Mutations in the hepatocyte nuclear factor 4 alpha (HNF-4α) gene have been shown to cause autosomal dominant early-onset diabetes in a number of MODY families. We have investigated the role that mutations in HNF-4α may play in type 2 diabetes in white caucasians. We report an analysis of the MODY1 gene in 3 subgroups of non-obese, islet cell antibody (ICA) negative and glutamic acid decarboxylase antibody (GADA) negative UK white caucasian diabetic subjects (i) severe β cell deficient with fasting plasma glucose (FPG) >12mmol/L (n=68) (ii) glucokinase-like diabetes with mild hyperglycemia FPG <8mmol/L (n=27) and (iii) randomly chosen type 2 diabetic subjects (n=100). The 11 exons and flanking introns of HNF-4α were screened by Single Strand Conformational Polymorphism (SSCP) analysis and RFLP for known and novel polymorphisms with the variants being sequenced. Two missense mutations have been found, the previously identified T/I130 and a novel E269D mutation. The T/I130 (Thr→Ile) has an allele frequency of 6% (glucokinase subgroup) and 2% (severe β-cell subgroup). This polymorphism was identified by Yamagata et al, who found it on the same allele as the amber mutation Q268X in the R-W pedigree and at a frequency of 5% in non diabetic white subjects. The missense mutation E269D is a result of a G→C nucleotide substitution at codon 269, Glu(GAG)→Asp(GAC) and has been found in a single glucokinase-like patient. This conservative amino acid substitution is unlikely to be a major cause of late onset diabetes. Two novel polymorphisms have also been found in exon 2, one silent and the other in the intron near the intron/exon junction. HNF-4α mutations are less prevalent than HNF-1α (MODY3) mutations.