Loss-of-function mutations in SLC30A8 protect against type 2 diabetes.
Abstract: Loss-of-function mutations protective against human disease provide in vivo validation of therapeutic targets, but none have yet been described for type 2 diabetes (T2D). Through sequencing or genotyping of ~150,000 individuals across 5 ancestry groups, we identified 12 rare protein-truncating variants in SLC30A8, which encodes an islet zinc transporter (ZnT8) and harbors a common variant (p.Trp325Arg) associated with T2D risk and glucose and proinsulin levels. Collectively, carriers of protein-truncating variants had 65% reduced T2D risk (P = 1.7 × 10(-6)), and non-diabetic Icelandic carriers of a frameshift variant (p.Lys34Serfs*50) demonstrated reduced glucose levels (-0.17 s.d., P = 4.6 × 10(-4)). The two most common protein-truncating variants (p.Arg138* and p.Lys34Serfs*50) individually associate with T2D protection and encode unstable ZnT8 proteins. Previous functional study of SLC30A8 suggested that reduced zinc transport increases T2D risk, and phenotypic heterogeneity was observed in mouse Slc30a8 knockouts. In contrast, loss-of-function mutations in humans provide strong evidence that SLC30A8 haploinsufficiency protects against T2D, suggesting ZnT8 inhibition as a therapeutic strategy in T2D prevention.

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