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# The phenotypic spectrum of CD151 deficiency: a family study and literature review

**Caroline M. Kolvenbach**
Caroline.Kolvenbach@med.uni-heidelberg.de
Heidelberg University
**Heike Gampp**
Heidelberg University
**Julia K. Winkler**
Heidelberg University
**Matias Simons**
Heidelberg University
**Christian P. Schaaf**
Heidelberg University
**Maja Hempel**
Heidelberg University

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## Abstract

*Background*: CD151 deficiency is a rare autosomal recessive disorder classically characterized by epidermolysis bullosa and nephropathy, although the full clinical spectrum remains incompletely defined.

*Methods*: We describe a consanguineous family with a homozygous truncating *CD151* variant and review all previously reported individuals to further delineate the multisystem phenotype of CD151 deficiency.

*Results*: The index patient presented with congenital unilateral kidney agenesis, nail dystrophy, juvenile-onset epidermolysis bullosa, nephrotic-range proteinuria with secondary focal segmental glomerulosclerosis, and progressive urogenital involvement including recurrent meatal stenosis, urethral strictures, and distal ureteral stenosis. In contrast, his sister, who also carries the homozygous *CD151* variant, exhibited isolated nail dystrophy without skin, kidney, or urogenital involvement, demonstrating striking intrafamilial phenotypic variability. A first cousin with isolated nail dystrophy may represent another mildly affected family member, although molecular confirmation was unavailable. The literature review confirms broad multisystem involvement in CD151 deficiency. Recurrent congenital kidney anomalies support CAKUT as part of the disease spectrum, while stenotic manifestations across several organ systems may represent an additional, previously underrecognized feature of the multisystem phenotype.

*Conclusions*: Collectively, these support consideration of CD151 deficiency as a basement-membrane-associated multisystem disorder and highlight the importance of longitudinal surveillance and awareness of progressive urogenital complications.

## INTRODUCTION

CD151 is a member of the tetraspanin family of transmembrane proteins and forms stable complexes with laminin-binding integrins, thereby regulating cell adhesion, migration, and basement membrane stability(1, 2). In the skin, CD151 is expressed in basal keratinocytes, where it associates with integrin α6β4 and contributes to hemidesmosome stability and dermal-epidermal adhesion(3). Within the glomerulus, CD151 is abundantly expressed in podocytes, where it interacts predominantly with integrin α3β1 to stabilize podocyte adhesion to the glomerular basement membrane and maintain the integrity of the glomerular filtration barrier(4–6).

Biallelic pathogenic variants in *CD151* are known to cause a rare multisystem disorder, epidermolysis bullosa with nephropathy and deafness (OMIM #609057), characterized by skin blistering, nail dystrophy, and kidney disease, typically manifesting as proteinuria and focal segmental glomerulosclerosis (FSGS)(6–12). Consistent with its role in podocyte adhesion, Cd151-deficient mice develop proteinuria and progressive glomerulosclerosis, supporting a direct role of CD151 deficiency in nephropathy(4, 5). Additional manifestations in patients include lacrimal duct abnormalities, and congenital anomalies of the kidneys and urinary tract (CAKUT)(6, 9). Notably, *CD151* is highly constrained against predicted loss-of-function variation in the general population, underscoring its critical biological function.

To date, only a small number of individuals with biallelic *CD151* variants have been reported. Here, we describe a consanguineous family demonstrating marked intrafamilial phenotypic variability and systematically compare the clinical findings with all previously published individuals to further refine the phenotypic spectrum of CD151-associated disease.

## METHODS

## Genetic analyses

Molecular genetic testing was performed as part of routine clinical diagnostics. Following the clinical suspicion of epidermolysis bullosa, targeted next-generation sequencing using an epidermolysis bullosa gene panel identified a homozygous truncating variant in *CD151* (NM_139030.3:c.346C > T; p.Gln116*; Table 1). Segregation analysis of available family members was subsequently performed by the same diagnostic laboratory.

Table 1
Clinical characteristics of affected family members with CD151 deficiency

| Patient | Sex | Ethnicity | Age | Variant | Zygosity | Skin/nails | Kidney/urogenital | Hearing | Other |
|---|---|---|---|---|---|---|---|---|---|
| Index IV-2 | M | Turkish | 19 y | c.346C > T; p.Gln116* | Hom | Blistering of the extremities, including dorsal hands and feet, nail dystrophy | Unilateral kidney agenesis, NS (secondary FSGS), hematuria, hydronephrosis grade III, meatal stenosis, urethral stricture, distal ureteral stenosis, unilateral cryptorchidism | – (subjective); NE (audiometry) | Polythelia, lacrimal duct stenosis, absence of MER2-antigen |
| Sister IV-3 | F | | 13 y | | Hom | Nail dystrophy | - | – (subjective); NE (audiometry) | - |
| Cousin IV-1 | F | | 22 y | | Presumed Hom | Nail dystrophy | - | – (subjective); NE (audiometry) | - |

Clinical characteristics of affected members of a consanguineous family with a homozygous truncating *CD151* variant (NM_139030.3:c. 346C > T; p.Arg116*). The cousin was not genetically tested and her reported phenotype was obtained from family history but is assumed to be homozygous based on the family pedigree and characteristic phenotype. F, female; Hom, homozygous; M, male; NE, not evaluated; NS, nephrotic syndrome; y, years; -, feature absent

## Literature review

To place the findings into context, a literature review was performed using PubMed. The following search terms were used: "CD151", "CD151 epidermolysis bullosa", "CD151 nephropathy", "CD151 kidney", "CD151 mutation", and "CD151 deficiency". The reference lists of all relevant publications were additionally screened to identify further eligible reports. Published case reports and case series describing the clinical phenotype of CD151-associated disease were reviewed, and relevant clinical characteristics were extracted from the original publications and summarized in Table 2.

Table 2
Published individuals with biallelic *CD151* variants identified through a literature review

| Reference | Fam. | Pat. | Sex | Ethnicity | Age | Variant | Zygosity | Skin/nails | Kidney/urogenital | Hearing | Othe |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Almokali et al., 2024 | A | 1 | M | Saudi | 13 y | c.493C > T; p.Arg165* | Hom | Pretibial blistering | NS, R small kidney | - | - |
| | | 2 | M | | Unknown | | Hom | Pretibial blistering | - | - | - |
| Dunn et al., 2022 | B | 3 | F | Unknown | 24 y | c.406C > T; p.Gln136* | Hom | Pretibial blistering, dystrophic nails, alopecia, poikiloderma | CKD, NS FSGS | Sensorineural hearing loss | Epile Cere dysp esop stric dent hypo pan insu |
| Naylor et al., 2022 | C | 4 | F | Unknown | 2 y | c.631A > T; p.Lys211* | Hom | Nail dystrophy, hypopigmented skin lesions | NS, hematuria, recurrent UTI, possible duplex system L with pelvis and distal ureter dilatation, increased echogenicity | NE | Abs MEF |
| Rahmani et al., 2022 | D | 5 | F | Iran | 16 y | c.351 + 2C > T; inframe del exon 5 | Hom | Mild pretibial lesions, dystrophic toenails | Unilateral kidney agenesis, proteinuria, ESKD | - | IUGF deca |
| | | 6 | M | | 30 y | | Hom | Mild pretibial and feet lesions, dystrophic nails, thin hair | Unilateral kidney agenesis, proteinuria, urinary incontinence | - | IUGF oligo |
| | | 7 | F | | 14 y | | Hom | Mild pretibial lesions, dystrophic toenails | Unilateral hypoplastic kidney, proteinuria | - | IUGF deca |
| Vahidnezhad et al., 2018 | E | 8 | M | Iran | 33 y | c.351 + 2C > T; inframe del exon 5 | Hom | Skin blistering and erosions, facial freckling, poikiloderma, skin atrophy, acrogeria, dystrophic nails, early-onset alopecia | Proteinuria, hematuria, recurrent pyelonephritis, urinary incontinence | NE | Lacr sten orop dysp esop web stru eder ectr corn vasc eros muc men |
| Karamatic Crew et al., 2004 | F | 9 | M | Israeli | unknown | c.382dupG; p.Asp128Glyfs*13 | Hom | pretibial blistering, dystrophic nails | Unilateral kidney agenesis, NS, ESKD | Sensorineural hearing loss | Lacr sten thal mino dyst teet of M anti |
| | | 10 | F | | unknown | | Hom | pretibial blistering, dystrophic nails | NS, ESKD, agenesis of the distal vagina | Sensorineural hearing loss | Lacr sten thal mino cerv abse MEF |
| | G | 11 | M | Israeli | unknown | c.383Cdup; p. Lys127fs | Hom | NE | NS, ESKD | NE | Abs MEF |

Clinical characteristics of all previously reported individuals with biallelic disease-causing *CD151* variants identified through a structured review of the publis literature. ESKD, end-stage kidney disease; F, female; Hom, homozygous; IUGR, intrauterine growth retardation; L, left; M, male; NE, not evaluated; NS, nephro syndrome; R, right; y, years; -, feature absent

| Reference | Fam. | Pat. | Sex | Ethnicity | Age | Variant | Zygosity | Skin/nails | Kidney/urogenital | Hearing | Othe |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | H | 12 | F | Turkish | unknown | c.533G > A; p.Arg178His | Hom | NE | NE | NE | Abs MEF |

Clinical characteristics of all previously reported individuals with biallelic disease-causing *CD151* variants identified through a structured review of the publis literature. ESKD, end-stage kidney disease; F, female; Hom, homozygous; IUGR, intrauterine growth retardation; L, left; M, male; NE, not evaluated; NS, nephro syndrome; R, right; y, years; -, feature absent

## RESULTS

# Clinical presentation

The index patient IV-2 was born with congenital left kidney agenesis, resulting in a solitary right kidney (Table 1). Additional findings during early childhood included left-sided cryptorchidism and polythelia (Table 1). Apart from low-set ears, physical examination was otherwise unremarkable. The patient experienced his first urinary tract infection at 16 months of age. From the age of six years, progressive nail dystrophy was noted, initially affecting both thumbnails and later involving all fingernails and toenails. At 14 years of age, trauma-induced blistering and erosions of the skin first became apparent and gradually progressed, predominantly affecting the extremities (Table 1, Fig. 1A). Dermatological examination demonstrated atrophic scarring, milia, and dystrophic nails consistent with epidermolysis bullosa. Oral and nasal mucosae were clinically unaffected. Bilateral lacrimal duct stenosis was present (Table 1). The patient denied hearing impairment. However, formal audiometric testing was not performed. No dental abnormalities were reported.

Kidney involvement became clinically apparent during adolescence. At 17 years of age, evaluation revealed nephrotic-range proteinuria, microscopic hematuria, arterial hypertension, and mildly impaired kidney function (Table 1). At the most recent follow-up, kidney function corresponded to CKD (chronic kidney disease) stage G2A3 (eGFR 71.6 mL/min/1.73 m²) with persistent nephrotic-range proteinuria (5.56 g/24 h). Kidney biopsy demonstrated FSGS with interstitial foam cells and segmental podocyte foot process effacement, without immune-complex deposition or ultrastructural abnormalities suggestive of Alport syndrome. Accordingly, targeted genetic testing for Alport syndrome was negative. The patient subsequently developed progressive urogenital involvement with recurrent meatal stenosis, urethral strictures, and distal ureteral stenosis, resulting in obstructive uropathy requiring multiple endoscopic and reconstructive urological procedures (Fig. 1A).

To further characterize the progressive cutaneous manifestations consistent with epidermolysis bullosa, targeted next-generation sequencing using an epidermolysis bullosa gene panel was performed. This identified a homozygous truncating *CD151* variant (NM_139030.3:c.346C > T; p.Gln116*) in exon 5 of 9, which was classified as likely pathogenic and predicted to result in nonsense-mediated mRNA decay (NMD) and loss of function (LOF). Notably, while *CD151* is not constrained against LOF variants (pLI = 0), no homozygous LOF variants are reported in the gnomAD population database, further supporting intolerance to complete loss of CD151 function. Consequently, the diagnosis of CD151-associated epidermolysis bullosa with nephropathy was established, providing a unifying explanation for the patient's cutaneous and kidney manifestations. The recurrent meatal and urethral stenoses were considered extracutaneous manifestations of CD151-associated epithelial fragility. Despite repeated surgical interventions, the patient developed recurrent urinary tract infections complicated by urosepsis and recurrent pyelonephritis. Owing to progressive cutaneous disease, treatment with dupilumab, a monoclonal antibody targeting interleukin-4 and − 13, is currently planned.

Given the known role of CD151 in the RAPH blood group system, molecular blood group typing was subsequently performed and identified a homozygous RAPH-null phenotype resulting from absent CD151 expression on erythrocytes (Table 1)(13). Consequently, the patient developed clinically relevant anti-MER2 alloantibodies, necessitating specialized transfusion management with early involvement of transfusion medicine before any red blood cell transfusions.

## Family investigation

Following establishment of the molecular diagnosis, genetic counselling was initiated for the extended family. The parents were first cousins and both were clinically unaffected (III-3 and III-4; Table 1). The patient's seven-year-old brother (IV-4) was likewise asymptomatic, whereas his 13-year-old sister (IV-3) had isolated nail dystrophy since the first year of life (Fig. 1B, Table 1). Kidney ultrasound examinations in both siblings and the parents were unremarkable, and urine analyses showed no evidence of proteinuria. The family history was otherwise negative for kidney disease, epidermolysis bullosa, or hearing impairment. Segregation analysis confirmed both parents and the unaffected brother to be heterozygous carriers of the familial *CD151* variant, whereas the sister was homozygous (Fig. 1C, Table 1). Despite carrying the identical homozygous truncating variant as the index patient, her phenotype remained limited to isolated nail dystrophy to this date, demonstrating marked intrafamilial phenotypic variability (Fig. 1C, Table 1).

A 22-year-old female first cousin of the index patient, whose parents were also related by consanguinity, was likewise reported by the family to have isolated nail dystrophy since birth (IV-1; Fig. 1C). She did not undergo systematic phenotypic evaluation and DNA was unavailable for molecular testing. However, based on the pedigree structure and her phenotype, she is likely to also be homozygous for the familial *CD151* variant, further supporting the broad phenotypic spectrum associated with biallelic CD151 deficiency.

Across 13 genetically confirmed individuals with informative phenotypic data, skin and/or nail abnormalities were present in 12/12 evaluable individuals (100%) and glomerular kidney disease in 11/13 (85%; Table 1). CAKUT was present in 7/13 individuals (54%), including unilateral kidney agenesis in 4/13 (31%), while sensorineural hearing loss was documented in 3/8 individuals with evaluable hearing data (38%; Table 1).

## DISCUSSION

By combining a detailed description of a consanguineous family with a review of all previously published individuals, our study further expands the phenotypic spectrum of CD151-associated disease (Fig. 1; Tables 1–2). The aggregated findings indicate two major, partly overlapping, phenotypic axes: progressive renal disease, comprising both glomerular and developmental abnormalities, and tissue fragility affecting the skin, nails, mucosal surfaces, teeth, and inner ear. Rather than representing a fixed combination of epidermolysis bullosa and nephropathy, biallelic *CD151* loss therefore appears to cause a pleiotropic cell-matrix adhesion disorder with highly variable organ involvement (Table 2). Notably, the only reported individual homozygous for a missense variant, p.Arg178His, was MER2-negative with no other organ involvement reported, suggesting that this allele may alter MER2 antigenicity without causing complete loss of CD151 function, although functional data are lacking.

The present family provides particularly strong evidence for variable expressivity. The index patient developed a severe multisystem phenotype, whereas his sister has thus far manifested only nail dystrophy. The similarly mild phenotype reported in their 22-year-old cousin further argues against age as the sole explanation. This variability is unlikely to result from substantial residual CD151 activity, as p.Gln116* is predicted to trigger NMD. If any mutant transcript escaped NMD, the resulting truncated protein would retain the first three transmembrane domains but lack almost the entire second extracellular loop, the fourth transmembrane domain, and the C-terminal intracellular tail (Fig. 2). Previous analyses indicated that such residual truncated proteins would be unlikely to reach the plasma membrane, and p.Gln116* truncates CD151 substantially further upstream than the previously reported p.Lys211* variant(12). Similar variable expressivity has been observed among individuals sharing the same variant in previously reported families (Table 2), indicating that the *CD151* genotype alone does not determine clinical severity. Age and environmental factors, both recognized modifiers of phenotypic expression in CAKUT, may contribute, while the strain-dependent kidney phenotype of Cd151-deficient mice provides direct evidence that genetic background modifies disease expression(4, 5). Additional modifiers may be particularly relevant in consanguineous families, in whom extended regions of homozygosity may harbor phenotype-modifying variants.

Kidney disease remains the principal determinant of long-term prognosis. Our findings further support CAKUT as an integral, rather than coincidental, component of the *CD151* phenotype. Including the present patient, unilateral kidney agenesis has now been described in at least four individuals from three families, while additional reported abnormalities include a hypoplastic kidney and a possible duplex collecting system. The underlying mechanism remains unresolved, but a developmental contribution of disrupted laminin-integrin signaling is biologically plausible. CD151 organizes laminin-binding β1-integrin complexes. Consistent with a role in nephrogenesis, single-cell RNA-sequencing data from the human fetal kidney show broad CD151 expression throughout the nephrogenic lineage, from nephron progenitors and pretubular aggregates to differentiating podocyte and tubular populations(14). Conditional deletion of Itgb1 in the developing ureteric bud impairs branching morphogenesis and can cause severe developmental kidney abnormalities, including kidney agenesis(15, 16). These observations suggest that deficient CD151-dependent integrin organization may disturb kidney morphogenesis.

The progressive urogenital stenoses in our patient extend a broader pattern of epithelial and mucosal complications in CD151 deficiency. Lacrimal duct stenosis, oral mucosal erosions, dysphagia, esophageal webs and strictures have been described previously, suggesting that repeated epithelial injury and fibrosis can affect several organ systems (Table 2). Recurrent meatal stenosis and urethral strictures have, to our knowledge, not previously been reported specifically in CD151-associated disease, but are consistent with this mechanism and with genitourinary complications observed in other forms of epidermolysis bullosa(17, 18). The distal ureteral stenosis may represent acquired scarring caused by epithelial fragility, but the coexisting kidney agenesis also raises the possibility of a developmental urinary tract anomaly(19, 20). Irrespective of mechanism, recurrent obstruction contributed directly to pyelonephritis and urosepsis in the index patient and therefore represents a potentially preventable source of morbidity.

The marked variability has direct implications for counselling and clinical care. Although evidence-based surveillance intervals cannot be derived from the small number of reported individuals, we suggest kidney ultrasound, regular blood pressure measurement, and assessment of kidney function and proteinuria. Because complete CD151 deficiency results in the RAPH-null phenotype, early coordination with transfusion medicine is important before red blood cell transfusion.

## CONCLUSIONS

The multisystem phenotype supports viewing CD151 deficiency as a highly variable basement-membrane-associated disorder. CD151 should be considered in individuals with unexplained nephropathy or CAKUT accompanied by skin, nail, hearing, or stenotic abnormalities, and confirmed cases warrant longitudinal multisystem follow-up, including documentation of RAPH blood group status. Larger cohorts and patient-derived models are needed to define genotype–phenotype relationships and disease modifiers.

## Abbreviations

CAKUT
congenital anomalies of the kidneys and urinary tract
CKD
chronic kidney disease
FSGS
focal segmental glomerulosclerosis
eGFR
estimated glomerular filtration rate
NMD

nonsense-mediated mRNA decay
LOF
loss of function

## Declarations

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of the Medical Faculty of Heidelberg University (S-632/2023) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent to participate was obtained from all participants and from the parents or legal guardians of participants of minors.

**Consent for publication**

Written informed consent for publication of their personal or clinical details along with any identifying images has been obtained from all the participants and the parents or legal guardians of minors.

**Availability of data and materials**

The here reported *CD151* variant has been submitted to the ClinVar database (ID: SCV007674013). All other data supporting the findings of this study are included in the article.

**Competing interests**

All authors declare no conflicts of interest.

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**Authors' contributions**

Conceptualization: C.M.K. and M.H. Visualization: C.M.K. Literature review: C.M.K. Resources: all authors. Writing – original draft preparation: C.M.K. Writing – review and editing: all authors. Supervision: M.H.

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## Figures

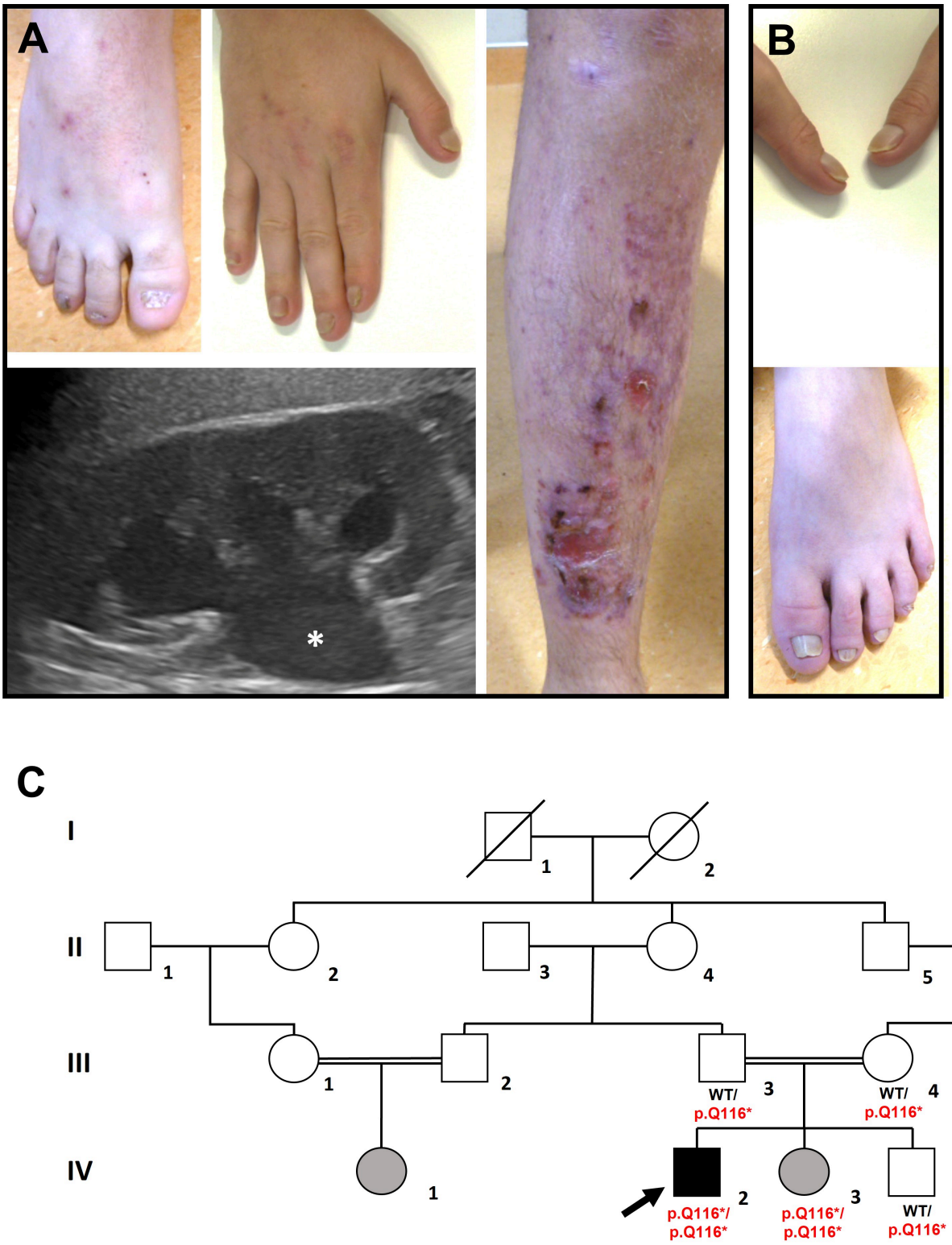



**Figure 1**

**Clinical findings and pedigree of the family with CD151 deficiency.**

**(A)** Clinical findings of the index patient IV-2, demonstrating mild blistering and erosive skin lesions on the dorsal aspects of the hands and feet with marked nail dystrophy, a pronounced pretibial lesion, and renal ultrasound of the solitary kidney showing grade III hydronephrosis secondary to urinary tract obstruction (white asterisk).

**(B)** Clinical findings of the affected sister IV-3, showing bilateral thumbnail dystrophy with otherwise normal fingernails and dystrophic toenails.

**(C)** Pedigree of the family. The index patient IV-2 is indicated by an arrow. Filled symbols indicate affected individuals, gray symbols indicate mildly affected individuals.

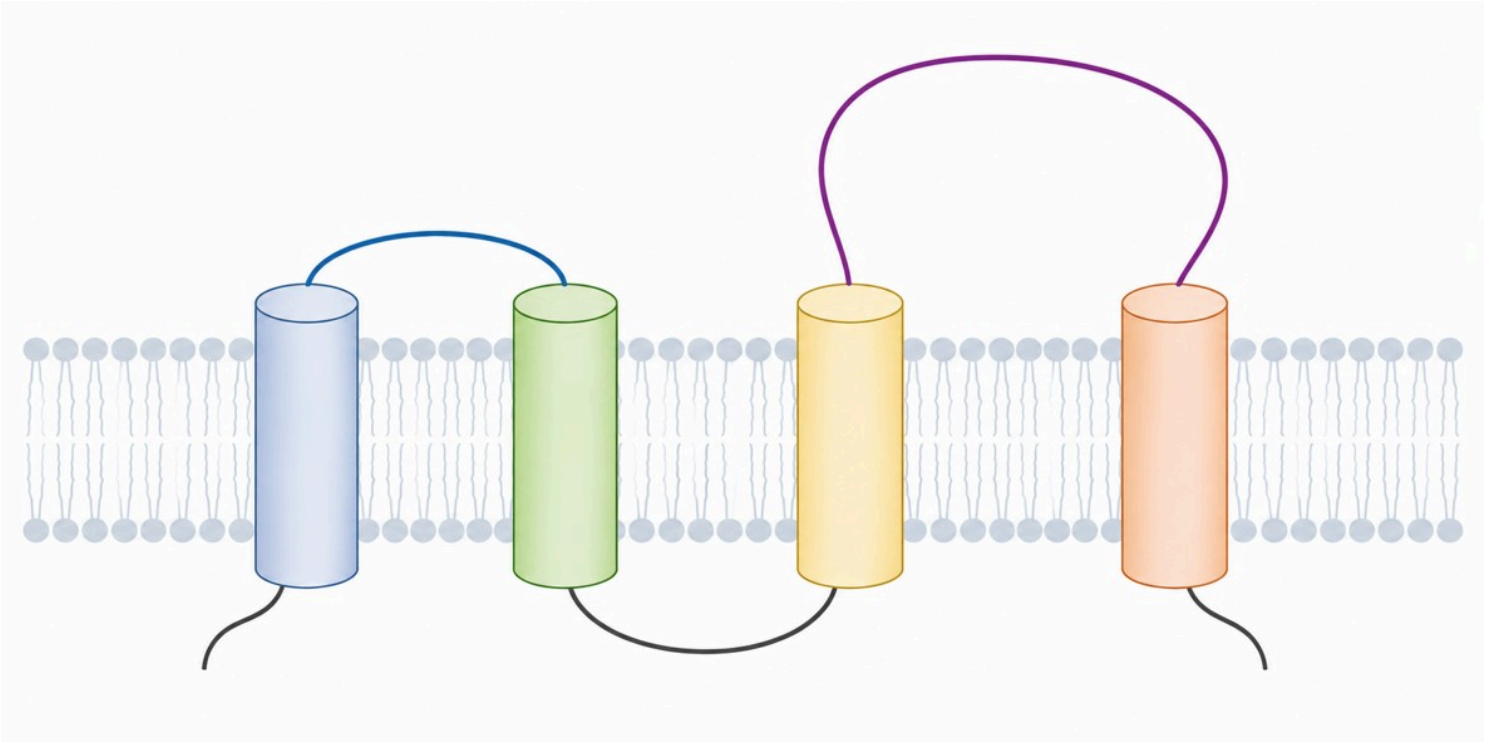


**Figure 2**

**Topological model of wild-type CD151 and the p.Gln116 residue.**

CD151 is a tetraspanin protein comprising four transmembrane domains (TM1–TM4), a small extracellular loop (EC1), a small intracellular loop (IC), and a large extracellular loop (EC2). According to the UniProt topology annotation (P48509), residue Gln116 is located immediately downstream of the third transmembrane domain at the beginning of EC2.  Created with OpenAI ChatGPT (GPT-5.5 image generation).