RATIONALE AND SIGNIFICANCE OF THE STUDY

Glaucoma is the largest cause of irreversible blindness with 1% global prevalence. Primary open angle glaucoma (POAG) is the most common subtype of glaucoma. POAG is a complex disease where multiple genetic factors contribute in development of the disease. So far 23 loci have been identified to be linked with the disease. When familial it usually follows autosomal dominant trait. Few genes have been identified via linkage studies however they explain only 5% of the disease in global scale. Apart from linkage studies several genome-wide association studies have reported various loci to be associated with disease. However poor reproducibility of associated loci across different population warrants further studies to establish their role in the disease. Despite a large number of familial based as well as population based (association study including GWAS) studies to discover genes responsible for POAG, a very small fraction can be explained. With the intent to explain as yet unknown part of this missing heritability we wanted to perform genome-wide study of copy number variation (CNV) region in POAG using a case control design.

CNV, being a major factor of genomic diversity, have been studied in various complex diseases. By definition it is a type of structural variation that causes alteration in DNA copy number. It is classified into two types either deletion or duplication which can be as large as few megabases. Non allelic homologous recombination (NAHR) is considered as the primary mechanism for CNV formation in genomes. CNV, disrupting genes or their potential regulatory elements, may cause aberrant gene expression. Sometimes this situation can lead to disease phenotype. Several previous studies have shown CNV association with neuron related diseases. Very few CNV based genome-wide association studies (GWAS) have been done on POAG, identifying several rare variants (Davis et al., 2011). However, still these variants have to be validated across populations which demands further studies to be performed. Poor overlap between all these findings warrant further studies in different populations to get a better understanding about involvement of these with development of the disease. From that perspective we are motivated to pursue the study on CNV in POAG which is the basis of this doctoral thesis.
Based on these questions, I have divided my objectives in three broad categories:

1. Large CNVs in Glaucomatous Neurodegeneration
2. Genome-wide CNVs association in Glaucomatou Neurodegeneration
3. Genome-wide identification of transcriptional targets of Foxe3 in RGC-5 cell line by ChIP-Seq