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

Consensus statement on standards and guidelines for the molecular diagnostics of Alport syndrome: refining the ACMG criteria

Savige, Judy et al.

European Journal of Human Genetics, April 15, 2021.

The Savige et al. paper is a technical "state-of-the-art" guideline for how to classify the diversity of thousands of Alport syndrome genetic variants.

As genetic sequencing becomes more commonplace, new variants are being discovered all the time.

The ability to predict which of these variants are benign, which are pathogenic, and to what degree of pathogenicity (i.e. "At what age can kidney failure be expected?", "Will hearing be impacted or not?", "Will vision be impacted or not?", etc.) is extremely critical for the Alport syndrome community.

For patients and parents-of-patients receiving a genetic diagnosis prior to experiencing kidney failure and/or hearing loss, guidance on severity of pathogenicity is key to optimizing their treatment and reducing anxiety.

Conversely, there are non-trivial populations of patients diagnosed with glomerular nephropathies (in particular FSGS, but also IgAN, MN, and even diabetes) that a genetic test would confirm they are actually Alport syndrome patients with a variant which has some degree of pathogenicity. This would then align the patient to the correct diagnosis, our community, and - importantly - alert their family for risk. It also informs future patients by increasing the number of known variants.

While some limited predictive ability is now possible with current understanding of the Collagen IV protein complex, aligning genetic diagnosis variants (genotypes) to experienced symptoms (phenotypes) from kidney patients around the world remains the best way to improve these guidelines on classification.

As more information becomes available, the authors hope to re-convene to update these guidelines accordingly.

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