



Impact of Novel Heterozygous Mutations on ADPKD: Genetic Testing, Clinical Implications and Personalized Management

Ntowe Olunuga*

Department of Surgery, Duke University Medical Center, Durham, United States of America

DESCRIPTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common genetic disorders, affecting approximately 1 in 1,000 live births. Characterized by the progressive formation of fluid-filled cysts in the kidneys, it leads to End-Stage Renal Disease (ESRD) in a significant number of patients. Although the disease is primarily caused by mutations in the *PKD1* and *PKD2* genes, the identification of novel mutations, particularly heterozygous ones, is crucial for advancing genetic understanding and patient management.

The timing of genetic testing in ADPKD is vital, particularly for individuals with a family history of the disease. Early genetic testing can provide essential information on the prognosis of the disease, guide clinical management, and offer genetic counselling for at-risk family members. Testing is most often conducted when the first symptoms of the disease, such as hypertension or haematuria, arise. However, in the context of novel mutations, testing may be prompted by the presentation of unusual disease progression or atypical clinical features that do not align with known mutation profiles. Moreover, genetic analysis can be utilized to confirm a diagnosis, particularly in patients with ambiguous clinical symptoms or family histories of ADPKD without clear genetic linkage. The primary genes responsible for ADPKD are *PKD1*, which accounts for approximately 85% of cases, and *PKD2*, responsible for around 15% of cases. Both genes encode proteins that are integral to the formation and function of renal tubules. Mutations in these genes disrupt the normal cellular processes, leading to the growth of cysts and renal damage over time. While the vast majority of mutations associated with ADPKD are heterozygous, meaning the individual carries a single copy of the mutated gene, the discovery of novel mutations provides a deeper understanding of the molecular mechanisms underlying the disease.

Heterozygous mutations refer to changes in one allele of a gene, which can result in a partial loss of function of the

corresponding protein. In ADPKD, these mutations can vary significantly, ranging from point mutations to larger deletions or duplications. The identification of novel mutations is particularly important for several reasons. First, it can reveal new genetic loci associated with the disease, expanding the knowledge base of genetic markers. Second, it can help to define the spectrum of clinical manifestations of ADPKD, which may vary depending on the nature of the mutation. Third, novel mutations may be linked to atypical forms of the disease, such as those with delayed onset or slower progression. Genetic analysis of ADPKD often involves sequencing both *PKD1* and *PKD2* genes, as well as screening for large deletions or duplications through techniques such as Multiplex Ligation-Dependent Probe Amplification (MLPA). Newer technologies, such as Whole-Exome Sequencing (WES), have also gained prominence in identifying novel mutations. WES allows for the examination of all protein-coding regions in the genome, enabling the discovery of previously unidentified mutations that could contribute to the development of ADPKD. When a novel mutation is identified, it is essential to verify its pathogenicity through functional studies, including in vitro assays or animal models, to understand its impact on protein function.

In cases involving novel heterozygous mutations, the clinical implications can be diverse. Some mutations may cause a mild form of ADPKD, with slow progression and relatively normal renal function for many years, while others may lead to a more severe phenotype, characterized by rapid cyst growth and early renal failure. Additionally, the presence of a heterozygous mutation in *PKD1* may be associated with a more severe disease course compared to mutations in *PKD2*. However, the exact relationship between genotype and phenotype in ADPKD is complex and influenced by other genetic, environmental, and epigenetic factors.

Genetic counseling plays a critical role in the management of ADPKD, particularly for families affected by novel mutations. Genetic counselors provide families with information about inheritance patterns, the risks of transmission to offspring, and

Correspondence to: Ntowe Olunuga, Department of Surgery, Duke University Medical Center, Durham, United States of America, E-mail: olunuga_n@gmail.com

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the potential for early diagnosis through genetic testing. For families with novel mutations, counseling becomes even more essential, as the implications of these mutations may not be fully understood, and the risks of transmission may vary. For instance, if a novel heterozygous mutation is identified in a parent, it is important to discuss the likelihood of offspring inheriting the mutation, as well as the potential age of onset and progression of the disease. Moreover, genetic counseling includes the discussion of available interventions, including lifestyle changes, medical therapies, and potential involvement in clinical trials for novel therapeutics.

In conclusion, genetic testing and counseling in ADPKD continue to evolve, the discovery of novel mutations presents

both challenges and opportunities. While the identification of these mutations expands our understanding of the disease's genetic basis, it also raises important questions about the clinical management of patients with less well-characterized mutations. The complex relationship between genotype and phenotype underscores the need for personalized care that takes into account not only the genetic mutation but also the individual's overall health, family history, and disease progression. Furthermore, advances in genetic testing technologies hold promise for uncovering more rare mutations and providing a more complete picture of the genetic underpinnings of ADPKD, potentially leading to new therapeutic strategies.