Genotype–Phenotype Correlations: Filling the Void

Afshin Parsa

Department of Nephrology, University of Maryland School of Medicine, Baltimore, Maryland

Classical Mendelian genetics often conjure the image of a well-defined mutation in the DNA sequence that causes a disruption in gene function and characteristic phenotype. However, Mendelian traits can often behave like complex disease traits. One level of complexity is that even a specific mutation may be associated with a wide spectrum of symptoms, with expression perhaps modified by the effects of other genes and/or environmental factors. Another source of phenotypic variation can arise from the fact that there may be multiple functional mutations in the same gene, each associated with its own set of symptoms depending on the effects of the mutation on altering gene product or function. For example, depending on the mutation type, there may be either total or partial loss or gain of function. In addition, many genes have multiple isoforms. Under this premise, the location and consequence of the mutation can differentially affect the various isoforms, resulting in variable aberrations of multiple gene products. This mutational diversity has limited our ability to diagnose diseases with primarily genetic causes, as well as to predict their natural histories.

In this issue of CJASN, Chernin et al. (1) present an extensive analysis of the genotype–phenotype correlation in steroid-resistant nephrotic syndrome (SRNS) caused by Wilms’ tumor–suppressor gene 1 (WT1) mutations, adding to our understanding of the complex association between WT1 mutations and associated renal phenotypes. This study comprises the largest case series yet reported of WT1 mutation–related SRNS and provides important confirmation of the role of the mutation type in WT1–associated phenotypes. Most important, by focusing on the prediction of developing Wilms’ tumor (WT), in nonsyndromic cases, this study helps to improve our prognostic ability and hence allows further refinement of clinical management.

WT1 gene encodes a zinc finger protein with alternative splicing resulting in at least four isoforms. The isoforms are due to the insertion of three amino acids (KTS) between zinc fingers 3 and 4 and the insertion alternatively spliced segment encoded by exon 5 (2). The isoforms can affect transcriptional and post-transcriptional activity as activators or repressors depending on the cellular context (2). WT1 is initially expressed primarily in the embryonic mesonephric kidney, then in the maturing podocytes, and to a lesser extent in the visceral epithelial cells (3). The resultant transcription factors influence kidney and urogenital tract development. In addition, there is some expression in other organs, notably the hematopoietic system, where it has been associated with a variety of malignancies (4). To date, WT1 mutations have been associated with three renal-related clinical syndromes, often presenting in the first decade of life: (1) Frasier syndrome (FS), which is characterized by SRNS in childhood with histologic findings of FSGS and often slow progression to ESRD in the second or third decade of life, male pseudohermaphroditism, and a high incidence of gonadoblastomas (OMIM 136680); (2) Denys-Drash syndrome (DDS), which is characterized by infantile SRNS with histologic findings of mesangial sclerosis with rapid progression to ESRD usually by age 4, ambiguous genitalia, and WT (OMIM 194080); and (3) isolated SRNS (OMIM 256370). In light of the high incidence of gonadoblastoma and WT in FS and DDS, respectively, prophylactic oophorectomies and nephrectomies have been advocated and practiced (5,6). A most difficult clinical decision pertains to individuals with SRNS as a result of WT1 mutations and without clinical evidence of FS or DDS. Should prophylactic bilateral nephrectomy be considered in such individuals?

The findings of Chernin et al. (1) largely confirm previous observations but then provide a more robust platform for decision making regarding the degree of surveillance and consideration for bilateral nephrectomy in such individuals. In their study, they found that all patients with nonsense mutations developed WT. In contrast, missense mutation caused WT in some but not all patients, whereas patients with KTS mutations and isolated SRNS did not develop WT. Drawing on these observations, the authors provide a flow chart to help decide clinical management on the basis of type of mutation and initial clinical presentation. Although a case series of 52 does not provide sufficient data for clinical certainty, it does provide a solid foundation on how to categorize risk broadly and is a welcome addition to the existing literature on WT1 mutations, notably in patients with isolated SRNS.

Chernin et al. (1) selectively sequenced only exons 8 and 9 of the WT1 gene. The reasoning behind this choice centered on previous findings that almost all identified WT1 mutations have been in these two regions (7). Although such selective sequencing might have previously been necessary because of practical limitations, the rapid progress of this technology (e.g., NextGen sequencing) and its decreasing cost make exome and
likely soon full genome sequencing of such individuals not only feasible but also arguably practical. Whereas the first human sequencing came at a cost of $3 billion, within a decade, the targeted $1000 genome seems to be within near reach. Bearing these advancements in mind, we can proceed beyond targeted sequencing and toward more comprehensive sequencing of SRNS and other disorders with suspected underlying Mendelian mutations. The recent identification of the Miller syndrome gene provides a good example of how newer technology can greatly facilitate further gene mutation discovery beyond what has been successfully accomplished with positional cloning (8). This needed extra information will allow us not only to better define genotype–phenotype associations for WT1 and other causes of SRNS in children and adults but also to explore and identify gene interactions that are responsible for some of the significant clinical heterogeneity of many Mendelian syndromes. Initial efforts can be targeted at the currently known WT1 target genes and genes with overlapping phenotypes, which are most likely to provide identifiable epistatic interactions, distinct from potential environmental effect modifiers.

As our ability to uncover and study DNA sequences has increased at a dizzying pace, our oversimplified concepts of genetic regulation and genotype–phenotype associations have been challenged. A nice summary of our evolving theories and understanding of the amazing complexity of genetic regulation along with a suggested updated definition of a gene was put forth by Gerstein et al. (9) on behalf of the ENCODE consortium.

The interaction of WT1 with its many targets at different points during development and throughout life would be expected to have a significant role in determining the variable phenotype noted with WT1, as with many other gene mutations. Genetic modifiers of other Mendelian disorders have been shown in numerous disorders, including polycystic kidney disease (10). In summary, although the extended sequencing and phenotyping will undoubtedly continue to shed light on genotype–phenotype associations, further study of interacting proteins and environmental modifying factors will often be necessary before we can reliably predict phenotype on the basis of genotype, not just for complex traits, but also in Mendelian diseases. As we move forward, we should remain cognizant that our earlier common teaching of the direct relationship between genetic sequence and phenotype contains a sizable gap and that we need to view single gene allelic variability as one of several factors that jointly determine phenotypes. Perhaps then we might move closer to our longstanding goal of understanding the highly dynamic genotype–phenotype relationship.

**Disclosures**

None.

**References**