Discordant phenotypes in monozygotic twins with identical de novo WT1 mutation

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Abstract
Mutations in the WT1 gene, leading to Denys-Drash syndrome and Frasier syndrome, can also cause isolated steroid-resistant nephrotic syndrome (ISRNS). Previous studies have reported six pairs of monozygotic twins with WT1 mutations, including one presenting with discordant phenotypes with identical WT1 mutations being of paternal origin and five pairs of monozygotic twins presenting the same phenotype with identical WT1 mutations. In this study, we report on female monozygotic twins showing discordant phenotypes with an identical de novo WT1 mutation, R394W, and presenting incomplete Denys-Drash syndrome and ISRNS.

Keywords: Denys-Drash syndrome; steroid-resistant nephrotic syndrome; WT1

Background
The WT1 gene, located on chromosome 11p13, plays a crucial role in kidney and genital system development [1]. Recent studies have demonstrated that mutations in WT1, leading to Frasier syndrome and Denys-Drash syndrome (DDS), can also cause isolated steroid-resistant nephrotic syndrome (ISRNS) [2]. Incomplete DDS is characterized as a nephrotic syndrome associated with Wilms' tumor or male pseudohermaphroditism [3]. A previous study has reported one pair of monozygotic twins presenting discordant phenotypes with identical WT1 mutations being of paternal origin [4]. Here, we report on discordant phenotypes in monozygotic twins with identical de novo WT1 mutations.

Case reports
Female monozygotic twins having very similar appearances and only one placenta were observed. Both twins had normal female phenotypes and karyotype 46, XX. Urinalyses of their parents and older sister were normal.

Twin A (Figure 1 (III4)) was admitted to the Department of Pediatrics, Fuzhou Dongfang Hospital, P. R. China for evaluation of edema at the age of two. A urine dipstick revealed 3+ albumin. Serum albumin was 22.8 g/L and creatinine 48 μmol/L. She failed to respond to 6 weeks of prednisone therapy (2 mg/kg/24 h). At the age of 3.49 years, she also presented with a right abdominal mass. Kidney ultrasound revealed a 9.85 cm by 8.32 cm Wilms' tumor in the right kidney, confirmed by computed tomography scan (Figure 2). She was diagnosed with incomplete DDS and died at the age of 3.50 years due to renal failure.

Twin B (Figure 1 (III5)) was examined at the age of two. Physical examination was unremarkable. A urine dipstick revealed 3+ albumin. Serum albumin was 25.3 g/L and creatinine 36 μmol/L. No therapeutic provision was implemented then because her parents refused to accept medical decision. She initially presented with eyelid edema at the age of 4.02 years. A urine dipstick revealed 3+ albumin. Serum albumin was 22 g/L and creatinine 42 μmol/L. She failed to respond to standard steroid therapy and was diagnosed with ISRNS. She had not displayed Wilms' tumor by kidney ultrasound by the age of 5.14 years, though her serum creatinine had increased to 66 μmol/L. She is now 5.85 years old and has not yet displayed Wilms' tumor, verified by both kidney ultrasound and computed tomography scan. Serum creatinine is 153 μmol/L.

With the subjects' informed consent, samples of blood were obtained for genetic analysis. A heterozygous variant in Exon 9 of WT1, 1180C > T, leading to an arginine to tryptophan substitution (R394W), was identified in both twins, whereas it was not found in 50 controls or the twins' parents or older sister. Three WT1 polymorphisms, 126C > T, 903A > G and IVS7–32C > A, were also found in the twins.

Discussion
In this study, we identified an identical de novo heterozygous WT1 mutation, R394W, in monozygotic twins presenting with incomplete DDS and ISRNS, which was not observed in the parents. Previous studies have reported WT1 mutation R394W can cause DDS or ISRNS [5]; therefore, we considered this mutation to be responsible for the phenotypes observed in the twins.

The twins, having very similar appearances, had only one placenta and three WT1 polymorphisms, 126C > T,
The twins possessed the same genotype and showed discordant phenotypes. Twin A presented with ISRNS at the age of 2 and developed unilateral Wilms’ tumor at the age of 3.49. Twin B presented with ISRNS at the age of 4.02 and did not present with any renal tumors at the last follow-up when she was 5.85.

The possible reason for our observations is that discordant phenotypes in our twins with identical WT1 mutation R394W could be associated with the ‘two-hit’ mutational model of Wilms’ tumorigenesis [6]. Although the onset age of Wilms’ tumor in DDS patients with WT1 mutation R394W was from 0.3 to 2.7 years [5, 7, 8], we will still continue a clinical follow-up and make a prompt report if Wilms’ tumor will appear in Twin B.

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Conflict of interest statement. None declared.

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