ABSTRACT

Dyslexia is a specific impairment in learning to read and write. Family and twin studies have shown that dyslexia is caused in large part by genetic factors. Dyslexia is most likely the result of the interplay of multiple genetic and environmental factors. Some or all of the subtypes of dyslexia have distinct genetic causes. Understanding the role of genetics in dyslexia could help to diagnose and treat susceptible children more effectively and rapidly than is currently possible and in ways that account for their individual disabilities. Depending on the phenotype dimension investigated, inherited factors are estimated to account for up to 80%. Linkage findings in dyslexia are relatively consistent across studies in comparison to findings for other neuropsychiatric disorders. This is particularly true for chromosome regions 1p34–p36, 6p21–p22, 15q21 and 18q11. Results indicate that a disturbance in neuronal migration is a pathological correlate of dyslexia at the functional level. However, even in studies those have shown negative linkage undetected Copy Number Variations (CNVs) playing a role cannot be ruled out. Genome-wide genotyping was performed using an Affymetrix Genome-wide Human SNP Array 6.0 chip having 1.8 million combined SNP and CNV markers with the median inter-marker distance of 500-600 bases. These chips provide maximum panel power and the highest physical coverage of the genome. Whole genome CNV scan identified 5 novel genes and one already identified candidate gene in 11 dyslexic subjects. Genes include \textit{PCDH11X, GABARAP, NEGR1, ACCN1 and DCDC5} and one already identified gene \textit{CNTNAP2}.

A 3.5 Mb region of the X chromosome underwent duplication and transposition to the Y chromosome ~ 5–6 million years ago. This X-transposed region (XTR) originated
at Xq21.3 and was inserted at Yp11.2. The two locations have a 98.78% homology and a high concentration of tandem repeats. In whole genome scans of eleven families with dyslexic members, transposed blocks comprising >102 kb of the Yp11.2 region in its homologous region at Xq21.3 in three females from three different families was identified. Although recombination is known to be limited only to the pseudoautosomal regions (PARs) of the X and Y chromosomes, allelic unequal recombination between the XTR region Yp11.2 and Xq21.3 indicating the presence of a new PAR, termed as PAR3 is reported here. This PAR3 region was also found in 2% of the general population. An additional layer of justification could be provided from six other dyslexic cases which harbored duplications and deletions in the same Xq21.3 and Yp11.2 regions through allelic unequal recombination.

Thus, the present investigation is a maiden report in the analysis of Copy Number Variations (CNVs) in the Indian dyslexic families. Although dyslexia has long been thought as a neuronal migration disorder, the present study suggests that dyslexia may also be viewed as a disorder due to defects in neurotransmission and cell adhesion processes.