

TRISOMY 21 WITH A SMALL SUPERNUMERARY MARKER CHROMOSOME DERIVED FROM CHROMOSOMES 13/21 AND 18

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ABSTRACT

We describe a trisomy 21 with a small supernumerary marker chromosome (sSMC) derived from chromosomes 13/21 and 18 in which the karyotype was 48,XY,+der(13 or 21)t(13 or 21;18)(13 or 21pter→13q11 or 21q11.1::18p11.21→18pter),+21. Of the 35 case reports in the literature for a karyotype 48,XN,+21,+mar, in only 12 was the origin of the sSMC determined by fluorescence *in situ* hybridization (FISH), and only one was a der(13 or 21) and none were derived from two chromosomes. The influence of the partial trisomy 18p on the clinical outcome was hard to determine, however, there are reports on clinically healthy subjects for partial trisomy 18p.

Key words: small supernumerary marker chromosome (sSMC), Partial trisomy 18p, Down syndrome

Background. Down syndrome (DS) is caused by trisomy of human chromosome 21 and occurs in about 0.45% of human conceptuses. The incidence is

influenced by maternal age and affected fetuses are at an increased risk of miscarriage [1]. Different theories are discussed how free trisomy 21 develops during maternal meiosis [2,3]. In 35 reported DS cases instead of a karyotype 47,XN,+21 there was a karyotype 48,XN,+21,+mar, *i.e.*, a small supernumerary marker chromosome (sSMC) was also present [4]. The sSMC are a morphologically heterogeneous group of structurally abnormal chromosomes which may represent different types of inverted duplicated chromosomes, minute chromosomes and ring chromosomes. They can be characterized unambiguously by molecular cytogenetics and are usually equal in size or smaller than a chromosome 20 in the same metaphase spread. They can also be present in: **1)** a karyotype of 46 normal chromosomes, **2)** a numerically abnormal karyotype (such as DS) or **3)** a structurally abnormal but balanced karyotype (*e.g.*, Robertsonian translocation) or ring chromosome formation [5]. About 10% of sSMC are complex rearranged, *i.e.*, they consist of more than one chromosomal region. Some 85% of this subgroup are present in Emanuel or der(22) syndrome with a karyotype 47,XN,+der(22)t(11;22)(q23;q11) [4]. The remainder may arise from any human chromosome and have different genetic contents [4,6]. Here we report on a unique case of trisomy 21 with an sSMC derived from chromosomes 13/21 and 18.

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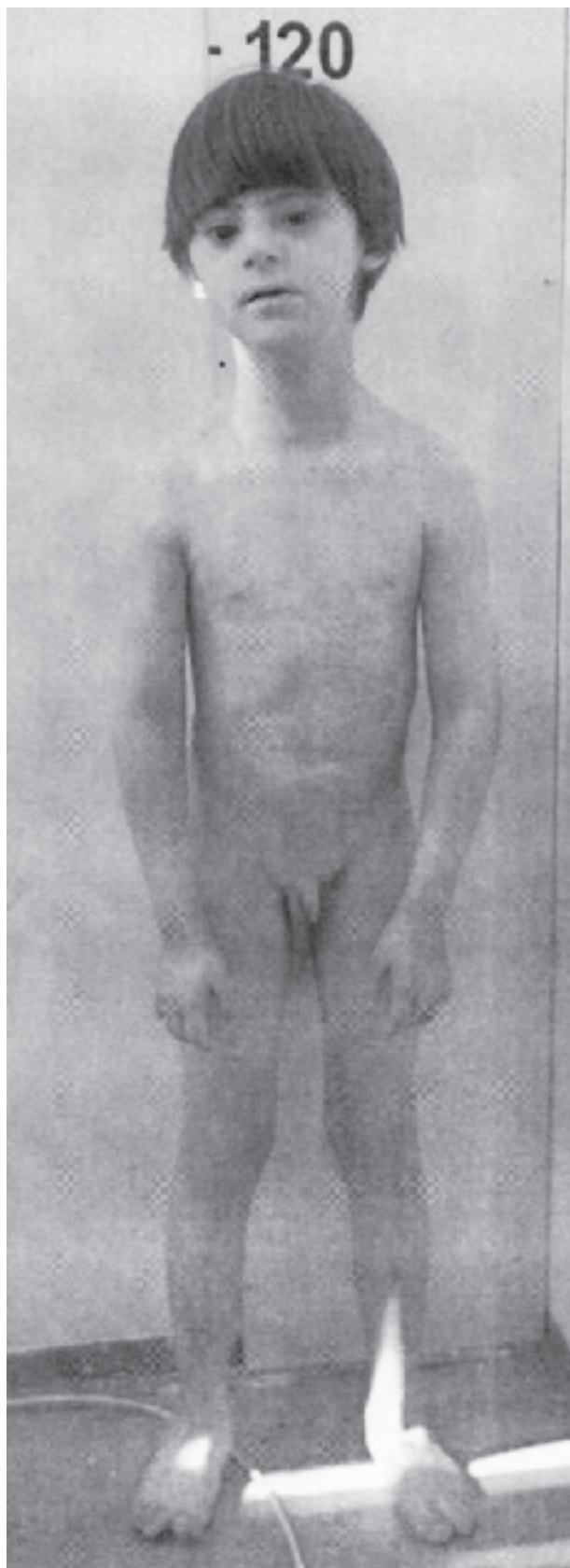


Figure 1 Photograph of the patient at 6 years of age.

Case Presentation. Characteristic clinical signs of DS were already present at birth, like the specific facial appearance (see Figure 1). He had a very pronounced retardation of motor development and only started to walk when he was 6 years old. He was moderately mentally retarded, had low body weight and an elongated neck, resembling his mother in the latter two characteristics.

Chromosomal analysis revealed a karyotype of 48,XY,+21,+mar in all analyzed cells. The karyotype of the parents was normal. Application of multiplex fluorescence *in situ* hybridization (M-FISH) [7] confirmed the presence of three chromosomes 21, one of which contained material from chromosome 18 and possibly from chromosome 21 (Figure 2A). Application of commercially available subtelomeric probes for chromosome 18 (Abbott, Wiesbaden, Germany) and a centromeric probe specific for chromosomes 13 and 21 (Kreatech Diagnostics, Amsterdam, The Netherlands) revealed p-arm material of chromosome 18 on the sSMC, which was derived from chromosome 13 or 21 (Figure 2B). The presence of three DS critical regions but not on the sSMC was demonstrated by an appropriate commercial probe (LSI 21; Abbott). By subcentromere-specific M-FISH [8] using specific probe sets for chromosomes 13, 18 and 21 (Figures 2D-2F) the final karyotype was determined as 48,XY,+der(13 or 21)t (13 or 21;18)(13 or 21pter→13q11 or 21q11.1::18p11.21→18pter),+21. The chromosomal origin of the sSMC could not be determined more exactly because of sequence identity of the centromeric regions of chromosomes 13 and 21.

DISCUSSION

The presence of 48 chromosomes in DS is a rare finding. It can be caused by an additional gonosome leading, *e.g.*, to a karyotype 48,XXX,+21 [9,10] or by an sSMC [4]. Up to now, for sSMC derived from chromosomes 4, 7, 13 (two cases), 14, 14/22, 15 (two cases) and 22 (three case) have been reported in DS [4]. Ours is the first report of an sSMC in DS derived from chromosome 13 or 21 and the first complex rearrangement of one.

Among the complex rearranged of sSMC, chromosome 13/21 is the second most frequently involved [6]. An sSMC like the one we describe

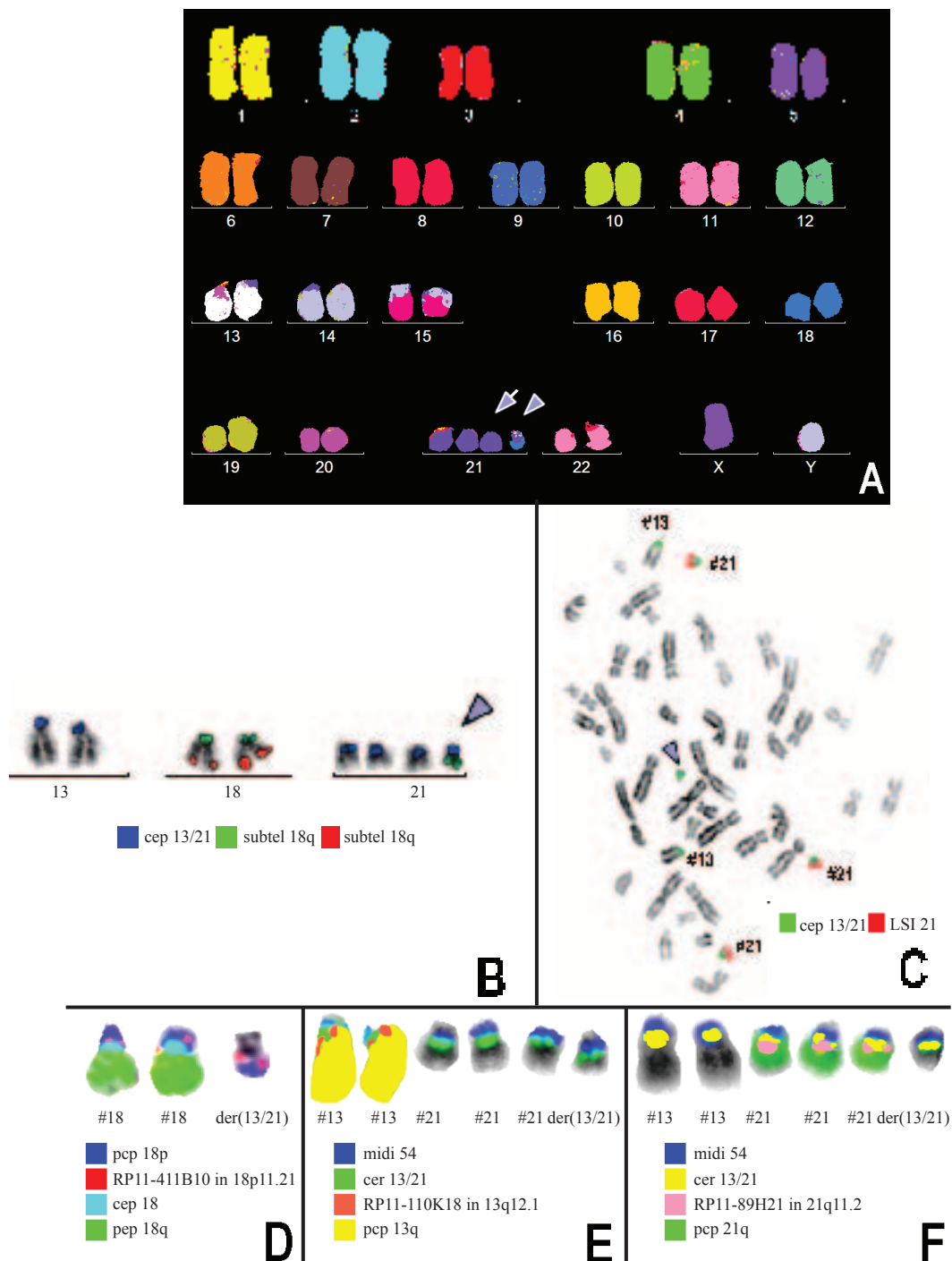


Figure 2 The FISH results obtained on the chromosomes of the reported patient. A) The M-FISH showed trisomy 21 (arrow) and an sSMC (arrowhead). B) Subtelomeric probes for chromosome 18 (subtel 18p and subtel 18q) and for the centromeric regions of chromosomes 13 and 21 (cep 13/21). Note the short arm material derived from chromosome 18 present on the sSMC. C) Down syndrome critical region (LSI 21) was present in the three chromosomes 21 but not on the sSMC (arrowhead). Abbreviation: cep 13/21:

centromeric probe specific for chromosomes 13 and 21. D-F) Subcentromeric probes for the chromosomes 18, 13 and 21. Note the short arm of chromosome 18 present on the sSMC but not the centromeric region of that chromosome. Locus-specific centromere-near probes for chromosomes 13 and 21 did not detect euchromatic sequences on the sSMC. Abbreviations: cep = centromeric probe; midi 54 = probe specific for the short arms of all acrocentric chromosomes [14]; pcp = partial chromosome paint.

here, leading to partial trisomy 18p was reported in five individuals [6,9-11] in four of which no, or only minor malformations and/or mental impairment, were found [6,11,12], in the fifth, no postnatal data were available, but sonography gave normal results [13]. Apart from the pronounced retardation in motor development, we observed no obvious influence of partial trisomy 18p in our patient. This suggests that some genes present on 18p cause severe problems when present as four copies, as in i(18p)-syndrome [5], but not when present as three copies.

Competing Interests. The author(s) declare that they have no competing interests.

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