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Sporadic ADPKD-*IFT140*: Absence of Family History as an Indicator of Clinical Mildness

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Polycystic kidney disease (PKD) has become recognized as a genetically and clinically heterogeneous condition, with new disease genes being discovered upon atypical presentation. Atypical presentation contrasts with the classic clinical picture of autosomal dominant PKD (ADPKD), which is characterized by symmetric bilateral kidney enlargement, presence of liver cysts, and a PKD-family history, often over several consecutive generations. Sequencing aberrations in the genes *PKD1*/*PKD2* account for the vast majority of typical ADPKD (>90%); however, variants in new disease genes are to be considered upon atypical imaging patterns (unilateral, asymmetric, segmental, lopsided, or bilateral cystic disease with unilateral or bilateral kidney atrophy) or absence of typical extrarenal manifestations (e.g., liver or pancreas cysts, intracranial aneurysms, cardiac valve disease, colonic diverticula). Mechanistically, the following 2 groups can be distinguished among these new PKD disease genes: (i) genes encoding for components of the endoplasmic reticulum (*ALG5*,[1] *ALG6*,[2] *ALG8*,[3] *ALG9*,[4] *DNAJB11*[5]) and (ii) genes whose products are located and functionally associated with the primary cilium (*IFT140*,[6] *NEK8*[7]) (Figure 1a). Upon biallelic alteration, virtually all these genes were previously associated with an early-onset syndromic condition within the spectrum of congenital disorders of glycosylation (*ALG5*, *ALG6*, *ALG8*, *ALG9*) or nephronophthisis related ciliopathies (*IFT140, NEK8*).

Among atypical presentations, PKD due to monoallelic pathogenic variants in *IFT140* appears to be the predominant entity, characterized by an attenuated, mild natural history, with little to no incidences of kidney failure in midlife.[6,8,9] In their current article, Fujimaru *et al.*[10] report on the relatively high prevalence of pathogenic *IFT140* variants specifically among PKD-patients without overt family history (4.5% vs. 1% in PKD-patients with a family history). The authors argue that 10% to 25% of the total PKD population negate familial affection and that such absence of family history may increase the likelihood of causal genetic findings in the spectrum of non-*PKD1/2*-mediated disease, notably ADPKD-*IFT140*. In their cohort of 157 adults with PKD (≥5 cysts/kidney), they employed a targeted panel of 69 to 92 cystic kidney disease genes, including *IFT140*. As a result, they found monoallelic diagnostic *IFT140* variants in 4.5% of the cohort, variants in *PKD1/2* in 32.5%, and variants in other cystic kidney disease genes (e.g., *HNF1B, PKHD1, OFD1, NPHP4*) in 4.5%. Similar to the initial description of ADPKD-*IFT140*,[6] the authors report on minor liver involvement, but atypical renal cyst size and locations (large, exophytic cysts) with lower total kidney volume and better renal function, compared to classical ADPKD-*PKD1/2*. Prevalence of arterial hypertension was similar to that of patients with pathogenic variants in *PKD1/2* and 3 out of 7 patients with pathogenic *IFT140* variants and adequate cerebral imaging actually showed an intracranial aneurysm.

Nevertheless, some knowledge gaps for ADPKD-*IFT140* remain. From this and previous studies, there is still insufficient data available on the prevalence of extrarenal disease: notably, the open question of whether intracranial aneurysms or retinal phenotypes are part of the disease spectrum, because the latter is commonly observed in patients with biallelic pathogenic variants in *IFT140* (MIM #266920 and MIM #617781).[6] Phenotypic variability may also be due to additional hypomorphic variants, including variants of unknown significance. Ultimately, monoallelic and biallelic disease are

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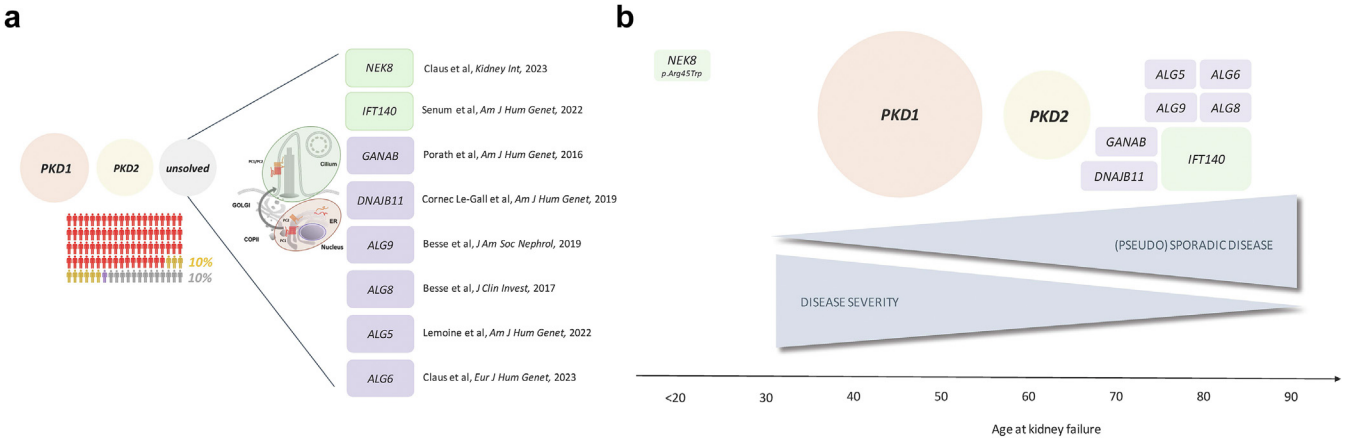

Figure 1. Overview on new autosomal dominant PKD genes with *IFT140* being the most prominent example. (a) Among the 10% of patients with genetically unresolved PKD, diagnostic variants in 1 of the 8 new disease genes can be found. Mechanistically, their gene products either play a role in the ER-based N-glycosylation process of the polycystins (PC1/2) (purple) or are associated with primary cilia function and signaling (light green). (b) Although renal disease severity decreases among the new ADPKD genes (with the exception of *NEK8* p.Arg45Trp), the likelihood of (pseudo) sporadic disease is increased in this group compared to typical ADPKD-*PKD1/2*. ADPKD, autosomal dominant polycystic kidney disease; COPII, coat protein complex II; ER, endoplasmic reticulum; PKD, polycystic kidney disease.

likely to represent 2 ends of a continuum.

Despite the growing list of cystic kidney disease genes, in the study of Fujimaru *et al.*,[10] pathogenic variants in cystic kidney disease genes have only been found in 41.4% of the 157 patients without familial affection. Even though an additional 20.4% of patients carried a variant of unknown significance in a cystic kidney disease gene, this still leaves almost 40% of the cohort genetically unresolved, compared to approximately 10% in patients with a family history. This may in part be explained by methodological limitations (e.g., panel sequencing). The diagnostic yield may have been higher with more sophisticated sequencing techniques such as (long-range) whole genome sequencing. Furthermore, other genetic (e.g., germline or somatic mosaicism) or nongenetic causes of kidney cysts (e.g., acquired renal cystic disease) remain a possibility. Nevertheless, the low estimated glomerular filtration rate (median 42.9 ml/min) and the relatively high prevalence of liver cysts (57.1%) suggest that *PKD1/2* variants might have been missed in these patients.

After all, the work by Fujimaru *et al.*[10] highlights the important contribution of pathogenic *IFT140* variants in ADPKD-like phenotypes, especially for patients with milder disease and no documented familial affection.

In genetics, sporadic disease typically suggests *de novo* status, somatic mosaicism, or recessive inheritance. However, in sporadic PKD with atypical adult-onset presentation, it is important to consider dominant inheritance with incomplete penetrance, due to a pathogenic variant in one of the newly discovered dominant PKD genes. With the exception of *NEK8*, where a distinct recurrent *de novo* missense allele (p.Arg45Trp) accounts for neonatal PKD,[7] this group of new PKD genes is overall associated with relatively mild cystic kidney disease. Sporadic cases are likely to be more frequent because parental affection was simply missed due to being oligosymptomatic or asymptomatic (Figure 1b). This phenomenon contrasts with true sporadic disease. Instead, the case of missed parental affection may therefore be referred to as "pseudosporadic".

Because family history is part of the clinical diagnostic criteria for imaging-based diagnosis of ADPKD (Pei-Ravine criteria), ADPKD-*IFT140* and other nonclassical forms of PKD can only be confirmed through genetic testing. Consequently, genetic testing has become increasingly important for the differential diagnosis of PKD in adults, aids in the prediction of disease progression, and guides targeted treatment. For now, we do not have sufficient evidence to recommend cascade testing of relatives for nonclassical forms of PKD. However, informing patients about the overall favorable prognosis of ADPKD-*IFT140* and other non *PKD1/2*-mediated disease is a key aspect of genetic counselling and may provide great relief for affected families.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Lemoine H, Raud L, Foulquier F, et al. Monoallelic pathogenic ALG5 variants cause atypical polycystic kidney disease and interstitial fibrosis. *Am J Hum Genet*. 2022;109:1484–1499. https://doi.org/10.1016/j.ajhg.2022.06.013
2. Boulogne F, Claus LR, Wiersma H, et al. KidneyNetwork: using kidney-derived gene expression data to predict and prioritize novel genes involved in kidney disease. *Eur J Hum Genet*. 2023;31:1300–1308. https://doi.org/10.1038/s41431-023-01296-x
3. Apple B, Sartori G, Moore B, et al. Individuals heterozygous for ALG8 protein-truncating variants are at increased risk of a mild cystic kidney disease. *Kidney Int*. 2023;103:607–615. https://doi.org/10.1016/j.kint.2022.11.025
4. Besse W, Chang AR, Luo JZ, et al. ALG9 mutation carriers develop kidney and liver cysts. *J Am Soc Nephrol*. 2019;30:2091–2102. https://doi.org/10.1681/ASN.2019030298
5. Huynh VT, Audrézet MP, Sayer JA, et al. Clinical spectrum, prognosis and estimated prevalence of DNAJB11-kidney disease. *Kidney Int*. 2020;98:476–487. https://doi.org/10.1016/j.kint.2020.02.022
6. Senum SR, Li YSM, Benson KA, et al. Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. *Am J Hum Genet*. 2022;109:136–156. https://doi.org/10.1016/j.ajhg.2021.11.016
7. Claus LR, Chen C, Stallworth J, et al. Certain heterozygous variants in the kinase domain of the serine/threonine kinase NEK8 can cause an autosomal dominant form of polycystic kidney disease. *Kidney Int*. 2023;104:995–1007. https://doi.org/10.1016/j.kint.2023.07.021
8. Dordoni C, Zeni L, Toso D, et al. Monoallelic pathogenic IFT140 variants are a common cause of autosomal dominant polycystic kidney disease-spectrum phenotype. *Clin Kidney J*. 2024;17:sfae026. https://doi.org/10.1093/ckj/sfae026
9. Salhi S, Doreille A, Dancer MS, et al. Monoallelic loss-of-function IFT140 pathogenic variants cause autosomal dominant polycystic kidney disease: a confirmatory study with suspicion of an additional cardiac phenotype. *Am J Kidney Dis*. 2024;83:688–691. https://doi.org/10.1053/j.ajkd.2023.08.019
10. Fujimaru T, Mori T, Sekine A, et al. Importance of IFT140 in patients with polycystic kidney disease without a family history. *Kidney Int Rep*. 2024;9:2685–2694. https://doi.org/10.1016/j.ekir.2024.06.021