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Rare variants in Protein tyrosine phosphatase, receptor type A (*PTPRA*) in schizophrenia: Evidence from a family based study

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Abstract

The contribution of both common and rare risk variants to the genetic architecture of schizophrenia (SZ) has been documented in genome-wide association studies, whole exome and whole genome sequencing approaches. As SZ is highly heritable and segregates in families, highly penetrant rare variants are more likely to be identified through analyses of multiply affected families. Further, much of the gene mapping studies in SZ have utilized individuals of Caucasian ancestry. Analysis of other ethnic groups may be informative. In this study, we aimed at identification of rare, penetrant risk variants utilizing whole exome sequencing (WES) in a three-generation Indian family with multiple members affected. Filtered data from WES, combined with *in silico* analyses revealed a novel heterozygous missense variant (NM_080841:c.1730C>G:p.T577R; exon18) in Protein tyrosine phosphatase, receptor type A *(PTPRA* 20p13). The variant was located in an evolutionary conserved position and predicted to be damaging. Screening for variants in this gene in the WES data of an independent SZ cohort (*n* = 350) of matched ethnicity, identified five additional rare missense variants with MAF < 0.003, which were also predicted to be damaging. In conclusion, the rare missense variants in *PTPRA* identified in this study could confer risk for SZ. This has also derived support from concordant

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Contributions

Prof. B.K. Thelma, Prof. S. N. Deshpande and Prof. V. L. Nimgaonkar designed the study and obtained research funding; Prof. S. N. Deshpande diagnosed and recruited the study samples; Dr. Jibin John performed all the WES data analysis, interpretation, and confirmation of variants by Sanger sequencing and linkage analysis. Dr. Triptish Bhatia contributed to sample recruitment and phenotype data documentation; Dr. Prachi Kukshal maintained the DNA repository and contributed to data analysis and interpretation; Mr. Aditya Sharma contributed to data analysis; Jibin John, B.K. Thelma and V. L. Nimgaonkar wrote the first draft of manuscript; all authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest in relation to the subject of this study.

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data from prior linkage and association, as well as animal studies which indicated a role for *PTPRA* in glutamate function.

1. Introduction

Schizophrenia (SZ) is a debilitating disorder, with a life time prevalence of ~1%. It is characterised by positive and negative symptoms and cognitive impairments which create emotional distress and lifelong disability in the affected individuals (Lewis and Lieberman, 2000). SZ is considered as a manifestation of an aberrant neurodevelopmental phenomenon (Lewis and Levitt, 2002) and abnormalities in neurotransmitter systems including dopaminergic, glutamatergic and gamma amino butyric acid (GABA) have been reported (Howes et al., 2015; Wassef et al., 2003). Genetic risk factors for SZ have been demonstrated through family based and twin and adoption studies, which also indicate the contribution of environmental perturbations (Gottesman and Gottesman, 1991; Tsuang, 2000). SZ is typically considered as an outcome of cumulative contribution of large number of genes with minor effects and transmitted in a non-Mendelian fashion. Based on this assumption, the last decade witnessed a large number of genome wide association studies (GWASs) carried out across ethnic groups, which identified a large number of common variants in several genes/loci. A recent meta-analysis using 36,989 cases and 113,075 controls identified 108 loci associated with disease with genome wide significance (Ripke et al., 2014). Of note, several of the genes encoded proteins involved in dopaminergic and glutamatergic functions. However, a recent study has shown that the associated SNPs only explain a small fraction (hg2 = 0.27) of genetic liability to the disease (Loh et al., 2015), warranting newer paradigms to uncover the components to explain total heritability.

The rapidly decreasing cost of next generation sequencing (NGS) technology facilitated one such approach, leading to rapid identification of rare variants in SZ etiology. Several studies using whole exome sequencing (WES) of case-parent trios have identified over 1000 rare *de novo* variants predicted to be disturbing protein function (Ambalavanan et al., 2016; Fromer et al., 2014; Girard et al., 2011; Guipponi et al., 2014; Gulsuner et al., 2013; Gulsuner and McClellan, 2014; Kranz et al., 2015; McCarthy et al., 2014; Singh et al., 2016; Takata et al., 2014; Xu et al., 2012). These *de novo* mutations are rare, nevertheless they were enriched in genes involved in synaptic transmission, glutamatergic post synaptic proteins and *N*-methyl-D-aspartate receptor (NMDAR) complexes the systems previously implicated in SZ pathogenesis. However, neither the common nor the *de novo* rare variants sufficiently explain the large fraction of genetic liability and/or the high heritability of SZ suggesting the presence of few rare high risk conferring variants transmitted across generations. At this juncture identifying such highly penetrant rare variants in functionally relevant gene(s) segregating with the disease phenotype in familial forms of SZ is appealing. We and others in the recent past have used small to medium size families with SZ and reported moderately to highly penetrant rare protein coding variants segregating with disease phenotype (Egawa et al., 2016; Homann et al., 2016; Hornig et al., 2017; John et al., 2018, 2017; Kos et al., 2016; Shirzad et al., 2017; Steinberg et al., 2017; Timms et al., 2013; Zhou et al., 2016) Several genes identified in these studies were broadly connected with glutamatergic pathway and supported the commonly accepted glutamatergic dysfunction hypothesis. These studies

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reaffirm the highly complex and heterogeneous nature of SZ and at the same time provide evidence for a major/predominant role of glutamatergic pathway genes in SZ etiology based on common and rare variants identified in GWASs and WES respectively. Yet, a substantial fraction of genetic determinants remains to be elucidated, encouraging additional studies. In the present study we analysed a small multigenerational SZ family using WES approach and identified a novel missense variant in *PTPRA* segregating with the phenotype. Furthermore, five additional rare coding variants in this gene were also observed on screening an independent SZ cohort.

2. Methods

2.1. Sample recruitment

The family in this study was recruited from Department of Psychiatry, Dr. Ram Manohar Lohia Hospital, New Delhi and was of north Indian origin. Consensus diagnosis of SZ was made by psychiatrists and well trained psychologists using DSMIV criteria. For getting additional information for the genetic studies, the Hindi version of Family Interview for Genetic Studies (FIGS) and Diagnostic interview for genetic studies (DIGS) were used (Deshpandeetal., 1998; John etal., 2016). The family comprised of seven affected, 11 unaffected and two other members with other psychiatric illness (Fig. 1). Of these, DNA from four affected and one unaffected individual was available for study. Any other psychiatric/behavioural phenotype in the unaffected individual was ruled out by same clinicians. The study was approved by institutional ethical committee of both participating institutions.

Whole Exome Sequencing (WES)—DNA from three affected members (Fig. 1) was used for WES. Agilent SureSelect Human All ExonV5+UTR kit was used for target enrichment and library preparation. Sequencing was performed in 101-bp paired-end mode using Illumina® HiSeq™ 2000. All these processes was carried out at a commercial facility (Medgenome; https://www.medgenome.com/).

2.2. Whole exome data analysis

The raw FastQ data were processed as per the recommendations of Genome Analysis Toolkit (GATK) “Best Practices for Germline SNP & Indel Discovery”. Basic QC checking of the raw data obtained from the service provider was performed using FastQC tool and Adapter and low quality sequences (phred score < 15) were removed using cutadapt (Martin, 2011). The QC passed sequences were aligned to the reference human genome (hg19) using BWA-MEM algorithm (Li, 2013; Li and Durbin, 2009). Aligned data in SAM format were then sorted, converted into BAM file and PCR duplicates were removed using Picard Tools (http://broadinstitute.github.io/picard/). Subsequently, realignment around indels and base recalibration were performed using GATK and cleaned BAM file was generated. Alignment QC and target region coverage in both depth and breadth were calculated from the BAM file generated from the preceding step using Qualimap (García-Alcalde et al., 2012). Variants in VCF format were created from the cleaned BAM file using GATK (McKenna et al., 2010). The variants were annotated using Kggseq (Li et al., 2012).

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2.3. Variant prioritisation

For the prioritisation of variants we followed the recommendations from three previous publications (Dashti and Gamieldien, 2017; Kircher et al., 2014; Richards et al., 2015) and used Kggseq (Li et al., 2012). Keeping in mind the small sized study family and therefore, a greater chance of identifying shared variants among affected just by chance alone, and thus to avoid false positive detection, we primarily focused on protein disturbing rare variants in previously reported and/or functionally relevant candidate genes (Purcell et al., 2014) and adopted the following steps for variant prioritisation. To start with, all the protein coding variants were extracted from the annotated file. All common variants (MAF > 0.001) catalogued in different public databases available namely 1000 genome (1000G), Exome Aggregation Consortium (ExAC r0.3.1), dbSNP, Genome Aggregation Database (gnomAD) browser and NHLBI GO Exome Sequencing Project (ESP) and all the synonymous variants were removed. Variants shared among three affected WES individuals were then taken forward to check for segregation in the remaining two individuals (one affected and one unaffected) using target capture sequencing. Only variants shared among all four affected individuals in the family were considered and variants in segmentally duplicated regions or in “polymorphic” genes (Fuentes Fajardo et al., 2012) and genes containing four or more variants each in an individual were removed from this list. Variants which were common (MAF > 0.001) in in-house WES data and shared with the unaffected member in the family were also removed. Finally, the variants that were present only in all affected members were further prioritised based on their predicted deleterious nature (by SIFT or Polyphen2_HDlV or Polyphen2_HVAR and with CADD score > 15) and on their relevance in SZ etiology, based on available reports of association/linkage/exome sequencing/animal studies/presence in pathways implicated in SZ and/or other neuropsychiatric disorders and gene functions. Variant (s) thus shortlisted were confirmed by Sanger sequencing (primer details in Supplementary Table 1; Supplementary Fig. 1).

2.4. In silico analysis of prioritised variants

To check if the variants were predicted to be damaging we used SlFT, Polyphen2_HDlV, Polyphen2_HVAR, LRT, MutationTaster, LR, FATHOM, MutationAssessor, MetaLR, PROVEAN, MetaSVM, RadialSVM, Variant Effect Scoring Tool3 (VEST3) and Combined Annotation Dependent Depletion (CADD) score. Evolutionary conservation score of the variant positions was calculated using phastCons7way_vertebrate, GERP+ +_RS, SiPhy_29way_logOdds and GERP+ +_NR and gene-based pathogenicity estimation were calculated using Residual Variation Intolerance Score (RVIS). All the algorithms were part of dbNSFP2.9 (Liu et al., 2013) and are included in Kggseq (Li et al., 2017, 2012).

2.5. Screening for additional rare variants in the prioritised gene(s) in an independent cohort

For screening of rare variants in the prioritised gene(s), we used WES data from i) unrelated SZ patients (n = 350) of matched ethnicity, recruited previously by the clinician (SND) based on consensus diagnosis using DSMlV criteria and available in the laboratory and ii) individuals without any psychiatric disorder (n = 150, considered as controls), both of which

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were also used in our previous study (John et al., 2018). All these samples were from the same geographical regions as the family recruited for the study.

3. Results

Three affected members namely III.1, III.2 and III.3 of the study family (Fig. 1) were used for WES. The mean target depth of sequencing observed across these three samples was 58.82×. On an average > 97% of the target regions were with 10× and >89% with 20× coverage. The mean mapping observed across the three samples was 46.99. Detailed information of target region both in depth and breadth aspects are given in Supplementary Table 2.

A scheme for prioritisation of variants detected with WES is provided in supplementary Table 3. After prioritisation, 20 variants were identified to be shared among all the affected but not in the unaffected member of the study family. Of these, 13 variants were predicted to be damaging by SIFT or Polyphen2_HDlV or Polyphen2_HVAR and CADD score > 15 (Supplementary Table 3). In order to identify high risk conferring variant(s) from among these, the 13 genes encompassing the rare variants were further scrutinised for their known/likely involvement in neurobiology. Among these, four genes namely *NRROS, L3MBTL1, RTTN* and *PTPRA* seemed to have some neurologically relevant functions. A critical review of all the available literature on genetic/knockout/over expression/pharmacological studies and animal models showing SZ or other neuropsychiatric disorder-related symptoms, suggesting the direct/indirect roles of these genes in disease biology (summarised in supplementary Table 6), revealed significant support for the involvement of Protein Tyrosine Phosphatase, Receptor Type A *(PTPRA)* but not the other three genes. Therefore, though the variants with complete annotation in these genes are catalogued (Supplementary Table 4), *NRROS, L3MBTL1* and *RTTN* were not considered for further analysis in the present study. However, this does not imply that these three genes may not have a role in SZ etiology, but sufficient support, based on functional and/or animal model studies are currently lacking. On the other hand, *PTPRA* is involved in various neurodevelopmental processes and also in glutamatergic and dopamine signalling pathways and previously implicated in SZ (as detailed in discussion below). The novel index variant (NM_080841:c.1730C>G: p.T577R; exon18) in *PTPRA* is in the Tyrosine-protein phosphatase 2 domain. The gene is expressed in different brain regions as evidenced in two public databases BrainSpan (http://www.brainspan.org) and Genotype-Tissue Expression (GTEx) portal (https://www.gtexportal.org/).

3.1. In silico analysis

The index variant (p.T577R) in *PTPRA* was located at an evolutionarily conserved residue (Supplementary Fig. 2) and is predicted to be damaging by seven of 13 *in-silico* tools and with a CADD score of 32. This indicates that the variant is among the top 0.1% of deleterious variants in the human genome (Supplementary Table 4).

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3.2. Gene level pathogenic analysis

Residual Variation lntolerance Score (RVIS) of *PTPRA* showed that the gene is among 7.15% of the most intolerant genes in human.

3.3. Additional variants identified in PTPRA in an independent SZ cohort

Based on all the findings presented above, screening for additional variants, if any, in *PTPRA* was undertaken in an independent SZ cohort. This would lend additional support to this gene being important in SZ etiology. WES data from a SZ cohort ($n = 350$) of matched ethnicity available in the laboratory and used in a previous study (John et al., 2018) were utilized for screening of variants in *PTPRA.* We identified five additional rare (MAF < 0.003) missense heterozygous variants namely; p.T57N, p.E506G, p.V664l and p.R759W in one individual each and p.A129V in two different individuals in the cohort. All these rare variants were also predicted to be damaging with several *in silico* tools and with CADD score was >15 (Supplementary Table 5). Except for p.T57N in *PTPRA* which was present in a heterozygous state in one healthy individual, none of the other variants were present in the exome data of 150 non-SZ individuals (non-disease controls) of lndian origin also available in the laboratory. All the five variants thus identified have been reported with MAF <0.003 in South Asian and few other populations in ExAC and gnomAD browsers (supplementary Table 5) and therefore, catalogued as rare in this study. lt may be relevant to mention here that p.T57N was reported in two SZ patients but was absent in 912 healthy controls in a Japanese population (Xing et al., 2014).

3.4. Analysis of PGC dataset

On screening the Psychiatric Genomics Consortium (PGC) data (https://www.med.unc.edu/pgc/), we found two common (MAF > 0.05) intronic SNPs namely rs6037443 ($p = 0.0006$) and rs1178029 ($p = 0.01$) in *PTPRA* nominally associated with SZ.

4. Discussion

We analysed a multi-member affected SZ family by WES and identified 13 rare variants that were predicted to be damaging and were present in all affected but not in the unaffected member in the study family. Based on multiple levels of contextual support from pre-existing genetic and animal studies (detailed below), the novel heterozygous missense variant (p.T577R) in *PTPRA* emerged as the most compelling contributor to the disease in study family (Fig. 1; Supplementary Fig. 1). Five additional rare missense variants in this gene were also identified among 350 unrelated SZ patients and four of these were not found in non-SZ exomes ($n = 150$) screened in the laboratory (Supplementary Table 5). A large number of *in silico* tools predicted all these variants to be deleterious and they are located in evolutionarily conserved positions (Supplementary Table 5). Furthermore, likely involvement of *PTPRA* is extensively supported by available literature. *PTPRA* is a member of protein tyrosine phosphatase (PTP) family. By regulating the phosphorylation of potassium channels (Kv1.1 and Kv1.2), *PTPRA* modulates acetylcholine and serotonin mediated activity response (Imbrici et al., 2000; Tsai, 1999). Kv1.2 is involved in D2 dopamine autoreceptor mediated dopamine release (Fulton et al., 2011; Martel et al., 2011). The gene is also known to regulate the kinase activity of Src and Fyn (Ponniah et al., 1999)

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and the role of Src in *N*-methyl-D-aspartate (NMDA) receptors hypofunction in SZ is evident from a previous report (Li et al., 2012). Fyn has also been shown to be involved in the phosphorylation and trafficking of NMDA receptors (Trepanier et al., 2012). Further as evident from literature, through the interactions with neural recognition molecules namely NB-3 and CHL1, *PTPRA* has been shown to be involved in apical dendrite development in the deep layer pyramidal neurons of the caudal neocortex (Ye et al., 2008). *PTPRA* is also involved in NCAM mediated neurite elongation (Bodrikov et al., 2008, 2005).

Interestingly *PTPRA* (20p13) has been previously reported to be linked to SZ in a large Arab Israeli pedigree (Teltsh et al., 2008) and with SZ and various psychotic illness in high-density Irish families with psychotic illness (Fanous et al., 2008). Two common intronic variants (rs6037443; $p = 0.0006$ and rs1178029; $p = 0.01$)} were shown to be nominally associated with SZ in Psychiatric Genomics Consortium (PGC) study (https://purces04.u.hpc.mssm.edu/ldookup/ldookup.cgi). A common intronic SNP (rs1016753) from this gene has been reported to be significantly associated ($p = 0.0008$) with SZ in a Japanese population (1420 cases, 1377 controls). Expression studies showing reduced expression of this gene in SZ brain samples compared to controls substantiated these findings and the same study also showed a trend of reduced expression in bipolar patients (Takahashi et al., 2011). In another study on Japanese population, where protein coding regions of the gene were re-sequenced in 382 SZ patients, eight rare variants were identified, which were further tested for association using 944 SZ patients, 336 autism spectrum disorders patients, and 912 healthy controls but no association was reported (possibly due to insufficient power). However, as already mentioned in the results section, in two individuals with SZ they observed PT57N (Xing et al., 2014), a rare variant that we also identified in one individual (Supplementary Table 5). Besides *PTPRA* variants in SZ, one *de novo* missense variant (NM_002836.3: c.2116G>C p.Gly706Arg) in this gene was also reported in an individual with autism spectrum disorder (Yuen et al., 2017). Two other intronic SNPs namely rs12151888 ($p = 0.02$) and rs77646362 ($p = 0.04$) from this gene have been reported to be nominally associated with autism (https://purces04.u.hpc.mssm.edu/ldookup/ldookup.cgi).

PTPRA knock out studies in mice further substantiate the relevance of this gene in brain functions. Association of this phosphatase with neurodevelopmental abnormalities include defects in pyramidal neuronal migration, synaptic plasticity, long-term potentiation (LTP) and hippocampal development (Petrone et al., 2003), oriented growth of apical dendrites of deep layer pyramidal neurons in caudal cortex (Ye et al., 2008), central nervous system myelination and oligodendrocyte differentiation (Wang et al., 2009). Knock out mice showed impaired src family kinases mediated NMDAR tyrosine phosphorylation and subsequent aberrant NMDAR-associated functions (Le et al., 2006; Lei et al., 2002). In another study on knock out mice, enhanced methamphetamine induced hyperactivity has been observed suggesting an augmented dopaminergic system and defect in prepulse inhibition (PPI) of the startle response and the defect in PPI is considered as an endophenotype of SZ (Takahashi et al., 2011). Thus, substantial evidence for involvement of *PTPRA* in SZ etiology is available.

However, it may be reiterated that prioritisation and identification of *PTPRA* from among the 20 variants that segregated with SZ in the study family has relied on previous knowledge

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only (as discussed above) and needs to be validated by functional experiments, but which are currently unavailable. Furthermore, contribution of other common/regulatory variants, CNVs *etc.* to disease in this family cannot also be ruled out considering the commonly accepted polygenic nature of this illness. In addition, a few other limitations in this study warrant mention. Replication cohort used in the study (350 SZ cases and 150 controls) is small. Data on genetic variation among the ethnically distinct Indian population is also limited to 1000 Genomes and ExAC databases bu. These together greatly limit identification of variants with a reliable population frequency to enable rare variant association testing. Nevertheless, the variant data presented in this study may be useful for meta-analysis. In conclusion, based on the genomic data from the present study, in conjunction with findings from previously reported biochemical and animal studies, the rare variants in *PTPRA* may be implicated for SZ etiology encouraging their functional validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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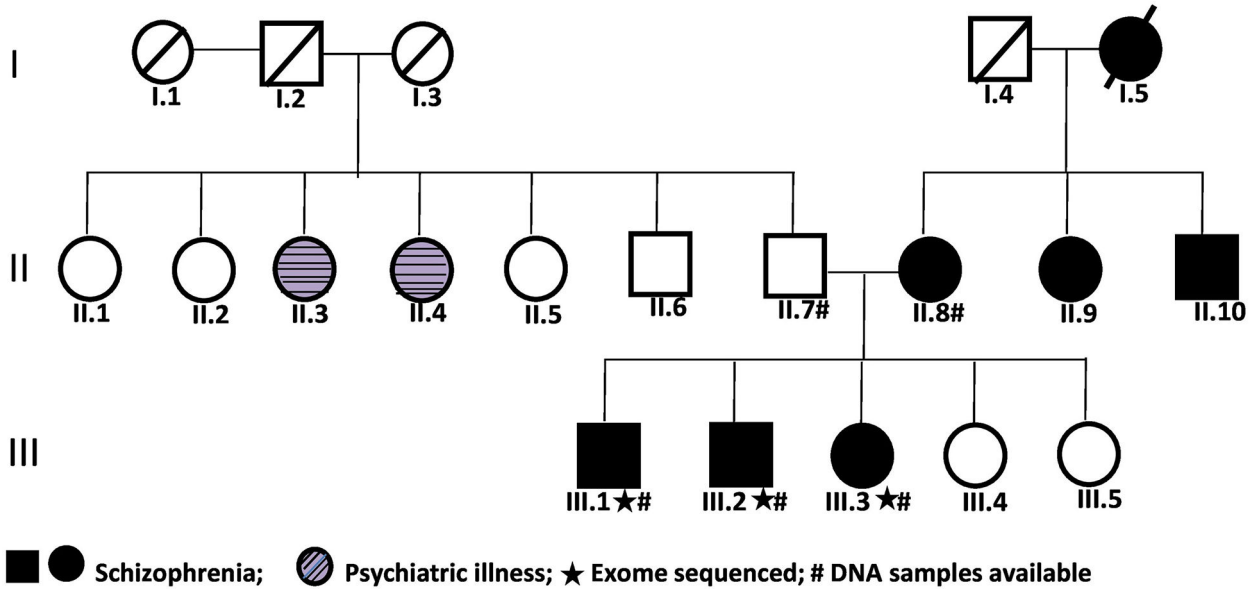

Fig. 1.
Pedigree of the multiplex family with schizophrenia.