Short Report

Silver–Russell syndrome due to maternal uniparental disomy 7 and a familial reciprocal translocation t(7;13)


Silver–Russell syndrome (SRS) is a genetically heterogeneous disorder characterized by intrauterine and postnatal growth retardation, typical facial features and a spectrum of additional features including body and limb asymmetry and clinodactyly. Maternal uniparental disomy for chromosome 7 ( upd(7)mat) was shown to occur in 5–10% of patients with SRS. Maternal UPD7 is clinically often associated with mild SRS. Parents of an affected child are given a negligible recurrence risk as all reported cases with upd(7)mat have been sporadic so far. In general, chromosomal rearrangements-like translocations increase the likelihood of uniparental disomy (UPD) for the chromosomes involved. However, SRS as the result of a upd(7)mat in association with an inherited chromosomal translocation involving chromosome 7 has only been reported once before. Here, we describe the second case of SRS with upd(7)mat due to a familial reciprocal translocation t(7;13). This emphasizes the importance of chromosome analysis in SRS patients with upd(7)mat to rule out chromosomal rearrangements despite their rare occurrence as they are of great relevance for genetic counseling of SRS families.

Conflict of interest

All authors declare that there is no actual or potential conflict of interest in relation to this article.

Silver–Russell syndrome (SRS) is a syndrome of pre- and postnatal growth retardation in combination with typical dysmorphic features, including a triangular face with down-turned corners of the mouth, micrognathia, relative macrocephaly and prominent forehead, asymmetry or hemihypoplasia of the face, limbs or trunk, clinodactyly V, developmental delay and other features (1). SRS is a clinically variable and genetically heterogeneous disorder with maternal uniparental disomy 7 ( upd(7)mat) being found in 5–10% of patients with SRS (2, 3). The term uniparental disomy (UPD) in general describes the inheritance of both homologous chromosomes from one parent, with no contribution of that chromosome from the other parent. Up to this point, more than 60 cases with SRS due to upd(7)mat have been published, and although the clinical phenotype by itself does not allow differentiation of the various causes of SRS, most SRS patients with upd(7)mat show a rather mild phenotype (3). A disturbed expression of imprinted genes on chromosome 7 most probably explains the phenotype of SRS in patients with upd(7)mat, and current research is focussing on different genes and candidate regions on chromosome 7 (1, 4).

Different mechanisms can lead to UPD. Chromosomal rearrangements such as chromosomal translocations which are associated with an increased risk of aneuploidy have been reported very rarely in patients with UPD. In fact, there is only one report of an SRS patient due to upd(7)mat, so far, who also carries a
translocation (5). We here describe the second case of upd(7)mat and a reciprocal, non-Robertsonian translocation and discuss the consequences of this chromosomal finding for genetic counseling of the family.

Clinical report

The boy was born as the first child of healthy non-consanguineous German parents following three prior miscarriages of the couple within the first trimester (Fig. 1a). Aside from one miscarriage in the third trimester reported by his maternal grandmother, both the maternal and the paternal family histories were unremarkable.

The propositus was born at 34 weeks of gestation by elective cesarean due to severe intrauterine growth restriction. Birth length was 38 cm (−2.5 SD), birth weight was 1400 g (−1.5 SD) and head circumference (OFC) was 28 cm (−1.8 SD). Due to initial apnoea and bradycardia he needed monitoring during his first days of life, but the following cardiological and internal examination did not reveal any organic diseases or anomalies.

From very early on, he presented with severe feeding difficulties, intermittent hypoglycemia and recurrent emesis. Insulin-like growth factor 1 level was below normal, and the possibility of growth hormone substitution therapy in the future was discussed with the parents. In contrast to his markedly delayed speech development, he started walking at the age of 15 months and continuously improved his motor skills.

When seen at the age of 2 years, he was severely growth retarded with a body length of 75 cm (−3.96 SD), a body weight of 7.6 kg (−3.99 SD) and an occipitofrontal circumference (OFC) of 49 cm (−0.55 SD). He presented with mild facial dysmorphism including a triangular face, down-turned corners of the mouth, thin lips, a prominent forehead and relative macrocephaly. Hemihypoplasia or clinodactyly was not observed. He presented with well-developed (fine) motor skills but still spoke only very few words.

Materials and methods

Cytogenetics and molecular genetics

High-resolution GTG-banding chromosome analyses were performed on metaphase preparations of peripheral blood lymphocytes from the patient and the parents using standard techniques. The chromosomes were

Fig. 1. (a) Pedigree of family. Affected boy (IV:4) labeled by filled-in square and arrow, carrier mother (III:4) marked by dot. Grandmother of the propositus (II:3) was not available for chromosomal analysis and is labeled by question mark. (b) Molecular testing for uniparental disomy revealing maternal UPD7, exemplarily shown by marker D7S493. (c) Schematic illustration of the results of molecular testing for UPD7 revealing maternal UPD7 in the boy with Silver–Russell syndrome. All the markers used are in accord with maternal uniparental disomy (UPD) of the whole chromosome 7. Arrows indicate the chromosome regions covered by informative markers (black) and those of assumingly maternal origin (gray).
analyzed and the karyotype described according to the International System for Cytogenetic Nomenclature (2009).

Fluorescence in situ hybridization (FISH) experiments were performed as described before (6) using specific probes for the subtelomeric regions of chromosomes 13q (PAC-163C9) and 7q (PAC-3K23) together with partial painting probes for the long arm of chromosomes 7 (pcp7q) and 13 (pcp13q), respectively.

Molecular genetic analysis

Genomic DNA was extracted from whole blood by use of standard salt precipitation protocols. Genotypes for chromosome 7-specific microsatellite markers D7S517 (7p22.2), D7S513 (7p21.3), D7S507 (7p21.1), D7S493 (7p15.3), D7S628 (7p14.3), D7S519 (7p12.3), D7S669 (7q21.11), D7S657 (7q21.3), IVS17BTA (7q31.2), D7S640 (7q33), D7S684 (7q34), D7S637 (7q36.2), and D7S2447 (7q36.2) were obtained by polymerase chain reaction, followed by polyacrylamide gel electrophoresis on an ALF express sequencer.

Results

Molecular testing revealed upd(7)mat and thereby confirmed the clinically suspected diagnosis of SRS (Fig. 1b,c). Hetero- as well as isodisomy were detected. Because of homozygosity in the mother, some markers (D7S517, D7S513, D7S507 and D7S657) did not allow differentiation between iso- and heterodisomic maternal inheritance. Although a few markers were not informative, all markers used were in accord with maternal UPD of the whole chromosome 7 (Fig. 1c).

In the following, high-resolution GTG banding of the mother’s metaphases revealed a balanced translocation t(7;13)(q11.2;q14). Subsequently, the translocation was shown in her son with SRS as well (Fig. 2). FISH confirmed these results (data not shown). The maternal grandmother of the propositus who reportedly had one miscarriage in the third trimester was not available for chromosome analysis.

Discussion

In the index patient SRS was suspected due to his clinical phenotype with growth retardation, delayed speech development, and mild facial dysmorphism. Testing of upd(7)mat was performed and confirmed the clinical diagnosis. Further cytogenetic analyses were initiated because of three preceding miscarriages and revealed that he is a carrier of the reciprocal translocation t(7;13)(q11.2;q14) inherited from his mother. This is only the second report of a patient with upd(7)mat in association with a reciprocal non-Robertsonian chromosomal translocation involving chromosome 7.

UPD has been described for nearly every chromosome, but only some of them show a different phenotype due to imprinting effects (7). Although structural chromosome abnormalities are expected to increase the likelihood of UPD for the chromosomes involved, the actual risk of UPD is difficult to estimate. Berend et al. (8) described an empiric risk of 0.6–0.9% of finding UPD in Robertsonian translocation carriers whereas cases of homologous acrocentric rearrangements seem to harbor a high risk of ~66%. Assumingly, the risk for another child with SRS in the present family is only mildly increased, the actual risk of UPD associated with non-Robertsonian translocation carriers, however, is currently unknown.

Theoretically, every chromosome abnormality that increases the occurrence of non-disjunction also increases the risk for UPD of the chromosomes involved. However, and not taking Robertsonian translocations into account, there are only very few cases published. To our knowledge there are only six reports of carriers of reciprocal translocations having offspring with UPD. Five of these translocations did not involve chromosome 7 and either led to the phenotypes of Prader-Willi or Angelman syndrome (9–13) or upd(16)mat with intrauterine growth retardation and minor facial anomalies (13). The only other case of an SRS patient with upd(7)mat and a familial reciprocal translocation was a girl with a maternally inherited t(7;16)(q21;q24) reciprocal translocation who showed a clinical phenotype of growth retardation and minor facial dysmorphism leading to a clinical tentative diagnosis of SRS (5). Further testing revealed maternal heterodisomy of chromosome 7.

In general, different mechanisms can lead to UPD and all result from an initial non-disjunctive event: trisomy rescue (loss of a supernumerary chromosome), monosomy rescue (duplication of an unique chromosome) and gamete complementation (fertilization of a disomic gamete by a nullisomic one) (14). In the presented case, the trisomy rescue hypothesis seems to be most plausible as the mechanism of formation can be explained best by 3:1 (interchange trisomy) segregation in oogenesis followed by the loss of the paternal chromosome 7 after fertilization of the oocyte (Fig. 3). Midro et al. (15) studied a family with reciprocal translocation carriers of the same chromosomes involved as in our case but with different breakpoints t(7;13)(q34;q13) and found a high rate of 3:1
Further genetic counseling of the family. We therefore suggest to add this diagnostic step to the algorithm scheme recently published by Eggermann et al. (17) whenever upd(7)mat has been confirmed in an SRS patient. In fact, if there had not been three miscarriages in the family history, karyotype analysis might not have been initiated at all, and the translocation with its consequences for the family would have been overlooked. Therefore, this case also recalls the importance of conventional karyotyping in the first line diagnostic approach in general as it proves to be an indispensable method for the detection of chromosomal rearrangements in patients with multiple congenital anomalies or mental retardation. Being unaware of the karyotype, the parents would have been given a negligible recurrence risk for another child with SRS as recurrence is generally very unlikely due to the complex mechanisms of formation leading to UPD. Recurrence risk is even considered to be so low that invasive prenatal diagnosis is normally not indicated. Instead, further investigation revealed that the constitutional karyotype of the mother harbors an increased risk of gametes with an unbalanced karyotype and consequently a high risk rate of miscarriages or children with severe malformations and mental retardation, respectively.

On the one hand this case supports the relevance/indication of UPD testing in pregnancies of carriers of chromosomal aberrations with participation of imprinted regions (12), on the other hand it has to be kept in mind that the clinical course of SRS as well as other imprinting disorders, e.g. Beckwith-Wiedemann syndrome, cannot be predicted when diagnosed prenatally. In consequence, all these situations require careful genetic counseling of the families.

Acknowledgements

We thank the patients and their parents whose help and participation made this work possible.

References


