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COMMENTARY

Genetic Testing Comes of Age: *WT1* Mutations in Steroid-Resistant Nephrotic Syndrome

Commentary on the article by Mucha *et al.* on page 325

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Nephrotic syndrome is a pathologic entity characterized by massive loss of protein in the urine, hypoalbuminemia, and edema. It constitutes one of the most common diagnoses made in pediatric nephrology (1). About 90% of all children with sporadic nephrotic syndrome, meaning nephrotic syndrome not associated with a positive family history, respond to steroid treatment (2). Unfortunately, the remaining steroid-resistant patients are at high risk for adverse effects of the required invasive drug therapy and prone to develop progressive disease, and renal failure. End-stage renal disease, requiring dialysis or transplantation therapy, occurs in a large number of these patients which places an enormous burden on these children and poses a huge challenge for the caring physicians and families (3). Thus, it comes as no surprise that the recent identification of genes involved in the pathogenesis of steroid-resistant nephrotic syndrome (SRNS) has generated a great deal of interest. It is now clear that mutations in genes encoding for proteins of the podocyte, the visceral epithelial cell of the kidney glomerulus, can cause nephrotic syndrome (4). *NPHS1*, encoding the podocyte protein nephrin, has been identified as the responsible gene in congenital nephrotic syndrome of the Finnish type (5). Podocin (6), α-actinin-4 (7), TRPC6 (8,9), and CD2AP (10) are all components of the podocyte foot processes that have been discovered subsequently through genetic approaches. Mutations in these genes cause focal-segmental glomerulosclerosis and proteinuria resistant to the treatment with corticosteroids. In fact, it is now getting clear that a majority of SRNS cases may have a genetic basis. I.e., mutations in the podocin-coding gene *NPHS2* account for about 20% of cases with sporadic SRNS (11–14).

Mutations in the Wilms' tumor predisposing gene *WT1* now join *NPHS2* as an important gene involved in the pathogenesis of sporadic SRNS. The study by Mucha and the APN investigators in this issue together with previous work from the same investigators shows that mutations in *WT1* account for sporadic SRNS in almost 10% of cases (15,16). *WT1*, the first gene found to be inactivated in Wilms' tumor, or nephroblastoma (17) encodes a zinc finger transcription factor that functions both as tumor suppressor (18) and as critical regulator of kidney and gonad development (19). This protein is expressed in a tightly regulated pattern within the embryonic kidney and is essential for renal development in mice (20). Germline deletions or mutations of *WT1* have been linked to WAGR (Wilms' tumor, aniridia, genitourinary abnormalities and mental retardation) syndrome (21,22), Drash syndrome (23) and Frasier syndrome (24). Mucha *et al.* now show that *WT1* mutations also have to be considered in patients with sporadic, nonsyndromic SRNS (15). All mutations in this study localized to exons 8 and 9 of *WT1* and patients with *WT1*-associated SRNS predominantly displayed primary focal and segmental glomerulosclerosis on kidney biopsy.

This study has important implications: The authors clearly show in a large cohort of SRNS patients that dominant *de novo* mutations of *WT1* account for a considerable number of SRNS cases in phenotypically female patients. Since these mutations can be associated with genitourinary malformations, male pseudohermaphroditism and tumorigenesis in offspring of these patients testing for *WT1* mutations should be included in the genetic work up and is required for genetic counseling. Pathogenic mutations exclusively localized to exons 8 and 9 of the *WT1* gene. Although intronic mutations could not be excluded in this study, these data indicate that screening of *WT1* exons 8 and 9 in patients with sporadic SRNS may be sufficient. Taken together, these data suggest that, in addition to screening all SRNS patients for *NPHS2* mutations, phenotypically female SRNS patients or male SRNS patients with genitourinary abnormalities should be readily screened for mutations in *WT1* exons 8 and 9.

The past several years have witnessed important advances in understanding the molecular basis of nephrotic syndrome and the importance of the glomerular podocyte for the function of the glomerular filter of the kidney (25,26). The recent emergence of the podocyte as the culprit in nephrotic syndrome has raised new hope for developing rational treatment strategies and provided novel diagnostic tools for the screening of SRNS-associated gene mutations (27,28). This rapidly increasing

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knowledge about the molecular genetics of nephrotic syndrome will not only help to identify novel therapeutic targets for patients with nephrotic syndrome but will soon allow predictions about whether a child will respond to invasive treatment strategies. Therefore, genetic testing is mandatory in all children with SRNS and has a huge promise for the future. Genetic testing comes of age: future is now.

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