Investigating the Etiology of Monogenic Stone Disease

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Background

•Lifetime prevalence of urinary stone disease (USD) is 7% in women and 12% in men in the U.S.[1]

•Up to 15% of cases of USD have monogenic causes[1]

•More than 100 genes suspected of causing USD are used for screening patients presenting with monogenic stone disease (MSD)[1]

•Next generation sequencing (NGS) important to improve diagnostics and new treatments or clinical trials for patients.[1]

Aims

Aim One: Genotype patients who present with a monogenic stone disease phenotypes[2]

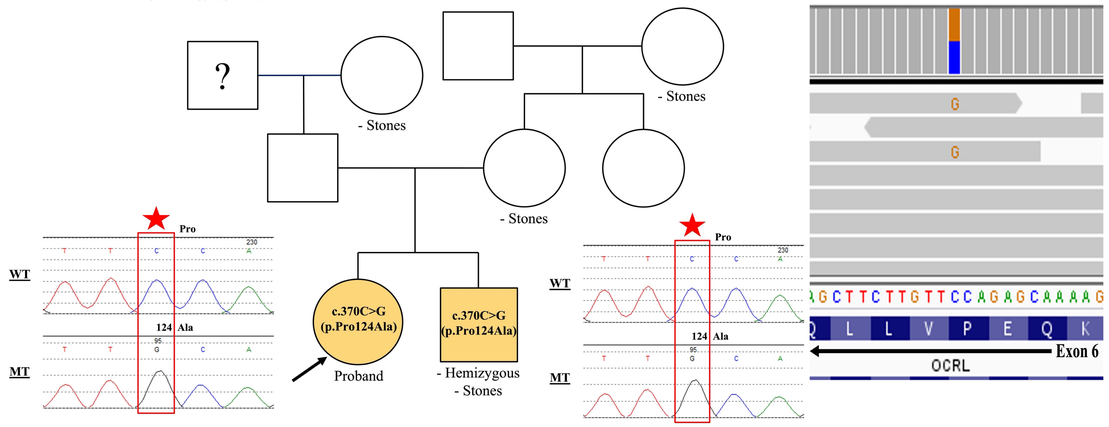
Aim Two: Classify and analyze genetic variants beyond being the causative agent in monogenic stone disease patients[2]

Methods

1. Obtain DNA sample from patient with suspected MSD
   - Run sample on NGS panel
2. Screen family members for mutations
   - In-house PCR sequencing
3. Submit PCR samples for sequencing
   - Analyze results using software

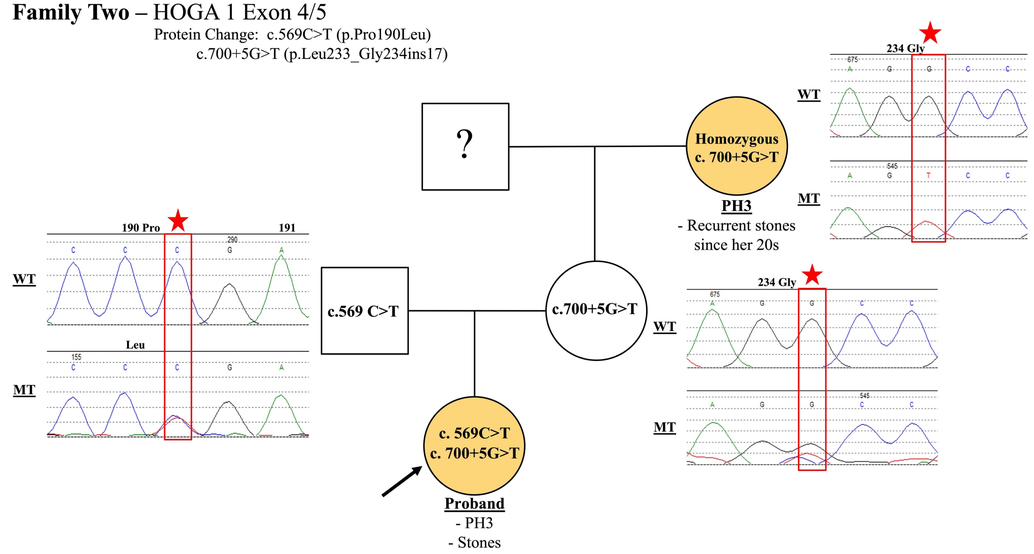
Results

Family One – OCRL Exon 6
Novel Missense Variant



Patient presented with mild Dent 2 disease with a family history of stones. Found to have a missense variant in the OCRL gene. Family members were sequenced, and no variants were found except for patient's brother. He is hemizygous for the variant and severely effected by Dent 2. Above is the proband's BAM file from NGS sequencing, showing the variant along with the Sanger sequencing files for both the proband and sibling, exhibiting the C to G base change.

Family Two – HOGA 1 Exon 4/5
Protein Change: c.569C>T (p.Pro190Leu)
c.700+5G>T (p.Leu233_Gly234ins17)



Proband diagnosed with the recessive USD, primary hyperoxaluria type 3 (PH3). Two variants were found in proband, and three family members sequenced. Each parent carry one of the variants, but neither is affected. The maternal grandmother is PH3 positive and homozygous for the intronic variant, suffering with stones since her 20s. Shown is Sanger sequencing for the family members.

Conclusions

•Sometimes familial complexity is discovered when analyzing affected families

- Two unique families
  - Family One exhibited very unusual inheritance of Dent 2 with only siblings affected
  - Family Two exhibited two different PH3 variants, with two affected individuals separated by a generation

•Sequencing family members allows for analysis of inheritance patterns of MSD variants.

Final Thoughts

•Research takes time and is full of trial and error

•SRS is an invaluable opportunity to gain experience and form networks.

•Useful skills are gained from this experience.

•The importance of research is better understood after this experience.

•SRS is a great resource for students

Resources

[1] Lieske, J., Harris, P., et. al. "RC2 - Employing tools to accurately characterize and study patients with monogenic kidney stones", 15 November 2019.

[2] "Monogenic R21 Mature Draft", 31 May 2019.