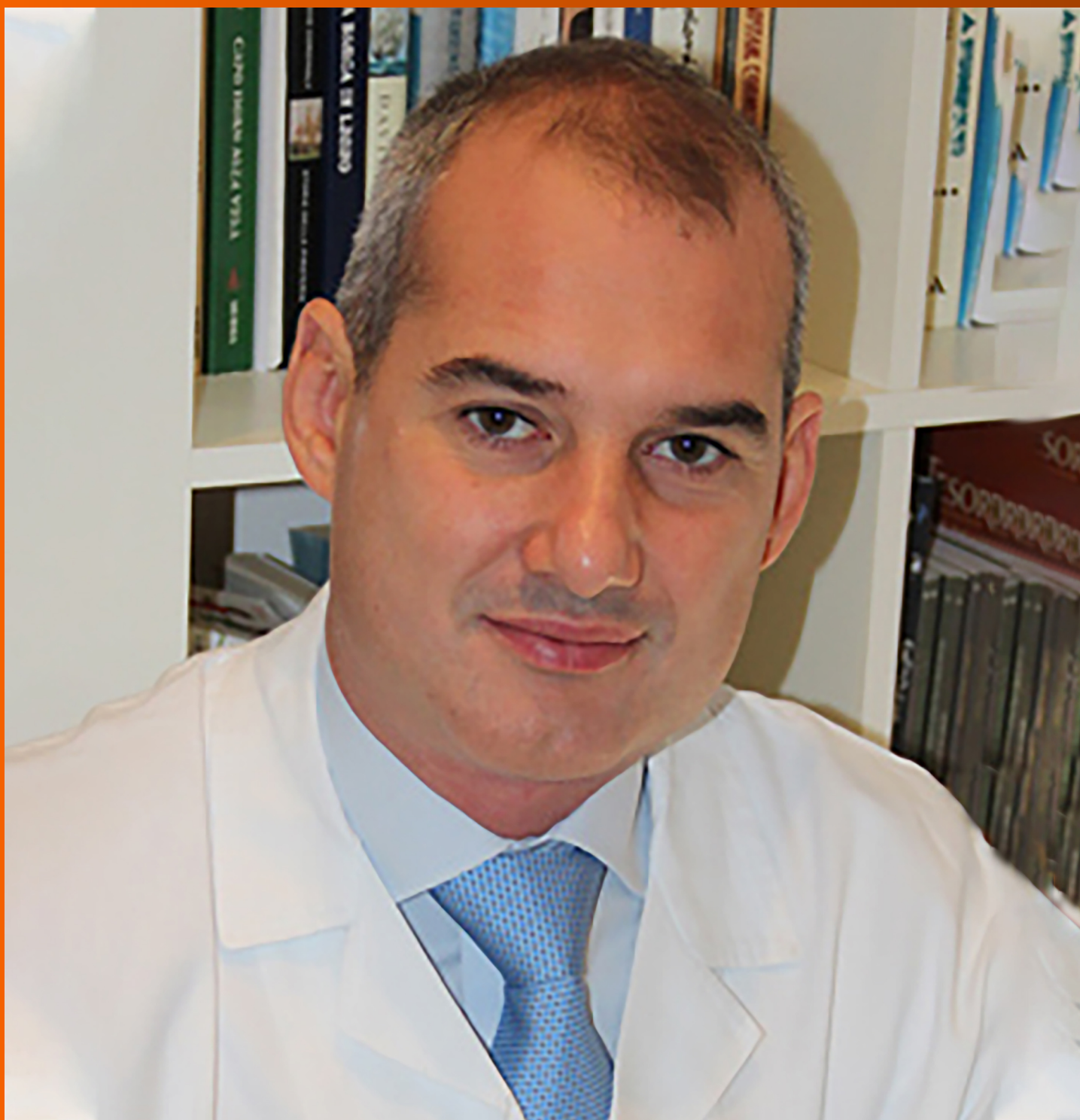


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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

August 16, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Prenatal diagnosis of triphalangeal thumb-polysyndactyly syndrome by ultrasonography combined with genetic testing: A case report

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Author contributions: Zhang SJ was involved in drafting the manuscript, acquiring the data, modifying the images, and revising the manuscript; Lin HB contributed to the physical examinations and clinical X-ray examinations, data acquisition, and the revision of the manuscript; Jiang QX and He SZ revised the manuscript critically for important intellectual content; Lyu GR made substantial contributions to the conception and design, revised the manuscript critically for important intellectual content, and gave final approval of the version to be published; all authors have approved the manuscript.

Supported by Fund of the Research Project of Collaborative Innovation Center for Maternal and Infant Health Service Application Technology, No. XJM1802.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement:

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Abstract

BACKGROUND

Triphalangeal thumb-polysyndactyly syndrome (TPT-PS) is a rare type of congenital limb deformity, and most studies focus on the genetics. Case reports of the sonographic characteristics of TPT-PS during pregnancy are rare.

CASE SUMMARY

A 30-year-old woman (G3P1) who had pregnancies with TPT-PS fetuses is presented. The possibility of TPT-PS was shown by ultrasound performed at the 19th wk of pregnancy, featuring hands with six metacarpals, an extra digit at the 5th finger side, and an abnormally widened thumb. Whole-exome sequencing was subsequently conducted. The results showed that exons 1-17 of the *LMBR1* gene had a heterozygous duplication, with a length of approximately 253 kb.

CONCLUSION

We suggest prenatal ultrasound examination combined with genetic testing to diagnose TPT-PS accurately and to help clinicians and patients make decisions.

Key Words: Congenital limb deformities; Ultrasound; Prenatal diagnosis; Polydactyly; Syndactyly; Case report

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There is no conflict of interest to report.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Manuscript source: Unsolicited manuscript

Specialty type: Obstetrics and gynecology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 2
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 24, 2021

Peer-review started: April 24, 2021

First decision: May 24, 2021

Revised: June 4, 2021

Accepted: June 16, 2021

Article in press: June 16, 2021

Published online: August 16, 2021

P-Reviewer: Watanabe A

S-Editor: Wu YXJ

L-Editor: Wang TQ

P-Editor: Xing YX



Core Tip: Triphalangeal thumb-polysyndactyly syndrome (TPT-PS) is a rare type of congenital limb deformity that has autosomal dominant inheritance. A case of TPT-PS diagnosed by ultrasound in pregnancy is presented. Features of antenatal ultrasound include hands with six metacarpals, an extra digit at the 5th finger side, an abnormally widened thumb or thumb shaped like a trident (bifida), and the absence of interphalangeal space between fingers. This case also shows that heterozygous duplication encompassing exons 1-17 of the *LMBR1* gene is related to TPT-PS.

Citation: Zhang SJ, Lin HB, Jiang QX, He SZ, Lyu GR. Prenatal diagnosis of triphalangeal thumb-polysyndactyly syndrome by ultrasonography combined with genetic testing: A case report. *World J Clin Cases* 2021; 9(23): 6832-6838

URL: <https://www.wjgnet.com/2307-8960/full/v9/i23/6832.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i23.6832>

INTRODUCTION

Triphalangeal thumb-polysyndactyly syndrome (TPT-PS, OMIM-174500), also known as preaxial polydactyly type II, is an autosomal dominant anomaly characterized by triphalangeal thumbs, pre- and post-axial polydactyly, complex polysyndactyly, and isolated syndactyly[1]. During limb development, sonic hedgehog (SHH), normally expressed in the zone of polarizing activity (ZPA) in the posterior limb bud, regulates the anterior-posterior axis of the limb bud[2]. The expression of SHH in the limb bud is regulated by an enhancer known as ZPA regulatory sequence (ZRS), which is a highly conserved noncoding sequence lying within intron 5 of the *LMBR1* gene, approximately 1 Mb upstream of SHH[3]. Disruption of ZRS can lead to additional expression of SHH at the anterior part of the limb bud, which finally causes TPT-PS[4]. A review of the literature shows that point mutations in ZRS[3,5,6], point mutations in pre-ZRS [4], and duplications including ZRS can cause TPT-PS[1,7-12]. A collection of genetic abnormalities causing TPT-PS is presented in Table 1.

Most of the literature reporting TPT-PS focuses on the genetics, but genetic testing is difficult to perform in prenatal screening because of its high cost. By ultrasonography, polydactyly can be detected as early as the 10th wk of gestation[13]. It is considered to be present if an extra digit containing bone is detected[14]. With improvements in ultrasound imaging technology, the detection rate of polydactyly has significantly increased. Whole-exome sequencing (WES) is an important way to detect abnormal genes associated with fetal structural malformations and can be an appropriate tool to confirm abnormal ultrasound findings during pregnancy[15]. At present, there is little literature reporting the sonographic characteristics of TPT-PS during pregnancy. Here, we report a case of TPT-PS with a summary of its prenatal sonographic features and show that heterozygous duplication encompassing exons 1-17 of the *LMBR1* gene with a length of approximately 253 kb is also related to TPT-PS.

CASE PRESENTATION

Chief complaints

In July 2020, a 30-year-old female patient at the 19th wk of pregnancy (G3P1) was admitted to our hospital due to a history of abnormal pregnancies.

History of present illness

The patient suffered from malformation of both hands and the right foot (Figure 1A-D).

History of past illness

In 2015, a baby boy was born with triphalangeal thumbs, pre- and post-axial polysyndactyly, and cutaneous fusion of the 3rd, 4th, and 5th fingers (Figure 1E-H). In 2017, a pregnancy ended in miscarriage with a fetus demonstrating triphalangeal thumbs and complex polysyndactyly. According to the sonogram, there was thumb polydactyly shaped like a trident (bifida) and the absence of interphalangeal space between the 3rd,

Table 1 Position of point mutations or range of duplications related to zone of polarizing activity regulatory sequence causing triphalangeal thumb-polysyndactyly syndrome

Ref.	Position/range
Lettice <i>et al</i> [3], 2003	Point mutation: 105C>G
Wang <i>et al</i> [6], 2007	Point mutation: 4420C>T
VanderMeer <i>et al</i> [5], 2012	Point mutation: 287C>A
Potuijt <i>et al</i> [4], 2018	Point mutation: Pre-ZRS (chr7: 156585476G>C)
Klopocki <i>et al</i> [1], 2008	Duplication: 589 kb
Sun <i>et al</i> [7], 2008	Duplication: 131-398 kb
Wieczorek <i>et al</i> [8], 2010	Duplication: 276 kb
Lohan <i>et al</i> [9], 2014	Duplication: 255 kb
Xing <i>et al</i> [10], 2014	Duplication: 442 kb
Liu <i>et al</i> [11], 2017	Duplication: 288 kb
Xu <i>et al</i> [12], 2020	Duplication: 180 kb

ZRS: Zone of polarizing activity regulatory sequence.

4th, and 5th fingers (Figure 1I-L).

Personal and family history

No deformity was found in the patient's parents or relatives.

Physical examination

Physical examination showed that the pregnant woman had triphalangeal thumbs, pre- and post-axial polysyndactyly, and cutaneous fusion of the 3rd, 4th, and 5th fingers, accompanied by deviant posture of the hands, while the index finger was unaffected. Her right foot manifested postaxial polysyndactyly (Figure 1A-D).

Laboratory examinations

Laboratory examinations showed no abnormalities.

Imaging examinations

On ultrasound, hands with six metacarpals were documented. Through multiplane scanning, an echo of the extra digit at the 5th finger side was evident, and the thumb appeared be doubled, leaving the thumb abnormally widened. The morphological appearance of the 3rd, 4th, and 5th fingers was plausibly normal at the beginning of our examination. However, no separation of those digits was detected throughout the examination, leading to a diagnosis of syndactyly (Figure 1O and P).

FINAL DIAGNOSIS

The final diagnosis was TPT-PS.

TREATMENT

According to the observed deformities, such as hands with six metacarpals, an extra digit at the 5th finger side, and an abnormally widened thumb, polysyndactyly was considered. Given that the patient had abnormal fetuses in three consecutive pregnancies and that the X-ray examination of herself and her son demonstrated a triphalangeal thumb, TPT-PS was diagnosed. After prenatal consultation, the patient chose WES to make a definite diagnosis and requested termination of the pregnancy.

At the 20th wk of gestation, ultrasound-guided cordocentesis was conducted with amniotic cavity injection of ethacridine lactate (Rivanol, Guangxi Hefeng Pharmaceutical Co., Ltd., China) for labor induction. Umbilical cord blood (3.5 mL) was



Figure 1 Limb features of patients with triphalangeal thumb-polysyndactyly syndrome. A and B: Physical and X-ray examinations showed that the mother had triphalangeal thumb, pre- and postaxial polysyndactyly, and cutaneous fusion of the 3rd, 4th, and 5th fingers accompanied by deviant posture of the hands, with unaffected index fingers; C and D: Physical and X-ray examinations showed that the mother's right foot had postaxial polysyndactyly; E-H: X-ray examination revealed that the son had an abnormality similar to that of his mother; I: Two-dimensional ultrasound showed triphalangeal thumb polysyndactyly; J and K: Two-dimensional ultrasound showed trident-like thumb; L: Three-dimensional ultrasound vividly showed postaxial webbing of the fingers; M: Postnatal autopsy of both hands showed pre- and postaxial polysyndactyly and webbing of the 3rd, 4th, and 5th fingers; N: Postnatal X-ray images of both hands showed triphalangeal thumb polysyndactyly and six metacarpals; O: Prenatal ultrasound image of the left hand showed an echo of an extra digit on the 5th finger side and double thumbs; P: Prenatal ultrasound image of the left hand showed no separation of the 3rd, 4th, and 5th fingers. LH: Left hand; L: Left; R: Right.

successfully obtained. The peripheral blood of the pregnant woman, her husband, and her son was also extracted for WES analysis. However, none of the patient's parents or relatives were willing to undergo a blood draw for genetic testing.

The fetus was stillborn 1 d after Rivanol injection. Postmortem and X-ray examination of the aborted fetus showed six metacarpals, triphalangeal thumbs, fused extra preaxial fingers, and cutaneous syndactyly of the 3rd, 4th, and 5th digits with a knob-like pedicled finger, while the index finger was unaffected (Figure 1M and N). Additionally, the right foot presented postaxial polysyndactyly.

OUTCOME AND FOLLOW-UP

Twenty-four days after the extraction, WES showed a heterozygous duplication encompassing exons 1-17 of the *LMBR1* gene (NM_022458.3) in the fetus, the pregnant woman, and her son. The size of their duplication was 253 kb. According to the inclusion criteria set by the American College of Medical Genetics and Genomics (ACMG), the Clinical Genome Resource (ClinGen), the disease gene variation database, and literature reports, the duplication was confirmed as a pathogenic

variation, and TPT-PS was confirmed. The duplication was absent from the patient's husband.

DISCUSSION

We report a case of prenatal sonographic detection of a fetus with TPT-PS. Subsequently, autopsy, X-ray examination, history investigation, and WES were used to verify the ultrasound diagnosis. In the history investigation, we found that the pregnant woman had abnormal fetuses in the last two pregnancies. WES revealed a duplication spanning exons 1-17 of the *LMBR1* gene, including ZRS. This research may shed light on methods for prenatal TPT-PS diagnosis.

First, there was a diversity of phenotypes, including triphalangeal thumbs, pre- and post-axial polydactyly, and webbing of the digits. Therefore, the sonographic features include the following: (1) An extremely widened or bifurcated thumb accompanied by additional echo of phalangeals and, in some cases, metacarpals; (2) A redundant echo of soft tissue with or without a bony echo at the postaxial field; and (3) A lack of interphalangeal space and/or fingers that never separate throughout the examination. Polydactyly and/or syndactyly of the lower extremities can sometimes be detected. These features can lead to a preliminary diagnosis of TPT-PS. When suspected by ultrasound, the triphalangeal thumb and polydactyly should be confirmed in the coronal and axial planes. Three-dimensional ultrasonography might be helpful to provide more details for the evaluation. Given that polydactyly is associated with approximately 300 syndromic abnormalities and that the presence of a triphalangeal thumb can be predictive of other combined congenital anomalies, further ultrasound scans are essential for the exclusion of other anomalies[16-18]. However, it is still difficult to diagnose TPT-PS accurately by prenatal ultrasonography only. Hence, additional information is needed to confirm this diagnosis.

Second, because TPT-PS is an autosomal dominant malformation, a detailed survey of the patient's history will be conducive to a prenatal diagnosis. It should be noted that mild and subclinical limb phenotypes without the presence of a triphalangeal thumb may occur in patients who are presumed to be unaffected. For instance, family members who do not have a triphalangeal thumb might have broadness of the thumb or a double flexion fold in the thumb. These mild anomalies might not cause evident aesthetic or functional problems, so the report will indicate that the individual is as unaffected. Consequently, the width, number of flexion folds, strength, and digital opposition of the thumb and whether the lunula of the thumb is duplicated should be evaluated when investigating the patient's history[19].

Last, the pathogenic gene of TPT-PS was confirmed to be the *LMBR1* gene, which is mapped to chromosome 7q36.3[1]. In our case, all the affected individuals with available samples for WES carried the mutation of the *LMBR1* gene, while the unaffected individual did not, confirming that the mutation is cosegregated in this family. Hence, genetic testing is an ideal approach to confirm the ultrasound diagnosis. Several case studies have reported the use of genetic testing after abnormal ultrasound findings[20-22]. Chen and Huang[20] reported a case of Apert syndrome diagnosed by prenatal ultrasound combined with magnetic resonance imaging and WES using a method similar to ours. As a screening tool, ultrasound mainly provides diagnostic information regarding the phenotypes of genetic syndromes. Additional genetic testing is performed for genotypic confirmation of the ultrasound findings. With the advent of the era of precision medicine, ultrasound screening combined with genetic testing may become a trend in the diagnosis of genetic syndromes. Moreover, genetic evaluation is indicated for likely unaffected family members for complete reassurance regarding whether they harbor the disease-related gene. This will contribute to the study of genetics and to the reproduction plans of affected families.

CONCLUSION

We suggest prenatal ultrasound examination combined with genetic testing to accurately diagnose TPT-PS and help clinicians and patients make decisions.

ACKNOWLEDGEMENTS

We sincerely thank the family and all participants for their cooperation in providing the medical data necessary for publication. We also wish to thank the BGI-Guangzhou Medical Laboratory for performing the whole-exome sequencing.

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