Letters to the Editor

Am. J. Hum. Genet. 48:1012–1013, 1991

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 χ^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.

GEORGIA CHENEVIX-TRENCH,* KATHLEEN JONES,† ADELE GREEN,† AND NICHOLAS MARTIN†
**Joint Oncology Programme of the Queensland Institute of Medical Research and Department of Pathology, University of Queensland; and*
†*Queensland Institute of Medical Research, Bramston Terrace, Herston, Brisbane*

Acknowledgments

We are most grateful to all the people who made this study possible: the patients, the surgeons (particularly D. McGuckin, P. Catt, M. Lanigan, and T. Finucan), the Children's Dental Hospital (particularly L. Baiano), the Royal Children's Hospital (particularly J. McGill and S. Neville), CLEFTPALs QLD Inc., and G. Bell (for providing the phTGF1-10-925 probe). This work was supported by a grant from the D. E. Hutchinson Estate Trust administered by Royal Children's Hospital, Brisbane.

References

Ardinger HH, Buetow KH, Bell GI, Bardach J, VanDemark DR, Murray JC (1989) Association of genetic variation of the transforming growth factor alpha gene with cleft lip and palate. Am J Hum Genet 45:348–353

Hayward NK, Nancarrow DJ, Bell DI (1987) A *Taq*I polymorphism of the human transforming growth factor alpha gene (TGFA). Nucleic Acids Res 15:5503

Hayward NK, Nancarrow D, Ellem K, Parsons P, Kidson C (1988) A *Taq*I RFLP of the human TGFα gene is significantly associated with cutaneous malignant melanoma. Int J Cancer 42:558–561

Hecht JT, Wang Y, Blanton SH, Daiger SP, Michels VV (1990) Nonsyndromic cleft lip with or without cleft palate: no evidence of linkage to transforming growth factor alpha. Am J Hum Genet 47:A220

Murray JC, Buetow KH, Bell GI (1986) RFLPs for the transforming growth factor alpha (TGFA) gene at 2p13. Nucleic Acids Res 14:7136

0002-9297/91/4805-0024$02.00