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Hypermethylation of the imprinted NNAT locus occurs frequently in pediatric acute leukemia.

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Abstract
Recent studies have demonstrated imprinting of the human neuronatin (NNAT) gene. NNAT maps to 20q11.2-q12, a region exhibiting loss of heterozygosity in acute myeloid leukemia and myelodysplastic/myeloproliferative disease. To investigate possible epigenetic dysregulation of genes in this region relevant to leukemogenesis, we analyzed methylation of the NNAT gene in normal tissues and in leukemias. We found a differential methylation pattern, typical of imprinted genes, at sites in the CpG island containing NNAT exon 1 in normal pituitary, peripheral blood cells and bone marrow-derived CD34-positive hematopoietic progenitor cells. Substantial or complete loss of the unmethylated NNAT allele was observed in leukemia cell lines and in 20 of 29 (69%) acute myeloid or lymphoid leukemia samples. While most highly expressed in brain, NNAT mRNA was also detected in normal hematopoietic progenitor cells and in leukemia cells exhibiting the normal methylation pattern, although not in hypermethylated leukemia cells. Demethylation by treatment of hypermethylated leukemia cells with 5-aza-2'-deoxycytidine resulted in reactivation of NNAT expression, concomitant with a reversion to the normal methylation pattern. The data demonstrate that hypermethylation of the NNAT locus is a frequent event in both myeloid and lymphoid acute leukemias of childhood. Aberrant hypermethylation of the NNAT locus suggests that the dysregulation of genes at 20q11.2-q12 in leukemia may be the result of epigenetic as well as genetic events.