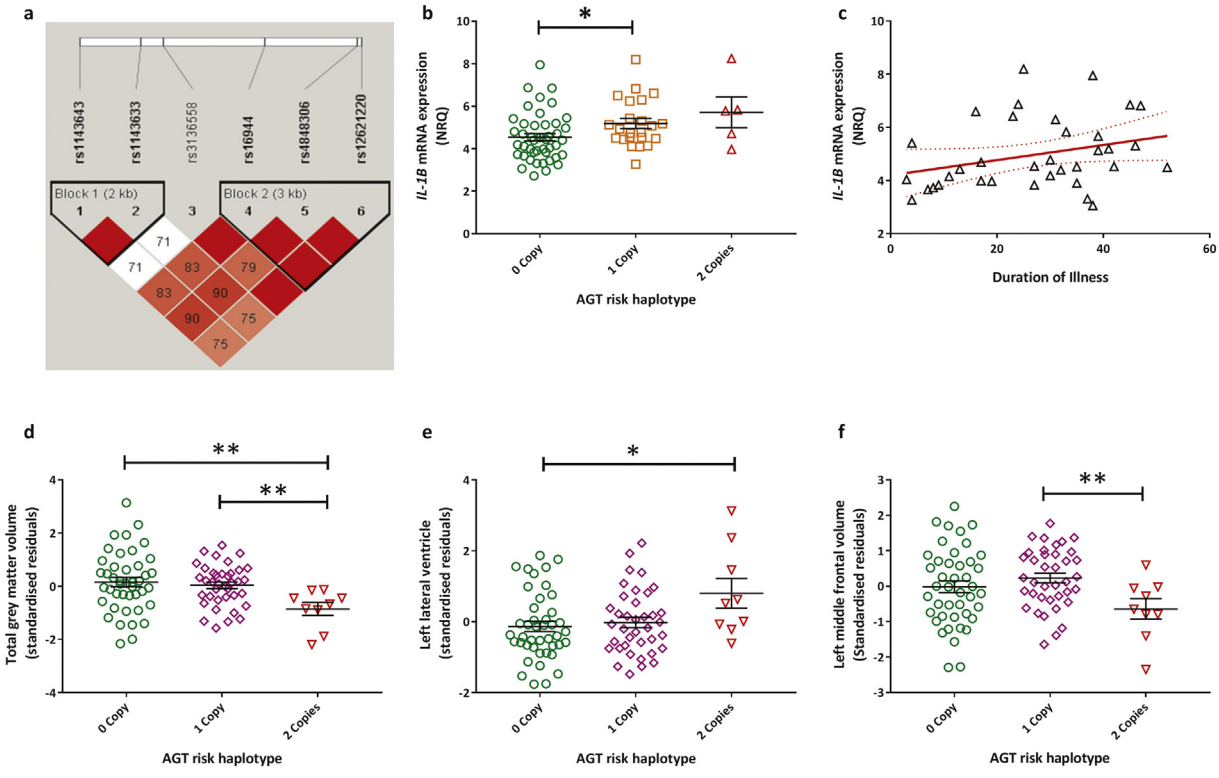

Fig. 1. *IL1B* genetic polymorphisms and its association with mRNA expression and brain morphology. **(a)** Linkage disequilibrium between *IL1B* SNPs in the post-mortem cohort; **(b)** Differences in gene expression between groups with different copy number of AGT risk haplotype (F = 3.99, df = 2, $p_{perm} = 0.023$; 0 copy vs 1 copy: $p_{perm} = 0.035$, 0 copy vs 2 copies: $p_{perm} = 0.093$, 1 copy vs 2 copies: $p_{perm} = 0.502$); **(c)** Spearman's correlation between *IL1B* mRNA expression in DLPFC and duration of illness (Spearman's rho = 0.341, $p_{perm} = 0.045$); **(d)** Differences in total grey matter volume between groups with different copy number of AGT risk haplotype (F = 4.10, df = 2, $p_{perm} = 0.20$; 0 copy vs 1 copy: $p_{perm} = 0.595$, 0 copy vs 2 copies: $p_{perm} = 0.002$, 1 copy vs 2 copies: $p_{perm} = 0.001$); **(e)** Differences in white matter volume between groups with different copy number of AGT risk haplotype (F = 3.46, df = 2, $p_{perm} = 0.036$; 0 copy vs 1 copy: $p_{perm} = 0.572$, 0 copy vs 2 copies: $p_{perm} = 0.030$, 1 copy vs 2 copies: $p_{perm} = 0.055$); **(f)** Differences in left middle frontal volume between groups with different copy number of AGT risk haplotype (F = 3.85, df = 2, $p_{perm} = 0.025$; 0 copy vs 1 copy: $p_{perm} = 0.142$, 0 copy vs 2 copies: $p_{perm} = 0.506$, 1 copy vs 2 copies: $p_{perm} = 0.002$); All the *p*-values are adjusted for covariates and were derived based on 1000 permutations. $^{*}p < 0.05$, $^{**}p < 0.027$ (Benjamini-Yekutieli multiple comparisons corrected threshold).

We also found that the same haplotype was associated with lower grey matter and left middle frontal volumes as well as greater left lateral ventricle volume.

Elevated levels of pro-inflammatory cytokines, such as *IL1B*, in post-mortem brain tissue have previously been shown in schizophrenia (Fillman et al. 2013). Likewise, reduced total grey matter volume and enlarged ventricular volumes are consistent with imaging phenotypes observed among those with schizophrenia (Haijma et al. 2013). Thus, our results suggest these intermediate phenotypes (i.e. mRNA expression, grey matter volume, ventricular volume) can, in part, be explained by *IL1B* genetic variation and supports the notion that the A-G-T haplotype could be a marker for psychosis risk.

These results provide additional evidence supporting the role of inflammation in mental illness and brain health. Although the biological mechanisms remain unclear, our results suggest *IL1B* genetic variation and more specifically the A-G-T haplotype moderates transcription of *IL1B* and as such is contributing to the elevated levels of pro-inflammatory cytokines detected by others (Fillman et al. 2013), which if sustained can precipitate neuronal degeneration and decrease neurogenesis, leading to morphological changes in the brain that could increase an individual's susceptibility to schizophrenia (Monji et al. 2009). However, the effects of the A-G-T haplotype on gene expression and brain structure were observed in both individuals with schizophrenia and controls, suggesting this haplotype is unlikely to be specific to schizophrenia risk. This is supported by evidence that not all individuals at ultra-high risk for psychosis who transition, receive a diagnosis of schizophrenia (Fusar-Poli et al. 2013). In fact, previous studies have shown that rs16944 (a SNP within the *IL1B* 'risk' haplotype) was associated with bifrontal-temporal grey matter deficits in schizophrenia (Meisenzahl et al. 2001) and bipolar disorder (Papiol et al. 2004). However, studies in the general population to determine if this haplotype confers a greater susceptibility to psychotic symptoms/experiences are needed to adequately test this hypothesis. If supported by future studies, this *IL1B* haplotype has potential for inclusion in current risk calculators (Cannon et al. 2016) to identify individuals at risk for transition to psychosis.

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None of the Funding Sources played any role in the study design; collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Author CAB, CP, and IPE designed the study and wrote the protocol. Author MSM managed the literature searches and analyses and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.09.008.

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