Screening of SUR 0 andKir 6.2 promoters for mutations in different types of type 2 diabetes.

AL. Gloyn, Y Hashim and R.C. Turner.

Diabetologia (1998); **41:** Suppl 1: A108

The β-cell ATP regulated K-channel (K-ATP) consists of 2 subunits, the sulphonylurea receptor (SUR 1) and the inwardly rectifying K-channel (Kir6.2). Mutations in the nuclear binding fold regions (NBFs) of SUR I and in Kir6.2 have been found to cause persistent hyperinsulinaemic hypoglycaemia of infancy. Population association studies have shown polymorphisms in SUR 1 at exon 18 (T761T) and intron 16 splice acceptor site -3tagGCC to -3cagGCC were significantly more prevalent in patients with type 2 diabetes than normal control subjects, suggesting that these polymorphisms could be in linkage disequilibrium with a pathogenic mutation. Mutations in the promoter region of either gene could result in abnormal expression and regulation of K-ATP channel with decreased insulin secretion. We have screened both promoter sequences and the remaining 20 exons of SUR 1, by single stranded conformational polymorphism (SSCP) analysis in β-cell deficient subtypes of white caucasian patients with type 2 diabetes who are islet cell antibody (ICA) and glutamic acid decarboxylase antibody (GADA) negative, and in normoglycaemic controls: (i) 20 non-obese (BMI < 27 $kg.m^{-2}$) who presented at age <50 yrs with fasting plasma glucose (FPG) < 8 mmol/l (i.e. similar to glucokinase deficient, MODY 2 patients) (ii) 20 non-obese subjects who presented with FPG >12mmol/l who have marked β-cell deficiency and a family history of diabetes (iii) 20 type 2 diabetic subjects with both exon 18 and intron 16 mutations (iv) 20 randomly selected patients with type 2 diabetes (v) 20 normoglycaemic controls. A silent variant in exon 12 of SUR 1 was not associated with diabetes. No polymorphisms were detected in the Kir6.2 promoter. A 3 base insertion/deletion was detected in SUR 1 promoter and is now being evaluated in larger numbers and different ethnic groups, (including the possibility of linkage disequilibrium with the 16/18 putative haplotype), to determine if abnormal expression of SUR 1 could contribute to type 2 diabetes.