Identifying causative variants in patients with monogenic stone disease

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Primary hyperoxaluria (PH) and Dent disease are rare monogenic diseases resulting in kidney stones and renal insufficiency. PH is caused by biallelic mutations to *AGXT*, *GRHPR*, or *HOGA1* while Dent disease (X-linked) is caused by single mutations to *CLCN5* or *OCRL*. Previously, Sanger screening resolved 53% of PH and 45% of Dent diagnosed families, and unresolved patients were screened with a next generation sequencing (NGS) panel of ~102 known or candidate stone-forming genes that solved a further 10% of these PH/Dent diagnosed families. The focus of the study was to identify patients carrying single heterozygous missense or atypical splicing variants in genes with autosomal dominant inheritance that could account for the stone phenotype. The pathogenicity of detected variants was evaluated with *in-silico* tools, including multisequence protein alignments, web-based prediction programs, tertiary/quaternary modeling, and population data. For the PH unresolved cases, 3 of 225 families were found to have monoallelic mutations to the genes *SLC4A1*, *SLC34A1,* and *SLC34A3*. In a further 51 families, a single potentially pathogenic variant was detected, but proof of causality was not reached. Of the 53 unresolved Dent families, 2 families were likely resolved with monoallelic mutations to the gene *HNF4A*. Additionally, the etiology of 5 families was likely solved with previously mis-scored biallelic variants in the genes *AGXT, SLC34A1* (X2), *SLC34A3,* or *SLC12A1.* This study shows the value of NGS and careful use of *in silico* methods for identifying pathogenic variants in our stone forming cohort, enhancing diagnostics and treatment options of monogenic kidney stone formers.