CHAPTER 7

General discussion and Conclusion
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Attention-deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders diagnosed in children and have a profound lifelong effect on the brain function. As the name implies, principal characteristics of this disorder are inattention, hyperactivity, and impulsivity. These symptoms appear early in a child’s life. Although they tend to diminish with age and social maturing, some children (approximately about 40–50%) have persisting symptoms till adulthood. ADHD may significantly affect a child’s life by impairing academic activities, relationships both in the family and with their contemporaries, thereby increasing the risk of social isolation [Kopeckova et al., 2006]. They also can lead to substance abuse and behavioural problems. These conditions become worse when ADHD subjects also have other co-morbid disorders (LDIs, CD, ODD, MD, and OCD etc.) [Bowen et al., 2008; Hurtig et al., 2007; Nijmeijer et al., 2008; Spencer, 2009]. As it is a symptomatic disorder, proper diagnosis and early detection are essential for intervention. Subjects with ADHD along with other co-morbid conditions if goes untreated may be a cause of serious concern depending on the severity of the problems faced by the ADHD patients.

ADHD is one of the common complex genetic disorders involving many susceptibility genes, each with a small effect [Qian et al., 2007; Tannock, 1998]. Heritability of ADHD is approximately 75%–91%) [Faraone et al., 2005; Levy et al., 1997;]. The genes currently identified as playing a causative role in ADHD account for only a small percentage of the total picture. Identification of additional candidate genes, and their interactions, holds the promise of identifying better methods for diagnosis and treatment, emphasizing the need for polypharmacy. Again, dysfunction of catecholamine, particularly dopamine (DA) has been postulated to be involved in ADHD [Castellanos et al., 1996; Zametkin and Rapoport 1987]. DA plays a key role in attention, motor function, reinforcing and rewarding behaviours that are deficient in ADHD patients. Hence dopaminergic system genes are targeted for most of the ADHD study. In the present study, six genes (DRD2, DRD4, DAT, NET, DBH and COMT) from the catecholaminergic system were chosen for determining their
association with ADHD and its associated co-morbid disorders in eastern Indian subjects. ADHD subjects were diagnosed according to DSM-IV criteria and without any chromosomal abnormality. Genotypic data obtained were tested for familial transmission (family based study) as well as compared with ethnically-matched control samples (population based study). Gene-gene interaction analyses were also done between the studied genes.

Both case-control and family-based data revealed association of DRD2 rs1799732 ‘C’ allele with ADHD+LDis. DRD4 rs4646983 ‘1R’ allele was significantly associated with all ADHD cases as well as ADHD+ CD, ADHD+ ODD and ADHD+MD while DRD4 rs4646984 ‘1R’ allele was only associated with ADHD+CD by case-control analysis. Family-based association analysis showed significant preferential transmission of rs6276 ‘A’ from parents to all ADHD cases, ADHD+CD, ADHD+LDis and ADHD+ODD cases. C-G and C-A haplotype formed between rs1799732-rs6276 also gave significant results by family-based study.

SLC6A3 rs40184 ‘G’ showed significant association with ADHD+LDis and ADHD+ODD while rs2652511 ‘T’ allele showed association with ADHD+CD. In case of SLC6A2, family-based analysis revealed significant association of ‘C’ allele from both the SNPs with the disorder.

From DBH gene 5’-ins/del consists of 19 base-pair insertion/deletion approximately 4.7 kb 5’ from the transcriptional start site and associated with plasma DBH activity was selected. Data obtained by the present study showed that the frequency of the ‘del’ allele was higher among the cases compared to controls, (though statistically not significant) indicating low serum DBH level in ADHD children from the eastern India.

Out of the four SNPs (rs4680, rs362204, rs165599, rs740603) selected in the COMT gene, significant associations of rs165599 ‘G’ with ADHD+LDis and rs740603 ‘G’ with ADHD+ODD as well as ADHD+MD were observed by case-control analysis. By family based analysis, only rs740603 ‘G’ showed significant result.

Gene-gene interaction analysis by MDR revealed significant independent main effect as well as epistatic interactions between the studied markers. Significant interactions were observed between rs2652511 and rs3785143 for
all ADHD cases and between rs40184 and DBH ins/del for ADHD + ODD. Here the synergistic interactions were observed for the genes which code for DA and NE transporters (SLC6A3, SLC6A2) and DA metabolising enzyme, DBH. Significant independent main effects were also found for rs6276, rs1799732, rs2652511, rs3785143, rs11568324. Significant independent effect and epistatic interaction between these loci indicates that they may affect dopaminergic neurotransmission in the Indian ADHD group.

Thus, the presently studied catecholaminergic genes may have roles in the complicated etiology of ADHD and associated co-morbid conditions of the eastern Indian ADHD probands. Because ADHD is one of the most common heritable psychiatric disorders and each ethnic group has a unique genetic set up, this study may help in understanding the disease etiology in this particular ethnic group while also extending the basic knowledge on the disorder.