Letters to the Editor

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Further Evidence for an Association Between Genetic Variation in Transforming Growth Factor Alpha and Cleft Lip and Palate

To the Editor:

Ardinger et al. (1989) hypothesized that there might be a nonrandom association between clefting and RFLPs of candidate genes which have a role in palate formation. They reported a significant association between two RFLPs of transforming growth-factor alpha (TGFα) and clefting in a group of 80 patients with nonsyndromic cleft lip with or without cleft palate (CL/P) and in a group of 102 controls (P = .0047 for the *Taq*I RFLP, and P = .0052 for the *Bam*HI RFLP). However, in another study of seven families with CL/P segregating in a dominant manner, none of the TGFα haplotype associations reported by Ardinger et al. was seen, and, in one family, clefting did not cosegregate with TGFα, ruling out tight linkage in these families (Hecht et al. 1990).

We have genotyped the *Taq*I RFLP in 96 unrelated nonsyndromic patients with CL/P and in 100 unrelated controls. Of the patients, 62 (65%) were male, and 48 (51%) of the 94 for whom information was available had a family history of CL/P (n = 44) or cleft palate alone (n = 4). The high percentage of patients with a family history of clefting probably reflects our method of ascertainment (mainly through newspaper articles in which we encouraged participation from familial cases). There were 20 patients (21%) with bilateral CL + P, 51 (54%) with unilateral CL + P, four (4%) with bilateral CL, and 19 (20%) with unilateral CL; clefting subtype for two patients was unavailable. The controls, all from the southeast Queensland region, were of unknown clefting status and comprised the following groups: healthy laboratory workers, geriatric patients, and mothers of twins. *Taq*I RFLP frequencies for 63 of the controls are taken from Hayward et al. (1988). Since the frequency of the rare *Taq*I allele (C2) was 4.8% in Hayward's controls and was 5.5% in the additional 37 controls genotyped here (homogeneity $\chi^2_1 = 0.4$; P = .75), frequencies from the combined control group were used for comparison with the patient group. All patients and controls were of Caucasian extraction, the majority being of Anglo-Celtic descent, and, in particular, all four grandparents of the patients were known to be Caucasian. The results of the genotyping for the *Taq*I TGFα RFLP (Hayward et al. 1987) by using phTGF1-10-925 (Murray et al. 1986) are seen in Table 1. Our results provide striking replication of the excess frequency of the *Taq*I C2 allele reported by Ardinger et al. (1989) in CL/P patients.

Table 1

***Taq*I RFLPs in CL/P Patients and Controls**

Group (N)	C1C1	C1C2	C2C2	Frequency[a] C1	Frequency[a] C2
Patients (96)	66	27	3	.823	.172
Controls (100) ...	90	9	1	.945	.055

[a] P = .0003 (two-tailed exact test).

The apparent absence, of linkage between TGFα and clefting in the seven families analyzed by Hecht et al. (1990), suggests that TGFα (or a linked gene) only plays a role in some families or contributes mainly to the development of sporadic CL/P. Of the 48 CL/P patients with a positive family history reported here, 14 (29%) carried at least one copy of the rare C2 *Taq*I allele, compared with 16 (35%) of the 46 sporadic patients (difference not significant). Thus, while our data do not support the hypothesis that TGFα is mainly involved in the etiology of sporadic CL/P, they do indicate that, in the majority of the families in our study, neither the *Taq*I polymorphism itself nor any polymorphism in tight linkage disequilibrium with it is responsible for the disorder. However, the strength of the association between TGFα and CL/P, an association which has now been found in two independent studies in two continents, suggests that either TGFα or a linked gene does indeed contribute to the development of clefting in some individuals.

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Association of Pigmentary Anomalies with Chromosomal and Genetic Mosaicism and Chimerism

To the Editor:

With regard to the intriguing points made by Thomas et al. (1989, 1990), I should like to add the following comments: In their recent letter Thomas and Frias (1990) imply that I suggested Lyonization to be the only mechanism producing the lines of Blaschko, and they do this by citing my statement that "the datable embryologic event of X-inactivation seems most suitable to explain the origin and nature of the lines of Blaschko." When cited completely, however, this sentence reads as follows: "Although it should be borne in mind that other genetic mechanisms such as somatic mutations or chimerism may give rise to the same linear pattern, . . ." (Happle 1985). Therefore I hope that Thomas et al. will agree that I do *not* disagree with regard to the different mechanisms giving rise to the lines of Blaschko.

The relationship between Blaschko lines and the mosaic phenotype of so-called hypomelanosis of Ito, as well as the similarity with allophenic mice (Mintz 1967), has been explicitly discussed already in the 1970s European literature on the subject (Happle 1977). Perhaps a thorough attempt to clarify the sequence of historical events may yield even earlier references suggesting such a relationship.

Second, I disagree with the authors on the point that the lines of Blaschko should always be "narrow linear streaks." The broadness of the bandlike zones of proliferation differs to a large degree when different ne-