

Insights into TNXB-Related Classical-Like Ehlers–Danlos Syndrome: A Study of Polish Patients

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Objective: Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders with diverse clinical and genetic backgrounds. Classical-like EDS (cEDS, OMIM 606408) is an extremely rare autosomal recessive subtype caused by biallelic variants in *TNXB*. Fewer than 100 cases have been described worldwide. This study aimed to identify and characterise *TNXB*-related variants in two Polish patients with clinical features suggestive of cEDS.

Methods: Two male patients, aged 13 and 14 years, underwent comprehensive genetic testing, including next-generation sequencing (NGS) using a connective tissue gene panel, Multiplex Ligation-dependent Probe Amplification (MLPA), and Sanger sequencing. Family segregation analysis was performed to confirm compound heterozygosity.

Results: NGS and confirmatory analyses identified compound heterozygous *TNXB* variants: c.[7222C>T];[8780T>C], p.[Pro2408Ser];[Ile2927Thr] in Patient 1, and c.[5947_5948delinsTT];[8300C>T], p.[Glu1983Leu];[Thr2767Ile] in Patient 2. Both variants were located in non-homologous *TNXB* exons, minimising the risk of misinterpretation due to pseudogene sequences. The clinical presentations of both patients were consistent with the major diagnostic criteria for classical-like EDS.

Conclusion: This report presents the first genetically confirmed Polish patients with a classical-like form of Ehlers–Danlos syndrome, expanding the known clinical and molecular spectrum of *TNXB*-related EDS. Our findings reinforce the notion that heterozygous *TNXB* variants, particularly frameshift alterations, may occasionally contribute to mild connective tissue manifestations in carriers, underscoring the complexity of genotype–phenotype correlations in this rare disorder.

Keywords: Ehlers–Danlos syndrome, *TNXB*, connective tissue disorders, genetic testing, next-generation sequencing, classical-like EDS

Introduction

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of heritable, non-inflammatory connective tissue disorders. The 2017 International Classification of EDS recognises 13 subtypes caused by pathogenic variants in 19 genes. These genes encode structural proteins critical for connective tissue integrity, including various types of collagen, proteins involved in collagen metabolism, and molecules that help maintain connective tissue stability. Among EDS subtypes are the more common classical (cEDS), vascular EDS (vEDS), and the hypermobile (hEDS) and rare types, eg, classical-like EDS (cLEDs) (OMIM 606408).^{1,2}

Classical-like EDS is an extremely rare type of EDS, up to now, less than 100 patients have been described^{3–9} cLEDs is an autosomal recessive disorder caused by homozygous or compound heterozygous mutations in the *TNXB* gene (NM_019105.6). The major criteria of cLEDs include hyperextensible, velvety skin without atrophic scarring; generalised joint hypermobility (GJH), which may or may not include recurrent dislocations; and a tendency for easy bruising or spontaneous ecchymoses. The minor criteria include: foot deformities, leg oedema, mild proximal and distal muscle

weakness, axonal polyneuropathy, hand and foot muscle atrophy, acrogeric hands, mallet finger(s), clinodactyly, brachydactyly, vaginal/uterus/rectal prolapse. To meet the diagnostic criteria for cEDS, a patient must meet all three major criteria and have a family history compatible with autosomal recessive inheritance.^{1,2,10}

The *TNXB* gene, mapped on chromosome 6 (6p21.33-p21.32), encodes the extracellular matrix protein (ECM) tenascin-X. The gene is located near the pseudogene *TNXA*, which shares over 97% sequence similarity with the 3' end of *TNXB* (exons 32–44, excluding exon 35), making variant detection challenging. The high homology between these genes can lead to non-allelic homologous recombination, resulting in hybrid genes and complicating genetic analysis.^{6–8}

Tenascin-X, a protein encoded by the *TNXB* gene, is a member of the tenascin family of extracellular matrix glycoproteins, which are crucial for tissue architecture and function. Tenascin-X is primarily expressed in connective tissues and is critical for ECM organisation and cellular interactions. Biochemically, tenascin-X is a large, modular protein with several domains, including fibronectin-type III repeats, which enable it to bind to various ECM components, such as collagen and elastin. These interactions help organise and stabilise the ECM, which is essential for the mechanical properties of connective tissues, including elasticity and tensile strength.^{5,6,11}

One of the primary roles of tenascin-X in the ECM is to modulate collagen fibril assembly. It interacts with collagen types I and III, facilitating proper alignment and stability of collagen fibres.

This interaction is fundamental to the structural integrity of tissues and organs such as the skin, joints, and blood vessels. Additionally, tenascin-X influences elastin fibres, which provide elasticity to tissues, allowing them to return to their original shape after stretching. This function is crucial in tissues such as the skin and blood vessels, which must withstand mechanical stress.^{7,12,13}

Tenascin-X also contributes to ECM remodelling by interacting with proteoglycans and regulating the activity of matrix metalloproteinases (MMPs). This regulation facilitates ECM remodelling during processes such as tissue repair and wound healing, where the ECM must remain both adaptable and structurally stable to support proper tissue function and integrity.^{12,13}

The diagnosis of classical-like Ehlers–Danlos syndrome (cEDS) is based on clinical evaluation in combination with molecular testing. This includes DNA sequencing techniques such as Next-Generation Sequencing (NGS), Sanger sequencing, and Multiplex Ligation-dependent Probe Amplification (MLPA), which are used to identify homozygous or compound heterozygous mutations in the *TNXB* gene.

Materials and Methods

The study included two patients (two males, aged 13–14 years) with a clinically established diagnosis of Ehlers–Danlos syndrome with suspicion of its classical-like type. The study was approved by the local Bioethics Committee of Collegium Medicum, Nicolaus Copernicus University. Institutional approval covered both the conduct of the study and the publication of the case details. Written informed consent for genetic testing and for publication of clinical data was obtained from the patients' parents. The patients underwent Next-Generation Sequencing (NGS) using a targeted connective tissue gene panel, followed by Multiplex Ligation-dependent Probe Amplification (MLPA) analysis. NGS findings were confirmed by Sanger sequencing. Upon identification of *TNXB* mutations, family segregation analysis was performed to determine whether the variants were located *in cis* or *in trans*. The clinical characteristics of the patients and their pedigrees are presented below.

Patient I

The 13-year-old boy fulfilled the cEDS major criteria: hyperextensible skin with no atrophic scarring, generalised joint hypermobility with no dislocations, and easy bruising. Additionally, the patient presented with one minor criterion: brachydactyly. Other symptoms included a gothic palate, kyphosis, valgus foot, inflammatory bowel disease, multiple food intolerances, tachycardia, microalbuminuria, MCAS (mast cell activation syndrome) (diagnosis not confirmed), and non-EDS-related asthma.

The patient is the only live-born child of non-consanguineous parents. The mother had a history of four previous pregnancy losses, all occurring in the early weeks of gestation due to unknown causes. He was born at term via cesarean

section (due to a foetal bradycardia) with a birth weight of 2890g and length of 53cm. No abnormalities in psychomotor development were observed; the child began walking around 12–13 months. The patient underwent rehabilitation at the age of 7 due to foot valgus.

The patient's parents were carriers of heterozygous *TNXB* variants; the mother had c.8780T>C, and the father had c.7222C>T. Parents did not present any symptoms of cEDS. The mother was diagnosed with hypothyroidism. The patient's pedigree is presented in Figure 1.

Patient 2

The 14-year-old boy met all three major criteria for cEDS: hyperextensible skin without atrophic scarring, generalised joint hypermobility (without dislocations), and easy bruising. Additional EDS symptoms included a gothic palate, scoliosis, flat feet, and muscle hypotonia. Other clinical data included: ADHD and autism spectrum disorder (ASD).

The patient was born to a non-consanguineous marriage as the first child from the first pregnancy. He was delivered preterm at 35 weeks of gestation, with a birth weight of 2390 g and a length of 48 cm. No abnormalities in psychomotor development were observed. He began walking at approximately 14 months of age. Rehabilitation was initiated from the first weeks of life due to muscle hypotonia.

The patient's mother was diagnosed with hypothyroidism and exhibited mild joint hypermobility. The father did not present any symptoms of cEDS. The patient's pedigree is presented in Figure 2.

Methods

Whole genomic DNA was extracted from nucleated cells using silica gel column methods according to the manufacturer's protocol (Qiagen) and Prepito TM for sequencing (NGS and Sanger), as well as for the MLPA assay.

A targeted next-generation sequencing was performed using a targeted multigene custom panel including genes *ADAMTS2*, *AEBP1*, *ATP7A*, *B3GALT6*, *B4GALT7*, *BGN*, *C1R*, *C1S*, *CHST14*, *COL12A1*, *COL1A1*, *COL1A2*, *COL2A1*, *COL3A1*, *COL5A1*, *COL5A2*, *CRTAP*, *DSE*, *FBN1*, *FKBP14*, *FLNA*, *P3H1*, *PLOD1*, *PRDM5*, *SLC39A13*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2*, *TNXB*, *ZNF469*. The sequencing library preparation was performed using SureSelectXT Custom (Agilent). The sample was sequenced with Illumina technology on a MiSeq sequencer with 2 ×

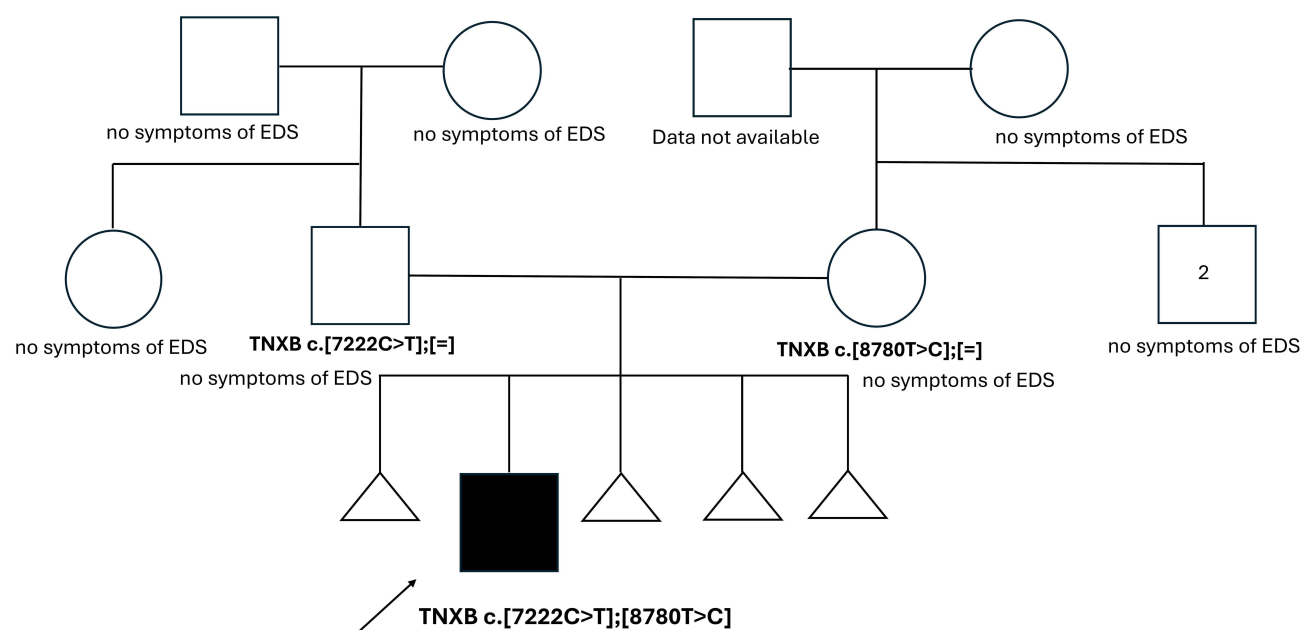


Figure 1 Pedigree of patient 1. The arrow indicates the proband; the black symbol shows a patient with cEDS; the white symbol shows a person without clinical features of cEDS; the circle represents a female; the square represents a male; and the triangle represents a pregnancy loss. *TNXB* variants identified in tested family members are listed under their pedigree symbols.

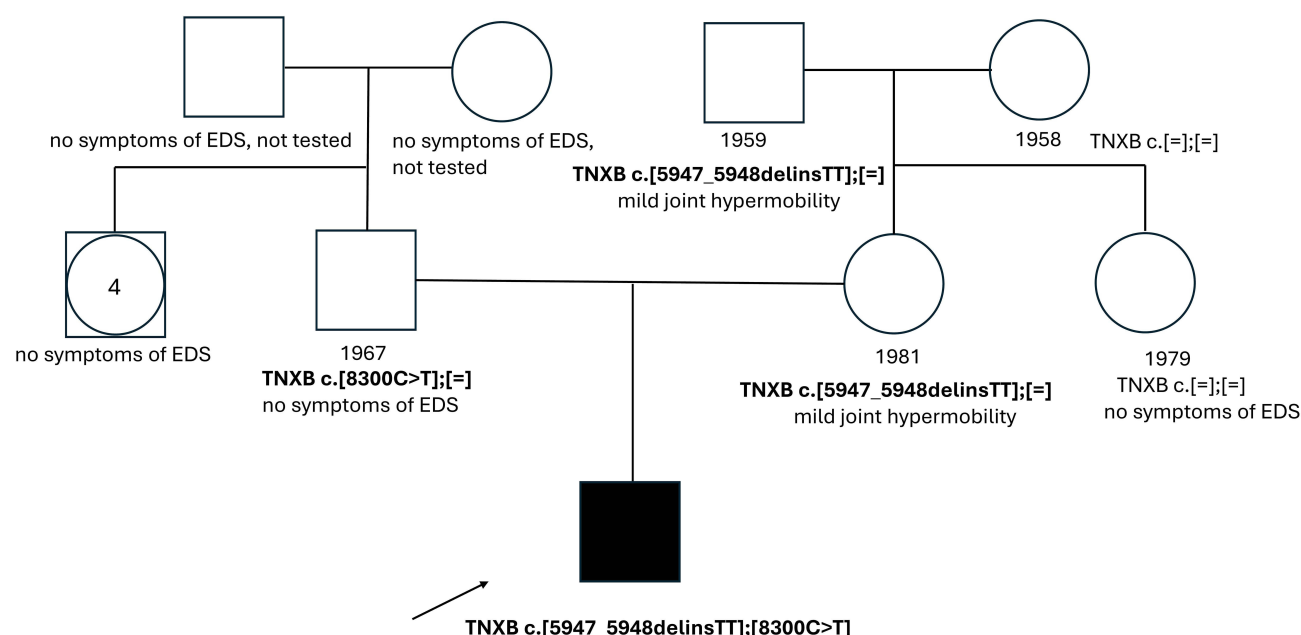


Figure 2 Pedigree of patient 2. The arrow indicates the proband; the black symbol shows a patient with cEDS; the white symbol shows a person without clinical features of cEDS; the circle represents a female; and the square represents a male. *TNXB* variants identified in each tested family member are listed under their pedigree symbols.

75 bp reads. Demultiplexing of the sequencing reads was performed with Illumina's bcl2fastq2 v2.19.0. Adapters were trimmed with Skewer version 0.2.9.¹⁴ BWA-MEM aligned the reads to the GRCh37/hg19 reference sequence.¹⁵ Read duplicates were removed using Picard 2.18.2 (<http://broadinstitute.github.io/picard/>). Variant call was performed with GATK v 4.0.3.0 HaplotypeCaller^{16,17} and FreeBayes (v1.2.0-2-g29c4002).¹⁸ Variants have been annotated with databases (i) VEP97:¹⁹ annotations Sift, Polyphen2, (ii) dbNSFPv4.0:²⁰ annotations MutationAssessor, MutationTaster, DANN, FATHMM, (iii) ESP6500, (iv) GnomAD, (v) dbSNP, (vi) ClinVar and (vii) 1000 Genomes.

Sanger Sequencing

Single-nucleotide variants (SNV), small deletions/insertions and familial segregation were revealed by Sanger sequencing on a 3130/3130XL Genetic Analyser (Applied Biosystem) using a BigDye Direct Cycle Sequencing Kit, specific primers and a BigDye XTerminator Purification Kit (Thermo Fisher Scientific), according to the manufacturer's protocol.

MLPA

Copy number variations (CNVs) detected in NGS were confirmed by MLPA using a SALSA MLPA Kit P155-D2 (MRC-Holland, Amsterdam, Netherlands). The kit includes 15 probes for exons 1, 2, 3, 5, 8, 11, 12, 14, 15, 16, 19, 23, 26, 31 and 35 of the *TNXB* gene. Electrophoresis was conducted on a 3130/3130XL Genetic Analyser (Applied Biosystem), and the data were analysed with GeneMarker (SoftGenetics).

Results

Genetic testing for *TNXB* gene mutations was conducted in patients with clinically diagnosed cEDS and their families. The analyses revealed compound heterozygous variants in the *TNXB* gene among the tested patients. No structural variants were detected using MLPA.

Patient 1 was a compound heterozygote carrier. *TNXB* c.[7222C>T];[8780T>C], p.[Pro2408Ser][Ile2927Thr]. *TNXB* variant c.7222C>T was not recorded in the dbSNP and gnomAD databases; population frequency was not determined. Variant *TNXB* c.8780T>C was described in dbSNP with the number rs781570593 and was deposited in the gnomAD database with a frequency of 0.00003 (in the European non-Finnish population). Neither variant was deposited in the LOVD database, and neither has been described in cEDS patients. According to the sequence (NM_019105.6), variants

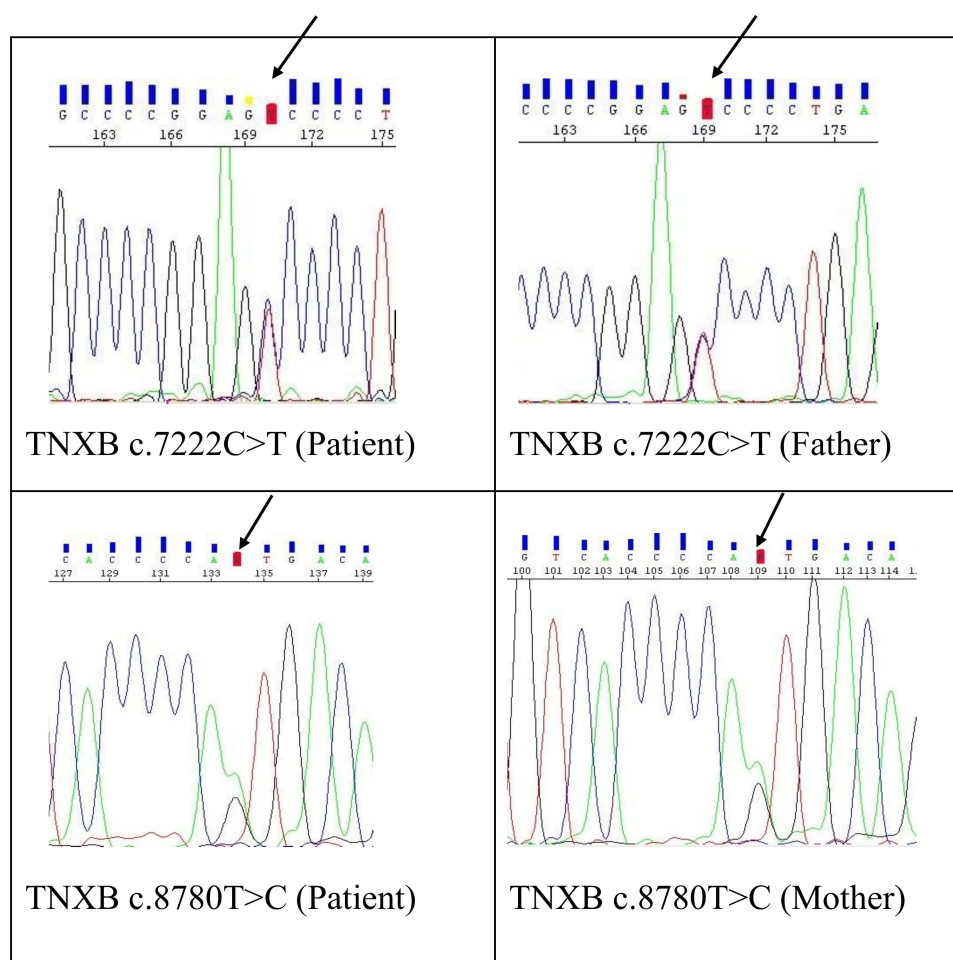


Figure 3 Sanger sequencing results of the patient and his parents. An arrow indicates the mutation site.

were localised in exons 21 and 25, respectively. Both patients' parents were carriers of single variants: the father carried *TNXB* c.7222C>T, and the mother carried *TNXB* c.8780T>C; neither parent presented any symptoms of cIEDS. This result confirms the patient's carrier status and determines the trans configuration of variants on both alleles. Electrophoregrams from Sanger sequencing are shown in [Figure 3](#).

Patient 2 harboured a compound heterozygous variant. *TNXB* c.[5947_5948delinsTT];[8300C>T], p.[p.Glu1983Leu];[p.Thr2767Ile]. The first change, c.5947_5948delinsTT, was not recorded in dbSNP or gnomAD. Population frequency was not evaluated. The mother and maternal grandfather were carriers of c.5947_5948delinsTT, a heterozygous variant, and exhibited mild joint hypermobility. Testing for a potential second mutation in the *TNXB* gene or pathogenic variants in any gene associated with Ehlers–Danlos syndrome or other connective tissue disorders revealed negative results. The patient's paternal grandmother and aunt were not carriers of c.5947_5948delinsTT and did not present any symptoms of cIEDS.

The second alteration, c.8300C>T, was set in dbSNP with the number rs201649053 and the gnomAD database with a population frequency of 0.0001 (in the European non-Finnish population). It was not placed in the LOVD registry. Segregation analysis revealed that the father was a carrier of the c.8300C>T variant with no symptoms of cIEDS. Electrophoregrams from Sanger sequencing are shown in [Figure 4](#).

Clinical characteristics and comparison among the patients are described in [Table 1](#).

Discussion

This study presents the first Polish patients clinically diagnosed with cIEDS, whose diagnoses were subsequently confirmed by the identification of pathogenic *TNXB* gene variants. Analysis of the inheritance patterns provides

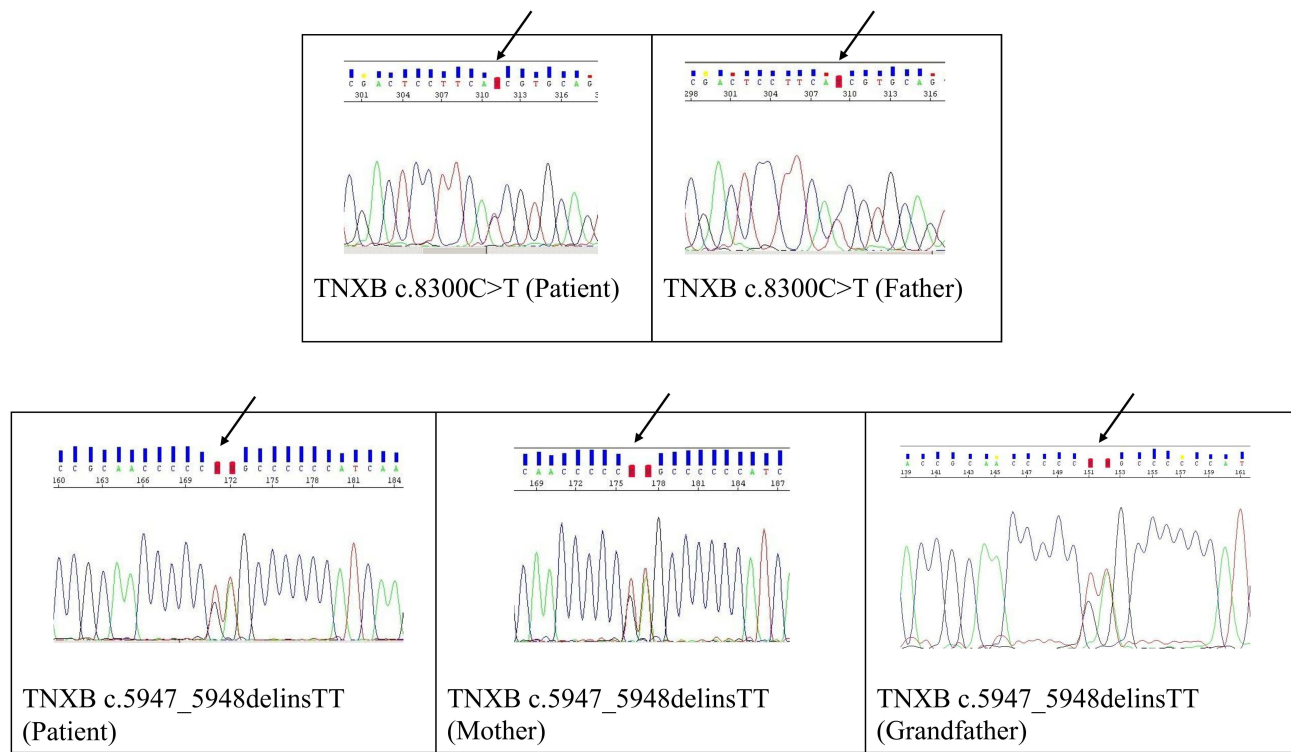


Figure 4 Sanger sequencing results for the patient, his parents, and his grandfather. An arrow indicates the mutation site.

additional insight into this condition’s clinical variability and genetic background. Diagnosis of cEDS is challenging due to the TNXA pseudogene, which shares high sequence similarity with TNXB. This homology increases the risk of diagnostic errors, particularly in Next-Generation sequencing, Sanger sequencing, and MLPA. However, in our study, the identified TNXB variants were located in non-homologous exons, which minimised the risk of misdiagnosis.^{5,7}

The identified variants expand the mutational spectrum associated with cEDS. All patients carried TNXB mutations previously unreported in cEDS, including missense and frameshift variants. Individuals described in earlier studies originated from various populations and did not exhibit recurrent, population-specific variants. Similarly, Polish patients — despite the small cohort — show no evidence of recurrent mutations or population-related patterns. Moreover, no recurrence was observed in the exons affected by mutations, further supporting previous findings that did not identify mutation hotspots linked to specific phenotypic features or population backgrounds.^{3,5,6,8,9}

In Patient 1, a compound heterozygous genotype in the TNXB gene — c.7222C>T (p.Pro2408Ser) and c.8780T>C (p.Ile2927Thr) — was identified, with both variants located in non-homologous exons (21 and 25). The c.7222C>T variant was absent from major population databases, including dbSNP and gnomAD. In contrast, c.8780T>C was reported in dbSNP (rs781570593) and found in gnomAD at a very low frequency (0.00003 in the non-Finnish

Table 1 Clinical Features of All Tested Patients

Patient	Hyperextensible Skin	Generalised Joint Hypermobility	Easy Bruising	Other Symptoms
P1	Yes	Yes (without dislocations)	Yes	Gothic palate, kyphosis, valgus foot, inflammatory bowel disease, multiple food intolerances, tachycardia, microalbuminuria, MCAS (diagnosis not confirmed), and non-EDS-related asthma
P2	Yes	Yes (without dislocations)	Yes	A gothic palate, scoliosis, flat feet, muscle hypotonia, ADHD and autism spectrum disorder (ASD)

European population). Neither variant was recorded in the LOVD database, and neither has been previously associated with cEDS. Segregation analysis confirmed that each variant was inherited from a different asymptomatic parent, establishing the trans configuration and supporting a recessive mode of inheritance. Although these variants have not been functionally characterised, their rarity in the general population, presence in functionally relevant exons, and consistency with the patient's clinical presentation suggest a likely contribution to the disease. This case underscores the importance of considering unreported *TNXB* variants in patients with a compatible phenotype and highlights the role of segregation analysis in supporting their clinical significance.

In the case of patient 2, a compound heterozygous variants in the *TNXB* gene were found: c.[5947_5948delinsTT]; [8300C>T], located in exons 17 and 24, respectively. The c.5947_5948delinsTT variant represents a novel frameshift mutation predicted to result in a truncated protein and likely undergo nonsense-mediated mRNA decay (NMD). This mechanism is consistent with previous reports suggesting that frameshift variants leading to NMD are associated with more severe phenotypes of cEDS patients.⁶ In contrast, the c.8300C>T variant is a missense substitution observed at low frequency in population databases and is of uncertain clinical significance (VUS). The variants were confirmed to be *in trans*, consistent with the expected autosomal recessive inheritance pattern of cEDS.

Interestingly, the patient's mother and maternal grandfather, both heterozygous carriers of the c.5947_5948delinsTT frameshift variant, presented with mild joint hypermobility. No additional pathogenic variants in *TNXB* or other genes associated with connective tissue disorders were identified. At this stage of the study, it remains unclear whether the mild phenotype observed in heterozygous relatives results from haploinsufficiency, as previously reported in some individuals with heterozygous *TNXB* mutations, or reflects unrelated etiologies beyond the scope of this study. It is also possible that an undetected pathogenic variant on the second allele (eg, a deep intronic mutation not captured by routine diagnostic methods) may contribute to the phenotype.^{4,21}

The patient's father, a carrier of the c.8300C>T missense variant, did not exhibit any signs or symptoms consistent with EDS. Similar observations were made in the families of Patients 1 and 2, whose heterozygous parents also harboured *TNXB* missense variants without phenotypic expression. Yamaguchi et al reported comparable findings, describing mild phenotypes (including skin involvement and joint hypermobility) in heterozygous relatives of cEDS patients with frameshift mutations; however, detailed clinical data were not available for all affected family members.⁹

These findings together highlight the potential pathogenic role of frameshift variants leading to NMD, such as c.5947_5948delinsTT, and show the variable expressivity and incomplete penetrance seen in heterozygous carriers.⁶ Due to the small sample size, it is not easy to draw definitive conclusions. Further research is needed to clarify the role of *TNXB* frameshift mutations in the pathogenesis of mild connective tissue symptoms.

Conclusion

This study presents the first Polish patients diagnosed with classical-like Ehlers–Danlos syndrome (cEDS), contributing to the growing knowledge on the disorder's clinical variability and genetic basis. The identification of variants in non-homologous *TNXB* exons reduces the risk of diagnostic misinterpretation caused by *TNXA* pseudogene homology, consistent with previous findings.

Importantly, our results support the observation that heterozygous *TNXB* mutations — particularly frameshift variants — may be associated with mild connective tissue symptoms in some patients and their relatives. This observation is consistent with previous reports describing mild phenotypes in patients carrying heterozygous *TNXB* variants.

Despite many years of molecular investigations of EDS patients in our laboratory — including *TNXB* sequencing and MLPA analysis — only two individuals with compound heterozygous pathogenic *TNXB* variants have been identified in our cohort. This underscores the extreme rarity of cEDS and the challenges in its genetic diagnosis.

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Disclosure

The authors declare no conflicts of interest related to this work.

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