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 TaqI RFLP, and P = .0052 for the BamHI RFLP). However, in another study of seven families with CLI 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 TaqI 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 unilateral 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. TaqI RFLP frequencies for 63 of the controls are taken from Hayward et al. (1988). Since the frequency of the rare TaqI allele (C2) was 4.8% in Hayward’s controls and was 5.5% in the additional 37 controls genotyped here (homogeneity χ² = 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 TaqI TGFα RFLP (Hayward et al. 1987) by using pcTGF1-10-925 (Murray et al. 1986) are seen in Table 1. Our results provide striking replication of the excess frequency of the TaqI C2 allele reported by Ardinger et al. (1989) in CL/P patients.

Table 1

<table>
<thead>
<tr>
<th>TaqI RFLPs in CL/P Patients and Controls</th>
<th>Frequency*</th>
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<tbody>
<tr>
<td>GROUP (N)</td>
<td>C1 C1 C1 C2 C2 C2 C1 C2</td>
</tr>
<tr>
<td>Patients (96)</td>
<td>96 66 27</td>
</tr>
<tr>
<td>Controls (100)</td>
<td>90 9</td>
</tr>
</tbody>
</table>

*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 TaqI 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 TaqI 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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References

Hayward NK, Nancarrow D, Ellem K, Parsons P, Kidson C (1988) A TaqI RFLP of the human TGFα gene is signifi-

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