Background: Silver-Russell Syndrome (SRS) is a genetic disorder characterized by intrauterine and postnatal growth restriction and normal head circumference with consequent relative macrocephaly. Additional findings are protruding forehead in early life, body asymmetry (of upper and lower limbs) and substantial feeding difficulties. Although several genetic mechanisms that cause the syndrome are known, more than 40% of patients with a SRS-like phenotype remain without an etiological diagnosis. In the last few years, different clinical reports have suggested that mutations or deletions of the HMGA2 gene can be responsible for a SRS-like phenotype in patients with negative results of the common diagnostic tests for this syndrome.

Case presentation: We present a 3-year-old male patient with clinical diagnosis of Silver-Russell Syndrome (SRS) associated with a de novo heterozygous deletion of the long arm of the chromosome 12 (12q14.3) encompassing the HMGA2 gene.

Conclusions: Our report confirms the etiological role of HMGA2 as a disease gene in the development of a SRS-like phenotype.

Keywords: Silver-Russell syndrome, Failure to thrive, HMGA2 gene, Netchine-Harbison clinical scoring system, Case report
In particular, the H19/IGF2:IG-DMR hypomethylation occurs in almost 40% of cases, followed by the maternal uniparental disomy of chromosome 7 (4–10% of cases), the maternal uniparental disomy of 11p15.5 region (less than 1% of cases), and the multilocus hypomethylation with or without ICR2 hypomethylation (less than 1% of cases). Chromosomal rearrangements, such as the duplication of maternal 11p15.5 region and other cryptic chromosomal aberrations, have been reported in less than 1% of cases respectively. However, all these genetic aberrations can be detected in less than 60% of SRS cases, and thus the clinical diagnosis remains without a genetic etiology [1–5].

In the last decade, several studies have suggested the role of HMGA2 as candidate gene in those patients with SRS phenotype and negative result of classical genetic tests for SRS. HMGA2 gene encodes for the HMGA2 protein, member of the “high-mobility group AT-hook” (HMG) family. These proteins act as architectural transcription factors that regulate the transcriptional activity of several genes. The expression of HMGA proteins is high in early developmental stages in embryos and mesenchymal stem cells, whilst it is almost absent or very low in adult tissues. Additionally, several studies have showed their role in adipocytes differentiation and their overexpression in some tumoral tissues [6–8].

In 2007, Menten et al. [9] reported SRS patients with the microdeletion of the 12q14.3 region encompassing different genes including HMGA2 and LEMD3 (an OMIM Disease Causing gene associated with Bushke-Ollendorff syndrome and Osteopoikilosis with or without melorheostosis). To our knowledge, other three heterozygous pathogenic variants and two exon deletions involving the HMGA2 gene have been described in patients with clinical diagnosis of SRS [8, 10–12].

We report the clinical and genetic characteristics of a patient with SRS phenotype and a de novo 425 Kb microdeletion of 12q14.3 region encompassing the HMGA2 gene but not the LEMD3 gene.

**Case presentation**

Our patient is a 3-year-old boy, third child of Caucasian, non-consanguineous and healthy parents. He was born at 39 weeks of gestation via natural delivery, after an unremarkable pregnancy. At birth he was small for gestational age: weight of 2350 g (<3rd centile), length 47 cm (2nd centile), head circumference (HC) 31 cm (<3rd centile). His Apgar scores were 9 at 1 min and 10 at 5 min. His past medical history was significant for a persistent failure to thrive during his first year of life. Several investigations, including a work-up for metabolic and gastrointestinal disorders, multiple urine tests, cranial ultrasound, echocardiogram and abdominal ultrasound, were normal. Endocrinological assessment showed a normal growth hormone (GH) function, but a moderate hypothyroidism, still treated with levothyroxine. At 8 months of age audiological evaluation was normal, while ophthalmologic exam revealed mild pseudostrabismus.

He was referred to our attention at the age of 10 months. His anthropometric parameters were: weight 5900 g (<−2 SDS), length 64 cm (<−2 SDS), head circumference (HC) 43.8 cm (9th – 25th centile). In addition, physical examination showed: triangular facies, closed anterior fontanelle, wide forehead, frontal bossing, deeply set eyes, epicantal inversus, downslanted palpebral fissures, blue sclerae, narrow chin with slight vertical crease, ears posteriorly rotated with prominent anterior crus of antihelix and underdeveloped tragus and antitragus, syndactyly of 2th/3th finger of the feet, clinodactyly of 5th finger of the hands, low muscle mass, asymmetric lower limbs (left almost 1 cm shorter than right). A neuropsychiatric consult was requested, and then a moderate speech delay was detected. The brain MRI was normal.

At 2 years, the clinical picture appeared unchanged. His weight was 7500 g (<3rd centile), his lenght was 81 cm at the left side and 80 cm at the right (<3rd centile), his HC was 47,3 cm (10rd centile) and his BMI was 11,7 (<3rd centile). During the last check-up at our Center, at the age of 3 years, no significant changes were revealed regarding the clinical presentation and growth parameters. His weight was 9450 g (<3rd centile), his lenght was 88 cm at the left side and 89 cm at the right (3rd centile), and his HC was 48,2 cm (3rd centile) (Fig. 1).

Applying the Netchine-Harbison CSS (NHCSS) we got a score of 5/6 (the proband met all the criteria for likely SRS except for relative macrocephaly at birth) [2].

**Genetic tests**

In accordance with the clinical suspicion of SRS assessed through the NHCSS, we proceeded according to the flowchart proposed by Azzi et al. and performed the classical genetic test for this syndrome. The Methylation-Specific Multiplex Legation-dependent Probe Amplification (MS-MLPA) at the imprinting region 11p15 did not reveal Loss Of Methylation (LOM) and the study of microsatellite markers of chromosome 7 did not detect UniParental Disomy (UPD). Subsequently, consistently with the aforementioned flow-chart, we proceeded with the research of genome-wide microdeletions or microduplications by Array-CGH (Array-Comparative Genome Hybridization). This analysis showed a de novo partial deletion of the long arm of the chromosome 12, 425 Kb-sized, from position 66,358,287, in which there is the most terminal probe delete on the array (cytogenetic locus 12q14.3) to 66,782,791 (cytogenetic locus 12q14.3) (Fig. 2). According with the build UCSC Genome Browser (Hg build 19) several genes lie in this region including the OMIM disease genes.
causing genes HMGA2 (OMIM 600698, partially involved), IRAK3 (OMIM 604459) and GRIP1 (OMIM 604597). This microdeletion is not reported in DECIPHER. However, the same database recorded a 1.67 Mb deletion (ID 337828) of unknown significance, encompassing the same genes and maternally inherited, in a female infant with episodic hyperhidrosis, failure to thrive, moderate short stature, facial asymmetry, prominent forehead, proptosis, scoliosis and history of intrauterine growth retardation. A deletion with the same genomic and clinical features (size, genomic coordinates, maternal origin, clinical picture except for the absence of hyperhidrosis) have been previously described by Heldt et al. in a family where it segregated along with Silver-Russell like phenotype. Even if neither Heldt nor the database DECIPHER refer to the case reported by the other, we believe it is reasonably to conclude that the deletions reported in DECIPHER and in Heldt paper are the same [2, 13].

**Materials and methods**

DNA of proband and his parents was extracted with QIAamp DNA blood Midi Kit (Qiagen Inc., Valencia, CA) according to the manufacturer’s instructions. The normal control was a commercially available male Promega (Promega Corporation, Madison, WI). Array-CGH analysis was performed using a Human Genome CGH Microarray Kit 8x60K (Agilent) with a resolution of 100–150 kb according to the manufacturer’s instructions. Array slides were analyzed with an Agilent G2505B scanner. Image were analyzed and visualized with CytoGenomics 3.0.6.6 (Agilent Technologies, Santa Clara, CA).

**Discussion & conclusions**

More than 40% of patients with a SRS-like phenotype remain without an etiological diagnosis [3, 4]. Several genes have been proposed as candidate genes. During
the last 10 years, different reports have suggested the role of \textit{HMGA2} in the etiology of SRS-like phenotype. To our knowledge, only 28 cases with a SRS-like phenotype due to the haploinsufficiency of \textit{HMGA2} have been reported (Table 1). In particular, 23 deletions, detected by a-CGH, have been described. The remaining 5 cases were: a 7 bp deletion \cite{11}, a nonsense variant and a frameshift variant \cite{10} and 2 deletions of exon 2 \cite{12} and exons 1–2 \cite{8}. The 23 deletions described so far range between 387 kb and 10.12 Mb, and involve other contiguous genes \cite{9, 12–23}. Despite the variable size of these deletions, a critical region of 2.61 Mb has been identified. The OMIM disease causing genes included in this region are: \textit{LEMD3} (OMIM 607844), \textit{MSRB3} (OMIM 613719), \textit{HMGA2} (OMIM 600698), \textit{IRAK3} (OMIM 604459), \textit{GRIP1} (OMIM 604597).

The \textit{HMGA2} gene encodes for the \textit{HMGA2} protein, member of the \textit{HMGA} family. This family of four proteins (HMGA1a, HMGA1b, HMGA1c and HMGA2), encoded by two genes (\textit{HMGA1} and \textit{HMGA2}), can interact with DNA altering its conformation and regulating the transcription of several genes. \textit{HMGA2} regulates the transcription of the known fetal growth factor IGF2. Multiple studies on human and animal models have demonstrated a high expression of \textit{HMGA2} during fetal period when it may play a crucial role in embryonic development and linear growth. Moreover, \textit{HMGA2} has showed to be essential in regulating cell growth, proliferation, differentiation and death, in promoting adipocyte differentiation. Over-expression of \textit{HMGA2} has also been found in some tumoral tissues (uterine leiomyoma, gastric cancer, pediatric lipoma) \cite{6–8, 12, 24–27}. These experimental studies, added to the clinical data reported in literature, converge in proving the key role of \textit{HMGA2} alterations in pre- and postnatal growth failure and failure to thrive that is otherwise unexplained.

As previously reported, \textit{LEMD3} is the causative gene of Buschke-Ollendorff syndrome and Osteopoikilosis with or without melorheostosis (OMIM 166700). All patients with characteristic features of this syndrome result carrying deletions involving also \textit{LEMD3}, as suggested by data in Table 1 (see superscripts and notes).

In regard to the other OMIM disease causing genes included in the critical region, biallelic mutations in \textit{MSRB3} gene have been described in cases of deafness autosomal recessive 74 (OMIM 613718), while several polymorphisms of \textit{IRAK3} have been associated with increased asthma susceptibility. The \textit{GRIP1} gene, known as causative gene of Fraser syndrome transmitted in recessive manner, has been considered as candidate gene for neurodevelopmental disorders in most patients carrying 12q14.3 deletions. This hypothesis arises from the evidence of his high expression in brain tissue in both fetal and postnatal period, and his clear role in synaptic functioning. However, developmental disorders, such as language and/or motor delay, learning difficulties and intellectual disability, have also been described in patients with a 12q14.3 deletion not involving \textit{GRIP1} gene \cite{15, 23}.

An exclusive role of \textit{HMGA2} gene in the pathogenesis of SRS-like cases is supported by the evidence that pre- and postnatal growth failure and underweight, typical features of SRS (the first two items of the Netchine-Harbison CSS), have been described in all patients carrying different aberrations of \textit{HMGA2} regardless of their dimension. In fact, there are not significant clinical difference among patients with more or less extensive deletions of the 12q14.3 region (involving multiple genes, as \textit{HMGA2}), and patients with pathogenic variants or intragenic deletions of \textit{HMGA2}. Moreover, recently a duplication involving \textit{HMG2A} in a patient with overgrowth, obesity and tall stature with advanced bone age has been reported \cite{28}, confirming the role of \textit{HMGA2} gene in growth regulation.

Regarding the other clinical features of the patients described in the literature (see Table 1), relative macrocephaly and a prominent forehead, two further items of
| Sex      | Genotype Microdeletion/ Mutation | Inheritance | IUGR | SGA | Failure To Thrive | Relative macrocephaly | Asimmetry | Fifth-finger clinodactyly | Frontal bossing/ prominent forehead | Triangular facies | Micrognathia/ Narrow chin | Short stature | Language delay | Other developmental disorders | Osteopoikilosis |
|----------|----------------------------------|-------------|------|-----|------------------|------------------------|------------|---------------------------|--------------------------------------|----------------|-------------------------|--------------|----------------|-------------------------------|----------------|
| Menten et al. 2007 [9] - Case 1* | F              | Del 6 Mb | Unknown | No  | No               | No                      | No         | No                        | No                                   | No            | No                      | No            | No             | Delayed neuromotor development and learning difficulties | Yes            |
| Menten et al. 2007 [9] - Case 2* | F              | Del 6 Mb | Unknown | No  | No               | No                      | No         | No                        | No                                   | No            | No                      | No            | No             | Learning difficulties and intellectual disability | Yes            |
| Menten et al. 2007 [9] - Case 3* | M              | Del 3.44 Mb | Unknown | Unknown | Yes               | No                      | No         | No                        | No                                   | No            | Yes                     | Yes           | No             | Delayed neuromotor development and learning difficulties | Yes            |
| Mail et al. 2009 [14]          | M              | Del 1.83 Mb | De novo | Yes | Yes              | No                      | No         | No                        | Yes                                   | Yes           | Yes                     | Yes           | Yes            | Motor delay | No            |
| Buysse et al. 2009 [12] - Case 1 | M              | Del exon 2 | Maternal | No  | No               | Yes                      | No         | No                        | No                                   | No            | No                      | No            | Yes            | No            | No            |
| Buysse et al. 2009 [12] - Case 2* | M              | Del 8.95 Mb | De novo | Yes | Yes              | Yes                      | No         | No                        | Yes                                   | No            | No                      | Yes           | No             | Global developmental delay | No            |
| Buysse et al. 2009 [12] - Case 3* | M              | Del 3.48 Mb | De novo | Yes | Yes              | No                      | No         | No                        | No                                   | No            | Yes                     | No            | Yes            | Mild developmental delay | No            |
| Spengler et al. 2010* [15]     | F              | Del 1.35 Mb | De novo | Yes | Yes              | Yes                      | Yes        | Yes                       | Yes                                   | No            | Yes                     | Yes           | No             | Motor delay | No            |
| Lynch et al. 2011 [16] - Case 1 | F              | Del 10.11 Mb | De novo | No  | No               | Yes                      | No         | No                        | No                                   | Yes           | Yes                     | Yes           | Yes            | Developmental delay | No            |
| Lynch et al. 2011 [16] - Case 2 | F              | Del 10.12 Mb | De novo | No  | No               | Yes                      | Yes        | No                        | No                                   | Yes           | No                      | Yes           | No             | Intellectual disability, ASD | No            |
| Bibb et al. 2012* [17]         | F              | Del 3.2 Mb | Maternal | No  | No               | Yes                      | No         | No                        | Yes                                   | No            | Yes                     | Yes           | Yes            | Mild intellectual disability and behavioural problems | No            |
| Bibb et al. 2012 [17] - Mother* | F              | Del 3.2 Mb | Unknown | Unknown | Yes               | Yes                      | No         | No                        | No                                   | Yes           | Yes                     | Yes           | Yes            | Learning disabilities | Yes            |
| Alyaajoub et al. 2012* [18]    | F              | Del 4.17 Mb | De novo | Yes | Yes              | No                      | No         | No                        | No                                   | Yes           | Yes                     | Yes           | No             | Hypotonia | No            |
| Takenouchi et al. 2012 [19]    | F              | Del 4 Mb | De novo | Yes | Yes              | Yes                      | No         | No                        | No                                   | No            | No                      | Yes           | No             | No            | No            |
| Nso-Roca et al. 2014 [20]      | F              | Del 8.35 Mb | De novo | No  | No               | No                      | No         | Yes                       | Yes                                   | No            | No                      | Yes           | No             | No            | No            |
Table 1 Summary of all cases with a SRS-like phenotype due to the haploinsufficiency of HMGA2 described in literature (Continued)

| Case                        | Sex | Genotype / Mutation | Inheritance | IUGR | SGA | Failure To Thrive | Relative Macrocephaly | Asymmetry | Fifth-finger Clinodactyly | Frontal bossing/ Prominent Forehead | Triangular Facies | Microporhania/ Narrow Chin | Short Stature | Language Delay | Other Developmental Disorders | Osteopoikilosis |
|-----------------------------|-----|---------------------|-------------|------|-----|-------------------|-----------------------|-----------|---------------------------|---------------------|------------------|--------------------------|---------------|----------------|-----------------------------|-----------------|
| McCormack et al. 2015       | M   | Del 3.8 Mb          | Unknown     | Yes  | No  | No                | Yes                   | No        | No                        | No                  | No               | Yes                      | No            | No            | No                          | No              |
| Raymond et al. 2015         | M   | Del 387 Kb          | De novo     | Yes  | No  | No                | Yes (ITG)             | No        | Yes                       | No                  | Yes              | Yes (ITG)                | No            | No            | No                          | No              |
| De Crescenzo et al. 2015    | F   | Del 7 bp at in et al. | Maternal    | Unknown | Yes | Yes               | Yes                   | No        | Yes                       | No                  | Yes              | Yes (ITG)                | No            | No            | No                          | No              |
| Abi Habib 2018              | F   | Nonsense mutation   | De novo     | Unknown | Yes | Yes               | Yes                   | No        | Yes                       | Yes                  | Yes              | Yes                      | Unknown       | Unknown       | No                          | No              |
| Leszinski et al. 2018       | F   | Del exon 1–2        | De novo     | Unknown | Yes | Yes               | No                    | No        | Yes                       | Yes                  | Yes              | Yes                      | No            | No            | No                          | No              |
| Heldt et al. 2018           | M   | Del 1.67 Mb         | Maternal    | No    | Yes | No                | Yes                   | No        | Yes                       | No                  | No               | Yes                      | No            | No            | No                          | No              |
| Our patient                 | M   | Del 425 Kb          | De novo     | Unknown | Yes | Yes               | Yes                   | Yes        | Yes                       | Yes                  | Yes              | Yes                      | Yes           | Yes           | No                          | No              |

*a Deletions involving also LEMD3 gene*
the NHCSS, present in our patient, to our knowledge, were described in literature in less than half of the cases. Another item of the NHCSS, the body asymmetry, does not seem to be a typical feature of the 12q14.3 microdeletion syndrome, while it is reported in our proband, who has lower limbs asymmetry. To date, our case represents the only one 12q14.3 microdeletion syndrome with limb asymmetry. Finally, our patient presents a moderate speech delay, in the absence of other neurodevelopmental disorders. The presence of neurodevelopmental disorders (language and/or motor delay, learning difficulties, intellectual disability, behavioural problems), seems to be a distinct and frequent feature of 12q14.3 microdeletion syndrome, as it is reported in about half of patients (see Table 1) [2].

In conclusion, we suggest to investigate HMGA2 gene in all the patients with evocative phenotype for SRS and negative genetic results for MS-MLPA at the imprinting region 11p15 and microsatellite markers of chromosome 7. In order to complete the diagnostic work-up of SRS we recommend array-CGH analysis, and subsequently the sequence analysis and the MLPA of HMGA2 gene.

Abbreviations
SRS: Silver-Russell syndrome; SD: Standard deviations; MR: Magnetic resonance imaging; MS-MLPA: Methylation-Specific Multiplex Legation-dependent Probe Amplification; LOM: Lost Of Methylation; UPD: UniParental Disomy; a-CGH: Array-Comparative Genome Hybridization

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Authors’ contributions
FM, MB and MP made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data. MM performed array-CGH analysis. FM and MB wrote the manuscript. TF and MP reviewed and revised the manuscript. FM, MB, ES, DP and MP were involved in the genetic diagnosis and care. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The parents of the patient described in this case report signed written informed consent for take part in the study.

Consent for publication
Written informed consent for publication of medical data, genetic testing results and identifying images was obtained from the patient’s parents.

Competing interests
The authors declare that they have no competing interests.

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