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Independent Replication of PSKH1-Associated Hepatorenal Ciliopathy: A Fifth Family with a Novel p.Ala195Thr Variant Expands the Phenotypic and Molecular Spectrum

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Case Report

Keywords: Hepatorenal ciliopathy, PSKH1, Pediatric cholestasis, Exome sequencing, Renal dysfunction

Posted Date: June 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9295478/v1

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Additional Declarations: No competing interests reported.

Abstract

Background:PSKH1-associated hepatorenal ciliopathy is an exceptionally rare and recently recognized autosomal recessive disorder characterized by neonatal-onset cholestasis and renal dysfunction. To date, the association between pathogenic variants in the PSKH1 gene and this phenotype has been reported in a single study describing four unrelated consanguineous families.

Objectives: To describe a fifth affected family carrying a novel homozygous PSKH1 variant and to compare the clinical findings with previously reported cases in order to further delineate the clinical and molecular spectrum of this emerging disorder.

Case presentation and results: We describe three affected siblings from a consanguineous Palestinian family who presented during early infancy with conjugatedhyperbilirubinemia, elevated gamma-glutamyl transferase (GGT), and hepatosplenomegaly. Renal involvement ranged from early dysfunction to progressive renal failure with metabolic acidosis. Liver biopsy revealed marked cholestasis with moderate portal fibrosis and focal bridging, without bile duct paucity or proliferation. Extrahepatic features included global developmental delay and cytopenias. Whole-exome sequencing identified a novel homozygous missense variant PSKH1(NM_006742.3):c.583G>A (p.(Ala195Thr)), which segregated with the disease in the family. Despite supportive management, all three children died in infancy or early childhood due to complications of their multisystem disease.

Conclusion: This study provides an independent support for the association between PSKH1 and hepatorenal ciliopathy and identifies a novel missense pathogenic variant (p.Ala195Thr) in a fifth affected family worldwide. These findings reinforce the role of PSKH1 in this severe disorder and highlight the importance of early genomic testing for clinical management and genetic counseling.

INTRODUCTION

Ciliopathies are a diverse group of genetic disorders arising from defects in the structure or function of primary cilia, specialized organelles critical for cellular signaling, development, and homeostasis [1]. Among them, hepatorenal ciliopathies are characterized by combined hepatic and renal involvement, often presenting with congenital hepatic fibrosis, cholestasis, and renal anomalies ranging from cystic dysplasia to tubulointerstitial disease [2].

A recently identified form of hepatorenal ciliopathy has been linked to biallelic mutations in *PSKH1*, a gene encoding a serine/threonine kinase localized to the centrosome and involved in the regulation of pre-mRNA processing. In a large exome-based study of pediatric cholestasis, *PSKH1* mutations were shown to cause elongated, dysfunctional cilia, confirming the gene's role in ciliary biology and establishing it as a novel cause of syndromic cholestasis with renal involvement [3, 4].

PSKH1-related ciliopathy represents a newly recognized monogenic etiology of pediatric cholestasis. Affected children typically present with early-onset cholestatic jaundice, elevated gamma-glutamyl

transferase (GGT), hepatosplenomegaly, and renal manifestations such as renal echogenicity, agenesis, or glomerulopathy, often progressing to organ failure [3].

Here, we report the first Palestinian family, and the fifth family worldwide, diagnosed with PSKH1-associated hepatorenal ciliopathy, presenting with neonatal-onset cholestasis and variable renal dysfunction, who were found to harbor a novel homozygous missense variant in PSKH1(NM_006742.3):c.583G > A (p.(Ala195Thr)). This variant, which has not previously been reported in the literature, fully segregated with the disease in the family. We describe the clinical, biochemical, and genetic features, thereby expanding the phenotypic and mutational spectrum of *PSKH1*-associated hepatorenal ciliopathy and reinforcing its relevance as a diagnostic consideration in pediatric cholestasis.

CASE REPORT

Individual IV-1:

A 17-day-old female sibling, born full-term via normal spontaneous vaginal delivery with birth weight of 3200 grams. She was presented with neonatal-onset jaundice that started on day 3 of life. No acholic stool was reported.

Physical examination revealed a deeply jaundiced infant with no distinctive features. Abdominal examination revealed hepatosplenomegaly. Neurological evaluation was initially unremarkable.

Laboratory investigations revealed direct hyperbilirubinemia (highest total serum bilirubin: 32 mg/dL, highest direct bilirubin: 19.9 mg/dL); elevated hepatic enzymes, including alanine aminotransferase (ALT: 90 U/L) and aspartate aminotransferase (AST: 85 U/L); elevated alkaline phosphatase (ALP: 1074 U/L); and GGT was reported to be elevated. Hepatic synthetic function was impaired, with hypoalbuminemia (albumin: 2.7 g/dL) but normal coagulation (INR: 1.1). Triglycerides were elevated at 173 mg/dL, and cholesterol at 305 mg/dL. Complete blood count revealed anemia with hemoglobin of 9.4 g/dL, and thrombocytopenia (lowest platelet count of 27,000/µL). Creatinine and BUN were elevated (Cr: 1.1 mg/dL, BUN: 23 mg/dL). The patient had metabolic acidosis with bicarbonate decreased to 12.7 mmol/L. Metabolic workup, including serum lactate, serum ammonia, urine organic acid and plasma amino acid analysis, revealed no abnormalities. Alpha-1 antitrypsin level was normal.

Abdominal ultrasound demonstrated hepatosplenomegaly with preserved parenchymal echotexture. Echocardiography was normal. Ophthalmic examination was unremarkable. Liver biopsy showed marked cholestasis with moderate portal fibrosis and focal bridging, no evidence of bile duct paucity or proliferation. Singleton whole exome sequencing was performed in 2016 and was non-informative.

The patient exhibited progressive liver and renal impairment, accompanied by failure to thrive, and global developmental delay. She lacked head control, did not demonstrate social responses such as laughing or

cooing, and had not achieved any developmental milestones by the time of her death at the age of 6 months.

Individual IV-2:

A 24-day-old female sibling, delivered vaginally at term after an uneventful pregnancy. Antenatal ultrasonography showed no structural anomalies. Her birth weight was 3100 grams. She was noted to have jaundice at the age of 2 days, no acholic stool was reported.

Physical examination revealed a deeply jaundiced girl with no dysmorphic features. Abdominal examination showed no hepatosplenomegaly. Neurological evaluation was unremarkable.

Laboratory investigations revealed direct hyperbilirubinemia (total serum bilirubin: 15 mg/dL, direct bilirubin: 12 mg/dL), elevated hepatic enzymes with alanine aminotransferase (ALT) of 177 U/L, aspartate aminotransferase (AST) of 284 U/L, alkaline phosphatase (ALP) of 514 U/L and gamma-glutamyl transferase (GGT) of 1317 U/L. She had abnormal hepatic synthetic function, evidenced by hypoalbuminemia and coagulopathy requiring albumin transfusions and vitamin K supplements. Renal failure was evidenced by elevated creatinine (up to 1.2 mg/dL) and BUN (up to 31 mg/dL) with severe metabolic acidosis that needed treatment with bicarbonate. Complete blood count showed anemia with hemoglobin as low as 7 g/dL and thrombocytopenia, with platelet counts decreasing to 45,000. Metabolic workup, including serum lactate, serum ammonia, urine organic acid and plasma amino analysis revealed no abnormalities, except for urine amino acid analysis which showed generalized aminoaciduria.

Abdominal ultrasound demonstrated hepatosplenomegaly with preserved parenchymal echotexture and renal ultrasonography showed mild left renal pelvic dilatation. Extensive investigations including T-cell subset, sweat chloride test, echocardiogram, ophthalmic examination, and skeletal survey were unremarkable. Liver biopsy showed marked cholestasis with moderate portal fibrosis and focal bridging, no evidence of bile duct paucity or proliferation; **(**Fig. 1d, e**)**. Singleton whole exome sequencing (WES) was performed in 2018 and was non-informative.

The patient exhibited progressive liver and renal impairment, with failure to thrive, and development of ascites, requiring repeated albumin transfusions. She ultimately died as a result of liver and renal failure at the age of 23 months. By that time, her developmental progress was limited: she was able to sit independently but could neither stand nor walk, could feed herself with a spoon, and had a limited expressive vocabulary of only three words.

Individual IV-3:

A 4-month-old male infant born to consanguineous parents. He was delivered vaginally at term after an uneventful pregnancy. Antenatal ultrasonography revealed polyhydramnios, with no other structural

anomalies detected. His birth weight measured 4200 grams. He was noted to have jaundice at the age of 3 days with a total serum bilirubin of 14 mg/dL and direct bilirubin of 6 mg/dL. No acholic stool was reported. He was referred to our hospital at the age of 4 months.

Physical examination revealed a deeply jaundiced baby with no dysmorphic features. His weight was 6100 grams (25th percentile), length was 62 cm (25th percentile) and head circumference was 41 cm (15th percentile). Abdominal examination revealed hepatomegaly and splenomegaly. Neurological evaluation showed mild axial hypotonia though peripheral tone was normal. Otherwise, his exam was unremarkable.

Laboratory investigations revealed direct hyperbilirubinemia (total serum bilirubin: 20.5 mg/dL, direct bilirubin: 18 mg/dL) and elevated hepatic enzymes, AST was 147 U/L, ALT was 54 U/L, ALP was 540 U/L, and GGT was 259 U/L. Hemoglobin was 11.2 g/dL, and serum creatinine was 0.4 mg/dL. Hepatic synthetic function remained intact, with normal coagulation profiles and albumin levels initially (albumin: 4 g/dL, INR: 1.06). Triglyceride level was mildly elevated at 168 mg/dL, while total cholesterol was normal at 164 mg/dL. Abdominal ultrasound demonstrated hepatosplenomegaly with preserved parenchymal echotexture. Echocardiogram revealed normal cardiac structure and function, and brain magnetic resonance imaging (MRI) showed no structural abnormalities. Metabolic workup, including urine organic acid and plasma amino analysis, revealed no abnormalities. Skeletal survey radiographs were unremarkable.

On follow-up at the age of 7 months, liver transaminases showed further elevation (AST: 323 U/L, ALT: 81 U/L), and hepatic synthetic function worsened, as indicated by an increased INR of 1.9. The patient exhibited axial hypotonia, was unable to sit without support, not holding objects and had not yet started cooing, suggestive of global developmental delay. He passed away during sleep at home at the age of 7.5 months, approximately two weeks after his last follow-up visit.

Genetic Analysis:

Genetic testing was undertaken in view of the family history of two similarly affected sisters who died in early childhood and the previously uninformative whole exome sequencing (WES) performed several years earlier. Accordingly, a reanalysis of WES for Individual IV-2 was requested in late 2024. This reanalysis identified a homozygous likely pathogenic variant in the *PSKH1* gene NC_000016.10:g.67909332G > A; NM_006742.3:c.583G > A; NP_006733.1:p.(Ala195Thr). To the best of our knowledge, this variant has not been previously reported in the medical literature. It is extremely rare in population databases, with a minor allele frequency of 6.20e-7 in gnomAD v4.1. Analysis of the UCSC Genome Browser 100-vertebrate conservation track, based on multiz multiple-species alignments and PHAST conservation scores, showed that Ala195 is completely conserved across 100 vertebrate species, supporting the structural and functional importance of this residue. *In silico* prediction tools consistently support a deleterious effect on protein function, including: AlphaMissense - pathogenic

(0.88); MetaRNN - pathogenic (0.97 D); CADD pathogenic (30); REVEL pathogenic (0.696); SIFT (deleterious), PolyPhen-2 (probably damaging).

Segregation analysis demonstrated that all three affected children (Individuals IV-1, IV-2, and IV-3) were homozygous for the identified variant, while both parents were heterozygous carriers, consistent with autosomal recessive inheritance (Fig. 1a). The two unaffected siblings were homozygous for the wild-type allele. Based on the American College of Medical Genetics and Genomics (ACMG) standards and guidelines, this variant was classified as likely pathogenic.

Structural Analysis:

To evaluate the potential structural and functional impact of the p.(Ala195Thr) variant, residue Ala195 was mapped onto the AlphaFold-predicted three-dimensional structure of PSKH1 (AF-P11801-F1) and visualized by ChimeraX-1.11.1. The Ala195 is located within the conserved catalytic kinase domain of PSKH1 (residues ~ 98–355) and lies in the N-terminal region of the C-lobe of the kinase fold right before the catalytic HRD motif (Fig. 1b). In the structural model, Ala195 is situated within a helical segment that contributes to the structural scaffold of the C-lobe adjacent to the catalytic loop (Fig. 1c). Substitution of alanine by threonine introduces a larger and polar side chain at this position, which may alter local packing interactions within the kinase core and potentially affect the structural stability of the catalytic region. Given its proximity to the catalytic HRD motif, such structural perturbation could disrupt the spatial orientation of these key catalytic residues or it might influence the conformation of the kinase active site, thereby impairing enzymatic activity.

Figure 1 *should appear here.*

DISCUSSION

PSKH1-associated hepatorenal ciliopathy is an ultra-rare autosomal-recessive disorder of primary cilium function [3]. We report three affected siblings from a consanguineous family with a novel homozygous missense variant, c.583G > A (p.Ala195Thr), and integrate these cases with the literature to further define this emerging disorder (Table 1).

Table 1

Summary of clinical, biochemical and genetic features, comparing the presented cases and previously reported cases.

Total cases	***Current study***	***Previous reported cases (percentage)***	***Combined cases (percentage)***
	3	**8**	**13**
Median age at last visit (range)	7 mo (6–24 mo)	26 mo (7 mo – 38 year)	23 mo (0–38 year)
Gender (Male: Female)	1:2	2:6	3:8
Consanguinity	3/3 (100%)	8/8 (100%)	11/11 (100%)
Family history	3/3 (100%)	8/8 (100%)	11/11 (100%)
Liver phenotype			
Liver impairment	3/3 (100%)	8/8 (100%)	11/11 (100%)
High GGT	3/3 (100%)	4/4 (100%)	7/7 (100%)
Abnormal abdominal ultrasound	3/3 (100%)	7/8 (87.5)	10/11 (90.9%)
Hepatomegaly	3/3 (100%)	6/8 (75%)	9/11 (81.8%)
Splenomegaly	3/3 (100%)	3/8 (37.5%)	6/11 (54.5%)
Ascites	1/3 (33.3%)	2/8 (25%)	3/11 (27.2%)
Liver biopsy performed	2/3 (66.6%)	5/8 (62.5%)	7/11 (63.6%)
Liver transplant	0/3 (0%)	5/8 (62.5%)	5/11 (45.4%)
Kidney phenotype			
Renal impairment	2/3 (66.6%)	4/8 (50%)	6/11 (54.5%)
Metabolic acidosis	2/3 (66.6%)	1/8 (12.5%)	3/11 (27.3%)
Abnormal renal ultrasound	1/3	6/8 (75%)	7/11 (63.6/%)
Increased echogenicity	0/3 (0%)	3/8 (37.5%)	
Solitary kidney	0/3 (0%)	3/8 (37.5%)	3/11 (27.2%)
Hydronephrosis	1/3 (33.3%)	0/8 (0%)	1/11 (9%)
Kidney biopsy performed	0/3 (0%)	2/8 (25%)	2/11 (18.1%)
Other phenotypes			
Global developmental delay	3/3 (100%)	3/8 (37.5%)	6/11 (54.5%)

Total cases	*Current study*	*Previous reported cases (percentage)*	*Combined cases (percentage)*
	3	**8**	**13**
Anemia	2/3 (66.6%)	1/8 (12.5%)	3/11 (27.2%)
Pancytopenia	2/3 (66.6%)	1/8 (12.5%)	3/11 (27.2%)
Genotype			
Transcript and predicted protein			
c.583G > A (p.Ala195Thr)	3/3 (100%)		3/11 (27.2%)
c.361C > T (p.Arg121Trp)		4/8 (50%)	4/11 (36.3%)
c.376A > G (p.Ile126Val)		2/8 (25%)	2/11 (18.1%)
c.547C > T (p.Arg183Cys)		2/8 (25%)	2/11 (18.1%)
Zygosity (Homozygous)	3/3 (100%)	8/8 (100%)	11/11 (100%)
Living status (Deceased)	3/3 (66.6%)	1/8 (12.5%)	4/11 (37%)

Neonatal-onset cholestasis is an early and characteristic feature of PSKH1-associated disease. In our cohort, all three siblings developed direct hyperbilirubinemia with high-GGT cholestasis within the first week of life, consistent with hepatic involvement reported previously. Across all cases with documented GGT levels (7 of 11 patients), all showed elevated GGT, suggesting that high-GGT cholestasis may represent a constant feature of PSKH1-associated disease. Cholestasis in all affected individuals was accompanied by evidence of hepatic impairment. Liver transplantation was required in most previously reported patients and appears essential for survival. None of our patients had access to transplantation, and all died in early childhood, highlighting the high fatality rate in the absence of liver transplantation.

Renal involvement is a core feature of PSKH1-associated disease, with considerable variability. In our family, two of three siblings developed progressive renal dysfunction with rising serum creatinine and metabolic acidosis, while the third maintained normal renal function. One patient had unilateral hydronephrosis on imaging. Among previously reported cases, six of eight patients showed structural renal abnormalities, and four exhibited clinical impairment; biopsies revealed chronic glomerulopathy with focal segmental glomerulosclerosis, thrombotic microangiopathy, and interstitial fibrosis, supporting a ciliopathy-related nephropathy. These findings underscore the broad renal phenotype and the need for longitudinal monitoring.

Beyond hepatic and renal manifestations, PSKH1-associated disease frequently involves multiple systems. All three of our patients (100%) exhibited global developmental delay, compared with 37.5% (3/8) in previously reported cases, suggesting that certain variants, including p.Ala195Thr, may confer a more severe neurodevelopmental phenotype, although ascertainment bias cannot be excluded.

Hematologic abnormalities were also notable, with anemia and pancytopenia observed in two siblings, consistent with prior reports and indicative of variable or underrecognized phenotypic expression.

Clinically, PSKH1-associated hepatorenal ciliopathy should be suspected in neonates with early-onset high-GGT cholestasis, particularly when accompanied by hepatosplenomegaly, renal dysfunction, or a family history suggestive of autosomal-recessive inheritance. Early implementation of next-generation sequencing, including reanalysis of whole exome data when needed, is critical for timely molecular diagnosis, guiding clinical management, enabling anticipatory monitoring, avoiding unnecessary invasive procedures, and providing accurate genetic counseling [5].

Management of PSKH1-associated disease is primarily supportive, including nutritional optimization, fat-soluble vitamin supplementation, albumin replacement, and correction of metabolic acidosis. Outcomes remain poor without access to liver transplantation in progressive hepatic disease.

The identification of PSKH1 p.Ala195Thr as the fourth validated pathogenic variant further highlights an unusual feature of the mutational spectrum of PSKH1. Despite the presence of 37 heterozygous predicted loss-of-function variants in the gnomAD v4.1 population database, biallelic truncating genotypes have not been reported in affected individuals. Instead, all currently described disease alleles consist of missense substitutions within the kinase catalytic domain, rather than truncating variants, suggesting that complete loss of PSKH1 may be incompatible with normal development or may lead to a clinically distinct phenotype. Notably, the previously reported p.Arg121Trp, p.Ile126Val, and p.Arg183Cys variants - and most likely our p.Ala195Thr variant - are predicted to preserve protein expression while markedly reducing catalytic activity. These observations support a model in which PSKH1-associated hepatorenal ciliopathy results from hypomorphic alleles that impair kinase activity rather than complete gene inactivation. Similar patterns have been described for other ciliopathy-associated kinases. For example, pathogenic variants in CILK1 (ICK) cluster within the kinase catalytic domain or adjacent regulatory elements rather than causing complete gene inactivation [6], and such variants typically reduce kinase activity and disrupt ciliary signaling.

Table 1 *should appear here*.

CONCLUSION

In summary, our findings provide independent replication of the recently reported association between PSKH1 variants and hepatorenal ciliopathy. Integrating the clinical and molecular features of our patients with previously reported cases further expands the phenotypic and mutational spectrum of this emerging disorder and reinforces its characterization as a severe multisystem disease with early hepatic involvement, variable renal manifestations, and possible neurodevelopmental features. Our findings also highlight the importance of periodic re-evaluation of whole-exome sequencing data, as emerging clinical and scientific knowledge can provide critical insights that may uncover previously unrecognized disease genes or lead to reclassification of variants according to updated ACMG criteria.

Abbreviations

PSKH1
Protein Serine Kinase H1
WES
Whole Exome Sequencing
ACMG
American College of Medical Genetics and Genomics
PHAST
Phylogenetic Analysis with Space/Time models

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and relevant institutional and national guidelines and regulations. Ethical approval was obtained from the Makassed Hospital Ethics Committee. Written informed consent to participate was obtained from the parents/legal guardians of all affected children.

Consent for publication

Written informed consent for publication of the patients' clinical details was obtained from the patients' parents. A copy of the written consent is available for review by the Editor upon request.

Availability of data and materials

The genetic variant identified in this study has been deposited in the ClinVar repository under accession numbers **VCV004850872.1** and **SCV007593453.1**, available at: **https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV004850872.1** The clinical and phenotypic data supporting the findings of this study are included within the article. Additional de-identified data may be made available from the corresponding author upon reasonable request and subject to institutional and ethical approvals.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors received no specific funding for this work.

Authors' contribution

Zeineddin Etkaidek: First author; led manuscript drafting, contributed to study design and data interpretation. **Mutaz Sultan:** Participated in study design and critically reviewed the manuscript. **Izzeddin Bakri:** Reviewed and interpreted the liver biopsies findings and contributed to the histopathological analysis. **Jihad Lehroob:** Participated in data collection and assisted with manuscript review. **Yaqoub Ashhab:** Contributed to protein *in silico* and structural analyses and manuscript review. **Nadirah Damseh:** Corresponding author; coordinated the project, contributed to study conception, data interpretation, and manuscript preparation.

Acknowledgement

The authors would like to thank the patients' family for their cooperation.

Disclosure of artificial intelligence (AI) usage

The authors acknowledge the use of ChatGPT-5.4 (OpenAI) for language editing and improvement of manuscript structure. All original research ideas, scientific content, experimental design, illustrations, and data interpretation were developed, drafted, and verified by the authors.

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Figures

Figure 1.

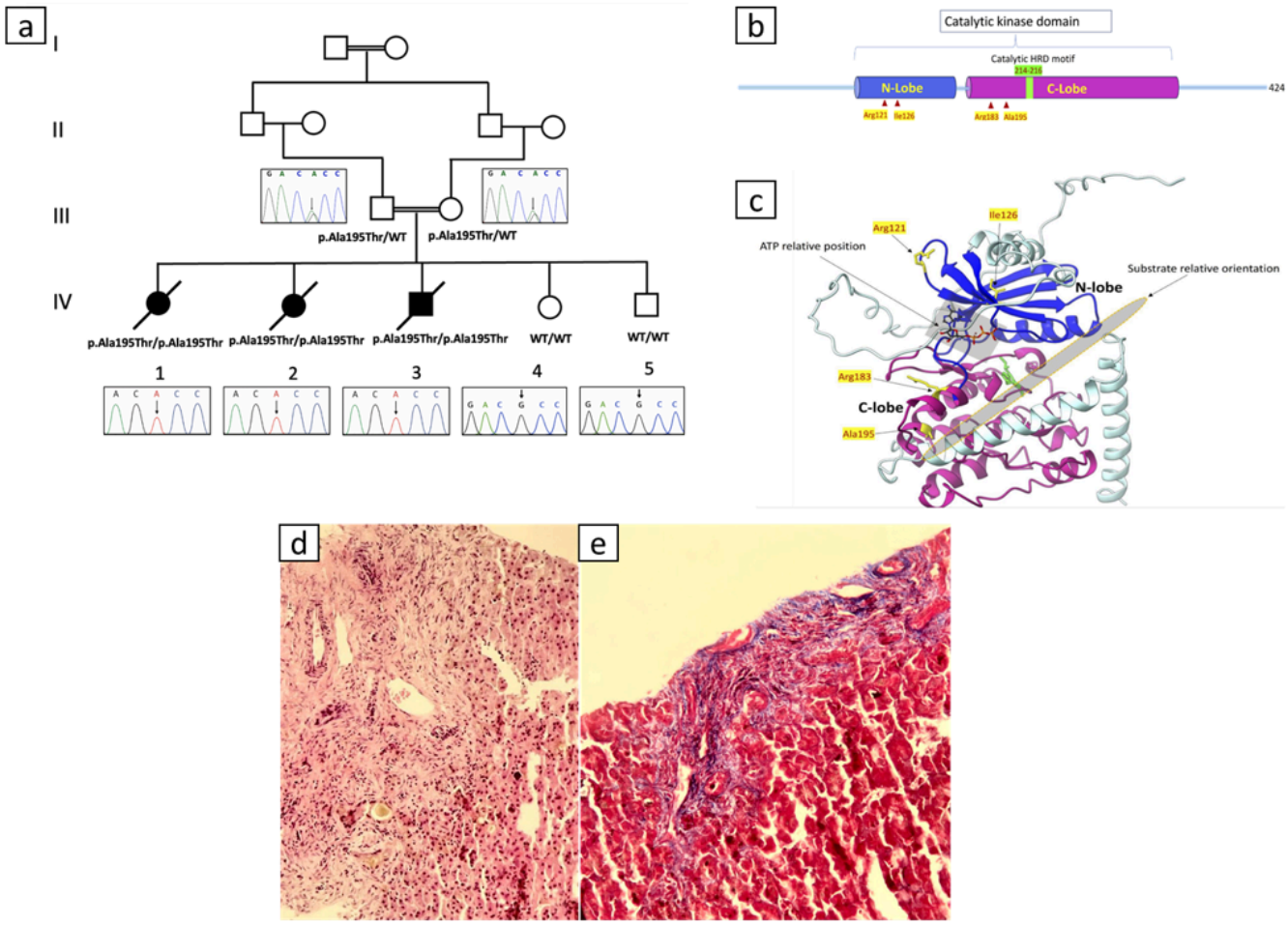


Figure 1

a. Family pedigree and segregation results.

b, c. Structural context of PSKH1 variants within the catalytic kinase domain. b. Linear schematic of human PSKH1 showing the catalytic kinase domain (~residues 98–355) composed of the N-lobe and C-lobe. The catalytic HRD motif (214–216) is indicated. Positions of the reported pathogenic variants (Arg121, Ile126, Arg183) and the novel variant identified in this study (Ala195) are marked. **c.** Three-dimensional model of PSKH1 generated from the AlphaFold structure (AF-P11801-F1) and visualized using ChimeraX. The N-lobe (blue) and C-lobe (magenta) form the catalytic cleft and the HRD catalytic motif (lime). Locations of the 4 variants (Arg121, Ile126, Arg183, and Ala195) are shown. The approximate positions of ATP and the peptide substrate are inferred from the PKA kinase structure

complexed with ATP and a substrate peptide (PDB: 1ATP), which shares the conserved catalytic architecture of serine/threonine kinases.

d, e. Representative histology sections of the liver biopsy of patient IV-2. d. H&E stain, original magnification ×10): Cores of liver tissue demonstrate preserved lobular architecture with portal tracts expanded by mild to moderate fibrosis and a sparse mixed inflammatory infiltrate, predominantly lymphocytic. Bile ducts are intact without evidence of injury, ductular reaction, or proliferation. The lobules show mild hepatocellular anisocytosis, focal multinucleated giant cell transformation, and scattered apoptotic bodies. Intralobular cholestasis is present, characterized by bile pigment accumulation within canaliculi. No significant ballooning degeneration, steatosis, or interface activity is identified. **e.**(Masson's trichrome stain, original magnification ×10): Trichrome stain highlights bridging portal-portal and portal-central fibrosis, with periportal and perivenular accentuation of collagen deposition. Blue-stained collagen extends into adjacent parenchyma, forming incomplete fibrous septa. No nodular regeneration is observed, and features diagnostic of established cirrhosis are absent.