Clinical Case Reports

CASE REPORT

A prenatal case of partial trisomy 21 (q22.2q22.3), resulting from a paternal insertion translocation ins(16;21) and uncovered by QF-PCR, and characterized by array CGH and FISH

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Key Clinical Message

In addition to detecting trisomies of whole chromosomes, QF-PCR can also detect partial trisomies of the chromosomes 13, 18, and 21, which can suggest an unbalanced translocation. Additional testing with other techniques, such as microarray or FISH, is recommended when an unbalanced translocation is suspected.

Keywords

What does this study add?

- QF-PCR can also detect partial trisomies of the chromosomes 13, 18, and 21, which can suggest an unbalanced translocation.
- Additional testing with other techniques, such as microarray or FISH, is recommended when an unbalanced translocation is suspected.

Aneuploidy of the sex chromosomes and of chromosomes 13, 18, and 21 can be detected by quantitative fluorescence polymerase chain reaction (QF-PCR) performed with STR markers for chromosomes X, Y, 13, 18, and 21. Although QF-PCR is designed for the detection of whole-chromosome trisomies, partial trisomies of the investigated chromosomes may be detected. A trisomy pattern of one STR marker may either point to a partial trisomy with serious clinical consequences or may indicate a polymorphic variant, a submicroscopic polymorphic duplication of microsatellites of this specific marker as is found in some healthy individuals [1].

Here, we report a case of a healthy 36-year-old female patient, gravidity 2 parity 0, who visited the Department of Maternal Fetal Medicine in our hospital. Her family history was noncontributory, and the patient and her partner were not consanguineous. In her first pregnancy at the age of 35 years, a first-trimester screening for Down syndrome revealed an increased risk of trisomy 21 when an increased nuchal translucency (NT) of 13 mm was detected. A chorionic villus biopsy was performed, and conventional karyotyping indeed showed trisomy 21. The fetus had a nonhereditary form of Down syndrome. The patient and her partner decided to terminate the pregnancy. In her second pregnancy at the age of 37 years, the patient opted for first-trimester screening. The NT was normal (1.3 mm); however, the pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (βHCG) were 371 mU/L and 157 μg/L, respectively, indicating an increased risk of a child with Down syndrome. Amniocentesis was performed at 14 weeks and 5 days of gestation, and QF-PCR

(Aneufast kit, version 2; Genomed Diagnostics AG, Switzerland) showed a triallelic trisomy pattern only for the STR marker D21S1411 (21q22.3) of chromosome 21. A minimum of two informative markers is required to confirm an abnormal result. Because only one of five markers was informative, additional markers were used. One other STR marker, D21S1412 (21q22.2), also showed a triallelic pattern (Fig. 1A and B). The two informative STR markers are located in adjacent sub-bands on chromosome 21q22. Therefore, a partial trisomy of chromosome 21 could not be excluded. Chromosomes 13 and 18 showed a normal pattern. The patient was referred to the Department of Clinical Genetics for counseling and additional testing. QF-PCR performed on DNA of the patient and her partner did not show the duplication of the STR markers concerned, and it revealed that the extra alleles of markers D21S1412 and D21S1411 in the fetus originated from the patient's partner. As QF-PCR is the first tier test in our center, conventional karyotyping was subsequently performed, which initially showed a normal male chromosomal pattern in the fetus. Additional targeted 180K array CGH (Agilent Technologies, Santa Clara, USA; Amadid 023363) showed a duplication of approximately 4.98 Mb of parts of chromosome bands 21q22.2 and q22.3 (ISCN: arr[hg18] 21q22.2q22.3 (39,119,758-44,102,267)x3) (Fig. 1C). In this particular region of chromosome 21, many RefSeq genes are located, which may be of consequence for the phenotype of the fetus. BRWD1 is located within the Down syndrome region-2, WRB has a potential role in the pathogenesis of Down syndrome congenital heart disease, WDR4 could be a candidate for the development of Down syndrome phenotypes, and DSCAM is linked to cardiac defects and contributes to defects in the central nervous system of patients with Down syndrome [2–7].

FISH testing, performed after the microarray, on cells of the fetus with probes that hybridize to chromosome band 21q22.3 showed a signal on both chromosome 21 and a third signal on chromosome 16. Conventional karyotyping and FISH on cells from the patient's partner showed a balanced interchromosomal insertion: 46,XY.ish ins(16;21)(q22;q22.2q22.3)(RP11-566C12+,RP11-891L10+, RP11-619I15+;RP11-566C12-,RP11-891L10-,RP11-619I15-) (Fig. 1E). The resulting karyotype of the fetus was 46, XY.ish der(16)ins(16;21)(q22;q22.2q22.3)(RP11-566C12+, RP11-891L10+,RP11-619I15+)pat, showing a submicroscopic insertion of chromosome band 21q22.2q22.3 in the long arm of chromosome 16 (Fig. 1D). The couple was counseled about the high risk of a Down syndrome phenotype and subsequently chose to terminate the pregnancy before 20 weeks of gestation. No ultrasound findings were seen during pregnancy. A viewing of the fetus after birth showed some mild dysmorphic features seen in Down syndrome (upslant of the eyes, telecanthus, low-set ears, increased nuchal fold, possibly a mild sandal gap). No autopsy was performed. The recurrence risk of an unbalanced insertion translocation in a next pregnancy theoretically is 50%. The couple opted for preimplantation genetic diagnosis (PGD) for future pregnancies, and the patient got pregnant after the first cycle. However, a miscarriage occurred. In the next PGD attempt, the patient became pregnant again and a healthy baby boy was born.

In the literature, several reports about 21q duplications have been published and most published partial duplications on 21q show a Down phenotype in the fetus or child. Reports that resemble our duplication the most are published by Qi et al. [8] and Lee et al. [9]. However, Qi's case shows a larger duplication at the same region with concomitant deletion and other duplications of small fragments in 21q and Lee et al. published a case with a duplication of chromosome region 21q22.13q22.2, which is more proximal than in our case. Additionally, in Lee's case microarray was not performed. Recently, a report was published in which a partial 21q duplication did not show an obvious abnormal phenotype. The duplicated region resembled our case [10]. It is difficult to say what the exact phenotype in our case would have been as the pregnancy was terminated. However, based on the literature at the time our case presented, we counseled a high risk of a Down phenotype in our fetus.

For the sake of completeness, the fetus from the patient's first pregnancy was investigated with FISH with the same probes specific for the duplicated region of chromosome 21. This fetus had a trisomy 21 due to nondisjunction, and it had the same balanced insertion translocation ins(16;21) as the patient's partner. There was no material left from the first fetus, and therefore, it was impossible to determine whether the trisomy 21 observed in the first fetus was due to a nondisjunction in the patient or her partner. An association between the two pregnancies seems attractive in theory, but an interchromosomal effect cannot be proven. A mechanism that would explain both abnormal pregnancies is unlikely on the basis of meiotic figures that are theoretically formed in the balanced carrier of the interchromosomal insertion. Our case illustrates the utilization of QF-PCR in prenatal samples to detect not only common trisomies, but also potential segmental trisomies and to precisely delineate the abnormality in conjunction with other techniques such as conventional karyotyping, FISH, and microarray. Additionally, our case shows the importance of parental testing to provide appropriate genetic counseling for managing future pregnancies.
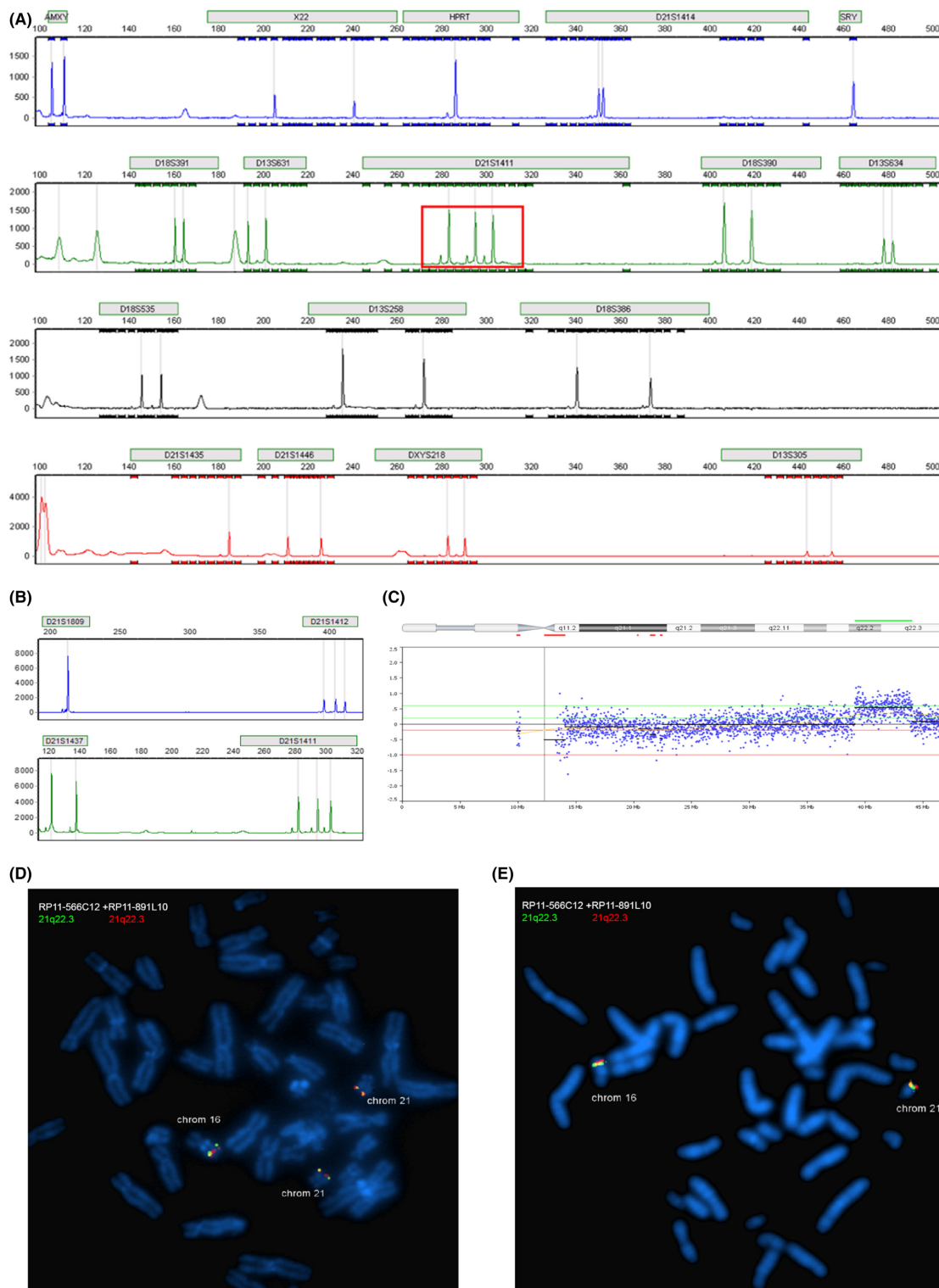
Figure 1. (A) QF-PCR of fetus showing triallelic trisomy pattern for the STR marker D21S1411 (21q22.3) (red box); (B) additional STR marker, D21S1412 (21q22.2), showing triallelic trisomy pattern; (C) 180K microarray showing a duplication approximately 4.98 Mb of parts of chromosome bands 21q22.2 and q22.3; (D) FISH on fetal material showing a submicroscopic insertion of chromosome band 21q22.2q22.3 in the long arm of chromosome 16; and (E) FISH on the patient's partner showing a balanced interchromosomal insertion: 46,XY.ish ins(16;21)(q22;q22.2q22.3).

Authorship

SLB and KES: wrote the manuscript. SLB: analyzed the prenatal tests. KES: counseled the patient. AWMN: participated in the analysis and reviewed the manuscript.

Conflict of Interest

None declared.

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