The following article summary was prepared by ASF's volunteer Research Program Chair and Board Member, André Weinstock, PhD, MSAS.

Wang, X., Zhang, Y., Ding, J., & Wang F. mRNA analysis identifies deep intronic variants causing Alport syndrome and overcomes the problem of negative results of exome sequencing. Sci Rep 11, 18097 (2021). https://doi.org/10.1038/s41598-021-97414-0

This article expands upon a potential reason why some patients/families that have a clear traditional diagnosis of Alport syndrome (AS) still exhibit negative genetic tests for AS.

5 families with confirmed AS via kidney biopsies but negative genetic tests were found to have novel COL4A4 and/or COL4A5 intronic variants. This is opposed to exonic variants which are much more obvious and detectable with modern NGS (Next Generation Sequencing) genetic tests. By analogy, exonic variants are like obvious spelling mistakes in the DNA genetic code while intronic variants are like subtle punctuation and spacing changes that modify the function and meaning of the sentence:

- Healthy variant: “Thank you! Your donation just helped someone cure Alport syndrome!”
- Exonic variants: “Think you! Your domation just just hooped anyone cure Airport syndrome!”
- Intronic variants: “Thankyou! You’re donation Just helped some one. Cure alport Syndrome!”

This research depended on looking at mRNA sequences from large urine sample collections and is not yet available to the general public. But it brings up a new and valid reason why, for some patients/families, AS is clearly present by traditional means (kidney biopsy, persistent proteinuria, hearing test, etc.) but not detected by current and standard genetic tests. It is hypothesized that as many as 20% of AS patients/families have intronic variants.