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P035 -Analysis of risk variants through whole exome sequencing in steroid resistant nephrotic syndrome from a UK cohort

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Idiopathic nephrotic syndrome (INS) describes a clinical spectrum of disease resulting from a disruption to the glomerular filtration barrier (GFB) and in particular the podocyte. The advent of next generation sequencing technologies has given a broader understanding of the genetic aspects of the condition with over 60 causative genes published to date. There remains a sub-set of steroid resistant patients with a particularly poor prognosis, in whom disease recurs post-transplant. An as yet unidentified 'circulating factor' (CF) is thought to be the cause. There are emerging reports that common genetic variation in a number of 'susceptibility genes' (FCG2RA/PLCG2/HLA-DQA1 for example) may be important in INS. Through this project we aim to validate and add to the published findings. A genetic 'risk signature' for these patients may be on the horizon.

Aim: To compare the frequency of common genetic variants in various 'risk/susceptibility' genes identified from the scientific literature, between a cohort of patients with steroid resistant nephrotic syndrome (SRNS) and the general population.

Methods: A literature search identified 22 genes in which single-nucleotide-variants (SNVs) had been identified as potential 'risk factors'/ 'modifiers' for INS. We screened these genes in 133 Caucasian patients from our UK paediatric SRNS cohort. Minor allele frequency (MAF) for each detected variant was compared with control (GnomAD European non-Finnish controls – exomes only; www.gnomad.broadinstitue.org). Sub-group analyses were performed for genetic SRNS / secondary SRNS + primary non-genetic SRNS with post-transplant recurrence (possible CF) / primary non-genetic SRNS without post-transplant recurrence and secondary SRNS with / without response to Rituximab.

Results: The supplementary table details the variants found to be significantly enriched ($p<0.001$) in our cohort compared to the general population. For HLA-DQA1 for example, published variants shown to be enriched in INS (RS1129740 & RS1071630) were significantly suppressed in our cohort. Published variants in ABCB1 were not detected in our cohort but an enriched variant was detected (7:87145881T/C, $p<0.05$). The published variant for TP53 was also present in our cohort but not enriched compared to control. An enriched variant ($p<0.05$) in TP53 was found however (17:7576543C/T, $p<0.05$). No significant results were found in SNAI1, FCG2RA, GCP5 or SCGB1A1. Sub-group analyses identified 12 significantly enriched variants ($p<0.001$) in HLA-DRB1 exclusively in the possible CFD group (example: 6:32549583T/C).

Conclusion: Using published INS risk factors as a starting point for further investigation, we have identified a number of SNVs that are significantly enriched in our SRNS cohort when compared to the general population. We have identified a large number of enriched variants (in HLA-DQB1 / HLA-DRB1 in particular) not previously cited in the literature as posing risk / susceptibility for INS, providing new avenues for further exploration. Stratifying these patients in the case of HLA-DRB1 for example, illustrates a sub-set of variants that are specifically enriched in (likely) CFD. This new data supports and adds to the hypothesis that there are a large number of genetic variants (residing outside of the known 'nephrotic' genes) working alone or in combination, to modify the pathogenesis of INS in some way.