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Clinical report

First report on concordant monozygotic twins with Silver–Russell syndrome and ICR1 hypomethylation

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ABSTRACT

Twin pairs with the imprinting disorder Silver–Russell syndrome (SRS) have rarely been reported. All six monozygotic (MZ) twin pairs described so far were clinically discordant. In two of the four SRS twin pairs with molecularly proven 11p15.5 epimutation, the healthy twin also showed the molecular alteration in blood cells, but not in the other tested tissues. The clinical discordance is a well-known but poorly understood observation because MZ twins derive from the same zygote. For the second 11p15.5-associated imprinting disorder, Beckwith-Wiedemann syndrome, a larger number of twins has been described, here the majority of pairs are MZ but clinically discordant as well. Interestingly, there is a considerable preponderance of females among the MZ twins with BWS, and a functional link between altered imprinting and X chromosome inactivation has been suggested. We now describe two further MZ SRS twins with H19/IGF2:IG-DMR hypomethylation, including the first clinically concordant pair. By summarizing the existing data, an excess of females in MZ twins with SRS is observed, thus confirming the hypothesis that X-chromosome inactivation might trigger the inaccurate methylation of imprinted loci at least in female twin conceptions. The occurrence of a MZ concordant SRS twin pair is exceptional. The detailed molecular characterization of both siblings of a twin pair enables a reliable diagnosis, furthermore it allows insights in the etiology of twinning in association with (aberrant) imprinting marking.

1. Introduction

Silver–Russell syndrome (SRS, OMIM180860) is a congenital imprinting disorder characterized by severe intrauterine and postnatal growth retardation, a typical triangular face, relative macrocephaly, and further less common clinical findings (Table 1) (for review Azzi et al., 2015). In up to 60% of patients, the clinical diagnosis can be confirmed by molecular testing. In approximately 10%, a maternal uniparental disomy of chromosome 7 (upd(7)mat) is detectable, but the major molecular subgroup carries a hypomethylation of the imprinting center region 1 (ICR1, H19/IGF2:IG-DMR) in 11p15.5, regulating the expression of the imprinted genes *H19* and *IGF2* (for review Azzi et al., 2015). In single patients, additional molecular disturbances have been reported (duplications/deletions of 11p15.5, upd(11p15)mat, *CDKN1C* or *IGF2* point mutations). Mutations and epimutations in 11p15.5 also result in another imprinting disorder, Beckwith-Wiedemann syndrome (BWS). This overgrowth disorder is caused by molecular disturbances opposite to those of SRS (for review Choufani et al., 2013).

In BWS, a large number of twins have been reported (for review Bliek et al., 2009). Interestingly, the majority of them were monozygotic (MZ), but clinically discordant, i.e. one twin presents the BWS phenotype whereas the other one is not affected. This discordance is a well-known but poorly understood observation because MZ twins derive from the same zygote and should therefore be genetically identical. Recent molecular characterization of MZ twins with BWS reveals that the majority carries a hypomethylation of the imprinting center region 2 (ICR2, KCNQ1OT1:TSS-DMR) in 11p15.5, which is close to the H19/IGF2:IG-DMR and disturbed in nearly 50% of BWS patients. This

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Table 1
Clinical features of the discordant and concordant MZ SRS twin pairs in our study. (IUGR intrauterine growth retardation, PNGR postnatal growth retardation).

Clinical feature	upd (7)mat (n = 20)	H19/IGF2 hypo (n = 44)	MZ discordant affected twin	MZ concordant affected twin 1	MZ concordant affected twin 2
Reference	(Wakeling et al., 2010)		This study	This study	This study
Gestational week			33	30 + 1	
IUGR (≤−**2 SDS**)					
length at birth			37 cm (−2.57 SDS)	31 cm (−3.4 SDS)	30 cm (−3.8 SDS)
weight at birth	70% ≤−2 SDS	82% ≤−2 SDS	1270 g (−2.0 SDS)	580 g (−3.4 SDS)	535 g (−3.6 SDS)
PNGR (≤−**2 SDS**)					
Height at examination	65% ≤−2 SDS	57% ≤−2 SDS	3 9/12 years: 85 cm (−4.81 SDS)	10 mon: 61.5 cm (−4.7 SDS)	10 mon: 61 cm (−4.9 SDS)
Weight at examination			$3^{9/12}$ years: 9.5 kg	10 mon: 5.4 kg	1 year: 5.3 kg
Craniofacial features:					
Rel. macrocephaly (head circumference at birth at least 1.5 SDSS above birth weight and/or length)	90%	70%	at birth: 30 cm (−0.72 SDS)	at birth: 25 cm (−1.8 SDS) 10 mon: 46 cm (−0.1 SDS)	at birth: 25 cm (−1.8 SDS) 10 mon: 45 cm (−0.1 SDS)
Triangular face	90%		yes	yes	yes
Prominent forehead	60%		yes	yes	yes
Ear anomalies (low set)	75%		no	yes	yes
Downturned corners of the mouth	20%		no	no	no
Other features:					
Asymmetry	30%	68%	no	yes	yes
Clinodactyly V	45%		no	no	no
Congenital heart defects	0%	9%	no	no	ventricular septum defect
Scoliosis	5%	9%	no	no	no
Irregular spacing of teeth	45%		yes	too young	too young
Café au lait naevi	15%		no	naevus flammeus	naevus flammeus
Feeding difficulties	90%	84%	yes	yes	yes
Hypoglycemia	29%	24%	no	yes	yes
Development:					
Speech delay	50%	39%	no	too young	too young
Global delay	65%	20%	no	too young	too young

epimutation was detectable in peripheral lymphocytes of the affected twins, but sometimes also in lymphocytes of the healthy sib. However, analyses of further tissues (buccal swab DNA, skin fibroblasts) then showed that the KCNQ1OT1:TSS-DMR hypomethylation was present in other tissues of the affected twin but not of the healthy child. This discrepant distribution of the molecular defect and the different phenotypic outcomes has been explained by the exchange of blood cells through vascular connections during pregnancy (Hall, 2003), for review (for review Bliek et al., 2009). Interestingly, there is a considerable preponderance of females among the MZ twins with BWS, and a functional link between altered imprinting and X chromosome inactivation has been suggested (Orstavik et al., 1995).

For SRS, reports on twins are rare, and all six MZ twins described so far were clinically discordant (Table 2). Five twin pairs were females, in four molecular testing had been performed revealing an H19/IGF2:IG-DMR hypomethylation. In two of these four twin pairs, the healthy twin also showed the molecular alteration in blood cells, but not in the other tested tissues (skin fibroblasts, buccal swab DNA) (Begemann et al., 2011; Gicquel et al., 2005).

We now describe two monozygotic SRS twin pairs (Table 1) with H19/IGF2:IG-DMR hypomethylation, including the first clinically concordant twin pair.

2. Clinical report

2.1. MZ discordant twin pair

The male twins were the second and the third child of a non-consanguineous German couple, the parents and the older sister were healthy and of normal height (father: 180 cm, mother: 165 cm). Family history was unremarkable. Pregnancy was uneventful, but delivery by caesarean section was induced because of severe intrauterine growth restriction of the affected child. Whereas the second twin did not show any clinical signs, the affected boy was short and showed severe growth failure and dysmorphic features (Table 1). Until the fifth months of life gastric tube feeding was required. At the age of 3 9/12 years, he was severely growth retarded, had relative macrocephaly and the facial gestalt was compatible with SRS. Scoring with the recently

Table 2
Overview on the MZ twin pairs with Silver–Russell reported in the literature and in this report. (f female, m male, hypo hypomethylation, ND not determined, NR not reported, ART assisted reproduction technology, ICSI intracytoplasmatic sperm injection).

Reference	ART	Sex	Clinical findings		Molecular findings	
			Concordant	Discordant	Affected twin(s)	Healthy twin
Twin pair 1, this study	no	m		1	ICR1 hypo	ICR1 normal in blood
Twin pair 2, this study	no	f	1		ICR1 hypo	*no healthy twin*
Cocchi et al., 2013	ICSI	f		1	ICR1 hypo	ICR1 normal in blood
Begemann et al., 2011	ART in preceding pregnancy	f		1	ICR1 hypo; MLID	ICR1 hypo in blood, normal in other tissues
Yamazawa et al., 2008	no	f		1	ICR1 hypo	ICR1 normal in blood
Gicquel et al., 2005	NR	f		1	ICR1 hypo	ICR1 hypo in blood, normal in other tissues
Bailey et al., 1995	NR	m		1	ND	ND
Samn et al., 1990	NR	f		1	ND	ND