

CLINICAL REPORT

Genome sequencing analysis of a family with a child displaying severe abdominal distention and recurrent hypoglycemia

Jidong Liu^{1,2} | Guolian Ding^{2,3,4} | Kexin Zou^{3,4} | Ziru Jiang^{3,4} | Junyu Zhang^{3,4} | Yunhua Lu⁵ | Antonella Pignata⁶ | Eric Venner⁷ | Pengfei Liu⁶ | Zhandong Liu⁸ | Michael F. Wangler^{6,8,9} | Zheng Sun^{2,10} 

¹Department of Endocrinology, Qilu Hospital of Shandong University, Jinan, China

²Department of Medicine-Endocrinology, Baylor College of Medicine, Houston, TX, USA

³The International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

⁴Shanghai Key Laboratory of Embryo Original Diseases, Shanghai, China

⁵Zhongxiang People's Hospital, Zhongxiang, Hubei, China

⁶Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

⁷Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA

⁸Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Houston, TX, USA

⁹Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

¹⁰Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA

Correspondence

Michael F. Wangler, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA.
Email: michael.wangler@bcm.edu

Zheng Sun, Department of Medicine-Endocrinology, Baylor College of Medicine, Houston, Texas, USA.
Email: zheng.sun@bcm.edu

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Abstract

Background: Germline mutations in *PTEN* are associated with the *PTEN* hamartoma tumor syndrome (PHTS), an umbrella term used to describe a spectrum of autosomal-dominant disorders characterized by variable phenotypic manifestations associated with cell or tissue overgrowth. We report a boy who developed severe progressive abdominal distention due to a dramatic adipose mass from the age of 7 months and developed recurrent hypoinsulinemic hypoglycemia that led to seizures at the age of 4 years. **Methods:** Trio-based whole-genome sequencing was performed by using blood DNA from the child and his parents. The possible pathogenic variants were verified by Sanger sequencing. Functional characterization of the identified variant was completed by western blot.

Results: The child inherited a single-nucleotide deletion NM_000314.6:c.849delA (p.Glu284Argfs) in the tumor suppressor gene *PTEN* from his father. The paternal family members have a history of cancer. It is conceivable that *PTEN* loss-of-function induced the adipose tumor growth and hypoglycemia, although the proband did not meet the usual diagnosis criteria of Cowden syndrome or Bannayan–Riley–Ruvalcaba syndrome that are characterized by germline mutations of *PTEN*.

Jidong Liu and Guolian Ding contributed equally to this work.

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Conclusion: This case underlines the variability of phenotypes associated with *PTEN* germline mutations and provides useful information for diagnosis and genetic counseling of *PTEN*-related diseases for pediatric patients.

KEYWORDS

adipose tissue tumor, hypoglycemia, *PTEN*, whole-genome sequencing

1 | INTRODUCTION

The *PTEN* gene (phosphatase and tensin homolog, OMIM number 601,728) located on chromosome 10q22-23 was originally described as a somatically mutated tumor-suppressor gene in brain, breast, and prostate cancer (Li et al., 1997). It encodes a phosphatase protein that deregulates the PI3K/AKT/mTOR pathway target of rapamycin, which affects angiogenesis, proliferation, and migration (Stambolic et al., 1998; Vivanco & Sawyers, 2002; Wu, Senechal, Neshat, Whang, & Sawyers, 1998). Germline mutations in *PTEN* are associated with the *PTEN* hamartoma tumor syndrome (PHTS), an umbrella term used to describe a spectrum of autosomal dominant disorders characterized by variable phenotypic manifestations associated with cell or tissue overgrowth. The PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (Eng, 2003; Hobert & Eng, 2009).

The genetic susceptibility to PHTS has been a subject of intensive study. Germline mutations in the tumor suppressor gene *PTEN* are identified in 80% of patients with the clinical features of CS and 60% of those with the clinical features of BRRS (Blumenthal & Dennis, 2008; Marsh et al., 1999). However, the variability of the clinical manifestations makes the diagnosis difficult (Leslie & Longy, 2016). Additional genetic and epigenetic changes could modulate the phenotypes in PHTS. On one hand, many of the presentations of PHTS are common in the general population, which makes the diagnosis a challenge (Mester & Eng, 2015; Yehia & Eng, 2018). These features, including benign lesions of the breast, uterus, and skin, may not be recognized as PHTS. On the other hand, patients with germline *PTEN* mutations can show phenotypes not matching the clinical diagnostic criteria for PHTS. For example, hypoglycemia is not a typical clinical presentation for PHTS. Recurrent hypoglycemia in children may result from congenital genetic defects in many genes involved in carbohydrate metabolism (De Leon & Stanley, 2017; Ponzi et al., 2018). Failure to recognize a catastrophic episode of hypoglycemia can lead to long-term neurodevelopmental disabilities or death. Efficient identification of the etiology underlying hypoglycemia in infants and children is critical for guiding therapeutic interventions. However, the phenotypic presentation of hypoglycemia is

quite heterogeneous and the underlying etiology is complex. Traditional diagnosis involves a series of hypotheses-driven metabolic tests that are often time-consuming and inefficient in pinpointing the underlying genetic causes (Alam & Schofield, 2018; Ponzi et al., 2018). The next-generation nucleotide sequencing technology allows efficient profiling of the genetic makeup and is increasingly used in the diagnosis of potential inborn errors of metabolism (Ponzi et al., 2018; Stark et al., 2016).

Here, we report a 7-year-old patient who presented with a dramatic abdominal distention caused by a suspected tumor mass, which developed from the abdominal white adipose tissue. The patient had severe hypoglycemia and was found to have a heterozygous germline mutation in the coding region of *PTEN*.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the Research Ethics Committee of Shandong University Qilu Hospital. Informed consent for the photos and publication was obtained from the participants.

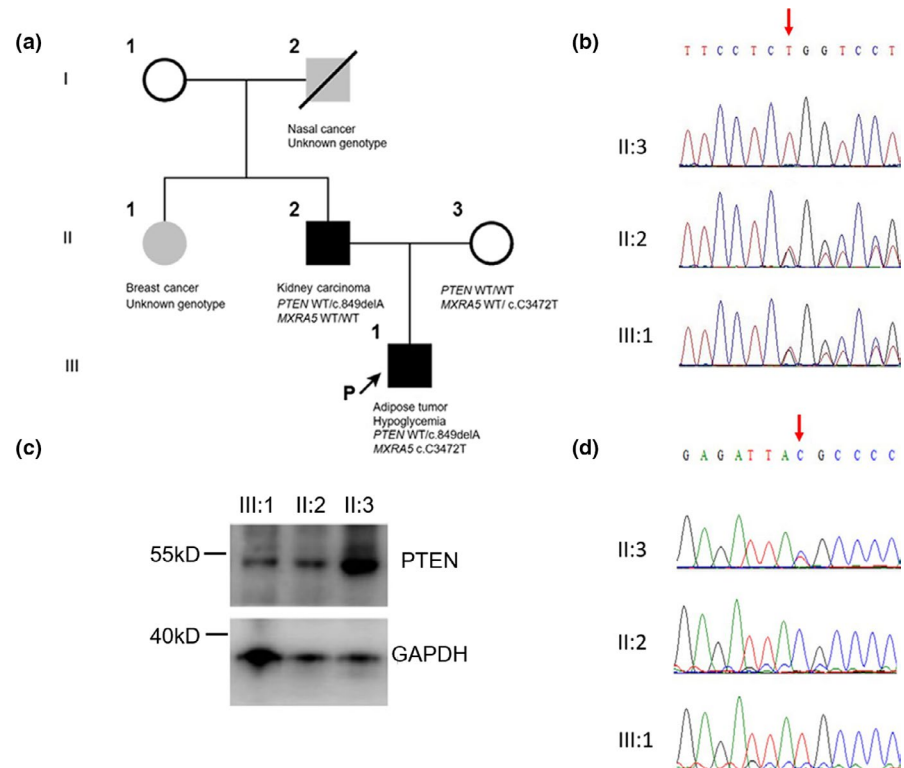
2.2 | Clinical report

The proband presented with massive abdominal distension and hypoglycemia. He was born to nonconsanguineous healthy parents as the first child after a full-term pregnancy. His clinical course during infancy was unremarkable. Parents report that abdominal distention was first noted at the age of 7 months and kept growing throughout childhood (Figure 1a). At the age of 4 years, the proband suffered recurrent episodes of hypoglycemic seizures, with the glucose level at 14–32 mg/dl while the normal range is 70–130 mg/dl. The fasting insulin was <2.0 μIU/ml. The occipitofrontal circumference was 35.8 cm and 51.5 cm at birth and at the age of 4 years, respectively. Computed tomography (CT) analysis at the age of 8 years revealed a large amount of fat accumulation in the abdomen and lower back, high fat density in the psoas muscle and erector

FIGURE 1 Clinical presentation of the proband. (a) Pictures of the proband at the age of 5 years with remarkable abdomen distension. (b) CT scan of the abdomen imaging showing a large amount of fat accumulation



FIGURE 2 Family tree and validation of the possibly pathogenic variants. (a) Family tree and genotype–phenotype relationship of the family. (b) Sanger sequencing confirmation of the *PTEN* NM_000314.6:c.849delA. The antisense DNA strand was sequenced using the Sanger method after PCR amplification. The arrow indicates the site of variant identified in the proband (III:1) and the father (II:2). (c) Western blot analysis of *PTEN* using protein extracts from the whole blood. (d) Sanger sequencing confirmation of *MXRA5* NM_015419.4:c.C3472T variation. The sense DNA strand was sequenced using the Sanger method after PCR amplification. The arrow indicates the site of variant identified in the proband (III:1) and the mother (II:3)



spinae muscles, and normal morphology of pancreas and liver. The imaging investigations pointed toward a provisional diagnosis of a tumor with high-fat content (Figure 1b). The proband (III:1) died of pneumonia and pathological examination of the fat mass could not be performed.

The proband's father (II:2) was diagnosed with clear cell kidney carcinoma at the age of 41 years. The proband's paternal grandfather (I:2) deceased from nasal cancer, and a paternal aunt (II:1) had a history of breast cancer. The proband's mother (II:3) was healthy (Figure 2a).

2.3 | Whole-genome sequencing (WGS)

Chromosomal microarray analysis did not detect potential pathogenic copy number variations. Whole blood samples were collected from the proband and his parents. Genomic DNA was extracted. WGS was performed by using Illumina HiSeq X Ten, with a target 30x coverage for 150 bp paired-end reads. Reads were aligned to the Genome Reference Consortium Human Build 37 (GRCh37/Hg19) using Burrows–Wheeler Aligner (version 0.7.12) (Li & Durbin, 2009). Picard tools (version 1.118, <https://broadinstitute.github.io/picard/>) were used to identify and remove duplicate reads. Single-nucleotide variants (SNVs) and short insertions and deletions (InDels) of ≤ 50 bp were detected using HaplotypeCaller of GATK (version 3.3.0) (McKenna et al., 2010).

2.4 | Variants analysis pipeline

All variants with a minimum depth of 5 were included for the downstream analysis. The Exome Aggregation Consortium (ExAC, version 0.3.1), the 1,000 Genomes Project database, the Genome Aggregation Database (gnomAD, version 2.0) were used to exclude common polymorphisms with a minor allele frequency (MAF) > 0.01 in any of these databases. Variants were then grouped into five categories: de novo, autosomal recessive, compound heterozygous, X-linked recessive, and inherited variants. All truncation, canonical splice-site, frame-shift, and missense variants were retained. ClinVar NCBI database (www.ncbi.nlm.nih.gov/clinvar/) and Online Mendelian Inheritance in Man (OMIM) were used to evaluate the functional impact of the variants. We used SIFT (sift.bii.a-star.edu.sg/), PolyPhen2 (genetics.bwh.harvard.edu/pph2/), CADD (cadd.gs.washington.edu/), and M-CAP (bejerano.stanford.edu/mcap/) to predict the pathogenic potential of variants.

2.5 | Sanger sequencing

A fragment of *PTEN* was amplified using PCR (forward primer: 5′CATCAGGGAAGTTGCACTCA3′; reverse primer: 5′AGTCAACAACCCCAACAAA3′). A fragment of *MXRA5* was amplified using PCR (forward primer: 5′AGACACCACAACAGCAACAA3′; reverse primer: 5′ACCCAAGCTGTAGGAACCAG3′). The PCR products reacted with BigDye Terminator v3.1 Cycle Sequencing kits (Applied Biosystems), using ABI 3,500 Dx Genetic Analyzer (Applied Biosystems), and were analyzed using CodonCode Aligner 8.0.2 (CodonCode Corporation).

2.6 | Western blot analysis

For western blot, the total protein was extracted from whole blood using the whole blood total protein extraction kit (BB-3140, BestBio). Protein samples were quantified using BCA protein assay. Lysates were resolved by Tris-glycine SDS–PAGE, transferred to a PVDF membrane, and blotted with antibodies for PTEN (#9188, Cell Signaling Tech, recognize the C-terminus region of human PTEN) and GAPDH (#60004-1-Ig, Proteintech).

3 | RESULTS

Approximately 3,394,895 single-nucleotide variants (SNVs) and 809,745 insertions or deletions (InDels) were identified in the proband (III:1). The analysis revealed a heterozygous frame-shift single-nucleotide deletion NM_000314.6:c.849delA (p.Glu284Argfs) in exon 8 of the tumor suppressor gene *PTEN*. This variant is recognized as pathogenic in ClinVar (www.ncbi.nlm.nih.gov/clinvar/variation/428233) (Table 1). Sanger sequencing confirmed the presence of the *PTEN* heterozygous variant in the proband (III:1) and his father (II:2) (Figure 2b). Western blot analysis further confirmed the significant reduction of the PTEN protein in the blood samples of the proband (III:1) and his father (II:2) (Figure 2c). The occipitofrontal circumference of the father (II:2) is 57.1cm. Of note, macrocephaly, thyroid nodule, penile freckling, and oral papilloma were not detected in the proband (III:1) or his father (II:2). Neither the proband (III:1) nor his father (II:2) met the National Comprehensive Cancer Network (NCCN) criteria or the threshold of Cleveland Clinic *PTEN* Risk Calculator due to a lack of symptoms (Daly et al., 2017; Tan et al., 2011).

In addition, we noted a missense variant NM_015419.4:c. C3472T (p.Arg1158Cys) inherited from the mother (II:3) in the gene *MXRA5* (matrix remodeling associated 5, OMIM number 300,938) on the X-chromosome (Table 1). This was confirmed by Sanger sequencing (Figure 2d). In silico analysis, SIFT, CADD, and M-CAP predicted the variant to be deleterious.

4 | DISCUSSION

In this study, we report a patient with *PTEN* germline mutation who represented a unique combination of severe hypoglycemia with remarkable abdominal distention caused by the adipose tumor.

PTEN is a canonical tumor suppressor. Heterozygous depletion of *PTEN* predisposes mice to a variety of tumors including lymphomas, dysplastic intestinal polyps, endometrial complex atypical hyperplasia, prostatic intraepithelial

TABLE 1 Annotation and functional prediction of possibly pathogenic variants in the proband

Gene	Locus (Hg19)	Accession number	Mutation type	Nucleotide change	Amino acid change	SIFT	Polyphen-2	CADD	M-CAP	MAF in gnomAD
<i>PTEN</i>	Chr10: 89,720,698	NM_000314.6	Frame-shift	c.849delA	Glu284Argfs	-	-	-	-	0
<i>MXRA5</i>	ChrX:3,240,254	NM_015419.4	Missense	c.C3472T	Arg1158Cys	0.001	0.899	24.8	0.17	0.00006431

Abbreviations: Hg19, GRCh37 reference genome; MAF, minor allele frequency.

neoplasia, and thyroid neoplasms (Podsypanina et al., 1999). In human, germline *PTEN* mutations are associated with increased lifetime risks for a variety of cancers, including 85% risk increase for breast cancer, 35% risk increase for thyroid cancer, 28% risk increase for endometrial cancer, 33% risk increase for renal cell carcinoma, and 9% risk increase for colorectal carcinoma (Tan et al., 2012). Lipoma was noted in about 40% of children with *PTEN* mutations and was identified as early as shortly after birth (Smpokou, Fox, & Tan, 2015). A family was reported with a distinct syndrome consisting of multiple lipomas with abdominal enlargement, which showed similar abdominal symptoms as our proband (Zonana, Rimoin, & Davis, 1976).

The hypoglycemia is not considered a clinical feature in pediatric patients affected by PHTS. Heterozygous loss of *PTEN* could also contribute to hypoglycemia through modulating the insulin signaling pathway. Insulin is the key hormone in systemic glucose homeostasis. Insulin functions by binding to the insulin receptor and activating the PI3K/AKT signaling. *PTEN* heterozygous null mice showed lower fasting glucose levels and remained much lower glucose levels after insulin injection (Wong et al., 2007). Human subjects with *PTEN* deficiency also showed profound insulin sensitization with 60% lower fasting insulin levels and 2 times higher glucose infusion rate in the hyperinsulinemic euglycemic clamp study (Pal et al., 2012). Two siblings harboring germline *PTEN* mutations were reported to display hypoinsulinemic hypoglycemia with fasting glucose and insulin at 14–38 mg/dl and <2 μ IU/ml, respectively (Granados, Eng, & Diaz, 2013). A pediatric patient affected by BRRS with a heterozygous p.K289Nfs frame-shift *PTEN* mutation reported hypoglycemia and precocious puberty with diffuse testicular microlithiasis. The hypoglycemic episodes occurred during fasting and sleeping until the age of 2 years and the serum glucose was lower than 40 mg/dl (Ozsu, Sen, & Ceylaner, 2018). In summary, the *PTEN* deficiency could be the molecular cause for the phenotypes in our proband.

Targeted gene panel represents a powerful tool for the diagnosis of inborn errors of metabolism including those with recurrent hypoglycemia. A panel of 65 genes was shown to provide a diagnosis for 33% of patients whose clinical and biochemical profiles failed to identify pathogenic genes (Ponzi et al., 2018). However, *PTEN* is not included in this hypoglycemia gene panel. Therefore, exome or whole-genome sequencing would be a more comprehensive and efficient approach for the genetic diagnosis of recurrent hypoglycemia in infants or children.

We considered whether the sequencing data could aid in identifying additional candidate modifiers given that the proband had a severe early-onset disease while his father had a very different presentation. Although the effect of a germline variant in *MXRA5* is not clear, somatic mutations in *MXRA5* were recently found highly enriched in liposarcoma and lung cancers

(Kanojia et al., 2015; Xiong et al., 2012). Given the variability of *PTEN*-related disorders, it is unclear whether *MXRA5* variants can actually modify the phenotypic differences in this family.

The major limitation of this study is that it is an observational study of a single family. The tumor tissue was not available due to the unfortunate death of the patient. This limited our analysis of the adipose mass from the patient. Indeed, one might expect that tumors would exhibit a loss-of-heterozygosity (LOH) for *PTEN*, and a second mutation in the gene developed in the mass. In conclusion, this case describes a pediatric patient with a *PTEN* germline mutation who represents a unique combination of severe hypoglycemia with remarkable abdominal distention caused by adipose tissue tumor. The study underlines the phenotypic variability and expands the phenotypes associated with *PTEN* germline mutations.

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CONFLICT OF INTEREST

The authors disclose no competing financial conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

ORCID

Zheng Sun  <https://orcid.org/0000-0002-6858-0633>

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