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Identification of Compound Heterozygous Variants in OBSCN Gene Associated With Rhabdomyolysis: A Case Report

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ABSTRACT

Background: The obscurin protein encoded by the *OBSCN* gene is an important structural protein in the regulation of myocyte sarcoplasmic nodule stability and sarcoplasmic reticulum function and is particularly closely associated with calcium ion (Ca^{2+}) signaling. With increasing genomic studies, pathogenic variants in the *OBSCN* gene have been shown to be associated with a variety of inherited diseases, such as cardiomyopathy. However, case reports of its variants causing rhabdomyolysis are more limited.

Methods: We performed whole exome sequencing on a patient with exercise-induced rhabdomyolysis to identify possible causative gene variants. In addition, functional prediction of the pathogenicity of the variants was performed by combining multiple bioinformatics analysis tools and in-depth analyses with clinical phenotypes and family history.

Results: The patient carried compound heterozygous variants, including c.21184C>T (nonsense variant) and c.15610+12C>T (intronic splicing variant). The c.21184C>T variant resulted in a premature termination of the protein, was not included in population-based databases, and was supported by multiple prediction tools as a potentially pathogenic variant. The c.15610+12C>T variant was also absent in the gnomAD_EAS database and predicted to disturb normal splicing, potentially creating a novel donor site. The pathogenicity of the variant is further supported by the fact that the patient's mother, with a homozygous *OBSCN* variant, also exhibited exercise-induced myalgia. Clinically, the patient presented with exercise-induced rhabdomyolysis accompanied by significant serum creatine kinase elevation, muscle pain, and MRI-demonstrated muscle edema of both lower limbs without significant muscle weakness or cardiac abnormalities.

Conclusion: We report the first case of rhabdomyolysis in China caused by *OBSCN* gene variants. This finding further extends the spectrum of the *OBSCN* gene variants. It also provides an important basis for genetic counseling and helps in the early diagnosis and management of similar cases.

1 | Introduction

OBSCN, located on chromosome 1q42, is a protein-coding gene that contains over 80 exons and encodes nearly 8000 amino acids (obscurins). Obscurin is a component of the sarcomere that binds near the M-line or the Z-disc. Previous studies showed that it could interact with titin, myosin, and small ankyrin1. It is thought to be a structural protein that links the M-line of the sarcomere to the sarcoplasmic reticulum (Fukuzawa et al. 2008; Kontrogianni-Konstantopoulos et al. 2009; Gautel 2011;

Fukuzawa et al. 2005). It is also considered to participate in the SR function and Ca^{2+} regulation (Lange et al. 2009; Blondelle et al. 2019).

The variant of the *OBSCN* gene has been reported in skeletal myopathy and cardiomyopathy, such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and left ventricular myocardial nondensification (LVNC) (Hu et al. 2017; Wu et al. 2021; Marston et al. 2015; Rossi et al. 2017). Recently, reports highlight the relevance of these variants in skeletal muscle disorders, particularly rhabdomyolysis. Bi-allelic loss-of-function OBSCN variants have been linked to rhabdomyolysis, with affected individuals presenting with myalgia, muscle spasms, and elevated creatine kinase (CK) levels following exercise or fever (Cabrera-Serrano et al. 2021; Zemorshidi et al. 2024). Macarena et al. present six patients who presented with severe and recurrent rhabdomyolysis. They found reduced expression of OBSCN and loss of obscurin protein in patient muscle, and impaired sarcoplasmic reticulum Ca^{2+} handling (Cabrera-Serrano et al. 2021). Fariba et al. reported two patients with *OBSCN* variants who also showed rhabdomyolysis without cardiomyopathy. The functional analysis showed that obscurin-deficient muscle fibers are more susceptible to damage induced by exercise, leading to rhabdomyolysis (Zemorshidi et al. 2024). These findings suggest a role for OBSCN in muscle function and highlight the need for further studies to better understand OBSCN-related disease.

Currently, few cases of rhabdomyolysis associated with OBSCN variants have been reported.

Here, we reported another rhabdomyolysis patient who presented with bilateral lower extremity pain and increased CK. The whole exome sequencing identified the complex heterogeneous variants in OBSCN (NM_001386125.1: c.21184C>T, p.Gln7062*; c.15610+12C>T). Our study further expands the spectrum of *OBSCN* gene variants. It is recommended that patients with unknown causes of rhabdomyolysis should undergo genetic testing.

2 | Methods

2.1 | Patient

We collected the clinical information, including the results of ultrasound, electrocardiogram, magnetic Resonance Imaging (Cabrera-Serrano et al. 2021), and CK level. This study was approved by the Human Ethics Committees of Jiangxi Provincial Children's Hospital.

2.2 | WES

The WES was performed to identify the genetic cause of rhabdomyolysis in our patients. The samples from the patient and her parents were sequenced on a NovaSeq 6000 (Illumina, USA) platform after being captured with the IDT xGen Exome Research Panel. The average coverage depth for the WES for our patient was 165.55×, and the percentage of bases covered at ≥ 20× is 99.49%. Raw data from the sequencer were converted from .bcl files to .fastq files using bcl2fastq, and reads were aligned to the human reference genome GRCh38/hg38 using BWA software, and the resulting .bam files were locally retargeted using GATK software. The resulting .bam files were locally recontrasted using GATK software, duplicate sequences were removed, and variants were detected. Variants were annotated using Annovar for variant call format (VCF) variant files.

Variants not carried by normal people or carried at a rate of little more than 5% were screened in databases such as Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org), 1000 Genomes Project (1000G, http://browser.1000genomes.org), Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org), and other databases that are not carried by normal people or have a minor allele frequency ≤ 5%, and exclude known polymorphic sites. Referring to dbSNP (http://www.ncbi.nlm.nih.gov/snp), OMIM (http://www.omim.org), HGMD (http://www.hgmd.cf.ac.uk), and ClinVar (https://www.ncbi.nlm.nih). Predictions of protein function caused by genetic variants are performed using various protein function prediction software such as SIFT, Polyphen2, MutationTaster, and dbscSNV software. Pathogenicity analyses were performed according to the variant interpretation guidelines issued by the American College of Medical Genetics and Genomics (ACMG). The candidate pathogenic variants detected with the WES that are associated with the patient's clinical phenotype are verified with Sanger sequencing technology.

3 | Results

3.1 | Case Report

The patient is an 11-year-and-6-month-old girl who presented with progressively worsening pain in both lower limbs after swimming for one hour daily over the past week. The pain was accompanied by tenderness in both thighs, and at its peak, the patient was unable to walk and was woken by the pain at night. She has a history of recurrent limb pain following intense physical activity, such as hiking and running, during which elevated serum CK levels were noted without other abnormalities. Family history revealed that her father is healthy, while her mother has experienced similar episodes of recurrent limb pain triggered by intense physical activity since childhood. The mother (39 years old) had previously undergone an outpatient CK test for pain in the lower limbs on exercise, and her CK level was over 2000. However, she was not hospitalized and was rehydrated at the local clinic.

Upon admission, laboratory tests showed a significantly elevated serum CK level (29,842.00 U/L), CK-MB level (126.6 U/L), and increased serum myoglobin (2740.50 ng/mL). Cardiac evaluations, including echocardiography and electrocardiography, were unremarkable. Lower extremity MRI indicated multiple abnormal signals in the bilateral thigh muscle groups, consistent with muscle edema (Figure 1). Muscle strength and electromyography were normal. The patient received routine pediatric care, including urine alkalinization, fluid replacement, and antioxidant therapy with vitamin C. Her symptoms significantly

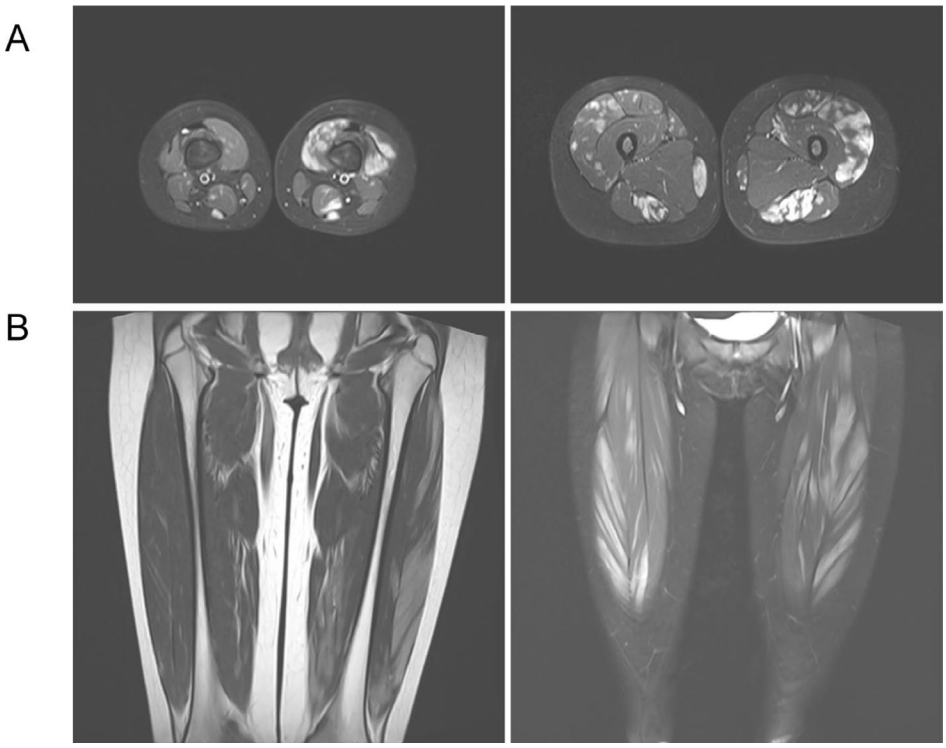

FIGURE 1 | MRI scans of bilateral thigh muscles in axial and coronal views. (A) Axial T2-weighted MRI images of the thigh muscles. They display cross-sectional views of the thigh. Axial T2-weighted imaging with fat suppression shows patchy hyperintense signals within the muscle. (B) Coronal T2-weighted MRI images of the bilateral thighs, showing longitudinal sections of the quadriceps muscles and adjacent structures. Left: T2-weighted imaging demonstrates mildly hyperintense abnormal signals within the muscle, with signal intensity lower than that of the adjacent subcutaneous fat. Right: Coronal T2-weighted imaging with fat suppression reveals patchy hyperintense signals within the muscle.

improved after five days of treatment, and she was discharged with no residual complaints.

Before discharge (on September 15, 2024), follow-up laboratory tests showed a persistently elevated serum CK level (20,401.00 U/L) and CK-MB level (124.2 U/L). Despite this, the patient exhibited no cardiac symptoms. Renal function tests were unremarkable, with no signs of acute kidney injury. The patient's symptoms significantly improved after five days of treatment. However, given the persistently high CK levels, she was advised to avoid strenuous physical activity.

3.2 | Identification of *OBSCN* Gene Variant in Our Patient

The WES was performed to further explore the etiology of the patient. The complex heterogeneous variants in OBSCN (NM_001386125.1: c.21184C>T, p.Gln7062*; c.15610+12C>T) were found in our patient. They were inherited from the parents, and they were confirmed through Sanger sequencing (Figure 2).

The c.21184C>T variant is absent from publicly available population frequency databases, such as gnomAD, 1000 Genomes, and ExAC, indicating it has not been observed in the general population. The predictions from multiple in silico tools, including LRT_pred ('D'), MutationTaster ('A'), and a CADD-RAW score of 17.141, strongly support the variant's potentially harmful nature. Although the REVEL score of 0.304 indicates a moderate impact, the collective evidence suggests this variant may contribute to the observed phenotype.

The minor allele frequency (MAF) for another c.15610+12C>T variant was 0 in the gnomAD_EAS database. The SpliceAI analysis of it highlights a substantial potential impact on splicing, with a Donor Loss score of 0.6 and a Donor Gain score of 0.91. These findings suggest that this variant could lead to aberrant splicing, possibly resulting in disrupted gene function or altered protein products. Additionally, MMSplice predicts a significant reduction in splicing efficiency (delta_logit_psi = −0.6738), which may lead to exon skipping or intron retention. Furthermore, MaxEntScan analysis indicates a notable increase in donor site strength (MesDonVar = 25.032), suggesting the activation of a cryptic donor site, potentially leading to abnormal transcript processing (Supporting Information Table).

4 | Discussion

OBSCN is a complex structural protein-coding gene that encodes an obscurin protein mainly involved in the stability of muscle cell sarcomeres and the functional regulation of SR, especially closely related to calcium ion (Ca^{2+}) signaling. With the progress of genomic studies, pathogenic variants of OBSCN have been gradually revealed as the cause of a variety of genetic diseases, including cardiomyopathy and rhabdomyolysis. In this study, we report a patient carrying compound heterozygous variants of OBSCN (c.21184C>T and c.15610+12C>T), which further

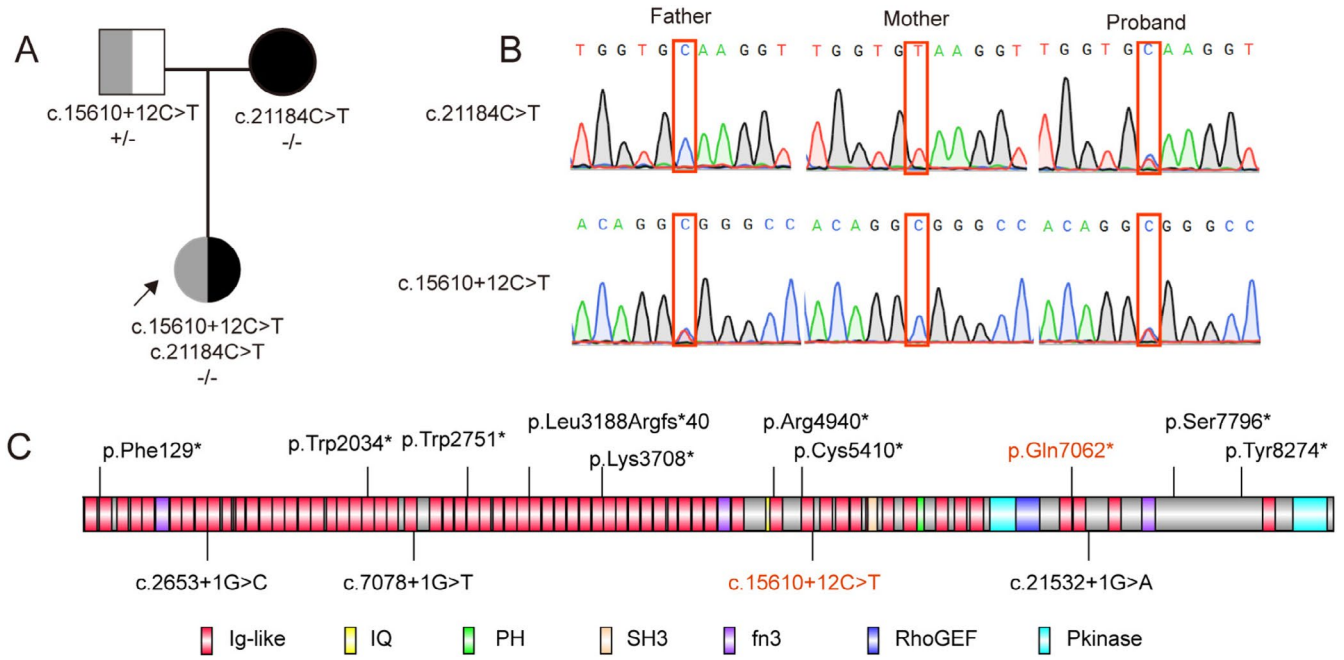

FIGURE 2 | Identification of the compound heterozygous variants in the proband. (A) Pedigree diagram of the family showing segregation of the identified variants. The proband (indicated by an arrow) carries compound heterozygous variants c.15610+12C>T and c.21184C>T. The father is heterozygous for c.15610+12C>T (+/−), and the mother is homozygous for c.21184C>T (−/−). (B) Sanger sequencing chromatograms for the c.15610+12C>T and c.21184C>T variants. Red boxes highlight the nucleotide changes in the father, mother, and proband. (C) Schematic representation of the gene structure with identified variants mapped. Previously reported pathogenic mutations (black text) and functional domains are shown. The c.15610+12C>T variant is marked in red. fn3, fibronectin type III domain; Ig-like, immunoglobulin-like domain; IQ, IQ calmodulin-binding motif; PH, Pleckstrin homology domain; Pkinase, protein kinase domain; RhoGEF, rho guanine nucleotide exchange factor domain; SH3, Src homology 3 domain.

extends the spectrum of *OBSCN* gene variants and further suggests the association of OBSCN variants with rhabdomyolysis.

Currently, *OBSCN* gene variants have been found to be associated with a variety of myopathies, including HCM, DCM, LVNC, and skeletal myopathies. In recent years, rhabdomyolysis has been gaining increasing attention. Obscurin proteins play an important role in maintaining the structural integrity and organizational stability of the membrane-associated microtubule by interacting with a wide range of sarcomeric proteins, such as tropomyosin, tropomyosin, and myosin-binding protein C (Randazzo et al. 2013), cytoskeleton, and the organizational stability of the myofibrillar membrane (Randazzo et al. 2013). Deficiency of obscurin increases the risk of rhabdomyolysis by making muscle fibers more sensitive to exercise-induced injury and decreasing membrane stability (Randazzo et al. 2017). In addition, obscurin is thought to play a key role in connecting the ganglionic contractile apparatus to the SR, in particular regulating the structure and function of the SR through the interaction of its COOH-terminal binding site with the small anchor protein 1 (sAnk1.5) in the SR (Lange et al. 2009; Bagnato et al. 2003). Studies have shown that both Obscn null and sAnk1.5 null mice exhibit reduced SR size, suggesting the importance of obscurin in maintaining SR integrity (Giacomello et al. 2015).

Loss-of-function variants of OBSCN have been shown to cause exercise-induced rhabdomyolysis (Cabrera-Serrano et al. 2021; Zemorshidi et al. 2024), such as myalgia, cramps, and significant elevations in serum CK. These symptoms are usually induced by high-intensity exercise or fever. Fourteen variants in nine patients have been reported (including our patient, Table 1). The main feature for these patients was childhood or adolescent onset, with exercise- or heat-induced rhabdomyolysis, accompanied by exercise intolerance (7/9) and myalgia (8/9). All patients presented with significant elevation of serum CK (mean value over 275,000 IU/L and maximum up to 603,000 IU/L), which was accompanied by muscle cramps (3/9) or mild muscle weakness (3/9) in some patients. Renal failure occurred in 3 patients (3/9), but cardiac function was normal in all patients. The patients in this study had exercise-induced rhabdomyolysis, which presented with muscle pain, elevated CK values, and MRI findings in both lower limbs that showed muscle edema, with no signs of muscle weakness or cardiac abnormalities. The phenotype was basically consistent with previous reports, further validating the relationship between *OBSCN* gene variants and exercise-induced rhabdomyolysis.

Our patient was tested by WES, which identified compound heterozygous variants inherited from each parent. One of the variants, c.21184C>T, is a nonsense variant that causes the protein to terminate prematurely at amino acid 7062, which is not found in the gnomAD, 1000 Genomes, and ExAC databases, and is supported by multiple prediction tools as potentially pathogenic, with a CADD-RAW score of 17.141, suggesting that it may have a large impact on protein function.

Another variant, c.15610+12C>T, is located in the intronic region, and its very low MAF (0.0000229779) and Donor Loss

TABLE 1 | The clinical information for reported patients with *OBSCN* variants.

Ref.	ID	Age/ sex (Age at first episode)	Onset of muscle symptoms and basal neurological examination	Peak CK (IU/l)/basal CK between episodes	Rhabdo trigger	Muscle pathology	LL muscle MRI	Cardiac abnormality	Exercise intolerance	Myalgia	Muscle weakness	Renal failure	Variants
Macarena et al.	AUS1	20 y/M (18 y)	Exercise-induced myalgia and muscle cramps in childhood, mild distal weakness and exercise intolerance	> 500,000/~200–500	Heat, exercise	Mild random variation in myofiber size, increased central nuclei, occasional necrotic and regenerating myofibers present	Normal	Normal	Y	Y	Y (distal)	Y	exon 62: c.16230C>A, p.(Cys5410*)—hmz
	AUS2	39 y/M (27 y)	Presented for review after exercise intolerance and rhabdomyolysis. Normal on examination	275,000/normal	Exercise	Central core disease with fiber type variation	N/A	N/A	Y	Y	N	N	exon 21: c.6102G>A, p.(Trp2034*) exon 24: c.7078+1G>T, p.(?)
	FIN1	38 y/M (15 y)	Occasional exercise-related myalgias in childhood	> 90,000/normal-mildly elevated	Exercise	Glycogen accumulation, dilated SR/T-tubules	Normal	N/A	N	Y	N	N	exon 36: c.9563_9576del, p.(Leu3188Argfs *40) exon 36: c.9563_9576del, p.(Leu3188Argfs *40)
	TUR1	20 y/F (17 y)	Exercise-related myalgia and muscle cramps	> 350,000/~400	Heat, exercise	Abnormal variation in myofiber size, increased internal nuclei. Some predominance of type 2 myofibers, lobulation of type 1 myofibers, core-like regions	N/A	N/A	Y	Y	N	Y	exon 46: c.14818C>T, p.(Arg4940*)—hmz

(Continues)

TABLE 1 | (Continued)

Ref.	ID	Age/sex (Age at first episode)	Onset of muscle symptoms and basal neurological examination	Peak CK (IU/l)/basal CK between episodes	Rhabdo trigger	Muscle pathology	LL muscle MRI	Cardiac abnormality	Exercise intolerance	Myalgia	Muscle weakness	Renal failure	Variants
	UK1	41 y/F (teens)	Recurrent rhabdomyolysis	17,000/normal	None	Within normal limits	Unremarkable	Normal	N	N	N	N	exon 31: c.8253G>A, p.(Trp2751*) exon 42: c.11122A>T, p.(Lys3708*)
	USA1	19 y/M (12 y)	Exercise-related myalgia in childhood. Physically very active. Elite high school athlete (lacrosse)	603,000/500–1000	None	N/A	N/A	N/A	N	Y	N	Y	exon 90: c.21532+1G>A, p.(?) exon 2: c.386_387delinsAA, p.(Phe129*)
Fariba et al.	PER1*	20/M	Exercise intolerance and rhabdomyolysis	27,600/260–1760 (normal < 190)	Exercise	Variation in fiber size, angular atrophic fibers, increased internalized nuclei, and type 2 fiber predominance	Mild fatty change in some muscles	Normal	N	Y	N	N	intron 8: c.2653+1G>C, p.(?)—hmz
	TUR1*	16/M	Exercise-induced rhabdomyolysis with myoglobinuria	337,000/1000–1597 (normal < 190)	Exercise	N/A	N/A	Normal	Y	Y	N	N	exon 105: c.24822C>A, p.(Tyr8274*)—hmz
Our study	Patient	11/M	Exercise-induced rhabdomyolysis	29,842/-(normal 22-270)	Heat, exercise	N/A	Muscle edema	Normal	Y	Y	N	N	exon87: c.21184C>T (p.Gln7062*) exon58: c.15610+12C>T
	The mother	39/M	Exercise-related myalgia	> 2000/-(normal 22-270)	Exercise	N/A	N/A	Normal	Y	N/A	N/A	N	exon87: c.21184C>T (p.Gln7062*)

Abbreviations: CK, creatine kinase; F, female; LL, lower limb; M, male; N, no; Ref, reference; SR/T, sarcoplasmic reticulum/transverse; Y, yes.

and Donor Gain scores predicted by SpliceAI (0.6 and 0.91, respectively) suggest that it may lead to aberrant splicing, which will ultimately affect protein function. Further supporting this, MMSplice predicts a possible reduction in splicing efficiency (delta_logit_psi = −0.6738), while MaxEntScan indicates a substantial increase in donor site strength (MesDonVar = 25.032), suggesting activation of a cryptic donor site. The fact that the mother harbored the homozygous *OBSCN* variant and also showed symptoms of exercise-induced myalgia provides further support for its pathogenicity. The variant in the patient in this study may have an effect on several important structural domains of the protein, potentially weakening support for the cytoskeleton, disrupting calcium signaling, and affecting membrane localization and signaling (Manring et al. 2017). The pathogenicity of the identified splicing variants could not be fully confirmed due to the lack of transcript analysis. Although in silico predictions support aberrant splicing, we were unable to perform experimental validation because patient-derived samples were not available for analysis. Additionally, the rarity of OBSCN-related ER cases and limited population-specific data constrain the interpretation of these variants. Further studies are needed to validate their functional and clinical significance.

In conclusion, we report the first case of rhabdomyolysis caused by an *OBSCN* gene variant in China. The compound heterozygous variants (c.21184C>T and c.15610+12C>T) carried by this patient were identified by WES. This finding further extends the spectrum of variants in the *OBSCN* gene and provides new evidence for its association with exercise-induced rhabdomyolysis.

Author Contributions

Xiaolan Sun collected the data, contributed to data and analysis tools, performed the analysis, and wrote and edited the manuscript. Jianmin Zhong conceived and designed the analysis and supervised the project. Hui Chen assisted with project supervision and analysis tools. Jihua Xie assisted with data collection. Ruiyan Wang assisted with project supervision and provided resources. All authors contributed to editing the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.