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Case report: Prenatal whole exome sequencing identifies familial autosomal dominant pathogenic GREB1 variant with incomplete penetrance

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Background

While whole exome sequencing (WES) has become integrated into case management for pediatric genetic cases, its utility in the prenatal arena is still being considered. The American College of Medical Genetics and Genomics (ACMG) has stated that exome sequencing can be used for pregnancies with ultrasound anomalies when standard karyotype and CMA have failed to present a diagnosis.[1] We present a case where fetal WES revealed an inherited pathogenic variant that showed differing presentations within a family.

Case presentation

A 31-year-old patient with a diamniotic, dichorionic twin gestation was referred for genetic counseling due to an abnormal ultrasound finding of severe oligohydramnios and suspected bilateral renal agenesis in both fetuses. The family history was significant for a previous pregnancy with anencephaly (46,XY karyotype and normal microarray test results) and a healthy 18-month-old son (Figure 1).

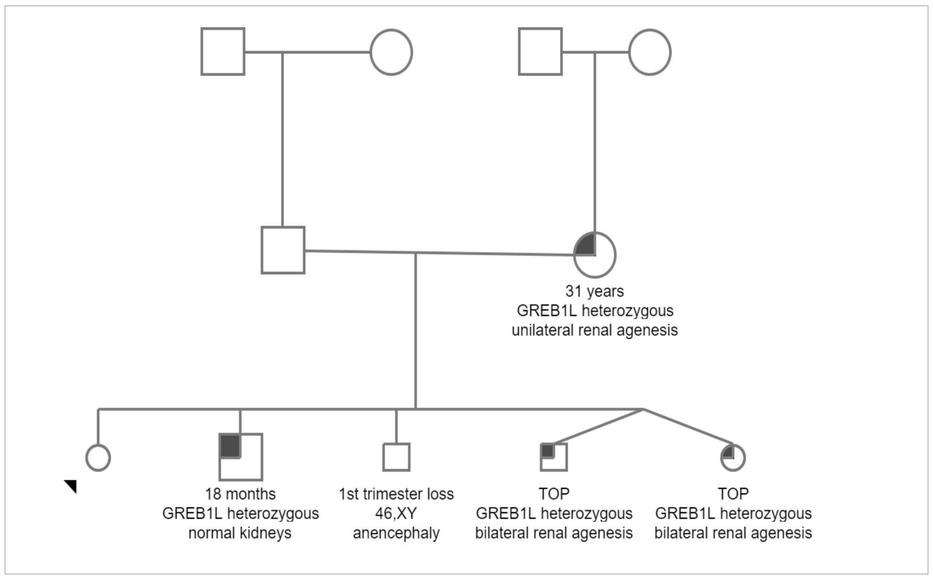
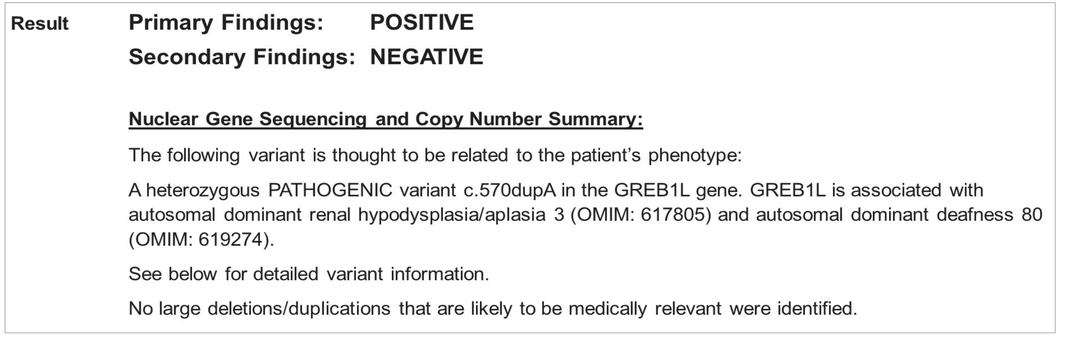


Figure 1. Pedigree.

Results

Chorionic villi sampling was performed for both fetuses and normal microarray results were obtained. The couple then elected to proceed with trio WES analysis, and results revealed that both fetuses were heterozygous for a maternally inherited pathogenic variant c.580dupA in the GREB1L gene (Figure 2). The couple elected to pursue termination of pregnancy given the poor prognosis. The patient subsequently had a renal ultrasound and was found to have unilateral renal agenesis. Their son also tested positive for the variant and had a reportedly normal renal ultrasound (Table 1).

The GREB1L gene has been found to affect cellular differentiation of the renal system in humans. The inheritance in observed cases has been consistent with autosomal dominant inheritance with incomplete penetrance. The phenotype can range from bilateral renal agenesis to milder manifestations such as unilateral renal agenesis and horseshoe kidney. Genomic studies of stillborn fetuses with multiple congenital anomalies revealed de novo mutations in GREB1L in two cases with bilateral renal agenesis.



Result **Primary Findings:** **POSITIVE**
Secondary Findings: **NEGATIVE**

Nuclear Gene Sequencing and Copy Number Summary:

The following variant is thought to be related to the patient's phenotype:

A heterozygous PATHOGENIC variant c.570dupA in the GREB1L gene. GREB1L is associated with autosomal dominant renal hypodysplasia/aplasia 3 (OMIM: 617805) and autosomal dominant deafness 80 (OMIM: 619274).

See below for detailed variant information.

No large deletions/duplications that are likely to be medically relevant were identified.

Figure 2. WES result.

Family member	Genotype	Phenotype
Fetus A (twin A)	GREB1L heterozygous	Bilateral renal agenesis
Fetus B (twin B)	GREB1L heterozygous	Bilateral renal agenesis
Patient's son	GREB1L heterozygous	Normal renal development
Patient	GREB1L heterozygous	Unilateral renal agenesis

Table 1. Familial pattern of inheritance and expression.

Conclusions

The risk for future pregnancies to inherit this variant is 50%; therefore, genetic counseling for the couple included discussions of IVF with preimplantation genetic testing. After discussion, the couple elected to pursue this option given the wide range of outcomes associated with GREB1L variants. WES is shedding light on the large phenotypic spectrum of many genetic disorders. This poses significant genetic counseling challenges in post-test counseling and difficult decisions for patients due to the difficulty of prediction of phenotype.

Reference

1. Monaghan KG, Leach NT, Pekarek D, Prasad P, Rose NC. The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22(4):675-680. doi:10.1038/s41436-019-0731-7

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