Nephrotic syndrome (NS) is a clinical syndrome characterized by heavy proteinuria, with consequent oedema, hypoalbuminaemia and hyperlipidaemia. It is the most frequent presenting feature of various glomerular diseases in both children and adults. There are no population based data on the incidence and prevalence of the disorder in Pakistani children. It constituted the most common indication of renal biopsies in a large series of renal biopsies performed on children with medical renal diseases at our center. The exact cause and pathogenesis of idiopathic NS (INS) in children still remain incompletely understood. The histopathological lesions underlying INS vary depending on different presenting characteristics of the syndrome, such as, age, ethnicity, and response to steroid therapy. In children, INS is mostly caused by minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) or mesangial proliferative glomerulonephritis (MesPGN). According to our earlier study, MCD and its variants are the leading cause of INS in children (43% of cases) followed by FSGS (38% of cases). The latter is the predominant pathological presentation in steroid-resistant NS (SRNS) and adolescent NS.

The clinical syndrome of NS has been classified in different ways. Its broad categorization into primary or secondary forms is of importance for proper management. The age of onset is the next important characteristic used for categorization. Based on the presenting age, childhood NS has been classified as congenital (CNS), infantile, early childhood, and adolescent types. Characterization of the disorder on the basis of underlying renal glomerular pathology is also important. Another commonly used classification is on the basis of initial response to corticosteroids as steroid-dependant (SDNS) and SRNS. Lastly, in the past two decades, the identification of genetic causes of NS has further contributed to the heterogeneity of the disorder. Results from these studies show that the majority of early onset INS cases have a genetic origin with a wide age of onset ranging from foetal life to early adulthood.

Many genes that are highly expressed in glomerular filtration barrier (GFB), especially the podocytes and slit diaphragms (SD), have been implicated. In a large European cohort of 89 children with INS occurring during first year of life, two thirds of the cases were attributable to mutations of one of the four genes; NPHS1, NPHS2, WT1 and LAMB2. The NPHS1 and NPHS2 genes together constituted the vast preponderance of genetic causes of NS in these children. Several other genes, including WT1, TRPC6, and ACTN4, have been implicated in the causation of NS in children and adolescents.

The NPHS1 gene encodes a podocyte transmembrane protein, nephrin, which is exclusively expressed at SD and forms the main component of the latter. Mutations in the NPHS1 gene were initially reported as the cause of vast majority of cases of CNS of "Finnish type" (CNF). The two common mutations, Finnmajor and Finminor were together found in >90% cases in Finland, and less frequently in other countries. These and many other mutations in NPHS1 account for 39-55% cases of childhood NS and 40% of all cases of CNS outside Finland indicating that this gene might cause a broad spectrum of clinical severity and age distribution in NS. It has also been suggested that NS caused by NPHS1 gene mutations constantly shows resistance to corticosteroid therapy and low recurrence after transplantation.

The NPHS2 gene encodes podocin protein, an integral podocyte membrane protein. It is exclusively expressed in podocytes, localizes to the insertion site of SD and has been shown to play a critical role in facilitating nephrin signaling. In humans, mutations in the NPHS2 cause a recessive form of SRNS with an early childhood onset of the disease and renal morphology of FSGS. The NPHS2 mutations have also been found in 51% of CNS cases of European origin and in adult onset form of FSGS. The incidence of NPHS2 mutations in familial SRNS also vary considerably from 40% in European and American children to 29% in Turkish children to no mutations in Japanese and Korean children. Our group is the first to accurately characterize the pathological lesions underlying different subsets of NS in children and adolescents in Pakistan. We are also the first to...
document the results of screening for mutations in the commonly implicated genes in NS in children in Pakistan. We identified 7 novel mutations out of 12 in NPHS1 and one novel mutation out of 2 in NPHS2 gene in a cohort of 145 children including 36 cases of congenital or infantile NS. The primary findings of this study show that mutations in the NPHS1 and NPHS2 genes are uncommon in childhood NS in our population. The observed low prevalence of these gene mutations in CNS and childhood onset NS also suggests the genetic heterogeneity of NS in our population. The results indicate that, in these children, there may be other genetic alterations that remain to be identified.6

In addition to the above monogenic causes of NS, gene polymorphisms in many other genes have also been studied for their association with the risk or progression of NS, mostly in children. Alterations in these genes may act as modifiers of the clinical course of NS. Recently, our group has also analyzed angiotensin converting enzyme (ACE) gene for insertion/deletion (I/D) polymorphism in 268 NS children. According to the results of this study, the II genotypic and allelic frequencies were found to be significantly associated with the disease in the Pakistani paediatric NS population (OR=6.755; C.I=3-14.9). No significant association was found between this polymorphism and the response to standard steroid therapy.10

In conclusion, the discovery and study of several genes underlying NS in children have significantly improved our understanding of molecular mechanisms underlying glomerular permselectivity and proteinuria. Many of the genes that were originally identified in rare forms of hereditary NS appear to be more broadly involved in the modulation of susceptibility to glomerular injury and proteinuria. A better understanding of these molecular mechanisms of the disease will be helpful in developing targeted therapies against the disease. Screening for the common genetic causes of NS will prevent unnecessary steroid therapy of these children.

References