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.
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.