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Chromosome 11p15 Duplication in Silver-Russell Syndrome Due To a Maternally Inherited Translocation t(11;15)

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The role of 11p15 disturbances in the aetiology of Silver-Russell syndrome (SRS) is well established: in addition to hypomethylation of the *H19/IGF2* differentially methylated regions, five patients with a duplication of maternal 11p15 material have been described. We report on a boy with SRS carrying a maternally inherited duplication of chromosome 11p15. The patient showed the typical clinical picture of SRS including severe intrauterine and postnatal growth restriction, relative macrocephaly, a prominent forehead, a triangular face, down-turned corners of the mouth and fifth digit clinodactyly. Body asymmetry was not observed. By molecular genetic analyses, MLPA and microsatellite typing detected a duplication of chromosome 11p15 and cytogenetic analysis showed an unbalanced translocation t(11;15)(p15.5:p12). The size of the duplicated region is ~8.8 Mb as determined by SNP-array analysis. The healthy mother carried a balanced reciprocal chromosome translocation t(11;15). Thus, there is an increased risk for further children with SRS due to 11p15 duplication. Additionally, the family is at risk for offspring with an 11p15 deletion and Beckwith-Wiedemann syndrome whereby the phenotype will be influenced by haploinsufficiency of additional genes at 11p15 due to the deletion. The balanced aberrant karyotype was identified in several other family members, but interestingly there was no history of recurrent miscarriages, intrauterine fetal death, or multiple congenital anomaly syndromes in the family.

Key words: Silver-Russell syndrome; Beckwith-Wiedemann syndrome; 11p15 duplication; 11p15 deletion; familial translocation

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INTRODUCTION

Silver-Russell syndrome (SRS) is a clinically and genetically heterogeneous syndrome. It is mainly characterized by intrauterine and postnatal growth restriction (<2nd centile) and a characteristic triangular face with a prominent forehead. Asymmetry of body and limbs, fifth finger clinodactyly and a relative macrocephaly are additional common clinical signs. Whereas about 10% of patients have a maternal uniparental disomy of chromosome 7 (UPD(7)mat), more than 38% carry a methylation defect in the telomeric imprinted region (imprinting center 1 region, ICR1) on chromosome 11p15 [Gicquel et al., 2005]. In addition, single cases carry chromosomal disturbances, among them duplications of maternal 11p15 material [Fisher et al., 2002; Eggermann et al., 2005]. Five patients with isolated 11p15 duplication have been reported; the size of the duplicated segment ranged from 5 to >14 Mb. All patients showed (severe) intrauterine and postnatal growth restriction, and four had SRS features. The parental karyotypes have not been reported for all of them but a maternal inheritance of a pure 11p15 duplication has never been described. South et al. [2008] described three families with unbalanced translocations consisting of a deletion of 4p16.3 and a duplication of 11p15, and the patients had modifications of the Wolf-Hirschhorn syndrome phenotype due to 11p15 partial trisomy in a parent-of-origin specific manner. We report on a SRS patient with a maternally inherited 11p15 duplication and the consequences of this familial rearrangement for genetic counseling.

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CLINICAL REPORT

The propositus is the first child of a healthy non-consanguineous German couple, a 27-year-old mother and a 29-year-old father. Both parents were of normal height (mother: 174 cm, father: 176 cm). The maternal family history was unremarkable. The paternal family history identified a brother of the grandfather with cleft palate who died at the age of 2 months. Miscarriages were not known in either family.

After an uncomplicated pregnancy, the patient was born at 32 gestational weeks by elective caesarean due to a severe intrauterine growth restriction and pathological Doppler and cardiotokography (CTG). Birth length was 34 cm (−3.0 SD), weight 790 g (−2.6 SD), head circumference 27 cm (−1.9 SD) (Table I). Due to respiratory insufficiency artificial respiration was necessary, and he developed a cerebral hemorrhage. He had an ostium secundum atrial septum defect (which spontaneously closed). At the age of 11 months he developed jackknife convulsions. He responded to therapeutic intervention and was seizure-free with normal EEG by the age of 2 years.

At the age of 2 years, he was severely growth restricted with a length of 75 cm (−4.1 SD) and a weight of 8 kg (−4.5 SD). His head circumference of 48 cm was within the low-normal range (−1.2 SD) (Table I, Fig. 1). He had distinctive craniofacial features, which included a relative macrocephaly, a large prominent forehead, a triangular face with a small jaw, thin lips, down-turned corners of the mouth, and deeply set ears. Clinodactyly of both fifth fingers and

TABLE I. Major Clinical Features in Our 11p15 Duplication Carrier in Comparison to Those in11p15 Epimutation Carriers, UPD(7)mat Carriers and SRS of Unexplained Origin

Clinical feature	This patient	11p15 epimutation carriers from the literature (n = 59)[a]	UPD(7)mat carriers (n = 44)[a]	SRS of unexplained origin (n = 14)[b]
Birth weight	−2.60 SD	−3.55	−2.79	−2.60
Birth length	−3.00 SD	−4.38	−3.10	−3.40
Birth OFC	−1.90 SD	−1.35	−1.26	−1.70
PNGR (<−2 SD)	Yes (−4.10 SD)	100%		−3.40
Relative macrocephaly	Yes (−1.20 SD)	91%	≥92%	64.3%
Muscular hypotrophia/hypotonia	no		9/13	
Motor/neuropsychological delay	Yes	20.5% (8/31)	43% (17/39)	19.3%
Asymmetry	No	77%	60% (18/30)	42.9%
Clinodactyly	Yes	78% (31/40)	82% (28/34)	42.9%
Triangular face	Yes	76%	97% (33/34)	
Prominent forehead	Yes	88%	>68%	78.6%

[a]Kotzot [2008].
[b]Netchine et al. [2007].

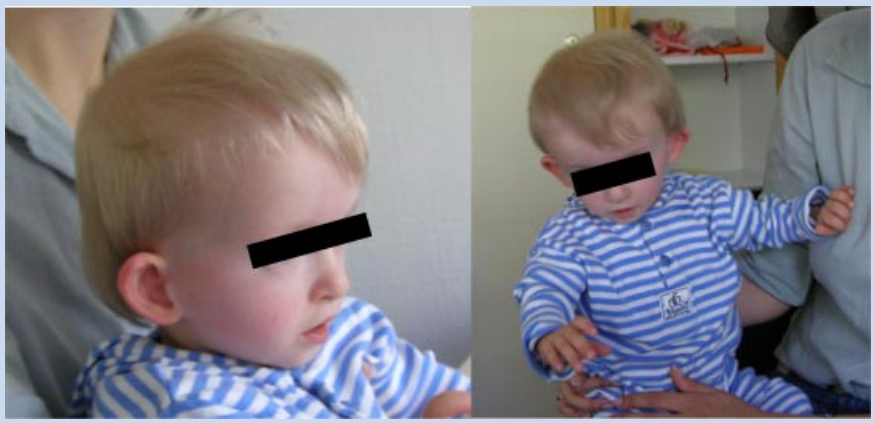

FIG. 1. Facial features of our patient with 11p15 duplication at 2 years of age.[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

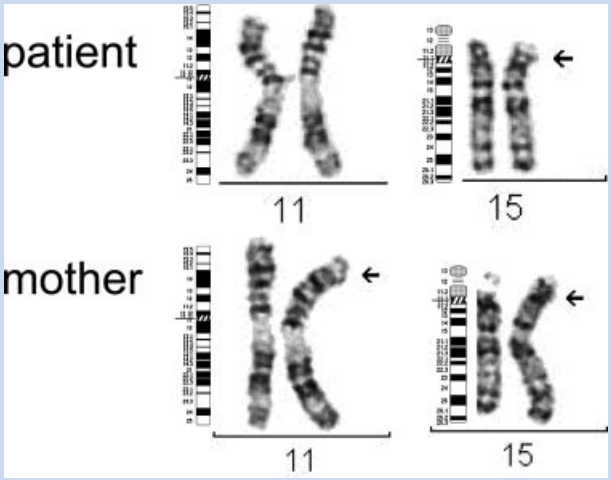

FIG. 2. Representative partial karyotypes of our patient and his mother. Visible aberrations are marked by arrows. (Karyotype of the mother: 46,XX.ish t(11;15)(p15.5;p12) (D11S2071−, MD54+;D11S2071+,MD54−), karyotype of the patient: 46,XY.ish der(15)t(11;15)(p15.5;p12)mat(D11S2071+;MD54−).)

partial syndactyly of second and third toes were also noted. Hemihypotrophy was not observed. His psychomotor development was delayed. He had just started crawling and spoke only a few words. Feeding difficulties were also reported.

GENETIC TESTING

Initial conventional GTG banding on the patients' peripheral lymphocytes was interpreted as normal without abnormalities of chromosome 11 (Fig. 2). After detection of a duplication of the region 11p15 by molecular genetic testing (see below), FISH analysis with a subtelomeric 11p probe (*D11S2071*, Abbott Molecular, Inc., Abbott Park, IL) showed an additional signal on the short arm of chromosome 15. This result was confirmed with a specific probe for the short arms of the acrocentric chromosomes (MD 54, kindly provided by PD Dr. Thomas Liehr, Jena) which showed absence of signal on one chromosome 15. Karyotyping of the maternal chromosomes detected an abnormal chromosome 11, but only when additional FISH analysis was done, with a balanced reciprocal translocation between 11p and 15p. The mother's karyotype was defined as 46,XX.ish t(11;15)(p15.5;p12)-(D11S2071−,MD54+;D11S2071+,MD54−). Thus, the index patient of this report is carrier of a maternally inherited, unbalanced translocation t(11;15) with the karyotype 46,XY.ish

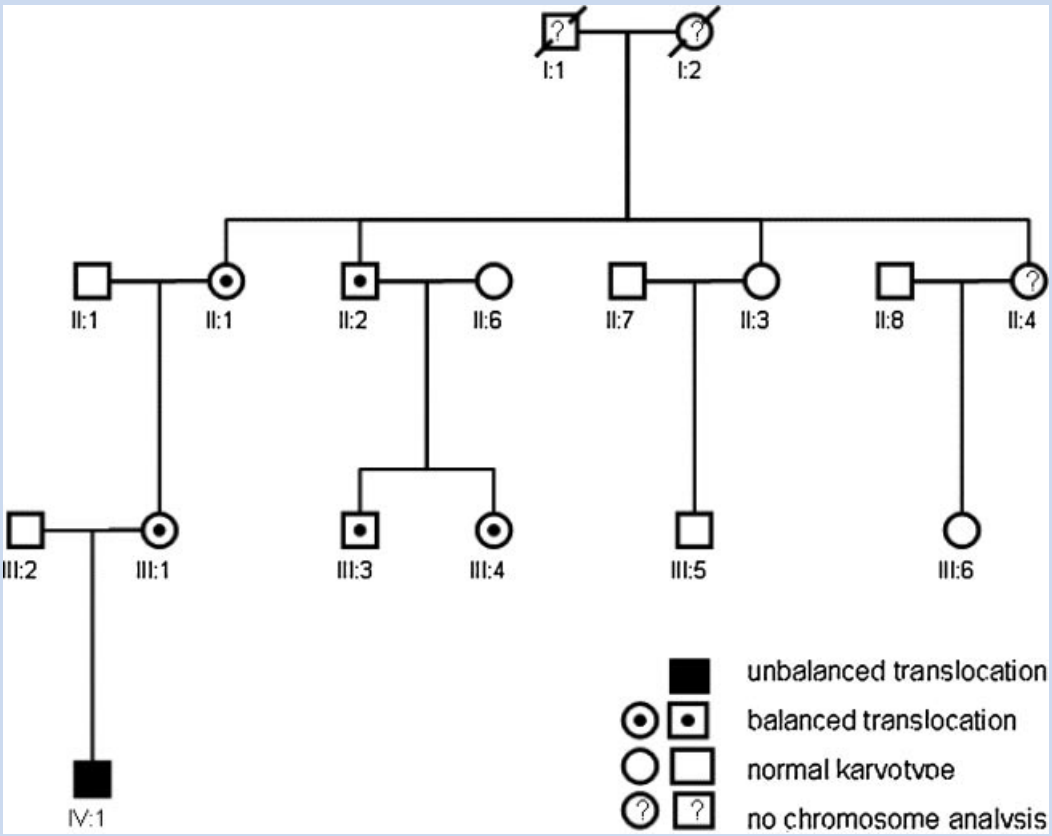

FIG. 3. Pedigree of the translocation family with the reciprocal translocation t(11;15). The index patient with the SRS phenotype is IV:1.

der(15)t(11;15)(p15.5;p12)mat(D11S2071+;MD54−). This is functionally a trisomy of the region 11p15, and monosomy 15p, which is clinically insignificant. Several additional family members were shown to carry the same balanced reciprocal translocation, but there is no history of abortions or malformations known in the family (Fig. 3).

For molecular testing, the patient's genomic DNA was isolated from peripheral lymphocytes by a simple salting-out procedure. We performed a methylation-specific MLPA assay (ME030-BWS/SRS, MRC Holland, Amsterdam, NL) to detect ICR1 epimutations and 11p15 copy number variations as described elsewhere [Eggermann et al., 2007]. Quantitative as well as methylation-specific MLPA hybridization patterns were consistent with a duplication in 11p15. Microsatellite typing in this family confirmed the duplication, and the maternal origin of the additional 11p15 material and a duplication size of ~10 Mb were delineated. The size of ~8.8 Mb was then confirmed by typing of an Affymetrix GeneChip®Genome-Wide Human SNP 6.0 array.

RESULTS AND DISCUSSION

The finding of a maternal duplication of 11p15 material in this patient with the clinical diagnosis of SRS supports the observation that gain of maternal chromosome 11p15 material belongs to the spectrum of (epi)genetic disturbances in this disease. Furthermore, this case illustrates that many cryptic chromosomal imbalances remain undetected by conventional cytogenetics in SRS [for review: Spengler et al., 2009]. After exclusion of 11p15 hypomethylation and UPD(7)mat, further genetic tests should include molecular analysis instead of conventional karyotyping.

In addition to the general relevance of maternal 11p15 duplications for the clinical outcome, genetic counseling in this family is complicated by the reciprocal translocation resulting in an 11p15 deletion in one of the homologue chromosomes 11 of the mother. This constitutional karyotype harbors the risk of gametes with 11p15 duplications and 11p15 deletions. While duplications of maternal 11p15 material have been described several times in the literature and are always associated with severe growth retardation and further SRS-like features, the clinical outcome of a maternal 11p15 deletion is difficult to predict. We speculate that an 11p15 deletion carrier will probably have Beckwith-Wiedemann syndrome, and the phenotype will be additionally influenced by haploinsufficiency of additional genes at 11p15 due to the deletion. So far, only one pregnancy with a mosaic deletion of the maternal 11p15 region has been reported [Robinson et al., 2007]. The fetus showed overgrowth with an enlarged heart and marked fetal ascites. Additional BWS features were not observed, and the fetus died in utero at 34 weeks. The fetal malformations were associated with a focal placental mesenchymal dysplasia. As aforementioned, the deletion in that case was present as a mosaic, thus it is conceivable that in the non-mosaic state the consequence of 11p15 deletions is so severe that it results in very early embryonic death. This would explain why miscarriages have not been reported by the family of this patient. We emphasize that the balanced translocation karyotype in this family was observed in several individuals, but miscarriages, intrauterine fetal deaths, and congenital malformation syndromes were not reported.

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