Novel compound heterozygous COL3A1 variants are associated with Vascular Ehlers-Danlos Syndrome

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Abstract

Aim: Vascular Ehlers-Danlos Syndrome (vEDS) is an autosomal- dominant inherited disorder result on collagen type III alpha-1 chain (COL3A1) gene mutation. vEDS is associated with a decreased life expectancy due to spontaneous arterial, intestinal, and uterine rupture. The diagnosis of vEDS is supported by genetic testing confirming the presence of pathogenic variations in COL3A1. Although how COL3A1 mutation in the precise mechanism can lead to the multiple vascular involvements seen at a pathological level remains unclear. COL3A1 encodes the Collagen alpha-1(III) chain in humans. The alterations in content and properties of type III collagen, can lead to organ fragility. Genome sequencing revealed heterozygous COL3A1 variants (c.4223C>T p.F1408S) as likely genetic cause of vEDS in this present case. **Methods**: We assessed the young adult diagnosed with Stanford A aortic dissection without a history of hypertension and undertook Sanger sequencing. **Results**: We identified novel compound heterozygous variant in COL3A1: a missense- c.4223C>T p.F1408S Conclusion: Given the clinical phenotype and identified variants we suggest that this is the first patient reported to date with vEDS due to c.4223C>T mutations in COL3A1.

INTRODUCTION

Vascular Ehlers-Danlos Syndrome (vEDS) is an autosomal-dominant inherited disorder result on collagen type III alpha-1 chain (COL3A1) gene mutation[1]. vEDS is commonly considered the most severe subtype of Ehlers-Danlos Syndrome (EDS) and is associated with a reduced life expectancy due to spontaneous arterial, intestinal, or uterine rupture. Some patients presented with thin skin cuticles, easy bruising, and increased brittleness of connective tissue of hollow organ wall. The diagnosis of vEDS is relays on confirming the pathogenic variations in COL3A1by genetic testing[2].

COL3A1 is located on the long arm of chromosome 2 and is about 38 kb long. COL3A1 encodes the alpha 1 chain of type III collagen, also known as Collagen alpha-1(III) chain in humans. Type III collagen, an extracellular matrix (ECM) protein, is synthesized by cells as a pre-procollagen. It is found a significant structural component in hollow organs such as large blood vessels, uterus and bowel[3]. The alterations in content and properties of type III collagen, can lead to organ fragility. Mutations in the*COL3A1* gene cause the vascular type of Ehlers-Danlos syndrome. Patients with vEDS have decreased type III pro-collagen[4]. The content of type III collagen accounts for about 5-20% among of the total collagen content of the human body. The reduction of type III collagen will lead to the loss of structural integrity of tissue, which directly leads to tissue brittleness and vascular endothelial dysfunction [5,6].

CASE STUDY

A 32-year-old Han Chinese male was sent into the emergency department of the Traditional Chinese medicine hospital of Guangdong Province because of acute substernal chest pain for 7 hours. Past medical history is negative for hypertension and cardiovascular disease, and his family medical history has no record of cardiovascular or aneurysmal disease. He denies smoking or excessive drinking history. When the patient firstly

came to the emergency department, his blood pressure came to 261/142 mmHg and with sinus tachycardia at a heart rate of 121 beats per minute. Computed tomography angiography (CTA) demonstrated Stanford A aortic dissection, accumulative three branches of the aortic arch, superior mesenteric artery, and celiac trunk artery; The left renal artery and the inferior mesenteric artery originates from the false lumen, while the right renal artery originates from the true lumen. (Fig. 1). He was transferred to the Cardiovascular department of the First Affiliated Hospital of Jinan University, where the patient was performed urgent surgery. Before the preoperative examination was accomplished the patient was continuously intravenous infusing of Nycomed and Esmolol for anti-hypertensive therapy (goal systolic blood pressure was less than 120 mmHg,and heart rate less than 80 beats per minute) to prevent worsening dissection and aortic dissection rupture. Bedside transthoracic echocardiography revealing ascending aortic dissection, severe aortic regurgitation. The level of hypersensitive troponin is within normal limits. After finishing all the necessary preoperative examination, urgent surgery was performed. The patient underwent hybrid aortic repair surgery, including Bentall procedure, total arch replacement and descending aortic stent implantation. The patient was subsequently discharged 12 days after the surgery without complications, on an oral medication regimen of warfarin (4.5 mg daily), bisoprolol (5 mg daily), amlodipine (5 mg daily), and spironolactone (20mg daily). He presented to his 3-month follow-up clinic appointments with adequate blood pressure control equal bilaterally of upper limbs at about 122/80 mmHg, with no evidence of postoperative complications. CTA showed postoperative aortic valve replacement; the ascending aorta, aortic arch and part of the descending aorta were changed after stent implantation. A little contrast agent entered into the false lumen of the thoracic aortic stent. The tear of the endangium involved the thoracic aorta to the right common iliac artery, innominate artery and left internal carotid artery. The celiac trunk, superior mesenteric artery and right renal artery opened into the false lumen. The left renal artery opens into the true lumen; Mural thrombosis in the lower thoracic aorta false lumen. Laboratory results demonstrated normal complete blood routine tests and blood biochemical tests. The prothrombin time (PT) was 18.1 sec, and international normalized ratio (INR) was 1.48. The decision was made continue to take warfarin, bisoprolol and amlodipine.

GENETIC EVALUATION

Genetic testing is the definitive tool for confirming the diagnosis of vEDS, Sanger sequencing of COL3A1 was undertaken, and pathological variants were identified. (Fig.2) The gene is 38 kb long and has 51 exons, which are numbered 1–51 to match the numbering of exons in the genes for other fibrillar collagens (Fig.3). In contrast, sequencing of COL3A1 identified new variant; c.4223C>T p.F1408S in exons 50 respectively (Fig.4) . After searching some database, like Google scholar, PubMed, Ehlers-Danlos Syndrome variant Database, Human Gene Mutation Database, gnom AD and ClinVar, we confirmed that this variant has not been previously reported. COL3A1 mutations introduce premature termination codons that lead to mRNA instability[7].The mutation of COL3A1 resulting in the defective synthesis of the type III collagen Pro A1 (III) chain. Most of the COL3A1 mutations were led to substitutions for glycine in the repeated Gly-X-Y triple motif of the triple-helical domain[7]. (Fig.4)

DISCUSSION

In this study, we applied whole-exome sequencing (WES) and Sanger sequencing and identified a new mutation in COL3A1(c.4223C>T p.F1408S) that led to vEDS.

vEDS is a rare, severe, autosomal dominant disease characterised by arterial dissections, arterial ruptures, bowel perforation, and organ ruptures [8,9]. The incidence of vEDS is 1/50,000-1/200000[4], the median survival has been reported at 24.6 and 48 years[9], and the cause of death is associated with arterial aneurysm and,or spontaneous rupture of dissection.The major cause of vEDS is mutations in COL3A1.

After sequencing of COL3A1 mutation was found in our patient, the diagnosis of vEDS was effectively confirmed with the identification of rare biallelic variants in COL3A1. Novel compound heterozygous COL3A1 variants c.4223C>T p.F1408S in exons 50 was found.

The detailed pathogenesis underlying the COL3A1 mutation causing vEDS has not been elucidated so far. Our report novel compound heterozygous COL3A1 variants associated with Vascular Ehlers-Danlos

Syndrome, thereby expanding the associated molecular spectrum and emphasising the devastating nature of this multi-system disease, and hoping to shed light on the mechanism how COL3A1 mutation causes vEDS.

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