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Reply to Burn and Chapman

To the Editor:

Burn and Chapman (1994) criticize our report (Stella et al. 1993), in which we exclude the adenomatous polyposis coli (APC) gene as the cause of a variant form of familial adenomatous polyposis (FAP). They assert that the surgical and diagnostic criterion for FAP is the presence of >100 polyps in the colon or, when this is not fulfilled, the presence of extracolonic features such as congenital hypertrophy of the retinal pigment epithelium. In both the families described in our paper at least one patient (one in one family and three in the other) presents >100 polyps, fulfilling one of the criteria mentioned by Burn and Chapman. Several observations make it difficult to distinguish clearly among classical polyposis, Gardner syndrome, and the attenuated form of polyposis: (1) the existence of FAP families showing a low and variable number of polyps, without extracolonic manifestations, as the only detectable symptom (Leppert et al. 1992; Spirio et al. 1992); (2) the linkage between the variant form of adenomatous polyposis segregating in these families and the APC locus (Spirio et al. 1993); and (3) the restriction of ocular fundus lesions to a specific subgroup of APC mutations in APC patients (Olschwang et al. 1993).

In our opinion the real question is, what criteria define an FAP family: the presence of APC gene mutations no matter how many polyps or extracolonic manifestations are present, or the presence of a well-defined group of clinical signs or symptoms no matter which gene is mutated? Our findings suggest that mutations in genes other than APC might cause a phenotype quite similar to FAP; consequently it may be important to consider such an eventuality whenever a family whose members show a variable number of polyps is referred for genetic counseling.

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D-Loop mtDNA Deletion as a Unique Marker of Chibchan Amerindians

To the Editor:

Torroni et al. (1993) presented an extensive restriction-site analysis of Native American mtDNAs from 17 widely distributed Na-Dene and Amerindian tribes. For sometime we have been analyzing mtDNA control region sequences of several Chibcha-speaking Amerindian tribes from Costa Rica and Panama. Some Huetar individuals from central Costa Rica (not included in Torroni et al.'s tribes) present a 6-bp deletion encompassing nucleotides 106–111 (not reported before), subsequently denominated "Huetar deletion" (Santos 1992, Santos et al., in press). This marker has been found in different frequencies in several Chibchan groups (Bribri, Cabecar, Guaymi, and Kuna), but not in another located in the northern region of lower Central America (Miskito). According to our sequence data, the Huetar deletion carriers have lost restriction site *Msp*I 104, as well as *Bsi*HKAI (BioLabs) or its isoschizomers (Santos and Barrantes 1994). Therefore the *−104i* mutation in haplotypes 51–53 from Chibchan groups (Torroni et al. 1993) corresponds exactly to the Huetar deletion.

This may represent a regional polymorphism, since it was previously shown to be absent from other non-Amerindian populations (Vigilant et al. 1989), and it is currently

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*