MONOALLELIC PATHOGENIC ALG5 VARIANTS CAUSE ATYPICAL POLYCYSTIC KIDNEY DISEASE AND INTERSTITIAL FIBROSIS

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Résumé

Background: Disorders of the Autosomal Dominant Polycystic Kidney Disease (ADPKD) spectrum are characterized by the development of kidney cysts and progressive kidney function decline. *PKD1* and *PKD2*, encoding polycystin (PC)1 and 2, are the two major genes associated with ADPKD; other genes include *IFT140*, *GANAB*, *DNAJB11* and *ALG9*. Genetic testing remains inconclusive in ~7% of the families. We hypothesized that other genes may be associated with ADPKD spectrum.
Methods: Whole-Exome Sequencing (WES) or targeted massively parallel sequencing were used in a cohort of 1214 ADPKD-like and/or Autosomal Dominant Tubulointerstitial Kidney Diseases (ADTKD) pedigrees. Genomics England 100,000 Genomes Project data was accessed to identify additional families. Homozygous and heterozygous knockout cellular models were created employing CRISPR/Cas9 on renal cortical tubular epithelial (RCTE) cells. N-glycan precursor were analyzed by high-performance liquid chromatography (HPLC) after (2-3H) mannose pulse metabolic labelling. PC1 maturation profiles were analyzed employing immunoblot and PC1/PC2 membrane and ciliary localization studied by immunofluorescence.

Results: We performed WES in a large multiplex genetically unresolved ADPKD-like family and identified a monoallelic frameshift variant (c.703_704delCA) in *ALG5. ALG5* encodes the dolichyl-phosphate beta-glucosyltransferase, an asparagine-linked glycosylation mechanism enzyme, that participates in the synthesis of the Dol-P-Glc donor substrate required for the addition of glucose molecules during the synthesis of the N-glycan precursor in the endoplasmic reticulum lumen. Four additional pedigrees with likely pathogenic variants in *ALG5* were identified. Clinical presentation was consistent in the 23 affected members, with non-enlarged cystic kidneys and few or no liver cysts; 8 subjects reached end-stage kidney disease from 62 to 91 years of age. We demonstrate that *ALG5* deficiency, whether heterozygous or homozygous, leads to the accumulation of incomplete Man9GlcNAc2 N-glycan precursors and their transfer onto proteins in human kidney epithelial cells. We also show by characterization of *ALG5*-null RCTE cells that *ALG5* is required for PC1 maturation and thus membrane and ciliary localization, and that heterozygous loss of *ALG5* affects PC1 maturation. While PC1 protein level and maturation were rescued in *ALG5-/-* cells by the transfection of a wild-type *ALG5* construct, identified *ALG5* missense variants (p.Arg208His and p.Arg212His) failed to rescue PC1 maturation.

*Intervenant

Conclusion: Our results indicate that monoallelic variants of *ALG5* are sufficient to alter PC1 maturation leading to a disorder of the ADPKD-spectrum characterized by multiple small kidney cysts, progressive interstitial fibrosis and kidney function decline.