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Abstract Topic:- Complex traits and polygenic disorders

Abstract Title:- Detection of a structural variant by long read sequencing in a patient with non-syndromic autism spectrum disorder.

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Aims:-The heritable component for autism spectrum disorders (ASD) has been estimated to be up to ~80%. Despite this, nearly 50% of ASD cases remain undiagnosed. Recent literature suggests the role of structural variants (SVs) impacting non-coding genomic elements in the etiology of autism. Long read whole genome sequencing (LR-WGS) provides ability to detect these SVs that previously went undetected by whole exome short read sequencing. We hereby present a novel case of non-syndromic ASD identified with a SV on LR-WGS in whom prior traditional genetic tests failed to provide a diagnosis.

Methods:- A two year ten months male proband was diagnosed with non-syndromic ASD according to the DSM-5 criteria. No genetic cause could be identified on karyotyping, Fragile-X analysis, chromosomal microarray and whole exome sequencing. LR-WGS was carried out using high molecular weight genomic DNA on the Oxford Nanopore Technology (Mk1C) sequencing platform with an average coverage of ~10x. Base calling was carried out using Guppy in high accuracy mode on fast5 files and the reads were aligned against GRCh38 reference genome build. SVs were called using four variant callers- sniffles2, cuteSV, SVIM, and npInv. SVs concordant across at least 2 variant callers were considered for downstream analysis that included filtration and prioritization, carried out using AnnotSV.

Results:- The proband was detected with an ~2.7 Mb heterozygous inversion, chr20:g.10183742_12846281inv. It was located on chromosome 20 with breakpoint 1 (BP1; g.10183741) disrupting the SNAP25 and SNAP25-AS1 genes at region 20p12.2 and breakpoint 2 (BP2; g.12846281) at an intergenic region, 20p12.1. Validation and segregation analysis in the proband and his similarly affected twin brother showed the presence of the inversion and was found to be inherited from their heterozygote mother. The father and their unaffected elder brother were not found to carry the variant.

Conclusions:- Multiple studies have implicated inherited non-coding elements along with a parental polygenic risk contribution, as well as a female protective effect in the genetics of ASD. In the present case, it is plausible that an aberrant synthesis of SNAP25-AS1 long non-coding RNA is likely to increase the risk of autism if not be the sole cause. Both genes are involved in the synaptic pathway and have previously been associated with autism. We present the first case from India where an SV was detected by LRS and was suggested to play a role in ASD etiology.

Keywords:- Autism spectrum disorder, structural variant, whole genome long read sequencing, inversion, non-coding genomic element