CHAPTER 9: INference

http://colinfarrelly.blogspot.com/2010_01_01_archive.html
The term Mental retardation (MR) is used to explain a state with significant limitations in intellectual functioning, self help skills and adaptive behavior [1]. Incidence of MR is estimated to be 1-3% in some countries and regions among children of 18 years or younger [24]. Since MR is manifested during the early growth phase, it affects a child's way of life and may become a cause of serious concern to the family depending on the severity of the condition. The situation becomes worse when MR is associated with co-morbid behavioral problems [109] and if remain untreated, they can cause life-threatening damages in adolescents [111, 112].

Since genetic heterogeneity that underlies cognitive impairment is unprecedented [17], understanding the biology of MR is really complicated. Dysfunction of proteins encoded by genes involved in a large spectrum of cognitive deficits extending from mild MR, with or without comorbid features, to severe MR might lead to defects in synaptic structure or function and neuronal connectivity thereby hampering ability of the brain to process information [17]. The resulting limited ability of the brain to process information would result in cognitive deficits. In view of these assumptions, the present study was designed to look into the genetic status of MR individuals by exploring functional polymorphisms in candidate genes like DRD4, SLC6A3, COMT, MAOA and SLC6A4. Products of these genes are known to regulate activities of principle neurotransmitters: dopamine (DA) and serotonin (5-HT), which control cognition, motor functions and behavioral symptoms of human being. To summarize the entire work, it could be stated that out of the five genes studied, four namely, DRD4, SLC6A3, COMT and MAOA, may have significant impact in the etiology of MR and could be considered as risk factors with sex-bias.

DRD4 exon3 VNTR "6R" allele conferring subnormal activity to the receptor showed significant association with MR (both IMR and DS) and more specifically in IMR probands with behavioral problems, while SLC6A3 3'UTR-VNTR lower repeat alleles (6R, 7R and 9R) and "9R/9R" genotype, intron 8 VNTR "5R" allele and "5R/5R" genotype also conferring subnormal function of the transporter, showed significant association with IMR probands and more specifically with IMR probands with behavioral problems. On the other hand, while COMT rs4680 low active "A" allele and "A/A" genotype showed preferential transmission to male IMR probands, low active COMT rs165599 "G" allele and MAOA rs6323 "T" allele showed association specifically with female MR (both IMR and DS) probands. No significant
impact of MAOA and COMT polymorphisms was found with MR probands having severe behavioral problems.

Significant results were also obtained by haplotype analyses where "6R-T" haplotype of the DRD4 gene and lower repeat haplotypes (7R-5R and 9R-5R) of the SLC6A3 gene, giving rise to receptor and transporter with reduced efficiencies respectively, showed bias in transmission. Then again, a significant bias in transmission of low active "3.5R-T" haplotype of MAOA gene was observed in female DS probands. All these variants (both allelic and haplotypic), ensuing suboptimal DRD4 and DAT function and less active MAOA and COMT enzyme, together may increase the level of DA and 5-HT in the system and therefore, abnormal DA and 5-HT neurotransmission could be associated with the disease etiology of Indian MR patients. Significant association of "S-12R" haplotype of SLC6A4 gene was also found with independent effect of both "S" allele of 5-HTTLPR and "12R" allele of STIN2 in MR. Both of these alleles act in opposite way and hence nullify the causal role of 5-HTT in MR. Therefore, it is yet to be proved whether SLC6A4 polymorphisms have a role in the etiology of MR individuals in this population.

Finally, analysis of genetic interaction by MDR revealed significant epistatis and additive effects between the markers along with independent main effects. In IMR and DS individuals significant interaction was observed between DRD4 rs1800955 (M2) and STIN2 (M10) indicating an interaction between the dopaminergic and serotonergic systems. Dominant by dominant (DD) interaction effects was observed between DRD4 rs1800955 (M2) and 5-HTTLPR (M9), rs1800955 (M2) and MAOA rs6323 (M8), rs1800955 (M2) and MAOA-u VNTR (M7), rs1800955 (M2) and SLC6A3 intron 8 VNTR (M4), intron 8 VNTR (M4) and rs6323 (M7), intron 8 VNTR (M4) and 5-HTTLPR (M9), intron 8 VNTR (M4) and STIN2 (M9), 5-HTTLPR (M9) and STIN2 (M10), MAOA-u VNTR (M7) and 5-HTTLPR (M9) and between MAOA-u VNTR (M7) and STIN2 (M10) with IMR. Significant additive effects were also observed between rs6323 (M8) and 5-HTTLPR (M9), rs1800955 (M2) and rs6323 (M8) and between rs6323 (M8) and STIN2 (M10). MDR Phenomics also revealed significant sex-bias in these interactions. The complexity of the interrelations between genetic variation and phenotypic covariates was efficiently captured by this nonparametric MDR approach.

In case of DS, DD effects were observed between MAOA-u VNTR (M7) and rs6323 (M8), MAOA-u VNTR (M7) and COMT rs165599 (M6) and between rs6323 (M8) and STIN2 (M10). Additive effects were observed between rs1800955 (M2) and 5-HTTLPR (M9),
rs1800955 (M2) and COMT rs4680 (M5), COMT rs165599 (M6) and 5-HTTLPR (M9), and between rs165599 (M6) and rs6323 (M8). No significant sex-bias was observed for DS by MDR Phenomics analysis.

The significant epistatis and additive effects observed between the markers in both IMR and DS may further affect functions or activities of the proteins encoded by DRD4, SLC6A3, COMT, MAOA and SLC6A4 genes that work together to regulate dopaminergic and serotonergic transmission and clearance of excess DA and 5-HT from the synaptic cleft by signal transduction, re-uptake and enzymatic degradation respectively and hence can alter the levels of these neurotransmitters in the system.

From the data obtained it can be hypothesized that there is a possibility of altered neurotransmission in the MR individuals as postulated in the Fig. 9-1. It is also indicative from the current study that though the studied genes have an impact in the disease etiology of both IMR and DS, their interaction with each other is different in the two disorders. However, biological interpretation based on statistical analysis [486] seems to be too simplified for a complex disorder like MR and could only be supported through more in-depth analysis of these pathways.

![Figure 9-1: Hypothetical representation of the involvement of different gene variants in the pathophysiology of MR.](image-url)