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Abstract Title:- Study on the Impact of MicroRNAs Present in the Autism Associated Copy Number Variations

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Aims:-To understand the significance of Copy Number Variation and their associated microRNAs for its role in the pathophysiology and genetic heterogeneity of autism in south Indian population.

Methods:- By using Insilco Analysis we identified the miRNAs present in copy number variation associated with autism. A total of 85 children diagnosed with autism were recruited for this study. Samples were also collected from 64 age-matched healthy children studying in different schools (n = 41) and from the unaffected sibling (n=23) who served as control group. Heparinized peripheral blood samples were used for isolation of total RNA using Qiagen RNA isolation kit. The expression analysis of miRNA was profiled using custom based stem-loop miRNA assay by qRT-PCR.

Results:- A systematic analysis of the CNV-miRNAs based on their interactions with the target genes enabled the identification of top 10 miRNAs (Vaishnavi et al., 2013). Using qRT-PCR, we profiled the expression of the top 10 CNV-miRNAs and ten neuronal specific miRNAs which were expressed in the peripheral blood. Out of top ten CNVs associated miRNAs hsa-miR-34a-5p, hsa-miR-195-5p and hsa-miR-497 were found to be over expressed in autism cases with significant p-value whereas hsa-miR-590- 3p showed overexpression without any statistical significance. The remaining six miRNAs were below the threshold level of real-time PCR based detection. The ten neuronal specific miRNAs selected from publication were also profiled for their expression in autism. The hsa-miR-34a-5p, hsa-miR-195-5p, hsa-miR-497, hsa-miR-19b-3p, hsa-miR-34b-3p, has-miR-320a, hsa-miR-486-3p, hsa-miR-1228-3p, Let-7a-5p, Let-7d-5p and hsa-miR-181-3p showed a significant differential expression profiling in autism children compared to control.

Heat map of miRNAs expression generated using QCanvas between cases and control, showed similar clustering pattern between cases (n=85) and sibling controls (n=23) and not with normal controls (n=41). The miRNAs hsa-miR-19b-3p, hsa-miR-103a-3p, hsa-miR-590- 3p and hsa-miR-106b-5p were up-regulated in sibling control compared with cases. In addition to understand the importance of miRNAs candidate genes the functional and pathway analysis were studied and majority of the target genes were found to be involved in the synaptic and neuronal functions.

Conclusions:- All together, the miRNA profiling in peripheral blood could be used as a surrogate system for studying brain specific miRNAs and this study provide a new insight on role of CNVs and miRNAs in the pathophysiology and genetic heterogeneity of autism.

Keywords:- Copy Number Variation, MicroRNAs.