Epigenetic mutations in 11p15 in Silver-Russell syndrome are restricted to the telomeric imprinting domain

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Abstract

Introduction Silver-Russell syndrome (Russell-Silver syndrome, SRS) is a heterogeneous syndrome which is characterised by severe intrauterine and postnatal growth retardation and typical dysmorphic features. Recently first SRS patients with (epi)genetic mutations in 11p15 affecting the telomeric imprinting domain have been identified. Interestingly, opposite mutations are associated with Beckwith-Wiedemann syndrome (BWS). However, the general significance of epigenetic mutations in 11p15 for the aetiology of SRS remained unclear.

Methods We screened a cohort of 51 SRS patients for epimutations in ICR1 and KCNQ1OT1 by methylation-sensitive Southern-Blot analyses.

Results ICR1 demethylation could be observed in 16 out of 51 SRS patients, corresponding to a frequency of approximately 31%. Changes in methylation at the KCNQ1OT1 locus were not detected.

Discussion Combining these data with those on maternal duplications in 11p15, nearly 35% of SRS cases are associated with detectable (epi)genetic disturbances in 11p15. We now also have to consider a general involvement of 11p15 alterations in growth retarded patients with only minor or without further dysmorphic features. SRS and BWS may now be regarded as two diseases caused by opposite (epi)genetic disturbances of the same chromosomal region displaying opposite clinical pictures.
To the editor:

Silver-Russell syndrome (Russell-Silver syndrome, SRS) is a heterogeneous syndrome which is mainly characterised by severe intrauterine and postnatal growth retardation (<3 percentile). The typical features include a prominent forehead, a triangular face, hemihypotrophy, and clinodactyly V. So far, only little is known about the causes of the disease: Several reports on SRS families as well as on chromosomal disturbances point to a genetic background (for review: 1). In 7-10% of SRS patients, a maternal uniparental disomy of chromosome 7 (UPD7) can be detected.

Recently, six growth retarded patients with duplications of maternal 11p15 were reported, four of these cases showed SRS(-like) features (for review: 2). This finding led to the hypothesis that (epi)genetic alterations in 11p15 opposite to Beckwith-Wiedemann syndrome (BWS) are involved in the aetiology of SRS2. Indeed, first SRS patients with epigenetic mutations in the telomeric imprinting domain of 11p15 have recently been identified: Gicquel et al.3 reported on an epimutation consisting of a (partial) loss of paternal methylation at the H19-IGF2 imprinting center (ICR1), at the H19 promoter and at the IGF2 DMR2 in five out of nine patients with the classical SRS phenotype. Methylation of KvDMR1 in KCNQ1OT1 was normal in this cohort.

However, the general significance of epigenetic mutations for the aetiology of SRS remained unclear due to the small number of patients investigated by Gicquel et al.3. We screened a cohort of 51 SRS patients for epimutations in ICR1 and KCNQ1OT1 by methylation-sensitive Southern-Blot analyses as reported previously3, 4: Total genomic DNA was digested over night with Rsal and HpaII for ICR1 and with BamHI and NotI for KvDMR1 in KCNQ1OT1. Samples were electrophoresed on 1.2% or 0.7% agarose gels, blotted and hybridised with digoxigenin-labelled PCR products for ICR1 or KCNQ1OT1. Methylation index was achieved by densitometry of autoradiographs using a GelDoc2000 system (BioRad, München, Germany). In these patients, maternal UPD7 and maternal duplications of 11p15 had been excluded before. All patients showed severe intrauterine and postnatal growth retardation (<3. percentile) and at least three further signs typical for SRS according to Wollmann et al.5.

ICR1 demethylation with an methylation index ranging from 0.20 to 0.37 could be observed in 16 out of 51 SRS patients, corresponding to a frequency of approximately 31%. In two further patients with maternal UPD7 ICR1 demethylation was also excluded. Changes in methylation at the KCNQ1OT1 locus were not detected in the 51 patients. More than 80% of the patients with ICR1 demethylation showed body asymmetry among other clinical features thus supporting a postzygotic origin and mosaicism of the disturbance as suggested by Gicquel et al.3. Assuming this formation mechanism, the number of epigenetic alterations in the telomeric imprinting region may be even larger than reported here but still remains undetected.

Our data show that ICR1 demethylation is indeed an important if not the most important genetic disturbance in SRS. Combining these data with those on maternal duplications in 11p152, nearly 35 % of SRS cases are associated with detectable (epi)genetic disturbances in 11p15 (table 1). Considering that 7-10% of SRS patients show maternal UPD7 and chromosomal rearrangements affecting 7p11.2-p13, a genetic alteration with probable functional significance can now be diagnosed in more than 45% of SRS cases. As a consequence, the diagnostic algorithm for SRS should comprise conventional cytogenetic analyses, ICR1 methylation analyses, and search for maternal UPD7.
Table 1

Comparison of genetic alterations and their frequencies in BWS and SRS. (a frequencies are leaned on Weksberg et al.8; b present study).

<table>
<thead>
<tr>
<th>Type of mutation</th>
<th>BWS(^a)</th>
<th>SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>uniparental disomy of 11p15</td>
<td>paternal 10-20%</td>
<td>maternal - (0/46)(^2)</td>
</tr>
<tr>
<td>structural chromosomal rearrangements of 11p15</td>
<td>paternal duplications 1%</td>
<td>maternal duplications 4% (2/46)(^2)</td>
</tr>
<tr>
<td>in telomeric 11p15 imprinting domain</td>
<td>hypermethylation of H19 2%</td>
<td>hypomethylation of ICR1 31-55%(^b,3) (16/51, 5/9)</td>
</tr>
<tr>
<td>in centromeric 11p15 imprinting domain</td>
<td>mutations in CDKNIC 5-10% sporadic 25% ant.-dominant</td>
<td>mutations in CDKNIC (^6)</td>
</tr>
<tr>
<td></td>
<td>hypomethylation of KvDMR1 50%</td>
<td>hypermethylation of KvDMR1 (^b,3) (0/60)</td>
</tr>
<tr>
<td>others</td>
<td>unknown 10-20%</td>
<td>maternal UPD7/ duplications in 7p 10%</td>
</tr>
</tbody>
</table>

In contrast to BWS, mutations in the centromeric imprinting domain of 11p15 may be neglected in the aetiology of SRS (table 1). Among 51 patients we did not find any epimutation of KvDMR1, mutations in the transcribed sequences of CDKNIC or KCNQ1OT1 were not detected either\(^6,7\). This is in agreement with results of Gicquel et al.\(^2\) who excluded changes in methylation of KvDMR1 in their cohort of nine patients.

The surprising data on the significance of 11p15 disturbances in SRS shed more light in the aetiology of the disease, on the other hand they raise a lot of questions:

If we assume that the growth retardation is caused by the defective expression of IGF2 as a factor of the IGF/IGF1R axis, probably several genes in the cascade may be disrupted resulting in similar phenotypes. Indeed, chromosomal aberrations observed in SRS affect the regions 7p11.2-p14 as well as 15q26 which harbour the genes IGFBP1, IGFBP3, GRB10 and IGF1R, respectively, but mutations in these genes have previously been excluded in SRS patients (for review: \(^1\)). In addition, body asymmetry is not restricted to SRS patients with proven 11p15 epimutations, mosaicism for undetected epigenetic alterations or chromosomal aberrations is therefore conceivable and needs further evaluation.

Interestingly, the clinical picture in patients with epigenetic mutations in the telomeric imprinting domain in 11p15 is more consistent with SRS than that in patients with maternal duplications of the same region: Among the six duplication carriers reported so far, only four showed SRS features (for review:\(^2\)). Thus many milder patients are likely to remain undiagnosed. Consequently, we now also have to consider a general involvement of 11p15 alterations in growth retarded patients with only minor or without further dysmorphic features.

With the identification of a major genetic disruption in SRS, an individual and more directed therapy is conceivable. Until recently it was nearly impossible to define genetic and functional subgroups of SRS, thus the treatment of the growth retardation was undirected. During growth hormone (GH) treatment, the response of SRS patients is highly variable, with approximately half of them showing a rapid catch-up growth. The potential for increasing final height using early GH treatment is still being assessed. Interestingly, one of the patients treated successfully is a carrier of maternal duplication 11p15\(^2\). It will be interesting to see whether this is a single case or whether SRS patients with 11p15 mutations or other 11p15 disturbances in general benefit from GH treatment in comparison to other SRS subgroups.
Similar to Prader-Willi and Angelman syndrome, SRS and BWS may now be regarded as two diseases caused by opposite (epi)genetic disturbances of the same chromosomal region. Apart from this exciting genetic background it is in particular spectacular that the two imprinting syndromes also display the opposite clinical picture.

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