A functional GNAQ promoter haplotype is associated with altered Gq expression and with insulin resistance and obesity in women with polycystic ovary syndrome.

Abstract:

The G-protein Gq, encoded by GNAQ, is involved in glucose metabolism. The GNAQ promoter harbours three polymorphisms. The TT(-695/-694)GC polymorphism was already shown to affect Gq transcription. Accordingly, we (i) characterized the GNAQ promoter polymorphisms G(-173)A and G(-168)A, (ii) investigated potential influences upon the TT(-695/-694)GC polymorphism and (iii) studied the associations with metabolic abnormalities in polycystic ovary syndrome (PCOS). Characterization of the polymorphisms was performed with electrophoretic mobility shift assays and reporter assays. Inhibition of lipolysis and Gq expression were measured in adipocytes isolated from female mammary tissue. We genotyped 266 healthy Caucasians, 265 women with PCOS, and 293 healthy, age-matched female controls to associate GNAQ promoter polymorphisms and haplotypes with anthropometric and metabolic variables. The A(-168) allele was associated with significantly decreased transcriptional activity and altered transcription factor binding, whereas the G(-173)A polymorphism appeared functionally silent. Linkage and haplotype frequencies analysis resulted in four common haplotypes. In adipose tissue, a 44% higher Gq mRNA concentration was observed in homozygous GC(-695/-694)-G(-168)
haplotypes compared with homozygous TT(-695/-694)-G(-168) haplotypes (P=0.046). This was associated with increased insulin inhibition of lipolysis in isolated adipocytes. In PCOS patients, the homozygous GC-G haplotype was associated with decreased insulin resistance and body mass index (BMI) compared with the homozygous TT-G haplotype (homeostatic model assessment of insulin resistance: 3.4+/-0.4 vs. 5.6+/-0.7 mmol/l x mmol/l, P=0.001; fasting insulin: 86.6+/-11.9 vs. 128.8+/-16.5 pmol/l, P=0.003; BMI: 29.3+/-1.2 vs. 33.9+/-1.3 kg/m2, P=0.002). No association with BMI was found in healthy women.G(-168)A is functionally relevant and in linkage with TT(-695/-694)GC. GNAQ promoter diplotypes are associated with insulin resistance and obesity in PCOS.