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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of a small supernumerary marker chromosome derived from chromosome 15 in a pregnancy associated with recurrent Down syndrome

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ABSTRACT

Objective: We present prenatal diagnosis and molecular cytogenetic characterization of a small supernumerary marker chromosome (sSMC) derived from chromosome 15 in a pregnancy associated with recurrent Down syndrome.

Case report: A 33-year-old, gravida 4, para 2, woman underwent amniocentesis at 16 weeks of gestation because of a previous child with Down syndrome and a karyotype of 46,XY,der(14;21)(q10; q10),+21. In this pregnancy, amniocentesis revealed a karyotype of 47,XX,+21[12]/48,XX,+21,+mar[3]. The parental karyotypes were normal. The pregnancy was terminated, and a malformed fetus was delivered with characteristic craniofacial appearance of Down syndrome and hypoplastic middle phalanx of the fifth fingers. The placenta had a karyotype of 47,XX,+21[37]/48,XX,+21,+mar[3]. The umbilical cord had a karyotype of 47,XX,+21[38]/48,XX,+21,+mar[2]. In addition to trisomy 21, array comparative genomic hybridization (aCGH) on the DNA extracted from umbilical cord revealed 40~50% mosaicism for a 2.604-Mb duplication of 15q25.2–q25.3, or arr 15q25.2q25.3 (83,229,665–85,834,131) × 2.4 [GRCh37 (hg19)] encompassing 19 Online Mendelian Inheritance in Man (OMIM) genes. Quantitative fluorescent polymerase chain reaction (QF-PCR) using the DNAs extracted from cultured amniocytes and parental bloods revealed maternal origin of the sSMC(15) and the extra chromosome 21.

Conclusion: aCGH is useful for identification of the nature of sSMC, and QF-PCR is useful for determination of the parental origin of the aberrant chromosomes.

Introduction

We previously reported identification of a small supernumerary marker chromosome (sSMC) derived from chromosome 15 [1–3]. Here, we present prenatal diagnosis and molecular cytogenetic characterization of an sSMC derived from chromosome 15 in a pregnancy associated with recurrent Down syndrome.

Case report

A 33-year-old, gravida 4, para 2, woman underwent amniocentesis at 16 weeks of gestation because of a previous child with Down syndrome and a karyotype of 46,XY,der(14;21)(q10;q10),+21. In this pregnancy, amniocentesis revealed a karyotype of 47,XX,+21 [12]/48,XX,+21,+mar [3] (Fig. 1). The parental karyotypes were normal. The pregnancy was terminated, and a malformed fetus was

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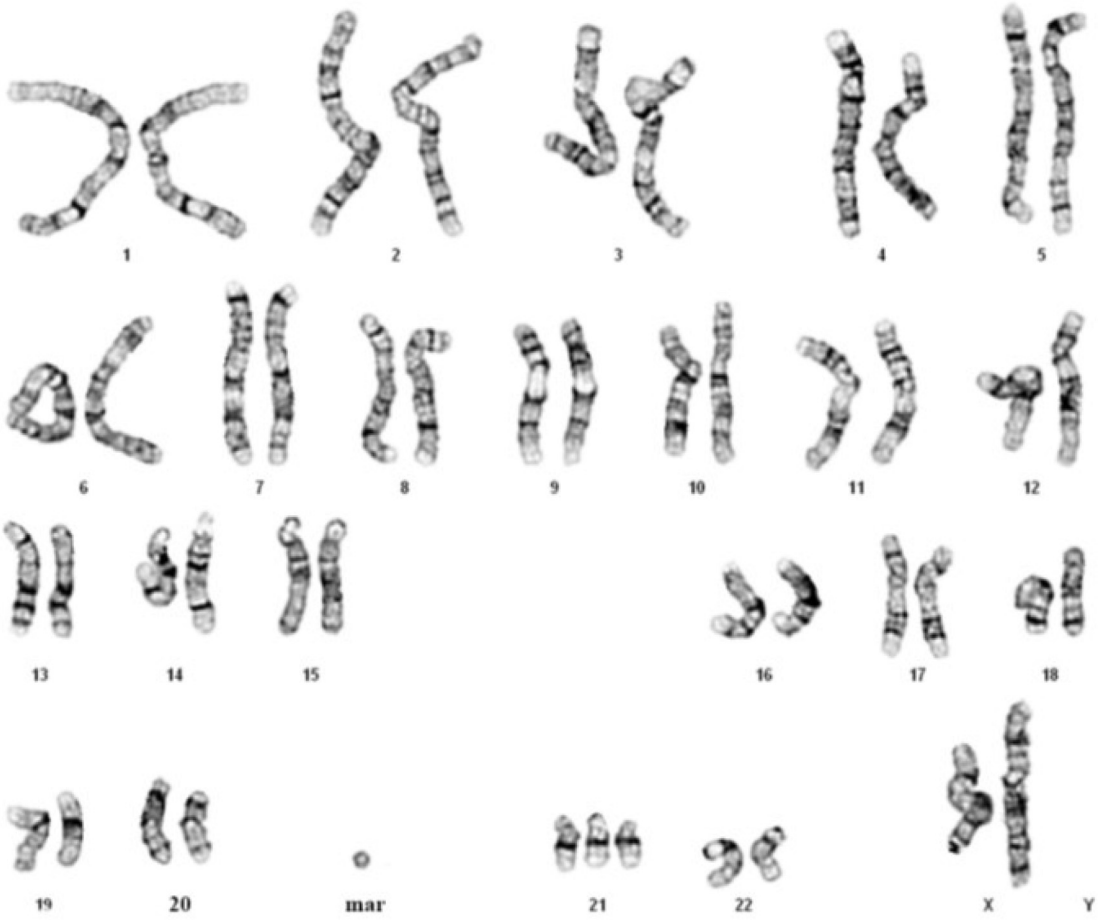

Fig. 1. A karyotype of 48,XX,+21,+mar. mar = marker chromosome.

delivered with characteristic craniofacial appearance of Down syndrome and hypoplastic middle phalanx of the fifth fingers. The placenta had a karyotype of 47,XX,+21[37]/48,XX,+21,+mar [3]. The umbilical cord had a karyotype of 47,XX,+21[38]/48,XX,+21,+mar [2]. In addition to trisomy 21, array comparative genomic hybridization (aCGH) on the DNA extracted from umbilical cord revealed 40~50% mosaicism for a 2.604-Mb duplication of 15q25.2-q25.3, or arr 15q25.2q25.3 (83,229,665–85,834,131) × 2.4 [GRCh37 (hg19)] encompassing 19 Online Mendelian Inheritance in Man (OMIM) genes of *CPEB1*, *AP3B2*, *SCARNA15*, *WHAMM*, *HOMER2*, *FAM103A1*, *BTBD1*, *TM6SF1*, *HDGFRP3*, *BNC1*, *SH3GL3*, *ADAMTSL3*, *WDR73*, *NMB*, *SEC11A*, *ZNF592*, *ALPK3*, *SLC28A1* and *PDE8A* (Fig. 2). Quantitative fluorescent polymerase chain reaction (QF-PCR) using the DNAs extracted from cultured amniocytes and parental bloods revealed maternal origin of the sSMC(15) and the extra chromosome 21 (Fig. 3).

Discussion

The present case had a 2.604-Mb gene dosage increase on 15q25.2-q25.3 encompassing 19 OMIM genes including *HOMER2*, *BNC1*, *AP3B2*, *WDR73*, *ALPK3*, *SLC28A1* and *HDGFRP3*. *HOMER2* (OMIM 604799) is associated with autosomal dominant deafness 68 (OMIM 616707). *BNC1* (OMIM 601930) is associated with autosomal dominant premature ovarian failure 16 (OMIM 618723). *AP3B2* (OMIM 602166) is associated with autosomal recessive early infantile epileptic encephalopathy 48 (OMIM 617276). *WDR73* (OMIM 616144) is associated with autosomal recessive Galloway-Mowat syndrome 1 (OMIM 251300). *ALPK3* (OMIM 617608) is associated with autosomal recessive familial hypertrophic cardiomyopathy 27 (OMIM 618052). *SLC28A1* (OMIM 606207) is associated with autosomal recessive uridine-cytidineuria (OMIM 618477). *HDGFRP3* (OMIM 616643) encodes hepatoma-derived growth factor-related protein 3 which is a novel angiogenic factor [4] and is involved in the progression of hepatocellular carcinoma [5]. *HDGFRP3* is a mitogenic, angiogenic and anti-apoptotic factor, and is also a neurotrophic and a neuroprotective factor that is related to proliferation, differentiation and maintenance of neurons [6].

Microdeletions and microduplications of 15q25.2 have been reported to be associated with phenotypic abnormalities. Monzani et al. [7] reported co-occurrence of duplication on Xp22.1 flanking the *SHOX* coding sequence and an additional duplication of 1.6–2.5 Mb on 15q25.2 that included 13 genes such as *RPS17*, *CPEB1* and *HOMER2* in a girl with short stature, precocious puberty, urogenital malformations and bone anomalies. Wat et al. [8] reported individual with recurrent microdeletions of 15q25.2 involving *CPEB1*, *AP3B2*, *HOMER2* and *HDGFRP3* in association with abnormal central nervous system development, cognitive deficits, congenital diaphragmatic hernia and anaemia. Monkam et al. [9] reported a case with a 15q25.2 microduplication, delayed speech, intellectual disability, splay foot, toe syndactyly, thin hand and short fifth fingers. DECIPHER database v10.1 [10] reported four patients with 15q25.2 microduplication with abnormal phenotype, *i.e.*, #316713 with abnormality of toe, delayed speech, eczema and retrognathia; #289343 with intellectual disability and macrocephaly; #260289 with global developmental delay, nasal speech and seizure; and

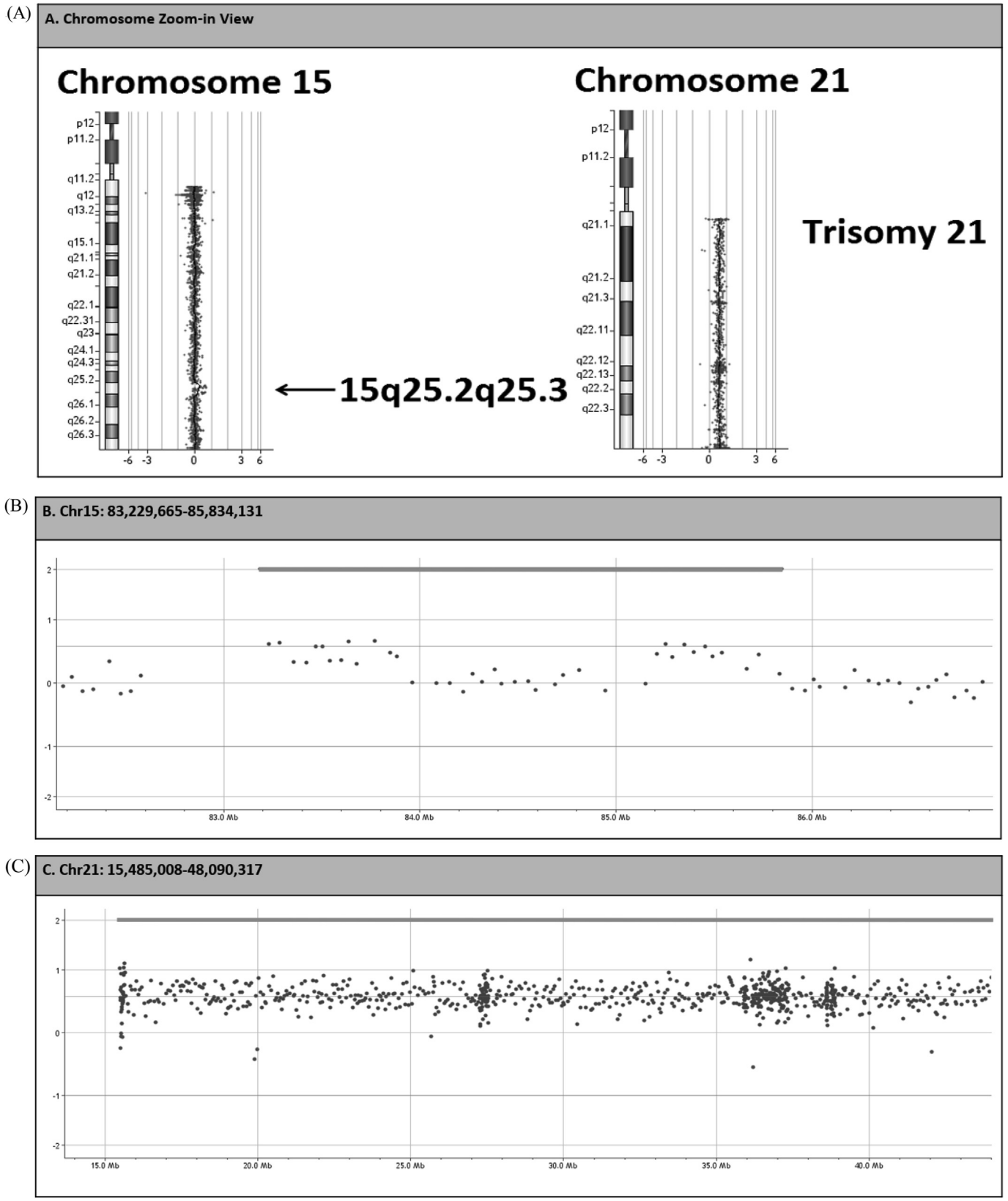

Fig. 2. (A), (B) and (C) Array comparative genomic hybridization analysis by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA) using the DNA extracted from umbilical cord shows the result of arr 15q25.2q25.3 (83,229,665–85,834,131) × 2.4, arr 21q11.2q22.3 (15,485,008–48,090,317) × 3.0 [GRCh37 (hg19)].

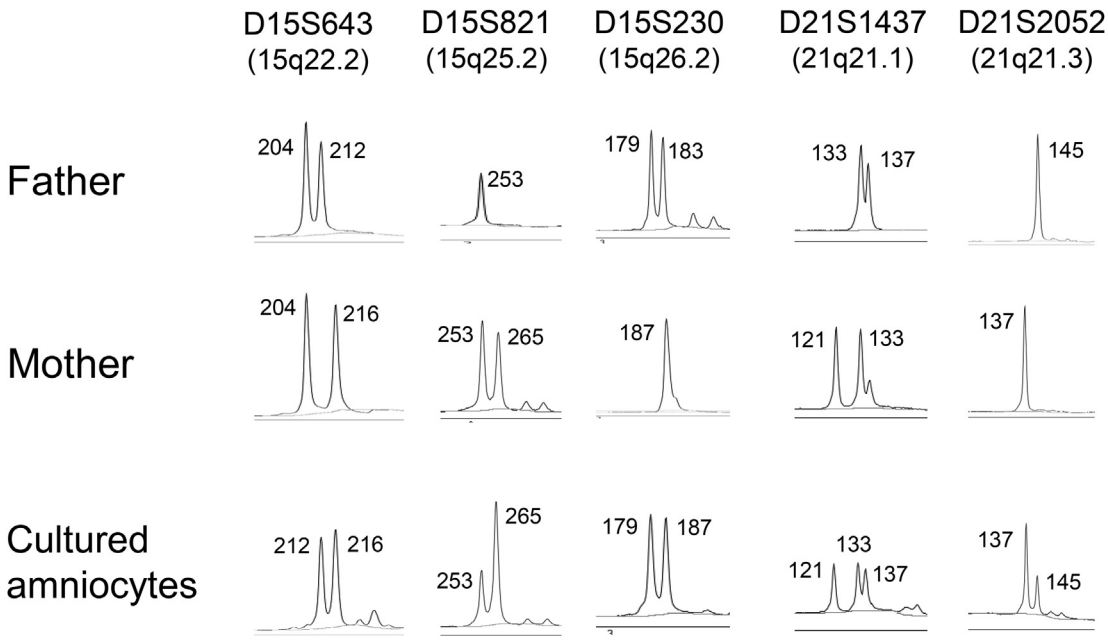

Fig. 3. Quantitative fluorescent polymerase chain reaction assays on the DNAs extracted from cultured amniocytes and parental bloods using the informative markers of D15S643 (15q22.2), D15S821 (15q25.2), D15S230 (15q26.2), D21S1437 (21q21.1) and D21S2052 (21q21.3) show that D15S821 (15q25.2) has gene dosage increase in the maternal allele of 265 bp, D21S2052 (21q21.3) has gene dosage increase in the maternal allele of 137 bp, and D21S1437 (21q21.1) contains three different alleles.

#263566 with delayed speech, macrocephaly, micrognathia and preaxial hand polydactyly. However, in our case, no other abnormalities in addition to Down syndrome have been observed.

The present case was associated with recurrent Down syndrome in two pregnancies. However, both parents had normal phenotypes by conventional cytogenetic analysis on peripheral bloods. The recurrent risk for Down syndrome in phenotypically normal young parents is about 1–2% [11]. The recurrent risk has been proposed to be caused by parental mosaic trisomy 21, parental gonadal mosaicism, maternal age-associated risk and genetic predisposition to non-disjunction [12,13]. Magalhães et al. [14] reported a woman with three trisomy 21 pregnancies. The woman and her husband had normal karyotypes by conventional cytogenetic analysis on peripheral bloods. However, interphase fluorescence *in situ* hybridization (FISH) analysis on 230 maternal blood cells detected one cell with trisomy 21, and FISH analysis on maternal oral mucosal cells detected three trisomy-21 cells in 100 cells. Hultén et al. [15] suggested the importance of detection of germinal and somatic trisomy 21 mosaicism in individual carrier parents. Down syndrome associated with parental mosaic trisomy 21 has been well reported previously [16–22]. The incidence of parental mosaic trisomy 21 in families with only one child with Down syndrome is about 2.7–4.3% [17]. Harris et al. [18] estimated that 3% of couples producing a child with trisomy 21 can be explained by parental mosaicism. However, the incidence of parental mosaic trisomy 21 has been reported to be higher (5/13) in families with recurrent trisomy 21 [21].

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of an sSMC derived from chromosome 15 in a pregnancy associated with recurrent Down syndrome. aCGH is useful for identification of the nature of sSMC, and QF-PCR is useful for determination of the parental origin of the aberrant chromosomes.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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