References

Elston RC (1973) Ascertainment and age of onset in pedigree analysis. Hum Hered 23:105–112

——— (1981) Segregation analysis. In: Harris H, Hirschhorn K (eds) Advances in human genetics, vol 11. Plenum, New York, pp 63–120

Hall JM, Friedman L, Guenther C, Lee MK, Weber JL, Black DM, King M-C (1992) Closing in on a breast cancer gene on chromosome 17q. Am J Hum Genet 50:1235–1242

Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King M-C (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250:1684–1689

Margaritte P, Bonaiti-Pellie C, King M-C, Clerget-Darpoux F (1992) Linkage of familial breast cancer to chromosome 17q21 may not be restricted to early-onset disease. Am J Hum Genet 50:1231–1234

Mérette C, King M-C, Ott J (1992) Heterogeneity analysis of breast cancer families by using age at onset as a covariate. Am J Hum Genet 50:515–519

Newman B, Austin MA, Lee M, King M-C (1988) Inheritance of human breast cancer: evidence for autosomal dominant transmission in high risk families. Proc Natl Acad Sci USA 85:3044–3048

Ott J (1991) Analysis of human genetic linkage, 2d ed. Johns Hopkins University Press, Baltimore

0002-9297/93/5203-0020$02.00

Am. J. Hum. Genet. 52:629–630, 1993

Reply to Ott and Mérette

To the Editor:

In their letter, Ott and Mérette propose an explanation for the discrepancies between their results (Mérette et al. 1992) and ours (Margaritte et al. 1992), with regard to the analysis of cancer family data reported by Hall et al. (1990). The reason invoked is our study's "failure of allowing for incomplete penetrance in genetic and nongenetic cases." It is certainly not the correct reason, since, in fact, in our analysis, the lifetime penetrances were set to .82 for the gene carriers and .081 for the noncarriers. These values are the same as those used by Mérette et al. (1992) and correspond to the estimations by Newman et al. (1988). Besides, our formulas $R(x)$ and $R'(x)$ do not require any assumption about the lifetime penetrance values, since they were established by using directly the incidence functions obtained from Newman et al. (1988). On the contrary, Mérette et al. modeled the incidence through a normal density function, which consequently has to be multiplied by the lifetime penetrance.

In our view, the discrepancy is probably due to the two studies' different assumptions about the age-at-onset distributions. Mérette et al. not only assumed normal distributions for inherited and sporadic cases but also fixed a mean age at onset $\mu_{dd} = 55.5$ years in sporadic cases, whereas we just used the step functions provided by Newman et al. (1988). The conclusion of a linkage homogeneity test is valid only on the condition that the assumptions are valid. In particular, the conclusion that there are two age-at-onset distributions among inherited cases in Mérette et al. (1992), as well as the results of table 1 in the letter by Ott and Mérette, depends on the correctness of the μ_{dd} value. Note that Mérette et al. (1992) estimated this value on the basis of data (Mettlin et al. 1990) other than those that Newman et al. (1988) used for estimating the lifetime penetrances. This value (55.5 years) is surprisingly low, compared with values published in the literature (68.99 in Claus et al. 1991). Furthermore, under their assumption of normality, this value implies that half the sporadic cases would have an age at onset that is more than 55.5 years. This is not compatible with the step functions of Newman et al. (1988), which predict that two-thirds of sporadic cases would have an age at onset that is more than 55 years.

The second point raised by Ott and Mérette is that "a difference in age at onset between linked and unlinked families is not strictly addressed" in our analysis. Is it not obvious that such a question did not have to be addressed, since our homogeneity tests did not indicate that families with late onset were unlinked but that they could be explained by the presence of sporadic cases? Of course, we do not exclude the existence of two (or more) age-at-onset distributions among inherited cases. However, at the present time there is no convincing argument for this. In particular, the data presented at the last meeting of The American Society of Human Genetics (Skolnick et al. 1992) do not favor the existence of such a heterogeneity.

FRANÇOISE CLERGET-DARPOUX,
PATRICIA MARGARITTE,
AND CATHERINE BONAÏTI-PELLIÉ
INSERM Unité 155
Château de Longchamp, Bois de Boulogne
Paris

References

Claus EB, Risch N, Thompson WD (1991) Genetic analysis of breast cancer in the Cancer and Steroid Hormone Study. Am J Hum Genet 48:232–242

Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250:1684–1689

Margaritte P, Bonaïti-Pellié C, King M-C, Clerget-Darpoux F (1992) Linkage of familial breast cancer to chromosome 17q21 may not be restricted to early-onset disease. Am J Hum Genet 50:1231–1234

Mérette C, King M-C, Ott J (1992) Heterogeneity analysis of breast cancer families by using age at onset as a covariate. Am J Hum Genet 50:515–519

Mettlin C, Croghan I, Nataragan N, Lane W (1990) The association of age and familial risk in case-control study of breast cancer. Am J Epidemiol 131:973–983

Newman B, Austin MA, Lee MK, King MC (1988) Inheritance of human breast cancer: evidence for autosomal dominant transmission in high risk families. Proc Natl Acad Sci USA 85:3044–3048

Skolnick MH, Goldgar DE, Albright LA, Lewis CM, Fields P, Linker G, Tran T (1992) Phenotypic effects of the BRCA1 locus in 8 linked kindreds. Am J Hum Genet Suppl 51:A38

0002-9297/93/5203-0021$02.00

Am. J. Hum. Genet. 52:630, 1993

When Single-stranded Conformations Are Polymorphic

To the Editor:

The technique of single-stranded conformation polymorphism (SSCP) analysis originally published by Orita et al. (1989) has been an important addition to the repertoire of techniques for molecular genetics. Perhaps the most extensive applications of the SSCP technique have been for identification of mutations; however, the technique continues to be of value in the identification of familial variants for segregation analysis and prenatal diagnosis. It is unfortunate that the majority of those who have employed this technique for the detection of rare variants or mutations continue to refer to it as "single stranded conformation *polymorphism,*" instead of as the more genetically correct "single-stranded conformation *analysis.*" The term "polymorphism" is one that can be found in a dictionary of genetic terms. There is a defined frequency at which the transition in terminology from "rare variant" to "polymorphism" takes place. This is when the gene frequency becomes .01 or greater and, hence, without a population survey being undertaken, the variants seen by the single-stranded conformation analysis must be considered just that, a variant. Therefore, when this technique is used to find mutations or to identify familial variants for segregation studies, it should be referred to as "single-stranded conformation analysis," or, simply, "SSCA." The term "SSCP" should be reserved for those instances where the allele frequency is known to reach .01 and, hence, becomes a true polymorphism.

DAVID I. HOAR

Immunology Laboratory
Vancouver General Hospital
Vancouver

Reference

Orita M, Iwahana H, Kanazawa H, Hayashi K, Sekiya T (1989) Detection of polymorphisms of human DNA by gel electrophoresis as single-stranded conformation polymorphisms. Proc Natl Acad Sci USA 86:2766–2770

0002-9297/93/5203-0022$02.00

Am. J. Hum. Genet. 52:630–631, 1993

Further Considerations of Caucasian Admixture

To the Editor:

I appreciate the additional information given in the reply of Chakraborty et al. (1992*a*) to my letter (Reed 1992). However, I must make several comments for clarification and correction:

1. The standard error of my admixture estimate μ *does* consider sampling errors of allele frequencies. Either the formula quoted or the simultaneous estimation of μ and Fy^a frequency by maximum likelihood gives the same estimate for μ: 22.0 ± 0.9%.

2. The Rh and Duffy loci were said (Reed 1992) to show no overt evidence for selection on allele frequencies because several large-scale studies, on American Caucasians and blacks by Reed (1967, 1968*a*, 1968*b*)