SECTION IV

Summary
1. Dyslexia, a disorder of reading and spelling, is a heterogeneous neurological syndrome with a complex genetic and environmental aetiology. People with dyslexia differ in their individual profiles across a range of cognitive, physiological, and behavioural measures related to reading disability.

2. An understanding of 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.

3. Genetic linkage analysis has identified regions of the genome that might harbour inherited variants that cause reading disability.

4. Several genes have been proposed as candidates for dyslexia susceptibility, including $DYX1C1$ on chromosome 15, $KIAA0319$ and $DCDC2$ on chromosome 6, $ROBO1$ on chromosome 3 and $MRPL19$ and $C2orf3$ on chromosome 2. Interestingly, these genes share a putative role in brain development.

5. A whole genome scan is a powerful tool for the identification of subtle changes in individuals with diseases. Genome-wide scan can be performed using several tools at varying resolutions. The advancement in the microarray well and bead based chip technologies led to the development of chips containing millions of SNPs and CNP probes. Comparatively these advanced DNA chips offer a higher resolution at base pair level intermarker distances compared to the earlier Mega base resolution.

6. A growing body of evidence suggests that structural variation, including CNVs, across the genome is common and likely contributes to human disease.

7. Even in studies that have shown negative linkage, the possible contribution of undetected CNVs cannot be dismissed.
8. This is maiden report in the analysis of copy number variations in the Indian dyslexic families. Identified 27 CNVs in a total of 14 dyslexic subjects and was validated in 100 unrelated control members. These 27 CNVs disrupted the exon structure of 5 novel genes PCDH11X, GABARAP, ACCNI, NEGR1, DCDC5 and one already identified candidate gene CNTNAP2.

9. Perusal of the literature revealed that PCDH11X in the Xq21.3 region is associated with verbal ability, language processing and cerebral asymmetry. The present finding is a maiden report indicating the association of PCDH11X with dyslexia.

10. Dyslexia has long been thought as a neuronal migration disorder. But the present study suggests that dyslexia may also as be viewed as a disorder due to defects in neurotransmission and cell adhesion processes. Dendritic spines help transmit electrical signals to the neuron's cell body and undergo changes in shape, volume and number. Taking into account the role of all five genes identified, suggests their involvement in dendritic spinal plasticity leading to cognition, learning and memory. This probably can explain how dyslexics start to perform better over an extensive learning and skill acquiring period, which can be attributed to the pruning of dendritic spines leading to stabilized presynaptic connections.

11. The dyslexia gene network model was established which controls six major functions: synaptic transmission, axon guidance, transmission of nerve impulse, neurogenesis, cell migration and protein domain specific binding based on weighted gene protein interaction network. Based on the current de novo CNV events, neuronal network and pathway studies, an attempt was made to visualize the ongoing cellular processes with an aim to understand the functional role of the
candidate genes identified in this study and also to study its implication on the other molecules and processes in the cellular network.

12. This study also identified transposed blocks consisting of >102 kb of Yp11.2 integrated into Xq21.3 region in three members. Allelic unequal recombination indicates the features of a new PAR, namely PAR3. ~ 5–6 million years ago, the Xq21.3 region has a history of duplication and transposition activity by means of a duplicated and later transposed block of 3.5 Mb from the X to the Y chromosome. This process is very similar to the origination of the PAR2. The PARs have a large amount of homology to each other, whereas the XTR alone has a 98.78% identity. The genes *PCDH11X* and *TGIF2LX* have 99.1% identity with their *PCDH11Y* and *TGIF2LY* homologues in the XTR. A few genes in PAR1 and PAR2 are known to escape inactivation in the inactivated chromosome. Likewise, a few genes in Xq21.3 escape inactivation. PAR2 and PAR3 share similar type of origin and creation. Thus, these recombination events are a maiden report to identify XTR as a PAR3 region.

13. The findings on CNVs contribute to the array of dyslexic phenotypes seen in families which demonstrates the importance of performing a high-resolution assessment of genomic background, even after the detection of a rare and likely damaging CNV. Although dyslexia has long been thought as a neuronal migration disorder, the present study suggests that dyslexia may also as be viewed as a disorder due to defects in neurotransmission and cell adhesion processes.

14. Understanding the biology of complex cognition is a major challenge, to which genetics can provide crucial clues because Dyslexia is an Invisible Handicap. This
study surrounds around families with multiple affected individuals. The methodology adopted here has a higher genome resolution but the number of families chosen for the study is less, which becomes a limitation and requires further whole genome studies on large extended families to identify more appropriate genes and relevant test. These will at large help to rehabilitate, treat, manage and cure the dyslexia subjects.

15. Understanding the biology of complex cognition is a major challenge, to which genetics can provide crucial clues because Dyslexia is an Invisible Handicap. Dyslexia has long been thought as a disorder with fewer implications on life. The methodology adopted here has a higher genome resolution and these will at large further help in the development of treatment to manage the dyslexia subjects.