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CLINICAL REPORT

A novel variant in the *QRICH1* gene was identified in a patient with severe developmental delay

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Abstract

Background: QRICH1 encodes the glutamine-rich protein 1, which contains one caspase activation recruitment domain and is likely to be involved in apoptosis and inflammation. However, the function of the QRICH1 gene was largely unknown. Recently, several studies have reported de novo variants in *QRICH1*, and the variants have been associated with Ververi-Brady syndrome characterized by developmental delay, nonspecific facial dysmorphism, and hypotonia.

Materials and Methods: Whole exome sequencing, clinical examinations, and functional experiments were performed to identify the etiology of our patient.

Results: Here, we added another patient with severe growth retardation, atrial septal defect, and slurred speech. Whole exome sequencing identified a novel truncation variant in the *QRICH1* gene (MN_017730.3: c.1788dupC, p.Tyr597Leufs*9). Furthermore, the functional experiments confirmed the effect of genetic variation.

Conclusion: Our findings expand the *QRICH1* variant spectrum in developmental disorders and provide evidence for the application of whole exome sequencing in Ververi-Brady syndrome.

KEYWORDS
developmental delay, QRICH1, Ververi-Brady syndrome, whole exome sequencing

1 | INTRODUCTION

QRICH1 (Glutamine Rich 1) encodes a transcriptional regulator, which acts as a mediator of the integrated stress response (ISR) by controlling protein homeostasis transcriptionally under conditions of ER stress (You et al., 2021). It contains two conserved domains: the caspase activation and recruitment (CARD) domain at the N-terminal, which is a protein–protein interaction domain, and the domain of unknown function (DUF3504) at the C-terminal (You et al., 2021).

The function of QRICH1 is mainly unclear; however, as the next sequencing technology has advanced, an increasing number of *QRICH1* gene variants have been found. So far, five articles have reported that variants in the *QRICH1* gene have been associated with Ververi-Brady syndrome (OMIM: 617982), which presented with developmental delay (DD), intellectual disability (ID), language delay, and facial dysmorphism (Baruch et al., 2021; Föhrenbach et al., 2021; Kumble et al., 2022; Lui et al., 2019; Ververi et al., 2018). Furthermore, it was reported to be involved in the process of chondrocyte hypertrophy, which is essential for healthy longitudinal bone growth (Lui et al., 2019).

Variations in the *QRICH1* gene are still rare, and more cases were beneficial in studying the role of QRICH1 in the nervous system. Here, we report a female patient

who presented severe growth retardation. The *QRICH1* variant was detected by the trio whole exome sequencing (WES). In vitro function experiments showed a decrease in QRICH1 expression in mRNA and protein levels. Our study expands the genotypic spectrum of individuals with *QRICH1* variants.

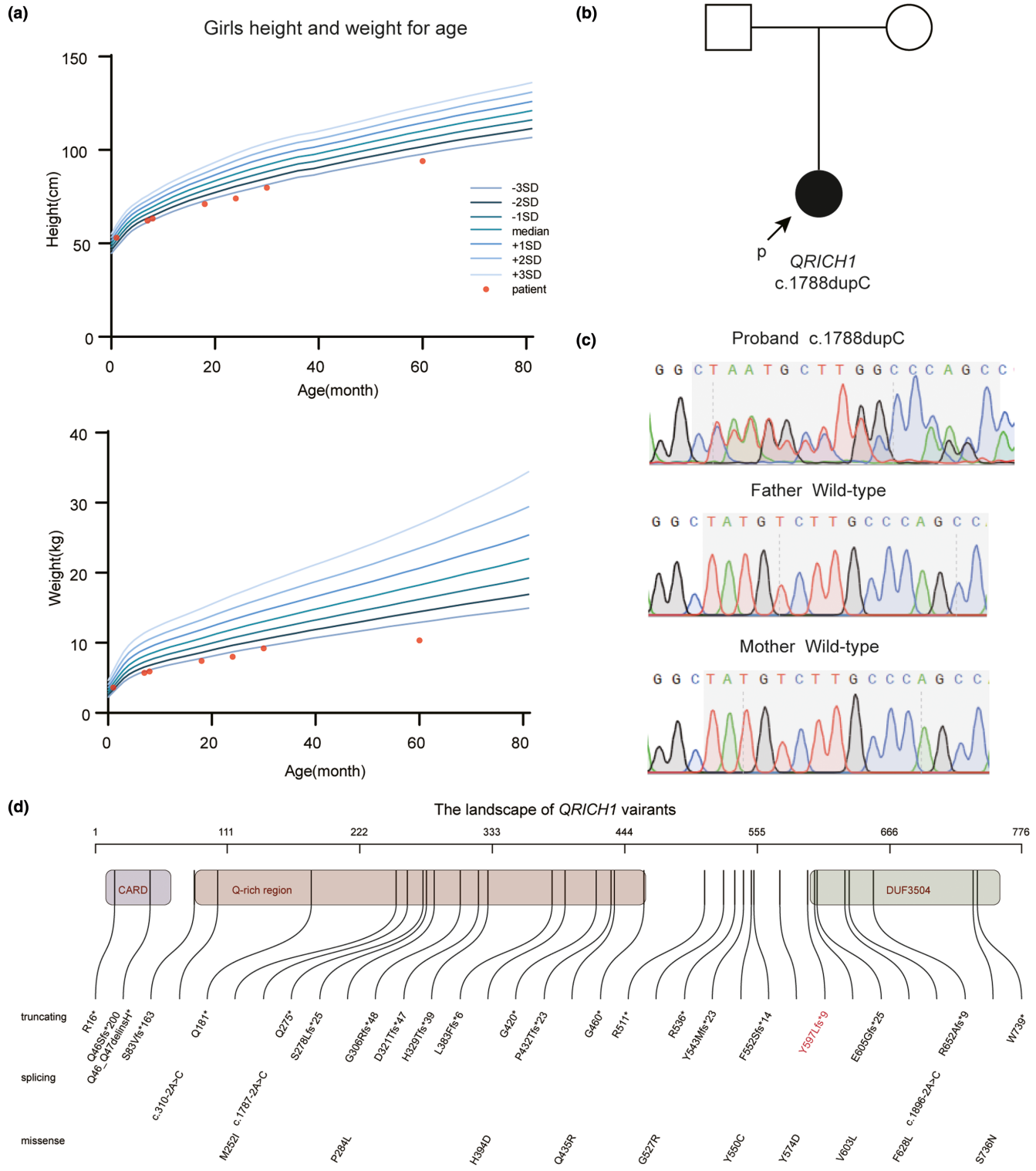

FIGURE 1 Identified the *QRICH1* variant in our patient. A pedigree of the affected family. (a) Height and weight distribution of patients. (b) Our patient was represented by the filled symbol with an arrow. (c) Whole exome sequencing identified a de novo truncated variant in the *QRICH1* gene. (d) The landscape of *QRICH1* variants .Variant in our patient was highlighted in red text.

2 | MATERIALS AND METHODS

2.1 | Patient

We report a Chinese female patient who had DD and slurred speech. This study was conducted according to the Helsinki declaration of human studies research. Informed consent was obtained from her parents. This study was approved by the Ethics Committee of the West China Second Hospital of Sichuan University. The patient's clinical examination included physical examinations, laboratory examinations, cardiac ultrasound, and genetic analysis.

2.2 | Whole exome sequencing and Sanger sequencing

Genomic DNA was extracted from the peripheral blood of the trio family, and IDT XGen Exome Research Panel was used to collect the genomic DNA library. Then WES was performed based on the NovaSeq 6000 Sequencing platform using Paired-End reads. And BWA (Li & Durbin, 2009), Samtools (Jaganathan et al., 2019), and Picard software (http://broadinstitute.github.io/picard/) were used to read the alignment to the human reference genome GRCh38/hg38. The generated files were partially recompared with GATK software (McKenna et al., 2010), and we used Annovar (Wang et al., 2010) to perform variants annotation. The average coverage depth for the WES is 227.24X, the ≥50% base coverage in the target region is 98.58%.

The detected variants were analyzed by using the HGMD, dbSNP, OMIM, and ClinVar databases. All detected variants were filtered by clinical characteristics, inherent patterns, and databases included gnomAD and ExAC. Sanger sequencing was then performed to confirm the variations found by WES.

2.3 | Functional examination of the variant

To determine the effect of variation on gene expression, recombinant expression vectors (phagh-QRICH1-wt/mut; pEGFP-C1-QRICH1-wt/mut) were created. The vector "phagh" and "pEGPF-C1" were self-constructed, and the full sequences were provided in the Supplementary materials. Sanger sequencing was used to validate the amplification products. In mutant vectors, the variation c.1788dupC was introduced. All primers used in the vectors construct were provided in Table S1.

The produced wild-type and mutant recombinant expression vectors were transfected into 293T cells using Lipo2000 in accordance with the manufacturer's instructions. Samples were taken 48 hours after transfection. Total RNA was extracted by Trizol, and cDNA were synthesized after DNA digestion, and differential expression

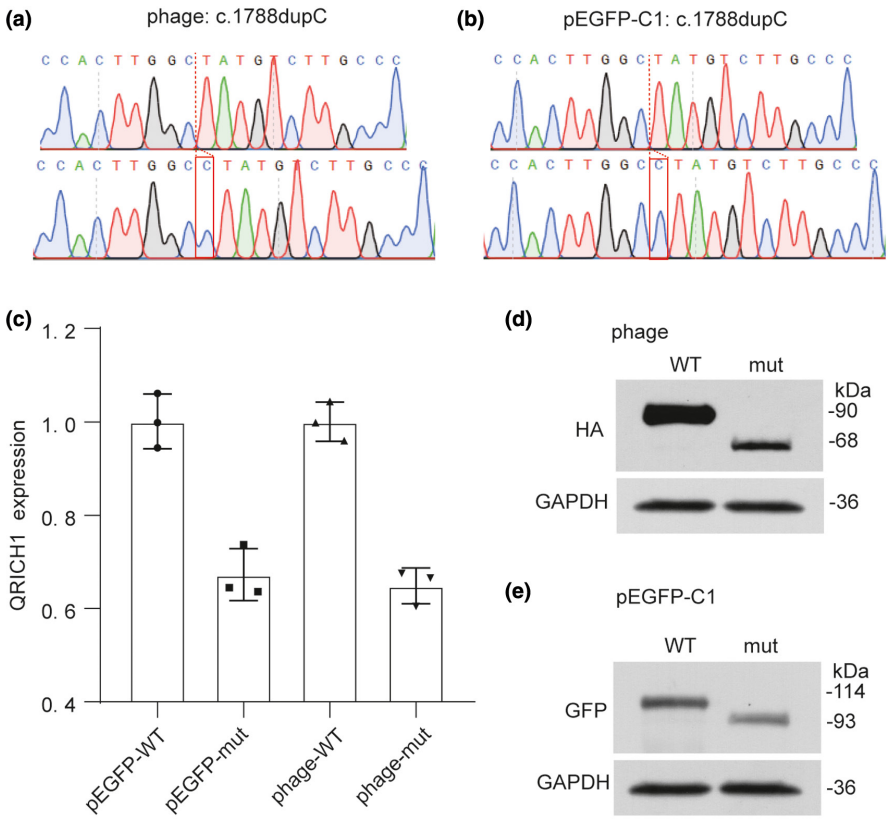

FIGURE 2 Functional analysis of the effect on the c.1788dupC variant. (a and b) The DNA fragments were subcloned from genomic DNA, and mutated fragments were successfully inserted successfully and confirmed by Sanger sequencing. And the mutagenesis was indicated by red boxes. (c) The quantitative PCR was performed in wild-type and mutant recombinant transfection cells, showing the different levels of QRICH1 mRNA. (d and e) Western blot of recombined phage and pEGPF-C1 vectors transfected in 293T cells showing the different levels and lengths of QRICH1 protein.

TABLE 1 Phenotypic features in individuals with *QRICH1* variants.

Individual number (ref)	Age and gender at evaluation	Variants information	QRICH1 domain	Exon/intron	ID or GDD	Autism	DD	Facial dysmorphism
1 (Kumble)	M, 10 y	c.46C>T, p.(Arg16*)	CARD	3	Normal	+	+	+
2 (Kumble)	M, 11 y	c.136del, p.(Gln46Serfs*200)	CARD	3	Mild	+	+	+
3 (Ververi)	F, 9 y	c.138_139delinsTT, p.(Gln46_Gln47delinsHis*)	CARD	3	Mild	−	+	+
4 (Baruch)	M, 4 y	c.246del, p.(Ser83Valfs*163)		3	Mild	−	+	+
5 (Kumble)	M, 22 m	c.310-2A>C, p.?		IVS3	Normal	−	+	+
6 (Kumble)	F, 10 y	c.541C>T, p.(Gln181*)	Gln-Rich	4	Normal	−	+	+
7 (Kumble)	F, 3 y	c.756G>T, p.(Met252Ile)	Gln-Rich	4	Severe	−	+	+
8 (Kumble)	F, 13 y	c.823C>T, p.(Gln275*)	Gln-Rich	4	Mild	−	+	+
9 (Föhrenbach)	F, 15.25 y	c.832_833del, p.(Ser278Leufs*25)	Gln-Rich	4	Normal	−	+	+
10 (Kumble)	M, 11 y	c.851C>T, p.(Pro284Leu)	Gln-Rich	4	Mod	+	+	+
11 (Kumble)	M, 26 y	c.914dup, p.(Gly306Argfs*48)	Gln-Rich	4	Mild	+	+	+
12 (Kumble)	F, 13 y	c.961del, p.(Asp321Thrfs*47)	Gln-Rich	4	Mild-mod	−	−	+
13 (Kumble)	M, 13 y	c.985del, p.(His329Thrfs*39)	Gln-Rich	4	Mod-severe	−	+	+
14 (Kumble)	M, 7 y	c.1147_1150del, p.(Leu383Phefs*6)	Gln-Rich	4	Mild	+	+	+
15 (Kumble)	M, 15 y	c.1180C>G, p.(His394Asp)	Gln-Rich	4	Mild	+	+	+
16 (Kumble)	F, 11 y	c.1258C>T, p.(Gln420*)	Gln-Rich	4	Severe	−	+	+
17 (Kumble)	F, 14 y	c.1292dup, p.(Pro432Thrfs*23)	Gln-Rich	4	Normal	−	+	+
18 (Kumble)	F, 6 y	c.1304A>G, p.(Gln435Arg)	Gln-Rich	4	Normal	−	+	+
19 (Cope)	F, 15 y	c.1378C>T, p.(Gln460*)	Gln-Rich	5	Mild	−	+	+
20 (Lui)	M, 11 y	c.1531C>T, p.(Arg511*)		6	Mild	−	+	+
21 (Kumble)	M, 6 y	c.1579G>A, p.(Gly527Arg)		6	Mild	−	+	+
22 (Lui)	F, 8 y	c.1606C>T, p.(Arg536*)		6	U	−	+	+
23 (Kumble)	M, 15 y	c.1626del, p.(Tyr543Metfs*23)		6	Mod	−	+	+
24 (Kumble)	F, 6 y	c.1649A>G, p.(Tyr550Cys)		6	Normal	−	+	+
25 (Kumble)	M, 8 y	c.1655del, p.(Phe552Serfs*14)		6	Mod	−	+	+
26 (Kumble)	M, 14 y	c.1720T>G, p.(Tyr574Asp)		7	Normal	+	+	−
27 (Kumble)	M, 3 y	c.1787-2A>G, p.?		IVS7	U	−	+	+
28 Present study	**F, 5 y**	**c.1788dupC, p.Tyr597Leufs*9**		**8**	**Mild**	**−**	**+**	**+**
29 (Kumble)	M, 3 y	c.1807G>T, p.(Val603Leu)	DUF3504	8	Normal	+	+	−
30 (Föhrenbach)	M, 12.5 y	c.1812_1813del, p.(Glu605Glyfs*25)	DUF3504	8	Normal	−	+	+
31 (Kumble)	M, 2 y	c.1884C>G, p.(Phe628Leu)	DUF3504	8	Normal	+	+	−
32 (Kumble)	F, 11 y	c.1896-2A>G, p.?		IVS8	Mild	−	+	+
33 (Ververi)	F, 14 y	c.1953dup, p.(Arg652Alafs*9)	DUF3504	9	Mod	−	+	+
34 (Kumble)	F, 4 y	c.1954C>T, p.(Arg652*)	DUF3504	9	Mod	+	+	+
35 (Kumble)	F, 4 y				Mild	−	+	+
36 (Ververi)	M, 8 y				Mild	+	+	+
37 (Föhrenbach)	M, 5.5 y				U	−	+	+
38 (Kumble)	F, 2.75 y	c.2207G>A, p.(Ser736Asn)	DUF3504	11	Mod	−	+	+
39 (Kumble)	M, 21 m	c.2216G>A, p.(Trp739*)	DUF3504	11	Mild	−	+	+

Bold indicates the phenotype in patient.

Abbreviations: F, female; GDD, global developmental delay; ID, intellectual disability; m, months; M, male; Mod, moderate; U, unspecified; y, year.

Height < −2SD	Weight < −2SD	Feeding difficulties	Seizures (age of onset)	Hypotonia	Chondrodysplasia	Scoliosis	Organ abnormalities	Brain abnormalities
−	−	−	+, 8 y	−	−	−	−	−
−	−	−	−	−	−	−	+	+
+	+	−	−	−	−	−	−	−
−	+	+	−	−	−	−	−	−
+	+	−	−	+	−	−	−	−
−	−	−	−	+	−	+	−	−
−	−	−	−	−	−	−	−	+
−	−	−	−	+	−	+	+	−
−	−	−	−	−	−	+	−	+
−	−	−	+, 5 y	−	−	−	−	−
−	+	−	−	−	−	−	−	−
−	+	−	+, 6 y	−	−	−	−	−
+	−	−	−	−	−	−	−	+
−	−	−	−	−	−	−	−	−
−	−	+	+, 14 y	+	−	−	−	−
+	+	−	+, 6 m	+	−	+	−	+
+	+	−	−	−	−	+	−	−
−	+	−	−	−	−	−	+	−
−	−	+	+, 6 y	−	−	−	+	+
−	−	−	−	−	+	−	+	−
+	+	−	−	+	−	−	−	−
+	+	−	−	+	+	+	−	−
−	−	−	−	−	−	−	−	+
+	−	−	−	+	−	−	−	−
+	−	−	−	−	−	−	−	−
−	−	−	+, 9 y	−	−	−	−	−
+	−	−	−	−	−	−	−	−
+	+	−	−	−	−	−	+	−
−	−	−	+	+	−	−	−	−
−	+	−	−	−	−	−	−	−
−	−	−	−	−	−	−	−	−
−	−	+	−	+	−	−	+	+
−	−	−	−	+	−	−	−	−
−	−	−	+, 18 m	+	−	−	+	+
−	−	+	−	+	−	−	−	−
−	−	−	−	−	−	−	−	−
−	−	−	−	+	−	+	+	+
+	−	+	−	−	−	−	−	−
+	−	+	−	−	−	−	−	−

of wild-type and mutant QRICH1 mRNA was detected by qPCR. The total protein in the cells was extracted using RIPA. The BSA kit was used to measure the protein concentration, followed by protein denaturation, and the Western Blot method was used to detect the difference in the expression of the wild-type and mutant QRICH1 proteins.

3 | RESULTS

3.1 | Case report

The patient is a five-year-old girl. She was born full-time with a weight of 3.05 kg and a height of 50 cm. She has severe growth retardation with short stature (height < −3SD) and low weight (weight < −3SD) (Figure 1a). She is lactose intolerant and allergic to milk and protein. She was admitted to our hospital at the age of 2 years and 8 months old due to DD. Laboratory examinations did not show any abnormalities. Cardiac ultrasound results showed that she had congenital heart disease with an atrial septal defect when she was born. But it became normal at subsequent check. She has a special face, presenting with forehead protrusion, nose collapse, low-set ears, and a high-arched palate; one-third of the outside of the eyebrows is sparse, and the distance between the eyes is wide. Her motor and intellectual development is normal, but she has slurred speech.

3.2 | Identification of the *QRICH1* variant in our patient

WES was performed to further clarify the etiology of our patient. The de novo heterozygous variant in the *QRICH1* gene (MN_017730.3: c.1788dupC, p.Tyr597Leufs*9) was found and confirmed by the Sanger sequencing (Figure 1b,c). It was not presented in her parents and was predicted to lead to the truncation of the QRICH1 protein. It is rare and has not been concluded in public databases, such as gnomAD, ClinVar, and ExAC. The variant c.1788dupC, p.Tyr597Leufs*9 in the *QRICH1* gene in our patient was categorized as "pathogenic" according to the ACMG guideline (PVS1 + PS2 + PM2). So far, rare *QRICH1* variants have been reported, and the landscape was shown in Figure 1d.

3.3 | Functional experiments for *QRICH1* mutant

To identify the potential functional effect for this variant, we construct the phage and pEGFP-C1 vectors and introduce the variant c.1788dupC. The mutant was successfully introduced and confirmed by Sanger sequencing (Figure 2a,b). The vectors were transferred to 293 T cells, and the whole mRNA and protein were collected after 48 hours of transfer. Quantitative real-time PCR (qPCR) and Western Blot experiments were performed to identify QRICH1 expression in mRNA and protein levels. The results are shown in Figure 2c–e. The mRNA and protein in QRICH1 mutant groups showed a significant decrease. These results showed that this variant c.1788dupC affected the transcription and translation of QRICH1.

4 | DISCUSSION

QRICH1 enables DNA binding activity and is involved in multiple processes; it is a key effector of the PERK-eIF2α axis of the unfolded protein response, controlling transcriptional programs associated with translation and secretion networks (You et al., 2021). Even so, the physiological and molecular functions of QRICH1 are largely unknown. The conserved DUF3504 domain in the QRICH1 protein may be involved in the transcription and be implicated in the pathogenesis of ASD (Kojima & Jurka, 2011). Apoptosis and inflammation are probably both impacted by the caspase activation recruiting domain. Patients with

TABLE 2 The height and weight of our patient.

Date	Age	Weight (kg)	Weight evaluation	Height (cm)	Height evaluation
2018/2/5	1 month	3.6	P4.2	53	P16.6
2018/8/6	7 months	5.7	P0.3	62.2	P0.3
2018/9/7	8 months	5.9	P0.2	63.3	P0.2
2019/7/18	19 months	7.4	P0.2	71	≤P0.1
2019/12/18	24 months	8	<P3	74	<P3
2020/8/5	31 months	9.2	<P2	79.8	<P1
2022/12/15	60 months	10.35	P1.9	93	P < 0.1

Abbreviation: P, percent.

neuromuscular diseases have highly elevated caspases in their muscle fibers because they are implicated in the apoptotic protease cascade, which causes muscle fiber atrophy (Tews et al., 2005). Furthermore, the siRNA was used to knock down Qrich1 expression in primary mouse epiphyseal chondrocytes, and the results showed that several genes involved in chondrocyte hypertrophy differentiation were downregulated (Lui et al., 2019). This may be one of the reasons why the *QRICH1* variants cause DDs in patients.

To date, five studies report 38 patients with *QRICH1* variants, the landscape of *QRICH1* gene variants was shown in Figure 1d. The phenotypes identified so far are nonspecific and include variable neurodevelopmental features, hypotonia, short stature, stunted growth, and mild facial deformities (Table 1). As previously reported (Kumble et al., 2022), we unfortunately did not find a clear association between the type of mutation and the phenotype. Only the LOF variant was associated with facial dysmorphism, which also corresponded to the phenotype of our patient. Our patient weight and height (Table 2, Figure 1c) continued were consistently below the standard (Li, 2009). Her weight and height continued below −3SD at her last follow-up at the age of 5 years old, and this is the most consistent feature of the patients (28/39 patients, including our patient). The radiograph for our patient was normal, bone age was basically consistent with actual age. It did not show the irregular metaphyseal boundaries of proximal phalangeal growth plates as previous reported (Lui et al., 2019). The presence of chondrodysplasia may vary with the degree of skeletal maturation and could be an age-related characteristic, which can make it challenging to compare between individuals. Long-term follow-up may be required to observe this feature. Additionally, severe short stature and structural cardiac anomalies were noted. She had congenital heart disease with an atrial septal defect, which is the same as the previous study (Kumble et al., 2022), 5 previous patients had cardiac anomalies. Furthermore, homozygous knockout Qrich1 mice also exhibited cleft palate, renal abnormalities, and congenital heart disease (San Agustin et al., 2016), which may be related to the function of QRICH1 in related systems. But the cardiac phenotype was normal when she was 5 years old. The short-term atrial septal defect may not be related to the *QRICH1* variant. Our patient also has slurred speech and mild facial abnormalities, but she has no intellectual or motor impairments.

The variants in the *QRICH1* gene were rare, and gnomAD databases include seven LoF variants in total, each with a frequency of <0.001 (https://gnomad.broadinstitute.org/gene/ENSG00000198218?dataset=gnomad_r2_1, accessed January 6, 2023). According to the gnomAD database, the probability of LoF intolerance for this gene is equal to 1, and the LOEUF score was 0.28, so QRICH1 is expected to be intolerant to LoF mutations, and this suggests that QRICH1 haploinsufficiency (pHaplo score = 0.89) may be the root cause of the patient's phenotype (Ververi et al., 2018). The truncation variant in our patient (c.1788dupC, p.Tyr597Leufs*9) was not reported before. Our functional experiments confirmed that the variant led to decreasing mRNA and protein (Figure 2), early termination of translation, and the impact of this variation is obvious. The variant in our patient was located in exon 8 (10 exons in total), and was predicted to cause protein frameshift. It may have triggered the Nonsense-mediated mRNA Decay (NMD) (Khajavi et al., 2006) mechanism, and lead to low expression in mRNA and protein level. The NMDEscPredictor tool (https://nmdprediction.shinyapps.io/nmdescpredictor/) showed that p.Tyr597Leufs*9 in *QRICH1* will subject to degradation by NMD. This is also consistent with the results of our functional verification.

In summary, our study added another patient with the *QRICH1* variant, who presented with severe short stature, slurred speech, and mild facial abnormalities. The functional experiments showed the harmful effects of p.Tyr597Leufs*9 variant. Our study expands the QRICH1 cohorts and expands the spectrum of genetic variations for *QRICH1*.

AUTHOR CONTRIBUTIONS

Study design: Jin Wu; Data collection: Dong Wang and Jin Wu; Functional experiments: Dong Wang and Jin Wu; Manuscript preparation: Jin Wu; Manuscript revisions: Dong Wang.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by the Ethics Committee of the West China Second Hospital of Sichuan University.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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