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mtDNA Analysis Shows Common Ancestry in Two Kindreds with X-Linked Recessive Hypoparathyroidism and Reveals a Heteroplasmic Silent Mutation

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Summary

Two kindreds residing in eastern Missouri and exhibiting X-linked recessive idiopathic hypoparathyroidism have been described. Genealogical records extending back five generations revealed no common ancestor. To investigate the possibility of relatedness, the DNA sequence of the mitochondrial D-loop was compared among several individuals in both kindreds. The mtDNA D-loop was amplified from the total DNA of individuals by use of nested PCR reactions, and the resulting 430-bp fragment was sequenced. The mtDNA sequence was identical among affected males and their maternal lineage for individuals in both kindreds. Conversely, the mtDNA sequence of the fathers of the affected males differed from that of the maternal lineage at three to six positions. These results demonstrate that the two kindreds exhibiting X-linked recessive hypoparathyroidism are indeed related and that an identical gene defect is responsible for the disease. A further feature of the inheritance pattern was examined when a unique point mutation was identified in the mtDNA of one branch of one of the kindreds. This mutation appears to be de novo and segregates in subsequent generations without obscuring relatedness. In addition, the results of our study of mtDNA analysis indicate that this approach may be of importance in investigating common ancestry in other X-linked disorders.

Introduction

X-linked recessive idiopathic hypoparathyroidism (HPT; OMIM 307700) has been mapped to Xq27 in two kindreds from eastern Missouri (Thakker et al. 1990). An autopsy study of one patient who died in an automobile accident showed no parathyroid tissue (Whyte et al. 1986). Hence, the disorder appears to be due to the absence of parathyroid glands from an early developmental defect. Chronic tetany with convulsions that are lethal within weeks after birth can be managed by vitamin D and calcium supplementation (Peden 1960; Whyte and Weldon 1981).

Despite first being described in 1960, the disorder has been reported in only two kindreds worldwide. One kindred included two affected infant boys, and, of the other 96 individuals, 11 boys had died with convulsions in infancy (Peden 1960). The second kindred was recognized after idiopathic HPT was diagnosed in two brothers (Whyte and Weldon 1981). Analysis of their large pedigree (167 individuals, with 4 confirmed affected males and 12 male deaths due to seizures early in life) also exhibited X-linked recessive inheritance spanning four generations. Until recently, no affected male in either kindred survived to have children. Therefore, there has been no opportunity to observe additional hallmarks of an X-linked disorder, including absence of male-to-male transmission or an obligate carrier state in the daughters of affected males.

These two kindreds are large, permitting the localization of the gene defect(s) to Xq27 in both (Thakker et al. 1990). Despite genealogical studies of five generations, no common ancestor has been identified. Both kindreds live in eastern Missouri and are known to have migrated there from Kentucky in the 1800s. The extreme rarity of HPT and the proximity of the kindreds suggest that the two kindreds are in fact related.

To test for HPT kindred relatedness, we analyzed their mtDNA. mtDNA provides markers that are as specific for maternal lineage as the Y chromosome is for paternal inheritance (Giles et al. 1980). Since both mtDNA and HPT are maternally inherited, linkage of the disease to maternal mtDNA should be complete (Giles et al. 1980). Thus, relatedness of the two HPT kindreds could be

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tested by comparing their mtDNA. In particular, the D-loop of mtDNA is a noncoding control region that is important in DNA replication and tRNA gene expression. Because the D-loop DNA has a mutation rate 5–10-fold higher than that of nuclear DNA, sequence comparisons among individuals (Ginther et al. 1992) and analysis in populations (Di Rienzo and Wilson 1991) provide useful indications of relatedness. In this article, we provide evidence, from mtDNA studies, that the two Missouri kindreds with HPT are related and that there is a single founder for HPT in the two kindreds. Furthermore, a new mtDNA allele was revealed in a branch of one kindred, permitting comparison of its inheritance and penetrance with the inheritance of fully established alleles.

Material and Methods

Genealogical Studies

The family structures were derived from extensive interviews with patients, with family members, and with groups at family reunions; they have been reported in the original clinical descriptions (Peden 1960; Whyte and Weldon 1981). All lineages were investigated, including male ancestors as well as females. The additional family members in this study are from follow-up work on the current generation.

Amplification of D-Loop

Total DNA was isolated from blood by use of standard protocols, and the mtDNA D-loop was amplified using primers described by Orrego and King (1990). The first PCR reaction was performed with primers L15926 and H00580 at a final concentration of 0.4 μM each. The PCR reactions were performed in 10-μl volumes containing Tris-ammonium-potassium (TNK) 50 buffer (Blanchard et al. 1993), 0.1 mM dNTP, and 0.4 unit *Taq* polymerase (Perkin-Elmer). PCR was performed in a Perkin-Elmer 9600 for 30 cycles of 94°C for 30 s, 55°C for 45 s, and 72°C for 45 s. This produces a product of 1,600 bp. The initial PCR-reaction mixture was diluted 1:20, and 1 μl was used as template in a second, nested PCR reaction using primers L15997 and H16401 at 0.4 μM each. Reaction and cycling conditions were the same, except that TNK 100 buffer (Blanchard et al. 1993) was used. The product is 443 bp.

Sequencing of the Amplified D-Loop

Published protocols for mtDNA D-loop analysis call for an initial standard amplification of a 1,600-bp fragment of the D-loop, followed by an asymmetrical amplification using the nested primers (Orrego and King 1990; Di Rienzo and Wilson 1991). This essentially "single-stranded" product is then sequenced. However, the asymmetrical PCR amplification is variably successful. It was therefore replaced by a nested pair of PCR reactions followed by cycle sequencing of the PCR products by use of end or internal primers. This approach produced completely reproducible results.

The amplified D-loop products were purified by electrophoresis on a 1% low-melting agarose gel with 1 × Tris-acetate EDTA buffer. The 443-bp bands were excised in minimal amounts of agar and were diluted with 10 μl H_2O. DNA sequencing was performed by use of the cycle-based method of Srivastava et al. (1992), slightly modified. Modifications included the use of TNK 100 buffer, 4.0 mM ddTTP stock solution, and 1.25 mM ddCTP stock solution. Cycling conditions in the Perkin-Elmer 9600 were 20 cycles of 94°C for 30 s, 55°C for 45 s, and 72°C for 60 s. Electrophoresis was performed on a standard 6% sequencing gel in Tris-borate EDTA buffer. Sequencing primers included L15997, H16401, L16099, and H16255 (Orrego and King 1990; Di Rienzo and Wilson 1991).

Results

The general approach was to amplify and sequence the highly polymorphic region of the mtDNA D-loop of individuals from the maternal lines of each HPT kindred. Between the two kindreds, sequence identity of this region would indicate that they are related, whereas sequence variation would indicate nonrelatedness. Initially, the D-loops from an affected male and his maternal grandmother were examined for each kindred (individuals 335 and 327 in the Peden kindred and individuals 215 and 208 in the Whyte kindred [fig. 1]). The DNA sequences of both patients and their grandmothers were identical over a 367-bp region.

As a critical control, the D-loop sequences of the patients' fathers were analyzed. They represent a sampling of the same local population and were found to vary from the maternal lineage sequence by 3 bp (in individual 213 of the Whyte kindred) to 6 bp (in individual 330 of the Peden kindred) (fig. 2). This analysis was then used for two more individuals (328 and 332) of maternal lineage from the Peden kindred and eight individuals (219, 238, 218, 220, 223, 224, 226, and 227) of maternal lineage from the Whyte kindred. All of these individuals showed the identical maternal lineage sequence already observed, except in one instance (see below). Again, the fathers chosen for study who were not in the maternal lineage (326 in the Peden kindred and 222 and 228 in the Whyte kindred) showed D-loop variation of 5, 4, and 5 bp, respectively, when compared with the maternal lineage (fig. 2). Additionally, the sequences of all the nonmaternally related fathers varied among themselves, providing a relevant example, in this population, of the high variability of the mtDNA D-loop. Examples of variation between nonrelated fathers

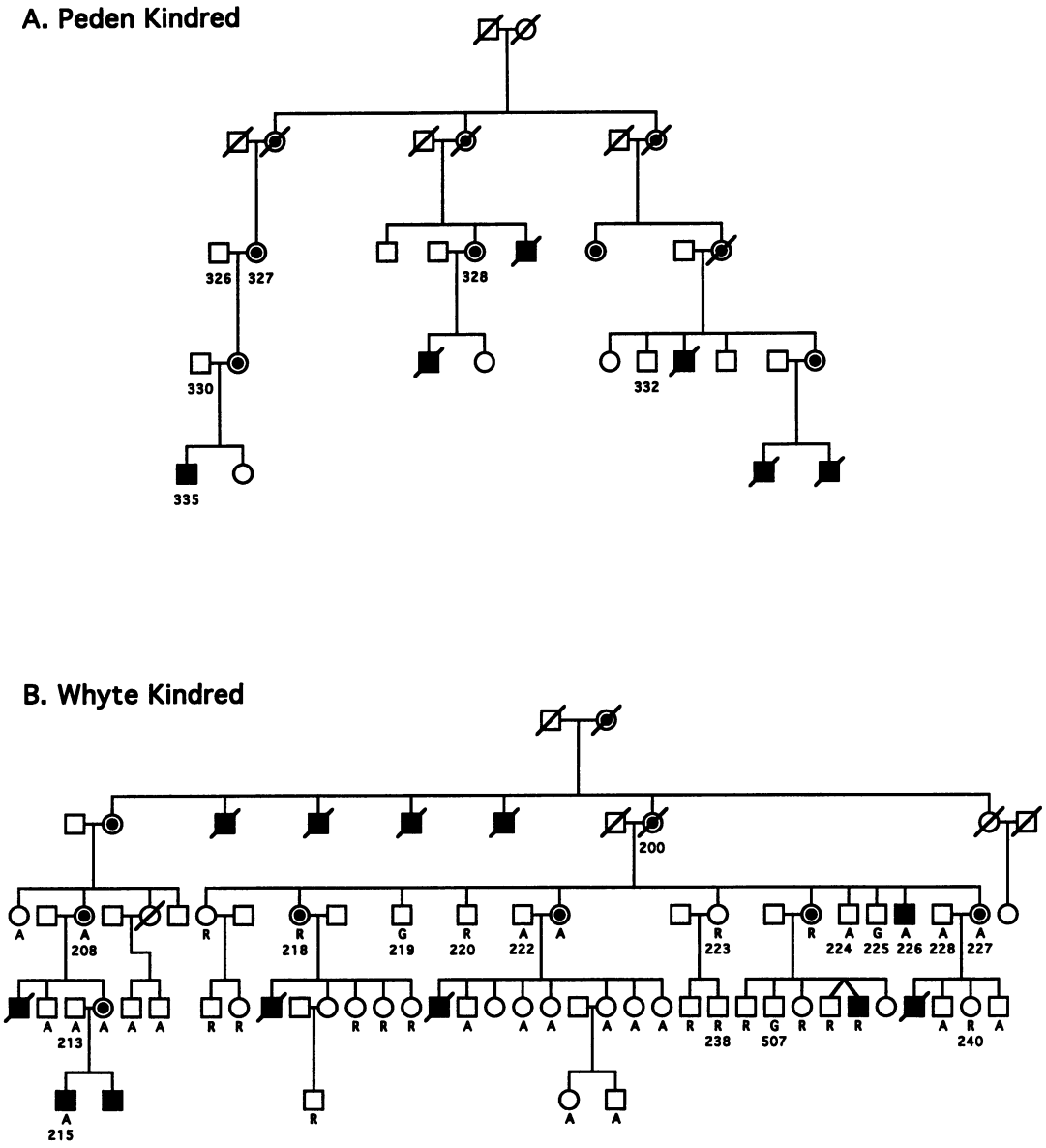

Figure 1 HPT kindreds. Current versions, including several new individuals, of the original HPT kindreds described by Peden (1960) and Whyte and Weldon (1981) are shown. The numbers refer to individuals mentioned in the text. Individuals 200, 208, 213, 219, 222, 225, 227, 228, and 507 have been referred to elsewhere as II.4, III.2, IV.3, V.1, III.6, III.9, III.14, III.17, III.16, and IV.9, respectively (Thakker et al. 1980). The letters in the Whyte kindred indicate the nucleotide at position 295 of the mtDNA D-loop ("R" indicates a heteroplasmic state with a mixture of A and G at position 295). Estimates of the levels of heteroplasmy for individuals is available on request.

and the maternal lineage are shown in figure 3. In an effort to identify these mutations more readily, the order of the samples on the sequencing gel was altered from the conventional display by grouping dideoxy terminating reactions for all individuals (fig. 4).

Comparison of the D-loop sequences of the selected fathers to that of the maternal lineage identified two bases that are idiosyncratic for the maternal lineage—a G at position 148 and a C at position 195. In a further assessment of the degree to which the maternal lineage sequence might be encountered, a search of the extensive records of mitochondrial D-loop sequences in the Genbank and European Molecular Biology Library databases has revealed no other person with the sequence of the maternal lineage in these HPT kindreds. These databases contain $\geq$779 unique human mtDNA D-loop sequences, including those of European descent. Hence, the sequence including those residues is, thus far, unique, among the world population, to the maternal lineage in these HPT kindreds, essentially representing a "signature" for this family.

It is possible, by use of standard statistical methods,

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....79.90.115.148.158.175.195.209.242.251.290.297.342.348
mat..T..C..G...G...T...T...C...C...C...A...T...T...T...T.
213.....A.....A.....T.....T.....T.....T.....T.....T.....
222..C.....A.....A.....T...T.....T.....T.....T.....T.....
228.....A...C.....T.....T.....C...C.....T.....T.....T.....
326..C..T.....A.....A.....T.....G.....T.....T.....T.....
330.....A...A.....C...T.....C...C.....T.....T.....T.....
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Figure 2 Nucleotide sequence differences, of the mtDNA D-loop, between fathers and the maternal lineage. Only differences in the D-loop of nonmaternally related fathers are shown below the maternal sequence. The numbers along the top indicate the nucleotide number in the 367-bp sequence of the mtDNA D-loop. The numbers at the left identify the nonmaternally related fathers depicted in the kindreds (see fig. 1); "mat" indicates the sequence of the maternal lineage.

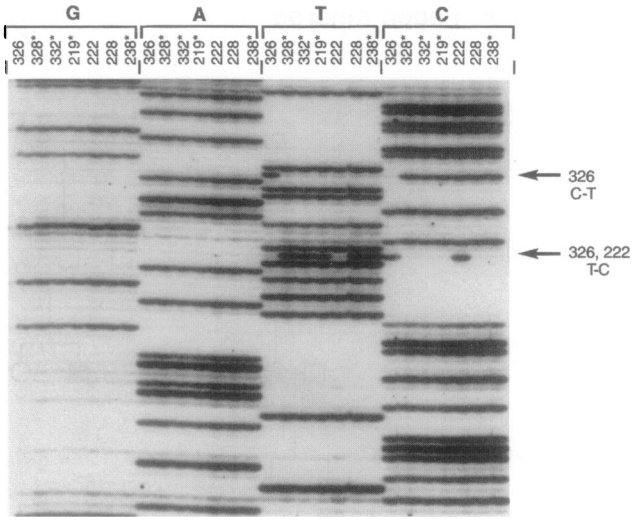

Figure 4 DNA sequence showing differences between the maternal lineage and nonmaternally related fathers. The conventional order of samples on the sequencing gel has been altered to more readily identify differences. Each nucleotide reaction is grouped for all individuals. Notation is as in figure 3.

to assess objectively the probability that the pattern of mtDNA variation described above is consistent with chance alone. Most simply, one can use the observed frequency of this haplotype in the Genbank compilation to assess the probability that these two kindreds would share this haplotype. As indicated above, this haplotype is unique, suggesting a worldwide prevalence of <1/779. Therefore, the probability that the two disease-carrying lineages would share this haplotype is the square of this frequency ($P < .0001$). However, this number is too conservative in that there is no a priori reason to ascribe any significance to this individual haplotype.

A more realistic estimate of the probability of sharing can be made from published data on the observed variability in this region in Caucasian populations. Orrego and King (1990) and, more recently, Piercy et al. (1993) have estimated the average number of differences between any pair of sequences to be 5.9 and 4.6, respectively. In view of the assumption that mtDNA nucleotide differences follow a Poisson distribution (Orrego and King 1990), these two numbers do not significantly differ from each other. Again, when a Poisson distribution of differences is assumed, the probabilities that no differences would be observed between the haplotypes sampled, by chance alone, from the two lines of descent are .0027 (Orrego and King 1990) and .0102 (Piercy et al. 1993).

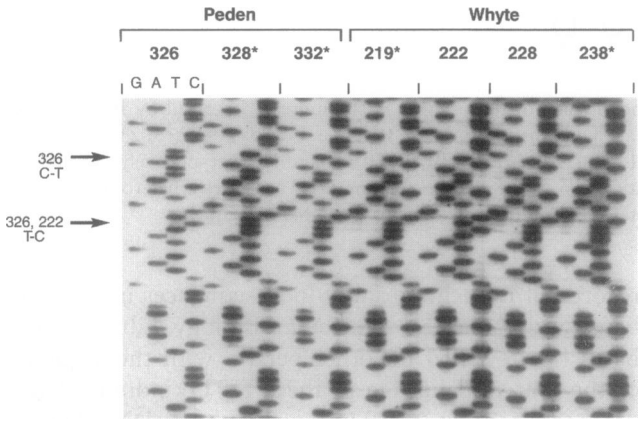

Figure 3 DNA sequence showing differences between the maternal lineage and nonmaternally related fathers. The sequencing gel has been run in the conventional manner, with the nucleotide order GATC. "326 C-T" indicates a C→T transition at position 40 in individual 326. "326, 222 T-C" indicates a T→C transition at position 29 in individuals 326 and 222. An asterisk (*) indicates individuals of maternal lineage.

It is reasonable to question whether the mtDNA identity between the two transmitting lineages might be a product of overall reduced mtDNA variability in this geographic region. It is possible to address this question by calculating the average number of differences observed among the six independent mtDNAs observed in this study. By use of the sequences obtained from the five nontransmitting males sequenced and the one transmitted mtDNA sequence, the average number of differences between any pair of sequences is 4.9. This value is not significantly different from either of the above estimates and suggests comparable levels of mtDNA variability in the DNA sequence in this geographic region. Again, when a Poisson distribution of differences is assumed, the probability that no differences are observed between the two transmitting kindreds is .008, on the basis of this locally derived number. The above results indicate that it is statistically unlikely that the two kindreds share mtDNA patterns by chance alone. Therefore, the findings of sequence identity between the

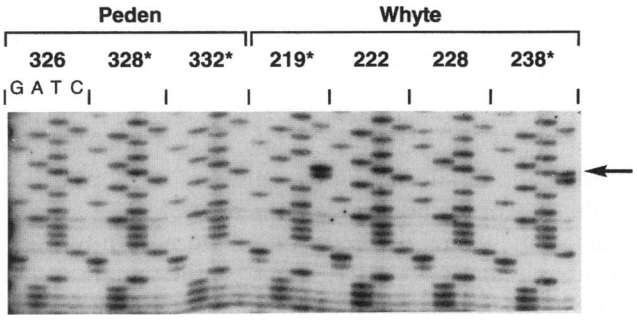

Figure 5 De novo mutation at nucleotide position 295 in the Whyte kindred. This sequencing reaction was performed using the reverse primer; hence the sequence is complementary to that shown in figure 2. The arrow indicates the A→G transition (shown here as a T→C transition) in individual 219. The heteroplasmic state can be seen in individual 238, in whom there is a mixture of A and G (shown here as T and C). Additionally, two differences between the maternal lineage and a nonmaternally related father can be seen as A→G transitions (for the fifth nucleotide above the arrow and the second nucleotide below the arrow) in individual 228. An asterisk (*) indicates individuals of maternal lineage.

mtDNA D-loops in the two kindreds studied strongly support the relatedness of the two kindreds exhibiting HPT.

Of interest within the Whyte kindred is a mutation that was noted at a particular base position. It was first detected in individuals 219 and 238, both of whom are in the maternal lineage and are descendants of individual 200. A clear A→G transition at position 295 of the 367 bp was detected in individual 219, compared with the maternal lineage (observed as a T→C transition in fig. 5, in which the sequence is from the complementary strand). In individuals 238, 218, 220, and 223, sequencing tracts showed a mixture of A and G at this position. In contrast, in individuals 224, 226, and 227 and a number of others of maternal lineage who were tested in both kindreds, this base was always an A. Thus, only individuals who are descendants of individual 200, in the Whyte kindred, exhibited a partial or complete transition at position 295.

On the basis of these results, it seemed possible that an A→G mutation had arisen de novo in the mtDNA of this branch of the kindred and that the variants were segregating in subsequent generations. To test this hypothesis, the mtDNA from all available individuals of this kindred was examined for this transition event. The results are depicted in the Whyte pedigree in figure 1. They are consistent with the interpretation that a new mutation has occurred in the mtDNA that was at first heteroplasmic in the population of mtDNA of individuals but that is gradually becoming homoplasmic in a series of subsequent generations (see Discussion).

Discussion

Sequence analysis of the mtDNA D-loop has been used to show relatedness between individuals and to assess the evolution and migration patterns of human populations (Di Rienzo and Wilson 1991; Ginther et al. 1992). In this study, we adopted this technique to establish the relatedness of two kindreds that share the same rare X-linked disease, HPT. Information has been obtained about the relative stability and usefulness of mtDNA for the analysis of founder effects in X-linked recessive disorders, with some correlative data about the establishment and stability of new mtDNA genotypes.

Rate and Extent of Establishment of a New mtDNA Variant

The use of mtDNA to assess relatedness depends on the balance of rates of mutation and rates of transmission of alleles in the relevant population (Hauswirth and Laipis 1985). On the basis of previous estimates, the rate of mutation of mtDNA is likely to be on the order of 10^{-4} (Brown et al. 1979). However, there are few instances where de novo mutations and subsequent segregation have been observed in a large kindred. Thus, although no systematic studies have been carried out, it is not surprising that an mtDNA D-loop mutation might be observed when a number of individuals from four generations of a large kindred are studied. In the instance reported here, the evidence for such an event is based on the observance of mixtures of A and G alleles at a presumptively mutant locus. This can best be explained as resulting from an A→G transition in the mtDNA of a female in one branch of the Whyte pedigree, shown in figure 1.

When hypothesizing how segregation leads to a homoplasmic state, we should note that the heteroplasmy in the Whyte kindred is due to an mtDNA mutation in a noncoding control region. This mutation presumably has no apparent phenotypic effect that could affect segregation. This is in direct contrast to many occurrences of mutations in mtDNA that do result in phenotypic changes (disease states) (Wallace 1992, 1994). In these cases, segregation may be affected by selection for or against the mutation.

Several observations can be made regarding mtDNA segregation in this kindred. The mutation that initiated heteroplasmy appears to have originated in individual 200, although the mutation could have arisen in a female predecessor (fig. 1). No DNA samples are available for this woman, who is deceased, so a direct test cannot be made. Among her children, all possible states exist—complete A, complete G, and the mix of A and G. Therefore, change from one homoplasmic state to another (complete A to complete G) can occur quickly, as observed in individuals 219 and 225. This observation has been observed in a large bovine pedigree (Hauswirth and Laipis 1985). Alternatively, heteroplasmy can be carried for several generations without necessarily reaching the homoplasmic state. This, in fact, is ob-

served in individual 218, whose children and grandchild retain the heteroplasmic state (fig. 1). Third, in one individual (227) who appeared to have the complete A allele, sufficient mutant allele (undetectable by standard sequence analysis) actually was present to convey the heteroplasmic state to one offspring (individual 240). Finally, in this kindred, only males (individuals 219, 225, and 507) have thus far obtained the complete mutant mtDNA allele. Hence, the mutant mtDNA allele is not yet firmly established in this kindred; establishment is dependent on the many females in the recent generations who are heteroplasmic.

It is uncertain how a mutation in a single molecule of mtDNA becomes established, since individual cells contain many mtDNA molecules. Several factors, discussed below, could contribute to the reduction of heteroplasmy to homoplasmy. First, in the absence of a segregation mechanism for mtDNA, progeny cells will tend to become pure for one or another mtDNA allele during a series of cycles of growth—much as bacterial plasmids with different genotypes tend to segregate to pure clones during cell outgrowth. However, in order for a random process to be efficient, it would require the relative expansion of the mutant allele over a number of generations. Instead, the transition either from a state of dominance of one allele over another or to a comparable representation of both alleles is very rapid at several points in the pedigree. The fact that the ratio of alleles can vary greatly in one generation can be explained most easily by the "bottleneck" theory whereby only one or a few mtDNA molecules replicate as "masters" for progeny mitochondria (Hauswirth and Laipis 1985; Poulton 1995). This model conceivably could be detailed further by use of additional quantitative studies of allele frequencies in the mtDNA of cloned cells from heteroplasmic individuals in the Whyte kindred.

Implications of the Results—for HPT and Other X-Linked Diseases

Introduction of new mtDNA alleles occasionally can be seen within family lineages, as observed here, but generally can be distinguished from the more stable genotypes. For HPT, statistical tests (see Results) are consistent with the inference that the rate of change of mtDNA is sufficient to provide alleles for an idiotypic "fingerprint" in the maternal lineage, without obscuring relatedness in families. From our results, the rarity of HPT almost certainly can be explained by a unique event expressed in a single founder. Since untreated boys do not survive, the founder was most likely a female or was due to gonadal mosaicism. Because the phenotype in affected boys is especially marked and consistent, the lack of any convincing reports of HPT in the intervening 35 years since the first description of the disease suggests that the causative hereditary change may have been of a unique type. A rare mutation event that must occur at one or a very few sites (whether point mutation, duplication, site-specific deletion, etc.) now seems a likely source of the disorder. Hence, a very extensive comparative study of DNA of the candidate region of Xq27 in affected and unaffected individuals may be required for establishment of the genetic basis of HPT.

Since these are the only two kindreds (now one) worldwide that have HPT, either (*a*) the mutation that arose in the founder must have occurred after the family immigrated to the United States or (*b*) a European branch died out. Otherwise, owing to the easily recognizable phenotype, the disease would be observed in Europe. Therefore, we propose that the mutation responsible for HPT arose near the time of the family's immigration to the United States. Subsequently, the Peden and Whyte kindreds diverged, and subsequent to this event, the heteroplasmic mutation in the mtDNA D-loop arose in the Whyte kindred.

Because of both the merger of the two kindreds into one large family and the recent localization of new polymorphic markers within the critical region, the linkage analysis for HPT is being reevaluated (Zucchi et al. 1996; P. H. Dixon and R. V. Thakker, unpublished data). Diallelic markers also are being developed across Xq27 in an effort to narrow the region by use of linkage disequilibrium. Furthermore, mtDNA sequence analysis may be useful for the assessment of founder effects and possible relatedness in other X-linked diseases. The approach is essentially limited to X-linked disorders in which affected males do not reproduce. In such instances, as here, the disease mutation and the mtDNA are inherited solely through the maternal lineage, making the inheritance mitochondrial linked as well as X linked. A perusal of OMIM shows ≥ 50 male lethal X-linked disorders to which the technique might be applicable. The technique also may be applicable to X-linked disorders in which affected males do reproduce, if the maternal lineage can be followed throughout the pedigree. For example, affected males in the current generation of the HPT kindred are surviving owing to both identification at birth and treatment of the associated hypocalcemia. Even though these males are surviving, the technique can be applied because the maternal lineage can be established by analysis of the pedigree. Finally, one advantage of using mtDNA analysis to show relatedness in X-linked diseases is the relative ease of the technique compared with linkage analysis. For example, one could easily examine a large number (≥ 100) of X-linked mental retardation patients by use of PCR and automated sequencing.

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