Rapid communication

Association of aldehyde dehydrogenase with inheritance of NIDDM


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Summary To investigate the influence of the mitochondrial aldehyde dehydrogenase 2 (ALDH2) genotype on the clinical features of diabetes, 212 Japanese patients with non-insulin-dependent diabetes mellitus (NIDDM) (154 males and 58 females aged 17–83 years; mean age 58.2 years) were investigated. Genotyping of ALDH2 was performed by the polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) method. The pattern of inheritance of diabetes and various clinical parameters was compared between active and inactive ALDH2 groups. Of the 212 subjects, 120 had active ALDH2 and 92 had inactive ALDH2. The percentage of patients with a diabetic mother was higher in the inactive ALDH2 group (32.6 %) than in the active ALDH2 group (19.2 %) (p < 0.05). The prevalence of proliferative retinopathy was lower in the inactive ALDH2 group than in the active ALDH2 group (p < 0.05). However, other clinical parameters showed no difference. We conclude that maternal inheritance of diabetes was common in the inactive ALDH2 group. The finding is suggestive of a relationship between alcohol intolerance and inheritance of diabetes. We speculate that the interaction between mitochondrial DNA and ALDH2 inactivity causes an increase of mitochondrial DNA mutations or deletions, thereby inducing the maternal inheritance of diabetes. The relationship of the ALDH2 genotype with proliferative retinopathy is interesting, because it resembles that of chlorpropamide alcohol flushing with severe diabetic retinopathy. The interaction of aldehyde dehydrogenase isoenzymes might have an aetiological role, since aldehyde dehydrogenase 1 plays an important part in oxidation of retinal to retinoic acid. However, the number of affected patients with proliferative retinopathy was small, hence, our result should be considered as a preliminary finding. [Diabetologia (1996) 39: 1115-1118]

Keywords Aldehyde dehydrogenase, chlorpropamide alcohol flushing test, diabetes mellitus, diabetic retinopathy, ALDH2.

In 1978, Pyke and Leslie [1] reported that chlorpropamide alcohol flushing (CPAF) is associated with inheritance of non-insulin-dependent diabetes mellitus (NIDDM). Subsequently, several studies have demonstrated that CPAF is associated with an increase in plasma acetaldehyde concentration. However, there are many papers criticizing the results of Pyke and Leslie. Desilva et al. [2] indicated the low incidence of CPAF in NIDDM, and Köbberling et al. [3] found no association of CPAF with inheritance of diabetes. Thus, the role of CPAF has been controversial.

Aldehyde dehydrogenase (ALDH) isoenzymes have been suggested to play a major role in the detoxification of aldehydes generated by alcohol metabolism and lipid peroxidation. Although there are multiple forms of ALDH in the liver, the mitochondrial enzyme, encoded by the aldehyde dehydrogenase 2
(ALDH2) locus on chromosome 12, has a very low \( K_m \) for acetaldehyde and hence is considered to play a major role in its oxidation.

New techniques for ALDH2 genotyping have been developed recently, but, the association of the genotype with diabetes remains undocumented. Accordingly, this study was performed to investigate the possible influence of the ALDH2 genotype on the clinical features of diabetes.

**Subjects and methods**

We investigated 212 patients with NIDDM including 154 males and 58 females aged 17–83 years (mean: 58.2 years). Patients who were already known to have diabetes associated with mitochondrial tRNA Leu(UUR) mutation at position 3243 were excluded, because many of them had alcohol intolerance [4].

The subjects were consecutively selected from our outpatient clinic and they were all unrelated. The diagnosis of diabetes was made according to World Health Organization criteria. All subjects gave their informed consent to this study and the investigation was performed in accordance with the principles of the Declaration of Helsinki.

Clinical parameters were investigated and each subject was questioned about diabetes in his or her parents. Data were ascertained by medical records and genealogical tree. To blind the data collectors to the patient’s tolerance of alcohol, information about alcohol intolerance or habituation was not obtained. The staging of diabetic retinopathy had been previously judged by ophthalmologist.

**Genotype analysis of ALDH2.** Genotyping of ALDH2 was performed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using DNA obtained from peripheral leukocytes. Briefly, portions of exon 12 of ALDH2 were amplified using PCR, digested with Mbo II, electrophoresed on 20 % acrylamide gel, and viewed after ethidium bromide staining. The ALDH2 alleles encoding the active and inactive subunits are termed ALDH2\(^1\) and ALDH2\(^2\), respectively. The phenotype of ALDH2 inactivity is compatible with possession of the genotype ALDH2\(^1/\)ALDH2\(^2\) or ALDH2\(^2/\)ALDH2\(^2\) [5].

**Statistical analysis**

Continuous variables were compared by Student’s \( t \)-test, and categorical variables were compared by chi-square analysis. All \( p \) values are two-tailed.

**Results**

Among the 212 NIDDM patients, 120 had the ALDH2\(^1/\)ALDH2\(^1\) genotype, 80 had ALDH2\(^1/\)ALDH2\(^2\), and 12 had ALDH2\(^2/\)ALDH2\(^2\). Thus, 92 patients had inactive ALDH2 (Table 1).

Regarding family history, 23 subjects in the active ALDH2 group had mothers with diabetes, compared with 30 in the inactive ALDH2 group (about 1.5 times higher than in the former group). The percentage of patients who had mothers with diabetes was significantly higher in the inactive ALDH2 group than in the active ALDH2 group (32.6 vs 19.2 %, \( p < 0.05 \)) (Table 1).

Of the clinical parameters investigated (age, gender, height, body weight, body mass index, age at diabetes onset, fasting plasma glucose, HbA\(_{1c}\), and current therapy), none was significantly different between the active and inactive ALDH2 groups. However, 11 (9.2 %) patients in the active ALDH2 group had diabetic proliferative retinopathy, compared to only 2 (2.1 %) in the inactive ALDH2 group, a significantly lower incidence (\( p < 0.05 \)).

**Discussion**

Epidemiologic studies of a spectrum of NIDDM patients have shown that diabetes is two to three times more frequently transmitted from the mother than from the father. While this maternal effect has been consistently attributed to gestational effects, Alcolado