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Challenges in genetic counseling for renal anomalies

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I. Introduction

We report on 2 families who presented with recurrent pregnancies with bilateral renal agenesis. Bilateral renal agenesis is on the severe end of the Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT) spectrum. The etiology of the CAKUT spectrum is complex and multifactorial. In recent years, alterations in more than 75 genes have been shown to cause isolated or syndromic CAKUT, in an autosomal dominant or, less frequently, recessive mode of inheritance. Identification of these genes allows for genetic testing of affected families. However, genetic counseling for CAKUT is still challenging due to genetic and phenotypic heterogeneity as well as incomplete penetrance. Consensus guidelines on genetic evaluation of CAKUT are currently lacking.

CAKUT Spectrum

- Complete renal agenesis
- Renal hypodysplasia
- Multicystic dysplastic kidneys
- Duplex renal collecting system
- Ureteropelvic junction obstruction
- Horseshoe kidney
- Hydronephrosis
- Megaureter
- Posterior urethral valve

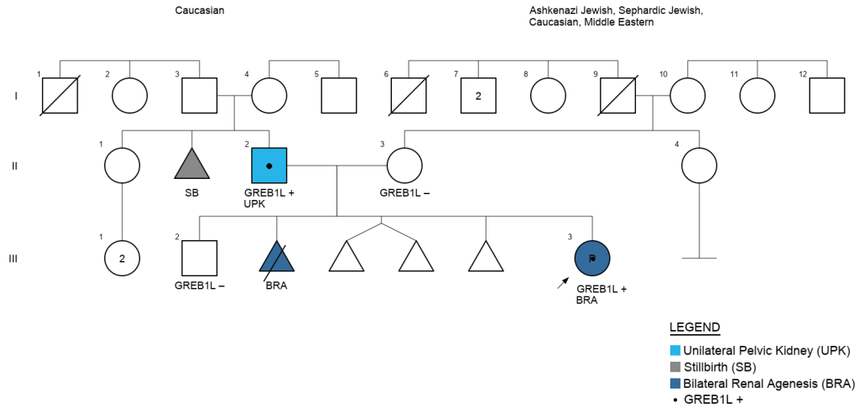
II. Case Reports

Case Report: Family 1

Family 1 presented to genetic counseling with a pregnancy affected with bilateral renal agenesis at 16 weeks gestation. The fetal bladder was not visualized but branched umbilical arteries were seen on color flow in the region of the bladder. Echogenic fetal bowel was seen. The couple's reproductive history also included termination of a previous pregnancy (female fetus) affected with bilateral renal agenesis, a healthy male offspring, an early spontaneous abortion of a twin pregnancy with unknown etiology, as well as a chemical pregnancy. The couple both denied any personal and family histories of CAKUT, although the father did report his sibling was stillborn.

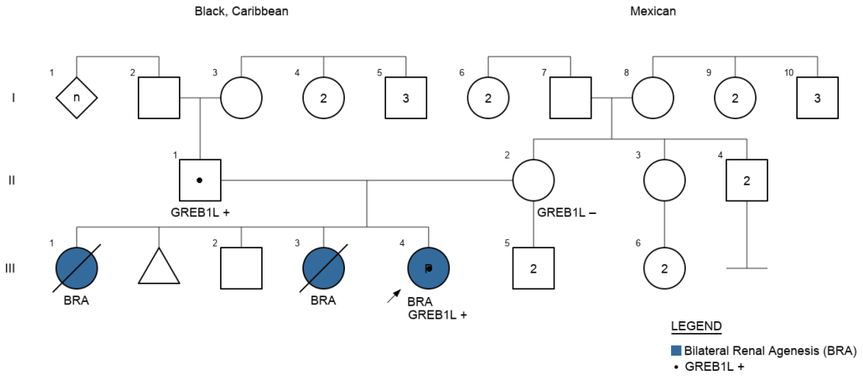
A CAKUT multi-gene panel was performed on the products of conception of this second affected pregnancy. A likely pathogenic variant (c.5356_5357del, p.Gln1786Valfs*13) was identified in *GREB1L*. This sequence variant was predicted to result in a frameshift and premature protein termination. This variant had not been reported previously, but was expected to be pathogenic. Fetal chromosomal microarray was normal female.

Targeted analysis of the couple found that the father carried the same variant. Although the father previously denied any personal history of CAKUT, his renal and bladder ultrasound revealed unilateral pelvic kidney. The couple's healthy son tested negative for the familial mutation.



Case Report: Family 2

Family 2 was referred to genetic counseling due to suspected recurrence of bilateral renal agenesis. The couple had two previous female pregnancies affected with bilateral renal agenesis that resulted in preterm neonatal death. For the current pregnancy, a detailed fetal anatomic survey performed at 17 weeks 5 days showed a smaller sized fetus measuring 16 weeks 1 day, right renal agenesis, suspected tiny nonfunctional left kidney, absent stomach, absent bladder, small thorax, echogenic intracardiac focus, and anhydramnios. Placental biopsy was performed for genetic studies. Results of chromosome microarray analysis showed a normal female complement. Whole exome sequencing trio results showed a variant in the *GREB1L* gene (c.5622T>A), which was classified as likely pathogenic. This variant has not been previously reported but is predicted to introduce a premature termination codon in the *GREB1L* protein, resulting in truncation or loss of *GREB1L* protein via nonsense mediated decay. The variant was also detected in the father. The couple's reproductive history also included an unaffected son (not tested) and one early miscarriage. The couple denied any personal or family history of CAKUT and reported having normal renal ultrasounds.



III. Discussion

GREB1L was identified as a CAKUT-susceptibility gene in 2017 and is associated with renal hypodysplasia/aplasia (RHDA3) (OMIM#617805). RHDA3 is autosomal dominant. It is characterized by high variability within families and incomplete penetrance. The variability reported with RHDA3 includes bilateral renal agenesis, as seen in our families, unilateral renal agenesis or even milder manifestations such as vesicoureteral reflux. Female mutation carriers may also have uterine or ovarian abnormalities.

Although the CAKUT in both families appeared autosomal recessive at initial presentation, genetic testing proved the condition to be autosomal dominant. Based on our experience, autosomal dominant inheritance should be considered even in the absence of affected first degree relatives. Clinical evaluation of the genitourinary system should be considered in apparently asymptomatic first degree relatives. If a clinically significant variant for an autosomal dominant condition is identified in the proband, testing first degree relatives for the variant should be considered even if the relatives are apparently asymptomatic.

IV. Conclusions

Our experience suggests that testing for CAKUT genes should be considered for renal agenesis, especially when chromosomal microarray is non-diagnostic. Identification of the genetic etiology helps define recurrence risks, allows for early prenatal diagnosis and preimplantation genetic testing (PGT), and informs subsequent diagnosis and follow up of family members who are at risk for CAKUT. Challenges remain in genetic counseling for CAKUT especially in the prenatal setting. The variable expressivity and reduced penetrance pose significant difficulties for clinicians to provide prognostic information on mutation-positive fetuses that are yet to show clinical signs of the condition. The extremely broad prognosis may make it difficult for prospective parents to make decisions regarding the pregnancy. Identification of additional genetic and environmental modifiers of the CAKUT phenotype can potentially help with these challenges.

V. References

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