Am. J. Hum. Genet. 64:896–897, 1999

Reply to Leder and Hodge

To the Editor:

On the basis of human leukocyte antigen (HLA) association studies, workers in the field of psoriasis have long been aware that the HLA complex plays an important role in determining psoriasis susceptibility. The question has always been why many families appear not to show linkage to HLA. We share in the pleasure of Drs. Leder and Hodge (1999 [in this issue]) now that the genetics of the HLA region in psoriasis is coming into sharper focus.

The general agreement between Leder and Hodge's studies (Leder et al. 1998), our own work (Jenisch et al. 1998 and in press), and the recent studies of Trembath et al. (1997) and Burden et al. (1998) provides welcome insight into this long-standing puzzle. By optimizing LOD scores over a variety of penetrance functions, assuming Hardy-Weinberg equilibrium, Leder and Hodge (Leder et al. 1998) found the highest LOD scores for dominant models specifying high disease allele frequency and low penetrance. We reached essentially the same conclusion, following the suggestions of Risch et al. (1989) for complex-trait data. It is well appreciated that power to detect linkage is diminished when the disease allele frequency is high and the penetrance is low. Given the smaller sample sizes of earlier studies, it is not surprising that linkage to the HLA region was not always apparent.

We have reported that linkage to HLA is more readily detected when marker-trait disequilibrium is taken into account, in part because of more-accurate specification of phase (Jenisch et al. 1998). Leder et al. (1998) and Trembath et al. (1997) report similar results. This effect was first pointed out 15 years ago (Clerget-Darpoux 1982) but has not been widely exploited in the genetic analysis of other common HLA-associated disorders. Even without incorporation of disease-marker haplotype frequencies, Leder et al. (1998) found strong evidence for linkage to HLA under a dominant model, whereas we did not. Leder et al.'s study made use of previously published pedigrees, and concerns regarding ascertainment bias in favor of linkage are inevitable in such a study. However, it is also possible that our sample yielded lower LOD scores because it contained a number of small pedigrees, thereby increasing the number of phase-unknown individuals.

We concur with Leder and Hodge (1999) that there is now excellent agreement regarding the importance of the HLA region in familial psoriasis and that this locus should now be referred to as PSORS1. We would emphasize that, because the HLA loci yielding the highest LOD scores in familial psoriasis are so similar to those observed in prior case-control association studies, there is unlikely to be any difference between familial and "sporadic" juvenile-onset psoriasis with respect to the involvement of PSORS1. We can also infer that genetic differences between juvenile- and adult-onset psoriasis must exist, because of their different HLA associations (Henseler and Christophers 1985). Whether an HLA locus different from PSORS1 is involved in the adult-onset form of this disease remains to be determined.

High disease allele frequencies and low penetrance values are likely to be the rule rather than the exception in common multifactorial diseases. We hope that these recent insights into the genetics of the HLA region in psoriasis will be of benefit to other groups studying complex genetic disorders.

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Protein-Truncation Mutations in the *RP2* Gene in a North American Cohort of Families with X-Linked Retinitis Pigmentosa

To the Editor:
X-linked forms of retinitis pigmentosa (XLRP) are a genetically heterogeneous group of retinal dystrophies that result in relatively severe clinical manifestations (Bird 1975; for a review, see Aldred et al. 1994). The two major XLRP loci, *RP2* (MIM 312600) and *RP3* (MIM 312610), have been mapped to Xp11.32-11.23 and Xp21.1, respectively (for a review see Aldred et al. 1994; Fujita et al. 1996; Fujita and Swaroop 1996; Thiselton et al. 1996). The *RP15* locus (MIM 300029) has been mapped to Xp22.13-22.11 in a single family with retinal degeneration (McGuire et al. 1995), and some evidence exists for a fourth locus, *RP6* (MIM 312612), at Xp21.3 (Musarella et al. 1990; Ott et al. 1990). We recently localized another genetic locus, *RP24* (MIM 300155), at Xq26-27 by using linkage analysis in an XLRP family (Gieser et al. 1998). In addition, the disease in some retinitis pigmentosa (RP) families with apparently X-linked inheritance does not seem to be linked to markers in the region of mapped XLRP loci (Teague et al. 1994; L. Gieser, R. Fujita, and A. Swaroop, unpublished data). It therefore appears that mutations in several genes on the X chromosome may lead to RP.

The first XLRP gene, *RPGR* (retinitis pigmentosa GTPase regulator), was isolated from the *RP3* region (Meindl et al. 1996; Roepman et al. 1996). Genetic analysis has suggested that *RP3* accounts for 70% of XLRP (Ott et al. 1990; Teague et al. 1994; Fujita et al. 1997). However, *RPGR* mutations are detected in only 20% of XLRP (and genetically defined *RP3*) families (Buraczynska et al. 1997; Fujita et al. 1997; M. Guevara-Fujita, S. Fahrner, and A. Swaroop, unpublished data). The *RP2* gene has recently been isolated by a positional cloning strategy (Schwahn et al. 1998) and is predicted to encode a protein of 350 amino acids with homology to cofactor C, which is involved in folding of β-tubulin (Tian et al.

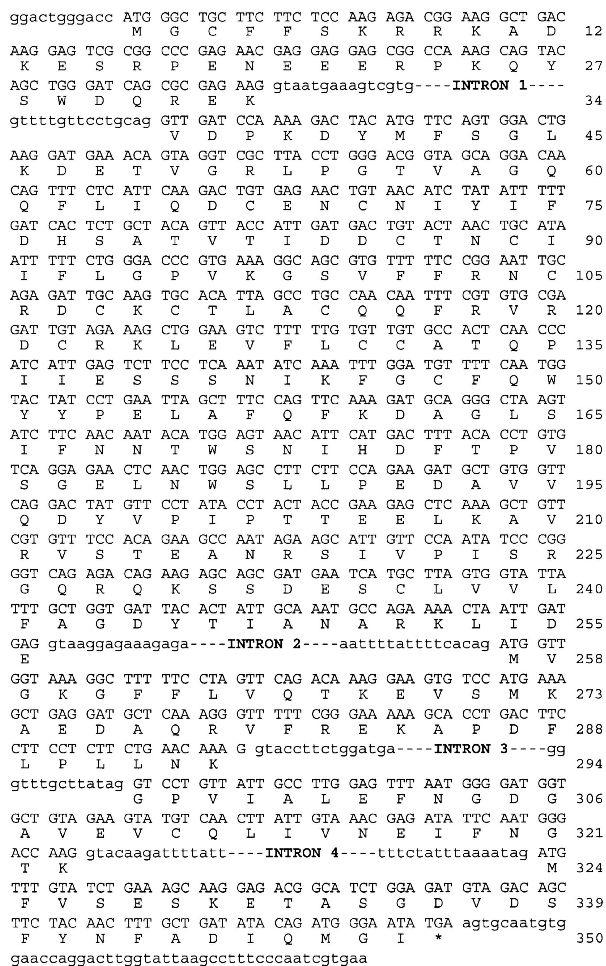

Figure 1 Composite nucleotide sequence showing *RP2* exons, including the coding region, and the exon-intron boundaries. The numbers on the right refer to the amino acid residues of the predicted RP2 protein.

1996). The *RP2* locus is believed to represent 20%–30% of XLRP in Europe (Ott et al. 1990; Teague et al. 1994), but little or no genetic evidence exists for an *RP2* subtype in the XLRP families from North America (Musarella et al. 1990; Ott et al. 1990). Because our haplotype analysis provided suggestive evidence for *RP2* in two North American families (R. Fujita, L. Gieser, S. G. Jacobson, P. A. Sieving, and A. Swaroop, unpublished data), we examined the genomic DNA from our cohort of XLRP patients for causative mutations in the *RP2* gene.

The procedures for clinical ascertainment of patients, obtaining blood samples, and preparation of genomic DNA have been reported elsewhere (Fujita et al. 1997). The families included in the present study showed an apparent X-linked inheritance and no male-to-male transmission. Affected male individuals had a clinical