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Multiple Independent Origins of the COII/tRNA^{Lys} Intergenic 9-bp mtDNA Deletion in Aboriginal Australians

To the Editor:

Most humans have a 9-bp tandem duplication in the COII/tRNA^{Lys} intergenic region of their mitochondrial genome (Cann and Wilson 1983; Wrischnik et al. 1987). A deletion of one copy occurs in some populations and has been used to infer affinities and migration patterns. We report that 4 of 290 Aboriginal Australians have this deletion, which has arisen in them independently at least twice.

The 9-bp deletion occurs at varying frequencies in some populations in Asia and Oceania (Horai and Matsunaga 1986; Hertzberg et al. 1989; Ballinger et al. 1992; Harihara et al. 1992; Passarino et al. 1993; Torroni et al. 1994; Redd et al., in press) and in most Amerindian populations (Schurr et al. 1990; Ward et al. 1991; Greenberg and Ruhlen 1992; Torroni et al. 1992; Horai et al. 1993). It occurs in Mongolia and Siberia, but not in Beringians and some other circum-Arctic populations (Shields et al. 1992, 1993). In Oceania, the deletion associates with Austronesian languages and forms a geographic cline (Hertzberg et al. 1989; Redd et al., in press). Previously, it has been reported absent in highland New Guineans and Aboriginal Australians, who speak non-Austronesian languages (Hertzberg et al. 1989; Stoneking et al. 1990; Lum et al. 1994).

Wrischnik et al. (1987) suggested that the deletion arose only once in an ancient Asian population. As subsequently developed, this model explains its distribution among Asian-derived populations around the Pacific basin by late-Pleistocene–early-Holocene movement and expansion of populations (Hertzberg et al. 1989; Stoneking and Wilson 1989; Cann 1993; Hagelberg and Clegg 1993, 1994; Lum et al. 1994; Redd et al., in press). It is presumed that modern circum-Pacific populations lacking the marker either arrived much earlier (Aboriginal Australians and highland New Guineans) or arrived later from a different source population (Beringians and Inuit).

We screened a total of 310 individuals for the deletion, comprising 290 Aboriginal Australians and 20 Cantonese (Southern Chinese) from Hong Kong, the latter representing a population in whom the deletion occurs at a moderate frequency. The Australians group by place of birth into four populations: 64 from the Kimberley region of Western Australia, 92 from the western desert of Western Australia, 85 from the "top end" (tropical north) of the Northern Territory, and 49 from the central (desert) region of the Northern Territory. Individuals with known or suspected non-Aborigi-

nal ancestry were excluded. Where genealogical information was available, we avoided screening more than one individual from a common maternal lineage.

Part of mtDNA region V (Cann and Wilson 1983) was amplified by PCR from all samples (Wrischnik et al. 1987). Length variation in the PCR product was detected by electrophoresis, staining, and UV fluorescence. In the first Aboriginal Australian found to have the fragment length polymorphism (AK27), the deletion was confirmed by cloning and sequencing the COII/ $tRNA^{Lys}$ intergenic region in both directions.

The deletion occurred in 4 of 156 Aboriginal Australians from Western Australia: two (AK27 and AK1110) from the Kimberley region and two (AW218 and AW220) from the western desert population. None of the 134 individuals screened from the Northern Territory had the deletion, but it did occur in 4 of the 20 Cantonese (HK3829, HK3850, HK3919, and HK3992).

The provenance of three of the four Aboriginal Australians with the deletion is supported by analysis of HLA class II haplotypes, determined either by hybridization with sequence-specific oligonucleotide probes (Gao and Serjeantson 1991; Gao et al. 1992) or by restriction digestion following PCR (Maeda et al. 1989; Nomura et al. 1991). In the fourth case (AK1110) there was insufficient genomic DNA to perform HLA typing. Results were as follows: DRB1*04, DQA1*0301, DQB1*0402 (AK27); DRB1*0405 and DRB1*0408, DQA1*0103 and DQA1*0301, DQB1*0402 (AW218); DRB1*1408, DQA1*0101, DQB1*0503 (AW222). These haplotypes are common among Aboriginal Australians, supporting the Aboriginal identity of AK27, AW218, and AW222.

Control region sequences from 24 individuals (all 20 Cantonese plus the 4 Aboriginal Australians with the deletion) were obtained by direct sequencing (table 1). The Kimberley individuals with the deletion (AK27 and AK1110) have similar sequences, differing at three sites. The Australian sequences are otherwise quite divergent, with AK1110 and AW222 differing at 18 sites. For comparison, we included two sequences from North American aborigines (Nuu-Cha-Nulth 27 and 28) known to have the deletion (Ward et al. 1991).

Horai et al. (1993) identified T→C transitions occurring at positions 16189, 16217, and 16519 of the reference sequence (Anderson et al. 1981) that are typical of carriers of the deletion in Asian-derived populations; 16519 is outside the region we sequenced. The four Cantonese with the deletion all had C at 16189, and two (HK3829 and HK3919) had the C at position 16217. Three of the four Australians with the deletion lack the C at positions 16189 or 16217. However, AW222 has C at position 16189; this individual's control region sequence persistently groups with the six Asia-Pacific individuals with the deletion (fig. 1). None of the eight individuals we found with the deletion shares the "Polynesian motif" comprising the C at position 16217, plus G at position 16247 and T at position 16261 (Hagelberg and Clegg 1994; Redd et al., in press).

Phylogenetic analysis was performed on the 26 mtDNA control region sequences using the Phylip 3.5c (Felsenstein 1993), and Mega 1.01 (Kumar et al. 1993) suites of programs. On neighbor-joining (NJ) analysis, the genotypes associated with the 9-bp deletion appear in three separate clades (fig. 1). These are (1) the two Kimberley genotypes (AK27 and AK1110) that group with HK5565, which is not linked to the deletion; (2) a western desert genotype (AW218) that groups with three Cantonese genotypes again not associated with the deletion (HK5633, HK5492, and HK5656); and (3), another western desert genotype (AW222) that groups with the six Asian-derived genotypes that do have the deletion (four Cantonese plus two Nuu-Cha-Nulth).

Other methods persistently gave the same three clades. These methods included an NJ tree using the gamma distance correction of Tamura and Nei (1993) and maximum parsimony analysis. A branch-and-bound search (Hendy and Penny 1982) of 1×10^6 trees from a 12-member subset representative of major branches (HK3829, HK3843, HK3850, HK3918, HK3960, HK5505, HK5565, NCN28, AK27, AK1110, AW218, and AW222) found 15 equally parsimonious solutions (56 steps), none of which united the three clades. A maximum-likelihood analysis on the same subset gave similar results. However, analysis of log-likelihood values of defined trees uniting all or any two of the clades failed to demonstrate statistical significance.

Sequences from AK27 and AK1110 group together in 1,000 bootstrap replications, applying both NJ and maximum parsimony algorithms in Phylip 3.5c to all 26 sequences. This pair never grouped in any tree with either AW218 or AW222 nor with the six Asian-derived individuals with the deletion; this indicates a common and independent origin for the deletion in this Kimberley clade. In all bootstrapped trees, the AW218 genotype never grouped with either the Kimberley clade or AW222 but associated with Cantonese genotypes that lack the deletion. This suggests a second independent origin among Aboriginal Australians.

In the Phylip bootstrap analysis, the AW222 genotype never grouped with the other three Aboriginal Australians and always grouped with the six Asian-derived genotypes with the deletion. However, the place of AW222 as an outgroup to the other six members of this group was not robust on bootstrapping, nor on maximum-likelihood analysis. MEGA 1.01 (Kumar et al. 1993) uses a bootstrap algorithm different from Phylip. Using MEGA, both the bootstrap value (gamma distance, $\gamma = 0.5$; Tamura-Nei algorithm) and the confi-

Table 1

Listing of the Variable Sites of 26 Sequences Studied, Relative to Positions 16024–16400 of the Reference Sequence (Anderson et al. 1981)

	16030	16051	16086	16092	16093	16095	16106	16108	16129	16140	16145	16148	16155	16162	16166	16172	16182	16183	16189	16192	16209	16213	16217	16223	16243	16245	16249	16256	16260	16261	16263	16264	16266	16270	16274	16278	16286	16289	16290	16291	16292	16293	16294	16295	16297	16298	16304	16311	16319	16325	16326	16327	16355	16356	16362	16368	16396	16399
Reference	C	A	T	T	T	C	G	C	G	T	G	C	A	A	A	T	A	A	T	C	T	G	T	C	T	C	T	C	C	C	T	C	C	C	G	C	C	A	C	C	C	A	C	C	T	T	T	T	G	T	A	C	C	T	T	T	T	A
AK27	.	G	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	T	C	T	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.
AK1110	T	G	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	T	C	T	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	.
AW218	.	.	C	.	.	.	.	.	A	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.
AW222	.	.	.	.	.	.	.	.	.	.	A	.	G	.	C	.	.	C	C	.	.	A	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	T	.	.	.	.	C	.	C	.	.	.	.	.	C	.	.
HK3829	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	C	C	C	.	.	.	C	.	.	.	.	.	.	T	.	.	.	.	A	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK3919	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	C	C	C	.	.	.	C	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK3850	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	C	C	.	C	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK3992	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	C	C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
NCN27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
NCN28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	C	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK3843	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	A	.	C	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.
HK3845	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	C	.	.	.	.	T	.	C	.	.	.
HK3853	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK3863	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	T	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.
HK3918	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	C	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.
HK3960	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	T	.	C	.	.	.
HK3968	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK3995	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.
HK5197	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	T	.	.	.	.	.	T
HK5303	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.
HK5492	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.
KH5505	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	C	.	.	.
HK5551	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK5565	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK5633	.	.	.	.	.	.	A	T	A	.	.	.	.	G	.	C	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
HK5656	.	.	.	.	.	.	.	.	A	.	.	.	.	G	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	C	.	.	.

NOTE.—Direct sequencing employed either single-stage PCR with primers L15996 and H16401 (Vigilant et al. 1989), or two-stage PCR using primers L15926 (Ward et al. 1991) and H629 (5′-TGTTTATGGGGTGATGTAA-3′) in the first stage and nested primers H16401 (Vigilant et al. 1989) and L15997 (Ward et al. 1991) in the second stage. At least one sequence was obtained in each orientation for all individuals with at least three sequences in total, except for AK1110 (only two obtained) in which position 16037 was ambiguous, being either A or C (not shown). HK5565 uniquely had a C inserted after position 16386 (not shown). OTUs comprise 20 Cantonese (Genbank accession numbers U37734 to U37753) from this study, four Aboriginal Australians (AK27, AK1110, AW218, and AW222: Genbank U37730 to U37733) we report as having the deletion, and also include two North American aborigines (NCN27 and NCN28: Genbank HUMMTAIAA, HUMMTAIAB) known to have the deletion (Ward et al. 1991). Other than the reference sequence, all control region genotypes in the upper part of the table (from AK27 to NCN29) are associated with a 9-bp deletion between positions 8271 and 8289 in the COII/tRNA^{Lys} intergenic region. Of these, the lower seven appear to belong in a clade widespread among Asian-derived populations.

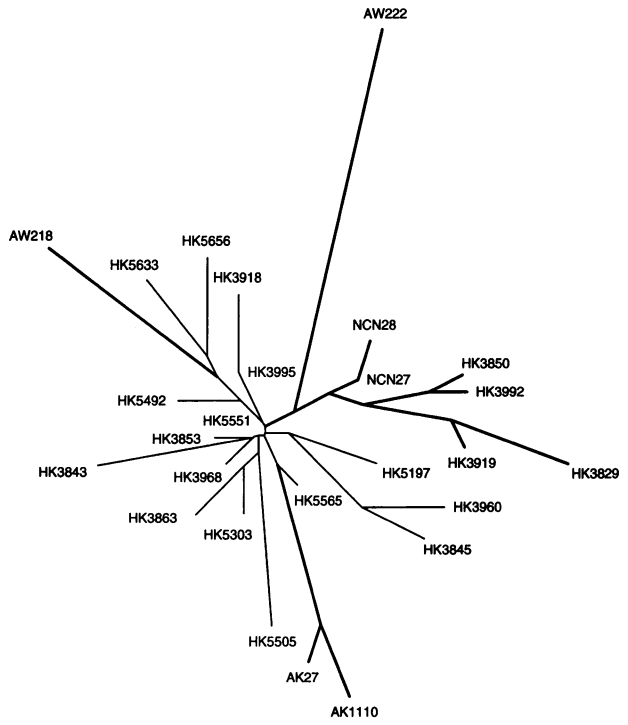

Figure 1 Unrooted NJ tree (Saitou and Nei 1987) comparing 26 mtDNA control region sequences from positions 16024 to 16400 of the reference sequence. OTUs are the same as for table 1. Branches drawn with heavy lines lead to sequences associated with the 9-bp deletion in region V. These sequences are found in three distinct clades, separated by branches leading to Asian-derived sequences *not* associated with the deletion. Distances were calculated by Kimura's two-parameter method (Kimura 1980), with transitions/transversions (t) = 15; varying t between 5 and 45 did not affect topology. The terminal branches to NCN27 and HK5551 are not significantly longer than zero; the latter sequence is at the base of an apparent trifurcation to HK3843, HK3853, and HK3968.

dence probability (Kimura two-parameter distance) for monophyly among those six sequences was 50%.

This result has several possible interpretations. If the AW222 mitochondrial genotype does form part of the major Asian-derived clade, then it may represent either an ancient divergence or a later introgression, or both. Alternatively, the few shared variable sites described above could represent homoplasy in a region with known high rates of mutation; in this case, AW222 could represent a third independent origin for the deletion. Table 1 shows that these seven sequences only share a T→C transition at position 16189 and that AW222 also shares an A→C transversion at 16183 with the four Cantonese individuals with the deletion. The reference sequence for positions 16180–16193 is AAAACCCCCTCCCC; this area is a hotspot for mutation including length variation (Horai et al. 1993), and the T→C transition at position 16189 may have occurred many times.

In summary, analysis of control region sequences from four Aboriginal Australians with the 9-bp deletion indicates that three of them represent two independent origins for the deletion. These findings are consistent with the time depth of occupancy of the continent: humans have been in Australia and New Guinea for at least 50,000 years (Roberts et al. 1990; Flood 1995), with little apparent intermarriage with later Southeast Asian or Pacific populations. The fourth Australian mtDNA genotype with the deletion could be part of a widespread Asia-Pacific clade, representing either later introgression or an early divergence from the main Asian-derived clade with the deletion.

There are other recent reports of independent deletion events in the COII/tRNA^{Lys} intergenic region (see, e.g., Ballinger et al. 1992; Passarino et al. 1993; Redd et al., in press). Three copies of the repeat also occur in some individuals, perhaps due to replication error (Shields et al. 1992; Passarino et al. 1993). It is now clear that there have been multiple deletions and insertions at this site. These findings do not remove the deletion's utility as a mitochondrial population marker. However, these results do mean that a common origin of the 9-bp mtDNA deletion in different individuals or populations must be tested, and not just assumed.

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Nomenclature for Inherited Diseases of the Retina

To the Editor:

McGuire et al., in the July 1995 issue of *American Journal of Human Genetics,* report an apparently new X-linked dominant locus for cone-rod degeneration. However, a close examination of the article leaves the reader wondering whether this is really a new locus and raises wider questions about nomenclature in the field of inherited retinal degenerations.

First, is the phenotype in this family really dominant? Males are consistently severely affected, with an age at onset of 10 years or so and with nonrecordable electroretinograms. Females, in contrast, have symptoms that range from very mild (unaware of any deficit) to a condition in one case comparable to that of the males. So far, this sounds much the same as X-linked retinitis pigmentosa (xlRP), with female carriers as mosaics affected to varying degrees according to the lottery of X-inactivation. Unless the gene in question escapes X-inactivation, the terms *dominant* and *recessive* are, one would have thought, inapplicable. The authors base their dominant classification on the observation that all females are affected to some degree and that their affectation status is on average greater than that of female carriers in other X-linked retinopathies. In making this assertion, they seem to be reviving a controversy of the 1960s. At that time, the consensus that emerged was that it was common for female carriers in all xlRP pedigrees to exhibit some symptoms on close examination and that high levels of intrafamilial variation in severity were common in heterozygotes. It was therefore concluded that there was no justification for categorizing xlRP into dominant, intermediate, and recessive forms, as had been proposed earlier (Berson et al 1969; Bird 1975). Since then the literature has simply talked of "X-linked RP" without the need to classify families further. Does this family really justify a change now?

Second, is this cone-rod degeneration or is it RP? The authors use both descriptions in their title, and in their introduction they suggest that both cone and cone-rod dystrophy are merely different forms of RP anyway. Clinical colleagues tell us that such a statement is not entirely unreasonable, since cone and macular involvement have been recorded in xlRP. On the other hand, cone-rod degeneration is defined, in the authors' own words, as "frequently including . . . minimal pigmentary changes" (p. 87). Perhaps then there is some justification on both sides of this debate. If so, however, one would have to say that this family does not differ greatly from xlRP as commonly described. Nevertheless, the subtypes cone dystrophy, cone-rod dystrophy, and RP are widely used and understood. Should all this now change? Should COD1 and CORDs 1 and 2 be reassigned as RP numbers; or, once again, might things not be better left as they are? In which case, the reader is still left wondering just what to call this family.

After all, locus symbols in RP are confusing enough to the uninitiated (see table 1). This is perhaps inevitable in such a heterogeneous disorder, but it appears to have been further confounded by a tendency to assign locus numbers while data were still only tentative. As a result, RP1 moved from chromosome 1 to chromosome 8 in 1991. Similarly, the loci designated RP5 and -6 were only ever hints, and at least one, RP5, is no longer thought to exist. RP8, in fact, never was a locus but instead was merely a family unlinked to the previous seven loci. As far as we are aware, it remains unlinked, to this day. As to rhodopsin (RP4) and peripherin/RDS (RP7), would it not be more helpful simply to refer to these loci by their gene names (as, in fact, most researchers do)? We note that, in the 2 years since it was reported as an RP locus, no number has yet been assigned to PDE-β, so perhaps this policy has already changed.

Now McGuire et al. (1995) propose to name this cone-rod degeneration "RP15"; this for a locus that they have already referred to as "CORD3" in one previous publication (Daiger et al 1995) and "X-linked dominant RP" in another (McGuire et al. 1994); a locus that anyway cannot definitely be resolved either clinically or genetically from the (itself only tentative) X-linked RP6 locus. Could this not simply be a genuine RP6 family, and might it not be wise to hold off on the assignment of a locus number until evidence for the existence of this locus was somewhat more substantial?

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