**Comments:**

First paragraph reads too much like a list. The words are stiff and lacks flow

**Testing:**

Adding line to see tracking on github.

**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 commonly kidney disease2. AS patients with kidney disease are diagnosed with glomerulonephritis, and present with symptoms of hematuria and proteinuria. Inevitably, their kidney functions deteriorate as the disease progresses and leads to End-Stage Renal Failure (ESRF) 2. It is well studied that ESRF due to AS is caused by genetic mutations in *Col4a3, Col4a4, and Col4a5*, which encode for the α3-5 chains of collagen IV proteins found in the glomerular basement membrane (GBM) of the kidney3. Of these three genes, mutations in *Col4a5*, located on the X chromosome, is responsible for 80% of AS. X-linked AS patients do not all present the disease in a similar manner, in fact AS is known be highly variable in their in age of onset and severity4. Additionally due to its X-linkage, the disease disproportionally affects males. Studies have observed that X-linked AS in males have an earlier onset and increase severity of the disease, with 50% of patients requiring dialysis or kidney transplants due to ESRF by the age of 25, 90% by the age of 40, 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, however the rate of ESRF increases to 30% at the age of 60, and 40% at the age of 80 years5.

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 are Angiotensin-converting-enzyme inhibitors (ACE-inhibitors), which is primarily used as treatment for hypertension4. Treatment with ACE-inhibitors are able to alleviate the mechanical pressure applied to the vulnerable 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 target for therapeutic interventions. Although *Col4a5* is known to cause AS, it is a poor therapeutic target as the disease progression vary dramatically. The varying age of onset and severity of AS suggests possibilities of other underlying mechanisms that are able to modify disease progression caused by the *Col4a5* mutation. Identifying these mechanisms and the genes involved may lead to the development of precise and novel therapeutic targets.

To our knowledge there has only been one study conducted to identify modifier genes that lead to the variability in age of onset and severity of 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 probable candidate genes8.

In this study we aimed to identify modifier genes of X-linked AS by introducing the *Col4a5* mutation into a diverse genetic background using the Diversity Outbred (DO) mice 9-11. 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. This heterogeneity observed in the DO population is currently the best model that reflects the genetic diversity in the human population. (Ending pending results)

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