

## Evidence That the Diabetes Gene Encodes the Leptin Receptor: Identification of a Mutation in the Leptin Receptor Gene in db/db Mice

The investigators identified an abnormality in the hypothalamic receptor for the fat-derived, anorectic OB peptide (leptin) in the db/db mouse, which is responsible for the phenotype of this animal. The phenotype is similar to that of the ob/ob mouse and characterized by early-onset obesity, insulin resistance, and susceptibility to diabetes. In the normal mouse there are short and long forms of leptin receptor (designated OB-R) that arise by alternative splicing of transcripts. The short OB-R has extracellular leptin-binding transmembrane and intracellular domains of 816, 23, and 34 amino acids, respectively. The long OB-R has an intracellular domain of 302 amino acids. The latter results from the inclusion of an exon that is not transcribed in the OB-R short form. It is the long form of the OB-R that probably is involved in intracellular signaling. It is related to the class I group of cytokine

receptors and contains motifs for interaction with janus kinase (JAK) and the signal transducer and activator of transcription (STAT). The db/db mouse pathologically expresses only the short form of the OB-R. It does so because of a mutation (G→T) in the OB-R gene that creates a new splice site that leads to the incorporation of 106 extra nucleotides in the transcript of the OB-R gene, including a stop codon that results in premature termination of the long intracellular portion of the OB-R.

Chen H, et al. *Cell* 1996;84: 491-495.

**Editor's comment:** Recent papers by Lee et al<sup>1</sup> and Chua et al<sup>2</sup> add further information to the genetic defect in the db/db mouse. Lee et al reported identical findings to those of Chen et al in the db/db mouse; they also observed 9 normal splicing variants of OB-R expressed in mouse brain, hypothalamus, adipose tissue, testes, and heart. Chua et al reported that the OB-R gene and those encoding the defects in the db/db mouse and fa/fa (Zucker fatty) rat are the same. Interestingly, the OB-R also is expressed in the ovaries (Chen et al). The human OB-R has been localized to chromosome 1p31.

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1. Lee G-H, et al. *Nature* 1996;379:632-635.
2. Chua SC Jr, et al. *Science* 1996;271:994-996.