Cutis Laxa Type 2E - Report of a New Case Highlighting Hypotonia as a Major Feature

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BACKGROUND

Cutis laxa syndrome type 2E (CL2E) is a very rare disorder caused by biallelic pathogenic variants in the latent transforming binding growth factor β1 (*LTBP1*) gene. *LTBP1* truncating variants may induce a defective binding of LTBP1 protein to the extracellular matrix components (ECM) and dysregulate the transforming growth factor β (TGFβ) signaling. CL2E patients share some common features to all cutis laxa syndromes such as cutis laxa and skin hyperextensivity. However, CL2E patients are characterized by short stature and skeletal abnormalities. To our knowledge, eight clinical cases from four different families have been reported so far. We present the case of a two-year-old male followed and assessed since birth for hypotonia. Hyperlaxity and cutis laxa were only noticeable later. Transmission electronic microscopy (TEM) on proband-derived dermal fibroblasts was performed to improve the phenotype-genotype correlation.

CASE REPORT

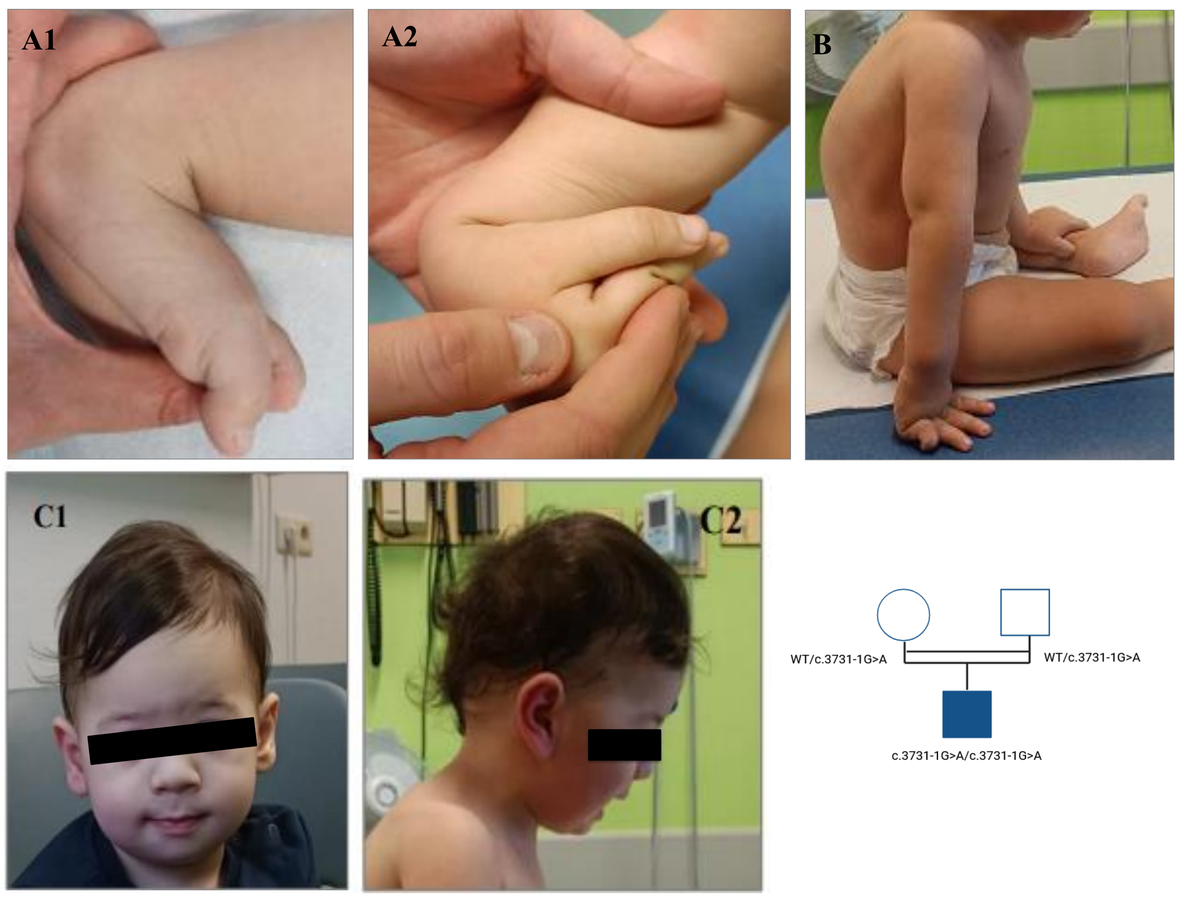

Figure 1 – Features at two years of age and familial history. Clinical examination showing joint hyperlaxity of the left foot (A1), and the right hand (A2), lumbar kyphosis and mild loose skin around the abdomen (B). Dysmorphic features were observed (C1, C2) such as a broad forehead, a bitemporal narrowing, large ears, a bilateral epicanthus with horizontal palpebral fissures, a bulbous nasal tip, a long philtrum and a thin upper lip and drooping cheeks. The patient is the first affected in the family and the first born from a consanguineous couple of Turkish origin.

The pregnancy was marked by the suspicion of a bilateral congenital talipes equinovarus. A varus was confirmed after birth on the left foot, and a talus foot on the right side. At birth, the patient was eutrophic with a normal birth height and weight. Axial and peripheral hypotonia was major. In the first days of life a kyphotic attitude was present. Metabolic and genetic work-up, including a trio-WES filtered on developmental delay disorders, were non contributive.

The patient showed no skin abnormalities nor hyperlaxity until the age of eight months. At the age of one year, a pectus excavatum started to become apparent. Clinical examination at the age of two (**Fig. 1**), including dysmorphic features, showed noticeable loose skin, cutis laxa, and joint hyperlaxity. Motor development showed slow progress due to the hyperlaxity.

Other features were a mild arytenoid malacia associated with a stridor, and a gastro-oesophageal reflux. Minor feeding difficulties were present.

WES analysis performed in research settings showed a novel homozygous likely pathogenic variant **c.3731-1G>A or p.(?)** in ***LTBP1***.

- This is the first intronic variant reported in the literature.
- This splice site variant is predicted to result in the skipping of a single exon and to not undergo nonsense-mediated decay (NMD).
- It is anticipated to alter only one of the last calcium EGF binding domain of the LTBP1 protein, which may explain the milder phenotype observed in our patient.

Our patient presented mild and likely delayed typical features of Cutis Laxa type 2E in comparison to previous patients reported in the literature. He showed no cardiac malformation, no brachydactyly, syndactyly nor clinodactyly, and most of all no short stature. TEM was performed and compatible with Cutis Laxa (**Fig. 2**). This served as an additional criterion for the pathogenicity of the variant and supported a strong phenotype-genotype correlation.

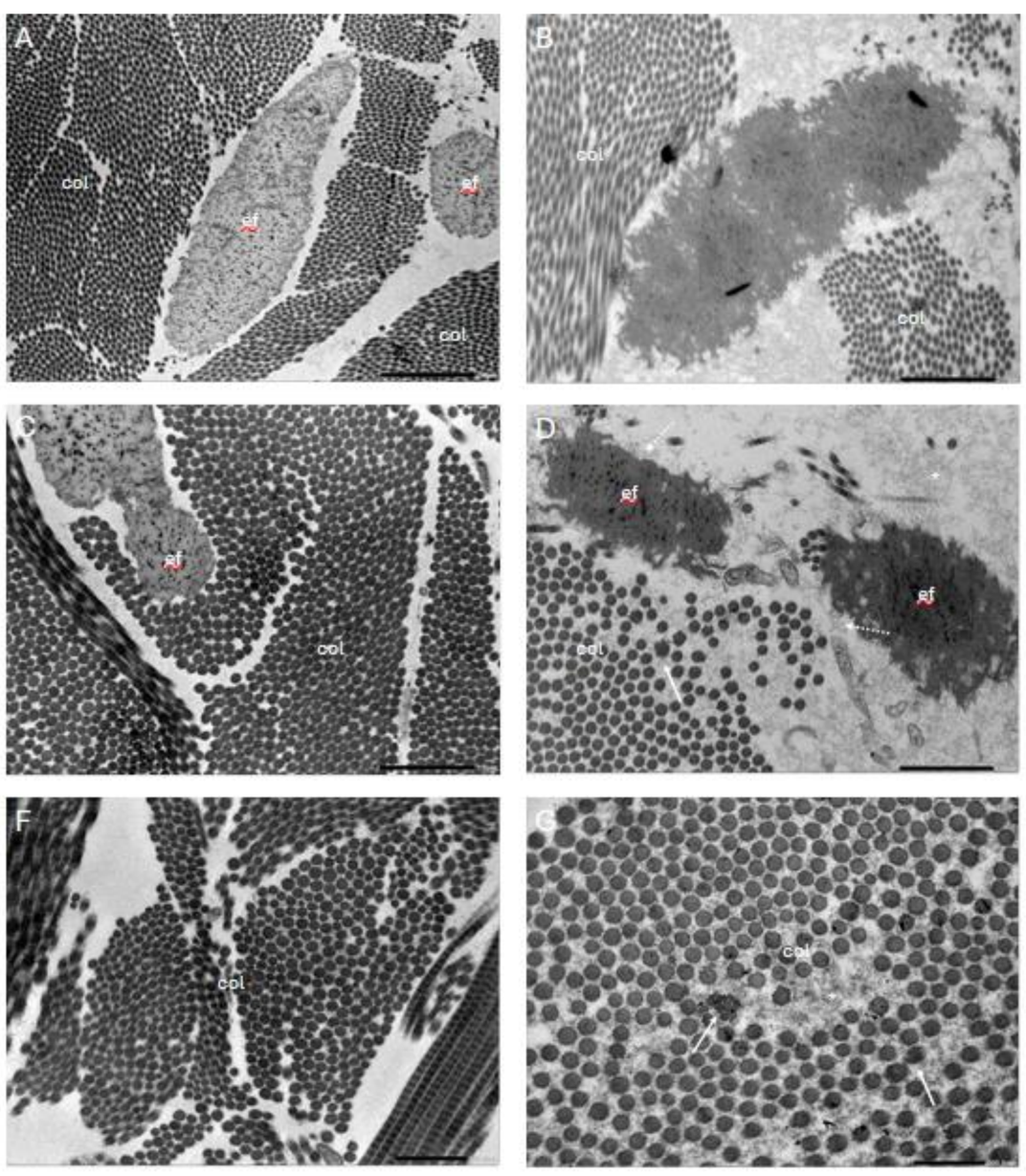

Figure 2 – TEM performed on proband derived-dermal fibroblasts (B, D, G) compared to a control (A, C, F). Patient's analyses show a mild fragmentation of elastin fibers and an interfibrillar spaces filled with amorphous granulofilamentous deposits. Abbreviations: *col*: collagene ; *el*: elastin.

CONCLUSION

- CL2E is an extremely rare disorder characterized by skin hyperextensivity, cutis laxa, skeletal abnormalities, occasionally cardiac malformation, and potentially other rare malformations. We report a new patient with a novel *LTBP1* variant and hypotonia as the major feature. This extends the phenotype and genotype of CL2E disorder.
- CL2E should be considered as a very rare cause of neonatal hypotonia.
- Diagnosis of a milder form of CL2E, such as observed in our patient, is challenging due to a non-specific initial clinical presentation and progressively apparent and more discriminant skin and joints features.
- A long-term follow-up of the patient is crucial to better understand the natural course of the disease.

References.

1 - Pottie L, Adamo CS, Beyens A, Lütke S, Tapaneeyaphan P, De Clercq A and al. *Bi-allelic premature truncating variants in LTBP1 cause cutis laxa syndrome*. Am J Hum Genet. 2021 Jun 3;108(6):1095-1114.

2 - Beyens A, Boel A, Symoens S, Callewaert B. Cutis laxa: *A comprehensive overview of clinical characteristics and pathophysiology*. Clin Genet. 2021 Jan;99(1):53-66.

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