Association studies of variants in promoter and coding regions of beta-cell ATP-sensitive K-channel genes SUR1 and Kir6.2 with Type 2 diabetes mellitus (UKPDS 53).

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AIMS: The beta-cell ATP-sensitive potassium channel consists of two subunits, SUR1 and Kir6.2. Population association studies have shown that three variants in SUR1 and one in Kir6.2 are associated with Type 2 diabetes. These polymorphisms do not result in a functional change or affect splicing, suggesting that they could be in linkage disequilibrium with a pathogenic mutation. The present study aimed firstly to screen the promoter regions of SUR1 and Kir6.2 to determine whether mutations in linkage disequilibrium with the silent variants lie in regulatory regions, which might lead to changes in gene expression. Secondly, novel and previously described variants associated with Type 2 diabetes (SUR1 exon 16-3t, exon 18 T, and Kir6.2 E23K) were investigated in the UKPDS cohort. METHODS: The promoter sequences of both genes were screened by single-stranded conformational polymorphism analysis for variants associated with Type 2 diabetes. The previously reported variants were evaluated in 364 Type 2 diabetic and 328 normoglycaemic control subjects. RESULTS: Two variants were detected in the SUR1 promoter, a three base insertion (caa) at -522 bp and a single base substitution at - 679 bp (c-->g). Neither of the variants were associated with diabetes, nor were they in a sequence consensus region for transcription factors. No association with diabetes was observed for either SUR1 variant. However, in contrast, analysis of the Kir6.2 E23K variant showed that the KK homozygosity was more frequent in Type 2 diabetic than control subjects. Variants were not associated with clinical characteristics nor did they affect response to sulphonylurea therapy CONCLUSION: There is no support at present for mutations in either Kir6.2 or SUR1 promoter sequences contributing to Type 2 diabetes. However, the minimal promoter region of SUR1 has yet to be investigated. The E23K variant of Kir6.2 is associated with Type 2 diabetes mellitus in the UKPDS cohort.