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The Leu72Met polymorphism of the *GHRL* gene prevents the development of diabetic nephropathy in Chinese patients with type 2 diabetes mellitus

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Abstract The preproghrelin (*GHRL*) Leu72Met polymorphism (rs 696217) is associated with obesity, reduced glucose-induced insulin secretion in healthy or diabetic subjects, and reduced serum creatinine (Scr) levels in type 2 diabetes. We evaluated the association of the Leu72Met polymorphism with measures of insulin sensitivity in non-diabetic control individuals and type 2 diabetics, and whether this variation contributes to the development of diabetic nephropathy (DN) in type 2 diabetes. A case–control study was performed of 291 non-diabetic control subjects and 466 patients with type 2 diabetes, of whom 238 had DN with overt albuminuria (DN group; albuminuric excretion rate [AER] $\geq$ 300 mg/24 h) and 228 did not have DN, but had diabetes for more than 10 years (non-DN group). Genotyping was performed using a TaqMan PCR assay. The Leu/Leu, Leu/Met, and Met/Met genotype frequencies were significantly different between the non-DN and DN groups ($p = 0.011$). The frequency of the variant genotypes (Leu/Met, Met/Met) was significantly lower in the DN group than the non-DN group (23.5 vs. 36.0 %, $p = 0.003$). Met/Met non-diabetic control subjects had lower BMI and Scr levels and higher eGFR level than Leu/Leu or Leu/Met individuals ($p < 0.05$). Leu/Met and Met/Met type 2 diabetics had significantly lower AER and Scr levels and higher eGFR level than Leu/Leu type 2 diabetics (all $p < 0.001$). The *GHRL* Leu72Met polymorphism may help to maintain normal renal function and may protect against the development of DN by reducing albuminuria and improving renal function in Chinese patients with type 2 diabetes.

Keywords Leu72Met polymorphism · Preproghrelin · GHRL · Albuminuria · Type 2 diabetes mellitus · Diabetic nephropathy

Introduction

Ghrelin, a recently discovered endogenous ligand, is mainly secreted from the stomach, but is also synthesized in other tissues including the kidney [1, 2]. Human ghrelin is a 28 amino acid peptide, which is produced from the 117 amino acid preproghrelin (*GHRL*) [3]. Ghrelin is the endogenous ligand of the growth hormone secretagogue receptor (GHSR) which stimulates the release of growth hormone (GH), regulates appetite and body weight, and plays an important role in glucose and insulin metabolism [4, 5].

Plasma ghrelin levels are inversely correlated with obesity, insulin resistance, and type 2 diabetes [6–8], and administration of ghrelin increases the level of plasma insulin and attenuates the symptoms of diabetes in type 2 diabetic newborn rats [9]. In addition, exogenous ghrelin increases the activity of the primary antioxidant defense

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