Am J Transl Res 2023;15(11):6476-6485
www.ajtr.org /ISSN:1943-8141/AJTR0152320

Original Article

Association of the *CDH13* gene variant rs9940180 with schizophrenia risk in North Indian population

Suruchi Gupta[1*], Indu Priya[1], Manu Arora[2], Hemender Singh[3,4*], Isar Sharma[1], Sakshi Sharma[1], Ritu Mahajan[1], Nisha Kapoor[1]

[1]*School of Biotechnology, University of Jammu, Jammu 180006, India;* [2]*Govt Psychiatric Disease Hospital, Govt Medical College, Jammu 180001, India;* [3]*School of Biotechnology, Shri Mata Vaishno Devi University, Katra 182320, India;* [4]*Pharmacology Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India.* [*]*Equal contributors.*

Received July 19, 2023; Accepted October 16, 2023; Epub November 15, 2023; Published November 30, 2023

Abstract: Background and Objectives: Cadherin13 (*CDH13*) is an uncommon cadherin family member, lacking a transmembrane domain, and attaches via a glycosylphosphatidylinositol anchor to the peripheral surface of the cell membrane. *CDH13* plays an important role in the development and maintenance of axonal growth cones, synapse morphogenesis, and the embryonic neural tube. Cadherin superfamily genes have been associated with many neuropsychiatric diseases. Studies have shown the Cadherin13 gene as a risk locus for Schizophrenia (SCZ). In this study, we investigated *CDH13* gene variants rs7204454 in the promotor region and rs9940180 in the intronic region of the gene with susceptibility to SCZ risk in the population of Jammu region of J&K, India. Methods: The genotyping was performed using TaqMan assay, where 560 individuals, comprising 164 patients and 396 healthy controls, were genotyped. Results: The result of the study suggested rs9940180 was significantly found to be associated with Schizophrenia and the "C" allele of rs9940180 was associated with increased risk for SCZ (P = 0.03817; OR = 1.527; 95% CI, 1.022-2.28) whereas the other variant rs7204454 of *CDH13* gene did not show significant association with schizophrenia risk with P = 0.8827, OR = 0.582-1.33 at 95% CI. Conclusion: This is the first report suggesting a significant association of polymorphism at *CDH13* rs9940180 with Schizophrenia in the Dogra population group of the Jammu region. The current study offers a piece of important information on the genetic reason for *CDH13* in the Jammu population of J&K. Also, it supports the GWAS findings on the correlation of *CDH13* in schizophrenia.

Keywords: Schizophrenia, Cadherin13, rs9940180, genetic variants, linkage disequilibrium

Introduction

Schizophrenia (SCZ) is a life-threatening mental illness with prevalence rates corresponding to 1% of the global disease burden (World Health Organization, 1996). SCZ symptoms include delusions, hallucinations, highly impaired behavior, and thinking that badly affects routine functions [1, 2]. The causes of Schizophrenia include both genetic as well as environmental aspects [3].

It is well established that various SNPs were associated with schizophrenia, and the SNP heritability has been estimated to be 64-80%, implying that genetic factors play a significant role in the disorder's etiology. It has also been reported that SCZ is associated with several abnormalities, like a reduction in the hippocampus, prefrontal cortex, and brain volume [4, 5]. Moreover, significant changes in morphology, neuron size, and synaptic connectivity also associated with SCZ risk [6, 7]. Previous research suggests that genes involved in neuronal growth and mature brain activity may also be associated with SCZ [7, 8].

Cadherins (*CDHs*) are a type of cell adhesion molecule that mediates cell adhesion and thus regulates morphogenesis. *CDHs* are essential for neural tube regionalization, differentiation of gray matter, neuronal migration, spine morphology, neural circuit formation, synapse formation, and remodeling in the nervous system

[9, 10]. Cadherin13 (*CDH13*) gene, also known as T-cadherin, is a member of the cadherin superfamily and is found on chromosome 16q23 in humans and has a length of 1,169.8 kbp. *CDH13* is a glycosylphosphatidylinositol linked protein that does not have cytoplasmic and transmembrane domains [11].

CDH13 is an important regulator of neurodevelopmental processes [11] like synapse formation and axonal outgrowth is regulated *by CDH13* [12]. *CDH13* encodes for calcium-dependent cell-cell adhesion protein [13] which regulates development of neurons and synaptic plasticity, demonstrating its importance in neurodevelopmental processes. Another study showed that *CDH13* knockout mice exhibited learning impairments and hyperlocomotion [14]. These results, along with the findings from other association studies in which *CHD13* is associated with, other neurodevelopmental disorders, make *CDH13* a potential candidate gene for SCZ [15]. Although, evidence supporting the functional implications of common gene variation in the *CDH13* gene in humans is limited. Cadherin-13 is highly expressed in the brain, where it plays role as a negative regulator of axon guidance and neurite outgrowth [16].

CDH13 has been implicated in the susceptibility to a variety of psychiatric diseases like SCZ, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD), and bipolar disorder (BD) [17-19]. At a genome wide level none of these associations have been significant, in GWAS studies, linking *CDH13* gene to psychosis comes from at least two different populations, *CDH13* is highly applicable candidate gene for psychosis [20].

According to a GWAS conducted on the Danish population, rs8057927 in the *CDH13* was associated with SCZ [22]. It was the first study to show a correlation between *CDH13* and schizophrenia. Several other studies have been conducted to determine the association between the *CDH13* SNP and SCZ [22, 23]. Another family-based study identifies a rare duplication i.e. DUP16q23.3 in the *CDH13* gene and linked with ID, delayed speech, language development, and global developmental delay [21]. It was observed that the functional variant in the *CDH13* gene rs22199430 has been linked to personality traits, and has been shown to alter neural processing while performing memory tasks [12].

Thus it is pertinent to screen other SNPs in linkage disequilibrium (LD) with the *CDH13* for their association with schizophrenia. In addition to this study the association of *DISC1* SNP rs3738401 has also been found in SCZ risk in Jammu population [24].

In the present study, we determined the association of rs9940180 and rs7204454 of *CDH13* with SCZ in the North Indian population. Also, we found linkage disequilibrium (LD) pattern between these two SNPs in our population as no such work has been done on the North Indian population of the Jammu region.

Materials and methods

Selection criteria

The study was carried out after seeking approval from the Institute's Ethics Committee (IEC), Government Medical College, Jammu, and the University of Jammu. All the experiments were carried out as per the guidelines and protocols of the Indian Council of Medical Research (ICMR) (IEC/2017/425). Hospital-based recruitment of cases and controls was performed. All the subjects have been confirmed with schizophrenia using the Diagnostic and Statistical Manual of Mental Illnesses, 4th edition criteria, by an experienced psychiatrist (American Psychiatric Association, 1994) at Psychiatric Diseases Hospital, GMC Jammu. Psychiatric conditions induced by physical disease, drugs, or other treatments; mentally retarded; family history of epilepsy or brain injury; substance abuse history; and drug abuse are among the subjects' exclusion criteria.

Non-psychiatric healthy controls were gathered from Jammu, and they underwent drug abuse, mental disease history, and family history of mental disorders screenings. Both the cases and the controls, as well as their respective guardians, were informed of the study design. Prior to the sample collection, they also provided their informed consent.

Subjects

The association study included 164 SCZ cases and 396 healthy controls. All the subjects

Table 1. Real-time PCR reaction mix

Components	384-well (5-µl reaction)
TaqMan® Master Mix (2×)	2.50 µl
Assay Working stock (40×)	0.125 µl
Water (Nuclease-Free)	1.375 µl
DNA sample	1.0 µl
Total volume per cell	5.0 µl

recruited in the study belong to the Jammu region (Jammu and Kashmir, North India). Informed consent from all subjects and family members of the schizophrenic patients was taken for their recruitment in the study.

Two SNPs (rs9940180 and rs7204454) were successfully genotyped and analyzed in 560 subjects. Out of 164 schizophrenic individuals, 68% were males and 32% were females, and 396 healthy individuals, 39% were males, and 61% were females. Both cases and controls belonged to the population of the Jammu region.

Sample collection and DNA extraction

Three ml of venous blood was taken from the affected and healthy individuals and placed in EDTA tubes using disposable sterile syringes. Later, samples were stored at -20°C until DNA was extracted. DNA isolation was done by using the phenol chloroform method [25]. The qualitative and quantitative analysis of all the DNA samples was done using 0.8% Agarose gel electrophoresis and NanoDrop™ 2000/2000c (Thermofisher), respectively.

SNP selection

In the promotor region of *CDH13,* one LD block in the population of Gujarati Indian in Houston, TX, from the International Genome Sample resource (https://www.internationalgenome.org/) was selected. Then two tag SNPs (rs7204454 promotor region variant rs9940180 intronic region variant) were selected from that LD block with an r^2 threshold greater than 0.8 and D' value greater than 0.9 that was further confirmed by HaploReg v.4.1.

TaqMan genotyping

The SNP genotyping for variants rs9940180 and rs7204454 was performed using TaqMan allele discrimination assay using Quantsudio Real-time PCR system (Thermofisher). The genotyping was carried out according to the manufacturer's instructions. The reaction mixture of the TaqMan assay is mentioned in **Table 1**. The allelic discrimination plot was generated for both SNPs to verify allele distribution in the samples (**Figures 1** and **2**). For the variant rs7204454 the red colour represents GG genotype, blue represents CC genotype, and green represents GC genotype. Similarly, for variant rs9940180 the red colour represents CC genotype, blue represents TT genotype, and green represents CT genotype.

Statistical analysis

All the data was entered into Microsoft Excel 2017 worksheet for data extraction and statistical analyses. The TaqMan assay's experimental data were analyzed using TaqMan® Genotyper Software.

The power of study was calculated using Genetic Association Study (GAS) power calculator (http://csg.sph.umich.edu/abecasis/cats/gas_power_calculator/index.html) where the significance level was set at 0.05, prevalence of the disease as 0.3, disease allele frequency as 0.5, and odds ratio as 1.5. The power of study was observed to be 99.2%. The Chi-Square test was employed in 2×2 and 2×3 tables to assess the significance of differences in allelic and genotypic distributions, respectively. The association of the variants was evaluated by calculating the odds ratio (OR) at a 95% confidence interval (CI) at a significance level of ≤ 0.05. The Genotypic and allelic frequencies were estimated and evaluated for Hardy-Weinberg equilibrium (HWE) and association of SNP in different models (Genotyping model, Allelic model, Dominant model, and recessive model) has been done using PLINK v.1.07 tool. The LD of the variants was evaluated and plotted using the Haploview v.4.2 tool. In addition, the gene-gene interaction analysis was performed to evaluate the interaction of the candidate gene with other genes of the related pathway and functions using STRING v.12.0 (https://string-db.org/).

Results

In the present study, the allelic and genotypic frequencies for rs9940180 and rs7204454 were determined in the studied population

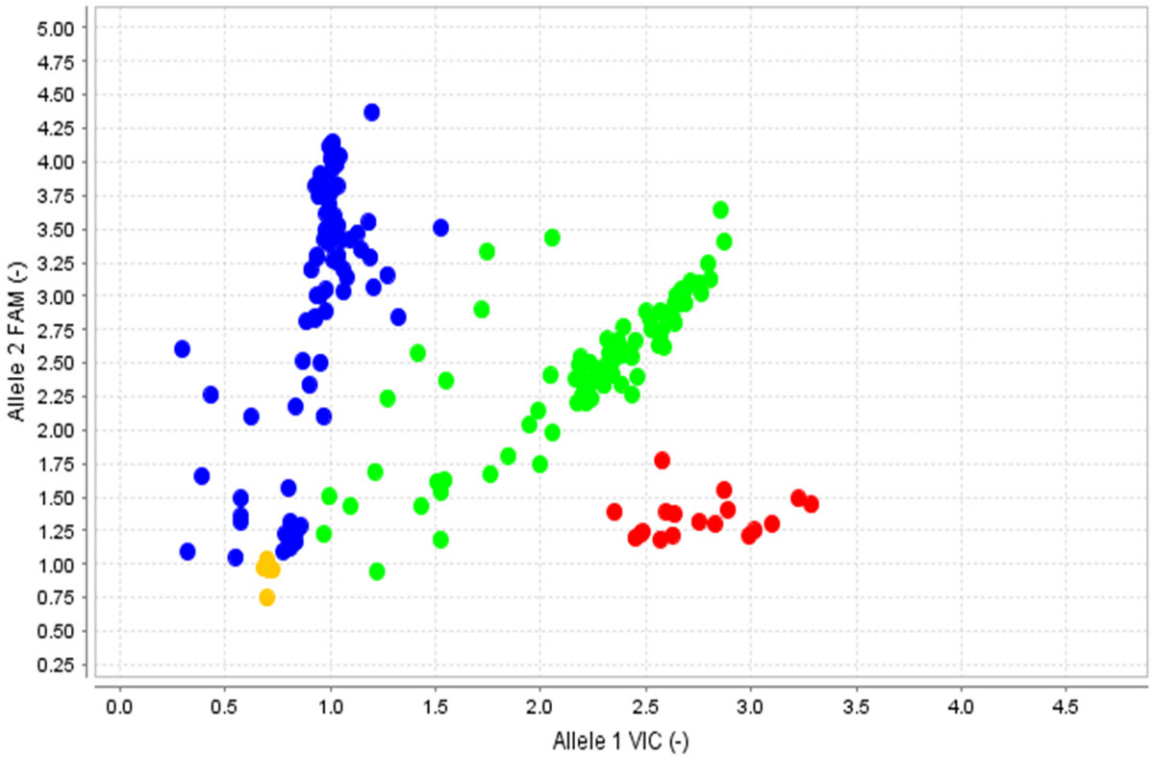

Figure 1. Allelic discrimination plot for the variant rs7204454.

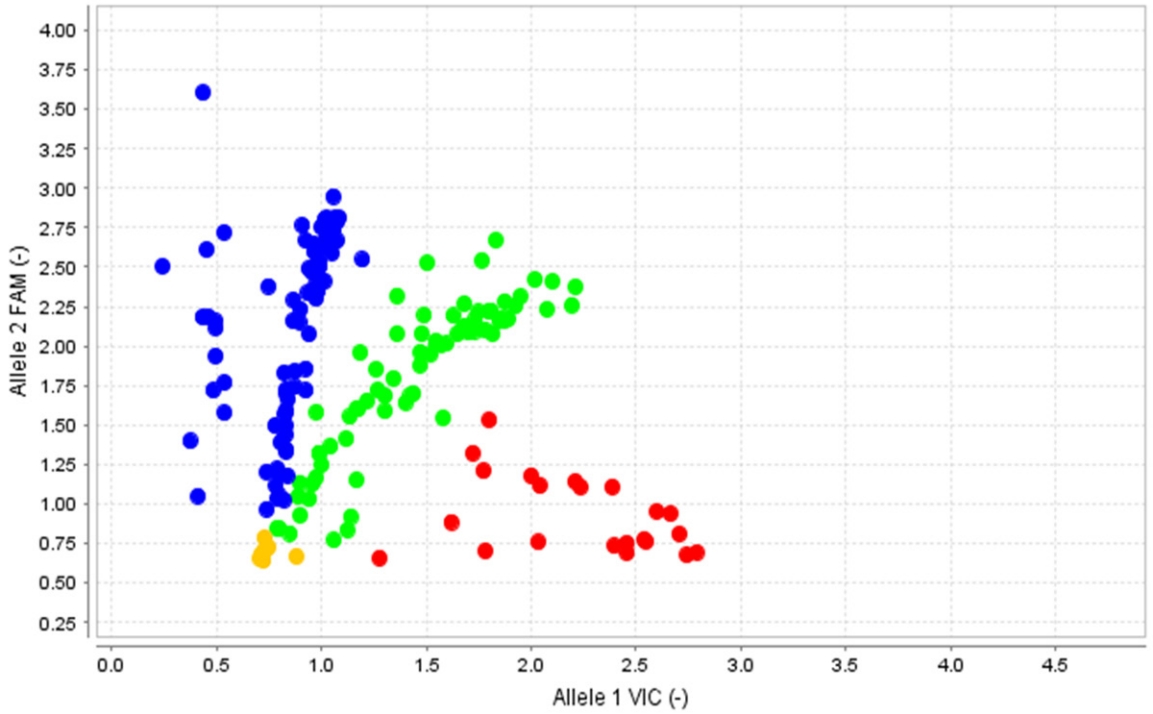

Figure 2. Allelic discrimination plot for the variant rs9940180.

(**Tables 2**, **3**). Both the variants rs9940180 and rs7204454 followed the HWE in our population with a *p*-value of 0.558 and 0.4433, respectively (**Table 4**).

Table 2. Distributions of allelic frequencies for rs7204454 and rs9940180 in individual studies

SNP ID	Allelic Frequencies			
	Schizophrenia		Control	
	C	T	C	T
rs9940180	0.432	0.568	0.333	0.667
	G	C	G	C
rs7204452	0.317	0.683	0.344	0.656

Table 3. Distributions of genotypic frequencies for rs7204454 and rs9940180 in individual studies

SNP ID	Genotypic Frequencies					
	Schizophrenia			Control		
	CC	CT	TT	CC	CT	TT
rs9940180	0.219	0.426	0.353	0.068	0.53	0.401
	GG	GC	CC	GG	GC	CC
rs7204452	0.085	0.463	0.451	0.106	0.477	0.416

Interestingly, the variant rs9940180 was significantly associated with schizophrenia at an OR = 1.527 and a 95% CI = 1.022-2.28 with a *p*-value of 0.03817. While another variant rs7204454 was not significantly associated with SCZ, with OR = 0.8827 with a 95% CI = 0.582-1.33 at a *p*-value of 0.5558 (**Table 4**).

Furthermore, the association of the variant rs9940180 in CDH13 gene was evaluated for different genetic models. In the allelic model (C versus T), the minor allele "C" of rs9940180 was significantly associated with schizophrenia with a *p*-value of 0.03817 in the studied population. The significant association was also observed under the recessive model (CC versus CT + TT) with a *p*-value of 0.00119. While, the genotypic model had also shown a significant association with schizophrenia predisposition with a *p*-value of 0.005025 in the North Indian population. However, no significant association was observed under the dominant model with *p*-value of 0.4839 (**Table 5**). Thus, it can be conferred that the variant rs9940180 correlates to Schizophrenia predisposition in the population of North India in the recessive condition.

Linkage disequilibrium

The LD pattern between rs9940180 and rs7204454 was also explored. For variant rs7204454, present at chromosome 16:82625589 (forward strand) in *CDH13* gene and regulatory variant rs9940180 at chromosome 16:82619839 (forward strand) in *CDH13* gene, the distance between these two variants is 5 kb. The LD analysis of studied SNPs showed moderate linkage with D' = 0.364, r-squared = 0.113 in our studied population, as shown in **Figure 3**.

Gene-gene interaction

The gene-gene interaction analysis was done so as to evaluate other potential candidate genes that might be correlated with Schizophrenia. It was observed that CDH13 gene was interacting with other genes of the related pathway; including *CDH10, CDH5, CDH9, CDH11, CDH17, CDH8, CTNNA1, CTNNB1, CTNND1*, and *JUP*.

Discussion

This study is the first genetic study evaluating the association of the genetic variants of the *CDH13* in the population group of North India. This study evaluated the association of the regulatory variant, and an intronic variant by a case-control study design in the population of the Jammu region (a North Indian population cohort). The genome-wide association study using Japanese population samples showed five tag SNPs (rs12925602, rs7193788, rs-736719, rs6565051, and rs7204454) to be associated with schizophrenia in the *CDH13* promoter region [23]. In our study, we selected rs7204454 in the promoter region and found a lack of association in our population. Although the susceptibility of *CDH13* to several psychiatric diseases was concerned [26]. Except for a recent GWAS of a Danish population study, there has been no report on the correlation between *CDH13* and schizophrenia [22].

For the first time, a report on Danish samples by Borglum et al., 2014 showed the involvement in of a SNP rs8057927 (intronic) of *CDH13* with schizophrenia. In the present study we examined the relationship in the Jammu population of other intronic SNPs rs9940180 of *CDH13* and schizophrenia. Our current research is the first to examine the relationship between *CDH13* SNPs rs9940180 and schizophrenia in the population of Jammu region and we found statistically significant association of rs9940180 with schizophrenia.

Table 4. Association analysis in *CDH13* gene in SCZ

S. No.	SNP ID	Affective allele frequency (cases-control)	*p*-value	Odds Ratio	Confidence interval	HWE *p*-value
1	rs9940180	0.4329-0.333	0.03817	1.527	1.022-2.28	0.558
2	rs7204454	0.3171-0.344	0.5558	0.8827	0.582-1.33	0.4433

Table 5. Association of rs9940180 with schizophrenia in different genetic models

SNP ID	Genotyping model (*p*-value)	Allelic model (*p*-value)	Dominant model (*p*-value)	Recessive model (*p*-value)
rs9940180	0.005025	0.03817	0.4839	0.00119

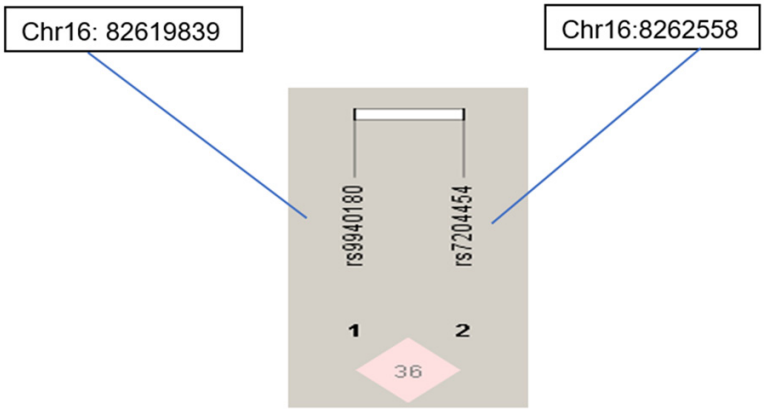

Figure 3. A systematic representation of LD plot between rs9940180 and rs7204454 (D' = 0.364, r-squared = 0.113).

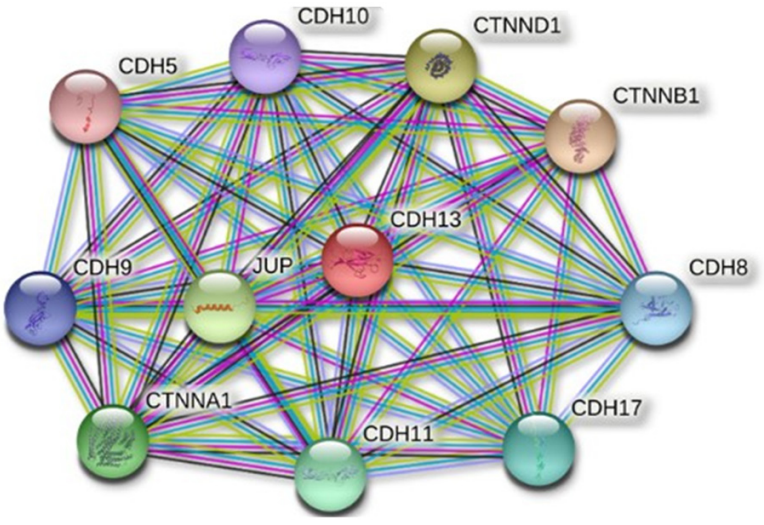

Figure 4. Interaction of *CDH13* with other genes (https://string-db.org/cgi/network).

The above results suggest that *CDH13* variant rs9940180 is significantly associated with SCZ. *CDH13* is significant as it plays a crucial role in morphogenesis and the maintenance of neuronal circuits, synapse formation, and remodeling [18] via interacting with various proteins, including *CDH5, CDH11, CTNB1, CTNND1,* etc., as shown in **Figure 4**. This suggest that the occurrence of Schizophrenia in a studied population might be due to the interplay of other interacting genes. Therefore, it is pertinent to conduct the fine mapping of these genes in future studies that, might give us a better insight about the Schizophrenia genetic predisposition. In addition, the function of the variants was investigated using the SNIPA tool. As shown in **Figure 5**, the genetic variant rs7204454 has a direct regulatory effect. In contrast, the variant rs9940180 indirectly impacts the functioning of the gene, so polymorphism in any region could potentially affect the neighboring SNPs and disrupt the overall physiology of the gene. This genetic variant has never been studied in SCZ in any Indian population, and this is the first study from the Jammu region.

We have selected intronic variant rs9940180 of *CDH13,* which is in strong LD with rs7204454 with D' = 1.0, r^2 = 0.946 in the GIH population,

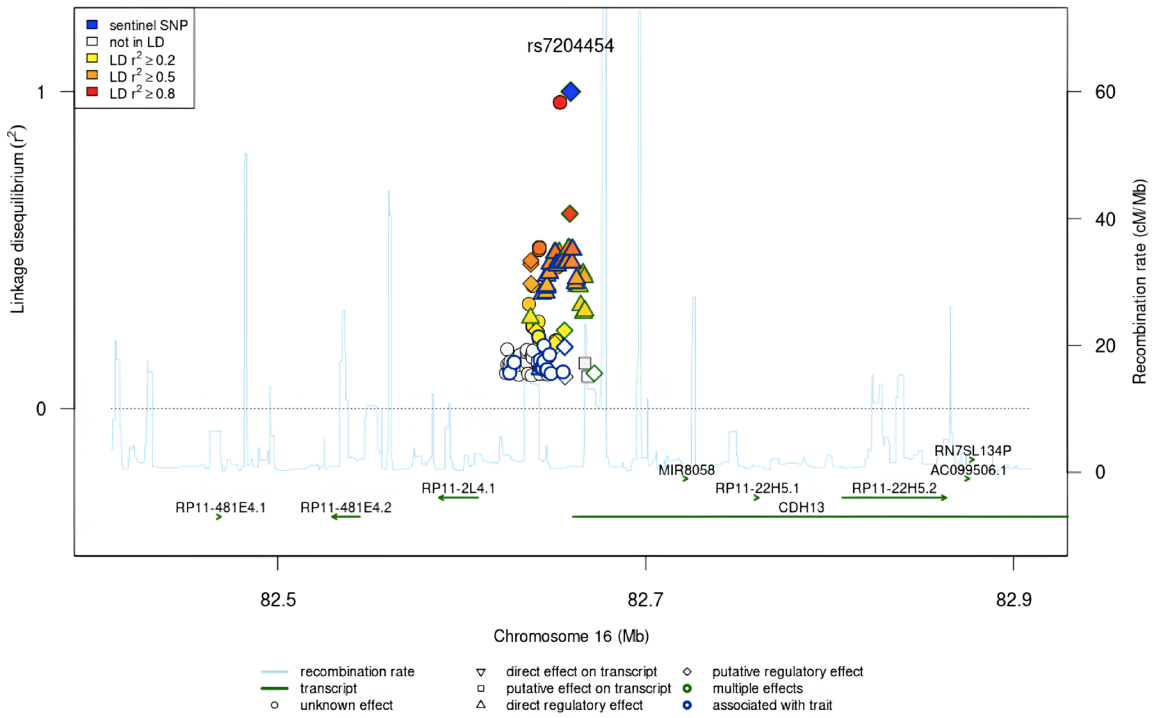

Figure 5. Linkage disequilibrium plot which shows the amount of correlation between a sentinel variant (blue colored) and its surrounding variants. The sentinel variant is upward triangle thus signifies that variant has regulatory effect (http://snipa.helmholtz-muenchen.de).

whereas in the present study, rs9940180 and rs7204454 are in moderate LD with each other with D' = 0.364 and r-squared = 0.113 in the population of Jammu.

The results of an association study in the Japanese population showed a substantial difference between SCZ patients and healthy controls in the distribution of the GACAG haplotype in the *CDH13* promoter region. They confirmed that haplotype variants in the *CDH13* promoter region alter in correlation to schizophrenia [23]. Based on the frequency of the haplotypes, it can be inferred that they may have a protective role. The distributions between different populations of SNP haplotypes (rs7204454) vary. Among Asian and Caucasian populations, the frequency of the GACAG haplotype is rare, 0.024-0.1266. There is the frequency of this haplotype in Africans [27].

CDH13 was identified as one of the most closely related genes in attention deficit hyperactivity disorder studies [26, 28, 29], and a meta-analysis of hyperactivity or attention deficit disorder link scans recognized the *CDH13* region as the only significant genome-wide region [30]. GWA studies have also reported the participation of *CDH13* in autism [31], depression [32], and a current study concerned CNVs associated with *CDH13* in autism susceptibility [33]. Consequently, our outcome, the correlation of the *CDH13* gene in schizophrenia, is confirmed by the primary function of *CDH13* in brain development and in controlling neural circuit essential accompanied by the evidence of *CDH13* participation in other psychiatric disorders.

While it was done using a small sample relative to current GWA research, this study has recognized a novel risk locus, suggesting that *p*-values in such a manner might act as a powerful tool. The accruing descriptions of independent communication signals from nearby placed SNPs support this [34, 35]. Furthermore, the variant in the intronic region displayed a significant association in the Danish population. Similarly, independent replication of another intronic variance in the Jammu population also reported a significant association. These previous studies indicated the role of *CDH13* in the

pathophysiology of schizophrenia. Consequently, the attention in this document to *CDH13* may be fair, and additional studies are required to confirm the correlation of *CDH13* to schizophrenia pathophysiology.

Furthermore, in multiple ethnic groups, the genetic association of *CDH13* SNPs with schizophrenia may be inconsistent. Therefore, additional studies with larger samples are warranted in South-Asian populations. Further studies involving large sample sizes and more probable SNPs could bring new biomarkers linked to the disorder's susceptibility, progression, or severity. They could prove enormously helpful in detecting persons at enhanced risk and in their clinical organization. It is theorized that further examination of such polymorphism studies may lead to a significant understanding of the genetic pathophysiology of schizophrenia.

Acknowledgements

The authors are grateful to all the participants who donated their blood samples for the study and all the doctors who diagnosed patients with the disorder. In addition, the authors are thankful to CSIR, New Delhi, Central facility and DBT funded Bioinformatics center at School of Biotechnology, university of Jammu and Thermofisher Scientific, New Delhi for support. This study is supported by JK DST Project (T-141), RUSA grant.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Nisha Kapoor, Immunology and Molecular Biology Lab, School of Biotechnology, University of Jammu, Jammu 180006, J&K, India. Tel: +91-9622049666; E-mail: immunogenomicsbtju@gmail.com; nishakapoor@jammuuniversity.ac.in

References

[1] van Os J and Kapur S. Schizophrenia. Lancet 2009; 374: 635-645.
[2] Patel KR, Cherian J, Gohil K and Atkinson D. Schizophrenia: overview and treatment options. P T 2014; 39: 638-45.
[3] Owen MJ, Sawa A and Mortensen PB. Schizophrenia. Lancet 2016; 388: 86-97.
[4] McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA and Shenton ME. MRI anatomy of schizophrenia. Biol Psychiatry 1999; 45: 1099-119.
[5] Shenton ME, Dickey CC, Frumin M and McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001; 49: 1-52.
[6] Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 1999; 122: 593-624.
[7] Stephan KE, Friston KJ and Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 2009; 35: 509-27.
[8] Gregório SP, Sallet PC, Do KA, Lin E, Gattaz WF and Dias-Neto E. Polymorphisms in genes involved in neurodevelopment may be associated with altered brain morphology in schizophrenia: preliminary evidence. Psychiatry Res 2009; 165: 1-9.
[9] Takeichi M. The cadherin superfamily in neuronal connections and interactions. Nat Rev Neurosci 2007; 8: 11-20.
[10] Hirano S and Takeichi M. Cadherins in brain morphogenesis and wiring. Physiol Rev 2012; 92: 597-634.
[11] Rivero O, Sich S, Popp S, Schmitt A, Franke B and Lesch KP. Impact of the ADHD-susceptibility gene CDH13 on development and function of brain networks. Eur Neuropsychopharmacol 2013; 23: 492-507.
[12] Ziegler GC, Ehlis AC, Weber H, Vitale MR, Zöller JEM, Ku HP, Schiele MA, Kürbitz LI, Romanos M, Pauli P, Kalisch R, Zwanzger P, Domschke K, Fallgatter AJ, Reif A and Lesch KP. A common CDH13 variant is associated with low agreeableness and neural responses to working memory tasks in ADHD. Genes (Basel) 2021; 12: 1356.
[13] Ribasés M, Ramos-Quiroga JA, Sánchez-Mora C, Bosch R, Richarte V, Palomar G, Gastaminza X, Bielsa A, Arcos-Burgos M, Muenke M, Castellanos FX, Cormand B, Bayés M and Casas M. Contribution of LPHN3 to the genetic susceptibility to ADHD in adulthood: a replication study. Genes Brain Behav 2011; 10: 149-57.
[14] Drgonova J, Walther D, Hartstein GL, Bukhari MO, Baumann MH, Katz J, Hall FS, Arnold ER, Flax S, Riley A, Rivero-Martin O, Lesch KP, Troncoso J, Ranscht B and Uhl GR. Cadherin 13: human cis-regulation and selectively-altered addiction phenotypes and cerebral cortical dopamine in knockout mice. Mol Med 2016; 22: 537-547.
[15] Grimm O, Kranz TM and Reif A. Genetics of ADHD: what should the clinician know? Curr Psychiatry Rep 2020; 22: 18.
[16] Rivero O, Sich S, Popp S, Schmitt A, Franke B and Lesch KP. Impact of the ADHD-susceptibility gene CDH13 on development and function

of brain networks. Eur Neuropsychopharmacol 2013; 23: 492-507.
[17] El-Amraoui A and Petit C. Cadherins as targets for genetic diseases. Cold Spring Harb Perspect Biol 2010; 2: a003095.
[18] Redies C, Hertel N and Hübner CA. Cadherins and neuropsychiatric disorders. Brain Res 2012; 1470: 130-44.
[19] Hawi Z, Tong J, Dark C, Yates H, Johnson B and Bellgrove MA. The role of cadherin genes in five major psychiatric disorders: a literature update. Am J Med Genet B Neuropsychiatr Genet 2018; 177: 168-180.
[20] Prata DP, Costa-Neves B, Cosme G and Vassos E. Unravelling the genetic basis of schizophrenia and bipolar disorder with GWAS: a systematic review. J Psychiatr Res 2019; 114: 178-207.
[21] Pol-Fuster J, Cañellas F, Ruiz-Guerra L, Medina-Dols A, Bisbal-Carrió B, Asensio V, Ortega-Vila B, Marzese D, Vidal C, Santos C, Lladó J, Olmos G, Heine-Suñer D, Strauch K, Flaquer A and Vives-Bauzà C. Familial psychosis associated with a missense mutation at MACF1 gene combined with the rare duplications DUP3p26.3 and DUP16q23.3, affecting the CNTN6 and CDH13 genes. Front Genet 2021; 12: 622886.
[22] Børglum AD, Demontis D, Grove J, Pallesen J, Hollegaard MV, Pedersen CB, Hedemand A and Mattheisen M; GROUP investigators10, Uitterlinden A, Nyegaard M, Ørntoft T, Wiuf C, Didriksen M, Nordentoft M, Nöthen MM, Rietschel M, Ophoff RA, Cichon S, Yolken RH, Hougaard DM, Mortensen PB and Mors O. Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. Mol Psychiatry 2014; 19: 325-33.
[23] Otsuka I, Watanabe Y, Hishimoto A, Boku S, Mouri K, Shiroiwa K, Okazaki S, Nunokawa A, Shirakawa O, Someya T and Sora I. Association analysis of the Cadherin13 gene with schizophrenia in the Japanese population. Neuropsychiatr Dis Treat 2015; 11: 1381-93.
[24] Priya I, Sharma I, Sharma S, Gupta S, Arora M, Bhat GR, Mahajan R and Kapoor N. Genetic association of DISC1 variant rs3738401 with susceptibility to Schizophrenia risk in North Indian population. Meta Gene 2021; 29: 100923.
[25] Guha P, Das A, Dutta S and Chaudhuri TK. A rapid and efficient DNA extraction protocol from fresh and frozen human blood samples. J Clin Lab Anal 2018; 32: e22181.
[26] Neale BM, Medland S, Ripke S, Anney RJ, Asherson P, Buitelaar J, Franke B, Gill M, Kent L, Holmans P, Middleton F, Thapar A, Lesch KP, Faraone SV, Daly M, Nguyen TT, Schäfer H, Steinhausen HC, Reif A, Renner TJ, Romanos M, Romanos J, Warnke A, Walitza S, Freitag C, Meyer J, Palmason H, Rothenberger A, Hawi Z, Sergeant J, Roeyers H, Mick E and Biederman J; IMAGE II Consortium Group. Case-control genome-wide association study of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2010; 49: 906-20.
[27] Barrett JC, Fry B, Maller J and Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005; 21: 263-5.
[28] Lasky-Su J, Neale BM, Franke B, Anney RJ, Zhou K, Maller JB, Vasquez AA, Chen W, Asherson P, Buitelaar J, Banaschewski T, Ebstein R, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen HC, Taylor E, Daly M, Laird N, Lange C and Faraone SV. Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations. Am J Med Genet B Neuropsychiatr Genet 2008; 147B: 1345-54.
[29] Lesch KP, Timmesfeld N, Renner TJ, Halperin R, Röser C, Nguyen TT, Craig DW, Romanos J, Heine M, Meyer J, Freitag C, Warnke A, Romanos M, Schäfer H, Walitza S, Reif A, Stephan DA and Jacob C. Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. J Neural Transm (Vienna) 2008; 115: 1573-85.
[30] Zhou K, Dempfle A, Arcos-Burgos M, Bakker SC, Banaschewski T, Biederman J, Buitelaar J, Castellanos FX, Doyle A, Ebstein RP, Ekholm J, Forabosco P, Franke B, Freitag C, Friedel S, Gill M, Hebebrand J, Hinney A, Jacob C, Lesch KP, Loo SK, Lopera F, McCracken JT, McGough JJ, Meyer J, Mick E, Miranda A, Muenke M, Mulas F, Nelson SF, Nguyen TT, Oades RD, Ogdie MN, Palacio JD, Pineda D, Reif A, Renner TJ, Roeyers H, Romanos M, Rothenberger A, Schäfer H, Sergeant J, Sinke RJ, Smalley SL, Sonuga-Barke E, Steinhausen HC, van der Meulen E, Walitza S, Warnke A, Lewis CM, Faraone SV and Asherson P. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 2008; 147B: 1392-8.
[31] Wang K, Zhang H, Ma D, Bucan M, Glessner JT, Abrahams BS, Salyakina D, Imielinski M, Bradfield JP, Sleiman PM, Kim CE, Hou C, Frackelton E, Chiavacci R, Takahashi N, Sakurai T, Rappaport E, Lajonchere CM, Munson J, Estes A, Korvatska O, Piven J, Sonnenblick LI, Alvarez Retuerto AI, Herman EI, Dong H, Hutman T, Sigman M, Ozonoff S, Klin A, Owley T, Sweeney JA, Brune CW, Cantor RM, Bernier R, Gilbert JR, Cuccaro ML, McMahon WM, Miller J, State

MW, Wassink TH, Coon H, Levy SE, Schultz RT, Nurnberger JI, Haines JL, Sutcliffe JS, Cook EH, Minshew NJ, Buxbaum JD, Dawson G, Grant SF, Geschwind DH, Pericak-Vance MA, Schellenberg GD and Hakonarson H. Common genetic variants on 5p14.1 associate with autism spectrum disorders. Nature 2009; 459: 528-33.

[32] Terracciano A, Tanaka T, Sutin AR, Sanna S, Deiana B, Lai S, Uda M, Schlessinger D, Abecasis GR, Ferrucci L and Costa PT Jr. Genome-wide association scan of trait depression. Biol Psychiatry 2010; 68: 811-7.

[33] Sanders SJ, Ercan-Sencicek AG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, Chu SH, Moreau MP, Gupta AR, Thomson SA, Mason CE, Bilguvar K, Celestino-Soper PB, Choi M, Crawford EL, Davis L, Wright NR, Dhodapkar RM, DiCola M, DiLullo NM, Fernandez TV, Fielding-Singh V, Fishman DO, Frahm S, Garagaloyan R, Goh GS, Kammela S, Klei L, Lowe JK, Lund SC, McGrew AD, Meyer KA, Moffat WJ, Murdoch JD, O'Roak BJ, Ober GT, Pottenger RS, Raubeson MJ, Song Y, Wang Q, Yaspan BL, Yu TW, Yurkiewicz IR, Beaudet AL, Cantor RM, Curland M, Grice DE, Günel M, Lifton RP, Mane SM, Martin DM, Shaw CA, Sheldon M, Tischfield JA, Walsh CA, Morrow EM, Ledbetter DH, Fombonne E, Lord C, Martin CL, Brooks AI, Sutcliffe JS, Cook EH Jr, Geschwind D, Roeder K, Devlin B and State MW. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. Neuron 2011; 70: 863-85.

[34] Steinberg S and de Jong S; Irish Schizophrenia Genomics Consortium, Andreassen OA, Werge T, Børglum AD, Mors O, Mortensen PB, Gustafsson O, Costas J, Pietiläinen OP, Demontis D, Papiol S, Huttenlocher J, Mattheisen M, Breuer R, Vassos E, Giegling I, Fraser G, Walker N, Tuulio-Henriksson A, Suvisaari J, Lönnqvist J, Paunio T, Agartz I, Melle I, Djurovic S, Strengman E; GROUP, Jürgens G, Glenthøj B, Terenius L, Hougaard DM, Ørntoft T, Wiuf C, Didriksen M, Hollegaard MV, Nordentoft M, van Winkel R, Kenis G, Abramova L, Kaleda V, Arrojo M, Sanjuán J, Arango C, Sperling S, Rossner M, Ribolsi M, Magni V, Siracusano A, Christiansen C, Kiemeney LA, Veldink J, van den Berg L, Ingason A, Muglia P, Murray R, Nöthen MM, Sigurdsson E, Petursson H, Thorsteinsdottir U, Kong A, Rubino IA, De Hert M, Réthelyi JM, Bitter I, Jönsson EG, Golimbet V, Carracedo A, Ehrenreich H, Craddock N, Owen MJ, O'Donovan MC; Wellcome Trust Case Control Consortium 2; Ruggeri M, Tosato S, Peltonen L, Ophoff RA, Collier DA, St Clair D, Rietschel M, Cichon S, Stefansson H, Rujescu D and Stefansson K. Common variants at VRK2 and TCF4 conferring risk of schizophrenia. Hum Mol Genet 2011; 20: 4076-81.

[35] Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. Nat Genet 2011; 43: 969-976.