**Title: TBD**

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Alport Syndrome (AS) is a hereditary disease affecting 1 in 5,000 births in the United States1. Children and young adults with AS suffer from hearing loss, vision abnormalities, and most notably kidney disease2. AS patients with kidney disease are diagnosed with glomerulonephritis, and present with symptoms of hematuria and proteinuria. Inevitably, their kidney functions progressively deteriorate and lead to End-Stage Renal Failure (ESRF) 2. It is well studied that ESRF in AS is caused by genetic mutations in the α3, α4, and α5 chains of type IV collagen, which are encoded by *COL4A3, COL4A4, and COL4A5*. In the kidney, the three type IV collagen proteins form heterotrimers and are exclusively found in the glomerular basement membrane (GBM)3. The lack of type IV collagen proteins causes the GBM to weaken and distend, and podocytes foot process effacement is also observed (REFERENCE). COL4A5 is the only type IV collagen protein encoded on the X chromosome, and is responsible for 80% of AS diagnosis. As the X-linkage suggests, males that are hemizygous to the *COL4A5* mutation are disproportionally affected compared to females. Males have an earlier onset and increased severity of the disease, with 50% of patients requiring dialysis or kidney transplants due to ESRF by the age of 25 and 100% by the age of 604. On the other hand females that are heterozygous for this X-linked AS have relatively later onset with only 12% developing ESRF by the age of 40 and 40% at the age of 80 years5. Curiously, patients with similar genetic mutations do not all present the disease in a similar manner, and studies have observed their age of onset and severity to be highly variable4.

In the 2015 International Workshop on AS, clinicians and researchers highlighted the need for an effective cure for AS6. Currently the only treatment option for AS patients is Angiotensin-converting-enzyme inhibitors (ACE-inhibitors), which are primarily used as treatment for hypertension4. Treatment with ACE-inhibitors are able to alleviate the mechanical pressures applied to the fragile GMB of AS patients and delay onset of ESRF, however treatment efficacy is highly dependent on timing6,7. In addition to the lack of treatment options, we still do not have a specific target for therapeutic interventions. Although *Col4a5* is known to cause AS, it is a poor therapeutic target as patients with this mutation vary dramatically in disease progression. It is widely accepted that the varying age of onset and severity of AS is in part due to underlying mechanisms that are able to modify disease progression. However, small samples sizes and other confounding factors preclude the ability to study such modifier in humans.

To our knowledge there has only been one study conducted to identify modifier genes in AS8. They observed variation between *Col4a3* knock out mice in 129X1/SvJ and C57BL/6J backgrounds, and identified 2 quantitative trail loci (QTL) on chromosome 9 and 16, however the intervals were not narrow enough to confidently identify candidate genes8.

In this study we aimed to effectively identify modifier genes of X-linked AS by introducing the *Col4a5* mutation into a diverse genetic background using the Diversity Outbred (DO) mice. DO mice are derived from eight inbred founder strains (A/J, C57BL/6J, 129S1/SvImJ, NOD/LtJ, NZO/HlLtJ, CAST/EiJ, PWK/PhJ, and WSB/EiJ), which captured nearly 90% of the known genetic variation present in laboratory mice12. The heterogeneity observed in the DO population allows for high resolution mapping and with a sufficient sample size this model is ideal for mapping modifier genes in X-linked AS 9-11.

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