Classic Ehlers–Danlos Syndrome in a Son and Father with a Heart Transplant Performed in the Father

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Abstract

Keywords

- ▶ classic Ehlers–Danlos syndrome with *COL5A1* gene variant
- ▶ joint hypermobility
- ▶ poor skin healing and easy bruising
- ▶ heart transplant

We report a 13-year-old male patient with severe orthopedic problems including features of a connective tissue disorder and a heterozygous c.305T > A variant found within exon 3 of the autosomal dominant collagen (*COL5A1*) gene causing the classic Ehlers–Danlos syndrome. This variant has not been reported previously and identified as having an unknown clinical significance but classified as trending damaging per in silico prediction with high conservation among species. Our patient's father had the same gene variant and similar features of stretchable skin, easy bruising, and multiple joint dislocations. The father had unexplained heart failure requiring cardiac transplantation at 43 years of age.

Introduction

The classic Ehlers–Danlos syndrome (EDS) is a heritable connective tissue disorder with features of hyperextensible, fragile soft skin, delayed wound healing and atrophic scars, easy bruising, and generalized joint hypermobility. Approximately 50% of patients with a clinical diagnosis of classic EDS show mutations in the *COL5A1* and *COL5A2* genes encoding the $\alpha 1$ and $\alpha 2$ chains of type V collagen, respectively.¹ Classic EDS is an autosomal dominant disorder with a prevalence of 1 in 20,000² individuals and first recognized in 1901.³ Major diagnostic criteria include skin hyperextensibility with wide atrophic scars, joint hypermobility with dislocations/subluxations, and pes planus. Minor criteria include soft smooth skin with healing irregularities, easy bruising, prone to hernias with cardiac involvement (usually mitral valve prolapse or aortic root dilation), and early termination of pregnancy due to premature rupture of membranes.⁴ EDS consists of a group of single gene conditions and termed classic, hypermobile, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis.^{4,5} Causative genes identified with advances in genetic technology have led to better awareness, improved diagnosis, and treatment by medical providers.

Here, we report a proband (son) and his father with a *COL5A1* gene variant coding for one of the low abundant

fibrillar collagens that relate to the major and minor connective tissue abnormalities seen in classic EDS. The father was similarly affected but had a heart transplant at 43 years of age due to heart failure with no known cause determined.

Clinical Report

Our patient is a 13-year-old male and the second child born to nonconsanguineous parents. His height was 166 cm (90th percentile), weight was 48.1 kg (45th percentile), and head circumference was 53.7 cm (50th percentile). He was born at full term by caesarean section and weighed 3.9 kg (75th percentile). The mother was under psychiatric care due to bipolar disorder during the pregnancy but no drug or alcohol use was noted. His growth and development were normal but did have chronic ear infections as a young child. Poor healing was noted following a tympanoplasty with subsequent hearing deficits. He participated in sport activities and fractured his wrist and elbow while playing basketball. He also experienced multiple spontaneous knee dislocations beginning at 9 years of age with knee pain and generalized joint hypermobility, loose skin, excessive bruising, and poor scarring.

During the genetics clinic visit, we assessed for hypermobility using the Beighton scale^{6,7} and recorded a numerical

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score of 8 out of 9. The score included passive dorsiflexion of fifth finger beyond 90 degrees (1 point), passive bilateral apposition of both thumbs to flexor aspects of forearms (2 points), hyperextension of the elbows beyond 180 degrees (2 points), hyperextension of the knees beyond 180 degrees (2 points), and forward flexion of the trunk with palms of hands resting on the floor. No heart murmur was detected with regular rate and rhythm. A previous echocardiogram showed normal intracardiac anatomy and size with no valvular heart disease but his aortic root was dilated. He exhibited skin marbling with atrophic scars on the posterior side of lower left leg and increased pigment secondary to easy bruising. Our patient also exhibited asymmetry of the anterior body wall segment (► Fig. 1).

A three-generation family history revealed a 24-year-old sister with no reported physical or health abnormalities. However, his 55-year-old father exhibited similar clinical features including stretchable thin skin, poor scarring, hypermobile joints with pain and easy bruising. He had a Beighton's hyperflexibility score 6 out of 9. Due to multiple knee surgeries, we were unable to assess bilateral knee range of motion. He had strabismus (exotropia) with repair at 12 years of age. The father also had surgery on the right knee due to frequent dislocations. Bilateral foot surgeries were performed due to pes planus. He had a stroke at 37 years of age but without hypertension. At 43 years of age, he underwent a cardiac transplant for heart failure with no known cause such as infections, anatomic defects, or metabolic problems. He also

Fig. 1 Views of hands, chest, and leg showing joint hyperflexibility, chest asymmetry, and poorly formed thin scars with excessive bruising on anterior lower leg in the 13-year-old male patient consistent with the classic Ehlers–Danlos syndrome with a *COL5A1* gene variant of unknown clinical significance.

underwent surgery at 54 years of age to fuse lower vertebrae and correct complications from nerve compression impacting ambulation. There were also no other paternal family members with features of a connective tissue disorder. Our patient's mother was a 42-year-old female with bipolar disorder and history of substance abuse. There were no maternal family members diagnosed with a connective tissue disorder.

Next Generation DNA Sequencing of Connective Tissue Disorder Gene Panel

We ordered a next generation DNA sequencing panel with deletion/duplication analysis of the following 50 genes related to connective tissue disorders: *ABCC6*, *ACTA2*, *ADAMTS2*, *ADAMTS10*, *ADAMTSL2*, *ALDH18A1*, *ATP6V0A2*, *ATP7A*, *CBS*, *CHST14*, *COL1A1*, *COL1A2*, *COL2A1*, *COL3A1*, *COL5A1*, *COL5A2*, *COL9A1*, *COL9A2*, *COL9A3*, *COL11A1*, *COL11A2*, *EFEMP2* (*FBLN4*), *ELN*, *FBLN5*, *FBN1*, *FBN2*, *FKBP14*, *FLNA*, *LTBP4*, *MED12*, *MYH11*, *MYLK*, *NOTCH1*, *PKD2*, *PLOD1*, *PRDM5*, *PRKG1*, *PYCR1*, *SKI*, *SLC2A10*, *SLC39A13*, *SMAD2*, *SMAD3*, *SMAD4*, *TGFB2*, *TGFB3*, *TGFBRI*, *TGFBRII*, *TNXB*, and *ZNF469*. The gene panel was analyzed commercially at the University of Nebraska Medical Center (Omaha, NE) using next generation sequencing protocols established in their laboratory from blood samples collected from the child and father. The DNA results from both patients showed a heterozygous missense *COL5A1* gene variant of exon 3 at chr9:137,591,782 at nucleotide c:305T > A with amino acid position at p.Ile102Asn.

Discussion

The classic type of EDS is a connective tissue disorder characterized by skin hyperextensibility, abnormal wound healing and scars, easy bruising, and joint hypermobility with pain. Both EDS type I and II include a continuum of clinical findings, allelic in nature and considered to be the same disorder. In both conditions, the skin is smooth, velvety, and hyperelastic with damage to the dermis occurring after relatively minor trauma. These areas occur especially over pressure points, such as the knees or elbows and areas prone to trauma including the lower legs, forehead, and chin. Wound healing is delayed with stretching of scars. Joint hypermobility can also lead to dislocations of the shoulder, clavicle, patella, digits, and hip but can resolve spontaneously. Other features include hypotonia, delayed motor development, fatigue, muscle spasms, and hernias. Less common findings include cardiac problems, such as mitral and tricuspid valve prolapse, aortic root dilatation, and spontaneous rupture of large arteries.¹ More than 100 variants of the *COL5A1* gene have been identified.⁸

The *COL5A1* gene codes for a component of type V collagen and spans 750 kb and 66 exons.^{8,9} Collagens include a family of proteins that strengthen and support tissues, such as skin, ligaments, bones, tendons, and muscles. A component of type V collagen called the pro- $\alpha 1$ (V) chain is produced from the *COL5A1* gene. Two combinations of α chains can generate type V collagen: three pro- $\alpha 1$ (V) chains or two pro- $\alpha 1$ (V) chains and one pro- $\alpha 2$ (V) chain (which is produced from the

COL5A2 gene). The triple-stranded procollagen molecules are processed by enzymes from outside of the cell to create mature collagen. They are arranged into long, thin fibrils of type I collagen. A separate collagen (type V) regulates the width (diameter) of these fibrils and control the assembly of other types of collagen into fibrils in several tissues.⁹ Type V collagen was first identified in human placenta and adult skin but present in other tissues and organs as a minor collagen component.

Several types of pathogenic variants were reported in 10 individuals with classic EDS⁹ identified in the literature as having structural variants exerting dominant-negative effects. These gene variants affect the structural integrity of type V collagen, resulting in a functionally defective collagen protein (dominant-negative variant). These structural variants are most commonly splice-site variants that result in exon skipping. However, a few single nucleotide variants have been reported to result in the substitution for glycine in the triple-helical region of the collagen molecule. A unique single nucleotide variant in *COL5A1* that changes a highly conserved cysteine residue to a serine in the C-terminal propeptide of the $\alpha 1$ (V) collagen chain has also been identified (p.Cys1639Ser; NM_000093.3:c.4916G > C). A nonsense mutation of the *COL5A1* gene at exon 2 (c.265C > T; p.Gln89*) has also been reported in a Chinese family (proband and father).¹⁰ The proband presented with soft velvety skin, dystrophic scars, and joint hypermobility.

A variety of mutations, deletions or duplications in the *COL5A1* gene can cause classic EDS. For example, our patient and his father were identified with a heterozygous variant c.305T > A (p.Ile102Asn) of exon 3 in the *COL5A1* gene. Their heterozygous missense variant is rare, highly conserved and causes a significant amino acid change from Isoleucine. Isoleucine is aliphatic and hydrophobic (nonreactive) while Asparagine has polar properties. This transition could impact the protein structure due to an affected change in the amino acid classification type. The amino acid substitution represented a high Grantham's distance of 194¹¹ which indicates that the amino acid change could be harmful and trending damaging by in silico prediction. The proband's father tested positive for the same mutation. He had a heart transplant at 43 years of age for heart failure for which no cause was determined. He also had multiple knee replacements due to chronic dislocations, eye, spine, and foot surgeries, easy bruisability, and joint pain with hyperflexibility.

In summary, we propose that the c.305T > A nucleotide transition (p.Ile102Asn) in *COL5A1* gene causes classic EDS. This missense mutation was not previously described and found in the son and similarly affected father with classic EDS. The father had undergone multiple surgical operations including joint replacements and a heart transplant. The heart transplant was done for heart failure for which no cause was determined. This clinical presentation should receive particular attention by existing cardiac transplantation services and a possible role of EDS in a subset of patients. We encourage the reporting of other similarly affected individuals in the literature and/or evaluation of connective tissue disorders in those with unexplained cardiac failure seeking heart transplantation.

Conflict of Interest

None declared.

Acknowledgments

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