Agarwala et al. (2017) Can J Biotech, Volume 1, Special Issue, Page 94
https://doi.org/10.24870/cjb.2017-a81

Canadian Journal of Biotechnology

ISSN 2560-8304

Poster Presentation OPEN ACCESS

Category: Clinical Genomics

Damaging stop gain/loss and frameshift mutations in autism subjects outline impairment in neuronal migration and adhesion pathways

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Abstract

Genetic heterogeneity makes it challenging to identify causal-genes responsible for autism pathogenesis. Till date, research studies report only a handful of high confidence genes for autism. There is a need to identify damaging genomic-variants, predisposing an individual towards autism manifestation. Of special interest is stop gain/loss mutations found in the exome. Such variants are prevalent, having an estimated number of 100-200 occurrences per human-genome. Stop-gains and frameshifts may lead to functional consequences. Based on stringent inclusion-exclusion criteria, the study recruited 150 autism subjects of Indian origin, of which 13 were used for WES. To understand the nature and possible consequences of these variants, we first analyzed their characteristics at the genome-level. Genome-wide analysis of more than 30000 variants provided statistical-significance to identify sequence-specific features for severity and to build a pathogenicity score. This sequence-based pathogenicity score was then applied to the analysis of variants in autism susceptibility. Several damaging stop gain/loss mutations encompassing autism genes *CDH5*, *DDX23*, *CLDN5*, and *DPP3* were identified with protein truncations ranging from 20-70%. Loss of function mutations disrupted protein domains involved in various autism related pathways such as neuronal migration, synaptogenesis, and neuronal adhesion. Mutations were identified with previous evidences for neuronal migration and adhesion pathways in *Drosophila sp, C. elegans* and *mice* models. Homozygosity mapping analysis to identify risk-homozygous-haplotypes showed evidence of recessive polymorphisms in *GIGYF1*, *SERPINE1*, and *EPHB6.* Recessive alleles were identified across all the samples while polymorphisms in *FOLH1*, *BCKDK*, *CDH11*, and *CTCF* were specific. Mutations in language-specific genes, *GCFC1* and *MRPL19* were associated with autism phenome. A novel autism candidate gene *CLDN5* that physically interacts with genes involved in various autism pathways was identified.*CLDN5* belongs to the leukocyte-transendothelial-migration pathway and elevated in autism cortex, impairing the blood brain barrier leading to compensatory gene expression and protein accumulation. This on-going study identified several damaging mutations specific for autism in Indian population, adding to the growing body of mutational spectrum. Validations through Sanger sequencing and allele specific PCR is being done for the mutations identified.

Citation: Agarwala, S., Shyamala, K.C., Padakannaya, P. and Ramachandra, N.B. Damaging stop gain/loss and frameshift mutations in autism subjects outline impairment in neuronal migration and adhesion pathways [Abstract]. In: Abstracts of the NGBT conference; Oct 02-04, 2017; Bhubaneswar, Odisha, India: Can J biotech, Volume 1, Special Issue, Page 94. https://doi.org/10.24870/cjb.2017-a81