

Novel Candidate Genes for Autism Spectrum Disorders Identified by Whole Exome Sequencing of Indian Autism Twin, Triplet, and Quadruplet Families

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Background: Autism spectrum disorder (ASD) is a childhood-onset complex neurodevelopmental disorder with a complex genetic architecture. There have been very few studies on the genetics of ASD in the Indian population: To identify the potential candidate genes of ASD, we carried out a whole exome sequencing (WES) study of ASD twin, triplet and quadruplet families in the Indian population.

Methods: Five monozygotic twin-, five dizygotic twin-, one monozygotic triplet-, and one multizygotic quadruplet- families participated in the study. Four monozygotic- and three dizygotic- twins were concordant for ASD, while one monozygotic twin, two dizygotic twins, triplet and quadruplet were discordant for ASD. WES was done for all the members of each family.

Findings: There were several deleterious variants among the proband-specific *de novo* and inherited (homozygous recessive and compound heterozygous) variants. Only few of these variants are listed in autism databases. Some of the novel ASD candidate genes identified in this study with well-known brain-related functions include, *GPRIN2*, *HDAC9*, *COL4A2*, *SHISA6*, *TRAM2*, *DGKD*, *OR5AC2*, *FLNB*, *TENM2*, and *ADAMTS18*. These genes play crucial roles in neurodevelopment, axon guidance and synaptic plasticity. Some of the candidate genes have been implicated in other neurological disorders such as epilepsy that share genetic etiologies and biological processes with ASD. Gene ontology enrichment analysis showed that the genes harboring the proband-specific *de novo* and inherited variants were enriched in the biological processes involving nervous system development, synaptic transmission and cell adhesion.

Interpretation: This study further emphasizes the role of early brain development, synaptic transmission and cell adhesion molecules in the pathogenesis of ASD. Aberrations in these biological processes may lead to altered neurogenesis causing ASD. Embryonic neurogenesis is a potentially important period in the pathogenesis of ASD. The onset of ASD is early in life during the period of rapid synaptogenesis. Increased brain mass in autistic children, severe deficit of neuronal nucleus and cytoplasm volume in autistic children, and desynchronized neuronal growth indicate altered neurogenesis in ASD. Cell adhesion molecules (CAMs) serve important roles in neurodevelopment, promoting neurogenesis, neuronal survival, neuritogenesis, axon guidance, synaptogenesis and synaptic function. Aberrations in CAMs contribute to the ASD phenotype, and can affect its severity. In a developing brain, alterations in these aspects result in neuronal network dysfunction, ultimately leading to complex cognitive and behavioral dysfunctions. This is the first comprehensive genetic study of ASD in an Indian population.

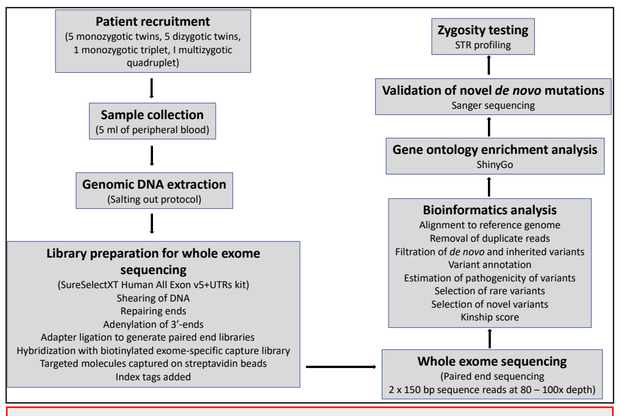


Figure 1: Flow chart of Methods

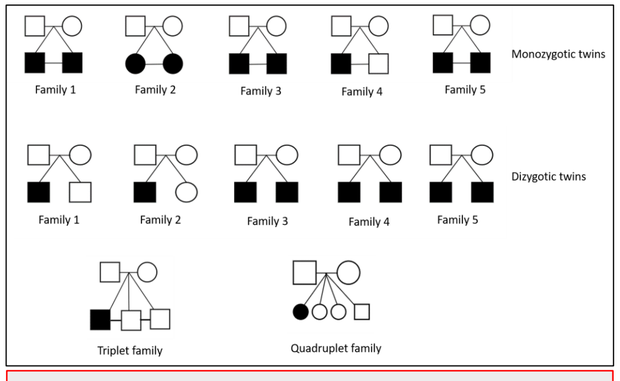


Figure 2: Study participants

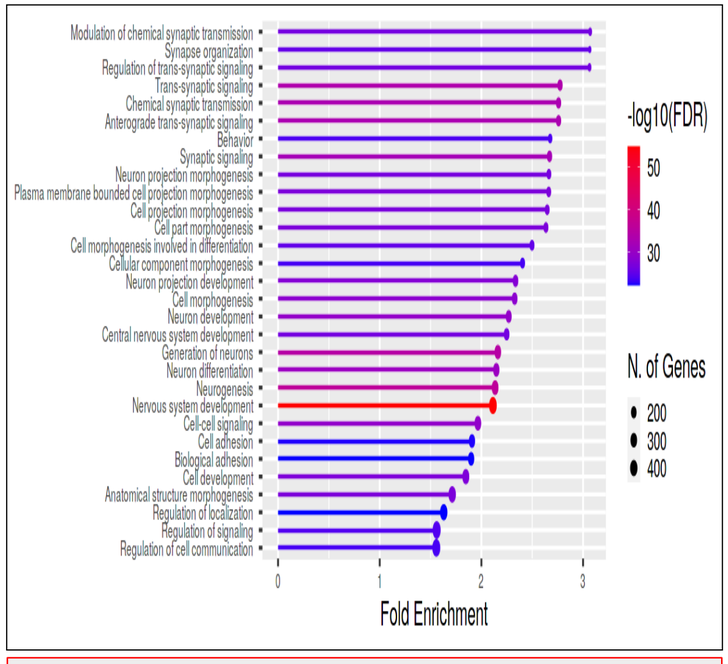


Figure 3: Gene ontology enrichment analysis showed that the genes harboring proband-specific *de novo* and inherited variants were enriched in the biological processes involving nervous system development, synaptic transmission and cell adhesion.

Gene	rs SNP ID	Variant type
KLF18	rs375887615	Nonsynonymous SNV
LRRC53	rs491922	Nonsynonymous SNV
PYDC5	rs41264051	Nonsynonymous SNV
ZC3H11B	rs2653989	Nonsynonymous SNV
ZC3H11B	rs3799941	Nonsynonymous SNV
OR5AC2	rs565646972	Nonsynonymous SNV
HDAC9	rs4721715	Nonsynonymous SNV
HDAC9	rs4721716	Nonsynonymous SNV
COL4A2-AS2	rs373030497	Nonsynonymous SNV
COL4A2-AS2	rs9521780	Nonsynonymous SNV
ADCK1	rs6574411	Nonsynonymous SNV
ADSS1	rs80097179	Start-loss
IVD	rs72733450	Nonsynonymous SNV
ABR	rs34309560	Nonsynonymous SNV
SHISA6	rs768794222	Nonsynonymous SNV
TEX13D	rs6649197	Nonsynonymous SNV
LRRC53	rs491922	Non-synonymous SNV
SIPA1L2	rs542865802	Non-synonymous SNV
CROCC2	rs12466789	Non-synonymous SNV
ING5	rs7573214	Non-synonymous SNV
MARCOL	rs9325091	Non-synonymous SNV
TRAM2	rs373852555	Non-synonymous SNV
SNAPC3	rs374540261	Non-synonymous SNV
LYSMD4	rs11631604	Non-synonymous SNV
FLNB	rs200567066	Nonsynonymous SNV
TENM2	rs564194314	Nonsynonymous SNV
ADAMTS18	rs150975249	Nonsynonymous SNV
ADAMTS18	rs143359890	Nonsynonymous SNV
DGKD	rs564205238	Nonsynonymous SNV
DGKD	rs760475646	Nonsynonymous SNV

Table 1: Proband-specific deleterious homozygous recessive and compound heterozygous variants in dizygotic twins and quadruplets.

Biography

Dr. Anitha Ayyappan Pillai did her Ph.D. at Rajiv Gandhi Centre for Biotechnology, Trivandrum in the field of Population Genetics. She then worked as Assistant Professor at Hamamatsu University School of Medicine, Japan. Now, she is an Associate Professor at Institute for Communicative and Cognitive Neurosciences (ICCONS), Shoranur. Her research area is Neurogenetics. She has received research grants from national and international funding agencies. She has authored >45 scientific papers in leading international journals and has co-authored book chapters.

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