Diabetologia (2002) 45:1605–1606
DOI 10.1007/s00125-002-0951-1

Diabetologia

Observation

Conflicting results on variation in the *IGFI* gene highlight methodological considerations in the design of genetic association studies

To the Editor: The fetal insulin hypothesis [1] proposes that genetic factors could explain the association between reduced fetal growth and Type II (non-insulin-dependent) diabetes mellitus. Vaessen et al. have recently tested this hypothesis by first identifying an association between a candidate gene polymorphism, the *IGFI* promoter microsatellite, and Type II diabetes [2] and then assessing the role of this variant in fetal growth within the same Dutch population [3]. Absence of the common allele was associated with both increased risk of Type II diabetes in 220 patients compared with 596 control subjects and with reduced fetal growth in 463 subjects from the Rotterdam study.

Received: 18 April 2002
Published online: 18 September 2002

We have analysed the same *IGFI* gene polymorphism in UK subjects and we did not observe any of the associations seen in the Dutch study (all trends seen were in the opposite direction). This highlights important methodological issues regarding the design of genetic association studies. We have analysed the *IGFI* gene polymorphism in 611 subjects from the UK Barry-Caerphilly cohort (BCG), and 348 patients with Type II diabetes [4] and a further 169 subjects from the Exeter Family study of childhood growth (EFS). All subjects gave informed consent with approval from the local research ethics committee in accordance with the declaration of Helsinki. We did not find that the absence of the common allele was associated with Type II diabetes or with any diabetic intermediate traits such as insulin resistance or beta-cell dysfunction. In addition, there was no association with birth weight (Table 1).

The following factors could have caused differences in results: (i) the microsatellite might be in linkage disequilibrium (LD) with the functional variant and patterns of LD might differ between the two populations; (ii) the environmental exposures experienced by the study populations, which differ greatly in age – may lead to genotype influencing outcomes in different ways; (iii) the initial study is possibly a false positive result, since the many plausible candidate genes and polymorphisms that could be involved in fetal growth and or Type II diabetes means that the a priori odds of finding a genuine association will be low; (iv) our results could be a false negative, particularly because larger sample sizes are needed to replicate initial genetic associations that are real, given the finding that initial reports tend to overstate the effect size [5].

Table 1. Association between the IGFI promoter polymorphism and birth weight

IGF-I genotype	BCG study				Exeter family study				Both studies combined			
	n	birth[a] weight (Kg)	95% CI	*p* value	*n*	birth weight (Kg)	95% CI	*p* value	*n*	birth weight (Kg)	95% CI	*p* value[b]
Absence of 192 bp allele	88	3.51	3.41 to 3.61		24	3.75	3.56 to 3.95		112	3.57	3.48 to 3.65	
Heterozygous 192 bp allele	286	3.45	3.38 to 3.51	0.38	85	3.60	3.48 to 3.72	0.21	371	3.49	3.43 to 3.54	0.18
Homozygous 192 bp allele	237	3.42	3.35 to 3.49	0.15	60	3.62	3.49 to 3.75	0.27	297	3.46	3.40 to 3.52	0.08

[a] Adjusted for male sex and gestational age in weeks between 35 to 44 weeks
[b] *p* value for trend on combined datasets was 0.10

Does the *IGFI* polymorphism or one in linkage disequilibrium with it affect fetal growth? The results from studies so far do not support this. However further studies may be warranted: a recent meta-analysis of 370 genetic association studies has highlighted the need to assess the evidence for or against an association over many studies [5]. In genetic studies of polygenic traits, conflicting results are far more common than concordant results. These problems can be partly overcome by using larger numbers of subjects, requiring smaller *p* values and by attempting to replicate results in additional cohorts and in family studies. This applies equally to fetal growth as it does to any other polygenic trait. These approaches have been widely advocated [6] but rarely implemented, even in high impact journals.

T. M. Frayling, A. T. Hattersley, G. D. Smith, Y. Ben-Shlomo

References

1. Hattersley AT, Tooke JE (1999) The fetal insulin hypothesis: an alternative explanation of the association of low birth weight with diabetes and vascular disease. Lancet 353: 1789–1792
2. Vaessen N, Heutink P, Janssen JA et al. (2001) A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. Diabetes 50: 637–642
3. Vaessen N, Janssen JA, Heutink P et al. (2002) Association between genetic variation in the gene for insulin-like growth factor-I and low birthweight. Lancet 359: 1036–1037
4. Frayling TM, Hattersley AT, McCarthy et al. (2002) A putative functional polymorphism in the IGF-I gene: association studies with type 2 diabetes, adult height, glucose tolerance, and fetal growth in UK populations. Diabetes 51: 2313–2316
5. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG (2001) Replication validity of genetic association studies. Nat Genet 29: 306–309
6. Freely associating (1999) Nat Gent 22: 1–2

Corresponding author: Dr. T. M. Frayling, Department of Diabetes and Vascular Medicine, Barrack Road, Exeter, EX2 5AX, UK, E-mail: T. M. Frayling@exeter. ac.uk