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Case Report

Chromosome 15q overgrowth syndrome: Prenatal diagnosis, molecular cytogenetic characterization, and perinatal findings in a fetus with dup(15)(q26.2q26.3)

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Abstract

Objective: To present molecular cytogenetic characterization of a prenatally detected duplication of 15q26.2 → q26.3 in a fetus with overgrowth.
Case Report: A 34-year-old para 0 woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a derivative chromosome 15, or der(15), with additional material at the end of the long arm of one chromosome 15. Parental karyotypes were normal. Fetal overgrowth was first noted at 21 weeks of gestation. Repeated amniocentesis was performed at 22 weeks of gestation. Array comparative genomic hybridization revealed a 4.71-Mb duplication from 15q26.2 to 15q26.3 encompassing the *IGF1R* gene. Fluorescence *in situ* hybridization analysis using the bacterial artificial chromosome clone probes specific for 15q26.2-q26.3 and the subtelomeric region of 15q showed a direct duplication and no terminal deletion in the der(15). Polymorphic DNA marker analysis determined a paternal origin of the duplication of 15q. Level II ultrasound at 23 weeks of gestation revealed a fetal biometry equivalent to 26 weeks. The pregnancy was subsequently terminated, and a 1062-g (>99th centile) malformed fetus was delivered at 24 weeks of gestation with craniofacial dysmorphism, craniosynostosis, and overgrowth.
Conclusion: The present case provides evidence for prenatal overgrowth, craniosynostosis, and characteristic facial dysmorphism in association with a duplication of 15q26.2 → q26.3 and a duplication of the *IGF1R* gene. Prenatal diagnosis of fetal overgrowth should include a differential diagnosis of the chromosome 15q overgrowth syndrome.
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Keywords: dup(15q); Duplication; 15q Overgrowth syndrome; Prenatal diagnosis

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Introduction

The chromosome 15q overgrowth syndrome is an overgrowth syndrome caused by increased gene dosage of *IGF1R* through duplication or triplication of the 15q26.1-qter region involving 15q26.3 because of trisomy and tetrasomy of distal chromosome 15q [1]. This syndrome is characterized by the clinical features of overgrowth, learning difficulties, a characteristic facial appearance of a long thin face with a prominent chin and nose, and renal anomalies of renal agenesis, horseshoe kidneys, and hydronephrosis [1]. Prenatal diagnosis of the chromosome 15q overgrowth syndrome is unusual. Here we report prenatal diagnosis, molecular cytogenetic characterization, and perinatal findings in a fetus with a duplication of 15q26.2 → q26.3 and overgrowth.

Case report

A 34-year-old, gravid 2, para 0, woman underwent amniocentesis at 18 weeks of gestation because of her advanced maternal age. The woman had experienced two spontaneous abortions. Her husband was 35 years old. Cytogenetic analysis then revealed a derivative chromosome 15, or der(15), with additional material at the end of the long arm of one chromosome 15 (Fig. 1). The parental karyotypes were normal. Prenatal ultrasound examinations had revealed a fetal biometry equivalent to 16 weeks [biparietal diameter (BPD) = 2.9 cm (16^{th} centile), femur length (FL) = 2.2 cm (79^{th} centile)] at 16 weeks of gestation and a fetal biometry equivalent to 23 weeks [BPD = 5.78 cm ($>99^{th}$ centile), FL = 3.54 cm (72^{nd} centile)] at 21 weeks of gestation. The woman requested amniocentesis at 22 weeks of gestation. Using uncultured amniocytes, oligonucleotide (oligo)-based array comparative genomic hybridization (aCGH) (CytoChip Oligo; BlueGnome, Cambridge, UK) demonstrated a 4.71-Mb duplication from 15q26.2 to 15q26.3 (95,490,272–100,200,967 bp) (NCBI build 36, March 2006) (Fig. 2). The result of oligo-aCGH was arr cgh 15q26.2q26.3 (95,490,272–100,200,967)×3. For fluorescence *in situ* hybridization (FISH) determination of the orientation of the duplication and no terminal deletion in the der(15), the bacterial artificial chromosome (BAC) clone probes mapping the genomic region of 15q26.2-q26.3 and the subtelomeric region of 15q were used. The BAC clone probes RP11-308P12 (96,148,983–96,341,797) (spectrum green) and RP11-66B24 (99,149,459–99,322,865) (spectrum red) were used to determine the orientation of the duplication. FISH analysis showed an orientation of green-[(red-green) or yellow]-red consistent with the diagnosis of a direct duplication of distal 15q (Fig. 3). The BAC clone probe RP11-259N2 (100,094,760–100,248,597) (spectrum green) was used to determine the presence of the subtelomeric region of the der(15). FISH analysis showed no terminal deletion in the der(15) (Fig. 4). The karyotype of the fetus was 46,XY,dup(15) (q26.2q26.3) (Fig. 1). Level II ultrasound at 23 weeks of gestation revealed a fetal biometry equivalent to 26 weeks [BPD = 6.7 cm ($>99^{th}$ centile), abdominal circumference = 21.6 cm ($>99^{th}$ centile), and FL = 4.56 cm ($>99^{th}$ centile). The internal organs were unremarkable. The parents elected to terminate the pregnancy, and a 1062-g ($>99^{th}$ centile) malformed fetus was delivered at 24 weeks of gestation. The fetus manifested macrocephaly, an elongated face, a sloping forehead, down-slanting palpebral fissures, hypertelorism, a down-turned mouth, and a prominent nose and chin (Fig. 5). Three-dimensional computed tomography scans of the skull showed premature synostosis of the metopic and coronal sutures (Fig. 6). Quantitative fluorescent polymerase chain reaction analysis using polymorphic DNA markers determined a paternal origin of the duplication (Fig. 7) (Table 1).

Discussion

The present case had a direct duplication of 15q26.2 → q26.3 and a duplication of the *IGF1R* gene, and manifested prenatal overgrowth, craniosynostosis, and characteristic facial dysmorphism. Insulin-like growth factor 1 receptor [Online Mendelian Inheritance in Man (OMIM) 147370] is the receptor for type 1 insulin-like growth factor (IGF1) (OMIM 147440). The *IGF1R* gene is mapped to 15q26.3 and is involved in growth, insulin-related phenotypes, and longevity. The *IGF1R* gene is expressed equally from the maternal and paternal alleles in humans and has not been known to be imprinted [2,3]. Insulin-like growth factor 1

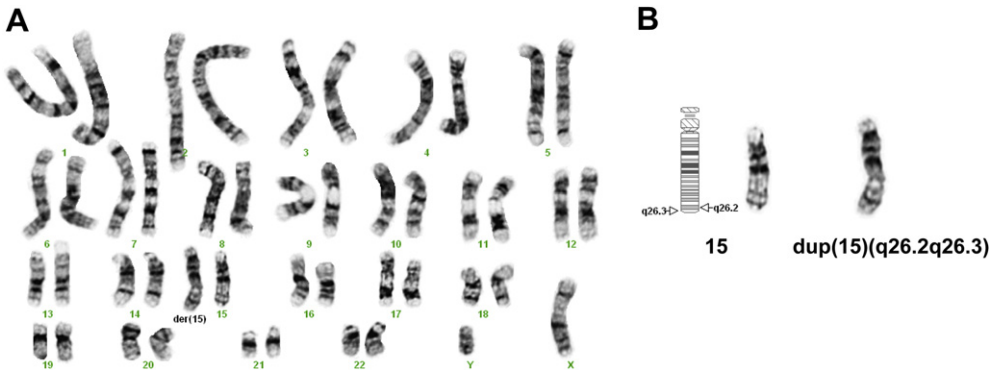

Fig. 1. (A) A karyotype 46,XY,dup(15)(q26.2q26.3) in the fetus. (B) Partial G-banded karyotype of the fetus showing one normal chromosome 15 and one derivative chromosome 15, or der(15), with dup(15q)(q26.2q26.3). The arrows indicate the breakpoints. dup = duplication.

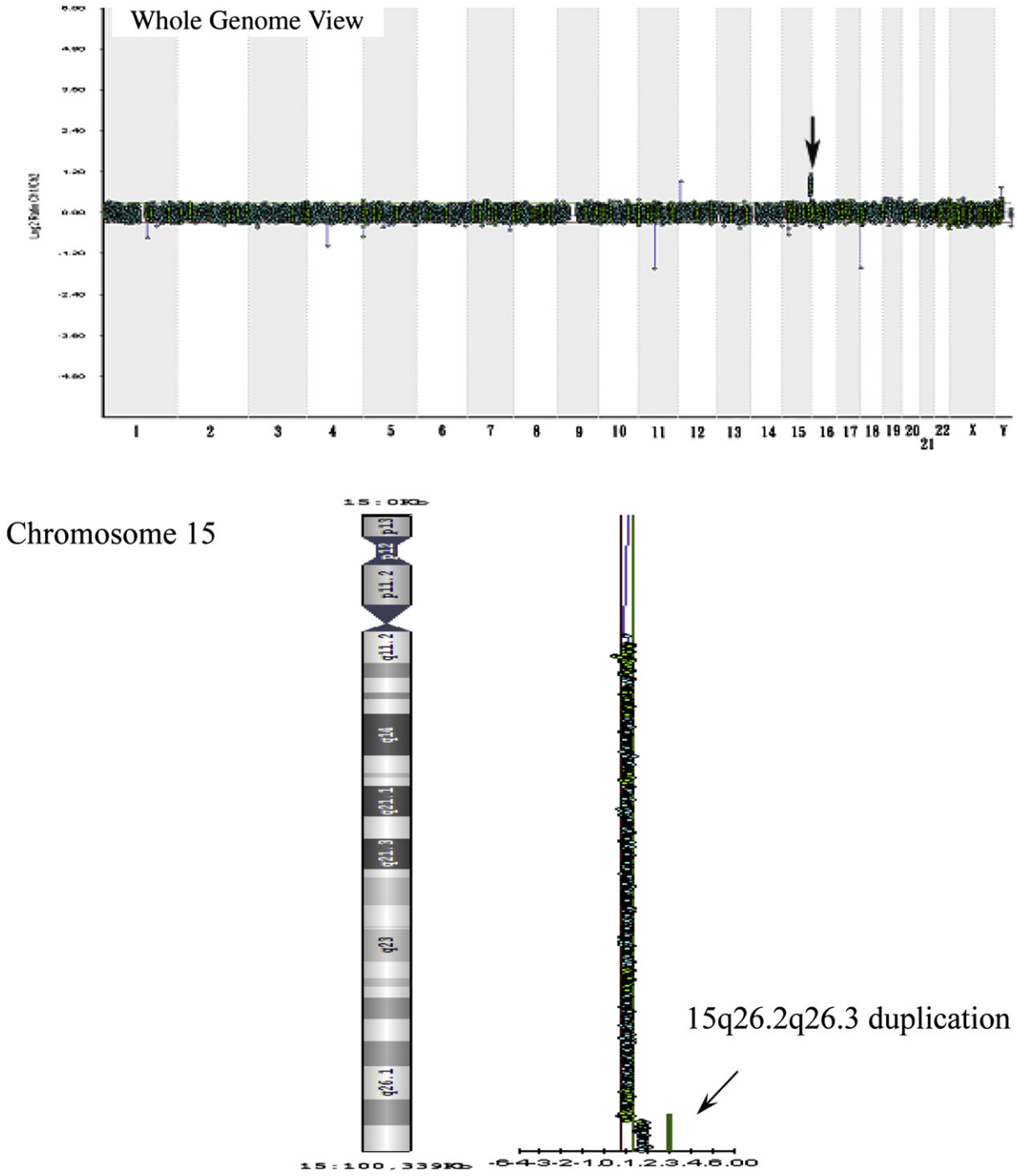

Fig. 2. Oligonucleotide-based array comparative genomic hybridization shows a 4.71-Mb duplication from 15q26.2 to 15q26.3 [arr cgh 15q26.2q26.3 (95,490,272–100,200,967)×3] (arrow). arr cgh = array comparative genomic hybridization.

receptor is required for normal fetal and postnatal growth. Gene dosage increase of *IGF1R* can lead to overgrowth, whereas gene dosage decrease of *IGF1R* can cause growth retardation. Okubo et al [4] reported accelerated growth of the skin fibroblasts in a tall child with three copies of the *IGF1R* gene and slower growth of the skin fibroblasts in a short child with one copy of the *IGF1R* gene. Faivre et al [5] observed a specific phenotype of macrosomia at birth, overgrowth, macrocephaly, and mild developmental delay in patients with trisomy 15q26.1-qter. Kant et al [6] reported tall stature and mental retardation in patients with trisomy 15q26-qter and a duplication of the *IGF1R* gene. Abuzzahab et al [7] postulated that mutations in the *IGF1R* gene may result in IGF1 resistance and underline intrauterine growth retardation and subsequent short stature. Bonafè et al [8] hypothesized that the polymorphic variants of *IGF1R* play a role in systemic IGF1 regulation and human longevity by down-regulating the IGF1 pathway or IGF1 plasma levels.

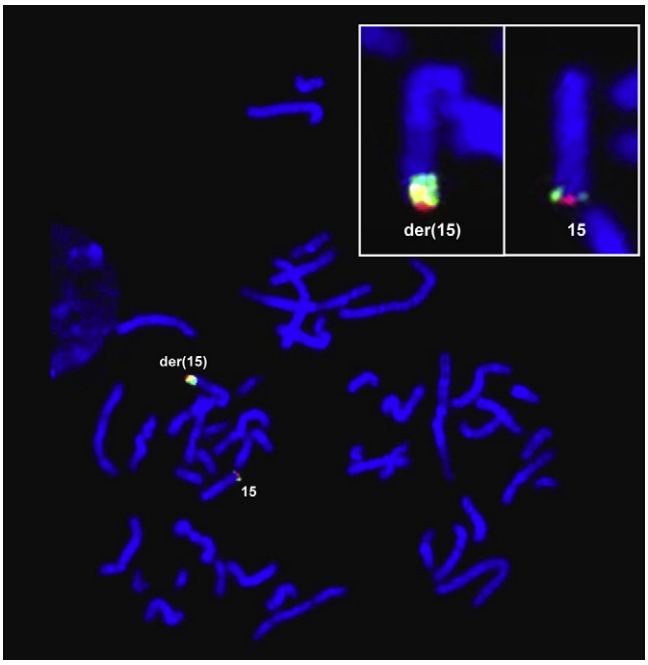

Fig. 3. Fluorescence *in situ* hybridization using bacterial artificial chromosome clone probes RP11-308P12 (96,148,983–96,341,797) (spectrum green) at 15q26.2-q26.3 and RP11-66B24 (99,149,459–99,322,865) (spectrum red) at 15q26.3. A direct duplication of 15q in the orientation of green-[(red-green) or yellow]-red is evident in the der(15). The inset shows the amplified der(15) and chromosome 15.

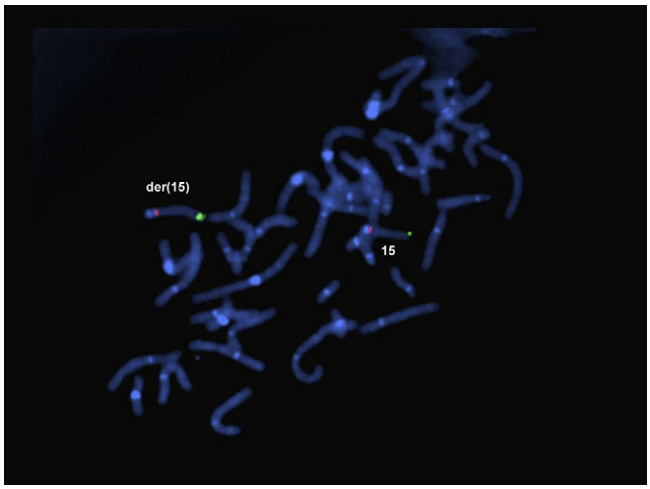

Fig. 4. Fluorescence *in situ* hybridization using bacterial artificial chromosome clone probes RP11-259N2 (100,094,760–100,248,597) (spectrum green) at 15q26.3 and RP11-138H15 (19,375,579–19,534,126) (spectrum red) at 15q11.2 as internal control shows presence of the green signal in the der(15).

Pure trisomy for distal 15q has been described in at least 15 patients [1,4,6,9–14]. In case of mixed or non-pure trisomy for distal 15q, the chromosome aberration has arisen from an unbalanced reciprocal translocation inherited from the parent and contains a deletion of another chromosome. The phenotype of such a case thus can be attributed to monosomy of the involved chromosome in addition to partial trisomy 15q. The reported monosomies associated with non-pure trisomy 15q include monosomic components of chromosomes 2q [6,15–18], 12p [19], 13q [5,20,21], 14p [1], 15p [1], and 20p [5]. Inv dup del(15q) has been reported in one case [30]. Genesio et al [30] reported an inverted duplication of 15q and a terminal 15q deletion in a case with three copies of the *IGF1R* gene, marked intrauterine growth restriction, congenital heart defects, horseshoe kidneys, hand contractures, and club feet. In case of tetrasomy for distal 15q, the tetrasomy is the result of an acentric inverted duplication of distal 15q in the form of mosaic or non-mosaic distribution of an analphoid supernumerary marker chromosome [1,22–29]. To date, about 41 patients with trisomy or tetrasomy for distal 15q have been reported. Among the 41 reported cases with trisomy or tetrasomy for distal 15q, only six cases manifested craniosynostosis [15,19–21,25]. Our case adds to the list of trisomy or tetrasomy for distal 15q with craniosynostosis.

Prenatal diagnosis of fetal overgrowth should include a differential diagnosis of incorrect gestational dating; normal

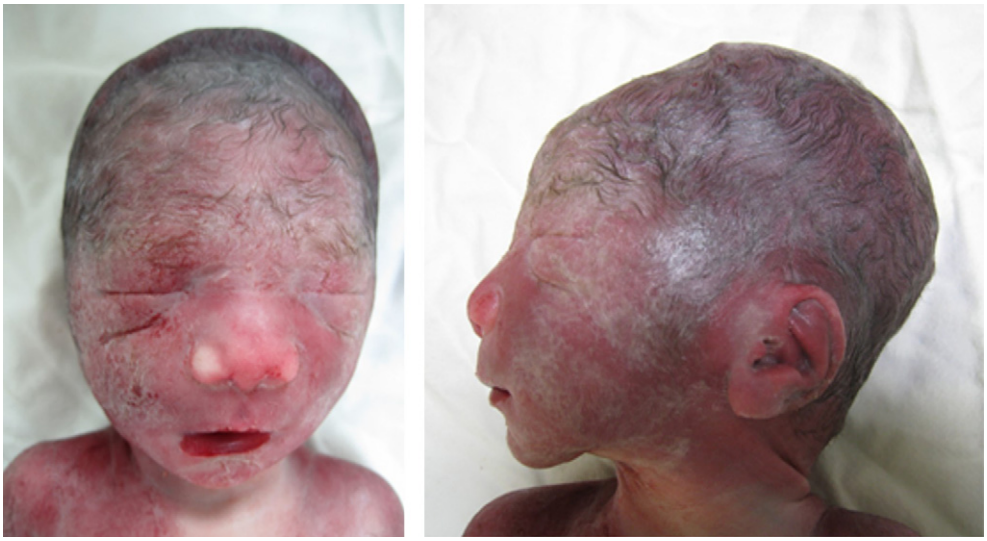

Fig. 5. The craniofacial appearance of the fetus at birth.

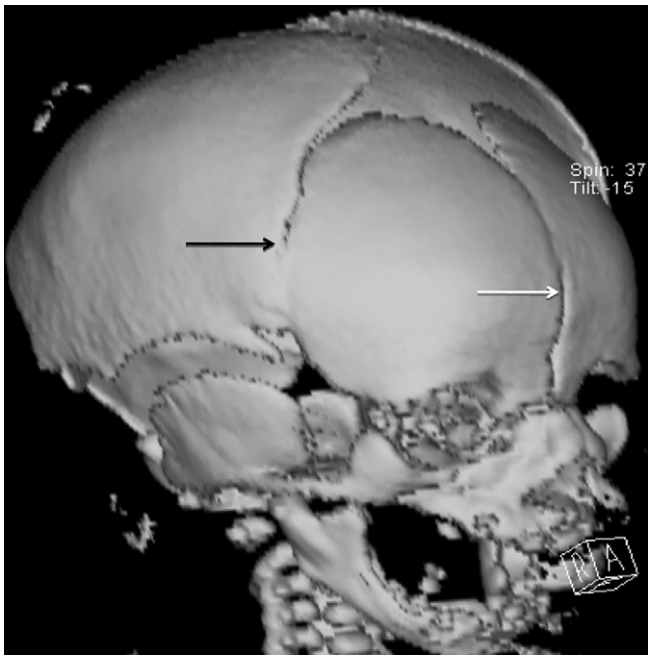

Fig. 6. Three-dimensional computed tomography scans of the skull shows premature synostosis of the metopic and coronal sutures.

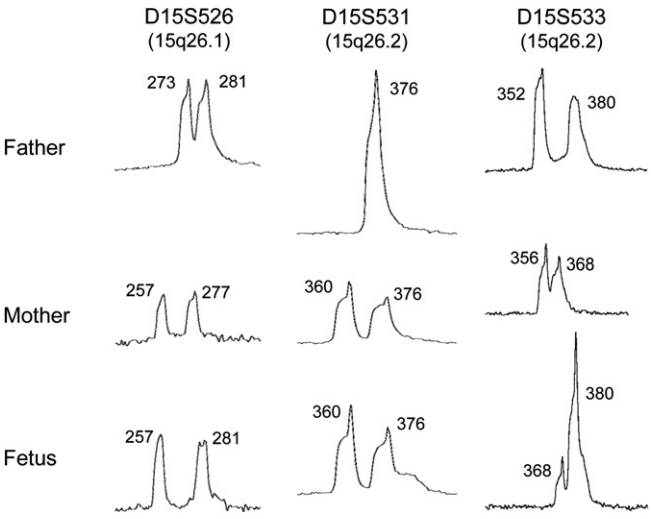

Fig. 7. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays. The marker D15S533 shows two peaks (368 bp: 380 bp; maternal and paternal, respectively) of unequal fluorescent activity from two different parental alleles in the fetal tissues with a dosage ratio of 1:2 (maternal:paternal) indicating a paternal origin of the duplication.

variants such as familial tall stature or familial rapid maturation; secondary overgrowth which is due to humorally mediated factors outside the skeletal system such as diabetic macrosomia or congenital nesidioblastosis; and primary overgrowth which is due to intrinsic cellular hyperplasia [31,32]. Genetic considerations of primary overgrowth in prenatal-onset overgrowth include trisomy or tetrasomy for distal 15q or the chromosome 15q overgrowth syndrome [1], proximal 4p deletion [33], deletion or microdeletion of 9q22.3 involving *PTCH1*, the gene responsible for Gorlin syndrome (OMIM 109400) (autosomal dominant at 9q22.3) [34–37], duplication of 4p16.3 [38], deletion of 22q13 [39,40], mosaic tetrasomy 12p or Pallister-Killian syndrome (OMIM 601803) (sporadic) [41–43], trisomy 12p [44], Beckwith-Wiedemann syndrome (OMIM 130650) (imprinting defects, sporadic or autosomal dominant) caused by loss of methylation at maternal imprinting center 2 or differentially methylated region 2, paternal uniparental disomy 11p15.5, mutations in *CDKN1C*, gain of methylation at maternal imprinting center 1 or differentially methylated region 1, 11p15.5 chromosome translocation/inversion or duplication, or unknown etiology [45,46], Sotos syndrome (OMIM 117550) (sporadic or autosomal dominant at 5q35) caused by *NSD1* disease-causing mutations, deletion or microdeletion of 5q35 [47,48], Weaver syndrome (OMIM 277590) (sporadic and autosomal dominant at 5q35) with some patients with mutations in the *NSD1* gene [49], Perlman syndrome (OMIM 267000) (autosomal recessive) [50,51], Simpson-Golabi-Behmel syndrome (type I, OMIM 312870; X-linked recessive at Xq26.2) (type II, OMIM 300209; X-linked recessive at Xp22) caused by *GPC3* mutations, deletion, or microdeletion of Xq26.2 in type I; and *CXORF5* mutations, deletion, or microdeletion of Xp22 in type II [52–55], Costello syndrome (OMIM 218040) (autosomal dominant at 11p15.5) caused by mutations in the *HRAS* gene [56–60], Macrocephaly-capillary malformation syndrome (OMIM 602501) (sporadic) [61–63], Nevo syndrome (OMIM 601451) (autosomal recessive) caused by mutations in *PLOD1* gene [64], and *PTEN* hamartoma tumor syndrome such as Bannayan-Riley-Ruvalcaba syndrome (OMIM 153480) (autosomal dominant at 10q23.31) [65,66] and Proteus syndrome (OMIM 176920) (sporadic) [66,67], caused by mutations in the *PTEN* gene.

In conclusion, the present case provides evidence for prenatal overgrowth, craniosynostosis, and characteristic facial dysmorphism in association with a duplication of 15q26.2 → q26.3 and a duplication of the *IGF1R* gene. Prenatal diagnosis of fetal overgrowth should include a differential diagnosis of the chromosome 15q overgrowth syndrome.

Table 1
Molecular results using polymorphic DNA markers specific for chromosome 15q[a]

Markers	Father	Mother	Fetus	Location
D15S526	273, 281	257, 277	257, 281	15q26.1 (90,387,342–90,387,627)
D15S531	376, 376	360, 376	360, 376	15q26.2 (94,521,647–94,521,997)
D15S533	352, 380	356, 368	368, 380, 380	15q26.2 (98,082,884–98,083,244)

[a] Alleles (base pair sizes) are listed below each individual.

Acknowledgments

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