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WHOLE EXOME SEQUENCING REVEALED A MUTATION IN *COL6A1* ASSOCIATED WITH ULLRICH CONGENITAL MUSCULAR DYSTROPHY

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SUMMARY

Collagen type VI-related disorders consist of Ullrich congenital muscular dystrophies (UCMD) and Bethlem myopathy, in which these entities are at two opposite extremes of the phenotype continuum. Clinical characteristics include proximal joint contracture, distal joint hyperlaxity, generalized muscle weakness, normal cognitive function, and pulmonary insufficiency. Affected individuals have trouble standing up and walking independently. Mutations in 3 genes (*COL6A1*, *COL6A2*, and *COL6A3*) are associated with decreasing collagen-VI production and disrupting the microfibrillar network between skeletal muscles. In the present study, using whole-exome sequencing (WES), a pathogenic variant in the *COL6A1* gene (NM_001848, c.868G>C, p.G290R) was detected in a Vietnamese family with UCMD patients. Segregation analysis by Sanger sequencing confirmed that this mutation was inherited in an autosomal dominant pattern. This study expands the breadth of congenital muscular dystrophies research landcape and underscores the efficiency of WES in investigating the etiology of this group of heterogeneous diseases. Insight about the underlying genetic causes could contribute to develop a well-timed treatment regimen and help patients make an informed decision about reproductive health.

Keywords: *COL6A1*, Sanger sequencing, UCMD, Vietnam, WES

INTRODUCTION

Congenital muscular dystrophies (CMD) are a group of genetically and clinically heterogeneous and early onset muscular conditions. Historically, CMD is classified based on clinical and imaging findings, yet with the continuous emerging of genetic causes and overlapping syndromes, this scheme is gradually replaced with a categorization by associated genes, which divides CMD into 7 subtypes (Bonnemann *et al.*, 2014). Among them are collagen VI-related myopathies, a continuous spectrum of muscular dystrophies, including Bethlem myopathy (BM) at the mild end and Ullrich congenital muscular dystrophy (UCMD) at the severe end, with an intermediate myopathic form in between. UCDM (OMIM # 254090) is a rare genetic disease characterized by progressive muscle weakness, contractures of proximal joints, rigid spine syndromes, hyperextensibility of distal joints such as wrist, ankle, and finger, and normal intelligence (Yonekawa, Nishino, 2015). The prevalence of this disease is 1.3/1000000 in the population of Northern England (Norwood *et al.*, 2009). Early

findings suggest that homozygous recessive mutation is the main inheritance mode, but later data point out that both heterozygous and dominant patterns also play a major role in the cause of this disease (Baker *et al.*, 2005; Giusti *et al.*, 2005).

Three genes (*COL6A1*, *COL6A2,* and *COL6A3)* encoding for the three alpha chains 1, 2, and 3 of collagen type VI, respectively have been identified as the causative genes for UCMD. While *COL6A2* (NM_001849.4) and *COL6A3* (NM_004369.4) have 28 and 43 exons and cover a region of 34.7 kb and 89.9 kb on 21q22.3 and 2q37.3, respectively, *COL6A1* (NM_001848) contains 35 exons spanning over a region of 23.3 kb, coding for a 140 kDa protein. Structures of alpha 1, alpha 2, and alpha 3 share a central triple-helical (TH) domain consisting of repeating Gly-X-Y motif, flanked by large globular von Willebrand factor type A domains (Chu *et al.*, 1990; Chu *et al.*, 1988). Heterotrimeric assembly of alpha 1, alpha 2, and alpha 3 constitutes the primary structural unit of collagen type VI inside the cell. Two peptide monomers align in antiparallel arrangement to form a sulfide-bonded dimer, which is constituted of tetramer (Ball *et al.*, 2003). Tetramers are then exported to the external environment to form microfibrils. As the completed collagen VI product, the microfibrillar matrix anchors the basement membrane of muscular tissue with the extracellular matrix, maintaining structural integrity (Chu *et al.*, 1989; Furthmayr *et al.*, 1983). Dysfunctional structure or lower production of collagen type VI protein could disrupt the connection between the extracellular matrix and muscular tissues, resulting in muscular dystrophy (Cescon *et al.*, 2015). Since alpha 1, alpha 2, and alpha 3 chain all take part in collagen assembly, pathogenic mutations in any of these 3 genes could give rise to UCMD/Bethlem myopathy.

In early 2009, whole exome sequencing (WES) emerged as a promising technique that could reshape the research landscape (O'Grady *et al.*, 2016). Ever since then, with the rapid cost reduction and continuous improvement in sensitivity and coverage, WES has gradually superseded Sanger sequencing in variant discovery (Chin *et al.*, 2013). Recently, a novel, likely pathogenic *COL6A1* mutation (c.G1667T) was found in two sisters in a consanguineous Sri-Lankan family using WES (Sirisena *et al.*, 2021). Using a similar approach, following up by functional analysis, Bardakol and his colleagues uncovered another novel homozygous recessive mutation (c.227 + 2T>C) in the *COL6A1* gene in 5 siblings of a Russian family, each of them exhibited a different degree of muscular contracture (Bardakov *et al.*, 2021).

In this study, we report a familial case with UCMD caused by a known variant (c.868G>C p.G290R) in *COL6A1* using whole-exome sequencing. To our knowledge, this is the first report of UCMD in a Vietnamese family using WES for mutation detection.

MATERIALS AND METHODS

Study subject and genomic DNA extraction

Blood samples from all family members were taken for segregation analysis. Genomic DNA was extracted and purified from peripheral blood using GeneJET Whole Blood Genomic DNA Purification Mini kit (ThermoFisher Scientific, USA), following the manufacturer's protocol. With the study approval from the Institutional Review Board of the Institute of Genome Research, Vietnam Academy of Science and Technology (No: 2-2019/NCHG-HĐĐĐ), written consent forms were obtained from the proband's parents.

Whole exome sequencing (WES)

WES was performed on the proband (II-1). DNA library was prepared using the SureSelectXT Human All Exon V6, and run on NovaSeq 6000 (Illumina, USA). Short reads were mapped onto the Human reference genome (UCSC hg19) using Novoalign (http://www.novocraft.com/products/novoalign/). PCR duplications were filtered out by Picard version 2.18.7 (http://broadinstitute.github.

io/picard/). Variant callings were performed following Genome Analysis Toolkit Best Practices (https://www.broadinstitute.org /gatk/ index.php).

PCR and Sanger sequencing

Validation of the causative variant was done on the proband (II-1) and her parents' samples. (I-1, and I-2). The target site and flanking regions were amplified using designed primers (primer sequence is available upon request). Purified PCR was sequenced with ABI Big Dye Terminator v3.1 Sequencing Standard Kit (Applied Biosystems, CA) on ABI 3500 Genetic Analyzer sequencer (Applied Biosystems).

Prediction tools

The pathogenicity of the variant was assessed in silico by several scales: SIFT (Sim *et al*., 2012), Polyphen-2 (Adzhubei *et al*., 2010), Mutation Taster (Schwarz *et al*., 2014), CADD (Rentzsch *et al*., 2021), and GERP (Cooper *et al*., 2005). Protein sequence conservation at amino acid position 290 was evaluated using ClustalOmega (Madeira *et al*., 2019)

RESULTS

Clinical presentation

Proband (II-1) was a nine-year-old female born to a non-consanguineous Vietnamese family. She started to walk around 18 months. Around the age of three, she developed proximal muscle weakness and Achilles tendon contracture that rendered her ability to walk or lift heavy things. Her creatine kinase (CK) serum level was 208.5 U/L (normal range <200 U/l). At the age of six, the proband weighed 16.2 kg (20.2±3) and had trouble standing up. At the age of seven, she weighed 20 kg (22.4±3.5), lost balance easily, and was unable to stand up without support. At the age of nine, her weight and height were 30 kg (28.2±4.8) and 130 cm (132.5±6.3), respectively. At the last examination of her age of nine, she did not exhibit any other postural abnormalities as demonstrated in a typical UCMD case (Figure 1A-C).

Patient I-2, a 37-year-old male, was the proband's father. His initial sign of muscle weakness appeared around 3 months old after a fever. Keloid formations were frequently formed in the knee area after an injury. He developed generalized muscle weakness, which became progressively worse over time, and eventually lost ambulation at the age of 30. At the time of our study, muscle atrophy had affected both upper and lower limbs (Figure 1D-E). His height was 162 cm and his weight was 27 kg, significantly underweighted.

The main clinical manifestations of the proband (II-1) and her father (I-2) are summarized in Table 1.

Genetic analysis

To identify the genetic cause of the disease, we performed WES, which showed the missense mutation (NM_001848, c.868G>C, p.G290R) (rs121912939) on exon 10 in the *COL6A1* gene. The identical missense variant was reported to be pathogenic previously (Giusti *et al.*, 2005). Sanger sequencing revealed the heterozygous pattern of the variant was present in both proband (II-1) and her father (I-2) but absent in her mother (I-1) (Figure 2A-B). Multiple sequence alignment of *COL6A1* peptide sequences between human and eight different species showed that this region is highly conserved (Figure 2C).

To predict the pathogenicity of the variant, in silico tools were performed. In particularly, prediction scores for SIFT, Polyphen2, and MutationTaster are 0, 1, and 1 respectively, reflecting the damaging effect of the variant. Given the corresponding thresholds of 15 and 4.4, the values of CADD (29.3) and GERP (4.4) are considered deleterious (Dong *et al.*, 2015).

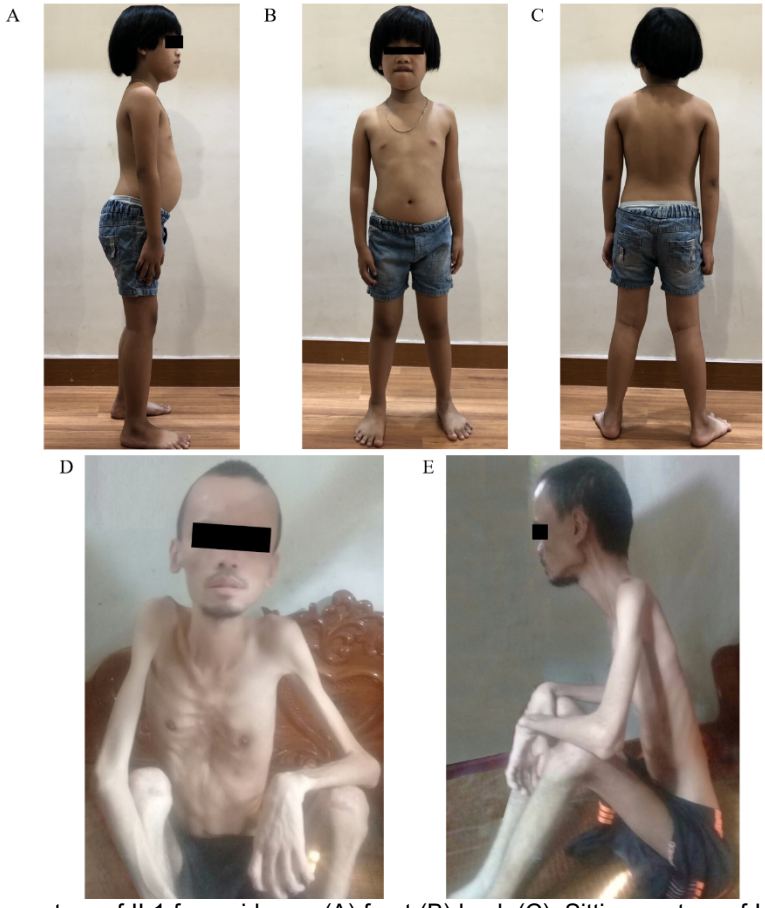

Figure 1. Standing posture of II-1 from sideway (A) front (B) back (C). Sitting posture of I-2 from front (D) and sideway (E).

Table 1. Major clinical phenotypes of the proband and her father and reported cases in literature with the same variant at amino acid position 290.

	Our study		**Pace *et al.***	**Giusti *et al.***	**Okada *et al.***	
Patient ID	I-2	II-1	P41	P5	#10	#11
Mutation form	Heterozygous c.G868C, pG290R	Heterozygous c.G868C, pG290R	Heterozygous c.G868A pG290R	Heterozygous c.G868C, pG290R	Heterozygous c.G868A, pG290R	Heterozygous c.G868A, pG290R
Sex	Male	Female	Female	Female	Female	Female
Age of review	37	9	13	18	5	6
Neonatal hypotonia	Yes	Yes	Yes	Yes	Mild	Yes
Torticollis	Absent	Absent	Absent	Absent	Absent	Absent
Hip dysplasia	Absent	Absent	Yes	Absent	Yes	Yes
Hyperlaxity	Absent	Absent	Yes	Yes	Yes	Yes

Muscle weakness (facial, neck flexors, pelvic girdle, feet, and hand)	Feet and hand	Feat and hand	-Slightly facial weakness -Proximal muscle -feet and hand	-Mild symptoms at neck flexors, pelvic girdle, feet, and hand	Not determined	Not determined
Contracture (knee, hip, ankles, finger)	Absent	Ankles	Elbows, knees, and ankle	Moderate symptoms at knee, hip, ankles, and finger	Absent	Yes, not specified
Scoliosis	Absent	Absent	Absent	Absent	Not determined	Not determined
Kyphosis	Absent	Absent	Absent	Yes	Not determined	Not determined
Protuberant calcanei	Not determined	Not determined	Absent	Not determined	Not determined	Yes
Abnormal scarring	Yes	Absent	Absent	Not determined	Not determined	Not determined
Age of walking	Not determined	18 months	18 months	30 months	Around 3- year-old	Around 3- year-old
Maximal motor capacity (to date of study)	Completely lost ambulation at 30-year-old.	Walking independently but easily losing balance	Walking short distance	Walking independently	Unable to run, but still achieve ambulation	Walking independently
Creatine Kinase (U/L)	Not determined	208.5	231	<250	417	138
Mental retardation	Absent	Absent	Absent	Absent	Absent	Absent
Respiratory complication	Absent	Absent	Absent	Absent	Absent	Absent

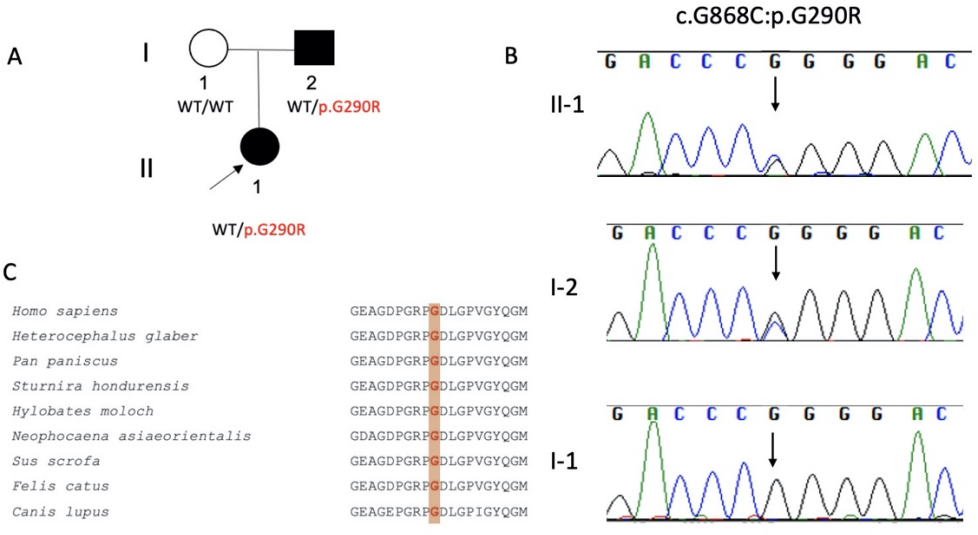

Figure 2. (A) Pedigree analysis of our studied family: I-1 did not show any clinical characteristics of UCMD, while I-2 and II-1 were diagnosed with UCMD. (B) Segregation analysis of all members in the family, in which I-2 and II-1 had a heterozygous G/C variant while I-1 had a homozygous wildtype G. (C) Multiple sequence alignment at amino acid position 290 (highlighted in red).

DISCUSSION

Here, we identified a known missense variant (c.868G>C, p.G290R) in *COL6A1*. At nucleotide 868, there are two variants G>C and G>A that both result in the amino acid change p.G290R. This protein substitution was described in at least 4 UCMD myopathy patients in several literatures, in which 3 of them harbored G>A mutation and 1 carried G>C (Giusti *et al.*, 2005; Okada *et al.*, 2016; Pace *et al.*, 2008). A detailed comparison of clinical phenotypes between our patients and these published cases is shown in Table 1, with a highlight on certain features that are typical to CMD. Neonatal hypotonia is present in all cases, while contractures are found in of our proband and 3/4 of previously reported cases. In 2/4 literature cases and both our patients, there is muscle weakness in different body parts. More distinctive features of UCMD such as hyperextension of distal joint or hip dislocation are absent in this study, but present in the literature cases. Ambulation is archived by all during childhood, but slowly impaired with age. Therefore, even with the same mutation, the clinical symptoms and their phenotypic expressivity are various on a case-by-case basis, indicating the challenge in establishing genotype-phenotype correlation for UCMD myopathy.

The peptide product of *COL6A1* gene, alpha I chain make up the monomers that construct collagen type VI through arrangement with other types of alpha chain. It comprises of two von Willebrand factors flanking on N- and C-terminal, with a signature TH domain in between (Lamande, Bateman, 2018). According to the UniProt database, the region of aa257-592 containing p.G290R, is a highly conserved TH domain that has repeated Gly-X-Y motifs. The glycine substitution in this repetitive motif does not affect the monomer formation of three alpha chains, but it interferes with tetramer assembles and interactions. Consequently, tetramer deposition to extracellular matrix and microfibril formation are significantly decreased, suggesting that damaging the level of microfibril matrix disruption has a positive correlation with the manifestation of clinical symptoms (Pace *et al.*, 2008). Another comprehensive study of 97 new patients and 97 patients reviewed in the literature suggested that those with glycine substitution in Gly-X-Y triplet 10-15th of TH domain manifest more severe symptoms than those with glycine substitution in other segments (Butterfield *et al.*, 2013). Though p.G290R is located on the 12th triplet within this critical region, the expressions of our patients' phenotypes are not on the severe end, further emphasizing on the complexity of this disease's genotype-phenotype correlation.

According to the public database of HGMD, about 66.3% (240/362) of reported variants on *COL6A1*, *COL6A2,* and *COL6A3* genes are either missense or small deletion/insertion of less than 20 bp mutations. On the other hand, both proband and her father lack of more UCMD-prominent features, yet retain all common ones shared with CMD. Neither the use of common genetic techniques such as CGH array or MLPA-PCR nor biochemical and clinical data are the most appropriate option to establish a concrete diagnostic for uncertain cases with nondistinguished phenotypes like our patients. Because of the limitation of financial and technological resources in Vietnam, NGS is not yet a part of the standard treatment. The delayed diagnosis places a burden on patients, not only in terms of finance but also on physical and mental wellness, as the patient might have to go through unnecessary invasive treatments and suffer anxiety. Our finding highlights the importance of whole-exome sequencing in identifying genetic diseases, especially in those that have general, overlapping symptoms. Knowing the precise disorder could also help physicians and patients anticipate respiratory complications, so that they can come up with a reasonable management plan. Finally, understanding the molecular underlying of UCMD can come into the future use for genetic counseling, family planning, and reproductive choice of affected individuals.

CONCLUSION

We report a known mutation (c.868G>C,

p.G290R) in the *COL6A1* gene, inherited in a heterozygous dominant pattern. The segregation of the mutation was confirmed in the family using Sanger sequencing. It was also found in her affected father but not in her healthy mother. Due to the slowly progressive nature of UCMD, we suggest regular check-ups with the patients to manage any potential manifestation promptly. With the advantages of using WES to detect variants in hereditary diseases that have non-specific symptoms, we encourage the implementation of WES into the gold standard of clinical routine to deliver optimal healthcare.

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XÁC ĐỊNH ĐỘT BIẾN GEN *COL6A1* GÂY BỆNH RỐI LOẠN CƠ BẨM SINH BẰNG GIẢI TRÌNH TỰ HỆ GEN MÃ HOÁ

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TÓM TẮT

Nhóm bệnh cơ liên quan đến protein collagen loại VI là một dạng loạn dưỡng cơ bẩm sinh gồm một phổ rộng các triệu chứng lâm sàng với mức độ nghiêm trọng khác nhau. Trong đó, bệnh cơ Bethlem là dạng nhẹ còn bệnh loạn dưỡng cơ Ullrich (UCMD) được xếp vào dạng nặng. Người mắc bệnh thường có các biểu hiện như co cứng các khớp gần, các khớp xa linh hoạt bất thường, yếu cơ toàn thân, có các vấn đề liên quan đến chức năng hô hấp và có nhận thức bình thường. Ngoài ra, khó

khăn trong việc vận động và tự di chuyển cũng là một dấu hiệu thường gặp. Đột biến ở ba gen *COL6A1*, *COL6A2* và *COL6A3* đã được chứng minh là có liên quan đến nhóm loạn dưỡng cơ collagen loại VI. Sử dụng giải trình tự hệ gen mã hoá (Whole exome sequencing - WES), chúng tôi đã tìm ra đột biến gây bệnh trên gen *COL6A1* (c.G868C, p.G290R) ở một gia đình người Việt Nam có bệnh nhân mắc UCMD. Kết quả giải trình tự Sanger sequencing trên bệnh nhân và bố mẹ bệnh nhân xác nhận rằng đột biến này được di truyền ở dạng dị hợp trội. Nghiên cứu này góp phần mở rộng hiểu biết về các bệnh loạn dưỡng cơ bẩm sinh, đồng thời nhấn mạnh tính hiệu quả của phương pháp WES trong việc xác định chính xác yếu tố di truyền trong chẩn đoán các bệnh loạn dưỡng cơ. Tìm ra nguyên nhân di truyền gây bệnh góp phần đáng kể vào việc xây dựng phác đồ điều trị lâu dài cho bệnh nhân, từ đó giúp họ có thể đưa ra những quyết định liên quan tới xây dựng cũng như kế hoạch hoá gia đình.

Từ khoá: *COL6A1*, giải trình tự Sanger, loạn dưỡng cơ Ullrich, Việt Nam, giải trình tự hệ gen mã hoá