G-protein β3 subunit gene 825C/T polymorphism and its association with the presence, severity, and duration of vasculogenic erectile dysfunction

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Objective: To investigate the association between G-protein β3 (GNB3) subunit gene 825C/T polymorphism and vasculogenic ED (VED).
Design: Case-control study.
Setting: Private urology and andrology clinic.
Patient(s): The study included 246 patients with VED and 492 healthy controls, Caucasians of Iranian descent.
Intervention(s): Typing of the polymorphism was performed using the polymerase chain reaction restriction fragment length polymorphism technique.
Main Outcome Measure(s): To test the hypothesis of whether the presence of the 825T allele of the GNB3 gene is associated with an increased risk of VED.
Result(s): The CT genotype was more prevalent in VED patients relative to healthy controls (adjusted odds ratio [OR] = 2.34; 95% confidence interval [CI], 1.10–4.26). Interaction between T allele carriership and VED was significant. The dominant model CT + TT variant was associated with a 3.74-fold increase in the adjusted risk (OR = 3.74; 95% CI, 1.11–12.4) for the occurrence of VED. Our results indicate that the GNB3 polymorphism is associated with higher systolic blood pressure, higher dyslipidemia, and higher body mass index. The 825TT genotype was associated with a more than five-fold increased risk of severe VED compared with the 825CC genotype (OR = 5.62; 95% CI, 3.54–9.25). Significantly different onset of age of VED was not found between the genotypes for the GNB3 polymorphism.
Conclusion(s): The GNB3 polymorphism is an independent risk factor for VED in Iranian males. Our findings confirm a role of GNB3 in the genetic susceptibility of VED and suggest that GNB3 polymorphism should be taken into consideration to improve the assessment of an individual's risk of VED. (Fertil Steril® 2013;99:69–75. ©2013 by American Society for Reproductive Medicine.)
Key Words: Polymorphism, single nucleotide, G-protein beta 3 subunit, impotence, vasculogenic, genotype, genetic association studies

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Heterotrimeric guanine nucleotide binding proteins (G proteins, GNB) communicate signals from a large superfamily of receptors to several distinct intracellular signaling pathways (1). These proteins are composed of three subunits, α, β, and γ, and each subunit is encoded by many different genes. The G-protein β3 subunit (GNB3) gene, which consists of 12 exons, is located on chromosome 12p13 and encodes the β3 subunit of heterotrimeric G proteins (2). Siffert et al. were the first to describe the C825T (C-to-T substitution at nucleotide 825 in exon 10) (rs5443) polymorphism of the GNB3 gene (3). This polymorphism leads to a truncated

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splice variant (Gβ3) in which the nucleotides 498–620 of exon 9 are deleted (3).

Penile arterial insufficiency is one of the most common causes of erectile dysfunction (ED). Atherosclerotic occlusive disease can decrease arterial flow to the corpus cavernosum sinusoidal spaces, thus impairing penile tumescence. Common risk factors associated with general atherosclerosis include hypertension, hyperlipidemia, diabetes mellitus, and cigarette smoking (4). The 825T allele is associated with increased signal transduction (5). This polymorphism has been shown to be associated with hypertension, atherosclerosis, obesity, and insulin resistance (6). Total cholesterol is significantly higher in subjects with the T allele (7). In a pilot study, Sperling et al. reported that homozygous 825T allele carriers had an improved erectile response to sildenafil (8). Taking into consideration the known influence of the 825C/T polymorphism on vascular risk factors for ED, this investigation was performed to test the hypothesis that the presence of the 825T allele of the GNB3 gene results in an increased risk of vasculogenic ED (VED).

MATERIALS AND METHODS

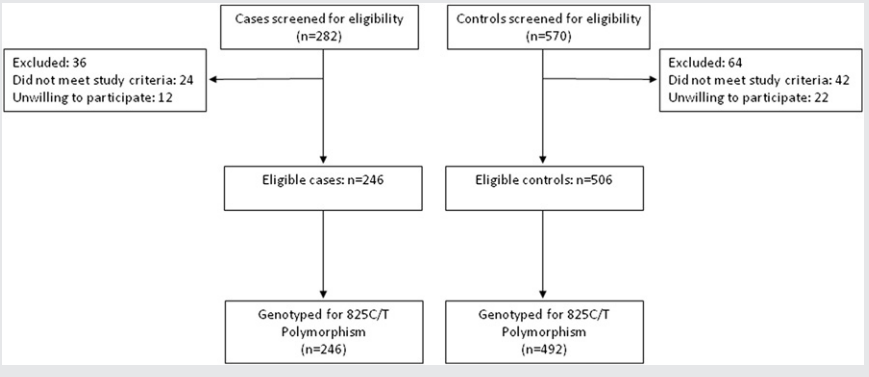
Study Population

A total of 246 unrelated patients with VED, aged between 41 and 62 years old, participated in this study. Patients were prospectively selected from the referrals to our clinic between March 2007 and March 2011. They were all naïve for treatment. ED was defined as the consistent inability to attain and/or maintain penile erection sufficient for satisfactory sexual function. A total of 492 unrelated healthy volunteers (two controls for each case), aged between 40 and 63 years old, were recruited from blood donors concurrently with the patient recruitment, in two approximately 8-week sessions (Fig. 1). They were matched to cases according to the age distribution and smoking history. The control subjects were from same linguistic and geographical area. All participants were Caucasian, $\geq$20 years old, and lived in Tehran County. All subjects gave their informed consent before enrollment into the study, which was performed in compliance with the International Conference on Harmonization and Good Clinical Practice Guidelines, as consistent with the Declaration of Helsinki 2002 and applicable laws. The study protocol was approved by Medical Ethics Committee at the study site.

Evaluation

All patients were seen with their wives and interviewed about their sexual activity and patient's erectile function (EF). To minimize the problem of response bias, patients and their wives were interviewed privately. For both groups, information was collected from self-reported questionnaires, a standardized clinical examination, and fasting venous blood samples. The questionnaires consisted of health-related questions, including the sexual history; medical, surgical, and psychosexual histories; use of any medication; and smoking status. The participants were also asked to state whether they had histories of cardiovascular disease (angina pectoris, myocardial infarction, and stroke) or diabetes mellitus. The physical examination included measurements of height, weight, and blood pressure. Biochemical analyses included complete blood count, fasting measures of blood sugar, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), thyroid function tests, LH, FSH, PRL, and T. Before proceeding to sophisticated tests for documentation of VED, all patients with ED completed the Dissociative Experiences Scale, the Hamilton Rating Scale for Anxiety, and the Liebowitz Social Anxiety Scale. Patients with normal psychiatric testes and normal serum hormonal profile underwent diagnostic tests for VED. VED diagnosis was established using penile color duplex Doppler ultrasound before and after intracavernosal injection with 20 μg prostaglandin E_1, pudendal nerve conduction tests, and impaired sensory-evoked potential studies. During penile color duplex Doppler ultrasound, the following penile arterial indices were measured: peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index (RI) of the left and right cavernous arteries. For establishing different types of VED, the following hemodynamic values were used: pure arterial insufficiency (AI), a PSV of $<$5 cm/second; borderline AI, PSV 25–30 cm/second; pure veno-occlusive dysfunction (VOD), PSV $>$30 cm/second

FIGURE 1



Flow diagram of recruited subjects through the study.

Safarinejad. GNB3 gene polymorphism and ED. Fertil Steril 2013.