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Case Report: 2-Year-old With Wilms Tumors, Familial Heterozygous *DIS3L2* Mutation, and Cutis Marmorata Telangiectatica Congenita

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Summary: Biallelic variants in DI3SL2 cause Perlman Syndrome, associated increased risk for Wilms tumor. Cutis Marmorata Telangiectatica Congenita (CMTC) is a rare congenital disorder characterized by cutaneous vascular anomalies. We report a 2-year-old boy with both Wilms tumor and CMTC. Genetic testing, prompted by his complex presentation, revealed 1 somatic mutation and 1 familial germline mutation in the *DIS3L2* gene, suggesting a 2-hit causation of Wilms tumor. Separately, a single *GNA11* somatic mutation was identified to explain the CMTC. We suggest that genetic testing for germline mutations associated with Wilms tumor susceptibility be considered even in cases without known family history.

Key Words: Perlman syndrome, Wilms tumor, CMTC, *DIS3L2*, *GNA11*

(*J Pediatr Hematol Oncol* 2023;45:e128–e130)

Wilms tumor, typically diagnosed before 5 years of age, is the most common renal malignancy in children.[1] It can be isolated or occur as a feature of multiple genetic overgrowth syndromes including Beckwith-Wiedemann Syndrome and Perlman Syndrome. Individuals with Perlman Syndrome typically have macrosomia, characteristic dysmorphic features (deep-set eyes, prominent forehead, inverted V-shaped upper lip, broad flat nasal bridge, and low set ears), hypotonia, renal anomalies, neurodevelopmental delay, a very elevated risk for Wilms tumor, and high neonatal mortality.[2]

As an autosomal recessive condition, Perlman Syndrome requires two germline mutations to occur, 1 in each allele of the *DIS3L2* gene.[2] The DIS3L2 protein is known to play an important role in kidney development, and mutations in the gene have been associated with disrupted miRNA processing and intracellular calcium homeostasis, predisposing to Wilms tumor formation.[3,4] In addition, the DIS3L2 protein has exonuclease activity which assists in creating appropriate mitotic checkpoint proteins.[5] Loss-of-function mutations in *DIS3L2* result in abnormal RNA metabolism. Cell proliferation plays a critical component in human tissue growth, regeneration, and wound healing.[6] This has been investigated using human kidney cells and the genetic model organism, *Drosophila melanogaster*, to show the absence of DIS3L2 protein leads to an increase in the PI3-Kinase/AKT signaling pathway which results in abnormal cell proliferation.[6] The dysregulation and proliferation of errors in the cell cycle can lead to cancer.[6]

Cutis Marmorata Telangiectatica Congenita (CMTC) is a rare congenital disorder characterized by localized or generalized cutaneous vascular anomalies, which may dissipate over time.[7,8] The skin findings are characterized by persistent reticulated marbled erythema and are often associated with cutaneous atrophy, ulcerations, and body asymmetry.[7,8] The genetics of CMTC and its associated findings are continuing to be elucidated. Genetic mutations associated with CMTC typically are postzygotic somatic mutations.

We describe a 2-year-old boy who had both a Wilms tumor and CMTC who was found to have 2 *DIS3L2* mutations, 1 somatic and 1 familial germline mutation that likely explain his Wilms tumor diagnosis. In addition, a single *GNA11* somatic mutation was identified to explain his diagnosis of CMTC. This study was approved by the Institutional Review Board at University Hospitals (STUDY20210117).

CASE REPORT

The patient was born at 39 weeks of gestation. Birth parameters were: 3.02 kg (10th to 50th percentile; head circumference measuring 33 cm (10th to 50th percentile); and length 51 cm (50th to 90th percentile). His Apgar score was 9 at 1 minute and at 5 minutes. In addition, he was noted to have a harlequin color change and spent 7 days in the NICU for hypoglycemia, temperature dysregulation, and bradycardia. These symptoms spontaneously resolved on their own. There was initial concern about possible craniosynostosis at birth because of diagnosis of a single Wormian bone and right sided plagiocephaly, but it was later determined that he only had some premature closure of sutures not requiring treatment. He was noted to have cryptorchidism at birth, but this resolved by 3 months of age. He was diagnosed with hypospadias at 10 days of age and a bifurcated urethra was identified, but this did not require surgical intervention. Pediatric cardiology was consulted, and an echocardiogram was reassuring. An aberrant right subclavian vessel, believed to be an artery, was diagnosed incidentally on a modified barium swallow ordered for a choking concern and failure to thrive. Finally, a diagnosis of CMTC was made by his pediatrician and a pediatric dermatologist because of mottling unresponsive to full body warming. Because of his multiple seemingly unrelated concerns, a genetics evaluation was conducted, and a chromosomal microarray sent. This testing was normal.

The patient was then evaluated at 2 years of age at Rainbow Babies & Children's Hospital in March 2020 after his father noted a right sided abdominal mass. A bilateral renal ultrasound diagnosed

Received for publication January 17, 2022; accepted May 16, 2022.
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The authors declare no conflict of interest.
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DOI: 10.1097/MPH.0000000000002498

a right sided Wilms tumor. The left kidney appeared normal. He underwent a right radical nephrectomy and adrenalectomy, and a skin biopsy was taken for further genetic testing. An area of nephrogenic rest (triphasic) was seen separate from the Wilms tumor on histopathology.

A genetics consult was requested to rule out possible genetic etiologies for his Wilms tumor. Physical exam noted some minor dysmorphic features including a slightly long face, micrognathia, and right occipital plagiocephaly (right ear displaced anteriorly). DNA from a blood sample was tested for Beckwith-Wiedemann Syndrome (BWS), including *CDKN1C* sequencing and deletion/duplication analysis (Invitae), and chromosome 11p15 methylation studies (Mayo Clinic Laboratory). Both were negative. He also was tested with a 7-gene Wilms tumor panel at Invitae that was notable for 2 findings. There was a heterozygous pathogenic mutation in *DIS3L2* c.695C > G (p.Ser232*) (NM_152383.4), and there was a heterozygous variant of unknown significance in *WT1* c.431C > G (p.Pro144Arg) (NM_024426.4).

Subsequently, his father was found to have the pathogenic *DIS3L2* mutation, while his unaffected mother had the WT1 variant of uncertain significance, suggesting it may be benign. One sister was also found to have the familial pathogenic *DIS3L2* mutation. The familial *DIS3L2* mutation was also identified in the patient's paternal grandfather, and then in other paternal relatives (Fig. 1).

A sample of the patient's Wilms tumor was sent to TEMPUS (648 genes tested), which not surprisingly identified both the *DIS3L2* and the *WT1* variants previously found on germline testing. However, the variant allele frequency of the *DIS3L2* mutation in the tumor was 97%, indicating a likely deletion of the second copy of the *DIS3L2* gene, or loss of heterozygosity in the tumor. Not suspected to be pathogenic, the variant allele frequency of the variant of unknown significance in the *WT1* gene was identified to be of similar frequency (~45%) in both the germline and in the tumor. No additional mutations were identified on somatic testing that were thought to be significant. In addition, it is unknown whether the nephrogenic rest area contained only a germline mutation or a second hit.

Concurrently, to evaluate possible genetic causes that would explain both the Wilms tumor and the CMTC diagnosis, fibroblasts from the skin biopsy and a blood sample were sent for genetic testing at Washington University, St. Louis. This included sequencing for *PIK3CA*-related overgrowth syndromes because of some rare reports of an association of CMTC and Wilms tumor,[9,10] despite the patient not showing the typical manifestations of *PIK3CA*-related overgrowth syndrome. This testing was negative. Reflex genetic testing in the context of CMTC was completed at Washington University, St. Louis, and a likely pathogenic mutation in *GNA11* (p.R183H) was detected. The lab classified the *GNA11* mutation as likely somatic in origin because of the allelic fraction in the skin biopsy, and the absence of the mutation in the blood specimen.

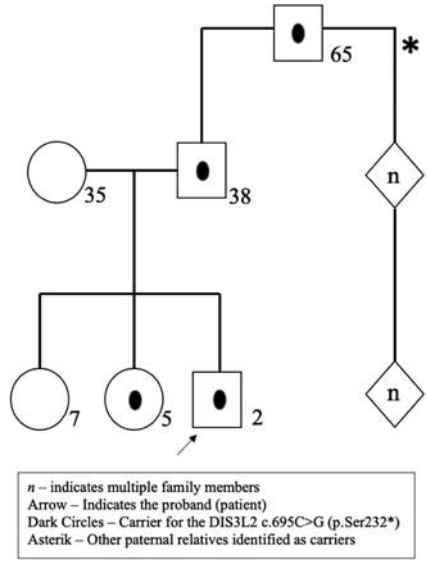

FIGURE 1. A pedigree detailing the familial *DIS3L2* mutation tracking throughout the family.

DISCUSSION

Despite initial concern for a unifying syndrome, this 2-year-old boy was found to have 2 distinct genetic explanations for his clinical features. The Wilms tumor is likely because of mutations in *DIS3L2*, 1 germline point mutation and 1 somatic loss of the normal allele. *DIS3L2* is associated with Perlman syndrome when 2 germline mutations are present. In our patient, genetic testing revealed that he is only a carrier for Perlman syndrome.

The prevalence of Perlman Syndrome is ~1 in 1 million,[11] and the carrier frequency is about 1 in 500 individuals, assuming Hardy-Weinberg equilibrium. The risk for developing Wilms tumor in Perlman Syndrome is ~55%, and bilateral renal tumors are common.[5] There has been limited research on the Wilms tumor risk for patients who are only carriers for Perlman Syndrome. One study identified a *DIS3L2* mutation in 3 of 53 studied Wilms tumor patients.[3] One individual, like this boy, was confirmed to have a second hit in the tumor (ie, became apparently homozygous in tumor).[3] Therefore, risks for those found to carry 1 *DIS3L2* mutation are currently unknown, but are likely not as high as those with 2 *DIS3L2* mutations. Germline *DIS3L2* mutations may be overrepresented in the population of patients with Wilms tumor, however, based on their frequency in the previous study.

DIS3L2 is a tumor suppressor gene.[12] In our patient, there was a second random, somatic loss of the second copy of the gene in tumor cells, which we suspect is responsible for the patient's Wilms tumor diagnosis. This theory is consistent with the idea of the 2-hit hypothesis for tumor development.[13] In our patient's family, both his father and grandfather are known *DIS3L2* carriers without a personal history of Wilms tumor. *DIS3L2* mutation carriers are not known to have additional cancer risks outside of the development of Wilms tumor.

Because our patient and his sister are in the age-range typical for development of Wilms tumor, we are following them using current Beckwith-Wiedemann guidelines for Wilms tumor screening, as these guidelines are most often extrapolated to those with other overgrowth syndromes.[14]

Although there was initial suspicion for a unifying genetic syndrome, our patient's CMTC appears to have a separate genetic cause, attributed to the likely pathogenic somatic mutation in *GNA11*. There have been no observed connections between *GNA11* mutations and the development of Wilms tumor in the medical literature. Our patient's particular mutation in *GNA11* has previously been described with CMTC, in association with Phakomatosis Pigmentovascularis, which is associated with port wine stains and additional skin findings including café-au-lait spots and melanocytosis.[15,16] Our patient does not have any of these additional skin findings upon clinical examination.

We do not suspect that the *DIS3L2* mutation is related to any of the patient's features aside from the Wilms tumor, because of the absence of reports of congenital anomalies associated with the carrier status of Perlman Syndrome. We do not have an explanation for all the patient's minor anomalies, but many are nonspecific and do not suggest a recognizable genetic syndrome. The patient is currently healthy.

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CONCLUSIONS

The need for genetic evaluation for children with Wilms tumor has long been recognized when a syndrome is suspected, or in familial cases. In this patient, concern for a syndromic presentation prompted extensive testing, but ultimately the Wilms tumor and skin findings were determined to have separate etiologies. Even when not part of a syndromic presentation, the same genes may be involved in the pathogenesis of Wilms tumor through a 2-hit model, so testing should be considered even in apparently nonsyndromic cases (particularly true when a nephrogenic rest is identified on pathology). In retrospect, the nephrogenic rests may have been a clue to the genetic findings, but the remainder of the clinical phenotype, we suspect to be unrelated to *DIS3L2*. Thus, he may be considered as having nonsyndromic Wilms tumor. More research dedicated to clarifying the role of germline monoallelic *D1S3L2* mutations in the development of Wilms tumor and the magnitude of risk is needed. In addition, this case reinforces that not all clinical symptoms can be linked and placed into a unifying diagnosis. This is evident by this patient who inherited 1 germline mutation and acquired 2 random somatic mutations, despite no specific mutagenic exposures.

Addendum

While this manuscript was in revision, Hol and colleagues published a report noting genetic or epigenetic predisposing factors in one-third of their sample of 126 patients with Wilms tumor.[17] This included 5 patients (4%) with a constitutional mutation in DIS2L3, and 4 of 5 of these tumors were confirmed to have a second somatic hit.[17] This lends additional support to the concept of DIS2L3 as a recurrent predisposing factor for which apparently nonsyndromic cases should be tested.

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