CORRESPONDENCE

Hypomethylation in the 11p15 telomeric imprinting domain in a patient with Silver–Russell syndrome with a CSH1 deletion (17q24) renders a functional role of this alteration unlikely

Silver–Russell syndrome (SRS) is a clinical and genetic heterogeneous malformation syndrome. Patients show intrauterine and postnatal growth retardation (<3rd centile), and numerous additional dysmorphisms such as a relative macrocephaly, a small triangular face, a prominent forehead, clinodactyly V and asymmetry of head, limbs and trunk (for a review, see Hitchins *et al*¹). Several genetic disturbances have meanwhile been described, among them cytogenetic aberrations affecting different chromosomes and maternal uniparental disomy of chromosome 7 in 7–10% of cases. Epimutations of the telomeric imprinting centre region 1 (ICR1) in 11p15 can be detected in at least 30% of cases (for a review, see Eggermann *et al*²). The functional link between these mutations and the phenotype is currently unclear, but the different genetic variations impressively illustrate the genetic heterogeneity of SRS. It has therefore been postulated that further loci are involved in the aetiology of the disease.

Among the rare chromosomal disturbances in SRS are two balanced translocations involving the region 17q24–q25.^{3,4} The description of these patients prompted several groups to search for an SRS candidate gene in the short arm of chromosome 17. Recently, Dörr *et al*⁵ characterised the 17q breakpoint in one of these patients more precisely, and thereby identified the *karyopherin α2* (*KNA2*)⁵ gene. Nevertheless, they excluded mutations in this positional candidate gene to be relevant to the aetiology of SRS. In the same chromosomal region, the growth hormone (*GH*) gene cluster is localised. The *GH* gene cluster consists of two growth hormone genes (*GH1* and *GH2*) and three somatomammotropin-like genes (*CSH1*,

CSH2 and *CSH-L*). Although the central role of *GH1* in human growth is well established, the roles of *CSH1* and other components of the cluster are ambiguous. We recently reported on heterozygotic deletions of *CSH1* in three of 64 patients with SRS without maternal uniparental disomy for chromosome 7.^{6,7} Further search for mutations in the *CSH1* and *GH2*, as well as the *GRB2* and *GRB7* genes, which are localised in the vicinity of the *GH* cluster, did not reveal any hint of a contribution of these factors to the formation of SRS.^{7,8}

On the basis of the recent identification of 11p15 hypomethylation in >30% of patients and the potential functional link to the SRS phenotype, we decided to test our three *CSH1* deletion carriers for this alteration using a methylation-sensitive Southern blot approach.⁹ Among our three patients, we could identify one *CSH1* deletion carrier with a nearly complete hypomethylation at the ICR1 locus. This patient⁷ showed the characteristic clinical signs of SRS, in particular asymmetry of limbs, which is typically associated with this epigenetic mutation in the ICR1. This asymmetry can be attributed to the mosaicism for the 11p15 epimutation, which probably originates from a postzygotic error.

To sum up, the identification of the ICR1 hypomethylation in a *CSH1* deletion carrier makes a relevant role of this deletion in the aetiology of SRS unlikely. The *CSH1* deletion can therefore be regarded as a polymorphism without any causal relationship to SRS.

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