

P017 A novel mutation in the *ABCC8/SUR1* gene is linked to type 2 diabetes in adults

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Background: Mutations in ATP-sensitive potassium (K_{ATP}) channel subunit genes have recently been implicated in both permanent and transient neonatal diabetes mellitus. Here, we describe a novel mutation in SUR1 subunit linked to disease onset in adults. Methods: Recombinant K_{ATP} channels were expressed using vector pIRES in HEK293 and INS1(832/13) cells. ATP-sensitivity was measured in inside-out patches and K_{ATP} channel distribution was analysed by confocal microscopy. Plasma membrane potential was monitored electrophysiologically, cytoplasmic $[Ca^{2+}]$ was imaged using Fura-red. Results: A heterozygous carrier of the Y356C mutation in *ABCC8* (SUR1) was diagnosed with type 2 diabetes at age 39. His two children, 33 and 35, carrying the same mutation, showed impaired insulin secretion. Currents through mutant K_{ATP} channels expressed homo- and heterozygously were blocked by MgATP with IC_{50} =95 μ mol/l and IC_{50} =88 μ mol/l respectively, compared to 24 μ mol/l for the wild-type channel. The mutation substantially diminished glucose-induced membrane depolarisation and cytosolic Ca^{2+} oscillations, but had no effect on SUR1 targeting to the plasma membrane. Conclusion: A relatively small shift in K_{ATP} channel ATP-sensitivity leads to impaired stimulus-secretion coupling in β -cells and may underlie diabetes susceptibility in SUR1-Y356C carriers.