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Schema For Resolution Of Genetic Variants Of Uncertain Significance In Patients With Suspected Genetic Glomerulopathies: DRAGON (Deciphering Diversities: Renal Asian Genetics Network)

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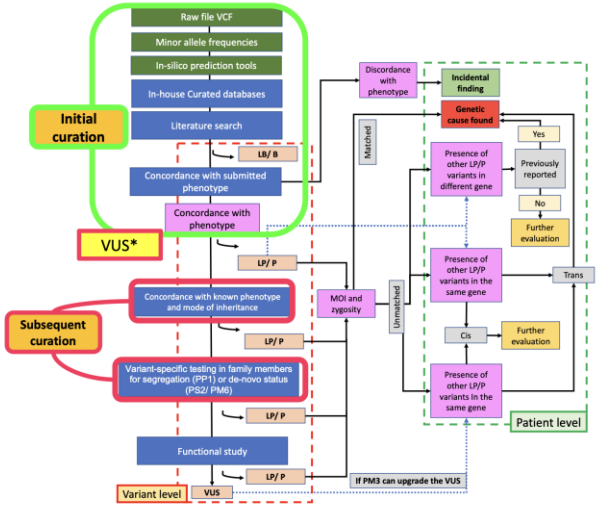
Objectives : Monogenic causes account for 10-30% of patients with primary glomerular disease. Variants of uncertain significance (VUS) are frequent in Asians. Variant interpretation is often complex. Here, we performed panel sequencing on patients with glomerulopathies and developed an in-house variant curation pipeline. We aimed to evaluate the steps in this pipeline.
Methods : We performed targeted analysis of 90 glomerular genes in 124 probands with primary glomerulopathies from South and Southeast Asia (20% with family history and 12% with consanguinity). Variant calling and filtering was based on Genome Analysis Toolkit. We excluded benign variants using computerised steps (initial curation) involving minor allele frequencies, in-silico prediction tools and literature search using Mastermind (Figure 1). With the remaining variants, we performed and evaluated two subsequent steps: (a) determining concordance with known phenotype and mode of inheritance of the gene, and (b) variant-specific testing in family members for segregation (PP1) or de-novo status (PS2/ PM6).
Results : After variant calling, we identified 442 variants. After initial curation, there were 35 (likely) pathogenic variants in 32 (26%) probands. Of these, 18 and 9 were excluded due to discordance with the mode of inheritance and gene-phenotype discordance respectively. We identified 34 VUS with high pathogenic likelihood in 27 (22%) probands. Seven VUS were excluded due to discordance between the gene and phenotypes. We performed variant-specific testing of family members for 16 VUS. 1 and 3 variants were conferred PP1 and PS2 respectively, resulting in their upgrade to (likely) pathogenic variants. In total, we identified 12 (likely) pathogenic variants in 12 (10%) probands, of whom 3 had Alport syndrome. 23 variants remained as VUS.
Conclusions : Determination of gene-phenotype discordance is a discerning step to rule out variants, while familial variant-specific testing is a useful step to rule in VUS.

Variant curation pipline.png



VUS – VUS with high pathogenic likelihood*

VCF – Variant call format, LB/B – Likely benign/ Benign, LP/P – Likely pathogenic/ Pathogenic, VUS – Variant of uncertain significance, MOI – Mode of inheritance

Figure 1: In-house variant curation pipeline.