found only in lower Central America. We agree with Torroni et al. (1994) that it most likely arose in the ancestral proto-Chibchan population from which modern Chibchan speakers derived and that it will be useful for Amerindian taxonomic research.

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Case-Parental Control Method in the Search for Disease-Susceptibility Genes

To the Editor:

In the past year, two articles have been published in the *Journal* on the use of nuclear families in the analysis of associations for candidate genes for common diseases (Knapp et al. 1993; Schaid and Sommer 1993). I would like to emphasize the importance and the promise of this approach in the search for disease-susceptibility genes and to point out two simple epidemiologic properties.

Historically, the search for disease-susceptibility genes has taken on two approaches, the linkage approach, traditionally the domain of the geneticist, and the association approach, traditionally the domain of the epidemiologist (Morton 1984). The problem with association studies has been the choice of an appropriate control group with which cases can be compared with respect to the allelic distribution. The choice of appropriate controls has been extensively discussed in the epidemiology literature (Wacholder et al. 1992). To deal with confounding due to population stratification, sibling controls have been used as one group to adjust for genetic background. In the approach discussed by Knapp et al. (1993) and Schaid and Sommer (1993), the control group is a "fictitious" group formed by the parental alleles (at the locus of interest) that have not been transmitted to the proband. Cases and controls can then be compared with respect to the distribution of marker alleles at this locus, and measures of relative risk (haplotype or genotype relative risks) can be derived.

One epidemiologic property of this approach is the one-to-one matching of this case-control study. Because each case is matched to a "parental" control, the appropriate method for analyzing and interpreting the findings will be a matched analysis. For example, if we are interested in testing whether a particular allele at a specified locus is associated with increased disease risk, then we would obtain genotypic information on all cases and their parents and derive the genotypic distribution of the nontransmitted parental alleles (i.e., control group), as shown in table 1. The grand total for this table is the total number of cases in the study (identical to the number of case-control pairs). The ratios of discordant pairs provide estimates of relative risk (odds ratio). The two odds ratios obtained estimate the relative risk of disease for carriers of one allele and two alleles, respectively, compared with individuals who carry none. In the case of a dominant susceptibility trait, both relative risks will be elevated (>1), while, in the case of a recessive susceptibility trait, only the second relative risk will be elevated. As with all matched analyses, there are standard methods (e.g., the McNemar test) to evaluate the statistical significance and variances of these relative-risk estimates (Rothman 1986, pp. 237–283; Kahn and Sempos 1989, pp. 85–136).

Another epidemiologic property of this approach is that it allows for testing for genotype-environment interaction in a simple way by stratifying the data according to the presence or absence of specific measured environmental exposures that are suspected to interact with the genotype of interest. For example, several studies have suggested that a genetic variant at the transforming growth-factor alpha locus (TGFA) is associated with increased risk of cleft lip and palate (Ardinger et al. 1989; Shiang et al.

Table 1

Case-Parental Control Analysis

	Cases		
	No Alleles	One Allele	Two Alleles
Controls:			
No alleles	*a*	*b*	*c*
One allele	*d*	*e*	*f*
Two alleles	*g*	*h*	*i*
Genotypic relative risk	1	*b/d*	*c/g*

1993). While this association is not found in all studies, it would be relatively easy to test the hypothesis by using nuclear family data and the approach discussed above. Furthermore, it has been suggested that maternal cigarette smoking during the first trimester is associated with increased risk of cleft lip and palate in the offspring (Ericson et al. 1979; Khoury et al. 1989). Again, while this finding is not observed in all studies, it would be relatively easy to evaluate whether there is biologic interaction between smoking and the TGFA allele in conferring risk of oral clefts. By stratifying the data into at least two tables as above (one for smokers and one for nonsmokers—or by level of smoking), one can evaluate whether genotype relative risks associated with the TGFA alleles are similar across strata of maternal smoking. For example, if TGFA alleles are associated with increased risk of clefting among smokers (genotypic odds ratios >1) but not among nonsmokers, then one can infer that there is a biologic interaction between maternal smoking and TGFA, in predicting the risk of oral clefts in the offspring. Statistical testing for interaction can be done by using standard epidemiologic methods (Rothman 1986, pp. 237–283; Kahn and Sempos 1989, pp. 85–136).

In summary, the use of parental controls can provide a valuable method to search for disease-susceptibility genes for common diseases and to look for evidence of genotype-environment interaction. It is hoped that this methodology will be increasingly used in genetic-epidemiologic studies of disease.

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