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Describing and Explaining ADPKD Variability Within Families

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Differences in the experience of kidney disease and other complications of autosomal dominant polycystic kidney disease (ADPKD) within families has long been a clinical conundrum.[1] Where large cohort studies have previously identified key associations between genetic etiology and ADPKD phenotype,[2,3] there has been a persistent observed and reported phenomena of unexpectedly mild disease in close to 1 in 5 patients.[4] These unexpectedly divergent cases have challenged the traditionally deterministic dogma of genotype-phenotype correlations in monogenic disease. Multiple different lines of evidence have emerged to help explain such phenotypic discordance, including polygenic contributions to phenotype,[5] incomplete penetrance,[6] sex or environmental exposures,[7] and an overarching theory of a polycystin signaling cystogenic threshold which relates to ADPKD phenotype[8] (Figure 1). The practical application of these has emerged in the form of the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score,[9] which combines many of these factors to practically prognosticate kidney phenotype in ADPKD in a more individualized way. Further causative genes which help to explain phenotypic variability and the broader spectrum of ADPKD have also been identified.[S1–S3] Despite these efforts, approximately 1 in 10 families affected by ADPKD experience substantial and otherwise unexpected kidney disease discordance,[S4] which continues to pose challenges for individual clinical management, prognostication and broader genetic counselling.

Recently, Elhassan *et al.*[S5] have replicated and expanded upon the previous findings around such intrafamily variability of ADPKD severity in an Irish family cohort. Similar to Lanktree *et al.*,[S4] they have identified that approximately 13% of families experience marked or extreme intrafamily variability. This is important in several important ways discussed next.

First, this study[S5] reconfirms these findings in a genetically distinct population which further aids in the translation of its findings. Although contemporary Canadian and Irish populations are diverse, it is likely that they remain overrepresented by those of White or Caucasian ancestry. Therefore, further replication in additional diverse communities and jurisdictions is likely still required, especially in Asia, Africa, and Oceania.

Second, these findings of Elhassan *et al.*[S5] critically confirm the establishment of key definitions of ADPKD phenotype severity and variability as follows:

- Severe Disease. Defined as patients who reached kidney failure before the age of 55 years, or with eGFR annual decline >5 ml/min/yr, or with PROPKD score >6, or with Mayo Clinic Imaging Classification (MCIC) class 1D or 1E, or with a kidney length on ultrasound >16.5 cm at age <45 years.
- Mild Disease. Defined as patients who developed kidney failure later than the age of 70 years, or with PROPKD score of 3 at an age later than 35 years, or with MCIC risk class 1A or 1B.
- Intermediate Disease. Failed to meet the criteria for either mild or severe disease.
- Marked/Discordant Intrafamily Variability. A family with at least 1 severe and 1 mild case.

The confirmed assertion of these definitions is critical to future application of such findings in practice given that this now enables an accepted ontology to be applied. It must however be noted that the application of the definition of intrafamily variability is dependent upon a family having at least 2 known and well-characterized family members. For *de novo* cases or those without known or well-characterized affected family members, alternate approaches to individualized prognostication and

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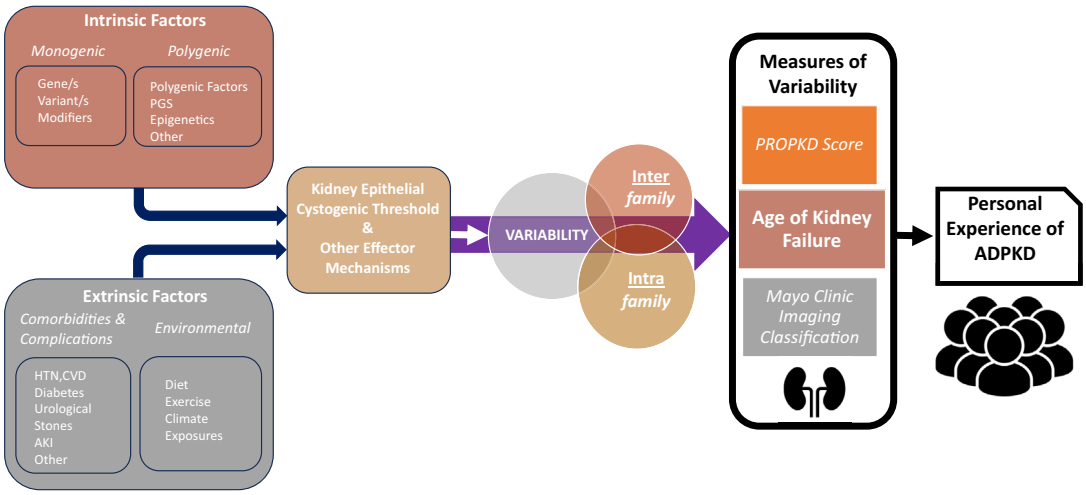

Figure 1. Factors contributing to ADPKD variability. ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; CVD, cardiovascular disease; HTN, hypertension; PGS, polygenic score.

counselling remain indicated, such as PROPKD score or MCIC.[S6]

Third, this analysis was able to compare different criteria of disease severity for both interfamily variability as well as intrafamily variability of ADPKD phenotype. This identified that interfamily phenotypic variability was most discordant according to PROPKD score (63.7%); however, this variability between different families was similar by age at kidney failure and MCIC (28.8% and 24%, respectively). In contrast, intrafamily variability was most discordant according to MCIC (24%) with both age at kidney failure and PROPKD score representing much more modest phenotypic discordance within individual families (7.7% and 8.4%, respectively). This suggests that a broad approach with multiple forms of severity assessment is indicated for individual and family characterization and prognostication. For a patient who might be encountered in clinic, appraisal of personal phenotype (kidney imaging, medical history), genetic information, and family history may all be required in addition to understanding of current kidney function in order to provide meaningful ADPKD prognostication for them.

Lastly, this study gives further practical insights into a more nuanced experience of being affected by a monogenic disease such as ADPKD. The potential disease-associated changes in our genome do not necessarily define the whole story of what might happen next. Rather, a broad combination of intrinsic and extrinsic factors is likely to together influence phenotypes and disease trajectories, and ADPKD is certainly illuminating this. Where this multilayered reality may be less binary or linear, the future challenge remains in applying it to the clinical care of affected or at-risk patients and families. Similar or larger high quality cohort studies across different populations and jurisdictions will assist with confirming these findings and enable globalized approaches to ADPDK research in partnership with patients. Areas for priority action might include longitudinal characterization for more granular prognostication evidence, novel gene and polygenic characterization, platform trial designs, research or clinical data reuse to minimize research waste, and dynamic consent approaches to patient-centric participation.

This study[S5] in concert with previous research and astute clinical investigation is enabling the delivery of a more personalized approach to ADPKD clinical care. It indicates that ~1 in 10 families experience marked or discordant intrafamily variability of ADPKD phenotype, with a well-defined approach to ADPKD phenotype ontology, and the indicated need to concurrently apply multiple approaches to disease severity assessment. Most importantly, it also highlights future avenues for clinical study and research to further refine the evidence base that underpins the patient-centric and increasingly personalized care paradigm in contemporary ADPKD practice.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

SSA and AJM drafted the manuscript with both coauthors providing input, review, and edits.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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