MTHFR gene variant is not associated with diabetic nephropathy in Japanese

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ABSTRACT
Genetic predisposition has been implicated in diabetic nephropathy. The C677T variant of the MTHFR gene has been suggested to play a role in the development of not only vascular diseases but also diabetic microangiopathies. By using polymerase chain reaction-restriction length polymorphism (PCR-RFLP) method using Hinf I, we investigated whether this variant is associated with diabetic nephropathy in Japanese. By analysing 274 unrelated Japanese patients with type II DM with or without nephropathy, there was no significant difference in the genotype distribution of this variant. The distribution of the three genotypes were not different among patients with micro- or macroalbuminuria and those without nephropathy. Although previous reports suggest a role of this variant with diabetic microangiopathies, our observations suggest that this variant is does not play an important role in the pathogenesis of diabetic nephropathy in Japanese.

INTRODUCTION
Diabetic nephropathy is one of the three major microangiopathies of diabetes mellitus, which is often related to mortality in diabetic patients. Genetic predisposition has been implicated in its development [1-2]. The C677T (Ala→Val) variant of the methylenetetrahydrofolate reductase (MTHFR) gene has been reported to result in reduced enzyme activity and impaired homocysteine/folate metabolism, leading to moderate hyper-homocysteinaemia [3-5], which has been demonstrated to an important cardiovascular risk factor [3]. And the C677T mutation of the MTHFR gene has been reported to be associated with increased susceptibility for the development of coronary heart disease [5]. A recent study also suggests that this mutation is associated with another major diabetic microangiopathy of retinopathy [6], which indicates a possible importance of this genetic variant in development of diabetic microangiopathies as well as vascular diseases. Recently, it was reported that this variant is associated with diabetic nephropathy [7]. A previous report also suggests an importance of hyperhomocysteinaemia in the development of diabetic nephropathy [8]. These observations suggest that the C677T mutation may be associated with diabetic nephropathy. To know the possible role of the C677T variant with diabetic nephropathy, we
investigated whether the variant is associated with diabetic nephropathy in Japanese.

**PATIENTS AND METHODS**

We randomly recruited 274 unrelated Japanese patients with type II DM with (77 males/66 females, mean[SD]: 59.4[12.2] years old, range: 29-87 years) or without (86 males/45 females, 57.4[10.6], 24-85 years) diabetic nephropathy for the presence of the C677T variant of the MTHFR gene. Age (p=0.14, t test), age at onset of diabetes (46.2[11.4] vs 46.0[11.4] years, p=0.92), duration of diabetes (15.5[10.8] vs 13.7[13.0], p=0.20), systolic and diastolic blood pressure (143.7[25.7] vs 140.3[20.3] mmHg/85.9[15.8] vs 84.6[12.2] mmHg, p=0.23/0.46) were not different between the patients with nephropathy and those without nephropathy. The PCR products were digested with Hinf I separated on 8% poly-acrylamide gel.

**RESULTS AND DISCUSSION**

The frequencies of C/C (Ala/Ala), C/T (Ala/Val) and T/T (Val/Val) genotypes were not different between the two groups (χ² =1.74, p=0.42). The proportion of the T/T genotype carriers was not increased in patients with diabetic nephropathy (χ²=0.037, p=0.85). The T allele frequency was not different between the two groups (Fisher's exact test, p=0.34). The genotype frequencies were not different by comparing patients with macro-(Urine >300 µg/day) or microalbuminuria (>30 µg/day) with those without nephropathy (<30 µg/day). Although the C->T mutation has been reported to be associated with diabetic retinopathy and nephropathy in the previous reports [6-7], its association was absent with diabetic nephropathy in the analysed population. As the role of homocysteine metabolism in the pathogenesis of diabetic microangiopathies is largely unknown, it is currently not possible to have appropriate explanations for its association with diabetic nephropathy in the previous study. In conclusion, although previous observations suggest a role of the C677T mutation of the MTHFR gene in the development of diabetic nephropathy, it seems to be premature to conclude that this mutation is associated with diabetic nephropathy in Japanese.

**References**