Case Reports

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(4) 1–11

DOI: 10.1177/03000605211010644
journals.sagepub.com/home/imr
SAGE

A novel compound heterozygous variant in *SMARCAL1* leading to mild Schimke immune-osseous dysplasia identified using whole-exome sequencing

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Abstract

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive inherited disorder that is caused by the *SMARCAL1* mutation. The phenotype can vary from mild to severe on the basis of the patient's age at onset. Herein, we report the case of a 14-year-old Chinese boy who presented with short stature, focal segmental glomerulosclerosis (FSGS), and facial dysmorphism. Genetic analysis revealed two compound heterozygous missense mutations, including a well-known mutation (c.1933C>T, p.R645C) and a novel mutation (c.2479G>A, p.V827M) in the *SMARCAL1* gene, which were inherited from his parents. *In silico* analyses showed that the c.2479G>A (p.V827M) variant affects a highly conserved residue within the ATPase catalytic domain. Finally, we established the diagnosis of mild SIOD and treated the patient with diuretics and angiotensin receptor blockers. This report expands the mutational spectrum of *SMARCAL1* and reinforces the importance of a detailed clinical evaluation, molecular detection, and appropriate genetic counseling.

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Keywords
Short stature, focal segmental glomerulosclerosis, Schimke immuno-osseous dysplasia, SMARCAL1, whole exome sequencing, novel mutation

Date received: 28 December 2020; accepted: 24 March 2021

Introduction

Schimke immuno-osseous dysplasia (SIOD, OMIM: 242900) is a rare autosomal recessive inherited disorder that was first reported by Schimke in 1971, and its main clinical findings are spondyloepiphyseal dysplasia, focal segmental glomerulosclerosis (FSGS), T-cell immunodeficiency, and facial dysmorphism.[1–3] Clinically, the severity of SIOD is determined primarily by the patient's age at onset, ultimate lifespan, and accompanying symptoms.[4] SIOD is divided into the following two forms: 1) severe or infantile; and 2) mild or juvenile on the basis of the age at onset. The severe or infantile form usually manifests early or even *in utero* with growth retardation and death early in life, whereas the mild or juvenile form usually displays growth failure and survival to adulthood if renal disease is appropriately treated.[3,5] Mortality with SIOD can be significant, particularly if the condition is not recognized. Fortunately, identification of biallelic pathogenic mutations in *SMARCAL1* on molecular genetic testing confirms the diagnosis if clinical features are inconclusive.

Boerkoel et al.[5] first determined that *SMARCAL1* (OMIM: 606622; hg19/GRCh37, NM_014140.4) gene mutations were responsible for SIOD. The *SMARCAL1* gene, which was mapped to 2q35, is composed of 18 exons, and the first two exons are non-coding. It also encodes the SMARCAL1 protein, which is also known as HepA-related protein (HARP) and has 954 amino acids; this protein plays an important role in transcriptional regulation, replication, repair, recombination, and covalent modification.[6] A deficiency in the SMARCAL1 protein could lead to impairment of cellular functions due to progressive DNA damage.[7] In this study, we present the case of a 14-year-old Chinese boy with short stature, FSGS, and some characteristic dysmorphic features. He was diagnosed with mild SIOD on the basis of clinical features and genetic analysis. We also present a review of other cases of mild SIOD in the literature.

Case presentation

A 14-year-old Chinese boy, who was the second child of nonconsanguineous parents, was admitted to our hospital because of foamy urine and lower extremity edema for 1 year. His parents and older brother were healthy, and no family history of short stature or renal disease was reported. He was born at 38^{+3} weeks gestation (birth weight, 2.6 kg) by cesarean section because of oligohydramnios and decreased fetal movement. Protracted diarrhea occurred frequently before 3 years of age, and his weight was 8.3 kg, which is in the <3rd percentile for that age.

On physical examination, he had developmental delay (37.0 kg, weight at 3rd percentile), short stature (137 cm, height <3rd percentile), and he had some characteristic facial features including a triangular shape and a broad nasal bridge with a rounded tip of the nose. He had swollen eyelids, short

neck, barrel-shaped chest, protruding abdomen, and two areas of jock itch, one on each of his inner thighs. His teeth appeared small and widely spaced (Figure 1). When walking, his legs made an X shape. Lymphopenia (1.04×10^9/L, 16.7%, Ref: $1.1–3.2 \times 10^9$/L, 20%–50%) was observed at different times, and it was further confirmed by flow cytometry analysis, which revealed significantly decreased levels of $CD4^+$ T-cells (208/μL, 14.57%, Ref: 550–1440/μL, 27%–51%) and $CD4^+/CD8^+$ T-cells (0.55/μL, Ref: 0.71–2.78/μL). Massive proteinuria (9.31 g) was detected using 24-hour proteinuria quantification, and proteinuria did not improve after treatment. Blood biochemistry evaluation revealed hypoproteinemia due to low total protein (47.3 g/L, Ref: 60–85 g/L) and albumin (24.9 g/L, Ref: 35–55 g/L), as well as dyslipidemia with high total cholesterol (TC; 7.87 mmol/L, Ref: <5.2 mmol/L) and low-density lipoprotein (LDL; 4.27 mmol/L, Ref: <3.61 mmol/L). However, urea nitrogen, creatinine, and glucose levels were all within their respective reference ranges. Endocrine hormone results revealed subclinical hypothyroidism (thyroid stimulating hormone [TSH] 8.75 μIU/mL, Ref: 0.27–4.2 μIU/mL), hypocalcemia (serum calcium 1.91 mmol/L, Ref: 2.0–2.7 mmol/L), and secondary hyperparathyroidism (parathyroid hormone [PTH] 178.1 μIU/mL, Ref: 15–68.3 μIU/mL) because 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] was insufficient (11 ng/μL, Ref: 30–100 ng/μL), whereas cortisol, adrenocorticotropic hormone (ACTH), and sex hormones (including follicle stimulating hormone [FSH], luteinizing hormone [LH], estradiol, prolactin, and progesterone) were all normal. Growth hormone provocation test results indicated that the peak secretion of growth hormone was up to 40,308 pg/mL at 30 minutes after medication (Table 1), with a normal insulin-like growth factor [IGF-1] level (298 ng/mL; Ref: 220–972 ng/mL). High levels were detected for C-reactive protein (CRP; 15.2 mg/L, Ref: 0–10 mg/L), procalcitonin (PCT; 0.061 ng/mL, Ref: 0–0.046 ng/mL), and erythrocyte sedimentation rate (ESR; 39 mm/hour, Ref: 0–15 mm/hour). No hepatitis infection was detected, and the markers of autoimmunity (antinuclear antibodies [ANA], antineutrophil cytoplasmic antibody [ANCA], anti-double-stranded DNA antibody [dsDNA]) were negative. Radiological examination of

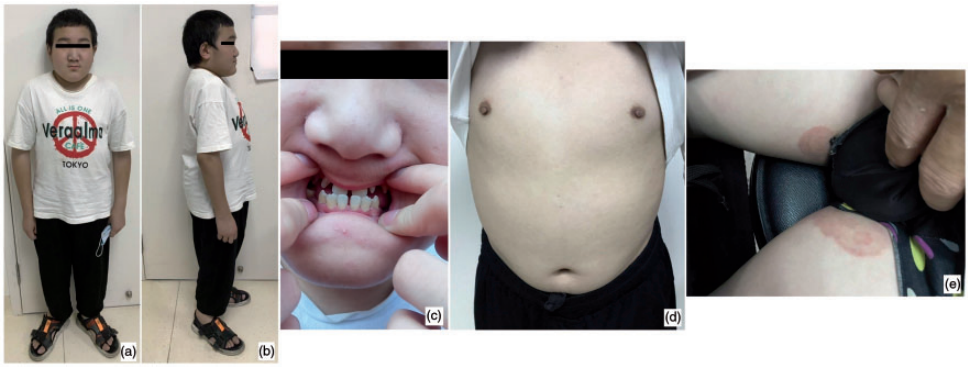

Figure 1. Clinical details of the patient at 14 years of age. (a–b) Photographs showing short stature, round face, and broad nasal bridge with a rounded tip of the nose. (c) Physical appearance of the patient's teeth noting microdontia and delayed eruption of permanent teeth. (d) Photographs showing a protruding abdomen. (e) Photographs showing two areas of jock itch, one on each of his inner thighs.

Table 1. The patient's growth hormone provocative test results.

	Growth hormone (pg/mL)
When medication was administered	685.9
15 minutes after medication	29297
30 minutes after medication	40308
1 hour after medication	29881
1.5 hours after medication	26718
2 hours after medication	13115

his hand demonstrated that the patient's bone age was 14.3 years, which was consistent with his calendar age. Osteoporosis was observed in both feet and ankles using an X-ray bone densitometer, but the features of his vertebrae, pelvis, and femoral heads were not available.

With his parents' consent, a renal biopsy was performed, and the results showed FSGS and mild mesangial proliferative glomerulonephritis. Whole exome sequencing (WES) revealed two compound heterozygous missense mutations in the *SMARCAL1* gene using the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA). Sanger sequencing confirmed that the two missense variants, c.1933C>T (p.R645C) and c.2479G>A (p.V827M), in the *SMARCAL1* gene were inherited from his parents (Figure 2). Results of bioinformatic analysis showed all of the five online prediction tools, including Mutation Taster (http://mutationtaster.org/),[9] Polymorphism Phenotyping v2 (Polyphen_2, http://genetics.bwh.harvard.edu/pph2),[10] Rare Exome Variant Ensemble Learner (REVEL, https://sites.google.com/site/revelgenomics/),[11] Sorting Intolerant from Tolerant (SIFT, https://sift.bii.a-star.edu.sg/),[12] and Protein Variation Effect Analyzer (PROVEAN) (http://provean.jcvi.org/index.php),[13] predicted the two missense mutations as disease-causing/damaging mutations. The prediction results were also supported by the extremely low allele frequencies of the two mutations (Table 2). Additionally, comparative amino acid sequence alignment of other SMARCAL1 proteins across different species revealed that the c.2479G>A (p.V827M) mutation occurred in highly conserved regions within the ATPase catlytic domain using homologene (http://www.ncbi.nlm.nih.gov/homologene) with UGene software (Figure 3).[14,15] In accordance with the ACMG guidelines for interpretation of genetic variants,[16] the c.1933C>T (p.R645C) and c.2479G>A (p.V827M) variants were classified as a "likely pathogenic variant" (PM2+PP4+PM3+PM5+PP3) and a "likely pathogenic variant" (PM2+PP4+PM3+PP3), respectively. Therefore, on the basis of the clinical and genetic features, the patient was diagnosed with mild SIOD. After receiving consent from his parents, the patient was treated with irbesartan, alfacalcidol capsule, levothyroxin sodium tablets, calcium carbonate, vitamin D_3 tablets, and thymopdypeptide enteric-coated tablets to reduce proteinuria, protect kidney function, prevent infection, maintain thyroid function, and regulate immune function. After treatment, his edema and infection improved. We followed-up with the patient until December 2020, and he had normal renal function.

Discussion

In the present study, we report the case of a male teenager who exhibited some clinical characteristics and was diagnosed with mild SIOD; these clinical characteristics included short stature, FSGS, and characteristic dysmorphic features. Moreover, there were two areas of jock itch, one on each of his inner thighs, which might have been caused by a fungal infection, and it was confirmed by

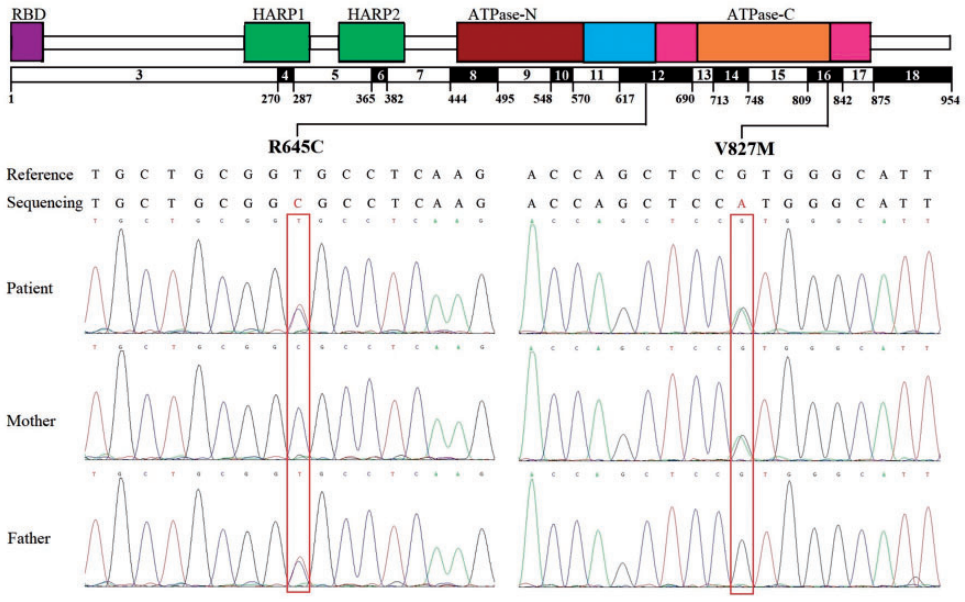

Figure 2. Schematic representation of the structure of the SMARCAL1 protein and Sanger sequencing results of the identified *SMARCAL1* (NM_014140.4) mutations. HepA-related protein domains are shaded green; replication protein A-binding domain (RBD) are purple; RecA-domains are brown and orange; and SNF2-specific inserted helical domains (HD) are light blue and pink. The figure is adapted from Barraza-García et al. (2016). The sequencing results showing the c.1933C>T transversion in exon 12 and exon 16 of SMARCAL1 resulting in the pathogenic substitution of an arginine for a cysteine residue at position 645 of the protein (p.R645C) and a valine for a methionine residue at position 827 of the protein (p.V827M). Affected residues are indicated with the red box.

the laboratory test results. This infection might have been associated with low immunity. The effect of $1,25(OH)_2D_3$ on secondary hyperparathyroidism with chronic renal failure was reported previously, and it showed that $1,25(OH)_2D_3$ could markedly suppress PTH levels while increasing serum calcium.[17,18] For our patient, hyperparathyroidism was considered to be the result of a $1,25(OH)_2D_3$ deficiency. Mild clinical features were compatible with the juvenile form of SIOD at 14 years of age.

As an ATP-dependent annealing helicase, the SMARCAL1 protein, contains two DNA/RNA HARP2 helicases at the C-terminal and has a SNF2 N terminal domain, and the SMARCAL1 protein can catalyze the rewinding of stably unwound DNA (Figure 2).[19,20] The professional HGMD database contains 100 mutations of the *SMARCAL1* gene, with 66 missense/nonsense mutations, 9 splicing substitutions, 14 small deletions, 8 small insertions/duplications, 1 small indel, and 2 gross deletions. Usually, the *SMARCAL1* missense mutations are typically associated with later onset disease, whereas nonsense, frameshift, and splicing mutations are more frequently detected in severe SIOD. In our patient, a mild phenotypic expression of SIOD was found to be associated with a new genotype consisting of compound heterozygosity for a well-known missense variant (c.1933C>T, p.R645C) and a novel missense variant (c.2479G>A, p.V827M). The missense

Table 2. The *SMARCAL1* variant pathogenicity was supported by multiple *in silico* analyses

Variant	Amino acid change	Mutation Taster[a]	Polyphen-2[b]	REVEL[c]	SIFT[d]	PROVEAN[e]	ExAC (total)[f]	1000 Genome (total)[g]	gnomAD_exome (total)[h]	gnomAD_genome (total)[i]
c.1933C>T	p.R645C	Disease-causing (1)	Probably damaging (1.000)	Damaging (0.974)	Damaging (0)	Damaging (−7.28)	–	–	1.219e-05	3.23e-05
c.2479G>A	p.V827M	Disease-causing (1)	Probably damaging (0.997)	Damaging (0.844)	Damaging (0)	Damaging (−2.81)	4.456e-05	0.000199681	1.38e-05	3.229e-05

a: For Mutation Taster, the probability value is the probability of the prediction (i.e., a value close to 1 indicates a high likelihood of prediction).
b: For Polyphen-2, the prediction scores ranged from 0 to 1, with high scores indicating probably or possibly damaging.
c: For REVEL, prediction scores ranged from 0 to 1, with high scores indicating probably or possibly damaging.
d: For SIFT, scores varied between 0 and 1. Variants with scores close or equal to 0 are predicted to be damaging.
e: For PROVEAN, variants with scores lower than −2.5 (cutoff) are predicted to be deleterious.
f: Allele frequency of variation in the total ExAC database.
g: Allele frequency of variation in the 1000 Genomes database.
h: Allele frequency of variation in the total gnomAD (a large database containing 123,136 exome sequences).
I: Allele frequency of variation in the total gnomAD (a large database containing 15,496 whole-genome sequences).
Polyphen-2, polymorphism phenotyping v2; REVEL, Rare Exome Variant Ensemble Learner; SIFT, Sorting Intolerant from Tolerant; PROVEAN, Protein Variation Effect Analyzer; ExAC, Exome Aggregation Consortium; gnomAD, Genome Aggregation database.

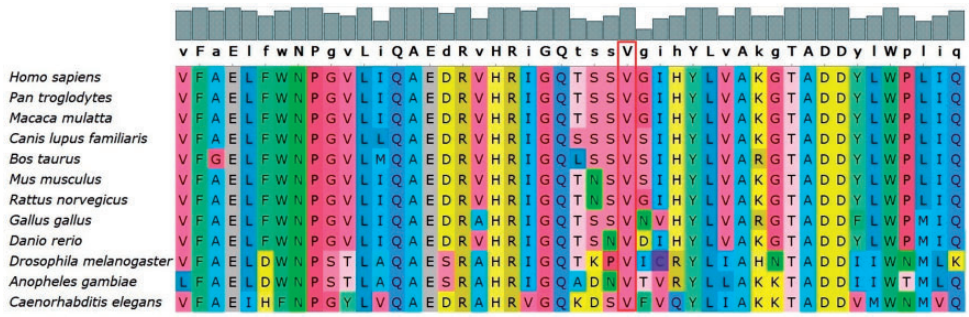

Figure 3. The conservative analysis of the amino acid at the mutant site in SMARCAL1 protein (NM_014140.4). The 827th amino acid valine in SMARCAL1 (indicating by the red box), which was changed to a methionine in the patient, is highly conserved in all the following species that were available on the National Centre for Biotechnology Information: *Homo sapiens*, *Pan troglodytes*, *Macaca mulatta*, *Canis lupus*, *Bos taurus*, *Mus musculus*, *Rattus norvegicus*, *Gallus*, *Danio rerio*, *Drosophila melanogaster*, *Anopheles gambiae*, and *Caenorhabditis elegans*.

variant (c.1933C>T, p.R645C) has been previously reported to be pathogenic, and it was detected in a patient who was clinically diagnosed with mild SIOD and survived into adulthood with medical therapy and renal transplantation.[21] This suggests that the missense variant c.1933C>T (p.R645C) is common in mild SIOD, which was previously reported in other SIOD patients with different ethnic origins.[5] This missense mutation c.2479G>A (p.V827M) occurred at a highly conserved site of the multi-sequence alignment within the ATPase catalytic domain (Figure 3). This indicates that there may be some residual function of the SMARCAL1 protein with the compound heterozygous missense mutations c.1933C>T (p.R645C) and c.2479G>A (p.V827M).

For a better understanding the phenotype and genotype, we summarized the reported cases of mild SIOD that were reported in the literature (Table 3).[4–6,20,22–26] Sixteen cases (including four pairs of siblings) with mild SIOD have been summarized. The male-to-female ratio was 7:9, and 81.25% (13/16) of the patients were over 10 years of age. Most mild SIOD cases occurred in people of German descent (4/16), Italian descent (3/16), and Turkish descent (3/16), and only one case was reported in a Chinese population. Skeletal abnormality (16/16) was the most frequent feature, and short stature was the most common reason for admission to the hospital. Nephrotic syndrome (13/16) and facial features (9/16) were also common features. Nine patients underwent renal biopsies, and FSGS was observed in seven patients. Thirteen patients underwent genetic analysis, and all (including four pairs of siblings) had five homozygous mutations (including two pairs of siblings) or eight compound heterozygous mutations in the *SMARCAL1* gene. Among these mutations, a nonsense mutation of E848X was identified in five out of 13 patients with a heterozygous mutation, indicating that it should be prevalent in the patients with mild SIOD. Both homozygous missense mutations of R586W and R561C were detected in two pairs of siblings who were born to consanguineous parents. The homozygous R561C mutation was detected in a young boy aged 18 months who presented with significantly diminished $CD4^+$ T cells, which is a typical immune defect, and this required long-term follow-up. Another homozygous K647T mutation was detected in a young Algerian

Table 3. Phenotype and genotype in mild SIOD patients.

Reference	Fam–Ind	Ethnicity	Sex	Age[#] (y)	Sk	Fac	Pig	NS	Rec	Lym	TSH	Dys	CNS	Ren	Treatment	Exon	Gene mutation
Hashimoto et al. (1994)[22]	1–1	Japanese	F	16	+	+	+	+	−	+	ND	+	−	FSGS	Peritoneal dialysis	−	ND
Boerkoel et al. (2002)[5]	16–1	Scottish/ French	M	25.9	+	+	+	+	−	+	ND	ND	−	ND	Kidney transplant	9/12	p.I548N/p.R645C
	18–1*	Italian	M	36.3	+	−	−	+	−	+	ND	ND	−	ND	Kidney transplant	11/11	p.R586W/p.R586W
	18–2*	Italian	F	23.9	+	−	−	+	−	+	ND	ND	−	ND	Kidney transplant	11/11	p.R586W/p.R586W
	27–1	Algerian	F	19.8	+	+	+	+	−	+	ND	ND	−	ND	Kidney transplant	12/12	p.K647T/p.K647T
Lücke et al. (2005)[4]	1–1*	German	M	22	+	−	+	+	−	−	−	ND	−	GS	Kidney transplant	4/17	p.F279S/p.E848X
	1–2*	German	M	19.9	+	+	+	+	+	+, mild	−	ND	+	FSGS	Kidney transplant	4/17	p.F279S/p.E848X
Bökenkamp et al. (2005)[23]	1–1*	Turkish	M	10	+	+	−	+	−	+	−	ND	−	FSGS	Enalapril and losartan	10/10	p.R561C/p.R561C
	1–2*	Turkish	M	1.5	−	−	−	−	−	diminished CD4+ cells	ND	ND	ND	ND	−	10/10	p.R561C/p.R561C
Zivicnjak et al. (2009)[24]	1–1*	German	F	19	+	−	−	+	+ (after kidney transplant)	ND	ND	ND	−	MGA	Kidney transplant	12/17	p.R645H/p.E848X
	1–2*	German	F	14	+	−	−	+	+ (after kidney transplant)	+	ND	ND	−	ND	Kidney transplant	12/17	p.R645H/p.E848X
Santangelo et al. (2014)[6]	1–1	Italian	F	7	+	−	−	+	−	+	+	ND	−	FSGS	Ramipril and irbesartan	3/17	p.R247P/p.E848X
Yavuz et al. (2015)[25]	1–1	Brazilian	F	9	+	+	+	+	+	+	+	ND	+	FSGS	Kidney transplant	−	ND
Pedrosa et al. (2016)[26]	1–1	Turkish	F	10	+	+	+	+	−	+	ND	ND	+	FSGS	Enalapril and losartan	−	ND
Liu et al. (2017)[20]	1–1	Chinese	F	10.8	+	+	+	−	−	+	ND	+	−	ND	ND	3/12	p.Q149X/p.R645C

(continued)

Table 3. Continued.

Reference	Fam–Ind	Ethnicity	Sex	Age[#] (y)	Sk	Fac	Pig	NS	Rec	Lym	TSH	Dys	CNS	Ren	Treatment	Exon	Gene mutation
Current report	1–1	Chinese	M	14	+	+	–	+	Protracted diarrhea until 3 years old	+	+	+	–	FSGS	Irbesartan	12/16	p.R645C/p.V827M

*1 and 2 are siblings.

[#]Age at publication or reported in the paper.

Fam, family; Ind, individual; y, years; Sk, skeleton; Fac, facial features; Pig, pigmentation; NS, nephrotic syndrome; Rec, recurrent infection; Lym, lymphopenia; Dys, dyslipidemia; Ren, renal biopsy; F, female; M, male; TSH, thyroid-stimulating hormone; CNS, central nervous system; ND, no data or not done; GS, global glomerulosclerosis; FSGS, focal segmental glomerulosclerosis; MGA, minor glomerular abnormalities.

woman who was 20 years old. Nine patients underwent kidney transplantation and remained stable because their urea nitrogen and creatinine levels were normal, but the long-term efficacy remains to be further evaluated.

Conclusion

We identified a novel missense mutation, c.2479G>A (p.V827M), in the *SMARCAL1* gene from a male teenager who was diagnosed with mild SIOD. This report highlights the significance of complete clinical data and molecular detection. Our findings provide some targeted guidance for the treatment and prognosis in patients with mild SIOD, and they also contribute to the information that is available in gene mutation databases.

Acknowledgements

The authors thank the patient and his family members for participation in this study and all of the patient advisers for their assistance with clinical examination and blood specimen collection.

Authors' contributions

WL designed the study, performed genetic testing, and drafted the initial manuscript. LJJ collected the patient data and current literature. WG made the diagnosis and completed the diagnostic work-up. KXD designed the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

Informed consent was obtained from the patient and his family before participating in our study. The study was approved by the Research Ethics Committee of Zhengzhou University (approval number KS-2018-KY-36), and it complies with

the CARE case report guidelines.[8] All identifying details of the patient's information have been deleted from the case report, and the identity of the patient cannot be ascertained in any way. The patient and his parents provided written consent for the treatment and publication of this paper.

Funding

This work was supported by the National Key Research and Development Project of China [grant number 2018YFC1002203].

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References

1. Schimke RN, Horton WA and King CR. Chondroitin-6-sulphaturia, defective cellular immunity, and nephrotic syndrome. *Lancet* 1971; 2: 1088–1089.
2. Spranger J, Hinkel GK, Stoss H, et al. Schimke immuno-osseous dysplasia: a newly recognized multisystem disease. *J Pediatr* 1991; 119: 64–72.
3. Boerkoel CF, O'Neill S, Andre JL, et al. Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. *Eur J Pediatr* 2000; 159: 1–7.
4. Lucke T, Billing H, Sloan EA, et al. Schimke-immuno-osseous dysplasia: new mutation with weak genotype-phenotype correlation in siblings. *Am J Med Genet A* 2005; 135: 202–205.
5. Boerkoel CF, Takashima H, John J, et al. Mutant chromatin remodeling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. *Nat Genet* 2002; 30: 215–220.
6. Santangelo L, Gigante M, Netti GS, et al. A novel SMARCAL1 mutation associated with a mild phenotype of Schimke immuno-osseous dysplasia (SIOD). *BMC Nephrol* 2014; 15: 41.
7. Lipska-Zietkiewicz BS, Gellermann J, Boyer O, et al. Low renal but high extrarenal phenotype variability in Schimke immuno-osseous dysplasia. *PLoS One* 2017; 12: e0180926.
8. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *BMJ Case Rep* 2013; 2013: bcr2013201554.
9. Schwarz JM, Cooper DN, Schuelke M, et al. MutationTaster2: mutation prediction for the deep-sequencing age. *Nat Methods* 2014; 11: 361–362.
10. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods* 2010; 7: 248–249.
11. Ioannidis NM, Rothstein JH, Pejaver V, et al. REVEL: an ensemble method for predicting the pathogenicity of rare missense variants. *Am J Hum Genet* 2016; 99: 877–885.
12. Sim NL, Kumar P, Hu J, et al. SIFT web server: predicting effects of amino acid substitutions on proteins. *Nucleic Acids Res* 2012; 40: W452–W457.
13. Choi Y, Sims GE, Murphy S, et al. Predicting the functional effect of amino acid substitutions and indels. *PLoS One* 2012; 7: e46688.
14. Protsyuk IV, Grekhov GA, Tiunov AV, et al. Shared bioinformatics databases within the Unipro UGENE platform. *J Integr Bioinform* 2015; 12: 257.
15. Rose R, Golosova O, Sukhomlinov D, et al. Flexible design of multiple metagenomics classification pipelines with UGENE. *Bioinformatics* 2019; 35: 1963–1965.
16. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17: 405–424.
17. Slatopolsky E, Weerts C, Thielan J, et al. Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxy-cholecalciferol in uremic patients. *J Clin Invest* 1984; 74: 2136–2143.
18. Hirata M, Endo K, Katsumata K, et al. A comparison between 1,25-dihydroxy-22-

oxavitamin D(3) and 1,25-dihydroxyvitamin D(3) regarding suppression of parathyroid hormone secretion and calcaemic action. *Nephrol Dial Transplant* 2002; 17: 41–45.
19. Barraza-Garcia J, Rivera-Pedroza CI, Belinchon A, et al. A novel SMARCAL1 missense mutation that affects splicing in a severely affected Schimke immunoosseous dysplasia patient. *Eur J Med Genet* 2016; 59: 363–366.
20. Liu S, Zhang M, Ni M, et al. A novel compound heterozygous mutation of the SMARCAL1 gene leading to mild Schimke immune-osseous dysplasia: a case report. *BMC Pediatr* 2017; 17: 217.
21. Mobeireek A, Saleemi S, Khalid M, et al. Tracheobronchial anomalies in a patient with Schimke immuno-osseous dysplasia (SIOD). *Am J Med Genet A* 2015; 167A: 434–437.
22. Hashimoto K, Takeuchi A, Ieshima A, et al. Juvenile variant of Schimke immunoosseous dysplasia. *Am J Med Genet* 1994; 49: 266–269.
23. Bokenkamp A, DeJong M, Van Wijk JA, et al. R561C missense mutation in the SMARCAL1 gene associated with mild Schimke immuno-osseous dysplasia. *Pediatr Nephrol* 2005; 20: 1724–1728.
24. Zivicnjak M, Franke D, Zenker M, et al. SMARCAL1 mutations: a cause of prepubertal idiopathic steroid-resistant nephrotic syndrome. *Pediatr Res* 2009; 65: 564–568.
25. Yavuz S, Bayazit AK, Anarat A, et al. Medullary nephrocalcinosis in Schimke immuno-osseous dysplasia. *Pediatr Int* 2015; 57: 310–313.
26. Pedrosa AK, Torres LF, Silva AC, et al. Rare case of nephrotic syndrome: Schimke syndrome. *J Bras Nefrol* 2016; 38: 370–373.