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-

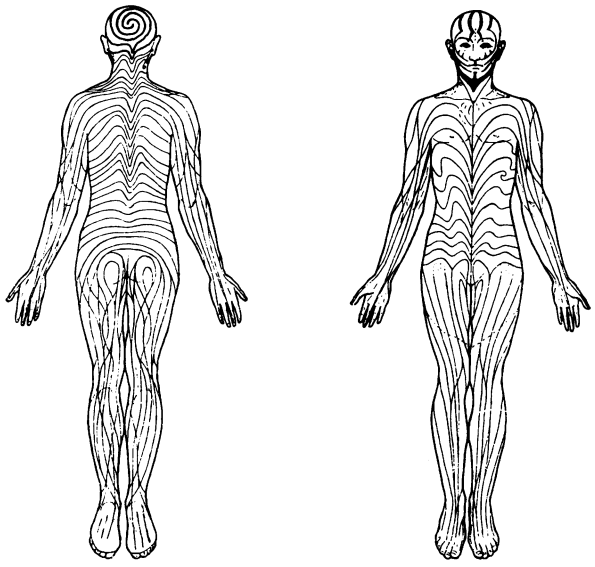

Figure 1 Lines of Blaschko. This figure is a reproduction of Blaschko's original drawing (1901), completed on the scalp according to Happle et al. (1984).

void conditions are considered. For example, the areas of hyperpigmentation present in the McCune-Albright syndrome are very broad and coarse. Nevertheless, there is convincing evidence that these pigmentary lesions can likewise be taken as a variation on the basic paradigm represented in humans by Blaschko lines.

On the other hand, I agree with Thomas et al. that women heterozygous for X-linked genes affecting the skin are as variously patterned as allophenic mice. This view is supported by the results obtained by Cattanach et al. (1972) in a comparative study of the coats of chimeric mice and those of heterozygotes for X-linked genes.

Finally, I disagree with Thomas et al. (1989, fig. 2) with regard to their diagram of Blaschko lines illustrating "the lack of information concerning the pattern over the head and face." The system of lines published by Blaschko (1901) covered the entire body including the face—but not the scalp, because of lack of pertinent case reports regarding this area. In the meantime this blank area has been filled in (Happle et al. 1984). On the scalp the lines of Blaschko are distributed in spiral streaks converging on the vertex. A completed diagram is presented in figure 1.

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Different Clinical Manifestations of Hyperphenylalaninemia in Three Siblings with Identical Phenylalanine Hydroxylase Genes

To the Editor:

Haplotype analysis at the phenylalanine hydroxylase (PAH) locus is currently used in the prenatal diagnosis of phenylketonuria (PKU) (Lidsky et al. 1985). LOD score analysis suggests that less severe serum phenylalanine elevations also result from mutation at the PAH locus (DiSilvestre et al. 1990*c*). We report a documented case of siblings who have the same phenylalanine hydroxylase (PAH) genotype, similar phenylalanine-loading-study results, normal neopterin-to-biopterin ratios, but different clinical manifestations of hyperphenylalaninemia (HPA). The results suggest that one should exercise caution when using genetic analysis at the PAH locus to predict the clinical outcome of HPA.

An informative Southern blot of DNAs isolated