We report a case of a 34-week-gestation male infant with prenatal overgrowth born to a 19-year-old G1P0 mother. No significant family history or consanguinity were reported. The infant was delivered emergently by cesarean section due to pregnancy-induced hypertension and polyhydramnios. At birth, the infant was noted to have anasarca and ascites with a massively distended abdomen and enlarged kidneys. Despite resuscitative efforts, the infant expired at one day of life. A complete autopsy demonstrated clinical and histologic features suggestive of Perlman syndrome. There were significant urinary tract abnormalities, including massive nephromegaly, hydronephrosis with megaureters, bilateral diffuse nephroblastomatosis, and renal dysplastic changes (Fig. 1). Also noted was organomegaly of the liver, spleen, and thymus. The lungs showed mild pulmonary hypoplasia with diffuse hyaline membrane disease. A skin biopsy was sent to our laboratory for genetic testing with suspicion of Perlman syndrome (mutation in DIS3L2 gene) or other potential causes for diseases with elevated cancer risk in an overgrown fetus, such as Simpson-Golabi-Behmel syndrome (GPC3). For these reasons, a comprehensive hereditary cancer panel of 130 genes (including DIS3L2) was performed.

The comprehensive hereditary cancer panel did not identify a pathogenic or likely pathogenic variant according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology germline variant classification guidelines,1 and no variants were observed in the DIS3L2 gene. However, analysis of regions with low sequence coverage on the panel discovered no sequence reads aligned to the genomic region of chr2:233028163-233028348, corresponding to exon 9 of DIS3L2 (NM_152383.4), indicating a homozygous deletion of exon 9 as visualized using Integrative Genomics Viewer (IGV) (Fig. 2A, next page). The deletion was confirmed by PCR specifically targeting DIS3L2 exon 9 using exon 6 as a positive PCR control (Fig. 2B, next page). Precise breakpoints could not be determined due to the nature of the targeted assay used. Homozygous deletions of exon 9 in DIS3L2 have been reported in multiple individuals from at least four families with Perlman syndrome2-4 and are listed in DECIPHER (#318416, https://decipher.sanger.ac.uk/). The deletion of exon 9 is predicted to result in an in-frame mRNA product, and it may be mediated by nonallelic homologous recombination between LINE-1 repeats located in the introns.3 The identification of the DIS3L2 exon 9 deletion is consistent withPerlman syndrome.
homozygous deletion is diagnostic of Perlman syndrome for the patient.

Next-generation sequencing technology allows interrogation of multiple genes in parallel to evaluate multiple variant types, including SNVs, small indels, exonic deletions/duplications, and gross copy number changes, as well as fusions and alternative splicing, through a single test, using DNA and RNA. PCR was used to confirm the exon 9 homozygous deletion in this case since we knew what we were looking for; however, this method would have had limited utility as a first-line test because it cannot detect the same spectrum of variants in as many genes as can NGS-based tests.

Perlman syndrome, first described in the 1970s, is a rare, autosomal recessive overgrowth syndrome that can present prenatally with fetal macrosomia and polyhydramnios. Patients also show characteristic dysmorphic facial features, including deep-set eyes, low-set ears, inverted V-shaped upper lip, prominent forehead, and a broad, flat nasal bridge. There is a high rate of neonatal mortality in patients with Perlman syndrome. Those who do survive commonly exhibit developmental delay and renal abnormalities and are at a high risk for developing nephroblastomatosis and Wilms tumor at an early age.

Astuti, et al., established a molecular basis for Perlman syndrome in 2012 by identifying regions of homozygosity in consanguineous Perlman syndrome families. With further genetic mapping, germline homozygous deletions of DIS3L2 exons were found in multiple consanguineous families, and additional biallelic DIS3L2 single nucleotide variants, including splice-site and missense mutations, were found to segregate with disease in non-consanguineous patients. The authors further demonstrated through functional in vitro studies that recombinant DIS3L2 protein with exon 9 homozygous deletion displayed substantially reduced ribonuclease activ-

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**Fig. 2.** Next-generation sequencing and PCR results showing homozygous deletion of DIS3L2 exon 9. A. Upper panel: screenshot from Integrative Genomics Viewer showing DIS3L2 exons 8, 9, and 10 of the patient's sequencing data compared with a normal control. Sequence reads (red and blue boxes) are seen as expected in exons 8 and 10 of DIS3L2 in the patient, but no reads for exon 9 are present. Lower panel: zoom-in screenshot of exons 8, 9, and 10 of DIS3L2 in the patient compared with a normal control. B. PCR confirmation visualized by TapeStation: A1, ladder; B1, patient's sample DIS3L2 exon 9 (no band); C1, control sample exon 9; D1, patient's DIS3L2 exon 6 (patient intragenic control); E1, control sample exon 6; F1, blank.
ity compared with wild-type DIS3L2. Additionally, loss of this gene in cell lines led to increased rates of aneuploidy, errors in mitosis, and abnormal expression of mitotic proteins.

In this case, a confirmed molecular diagnosis of Perlman syndrome has two primary impacts on patient care. First, in a situation of a neonatal death, a definitive diagnosis can help bring closure to the pregnancy for this family by providing a direct answer to what caused their loss. Second, and most significantly, this diagnosis has important clinical implications for this couple’s family planning and future pregnancies. As part of the report issued in this case, we recommended genetic testing for this family to aid in the assessment of recurrence risk. If both parents are found to be asymptomatic carriers for heterozygous pathogenic variants in DIS3L2, there is a 25 percent chance of their having another child with Perlman syndrome and a 50 percent chance of their having a child who is a carrier.

In sum, we identified a homozygous deletion of a single exon of DIS3L2 gene using an NGS-based hereditary cancer panel in a patient who died soon after birth. This result not only provides a molecular diagnosis of Perlman syndrome but also carries important implications for the family in its decision-making for future pregnancies. Our experience demonstrates that an NGS-based assay can detect copy number variants at the single exon level through use of a carefully designed bioinformatics pipeline and thorough sequence data investigation.


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