A de novo 11p13 Microduplication in a Patient with Some Features Invoking Silver-Russell Syndrome

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Abstract

Patients with Silver-Russell syndrome (SRS) show an intra-uterine and postnatal growth restriction associated with a variable spectrum of additional features. Genetic or epigenetic alterations on chromosomes 7 and 11 can be detected in several SRS patients; however, a large fraction of cases remains with unknown genetic etiology. Here, we describe the clinical and molecular findings of a patient with a phenotype invoking SRS showing intrauterine and postnatal growth retardation, psychomotor retardation, relative macrocephaly, slightly triangular face with pointed chin, clinodactyly, and a slight body asymmetry, in whom single-nucleotide polymorphism oligonucleotide array analysis led to the identification of a de novo 11p13 duplication containing many genes that could be functionally related with the observed clinical features. Many deletions of chromosome 11p13, resulting in WAGR (Wilms tumor, aniridia, genital anomalies, mental retardation) syndrome, have been described, while only few duplications spanning the same region have been

reported so far. To our knowledge, this is the first reported case presenting a SRS carrier of an 11p13 duplication. We propose candidate genes for the observed traits, and in particular, we discuss the possible role of the involvement of 2 noncoding RNAs in the etiology of the phenotype.

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Silver-Russell syndrome (SRS, OMIM 180860) is a clinically and genetically heterogeneous disorder characterized by intrauterine and postnatal growth restriction as well as body asymmetry associated with a variable spectrum of additional features: relative macrocephaly, triangular face with a prominent forehead, pointed chin, and 5th finger clinodactyly. Some patients show a mild motor and cognitive delay (learning difficulties and speech delay). By molecular genetic testing, in about 50% of patients, genetic/epigenetic alterations can be detected: in 7–10% of cases, a maternal uniparental disomy of chromosome 7 [UPD(7)mat] can be found, while a methylation defect of the imprinting control region 1 in 11p15 is reported in more than 38% of patients. Usually, the 11p15 epimutation carriers show the more classical SRS phenotype, while UPD(7)mat carriers are more mildly affected.

Fig. 1. Growth curves. **A** Weight-for-age percentile, 0–20 years. **B** Height-for-age percentile, 0–20 years.

Nevertheless, many exceptions have been reported, thereby making a strict genotype-phenotype correlation difficult. In addition to these 2 major disturbances, microscopically detectable structural aberrations affecting numerous chromosomes have been documented, but only the ones involving chromosomes 7, 11 and 17 were consistent with strict diagnostic criteria of SRS [Abu-Amro et al., 2008; Coutton et al., 2012]. However, about 50% of the remaining SRS patients are molecularly unexplained (idiopathic) [Eggermann et al., 2010]. In this study, we report on a 5-years-old boy showing growth retardation, slight body asymmetry and many of the clinical features of SRS, in which single-nucleotide polymorphism (SNP) array analysis identified a de novo duplication of chromosome 11p13 encompassing 4.3 Mb that include 42 genes. To date, only few studies have described submicroscopic chromosomal alterations in SRS or SRS-like cases, and

none of them involves the region 11p13 [Bruce et al., 2010; Spengler et al., 2012]. Also, we discuss the phenotype of the patient in relationship to the gene content of the identified microduplication, and in particular, we propose *CAPRIN1*, *SLC1A2* and *FJX1* as possible candidate genes for the psychomotor delay and *ELP4* for the intrauterine and postnatal growth restriction. Finally, we suggest a possible involvement of *MIR1343* and *LINC00294* in the 11p13-duplication phenotype observed in our patient.

Clinical Report

The male patient was born at the 41st week of gestation from nonconsanguineous healthy parents with no family history of congenital anomalies or developmental delay. During pregnancy, intrauterine growth retardation was reported. At birth, he was small for gestational age with a weight of 2,680 g (<3rd percentile), a

length of 49 cm (3–10th percentile) and a head circumference of 35 cm (50th percentile). He did not show either icterus or asphyxia. The sucking was documented as valid. He was referred at 18 months for evaluation of dysmorphic features, pre- and postnatal growth retardation, psychomotor retardation, and skeletal asymmetry. At that time, his weight was 8 kg (<<3rd percentile), his length 76 cm (<<3rd percentile) and his head circumference 46.6 cm (10–25th percentile). He held the head at 5 months, sat independently at 8 months and walked without support at 15 months. Because of the right truncal hypotonia, he performed physiotherapy from months 9 to 15. Recurrent respiratory infections were reported. At 4 years, he showed a delayed skeletal age of 2 years and also left cryptorchidism which was surgically corrected. An evaluation at 5 years noted a weight of 13 kg (<3rd percentile), a height of 100 cm (<3rd percentile) and a head circumference of 49.5 cm (25–50th percentile) (fig. 1). Physical examination showed hypotrophic and normotonic muscle masses, slight body asymmetry and mild dysmorphic features including: relative macrocephaly, slightly triangular face with high forehead and pointed chin, deep-set eyes, horizontal palpebral fissures, long eyelashes, left convergent strabismus, high and wide nose bridge, large low-set and anteverted ears, hypoplastic tragus, downturned corners of the mouth, slight retrognathia, hands and feet with a 4th and 5th finger clinodactyly, scapular winging, and valgus knees (fig. 2). At brain magnetic resonance, nonspecific white matter anomalies were noticed.

A diagnosis of SRS has been proposed based on the following criteria: intrauterine growth retardation (birth weight or length below the 3rd percentile), lack of postnatal catch-up growth (at 18 months of age, the weight and the length were both <<3rd percentile) and at least 2 of the following criteria: typical face (slightly triangular face with high forehead and pointed chin, downturned corners of the mouth, and ear anomalies), relative macrocephaly, body asymmetry, and 5th finger clinodactyly. The standard G-banding karyotype analysis and the search for epimutations in 11p15 and UPD(7)mat were all negative.

Material and Methods

Blood was obtained from the proband and his parents after signed informed consent. Genomic DNA samples were isolated from peripheral blood lymphocytes by using BioRobot EZ1 (Qiagen, Solna, Sweden). DNA concentration and purity were determined with a ND-1000 Spectrophotometer (NanoDrop Technologies, Berlin, Germany), while for the detection of submicroscopic genomic imbalances, we typed genomic DNA by using the Genome-Wide Human SNP 6.0 Array (Affymetrix, Santa Clara, Calif., USA), including 1.8 M oligonucleotide markers, as previously described [Palumbo et al., 2012]. Microarrays were washed and stained with the Affymetrix Fluidics Station 450 and scanned with the Affymetrix GeneChip Scanner 3000 using the Command Console software (Affymetrix). Copy number analysis was performed with the Genotyping Console software version 4.1 (Affymetrix) using annotation file version NA32 (hg19) and an in-house reference file consisting of 90 samples. Physical mapping and gene locations were obtained from the University of California Santa Cruz (UCSC, <http://genome.ucsc.edu/cgi-bin/hgGateway>) Genome Browser, assembly GRCh37.

Fig. 2. **A** Patient at the age of 5 years. Note hypotrophic and normotonic muscle masses and body asymmetry. **B** Facial features. Note the relative macrocephaly, high forehead with pointed chin, deep-set eyes, horizontal palpebral fissures, long eyelashes, left convergent strabismus, high and wide nose bridge, downturned corners of the mouth, and slight retrognathia. **C** Hands. Note the 4th and 5th finger clinodactyly.

Results

The SNP array analysis revealed an approximately 4.3-Mb-sized duplication in 11p13, from CN_576312 (31,464,790 bp) to SNP_A-2303898 (35,788,567 bp) which were the first and the last duplicated oligonucleotide starting from the telomere, respectively. The flanking normal probes were SNP_A-1958585 (31,454,975 bp, telomeric) and CN_567779 (35,790,243 bp, centromeric). The duplication was absent in the parent (fig. 3A), indicating a de novo origin of the rearrangement, and encompassed 42 genes (fig. 3B). According to the ISCN 2013 nomenclature, the rearrangement can be described as: $\text{arr}[\text{hg}19] \ 11\text{p}13(31,454,975 \times 2, 31,464,790 - 35,788,567 \times 3, 35,790,243 \times 2)\text{dn}$. The 11p13 microduplication in the patient was then confirmed by a second experiment using the GeneChip Human Mapping 250K NspI Array (Affymetrix) (data not shown).

Table 1. Comparison of clinical features of SRS patients, 11p13 duplication carriers reported in the literature and our patient

	Present case	Sanchez et al. [1974]	Palutke et al. [1980]	Strobel et al. [1980]	Lavedan et al. [1989]	Speleman et al. [1991]	Aalfs et al. [1997]	Aradhya et al. [2011]	Dolan et al. [2011]
Duplicated region	11p13	11p12p14	11p12p14	11p11.3p14.1	11p12p14	11p13p14 or 11p14p15	11p12p13	11p13	11p13p14.1
Coordinates of the minimal duplication, bp (hg19)	31,464,790–35,788,567	na	na	na	na	na	na	31,722,682–31,857,737	29,704,680–35,198,172
Coordinates of the maximal duplication, bp (hg19)	31,454,975–35,790,243	na	na	na	na	na	na	31,705,077–31,870,663	29,634,121–35,209,552
Technique of karyotyping	SNP array	G-banding	G-banding	G-banding	G-banding, RFLP	G-banding, FISH	G-banding, FISH	G-banding, FISH, array CGH	G-banding, FISH, array CGH
Growth									
Intrauterine growth retardation	+	–	–	–	–	–	–	–	nr
Postnatal growth retardation	+	–	–	–	–	–	–	–	–
Craniofacial									
Relative macrocephaly	+	–	–	–	–	–	–	–	–
Triangular face	–	–	–	–	–	–	–	–	–
High forehead	+	–	–	–	–	+	–	–	+
Pointed chin	+	–	–	–	–	–	–	–	–
Micrognathia	–	–	–	–	–	–	–	+	–
Downturned corners of the mouth	+	–	–	–	–	–	–	–	–
Ear anomalies	+	–	–	–	–	–	–	–	–
Physical									
Body asymmetry	slight skeletal asymmetry	–	–	–	–	–	–	–	–
Muscular hypotonia	–	–	–	–	–	–	–	+	–
Clinodactyly 5th finger	+	–	–	–	–	–	–	+	–
Other									
Intellectual disability	+	+	–	nr	+	+	+	+	–
Motor developmental delay	+	+	–	nr	–	–	+	–	nr
Speech delay	+	nr	–	nr	–	+	–	+	–

+ = Feature present; – = feature absent; na = not available; nr = feature not reported.

In the literature, deletions in 11p13 encompassing *PAX6* and *WT1* genes have long been known and associated with the WAGR syndrome that is characterized by Wilms tumor, aniridia, genital abnormalities, and mental retardation. In particular, loss-of-function mutations in *PAX6* cause the aniridia phenotype while the deletion of the *WT1* gene has been associated with the increased risk to develop a Wilms tumor [Fischbach et al., 2005].

The phenotype of the reciprocal 11p13 duplication and the dose effect of the genes included in the region are less well-known. To our knowledge, there are a total of 14 patients reported in the literature and only one, described by Aradhya et al. [2011], had a duplication smaller than

the one reported in our patient. Among the 14 published cases of duplications, 6 have been excluded in the clinical comparison since their extent into the 11p15 imprinted region.

Of the remaining 8 patients, none showed a phenotype invoking the Silver-Russell syndrome in contrast to our patient. The clinical comparison between these patients and the diagnostic criteria for SRS are reported in table 1.

In detail, Sanchez et al. [1974] described a partial trisomy 11 in a child with severe psychomotor retardation, intermittent exotropia, oval shaped pupils, leg spasticity, intestinal malrotation, and some craniofacial dysmorphisms; later, Palutke et al. [1980] reported a female pa-

Table 2. Candidate genes for the observed phenotypes in our patient

Gene symbol	Description
<i>ELP4</i>	elongator acetyltransferase complex subunit 4
<i>CAPRIN1</i>	cell cycle-associated protein 1
<i>SLC1A2</i>	solute carrier family 1 (glial high-affinity glutamate transporter), member 2
<i>FJX1</i>	four jointed box 1 (Drosophila)
<i>MIR1343</i>	microRNA 1343
<i>LINC00294</i>	long intergenic non-protein coding RNA 294

tient with a dup11p12p14 showing disconjugate eye movements, ventricular septal defects and dysmorphic features, while Strobel et al. [1980] described an infant with macular dysfunction, cleft lip and palate and developmental delay who was a carrier of a large duplication involving the 11p11.3 band.

Few years later, a mentally retarded child with a dup(11)(p13) [Lavedan et al., 1989] and a child with mild mental retardation, but no other remarkable dysmorphic characteristics [Speleman et al., 1991] were described. Subsequently, Aalfs et al. [1997] reported the data of a girl with a duplication of chromosome band 11p12p13 with borderline developmental delay, mild facial anomalies and eye abnormalities. More recently, a girl, carrier of a small 11p13 duplication comprising 135–168 kb and encompassing only the *PAX6* gene, with seizures, developmental delay, microcephaly, and ocular findings has been described by Aradhya et al. [2011], and a duplication of 5.5–5.8 Mb in size has been reported in a healthy patient by Dolan et al. [2011].

The variable phenotypes in patients described with 11p13 duplications may be related to the different sizes of the rearrangements, to polymorphisms, mutations or different genetic factors elsewhere in the genome, environmental factors, incomplete penetrance, or variable expressivity. Obviously, further molecular analyses are essential to clarify this point.

The potential clinical relevance of the duplication present in our patient is supported by its gene content. The 4.3-Mb duplicated region contains 42 genes (30 known protein-coding genes, 8 pseudogenes, 2 open reading frames, 1 miRNA gene, and 1 long noncoding RNA gene); we suggest and discuss some of them as functional candidates contributing to the phenotype observed in the patient (table 2). In particular, we suggest as candidates for the psychomotor retardation *CAPRIN1*, *SLC1A2* and *FJX1*.

CAPRIN1 encodes a protein that induces the formation of RNA granules, which regulate the transport and translation of mRNAs of proteins involved with synaptic plasticity in neurons. Loss of these control mechanisms is implicated in neuronal disorders. In particular, Shiina et al. [2010] demonstrated that *CAPRIN1* deficiency impairs the dendritic localization of mRNAs for Na⁺/K⁺ ATPase subunit isoforms leading to the degeneration of neuronal networks. Also, the protein *CAPRIN1* interacts with the fragile X mental retardation protein, involved in Fragile-X syndrome phenotype, in neuronal ribonucleoprotein complexes modulating its function [El Fatimy et al., 2012].

The gene *SLC1A2* encodes a member of a family of solute transporter proteins that transports L-glutamate and L- and D-aspartate. In particular, it is essential for terminating the postsynaptic action of glutamate by removing it from the extracellular space at synapses in the central nervous system. Some authors proposed the down-regulation of this gene as an adaptive response to neuronal death or a causative event contributing to neuronal death, suggesting it as a possible susceptibility gene to idiopathic epilepsy [Sarac et al., 2009]. Also, in the 11p13 microdeletion patients, Xu et al. [2008] proposed *SLC1A2* and *BDNF* as candidates that may contribute to autism and mental retardation.

Although the experimental evidences show that haploinsufficiency of these genes, *CAPRIN1* and *SLC1A2*, can give a neurological phenotype, we cannot exclude that also the duplication of the same has a negative effect on the phenotype as already demonstrated for several other genes [Franco et al., 2010; Mattina et al., 2012].

In addition, as regards the psychomotor retardation, we propose the gene *FJX1* as a good candidate. The protein encoded by this gene is the human ortholog of *Drosophila* and mouse four jointed gene product. The *Drosophila* gene four jointed is important for growth and differentiation of legs and wings and for proper development of the eyes while the mouse four jointed gene is expressed in the brain during embryogenesis and in the adult. Although the exact function of the protein encoded by this gene in humans is not known, animal models identify the four jointed gene as an inhibitor of dendrite extension and branching [Probst et al., 2007].

A possible candidate for the prenatal and postnatal growth retardation may be the *ELP4* gene, the product of which is a histone acetyltransferase component of the RNA polymerase II holoenzyme. It is involved in transcriptional elongation. Elongators may play a role in chromatin remodeling and are involved in acetylation of

histone H3 and probably H4. Chromatin dynamism is critical to basic cellular processes and is modulated by epigenetic mechanisms that alter the structure of the chromatin providing binding sites for a wide variety of regulatory proteins. Over the last decade, it has become increasingly clear that genetic alterations of genes involved in epigenetic mechanism are linked to human disorders and in particular to genetic conditions presenting pre- and/or postnatal growth alterations [Hennekam, 2006, Franco et al., 2010]. Also, some authors described carrier patients showing clear growth retardation and deletions or duplications of genes involved in chromatin remodeling, like *CHD1L* [Spengler et al., 2012] and *CREBBP* [Mattina et al., 2012], supporting the hypothesis that alterations of this pathway may result in growth defects. Although, to date, there are no reported cases in the literature documenting that the overexpression and/or microduplication of *ELP4* may have phenotypic consequences, given its functional role, we believe that *ELP4* is a good candidate for the features of growth retardation reported in our case. Of course, to confirm or reject our hypothesis, it is necessary that other patients, perhaps with a small duplication of only *ELP4*, are described.

Interestingly, 2 noncoding RNAs, *MIR1343* and *LINC00294*, are located within the duplicated region. Several reports indicated a role of noncoding RNAs in the molecular pathogenesis of different developmental disorders as well as that alterations of miRNA pathways could be implicated in the etiology of several genomic disorders [Xu et al., 2010]. We searched in the miRBase database (<http://mirdb.org/miRDB/>) for mRNAs containing a putative *MIR1343* binding site. This analysis revealed a large number of putative *MIR1343* target mRNAs (data not shown). Among these mRNAs, the most interesting one, with one of the highest scores, was *IGFBP5* that could be related with the growth retardation observed in our patient.

IGFBP5 codes for a protein, belonging to the insulin-like growth factor-binding protein family that contributes to modulate insulin-like growth factor actions. Mouse models have shown that alteration of the expression levels of *IGFBP5* is associated with growth retardation [Salih et al., 2004]. Although we have no experimental evidences, we suppose that alterations of its expression pattern could be causative of or jointly responsible for growth delay in our patient. As miRNAs function as negative regulators of gene expression, we hypothesize that the duplication of one of these noncoding RNAs could cause an altered expression of the target genes. This hypothesis is compatible with what is already documented

in some microdeletion syndromes, for example in 22q11.2 [Xu et al., 2013], or is proposed for other microduplication syndromes, such as for 8p23.1 [Barber et al., 2013]. Thus, we suggest that *IGFBP5* could be characterized by a similar mechanism, and therefore, growth retardation in our patient may be caused by *MIR1343* duplication.

The last gene that we proposed to play a role in the etiology of the clinical features shown by our patient is *LINC00294* which encodes a long noncoding RNA. The majority of the long noncoding RNAs have very high levels of expression in the central nervous system in a cell type-specific manner, of which some have already been implicated in neurological and developmental disorders [Qureshi et al., 2010]. It is assumed that they regulate gene expression notably via chromatin remodeling at their original locus (in cis) and/or elsewhere in the genome (in trans). This property considerably increases the difficulty to identify their triggers and to understand their physiological roles. Nevertheless, since they are mainly expressed and perform their functions in the central nervous system and given that they regulate gene expression through mechanisms of chromatin remodeling, *LINC00294* still remains a good candidate to explain psychomotor retardation and growth delay observed in our proband. Obviously, to confirm this suggestive hypothesis, gene expression or functional analyses are needed. In conclusion, this is the first paper describing a SRS-like patient being a carrier of a 11p13 microduplication detected by SNP array analysis. We suggest that *CAPRN1*, *SLC1A2*, *FJX1*, and *ELP4* are good candidate genes responsible for the observed traits, and we propose, for the first time, the possible involvement of *MIR1343* and *LINC00294* in the determination of the phenotype. Detailed clinical and molecular examinations of additional patients with a similar microduplication are needed to establish a more accurate genotype-phenotype correlation. Finally, this study demonstrates the utility of molecular karyotyping to discover submicroscopic imbalances in idiopathic SRS or SRS-like patients.

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