6.0 Introduction:

Genetic interactions have been studied years in model organisms as a means of identifying there functional relationships among genes or their corresponding gene products and also, with the nature of these relationships depending on the types of interactions (1). Sometimes mutations in two genes produce a phenotype that is surprising in light of each mutation’s individual effects. This phenomenon, which defines genetic interaction, can reveal functional relationships between genes and pathways. Gene interaction between multiple genes has an impact on the expression of an organism’s phenotype. The genetic interplay between podocyte genes and their influence on the clinical phenotype of NS has been previously studied as for instance, both nephrin and podocin may interact directly or indirectly and are important for maintenance of the glomerular capillary permeability barrier (1-4). To the best of my knowledge, there has been no report so far on interactions between podocyte genes (NPHS1, NPHS2) in combination with the genes involved in regulating fluid circulation (ACE) and drug traffic (MDR1) at the target cell. Hence, I have extended the analysis on the interactions of podocyte encoding genes in combination with ACE and MDR1 SNPs, towards steroid responsiveness in NS patients.

6.1 Comparison between MDR1 G2677T/A genotype and podocyte gene mutations:

Mutations in NPHS1 and NPHS2 genes, which are the candidate genes involved in regulating the podocyte structure and functions in the study population and the results were presented in chapter 3 and 4 of this thesis respectively. It is important to mention that 9% and 18% of the SRNS group (n=100) showed a mutation in those respective genes. Further the SNP G2677T/A genotypes of MDR1 shows an association to steroid response in SRNS patients only among the study subjects; i.e. healthy volunteers and SSNS group (Chapter-5). Since the SNP is a triallele, the possible genotypes are homozygous GG, TT, AA or heterozygous GT, GA and TA; of the expected six different genotypes, the proportion of available/majority in the SRNS subjects are (9% had GG, 34% were TT, 0% were AA, 41% had GT, 11% were GA and 5% were TA genotypes).
Combination of those different genotypes with *NPHS1* and *NPHS2* mutation towards the steroid resistance is presented Figure-6.0. As represented in Figure 6.0, 9% of SRNS patients carrying mutations in *NPHS1*; amongst, 7% of them showed the GT genotype and 2% showed the GA genotype for the SNP. Similarly, SRNS patients with *NPHS2* mutations (18%), 12% of them had the GT genotype, 3% had GA genotype and the remaining 3% patients had the TT genotype for the SNP. This suggests that this SNP both independently and in combination with mutations in the *NPHS1/NPHS2* genes is a potential genetic marker to detect drug resistance and responsiveness to steroids.

**Figure 6.0: Correlation between *NPHS1* and *NPHS2* mutations with *MDRI* G2677T/A polymorphism towards drug response in SRNS patients**

If our hypothesis is correct, then one can expect a mutation in the candidate genes (*NPHS1, NPHS2*) in all the SRNS patients. However, only 27% of the patients showed mutation despite the entire candidate gens (29 exons in *NPHS1* and 8 exons in *NPHS2*) were
sequenced. Of which, 17% are novel and has not been reported in any population. It supports the notion that the type and frequency of mutation may depend upon the life-style and/or ethnic variation; in addition to those candidate genes other genes such as PLCE1, CD2AP, LAMB2, TRPC6 and many other genes might play an equally important role in regulating the renal physiology and dysregulation could result in NS.

Screening for the common genetic causes of NS will prevent unnecessary steroid therapy of these children. For better understanding of the correlation between these gene polymorphisms, allele frequency and diseases conditions, large cohort studies in different areas need to be conducted. A perceptive of the molecular mechanisms of the disease may also yield new information about etiology and will be helpful in developing targeted therapies against the disease.
References:


