

Calcium-Sensing Receptor Genes Mutate and Produce Metabolic Disease

Ca^{2+} associated with a specific cell membrane component had been postulated for several years to explain, in part, the mechanism by which Ca^{2+} regulates the secretion of parathyroid hormone,¹ but the structure of the membrane component was unknown until Brown and coworkers isolated the bovine gene for this receptor from parathyroid tissue and expressed and characterized it. The bovine gene encodes a 120 kd, 1,085 amino acid, 7 transmembrane polypeptide characteristic of receptors that activate guanyl triphosphate (GTP) binding proteins. This activation initiates a cascade of intracellular signals that produce the characteristic biologic response of the cell to the ligand. The receptor is expressed in the bovine parathyroid gland, kidney, thyroid, and some areas of the brain.

Subsequently, the 6 exon of the human gene was isolated and mapped to chromosome 3q2. It encodes a 1,059 amino acid with an extremely long (613 amino acids) amino terminal extracellular region to which Ca^{2+} is thought to bind. Hypothesizing that the Ca^{2+} receptor gene was abnormal in patients with familial hypercalcemic hypocalciuria, the composition of this gene was analyzed in patients with this disorder and its more severe variant, neonatal severe hyperparathyroidism. All of the affected members of the families studied had base pair changes, although the genetic error varied in different families. Three variants were identified. In the amino terminal region, a G → A mutation in codon 186 altered arginine to glutamine and a C → T mutation in codon 298 changed wild-type glutamine to lysine. These mutations might affect Ca^{2+} binding to the receptor or alter polypeptide processing, receptor stability, or other necessary function. In the third intracellular domain, a C → T mutation in codon 796 altered arginine to tryptophan; this amino acid is near the site of receptor coupling to the GTP-binding protein. One subject with severe, and often fatal,

neonatal hyperparathyroidism had 2 copies of the abnormal gene at codon 298, thus lacking 2 functional Ca^{2+} receptor molecules. These observations suggest that familial hypercalcemic hypocalciuria is due to abnormalities within the gene coding for the membrane Ca^{2+} receptor and is genetically heterogeneous.

REFERENCES

1. Brown EM, et al. *Nature* 1993;366:575-580.
2. Pollak MR, et al. *Cell* 1993;75:1297-1303.

Editor's comment: *These articles provide an important advance in our understanding of the manner in which Ca^{2+} regulates the secretion of parathyroid hormone. Acting through the membrane Ca^{2+} receptor, Ca^{2+} activates GTP-binding proteins that increase activity of phospholipase C, thus hydrolyzing membrane phosphoinositide and increasing intracellular concentrations of inositol triphosphate, thereby releasing Ca^{2+} from its storage sites in calciosomes; Ca^{2+} and the GTP-binding proteins may also "open" Ca^{2+} channels directly. As the intracellular concentration of Ca^{2+} increases, neutral proteases, termed "calpains," are activated and increase the rate of degradation of parathyroid hormone.² High intracellular Ca^{2+} levels also decrease the rate of transcription of the gene for parathyroid hormone. It is possible that an abnormality in the Ca^{2+} receptor may account for the parathyroid hyperplasia seen in patients with multiple endocrine neoplasia or in a clone of parathyroid cells leading to a parathyroid adenoma. These unique observations suggest that there may be membrane receptors for other ions as well (ie, K^+ , MG^{++}).*

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Genetic Mapping of Quantitative Trait Loci for Growth Fatness in Pigs

Quantitative inheritance of a trait implies that the expression of that trait is dependent on the interaction of several genes at different loci and, often, environmental factors. In order to identify the chromosome(s) on which the traits for growth and fatness in pigs may reside, the investigators analyzed the quantitative trait loci (QTL) in second generation crossbred progeny of European domesticated pigs (selected for large growth and leanness) and the European wild boar (characterized by increased body fat content but smaller size) utilizing a linkage map and genetic markers for the porcine genome of 18 autosomes. The authors measured birth weight, growth rate, abdominal and back fat, and length of the small intestine (a trait that correlates positively with growth) and reported that wild boar alleles on chromosome 4 were associated with decreased growth, shorter small intestinal length, and increased body fat content. There was also a QTL for birth weight and early growth on chromosome 13. There was no relationship between the detected QTLs and sex or feeding. The precision of chromosomal location of these QTL is relatively low; therefore, the authors could not determine whether these chromosomal sites contained 1 or multiple genes affecting the quantitative trait.

The loci for the genes for growth hormone (chromosome 12), its receptor (chromosome 16), and insulin-like growth factor 1 (chromosome 5) were not related to the QTL for growth, body fat, or intestinal length. Loci corresponding to porcine chromosome 4 are found on chromosome 1 in humans.

Andersson et al. *Science* 1994;263:1771-1774.

Editor's comment: *The relevance of these observations to obesity in humans is uncertain, but it is of interest to note that in the mouse there are 2 genetic mutations associated with an obese phenotype (diabetes on mouse chromosome 4 and fat on chromosome 8) linked to genes with homologues on the first human chromosome. This observation points to a potential focus of attention in the study of human obesity and growth. The lack of association of body fat content with feeding regimen points to the importance of genetic factors in fat accumulation. It was a bit surprising that growth was not genetically linked to the loci for growth hormone, its receptor, or IGF-1, particularly since growth hormone-deficient pigs are dwarfed.*

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