BMC Nephrology

CASE REPORT

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Co-occurrence of Charcot-Marie-Tooth disease type 1 and glomerulosclerosis in a patient with a de novo *INF2* variant

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Abstract

Background Renal disease is associated with Charcot-Marie-Tooth disease (CMT), a common inherited neurological disorder. Three forms of CMT have been identified: CMT1 of the demyelinating type, CMT2 of the axonal defect type, and intermediate type (Int-CMT). *INF2* is an important target for variants that cause the complex symptoms of focal segmental glomerulosclerosis (FSGS) and CMT.

Case presentation We report the case of a 13-year-old female Chinese patient (born in 2011) with a rare co-occurrence of CMT1 and glomerulosclerosis (GS) (CMT1-GS). The patient presented with slowly progressive gait disorder with unsteadiness during walking, pes cavus, and kyphoscoliosis since the age of 1 year. Electrophysiological studies and brain magnetic resonance imaging revealed demyelinating features consistent with CMT1. At 12 years of age, she was hospitalised for hypertension and dizziness; her serum albumin was 27.9 g/L, serum creatinine was 87 μmol/L, estimated glomerular filtration rate was 88.6 mL/min, and 24-h urine protein was 4.95 g. A renal biopsy showed glomerulosclerosis. Renal function deteriorated further during the follow-up period, and she received a kidney transplant at the age of 13. Whole-exome sequencing identified a de novo heterozygous c.326T > G (p.Met109Arg) variant in exon 2 of *INF2*. The variant was classified as "pathogenic" according to the American College of Medical Genetics and Genomics criteria.

Conclusions We describe a rare clinical phenotype of CMT1-GS associated with a de novo variant of *INF2*. Our findings expand the phenotypic and genotypic spectrums of *INF2*-associated disorders.

Keywords Glomerulosclerosis, Charcot-Marie-Tooth disease type 1, *INF2*

Background

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome in both children and adults around the world, accounting for up to 20% of cases of end-stage renal disease (ESRD) [1, 2]. Substantial insights into the genetics of FSGS have accumulated, and an updated list of 13 genes have been reported as causes of FSGS [3]. Recent literature suggests that variants in *INF2* (inverted formin-2) gene are more frequent than in other genes [4]. It has been estimated that *INF2* variants are responsible for 9–17% of cases of autosomal dominant familial FSGS and 1% of sporadic cases [5, 6].

Charcot-Marie-Tooth (CMT) disease is the most common inherited peripheral neuropathy, with an estimated prevalence of 1/2500 [7]. Common symptoms appear to be clinically and genetically heterogeneous and cause the gradual degeneration of peripheral motor and sensory neurons. Based on the median motor nerve

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conduction velocity (MNCV), CMT is divided into CMT1 or 'demyelinating' (MNCV < 38 m/s), CMT2 or 'axonal' (MNCV > 38 m/s), and intermediate CMT (Int-CMT), with an MNCV between 25 and 45 m/s. CMT1 has been reported to be the major subtype present in 37.6–84.0% of cases [8]. An increased prevalence of nephropathy, particularly FSGS, has been reported in patients undergoing CMT [6]. *INF2* variants were found in approximately 75% of cases with complex symptoms of CMT and FSGS (CMT-FSGS). Among these cases, most patients presented with Int-CMT, and 91% of them developed ESRD with a median age of 20 years [9, 10].

INF2 is a member of the diaphanous formin family of actin-regulating proteins, which is strongly expressed in Schwann cells and podocytes. It plays an important role in the nucleation, elongation, and depolymerization of actin filaments. Both dual CMT-FSGS and single FSGS phenotypes associated with *INF2* variants render cellular defects through a common pathway that primarily affects the actin-microtubule network. However, variants related to CMT-FSGS have more severe effects than variants that cause FSGS alone [9, 10].

Here, we report a 13-year-old female Chinese patient (born in 2011) with a de novo heterozygous variant in *INF2* causing an uncommon clinical profile: CMT1 and glomerulosclerosis (GS) (CMT1-GS). Our findings demonstrated *INF2*-associated renal and neurological disorders and that the genotype–phenotype relationship may be more complicated than previously considered.

Case presentation

Patient and pedigree

The patient (II:1, Fig. 1A) presented with a slowly progressive unsteady gait, easy falls, and pes cavus (Fig. 2A) since 1 year of age. Cerebral palsy was excluded because the patient did not present with typical central nervous system disorders. In early childhood, she was fitted with orthopaedic shoes. At 10 years of age, she was diagnosed with kyphoscoliosis and treated with external fixation (Fig. 2B). Slowly, she developed moderate bilateral distal muscle weakness in the lower limbs, and was unable to

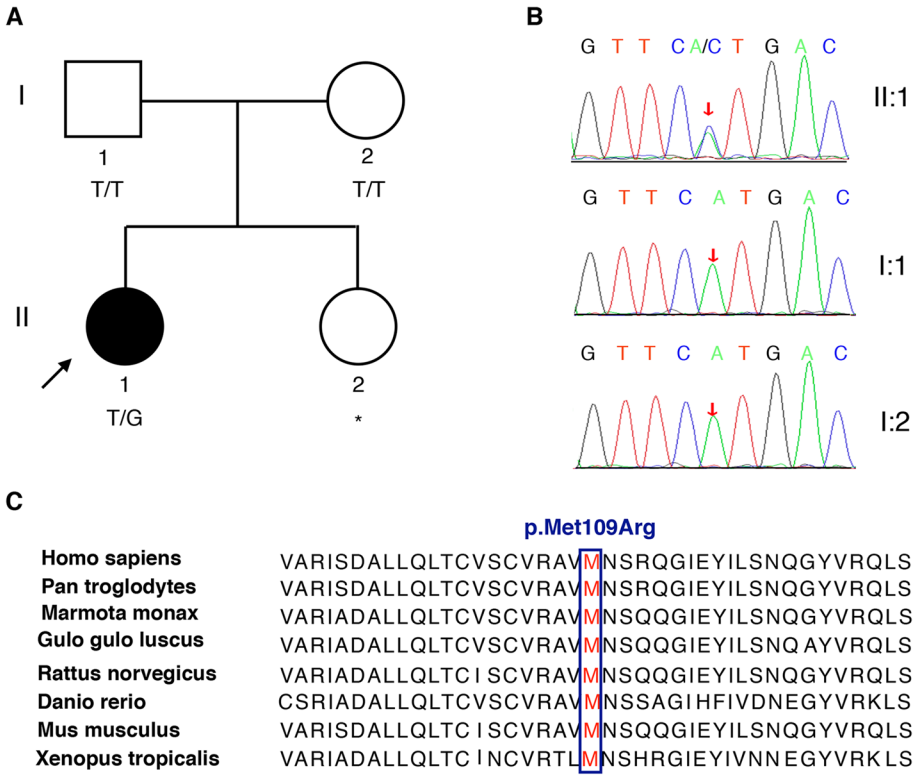

Fig. 1 Family pedigree, Sanger sequencing chromatograms and evolutionary conservation. **A** Pedigree structure of the family. Squares and circles denote males and females respectively. Roman numbers indicate generations. Genotypes associated with the *INF2* genetic variant (c.326T > G; p.Met109Arg) are indicated at the bottom of all the examined individuals. The patient (arrow, II:1) had the TG genotype for c.326T > G, whereas both unaffected parents showed no mutant allele. The asterisk* represents that genetic sequencing was not performed in the patient's younger sister (II:2). Unfilled symbols: unaffected individuals; filled symbols: individuals with CMT1-GS. **B** Sequence electropherograms show the heterozygous *INF2* c.326T > G substitution (arrow) in the patient, absent in her parents (I:1 and I:2). **C** Alignment of the INF2 protein in different species shows the conservation of the Met109 residue. The concerned amino acids are boxed

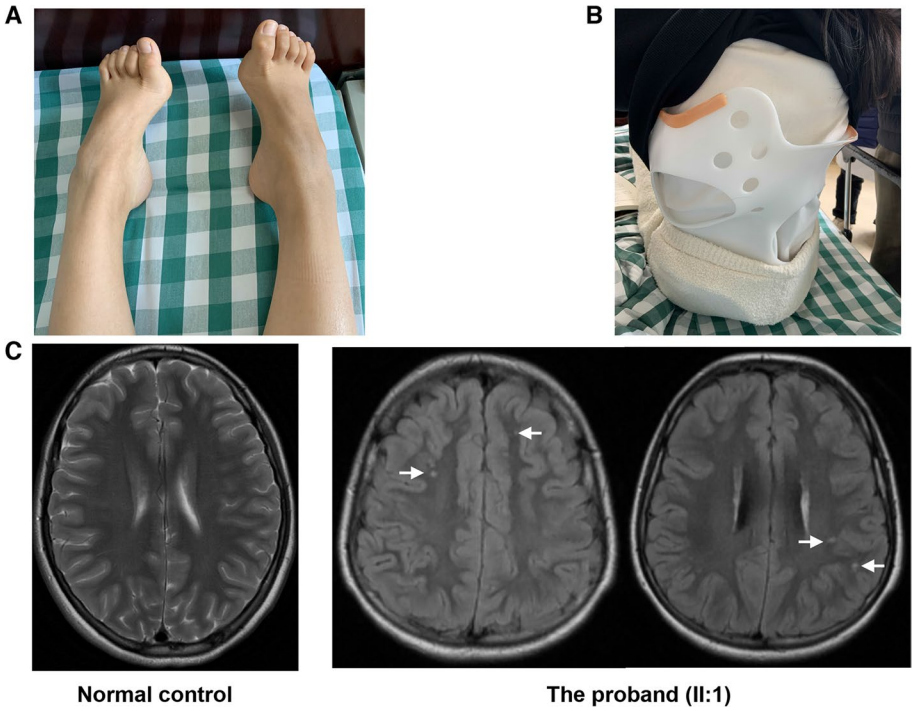

Fig. 2 Anomalies on physical examination and neuroimaging in the proband. **A** Pes cavus. **B** Kyphoscoliosis treated with external fixation. **C** Magnetic resonance imaging of the brain (fluid-attenuated inversion recovery sequences) of a normal control (on the left) and the proband (on the right). Arrows point to hyperintensities visible in bilateral frontal and parietal lobe white matter

run or jump. No sensorineural hearing impairment was detected. She had visited several hospitals and was clinically diagnosed with peripheral neuropathy.

At 12 years of age, she was hospitalised after experiencing hypertension and dizziness for more than a year. Her maximal blood pressure was 180/105 mmHg. Urinalysis showed 4 + proteinuria and 0–1 red blood cells per high-power field and her 24-h urine protein was 4.95 g/day. Urine protein profiles demonstrated non-selective glomerular proteinuria. Serum albumin was 27.9 g/L, serum creatinine level was 87 μmol/L, and the estimated glomerular filtration rate using the CKD-EPI equation was 88.6 mL/min. The following tests were negative: antinuclear antibodies, antineutrophil cytoplasmic autoantibodies, antiglomerular basement membrane autoantibodies, rheumatoid factor, serum and urine immunoelectrophoresis for free monoclonal light chains, hepatitis B surface antigen, and hepatitis C antibodies. Her father (I:1), her mother (I:2), and her younger sister (II:2) were phenotypically normal (Fig. 1A).

Renal ultrasonography revealed an 8.6 × 4.0 cm (reference value: 9.21 ± 0.62 × 4.91 ± 0.32 cm) left kidney and a 10.0 × 4.0 cm (reference value: 8.95 ± 0.64 × 4.83 ± 0.29 cm) right kidney with bilateral diffuse changes [11]. Subsequently, percutaneous renal biopsy was performed. The tissue for light microscopy (Fig. 3A-C) contained 21 glomeruli, of which 18 were globally sclerotic and three showed mesangial hypercellularity and mesangial matrix expansion. Tubular dilation with protein casts, interstitial fibrosis, non-specific inflammatory infiltrates, and small renal artery stenosis were present. Immunofluorescence studies showed marked IgM deposition (++) in the mesangial region ((Fig. 3D), normal expression of α2 and α5 chains of type IV collagen, and no positivity for IgA, IgG, C3, C4, C1q, and fibrinogen. Electron microscopy of the non-sclerosed glomeruli revealed no significant thickening of the glomerular basement membrane and partial effacement of the foot process (Fig. 3E, F).

Electrophysiological studies and brain imaging analysis

Electrophysiological studies were performed on the patient and her family members (Supplemental Table S1). The nerve conduction findings of the patient were consistent with those of CMT1; the mean MNCVs of the median nerves was 17.4 m/s. Normal MNCVs were observed in her parents and younger sister. In addition, her brain magnetic resonance imaging showed central nervous system anomalies characterized by point-shaped white matter hyperintensities in the bilateral frontal and parietal lobes (fluid-attenuated inversion recovery sequences) (Fig. 2C).

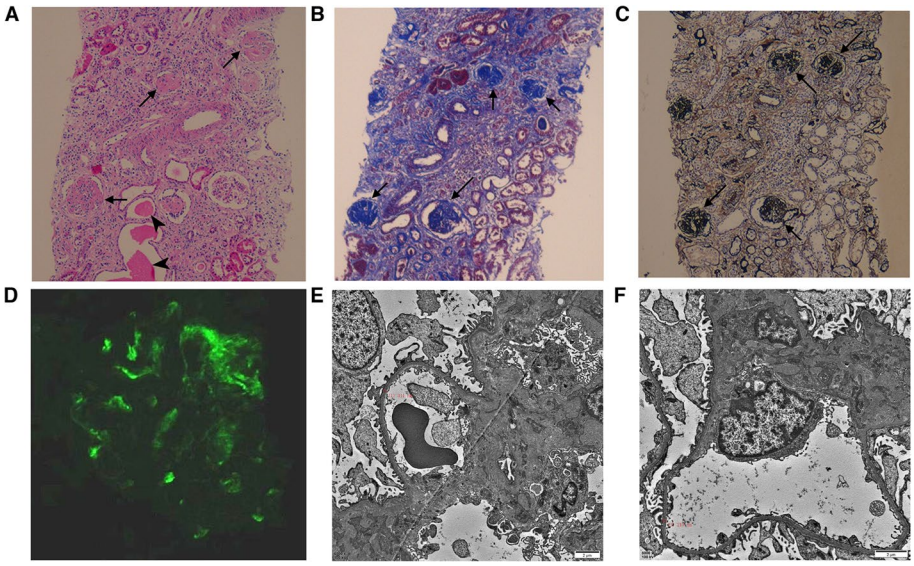

Fig. 3 The pathological features of kidney sections in the patient. Light micrograph: Mostly globally sclerotic glomeruli (arrows), individual glomeruli with mesangial hypercellularity and mesangial matrix expansion, tubular dilation with protein casts (arrowheads) (**A**, HE × 100). Obvious glomerular sclerosis (arrows), tubular atrophy, interstitial fibrosis, nonspecific inflammatory infiltrate, and small renal artery stenosis (**B**, Masson × 100 and **C**, PASM × 100). Immunofluorescence: IgM-dominant deposits in the mesangium (**D**, IF × 200). Electron micrograph: No significant thickening of the glomerular basement membrane and partial effacement of foot process (**E**, × 6000; **F**, × 8000). HE, haematoxylin and eosin. PASM, periodic Schiff-methenamine. IF, immunofluorescence

Genetic analysis

Using whole-exome sequencing, we identified a heterozygous *INF2* variant in the patient, which was confirmed by Sanger sequencing (Fig. 1A, B). Sanger sequencing showed that the variant was absent from the patient's unaffected parents. Further segregation analysis showed that the *INF2* c.326T > G variant occurred de novo. This variant consisted of thymine-to-guanine nucleotide substitution in exon 2, which was predicted to substitute an arginine residue with a methionine residue in the INF2 protein (p.Met109Arg) (Table 1). This variant was not found in any population databases (such as gnomAD and ExAC) or any publications. No DNA was available from the patient's unaffected younger sister.

Molecular characterisation and structural modelling

The residue Met109 is in the 8th α-helix within the regulatory N-terminal diaphanous-inhibitory domain (DID) of INF2 and is an evolutionarily highly conserved residue among organisms (Fig. 1C). The c.326T > G variant in *INF2* leads to a polar change from a neutral uncharged residue to a negatively charged residue. In silico prediction tools independently predicted that the substitution was deleterious to protein structure and function (MutationTaster: disease-causing; PolyPhen-2: 0.999; PROVEAN: -4.75) (Table 1). Based on homology modelling, the 3D representation of INF2 remained unchanged after the substitution of Met109 with an Arg residue (Fig. 4A); however, changes in the nature and size of the residue altered the local intramolecular hydrogen bonds between the side chain and its neighbouring residues (Val105 and Arg106) (Figs. 4B, C).

Discussion and conclusions

In the kidney, *INF2* gene expression occurs predominantly in podocytes, which are sensitive to changes in the cytoskeleton. Variants in *INF2* can induce a monogenic FSGS phenotype [12]. Meanwhile, INF2 is highly

Table 1 Bioinformatics analysis of *INF2* c.326T > G variant

Gene	Nucleotide change	Protein change	ClinVAR		dbSNP	Population database		In silico analysis		
			Interpretation	Assession		gnomAD	ExAC	MutationTaster	PolyPhen-2	PROVEAN
INF2*	c.326T > G	p.Met109Arg	LP	VCV000447578.1	rs1555373368	NF	NF	Disease causing	Probably damaging	Deleterious

Abbreviations: *Reference sequences of nucleotides are NM_022489.4. In ClinVar annotations, variants are classified according to recommendation by the American College of Medical Genetics and Genomics: LP, Likely Pathogenic. gnomAD, genome aggregation database; ExAC, exome aggregation consortium; NF, not found; PolyPhen-2, polymorphism phenotyping-2; PROVEAN, protein variation effect analyzer

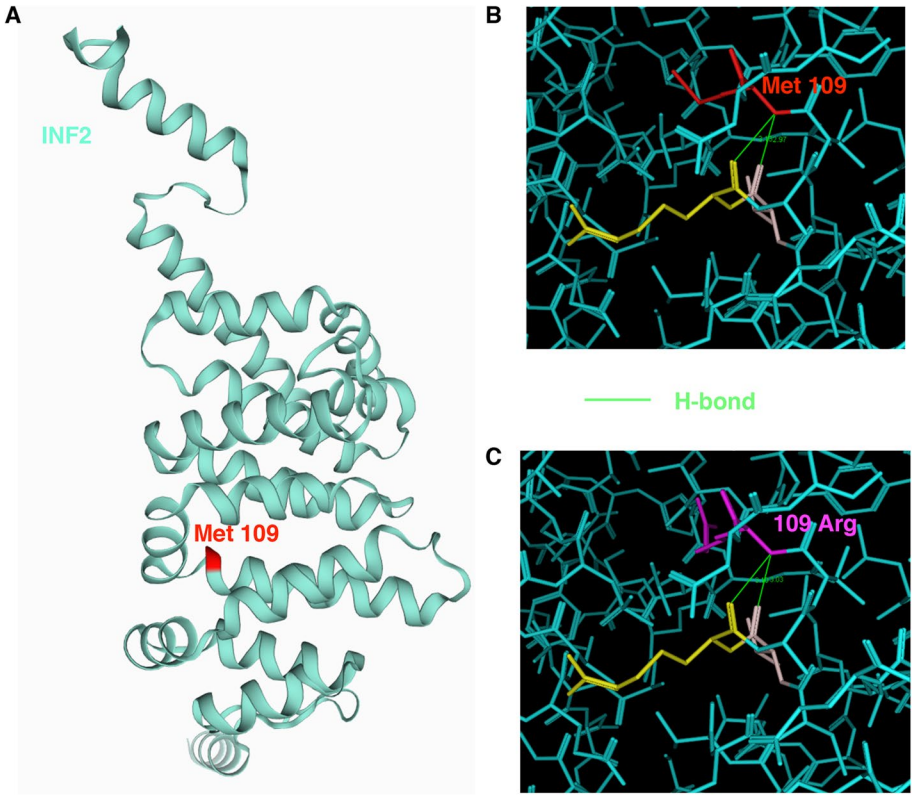

Fig. 4 Three-dimensional model of INF2 protein. **A** Amino acids 5 through 289 of INF2 are presented in blue using the Swiss-model program. The residue Met109 is shown in red, and it is located at the 8th α-helix of the diaphanous-inhibitory domain (DID). Generated models show the discrimination of local intramolecular hydrogen bonding interactions between Met109 (**B**) and 109Arg (**C**) by Molecular Operating Environment (MOE). Hydrogen bonds are shown as fluorescent green lines

expressed in Schwann cells and neurones. Recent research has revealed that INF2 interacts with the Rho GTPase CDC42 and myelin and lymphocyte (MAL) proteins, which are implicated in the essential steps of myelination and myelin maintenance. *INF2* variants are also responsible for the dual-faceted nature of CMT-FSGS [9].

The clinical and genetic findings of patients with concurrent CMT and renal involvement (mostly FSGS) in the literature are shown in Table 2. In accordance with previous reports, the renal phenotype of the patient in our study appeared after CMT symptoms but progressed faster. Although the CMT types associated with *INF2* variants have been almost exclusively Int-CMT, the patient was diagnosed with CMT1 based on neurophysiological and brain imaging findings. Furthermore, her kidney biopsy showed diffuse GS with marked IgM deposition in the mesangial region. Thrombotic microangiopathy and podocyte infolding glomerulopathy have also been reported to be associated with *INF2* variants [13, 14]. All patterns of glomerulonephritis can later lead to a pattern of GS. IgM deposition suggests late-stage FSGS, and we speculate that the GS of the patient may have gradually evolved from FSGS rather than other possible renal involvements. However, it has been sporadically reported that a cryptic splicing variant in *INF2* causes Int-CMT with minimal glomerular dysfunction [15]. Therefore, the genotype–phenotype correlation may be more complex.

In our study, the proband (II:1) presented with early onset and slowly progressive distal lower limb weakness, pes cavus, and kyphoscoliosis since 1 year of age. At the age of 12, she was found to have concomitant kidney disease characterised by nephrotic syndrome and renal insufficiency. Her parents (I:1, I:2) and younger sister (II:2) were phenotypically normal. Whole-exome sequencing identified a heterozygous missense variant (c.326T > G) in *INF2* in the patient. Subsequent Sanger sequencing and segregation analysis showed that the alteration occurred de novo. However, it cannot be completely ruled out that one of the patient's parents had germline mosaicism, and so we suggested that the patient' younger sister should undergo genetic sequencing and follow-up. In addition, other possible de novo *INF2* variants may have been missed owing to unfavourable

Table 2 Characteristics overview of previously reported patients and the patient in our study with concurrent CMT and renal involvement with *INF2* variant

Patient	Familial/ Sporadic	Ethnicity (Country)	*INF2* variant		Zygosity	Exon	Age at onset CMT (y)	Neuropathy type (FDS)[a]	Age at onset proteinuria (y)	Age at onset ESRD (y)	Renal phenotype	References
			cDNA Mut	Pro Mut								
1	S	Caucasian (France)	c.170 T > C	p.Leu57Pro	Hetero	2	10	NA (3)	10	20	FSGS	[9, 10]
2	S	Caucasian (Germany)	c.170 T > G	p.Leu57Arg	Hetero	2	1.5	NA (1)	12	15	FSGS	[16]
3	S	Caucasian (Germany)	c.203 T > C	p.Phe68Ser	Hetero	2	4	NA (3)	16	19	GS	[16]
4	F	Asian (Japan)	c.206 T > C	p.Leu69Pro	Hetero[b]	2	14	CMT1 (3)	11	14	FSGS	[17, 18]
5							12	Int-CMT (3)	6	15		
6	S	Caucasian (Greece)	c.205_216del	p.Leu69_Ser72del	Hetero	2	3.5	CMT1 (3)	10	20	FSGS	[10, 19]
7	S	Asian (Japan)	c.218 G > A	p.Gly73Asp	Hetero	2	< 11	CMT1 (3)	11	16	FSGS	[18]
8	S	Asian (Japan)	c.218 G > T	p.Gly73Val	Hetero	2	NA	NA	11	14	FSGS	[20]
9	S	Asian (Japan)	c.218 G > T	p.Gly73Val	Hetero	2	15	Int-CMT (3)	11	14	FSGS	[18]
10	F	Asian (Uzbekistan)	c.230 T > C	p.Leu77Pro	Hetero	2	4	Int-CMT (2)	15	No ESRD to date (at 18 yr)	FSGS	[10, 21]
11	S	Caucasian (Belgium)	c.230 T > G	p.Leu77Arg	Hetero	2	4	CMT1 (3)	14	18	FSGS	[10, 19]
12	S	Asian (Korea)	c.233 T > C	p.Leu78Pro	Hetero	2	1	CMT1 (3)	13	15	FSGS	[22]
13	F	Caucasian (France)	c.271 C > G	p.Arg91Gly	Hetero	2	17	Int-CMT (2)	87	No ESRD to date (at 87 yr)	No renal biopsy	[15]
14							3	Int-CMT (2)	61	No ESRD to date (at 61 yr)		
15							16	Int-CMT (2)	Normal at 30 yr	No ESRD to date (at 30 yr)		
16							10	Int-CMT (2)	26	No ESRD to date (at 26 yr)		
17	F	Caucasian (United Kingdom)	c.305 T > A	p.Val102Asp	Hetero	2	7	NA (3)	15	15	GS, TMA	[13]
18							10	NA (3)	17	17		
19	S	Caucasian (Morocco)	c.310 T > C	p.Cys104Arg	Hetero	2	6	NA (3)	12	12	FSGS	[9, 10]
20	S	Caucasian/African (French West Indies)	c.311 G > T	p.Cys104Phe	Hetero	2	12	NA (2)	11	15	FSGS	[9, 10]
21	F	Caucasian (Canada/ Quebec)	c.312 C > G	p.Cys104Trp	Hetero	2	8	Int-CMT (3)	19	26	FSGS	[9, 10]
22	S	Caucasian (France)	c.317 G > C	p.Arg106Pro	Hetero	2	24	Int-CMT (3)	18	18	FSGS	[9, 10]
23	S	Asian (Japan)	c.323 T > A	p.Val108Asp	Hetero	2	10	CMT1 (3)	14	17	FSGS	[18]
24	S	Asian (China)	c.326 T > G	p.Met109Arg	Hetero	2	1	CMT1 (3)	12	13	GS	This study
25	S	Caucasian (Germany)	c.341 G > A	p.Gly114Asp	Hetero	2	6	Int-CMT (1)	10	15	FSGS	[19]

Table 2 (continued)

Patient	Familial/ Sporadic	Ethnicity (Country)	*INF2* variant		Zygosity	Exon	Age at onset CMT (y)	Neuropathy type (FDS)[a]	Age at onset proteinuria (y)	Age at onset ESRD (y)	Renal phenotype	References
			cDNA Mut	Pro Mut								
26	S	Caucasian (Portugal)	c.383 T > C	p.Leu128Pro	Hetero	2	5	Int-CMT (3)	14	23	FSGS	[9, 10]
27	S	Caucasian (France)	c.383 T > C	p.Leu128Pro	Hetero	2	5	NA (3)	14	22	FSGS	[9, 10]
28	S	Caucasian (Austria)	c.383 T > C	p.Leu128Pro	Hetero	2	3	CMT1 (3)	16	17	FSGS	[21]
29	F	Caucasian (France)	c.395 T > G	p.Leu132Arg	Hetero	3	20	Int-CMT (3)	19	29	FSGS	[9, 10]
30	S	Caucasian (France)	c.395 T > G	p.Leu132Arg	Hetero	3	10	Int-CMT (3)	21	21	FSGS	[9, 10]
31	F	Asian (Korea)	c.395 T > C	p.Leu132Pro	Hetero	3	17	Int-CMT (2)	18	45	FSGS	[22, 23]
32							16	Int-CMT (1)	17	19		
33	F	Caucasian (Spain)	c.490_498del	p.Ala164_Asp166del	Hetero	3	28	NA (1)	21	No ESRD to date (at 32 yr)	FSGS	[9, 10]
34	F	Caucasian (Italy)	c.490_498del	p.Ala164_Asp166del	Hetero	3	20	NA (3)	20	20	FSGS	[9, 10]
35	F	Caucasian (France)	c.493 T > C	p.Leu165Pro	Hetero	3	20	Int-CMT (1)	20	47	FSGS	[9, 10]
36	F	Caucasian (Austria)	c.550 G > A	p.Glu184Lys	Hetero	4	< 10	Int-CMT (3)	27	30	FSGS	[16]

Abbreviations: *CMT* Charcot-Marie-Tooth disease, *FDS* functional disablity scale, *ESRD* end-stage renal disease, *NA* not available, *FSGS* focal segmental glomerulosclerosis, *GS* glomerulosclerosis, *CMT1* Charcot-Marie-Tooth disease type 1, *Int-CMT* intermediate Charcot-Marie-Tooth disease, *TMA* thrombotic microangiopathy, *Note*: FDS[a]: 0: normal, 1: normal but with cramps and fatigability, 2: inability to run, 3: walking difficulty but still possible unaided; [b], mosaicism

Table 3 Criteria met by *INF2* c.326T > G variant

ACMG criteria met	Evidence
PS2—De novo (both maternity and paternity confirmed) in a patient with the disease and no family history	Variant was confirmed to have arisen de novo following parental testing
PM1—Located in a mutational hot spot or functional domain that is not affected by benign variants	Variant was in the proximal half of the DID domain causing a dual-phenotype involving peripheral neurons and podocytes
PM2—Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project or Exome Aggregation Consortium	Variant was not found from controls in population databases or any publications
PP3—Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.)	Variant was highly conserved across species and predicted damaging by MutationTaster, PolyPhen-2 and SIFT
PP4—Patient's phenotype is highly specific for a disease with a single genetic etiology	*INF2* gene mutations were found in approximately 75% of the cases with the complex symptoms of CMT and FSGS

The above table lays out the evidence for calling the *INF2* variant as pathogenic according to ACMG guidelines

Abbreviations: *PS* strong pathogenic criterion, *PM* moderate pathogenic criterion, *PP* supporting pathogenic criterion, *ACMG* American College of Medical Genetics and Genomics, *DID* N-terminal diaphanous inhibitory domain

insurance coverage or for other reasons. Alternatively, there could be a rare deep intronic variant affecting splicing and only detectable by RNA analysis.

INF2 encodes a multidomain protein containing an N-terminal DID, formin homology 1 and 2 domains, and a C-terminal diaphanous-autoregulatory domain. To date, all *INF2* variants causing isolated FSGS and those in the syndromic form involving peripheral neurones and podocytes are clustered in exons 2–4 but segregate in distinctive regions of the DID [9, 10, 13, 15–23]. Variants in the proximal half of the DID (residues Leu57–Glu184) are located between two putative DID-binding pockets that typically cause a syndromic form (Table 2). *INF2* c.326T > G is in the N-terminal disease hotspot area and is highly conserved among organisms. In silico programs independently indicated the substitution as a potential functional variant. Based on the 3D homology-modelled structures, the alteration at amino acid position 109 changed the local intramolecular hydrogen bonds. We interpreted this variant as "pathogenic" (PS2 + PM1 + PM2 + PP3 + PP4) based on the American College of Medical Genetics and Genomics standards (Table 3).

Molecular dynamics analysis and cell immunocytochemistry can be performed to understand the cytoskeletal and structural effects of *INF2* variants. Over the past several years, multiple studies have shown that INF2 regulates various processes in cells [6, 18]. A recent translational study compared responses to puromycin aminonucleoside (PAN)-induced kidney injury between *INF2* R218Q mice (a mouse model with a point mutation in *INF2*) and *INF2* knockout mice [24]. The results showed that, in contrast to *INF2* knockout mice, R218Q knock-in mutant mice were susceptible to developing proteinuria and FSGS in response to PAN injury. Furthermore, *INF2* R218Q conferred gain-of-function effects on the actin cytoskeleton, podocyte adhesion and mitochondria, which were consistent with findings on human kidney organoids with an *INF2* variant (S186P). These data help explain that *INF2* variants cause kidney disease through a gain-of-function mechanism. Further studies are needed to clarify tissue-specific pathways and their cellular significance implicated in *INF2*-related phenotypes.

At present, there are no effective treatments for CMT [25]. The genetic origin of FSGS caused by *INF2* variants indicated that treatment with corticosteroids or immunosuppressants was ineffective. Supportive measures are the focus: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors can be used to control proteinuria and or blood pressure to delay the development of ESRD; however, the prognosis is generally poor [10, 26, 27]. Kidney transplantation is an option available for the complete correction of renal defects caused by pathogenic *INF2* [6]. In our study, the patient was initially administered an additional medicine called dapagliflozin to be taken with losartan, which was later replaced with finerenone. Unfortunately, her renal function progressively deteriorated, and she received a kidney transplant at the age of 13.

Knowledge of the molecular basis and disease relevance is crucial for patients and physicians. Screening for *INF2* variants is strongly recommended in patients presenting with CMT disease and renal disease. Our findings expand the genetic spectrum of *INF2*-associated disorders and broaden clinical phenotypes by the identification of CMT1-GS. Besides, neurological signs typically appear before onset of proteinuria, so we recommend routinely screening for proteinuria of CMT patients from children's age, and initiation of supportive treatment should be discussed.

Abbreviations

CMT	Charcot-Marie-Tooth disease
CMT1	Charcot-Marie-Tooth disease type 1
Int-CMT	Intermediate Charcot-Marie-Tooth disease
DID	Diaphanous-inhibitory domain
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
GS	Glomerulosclerosis
INF2	Inverted formin-2
MNCV	Median motor nerve conduction velocity

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03891-6.

Supplementary Material 1.

Acknowledgements
We thank all the individuals who participated in this study.

Authors' contributions
YD: formal analysis-lead, investigation-lead, resources-lead, data curation-lead, writing—original draft, writing—review and editing-equal; ZW: resources-support, data curation-support; XT: formal analysis-support; XL: formal analysis-support, writing—review and editing-equal. All authors read and approved the final manuscript.

Funding
This work was supported by grants from Medical and Health Technology Program of Zhejiang Province of China (No.2021KY915). The funding body had no role in the design of the study, collection, analysis and interpretation of data and in writing the manuscript.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The totality of the data cannot be shared based on patient confidentiality concerns.

Declarations

Ethics approval and consent to participate
This study was approved by Ethics Committee of the Hangzhou hospital of traditional Chinese medicine (institutional review board approval number: 2020KY055). Written informed consents were obtained from the patient's parents.

Consent for publication
Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Competing interests
The authors declare no competing interests.

Received: 31 August 2024 Accepted: 26 November 2024
Published online: 28 November 2024

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