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Identification of a *PKD1* Non-truncating Variant Presenting with a Rapid Progression: A Case Report

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Abstract

Background: Genetic diagnosis in cases with autosomal dominant polycystic kidney disease (ADPKD)is important in determining prognosis and enabling risk recurrence in the family. *PKD1* is the commonest gene in ADPKD and genotype phenotype correlation with the type of variant has been reported. Studies on the molecular genetic diagnosis of ADPKD have identified several variants classified as variants of uncertain significance presenting a challenge in interpreting their significance in disease progression.

Methods: The proband presented with a family history of ADPKD and severe progression of his condition. Molecular genetic diagnosis of the proband using a gene panel NGS identified a non-truncating missense variant of uncertain significance in the *PKD1* gene (c.9397G>T). Segregation studies in the family confirmed that the variant segregated with the disease and studies using quantitative PCR confirmed its effect on gene.

Results: The segregation and RNA expression studies enabled the re-classification of the variant from variant of uncertain significance to likely pathogenic which correlated well with his clinical presentation. This case highlights the importance of accurate classification of genetic variants in patients with ADPKD to enable correct prognosis and management and indicates the possibility of additional factors that may influence genotype phenotype correlation.

Introduction

PKD1 is the commonest gene implicated in autosomal dominant polycystic kidney disease (ADPKD), followed by PKD2, whereas several other genes have also been described in a fewer number of patients (Porath et al., 2016; Besse Whitney et al., 2019; Masyuk et al., 2022; Senum et al., 2022). The phenotypic expression of ADPKD varies significantly depending on the specific gene involved and is also influenced by the type of genetic variant present at a single gene locus. Truncating variants in the *PKD1* gene are associated with a poorer renal survival rate, with the onset of ESRD occurring at a median age of 55.6 years; 51 years (Cornec-Le Gall et al., 2013; Ciantar et al., 2024). In contrast, non-truncating *PKD1* variants (such as in-frame deletions and missense variants) have been associated with a later median onset of ESRD at 67.9 years; 58 years, indicating a difference in disease progression, contributing to milder phenotypic outcomes (Cornec-Le Gall et al., 2013, Ciantar et al., 2024).

Molecular diagnosis of cases with ADPKD is clinically important even in cases with a clinical diagnosis as it enables better prognosis and management. It is one of the parameters considered in predictive tools such as PROPKD (Cornec-Le Gall et al., 2016). Furthermore, reaching a genetic diagnosis in the affected patient makes predictive testing in the family possible. Genetic studies on cohorts of patients with ADPKD have consistently identified a number of novel variants some of which are classified as variants of uncertain significance (Hosseinpour et al., 2022; Yu, Chih-Chuan et al., 2022; Nigro et al., 2023). The genotype phenotype corrrelation of specific variants is important as it helps clarify the prognostic clinical implications of a specific variant. We present here a case of a family with a clinical diagnosis of ADPKD in whom a missense variant in the PKD1 gene initially classified as a VUS was associated with a severe phenotype.

Case Presentation

The proband is a 36-year-old male born to non-consanguineous Maltese parents who consented to participate in a study. He was first referred to the Nephrology Clinic at the age of 25 years for screening in view of a family history of ADPKD. His father had been clinically diagnosed with ADPKD, but his genotype never determined. Ultrasound imaging at the time showed multiple cysts on both kidneys up to 4.5cm in diameter. Liver cysts were also noted. A clinical diagnosis of ADPKD was thus made. At the age of 25, his creatinine was 113 umol/L with an eGFR of 68 ml/min/1.73m². His renal profile was then regularly monitored, and imaging was conducted frequently. At the age of 29, he presented with haematuria and loin pains and was diagnosed with hypertension one year later.

At the time of recruitment for the study (36 years), he was at stage 4 chronic kidney disease (CKD). 18 months later, his eGFR dropped below 10 ml/min/1.73m^2 and he was started on haemodialysis. His kidney volumes were also looked at retrospectively. Cross-sectional imaging was first done at the age of 34 years. A total of three CT Kidneys, Ureters, and Bladder (KUB) were done from 34 until 38 years of age. A marked increase in volume could be appreciated, in line with the deterioration in kidney function (Table 1). The kidney volumes classified the patient as Mayo 1E at the age of 34 years. The PROPKD score at the same time was 5, classifying as intermediate risk.

Table 1: Progression of eGFR and kidney volume.

Age (years)	Creatinine (umol/L)	eGFR (ml/min/1.73m^2)	Right Kidney Volume (mL)	Left Kidney Volume (mL)	Total Kidney Volume (mL)
26	123	66	not available	not available	not available
28	152	50	not available	not available	not available
34	244	29	1298	1403	2701
36	368	17	1588	1672	3260
38	640	8	2126	2181	4307

Molecular Genetics

A heterozygous missense variant at the *PKD1* locus, classified as a VUS by ACMG/AMP was identified using the target gene panel NGS for *PKD1*, *PKD2*, *GANAB*, *DNAJB11*, *PKHD1* and *DZIP1L* genes (Supplementary Material 1). Sanger sequencing confirmed the variant in the proband (Supplementary Material 2). The variant *PKD1*:c.9397G>T (RefSeq accession number NM_001009944.2) results in a missense change in exon 26, where Glycine (Gly, G) is replaced by Cysteine (Cys, C) at position 3133. The variant is located within the PLAT domain of the encoded protein, a region crucial for calcium-dependent lipid or protein binding. Additionally, the variant is near the exon/intron junction, where exonic nucleotides can influence splicing (Aron et al., 2022).

The PhyloCons100Way conservation score of 1.0 underscores the significant conservation of this region. In silico studies provided supporting evidence of pathogenicity, with strong pathogenic predictions from 16 tools (MetaRNN, BayesDel addAF, BayesDel noAF, dbscSN, EIGEN, FATHMM-MKL, FATHMM-XF, M-CAP, MutPred, PROVEAN, EIGEN PC, MaxEntScan, Mutation assessor, Primate AI, SIFT, SIFT4G). The CADD, DANN and REVEL scores indicated that the variant is disease causing. This variant has no associated rs number, allele frequency data is unavailable, and searches in dbSNP, PubMed, and Google returned no results, confirming that this variant has not been previously reported in databases or publications, thereby indicating its novelty. According to ACMG classification, the variant is classified as PM1_Moderate (UniProt protein PKD1_HUMAN domain 'PLAT' has 164 missense/in-frame variants (57 pathogenic variants, 105 uncertain variants, and 2 benign variants), which qualifies as moderate pathogenic), PP3_Moderate (Variant is predicted splicing: scSNV-ADA = 0.999964 is greater than 0.999925, and LOF in gene *PKD1* is known to cause disease (gene has 2 443 reported pathogenic LOF variants), furthermore AlphaMissense = 0.88 is between 0.787 and 0.956 ⇒ supporting pathogenic) and PM2_Supporting (Variant not found in gnomAD genomes, good gnomAD genomes coverage = 31.9). Using the ACMG rules, this combination typically classifies the variant as VUS.

Familial Segregation Studies

To strengthen the causal relationship between this variant and ADPKD, genetic investigation was extended to the proband's affected brother (II.1) and unaffected sister (II.2) who accepted to be included in the study (Figure 1). The affected parent (I.1) had passed away, so genetic testing was not possible, and the proband's children (III.1, III.2, III.3) were minors, excluding them from the study. The exclusion of the proband's children from the study due to their minor status precludes the possibility of examining the penetrance of this variant in the next generation.

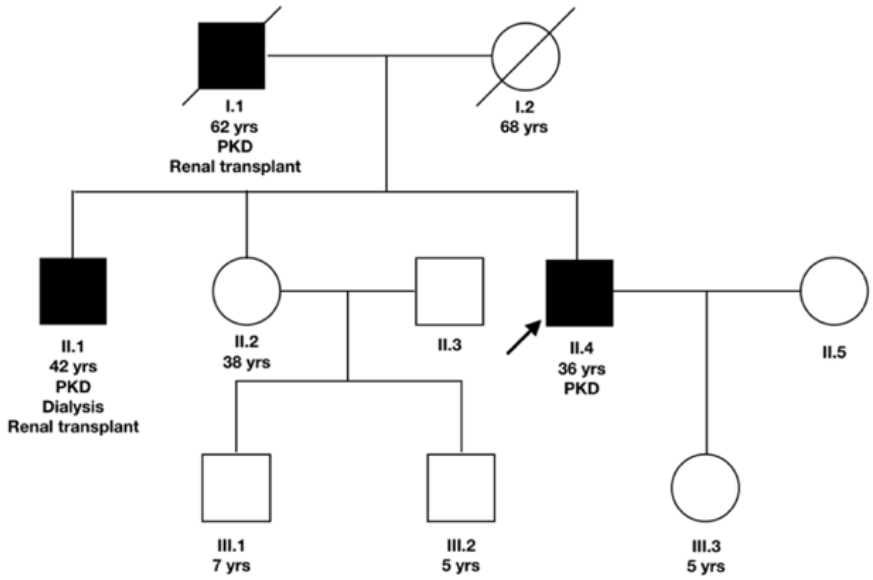


Figure 1: Family pedigree of proband (II.4).

Sanger sequencing confirmed that the proband's brother (II.1) had the same missense *PKD1* variant c.9397G>T (p.Gly3133Cys) variant and the variant was not identified in his unaffected sister (II.2) (Supplementary material 2). These results showed that the variant co-segregated with the disease in the family indicating that it was clinically significant in this family. The proband's affected brother (II.1) had a similar clinical presentation while the unaffected sister (II.2) lacked both the clinical features and the variant. The variant segregated in an autosomal dominant mode with the clinical condition in the family strongly supporting a causal relationship between the identified variant and the observed clinical phenotype.

Supplementary Material 1

Details of Gene Panel

The target gene panel yielded a total of 60 variants, of which 56 were classified as SNVs, 2 as insertions, 1 as a deletion and 1 as a substitution. Variants were filtered according to allele frequency, ACMG/AMP guidelines, functional consequences and clinical phenotype.

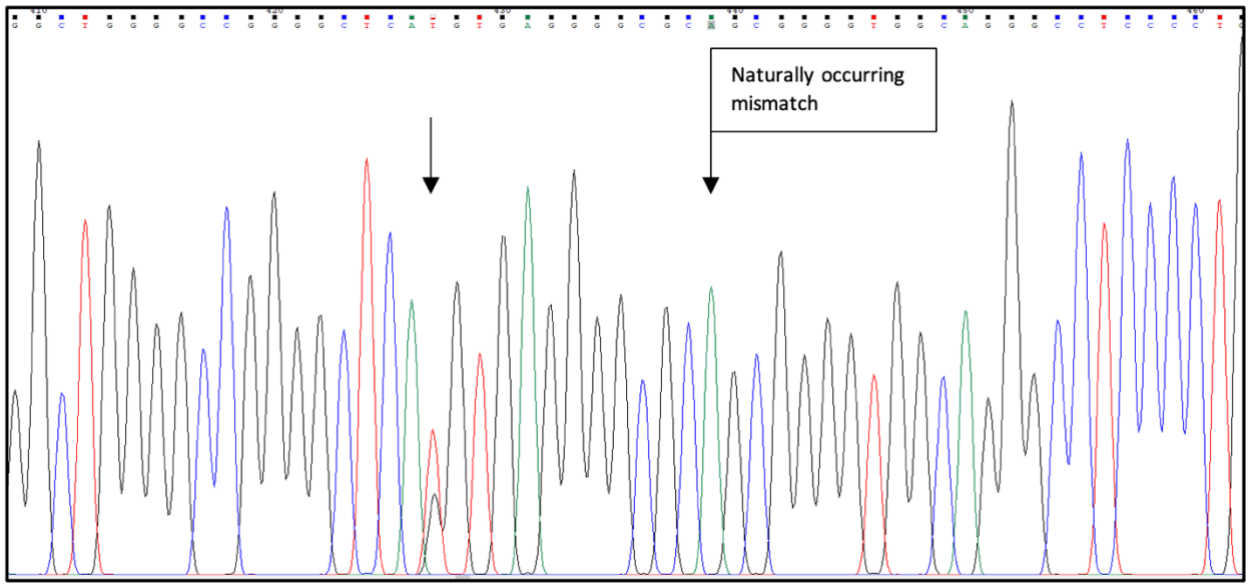
Table 1: Customized gene panel NGS detail of coverage and number of reads.

Total number of reads in raw sequence	100,292
Number of duplicates	0%
Number of reads singly mapped	86.92%
Number of reads singly mapped to the target region	80.41%
Average depth - on target	97%
Coverage 10x	99.4%
Coverage 20x	99.4%
Coverage 30x	99.4%

Targeted next-generation sequencing did not identify any other disease-causing variants, and no other variants were retained. Further whole-exome sequencing confirmed the presence of the *PKD1* variant, with no other disease-causing variants in kidney disease genes. Clinically, there was a high suspicion of ADPKD, with no other variants explaining the phenotype and so further studies were indicated.

Supplementary Material 2

1. Sanger sequencing of variant *PKD1* variant c.9397G>T (p.Gly3133Cys).



Supplementary Figure: Sanger sequencing trace showing mutated sequence. The sequence includes the naturally occurring mismatches which ensure that the variant is in the genuine gene and not the pseudogene.

Gene Expression

Gene expression studies were performed to assess this variant which is predicted to be disease causing. The significance of the expression levels of the *PKD1* aberrant transcript was assessed using a one-sample t-test with IBM SPSS Statistics Version 28. Gene expression analysis, performed by quantitative real-time PCR (qPCR), demonstrated a dysregulated expression pattern associated with the variant, supporting its clinically significant role. The case showed a statistically significant effect on the expression of the aberrant transcript (p-value <0.05).

Variant Classification

According to ACMG classification, this variant was originally classified as a VUS based on PM1_Moderate, PP3_Moderate and PM2_Supporting. With this segregation analysis variant could be classified as a likely pathogenic variant based on PM2_Moderate, PP1_Supporting, PP3_Supporting and PP4_Supporting. In accordance with the ACMG/AMP guideline framework for variant classification, these findings fulfill key criteria that justify an upgrade in classification from a 'Variant of Uncertain Significance (VUS)' to 'Likely Pathogenic'.

Risk Stratification

At the age of 26, the patient scored 3 using the PROPKD tool, indicating a low risk of rapid disease progression (total score = 3: male, 1 point). The Mayo classification could not be used as no cross-sectional imaging was available at the time. After presenting with loin pains and haematuria at the age of 29 and being diagnosed with hypertension aged 30, the PROPKD score rose to 5 (male, 1 point; urological event before 35 years, 2 points; hypertension before 35 years, 2 points), now suggesting an intermediate score.

Mayo classification at the age of 34, when the eGFR was already 29 ml/min/1.73m^2, also indicating a high risk for rapid disease progression. At the time of testing, at 36 years of age, the PROPKD score was 5 as the non-truncating variant was classified as a VUS. The PROPKD score only identified the patient's risk correctly after the re-classification of the variant with a score of 7 (male, 1 point; urological event before 35 years, 2 points; hypertension before 35 years, 2 points; non-truncating *PKD1* mutation, 2 points) indicating a high risk.

Discussion

This case highlights the importance of accurate genetic diagnosis in cases of ADPKD. At the time of clinical and genetic diagnosis, the PROPKD score indicated a low risk of rapid disease progression. Despite this favourable prognostic classification, the patient experienced unexpectedly rapid disease progression. Prognostic scores need to be continually re-assessed during follow-up, particularly in young patients, in whom age-dependent clinical features may not yet be fully expressed. The PROPKD score accurately determined the patient's disease progression as high risk only after re-classification of the variant. This case also highlights the fact that while the lack of cross-sectional imaging early during follow-up prevented the calculation of the Mayo classification. Other potential prognostic markers, such as a family history of end stage kidney disease (ESKD) and the presence of hepatic cysts, are not included in these established prognostic tools.

The association of non-truncating *PKD1* variant presenting with a severe progression of disease raises the possibility that additional genetic, epigenetic, environmental modifiers or molecular domain may be contributing to the aggressive clinical course. A study (Sucholeiki et al., 2025) has shown that the molecular domain location of nontruncating variants in *PKD1* may potentially affect the impact of a particular variant on disease progression.

Genetic testing is revolutionizing the diagnosis of cystic kidney diseases, particularly in pinpointing pathogenic variants in the *PKD1* gene. However, the rise of NGS has also highlighted a critical diagnostic bottleneck: the classification of variants of uncertain significance (VUS) (Aklilu et al., 2024). While VUS cases embody the promise of advanced genetic testing, they also expose its limitations, leaving patients in diagnostic limbo and clinicians with unresolved questions regarding disease management. This study addresses the challenge of VUS by detailed phenotypic characterization of affected individuals, comprehensive review of family and medical history of relatives.

The current reliance on statistical and bioinformatic tools for VUS classification, including ACMG/AMP guidelines, minor allele frequency (MAF) thresholds (Lasky-Su, 2017), and in silico prediction tools, falls short of providing definitive answers. These tools, though valuable, operate within the confines of computational predictions, often lacking functional or clinical validation. This creates a systemic issue in reaching a definite genetic diagnosis. Without supported evidence from family-based segregation studies or functional studies, statistical thresholds alone cannot establish pathogenicity with confidence (Aklilu et al., 2024).

In accordance with ACMG/AMP guidelines, this variant meets the criteria for reclassification of the VUS to 'likely pathogenic', supported by evidence corresponding to PM2, PP1-PP4 (Richards et al., 2015). By integrating molecular data with observed genotype-phenotype correlations, this approach increases diagnostic accuracy and allows more definitive genetic interpretations. A definitive genetic diagnosis guides more informed clinical management, from monitoring disease progression to tailoring interventions, and enhances genetic counselling for affected families. The combination of molecular genetic data together with a thorough clinical genetic assessment highlights the necessity of a multidisciplinary approach in the interpretation of VUS in a clinical genomics context.

Conclusion

This case report highlights the importance of complete characterization of the genetic profile of patients with ADPKD and the accurate correlation with the clinical presentation to correctly predict the disease progression. Our findings demonstrate that the molecular domain locations of nontruncating variants in *PKD1* should be explored as potential prognostic markers of early-stage ADPKD. Furthermore, it indicates that additional factors such as environmental and epigenetic may play a role in determining the predictive significance of a particular genetic variant.

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Author's Contributions

Natalie Ciantar: Conceptualization, Formal analysis, Investigation, Methodology, Writing - original draft.

Graziella Zahra: Methodology, Supervision, Resources.

Julian Delicata: Collection of patient clinical data, Investigation, review.

Emmanuel Farrugia: Project administration, Funding acquisition, Patient recruitment.

Edith Said: Conceptualization, Project administration, Funding acquisition, Genetic counselling, Investigation, Methodology, Supervision, Writing - review & editing.

Ethical Consideration

The study was reviewed and approved by the University of Malta Research Ethics Committee (ethics number - 2505_09082019 on 08.04.2020).

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Disclosure of Conflict of Interest

The authors declared that they have no conflict of interest.

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