R127W in HNF4α is a loss-of-function mutation causing maturity-onset diabetes of the young (MODY) in a UK Caucasian family

Dear Sir,

Whether a change in the coding region in a known *MODY* gene causes diabetes is a difficult dilemma and one which requires both functional studies and clinical observations within families. We read with great interest the paper by Yang et al [1] showing that the R127W mutation in the *HNF-4α* gene seems to be a loss-of-function mutation causing early onset Type II (non-insulin-dependent) diabetes mellitus in a Japanese family. We describe a MODY family from the United Kingdom with the same mutation that shows clear co-inheritance with diabetes (Fig. 1). This, along with further functional data from our group clearly supports the evidence for the pathogenic role of this mutation which has been described previously as a non-functional polymorphism [2].

Yang et al. present clear functional data showing that R127W exhibits about 30 % reduction in transactivation activity in vitro compared with wild-type *HNF-4α* [1]. This data is in contrast to a previous report which found this mutation had similar activity to wild-type *HNF-4α* [2]. We have also found that the functional activity of the R127W mutant is reduced in vitro. When this mutant was expressed in HeLa cells it retained about 50 % of wild-type activity under saturating conditions and gave a two to threefold lower transactivation at all concentrations of expression vector tested [3].

Whether a mutation in a gene causes diabetes can be difficult to ascertain particularly when functional data is controversial. In favour of R127W being a significant missense mutation is that it involves the alteration of an amino acid that is phylogenetically conserved (arginine is present in human, rat, mouse and *Xenopus* α and *β*) and is not present controls.

The final evidence required to establish if a mutation has an aetiological role is the co-inheritance with diabetes within families. In the Japanese family described previously [1, 4] there is a bilineal inheritance in both parents affected, making interpretation difficult. The R127W mutation is only present in diabetic subjects (three and one family member who is assumed affected given that the children are affected and the spouses unaffected) but one was diagnosed at the age of 90 and there are two diabetic subjects who do not have the mutation [1, 4]. We have found the same R127W mutation in a Caucasian family in the United Kingdom (Fig. 1). In this family there is clear co-segregation of the mutation with diabetes. All three affected members of the family (diagnosed diabetic at 17, 20 and 21 years of age) harbour the mutant allele, whereas none of the unaffected individuals tested have the mutation.

In conclusion, we describe a second family from a different race with R127W-HNF4α that shows clear co-segregation of the mutant allele in affected patients and also refer to further evidence for an in vitro functional effect. The combination of these additional observations, even in the absence of a statistically significant LOD score when the families are combined would support the work of Yang et al suggesting that R127W is a loss-of-function mutation rather than a rare polymorphism. As diagnostic molecular genetic testing is being introduced in diabetes, the differentiation of mutations and rare coding polymorphisms is going to become of increasing clinical importance. These questions are best resolved by the combination of clinical and functional observations.

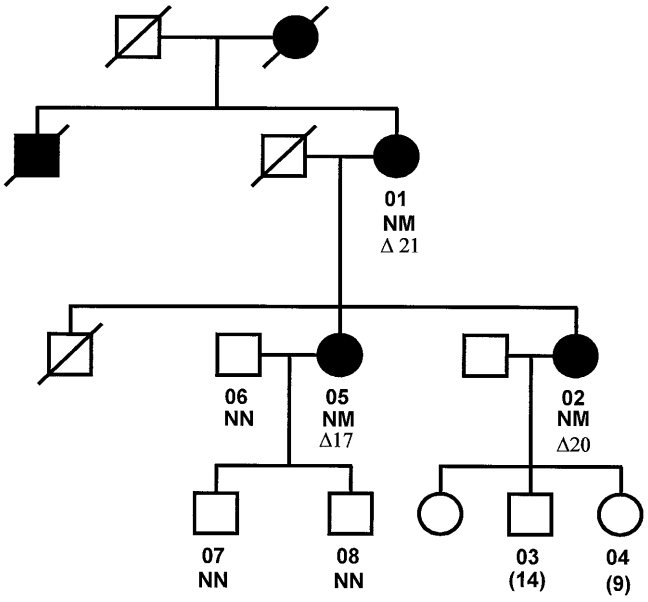

Fig. 1. UK MODY pedigree BDA 47 showing co-segregation of the R127W mutation in exon 4 of the HNF4α gene with diabetes. The genotypes of subjects are indicated: N, normal (wild type) allele; M, mutant R127W allele. The ages of diagnosis in affected subjects (△). Subjects 03 and 04 were not tested as they are younger than 16 years of age (current ages shown in brackets)

Yours faithfully,
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