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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Silver–Russell syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Silver–Russell syndrome.

1.2 OMIM# of the disease
180860.

1.3 Name of the analysed genes or DNA/chromosome segments
7, 11p15.5.

1.4 OMIM# of the gene(s)
Not applicable.

1.5 Mutational spectrum[1]

#7	UPD(7)mat	4–10%
#11p15.5	ICR1 hypomethylation	~40%
	Duplication of maternal chromosome 11p15.5	<1%
	UPD(11p15)mat	<1%
Multilocus hypomethylation with or without ICR2 hypomethylation[2,3]		<1%
Cryptic chromosomal aberrations		~1%

1.6 Analytical methods
Methylation-specific PCR, microsatellite typing, methylation-specific MLPA, microarray.

1.7 Analytical validation
Parallel analysis of negative and positive controls.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
Unknown.

1.9 If applicable, prevalence in the ethnic group of the investigated person
Unknown.

1.10 Diagnostic setting

	Yes.	No.
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☐	☒
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment:
Prenatal diagnosis is rarely required for SRS but may occasionally be requested in cases of a familial chromosomal rearrangement affecting chromosomes 11p15 and 7, or in cases of trisomy 7 mosaicism in CVS.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Negative	C	D	Positive predictive value:	A/(A+B)
			Negative predictive value:	D/(C+D)

2.1 Analytical sensitivity (proportion of positive tests if the genotype is present)

UPD(7)mat		
11p15.5	ICR1 hypomethylation	Nearly 100%*
	Duplication of maternal chromosome 11p15.5	Nearly 100%
	UPD(11p15)mat	Nearly 100%
Imbalanced cryptic chromosomal aberrations		**

*Low-grade mosaics might not be detected
**Depends on the method used

2.2 Analytical specificity (proportion of negative tests if the genotype is not present)
Nearly 100%.

2.3 Clinical Sensitivity (proportion of positive tests if the disease is present)
Clinical sensitivity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.
Approximately 50%.

2.4 Clinical specificity (proportion of negative tests if the disease is not present)
Clinical specificity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.
Nearly 100%.

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2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
100%.

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
Not applicable.

Index case in that family had not been tested:
Not applicable.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

The differential diagnosis includes any condition that can cause intrauterine growth retardation and short stature. This includes 3M syndrome and Mulibrey nanism.

3.1.1 Can a diagnosis be made other than through a genetic test?

No (continue with 3.1.4)	☐
Yes	☒
Clinically	☒
Imaging	☐
Endoscopy	☐
Biochemistry	☐
Electrophysiology	☐
Other (please describe)	☐
	A clinical examination may suggest the diagnosis even if genetic testing cannot confirm it.

3.1.2 Describe the burden of alternative diagnostic methods for the patient
The clinical characterization is not associated with additional invasive procedures for the patient.

3.1.3 How is the cost-effectiveness of alternative diagnostic methods to be judged?
Because of clinical heterogeneity, the clinical diagnosis is often uncertain. Furthermore, some of the characteristic craniofacial symptoms are not detectable in adult patients.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐	
Yes	☒	
Therapy (please describe)		*Certainty of diagnosis aids medical management and precludes further investigations for short stature and faltering growth in early childhood. However, the use of growth hormone treatment, physiotherapy, control of the calorific intake, percutaneous endoscopic gastrostomy, and managing of hypoglycaemia are based on symptoms rather than on the genetic diagnosis.*
Prognosis (please describe)		*Relatively good; minimal intellectual incapacities, final height without growth hormone treatment estimated at 151.2 cm for boys and 139.9 cm for girls, although it is very variable and may fall within normal limits. Some patients have congenital malformations such as cleft palate and genital abnormalities and these may affect, for example, fertility.*
Management (please describe)		—

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.10 'B' was marked).

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test result is positive (please describe):
Not applicable.

If the test result is negative (please describe):
Not applicable.

If the test is positive, it is important that the dietary supplements be calculated in a manner that is suitable for the actual height and not for the predicted height by age to avoid obesity.

3.2.2 Which options in view of lifestyle and prevention does a person at risk have if no genetic test has been carried out? (please describe)
As above, where possible, but the uncertainty over diagnosis and the wide differential diagnosis can make it more difficult to follow.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

In case of 11p15.5 duplication or other submicroscopic chromosomal aberrations, up to 50%.

Unknown for the other aberrations.

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
No.

3.4 Prenatal diagnosis
(To be answered if in 2.10 'D' was marked).

Prenatal diagnosis may be requested.

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes, particularly when there is a genetic rearrangement to account for SRS. Systematic testing to confirm that prenatal diagnosis is possible on CVS for epigenetic aberrations has not been performed for this condition.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or for his/her relatives? (Please describe)

The identification of an (epi)mutation allows a more precise delineation of a recurrence risk for the patient and his family.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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