Absence of BiP co-chaperone DNAJC3 causes diabetes mellitus and multisystemic neurodegeneration.

Abstract:
Diabetes mellitus and neurodegeneration are common diseases for which shared genetic factors are still only partly known. Here, we show that loss of the BiP (immunoglobulin heavy-chain binding protein) co-chaperone DNAJC3 leads to diabetes mellitus and widespread neurodegeneration. We investigated three siblings with juvenile-onset diabetes and central and peripheral neurodegeneration, including ataxia, upper-motor-neuron damage, peripheral neuropathy, hearing loss, and cerebral atrophy. Exome sequencing identified a homozygous stop mutation in DNAJC3. Screening of a diabetes database with 226,194 individuals yielded eight phenotypically similar individuals and one family carrying a homozygous DNAJC3 deletion. DNAJC3 was absent in fibroblasts from all affected subjects in both families. To delineate the phenotypic and mutational spectrum and the genetic variability of DNAJC3, we analyzed 8,603 exomes, including 506 from families affected by diabetes, ataxia, upper-motor-neuron damage, peripheral neuropathy, or hearing loss. This analysis revealed only one further loss-of-function allele.
in DNAJC3 and no further associations in subjects with only a subset of the features of the main phenotype. Our findings demonstrate that loss-of-function DNAJC3 mutations lead to a monogenic, recessive form of diabetes mellitus in humans. Moreover, they present a common denominator for diabetes and widespread neurodegeneration. This complements findings from mice in which knockout of Dnajc3 leads to diabetes and modifies disease in a neurodegenerative model of Marinesco-Sjögren syndrome.