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A Newly Identified Mutation in the WT1 Gene in Denys-Drash Syndrome

Denys-Drash Sendromunda WT1 Geninde Yeni Tanımlanan Bir Mutasyon

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ABSTRACT

Denys-Drash syndrome (DDS) is a rare autosomal dominant disorder characterized by genital abnormalities, nephropathy, and Wilms' tumor (WT), typically caused by heterozygous mutations in the Wilms' tumor suppressor 1 (WT1) gene. Here, a 2-year-old male admitted with fever and abdominal pain was presented. Physical examination revealed ambiguous genitalia and a palpable abdominal mass. Imaging identified a heterogeneous mass in the left kidney, consistent with WT. Genetic analysis detected a novel heterozygous frameshift mutation in exon 8 of the WT1 gene [p.H245Tfs*2 (c.1393delC)]. WT is the most common renal tumor in children and is frequently associated with WT1 gene mutations in DDS. Given the early onset and severity of symptoms, early genetic screening for WT1 gene mutations should be considered in patients admitted with ambiguous genitalia and nephrotic syndrome. This case contributes to the understanding of WT1 gene mutations and highlights the importance of molecular analysis in children with genitourinary anomalies.
Keywords: Ambiguous genitalia; Denys-Drash syndrome; WT1 gene.

ÖZ

Denys-Drash sendromu (DDS), genital anormallikler, nefropati ve Wilms tümörü (WT) ile karakterize, tipik olarak Wilms tümör baskılayıcı 1 (WT1) genindeki heterozigot mutasyonların neden olduğu nadir görülen otozomal dominant bir hastalıktır. Bu yazıda ateş ve karın ağrısı ile başvuran 2 yaşında bir erkek hasta sunulmuştur. Fizik muayenede belirsiz genital organlar ve karında ele gelen bir kitle saptandı. Görüntülemede sol böbrekte WT ile uyumlu heterojen bir kitle tespit edildi. Genetik analizde WT1 geninin 8. ekzonunda yeni bir heterozigot çerçeve kayması mutasyonu tespit edildi [p.H245Tfs*2 (c.1393delC)]. WT çocuklarda en sık görülen böbrek tümörüdür ve DDS'de sıklıkla WT1 gen mutasyonları ile ilişkilidir. Semptomların erken başlangıcı ve ciddiyeti göz önüne alındığında, belirsiz genital organlar ve nefrotik sendrom ile başvuran hastalarda WT1 gen mutasyonları için erken genetik tarama düşünülmelidir. Bu vaka, WT1 gen mutasyonlarının anlaşılmasına katkıda bulunmakta ve genitoüriner anomalileri olan çocuklarda moleküler analizin önemini vurgulamaktadır.
Anahtar kelimeler: Ambigus genitalya; Denys-Drash sendromu; WT1 geni.

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INTRODUCTION

Denys-Drash syndrome (DDS) is a rare inherited disorder with an autosomal dominant transmission pattern. The majority of patients present with early-onset nephropathy accompanied by 46,XY disorders of sex development and an increased risk of developing Wilms' tumor (WT) (1). Approximately 90% of cases of DDS are

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characterized by heterozygous mutations in the Wilms' tumor suppressor 1 (WT1) gene (2,3).

The WT1 gene spans 50 kb and comprises 10 exons. It is located on chromosome 11 (4). The gene was first described in 1990 (5), and since then, several novel mutations have been reported (6,7). Additional studies have described atypical or milder phenotypes associated with newly identified WT1 gene variants (8,9). The WT1 gene is essential for the development of the genitourinary system, and pathogenic variants of this gene have been linked to conditions such as DDS and Frasier syndrome (10). Moreover, the involvement of the WT1 gene in gonadal development and disorders of sex development has also been emphasized in recent literature (11).

During the neonatal period, DDS typically presents with ambiguous genitalia (10). Most individuals with a 46,XY karyotype exhibit signs such as bilateral cryptorchidism, hypospadias, or a phenotypically female appearance (12). Renal involvement generally appears in the first year of life, often within the first 12 months (10), and kidney biopsies commonly reveal mesangial sclerosis (13). Clinical manifestations frequently include nephrotic syndrome or progressive renal failure, usually emerging between two months and two years of age. In DDS, WT is often detected at an earlier age than in the general population, primarily due to specific WT1 gene mutations (12).

Here, a child with DDS carrying a previously undescribed WT1 gene frameshift mutation [p.H245Tfs*2 (c.1393delC)] was presented, contributing to the understanding of genotype-phenotype correlations and emphasizing the importance of molecular analysis in patients with genitourinary anomalies.

CASE REPORT

The patient initially presented at 6 months of age to another center with nephrotic-range proteinuria and edema. A kidney biopsy performed at that time revealed diffuse mesangial sclerosis, and corticosteroid therapy was initiated. A partial response was achieved; however, complete remission was not obtained. Genetic analysis was not performed at that stage due to technical limitations. The family subsequently discontinued both medical follow-up and steroid therapy. At 28 months of age, the patient was admitted to our center with a 20-day history of persistent fever and abdominal pain. On physical examination, a palpable mass was detected in the left lower abdominal quadrant, and the patient exhibited ambiguous genitalia. Ophthalmologic evaluation was within normal limits, and no signs of neurodevelopmental delay were observed. Urinalysis demonstrated 4+ proteinuria.

Doppler ultrasonography revealed a 5x6 cm heterogeneous mass in the left kidney, consistent with WT. Further imaging with computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) revealed hepatic and pulmonary metastases. Based on the criteria of the National Wilms' Tumor Study-5 (NWTS-5), the disease was classified as stage 4 (14).

The patient subsequently underwent a left nephrectomy for WT, followed by chemotherapy. During follow-up, progressive renal dysfunction developed, and hemodialysis was initiated. The patient later experienced febrile neutropenia during chemotherapy and radiotherapy and subsequently succumbed to sepsis.

Genetic analysis identified a previously undescribed heterozygous frameshift mutation in exon 8 of the WT1 gene, designated as p.H245Tfs*2 (c.1393delC), as illustrated in Figure 1. This mutation introduces a premature stop codon two residues downstream of the altered amino acid at position 245, resulting in the synthesis of a truncated WT1 protein.

Written informed consent was obtained from the patient's legal guardian for publication and image use.

DISCUSSION

In this report, a patient diagnosed with DDS, characterized by ambiguous genitalia, early-onset proteinuria, renal insufficiency, diffuse mesangial sclerosis on kidney biopsy, and the development of WT, was presented.

WT is the most common renal malignancy in children, with approximately 80% of cases diagnosed before the age of five (11). Characteristic findings in DDS include genital abnormalities, nephrotic syndrome, and diffuse or focal mesangial sclerosis (10). In most cases, renal failure develops by the age of three, and the risk of WT is markedly increased (1,15).

In our patient, nephropathy presented at 6 months of age with diffuse mesangial sclerosis and steroid resistance, followed by WT with metastatic spread at 28 months. This severe clinical course is consistent with the aggressive phenotype frequently associated with structural mutations in the WT1 gene. Previous studies have shown that missense mutations in exons 8 and 9 of the WT1 gene are the most frequent alterations in DDS, while frameshift and nonsense variants, though less common, may be linked to more severe phenotypic manifestations and rapid progression to end-stage renal disease (16,17). Our case supports this genotype-phenotype correlation, as the novel frameshift mutation p.H245Tfs*2 (c.1393delC) was associated with early nephropathy, steroid resistance, and early-onset WT.

These findings emphasize the importance of early genetic testing in patients with ambiguous genitalia and nephrotic syndrome. Identification of WT1 gene mutations at an early

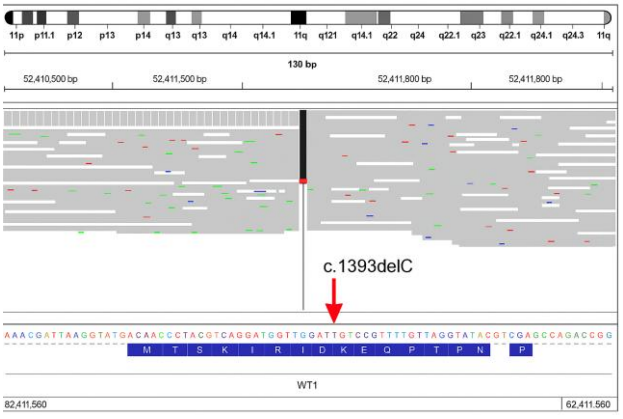


Figure 1. Visualization of a novel heterozygous frameshift mutation in exon 8 of the WT1 gene [p.H245Tfs*2 (c.1393delC)] using next-generation sequencing. The deleted nucleotide (c.1393delC) is indicated by a red arrow. This deletion introduces a premature stop codon two residues downstream of the altered amino acid at position 245, resulting in the synthesis of a truncated WT1 protein

stage could allow closer monitoring, timely diagnosis of tumor development, and more informed management strategies.

Several factors may account for the severe clinical presentation observed in our patient, including the rapid disease progression, the disruptive nature of the frameshift mutation, and possible involvement of downstream signaling pathways. Prophylactic nephrectomy may be considered only in selected cases after the development of chronic kidney disease; therefore, careful patient selection is crucial. Prompt genetic screening for WT1 gene mutations should be considered in patients presenting with nephrotic syndrome and disorders of sex development. Further genetic studies involving larger cohorts are warranted to identify novel mutations and enhance our understanding of the molecular pathogenesis of DDS.

CONCLUSION

In conclusion, we report a novel heterozygous WT1 gene frameshift mutation associated with DDS. This case highlights the importance of early genetic screening in patients presenting with ambiguous genitalia and nephrotic syndrome. Timely molecular diagnosis may guide clinical management and facilitate appropriate follow-up. Further studies are needed to clarify the clinical impact of newly identified WT1 gene variants.

Informed Consent: Written informed consent was obtained from the patient for publication and accompanying images.

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