offer a new perspective on $(TTAGGG)_n$ maximum length and on the relative stability of this telomeric hexamer, both in vitro and in vivo.

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A retGC-1 Mutation in Autosomal Dominant Cone-Rod Dystrophy

To the Editor:

Choroidoretinal dystrophies represent a clinically and genetically heterogeneous group of disorders that in-

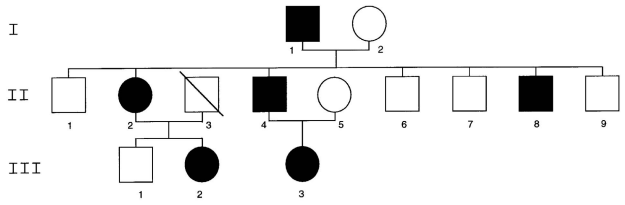

Figure 1 Pedigree of family segregating autosomal dominant cone-rod dystrophy (CORD6).

cludes retinitis pigmentosa (RP). On the other hand, cone-rod dystrophies (CRDs) long have been regarded as inverse RP and are characterized clinically by an initial cone dysfunction followed by a progressive peripheral disease (Rabb et al. 1986; Heckenlively 1987). The main symptoms at onset of the disease are a decrease of visual acuity, with loss of color discrimination and photophobia. As the disease progresses, nyctalopia, progressive peripheral visual field deficit, and decreasing scotopic electroretinogram (ERG) amplitudes are observed (Moore 1995). Autosomal dominant, autosomal recessive, and X-linked recessive patterns of inheritance have been observed (Bird 1995), and five CRD loci have been mapped: CORD1 to 18q21.1 (Warburg et al. 1991), CORD2 to 19q13 (Evans et al. 1994), CORD3 to Xp22.13-p22.11 (McGuire et al. 1995), the peripherin/retinal degeneration slow (RDS) gene to 6p21.2-cen (Travis et al. 1991), and CORD6 to 17p12-p13 (Kelsell et al. 1997). Yet, only two disease-causing genes have been identified for CRD—namely, the peripherin/RDS gene (Nakazawa et al. 1994, 1996; Kohl et al. 1997) and the photoreceptor-specific homeobox gene, CRX, corresponding to CORD2 (Freund et al. 1997).

Since CORD6 maps to the genetic interval encompassing the retinal-specific guanylate cyclase gene (retGC-1) and especially since retGC-1 mutations have been reported elsewhere for Leber congenital amaurosis (LCA1) (Perrault et al. 1996), we screened retGC-1 for mutations in a large CRD pedigree consistent with linkage to CORD6. In addition, very recently a large deletion of the GC1 gene, the avian orthologue of retGC-1, had been reported in the rd/rd chicken affected with a congenital retinal degeneration similar to LCA (Semple-Rowland et al. 1997).

All affected individuals displayed an early cone dysfunction characterized by decreased vision acuity, with severe color dyschromatopsia and photophobia, during the 1st decade of life. At this stage, ophthalmoscopical examinations were not specific. By contrast, electrophysiological testing revealed marked loss of photopic function, with scotopic function relatively well preserved, and the visual field showed a consistent central scotoma. During the 2d and 3d decades, visual acuity decreased dramatically, and the color-vision defect was confined to achromatopsia, hampering normal schooling and professional insertion. After 40 years, peripheral visual field loss and progressive night blindness were observed, and the ERG became unrecordable (individual I-1; fig. 1).

For PCR-based genotypic analyses, genomic DNA

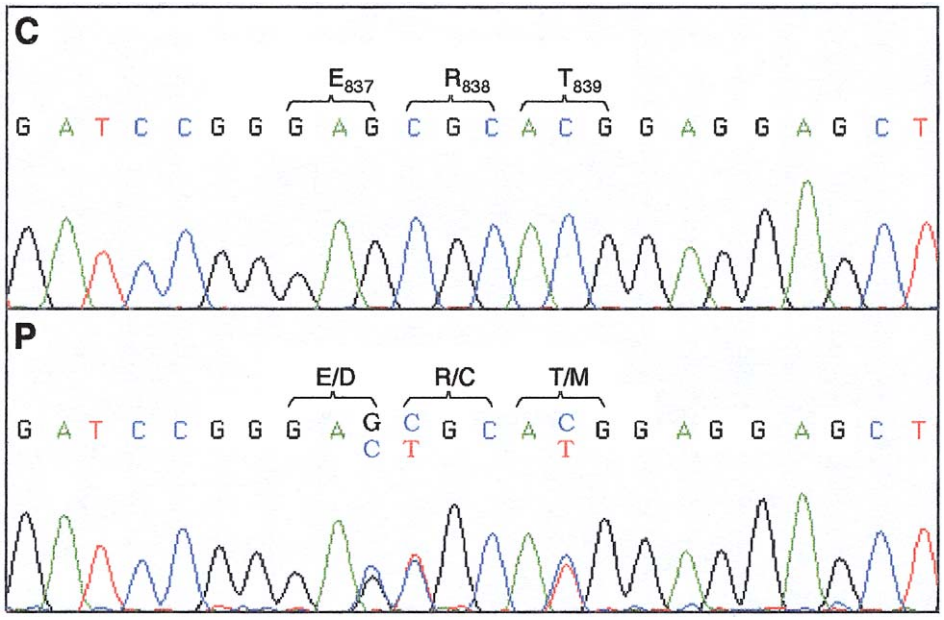

Figure 2 Identification of a heterozygote mutant genotype of the retGC-1 gene in CORD6. *C*, Control. *P*, Patient.

(200 ng) was tested as described elsewhere (Perrault et al. 1998), and linkage analyses were performed by use of the MLINK and LINKMAP options of the LINKAGE program, version 5.1 (Lathrop et al. 1985). For mutation screening of the 18 coding exons of the retGC-1 gene, genomic DNA (200 ng) was PCR amplified by use of 1 μM of the intronic primers, as described elsewhere (Perrault et al. 1996). Amplification products were loaded onto a 1% agarose low–melting-temperature gel, were purified by phenol-chloroform extraction, and were recovered by ethanol precipitation. Purified fragments were sequenced directly, by use of primers specific for the cDNA sequence and the Big Dye Terminator Cycle Sequencing kit (Perkin Elmer), on an automatic fluorometric DNA sequencer (Applied Biosystems).

Positive LOD-score values were obtained with polymorphic markers flanking retGC-1 at loci D17S1796 and D17S1881 (maximum LOD score of 2.71 at recombination fraction 0, for both markers). The coding sequence of the retGC-1 gene was screened for point mutations or minute changes, by direct-sequencing analysis of genomic DNA. The proband was heterozygous for a complex mutational event including three consecutive missense mutations in exon 13: (1) a G→C transversion at nucleotide 2584, changing a glutamate to an aspartate at codon 837 (E837D); (2) a C→T transition at nucleotide 2585, changing an arginine to a cysteine at codon 838 (R838C); and (3) a C→T transition at nucleotide 2589, changing a threonine to a methionine at codon 839 (T839M) (see fig. 2). This mutational event was found in all affected individuals and was absent in all healthy members of the family. No base change was found in the remaining exons.

retGC-1 mutations previously had been shown to account for LCA1. Interestingly, none of the 17 retGC-1 mutations identified in 20 unrelated LCA1 families involved the putative dimerization domain encoded by exons 11–13 (Laura et al. 1996). Conversely, no visual impairment was present in individuals heterozygous for the LCA1 mutations. We speculate that mutations at these codons led to the production of a mutant cyclase that interfered with normal protein dimerization, thereby limiting the production of cGMP in the retina, via a dominant negative effect of the mutant protein on the wild-type gene product.

In conclusion, it appears that the same gene—namely, retGC-1—can result in either an autosomal dominant cone-rod dystrophy or an autosomal recessive retinal degeneration (Leber disease), depending on the location of the mutation in the gene. The wide clinical spectrum of retGC-1 mutations gives additional support to the relevance of visual-transduction–cascade genes in a variety of retinal diseases.

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Mapping Genes by Drift-Generated Linkage Disequilibrium

To the Editor:

In human populations that have remained of small and constant size, high levels of linkage disequilibrium (LD) are generated by genetic drift (Slatkin 1994; Laan and Pääbo 1997). Theoretical considerations suggest that such LD can be used to identify chromosomal regions involved in diseases or other traits, by "drift mapping" (Terwilliger et al. 1998). This concept relies on the assumption that when "cases" and "controls" are compared within a population in which extensive LD exists, disequilibrium will be observed between the trait and marker loci close to the gene(s) that contributes to the trait. Furthermore, genetic differentiation between the cases and controls will be observed in genomic regions contributing to the trait, whereas no differentiation will be seen in other parts of the genome. Computer simulations indicate that, under reasonable assumptions with regard to population size, population age, and marker heterozygosity (Terwilliger et al. 1998), it might be possible to map genes by use of this approach.

To empirically evaluate this idea, we have studied polymorphic loci in and around the gene that encodes the renin-binding protein (RnBP), a component of the renin-angiotensin system involved in the regulation of blood pressure. The RnBP gene is located on Xq28 and contains a point mutation, T61C, that occurs with a frequency of .18 in Germans (Knöll et al. 1997). We scored this polymorphism in males from the Saami and the Finns, two populations that differ radically in their demographic history. Whereas the Saami have not expanded during historical times and show no indication of expansion in tests based on DNA sequence variability (von Haeseler et al. 1996), the Finns are thought to have expanded drastically during the past few thousand years, on the basis of both epidemiological (Peltonen et al. 1995) and genetic evidence (Sajantila et al. 1996). The frequencies of the C allele were found to be .21 and .19 in the Saami and the Finns, respectively. The fact that the C allele occurs at appreciable frequencies in three European populations indicates that it is older than these populations. It is therefore a useful model of alleles involved in complex traits, since such alleles are expected to be both frequent in the population and of old age.

Four microsatellites located ~1.0–7.8 cM from the RnBP gene (fig. 1), as well as the T61C polymorphism, were typed in 53 Saami and 80 Finns. In addition, 10 microsatellite loci on Xp22 and Xq13, which had numbers of alleles comparable to the numbers of those around the RnBP gene, were typed in the same individuals (Laan and Pääbo 1997; authors' unpublished data), to assess the extent to which loci situated far from the RnBP gene might yield spurious associations with the T61C polymorphism. When the RnBP polymorphism and the microsatellite loci were analyzed for allelic as-

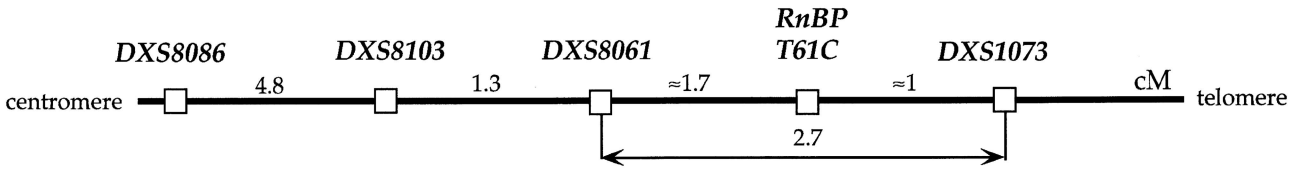

Figure 1 Genetic map (Nelson et al. 1995; Dib et al. 1996; Esposito et al. 1997; Nagaraja et al. 1997) of studied microsatellite loci around the RnBP gene.