The IRF6 p.274V polymorphism is not a risk factor for isolated cleft lip

To the Editor:

Cleft lip (CL) with or without cleft palate (CP) is one of the most common birth defects in humans, with a prevalence of 1 in 700 worldwide.[1] The majority of clefts are thought to display a multifactorial mode of inheritance.[2] Recently, significant progress has been made with the identification of gene mutations in several forms of CL/P and CP, including the cell adhesion molecule PVRL1[3] and the transcription factors MSX1,[4,5] TBX22,[6] and IRF6,[7] respectively. Originally, mutations in the *IRF6* gene[7] have been found to be associated with Van der Woude syndrome, a rare monogenic and syndromic form of cleft lip and palate associated with lip pits. However, Zucchero and coworkers[8] recently suggested that a frequent polymorphism in the *IRF6* gene might influence the development of nonsyndromic cleft lip. The authors state that the common p.274V polymorphism in the *IRF6* gene triples the risk of recurrence of isolated cleft lips in families with one affected child.[8] Because this fact would be an important consideration in genetic counseling, we investigated this polymorphism in a healthy German population.

In general, one can safely assume that a subpopulation with a 3-fold increased risk must not exceed one third of the entire population. The authors defined the risk population as couples who might have a child homozygous for the p.274V polymorphism.[8] Accordingly, the frequency of the risk allele should not exceed 35% in order to explain a 3-fold risk, among parents with an affected child as well as in the entire population. In Asians, which were predominantly investigated, the p.274V allele frequency has been estimated to be 66%.[7,8] Congruously, 78% of Asian couples are expected to belong to the so called "risk population." Based on these data, a 3-fold risk is not allegeable.

Zucchero and coworkers[8] describe p.274V allele frequencies of 100% in 102 Europeans and 156 Africans, and of 97.5% in 200 Pakistani, respectively. We therefore investigated 193 German control individuals, all of whom displayed the p.274V variant. Of these, 192 subjects were homozygous, and one subject was heterozygous for the p.274V variant (allele frequency 97.7%). These results indicate that nearly all individuals of Caucasian, African, and Pakistani descent are carriers of the "risk allele." We therefore argue that p.274V is not suitable for specifying the risk of recurrence of isolated cleft lip. Thus the p.274V polymorphism is irrelevant for genetic counseling.

Robert Hering, MD
Kathrin Grundmann, MD
Institute of Human Genetics
University of Tübingen
Tübingen, Germany

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