UTHealth Houston
McGovern Medical School
Obstetrics, Gynecology and Reproductive Sciences

It Takes a Village: When Your Network Has Your Back

TEXAS SOCIETY OF GENETIC COUNSELORS AEC

Theresa Wittman, MS, CGC
Assistant Professor, The Department of Obstetrics, Gynecology, & Reproductive Sciences
McGovern Medical School at UTHealth Houston

Patient K.M (El Campo, Texas)

- 31 yo G3P2002 self referral at 24 0/7 weeks gestation due to severe symptomatic polyhydramnios
- Past medical/social history:
  - History of secondary infertility, natural conception
  - low risk NIPT (XY), neg TORCH
  - no medical insurance
  - normal glucose tolerance test
- Polyhydramnios first identified at 21 0/7 weeks gestation (AFI of 29.3 cm, nml 5-25)
  - No structural abnormalities noted on anatomy scan

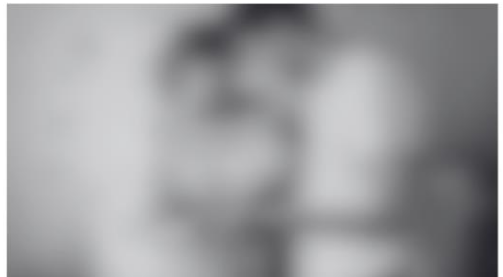
Patient K.M

- 23 0/7 increasing symptomatic, AFI of 38
  - Given the choice of in house management (Austin)
  - Self refers to UT Fetal Center

- 23 5/7 week initial limited ED ultrasound did not note any fetal anomalies
  - AFI 50, EFW 48th percentile
  - 4.2 liters of amniotic fluid removed, post procedure AFI 23
  - Fluid sent for CMA

Patient K.M

- 24 2/7 weeks comprehensive anatomy scan
  - Polyhydramnios (AFI 32.4 cm), mild tricuspid valve regurgitation, aliased flow in the ductus arteriosus with increased velocities and increased diastolic flow, concern for ductal constriction, double aortic arch, duplicated left collecting system, mild bilateral pyelectasis, normal urinary bladder



Caucasian/Northern European

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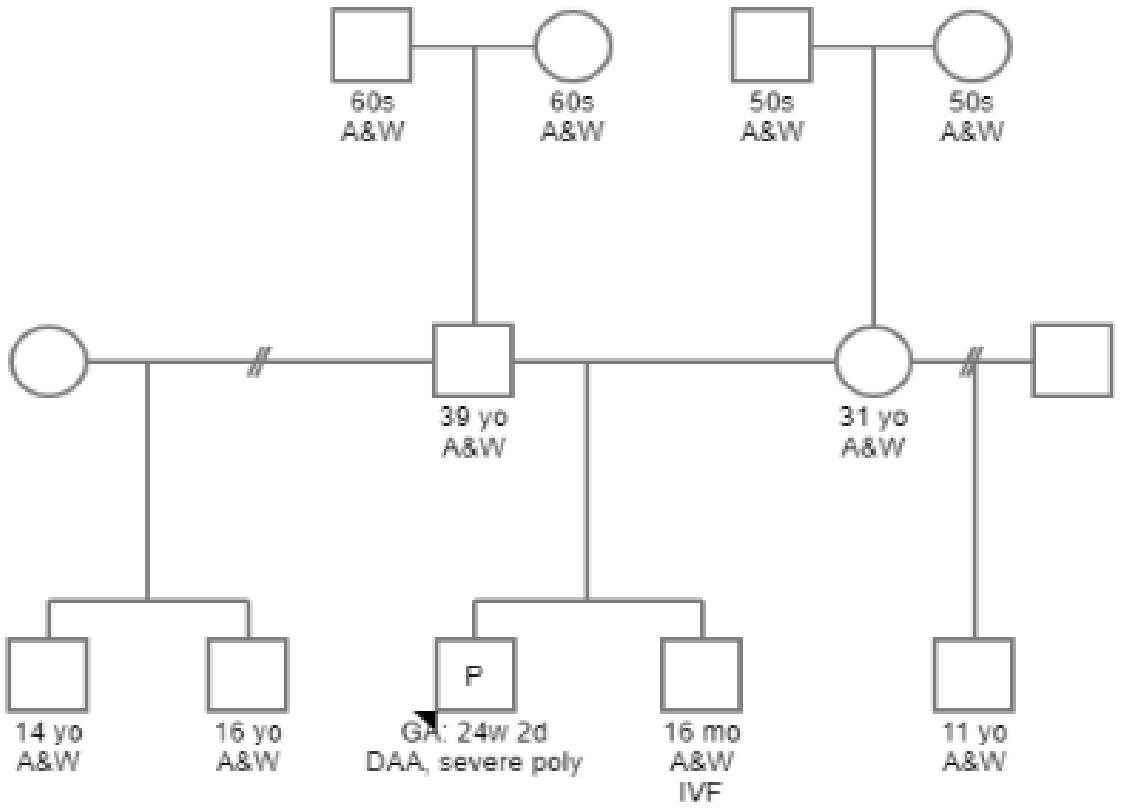


(+/-)
RSABs/SB
MR/LD
Birth defects
Consanguinity
Genetic

Patient K.M

- Chromosome microarray: normal male
- Patient consented for Prenatal SEQ (Columbia University) study for whole exome sequencing
- Fluid also sent to Children Mercy in Kansas for additional metabolic and analyte studies including potassium and chloride and possible further genetic studies

Whole Exome Sequencing Results (NGS)

RESULTS SUMMARY

INDETERMINATE FINDINGS

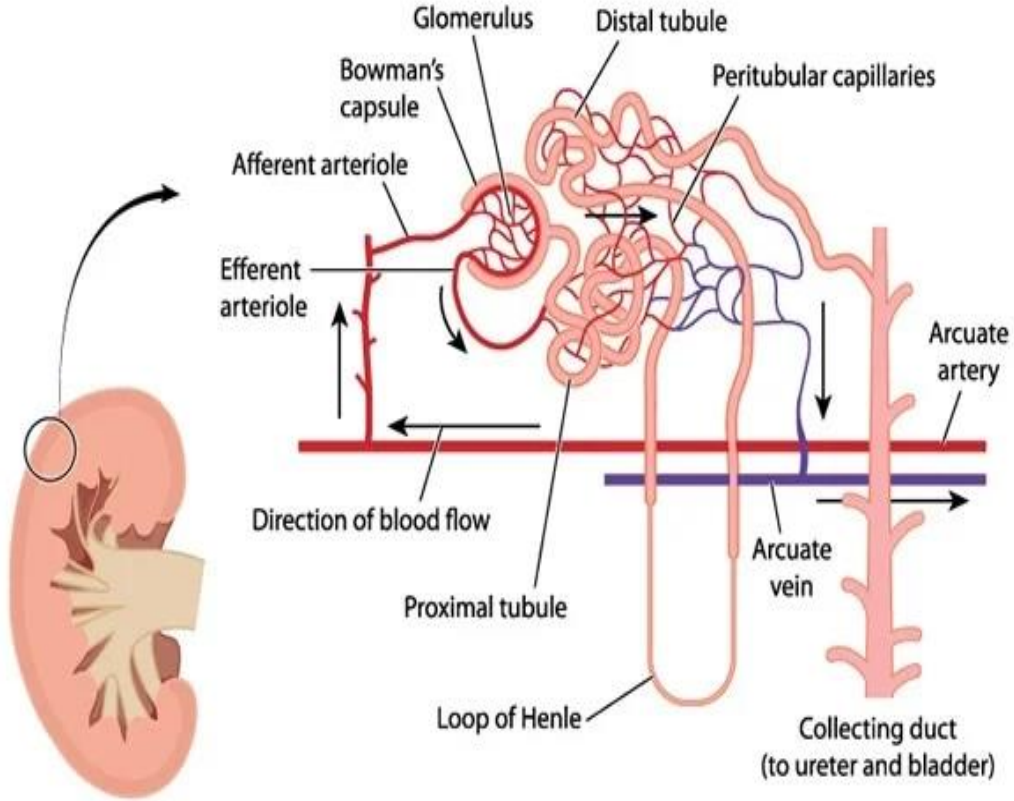
SUMMARY

Hemizygous De Novo Variant of Uncertain Significance (VUS) in MAGED2 detected.

POSSIBLE HIGH IMPACT FINDING(S)

Bartter Syndrome

- 1 in 1,000,000 individuals
- Renal tubular salt-wasting disorder in which the kidneys cannot reabsorb sodium and chloride in the thick ascending limb of the loop of Henle
- Common symptoms include hypokalemia, hypochloremic metabolic alkalosis, and low normal blood pressures
- 5 types of varying severity and presentation
  - types 1-4 AR
  - type 5 (XLR, MAGED2), most severe and earliest onset, transient (neonatal period)



Antenatal Bartter Syndrome (MAGED2 Related)

- Severe polyhydramnios occurs secondary to alterations in ion channels located in the thick ascending limb of Henle's loop
- High mortality due to preterm birth
- Perinatal management has included:
  - ✓ Serial amniotic fluid reductions
  - ? Maternal treatment with Indomethacin-> collaboration with neonatology/nephrology
    - increased risk of constriction of the ductus arteriosus
- Patient received several doses during pregnancy that seemed to decrease (but not eliminate) polyhydramnios

Patient K.M

Amnioreduction #	Gestational age (Weeks)	Amnioreduction volume (L)	Preop AFI* (cm)	Postop AFI (cm)
1	23 3/7	4.2	50	23
2	24 5/7	2.0	39	18
3	26 2/7	1.0	36.6	29
4	27 0/7	2.0	33.8	--
5	28 3/7	3.7	51	30
6	29 3/7	2.8	36.9	16.7
7	30 6/7	4.0	40	13
8	31 6/7	2.8	39	8
9	32 5/7	2.0	42	22
10	33 0/7	1.5	32	20

Patient K.M

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Secondary Findings

INTERPRETATION - SECONDARY FINDING

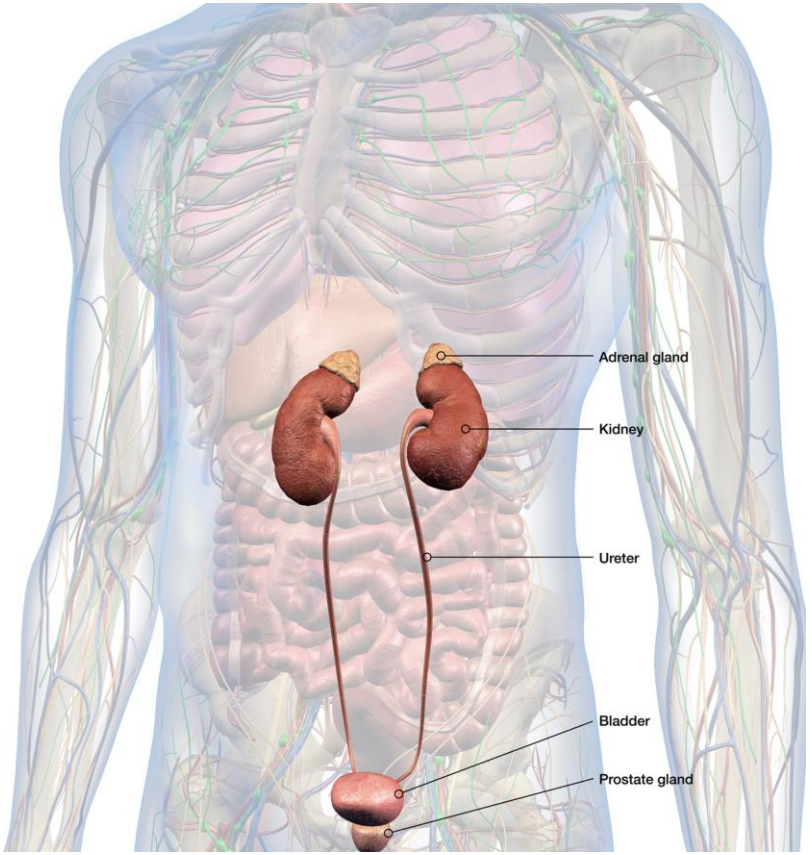
PATHOGENIC VARIANT IN TMEM127

TYPE	DISEASE	INHERITANCE	GE
SNV	Pheochromocytoma	AD	N

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome (TMEM127 related)

- Increased risk for paragangliomas, pheochromocytomas and possible increased risk for clear cell renal cell carcinoma
- Symptoms of PCC/PGL can include HBP, headaches, sweating palpitations, anxiety depending on tumor location
- Consider surveillance via annual biochemical testing and imaging, whole body MRIs every 2-3 years
- Familial testing

https://netrf.org/old-for-patients/nets-info/tumor-site/adrenal/



Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome (TMEM127 related)

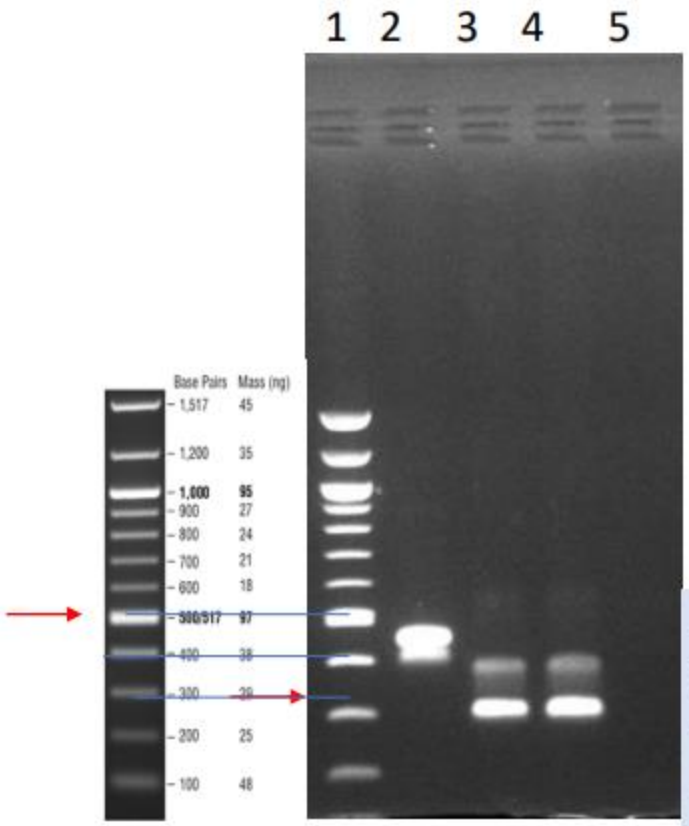
- FOB informed of diagnosis
- He had been having fainting/dizzy spells
- Two teenage sons from a previous relationship, parents in their 60s
- Referred to MD Anderson, later UTMB (due to insurance)
  - Thank you Christina Falugi, MS, CGC!

MAGED2 Variant Reclassification

- CDNA studies performed at Genomic Medicine Center at Children's Mercy in KC

Small bands of cDNA amplification—confirmed deletions by abn splicing of exon 5-6

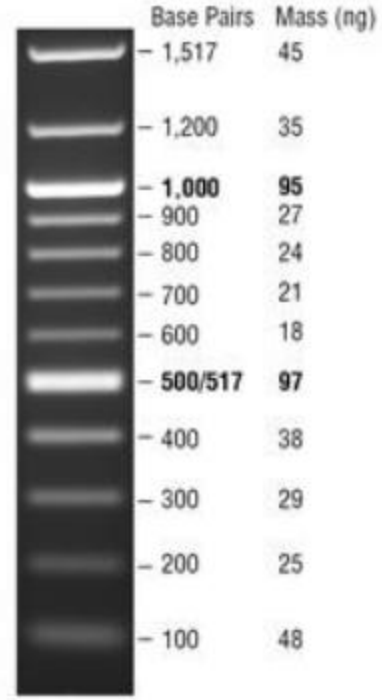
Exon 5 and 6 deleted



1. 100 bp Ladder
2. Deidentified control amnio RNA
3. MK amnio 2-2 RNA
4. MK amnio 2-3 RNA
5. Blank

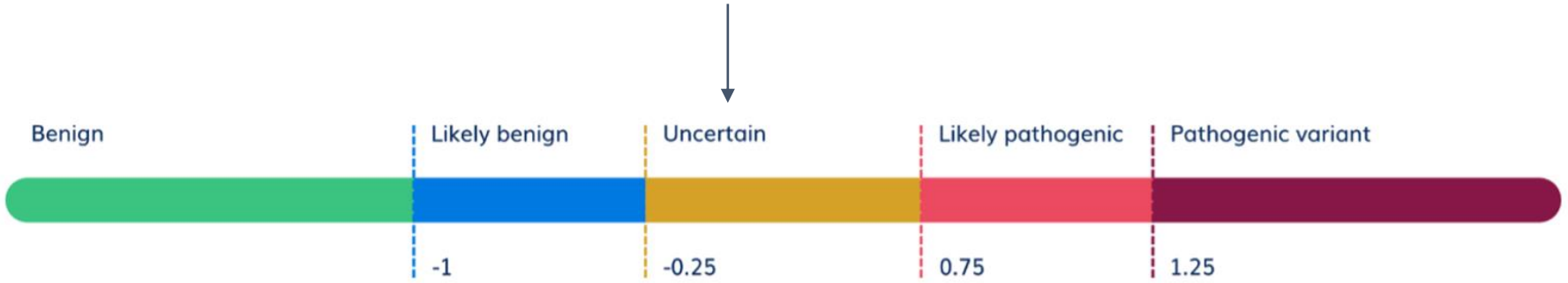
- Product size per primer design: **451bp**
- Abn product is around **~300bp**

- **Exon5 (63bp) exon6 (79bp) =142bp**



Variant Reclassification

- Targeted RNA, cDNA amplification confirmed that an abnormal protein product (~300 bp versus ~450 bo) is made with this variant due to abnormal splicing of exons 5 and 6
- Presented to performing lab (Baylor Genetics), agreement about reclassification (formal reclassification December 2023)
- Clinically diagnosed by UT Pediatric Genetics



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- MAGED2 VUS --> Likely Pathogenic

Patient K.M

- Induced at 33 weeks 0 days due to polyhydramnios, decreased tolerance to amniotic fluid reductions, global membrane separation
- 5 week NICU stay
  - Vascular ring division, tracheal compression and laryngotracheomalacia noted
  - Intolerance to postnatal indomethacin (gastritis)
  - Oral potassium
- Initial wet diapers ~26 per day gradually reduced to ~14 and later 8-9 (5 months old)

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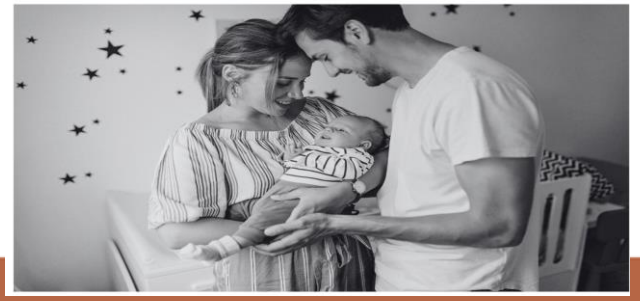

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