A Novel *COL3A1* c.2644G>T; p.(Gly882Cys) Variant in a Turkish Family with Vascular Ehlers-Danlos Syndrome

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Established Facts

- Vascular Ehlers-Danlos syndrome (vEDS) is caused by heterozygous mutation in the *COL3A1* gene at chromosome 2q32.

Novel Insights

- The authors present a family affected by vEDS and a novel *COL3A1* pathogenic variant that has not been defined before.

Keywords

Carotid artery · Iliac artery · Pathologic variation · Pseudoaneurysm · Spontaneous dissection · Vascular Ehlers-Danlos syndrome

Abstract

Vascular Ehlers-Danlos syndrome (vEDS) is an autosomal dominant disease, also known as EDS type IV. The estimated prevalence for all EDS varies between 1/10,000 and 1/25,000 with EDS type IV representing approximately 5–10% of the cases. The vascular complications may affect all anatomical areas, with a tendency toward arteries of large and medium diameter. vEDS diagnosis is a challeng-

ing process. Patients usually have different phenotypic features and are unaware of the diagnosis at the time of initial vascular complications. The authors report the case of a 39-year-old male patient with EDS type IV, who developed internal carotid artery dissection and was diagnosed with clinical findings, imaging modalities, and a novel pathogenic *COL3A1* variant.

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Vascular Ehlers-Danlos syndrome (vEDS) is an autosomal dominant disease that causes arterial dissection, pneumothorax, and intestinal and uterine rupture due to decreased production of type III procollagen. The average

Fig. 1. Brain MRI of the patient revealing acute dissection of the right internal carotid artery, 190 hematoma in the pseudo-lumen, and hyperintense on T1- and T2-weighted images.

Fig. 2. CT angiography examination after 2 weeks. Recanalization is present in the internal carotid artery and the lumen is clearly seen.

age at death is 48 years, and it is considered to be the most severe form of EDS [Malfait et al., 2017; Shalhub et al., 2019]. Some people with vEDS have a characteristic facial appearance, thin skin, and tissue fragility that could indicate the condition is present before there is a major complication. vEDS is caused by pathogenic variations in *COL3A1*, a gene that directs the synthesis of type III collagen that is a major component of blood vessels, bowel walls, and skin. The diagnosis is generally suspected through a clinical exam because other family members are affected or because of a bowel or arterial rupture and finally is confirmed by genetic testing. Herein, we present a family affected by vEDS and a novel pathogenic variant that has not been defined before [Germain, 2007; Jørgensen et al., 2014].

Patients and Methods

A 39-year-old male patient was admitted to the hospital with blurred vision of the right eye and right hemispheric headache. His symptoms had started 2 weeks before and partially resolved over time. He had no medical history, and he was not on any medication. There was no history of illegal drug use or alcohol consumption. Medical examination was normal. All pulses were palpable, lungs were clear with auscultation, and he had no murmur. His blood pressure was 110/80 mm hg and pulse rate was 80 bpm. His family history was remarkable with loss of his father at 41 due to intracranial aneurysm rupture and intracranial hemorrhagia as well as loss of 2 uncles at 42 and 45 years of age. Autopsy was performed on one of his uncles and De Bakey type 1 aortic dissection was diagnosed. Brain MRI and angiography of carotid and vertebral arteries showed dissection and total occlusion of the right internal carotid artery (Fig. 1). Enoxaparin, acetylsalicylic acid, and clopidogrel therapy was started. Two weeks later, control CT angiography was done and recanalization of the internal

Fig. 3. MR angiography examination after 6 months. The right internal carotid artery is evident in the MIP images.

Fig. 4. MR angiography of the lower extremities performed 2 years later because of left groin pain in the patient shows a dissected aneurysm at the level of the left common iliac artery distal bifurcation.

carotid artery was observed (Fig. 2, 3). Enoxoparin was stopped, and clopidogrel together with acetylsalicylic acid was continued [Imamura et al., 2001; Nasser et al., 2013]. All exons of the *ACTA2* gene were amplified and sequenced for Moya Moya disease. Any pathogenic variant was not detected. Two years later, he had left lumbar and lower quadrant abdominal pain. Abdominal imaging and MRI angiography showed a dissected aneurysm of the left common iliac artery of approximately 3.5 cm (Fig. 4). Treatment of the aneurismal segment was planned with surgery, and he underwent aneurysm resection and anastomosis [Mehta et al., 2012; Abayazeed et al., 2014]. On the third day, he experienced severe bleeding and was reoperated. The graft was functioning normally, but capillary bleeding was observed. After revision and blood transfusions, he recovered uneventfully. During follow-up, whole-exome sequencing was done to evaluate genetic alterations. Genomic DNA was isolated from peripheral blood then enzymatically fragmented, and regions of interest were selectively enriched using capture probes targeted against coding regions for whole-exome sequencing. Libraries were generated with Illumina compatible adaptors and sequenced on an Illumina platform. Relevant

variants reported in HGMD, ClinVar, and all variants with a minor allele frequency less than 1% in the gnomAD database were considered.

Results

A missense variation, c.2644G>T; p.(Gly882Cys), was found in heterozygous form in the *COL3A1* gene. Pathogenic variants in the *COL3A1* gene have been associated with aortic aneurysms. Next-generation sequencing result was confirmed by standard fluorescent dideoxy sequencing (Big Dye Terminator ver 3.1, 3500xl Analyzer, Applied Biosystems, CA, USA) as shown in Figure 5. There is no data for this variation in the literature and ClinVar. The c.2644G>T variation was determined to be disease-causing by using in silico prediction tools (Muta-

Fig. 5. Electropherogram of the patient.

tionTaster: disease causing, PolyPhen-2: probably damaging with a 0.97 score, SIFT: deleterious, MetaLR: deleterious with a 0.993 score). The patient was diagnosed with vEDS and Celiprolol 200 mg twice a day was started. During follow-up, serial CT and MRI scans were done, and the last 4 years were uneventful. In addition, 2 years ago, his female cousin (32-year-old female without any previous illness and with 1 uncomplicated pregnancy 2 years ago) – from his deceased uncle diagnosed with De Baeyer type 1 aortic dissection – had abdominal aortic dissection and rupture, and was treated with endovascular aneurysm repair. The same genetic variant was also found in her DNA sample. She is on celiprolol therapy and symptom free. Due to the same clinical history and the same heterozygous variant, it was considered as autosomal dominant.

Discussion

Approximately 98% of the vEDS cases are caused by a pathogenic variation in the *COL3A1* gene [Mehta et al., 2012; Nasser et al. 2013; Shalhub et al. 2019]. *COL3A1* (NG_007404.1) is located at chr2q31 and composed of 51 exons. Mutations in this gene cause aortic aneurysms, aortic dissection and rupture, gastrointestinal hemorrhage and perforation, uterine rupture, pneumothorax, hemothorax, and sudden death in some cases [Germain 2007; Nasser et al. 2013; Shalhub et al. 2019]. More than 200 mutations in the *COL3A1* gene have been described so far, all of which lead to synthesis of an abnormal type III collagen protein [Malfait et al., 2017]. Our patients showed a mutation in exon 38 of the *COL3A1* gene. This is the first time that this heterozygous missense variant, c.2644G>T; p.(Gly882Cys), is reported. Celiprolol is a guideline-recommended therapy and drug of choice in

vEDS. 400 mg/day is the recommended dose. We titrated Celiprolol to 400 mg/day in both of our patients. There is no accepted recommendation for frequency of imaging studies in vEDS patients. To avoid contrast-induced nephropathy and potential radiation hazard, we routinely perform doppler ultrasonography screenings at a 6-month interval. During a 1-year follow-up, no additional dissection was observed in our patients.

In conclusion, genetic screening is an important part of diagnosis in vEDS. Periodic screening and adequate therapy is essential for follow-up.

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Statement of Ethics

The study was approved by the local ethics committee and was performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

O.A. and V.S.H. designed the study, performed the experiments and analysis of the data, and wrote the manuscript.

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