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Association of G-protein beta-3 subunit gene (GNB3) T825 allele with Type II Diabetes

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Abstract

To date, the human G-protein beta 3 subunit (*GNB3*) gene and some of its variants represent some of the best examples of genetic influences that are involved in the determination of hypertension and obesity, which make it a sensible candidate gene for type 2 diabetes. To assess the influence of *GNB3* in type II diabetes mellitus (NIDDM), we carried out a retrospective, case-control study of variant *GNB3* 825C>T for putative correlations with NIDDM amongst nationals from the United Arab Emirates (Emirati) – an ethnic group characterized by no alcohol intake and no cigarette smoking.

We investigated a sample population of 510 Emirati (257 men, 253 women) comprising two groups – 254 controls and 256 patients with clinical diagnoses of type 2 diabetes (cases). The *GNB3* C825T dimorphism showed an association with NIDDM (χ^2=22.5, 2 df, P<0.001). Further analysis revealed that the *GNB3* T/T 825 genotype was positively associated with NIDDM (Yates corrected χ^2=20.6, 2 df, P<0.001; odds ratio of 2.44 with a 95% confidence interval of 1.64–3.63) compared to pooled CC/CT genotypes.

Our data shows that *GNB3* T825 allele may be involved in the pathogenesis of DM through a pathway that is different from the one implicated in obesity.

The G-protein beta-3 subunit gene (*GNB3*) encodes the β3 subunit of hetero-trimeric G proteins, and its 825T allele is associated with enhanced signal transduction via G proteins through the generation of a splice variant termed Gβ3s [6]. Cultured fibroblasts from patients with type 2 diabetes mellitus (DM) display enhanced Na^+–H^+ exchange activity [8], which has been shown to be secondary to enhanced G protein activation [6]. Dzida et al. recently demonstrated, using a moderate sample cohort, that the T825 allele was more frequent in a DM Polish population [1]. The associa-

Table 1. Distributions of *GNB3* 825 C>T genotypes and allele frequencies in the two groups, non-diabetic controls and type 2 diabetic patients (DM) of Emirati subjects.

Genotype / Allelefrequencies	Controls (n=254)	DM (n=256)
TT	60 (23.6)	110 (43.0)
TC	142 (55.9)	114 (44.5)
CC	52 (20.5)	32 (12.5)
T 825	0.52 ± 0.02	0.65 ± 0.02
C 825	0.48 ± 0.02	0.35 ± 0.02

( ) Numbers in parentheses indicate percentages

tion that they reported, however, was confounded by hypertension (HT) for which body mass index (BMI) emerged as an independent risk factor [1]. The *GNB3* T825 homozygous genotype has been associated with increased BMI in several populations worldwide [5], and the association with obesity is stronger than with HT, which explains why the 825T allele is associated more with late- rather than early-onset HT [7]. To eliminate the confounding effect of obesity on the association of *GNB3* and DM, we carried out a study on 510 overweight to obese subjects (BMI ≥ 28 kg/m^2).

This retrospective, case-control study was done on a population that has been previously described [4]. There were 510 Emirati (nationals from the United Arab Emirates) subjects (257 men, 253 women) with a mean age of 55.7±13.1 years – 256 DM (130 men, 126 women) and 254 controls (127 men, 127 women). This ethnic group provided another advantage – absence of alcohol intake and of smoking, which are the usual confounding, environmental factors in these types of studies. This project was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences (UAE University, Al Ain, UAE) and informed consent was obtained from all subjects.

Patients were classified as DM based on fasting blood glucose levels greater than 126 mg/dL. The DM patients and disease-free subjects were age, BMI and gender-matched. The BMI of DM patients and control subjects was 30.1 ± 6.0 kg/m^2 and 29.1 ± 6.5 kg/m^2 respectively. Genotyping for the *GNB3* 825 C>T polymorphism was carried out using a PCR and restriction endonuclease assay previously described [6]. Statistical analysis was performed using SPSS® version 10.0 for Windows® software package (Gorinchem, The Netherlands). Prevalence of alleles and genotypes among cases were counted and compared using χ^2 test with Hardy-Weinberg predictions. For all analyses, statistical significance was considered when significance level (*P*) values were <0.05.

Table 1 shows the distribution of alleles and genotypes of the *GNB3* 825 C>T marker in the two groups of subjects. *GNB3* genotypes occurred in Hardy-Weinberg equilibrium in both groups (DM: χ^2= 0.07, *P*=0.96; Controls: χ^2=1.90, *P*=0.39). Differences in the distributions of the three genotypes were highly significant for DM (χ^2=22.5, 2 df, *P*<0.001). T835 alleles occurred more frequently in the DM group (0.65 ± 0.02 *vs.* 0.52 ± 0.02, *P*<0.05); patients having the homozygous 825T genotype were predisposed to DM (Yates corrected χ^2=20.6, 2 df, *P*<0.001; odds ratio of 2.44 with a 95% confidence interval of 1.64 –3.63) compared to pooled CC/CT genotypes.

The *GNB3* T825 allele is thought to influence obesity by cellular hypertrophy of adipocytes via its effect on the Na^+–H^+ exchanger [6], which is counteracted by exercise [5,3]. Fernandez-Real et al. showed that T825 carriers had significantly improved insulin sensitivity in response to optimized therapy for DM [2]. We show here a striking association of T825 alleles with DM, and our data shows that the T825 allele is involved in the pathogenesis of DM through a pathway that is different from the one implicated in obesity.

Taken together, these findings indicate that the *GNB3* 825 C>T polymorphism is placed at the crossroads of metabolic and cardiovascular disorders mediating bodily responses to environmental stimuli.

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