A Novel Variant of COL6A2 Gene Causing Bethlem Myopathy and Evaluation of Essential Hypertension

To the Editor,

Collagen VI is an extracellular matrix protein and is closely associated with the basement membrane in most tissues.[1] Collagen-VI-related myopathies are caused by both dominant and recessive mutations in the three collagen-VI-related genes (COL6A1, COL6A2, and COL6A3) and present as Bethlem myopathy (BM), Ullrich congenital muscular dystrophy (UCMD), autosomal recessive myosclerosis myopathy, and autosomal dominant limb-girdle muscular dystrophy (LGMD).[2] Classification is based on phenotype; UCMD is more severe; and BM is characterized by mild proximal muscle weakness and typical distal contractures of the fingers and ankle joints, with a late-onset and slow progression. Cardiac and cognitive functions are not affected.[3] BM is mostly inherited dominantly, although a few cases of autosomal recessive inheritance have been reported.[2] MRI findings are characteristics for collagen-VI-related myopathies, caused by fatty infiltration mostly in anterior thigh muscles.[3] We are presenting a father as the index case and his two children with essential hypertension and a heterozygous c.2096G > A variant in the COL6A2 gene causing BM [Figure 1].

The proband was a 48-year-old male born of consanguineous parentage presenting with recurrent falls, contractures at metacarpals, elbow, and ankle with hyperextensibility of fingers, and keloids due to his injuries since the age of 10 years. His mental and motor milestones were normal. He had difficulty in climbing stairs and rising from the floor. He noticed a predominantly proximal weakness of all four limbs (Medical Research Council (MRC) grade 3-4/5 proximally and 4-5/5 distally) and continued to perform his daily activities without assistance. The weakness progressed very slowly until 35 years of age. He had sustained multiple injuries from recurrent falls resulting in multiple keloids over the left forearm and both hands over sites of injury [Figure 2]. Cranial nerve functions and sensations were intact, while muscle stretch reflexes were absent. He first presented to medical attention when his son also had muscle weakness, frequent falls, and keloids as same as him.

Both his son and daughter presented with predominant proximal muscle weakness (MRC grade 4-5/5 proximally) of all four limbs, follicular hyperkeratosis [Figure 2], and distal hyperextensibility of fingers. The elder son was 16-year-old with symptom onset at 12 years of age. He had recurrent falls, resulting in keloids over the left arm, and both hands [Figure 2] and contractures were seen at metacarpals. The second child, the daughter, was 13 yearold with disease onset at 12 years of age. She had mild proximal weakness of all four limbs and had occasional falls. She had not had any contractures or keloids yet. Higher mental functions and respiratory functions were normal for all three patients. The father's muscle enzymes were normal and mildly elevated for both children. The needle electromyography for all three patients revealed myopathic features with normal nerve conduction studies. The father's left quadriceps muscle biopsy revealed distinct features supporting BM. Also, the father's muscle MRI showed a specific pattern on the anterior thigh muscles with peripheral fatty infiltration with central sparing in vastus muscles and an anterocentral and peripheral infiltration of rectus femoris. His son's MRI showed anterocentral fatty infiltration of rectus femoris, and his daughter's MRI was normal.

Unlike usual BM patients, both children suffered from headaches around 10 years of age and were diagnosed with migraine. Throughout follow-ups, both developed hypertension at 12 years of age. The father was diagnosed with hypertension

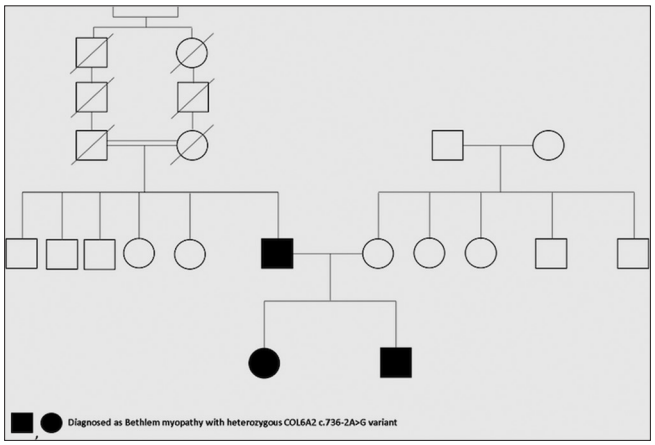

Figure 1: Pedigree of the family with BM

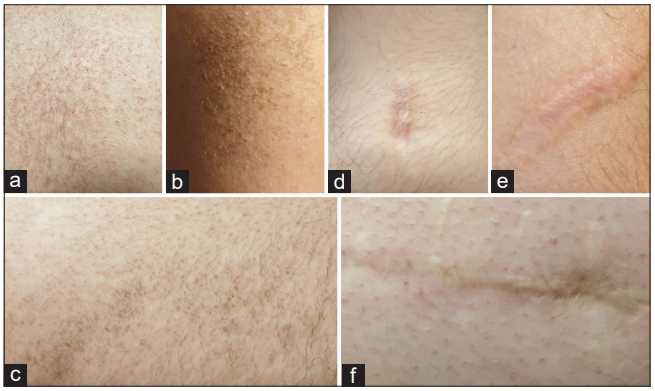

Figure 2: Follicular hyperkeratosis on the daughter's back and arm (a and b) and son's arm (c). Keloids over the upper extremity of the son (d and e) and father (f)

in the third decade. Electrocardiography, echocardiography, renal ultrasound, and renal Doppler ultrasound studies were normal for all three probands. Laboratory examinations for urine analysis, renin-angiotensin level, and lipid profile were normal. Therefore, all of the causes of secondary hypertension were eliminated.

Due to clinical findings, the patients were diagnosed as BM, and all coding exons and exonic-intronic junctions of the COL6A1, COL6A2, and COL6A3 genes were sequenced. We detected a heterozygous c.2096G > A variant in the COL6A2 gene. Although the pathogenicity prediction in ClinVar is not clear, we classified this variant as pathogenic according to the ACMG criteria that are two pathogenic moderates and three pathogenic supporting (PM1, PM2, PP1, PP3, PP4_strong).[4]

Early onset proximal muscle weakness associated with contractures accompany such diseases as Emery-Dreifuss muscular dystrophy (EDMD), UCMD, and BM.[5] UCMD patients have severe muscle weakness comparing to BM, progressing to respiratory insufficiency, velvety skin, and posteriorly prominent calcanei.[3] Mild and late-onset clinic presentation and absence of arrhythmia or cardiac involvement lead us to the differential diagnosis of UCMD and EDMD, respectively.

Dermatological examination of muscular dystrophy patients is highly important, leading the clinicians to diagnose particular muscular dystrophies. UCMD, BM, megaconial congenital muscular dystrophy (MCMD), and LGMD2Q have previously described skin changes and should be considered in the differential diagnosis.[6] Keloid or atrophic scar formation, hyperkeratosis pilaris, soft and thin skin on palms and soles are seen in collagen-VI-related dystrophies, including UCMD and BM.[3] MCMD has ichthyosis-like skin changes, and LGMD2Q (PLEC1 mutation) has epidermolysis bullosa simplex.[6,7]

Muscle MRI findings, fatty infiltration of different muscle groups, could be used in describing different muscular dystrophies. In BM, there is predominantly anterior thigh involvement. The central part of the rectus femoris and peripheral part of the vastus muscles involvement is the most characteristic finding for BM.[3]

Essential hypertension is rare in neuromuscular diseases. Hypertension usually develops secondarily as in DMD patients, due to steroid use and cardiac involvement.[8] A patient who had LMNA mutation was reported with lipodystrophy, hyperlipidaemia, and early onset hypertension.[9] To our knowledge, hypertension is not a cardinal feature of BM. In cohort studies conducted to date, essential hypertension has not been reported in patients with Collagen-VI-related myopathy but van der Kooi and colleagues reported hypertension for 2 BM patients who had cardiac abnormalities from the same family.[10] Bao and colleagues reported a patient with recurrent haematuria. After a whole-exome sequencing analysis, they speculated that impaired interaction between collagen VI and collagen IV results in haematuria.[1] Because collagen is present throughout the body, all organs or systems could be affected by any loss of function. Therefore, we suggested that the overlapping of clinical findings is not unexpected.

In this article, we reported a family with BM and essential hypertension. While the relation of the Collagen-VI-related disorders and hypertension is unclear, based on our knowledge about the functions of collagen and clinical findings of our patients, we speculated that essential hypertension might not be coincidental and COL6A mutations could play a role in hypertension. As we discover novel variations, clinicians should consider about new clinical findings in disorders previously described. However, there is still room for other possibilities because we did not analyse any other genes than COL6A genes. Further analyses are needed to prove the association between hypertension and COL6A2 mutations.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Submitted: 10-Apr-2020 **Revised:** 06-May-2020 **Accepted:** 27-May-2020
Published: 02-Sep-2020

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DOI: 10.4103/aian.AIAN_247_20