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Convergent Lines of Evidence Support LRP8 as a Susceptibility Gene for Psychosis

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Abstract Reelin (RELN) is identified as a risk gene for major psychiatric disorders such as schizophrenia (SCZ) and bipolar disorder (BPD). However, the role of its downstream signaling molecule, the low-density lipoprotein receptor-related protein 8 (LRP8) in these illnesses is still unclear. To detect whether LRP8 is a susceptibility gene for SCZ and BPD, we analyzed the associations of single nucleotide polymorphisms (SNPs) in LRP8 in a total of 47,187 subjects (including 9379 SCZ patients; 6990 BPD patients; and 12,556 controls in a screening sample, and 1397 SCZ families, 3947 BPD patients, and 8387 controls in independent replications), and identified a non-synonymous SNP rs5174 in LRP8 significantly

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associated with SCZ and BPD as well as the combined psychosis phenotype ($P_{meta}=1.99\times10^{-5}$, odds ratio (OR)=1.066, 95 % confidence interval (CI)=1.035–1.098). The risk SNP rs5174 was also associated with LRP8 messenger RNA (mRNA) expression in multiple brain tissues across independent samples (lowest $P=0.00005$). Further exploratory analysis revealed that LRP8 was preferentially expressed in fetal brain tissues. Protein-protein interaction (PPI) analysis demonstrated that LRP8 significantly participated in a highly interconnected PPI network build by top risk genes for SCZ and BPD ($P=7.0\times10^{-4}$). Collectively, we confirmed that LRP8 is a risk gene for psychosis, and our results provide useful information toward a better understanding of genetic mechanism involving LRP8 underlying risk of complex psychiatric disorders.

Keywords LRP8 · rs5174 · Schizophrenia · Bipolar disorder · mRNA expression

Introduction

Schizophrenia (SCZ) and bipolar disorder (BPD) are two major psychiatric disorders which affect together approximately 3 % of the world's population and are recognized as leading causes of morbidity [1, 2]. Family, twin, and adoption studies suggested a substantial genetic component together with environmental risk factors in the pathogenesis of these illnesses [3]. During the past few decades, genetic analyses including genome-wide association studies (GWAS) have identified a wealth of risk loci for SCZ and BPD in diverse populations [4–8]. Meanwhile, studies considering SCZ and BPD as a single major psychosis phenotype revealed shared risk alleles [9–12] and an overlapping polygenic component [13, 14]. These data are consistent with current clinical and epidemiological analyses, which predict substantial overlap of risk factors and genetic predisposition between SCZ and BPD [3].

Reelin (RELN) is a susceptibility gene for SCZ with genetic evidence from a GWAS using DNA pooling strategy [15] and several hypothesis-driven association studies across diverse populations [16–19], and variants in RELN have been reported to confer risk for BPD as well [20]. Recent studies have also demonstrated a reduction in RELN messenger RNA (mRNA) and protein expression in postmortem brain tissues of patients with SCZ and BPD [21, 22], and other analyses indicated epigenetic aberrations of RELN in psychiatric disorders [23]. These lines of evidence suggest that RELN seems a promising susceptibility gene for major psychiatric disorders. In addition, evidence from animal studies showed that dysfunctional RELN-mediated signaling might be related to neuropsychiatric diseases [24], which was further supported by the clinical observation of abnormal expression of RELN downstream cytomembrane receptors (very-low-density-lipoprotein receptor, VLDLR) in SCZ patients [25]. However, the role of another receptor of RELN, the low-density lipoprotein receptor-related protein 8 (LRP8), still remains obscure in the pathogenesis of major psychiatric disorders.

Here, to evaluate whether LRP8 is a risk gene for SCZ and BPD, we performed genetic analyses in large-scale samples, and identified a non-synonymous single nucleotide polymorphism (SNP) rs5174 showing strong association ($P_{meta}=1.99\times10^{-5}$). The risk SNP was also significantly associated with LRP8 mRNA expression in multiple independent healthy control samples. Subsequently, gene expression analyses in diverse tissues indicated that LRP8 was preferentially expressed in human brain samples, and protein-protein interaction (PPI) analyses showed that LRP8 significantly and directly interacted with several top susceptibility genes for psychiatric disorders.

Methods and Materials

Genetic Association Samples

Our screening sample consisted of the SCZ and BPD cases and the corresponding control subjects from the Psychiatric Genomics Consortium (PGC) GWAS [26]. Briefly, the screening sample included two sub-sample sets—sample set 1 includes 9379 SCZ and 7736 controls, and sample set 2 contains 6990 BPD and 4820 controls with no overlapping individuals among these samples. All included subjects were of European ancestry. Further information about the samples,

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including diagnostic assessments, genotyping, quality control, and association analyses can be found in the original publication [26].

Replication analyses were performed on 11 independent samples including a total of 1397 SCZ families, 3947 BPD patients, and 8387 controls that did not overlap with the screening samples. Detailed information on individual samples concerning diagnostic assessment, genotyping, and quality control is shown in the Supplemental Data.

The replication SCZ samples include the following: (1) The European family sample (794 SCZ families with 2740 individuals) [27], (2) The African-American family sample (438 SCZ families with 1262 subjects) [27], (3) The Arab-Israeli sample (58 SCZ families with 198 subjects) [28], and (4) The Jewish-Israeli sample (107 SCZ families with 331 individuals) [29].

The replication BPD samples are comprised of the following: (1) Sweden I (836 cases and 2093 controls) [30, 31], (2) Sweden II (1415 cases and 1271 controls) [31], (3) Romania (244 cases and 174 controls) [7, 31], (4) France (451 cases and 1631 controls) [5, 6], (5) Germany II (181 cases and 527 controls) [5, 7], (6) Germany III (490 cases and 880 controls) [5, 7], (7) Australia (330 cases and 1811 controls) [5, 7].

Most of these replication samples have been previously reported in earlier large-scale collaborative studies, and were shown to be effective samples in detecting genetic risk variants for major psychiatric disorders [5, 7, 31]. Each of the original samples was recruited under appropriate ethical approvals, and written informed consent was obtained from all subjects.

SNP Selection and Statistical Analysis

For the initial screening, a total of 20 SNPs in LRP8 gene were selected. We examined the linkage disequilibrium (LD) pattern of LRP8 gene in the European population using genotype data from 1000-Human-Genome [32] and we selected 19 tagging SNPs using the tagger procedure implemented in Haploview (pairwise tagging only, r^2 threshold=0.8). The 19 tagging SNPs include one non-synonymous SNP (rs5174, Arg952Gln). We also chose another LRP8 missense SNP (rs3820198, Asp64Glu). All the selected SNPs are biallelic. The significant SNPs in the screening samples were selected for replication in the additional independent samples. The genomic structure of the LRP8 gene, the locations of the tested SNPs, and their LD patterns in European populations are shown in Fig. 1. The SNP information is shown in Table S1.

The SNP genotyping in our replication samples was primarily performed on Illumina (San Diego, CA, USA) and Affymetrix platforms (details shown in Supplemental Data). The control subjects were tested for deviation from Hardy-Weinberg Equilibrium (HWE). The investigated SNPs did not deviate from HWE in any individual sample.

For each individual case-control sample, association P values, allele-specific odds ratios (ORs) and standard error (SE) were calculated by a logistic regression model with an additive effect using PLINK v1.07 program [33]. For the family based samples, the OR of transmission disequilibrium test (TDT) and its associated SE were calculated as follows [34]:

$$\mathrm{OR} = a/b$$

$$\mathrm{SE} = \mathrm{SQRT}(1/a + 1/b)$$

where a means number of times A1 allele transmitted from heterozygous parents to affected proband, and b means number of times A1 allele was not transmitted.

In the meta-analysis of the overall samples, we used OR and SE from each individual study to estimate heterogeneity between samples and to calculate the pooled OR and 95 % confidence interval (CI). To combine the results from individual samples, we calculated the heterogeneity between each samples using Cochran's (Q) χ^2 test, which is a weighted sum of the squares of deviations of individual OR estimates from the overall estimate. When the ORs are homogeneous, Q follows an χ^2 distribution with degrees of freedom. If $P_Q<$ 0.10, the heterogeneity is considered statistically significant. Inconsistency across studies was quantified with the I^2 metric ($I^2=Q-\mathrm{d.f.}/Q$), which can be interpreted as the percentage of total variation across several studies due to heterogeneity. I^2 takes values between 0 and 100 %, with higher values denoting a greater degree of heterogeneity (0–25 %=no heterogeneity, 25–50 %=moderate heterogeneity, 50–75 %=large heterogeneity, and 75–100 %=extreme heterogeneity). In the presence of heterogeneity among individual studies, we used random effect models to combine the samples and to calculate the OR and the corresponding 95 % CIs; otherwise, a fixed-effect model was used.

The meta-analyses were performed using the classical inverse variance weighted methods with the R package (metafor module, https://cran.r-project.org/web/packages/metafor/metafor.pdf). As described in a previous GWAS meta-analysis [6], P values for replication samples are reported as one-tailed tests and P values for all combined samples are shown as two-tailed tests. We used a forest plot to graphically present the pooled ORs and the 95 % CIs. Each study was represented by a square in the plot, and the weight of each study was also shown.

Healthy Subjects for Expression Quantitative Trait Loci Analysis

To identify the impact of risk SNPs on LRP8 mRNA expression, we utilized two well-characterized gene expression databases. A brief description of the expression resources is

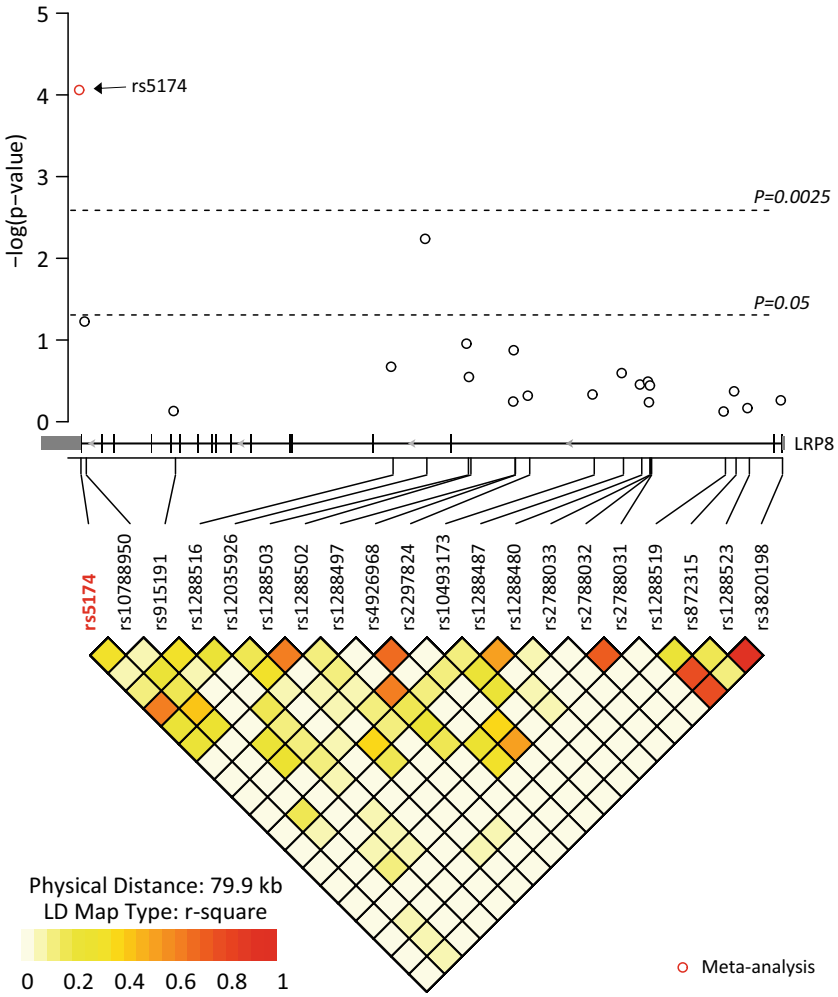

Fig. 1 Genetic association of LRP8 with risk for psychosis. A physical map of the region is given and depicts known genes within the region. *Bottom* the linkage disequilibrium structure of the tested markers for 85 unrelated healthy control subjects of European descent and depicted as r^2

provided in the following section; more detailed information can be found in the original reports: (i) BrainCloud [35] (http://braincloud.jhmi.edu/) and (ii) Genotype-Tissue Expression project (GTEx) [36].

The data in BrainCloud is aimed at increasing our understanding of the regulation of gene expression in the human brain and will be of value to others pursuing functional follow-up of disease-associated variants. The BrainCloud is comprised of 261 postmortem dorsolateral prefrontal cortex (DLPFC) of non-psychiatric normal individuals, including 113 Caucasian subjects and 148 African-American individuals across the lifespan. The raw genotype data were extracted from BrainCloud; expression data and demographic information such as RNA integrity number (RIN), race, sex, and age were also obtained. The prenatal subjects were removed from the expression quantitative trait loci (eQTL) analysis since LRP8 mRNA expression is differentially expressed in fetal subjects compared with postnatal subjects. The statistical analysis was conducted using linear regression in each ethnic sample, with RIN, sex, and age as covariates.

Compared with BrainCloud which focuses on brain DLPFC regions, the GTEx [36] contains information at the level of both genetic variation and gene expression from a diverse set of human tissues. So far, 3797 tissues from 150 postmortem donors have been collected and subsequently analyzed using a RNA sequencing (RNA-seq) based gene expression approach. Considering schizophrenia is a disorder almost exclusively originating from brain dysfunctions, we have used the brain tissues from GTEx to analyze the eQTL effects of the risk SNP, including frontal cortex, amygdala, cerebellum, caudate, putamen, hypothalamus, etc.

Frequency Distribution of the Risk Variants in Global Populations

We examined the frequency distribution of the risk alleles in global populations using genotype information from the Human Genome Diversity Project (HGDP) selection browser (http://hgdp.uchicago.edu/cgi-bin/gbrowse/HGDP/), which contains the genotype data of 53 worldwide populations.

LRP8 mRNA Expression Analysis in Human Tissues

We explored the temporal-spatial mRNA expression pattern of LRP8 in human tissues using different sets of gene expression data. We first investigated the tissue-specific expression distributions of LRP8 in diverse human tissues using the Genotype-Tissue Expression portal (GTEx) [36] and Gene Enrichment Profiler [37], a database that contains gene expression data for 126 different cell types/tissues (details shown in Supplemental Data). We also examined the temporal-spatial expression pattern of LRP8 in developing human brains using the BrainCloud [35] and the Human Brain Transcriptome [38] databases (described in Supplemental Data).

Protein-Protein Interaction Analysis

Normally, proteins play important roles in the cellular system through interacting with (e.g., binding to) other proteins or molecules. One example is the protein complex dysbindin in schizophrenia, an essential component of the biogenesis of lysosome-related organelles complex 1 (BLOC-1), that interacts with all other components of BLOC-1 [39]. Therefore, the malfunction of a member of the protein complex may lead to cascading functional consequences. Along with this theory, numerous studies have shown that disease-associated proteins tend to interact more with each other than random proteins in the protein-protein interaction (PPI) network; proteins located at the same genomic locus tend to interact within the PPI network [40, 41]. Accumulating data have suggested that PPIs play pivotal roles in the identification and prioritization of disease candidate genes [42, 43]. In fact, our recent studies suggest that proteins encoded by SCZ susceptibility genes significantly and physically interact and encode a highly interconnected PPI network [44, 45].

We selected two well-characterized data sets that contained promising psychosis susceptibility genes. The first data set consisted of candidate genes identified by recent GWAS or large-scale association studies on SCZ and BPD (e.g., ZNF804A and CACNA1C). The second data set was from a recent work of Ayalew et al. [46]. Ayalew et al. [46] prioritized several top SCZ (and BPD) candidate genes through translational convergent functional genomics (CFG) approach, which was firstly developed by Niculescu et al. [47]. CFG integrates GWAS data with other genetic and gene expression studies in human and animal models, and has proved to be a powerful and promising approach to identify the genes associated with major psychosis [47–51]. The top susceptibility genes from these two data sets represent promising candidate genes for psychosis (Table S2). Therefore, it is important to investigate whether the LRP8 gene is involved in the PPI network that is formed by proteins encoded by top susceptibility genes for psychosis.

Protein products of these genes were used as seed proteins. If there is in vitro evidence of physical interaction between two seed proteins, they will be linked by one edge. In a PPI network, the nodes represent proteins, while the edges represent physical interaction. DAPPLE (Disease Association Protein-Protein Link Evaluator, http://www.broadinstitute.org/mpg/dapple/dapple.php) was used to extract and reconstruct the PPI network [52]. The significance of the network built from PPI data was assessed through permutation tests (N=5000). More detailed information about PPI network construction and significance evaluation can be found in previous studies [52].

Results

A Non-Synonymous SNP rs5174 in LRP8 is Associated with Schizophrenia and Bipolar Disorder

To test whether LRP8 variants contribute to genetic risk of SCZ and BPD, we analyzed a total of 20 SNPs within LRP8 gene for their associations with these two disorders. The screening samples were drawn from the published PGC-GWAS [26], with no overlapping subjects between diagnostic groups. To date, several GWAS have been conducted in various SCZ and BPD samples, identifying a few genome-wide significant genes, such as MIR137, ZNF804A, CACNA1C, and the like [6, 8, 53, 54]. However, even these risk genes can only explain a small portion of the genetic liability, and the missing heritability is still unclear. A recent aggregated analyses [13] indicated that SCZ and BPD are polygenic disorders involving multiple susceptibility variants, with each of them having a tiny effect on the risk, and there may be true findings among those markers passing only nominal significance in the initial GWAS of psychiatric disorders, but later were consistently replicated in independent samples, such as CMYA5 [55], FGFR2 [56], CAMKK2 [57], and CREB1 [30]. Hence, dissection of the GWAS datasets is still valuable for further identification of the risk genes, and we believe this is also one of the most important contributions of GWAS.

Among these 20 SNPs, a non-synonymous SNP rs5174 in the exon 9 of LRP8 was significantly associated with SCZ ($P=2.64\times10^{-4}$, OR=1.089, 95 % CI=1.040–1.141, Table S1), and also showed a marginal association with BPD in the same direction of allelic effect ($P=0.080$, OR=1.051, 95 % CI=0.994–1.111, Table S1). A joint analysis considering SCZ and BPD as a single psychosis phenotype revealed a stronger association ($P=8.70\times10^{-5}$, OR=1.074, 95 % CI=1.036–1.112, Table S1 and Fig. 1). By contrast, the other SNPs did not show any evidence of association (Table S1 and Fig. 1). The LD structure analysis found that rs5174 is in low to moderate LD with the other tested SNPs (Fig. 1).

To further confirm the associations between rs5174 and these psychiatric disorders, we conducted the replication analysis in a large collection of independent SCZ and BPD samples (including a total of 1397 SCZ families, 3947 BPD patients, and 8387 controls). The forest plot of the meta-analysis results of all samples is presented in Fig. 2. The SNP rs5174 again showed nominally significant association with psychosis in the replication samples (one-tailed $P=3.53\times10^{-2}$, OR=1.050, 95 % CI=1.000–1.107, Fig. 2a). The meta-analysis of the combined screening and replication samples indicated a stronger significance level (two-tailed $P=1.99\times10^{-5}$, OR=1.066, 95 % CI=1.035–1.098, Fig. 2b), with no heterogeneity among the individual samples ($P=0.902$, $I^2=0$). The subgroup analysis by diagnostic phenotype showed that rs5174 is significantly associated with both SCZ ($P=3.07\times10^{-4}$, OR=1.083, 95 % CI=1.037–1.131, Fig. 2c) and BPD ($P=1.35\times10^{-2}$, OR=1.052, 95 % CI=1.011–1.095, Fig. 2d). The pooled ORs in the cumulative analysis (Fig. 2) are comparable with other loci reported as significantly associated with psychiatric disorders in larger meta-analyses and exceed the Venice interim criteria for "small summary" findings [30, 57]. Taken collectively, the genetic association analysis suggests that SNPs in LRP8 may confer risk for major psychosis like SCZ and BPD in the general population.

Rs5174 Allele is Associated with LRP8 mRNA Expression

The association between rs5174 with SCZ and BPD in multiple independent samples lends statistical and biological support to the involvement of this genomic region in the risk for these disorders. However, these findings do not identify the underlying molecular mechanism. Accumulating evidence suggests that molecular mechanisms of risk association are likely via differential effects on the variation of gene expression [58–60]. To explore the possibility that the molecular mechanism of clinical associations with rs5174 involves transcriptional regulation, we utilized several existing expression quantitative trait loci (eQTL) databases. We firstly used the BrainCloud expression database [35], consisting of human prefrontal cortex tissues from 113 Caucasian subjects and 148 African-American individuals, and we found that rs5174 is significantly associated with LRP8 expression ($P=0.0057$ in Caucasians and $P=0.05$ in African-Americans, Fig. 3a, b), with the risk allele [C] showing higher expression.

In another gene expression database GTEx [36], in multiple human brain tissues, such as prefrontal cortex, amygdala, cerebellum, etc., the risk allele (C) of rs5174 was again significantly associated with higher LRP8 expression (lowest $P=0.00005$, Fig. 3c). These highly consistent results suggest one of the molecular mechanisms for the risk SNP likely acts via regulation of LRP8 expression, particularly in brain regions.

A proxy search for SNPs in high LD with rs5174 was performed on the SNAP website (http://www.broadinstitute.org/mpg/snap/ldsearch.php) with the European panel from the 1000-Human-Genome. This identified 35 SNPs in high LD ($r^2>0.8$) with rs5174, all of which are located within LRP8 regions (Fig. 4a). However, none of them are located in functional regions (e.g., coding, UTR or non-coding RNA).

Further, rs5174 leads to an amino acid change from arginine (major C allele, the risk allele) to glutamine (minor T allele), a charge-status change that may have functional consequence. We performed functional predictions using Polyphen2 [61] and the results showed that arginine to glutamine substitution at rs5174 is likely to be damaging, implying that this SNP may influence the function of LRP8. However, since the risk allele (major allele) of rs5174 is also prevalent in control populations (>50 %), there is the possibility that rs5174 itself might not have a functional role but be in LD with causal variants.

Rs5174 Shows Dramatic Allele Frequency Difference in Worldwide Populations

Recent studies suggest that genetic variants conferring risk for major psychiatric disorders show significant frequency differences among worldwide populations [30, 62]. Thus, we examined the allele frequency distribution of the risk variants identified in this study in global populations. We used the genotype data from the HGDP selection database. We found that the risk allele (C allele) of rs5174 showed dramatic frequency differences in worldwide populations (Fig. 4b). Interestingly, the risk allele (C) of rs5174 is common in most world populations (e.g., fixed in some populations, red arrows in Fig. 4b), but is relatively low in some populations (green arrows in Fig. 4b).

LRP8 is Preferentially Expressed in Human Brain Tissues and Fetal Stage

We studied the spatial expression profiling of LRP8 in multiple human tissues to see if they are enriched in brain tissues, as major psychiatric disorders mainly originate from abnormal brain function. If LRP8 were preferentially expressed in the brain, it would make more sense to consider it as a potential risk gene. We firstly used the expression data from GTEx [36], in which 3797 tissues from 150 postmortem donors have been collected and subsequently analyzed using RNA sequencing (RNA-seq)-based gene expression approach. Notably, we found that LRP8 is abundantly expressed in human brain tissues such as cerebellum (Fig. 5a), while the expression level of LRP8 is generally low in non-neural tissues. The analysis of the LRP8 expression in another gene expression database, Gene Enrichment Profiler [37],

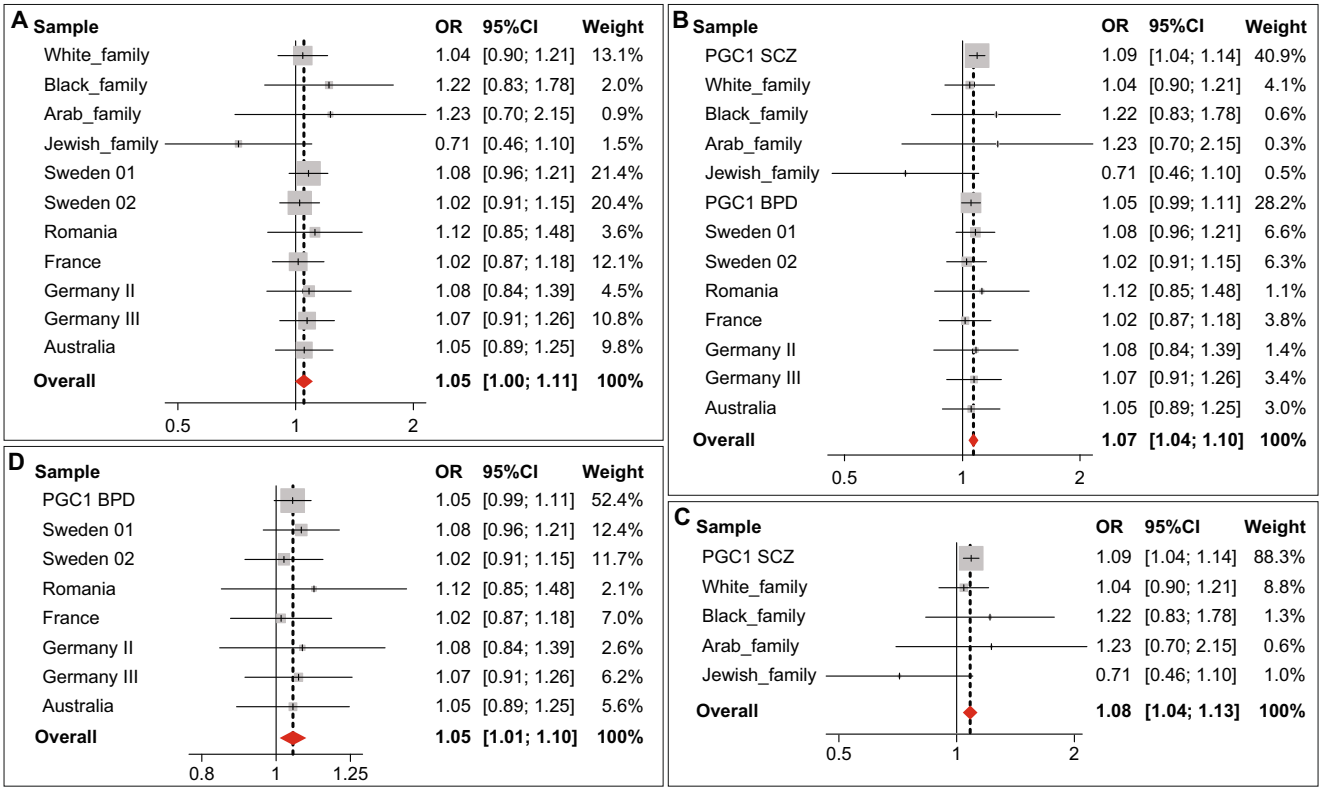

Fig. 2 Forest plot of odds ratios with 95 % confidence interval for SCZ and BPD samples included in meta-analysis of 5174 [C]. **a** Replication samples of schizophrenia and bipolar disorder combined. **b** All screening and replication samples of schizophrenia and bipolar disorder combined. **c** Schizophrenia samples. **d** Bipolar disorder samples

based on microarray techniques revealed similar results; LRP8 is better expressed in brain tissues such as hippocampus and amygdala (Fig. 5b), which have been repeatedly reported to have aberrant function in patients with SCZ and BPD [63, 64].

Temporal expression analysis in BrainCloud database [35] showed that the expression level of LRP8 in prefrontal cortex is high at early developmental stages (fetal age), but gradually decreases as development progresses (Fig. 5c). The investigation in another database Human Brain Transcriptome [38] confirmed the same developmental course of LRP8 in brain tissues (e.g., hippocampus, amygdala) (Fig. 5d). The above-mentioned data are consistent with recent studies [65, 66] reporting that genes associated with psychiatric disorders are potentially enriched in transcriptional activity in fetal life and

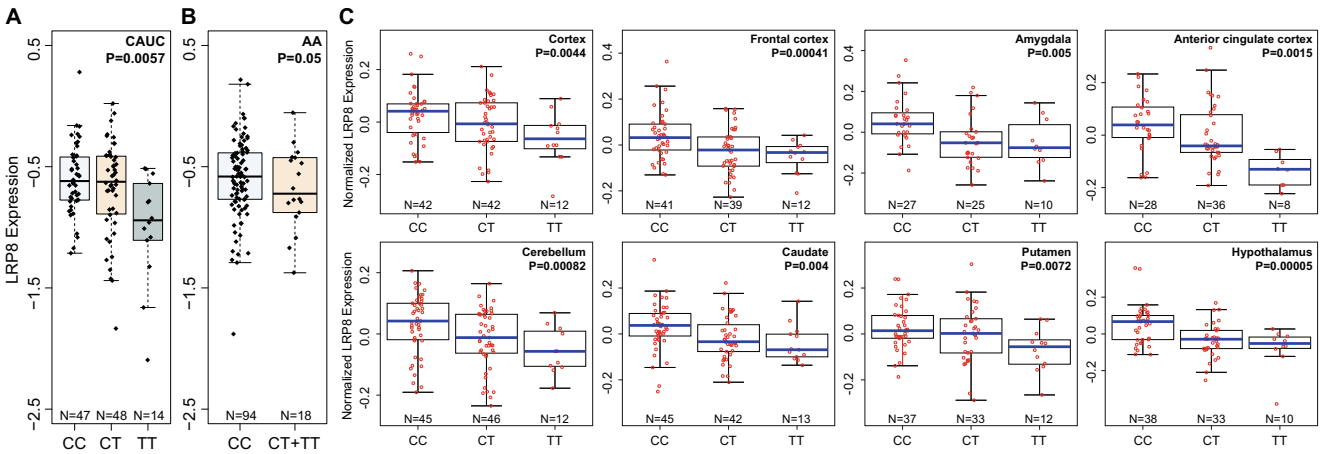

Fig. 3 Rs5174 is significantly associated with LRP8 mRNA expression. **a** Results in 109 healthy human brain DLPFC samples of Caucasian individuals. **b** Results in 112 healthy human brain DLPFC samples of African-American individuals. **c** Results in diverse brain tissues from GTEx datasets

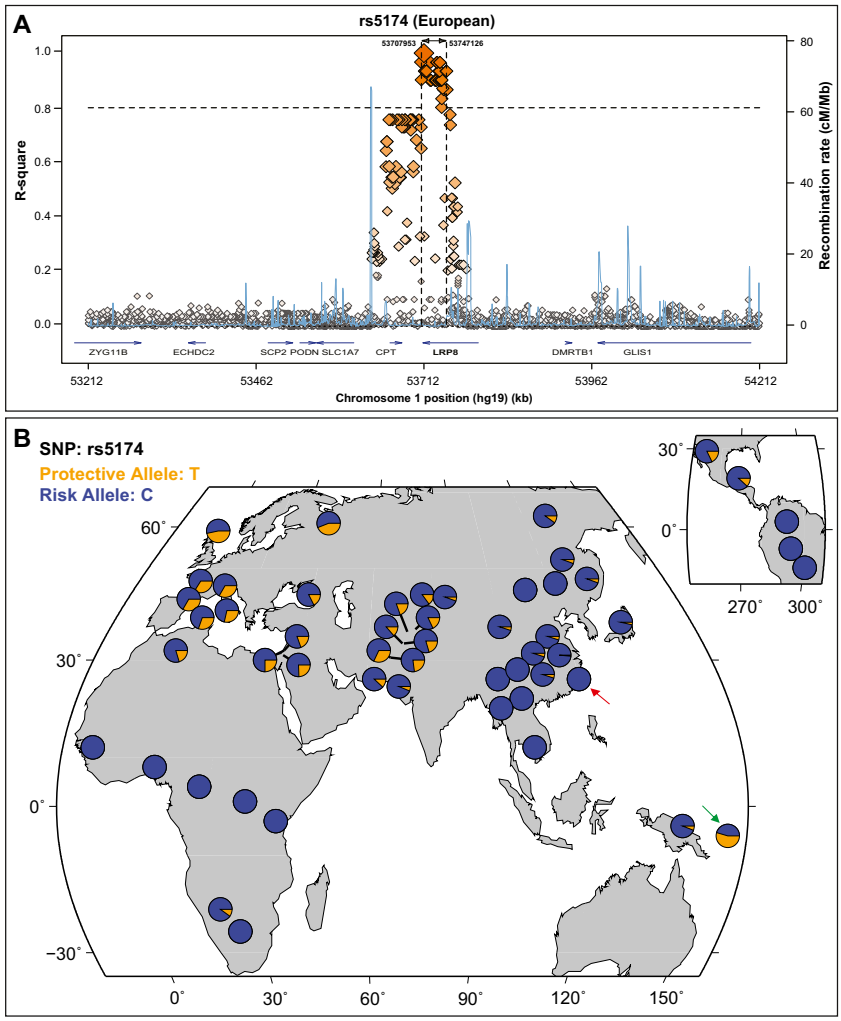

Fig. 4 **a** Plot of chromosome region showing a genomic area of high linkage disequilibrium with rs5174 in European populations. **b** Frequency distribution of the risk allele of SNP. The risk allele of rs5174 showed dramatic differences in its frequency among global populations. Of note, the C allele (risk allele) is fixed in some populations

their pathogenic effects might be exerted during this early developmental stage.

LRP8 Participates in a Highly Interconnected PPI Network Formed by Risk Genes for Psychosis

Recent studies support the idea that disturbances in a common but limited set of underlying molecular processes or pathways may modulate the risk to psychiatric disorders [44, 67]. Therefore, using high-confidence PPIs from well-characterized databases, we constructed a PPI network to investigate whether LRP8 interacts with proteins encoded by other risk genes for psychosis such as SCZ and BPD.

We found that top susceptibility genes for SCZ and BPD encode a densely interconnected PPI network (Fig. 6a). We tested the degree of interconnectivity by permutations (N= 5000) and found that the direct PPI network of risk genes had significantly more edges than expected by chance (corrected P=7.0×10^{-4}). Intriguingly, LRP8 participates in the highly interconnected network formed by these susceptibility genes (corrected P=0.0048, Fig. 6a), implying that LRP8 is involved in the common molecular network that modulates the risk for psychosis. In particular, LRP8 directly interacts with proteins encoded by RELN and apolipoprotein E (APOE) (Fig. 6b), in which the latter genes have been repeatedly reported conferring risk for psychosis in distinct samples [15, 16, 68].

Discussion

In recent years, numerous GWAS performed on a variety of SCZ and BPD samples revealed several genes significantly associated with these psychiatric disorders. However, fewer genes have been demonstrated to confer risk of both disorders, thus explaining a part of the shared genetic liability of the two illnesses. In this study, we showed that a common non-synonymous SNP rs5174 in LRP8 gene is significantly associated with both SCZ and BPD across independent and separate diagnostic samples. The non-synonymous SNP rs5174 as a potential genetic susceptibility locus seems to be dependent on changes in gene expression. Although the exact risk variant

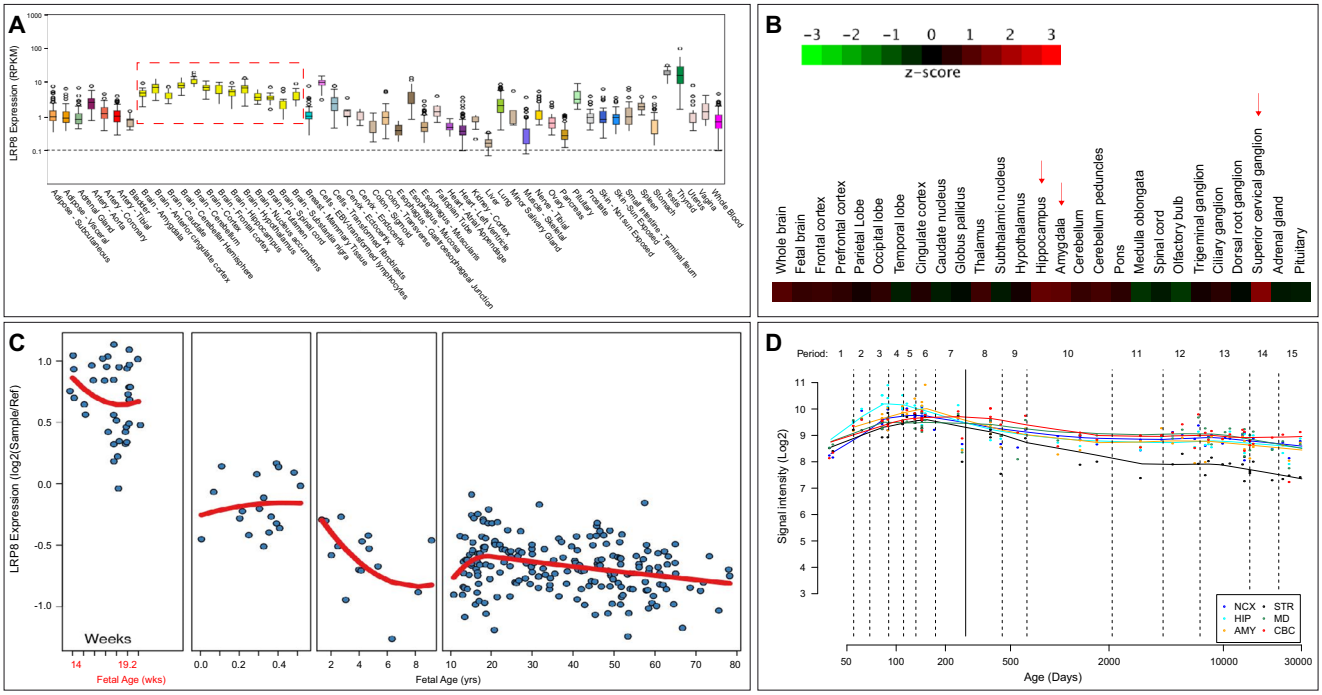

Fig. 5 Temporal-spatial expression profiling of LRP8 in human brain tissues. **a** LRP8 is abundantly expressed in human brain tissues in GTEx. **b** Expression of LRP8 is enriched in human brain tissues in Gene Enrichment Profiler, the hippocampus, amygdala, and superior cervical ganglion showed relatively higher enrichment scores. **c** Temporal expression profile of LRP8 in human postmortem dorsolateral prefrontal cortex (DLPFC) of BrainCloud. The expression level of LRP8 in human brain is relatively high at early developmental stage. As development progresses, LRP8 expression level decreases. **d** Temporal expression pattern of LRP8 in different human brain regions in Human Brain Transcriptome. *AMY* amygdala, *CBC* cerebellar cortex, *HIP* hippocampus, *MD* mediodorsal nucleus of the thalamus, *NCX* neocortex, *STR* striatum

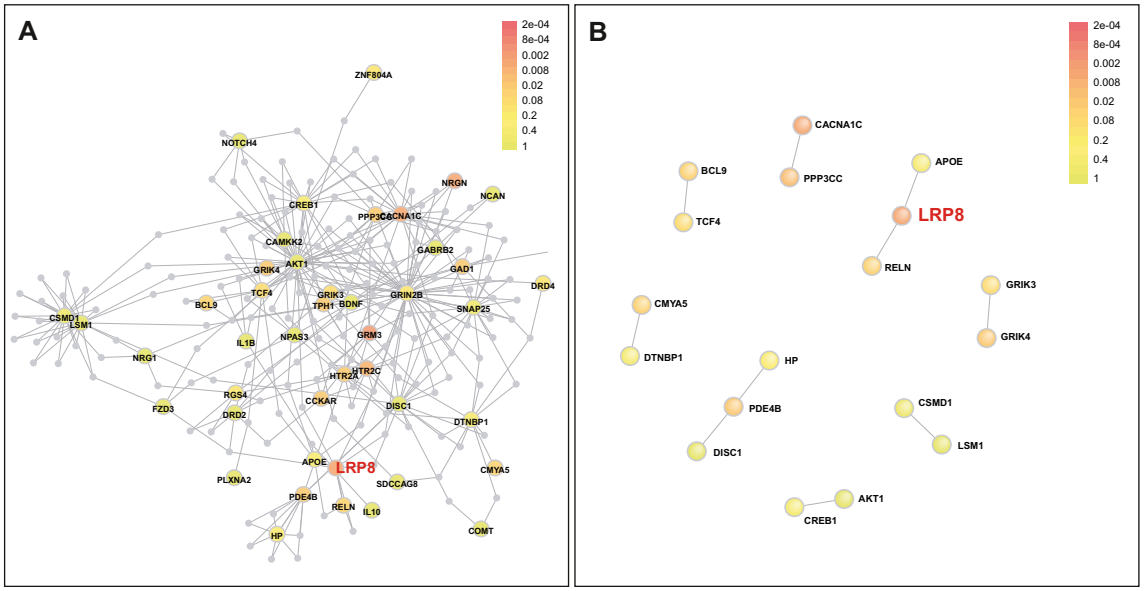

Fig. 6 Low density lipoprotein receptor-related protein 8 in a densely interconnected protein-protein interaction (PPI) network formed by top susceptibility genes for psychosis. **a** Proteins encoded by top psychosis susceptibility genes formed a highly interconnected network and LRP8 participates in this network, suggesting LRP8 is an important psychosis susceptibility gene that is involved in common molecular network that modulate risk to psychosis. The direct connectivity network is statistically highly significant (has more edges) compared with 5000 random networks ($P=7.0\times10^{-4}$, corrected), suggesting perturbations of common underlying molecular processes or pathways that modulate risk to psychosis. **b** LRP8 protein is physically interacted with RELN and APOE proteins

and genomic structure of this loci might vary in different populations, the SNP location might have an overall effect on LRP8 gene functioning that could still confer risk for SCZ and BPD.

Although only a moderate effect of the risk SNP in LRP8 was detected and the associations were not statistically significant at genome-wide level ($<5.0\times10^{-8}$), the observed ORs are comparable with other susceptibility loci identified through large-scale genetic association studies on SCZ and BPD [30, 57]. Moreover, PPI analysis identified LRP8 directly interacting with top risk genes for psychosis. As SCZ and BPD are highly polygenic disorders with a complex array of contributing risk loci across the allelic frequency spectrum [69], results from our analyses might provide genetic evidence for the interactive effects between LRP8 and other risk genes for major psychosis in the pathogenesis of the two disorders.

LRP8 is a cell surface receptor for RELN and apolipoprotein E (APOE), which contains ligands and participates in transmitting the extracellular RELN signal to intracellular signaling processes by binding to DAB1 on its cytoplasmic tail. RELN acts via both the VLDL receptor (VLDLR) and LRP8 to regulate DAB1 tyrosine phosphorylation and microtubule function in neurons, but LRP8 has higher affinity for RELN than VLDLR; thus, it is a key component of the RELN pathway which governs neuronal layering of the forebrain during embryonic brain development. These lines of convergent evidence strongly suggest that LRP8 interacts with other risk genes for SCZ and BPD from the RELN signaling pathway and plays a pivotal role in brain development. Considering that accumulating evidence supports the hypothesis that SCZ and BPD are neurodevelopmental disorders [70], our results suggest that LRP8 might be involved in their pathogenesis by influencing brain development. Further investigation of LRP8 is thus warranted.

While this study offers some interesting observations, it should be noted that the present evidence is limited, and we are cautious in interpreting our results. Firstly, although we identified a risk SNP in LRP8, the SNP coverage is still relatively low and other true risk SNPs may have been missed. Due to the dearth of functional data, it is difficult to identify the causative variant(s). Likewise, we cannot exclude the possibility that the positive association signal was actually caused by the hitch-hiking effect of rare missense mutations, copy number variations, or variants in a distant region. Further focused studies may provide a more complete survey. Secondly, the exact regulative mechanism of LRP8 expression by rs5174 is still unclear, and this might not be the only underlying molecular mechanism of risk associations, especially if we take into account that rs5174 is a non-synonymous variation.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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