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European differences in the association between the UCP2 −866G > A common gene variant and markers of body mass and fasting plasma insulin

To the Editor:

There is considerable interest in the role of the UCP2 −866G > A promoter variant in determining obesity, insulin secretion [1–5] and cardiovascular risk [6]. In two Austrian Caucasian samples, the −866G allele was associated with higher body mass index (BMI) and lower transcription in intraperitoneal adipose tissue [2]. The −866A was associated with type 2 diabetes, and AA subjects had a lower disposition index (insulin sensitivity × acute insulin response to glucose) [3]. Similar results have also been reported in Italian subjects [1]. However, in a mixed race American sample, the AA genotype was associated with *lower* mRNA in subcutaneous adipose tissue [4] with no difference in disposition index between AA and GG subjects. The description 'Adiposity angel and diabetes devil' (O'Rahilly [5]) aptly fits the association of the variant allele with type 2 diabetes but lower BMI. Different genetic and geographical backgrounds in the American study may explain their conflicting findings.

Therefore, we investigated the −866G > A variant in the HIFMECH study [7] to assess whether the genotype association with the measures of obesity and insulin sensitivity would differ by geographical location within Europe. Caucasian male first myocardial infarction survivors were recruited (Northern European-Stockholm, London; Southern European-Marseille, San Giovani Rotondo) (n = 598) with age-matched healthy controls (n = 653). Statistical analysis followed the *a priori* design, comparing risk factors associated with cardiovascular risk in relation to the North and South of Europe [7].

All samples were in Hardy–Weinburg equilibrium. There was not a significant relationship between BMI and genotype; however, in the Northern control group, a non-significant association was observed (GG vs. GA vs. AA: 26.2 ± 3.1 vs. 25.7 ± 3.1 vs. 24.9 ± 3.2 kg/m^2, p = 0.13) but no association in the South (GG vs. GA vs. AA: 26.4 ± 3.3 vs. 26.4 ± 3.3 vs. 26.0 ± 3.6 kg/m^2, p = 0.86) with similar relationships in the case groups. However, waist : hip ratio (WHR) was significantly greater in Gallele carriers (GG + GA vs. AA; North: 1.0 ± 0.06 vs. 0.98 ± 0.07 m, p = 0.03; South: 0.95 ± 0.05 vs. 0.93 ± 0.07 m, p = 0.04) in both North and South controls (figure 1) but not cases. By contrast, fasting plasma insulin was lower in AA subjects (controls: 25% lower; cases: 16% lower) compared with G allele carriers in the North only (figure 1). The frequency of the A allele was not different between North and South (p = 0.15); however, in cases the frequency of the −866A allele was higher in the North (North: 0.43 [0.38–0.47] vs. South: 0.33 [0.30–0.37]; p = 0.003), so the AA genotype was associated with a modestly higher odds ratio for MI in the North of 1.30 [95%CI 0.76–2.23] but not in the South 1.00 [0.60–1.68].

These results confirm the previous European studies, showing that AA subjects are leaner (2% lower WHR), and it also shows AA subjects have lower fasting plasma insulin levels, although this effect was greater in the north compared with southern Europe. This provides further evidence of the paradoxical association between the variant UCP2 −866A allele, higher diabetes risk and lower adiposity. The putative mechanism [5] would support enhanced function of the A allele. Why the associations are stronger in the North is not clear. The UCP2 gene is known to be induced under oxidative stress load [8], through binding sites for stress signals such as the aryl-hydrocarbon receptor and receptor nuclear translocator and hypoxia-inducible factor 1a [2]. In southern Europe, lifestyle differences with respect to diet and others may alter the cellular oxidative stress load, which could influence the effect of this promoter variant on transcription. The average WHR was also higher in the North than in the South (controls: 1 vs. 0.95, p < 0.001; cases: 0.98 vs. 0.93, p < 0.001), and it may be that the effect on insulin secretion is more pronounced under this extra insulin demand.

This study was underpowered to detect an association between genotype and cardiovascular risk, but a modestly higher odds ratio for MI associated with the AA genotype

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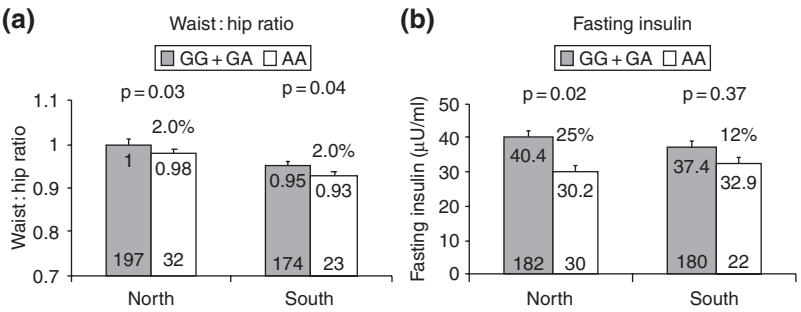

Fig. 1 Waist : hip ratio and plasma fasting insulin concentration in the HIFMECH study (northern and southern Europe controls) and the UCP2 −866G > A gene variant.

was seen in the North, in keeping with other data showing association of the A allele with cardiovascular disease (healthy men [6]), carotid atherosclerosis (women [9]) and higher oxidative stress markers (men with diabetes [6]). These studies imply lower 'uncoupling' with the A allele failing to protect the cell from oxidative stress and increasing the risk of atheromatous disease, in contrast to the insulin secretion/obesity data where the A allele improves 'uncoupling'. This could be explained if different alleles behave in different ways at baseline and under ROS loads, such as that produced by cardiovascular risk factors, e.g. smoking and glucose. Differential effects of UCP2 G and A promoter construct in pancreatic (INSE-1) and COS-7 cells under PAX6 stimulation have been reported [3]. We have identified yet another paradox when it comes to understanding the role of UCP2 in metabolism and atherosclerosis. Further study of the UCP2 promoter and its gene variants is warranted to determine the mechanism of these associations.

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