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A novel *COL5A1* mutation in a classic type of Ehlers-Danlos syndrome

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Introduction

The Ehlers-Danlos syndrome(EDS) is a hereditary connective tissue disorder characterized by skin hyperextensibility, joint hypermobility, and vascular fragility.[1)] The EDS is divided into 13 types according to the 2017 International Classification of the Ehlers-Danlos syndrome. Classical EDS (cEDS) is characterized by joint hypermobility, skin hyperextensibility, and atrophic scar.[2)] In more than 90% of patients with cEDS, autosomal dominant collagen V mutations have been identified, and approximately half are null- allele mutations resulting in *COL5A1* haploinsufficiency. [3)]

Case report

Case

A 18 year-old Japanese female who is the second child of healthy and nonconsanguineous parents. Her growth and development were normal. She had played volleyball and dislocated her left shoulder, after that she suffered from recurrent dislocation and underwent surgery. She also noticed loose skin. Her father and sister showed a similar clinical manifestation with a stretchable skin.

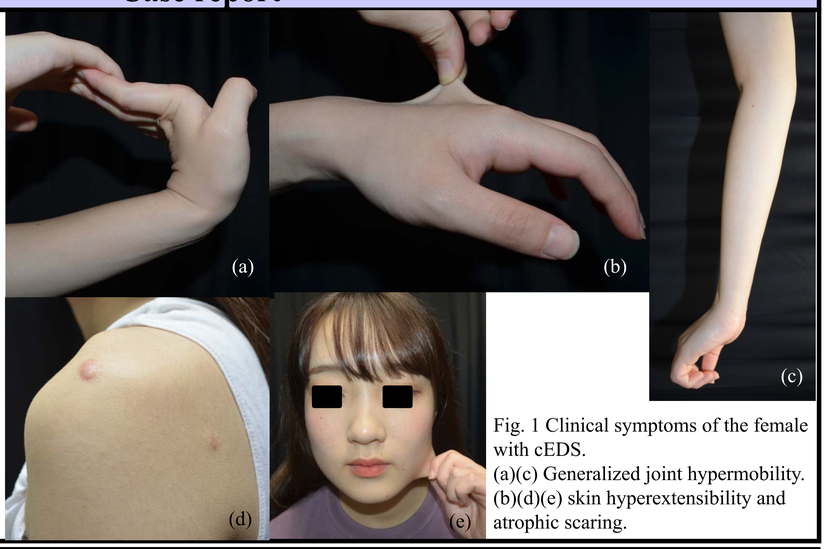

Fig. 1 Clinical symptoms of the female with cEDS.
(a)(c) Generalized joint hypermobility.
(b)(d)(e) skin hyperextensibility and atrophic scaring.

Molecular analysis

Each genomic DNA was purified from blood samples of the family. For molecular diagnosis, target exome sequencing was performed by MLPA (Multiplex Ligation- dependent Probe Amplification). Evaluation of potential pathogenicity of detected missense mutation was conducted using PolyPhen-2, Mutation testing.

Results

The 2017 International Classification of the cEDS

- Major criteria
  1. Skin hyperextensibility and atrophic scarring
  2. Generalized joint hypermobility(GJH)
- Minor criteria
  1. Easy bruising
  2. Soft, doughy skin
  3. Skin fragility (or traumatic splitting)
  4. Molluscoid pseudotumors
  5. Subcutaneous spheroids
  6. Hernia (or history thereof)
  7. Epicanthal folds
  8. Complications of joint hypermobility (eg, sprains, luxation/subluxation, pain, flexible flatfoot)
  9. Family history of a first degree relative who meets clinical criteria
- Minimal criteria suggestive for cEDS:
  Major criterion (1): skin hyperextensibility and atrophic scarring
  Plus
  -Either major criterion (2): GJH
  - And/or: at least three minor criteria

- Confirmatory molecular testing is obligatory to reach a final diagnosis.

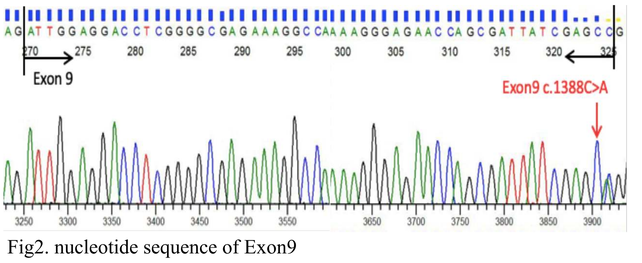

Fig2. nucleotide sequence of Exon9

MLPA revealed c. 1388C>A (p. P463Q) at exon9, which has not been reported previously, and PolyPhen-2 and Mutation testing showed it's a pathogenic mutation. The same variant was detected in her father and sister, but intra-familial phenotypic heterogeneity was observed.

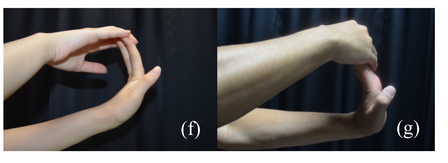

Fig3. The carrier, (f) sister and (g) father, have no clinical symptoms.

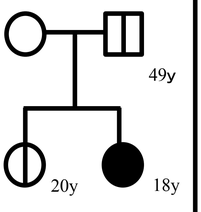

Fig4. Family pedigree

Discussion

In the most recent updates of the LOVD EDS Variant Datebase lists, 224 different mutations of *COL5A1* ware reported. Specifically, 64 (approximately 28 %) are frame shifts, 52 (23 %) are substitution (August, 2019). This results in a deficiency or structural defect in collagen V protein, which acts as a regulator of fibrillogenesis in dermis, tendons, ligaments, bones, blood vessels, and cornea.[4)] We report a family with a cEDS phenotype and the *COL5A1* c. 1388C>A (p. P463Q) mutation.

Conclusion

The mutation has not been reported previously. The same variant was detected in the family, but intra-familial phenotypic heterogeneity was observed. In some cases, adequate evaluation and classification of EDS patients based only on clinical features may be difficult.

1) Steinmann, et al. New York: Wiley Liss. 431-532.
2) 2017 International Classification of the Ehlers-Danlos syndrome
3) Symoens, et al. Hum mutat 2012; 33(10)
4) Ritelli M, et al. Orphanet J Rare Dis 2013; 8; 58.

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