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CLINICAL REPORT

Prenatal case of Simpson–Golabi–Behmel syndrome with a *de novo* 370Kb-sized microdeletion of Xq26.2 compassing partial *GPC3* gene and review

Jing Liu[1,2] | Qin Liu[1] | Shuting Yang[1] | Na Ma[1] | Jialun Pang[1] | Ying Peng[1,2] | Hui Xi[1,2] | Zhengjun Jia[1] | Yingchun Luo[1,2] | Meiping Jiang[1] | Yanling Teng[3] | Wenxian Yu[1] | Zhuo Li[4] | Hua Wang[1,2]

[1]Department of Medical Genetics, Hunan Provincial Maternal and Child Health Care Hospital, Changsha, Hunan, China

[2]National Health Commission Key Laboratory of Birth Defects Research, Prevention and Treatment, Changsha, Hunan, China

[3]Hunan Jiahui Genetics Hospital, Changsha, Hunan, China

[4]Center for Medical Genetics & Hunan Key Laboratory of Medical Genetics & Hunan Key Laboratory of Animal Models for Human Diseases, School of Life Sciences, Central South University, Changsha, Hunan, China

Correspondence
Zhuo Li, Center for Medical Genetics & Hunan Key Laboratory of Medical Genetics & Hunan Key Laboratory of Animal Models for Human Diseases, School of Life Sciences, Central South University, 110 Xiangya Road, Changsha, Hunan 410078, China.
Email: lizhuo@sklmg.edu.cn

Hua Wang, Department of Medical Genetics, Hunan Provincial Maternal and Child Health Care Hospital, Changsha, Hunan 410008, China.
Email: wanghua213@aliyun.com

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Abstract

Background: Simpson–Golabi–Behmel syndrome type 1 (SGBS1) is a rare X-linked recessive disorder characterized by pre- and postnatal overgrowth and a broad spectrum of anomalies including craniofacial dysmorphism, heart defects, renal, and genital anomalies. Due to the ultrasound findings are not pathognomonic for this syndrome, most clinical diagnosis of SGBS1 are made postnatally.

Methods: A pregnant woman with abnormal prenatal sonographic findings was advised to perform molecular diagnosis. Single nucleotide polymorphism array (SNP array) was performed in the fetus, and the result was validated with multiplex ligation-dependent probe amplification (MLPA) and real-time quantitative PCR (qPCR).

Results: The prenatal sonographic presented with increased nuchal translucency at 13 gestational weeks, and later at 21 weeks with cleft lip and palate, heart defect, increased amniotic fluid index and over growth. A *de novo* 370Kb-deletion covering the 5′-UTR and exon 1 of *GPC3* gene was detected in the fetus by SNP array, which was subsequently confirmed by MLPA and qPCR.

Conclusion: The *de novo* 370Kb hemizygous deletion of 5′-UTR and exon 1 of *GPC3* results in the SGBS1 of this Chinese family. Combination of ultrasound and genetics tests helped us effectively to diagnose the prenatal cases of SGBS1. Our findings also enlarge the spectrum of mutations in *GPC3* gene.

KEYWORDS

GPC3, prenatal diagnosis, Simpson–Golabi–Behmel syndrome 1, SNP array, ultrasound

1 | INTRODUCTION

Simpson–Golabi–Behmel syndrome 1 (SGBS 1, OMIM312870) is a rare X-linked recessive disorder. It was first described by Simpson et al in 1975 (Simpson et al., 1975). Later in 1988, Neri et al reported a pedigree with three affected males who displayed the same symptoms, since then a new syndrome was named as Simpson–Golabi–Behmel syndrome (Neri et al., 1988). Typical features of SGBS1 include macrosomia, facies, macroglossia, diaphragmatic henia, supernumerary nipples, genitourinary and gastrointestinal anomalies, skeletal anomalies, and increased risk for embryonal tumors (Tenorio et al., 2014). Multiple congenital anomalies have been described in SGBS1, most are described in postnatal series (Tenorio et al., 2014; Vuillaume et al., 2018).

The Xq26.2 region is an important region for the regulation of body size, specifically containing two contiguous genes, *GPC3* (OMIM 300037) and *GPC4* (OMIM 300168), which encode glypican-3 and glypican-4, respectively (Karna & Myers, 2020). The majority of SGBS1 patients have point mutations or deletions in *GPC3* (Schirwani et al., 2019; Vuillaume et al., 2018). Only a few SGBS1 families had been reported with duplication involving the entire of *GPC*3 and *GPC*4 (Mujezinovic et al., 2016; Schirwani et al., 2019; Vuillaume et al., 2018; Zimmermann & Stanek, 2017). Most of the mutations in the cases are inherited from the mother, and ~25% are *de novo* (Chen et al., 1993).

Here we report a prenatal case with fetal overgrowth and craniofacial anomalies during the first pregnancy of an unaffected mother. A *de novo* deletion covering 5′-UTR and exon1 in *GPC3* was identified in the fetus by SNP array and confirmed via MLPA and qPCR. The subsequent genetic counseling was performed according to the results. To our knowledge, this is the first report of partial *GPC3* deletion for a fetus with SGBS1 in Chinese population.

2 | CLINICAL REPORT

The research was approved by the Ethics Committee of the Maternal and Child Health Hospital of Hunan Province (EC20190105). A gravida 1, para 0 woman came to our clinical genetics center at 16 weeks of gestation for genetics counseling due to her first-trimester ultrasound screening result which was performed at 13 weeks. The mother (I:2) was 24-year-old and her husband (I:1) was 25-year-old. Both of them were non-consanguineous Chinese. And the mother mentioned that she had repaired her unilateral cleft lip when she was a child. There is no family history for genetic disorders. The ultrasound examination in 13 weeks for the fetus (II:1) revealed a markedly thickened nuchal

TABLE 1 Antenatal features of confirmed cases of SGBS with *GPC3* or *GPC4* gross rearrangements

	Present case	Hughes-Benzie et al., (1996)	Chen et al., (1993)			Weichert et al., (2011)
			Case 1	Case 2	Case 3	
Gestational age (week)	21		22	18	21	22
Prenatal findings						
MSAFP ↑	n/a	✓	✓	—	✓	✓
NT/Cystic hygroma ↑	✓	n/a	✓	—	✓	✓
Craniofacial anomaly	✓	✓	—	—	✓	✓
Macrosomia	✓	✓	—	✓	—	✓
Polyhydramnios	✓	✓	—	✓	—	✓
CDH	—	—	✓	✓	✓	n/a
Renal anomaly	—	—	✓	—	—	n/a
Outcome	TOP 21 weeks	Died at age 4.5 months	Died at age 3 days	n/a	TOP 21 weeks	TOP 24 weeks
Mutational analysis	GPC3 5′UTR and exon 1 deletion	GPC3 exon 1 deletion	GPC4 duplication	GPC3 and GPC4 deletion	GPC3 exon 7 duplication	GPC4 and GPC3 exon 3–6 duplication

Abbreviations: CDH, congenital diaphragmatic hernia; MSAFP, maternal serum alpha fetoprotein; n/a, not applicable; NT, nuchal translucency; TOP, termination of the pregnancy; week, gestational week.

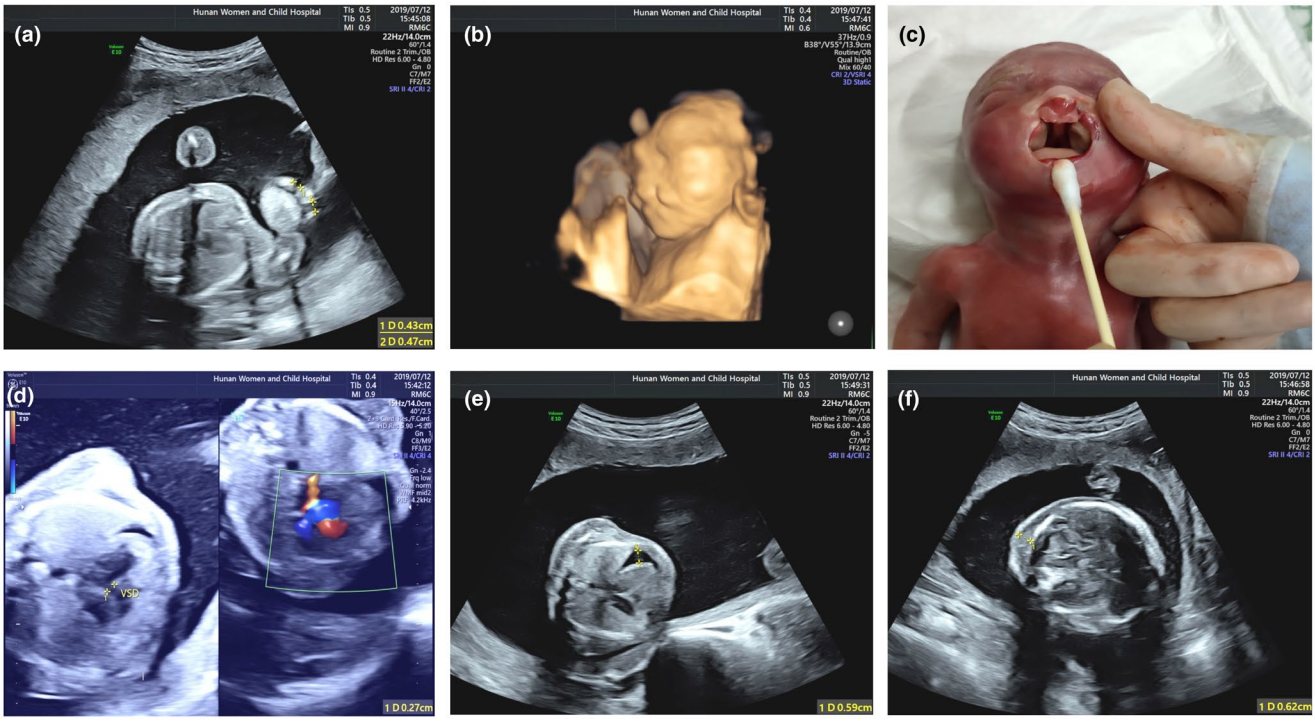

FIGURE 1 Appearance of the fetus at 21 weeks. (a) Gray-scale imaging showing the bilateral cleft lip and palate; (b) The 3-D image of face; (c) Clinical presentation after TOP at 21 weeks confirming severe bilateral cleft lip and palate; (d) Ultrasound features of heart-VSD; (e) Pericardial cavity effusion; (f) Thickened NF

Vuillaume et al., (2018)		Zimmermann and Stanek, (2017)	Mujezinovic et al., (2016)	Stove et al., (2017)	Kehrer et al., (2016)	Ochiai et al., (2013)	Magini et al., (2016)
Case 1	**Case 2**						**family 2**
n/a	n/a	37		13	17	18	16
✓	✓	✓	n/a	✓	n/a	n/a	n/a
n/a	n/a	✓	n/a	—	✓	n/a	✓
n/a	n/a	✓	—	✓	—	✓	✓
✓	✓	✓	✓	—	✓	✓	✓
✓	—	n/a	✓	—	✓	n/a	✓
—	—	✓	—	—	✓	✓	—
—	✓	—	—	—	✓	✓	✓
n/a	n/a	Died after birth		TOP 15 weeks	TOP	TOP 20 weeks	TOP
Xq26.2 with loss of portion GPC3	GPC3 and GPC4 duplication	GPC3 exon 2 deletion	GPC3 exon 3–7 Duplication	GPC3 exon 2b Duplication	Xq26.2(132834006–132986815)×0		

translucency (NT) (5.6 mm), with crown-lump length (CRL) was 64mm. Prenatal diagnosis was suggested according to thickened NT. Amniotic fluid and blood samples were obtained from the fetus and the couple separately after informed consent at 16 weeks. A traditional karyotype and SNP array were performed on the fetus firstly. According to the genetic testing results, a second round of ultrasound screening was scheduled at 21 weeks of gestation. The followed up scan of the fetus showed several craniofacial abnormalities such as bilateral cleft lip and palate (Figure 1a–c), heart defect such as ventricular septal defect (VSD) (Figure 1d), pericardial cavity effusion was 0.44–0.59cm (Figure 1e), nuchal fold (NF) thickness was 6.2mm (Figure 1f), amniotic fluid index (AFI) was 27.6cm, biparietal diameter was 5.3 cm (+1.13SD), head circumference was 19.1 cm (+1.11SD), abdominal circumference (AC) was 19.0 cm (+3.61SD), and estimated weight was 505 grams (+2.48SD). The couple finally decided to terminate the pregnancy after the CMA and ultrasound screening results, but refused to perform an autopsy.

3 | CYTOGENETICS AND SINGLE NUCLEOTIDE POLYMORPHISM ARRAY

After culturing amniotic fluid cells obtained from the fetus, routine chromosome G-banded (320–400 bands) karyotyping analysis was performed on metaphase cells according to standard protocols.

SNP array analysis: Genomic DNA was extracted from the amniotic fluid cells using DNA Extraction Kit (Tissue and cells). SNP array was performed using Affymetrix CytoScan®750 K Array (Affymetrix Inc), according to the manufacturer's protocol. Array results were analyzed using Chromosome Analysis Suite (ChAS; version 2.1). All genomic coordinates were taken from the February 2009 (hg19) human reference sequence (NCBI Build 37). Genes and Online Mendelian Inheritance in Man (OMIM) references were from RefSeq and OMIM entries, respectively.

4 | MULTIPLE LIGATION DEPENDENT PROBE AMPLIFICATION (MLPA) AND QUANTITATIVE PCR DETECTION

After the pregnancy was terminated, further confirmation of CNV and the origin by SNP array, MLPA, and qPCR were done to the mother and the fetus. The SALSA MLPA P154-C2 GPC3-GPC4 kit (MRC-Holland, Amsterdam, The Netherlands) was performed to determine the DNA copy number of a single DNA sequence in each of 37 reference probes, which include 26 probes within the GPC3-GPC4 gene and other 11 reference probes on the X-chromosome. MLPA analysis was performed following the manufacturer's instructions. MLPA products were examined by ABI 3500Dx genetic analyzer (Thermo Fisher, USA), quantitative data were analyzed using the software of Coffalyser V8.0 (http://www.mlpa.com/coffalyser). Mean cut-off for normalized peak height ratio of patient to the control sample was less than 0.65 in case of deletions and more than 1.40 in case of duplications. qPCR primers used for the confirmation of the Xq26.2 deletion are listed in Table S1.

5 | RESULTS

G-banded analysis of fetus showed a normal male karyotype: 46, XY (resolution 320–400 bphs). The SNP array was performed at the 16 weeks of gestation, and the results revealed a 370 Kb-sized deletion on Xq26.2 (arr[hg19] Xq26.2 (133,090,741–133,461,501)×0), encompassing part of only one OMIM gene (*GPC3*) (Figure 2a), which included the 5′-UTR and exon 1 of *GPC3*. After the medical termination of pregnancy at 21 weeks, both the MLPA and qPCR results on the amniotic fluid cells and the mother's blood also validated the absence of the copy number of 5′UTR and exon 1 in *GPC3* of the fetus, suggesting a hemizygous deletion, but not found in the mother's genome (Figure 2b–e). Then the deletion was considered to be a *de novo* mutation. This 370Kb deletion has not been reported yet, nor recorded in related databases.

6 | DISCUSSION

In this study, we reported a fetus who presented with a markedly increased NT (5.6 mm) at 13 weeks of gestation and then developed fetal overgrowth and craniofacial anomalies at 21 weeks of gestation. A novel 370Kb deletion covering 5′-UTR and exon1 of *GPC3* was identified to be the genetic cause for the affected fetus, who was thus diagnosed to be SGBS1. Due to the overlapping clinical features of a number of overgrowth syndromes (Vora & Bianchi, 2009), prenatal cases of SGBS have only rarely been reported in the current literature, and the clinical diagnosis are usually made postnatally.

Typical features of SGBS include macrosomia, facies, macroglossia, diaphragmatic hernia, supernumerary nipples, genitourinary and gastrointestinal anomalies, skeletal anomalies, neonatal hypoglycemia, and increased risk for embryonal tumors (Manor & Lalani, 2020; Tenorio et al., 2014; Vuillaume et al., 2019). The differential diagnosis of SGBS includes conditions presenting with craniofacial

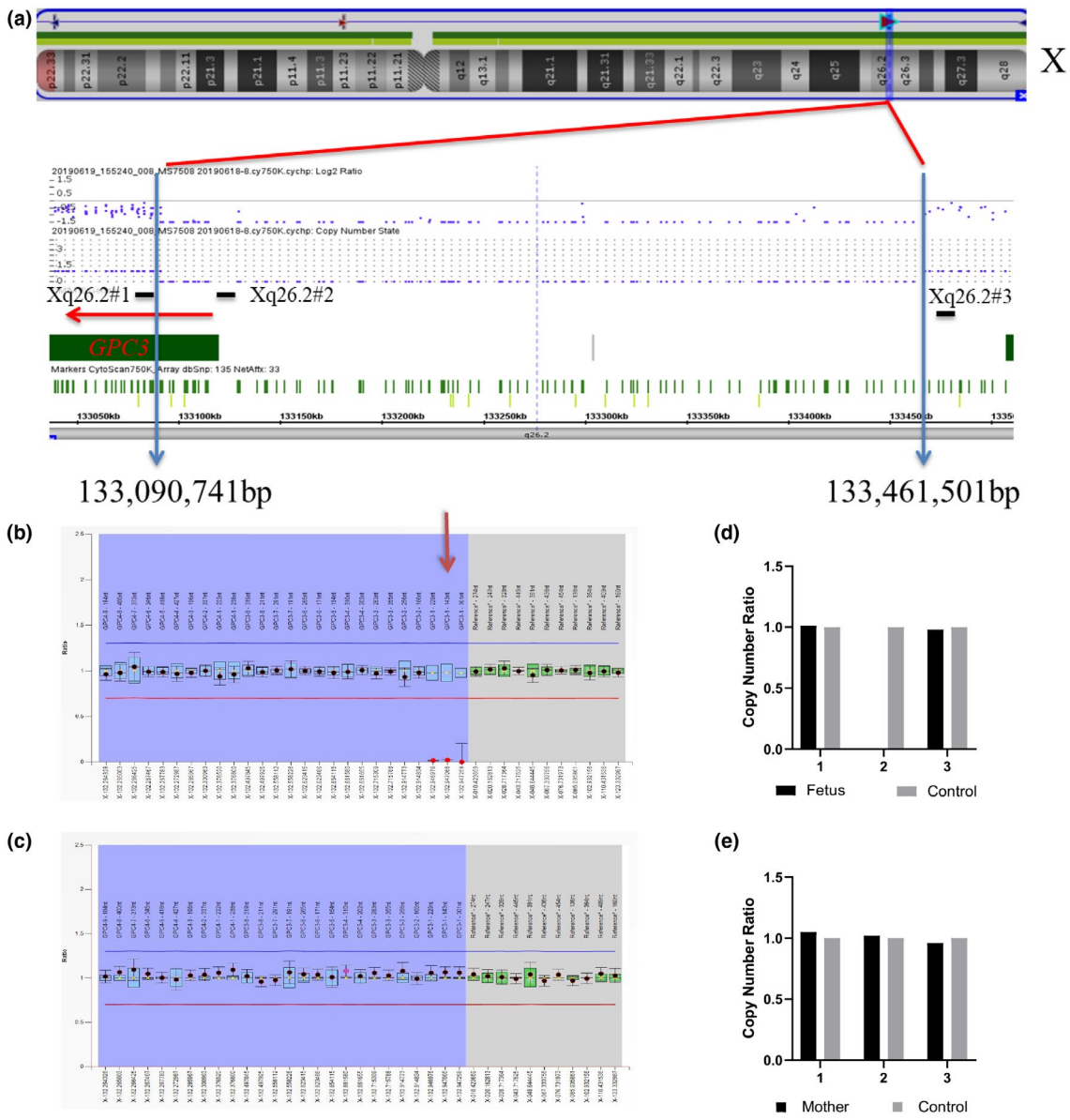

FIGURE 2 Genetic tests for the family. (a) SNP array revealed a 370 Kb deletion on chromosome Xq26.2 of the fetus: arr[hg19] Xq26.2 (133,090,741–133,461,501)×0. This deletion covered partial of GPC3 gene. qPCR for locations of Xq26.2#1, Xq26.2#2, Xq26.2#3 marked as the three black blocks. (b) MLPA also showed a total decreased bar height of exon 1 in TCOF1 gene, indicating a hemizygous deletion in the fetus. (c) MLPA for the mother showed normal height bar of all exons in GPC3 and GPC4 gene. (d) qPCR confirmed a 0-dose for Xq26.2#2 region in the affected fetus compared with the normal individual. Xq26.2#1 and Xq26.2#3 was set up as a normal control. (e) qPCR for these three locations were all in normal dosage in the mother

dysmorphology and fetal macrosomia, such as Beckwith-Wiedemann syndrome (BWS) (OMIM 130650), Sotos syndrome (OMIM 117550), Weaver syndrome (OMIM 277590), Perlman syndrome (OMIM 267000) or Pallister-Killian syndrome (PKS; OMIM 601803). The main overlap in clinical presentations in the prenatal setting for SGBS would be with BWS (Ridnoi et al., 2018). Therefore, it is still challenging to make a definite diagnosis for prenatal SGBS just based on the limited information from ultrasound imaging.

In our case, the fetus displayed significantly enlarged NT at 13 weeks. Although NT is a well-known soft marker of chromosomal anomalies, enlarged NT may also present in many monogenic defect syndromes, such as Noonan syndrome (Pergament et al., 2011). According to some previous prenatal reports on SGBS, elevated maternal serum alpha-fetoprotein (MSAFP) levels, increased NT or thickened NF were also suggested as antenatal markers for SGBS (Chen et al., 1993; Li & McDonald, 2009; Ridnoi et al., 2018; Young et al., 2006). In another review for prenatal symptoms

of SGBS1, it was described that fetal macrosomia accounted for 86% of the cases, polyhydramnios was reported in 70% of cases, and organomegaly was found in 60% of cases (Ridnoi et al., 2018). At 21 weeks of gestation, our case also manifested with macrosomia, polyhydramnios, organomegaly, facial clefts, and congenital heart defects. But it was still hard to differentially define as SGBS just depending on the ultrasound results. Combination with the results of SNP array, the fetus was finally diagnosed with SGBS1 and then the pregnancy was terminated according to the parent's decision. The appearance of the aborted fetus also confirmed part of prenatal symptoms, such as severe bilateral cleft lip and palate.

Using genetic testing, more and more dysmorphic prenatal cases have been accurately diagnosed. In our case, the 370-Kb deletion within the Xq26.2 region was first prenatally detected by SNP array, and then further confirmed by MLPA and qPCR after TOP. The *de novo* 370-Kb deletion encompasses a deletion of 5′UTR and exon 1 of *GPC3* gene, which might result in complete loss of function. As we know, the Xq26.2 region is a vital region for regulation of body size, especially *GPC3* plays a key role in regulating cell proliferation in embryonic mesodermal tissues and is likely involved in modulating cellular responses to intrinsic growth factors (Weichert et al., 2011). All male with mutations or deletions of this gene (resulting in a protein of severely curtailed or even loss of function) will exhibit clinical findings of SGBS1 (Weichert et al., 2011). Up to date, more than 103 distinct mutations have been identified in the *GPC3* gene collected in the Human Gene Mutation Database® (HGMD), most of which are gross deletions or missense/nonsence mutations. Only a few cases diagnosed as SGBS1 involving the deletion of the exon 1 in *GPC3* gene (Cottereau et al., 2013; Hughes-Benzie et al., 1996; Lindsay et al., 1997). Beside the mutations of *GPC3* gene, deletions or duplications involving *GPC4* gene were also related to SGBS1 (Chen et al., 1993; Vuillaume et al., 2018; Weichert et al., 2011). We conducted a system review (Table 1) of the previous reported prenatal features with *GPC3* or *GPC4* rearrangements, but it was still hard to find the genotype-phenotype correlation, and most cases chose TOP or died after birth. According to previous studies, SGBS1 was rarely reported in Asian countries. There were only 9 cases reported in the Japanese population (Ochiai et al., 2013; Okamoto et al., 1999; Sakazume et al., 2007), Zhang et al reported the first SGBS1 with subclinical hypothyroidism in Chinese population postnataly (Zhang et al., 2019), and Xiang et al described the first prenatal SGBS1 causing by nonsense variant of *GPC3* (Xiang et al.,l., 2020). In these cases, only one patient carried a deletion of 35,074-bp (between g.132445395 and g.132480524) spanning introns 6 and 7 and including entire exon 7 of *GPC3* (Sakazume et al., 2007) and the other one carried a duplication of exon 2b of *GPC3* (Ochiai et al., 2013).

In this study, we performed SNP array on the affected fetus for prenatal diagnosis due to the enlarged NT detected in the first round of ultrasound screening. A *de novo* 370Kb deletion within Xq26.2 region covered 5′-UTR and exon 1 in *GPC3* was identified and confirmed by MLPA and qPCR. Combining with the sonographic findings and the genetics results, we confirmed the diagnosis of SGBS1 for the family. This gross deletion was never reported in literatures and might lead to loss of protein function. And this is the first prenatal report of SGBS1 due to partial *GPC3* deletion in the mainland of China. For the *de novo* 370kb deletion, the recurrence risk of SGBS1 in this family is low, but prenatal diagnosis is still suggested in the next pregnancy in case of gonadal mosaicism. Our study also indicates that when facing with a similar case with enlarged NT/macrosomia/polyhydramnios in prenatal stage, molecular genetics testing such as SNP array would help a lot to make definite diagnosis to guide the following genetic counseling.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Jing Liu, Zhuo Li, and Hua Wang had major roles in the design of the study. Jing Liu and Zhuo Li drafted the manuscript. Jing Liu, Qin Liu, Jialun Pang, Wenxian Yu, Yanling Teng, and Na Ma performed the molecular genetic experiments and analyzed the data. Shuting Yang, Yingchun Luo, Meiping Jiang, Ying Peng, and Hui Xi analyzed the clinical data. Zhuo Li and Hua Wang are corresponding authors of this manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared at request of qualified investigators.

ORCID

Na Ma https://orcid.org/0000-0003-0089-7789
Ying Peng https://orcid.org/0000-0002-0602-6063
Zhuo Li https://orcid.org/0000-0001-6010-6139

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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