



## **Final Report Summary for the 2020 Alport Syndrome Foundation Research Award**

**\$125,000 over two years**

Title: Sex Specific Genotype Penetrance for Predictive Diagnosis in Alport Syndrome

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Chronic kidney disease (CKD) represents a diverse group of disorders that result in irreversible scarring of the kidney over time. It affects more than 750 million people globally. In 2019, we reported that gene mutations account for ~11% of adults with a form of CKD called focal and segmental glomerulosclerosis (FSGS) and of these genetic cases, unrecognized Alport syndrome (AS) is the leading cause.

Alport syndrome has a wide clinical spectrum ranging from mild to more severe forms of disease. Studies in the past have been biased towards individuals with more classic and severe manifestations that lead to specialist care. We hypothesized that the prevalence of Alport syndrome is higher than previous estimates, commonly stated to be 1 in 50,000 or 0.002% (Levy M, Feingold J. *Kidney Int.* 2000), as a result of this inherent bias.

Using funding from the Alport syndrome Foundation (ASF) awarded in September 2020, we have started to unravel the prevalence of kidney phenotypes associated with Alport syndrome gene (type IV collagen) mutations in the general population. We captured milder forms by studying participants in the UK Biobank, a large dataset that links genome-wide genetic data to clinical traits.

Characteristic renal phenotypes in Alport syndrome are blood in the urine called hematuria and urinary protein excretion called albuminuria. Hematuria is a distinguishing feature for Alport syndrome and select renal diseases whereas albuminuria is observed in a broader range of conditions. Thus, we began by evaluating 16,866 hematuria cases to enrich for Alport syndrome and 391,420 controls in the

European subset of the UK Biobank. The average age at the time of recruitment was 60 years in cases and 57 years in controls. Cases were found to have higher albuminuria and a higher rate of self-reported hearing loss. Cases compared to controls had lower kidney function, measured by eGFR and calculated to be 87 and 91 mL/min/1.72m<sup>2</sup>, respectively. These clinical characteristics are consistent with very mild disease. Six genomic regions called loci were significantly associated with hematuria, the strongest of which was type IV collagen, *COL4A3* and *COL4A4*, residing on chromosome 2.

A variant in *COL4A4*, p.Ser969X, had the most significant association, and two variants in the locus remained associated with hematuria after conditioning on it: *COL4A3* p.Gly695Arg and a common *COL4A4* intron 25 variant (not previously reported). *COL4A4* p.Ser969X was found 283 times in the entire European subset (n=355,319), mostly as a single copy in an individual and of the 3 independent associated variants, had the highest odds ratio for hematuria at 87.3. However, not all individuals with *COL4A4* p.Ser969X had documented hematuria and the proportion of people with the variant that had hematuria was 21% for females and 20% for males. Therefore, the estimated hematuria prevalence due to this single variant *COL4A4* p.Ser969X, taking into account its incomplete penetrance, was 0.02% and 10 fold higher than previous overall estimates for Alport syndrome. This is a minimum estimate given that there are other type IV variants that contribute to disease. Interaction with other risk genes across the genome influencing penetrance/disease progression will be evaluated but requires the addition of more severe cases to capture the clinical spectrum in Alport syndrome.

In the 18 months since receiving the ASF award, we have published 1 manuscript in *Pediatric Nephrology* (Feb 2021) describing UK Biobank studies of renal traits observed in Alport syndrome, thereby raising awareness of the disorder in the nephrology community. We currently have 1 manuscript describing our research results submitted for publication consideration and another in preparation.

We are grateful to the Alport syndrome Foundation for this support and we remain committed to advancing knowledge in this field beyond the duration of the award.