

P036

P036 -Interpretation of rare heterozygous variants in recessive genes in a UK cohort of children with steroid resistant nephrotic syndrome

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Steroid resistant nephrotic syndrome (SRNS) is a rare condition in childhood (up to 1.8 / 100,000 population) associated with considerable morbidity, particularly in those with early onset. Advancing genetic technologies show that approximately 30% of children have a monogenic cause, and research is focusing on stratifying patients at an early stage in order to 'personalise' their treatments.

There have been over 60 'nephrotic' genes identified to date in SRNS patients, most of them autosomal recessive (AR). Genetic test results will not infrequently identify single rare heterozygous variants within AR genes and their presence causes uncertainty. Often, the possibility that current sequencing platforms are not able to detect a second variant where one exists (as a compound heterozygote for example), or alternatively, that a second variant resides within the non-coding genome is assumed, and pathogenicity inferred.

Aim: To compare the frequency of rare (minor allele frequency (MAF) <0.01) heterozygous variants in known nephrotic AR genes in a cohort of paediatric SRNS patients (excluding patients with genetic / monogenic disease) with a control population using the GnomAD database. If the difference is significant, these patients are likely to be genetic. If the difference is not significant, they are likely to be co-incidental.

Methods: Whole exome analysis (WES) and sequencing was performed for 133 caucasian patients within the UK SRNS cohort. Non-synonymous heterozygous single nucleotide variants (SNVs) and SNVs within splice sites (+/-10 base pairs from intron / exon boundary) were filtered out if their MAF was >0.01 leaving a set of rare heterozygous variants for each of a selection of AR nephrotic genes for the SRNS patients. The same filtering process was performed for the corresponding genes in GnomAD (www.gnomad.broadinstitute.org, exomes only) to create a control population (matched ethnicity). Known and presumed genetic patients were excluded from the analysis. To assign pathogenicity, the non-synonymous heterozygous variants were analysed using the VEP (http://grch37.ensembl.org/Homo_sapiens/Tools/VEP) programme and analysed along with indels to further explore the role of 'likely pathogenic' heterozygous variants in the cohort compared with control.

Results: 15 AR genes known to be associated with SRNS (including ADCK4 / ALG1 / CD151) were analysed. Across the 15 genes, 27.5% of the cohort had a rare heterozygous variant compared with 24.6% of the 'general' (European non-Finnish) population (not statistically significant). 7 of these genes (NPHS1 / ADCK4 / NPHS2 / COL4A4 / CRB2 / CD2AP / KANK1) were further interrogated for the presence of 'likely pathogenic' heterozygous variants. Overall 7.7% of the cohort and 8.1% of the control population have one of these likely pathogenic heterozygous variants in one of these 7 genes (not statistically significant).

Conclusion: Through analysis of a subset of AR genes known to be associated with SRNS we have shown that there is no significant difference in the frequency at which rare heterozygous SNVs and rare heterozygous likely pathogenic SNVs are found when compared to a population of ethnically matched controls from a large population database. This would suggest that when such variants are found in an individual that they

are incidental and not an indication of an unidentified 'second hit'. It is important to recognize the limitations introduced by our small sample size when considering these conclusions however.