Letter to the Editor

Isolated hypermethylation of GRB10 (7p12.2) in a Silver–Russell syndrome patient carrying a 20p13 microdeletion

To the Editor:

Silver–Russell syndrome (SRS; OMIM 180860) is an imprinting disorder characterized by primordial growth retardation and a typical facial gestalt. Maternal uniparental disomy of chromosome 7 (upd(7)mat) is detectable in 7–10% of patients, and hypomethylation of the imprinting control region 1 (ICR1) in 11p15 accounts for up to 62%. On chromosome 7, two candidate genes have been suggested: MEST (7q32) and GRB10 (7p12.2). Whereas carriers of segmental upd(7q)mat and 7q32.2 deletions indicate a functional role of MEST, the findings in 7p12.2 aberrations are ambiguous (for review: 1). GRB10 is an imprinted gene exhibiting a tissue-dependent regulation with biallelic expression in many tissues but maternal expression in muscle and placenta as well as paternal expression in fetal brain (2, 3). In mice, Grb10 negatively regulates the Igf-growth cascade.

Here, we report on the first case with isolated hypermethylation of GRB10. The 5 11/12-year-old boy is the second child of a healthy, non-consanguineous Vietnamese couple (paternal height: 164 cm, maternal height: 156 cm). After an uneventful pregnancy, the boy was born spontaneously [gw 37; birth weight: 2180 g [standard deviation score (SDS) 2.07], length: 45 cm (SDS 2.17)]. Growth restriction persisted at the age of 5 11/12 years (height: 106 cm/SDS 2.34, weight 14.9 kg/body mass index 13.26) whereas head circumference was nearly normal (52 cm, SDS 0.22). Feeding difficulties were reported. The patient showed a triangular face (Fig. 1). He attends a regular kindergarten; psychomotoric development is normal.

Initial molecular analysis of DNA from peripheral lymphocytes by methylation-specific (MS) polymerase chain reaction revealed a GRB10 hypermethylation but gave a normal result for MEST. Deletions and uniparental disomy at the GRB10 locus were excluded. MS single nucleotide primer extension (MS-SNuPE) analysis confirmed the GRB10 hypermethylation, other tested loci gave normal methylation patterns (PLAGLI, IGF1R, MEST, H19, KvDMR1, IG-DMR, MEG3, and SNRPN) (Fig. 2). Molecular karyotyping (Affymetrix GeneChip®, Santa Clara, CA, USA; Genome-Wide Human SNP 6.0 array) revealed a heterozygous de novo 1.03 Mb deletion in 20p13 (hg19: chr20:61292-1090679), including 21 genes.

Up to now, only hypomethylation at the GRB10 locus has been reported (for review: 4), in these patients an influence of the GRB10 hypomethylation on the phenotype was not obvious. In contrast to the uncertain relevance of GRB10 hypomethylation, we hypothesize that isolated hypermethylation contributes to the phenotype as GRB10 is maternally methylated and maternally expressed in several tissues. A GRB10 hypermethylation might cause an overexpression in specific tissues leading to downregulation of the growth promoting insulin-like growth factor (IGF) cascade.

However, we have to consider the role of the de novo deletion in 20p13 in our patient. Several patients with 20p13 deletions have been reported (for review: 5, 6; DECIPHER http://decipher.sanger.ac.uk/), but only few of them were comparable to our patient in respect to size and gene content of the deletions. All these patients were ascertained because of mental retardation, but the clinical findings were inconsistent and only three showed features compatible with SRS (6; DECIPHER: 2628, 249088). As our patient exhibits...
Fig. 2. Methylation-specific single nucleotide primer extension results for 10 imprinted loci, for each locus two different CpGs were tested. The maternally methylated locus GRB10 showed an increased methylation (nMI > 0.7) whereas the other loci showed a normal index (nMI = 0.5).

When considering typical features of SRS, and upd(7)mat as a characteristic molecular finding in SRS functionally corresponds to a GRB10 hypermethylation, we rather suggest that the clinical features are attributable to the GRB10 epimutation. Nevertheless it has to keep in mind (i) that segmental upd(7q)mat is sufficient to cause SRS, pointing to a minor relevance of 7p, and (ii) screening for GRB10 (epi)mutations were negative (2, 3).

Thus, the final proof for the contribution of the GRB10 hypermethylation to the phenotype of our patient is missing, and the influence of the 20p13 deletion cannot be specified. Further studies on the biological role of GRB10 in growth and development are needed.

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