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A variant of uncertain significance in *HMGA2* gene, in a child with Silver-Russell syndrome like phenotype: A case report

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Abstract

Silver-Russell Syndrome 5 (SRS5) is characterized by asymmetric Intrauterine Growth Restriction (IUGR), poor postnatal growth, macrocephaly at birth and feeding difficulties. Other possible features include triangular shaped face, prominent forehead, hypertelorism, epicanthus, micrognathia, brachydactyly, clinodactyly of the 5th hand finger, and syndactyly of the 2nd and 3rd toe fingers. Pathogenic variants of the *HMGA2* gene, on chromosome 12q14, which regulates the transcription of the growth factor IGF2, havebeen recently associated with this syndrome. Here in we present a 2.5-year-old boy with growth delay, SRS-like phenotype, and a variant of uncertain significance in the *HMGA2* gene, which hasn't been described yet in the medical literature. So far, twenty-eightpathogenic variants in the *HMGA2* gene, inpatients with clinical SRS phenotype have been recently reported. Therefore, *HMGA2* gene testing should be always checked in the SRS patients that are found negative for the typical 11p15 (epi) mutations and mat UPD7, as well as be added to growth retardation disorder panels.

Background

Silver-Russell Syndrome (SRS) was first reported by Silver et al [1]. In 1953 and Russell in 1954 [2]. They both described different children with body asymmetry, short stature, intrauterine growth retardation and characteristic facial features, including triangular shaped face with a broad forehead and small chin with a wide, thin mouth. Although they both had described different phenotypic features, the whole picture was later defined as the "Russell-Silver syndrome", by Patton in 1988 [3].

SRS occurs in all populations and affects males and females equally. Due to diagnostic issues, it is difficult to determine the true incidence of the syndrome in the general population. Recent data suggests that around 1 in 15,000 children will have SRS [4].

Silver-Russell Syndrome (SRS) is a clinically heterogeneous condition which is characterized by asymmetric Intrauterine Growth Restriction (IUGR), poor postnatal growth, macrocephaly at birth and feeding difficulties. Other clinical features include triangular facies, prominent forehead with frontal bossing, broad nasal tip and bridge, micrognathia with narrow chin, fifth-finger clinodactyly and body asymmetry. Except for the limb length asymmetry, the growth failure is proportionate and head growth normal. These phenotypic characteristics change during childhood and adolescence, with the facial features and asymmetry usually becoming more indistinct with age [5,6]. The most common genetic causes for SRS are an epimutation of the Imprinting Center Region 1 (ICR1) on chromosome 11p15 or a maternal uniparental disomy of chromosome 7; these pathogenic variantscan be identified in around 60% of cases. The remaining 40% involves genetic heterogeneity and

mutations in other genes (IGF2, CDKN1C, PLAG1, HMGA2) [7]. Twenty-eightpathogenic variants have been recently described in the HMGA2 gene with a clinical phenotype of SRS. In particular, 23 deletions, detected by a-CGH, have been reported. The remaining 5 cases were: a 7 bp deletion, a nonsense variant and a frameshift variant and 2 deletions of exon 2 and exons 1–2 [8].

Herein we describe a 2-year-old boy with growth delay, Silver-Russell syndrome'scharacteristics and a variant of unknown significance in HMGA2 gene, which as far as we know, hasn't been described yet in the medical literature.

Case presentation

A 2-year-old boy was referred because of growth delay. From the perinatal history he was born at gestational age of 37 weeks from Caucasian and non-consanguineous parents. His birth weight was 2260 gr and birth length 46 cm (IUGR). The family history was reported unremarkable. The clinical examination showed a triangular face, hypertelorism, micrognathia and long eyelashes. Rest examination was normal. Furthermore, his weight (8 kg) and height (75 cm) were from birth, below the third percentile. Cardiac examination, renal ultrasound, hormonal and basic laboratory tests including celiac disease antibodies were performed and found to be unremarkable. His bone age was delayed by 7 months. The maternal height is 162 cm and the paternal height is 172 cm. His mid parental height will be between 165 cm and 182 cm with a target height calculated at 173.5 cm. Due to his clinical features, a genetic consult was requested. In view of normal Array Comparative Genomic Hybridization (aCGH) and negative result for epimutation at chromosome 11p15 and maternal uniparental disomy of chromosome 7, a Whole Exome Sequence (WES) was performed and revealed the variantc. 111+5G>A in the HMGA2 gene, which may cause a disruption in the splicing process. According to the guidelines of the American College of Medical Genetics this variant considered to be of uncertain significance (VUS). Unfortunately, parentalmolecular testing was not performed. At last, our patient was commenced on replacement therapy with recombinant Human Growth Hormone (HGH) with a good response.

Discussion and conclusion

Silver-Russell Syndrome-1 (SRS1) is caused by hypomethylation at distal chromosome 11p15 (ICR1). Opposite epimutations, such as hypermethylation at the same region on 11p15, are detected in about 5 to 10% of patients with Beck with-Wiedemann syndrome, an overgrowth syndrome [9]. Silver-Russell Syndrome 2 (SRS2) is caused by maternal uniparental disomy of chromosome 7, SRS3 by mutation in the IGF2 geneon chromosome 11p15, SRS4 by mutation in the PLAG1 geneon chromosome 8q12 and SRS5 by mutation in the *HMGA2* geneon chromosome 12q14.

HMGA2 is a transcription factor and one of the four members of the "High Mobility Group A" (HMGA) protein family that function as architectural transcription factors, and is encoded by HMGA2 gene. It is involved in a wide variety of biological processes, such as somatic growth control, proliferation, differentiation and death. In humans, chromosome anomalies thatcausing gain-of-function of HMGA2 are associated with overgrowth and mesenchymal tumors such asuterine leiomyoma, gastric cancer and pediatric lipoma [10]. While a common SNP in HMGA2 is associated with height variation in the general population [11]. Furthermore, expression of HMGA2 is suppressed in normal adult cells, contrary to embryogenesis, when it is high. Many studies have shown so far, a decrease of IGF2 expression when HMGA2 is silenced [12]. IGF2 is a main factor in human growth regulation, while in SRS its downregulation by LOM of the IC1 in 11p15.5 and by pathogenic variants which cause growth restriction [13,14].

Another role of *HMGA2* gene in the pathogenesis of SRS-like cases is supported by the evidence that pre and post natal growth failure and underweight – characteristic SRS features - have been described in all patients carrying different mutations of HMGA2 gene.

Ali Habib et al in a cohort of 192 patients with a suspected diagnosis of SRS, identified 2 unrelated patients with heterozygous de novo mutations in the HMGA2 gene. In 6 more patients from 4 families in this cohort, mutations in the PLAG1and IGF2 genes were identified. Experiments in Hep3b cells proved that *HMGA2* and PLAG1 regulate positively the expression of the IGF2 promoter P3, independently and via an *HMGA2*-PLAG1-IGF2 pathway. It was noted that disruption of any gene in the pathway results in a decrease in IGF2 expression, which subsequently produces an SRS phenotype similar to patients carrying 11p15.5 epigenetic defects (SRS1), except for body asymmetry [15].

We suggest that *HMGA2* mutations might be a cause of SRS and should be checked in the SRS patients that are found negative for the typical 11p15 (epi) mutations and mat UPD7, as well as beadded to growth retardation disorder panels.

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