

Congenital Leptin Deficiency Is Associated With Severe Early-Onset Obesity in Humans

The investigators report that 2 consanguineous, first-cousin offspring with hyperphagia and morbid obesity beginning in infancy had a homozygous abnormality of the *OB* gene encoding leptin, the appetite-regulating protein secreted by the fat cell. Each child had a homozygous deletion of 1 guanine nucleotide in codon 133 leading to a frameshift mutation and 14 altered amino acids. This truncated leptin protein could be synthesized but not secreted from Chinese hamster ovary (CHO) cells transfected with the mutant gene, and both children had extremely low serum immunoreactive leptin levels. They were hyperinsulinemic and normocortisolemic. The parents of both children and 1 sibling were heterozygous for this mutation; their serum leptin levels were normal, as was their body fat content.

Montague CT, et al. *Nature* 1997;387:903-908.

Editor's comment: These observations directly demonstrate for the first time the importance of leptin in appetite regulation in humans. All the obese subjects studied previously have not had an abnormality of genes encoding leptin or its receptor. The data also reveal that the heterozygote with 1 abnormal *OB* is normal. The phenotype of these children with hyperphagia, obesity, and hyperinsulinemia was quite similar to that of the

ob/ob mouse. It differed from the animal model in that the linear growth of the children was normal (75th percentile for chronologic age; no bone age data given), and they were not hypercortisolemic.

Jackson et al described a patient with childhood-onset obesity with dual mutations in the gene encoding prohormone convertase 1 (*PC1*), an endopeptidase necessary for prohormone processing. The patient was a compound heterozygote. One *PC1* gene contained a Gly483Arg mutation that caused trapping of the gene product within the endoplasmic reticulum. The other *PC1* gene had an A→C transversion in the donor splice site of exon 5, leading to deletion of this exon and a frameshift that resulted in a premature stop codon and truncated *PC1* protein. The investigators hypothesized that loss of *PC1* activity led to impaired processing of many protein prohormones, including neuropeptides involved in appetite regulation such as α -melanocyte-stimulating hormone and glucagon-like peptide 1.

We truly are on the threshold of understanding the relationship between leptin, genetics, and obesity.

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Jackson RS, et al. *Nat Genet* 1997;16:303-306.

Relationship Between Serum Leptin Concentration and Fetal Growth

Two recent articles in the *Journal of Clinical Endocrinology and Metabolism* concerned the relationship between the concentration of serum leptin and fetal growth.

Harigaya et al elucidated the role of leptin in the fetus. Blood samples from 116 infants were analyzed within 6 hours after birth. There was no difference in the concentration of leptin found in umbilical cord sera and infants' sera obtained within that 6-hour period. Ninety-one of these infants were term; 44 were classified as AGA (birth weight appropriate for gestational age); 28 were LGA (birth weight large for gestational age); and 19 were SGA (birth weight small for gestational age). Twenty-five were preterm. Infants with dysmorphic features, intrauterine infections, organic disorders, or chromosomal anomalies were excluded. Blood samples were compared with 28 umbilical cord samples taken at birth from the term group and 25 samples from healthy adults. Serum concentration of leptin and insulin levels were determined by radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA), respectively. Follow-up samples were taken from 48 of the 116 infants between 2 and 7 days of life. Leptin levels in term AGA infants were significantly lower than those of normal adults. The serum leptin concentration in LGA infants was significantly higher (12.8 ± 10.2 ng/mL) and those in SGA infants (1.6 ± 1.1 ng/mL) was significantly lower than in AGA

infants ($P < 0.01$). The follow-up leptin concentration in 48 term infants in the LGA and AGA groups dramatically decreased within 48 hours of delivery; the leptin concentration did not change in the SGA group. A positive correlation was found between leptin concentrations within 6 hours of life and birth weights ($r = 0.59$, $P < 0.01$). Leptin levels within 6 hours of life positively correlated with gestational age. The authors concluded that serum levels of leptin correlate with the fetal body weight gain.

Koistinen and colleagues looked at leptin concentrations in cord blood to see if there was a correlation with intrauterine growth. To determine how fetal growth compares with leptin levels at birth, 50 full-term infants were studied (28 = AGA; 9 = LGA; and 13 = SGA). Blood samples to measure leptin and insulin levels were taken from umbilical cord at birth. Amniotic fluid samples were obtained by amniocentesis from 10 mothers within 1 to 8 days before delivery and from 20 mothers at the time of Cesarean section. Umbilical leptin levels were higher in LGA infants (35.7 ± 8.0 μ g/L; $P < 0.005$) but lower in the SGA infants (3.3 ± 0.05 μ g/L; $P < 0.001$) than in AGA infants (14.5 ± 2.8 μ g/L; $P < 0.005$). Cord leptin levels correlated with birth weights, cord insulin concentrations, placental weight, and amniotic fluid leptin concentrations. Leptin concentrations in amniotic fluid were higher in LGA infants