The gene INPPL1, encoding the lipid phosphatase SHIP2, is a candidate for type 2 diabetes in rat and man.


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Abstract
Genetic susceptibility to type 2 diabetes involves many genes, most of which are still unknown. The lipid phosphatase SHIP2 is a potent negative regulator of insulin signaling and sensitivity in vivo and is thus a good candidate gene. Here we report the presence of SHIP2 gene mutations associated with type 2 diabetes in rats and humans. The R1142C mutation specifically identified in Goto-Kakizaki (GK) and spontaneously hypertensive rat strains disrupts a potential class II ligand for Src homology (SH)-3 domain and slightly impairs insulin signaling in cell culture. In humans, a deletion identified in the SHIP2 3’ untranslated region (UTR) of type 2 diabetic subjects includes a motif implicated in the control of protein synthesis. In cell culture, the deletion results in reporter messenger RNA and protein overexpression. Finally, genotyping of a cohort of type 2 diabetic and control subjects showed a significant association between the deletion and type 2 diabetes. Altogether, our results show that mutations in the SHIP2 gene contribute to the genetic susceptibility to type 2 diabetes in rats and humans.