Muhsin Elmas et al, 2019;1(2):81–83.
https://doi.org/10.24911/JBCGenetics/183-1541166651

CASE REPORT

A case of Bethlem myopathy with autosomal recessive inheritance with a novel mutation in the *COL6A2* gene

Muhsin Elmas[1]*, Başak Gogus[1]

ABSTRACT

Background: Mutations in the collagen VI genes (*COL6A1, COL6A2*, and *COL6A3*) cause Ullrich congenital muscular dystrophy (UCMD) [UCMD; Mendelian Inheritance in Man (MIM) 254090], Bethlem myopathy (BM) (BM; MIM 158810), and phenotypes between BM and UCMD. Both of UCMD and BM are inherited as autosomal dominant and autosomal recessive.

Case Presentation: A 4-year-old patient presented to the clinical genetic department with complaints of mental motor retardation, epilepsy, and joint contractures. The patient's physical examination, biochemical test results, magnetic resonance image, and echocardiography led us to suspect congenital muscular dystrophy. Then whole exome sequencing (WES) analysis was performed. As a result of WES analysis, the homozygous mutation was detected in the *COL6A2* gene.

Conclusion: WES analysis is a good method for diseases with recessive inheritance. In addition, a detailed and holistic assessment of patients is important.

Keywords: Myopathies, drug-resistant epilepsy, microcephaly.

Introduction

At collagen VI gene mutations cause the group of disease entitled as collagen VI related myopathies. The clinical severity of these diseases is broad (1). Bethlem myopathy (BM) was first identified by Bethlem and van Wijngaarden in 1976. According to this; in addition with slow progressing muscle weakness and long-finger flexors, w rists, e lbows, p ectoral m uscle g roups, a nd ankles typical flexion contractures have been followed and defined autosomal dominant inherited muscular dystrophy (2). Patients with BM usually become symptomatic with hypotonia after birth. However, they may become symptomatic in the first or second decade (3). Ullrich congenital muscular dystrophy (UCMD) is a congenital disease that progresses with joint contractures, weakness, and joint hyperlaxity (4).

In most of the patients with BM and UCMD, mutations occur in three genes encoding type IV collagen. These three genes and their locations are as follows: *COL6A1* and *COL6A2* (located on chromosome 21), *COL6A3* (located on chromosome 2) (5). Mutations identified associated with BM are usually inherited as autosomal dominant (mostly seen in exon 14 in COL6A1). Firstly reported by Gualandi et al. mutation with autosomal recessive inheritance has been reported at BM. But these are seen much less frequent (1,5). Mutations that cause UCMD are inherited as autosomal dominant and autosomal recessive. It was revealed that the mechanism under the autosomal dominant form was caused by the dominant negative effect (6).

We have detected one patient with BM findings (severe joint contractures) with homozygous in the *COL6A2* gene, inherited from healthy heterozygous parents. This is previously unreported a missense mutation.

Case Presentation

A 4-year-old male patient was referred to us by pediatric neurology with symptoms of neuromotor developmental delay, severe learning disability, delayed psychosocial development, joint contractures drug-resistant epilepsy, chronic constipation, and strabismus. At patient's

Correspondence to: Muhsin Elmas
*Faculty of Medicine, Medical Genetics Department, Afyon Sağlık Bilimleri University, Afyonkarahisar, Turkey.
Email: drmelmas@gmail.com
Full list of author information is available at the end of the article.
Received: 02 April 2018 | **Accepted:** 23 May 2018

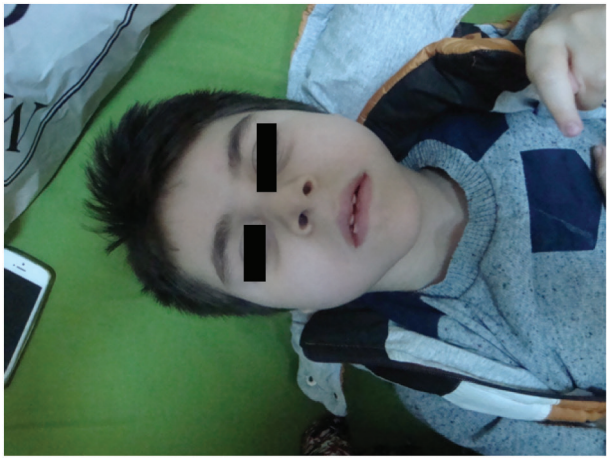

Figure 1. *Dysmorphic findings of the patient.*

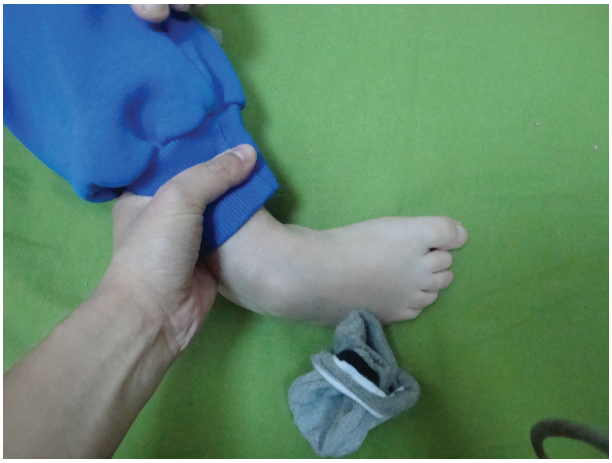

Figure 2. *Example of contractures in the patient.*

anamnesis informed fetal akinesia in the prenatal period. The birth information of the patient was 3,880 g with spontaneous vaginal delivery at term. The patient did not have a history of hypoxic birth and the fifth-minute birth APGAR score was 8–9. His breastfeeding duration was 7 months. Motor development retardation was detected when the patient's motor development stages were questioned (Head and neck control time: 1 year). Yet unsupported sitting, walking, and speaking were not available. He had first epilepsy attack when he was 30 days old and continued continuously. After 7 months, he had 20 seizures lasting 20 seconds on average in 1 day. Currently, he has two to three epilepsy attack per month average.

In the pedigree of the patient, it was seen that the parents were not consanguinity but they are from the same village. He had a 9-year-old healthy sister. At the same time, his mother had one abortion (6-week embryo).

At physical examination revealed head circumference below 3 percentile (microcephaly). At the dysmorphic examination, brachycephaly, flat occiput, square face, narrow forehead, sloping forehead, malar flatting, pointed chin, deeply set eyes, thick eyebrows, almond-shaped palpebral fissure, telecanthus, prominent inferior crus of antihelix, prominent antihelix stem, prominent superior crus of antihelix, underdeveloped crus helix, large lobe, low insertion of columella, enlarges nares, wide nasal bridge, depressed nasal bridge, wide nasal ridge, midline sinus of philtrum, thin upper lip vermilion, and thick lower lip vermillion were found (Figure 1). There are also contractures at the four extremities of the tetraplegic patient (Figure 2). Muscle atrophy that was more distinct at proximal groups was present in the upper extremities muscles.

No abnormal value was found in the biochemical tests of the patient. His creatine kinase levels were normal. At magnetic resonance images of the patient, thin corpus callosum and benign external hydrocephalus were shown. Hips arrhythmia was detected in electroencephalography. Echocardiography of the patient without any cardiac problems was reported as normal.

The patient was diagnosed with a severe congenital muscular dystrophy group disease but a specific disease could not be considered within this group of diseases. At this stage, it was decided that the best genetic test to be chosen was whole exome sequencing (WES). WES identified a homozygous mutation in the *COL6A2* gene [NM_001849.3 (COL6A2): c.2584C > T (p.Arg862Trp)]. It has not been previously reported in the literature. But according to genetic databases evaluation tools, it is highly likely presented as a disease-causing mutation. The patient was found to be compatible with the BM and thus a definitive diagnosis was evidenced.

Discussion

We described a novel mutation for recessive inheritance BM with our patient. Compared to the clinical findings of dominant inherited BM mutations, our patient had more severe clinical findings.

Generally, the onset of the disease was reported as the first and second decade (3). However, in our patient, the disease manifested itself in the first month after birth. Even, if we pay attention to the presence of fetal akinesia, the disease started to show its findings in the prenatal period. At the study of patients with autosomal recessive BM, patients reported to start the disease at the age of 43 and 41 years (7). In another study in which BM patients with recessive inheritance were presented, the age of onset of the disease was reported as 25 (1). When compared with other BM patients with autosomal recessive inheritance, it was observed that our patient had a much earlier onset. One reason for the presence of these severe clinical symptoms is thought to be early-onset and drug-resistant epilepsy. In addition, epilepsy has not been reported in other cases. We think that the new mutation in the *COL6A2* gene may cause this condition.

Another important point we want to focus on is the relationship with autosomal recessive inheritance and consanguinity marriage. Patients often state that they are not relatives but are from the same village. As seen in our

case, the frequency of recessive diseases is increasing in people from the same village. The reason for this situation may be that they have a common ancestor from the old generation. It is important that physicians pay attention to this issue, especially when drawing a pedigree.

The gene in the mutation detected in the patient's WES leads to two diseases. The presence of fetal akinesia, severe mental retardation (Normal intelligence is expected at UCMD), proximal muscular atrophy, and the absence of expected skin involvement in UCMD made possible to diagnose BM at our patient. This situation shows a detailed anamnesis and the importance of physical examination at genetics clinical department.

Conclusion

WES is a good method for many diseases that cannot be diagnosed despite the use of many laboratories and imaging techniques. Diagnosis of diseases with genetic etiology has made physicians much easier due to new methods such as WES parallel to the development of technology. Thus, nowadays, diseases are defined by mutations rather than syndromes. The other is that detailed clinical information is particularly necessary for the bioinformatics part of WES. Technology is advancing with each passing day, but the importance of a holistic approach to classical medicine is increasing.

Acknowledgment
First of all, we thank the patient and his family. Then we thank the Intergen Genetic Center for molecular analysis.

Declaration of conflicting interests
The authors declare that there are no conflicts of interest.

Funding
None.

Consent for publication
Written informed consent was obtained from the parents of the patients for publication of this paper and any accompanying images.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Author details
Muhsin Elmas[1], Basak Gogus[1]
1. Faculty of Medicine, Medical Genetics Department, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

References

1. Gualandi F, Urciuolo A, Martoni E, Sabatelli P, Squarzoni S, Bovolenta M, et al. Autosomal recessive Bethlem myopathy. Neurology 2009; 73(22):1883–91. https://doi.org/10.1212/WNL.0b013e3181c3fd2a
2. Bethlem J, Wijngaarden GK. Benign myopathy, with autosomal dominant inheritance. A report on three pedigrees. Brain 1976; 99(1):91–100. https://doi.org/10.1093/brain/99.1.91
3. Jöbsis GJ, Boers JM, Barth PG, De Visser M. Bethlem myopathy : a slowly progressive congenital muscular dystrophy with contractures. Brain 1999; 122(4):649–55.
4. Bozorgmehr B, Kariminejad A, Nafissi S, Jebelli B, Andoni U, Gartioux C, et al. Ullrich congenital muscular dystrophy (UCMD): clinical and genetic correlations. Iran J child Neurol 2013; 7(3):15–22.
5. Lampe AK, Bushby KMD. Collagen VI related muscle disorders. J Med Genet 2005; 42(9):673–85. https://doi.org/10.1136/jmg.2002.002311
6. Camacho Vanegas O, Bertini E, Zhang RZ, Petrini S, Minosse C, Sabatelli P, et al. Ullrich scleroatonic muscular dystrophy is caused by recessive mutations in collagen type VI. Proc Natl Acad Sci USA 2001; 98(13):7516–21. https://doi.org/10.1073/pnas.121027598
7. Foley AR, Hu Y, Zou Y, Columbus A, Shoffner J, Dunn DM, et al. Neuromuscular disorders autosomal recessive inheritance of classic Bethlem myopathy. Neuromuscul Disord 2009; 19(12):813–7. https://doi.org/10.1016/j.nmd.2009.09.010