CROSSTALK OF SYNAPTIC GENES WITH IMMUNE FUNCTIONS BURDENING AUTISM SPECTRUM DISORDER: A WHOLE EXOME SEQUENCING STUDY

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ABSTRACT

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social and communication deficits, restricted repetitive behaviors and interests. Although the prevalence of ASD in India is between 0.09-0.11, its genetic research in India has been limited to well-known polymorphisms and lacks holistic genetic studies. Careful examination of the genetic diversity within the Indian ASD population is necessary. Recent studies in rats indicate immune activation deregulates the expression of genes associated with synaptogenesis, axonal guidance, synaptic contact and neurogenesis. Since alterations in neuronal excitatory and inhibitory balance is the most unifying pathology underlying ASD manifestation, we investigated the mutational burden on synaptic genes with potential roles in immune functions in patients using Whole Exome Sequencing (WES).

WES was performed on 15 Indian ASD children on Illumina HiSeq 2500 using Agilent SureSelect Human All Exome V5+UTRs kit. Data was processed in BWA, GATK and VarScan. Variants were annotated using VEP, deleterious variants were identified using 30 different effect prediction tools.

A total of 22 synaptic genes were identified with the most pathogenic missense and truncating variations. This included high-confidence ASD synaptic genes like *ANK3, DSCAM, RELN, SCN2A, NRXN2, SETD5, CACNA1E, TSHZ3*; followed by strong-candidate ASD genes *ACHE, GABRG3, PLXNB1, SCN9A* genes and *CAMK2A, PPFIA1, SCN4A, CTNNA2, SYT1* providing suggestive evidence. Gene *CAMK2A* was the most potent immune gene involved in Interferon signaling potentially mediating a crosstalk between synaptic and immune systems. WES provided the necessary coverage of exonic regions in an unexplored population and confirmed that Indian ASD subjects bore similar genetic risks as that of the western populations. The study is ongoing and we will further explore mutations in immune genes with other neuronal functions.