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Case Report

Chromosome 7 Isodisomy in a Child with Silver-Russell Syndrome

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Abstract

Silver-Rusell syndrome is a rare genetic disease. There is evidence that the genetic causes of the disorder are heterogeneous, with predominant alterations in the imprinted regions of chromosomes 11 and 7, in addition to other genomic alterations, such as chromosomal structural aberrations, single nucleotide polymorphisms, copy number variations, and small insertions and deletions. The most prevalent clinical manifestations include prenatal and postnatal growth retardation, dysmorphic features, and feeding difficulties. We present a case of a 4-year-old boy with phenotypic features consistent with Silver-Russell syndrome. The sample was subjected to conventional karyotyping analysis. The analysis was also conducted using the SALSA MLPA Probemix ME032-A1 UDP7-UDP14 and Applied Biosystems CytoScan 750K Suite. MS-MLPA analysis revealed the presence of hypermethylation in the *GRB-10* and *MEST* genes on chromosome 7. SNP-array analysis revealed a loss of

heterozygosity (LOH) at 7q11.22q31.1 (38.7 Mb). The methylation of the genes involved in this epigenetic event, in conjunction with LOH and the clinical characterization of this child, indicates that the origin of the disease is due to an isodisomy of maternal chromosome 7. This report of a child who exhibits the clinical characteristics of SRS and presents a UPD of chromosome 7, most likely originating from the mother, once again demonstrates the involvement of these genes in SRS despite the incomplete understanding of the underlying mechanism. A multidisciplinary strategy has been proposed for the follow-up and treatment of this disease according to its etiology in the proband.

Keywords
Silver-Rusell syndrome; Isodisomy 7; methylation *GRB-10* and *MEST*; loss of heterozygosity; SNP-array analysis

1. Introduction

Silver-Russell syndrome (SRS, OMIM 180860) is clinically characterized by prenatal and postnatal growth failure, triangular face, varying degrees of body asymmetry (usually in the length of limbs), protruding forehead, clinodactyly of the 5th finger, and severe feeding difficulties. Most individuals have almost average intelligence. However, a learning disability has been reported in several cases [1]. It is thought that the incidence of this syndrome may range from 1:30,000 to 1:100,000 because many cases remain undiagnosed [2, 3].

SRS is a genetically heterogeneous disease. According to Sing et al., in their review of 3475 reported cases, half of the patients had no identified molecular cause. In those cases with an established diagnosis, methylation defects in the 11p15 region accounted for about 38% of all reported cases. These authors also report that UPDs account for approximately 7% of cases, most of which are mUPD7. Other genomic alterations, such as chromosome structural aberrations (3%) [3-6] and single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and small insertions and deletions (indels) (together constituting 1.6%) were also observed in these cases [7]. In addition, sequence variants of the high-mobility group AT-Hook 2 (HMGA2) and pleomorphic adenoma gene 1 (*PLAG1*), two non-imprinted genes, have been implicated in SRS [8, 9].

Although different genomic regions are involved, SRS shares many clinical features with other imprinting disorders (IDs), posing challenges for accurate diagnosis. For example, SRS, Temple syndrome (TS14), and Prader-Willi syndrome (PWS) share clinical features of growth retardation (pre- and postnatal), early feeding difficulties, small hands/feet, and hypotonia. Precocious puberty, clinodactyly of the 5th finger, and prominent forehead are more frequent only in SRS and TS14, whereas genital anomalies are more frequent only in SRS and PWS [10, 11].

In this case, we propose to describe the clinical features of a child with a suspected diagnosis of SRS, which was confirmed by molecular methods. Furthermore, we propose a potential syndrome etiology and a strategy for managing this disease in this patient.

2. Materials and Methods

A comprehensive medical history, anthropometric evaluation, and laboratory tests (glucose, insulin, hemoglobin, and growth hormone levels) were taken. Audiometry and ocular refraction were conducted.

The techniques described in The AGT Cytogenetics Laboratory Manual and adapted to laboratory conditions were employed to perform a karyotype analysis on the child using peripheral blood [12].

Genomic DNA was isolated from peripheral blood leukocytes on the QIA symphony SP automatic nucleic acid extractor using the QIAsymphony DNA Midi Kit (QIAGEN, Germany). The methylation alterations and copy number variations at chromosome 7 were measured by methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). According to the manufacturer's instructions, the analysis was conducted using the SALSA MLPA Probemix ME032-A1 UDP7-UDP14 (hg 18) (MRC Holland, The Netherlands).

Probemix ME032 UPD7-UPD14 interrogates imprinted 7p12, 7q32 and 14q32 regions, including the *GRB10* and *MEST* genes. Probes were hybridized to denatured genomic DNA. The hybridized sample was divided into two portions for separate analyses: direct ligation (to test CNVs) and digestion with the HhaI methylation-specific restriction enzyme before ligation (to test the methylation status). After ligation, PCR was performed using fluorescence-labeled unique primers for probe sets provided in the SALSA MLPA kit. Amplified products were separated on an ABI3100 Genetic Analyzer and analyzed using Coffalyser.Net software v.131211. The probe sequence sheet ME032 UPD7-UPD14-A1 (NCBI36/hg18) was used to determine the hybridizing sequence and location of the probes in the SALSA MLPA probemix.

Applied Biosystems CytoScan 750K Suite (Thermo Fisher Scientific, USA) was used to analyze genomic imbalances and loss of heterozygosity (LOH) determination.

The Institutional Review Board approved this study of the institutions involved in the study. Written consent and permission to publish the patient’s image, as shown in Figure 1 were obtained from the parents.

3. Results

A 4 year and 10-month-old boy presented with a height of 91 cm (<3 percentile), a weight of 10 kg (<3 percentile), a head circumference of 50.5 cm (75 percentile), dolichocephaly, triangular face, palpebral fissures upwards, long and abundant eyelashes, wide mouth with multiple cavities, thickened upper lip, high palate, micrognathia, short philtrum, joint hyperlaxity, large auricles unfolded from the plane of the face, with lax cartilage, right inguinal hernia and normal genitalia (Figure 1).

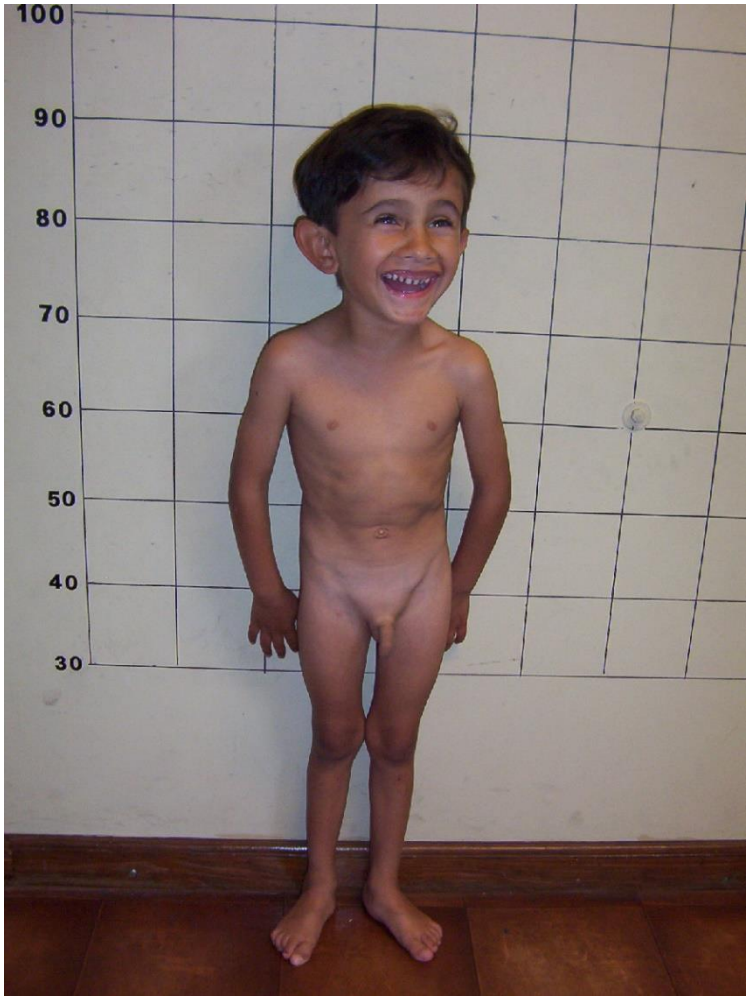

Figure 1 Child with Silver-Rusell syndrome. Some of the phenotypic characteristics described in the text can be observed, such as short stature, triangular face, relatively large head circumference, and wide mouth.

The child is the product of the fourth pregnancy of a non-consanguineous couple and is the first reported in the family with these phenotypic features. The mother's age at birth was 41 years, and the father was 47. Prenatal ultrasound detected intrauterine growth retardation. Delivery was expected at 33 weeks gestation. Birth weight was 1795 grams (<3 percentile). A lack of interest in suckling was reported from birth. Child's feeding was difficult due to the apparent lack of appetite. He was supplemented with nutritional supplements.

Laboratory tests revealed no abnormalities, except low growth hormone (GH) levels (0.15 ng/ml). The subject does not exhibit any evidence of delayed psychomotor development. He has no hearing deficit, and his vision is within the normal range.

Karyotype was found to lack abnormalities (46, XY).

Figure 2 (top) depicts the electropherogram of the sample digested with the HhaI enzyme. The bottom graph is a probe ratio chart generated by the Coffalyser.Net software from the analysis of the digested sample data. The MS-MLPA study demonstrated hypermethylation in the *GRB10* and *MEST* genes (Figure 2) located on 7p12 and 7q32.2, respectively. In conjunction with the patient's clinical characteristics, this suggests a maternal uniparental disomy of chromosome 7.

No CNV alterations were reported in the patient. Unfortunately, the copy number ratio chart for this sample is not available.

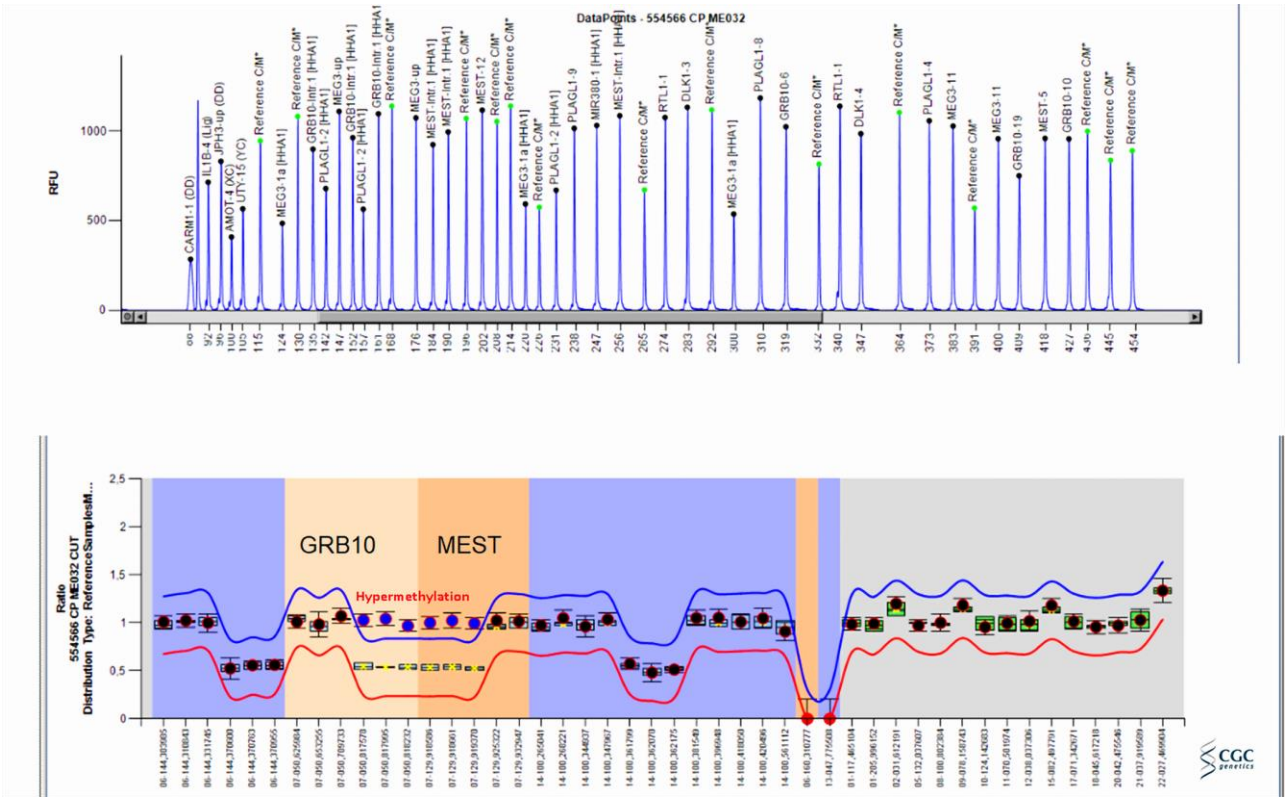

Figure 2 MS-MLPA profile of the imprinted loci at chromosomes 7 in the proband. Methylation ratio for *GRB10*:alt-TSS-DMR and *MEST*:alt-TSS-DMR are shown (bottom graphic). Each dot displays the final probe ratio for each locus analyzed. Black dots indicate the probing ratio is within the 95% confidence interval (CI) of the reference sample population, and the blue dots suggests the ratio is out of the 95% CI and over the arbitrary borders, upper border: blue line. The graphic shows that these six target probes (blue dots) are 100% methylated in the test sample and 50% in the reference sample (yellow rectangle) derived from healthy individuals. The top graphic (Capillary electrophoresis pattern) shows the probes sorted by length. It constitutes a quality control of the test that demonstrates the probes to be tested have been correctly digested and separated.

However, it is not known whether maternal UPD is a heterodisomy or an isodisomy. We then performed microarray-based SNP (hg-19) genotyping presenting the following results: arr 7q11.22q31.1(71547269-110322061) ×2, 11p15.4(9947192-9976320) ×1. A loss of heterozygosity at 7q11.22q31.1 (38.7 Mb) was identified (Figure 3). This large region of lost heterozygosity suggests that it is an isodisomy of maternally inherited chromosome 7.

Figure 3 Region with loss of heterozygosity (purple line) in segment 7q11.23-7q31.1. Denotes an isodisomy of chromosome 7.

4. Discussion

We present the case of a child whose clinical characteristics meet many of the Netchine Harbison SRS Clinical Scoring System criteria for SRS classification [13]. This patient shows in his phenotype prenatal and postnatal growth retardation, low birth weight, the onset of feeding difficulties in the neonatal period, relative macrocephaly, with a protruding forehead and triangular face, fulfilling in total 5 of the 6 criteria of the Netchine Harbison system for phenotype classification with SRS. Our study did not report Body asymmetry, which was found in 45% of the cases with mat UPD 7 [14]. Table 1 presents a comparative analysis of the clinical features of our proband with those reported in the literature on the whole mUPD of chromosome 7.

Table 1 Comparison of clinical data of our patient with 7 UPD with similar cases from the literature.

Clinical features	**Hitchins [14] n = 24 (%) whole chrom. 7**	**Ishida [15] n = 20 (%) whole chrom. 7**	**Lin [16] n = 10 (%) whole chrom. 7**	**Eggermann [17] § n (%) whole chrom. 7**	**Present case. Whole chrom. 7**
Growth parameters					
IUGR	Not reported	Not reported	Not reported	32(SD-2.79)	+
PGR	100	65	90	38 (SD-3.37)	+
low birth weight	87.5	70	100	37(SD-2.79)	+

Craniofacial features					
relative macrocephaly	71	90	50	92%	+
triangular face	29	90	50	34 (97)	+
prominent forehead	80	60	80	68%	+
downturned corners of the mouth	0	20	Not reported	22(50)	-
micrognathia	No reported	35	Not reported	9 (55)	-
ear anomalies	21	75	Not reported	14(78.6)	+
teeth anomalies	4		Not reported	14(64)	-
Others Features					
Feeding difficulties	33	90	100	Not reported	+
Body asymmetry	45	30	50	30 (60)	-
developmental delay	25 (Speech delay)	65	20	39(43)	-
clinodactyly V	37.5	45	20	34(82)	-
muscular hypotonia	12	Not reported	Not reported	13 (69,2)	-

§ Clinical features in SRS and their frequencies combined from different studies.
IUGR- Intrauterine growth retardation, PGR- Postnatal growth retardation.

This study suggests that the cause of SRS is due to a maternal uniparental isodisomy of the whole chromosome 7 i) due to the detection of a 38.7 Mb region in the long arm with loss of heterozygosity, ii) because the genes *GRB10* (7p12) and *MEST* (7q32.2), in which hypermethylation was demonstrated are outside this region of loss of heterozygosity and iii) after crossing over in prophase I of meiosis I, the chromosomes, although isodisomics have segments of different parental origin.

4.1 Genes Involved

Human growth factor binding protein 10 (*GRB10*) has been suggested as a candidate gene for SRS. A role of *GRB10,* at least for prenatal human growth, has been proposed. Besides, the negative correlation between *GRB10* expression and head circumference could also explain relative macrocephaly and/or developmental delay as another characteristic feature of SRS [18, 19]. In addition to uniparental disomy, some cases with duplications involving *GRB10* on the maternal allele have been described in patients with growth retardation and features of SRS. This reinforces the criterion that it is a candidate gene for the appearance of this disease when it has a maternal origin. However, the precise mechanism of this phenotypic effect is currently unknown [5, 20].

On the other hand, the *MEST* gene (*PEG1/MEST* paternally expressed gene 1/mesoderm-specific transcript) on 7q32.2 has been identified as one of the genes that could decisively influence the

onset of the disease, as it is methylated on the maternal chromosome 7. There is evidence that molecular changes at the imprinted *MEST* region in 7q32.2 are associated with a phenotype of SRS. Vincent et al. reported a 79 kb microdeletion in the paternal 7q32.2 region involving the *MEST* gene in a child with SRS phenotype. This microdeletion involving the *MEST* gene corroborates the hypothesis that *MEST* plays a significant role in the 7q32.2 microdeletion growth disorder and provides further evidence for the involvement of *MEST* in SRS UPD (7)mat itself [21]. Another case very similar to the previous one is reported by Carrera et al. [22]. Also, in prenatal diagnosis, intrauterine growth retardation has been detected in a fetus that presented a line with maternal UPD 7 and another line with trisomy 7; in the placenta, the line with UPD 7 predominated. The placental histological study detected an angiogenesis defect caused by the absence of the *PEG1/MEST* product. This finding suggests that this is the cause of fetal growth retardation, a very typical feature of SRS, although the authors do not rule out the effect of the trisomy 7 line [23].

Although this study only demonstrated hypermethylation in the genes mentioned above, it is worth noting that in the LOH segment of the proband (7q11.22q31.1), there are two candidate regions with genes that are reported to be imprinted. The 7q21.3 and 7q31.1 regions. The 7q31.1-7qter region contains four imprinted genes (*CPA4, MEST, COPG2, KLF4*) and two non-coding imprinted RNAs (*MESTIT1* and *COPG2IT1*) [24-27].

The imprinted PEG10/SGCE cluster (at 7q21.3) has been shown to contain the *DLX5* gene, which is expressed biallelically in mice but imprinted in humans [15].

One of the limitations of the present study is that neither of the two parents of the child studied agreed to provide DNA samples to corroborate the origin of this DUP. However, considering the results of the MS-MLPA (with the hypermethylated *GBR10* and *MEST* genes) and the clinical evidence of the proband's phenotype and loss of heterozygosity in an area of chromosome 7 that includes candidate regions with imprinted genes involved in SRS, the most harmonious option according to the literature consulted [7, 14, 19, 27] is that the UPD is maternally inherited.

4.2 SRS Management Strategy in This Child

Treatment strategies should be individualized because SRS is associated with many physical and functional abnormalities. Diagnosis and treatment should be performed in affected children as soon as possible to obtain the best possible results. This child was definitively diagnosed with the disease at the age of four. In cases of UPD 7, physical and neurodevelopmental disorders exhibit certain peculiarities that necessitate a longitudinal follow-up of the patient and a multidisciplinary approach to care involving various medical specialties. For example, it should be attended by gastroenterologists to help alleviate the lack of appetite of the child, which in the medium and long term causes a delay in development and may be due to multiple factors such as oralmotor dysfunction, functional and structural gastrointestinal problems, constipation (especially after the age of two). Pediatricians should also see the child because feeding difficulties increase the risk of fasting hypoglycemia and its potential neurocognitive consequences [2].

Given the low levels of growth hormone in the child, it is recommended that the child undergo GH treatment, which will help him to be taller in adulthood [28, 29]. In addition, this treatment will increase the child's muscle mass, improve appetite, and reduce the risk of hypoglycemia.

As this patient has a UPD 7 mat, it is highly recommended to monitor the symptoms of myoclonus dystonia. If these involuntary muscle movements appear, he should be promptly referred to a

pediatric neurologist. Furthermore, it is essential to closely monitor the child for signs of verbal or oral dyspraxia, as well as for indications of autism spectrum disorders. Monitoring for any signs of learning difficulties, psychosocial problems, or cognitive delays is essential. It is recommended that parents be informed of the potential for these issues to arise during the development of the proband [2]. This approach will facilitate the implementation of early intervention measures, thereby reducing the potential for psychosocial harm to the child and family.

This child exhibited multiple dental caries in all teeth, likely due to an unhealthy diet that attempted to compensate for a lack of appetite (excessive sugar consumption). Educating parents about these unhealthy habits and the importance of proper oral hygiene to prevent dental caries in adulthood is crucial.

The risk of recurrence of the disease is shallow, and the child's parents were informed accordingly. This information was a significant source of reassurance for all family members of reproductive age. Nevertheless, prenatal diagnosis is a strategy offered to alleviate parental (and other family members) anxiety about future pregnancies.

5. Conclusion

This report of a child who exhibits the clinical characteristics of SRS and presents a UPD of chromosome 7, most likely originating from the mother, once again demonstrates the involvement of these genes in SRS despite the incomplete understanding of the underlying mechanism. A multidisciplinary strategy has been proposed for the follow-up and treatment of this disease according to its etiology in the proband.

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Author Contributions

LAMR, IYI, AV: conceptualized and designed the research study. Reviewed and edited the manuscript. AV: clinical patient analysis. JPB: wrote the draft manuscript. Clinical patient analysis. Reviewed the final versión. RLF and ACS: were involved in supervision and funding acquisition. Reviewed and adequately modified the final versión. AE, LAMR: Proper interpretation of results. Reviewed and edited the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Saal HM, Pagon RA, Pepin MG. Reevaluation of Russell-Silver syndrome. J Pediatric. 1985; 107: 733-737.
2. Wakeling EL, Brioude F, Lokulo-Sodipe O, O'Connell SM, Salem J, Bliek J, et al. Diagnosis and management of Silver-Russell syndrome: First international consensus statement. Nat Rev Endocrinol. 2017; 13: 105-124.

3. Spiteri BS, Stafrace Y, Calleja-Agius J. Silver-Russell syndrome: A review. Neonatal Netw. 2017; 36: 206-212.
4. Zhang YL, Jing XY, Wan JH, Pan M, Li DZ. Prenatal Silver-Russell syndrome in a Chinese family identified by non-invasive prenatal testing. Mol Syndromol. 2022; 13: 323-327.
5. Catusi I, Bonati MT, Mainini E, Russo S, Orlandini E, Larizza L, et al. Recombinant chromosome 7 driven by maternal chromosome 7 pericentric inversion in a girl with features of Silver-Russell syndrome. Int J Mol Sci. 2020; 21: 8487.
6. Fokstuen S, Kotzot D. Chromosomal rearrangements in patients with clinical features of Silver–Russell syndrome. Am J Med Genet Part A. 2014; 164: 1595-1605.
7. Singh A, Pajni K, Panigrahi I, Khetarpal P. Clinical and molecular heterogeneity of Silver-Russell syndrome and therapeutic challenges: A systematic review. Curr Pediatr Rev. 2023; 19: 157-168.
8. Hübner C, Meyer R, Kenawy A, Ambrozaityte L, Matuleviciene A, Kraft F, et al. HMGA2 variants in Silver-Russell syndrome: Homozygous and heterozygous occurrence. J Clin Endocrinol Metab. 2020; 105: 2401-2407.
9. Vado Y, Pereda A, Llano-Rivas I, Gorria-Redondo N, Díez I, Perez de Nanclares G. Novel variant in PLAG1 in a familial case with Silver-Russell syndrome suspicion. Genes. 2020; 11: 1461.
10. Abi Habib W, Brioude F, Azzi S, Rossignol S, Linglart A, Sobrier ML, et al. Transcriptional profiling at the DLK1/MEG3 domain explains clinical overlap between imprinting disorders. Sci Adv. 2019; 5: eaau9425.
11. Juriaans AF, Kerkhof GF, Mahabier EF, Sas TCJ, Zwaveling-Soonawala N, Touwslager RN, et al. Temple syndrome: Clinical findings, body composition and cognition in 15 patients. J Clin Med. 2022; 11: 6289.
12. Arsham MS, Barch MJ, Lawce HJ. The AGT cytogenetics laboratory manual. Hoboken, NJ: John Wiley & Sons; 2017.
13. Netchine I, Rossignol S, Dufourg MN, Azzi S, Rousseau A, Perin L, et al. Imprinting center region 1 loss of methylation is a common and specific cause of typical Russell-Silver syndrome: Clinical scoring system and epigenetic-phenotypic correlations. J Clin Endocrinol Metab. 2007; 92: 3148-3154.
14. Hitchins MP, Stanier P, Preece MA, Moore GE. Silver-Russell syndrome: A dissection of the genetic aetiology and candidate chromosomal regions. J Med Genet. 2001; 38: 810-819.
15. Ishida M. New developments in Silver-Russell syndrome and implications for clinical practice. Epigenomics. 2016; 8: 563-580.
16. Lin HY, Lee CL, Fran S, Tu RY, Chang YH, Niu DM, et al. Epigenotype, genotype, and phenotype analysis of taiwanese patients with Silver-Russell syndrome. J Pers Med. 2021; 11: 1197.
17. Eggermann T, Begemann M, Binder G, Spengler S. Silver-Russell syndrome: Genetic basis and molecular genetic testing. Orphanet J Rare Dis. 2010; 5: 19.
18. Moore GE, Ishida M, Demetriou C, Al-Olabi L, Leon LJ, Thomas AC, et al. The role and interaction of imprinted genes in human fetal growth. Philos Trans R Soc B Biol Sci. 2015; 370: 20140074.
19. Eggermann T, Begemann M, Kurth I, Elbracht M. Contribution of GRB10 to the prenatal phenotype in Silver-Russell syndrome? Lessons from 7p12 copy number variations. Eur J Med Genet. 2019; 62: 103671.

20. Monk D, Bentley L, Hitchins M, Myler M, Clayton-Smith RA, Ismail J, et al. Chromosome 7p disruptions in Silver Russell syndrome: Delineating an imprinted candidate gene region. Hum Genet. 2002; 111: 376-387.
21. Vincent KM, Stavropoulos DJ, Beaulieu-Bergeron M, Yang C, Jiang M, Zuijdwijk C, et al. A 79-kb paternally inherited 7q32.2 microdeletion involving MEST in a patient with a Silver-Russell syndrome-like phenotype. Am J Med Genet A. 2022; 188: 2421-2428.
22. Carrera IA, de Zaldívar MS, Martín R, Begemann M, Soellner L, Eggermann T. Microdeletions of the 7q32.2 imprinted region are associated with Silver–Russell syndrome features. Am J Med Genet Part A. 2016; 170: 743-749.
23. Miozzo M, Grati FR, Bulfamante G, Rossella F, Cribiù M, Radaelli T, et al. Post-zygotic origin of complete maternal chromosome 7 isodisomy and consequent loss of placental PEG1/MEST expression. Placenta. 2001; 22: 813-821.
24. Iourov IY, Vorsanova SG, Korostelev SA, Zelenova MA, Yurov YB. Long contiguous stretches of homozygosity spanning shortly the imprinted loci are associated with intellectual disability, autism and/or epilepsy. Mol Cytogenet. 2015; 8: 77.
25. Kim SY, Shin CH, Lee YA, Shin CH, Yang SW, Tae-Joon C, et al. Clinical application of sequential epigenetic analysis for diagnosis of Silver-Russell syndrome. Ann Lab Med. 2021; 41: 401-408.
26. Hannula K, Lipsanen-Nyman M, Kontiokari T, Kere J. A narrow segment of maternal uniparental disomy of chromosome 7q31-qter in Silver-Russell syndrome delimits a candidate gene region. Am J Hum Genet. 2001; 68: 247-253.
27. Iourov IY, Vorsanova SG, Zelenova MA, Vasin KS, Kurinnaia OS, Korostelev SA, et al. Epigenomic variations manifesting as a loss of heterozygosity affecting imprinted genes represent a molecular mechanism of autism spectrum disorders and intellectual disability in children. Zh Nevrol Psikhiatr Im S S Korsakova. 2019; 119: 91-97.
28. Ranke MB, Lindberg A, KIGS International Board. Height at start, first-year growth response and cause of shortness at birth are major determinants of adult height outcomes of short children born small for gestational age and Silver-Russell syndrome treated with growth hormone: Analysis of data from KIGS. Horm Res Paediatr. 2010; 74: 259-266.
29. Azcona C, Albanese A, Bareille P, Stanhope R. Growth hormone treatment in growth hormone-sufficient and -insufficient children with intrauterine growth retardation/Russell-Silver syndrome. Horm Res. 1998; 50: 22-27.