IFT140-related ADPKD

To the Editor: As an Italian referral center for autosomal dominant polycystic kidney disease (ADPKD) for over 15 years , we read with great interest the article by Fujimaru *et al.*,[1] highlighting the contribution of pathogenic variants of *IFT140* to the spectrum of ADPKD, particularly in patients without family history. Given our clinical and genomic experience, we present the case of a 51-year-old woman, without family history of ADPKD, harboring a heterozygous loss-of-function variant of *IFT140* (NM_014714.4: c.2214_2217delCAGA; p.Asp738GlufsTer47) and negative pathogenic variants in other genes associated with monoallelic cystic kidney diseases. This proband exhibited a mild phenotype, further supporting the phenotypic variability of *IFT140*-associated ADPKD.

Our patient, diagnosed incidentally at the age of 20 years, presented with significant renal asymmetry and relatively preserved renal function, contrasting with the typical bilateral renal involvement seen in *PKD1*/*PKD2* variants. Despite her longstanding diagnosis, the patient remains in good health, with moderate hypertension and no liver involvement. Magnetic resonance imaging revealed very large cysts primarily in her left kidney, which was enlarged, whereas the right kidney maintained normal size and function with only minor cysts (Figure 1). Renal scintigraphy showed almost complete functional exclusion of the left kidney, whereas the right kidney compensated with stable function over time (eGFR, 90 ml/min).

This case highlights the differences between ADPKD-*IFT140* and the more common forms caused by *PKD1* or *PKD2* variants. Patients with *IFT140* variants exhibit fewer cysts, minimal liver involvement, and better renal outcome.[2,3] The pronounced renal asymmetry in our case confirms complexity, deviating from the typical ADPKD phenotype, where both kidneys usually enlarge progressively.

Interestingly, because of their nearby localization in 16p13.3, coinheritance of *PKD1* variants has been postulated as a phenotype modifier in *IFT140*-associated disease,[4] further emphasizing the need for precise genetic testing to distinguish between these variants and clarify the underlying cause. Expanding genetic testing beyond *PKD1* and *PKD2* is crucial for accurate diagnosis and management, especially in atypical cases. Regular follow-up is essential, because even mild cases may present delayed complications.

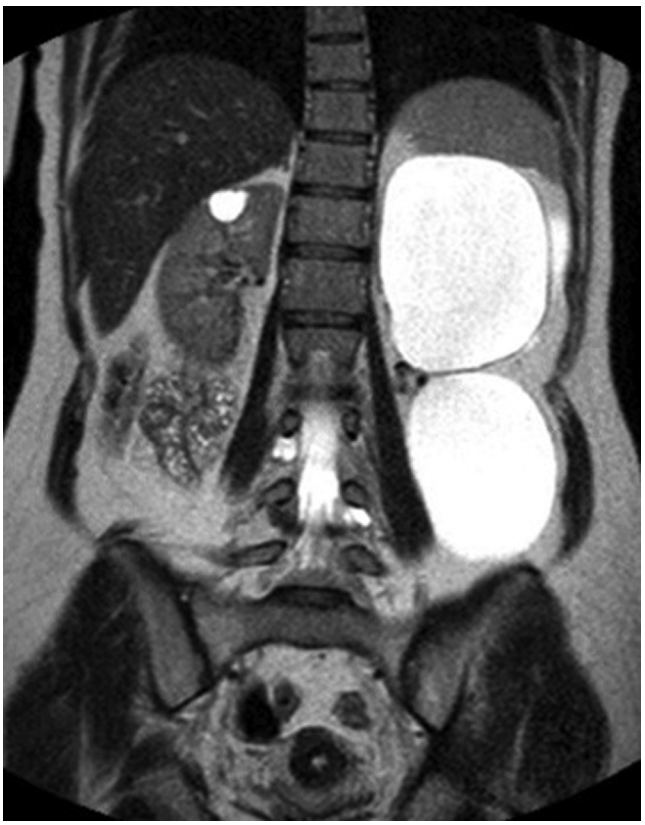

Figure 1. Asymmetric presentation of renal involvement.

In conclusion, we strongly advocate for expanding genetic testing to include genes such as *IFT140*, improving diagnostic precision and facilitating personalized care in ADPKD.

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1. 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
2. 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
3. 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
4. Chang AR, Moore BS, Luo JZ, et al. Exome sequencing of a clinical population for autosomal dominant polycystic kidney disease. *JAMA*. 2022;328:2412–2421. https://doi.org/10.1001/jama.2022.22847

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