Nephrotic Syndrome (NS) represents a non-specific symptom complex resulting from a multitude of both primary and secondary medical diseases of the kidney. It constitutes one of the commonest presenting features of kidney diseases and the most common indication of renal biopsies in nephrological practice. However, it is not a single disease. NS is classified in a number of ways. A primary categorization into primary or idiopathic and secondary types provides the basis for further investigations and management of the disorder. The primary or idiopathic form predominates in children while secondary NS is more common in adults. Another important basis of classification, especially in children, is that based on the response to initial standard steroid therapy. Three forms of the disease are recognized; Steroid-Sensitive NS (SSNS), Steroid-Dependant NS (SDNS) and Steroid-Resistant NS (SRNS). Among these, SRNS poses significant diagnostic, prognostic and therapeutic challenges to both the nephrologists and nephropathologists alike.

The prevalence of steroid resistance in Idiopathic NS (INS) varies from 10 to 40% depending on a number of factors. Part of the problem also stems from variations in the definitions of steroid resistance employed in different studies. Overall, SRNS constitutes upto one-third of INS in most reported series from different parts of the world. Similarly, SRNS constituted 31.1% of the cases undergoing renal biopsies in a cohort of 538 children at our center. A significant number of patients with SRNS (upto 40 to 50%) progresses to End-Stage Renal Disease (ESRD) over 5 to 10 years of follow-up. This together with the prevalence of the disorder has resulted in considerable research interest in understanding the pathogenetic mechanisms underlying steroid resistance in INS.

The pathogenesis of SRNS has traditionally been considered an immune-mediated mechanism, but with the discovery of mutations in NPHS1 as the underlying cause of Congenital NS (CNS), the role of genetic factors has become the focus of investigation. Numerous proteins and their corresponding genes have been identified and their mutations described in cases of SRNS, especially in children. The most common genes include; NPHS1, NPHS2, ACTN4, WT1, TRPC6, MYO1E, INF2, PLCE1, and many others. These proteins are mostly expressed in podocytes and perform both structural and signaling roles in podocyte physiology. Thus, the podocytes have become the center stage of study of mechanisms of proteinuric disorders. Both autosomal recessive and dominant forms of the genetic disease are described.

SRNS typically has constituted one of the most common indications of performing renal biopsy in INS, especially in children. The histology of SRNS has encompassed a variety of lesions, ranging from Minimal Change Disease (MCD) to Focal Segmental Glomerulosclerosis (FSGS) to Mesangial Proliferative Glomerulonephritis (MesPGN). FSGS was the single most common histopathological lesion underlying SRNS in children at our center, constituting 38.5% of all diagnoses. However, similar to the clinical presentation, the morphology also lacks specificity in glomerular pathology, especially in the era of molecular and genetic diagnostics. This principle also applies to the histology of SRNS. The morphological appearances do not accurately reflect the underlying pathobiological processes and transitions in morphology are commonly seen in repeat biopsies.

An investigation of the genetic basis of SRNS is not only important from point of view of understanding the pathobiology of the disease process, but has also considerable diagnostic, prognostic and therapeutic implications. Cases of INS with genetic basis are resistant to steroid therapy, frequently progress to ESRD and typically do not recur following transplantation. Paradigm shifts in the investigation of childhood INS are being contemplated and screening strategies and algorithms for genetic testing are being proposed based on the age of onset and sporadic or familial occurrence of the disease. A better understanding of the contribution of these genetic abnormalities to the pathogenesis of SRNS will pave the way for molecular and targeted therapeutic approaches to be developed in near future.

The progress on this front has been rather slow in Pakistan as compared with the developed parts of the world. However, now attention is being focused on the molecular investigation of INS, especially SRNS in Pakistan.
children. Our group has previously published results on a cohort of 141 children with SRNS. The prevalence of mutations in the two most commonly mutated genes (NPHS1 and NPHS2) was low in our cohort. However, our results are comparable with other regional studies. The exact reason for these discrepancies is not clear but may relate to racial factors. Further large-scale studies are needed to further confirm these observations. In addition, the repertoire of genes to be investigated also needs to be expanded. Next generation sequencing technology will definitely improve our ability to screen large number of genes in a timely and cost-effective manner.

In conclusion, the role of genetic factors in the pathogenesis of SRNS is being increasingly recognized in studies investigating the molecular mechanisms of the disease. These findings may pave the way for refinements in the diagnostic and prognostic testing of the disease in near future and ultimately to the targeted, molecular based therapeutics in near future.

REFERENCES