Silver–Russell Syndrome

Contents

Silver–Russell syndrome (SRS) is a clinically and genetically heterogeneous disorder, characterized by severe prenatal/postnatal growth retardation, characteristic facies, skeletal asymmetry, and other congenital anomalies. The incidence is estimated as 1:50,000–1:100,000 live births.

Synonyms and Related Disorders

Primordial dwarfism; Russell–Silver syndrome; Silver–Russell dwarfism

Genetic/Basic Defects

1. Inheritance (Duncan et al. 1990; Preece 2002):
    1. Sporadic occurrence in majority of cases
    2. 19% of cases with more than one affected individuals in the family, providing evidence for a genetic cause
    3. A genetically (and clinically) heterogeneous disorder:
        1. Autosomal recessive (17.4%) (Fuleihan et al. 1971; Teebi 1992)
        2. Autosomal dominant (8.7%) (Al-Fifi et al. 1996)
        3. X-linked dominant (74%) (Partington 1986)
2. Chromosomal basis (Preece 2002):
    1. Small number of cases with Silver–Russell syndrome reported in association with numerous chromosomal abnormalities:
        1. R(15) and deletion of 15q (Wilson et al. 1985; Rogan et al. 1996)
        2. Diploid–triploid mixoploidy (Graham et al. 1981)
        3. 45,X/46,XY
        4. XXY (Bianchi et al. 1983)
        5. Trisomy 18 mosaicism
        6. Del(8)(q11-q13) (Schinzel et al. 1994)
        7. Del(18p) (Christensen and Nielson 1978)
        8. Dup(1)(q32.1-q42.1) (van Haelst et al. 2002)
        9. Dup(7p12.1-p13), including GRB10 and IGFBP1, in a mother and daughter with features of Silver–Russell syndrome (Joyce et al. 1999)
        10. One had a partial duplication [46, XX, dup(7)(p12 p14)] and the second contained a paracentric inversion [46, XY, inv(7)(p14 p21)] (Nakabayashi et al. 2002)

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_216

11. Familial reciprocal translocation t(7;16) associated with maternal uniparental disomy 7 in a Silver–Russell patient (Dupont et al. 2002)
12. Distal chromosome 17q (Hitchins et al. 2002):
    1. Balanced translocation (17;20)(q25; q13) and severe Russell–Silver syndrome (Ramírez-Dueñas et al. 1992) inherited from clinically normal father.
    2. De novo translocation (1;17)(q31; q25) with breakpoint recently cloned and localized to 17q23.3-q24.
    3. Heterozygous deletion of the chorionic somatomammotropin hormone 1 (*CSH1*) gene located within the growth hormone and CSH gene cluster on 17q24.1 (Eggermann et al. 1998). The deletion was inherited from the father who appeared clinically normal but had short stature.

2. Maternal uniparental disomy (UPD) for chromosome 7 (about 7–10% of cases) (Preece et al. 1997; Bernard et al. 1999; Hannula et al. 2001b; Eggermann et al. 2001; Hitchins et al. 2001):
    1. Inheritance of both chromosome 7 from the mother: Maternal UPD7 was detected in several SRS patients, accounting for approximately 7-10% of the tested SRS patients (Eggermann et al. 1997; Preece et al. 1999).
    2. A possible novel imprinted region at 7p12-p14 (Monk et al. 2002), 7q32, and 7q31-ter: UPD can disrupt the balance between imprinted genes and thereby lead to phenotypic manifestations.
    3. Strong evidence of disruption of imprinted gene expression rather than mutation of a recessive gene underlying the Silver–Russell phenotype in these cases.
3. Genetic and epigenetic disturbances can meanwhile be detected in approximately 50% of patients with typical SRS features (Eggermann et al. 2010):
    1. Nearly one tenth of patients carry a maternal uniparental disomy of chromosome 7 (UPD(7)mat).
    2. More than 38% show a hypomethylation in the imprinting control region 1 in 11p15.
    3. More than 1% of patients show (sub) microscopic chromosomal aberrations.
    4. Interestingly, in 7% of 11p15 hypomethylation carriers, demethylation of other imprinted loci can be detected.
4. A splicing mutation of the *HMGA2* gene is associated with Silver–Russell syndrome phenotype (De Crescenzo et al. 2015).
5. Silver–Russell syndrome without body asymmetry in three patients with duplications of maternally derived chromosome 11p15 involving *CDKN1C* (Nakashima et al. 2015).
6. 14q32 disturbances significantly contribute to the mutation spectrum in this cohort. Furthermore, maternal uniparental disomy of chromosomes 6, 16, and 20 can be observed, but are rare. In case they occur, they can be regarded as causative for clinical features (Sachwitz et al. 2016b).

3. Clinical findings and molecular aberrations in the three congenital disorders associated with *CDKN1C* mutations (Eggermann et al. 2014):
    1. Silver–Russell syndrome:
        1. Frequency, 1:100,000
        2. Clinical findings (please see this chapter)
        3. Molecular aberrations:
            1. Aberrant *ICR1* (H19/IGF2) methylation: hypomethylation (40%)
            2. Large 11p15 duplications (including *ICR1* and *ICR2*): maternal (1%)
            3. Small *ICR2* duplications and deletions: single cases (the clinical outcome depends on the size and genomic content of the affected segment)
            4. Genomic imbalance in the centromeric 11p15 imprinting center in three families: further evidence of a role for *IC2* (or *ICR2*) as a cause of

Russell–Silver syndrome (Cytrynbaum et al. 2016)
5. UPD 11p15: upd(11p15)mat (single cases)
6. *CDKN1C* point mutations: gain-of-function mutations (sporadic cases, $n = 128$; familial cases, one case)

2. Beckwith–Wiedemann syndrome:
   1. Frequency: 1:13,700
   2. Clinical findings (please see the chapter on "► Beckwith-Wiedemann Syndrome")
   3. Molecular aberrations:
      1. Aberrant *ICR1* (H19/IGF2) methylation: hypermethylation (5–7%)
      2. Aberrant ICR2 (LIT1/KvDMR1) methylation: hypomethylation (50–60%)
      3. Large 11p15 duplications (including *ICR1* and *ICR2*): paternal (1%)
      4. Small *ICR2* duplications and deletions: single cases (the clinical outcome depends on the size and genomic content of the affected segment)
      5. UPD 11p15: upd(11p15)pat (20–25%)
      6. *CDKN1C* point mutations: loss-of-function mutations (sporadic cases, 5%; familial cases, 50%)
3. IMAGe syndrome: named for the acronym of its major features (intrauterine growth retardation (IUGR), metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies) (Bergadá et al. 2005; Bennett et al. 2014):
   1. Frequency, 25 patients reported worldwide
   2. Clinical findings:
      1. IUGR
      2. Skeletal abnormalities (most commonly delayed bone age and short stature; occasionally, metaphyseal and epiphyseal dysplasia of varying severity)
      3. Adrenal insufficiency presenting typically in the first month of life as an adrenal crisis or, rarely, later in childhood with failure to thrive and recurrent vomiting
      4. Genital abnormalities in males (cryptorchidism, micropenis, and hypospadias)
   3. Molecular aberrations: *CDKN1C* point mutations (gain-of-function mutations)
4. Epimutations of the IG-DMR and the MEG3-DMR at the 14q32.2 imprinted region in two patients with Silver–Russell Syndrome-compatible phenotype (Kagami et al. 2015)

Clinical Features

1. Existence of both the "Silver" (Silver et al. 1953; Silver 1964) and "Russell" (1954) variants in a nuclear family: provides additional evidence for considering SRS to be a single syndrome with a wide spectrum of clinical manifestations (Robichaux et al. 1981).
2. Diagnostic criteria: the presence of three major features plus one or more minor features is generally required for a positive diagnosis:
   1. Major criteria:
      1. Low birth weight (intrauterine growth retardation)
      2. Proportionate short stature (postnatal growth retardation): mature height about −3.6 standard deviation scores in both sexes (Tanner et al. 1975; Davies et al. 1988)
      3. Small triangular face
      4. Fifth finger clinodactyly
   2. Minor criteria:
      1. Relative macrocephaly due to sparing of cranial growth
      2. Ear anomalies
      3. Skeletal asymmetry (face, limb, or body)
      4. Brachydactyly of the fifth fingers
      5. Bilateral camptodactyly with terminal interphalangeal contractures
      6. Syndactyly
      7. Transverse palmar crease
      8. Downward-slanting corner of the mouth
      9. Muscular hypotrophy/hypotonia

10. Motor/neurological delay
11. Irregular spacing of the teeth
12. Café-au-lait spots
13. Precocious puberty
14. Squeaky voice
15. Genital abnormalities
16. Speech delay
17. Feeding difficulties (Blissett et al. 2001)

3. Other manifestations:
   1. Significant cognitive impairment (50%) (Lai et al. 1994)
   2. Gastrointestinal symptoms (77%):
      1. Gastroesophageal reflux disease (34%)
      2. Esophagitis (25%)
      3. Food aversion (32%)
      4. Failure to thrive (63%)
   3. Skeletal anomalies:
      1. Large anterior fontanelle (delayed closure)
      2. Absence of asymmetry (Gareis et al. 1971)
      3. Syndactyly of the toes
   4. Genitourinary anomalies:
      1. Hypospadias
      2. Posterior urethral valves
   5. Cardiac defects
   6. Various tumors:
      1. Craniopharyngioma
      2. Testicular seminoma (Funada et al. 2016)
      3. Hepatocellular carcinoma
      4. Wilms tumor
   7. Essentially normal pattern of puberty and adolescent growth (Davies et al. 1988)
   8. Fertility not necessarily impaired, at least in females (Abramowicz and Nitowsky 1977)
   9. Other features:
      1. Blue sclera
      2. Café-au-lait spots
      3. Excessive sweating
      4. Hypoglycemia
4. Silver–Russell syndrome should be considered in the differential diagnosis of children with severe pre- and postnatal growth deficiency (Donnai et al. 1989).
5. Netchine–Harbison clinical scoring system (Azzi et al. 2015): Patients with four or more items of the score are suspected to have Silver–Russell syndrome and should undergo molecular testing (Giabicani et al. 2016):
   1. Factor 1: Being born small-for-gestational-age: $\leq$2 (standard deviation score)* birth length and/or weight adjusted for gestational age (GA).
   2. Factor 2: Relative macrocephaly at birth: Head circumference at birth $\geq$1.5 SDS above birth weight and/or length adjusted for GA.
   3. Factor 3: Postnatal growth failure: Height $\leq$ 2 SDS at 24 months relative to mean or to midparental target height.
   4. Factor 4: Feeding difficulties and/or low BMI at 24 months: BMI $\leq$2 SDS at 24 months OR tube feeding OR cyproheptadine for appetite stimulation.
   5. Factor 5: Protruding forehead: The forehead protrudes from the facial plan (viewed laterally) between 1 and 3 years of age.
   6. Factor 6: Body asymmetry: Leg length discrepancy (LLD) of $\geq$ 0.5 cm OR arm asymmetry OR LLD $<$ 0.5 cm with at least two; other asymmetric body parts (with one being a nonface part).
6. A possible associations of Mayer–Rokitansky–Küster–Hauser syndrome and Silver–Russell syndrome (Abraham et al. 2016).
7. Clinical characterization (Hannula et al. 2001a; Binder et al. 2008; Bruce et al. 2009; Eggermann et al. 2010):
   1. Phenotype of maternal UPD7 carriers is generally milder.
   2. 11p15 epimutation (*H19* imprinting control region hypomethylation) carriers usually present the typical picture of SRS.
8. Differential diagnosis (Patton 1988):
   1. Intrauterine growth retardation owing to placental insufficiency:
      1. Chronic intrauterine growth retardation leads to a decrease in all growth parameters, that is, a "perfect miniature," and is

followed in most cases by catch-up growth in the first year of life.
    2. Late intrauterine growth retardation, especially in the postmature fetus, leads to a thin, low birth weight baby with normal length and head circumference
2. Chromosomal mosaicism:
    1. The phenotype has been reported in patients with mosaic trisomy 18 (Chauvel et al. 1975) a diploid–triploid mosaicism (Ferrier et al. 1964) and a 45,X/46,XY mosaicism. Consideration should be given to examining skin fibroblasts in addition to peripheral blood, especially where there is mental retardation or sexual ambiguity.
3. 3-M syndrome (Winter et al. 1984) This autosomal recessive syndrome has several features in common with the Russell–Silver syndrome, including intrauterine growth retardation, relatively large head, and short fifth fingers. It can be distinguished from the Russell–Silver syndrome by the presence of prominent heels, tall vertebral bodies, and facial features, which include a broad, fleshy nose and a hatchet-shaped profile.
4. X-linked short stature with skin pigmentation (Partington) (Partington 1986) This syndrome has been described as a variant of the Russell–Silver syndrome. There is a diffuse brown pigmentation with some achromic patches.
5. Neonatal progeroid (Rautenstrauch) (Wiedermann 1979) This syndrome has pseudohydrocephalus, generalized deficiency of subcutaneous fat, and natal teeth.

9. Subtypes existing in primordial dwarfism, their inheritance pattern, and distinguishing clinical features (Khetarpal et al. 2016):
    1. Seckel syndrome (please see the chapter on "► Seckel Syndrome")
        1. Autosomal recessive
        2. Microcephalic primordial dwarfism (brain size reduced to a third of normal volume)
        3. Extremely small head with narrow face, dental alterations, beak-like protrusion of nose, and receding mandible
    2. Majewski/microcephalic osteodysplastic primordial dwarfism (MOPD) types I/III
        1. Autosomal recessive
        2. Dry skin
        3. Sparsity of hairs and eyebrows
    3. MOPD type II
        1. Autosomal recessive
        2. Prominent nose and eyes
        3. Abnormally small or missing teeth
        4. A high squeaky voice
    4. Meier–Gorlin syndrome
        1. Autosomal recessive
        2. Underdeveloped ears
        3. Absent/hypoplastic patellae
    5. Silver–Russel syndrome
        1. Autosomal dominant or autosomal recessive and genomic imprinting
        2. Normal head size
        3. Small triangular face
        4. Micrognathia
        5. Dental anomalies

Diagnostic Investigations

1. Increased serum or urinary gonadotropin levels in the prepubertal age (Curi et al. 1967)
2. Hypoglycemia
3. Growth hormone studies
4. Metabolic acidosis due to renal tubular acidosis in a few patients
5. Radiography (Herman et al. 1987)
    1. Delayed bone age
    2. Limb asymmetry
    3. Ivory epiphyses of the distal phalanges
    4. Clinodactyly of the fifth fingers
    5. Fifth middle or distal phalangeal hypoplasia
    6. Pseudoepiphyses at the base of the second metacarpal
6. Chromosome analysis to define chromosome basis
    1. Mosaic trisomy 7 (Flori et al. 2005; Font-Montgomery et al. 2005)

2. Interstitial deletion of chromosome 7q [del (7)(q21.1q21.3)] (Courtens et al. 2005)
7. Molecular karyotyping in patients with SRS features: NSD1 duplication in Silver–Russell syndrome (Sachwitz et al. 2016a)
8. Molecular genetic testing (Eggermann et al. 2009; Saal 2007)
    1. Maternal uniparental disomy (UDP) of chromosome 7 (7–10%) clinically available: both maternal isodisomy and heterodisomy have been reported (Bernard et al. 1999; Price et al. 1999).
    2. Genetic or epigenetic mutations in the imprinted region on chromosome 11p15.5: methylation analysis of *H19* (35%) clinically available.
    3. 11p15 epimutation and UPD (7) mat carriers do not always show the unambiguous SRS phenotype.
    4. In addition to patients with the classical SRS phenotype fulfilling the SRS-specific scores, genetic testing for the 11p15 epimutation and/or UPD (7) mat should also be considered in case of SRS-like phenotypes, for example, mild IUGR and postnatal growth retardation (more than −2 SD) associated with a prominent forehead and triangular face or asymmetry as the only clinical sign.
    5. In particular, the lack of IUGR in patients with an SRS-like phenotype should not automatically result in exclusion from molecular testing.
    6. Silver–Russell syndrome in a patient with somatic mosaicism for upd(11)mat identified by buccal cell analysis (Luk et al. 2016).

Genetic Counseling

1. Recurrence risk (Saal 2007)
    1. Multiple etiologies of SRS
        1. Maternal uniparental disomy for chromosome 7: both parents are predicted to be unaffected.
        2. Possible mutations or epigenetic changes that modify expression of genes in the imprinted region of chromosome 11p15.5.
        3. Autosomal dominant inheritance.
        4. Autosomal recessive inheritance.
    2. Patient's sibs
        1. Not increased in a nongenetic sporadic case or as the result of maternal uniparental disomy for chromosome 7 (both parents are predicted to be unaffected)
        2. Increased depending on the inheritance pattern
    3. Patient's offspring
        1. Not increased in a nongenetic sporadic case and probably low in case of maternal uniparental disomy for chromosome 7
        2. Increased depending on the inheritance pattern
2. Recurrence risk estimation in SRS and Beckwith–Wiedemann syndrome (BWS) (Eggermann et al. 2016a)
    1. The majority of cases with SRS and BWS have been reported to occur sporadically. This is reflected by the type of (epi)mutations in both disorders (ICR1 hypomethylation in SRS as well as ICR2 hypomethylation and upd(11)pat in BWS) mainly occur as mosaicism and probably originate from postzygotic errors.
    2. In contrast, constitutional mutations (point mutations, duplications/deletions) are associated with a significantly increased recurrence risk of up to 50% depending from the affected paternal allele.
3. Molecular subtypes and recurrence risk (Eggermann et al. 2016b)
    1. 11p15.5
        1. *H19*/*IGF2*:IG-DMR hypomethylation: empirically low, only in rare cases increased due to genomic transacting mutations
        2. Duplications/deletions: Up to 50%, depending on the gene content of the aberration and the sex of the parent contributing the affected allele (in case of

duplication of the whole 11p15 region; in case of a maternal transmission)
3. UPD: empirically low
4. *CDKN1C* point mutation: 0% or 50%, depending on the sex of the parent contributing the affected allele
5. *IGF2* point mutation: 0 or 50%, depending on the sex of the parent contributing the affected allele

2. 7
1. upd(7)mat: empirically low, but some may be high because of familial translocations
2. upd(7q)mat: empirically low
3. Duplications/deletions/translocations affecting 7p13 and 7q32: up to 50%

3. 14q32
1. upd(14)mat, epimutation, duplications.
2. A number of SRS patients exhibiting (epi)mutations in 14q32 have recently been reported, and these molecular alterations correspond to findings in patients with Temple syndrome (Goto et al. 2016; TS14, OMIM616222).
3. TS14 is an ID with changes affecting the IG-DMR and/or MEG3-DMR in 14q32, and its phenotype (Ioannides et al. 2014) overlaps with SRS (for a review see Kagami et al. (2015)).
4. In single cases, maternal uniparental disomy of chromosomes 16 and 20 (upd(16)mat, upd(20)mat) has been reported (Azzi et al. 2015; Mulchandani et al. 2015) (for a review see Eggermann et al. (2015)).

4. Whole genome
1. (Mosaic) maternal unidiploidy: no
2. (Submicroscopic) chromosomal imbalances: up 50%, depending on the chromosome and type of rearrangement

4. Prenatal diagnosis
1. Ultrasonography of the fetus at risk by family history.
1. Delayed fetal skeletal growth may not be evident until the late second trimester.
2. Asymmetry of fetal limbs may not be evident until the third trimester.
2. Usually not possible because most occurrences are in a single individual in a family; therefore, most pregnancies are not identified to be at increased risk for recurrence (Saal 2007).
3. Russel–Silver syndrome should be considered in the differential diagnosis of fetal growth restriction with short, asymmetric, but morphologically normal limbs (Wax et al. 1996).
4. Molecular findings and interpretations in prenatal testing of SRS (and BWS) (Eggermann et al. 2016a).
1. Type of mutation: UPD, CNVs (copy number variations), epimutation, and point mutation.
2. Mosaicism: In case of a positive testing result, the suspected diagnosis can be confirmed, but a prediction of the phenotypic outcome is not possible but might be delineated from the ultrasound findings.
3. Mosaicism: In case of a negative testing result, the mosaic presence of UPD or epimutations can never be excluded. Mosaicism in case of constitutional mutations (CNVs, monogenic point mutations) can be neglected.
4. How to interpret the results in case of a twin pregnancy (the majority of monozygotic twins are clinically discordant)?

5. Management
1. Growth deficiency
1. Optimize caloric intake.
2. Consider nasogastric or gastrostomy feeding for severe gastroesophageal reflux and failure to thrive.
3. Consider growth hormone treatment in patients with documented growth hormone deficiency.
4. Growth hormone treatment of short children born small for gestational age or with Silver–Russell syndrome (Ranke and Lindberg 1996).
2. Dental cares for overcrowding of teeth
3. Orthopedic management for asymmetry of legs

4. Early intervention programs including physical therapy for developmental delay due to hypotonia
5. Special education for learning disabilities
6. Psychological counseling related to body image and peer relationship

References

Abraham, M. B., Carpenter, K., Baynam, G. S., et al. (2016). Report and review of described associations of Mayer-Rokitansky-Küster-Hauser syndrome and Silver–Russell syndrome. *Journal of Paediatrics and Child Health, 51*, 555–560.

Abramowicz, H. K., & Nitowsky, H. M. (1977). Reproductive ability of an adult female with Silver–Russell syndrome. *Journal of Medical Genetics, 14*, 134–136.

Al-Fifi, S., Teebi, A. S., & Shevell, M. (1996). Autosomal dominant Russell–Silver syndrome. *American Journal of Medical Genetics, 61*, 96–97.

Azzi, S., Salem, J., Thibaud, N., et al. (2015). A prospective study validating a clinical scoring system and demonstrating phenotypical-genotypical correlations in Silver–Russell syndrome. *Journal of Medical Genetics, 52*, 446–453.

Bennett, J., Bergano, S. A. S., & Deardorff, M. A. et al. (2014). IMAGe syndrome. GeneReviews. Updated 13 Mar 2014. Available at http://www.ncbi.nlm.nih.gov/books/NBK190103/

Bergadá, I., Dek Rey, G., Lapunzina, P., et al. (2005). Familial occurrence of the IMAGe association: Additional clinical variants and a proposed mode of inheritance. *Journal of Clinical Endocrinology and Metabolism, 90*, 3186–3190.

Bernard, L. E., Peñaherrera, M. S., Van Allen, M. I., et al. (1999). Clinical and molecular findings in two patients with Russell–Silver syndrome and UPD7: Comparison with non-UPD7 cases. *American Journal of Medical Genetics, 87*, 230–236.

Bianchi, M., Arico, M., Severi, F., et al. (1983). Russell–Silver syndrome and XXY karyotype. *Pediatrics, 71*, 669.

Binder, G., Seidel, A.-K., Martin, D. D., et al. (2008). The endocrine phenotype in Silver–Russell syndrome is defined by the underlying epigenetic alteration. *Journal of Clinical Endocrinology and Metabolism, 93*, 1402–1407.

Blissett, J., Harris, G., & Kirk, J. (2001). Feeding problems in Silver–Russell syndrome. *Developmental Medicine and Child Neurology, 43*, 39–44.

Bruce, S., Hannula-Jouppi, K., Peltonen, J., et al. (2009). Clinically distinct epigenetic subgroups in Silver–Russell syndrome: The degree of *H19* hypomethylation associates with phenotype severity and genital and skeletal anomalies. *Journal of Clinical Endocrinology and Metabolism, 94*, 579–587.

Chauvel, P. J., Moore, C. M., & Haslam, R. H. (1975). Trisomy 18 mosaicism with features of Russell–Silver syndrome. *Developmental Medicine and Child Neurology, 17*, 220–243.

Christensen, M. F., & Nielson, J. (1978). Deletion short arm 18 and Silver–Russell syndrome. *Acta Paediatrica Scandinavica, 67*, 101–103.

Courtens, W., Vermeulen, S., Wuyts, W., et al. (2005). An interstitial deletion of chromosome 7 at band q21: A case report and review. *American Journal of Medical Genetics Part A, 134*, 12–23.

Curi, J. F. J., Vanucci, R. C., Grossman, H., et al. (1967). Elevated serum gonadotrophins in Silver's syndrome. *American Journal of Diseases of Children, 114*, 658–661.

Cytrynbaum, C., Chong, K., Hannig, V., et al. (2016). Genomic imbalance in the centromeric 11p15 imprinting center in three families: Further evidence of a role for IC2 as a cause of Russell–Silver syndrome. *American Journal of Medical Genetics Part A, 9999A*, 1–9.

Davies, P. S. W., Valley, R., & Preece, M. A. (1988). Adolescent growth and pubertal progression in the Silver–Russell syndrome. *Archives of Disease in Childhood, 63*, 130–135.

De Crescenzo, A., Citro, V., Freschi, A., et al. (2015). A splicing mutation of the HMGA2 gene is associated with Silver–Russell syndrome phenotype. *Journal of Human Genetics, 2015*, 1–7.

Donnai, D., Thompson, E., Allanson, J., et al. (1989). Severe Silver–Russell syndrome. *Journal of Medical Genetics, 26*, 447–451.

Duncan, P. A., Hall, J. G., Shapiro, L. R., et al. (1990). Three-generation dominant transmission of the Silver–Russell syndrome. *American Journal of Medical Genetics, 35*, 245–250.

Dupont, J. M., Cuisset, L., Cartigny, M., et al. (2002). Familial reciprocal translocation t(7;16) associated with maternal uniparental disomy 7 in a Silver–Russell patient. *American Journal of Medical Genetics, 111*, 405–408.

Eggermann, T., Wollman, H. A., Kuner, R., et al. (1997). Molecular studies in 37 Silver–Russell syndrome patients: Frequency and etiology of uniparental disomy. *Human Genetics, 100*, 415–419.

Eggermann, T., Eggermann, K., Mergenthale, S., et al. (1998). Paternally inherited deletion of CSH1 in a patient with Silver–Russell syndrome. *Journal of Medical Genetics, 35*, 784–786.

Eggermann, T., Mergenthaler, S., Eggermann, K., et al. (2001). Segmental uniparental disomy of 7q31-qter is rare in Silver–Russell syndrome. *Clinical Genetics, 60*, 395–396.

Eggermann, T., Gonzalez, D., Spengler, S., et al. (2009). Broad clinical spectrum in Silver–Russell syndrome and consequences for genetic testing in growth retardation. *Pediatrics, 123*, e929–e931.

Eggermann, T., Begemann, M., Binder, G., et al. (2010). Silver–Russell syndrome: Genetic basis and molecular genetic testing. *Orphanet Journal of Rare Diseases, 5*, 19–26.

Eggermann, T., Binder, G., Brioude, F., et al. (2014). *CDKN1C* mutations: Two sides of the same coin. *Trends in Molecular Medicine, 20*, 614–622.

Eggermann, T., Perez de Nanclares, G., Maher, E. R., et al. (2015). Imprinting disorders: A group of congenital disorders with overlapping patterns of molecular changes affecting imprinted loci. *Clinical Epigenetics, 7*, 123.

Eggermann, T., Brioude, F., Russo, S., et al. (2016a). Prenatal molecular testing for Beckwith–Wiedemann and Silver–Russell syndromes: A challenge for molecular analysis and genetic counseling. *European Journal of Human Genetics, 24*, 784–793.

Eggermann, T., Bliek, J., Brioude, F., et al. (2016b). EMQN best practice guidelines for the molecular genetic testing and reporting of chromosome 11p15 imprinting disorders: Silver–Russell and Beckwith–Wiedemann syndrome. *European Journal of Human Genetics, 2016*, 1–11.

Ferrier, P., Stalder, G., Bamatter, F., et al. (1964). Congenital asymmetry associated with diploid-triploid mosaicism and large satellites. *Lancet, 1*, 80–82.

Flori, E., Girodon, E., Samama, B., et al. (2005). Trisomy 7 mosaicism, maternal uniparental heterodisomy 7 and Hirschsprung's disease in a child with Silver–Russell syndrome. *European Journal of Human Genetics, 13*, 1013–1018.

Font-Montgomery, E., Stone, K. M., Weaver, D. D., et al. (2005). Clinical outcome and follow-up of the first reported case of Russell–Silver syndrome with the unique combination of maternal uniparental heterodisomy 7 and mosaic trisomy 7. *Birth Defects Research, Part A: Clinical and Molecular Teratology, 73*, 577–582.

Fuleihan, D. S., DerKaloustian, V. M., & Najjar, S. S. (1971). The Russell–Silver syndrome: Report of three siblings. *Journal of Pediatrics, 78*, 654–657.

Funada, S., Ikeuchi, R., Yoshida, T., et al. (2016). Seminoma in a man with Russell–Silver syndrome presenting with testicular torsion. *Case Reports in Urology, 2016*, 1–3.

Gareis, F. J., Smith, D. W., & Summitt, R. L. (1971). The Russell–Silver syndrome without asymmetry. *Journal of Pediatrics, 79*, 775–781.

Giabicani, E., Netchine, I., & Brioude, F. (2016). New clinical and molecular insights into Silver–Russell syndrome. *Current Opinion in Pediatrics, 28*, 529–535.

Goto, M., Kagami, M., Nishimura, G., et al. (2016). A patient with temple syndrome satisfying the clinical diagnostic criteria of Silver–Russell syndrome. *American Journal of Medical Genetics Part A, 170A*, 2483–2485.

Graham, J. M., Hoehn, H., Liu, M. S., et al. (1981). Diploid-triploid mixoploidy. Clinical and cytogenetic aspects. *Pediatrics, 68*, 23.

Hannula, K., Kere, J., Pirinen, S., Holmberg, C., et al. (2001a). Do patients with maternal uniparental disomy for chromosome 7 have a distinct mild Silver–Russell phenotype? *Journal of Medical Genetics, 38*, 273–278.

Hannula, K., Lipsanen-Nyman, M., Kontiokari, T., et al. (2001b). A narrow segment of maternal uniparental disomy of chromosome 7q31-qter in Silver–Russell syndrome delimits a candidate gene region. *American Journal of Human Genetics, 68*, 247–253.

Herman, T. E., Crawford, J. D., Cleveland, R. H., et al. (1987). Hand radiographs in Russell–Silver syndrome. *Pediatrics, 79*, 743–744.

Hitchins, M. P., Stanier, P., Preece, M. A., et al. (2001). Silver–Russell syndrome: A dissection of the genetic aetiology and candidate chromosomal regions. *Journal of Medical Genetics, 38*, 810–819.

Hitchins, M. P., Abu-Amero, S., Apostolidou, S., et al. (2002). Investigation of the GRB2, GRB7, and CSH1 genes as candidates for the Silver–Russell syndrome (SRS) on chromosome 17q. *Journal of Medical Genetics, 39*, e13.

Ioannides, Y., Lokulo-Sodipe, K., Mackay, D. J., et al. (2014). Temple syndrome: Improving the recognition of an underdiagnosed chromosome 14 imprinting disorder: An analysis of 51 published cases. *Journal of Medical Genetics, 51*, 495–501.

Joyce, C. A., Sharp, A., Walker, J. M., et al. (1999). Duplication of 7p12.1-13, including GRB10 and IGFBP1, in a mother and daughter with features of Silver–Russell syndrome. *Human Genetics, 105*, 273–280.

Kagami, M., Mizuno, S., Matsubara, K., et al. (2015). Epimutations of the IG-DMR and the MEG3-DMR at the 14q32.2 imprinted region in two patients with Silver–Russell Syndrome-compatible phenotype. *European Journal of Human Genetics, 23*, 1062–1067.

Khetarpal, P., Das, S., Panigrahi, I., et al. (2016). Primordial dwarfism: Overview of clinical and genetic aspects. *Molecular Genetics and Genomics, 291*, 1–15.

Lai, K. Y. C., Skuse, D., Stanhope, R., et al. (1994). Cognitive abilities associated with the Silver–Russell syndrome. *Archives of Disease in Childhood, 71*, 490–496.

Luk, H.-M., Ivan Lo, F.-M., Sano, S., et al. (2016). Silver–Russell syndrome in a patient with somatic mosaicism for upd(11)mat identified by buccal cell analysis. *American Journal of Medical Genetics Part A, 170A*, 1938–1941.

Monk, D., Bentley, L., Hitchins, M., et al. (2002). Chromosome 7p disruptions in Silver Russell syndrome: Delineating an imprinted candidate gene region. *Human Genetics, 111*, 376–387.

Mulchandani, S., Bhoj, E. J., Luo, M., et al. (2015). Maternal uniparental disomy of chromosome 20: A novel imprinting disorder of growth failure. *Genetics in Medicine, 18*, 309–315.

Nakabayashi, K., Fernandez, B. A., Teshima, I., et al. (2002). Molecular genetic studies of human chromosome 7 in Russell–Silver syndrome. *Genomics, 79*, 186–196.

Nakashima, S., Kato, F., Kosho, T., et al. (2015). Silver–Russell syndrome without body asymmetry in three patients with duplications of maternally derived chromosome 11p15 involving *CDKN1C*. *Journal of Human Genetics, 60*, 91–95.

Partington, M. W. (1986). X-linked short stature with skin pigmentation: Evidence for heterogeneity of the Russell–silver syndrome. *Clinical Genetics, 29*, 151–156.

Patton, M. A. (1988). Russell–Silver syndrome. *Journal of Medical Genetics, 25*, 557–560.

Preece, M. A. (2002). The genetics of the Silver–Russell syndrome. *Reviews in Endocrine & Metabolic Disorders, 3*, 369–379.

Preece, M. A., Price, S. M., Davies, V., et al. (1997). Maternal uniparental disomy 7 in Silver–Russell syndrome. *Journal of Medical Genetics, 34*, 6–9.

Preece, M. A., Abu-Amero, S. N., Ali, Z., et al. (1999). An analysis of the distribution of hetero- and isodisomic regions of chromosome 7 in five mUPD7 Silver–Russell syndrome probands. *Journal of Medical Genetics, 36*, 457–460.

Price, S. M., Stanhope, R., Garrett, C., et al. (1999). The spectrum of Silver–Russell syndrome: A clinical and genetic study and new diagnostic criteria. *Journal of Medical Genetics, 36*, 837–842.

Ramírez-Dueñas, M. L., Medina, C., Ocampo-Campos, R., et al. (1992). Severe Russell–Silver syndrome and translocation (17;20)(q25;q13). *Clinical Genetics, 41*, 51–53.

Ranke, M. B., & Lindberg, A. (1996). Growth hormone treatment of short children born small for gestational age or with Silver–Russell syndrome: Results from KIGS (Kabi International Growth Study), including the first report on final height. *Acta Paediatrica. Supplement, 417*, 18–26.

Robichaux, V., Fraikor, A., Favara, B., et al. (1981). Silver–Russell syndrome: A family with symmetric and asymmetric siblings. *Archives of Pathology & Laboratory Medicine, 105*, 157–159.

Rogan, P. K., Seip, J. R., Driscoll, D. J., et al. (1996). Distinct 15q genotypes in Russell–Silver and ring 15 syndrome. *American Journal of Medical Genetics, 62*, 10–15.

Russell, A. (1954). A syndrome of intra-uterine dwarfism recognizable at birth with cranio-facial synostosis, disproportionately short arms and other anomalies. *Proceedings of the Royal Society of Medicine, 47*, 1040–1044.

Saal, H. M. (2007). Russell–Silver syndrome. *GeneReviews*. Updated 9 Mar 2007. Available at http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=rss

Sachwitz, J., Meyer, R., Fekete, G., et al. (2016a). *NSD1* duplication in Silver–Russell syndrome (SRS): Molecular karyotyping in patients with SRS features. *Clinical Genetics, 2016*, 1–6.

Sachwitz, J., Strobl-Wildemann, G., Fekete, G., et al. (2016b). Examinations of maternal uniparental disomy and epimutations for chromosomes 6, 14, 16 and 20 in Silver–Russell syndrome-like phenotypes. *BMC Medical Genetics, 17*, 1–7.

Schinzel, A. A., Robinson, W. P., Binkert, F., et al. (1994). An interstitial deletion of proximal 8q (q11-q13) in a girl with Silver–Russell syndrome-like features. *Clinical Dysmorphology, 3*, 63–69.

Silver, H. K. (1964). Asymmetry, short stature, and variations in sexual development: A syndrome of congenital malformations. *American Journal of Diseases of Children, 107*, 495–515.

Silver, H. K., Kiyasu, W., George, J., et al. (1953). Syndrome of congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropins. *Pediatrics, 12*, 368–376.

Tanner, J. M., Lejarraga, H., & Cameron, N. (1975). The natural history of the Silver–Russell syndrome: A longitudinal study of thirty-nine cases. *Pediatric Research, 9*, 611–623.

Teebi, A. S. (1992). Autosomal recessive Silver–Russell syndrome. *Clinical Dysmorphology, 1*, 151–156.

van Haelst, M. M., Eussen, H. J., Visscher, F., et al. (2002). Silver–Russell phenotype in a patient with pure trisomy 1q32.1-q42.1: Further delineation of the pure 1q trisomy syndrome. *Journal of Medical Genetics, 39*, 582–585.

Wax, J. R., Burroughs, R., & Wright, M. S. (1996). Prenatal sonographic features of Russell–Silver syndrome. *Journal of Ultrasound in Medicine, 15*, 253–255.

Wiedermann, H. R. (1979). An unidentified neonatal progeroid syndrome: Follow up report. *European Journal of Pediatrics, 130*, 65–70.

Wilson, G. N., Sauder, S. E., Bush, M., et al. (1985). Phenotypic delineation of ring chromosome 15 and Russell–Silver syndromes. *Journal of Medical Genetics, 22*, 233–236.

Winter, R. M., Baraitser, M., Grant, D. B., et al. (1984). The 3-M syndrome. *Journal of Medical Genetics, 21*, 124–128.

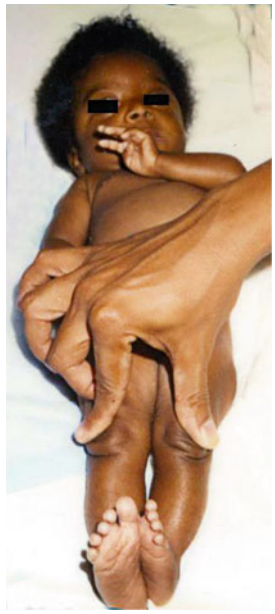

Fig. 1 An infant with Silver–Russell syndrome showing prenatal and postnatal growth deficiency, triangular face, and asymmetry of legs

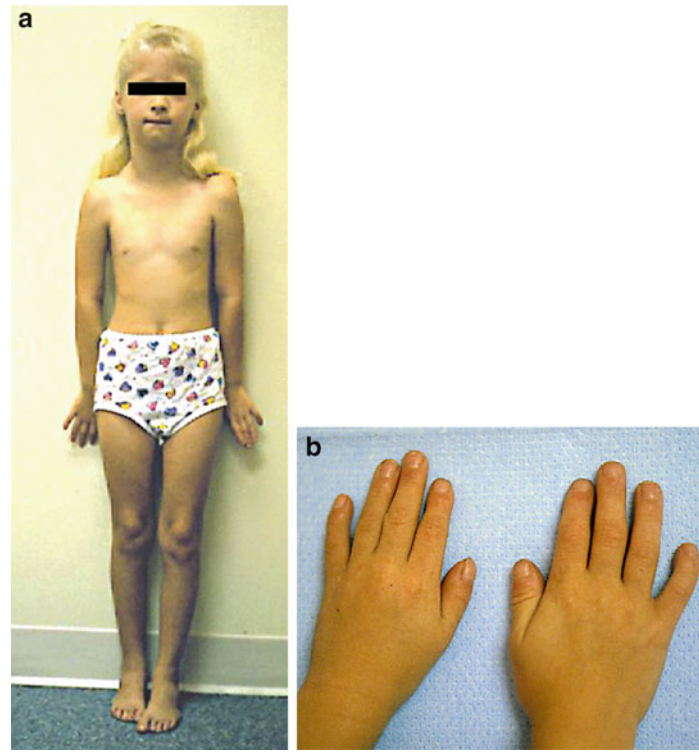

Fig. 2 (**a**, **b**) A girl (**a**) with Silver–Russell syndrome showing prenatal and postnatal growth deficiency, triangular face, and clinodactyly of the fifth fingers (**b**)

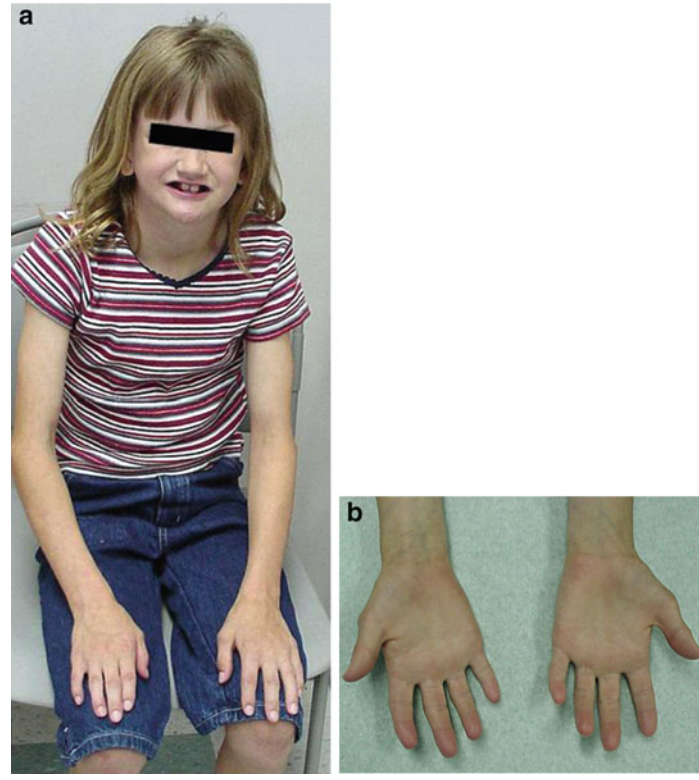

Fig. 3 (**a**, **b**) A girl (**a**) with Silver–Russell syndrome showing prenatal and postnatal growth deficiency with brachydactyly and clinodactyly of the fifth fingers (**b**)

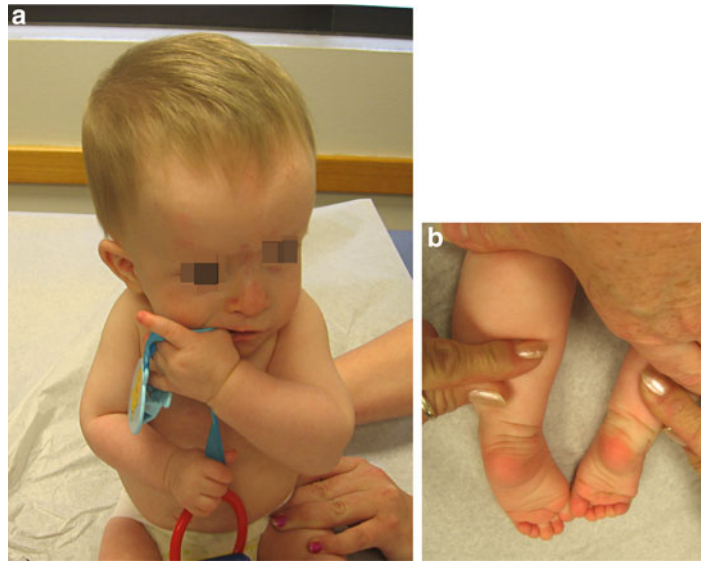

Fig. 4 (**a**, **b**) A 6-month-old male infant (**a**) was evaluated for intrauterine growth retardation, postnatal growth retardation, a relatively large head, a triangular face, and left side of the body larger than the right (**a**, **b**). Clinically, he was suspected to have Silver–Russell syndrome. Molecular genetic testing detected loss of methylation at differentially methylated region 1 (*DMR1*), upstream of the *H19* gene at 11p15. This result is consistent with a diagnosis of Silver–Russell syndrome due to hypomethylation of DMR1