Genotype-phenotype correlation in vascular Ehlers-Danlos syndrome: Novel duplication mutation of *COL3A1* gene in a large pedigree

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Introduction

Vascular Ehlers-Danlos syndrome (vEDS, EDS type IV, OMIM 130050) is a rare autosomal dominantly inherited connective tissue disorder characterized by generalized connective tissue fragility. Affected individuals are at risk of arterial rupture, aneurysm, or dissection; gastrointestinal perforation or rupture; and uterine rupture during pregnancy. The disease is caused by structural defects in the pro α 1(III) chain of collagen type III encoded by the *COL3A1* gene. Here we present a vEDS patient with complex severe clinical symptoms. We investigated genomic DNA sample of vEDS index patient with full-gene Sanger sequencing of *COL3A1* gene.

Material and methods

Phenotype of the index patient

A 42-year-old female patient was investigated with thin, translucent and slightly extensible skin, with highly visible subcutaneous vessels, characteristic facial appearance with blue sclera, gingival recession, small joints hypermobility, acrogeria, generalized vascular fragility, hemothorax, pes planus and scoliosis.

Pedigree analysis diagram

The pedigree analysis of the index patient (III/5.) suggest autosomal dominant inheritance and the vEDS phenotype appears three generation.

Methods

- Isolation of genomic DNA from peripheral blood leukocytes
- Full-gene Sanger sequencing of *COL3A1* gene (OMIM 120180) (CENTOGENE Rostock)
- In silico analyses (Exome Aggregation Consortium, Exome Sequencing Project, 1000 Genomes Browser)
- Family screening by Sanger sequencing (exon 43 of *COL3A1* gene)

Results

We detected a previously unreported heterozygous variant of *COL3A1* gene, **c.3124_3141dup (p.Ala1042_Gly1047dup)**. The duplication of that 18 bp causes duplication of 6 residues including two glycines within the triplehelical region (Ala-Pro-Gly-Ala-Pro-Gly) of the type III procollagen molecule.

Genotype-phenotype correlation study

Pedigree patient ID	Skin manifestation	Extracutaneous manifestations	Phenotype	Genotype
I/2.	-	-	-	wild type/wild type
II/5.	-	-	-	wild type/wild type
II/6.	Thin, translucent skin; acrogeria	Joint hypermobility; facial appearance; blue sclera	vEDS	Heterozygous c.3124_3141dup/wild type
III/4.	-	-	-	wild type/wild type
III/5.	Thin, translucent skin; extensive bruising; acrogeria	Arterial rupture; hemothorax; facial appearance; blue sclera; gingival recession; joint hypermobility; pes planus; scoliosis	vEDS	Heterozygous c.3124_3141dup/wild type
III/6.	Thin, translucent skin; extensive bruising; acrogeria; psoriasis	Intrapartum uterine rupture; facial appearance; blue sclera; joint hypermobility; Scoliosis	vEDS	Heterozygous c.3124_3141dup/wild type
III/10.	-	-	-	wild type/wild type
IV/1.	Thin, translucent skin	Blue sclera; facial appearance; pes planus; scoliosis	vEDS	Heterozygous c.3124_3141dup/wild type

Conclusions

The novel duplication mutation co-segregated with the vEDS-phenotype in the large family of the index patient. This previously unpublished insertion in the *COL3A1* gene expands the spectrum of mutations underlying vEDS and helps to perform genetic counselling.