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References

- Ardinger HH, Buetow KH, Bell GI, Bardach J, VanDemark DR, Murray JC (1989) Association of genetic variation of the transforming growth factor- α gene with cleft lip and palate. *Am J Hum Genet* 45:348-353
- Blanco R, Rosales C (1988) Diferencias étnicas y dimorfismo sexual de la fisura labiopalatina. *Rev Med Chil* 24:216-225
- Chenevix-Trench G, Jones K, Green AC, Duffy DL, Martin NG (1992) Cleft lip with or without cleft palate: associations with transforming growth factor alpha and retinoic acid receptor loci. *Am J Hum Genet* 51:1377-1385
- Chenevix-Trench G, Jones K, Green A, Martin N (1991) Further evidence for an association between genetic variation in transforming growth factor alpha and cleft lip and palate. *Am J Hum Genet* 48:1012-1013
- Holder SE, Vintiner GM, Farren B, Malcolm S, Winter RM (1992) Confirmation of an association between RFLP's at the transforming growth factor alpha locus and non-syndromic cleft lip and palate. *J Med Genet* 29:390-392
- Murray JC, Buetow KH, Bell GI (1986) RFLP's for the transforming growth factor alpha (TGFA) gene at 2p13. *Nucleic Acids Res* 14:7136
- Palomino HM, Palomino H, Cauvi D (1990) Variación sociogenética en la susceptibilidad a las fisuras faciales en Santiago, Chile. *Odontol Chil* 38:86-92
- Palomino H, Palomino HM, Goycoolea A (1991) Correlación de la frecuencia de fisuras faciales con atributos sociogenéticos y del medioambiente en Chile. *An Acad Estud Prof A Leng* 9: 16-24
- Rothhammer F, Lasserre E, Blanco R, Covarrubias E, Dixon M (1968) Microevolution in human Chilean populations. *Z Morphol Anthropol* 60:162-169
- Sassani R, Bartlett SP, Hongshu F, Goldner-Sauve A, Haq AK, Buetow KH, Gasser DL (1993) Association between alleles of the transforming growth factor alpha locus and the occurrence of cleft lip. *J Med Genet* 45:565-569
- Stoll C, Qian JF, Feingold J, Sauvage P, May E (1992) Genetic variation in transforming growth factor alpha: possible association of *Bam*HI polymorphism with bilateral sporadic cleft lip and palate. *Am J Hum Genet* 50:870-871
- Valenzuela C (1984) Letter to the editor. *Nature* 309:398
- (1988) On sociogenetic clines. *Ethol Sociobiol* 9:259-268
- Valenzuela C, Acuña M, Harb Z (1987) Gradiente sociogenético en la población chilena. *Rev Med Chil* 115:295-299
- Valenzuela C, Harb Z (1977) Socioeconomic assortative mating in Santiago, Chile: a demonstration using stochastic matrices of mother-child relationships applied to ABO blood groups. *Soc Biol* 24:225-233

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Heterogeneity of the Autosomal Dominant Split Hand/Split Foot Malformation

To the Editor:

I read with interest the three articles relating to the split hand/split foot (SHSF) malformation in the July issue of the *Journal* (Palmer et al. 1994; Roberts and Tabin 1994; Scherer et al. 1994). While one gene for the autosomal dominant SHSF malformation is mapped to the chromosome 7q21-22 region, there is at least one other gene responsible for the malformation.

A similar heterogeneity of the nonsyndromal autosomal dominant SHSF malformation was demonstrated from the clinical analysis of 55 families from the literature (Zlotogora 1994). It appears that there are *at least* two types of autosomal dominant SHSF: one in which the malformation is isolated (type I; McKusick 183600), the other in which at least one individual in the pedigree had other limb defects, in particular tibial hypoplasia (type II; McKusick 119100). While variability is evident in both types, the penetrance among the obligatory carriers of the descendant of the first affected individual is high in type I (96%) and low in type II (66%). In type II, within one family SHSF may be isolated in some individuals and associated with other limb defects in others. Genuardi et al. (1993) reported on a family with SHSF malformation type II that segregated with a translocation t(2,7). In this family the penetrance was low; isolated SHSF was the malformation in all affected individuals but one infant who had also left tibial hypoplasia. Since this translocation was one of the chromosomal aberrations used for the fine mapping of the gene for SHSF on chromosome 7 (Scherer et al. 1994), it may be concluded that this gene is the one associated with SHSF malformation type II.

In many of the families with SHSF type II, the obligatory carriers of the gene are unaffected sometimes for generations before the birth of the first affected individual (Zlotogora 1994). This phenomenon, which is not observed in SHSF type I, was referred to as *premutation* by Spranger and Shapera (1988). This suggests that SHSF type II may be causally related to the expansion of a trinucleotide repeat sequence as it was demonstrated in other diseases with anticipation. This trinucleotide repeat sequence may be lo-

cated close to the gene or perhaps within another gene controlling the expression of the SHSF gene.

The family reported by Palmer et al. (1994) is affected with SHSF type I, according to the classification proposed here, since the malformation in affected individuals is isolated and the penetrance is 100%. As expected, the authors demonstrated that the gene responsible for the malformation in this family is not linked to the one for SHSF type II (Palmer et al. 1994).

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References

- Genuardi M, Pomponi MG, Sammito V, Bellussi A, Zollino M, Neri G (1993) Split hand/split foot anomaly in a family segregating a balanced translocation with breakpoint on 7q22.1. *Am J Med Genet* 47:823-831
- Roberts DJ, Tabin C (1994) The genetics of human limb development. *Am J Hum Genet* 50:1-6
- Scherer SW, Poorkaj P, Allen T, Kim J, Geshuri D, Nunes M, Soder S, et al (1994) Fine mapping of the autosomal dominant split hand/split foot locus on chromosome 7, band q21.3-q22.1. *Am J Hum Genet* 50:12-20
- Spranger M, Schapera J (1988) Anomalous inheritance in a kindred with split hand, split foot malformation. *Eur J Pediatr* 147:202-205
- Palmer SE, Scherer SW, Kukolich M, Wijsman EM, Tsui L-C, Stephens K, Evans JP (1994) Evidence for locus heterogeneity in human autosomal dominant split hand/split foot malformation. *Am J Hum Genet* 50:21-26
- Zlotogora J (1994) On the inheritance of the split hand/split foot malformation. *Am J Med Genet* 53:29-32

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Reply to Zlotogora

To the Editor:

Dr. Zlotogora raises a number of interesting issues regarding the inheritance of split hand/split foot (SHSF). His study (Zlotogora 1994) represents an important systematic analysis of this confusing clinical entity. He finds that penetrance is high in families characterized by abnormalities limited to the hands and feet (type I SHSF), whereas low penetrance is observed in families with at least one individual clinically affected by other limb defects (type II SHSF). This is a useful observation, and, in addition to providing the basis for hypotheses regarding the molecular

genetics of SHSF, it may have implications for improved genetic counseling in SHSF.

Dr. Zlotogora speculates that the differences seen between type I and type II SHSF result from locus heterogeneity. Specifically, he argues that type II SHSF is likely to be caused by mutations in the locus at 7q21-q22, whereas type I SHSF is caused by mutations at another autosomal locus (which we have designated as *SHSF 2*; Palmer et al. 1994). This hypothesis is largely based on the report of a familial translocation in which there is reduced penetrance and an affected family member with tibial hypoplasia (Genuardi et al. 1993). The hypothesis could be further strengthened by also citing a report by Morey and Higgins (1990), in which a child with a deletion of 7q had SHSF of an upper extremity and absence of the lower extremities.

Unfortunately, however, the issue does not appear to be straightforward. In a recent report (Marinoni et al. 1994) a large pedigree was described in which there was significantly reduced penetrance and long-bone involvement consisting of tibial hypoplasia. In keeping with the hypothesis proposed by Dr. Zlotogora, this family represents type II SHSF, and the causative locus would be predicted to reside at 7q21-q22. However, the family is unlinked to the critical region on chromosome 7.

There may well be several autosomal genes, which, when mutated, result in SHSF. While it may be that the various genetic forms of this disorder are each caused by mutations in a different locus, it is not necessary to postulate locus heterogeneity as the entire cause of the observed variability. For example, one can certainly envision allelic heterogeneity giving rise to different phenotypes and different degrees of penetrance. Thus, in the final analysis, both locus heterogeneity and allelic heterogeneity (as well as modifying genes, stochastic events, and environmental factors) may be important in generating the complex clinical picture that characterizes SHSF.

Regarding speculation that SHSF may be secondary to expansion of a trinucleotide repeat motif, this is one of several avenues of investigation that we are following in our current efforts to isolate the SHSF genes. Only isolation of the actual genes will definitively address this possibility.

Studies such as Zlotogora's are invaluable in our attempts to reconcile molecular and clinical data. On eventual isolation of the genes that are responsible for SHSF, we should be in a position to address, in a definitive manner, the complex genetics of this intriguing human developmental disorder.

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