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Diabetologia

Letters

Comment

To: J. Hoffstedt et al. (2002) The common –675 4G/5G polymorphism in the plasminogen activator inhibitor–1 gene is strongly associated with obesity

To the Editor: Obesity, a major risk factor for Type II (non-insulin-dependent) diabetes mellitus and other morbidities is a polygenic disorder and recently has become the focus of many genetic analyses. The ultimate aim of these analyses is to identify the genes influencing obesity. As PAI-1 antigen concentrations are associated with adiposity, Hoffstedt et al. [1] have examined the relationship between the PAI-1 4G/5G polymorphism, associated with insulin resistance, and BMI. Although they found a relationship between BMI and possession of 4G alleles, we feel their conclusions regarding the strength of this association could be somewhat overstated.

The cohort was recruited from two sources, an obesity clinic and by local advertisement. This could have led to population stratification. The results are likely to be a post-hoc finding and it is not clear what the main hypothesis of the study was or which other candidate genes were examined. Although the aim of the authors was to investigate whether the PAI-1 gene might be a candidate for obesity, there is no data relating to either the total genetic contribution to BMI variance or the proportion of this variance influenced by the PAI-1 gene in this cohort. Finally if the influence of the 4G/5G polymorphism on BMI was strong, it should be detectable in studies from similar populations.

The authors suggest that such further studies should preferably be based on population cohorts or on families. We studied 532 subjects recruited from 89 healthy families in a community-based cohort, the characteristics and analysis of which have been published earlier [2].

Although there was a trend to higher BMI values in the 4G/4G genotype (mean values 26.3 kg/m^2, 4G/4G; 25.9, 4G/5G: 25.4 5G/5G), this was not significant either in the population as a whole (p=0.29), or when analysed by sex. When the cohort was divided into groups according to WHO definitions: lean (BMI<25 kg/m^2), overweight (BMI 25–30 kg/m^2) and obese (BMI>30 kg/m^2), there was no difference in genotype frequency between the groups (Table 1). Adjusted for age and sex, the heritability of BMI in these healthy families was 37% (95%CI 19–55). Evaluating contributors to variance of BMI shows problems due to the nature of the clustering in the insulin resistance syndrome where the distinction between cause and effect is often difficult to establish. However, 8% of BMI variance could be explained by epidemiological factors including age, sex, smoking habits and alcohol consumption. The PAI-1 4G/5G genotype was not a significant contributor to BMI variance (p=0.43) and was only a very minor contributor to the variance of PAI-1 (2%, p=0.001) in this population of healthy families [2]. Whilst the PAI-1 gene 4G/5G polymorphism has been shown to have a weak influence on PAI-1 levels [3] and PAI-1 levels are related to features of insulin resistance [4], there is little evidence to suggest that the PAI-1 4G/5G genotype has a strong

Table 1. PAI-1 genotype frequencies in lean, overweight and obese subjects (n=532)

	4G/4G n=134	4G/5G n=297	5G/5G n=101	p
Lean subjects (n=277)	0.48	0.51	0.61	
Overweight subjects (n=147)	0.30	0.29	0.21	0.29
Obese subjects (n=108)	0.22	0.20	0.18	

Values were compared by Chi square analysis
The genotype distribution differed from the Hardy-Weinberg equilibrium due to the familial nature of the cohort

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influence on any other features of insulin resistance or BMI. In conclusion, the results from Hoffstedt et al. are of interest but, particularly when interpreted in the context of other studies, do not support a strong role for PAI-1 4G/5G genotype in obesity. Further family studies to identify other sites of genetic variation (quantitative trait loci) which underlie the heritability of body mass index are under way.

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