Letters to the Editor

Linkage studies of maturity onset diabetes of the young – R.W. pedigree

Dear Sir,

Maturity onset diabetes of the young (MODY) families [1] provide a unique opportunity for identifying the gene(s) that cause glucose intolerance in affected individuals through the use of genetic linkage strategies. Previous linkage studies have excluded tight linkage between MODY and the insulin gene on chromosome 11p15.5 (at recombination frequencies less than 0.10 [2]) as well as the insulin receptor gene on chromosome 19p13.3–p13.2 (at recombination frequencies less than 0.15 [3]). Using the R.W. pedigree [4], we have confirmed that tight linkage between MODY and the insulin receptor gene can be excluded, and in addition, have examined two other candidate genes, the erythrocyte/HepG2 glucose transporter locus (GLUT) on chromosome 1p35–p31.3 (Xba I RFLP [5]) and the apolipoprotein B locus (APOB) on chromosome 2p24–p23 (Xba I RFLP [6]). The latter locus was considered as a possible candidate gene for MODY because of its association with Type 2 (non-insulin-dependent) diabetes mellitus in a Chinese population [7].

In our linkage analyses, MODY is assumed to be homogeneous within the R.W. pedigree and transmitted as an autosomal dominant trait. We used LIPED [8] for lod score calculations, with a straight-line age-of-onset correction. Using this correction, the probability that an unaffected susceptible homozygote is diagnosed with MODY increases from 0 at age 8 to 1.0 at age 25; the probability that a heterozygote is diagnosed with MODY increases from 0 at age 8 to 0.95 at age 25 (allowing for the possibility that not all heterozygotes will develop MODY); the probability that a normal homozygote is diagnosed with MODY is 0 throughout. The MODY susceptibility allele frequency was assumed to be 0.001, consistent with a lifetime population prevalence for MODY of 0.002. Results of analyses are summarized below (Table 1); male and female recombination frequencies (θ) were assumed to be equal. Tight linkage between MODY and either GLUT (for $\theta < 0.01$) or APOB (for $\theta < 0.05$) can be rejected. The results do not depend qualitatively on the value used for the MODY susceptibility allele frequency or on the assumption of zero penetrance in normal homozygotes. Both loci have large negative lod scores for $\theta = 0.0$ but slightly positive lod scores for larger values of θ . This is due partly to the fact that MODY appears to be transmitted with different RFLP alleles in different branches of the pedigree (requiring at least one recombination event), whereas no obligate recombinants are observed within these branches because the RFLPs studied are not very informative. How-

ever, at both the GLUT and APOB loci, there is at least one branch within the pedigree demonstrating that these loci cannot be closely linked to the MODY phenotype; for example, there are affected siblings who share no parental alleles at the relevant locus, or there are multiply affected and unaffected siblings who have inherited the same alleles from both parents. Thus, while genetic variation at these genes can be excluded as the cause of MODY in this pedigree, additional studies with other RFLPs are required to extend the exclusion regions around these genes.

Yours sincerely,

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References

1. Fajans SS (1987) MODY – a model for understanding the pathogenesis and natural history of Type II diabetes. *Horm Metabol Res* 19: 591–599
2. Andreone T, Fajans S, Rotwein P, Skolnick M, Permutt MA (1985) Insulin gene analysis in a family with maturity-onset diabetes of the young. *Diabetes* 34: 108–114
3. Elbein SC, Borecki I, Corsetti L, Fajans SS, Hansen AT, Nerup J, Province M, Permutt MA (1987) Linkage analysis of the human insulin receptor gene and maturity onset diabetes of the young. *Diabetologia* 30: 641–647
4. Fajans SS, Cloutier MC, Crowther RL (1978) Clinical and etiologic heterogeneity of idiopathic diabetes mellitus. *Diabetes* 27: 1112–1125
5. Shows TB, Eddy RL, Byers MG, Fukushima Y, DeHaven CR, Murray JC, Bell GI (1987) Polymorphic human glucose transporter gene (GLUT) is on chromosome 1p31.3–p35. *Diabetes* 36: 546–549
6. Priestley L, Knott T, Wallis S, Powell L, Pease R, Brunt H, Scott J (1985) RFLP for the human apolipoprotein B gene: V; XBAI. *Nucl Acids Res* 13: 6793
7. Xiang K, Cox NJ, Sanz N, Huang P, Karam JH, Bell GI (1989) Insulin receptor and apolipoprotein genes contribute to the development of non-insulin dependent diabetes mellitus in Chinese Americans. *Diabetes* 38: (in press)
8. Ott J (1976) A computer program for linkage analysis of general human pedigrees. *Am J Hum Genet* 28: 528–529

Table 1. Recombination frequency

	0.0	0.01	0.05	0.1	0.2	0.3	0.4
Lod score with APOB	–4.89	–3.58	–1.83	–0.89	–0.13	0.07	0.04
Lod score with GLUT	–7.17	–1.78	–0.19	0.42	0.73	0.57	0.23

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