Sequencing MODY1-6 genes in Uyghur Early-onset diabetes pedigree

Sir,

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes mellitus characterized by autosomal dominant inheritance, early age of onset, and pancreatic beta cell dysfunction.[1] With advancement in genomic technology, at least 11 distinct MODY genes have been identified to date and more are believed to exist.

The prevalence of Type 2 diabetes was 8% in China and 8.16% in the Uyghur population;[2] the cause of high prevalence is unknown. There is no prior study of the molecular genetics of early-onset Type 2 diabetes in Xinjiang and there is no report on mutations in MODY genes in the Uyghur ethnic population. We had undertaken the study to screen for mutations and polymorphisms in six known MODY genes in a Uyghur probable MODY family.

We collected two Uyghur early-onset diabetes pedigrees from Kashikar city of Xinjiang Uyghur Autonomous Region. We clinically diagnosed one pedigree as a probable MODY family according to the MODY criteria.[3] Two cases (Participants II.1 and III.2) from a family were involved in this research with their informed consents [Figure 1]. Genomic DNA was isolated. All exons and flanking intron regions of *HNF-4a, GCK, HNF-1a, IPF-1, HNF-1ß,* and *NEUROD1* genes were amplified from a genomic DNA sample by polymerase chain reaction (PCR). All sequences were analyzed and compared with the reference sequence from NCBI with the Lasergene software (DNASTAR, Wisconsin, USA). Changes in the sequence were checked against published polymorphisms and mutations from the Human Genome Variation Society (HGVS, http://www.HGVS.org).

The six MODY genes represent an excellent candidate gene set for identification of genetic variation in the MODY

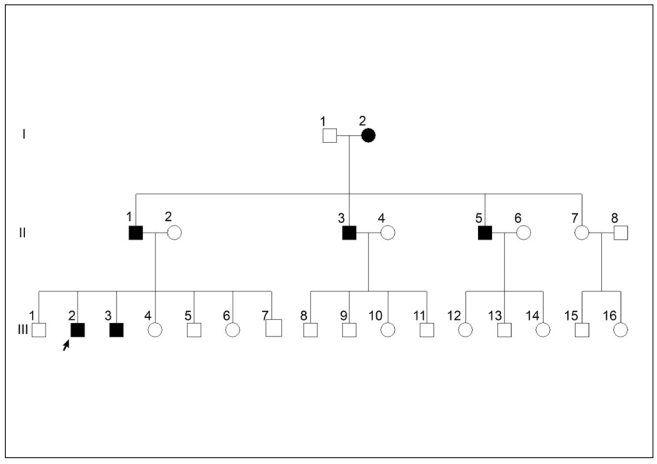

Figure 1: Arrow identifies the proband. Squares denote male family members, and circles denote female family members. Solid symbols represent subjects with Type 2 diabetes, open symbols represent non-diabetic individuals

family. Seventeen sequence variations were identified and none of them were classified as pathogenic mutation. Sequence variants of *HNF-1a* gene were relatively more common [Figure 2]. *HNF-1a* exon7 *p.Gln497Gln* and *NEUROD1* Exon1 *c.164G>A* were novel variations. Others were previously described common polymorphisms. No pathogenic mutations or polymorphisms were found in *GCK*.

A Chinese study suggested that the *S487N, I27L* variants might be associated with Type 2 diabetes mellitus (DM) in Chinese subjects, but these variants' significance in the development of Type 2 DM needs to be further investigated.[4] In this study, we also sequenced the *S487N, I27L* variants of the *HNF-1a* gene. A recent study suggested that variants of MODY genes can enhance the risk of susceptibility to Type 2 DM.[5]

In summary, this is the first report in which six known MODY genes were screened for mutations in the Uyghur ethnic group. Moreover, in the thorough analysis of the six MODY genes we did not identify any HNF-1α risk haplotype in this family, while HNF-4α, GCK, HNF-1ß, IPF-1and NEUROD1 apparently failed to contribute to the etiology of early-onset diabetes in this Uyghur family, providing further support for the high heterogeneity of this disease.

This is the first step of our researches on the MODY genes in a Uyghur probable MODY family. These variations which were identified in this study may indicate a relatively higher susceptibility to MODY or Type 2 DM in the Uyghurs.

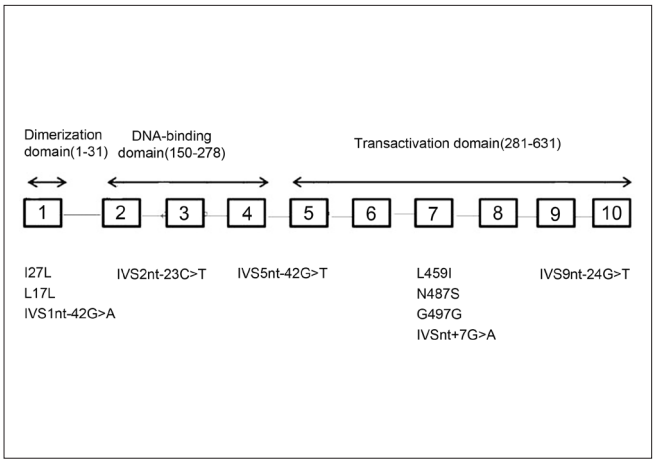

Figure 2: Location of variations within the 10 exons and introns of HNF-1α identified in this study

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