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LRRTM3 Genetic Variations, rs1925575, and rs1925608 Contributed to Autism Spectrum Disorder Trait Severity: An Observation in The Indian Probands

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ABSTRACT

Surface proteins containing leucine-rich repeat (LRR) are essential for the formation of synapses. Therefore, proteins containing aberrant LRR regions are speculated to cause synaptic dysfunction, an abnormality often associated with Autism spectrum disorder (ASD). LRR transmembrane 3 (LRRTM3) genetic variants showed association with ASD in the Caucasoid probands. We for the first time, analyzed two LRRTM3 genetic variants, rs1925575, and rs1925608, in Indian subjects (N=1048), including ASD probands (N=270), their parents (N=428), and healthy controls (N=350). ASD severity was assessed by the Childhood Autism Rating Scale2-standard test (CARS2-ST). Peripheral blood was collected after obtaining informed written consent for participation, and target sites were amplified by polymerase chain reaction using genomic DNA. Amplicons generated were subjected to differential digestion using a restriction enzyme, and the genotype data were analyzed for association with ASD by both population and family-based methods. Frequencies of rs1925608 and rs1925575 "CC" genotypes and C-C haplotype were higher in the probands (P=0.001). Analysis of parental data revealed a higher frequency of rs1925575 "T" in the fathers (P=0.01) and biased paternal transmission of rs1925575 "C" allele (P=0.03). The "Activity level" was higher in the ASD probands having rs1925608 "CC". Additionally, the score for "Relating to people" was higher in the presence of rs1925575 "TC" genotypes. The gender-based stratified analysis revealed the influence of the variants on a higher number of traits of the female probands. This pilot investigation indicated an influence of *LRRTM3* genetic variants on the trait severity of Indian ASD probands.

Keywords: ASD, CARS2-ST, LRRTM3, rs1925608, rs1925575

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Introduction

The occurrence of Autism Spectrum Disorder (ASD) is on the rise all over the world (1). Amongst the neurodevelopmentally challenged individuals attending our outpatient department,>65% were diagnosed with ASD. In the US Caucasoid population, ASD was reported to be 1.85% (2). On the other hand, among children and adolescents, the prevalence of ASD was found to be 0.23% in populations from southern (3) and eastern (4) India. A higher occurrence rate in males than females (4.5:1) was also reported (2).

Social communication skills and several behavioral attributes are affected in the ASD probands (1), though the cause still remains unknown. Aberrant functioning of the nervous system, including the improper formation of the excitatory or inhibitory synapses leading to excitation/inhibition imbalances (5,6), was found to affect the overall cognitive, emotional, social, and physical health of subjects with ASD (5-7). Studies involving syndromic ASD cases documented impaired synapse development as one of the prevalent causes of ASD (8, 9). The role of genetic factors in the etiology is speculated from studies on twins (10). Environmental factors were also reported to affect ASD etiology (11).

Surface proteins containing leucine-rich repeat (LRR) regions play a crucial role in forming excitatory and inhibitory synapses (12). Specific LRR proteins expressed on different cell types interact with various pre- and post-synaptic proteins and coordinate synapse formation, differentiation, pathway-specific synapse development, and synaptic plasticity (12, 13). Earlier investigators reported that LRR Transmembrane (LRRTM) proteins are involved in the organization and excitatory presynaptic differentiation along with mediation of the post-synaptic specializations (13). As a result, LRR protein dysfunction was speculated to contribute to different neuropsychiatric disorders, including ASD (14-17).

Mutations in the *LRR* genes have been linked with the occurrence of ASD (14), Intellectual disability (15), Schizophrenia (16), and Tourette syndrome (16). Subfamilies of LRR are distinguished by the consensus sequence of the repeat and combinations of the domains (18, 19). In experimental animal models, LRRTM3 showed association with excitatory synapse development in the hippocampal dentate gyrus (20) while overexpression of LRRTM3 was found to increase excitatory synapse density (21). LRRTM3 was also reported to promote the processing of amyloid precursor protein, a molecule crucial for amyloid beta secretion (22).

Amongst various LRRTM members, the *LRRTM3* gene is nested within the intron 7 of the alpha-T-catenin (*CTNNA3*) gene, a molecule speculated to have a role in ASD (19, 23). In the Caucasoid population, *LRRTM3* genetic variants exhibited statistically significant associations with ASD (14). Considering the data of previous reports and a comprehensive review of relevant literature, we aimed to analyze two LRRTM3 genetic variants, rs1925608, and rs1925575, for the first time in a group of Indo-Caucasoid subjects including ASD probands to determine their association with the disorder. Moreover, we assessed the association of these variants with ASD trait severity in a gender-dependent manner.

Materials and methods

Recruitment of Subjects

Inclusion criteria

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Unrelated nuclear families with ASD probands (N=270), and their parents (N=428), were recruited following the Diagnostic and Statistical Manual (DSM) - 4th edition, text revised (24).

The severity of ASD was evaluated using the Childhood Autism Rating Scale 2-Standard Test (CARS2-ST) (25). Under the CARS2- ST, 15 traits such as (i) Relating to people, (ii) Imitation, (iii) Emotional response, (iv) Body use, (v) Object use, (vi) Adaption to change, (vii) Visual response, (viii) Listening response, (ix) Taste, Smell and touch response and use, (x) Fear or nervousness, (xi) Verbal communication, (xii) Nonverbal communication, (xiii) Activity level, (xiv) Level and consistency of intellectual response, and (xv) General impression, are assessed. The scores for each trait vary between 1 to 4 with 0.5 intervals, and subjects are categorized as mild to moderate (score 30.0-36.5) and severe (score 37.0-60.0) based on the total score.

We have also recruited ethnically matched controls (N=350), devoid of any developmental or neurological disorders and falling under no symptom category of CARS2-ST (score <30), for population-based comparative analysis. The study protocol was approved by the institutional Human Ethics Committee (PR-007-19).

Exclusion criteria

Individuals with psychiatric or genetic disorders were excluded from the investigation.

***In-Silico* analysis**

Interaction of LRRTM3 with other proteins was identified using the Search Tool for the Retrieval of Interacting Genes (STRING Version 11.5) (https://string-db.org/) (26), keeping the confidence score high (0.70). The STRING network predicts interactions or links between two proteins based on both physical (direct) and functional (indirect) associations distinguished by different colored lines.

Genotyping of the target sites

The rs1925608 and rs1925575 were selected based on their zygosity status [(http:// www. ncbi.nlm. nih.gov); minor allele frequency> 0.05] and reports of association in other ethnic populations (27). Peripheral blood was collected from the recruited subjects after obtaining informed written consent from the participants/parents/caregivers. Genomic DNA was extracted (28), followed by the analysis of the target sites by polymerase chain reaction and fragment length polymorphism analysis using the DpnII (New England Biolabs) enzyme.

Statistical analysis

Information on the allelic frequencies was collected from the dbSNP database and compared with the frequencies reported for the European (EUR), African (AFR), African American (AFA), Asian (ASN), east Asian (EAS), Other Asian (OAS), and South Asian (SAS), populations using rxc contingency table (https://www.socscistatistics.com/tests/chisquare2/default2.aspx). The UNPHASED (v.3.1.7) program (29) was used for the population-based (Cocaphase) as well as family-based (Transmission Disequilibrium Test; TDT) comparative analysis using 1000 permutations to take care of the errors for multiple corrections. The Odds ratio (OR) was calculated by the online Odd ratio calculator (www.hutchon.net). Association between the studied variants and the total CARS2-ST score as well as independent scores for each trait was calculated,using the Quantitative trait (QT) analysis under the UNPHASED program; a positive AddVal

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indicates an increase in the trait severity in the presence of a particular allele or genotype while negative AddVal indicate the opposite effects.

Results

Case-control association analysis

The genotyping success rate for rs1925608 and rs1925575 was more than 90% in this population. Genotypic frequencies of both variants followed the Hardy-Weinberg equilibrium in the cases and controls. Comparative analysis with other ethnic groups failed to show any statistically significant difference in the allelic distribution pattern (Table 1).

Table 1. Comparative analysis on the frequency of the studied *LRRTM3* variants in different populations.

Population	Frequency of the derived allele of the studied variants	
	rs1925608 C	**rs1925575 C**
European	0.42	0.63
African	0.56	0.58
African American	0.56	0.58
Asian	0.44	0.49
East Asian	0.42	0.55
Other Asian	0.49	0.38
South Asian	0.37	0.47
Eastern Indian	0.38	0.55

Case-control comparative analysis showed significantly higher frequencies of rs1925608 "CC"(P= 0.0005; OR=2.94) and rs1925575 "CC" (P=0.0001; OR=2.07) genotypes in the ASD probands (Table 2). The frequency of the rs1925575 "C" allele was also higher (P=0.001; OR=1.47) in the probands. The gender-based stratified analysis revealed higher frequencies of rs1925575 "C" allele (P=0.005; OR=1.56) and "CC" genotype (P =0.001; OR=2.25), and rs1925608 "CC" genotype (P=0.02) in the male probands in comparison to the gender-matched controls (Table 2). The frequency of rs1925608 "CC" genotype (P=0.03; OR=6.02) was also higher in the female probands.

Analysis of haplotype frequencies (rs1925608-rs1925575) revealed a higher occurrence of the C-C haplotype ($\chi 2$ = 5.24; P=0.02; OR=1.27) with a concurrently lower frequency of the A-T haplotype ($\chi 2$= 10.72; P=0.001) in the probands as compared to the controls.

Family-based analysis

Analysis of the parental data showed a higher occurrence of rs1925575 "C" allele ($\chi 2$= 4.58; P=0.03; OR=1.36) and rs1925608 "CC" genotype ($\chi 2$=42.42; p<0.0001; OR=5.12) in the mothers of the ASD probands, while the rs1925575 "T' allele ($\chi 2$= 6.25; P=0.01; OR=2.12) and "TC" genotype ($\chi 2$= 9.91; P=0.007; OR=2.69) frequencies were higher in the fathers as compared to the controls matched for gender.

Family-based TDT analysis (Table 3) revealed a paternal bias in the transmission of the rs1925575 "C" allele (P=0.03; RR=1.51).

Effect of genetic variants on the trait scores measured by the CARS2-ST

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Table 2. Case-control comparative analysis on the *LRRTM3* variants.

Variant	Allele/ Genotype	Controls	ASD Probands	χ2 (P)	OR (95% CI)	Male control	Male probands	χ2 (P)	OR (95% CI)	Female control	Female probands	χ2 (P)	OR (95% CI)
rs1925608	A	0.62	0.59	0.38 (0.54)	0.93 (0.73 - 1.18)	0.62	0.60	0.67 (0.41)	0.87 (0.64-1.20)	0.60	0.60	0.02 (0.88)	0.97 (0.61-1.54)
	C	0.38	0.41		1.08 (0.85 - 1.37)	0.38	0.40		1.14 (0.83-1.57)	0.40	0.40		1.03 (0.65-1.65)
	AA	0.27	0.30	14.91 (0.0005)	1.22 (0.85-1.77)	0.29	0.30	7.17 (0.02)	1.07 (0.66-1.73)	0.24	0.32	7.19 (0.03)	1.49 (0.71-3.10)
	AC	0.69	0.58		0.60 (0.43-0.84)	0.66	0.58		0.68 (0.43-1.06)	0.72	0.55		0.46 (0.23-0.91)
	CC	0.04	0.12		2.94 (1.58-5.44)	0.05	0.12		0.21 (0.14-0.32)	0.03	0.13		6.02 (1.46-24.81)
rs1925575	T	0.45	0.36	10.08 (0.001)	0.68 (0.54-0.86)	0.44	0.33	7.85 (0.005)	0.64 (0.47-0.87)	0.46	0.48	0.09 (0.7)	1.08 (0.67-1.72)
	C	0.55	0.64		1.47 (1.16 - 1.86)	0.56	0.67		1.56 (1.14-2.14)	0.54	0.52		0.93 (0.58-1.49)
	TT	0.17	0.15	17.38 (0.0001)	0.36 (0.25-0.51)	0.15	0.14	14.16 (0.001)	0.88 (0.48-1.62)	0.18	0.21	0.16 (0.9)	1.19 (0.51-2.79)
	TC	0.56	0.42		0.56 (0.41-0.78)	0.57	0.39		0.49 (0.32-0.75)	0.55	0.53		0.93 (0.48-1.81)
	CC	0.27	0.43		2.07 (1.46-2.92)	0.28	0.47		2.25 (1.45-3.49)	0.27	0.26		0.95 (0.45-2.02)

χ2=chi square; P=p value; OR=odds ratio; 95% CI=95% confidence Interval; statistically significant differences are presented in bold.

The scores for Activity level were higher in the presence of the rs1925608 "CC" genotype (AddVal=4.67; χ2 =4.76; P=0.03), while the scores for Level and consistency of intellectual response were lower in the presence of this genotype (AddVal= - 0.54; χ2 =3.64; P=0.05; Table 4). The probands with rs1925575 "CC" showed lower scores for Relating to people (AddVal= - 0.64; χ2 =3.73; P=0.05), while those with the "TC" genotype showed higher scores. The gender-based stratified analysis revealed that impacts on the traits were principally due to significant effects on the traits of the female probands (Table4); trait scores for Relating to people, Verbal communication, Activity level, Fear or nervousness, Level and consistency of intellectual response were higher in the presence of rs1925608 "CC" genotype (p<0.05; Table 4). Whereas, in the presence of the rs1925575 "TT" genotype, female ASD subjects exhibited

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Table 3. Transmission disequilibrium test performed for informative nuclear families with ASD probands.

SNP ID	Parents	Allele/ Genotype	T	NT	χ2 (P)	RR (95%CI)
rs1925608	Both	A	0.59	0.60	0.13 (0.71)	0.95 (0.68-1.31)
		C	0.41	0.40		1.06 (0.76-1.47)
	Father	A	0.59	0.61	0.11 (0.7)	0.93 (0.72-1.19)
		C	0.41	0.39		1.08 (0.84-1.38)
	Mother	A	0.59	0.55	0.96 (0.3)	1.20 (0.94-1.54)
		C	0.41	0.45		0.83 (0.65-1.07)
rs1925575	Both	T	0.35	0.57	3.10 (0.07)	0.74 (0.54-1.02)
		C	0.65	0.43		1.35 (0.98-1.85)
	Father	T	0.36	0.46	4.26 **(0.03)**	0.66 (0.52-0.85)
		C	0.64	0.54		1.51 (1.17-1.94)
	Mother	T	0.36	0.38	0.32 (0.5)	0.90 (0.70-1.16)
		C	0.64	0.62		1.11 (0.86-1.44)

χ2=chi square; P=p value; RR=relative risk; 95% CI=95% confidence Interval; statistically significant differences are presented in bold

lower scores for Emotional response and Object use (p<0. 03; Table 4). The male ASD probands with rs1925575 "CC" genotype exhibited higher trait scores for Activity level (Table 4). In the presence of the rs1925608 "CC" genotype, scores for the Activity level were higher, especially in the female probands (Table 4).

Protein-protein interaction analysis

In silico analysis revealed the interaction of LRRTM3 with proteins involved in synaptic regulation

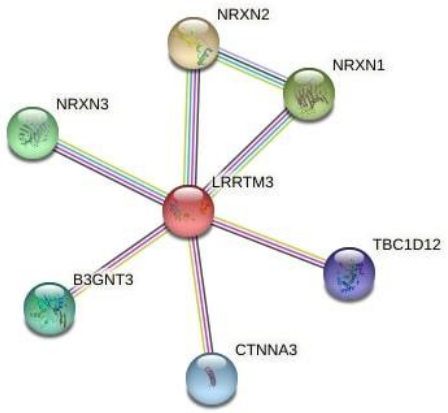


Fig. 1. Protein-protein interaction of LRRTM3 was identified by the STRING (v 11.5) program. Proteins showing association by text mining data are documented by yellow lines. The turquoise lines indicate data obtained from curated databases. Black lines link co-expressed proteins, while the magenta line indicates those showing association based on experimental data. Proteins with filled nodes have information on 3D protein structure. LRRTM3 was found to be co-expressed with Neuritin 1 (NRN1), Neurexin 2 (NRXN2), Neurexin 3 (NRXN3), Catenin alpha 3 (CTNNA3), TBC1 domain family member 12 (TBC1D12), and UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 3 (B3GNT3). Analyses of experimental and text-mining data also revealed an association between these proteins. Moreover, LRRTM3 was associated with NRN1, NRX2, and NRXN3 as per the curated database.

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(Figure 1); LRRTM3 was co-expressed with neurexin 1(0.300), neurexin 2 (0.600), neurexin 3 (0.600), and catenin alpha 3 (0.333). Analysis of data obtained from curated databases revealed significant interaction of LRRTM3 with neurexin 1 (0.600), neurexin 2 (0.183), and neurexin 3 (0.132). Text mining data showed strong interaction of LRRTM3 with neurexin 1 (0.557), neurexin 2 (0.753), neurexin 3 (0.558), and catenin alpha 3 (0.723).

Table 4. Quantitative Trait analysis to identify the association between *LRRTM3* variants and autistic traits.

Proband	rsID	CARS domain	Genotype	AddVal	$\chi 2$ (P)
All	rs1925608	Activity level	AA	0.27	2.03 (0.15)
			AC	-0.41	0.003 (0.96)
			CC	4.67	4.76 **(0.03)**
		Level and consistency of intellectual response	AA	-0.54	3.64 **(0.05)**
			AC	0.67	2.59 (0.12)
			CC	-0.1	0.12 (0.73)
	rs1925575	Relating to people	TT	0.59	0.52 (0.47)
			TC	0.66	5.82 **(0.02)**
			CC	-0.64	3.73 **(0.05)**
Male	rs1925608	Activity level	AA	0.54	4.05 **(0.04)**
			AC	0.64	6.42 **(0.01)**
			CC	-0.001	1.11 (0.29)
	rs1925575		TT	-0.70	1.88 (0.17)
			TC	-0.43	1.17 (0.28)
			CC	0.50	4.10 **(0.04)**
Female	rs1925608	Relating to people	AA	-0.36	0.16 (0.68)
			AC	0.33	1.71 (0.19)
			CC	41.06	6.74 **(0.009)**
	rs1925575		TT	0.70	0.52 (0.47)
			TC	2.81	5.82 **(0.02)**
			CC	-2	3.73 **(0.05)**
	rs1925608	Verbal communication	AA	-2.47	7.86 **(0.005)**
			AC	2.54	5.54 **(0.01)**
			CC	2.02	0.28 (0.59)
		Activity level	AA	-0.79	2.03 (0.15)
			AC	0.54	0.003 (0.96)
			CC	2	4.76 **(0.03)**
		Fear or nervousness	AA	0.08	0.009 (0.93)
			AC	-0.70	1.81 (0.18)
			CC	2.15	3.68 **(0.05)**
		Level and consistency of intellectual response	AA	-1.58	3.64 **(0.05)**
			AC	1.63	2.59 (0.11)
			CC	1.34	0.12 (0.73)
	rs1925575	Emotional response	TT	-0.92	3.09 (0.08)
			TC	1.27	4.83 (0.03)
			CC	-0.56	0.63 (0.43)
		Object use	TT	-1.94	4.08 (0.04)
			TC	-0.3	0.55 (0.46)
			CC	0.88	0.97 (0.32)

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Discussion

The present study on the Indo-Caucasoid population for the first time documented higher frequencies of the derived alleles of two *LRRTM3* genetic variants, rs1925608 “C” and rs1925575 "C" in the ASD probands. Our analysis revealed a higher frequency of the “C-C” haplotype (rs1925608-rs1925575) and biased paternal transmission of the rs1925575 "C" allele in the ASD proband group. We also found that female probands carrying the rs1925608 “CC” genotype exhibited higher trait scores. Based on our observation, we conclude that the "C" variant of these SNPs may increase ASD trait severity, at least in this population.

Synaptic connections are crucial for the regulation of information processing as well as information transmission (30) and investigations on LRR-containing proteins revealed their expression in cell types involved in the development and plasticity of synapses (12,13,15,16). Rare genetic mutations in LRR containing the SLITRK5 gene were identified as a risk factor for neuropsychiatric disorders (16, 31). Targeted gene sequencing revealed the presence of missense mutation in SALM1, another LRR-containing protein, in individuals with ASD (32). Additionally, exome sequencing in families with autistic probands identified a point mutation in the SALM5 gene (33). Leucine-rich repeat-containing protein 40 was identified as a candidate for ASD (34). Amongst different LRRTM variants, abnormal expression of the *LRRTM3* gene was found to affect the etiology of ASD (14) and Alzheimer's disease (22, 35). Family-based analysis in Caucasoid ASD subjects revealed a significant association of two *LRRTM3* variants, rs1998753 and rs12266823; genotyping failure was reported for rs1925575 (14). We for the first time have observed a significant association of *LRRTM3* rs1925608 and rs1925575 with ASD in the Indo-Caucasoid subjects. Stratified analysis on the trait scores of the probands confirmed the SNP data; scores for Activity level and Relating to people were higher in the ASD probands having rs1925608 "CC" and rs1925575 "TC" genotypes. Furthermore, gender-based stratified analysis revealed a noteworthy impact of the *LRRTM3* genetic variants on traits of the female probands; scores for Relating to people, Verbal communication, Activity level, Fear or Nervousness, and Level and consistency of intellectual response were affected in the female probands. In contrast, in the male probands, only a significant effect was observed on the Activity level. This differential effect in different genders could be due to the higher occurrence of the rs1925608 "CC" variant in the female probands, with a significantly high OR of 5.36, compared to the male. Based on these observations, we infer that, based on the gender of the probands, the studied variants may differentially affect the trait scores of the probands.

In Silico analysis showed a strong association between LRRTM3 and proteins involved in cell-cell adhesion (CTNNA3, NRXN2, NRXN3) and neurotransmitter release (NRXN1), crucial for synaptosomal development (23, 36,37, 38). Mild interaction was also observed with the intracellular protein transport TBC1 domain family member 12 (TBC1D12) and the carcinogenic factor Beta-1, 3-N-acetylglucosaminyltransferase (B3GNT3). The protein molecules showing stronger interaction with LRRTM3 are primarily involved in neuronal regulation (23, 36, 37, 38). This protein-protein interaction may be perturbed by the derived alleles of the two studied *LRRTM3* genetic variants since both are located near the regulatory region (35) and may have a role in synaptic function, which warrants further in-depth analysis.

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We infer from these observations that the *LRRTM3* rs1925608 and rs1925575 "C" alleles may be considered as risk variants for ASD, especially in the female probands. The major limitations of the present study include (a) recruitment of a small number of female ASD cases, and (b) analysis of only two *LRRTM3* variants. Further analyses, involving other exonic polymorphisms and more female ASD probands, would help in confirming the role of LRRTM3 in the etiology of ASD.

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