Ehlers-Danlos Syndrome Type IV, Vascular Type, Which Demonstrated a Novel Point Mutation in the COL3A1 Gene

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Abstract

Ehlers-Danlos syndrome type IV (EDS type IV), vascular type, an autosomal dominant disorder caused by a mutation of the type III procollagen gene (COL3A1) is the most severe form of EDS and often presents with aortic hemorrhage or organ perforation. This report discusses a male patient with EDS type IV with dyspnea due to hemopneumothorax. He had thin skin and hypermobile joints and was clinically confirmed as having EDS type IV. The diagnosis was genetically confirmed by a mutation c.2528 G>A (p.Gly843Glu) in the COL3A1 gene. The position of the mutation has never been reported.

Key words: Ehlers-Danlos syndrome type IV, collagen type III, mutation, Col3A1

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Introduction

Ehlers-Danlos syndrome, type IV (EDS IV: MIM 130050), also known as EDS vascular type, is a rare autosomal dominant disease seen at a frequency of 1:250,000 (1) and is characterized by elastic skin, fragile tissue and fragile arteries that lead to arterial rupture, aortic dissection and gastrointestinal perforation. EDS type IV is caused by a mutation in the COL3A1 gene located on 2q31 that encodes pro-α1 chain of type III collagen (2), and the penetrance of the mutated gene is thought to be 1.0. The mutation causes reduced production or decreased function of the type III collagen, resulting in the signs and symptoms observed in the patients (1, 3).

We present the case of a male patient with EDS type IV which was clinically diagnosed and was genetically confirmed by a mutation c.2528 G>A (p.Gly843Glu) in the COL3A1 gene.

Case Report

A 23-year-old male presented with chest pain and dyspnea. He had a thin nose, thin lips and philtrum, small chin, thin and translucent skin, and hypermobile small joints. Thoracic CT revealed pneumothorax and pleural effusion, and the diagnosis of hemopneumothorax was established by thoracentesis (Fig. 1). He was noted to have clubfoot when he was 6 months old and had epilepsy when he was 7 months old (Fig. 2). Diagnostic criteria and standardized nomenclature for the Ehlers-Danlos syndromes has been suggested (Table 1) (4). The presence of one or more major criteria is necessary to establish clinical diagnosis. The presence of one or more minor criteria contributes to the classification into a subtype. This case fulfilled 2 major criteria; thin, translucent skin and characteristic facial appearance, and 4 minor criteria; hypermobility of small joints, talipes equinovarus (clubfoot), pneumothorax/pneumohemothorax, and positive family history, sudden death in a close relative, and the diagnosis of EDS type IV was established.

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Thoracic CT. Thoracic CT and thoracentesis revealed hemopneumothorax.

Figure 2. Right foot. The skin was translucent. The wound on his heel was a scar that remained after undergoing surgery for his clubfoot.

A skin biopsy was performed on his upper-arm and the fibroblasts were cultured in order to biochemically and genetically confirm the diagnosis. The fibroblasts were cultured with [3H]proline. Here, most of the radioactive proteins secreted in the culture medium were the type III collagens synthesized by the fibroblasts. They were separated by sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE), imaged by fluorography, and the intensity of each band was measured by a densitometer. The amount of the α1 chain of the type III collagen secreted into the culture medium was only 11% of that of the fibroblasts from sex- and age-matched control (Fig. 3). An investigation of the entire coding sequence of the COL3A1 mRNA revealed a heterozygous point mutation c.2528 G>A in exon 37 that substitutes Gly843 to Glu (Fig. 4). The mutation was then confirmed by the sequence analysis of genomic DNA. Although the mutation was not one of the previously reported mutations, Gly843 is located in one of the Gly-X-Y triplet backbone sequences of the collagen alpha chain where a Gly is required for the trimer of procollagen molecules to form a triple-helix structure. Therefore, the procollagen molecule with a Gly843Glu substitution would have a reduced capacity to form a triple-helix structure and thus re-

Table 1. Diagnostic Criteria of EDS Type IV (4)

i) Major diagnostic criteria.

- Thin, translucent skin.
- Arterial/intestinal/uterine fragility or rupture.
- Extensive bruising.
- Characteristic facial appearance.

ii) Minor diagnostic criteria.

- Acrogeria.
- Hypermobility of small joints.
- Tendon and muscle rupture.
- Talipes equinovarus (clubfoot).
- Early-onset varicose veins.
- Arteriovenous, carotid-cavernous sinus fistula.
- Pneumothorax/pneumohemothorax.
- Gingival recession.
- Positive family history, sudden death in a close relative(s).

![Autoradiofluorogram of procollagens secreted from fibroblasts.](image)

Table 1:

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![Autoradiofluorogram of procollagens secreted from fibroblasts.](image)
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Figure 4. Heterozygous point mutation in exon 37 of the COL3A1 gene. Fibroblast mRNA was reverse-transcribed and the entire coding sequence of COL3A1 was amplified using the overlapping primers. Direct sequencing of the amplicons revealed c.2,528G>A (p. Gly843Glu) mutation. Wild-type allele and mutant allele were expressed at a similar amount. The presence of mutation was confirmed by the direct sequencing of genomic DNA.

markedly reduce the secretion of α1(III) chain of the type III procollagen molecules. We thereby concluded that the mutation was the cause of the EDS type IV in this patient.

During the 2 years that followed the establishment of the diagnosis, he had a total of 6 episodes of pneumothorax and alveolar hemorrhage. A cavity has been formed where once a hematoma was formed. In addition, he developed epileptic seizures, and has been given an anti-epileptic medication.

Discussion

The characteristic clinical signs and symptoms of the EDS type IV have been summarized into the major and the minor diagnostic criteria (1, 4). Over 98% of the patients with EDS type IV have been revealed to have a COL3A1 mutation (1). The patient in the current report is thus demonstrated as a characteristic case with EDS type IV.

Although patients with EDS type IV may have a history of visiting doctors due to minor symptoms such as club-foot or epilepsy, the diagnosis of EDS type IV is often not established until a catastrophic complication appears. The rates of the first symptoms in one study were arterial complications, 46%; gastrointestinal complications, 19%; and other organ complications, 5%. Only 30% of the patients are diagnosed of their disease before a serious complication developed. The median age of the first complication is 23.5 years old, and 12% of them did not survive such a complication (5). EDS type IV is the only EDS that has pneumothorax as one of the diagnostic criteria, and the presence of pneumothorax supports the diagnosis of EDS type IV. Spontaneous pneumothorax has been observed in 16% of the patients with EDS type IV (6, 7).

Surgical treatment is often difficult to perform once a complication develops because of the fragility of vessels (8). Conditions that require surgery include both non-vascular complications such as rupture of bowel, abdominal wall hernias, and miscarriages and vascular complications such as rupture of aneurysm, and arterial fistula that may lead to compartment syndrome when it occurs within a closed space. The present patient may have future episodes that require surgical treatment and they are a serious concern (9).

Genetic counseling gives potential benefit to the family members of the proband. The penetrance of the gene is close to 1.0, and the disease very often becomes lethal. Taking these factors into consideration, genetic counseling should be considered and deliberately performed.

The mutations of COL3A1 include point mutations in the coding sequence, point mutations in the splicing donor consensus sequence, and deletions (5). Most of the point mutations in the coding sequence changes glycine in one of the Gly-X-Y triplet sequences in the triple-helix domain to another amino acid (5). The substitution of Gly to another amino acid has been found in other hereditary diseases in which causative genes are one of the collagen genes: osteogenesis imperfecta for type I collagen, Alport syndrome for type IV collagen, and dystrophic epidermolysis bullosa for type VII collagen. The substitution of Gly in these collagen molecules is known to destabilize the triple-helix, and thus contributes to the occurrence of pathogenicity (10). The mutated collagen molecule exerts a dominant negative effect to cripple the function of normal collagen molecules produced by the wild-type allele. The c.2528 G>A (p. Gly843Glu) observed in the current patient matched the characteristics of pathogenic mutation.

The current report described a case of EDS type IV that presented a novel mutation in the COL3A1 gene. The information presented here will provide important information for the EDS type IV as well as for the biochemistry of collagen type III.

References