

Single Case

A Case of Hyperinsulinemic Hypoglycaemia Associated with Atypical Fanconi Renal Tubulopathy Syndrome Caused by an HNF4A Variant

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Keywords

Case report · Clinical molecular diagnostics · Fanconi syndrome · Hyperinsulinism · Hypoglycaemia · *HNF4A* variant · Kidney and urinary tract diseases · Paediatrics · Tubulopathy

Abstract

Introduction: This case illustrates the challenges in the diagnosis of a rare disease with an intricate orientation. The definitive genetic diagnosis was carried out after establishing crucial correlations between the preliminary clinical indications and the laboratory findings. **Case Presentation:** The initial presentation was myoclonic jerks. This was a direct consequence of hyperinsulinaemic hypoglycaemia (HH), and not a phenotypic characteristic described in previous case reports. Linking this to glycaemia led to the evaluation of response to fasting, where inadequate insulin suppression resulted in hypoketotic hypoglycaemia. The diagnosis of chronic kidney dysfunction associated with atypical Fanconi renal tubulopathy syndrome type 4 (FRTS4) was indicated on the basis of a decreased estimated glomerular filtration rate, nephrocalcinosis, millimetric lithiasis, rickets, and complex proximal tubulopathy. This indicated atypical FRTS4 as associated with HH and necessitated further molecular genetic

testing. **Conclusion:** The patient was identified as a carrier of the c.187C>T (p.Arg63Trp) variant in the *HNF4A* gene, which is a heterozygous missense variant classified as pathogenic. This entity is rare, and the published literature reporting *HNF4A* gene variants associated with atypical FRTS and HH is limited. It is therefore important to report such cases to contribute to the growing body of evidence and help identify pathogenic *HNF4A* variants and their implications.

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Introduction

The hepatic nuclear factor 4 (*HNF4A*) is a transcription factor that is highly expressed in the liver, pancreas, and kidney tubules. Mutations in the gene encoding for *HNF4A* were first shown to be associated with a form of familial monogenic diabetes known as maturity-onset diabetes of youth (MODY) type 1 [1]. On the one hand, the studies from Pearson et al. [2] and Fajans et al. [3] were the first to link mutations in *HNF4A* gene as a cause of mild, transient congenital hyperinsulinism (CHI) associated with macrosomia [4]. On the other hand, Hamilton et al. [5] were the first to recognise that one specific heterozygous missense mutation in the DNA-binding domain of *HNF4A* (p.R85W) caused an unusual MODY type 1 patient with features of renal Fanconi syndrome, although a case had been described previously [6].

CHI is the most common cause of severe hypoglycaemia in the newborn and childhood period and is determined by inadequate insulin secretion. Due to the inhibitory effect of insulin on lipolysis and ketogenesis, there is suppressed ketone body formation in the presence of hypoglycaemia thus leading to increased risk of hypoglycaemic brain injury. Therefore, a prompt diagnosis and immediate management of hyperinsulinaemic hypoglycaemia (HH) is essential to avoid hypoglycaemic brain injury and long-term neurological complications in children [7, 8].

Any complex proximal tubular dysfunction is classified as Fanconi renal tubulopathy syndrome (FRTS). It is characterised by the presence in the urine of compounds that are managed by particular tubular regions, indicating the impairment of one or more proximal tubule transporters [5]. FRTS may originate due to a range of different mechanisms and also includes different possible manifestations, from the classical forms to more recently described subtypes, the latest being linked to specific gene mutations and referred to as atypical FRTS [1].

Since this association of *HNF4A* with a renal tubulopathy phenotype was described, a number of cases have been reported [5, 6, 9–24]. Nevertheless, this gene is not always included in the genetic panels for tubulopathies. Therefore, in some cases, the study of this gene could be neglected, and hence, the presence of pathogenic variants goes unrecognised. The present case involves a patient with a genetic defect in the *HNF4A* gene who experienced myoclonic jerks associated with hypoglycaemia and tubulopathy. The initial case orientation entailed many challenges, which required comprehensive anamnesis and a series of laboratory analyses concluding with a genetic confirmation of the diagnosis.

Case Report

A three-year-old girl with no outstanding perinatal or family history (born at term after an uneventful pregnancy, with a birth weight of 3,300 g) was referred to our hospital after being evaluated at the emergency department of her regional hospital because of a tonic-

clonic convulsive episode. Upon presentation, the patient's electroencephalogram demonstrated the presence of frontal crisis. Consequently, the patient was classified as having epilepsy, and treatment with valproate was initiated. Previously, she had been in our hospital at the age of 14 months for myoclonic jerks upon awakening, which were diagnosed as benign myoclonus of infancy. Furthermore, she had been under the care of the traumatology department since the age of two because of a genu varum, which was considered to be a physiological condition. The neurological exam revealed a normally developing child with subtle dysmorphic features, such as relative macrocephaly with frontal bossing and elongated eyelashes and a short stature with a genu varum. Laboratory investigations showed hypoglycaemia (2.8 mmol/L; reference range [RR]: 3.3–5.6 mmol/L) and renal dysfunction with elevated blood urea (6.83 mmol/L; RR: 1.8–6.4 mmol/L) and blood creatinine (40.67 µmol/L; RR: 21.22–33.59 µmol/L) levels, with an estimated glomerular filtration rate (eGFR) of 66.6 mL/min/1.73 m² (CKiD U25 calculation [25, 26]). Other findings included low blood uric acid, increased urinary uric acid excretion, generalised hyperaminoaciduria and glycosuria, all compatible with complex proximal tubular dysfunction. Liver biochemistry was unremarkable. Concurrently, mild increases in the levels of Krebs cycle intermediates and lactate were observed, which is consistent with mitochondrial dysfunction, either primary or secondary. Considering the laboratory findings, the medical history was reviewed with the patient's family. The myoclonic jerks that occurred during infancy usually subsided with feeding and manifested mainly after long periods of fasting or during intense physical activity. The aetiology of such episodes was considered to be metabolic and associated with hypoglycaemia. The patient was admitted to the hospital for a multidisciplinary assessment by the neurology, endocrinology, and nephrology departments. Given that valproate can cause proximal tubulopathy and is contraindicated in case of mitochondrial pathology [27], its use was suspended.

Renal function was further evaluated. Renovesical ultrasound revealed the presence of mild medullary bilateral nephrocalcinosis and millimetric lithiasis. The laboratory examination included comprehensive blood analysis, with calcium and phosphate metabolism markers, and analyses of a spot urine sample and two 24-h urine samples, one of which was acidified for the determination of oxaluria (shown in Table 1). The results of the urine analysis indicated a normal urine-concentrating capacity, which could have been overestimated because of glycosuria without polyuria. The excretion of electrolytes was within the normal ranges, with no evidence of saline loss (FENa+ and FECl− [%] within the range) and normal aldosterone activity (evaluated through FEK+ and TTKG). Hypouricaemia, increased uric acid excretion and a slightly decreased phosphorus reabsorption rate (TRP: 82.5%, TmP/FGR: 1.15 mmol/L) were indicative of a heightened risk of lithiasis. Nephrotic-range proteinuria was detected, with a combination of characteristics, among which the tubular profile was the most prominent. Blood analysis confirmed renal dysfunction, with an increased plasma creatinine level (37.14 µmol/L; RR: 21.22–33.59 µmol/L) and an eGFR of 72.8 mL/min/1.73 m² (CKiD U25 calculation [25, 26]). Urinary metabolic acidosis with a conserved anion gap was subsequently observed (urinary pH: 6.5). Other findings included a low carnitine plasma concentration, which was compatible with renal loss due to proximal tubulopathy, and hyperparathyroidism, which was most likely secondary to hypovitaminosis D (PTH: 121 ng/L, RR: 14.5–87.1 ng/L; 25[OH]D: 36.19 nmol/L; RR: >49.92 nmol/L). However, cystinosis was excluded because the intraleucocyte cystine concentration fell within the RR. Finally, X-ray demonstrated alterations compatible with rickets. The patient was diagnosed with chronic kidney dysfunction associated with atypical FRTS.

Furthermore, a fasting functional test was conducted to investigate the origin of the hypoglycaemia. Serial measurements of glycaemia and ketonaemia revealed a hypoglycaemic state after 13 h of fasting. Afterwards, blood and urine samples were collected to

Table 1. The results of the urine analysis indicated renal dysfunction at admission

Analyte	Result	RR
Single urine specimen analysis		
Osmolarity, mOsm/kg	848	300–900
pH	6.5	4.5–8
Creatinine, $\mu\text{mol/L}$	5,128.36	n/a
Sodium, mmol/L	79.9	n/a
FENa ⁺ , %	0.7	0.63±0.21
Potassium, mmol/L	119.7	n/a
FEK ⁺ , %	15.9	8.43±3.24
TTKG, %	4.9	4.1–10.5
Chloride, mmol/L	107.1	n/a
FECl [−] , %	0.9	0.84±0.27
Calcium/creatinine, mol/mol creatinine	0.8	<0.8
Inorganic phosphorus/creatinine, mmol/mmol creatinine	5.73	0.73–3.63
TRP, %	82.5	86.34–95.76
TmP/GFR, mmol/L	1.15	1.49±0.19
Uric acid/creatinine, mmol/mmol creatinine	0.89	0.31±0.11
FEUa, %	23.5	11–17
Proteinuria, mg/mmol creatinine	559.11	<22.6
Albuminuria, mg/mmol creatinine	86.45	<3.39
$\beta 2$ -Microglobulin, mg/L	>4.0	<0.10
24-h urine analysis ^a		
Volume, mL/24 h	400	440–680
Creatinine, mmol/24 h	15.7	21.5–28.3
Glucose, mmol/24 h	343.68	<54.4
Sodium/potassium	1.37	<2.5
Natriuresis, mmol/kg/24 h	2.9	3.87±1.3
Uricosuria, $\mu\text{mol}/1.73 \text{ m}^2/24 \text{ h}$	2,813.3	437.6–1,548
Phosphaturia, mmol/1.73 m ² /24 h	30.58	<322.9
Calciuria, mmol/kg/24 h	0.16	0.059±0.017
Magnesiumuria, mmol/kg/24 h	0.19	0.086±0.045
Citrate/creatinine, mmol/mol	791	25–250
Citraturia, mg/24 h	237.69	<230
Calcium/citrate, mg/mg	0.37	>0.33
Oxaluria, mg/dL	25.3	<40

GFR, glomerular filtration rate; FE, fractional excretion; n/a, not applicable; TmP, tubular maximum reabsorption of phosphate; TRP, tubular reabsorption of phosphate; TTKG, transtubular potassium gradient. The formulas and RRs from [1]. Most urinary analytes were measured on Atellica Solutions (Siemens Healthineers, Erlangen, Germany). Osmolarity was measured using A20 (Tecil, Barcelona, Spain). Urinary pH was measured with SediMAX (A. Menarini). Urine sampling was performed by using a 10-mL Urirecen round-base tube (Vacutest Kima srl, Arzergrande, Italy). For urinary oxalate measurement, 24-h urine was collected in an acidified container and analysed on A15 (Biosystems, Barcelona, Spain). For 24-h urine collection, the patient's first voided morning urine was discarded; subsequent urine produced over the next 24 h, including the next morning's first voided sample, was collected in laboratory-provided containers. The total volume was recorded after a full 24 h of urine collection. A representative sample from the total collection was then submitted to the laboratory for analysis. ^aRathi CJCMB, Sharif S, Leslie SW. StatPearls Publishing LLC. 2024 [cited 2024 Nov 11]. 24-Hour Urinalysis. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482482/>.

Table 2. Plasma analytes indicating a low metabolic response to hypoglycemia

Analyte	Result	RR
Ketone bodies		
Free fatty acids, mmol/L	1.83	0.60–1.30
β-Hydroxybutyrate, μmol/L	712.2	15–600
Ketogenic amino acids		
Valine, μmol/L	343.4	85–334
Isoleucine, μmol/L	113.2	13–81
Leucine, μmol/L	207.5	40–158
Hormones		
Insulin, mU/L	1.1	N/A
C-peptide, ng/mL	0.24	N/A

N/A, not applicable. Serum analytes were measured on Atellica Solutions (Siemens Healthineers, Erlangen, Germany). Serum sampling was performed by using a 4-mL BD Vacutainer CAT (clot activator tube) (Becton, Dickinson and Company, Plymouth, United Kingdom). Plasma samples were collected in BD Vacutainer K2EDTA (Becton, Dickinson and Company, Plymouth, United Kingdom).

investigate the metabolic and endocrine responses to fasting. The concentrations of ketogenic amino acids (valine, leucine, and isoleucine), free fatty acids, and ketone bodies in the blood exhibited a profile consistent with hypoketotic hypoglycaemia (lower glycaemia ≤ 2.22 mmol/L) in the absence of insulin and C-peptide suppression (shown in Table 2). These data led to the diagnosis of HH.

Since the concurrence of atypical FRTS and HH was an indication for molecular genetic testing, exome analysis was performed. This included capturing of exonic regions using the xGen Exome Panel v2.0 (Integrated DNA Technologies, Coralville, USA) kit, generation of paired-end libraries, ultrasequencing (2 × 100 bp; NovaSeq 600 sequencing platform Illumina, San Diego, USA) and bioinformatic analysis of the data using the Data Genomics Exome Pipeline software (version v19.1). The following human phenotype ontology codes associated with the patient's phenotype were used to identify the genes included in the analysis: rickets (HP: 0002748), renal Fanconi syndrome (HP: 0001994), hypoglycaemia (HP: 0001943), and hyperinsulinaemia (HP: 0000842). The patient was found to be a heterozygous carrier of the pathogenic variant NM_175914.5:c.187C>T (p.Arg63Trp) in the *HNF4A* gene (VCV000156152.27, ClinVar, NCBI), which confirmed the diagnosis of HH with FRTS4 [28].

The treatment plan included diazoxide, an inhibitor of β-cell insulin secretion, which was administered in conjunction with metabolic supplements, including citrate salts, phosphate, carnitine, and vitamin D. Adequate water intake was also recommended. Later, a study was conducted to ascertain the extent of segregation between the parents. The mother was identified as an asymptomatic carrier of the variant, with unremarkable blood and urine results in the laboratory analysis. Written informed consent was obtained from the family for the purpose of publishing this case report and the CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000549545>).

Currently, the patient is under follow-up. Metabolic acidosis is being managed with citrate salts. At 7 years old, the patient is still being treated with diazoxide. She has also

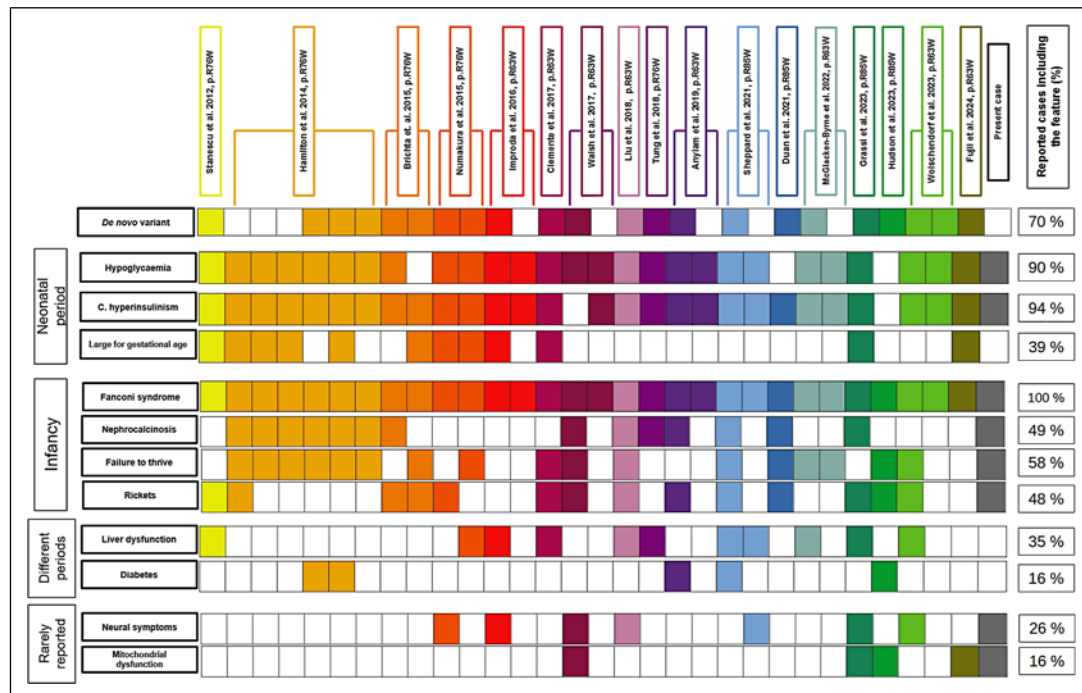


Fig. 1. Summary of previous published case reports. Adapted from Liu et al. [15] Hudson et al. [22], Grassi et al. [21] and actualised.

presented with episodes of nephrotic-range proteinuria of mixed origin although predominantly tubular. For it, treatment with angiotensin-converting enzyme inhibitors (enalapril) has been initiated and adjusted until reaching the maximum doses tolerated. Bilateral medullary nephrocalcinosis with non-obstructive microlithiasis, as well as secondary rickets and growth retardation, has resolved.

Discussion

The patient in this case was identified as a carrier of the c.187C>T (p.Arg63Trp) variant in the *HNF4A* gene, which codes for a transcription factor belonging to the nuclear receptor family and is mainly expressed in the intestine, kidney, liver, and pancreas (UniProt: P41235) [29]. The genes known to be regulated by *HNF4A* include those encoding glucose transporter-2, glycolytic enzymes, and enzymes involved in mitochondrial metabolism [7]. This is a heterozygous missense variant classified as pathogenic (ClinVar ID: 156152 and HGMD ID: CM102622) [26]. Different nomenclatures have been used to refer to it, including p.Arg60Trp, p.Arg63Trp, p.Arg76Trp, p.Arg85Trp, or p.Arg78Trp; depending on which mRNA spliced isoform is used as a reference. Notably, all of these refer to the same genetic variant and the same clinical syndrome. Although the MANE (matched annotation from the NCBI and EMBL-EBI) transcript corresponds to the p.Arg63Trp nomenclature, some authors suggest the use of the spliced isoform that contains p.Arg85Trp as the reference for FRTS since this is the major isoform expressed in the renal tubules [1, 20].

The pancreatic phenotype of the case is explained by the fact that the *HNF4A* gene harbours two distinct promoter regions, known as P1 and P2. The transcription from the

Table 3. Frequency of reported phenotypic characteristics of FRTS4 as described in Lemaire 2021

Characteristic	Number of cases (%), <i>n</i> = 30	References
Urinary phosphate wasting	12 (40)	[11–14, 16, 18, 21, 22]
Glycosuria	14 (47)	[10, 11, 13–15, 18, 19, 21, 22, 24]
Hyperaminoaciduria	11 (37)	[10, 11, 13, 14, 19, 21, 22, 24]
LMW proteinuria	15 (50)	[10–15, 17–19, 21, 22, 24]
Renal tubular acidosis	12 (40)	[9–15, 17, 21, 23, 24]
Hypercalciuria	14 (47)	[5, 10, 12–15, 19, 21]
Potassium wasting	3 (10)	[16, 21, 22]
Hyperuricosuria	3 (10)	[19, 24]
Renal insufficiency	10 (33)	[12, 14–17, 19, 21, 22, 24]
Nephrocalcinosis	17 (57)	[5, 10, 11, 14–19, 21]
Renal stones	1 (3)	[17]
Rickets	12 (40)	[9–11, 13–15, 17, 18, 21–23]
Hypermagnesemia	9 (30)	[5, 9, 12]
Other characteristics	Carnitine deficiency, hypermagnesuria, hypophosphatemia, elevated alkaline phosphatase, low vitamin D, oxaluria	[5, 9, 11–15, 18, 19, 23]

The initial column enumerates the primary renal phenotypic characteristics; those that are exhibited in our case are highlighted with a green background, while those not registered have a white background. In the second column, the published cases reporting each phenotypic characteristic are presented. It should be noted that not all the published literature reports the presence or absence of every phenotypic characteristic described in the table. Consequently, the total counts may not be comprehensive of the real incidence of each characteristic. The third column displays the references which report each phenotypic characteristic in a given row.

latter promoter is increased in pancreatic β cells, where *HNF4A* regulates key genes involved in glucose-stimulated insulin secretion [13].

The renal phenotype associated with *HNF4A* variants was not recognised until the identification of this specific mutation [p.Arg63Trp or p.R63W] in the DNA-binding domain of *HNF4A*, resulting in a change in electronegativity and hydrophobicity. In the kidney, *HNF4A* is exclusively expressed in proximal tubules, which is consistent with the atypical FRTS phenotype of the variant, called FRTS4. Nevertheless, why this specific mutation in *HNF4A* is the only mutation causing this phenotype remains unclear. Recent studies have described its interference with mitochondrial function, the reduction in transcriptional output in a dominant-negative manner and the formation of cytotoxic aggregates in the cytosol through in vitro models. These data contrast with the effects of other known mutations involving the DNA-binding domain of *HNF4A*, which do not cause the renal phenotype [30]. Studies in *HNF4A* knockout mouse models have shown that its deletion causes kidney tubular dysgenesis and nephrocalcinosis [22].

The cases associated with the *HNF4A* p.Arg63Trp variant present diverse clinical manifestations as summarised in Figure 1. The predominant phenotypes that have been described include large for gestational age and hyperinsulinaemic hypoglycaemia, which manifest during the neonatal period; and rickets, FRTS, and nephrocalcinosis, which emerge during infancy. Besides, some patients present with liver dysfunction and maturity-onset diabetes of the young (MODY), which can be the latest manifestation. Sporadically,

developmental delays secondary to brain damage, hearing loss, and cardiac abnormalities have been reported. On top of that, mitochondrial dysfunction has been highlighted in recent case reports. In our case, the laboratory analysis showed alterations that pointed to it, while in other cases it was confirmed either by electronic microscopy in a kidney biopsy or by respirometric analysis and enzymatic activity assays [5, 6, 9–24].

Fanconi tubulopathy in association with HH is a rare disease that requires a complex multidisciplinary diagnostic approach, given that its clinical presentation can be unspecific and a delay in diagnosis could lead to disabling and/or potentially life-threatening complications due to renal dysfunction and neuroglycopenia. In this case, the definitive genetic diagnosis was carried out after establishing crucial correlations between the preliminary clinical indications and the laboratory findings. The initial presentation was myoclonic jerks. Although this was a direct consequence of HH, this is not a phenotypic characteristic described on the previous case reports. Linking the myoclonic jerks with the glycaemic state led to the evaluation of the response to fasting. Inadequate insulin suppression with hypoketotic hypoglycaemia oriented the endocrine component of the pathology to hyperinsulinaemia. The re-evaluation of the genu varum, initially misclassified as benign, was another key point. Its association with rickets due to calcium loss and vitamin D deficiency suggested the renal dysfunction and tubulopathy. At this point, after dismissing the plausible cause of pharmacological valproate treatment, the increased excretion of multiple analytes in the urine indicated alterations in the proximal tubular region. Upon further examination, the majority of renal proximal tubulopathy types could be excluded, and the detailed characterisation of the renal phenotype allowed to direct the case towards atypical FRTS type 4 (Table 3). This specific renal phenotype determination and its connection to HH is of outmost value here, since the variant could never be detected if a panel of genes for the most common renal tubulopathies is performed as genetic testing. Finally, after several years of follow-up, the patient did not exhibit signs of developmental delay, liver dysfunction, or MODY.

The identification of a pathogenic variant of *HNF4A* in this clinical case represents a significant undertaking in view of the potential implications for clinical practice and research. In rare disease cases, it is crucial to adopt a clinical approach based on the information provided by previous similar cases that are reported in the literature by other professionals. Once a diagnostic suspicion is raised, identifying the underlying genetic variant is vital for the final diagnosis and subsequent monitoring of the patient. Lastly, it is essential to conduct genetic counselling and segregation studies within the family.

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Statement of Ethics

Ethical approval is not required for case reports in accordance with local or national guidelines. Written informed consent was obtained from the parents of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.G.-E. and L.P.-S.: contributed writing the original draft and the final manuscript; H.R.D.: interpreted the patient data regarding the renal disease, contributed writing the original draft and reviewing and editing the manuscript; M.G., N.D.-T., and R.F.: interpreted the patient data regarding laboratory analysis and contributed reviewing and editing the manuscript; M.A.M.: interpreted the patient data regarding genetic analysis and contributed reviewing and editing the manuscript; B.P.D.: interpreted the patient data regarding neurological pathology and contributed reviewing and editing the manuscript; M.C.: interpreted the patient data regarding the endocrine disease, contributed writing the original draft and reviewing and editing the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding authors.

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