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Polydactyly and syndactyly linked to GLI3 and TBX5 mutations: A pediatric case report

R. Leonardi[a], G. Pellino[b], E. Floridia[c], M. Lo Bianco[a], M. Ruggieri[d], SY. Cho[e], V. Pavone[f], P. Pavone[d,g,*,1], A. Polizzi[d,h,1]

[a] Postgraduate Training Program in Pediatrics, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[b] Postgraduate Training Program in Genetics, Department of Clinical and Molecular Biomedicine Ingrassia, University of Catania, Italy
[c] School of Medicine, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[d] Unit of Clinical Pediatrics, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[e] Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[f] Department of General Surgery and Medical Surgical Specialties, Section of Orthopedics and Traumatology, A.O.U. Policlinico, University of Catania, Via Santa Sofia 78, Catania 95123, Italy
[g] Unit of Catania, Institute for Biomedical Research and Innovation, National Council of Research, Catania, Italy
[h] Department of Educational Science, University of Catania, Catania 95100, Italy

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ABSTRACT

Background: Polydactyly and syndactyly, which are commonly encountered congenital limb deformities, rarely occur together and are linked with significant genetic mutations. This report sheds light on a unique co-presentation involving mutations in both the GLI3 and TBX5 genes, offering a deeper understanding of the genetic interactions that may influence limb development. This case report is important to increase our knowledge on genetic bases of limb malformations.
Case presentation: We report the case of an 8-month-old boy, born to non-consanguineous parents, presenting with both polydactyly and syndactyly in his limbs, in particular, complete syndactyly between the third to fifth fingers and post-axial polydactyly of the feet. His father showed a similar phenotype. Genetic testing identified a pathogenic heterozygous variant in the GLI3 gene (c .3762 T > A, p.(Tyr1254 *)) and a variant of uncertain significance in the TBX5 gene (c .1063 C > T, p.(Arg355Cys)).
Conclusions: This case highlights the complex nature of diagnosing and managing congenital limb deformities driven by genetic factors. It underscores the critical importance of comprehensive genetic testing in determining the etiology of limb malformations. The GLI3 variant, classified according to ACMG guidelines as a class IV mutation, likely results in a truncated protein due to a premature stop codon, confirmed by family segregation analysis indicating its paternal origin, suggesting autosomal dominant inheritance. Notably, the TBX5 gene variant, often associated with Holt-Oram syndrome—which is characterized by only hand skeletal anomalies and early-onset atrial fibrillation—suggests a risk of developing cardiac issues that are not currently present but may emerge as the child grows. This potential for evolving clinical manifestations necessitates vigilant long-term monitoring and may influence future medical management and therapeutic approaches.

* Correspondence to: Department of Pediatrics, AOU Policlinico, University of Catania, Via S. Sofia 78, Catania 95123, Italy.
E-mail address: ppavone@unict.it (P. Pavone).
[1] These Authors contributed equally

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Introduction

Polydactyly and syndactyly are two of the most common congenital limb malformations.

Polydactyly one with the highest frequency of limb - related anomalies and it is characterised by presence of a higher number of digits or toes as normal. Polydactyly can present with different phenotypes classified with various approaches [1].

Polydactyly occurs with an incidence from 0,37 to 1,2 per 1000 live births, varying across the different racial groups [2].

In general it tends to involve more frequently the upper limbs over the lower ones, with a preference for the right hand over the left, and the left foot over the right [1,3].

Two commonly observed manifestations include pre-axial polydactyly (PPD) (an extra digit attached to the first digit) and postaxial polydactyly (an additional digit along the fifth digit). Meso-axial polydactyly involving the second, third, or fourth digits are unusual findings [1,3].

Polydactyly occurs due to a defect on the anterior - posterior patterning during the limb development. Mostly this malformation presents with an inheritance pattern autosomal dominant [4].

Polydactyly morphogenetically arises from an abnormal bifurcation that progresses from distal to proximal end on the longitudinal axis of digits [5].

As a result of a sporadic mutation, it manifests itself unilaterally, while familial forms are often bilateral and symmetrical [3,6].

Furthermore, polydactyly can be an isolated phenomenon or, less frequently, associated to other malformations in the context of syndromes [4,7] (Table 1. Non syndromic Polydactyly).

For example, syndromes associated to hand and foot polydactyly are: Bardet-Biedl syndrome, McKusick-Kaufman syndrome, Carpenter syndrome, Poland syndrome, Smith-Lemli-Opitz syndrome [8]. Additionally, anomalies of the thumb-radius can be found in rare forms of Fanconi anemia, and polydactyly might be the unique manifestation in some cases of Diamond-Blackfan anemia [4] (Table 2. Syndromic Polydactyly).

Because of a multifactorial origin, polydactyly can also be a consequence of teratogens, like, for example, busulfan, a chemotherapeutic agent [9].

The diagnosis of polydactyly can be prenatally through ultrasound or clinically detected at birth and treatment requires surgical procedures [4].

The Temtamy and McKusick classification [10] identified various types of polydactyly, including pre-axial and post-axial forms, almost all inherited in a dominant manner. Building upon this classification, Goldstein et al.[11] expanded the scheme to include additional subtypes, with most showing autosomal dominant inheritance and variable expression. Castilla et al. [12] suggested that post-axial polydactyly in the hands and feet should be considered separately, while Orioli and Castilla [13] proposed that thumb and big toe polydactyly might have different genetic origins.

Postaxial polydactyly, a common congenital hand malformation has been defined as the presence of duplications of the fifth digit in both hands and/or feet. It has been classified into types A and B, and type A has 6 subtypes. It has a prevalence ranging from 1 in 630 to 1 in 3300 among individuals of Caucasian descent, and from 1 in 100 to 1 in 300 among individuals of Black descent [8].

The preaxial type of polydactyly, the second most prevalent phenotype after the postaxial type, has an estimated occurrence of around 0.8–2.3 in 10,000 live births. It has been described as the presence of an additional digit on the inner side of the limb and has been classified into four clinical types [8].

Syndactyly is an inherited deformity that occurs with the fusion of two neighbouring fingers or toes.

It is caused by a defect in the separation process during the limb development [14].

Syndactyly has an estimated occurrence of about 1 in 2000–3000 live births and it manifests in males twice as much as females. It can be associated to environmental factors such as smoking during pregnancy, elevated maternal intake of meat and eggs, malnutrition [15].

Phenotypically is considered one of the most diverse congenital malformations, manifesting in many different phenotypes, asymmetrical or symmetrical, involving hands and /or feet [14].

Syndactyly can be considered as a “simple syndactyly” if the digits are jointed only by soft tissue or as a “complex syndactyly” if there are also bones or cartilaginous malformations [15]. Complex syndactyly are the 16.5 % of cases of syndactyly and are the most common manifestation of syndactyly in females [16].

Furthermore, syndactyly can be “non syndromic”, distinguished in 9 different types (Table 3. Non syndromic syndactyly), or “syndromic”, being a feature of at least 300 anomalies. Some of the syndromes that can present syndactyly are: Acrocephalosyndactyly, Bardet - Biedl syndrome, Greig Cephalopolysyndactyly Syndrome, Pallister - Hall Syndrome, Poland Syndrome, Smith - Lemli - Optiz Syndrome, Triphalangeal Thumb - Polydactyly Syndrome [17].

This case report details the clinical journey of an 8-month-old infant diagnosed with both polydactyly and syndactyly, where advanced genetic testing revealed mutations in both the GLI3 and TBX5 genes—a rare combination that potentially heightens the complexity of the phenotypic outcome. The GLI3 gene is often implicated in cases of polydactyly associated with syndromic features, as seen in Greig cephalopolysyndactyly syndrome, while mutations in TBX5 are classically linked to Holt-Oram syndrome, which is characterized by skeletal and cardiac defects [7,18]. The coexistence of mutations in these two genes in the same patient underscores a rare intersect of syndromic pathways that might influence clinical decisions and long-term management strategies. This intersection of genetic factors contributes to making this case particularly rare and of significant interest to the medical community, offering profound insights into the complexities of genetic influence on limb development.

Case report

We present a case of an 8-month-old male infant referred to our clinic for polydactyly and syndactyly. He was the only child of non-consanguineous parents.

The family history revealed an obese mother with unspecified thyroid disorder and mild cognitive impairment, a father with polydactyly (operated on the hands, hexadactyly on the left foot, and seventh toe on the right foot) [Picture 3 ***(a), (b), and (c)***]. The rest of the family medical history was not relevant.

He was born at 39 + 4 weeks of gestation through spontaneous delivery, with birthweigh of 3200 g. The pregnancy was complicated by gestational hypertension and a SARS-CoV-2 infection at the eighth month. About developmental milestones, he had not achieved standing or walking, and his speech development was limited.

Upon admission, the child was in good overall condition with a notable composite facial expression. The colour of the skin exhibited a rosy-pale tone, and the mucous membranes were observed to be rosy. Noteworthy cutaneous findings included a Mongolian spot on the sacral region and a small café -au-lait spot (1 × 2.5 cm) located in the flexor region of the right arm. Vital signs were within normal limits, with a temperature of 36.2 °C, a weight of 10.200 kg (> 90th percentile), a height of 63 cm (< 3rd percentile), and a head circumference of 43.5 cm (between the 50th and 25th percentiles). Abundantly represented subcutaneous tissue was noted. Upon examination of the musculoskeletal system, muscle mass appeared normotrophic, but mild hypotonia was observed in the upper limbs.

Both hands exhibited complete syndactyly of the III, IV, and V fingers, accompanied by the presence of an appendage at the base of the V finger. [Picture 1 ***(a), (b), (c), (d), (e), (f), (g)]*** The right foot revealed an increased space between the third and fourth toes, while the left foot presented polydactyly with the presence of an extra (sixth) toe. [Picture 2 ***(a), (b)].***

Facial characteristics included hypertelorism and a short neck. Mild facial asymmetry was observed, with a slight prominence on the right side compared to the left. Lower incisors and upper incisor teeth erupted. The eyelid fissures displayed a downward orientation, furthermore, he presented a broad nasal bridge, a slight deviation of the mouth rim, and macrotia (larger-than-usual ears). The ears displayed a normal appearance, and the male genitalia were consistent with the child's age, with non-descended testicles.The cardio-pulmonary physical examination was negative. The abdomen appeared globular due to adiposity and was treatable on both superficial and deep palpation.

Neurological examination indicated intact sensorium, alertness, and responsiveness. The child demonstrated visual tracking, social smiling, object grasping, and transferring between hands. Additionally, he could maintain a sitting position independently. Anyway, at 8 months old, the child had not yet achieved a standing position or independent ambulation. Lallation was present, but the child had not pronounced any words.

Various diagnostic tests were conducted, including ECG and echocardiography, abdominal ultrasound, and consultations with ophthalmic examination with fundoscopy. These examinations did not reveal significant abnormalities, except for the upper and lower limbs X-Ray [Picture 4 ***(a), (b), (c)]***, which confirmed the presence of polydactyly and syndactyly, in absence of bone lesions. The orthopaedic consultation suggested the need for surgical intervention, scheduled to be performed after the age of 12 months. Genetic counselling recommended the execution of whole exome sequencing (WES), specifically targeting genes associated with limb anomalies and polydactyly/syndactyly. The sequence analysis revealed the presence of the heterozygous variant c .3762 T > A p.(Tyr1254 *) in the GLI3 gene (NM_000168) with likely pathogenic significance.

Additionally, the heterozygous variant c .1063 C > T p.(Arg355Cys) in the TBX5 gene (NM_181486) was identified.

The analysis indicated the heterozygous presence of the variant c .3762 T > A p.(Tyr1254 *) in the GLI3 gene, following autosomal dominant inheritance. According to ACMG, this variant is classified as class IV, generating a premature stop codon, likely leading to a truncated protein. Family segregation analysis confirmed the presence of the variant and identified its paternal origin. Variants in the GLI3 gene (OMIM 165240) are associated with Postaxial Polydactyly, Type A1 and B (OMIM 174200) and Preaxial Polydactyly, Type IV (OMIM 174700), both corresponding to the clinical characteristics observed in the proband.

Furthermore, the heterozygous variant c .1063 C > T p.(Arg355Cys) in the TBX5 gene, following autosomal dominant inheritance, was identified. Literature reports describe this variant in a patient with early-onset atrial fibrillation, a condition not present in the proband. Given this finding, a cardiological examination and subsequent follow-up in the years ahead are recommended. Family segregation analysis confirmed the presence of the variant in the proband and excluded it in the father.

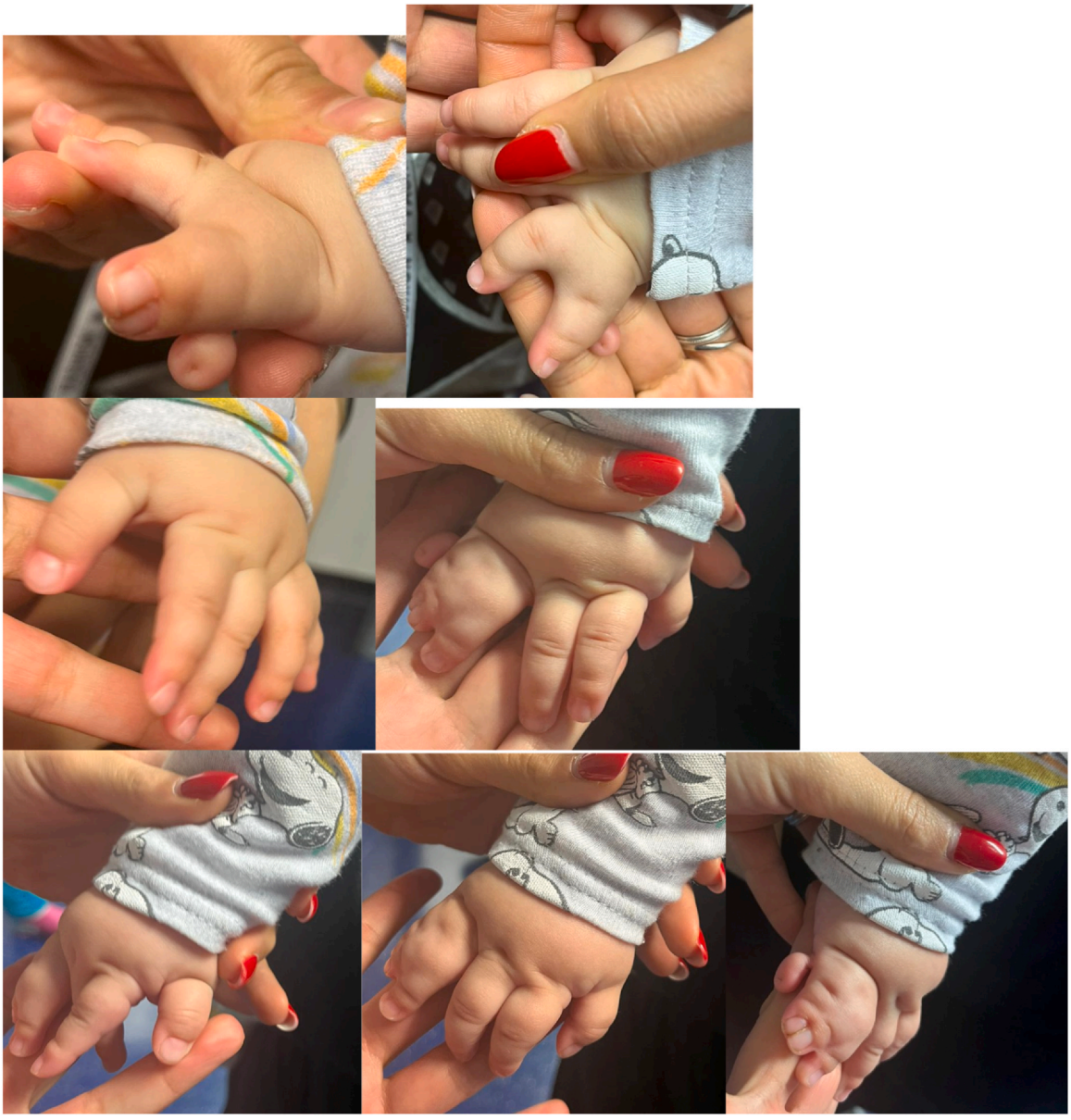
The recurrence risk for both variants in any potential offspring of the consultee is 50 % (1 in 2 chances) with each conception.

Discussion

Polydactyly represents the most frequent congenital deformity of the hands and feet.

The phenotype of our case appears to be consistent with isolated post-axial polydactyly types A and B and preaxial polydactyly Type IV. Based on the position of the extra digits, it is possible to classify polydactyly as preaxial, involving the thumb or big toe, and post-axial, affecting the fifth digit. Instead, when it involves the three central digits of the hands and foot is defined as central polydactyly (OMIM 174200), a very rare phenotype [8].

Post-axial polydactyly (PAP) is classified into two forms: Post-axial polydactyly type A is the presence of a well-formed extra digit articulating with the fifth or sixth metacarpal, while post-axial polydactyly type B is defined by the presence of a rudimentary and poorly developed extra digit in the same position as the previous one[1]. Both types can be inherited in an autosomal dominant or recessive manner [19]. Type A postaxial polydactyly has six subcategories [2,8]. The most common category of polydactyly is type B, which is often found in association to GLI3 gene mutations [20].



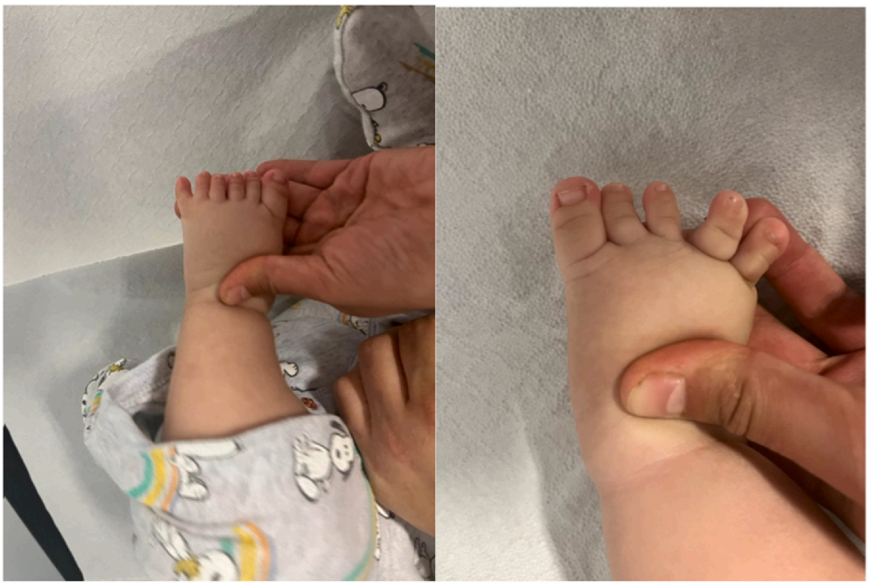
Picture 1. (a), (b), (c), (d), (e), (f), (g): the left (a,b) and the right hands of the patient.

Preaxial polydactyly type IV mainly involving the feet, is defined by the duplication of part or all of the first and second toes. In the hand, mild duplications of the thumb can also be observed. Both Pre-axial IV and Post-axial A1 (types A/B) are autosomal dominant hereditary forms. Furthermore, the Haas type is an autosomal dominant inherited polysyndactyly defined as a total fusion of the skin between all fingers with an extra digit ray in the interdigital space; it involves all hand fingers and occasionally foot toes [1,21]. Mapped the locus for Haas-type polysindactyly on 7q36, this form has been associated to mutations of the ZRS region of LMBR1 gene [8,14,22,23].

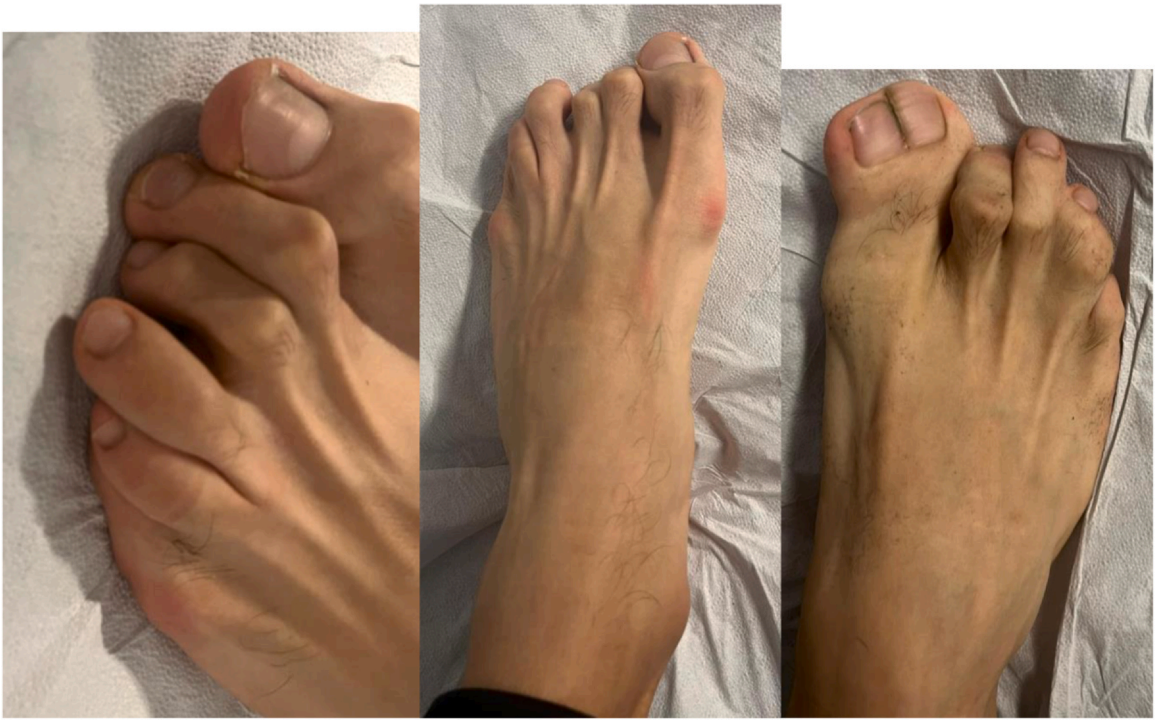
In suspicion of a genetic condition underlying the clinical picture, a Whole Exome Sequencing (WES) was performed, showing the presence of two pathogenetic variations: the heterozygous presence of the variant c .3762 T > A p.(Tyr1254 *) in the GLI3 gene and the heterozygous presence of the variant c .1063 C > T p.(Arg355Cys) in the TBX5 gene.

The variant c .3762 T > A p.(Tyr1254 *) in heterozygosity in the GLI3 gene, in accordance with ACMG guidelines, is classified as a likely pathogenic variant (class IV), inducing the introduction of a premature stop codon, presumably resulting in the encoding of a truncated protein. Family segregation analysis indicated the paternal origin of this variant: indeed, the father exhibited a phenotype compatible with the genetic variant.

The GLI3 gene is located on the short arm of chromosome 7 (7p14.1) and consists of 14 exons [24]. It encodes a transcription factor belonging to the C2H2 zinc finger protein subclass of the Gli family. The human GLI3 gene has a length of 276,261 base pairs.



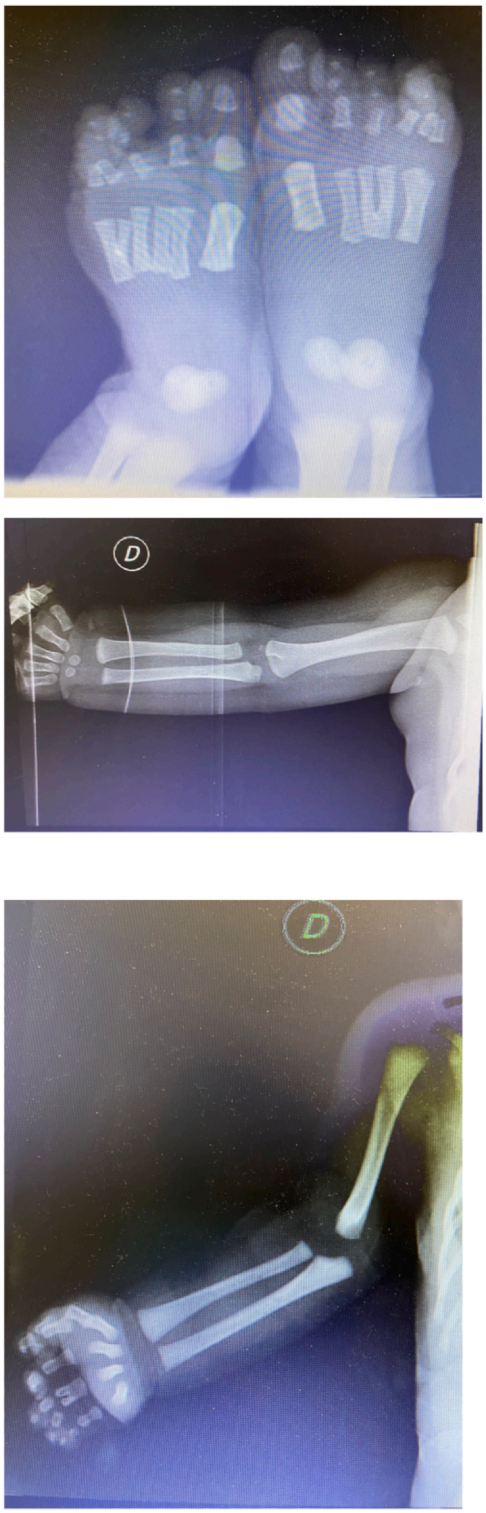
Picture 2. (a), (b): the left (a) and right (b) feet of the patient.



Picture 3. (a), (b), and (c): the left (a, b) and right (c) feet of the patient's father.

The GLI3 protein is predominantly located in the cytoplasm and has a dual function of transcriptional activation and repression of the Sonic hedgehog (Shh) signaling pathway. It also plays a role in the proper development of limbs. Additionally, it appears to have a significant role in embryogenesis [25].

This transcription factor is involved in tissue development and regulates the function of certain immune cells (B, T, NK). It also plays a role in the etiology of cancer, being overexpressed in various malignancies such as colorectal [26] and liver cancers [27]. The GLI3 factor exhibits a pro-growth phenotype, playing a crucial role in cellular proliferation and migration processes.



Picture 4. (a), (b), (c): foot X-Ray (a), arms and hands X-ray (b), (c).

Furthermore, the GLI3 protein, along with GLI2, is upregulated in ischemic limb muscles and seems to participate in tissue damage repair, angiogenesis [28], and myogenesis.

Studies have highlighted the antitumoral role of GLI3 in certain neoplastic forms, such as acute myeloid leukaemia and medulloblastoma [29].

Deleterious variants of the GLI3 gene are associated with various genetic conditions with autosomal dominant inheritance:

- **Greig cephalopolysyndactyly syndrome** [18, 30] **(OMIM 175700):** autosomal dominant inherited syndrome in which preaxial polydactyly (more frequently of the feet) and postaxial polydactyly (more frequently of the hands) are associated to macrocephaly and hypertelorism.
- **Pallister-Hall syndrome** [24] **(OMIM 146510):** postaxial polydactyly and syndactyly are associated to hypothalamic hamartoma, pituitary dysfunction, bifid epiglottis, and, less frequently, renal and genitourinary anomalies.
  Postaxial polydactyly types A1 and B (OMIM 174200)
- **Preaxial polydactyly, type IV (OMIM 174700)**: An autosomal dominant inherited condition characterised by mild duplication of the thumb, syndactyly of the third and fourth fingers/toes, duplication of the first or second toes, and toes syndactyly. Recently described in two families heterozygous for p.L1216PfsX31 and p.R290X mutations in the GLI3 gene [31]

The analysis conducted during our patient's consultation also highlighted the presence of the variant c .1063 C > T p.(Arg355Cys) in heterozygosity in the TBX5 gene. This variant is classified, in the main reference databases (ClinVar, Franklin), and in accordance with ACMG guidelines, as a variant of uncertain clinical significance (class III). Segregation analysis conducted in the parents confirmed the de novo origin of this variant.

This variant is located in exon 8 of the TBX5 gene and results from a substitution of arginine in codon 355 with cysteine.

Deleterious variants of the TBX5 gene are typically associated with Holt-Oram syndrome and pathological conditions related to cardiac conduction disorders, both inherited in an autosomal dominant manner [32, 33].

The TBX5 gene is located on 12q24.21, comprising 9 exons and spanning over 47 kb. It encodes for the protein TBX5, which plays a crucial role in limb and heart development. It is the main gene implicated in Holt-Oram syndrome, characterised by skeletal deformities of the limbs and heart. This protein product modulates the cardiac conduction system by regulating the gene expression of SCN5A, which encodes for the cardiac sodium channel NaV1.5, and through connexin 40.[34].

Holt-Oram syndrome is an autosomal dominant genetic disorder, with complete penetrance and variable expressivity, representing the most common form of heart-hand syndrome [35]. It is characterized by a heterogeneous phenotype consisting of skeletal abnormalities primarily affecting the upper limbs and congenital heart defects ranging from mild to severe, often associated with conduction abnormalities. It is possible to observe the presence of atrial septal defects and ventricular septal defects, the most common cardiac anomalies in this syndrome [36, 37]. In addition, it has been demonstrated a relationship between the severity of limb and heart anomalies [38] The limb deformities in these patients include absence/hypoplasia of the thumb, brachydactyly, clinodactyly, polydactyly of hands[39]; while lower limb anomalies are infrequent [37].

The variant identified in the proband has been reported in the literature in a patient with atrial fibrillation (AF). This variant appears to be associated with early-onset atrial fibrillation and seems to have a functional impact. Studies conducted have highlighted an important role of the TBX5 gene in the pathogenesis of AF [40,41].

Multiple studies have been conducted to identify the potential causative effect of the p.R355C mutation in atrial fibrillation. These studies have shown that zebrafish overexpressing the p.R355C mutant do not exhibit structural cardiac abnormalities. Only approximately 20 % of zebrafish with p.R355C overexpression studied showed cardiac rhythm abnormalities, including AF and conduction block. Therefore, the TBX5 gene has been proposed as a candidate gene implicated in atrial fibrillation [40].

Therefore, since the variant c .1063 C > T p.(Arg355Cys) in the TBX5 gene is classified as a variant of uncertain clinical significance and there are no evident cardiac issues present in the proband, this variant cannot be considered causative of our patient's clinical presentation.

Based on current knowledge, we cannot definitively diagnose the patient with Holt-Oram syndrome. However, continuous and annual evaluation of the patient is necessary to assess the emergence of significant clinical developments and the potential reclassification of the variant.

Nevertheless, we cannot exclude the possibility that the presence of this variant may contribute to the clinical picture presented by the little patient.

The genetic analysis that identified mutations in both the GLI3 and TBX5 genes provides a rare glimpse into the genetic underpinnings of limb malformations. This adds to the limited pool of data on the co-occurrence of these mutations and their phenotypic manifestations. Furthermore, the comprehensive clinical characterization of the patient, combined with the family genetic history and imaging techniques, ensures a robust diagnostic approach, allowing for a genotype-phenotype correlation. Nevertheless, the single-case nature of this report is a significant limitation as it may not necessarily provide a broad view of the genetic variability and full spectrum of clinical manifestations associated with these gene mutations. Another limitation is the lack of long-term follow-up data, which restricts understanding of the full clinical progression and long-term outcomes of the surgical and medical interventions proposed. Further studies describing larger cohorts or longitudinal studies are needed to broaden the description of the spectrum of clinical manifestations associated with the described genetic mutations.

Conclusion

Our case presents with isolated post-axial polydactyly types A and B and preaxial polydactyly Type IV, common congenital deformities affecting the hands and feet. Genetic testing revealed two variants: a likely pathogenic variant in the GLI3 gene and a variant of uncertain clinical significance in the TBX5 gene. While the GLI3 variant is associated with limb development disorders, the TBX5 variant's significance remains uncertain. Although the TBX5 variant is currently of uncertain clinical significance and no cardiac issues are evident in the proband, ongoing evaluation is necessary to monitor potential clinical developments and variant

reclassification. While the patient cannot be definitively diagnosed with Holt-Oram syndrome at present, the possibility of the TBX5 variant contributing to the clinical presentation cannot be ruled out.

This case may contribute to enhancing the genotype-phenotype correlations in foot and hand polysyndactyly. Recent analyses reveal distinct phenotypic changes in extra digit formation, suggesting a spectrum of evolution. Genome sequencing offers potential for uncovering new gene mutations linked to polysyndactyly. Bioinformatics analysis can further establish genetic correlations, supporting prenatal diagnosis and potential gene therapies.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

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Data Availability

Data shared are in accordance with consent provided by participants on the use of confidential data.

Conflicts of Interest

The authors declare no conflict of interest.

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