on CF Genetics 1990) has shown a southeast-to-northwest gradient in the frequency of this mutation. On the basis of these results, a single origin and a subsequent diffusion of the mutation, consistent with the migrations of early farmers from the Middle East, slowly progressed toward the northwest of Europe has been suggested (Ammerman and Cavalli-Sforza 1984).

We have tested 92 unrelated CF chromosomes from different regions of Albania (Tirane, Shkodra, Vlora, Fier, Korça, Durres, Elbasan, Lushnja, and Gjirokastra) by using allelic-specific PCR according to the protocol of Ballabio et al. (1990) and have found a ΔF508 frequency of 75% (69/92) ± 4.5%. This figure is the highest observed in southern Europe and compares well with the frequency detected in northern European populations. Our data do not seem to be consistent with the proposed southeast-to-northeast gradient.

A reverse gradient (north to south) has been suggested by Baranov et al. (1991). Thus, the Albanian data rather suggest the existence of multiple components of the gene which are spreading in Europe (Menozzi et al. 1978; Piazza et al. 1981). The Illyurian origin of the Albanians and the nomadic migration during the third millennium B.C. (Zvelebil 1980), together with the historical and cultural isolation of this ethnic group (Buda 1985), could explain the high frequency of the ΔF508 mutation in this country. On the basis of the present data, carrier screening in the general Albanian population would lead to the detection of approximately 60% of the couples at risk, for whom prenatal diagnosis can be performed by direct mutation analysis.

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Recurrent 3-bp Deletion at Codon 255/256 of the Rhodopsin Gene in a German Pedigree with Autosomal Dominant Retinitis Pigmentosa

To the Editor:

Recently a 3-bp deletion at codon 255/256 of the rhodopsin gene has been reported in the Journal (Inglehearn et al. 1991) and has been suggested to be the primary cause of autosomal dominant retinitis pigmentosa (RP) in a large British kindred. In an attempt to identify mutations in the rhodopsin gene in 120 patients from western Europe who have autosomal dominant RP, we are presently screening PCR-amplified products of the five exons by heteroduplex analysis essentially as described by Keen et al. (1991).

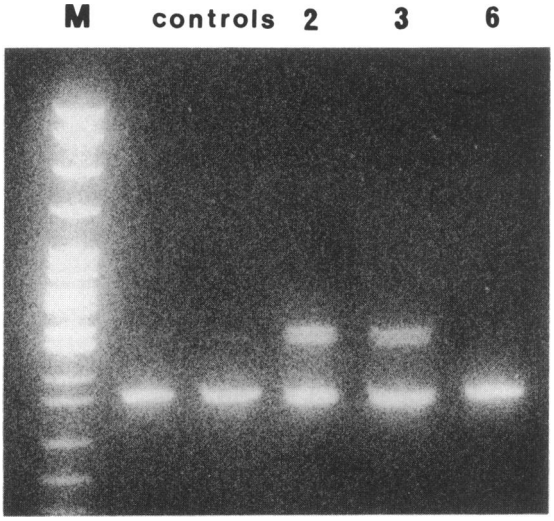

Figure 1 Analysis of patients with autosomal dominant RP. Patients are from a British family (lane 1) and from a German kindred including son (lane 2), mother (lane 3), daughter (lane 4), and granddaughter (lane 5), all of them affected, and mother's nonaffected sister (lane 6). M = marker DNA pBR322 cut by *Msp*I. Heteroduplex formation of PCR-amplified products from exon 4 of the human rhodopsin gene indicates mutations in subjects 2 and 3.

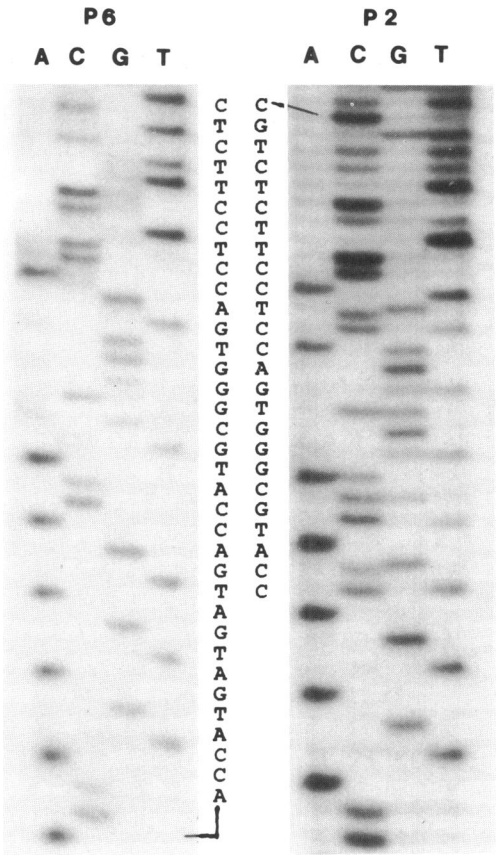

Figure 2 DNA sequence of exon 4, indicating 3-bp deletion at codon 255/256. Labeling of samples is as in fig. 1.

An additional band of slower mobility was detected by the analysis of exon 4 in one patient and, subsequently, in three other members of his family who are affected by autosomal dominant RP. This band was not seen in an unaffected relative (fig. 1). The presence of a mutation was confirmed by direct sequencing of double-stranded PCR products and was found to be a 3-bp deletion at codon 255/256 identical to that described by Inglehearn et al. (1991; also see fig. 2).

Several different point mutations and two in-frame deletions in families with autosomal dominant RP have been published in detail so far (Naylor and Carritt, in press). The prevalence of individual rhodopsin mutations is variable. Thr-58-Arg and Pro-347-Ser, for example, are reported only once, whereas Pro-23-His and Pro-347-Leu are found in 12% and 6%, respectively, of U.S. patients with autosomal dominant RP (Dryja et al. 1990). It has been suggested by those studying DNA polymorphisms of the rhodopsin gene that all families carrying the Pro-23-His mutation are descended from one common ancestor. In order to determine whether the German family is related to the British family described by Inglehearn et al. (1991), we analyzed a polymorphic CA-repeat located in intron 1 of the rhodopsin gene (Weber and May 1989). Clearly, all affected members of the German family share only one allele, which is, however, different from that of the British patient (Fig. 3), indicating that the mutation is most probably a recurrent event.

From a clinical perspective, intrafamilial variability in the German family appears to be low. All affected family members complain of night blindness from

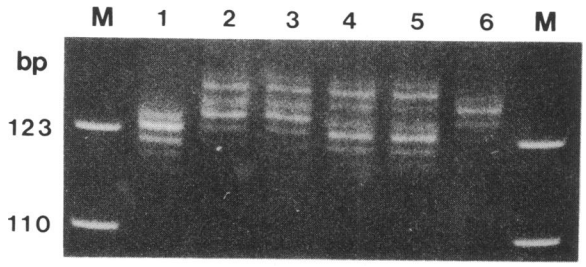

Figure 3 Polymorphic CA-repeat from intron 1 of human rhodopsin gene. Labeling of samples is as in fig. 1.

early childhood on. Although visual acuity was reduced to 14/20 in one patient at the age of 5 years, visual difficulties by day were usually not experienced during the first 2 decades. Visual fields are significantly reduced by the age of 30 years. Electroretinography shows reduced (ages 5, 32, and 41 years) to extinguished (age 71 years) scotopic responses. Peripheral retinal changes with regional patchy depigmentation can be detected at a very young age (3 years). Pigment migration into the neural retina is comparatively sparse even during the eighth decade, with well-preserved macular structures. The clinical changes appear similar to those described in the British kindred (Inglehearn et al. 1991) and are consistent with class I or diffuse autosomal dominant RP.

The mutation at codon 255/256 described here occurred at a site of three TCA repeats. One can speculate on different mechanisms leading to this 3-bp deletion, such as unequal crossing-over or replication slippage at meiosis. The latter is more likely in minisatellite sequence blocks in noncoding regions (Levinson and Gutman 1987; Wolff et al. 1988). It is conceivable that this slippage process can also predispose to mutational events in certain sequence blocks within coding regions. Indeed, certain regions of the cystic fibrosis gene have been shown to be particularly prone to mutation (Reiss et al. 1991). Mechanisms that predispose certain sequence elements to mutations will increase the likelihood of the same mutation occurring independently in several unrelated families.

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