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Three Different Frameshift Mutations of the Tyrosinase Gene in Type IA Oculocutaneous Albinism

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Summary

Mutations in the gene for the pigment-producing enzyme tyrosinase are responsible for type IA (tyrosinase-negative) oculocutaneous albinism (OCA). Most reported mutations have been single base substitutions. We now report three different frameshift mutations in three unrelated individuals with type IA OCA. The first individual has a single base deletion within a series of five guanidines, resulting in a premature stop codon in exon I on one allele and a missense mutation at codon 382 in exon III on the homologous allele. The second individual is a genetic compound of two separate frameshift mutations, including both the same exon I single base deletion found in the first individual and a deletion of a thymidine-guanidine pair, within the sequence GTGTG, forming a termination codon (TAG) in exon I on the homologous allele. The third individual has a single base insertion in exon I on one allele and a missense mutation at codon 373 in exon III on the homologous allele. The two missense mutations occur within the copper Bbinding region and may interfere with either copper binding to the enzyme or oxygen binding to the copper. These five different mutations disrupt tyrosinase function and are associated with a total lack of melanin biosynthesis.

Introduction

Oculocutaneous albinism (OCA) is a group of common genetic abnormalities with devastating effects on the affected individuals (King and Summers 1988). A reduction of melanin production in the skin results in an increased sensitivity to UV radiation and in a cumulative predisposition to skin cancer. Reduction of melanin in the eye during development is associated with nystagmus, foveal hypoplasia with reduced visual acuity (color perception is normal), and abnormal neural routing from the eyes to the brain, resulting in strabismus and loss of binocular vision.

Melanin synthesis is a multistep process that produces red-yellow pheomelanin, black-brown eumelanin, or, more commonly, a mixture of the two melanins (Prota 1980). The enzyme tyrosinase plays a pivotal role in this process by catalyzing the first two steps of the pathway, the hydroxylation of tyrosine to dihydroxyphenylalanine (dopa) and the oxidation of dopa to dopaquinone (Lerner and Fitzpatrick 1950; Prota 1980). Tyrosinase is a monooxygenase (E.C.1.14.18.1) with two copper-binding regions, a transmembrane region and a cytoplasmic tail (Hearing and Jimenez 1989).

Human OCA has been divided into two general groups that are based on the function of tyrosinase. Type I, or tyrosinase-related, OCA is associated with a loss of tyrosinase function, and several categories of type I OCA—including type IA (tyrosinase negative), type IB (yellow), type Its (temperature sensitive), and type III (minimal pigment)—have been defined by clinical and biochemical characterization (Nance et al. 1970; King et al. 1986, 1991; Witkop et al. 1989). Type II, or tyrosinase-positive, OCA is associated with normal tyrosinase function, and the biochemical

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or genetic mechanism for this type has not been determined.

The gene for tyrosinase has been mapped to the long arm of chromosome 11 at 11q14→21 (Barton et al. 1988). The gene is at least 50 kb in length, and its coding region is divided into five exons (Giebel et al., in press-*b*). Exon I is the largest exon, containing over half of the coding sequence (Tomita et al. 1989). Currently, several mutations of the tyrosinase gene within humans having type I OCA have been reported (Tomita et al. 1989; Giebel et al. 1990, 1991*a*, 1991*b*, and in press-*a*; Kikuchi et al. 1990; Spritz et al. 1990, 1991; Takeda et al. 1990; Oetting et al., in press). All but two of these are missense mutations. The mutation reported by Tomita et al. (1989) is a single base insertion within exon II, causing a premature termination codon, and the mutation reported by Giebel et al. (in press-*a*) is a nonsense mutation. We report three new frameshift mutations that are responsible for loss of tyrosinase activity in three unrelated individuals with type IA OCA.

Material and Methods

Hairbulb Melanocyte Tyrosinase Activity

Tyrosine hydroxylase activity of tyrosinase was determined with enzyme extracted from 10 fresh anagen hairbulbs, using a tritiated tyrosine assay (King and Olds 1985). Hairbulbs were incubated on ice in 0.2 ml of 0.1 M $NaPO_4$ buffer pH 6.8, containing 0.5% Triton X-100 for 60 min, and the supernatant was used as the enzyme extract. The reaction mixture contained 0.5 μM L-tyrosine-3,5-^3H (2 or 50 Ci/mmol) and 0.1 μM L-dopa in 0.1 M $NaPO_4$ buffer pH 6.8 and 20 μl of the enzyme extract in a total volume of 60 μl. The reaction mixture was incubated at 37°C. At 0, 60, and 120 min a 10-μl aliquot was placed on a small Dowex 50W column, and the ^3HOH generated by the oxidation of tyrosine was recovered with a citrate wash. Enzyme activity is expressed in picomoles of tyrosine oxidized per hairbulb per hour.

Hairbulb Melanocyte Ultrastructure

Fresh anagen scalp hairbulbs were fixed in 3% glutaraldehydre for electron microscopy. Samples were then processed using standard techniques.

Preparation of Genomic DNA

Peripheral blood was collected from each member of the nuclear family, and the lymphocytes were isolated by osmotic lysis (Litz et al. 1988). The isolated lymphocytes were lysed with 1% SDS and incubated with 75 μg Proteinase K/ml (Boehringer-Mannheim, Indianapolis) at 65°C overnight. The DNA was isolated by extraction of the aqueous phase, with phenol and chloroform, and the DNA was recovered with ethanol precipitation.

DNA Amplification

Individual exons I–V of the tyrosinase-coding region were amplified separately by using the PCR (Saiki et al. 1988). Synthesized primers for amplification of each exon are listed in table 1 (Shibahara et al. 1988; Giebel et al. 1990; Kikuchi et al. 1990). PCR primer sequences are derived from intron sequences, which allow the entire coding region of these exons, as well as the intron/exon boundary, to be available for sequence analysis. Each exon was amplified for 30 cycles as follows: 1 min at 94°C, 1 min at $T_m - 5$°C (where T_m equals the lowest T_m for the two primers), and 1 min at 72°C (except for exon I, for which the time was 1.5 min). The amplified product was concentrated, and primers were removed by using a Millipore 30,000 NMWL filter (Millipore, Bedford, MA). The filtered products were used directly for double-stranded DNA sequencing of exon I. For asymmetric DNA amplification, an aliquot of the processed amplified products were again amplified, under identical conditions, with one of the two primers diluted to a final concentration of 0.01 μM. The asymmetric amplified DNA was concentrated with a Millipore 30,000 NMWL filter. Asymmetric amplified DNA was used for sequencing exons II–V.

DNA Sequencing

The amplified exons were sequenced using a *Taq* DNA polymerase sequencing kit (United States Bio-

Table 1

Oligonucleotide Sequences Used to Amplify Exons I–V of Tyrosinase Gene

Exon	Primer Sequences
I	5′-TCTTCAAACATTGTAGCCTC-3′ 5′-TTAACAGGGCACCATTTCTG-3′
II	5′-CTCAGGAGAAGTCTAACAAC-3′ 5′-AACTCAGAAATTCTGAATTC-3′
III	5′-AGTCTCAATACGGAATGAA-3′ 5′-TTTAAATCCAATGAGCACGT-3′
IV	5′-ACAATATGTTTCTTAGTCTG-3′ 5′-TGGTAACACTAGATTCAGC-3′
V	5′-CTCCAAAGGACTGTGAAAGG-3′ 5′-AGGCTACACTTTGTATTAGG-3′

chemical Corporation, Cleveland), with modifications. This sequencing protocol is based on the dideoxy chain–termination technique and permits sequencing of 250 bp/reaction (Sanger et al. 1977). For exons II–V, sequencing primers were synthesized for hybridization to both the (+) and (−) strands, and both strands of the exon were sequenced. For exon I, a series of six primers that hybridized to the (−) strand were synthesized to produce a series of overlapping sequencing reactions.

All sequencing reactions used the products from asymmetric DNA amplification, except for exon I, for which double-stranded DNA was used as the sequencing template. The sequencing primer was radioactively labeled with [γ-^{32}P] ATP and T4 polynucleotide kinase (Bethesda Research Laboratories) and was annealed to the DNA template by boiling for 5 min and snap cooling on ice. The primer/template mixture was then allowed to incubate at room temperature for 20 min. The sequencing reaction mixture was made as recommended in the directions. The reaction was incubated for 10 min at T_m − 5°C and then incubated for 10 min at 72°C. After the samples were microfuged, 2 µl of an extension mix containing 7.5 µM of each dNTP was added to each of the four reaction tubes, and the reaction was continued at 72°C for another 10 min. After the addition of the stop solution, the reaction product was heated at 95°C and then was separated on an 8% urea-acrylamide sequencing gel, and the pattern was visualized by autoradiography. Each family was analyzed by the simultaneous sequencing of DNA from the affected individual and the parents.

Sequence Analysis

The sequence of Shibahara et al. (1988) was used as the standard normal sequence for human tyrosinase. For purposes of identifying the location of mutations within the coding region, the initial methionine is counted as codon 1.

Results

Clinical Findings

Three type IA OCA individuals and their parents were studied. All three individuals with albinism had white hair and white skin with no pigmented lesions. Figure 1 shows individual 1, to demonstrate this phenotype. On ocular examination all three had blue translucent irides, nystagmus, reduced visual acuity, foveal hypoplasia, and no retinal pigment (ocular photographs of individual 1 are shown in fig. 2). No tyrosinase activity could be detected in hairbulbs from individual 1 (female, age 4 years) or from her parents. Hairbulbs could not be obtained from the individual 2 (male, age 6 mo), but his parents had no detectable hairbulb tyrosinase activity. No tyrosinase activity could be detected in hairbulbs from individual 3 (male, age 2 years).

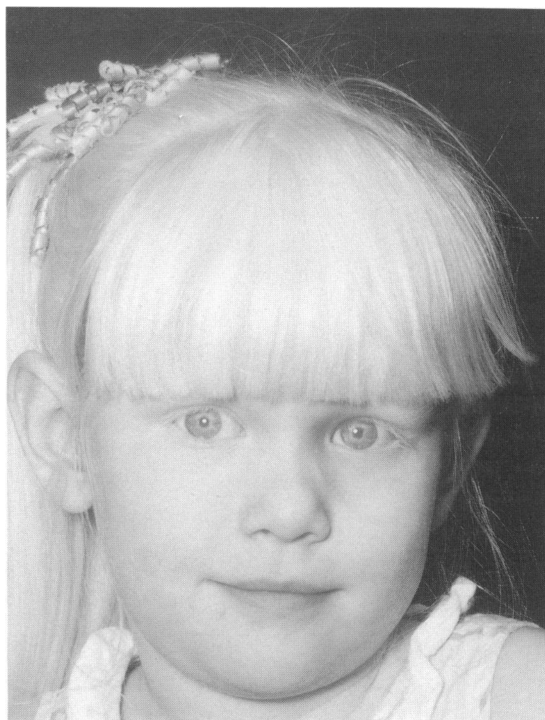


Figure 1 Individual 1, age 4 years, showing white skin and hair and blue eyes.

Sequence Analysis

Molecular sequence analysis of individual 1 revealed the presence of both a frameshift mutation and a missense mutation (fig. 3, *top*). The paternally inherited allele contained a single base deletion of a guanidine within a series of five guanidines, at codon 191 in exon I. The resulting frameshift produced a premature termination signal (TGA) at codon 225 (fig. 4*A*). The maternally inherited allele contained a base substitution of C→A, causing a missense mutation of asparagine to lysine at codon 382 in exon III. Both the parents and individual I were heterozygous for the polymorphism at codon 192 (TAT/TCT) (Giebel and Spritz 1990; Handoko et al. 1990). This is a nonpathogenic polymorphism in which the TAT codon codes for the

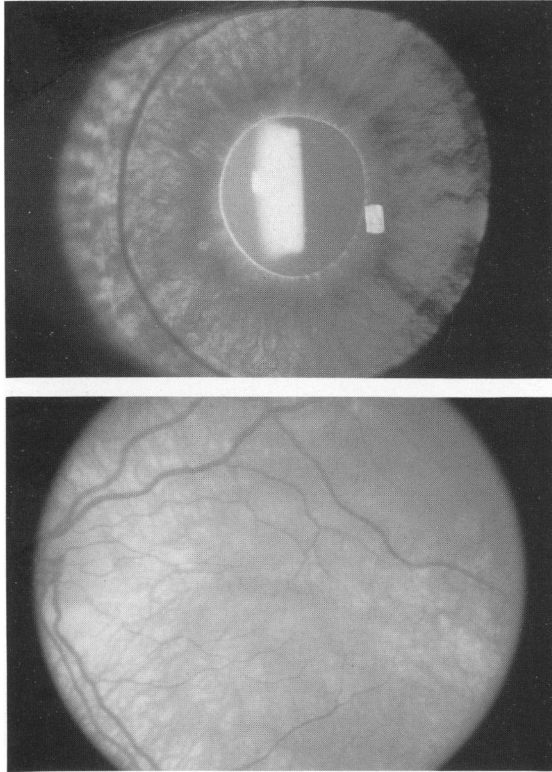
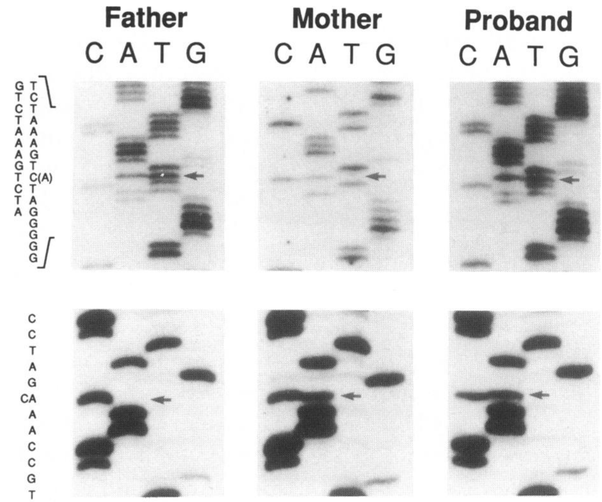
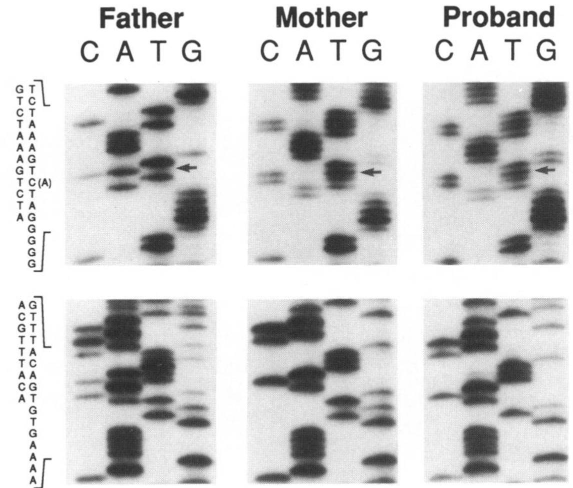


Figure 2 Ocular photographs of individual 1. *Top,* Iris transillumination showing translucent iris without pigment. *Bottom,* Fundus showing no retinal pigment or foveal development and full visualization of the choroidal vessels.





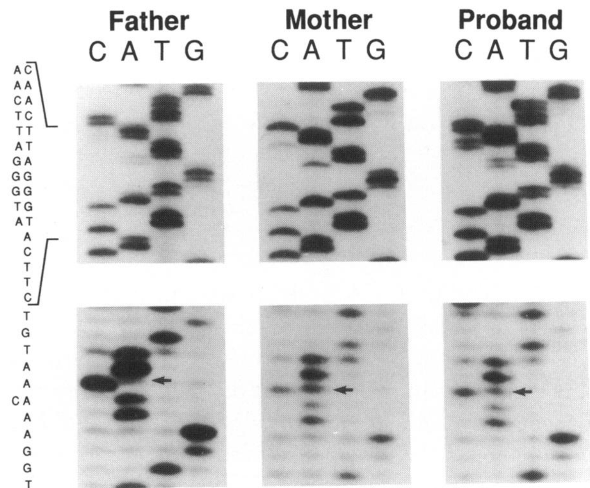


Figure 3 *Top,* Sequencing results for individual 1. The frameshift mutation on the paternal allele is located at codon 191. The arrow shows the location of the polymorphism at codon 192. The missense mutation on the maternal allele is identified by the arrow on the lower row of sequences and is located at codon 382. *Middle,* Sequencing results for individual 2. The frameshift mutation on the maternal allele is located at codon 191. The arrow identifies the location of the polymorphism at codon 192. The frameshift mutation on the paternal mutation is shown on the lower row of sequences and is located at codon 244. The sequence showing the mutation at codon 244 does not exhibit a sequence for both alleles for the proband because the mutation at codon 191 of the maternal allele interferes with the binding of the sequencing primer which hybridizes at this location. *Bottom,* Sequencing results for individual 3. The frameshift mutation on the parental allele is located at codon 96. The missense mutation on the maternal allele is identified by the arrow on the lower row of sequences and is located at codon 373.

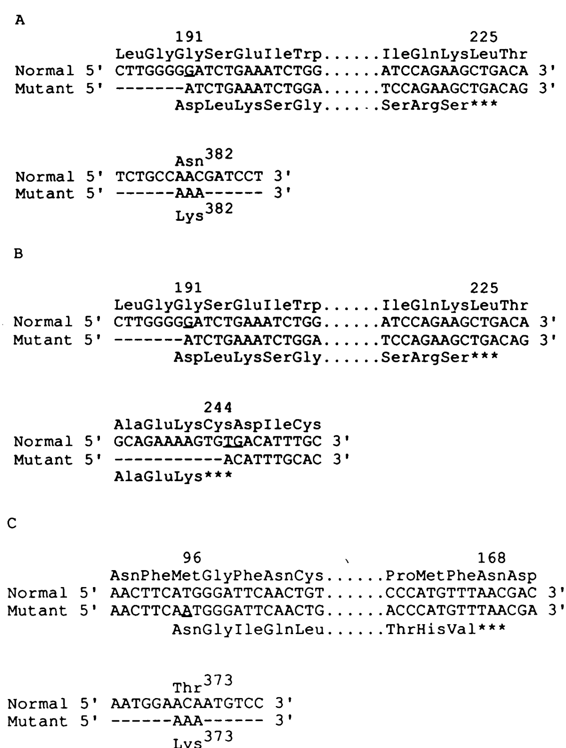


Figure 4 *A,* Individual 1, containing a missense mutation and single base deletion. One mutation occurs within codon 191 which contains a single base deletion as shown by the underlined base, resulting in a premature termination signal at codon 225. The second mutation occurs at codon 382, resulting in an amino acid substitution (Asn→Lys). *B,* Individual 2, containing a single base deletion at one allele and double base mutation at the second allele. One mutation is a deletion of a guanidine at codon 191, resulting in a premature termination at codon 225. The second mutation is a two-base deletion of a thymidine and a guanidine at codon 244, resulting in a nonsense (termination codon) mutation at this location. *C,* Individual 3, containing a single base insertion at one allele and missense mutation at second allele. The single base insertion is an adenine inserted within codon 96, resulting in a premature termination signal at codon 168. The second mutation occurs at codon 373, resulting in an amino acid substitution (Thr→Lys).

amino acid tyrosine and lacks an *Mbo*I site, while the TCT codon codes for serine and has an *Mbo*I site.

Analysis of individual 2 revealed the presence of two separate frameshift mutations (fig. 3, *middle*). The maternally inherited mutation is identical to the single base deletion at codon 191 of individual 1; however, there is no clinical or historical evidence that the family of individual 1 and that of individual 2 are related, which suggests that this is a case of a recurrent frameshift mutation. The paternally inherited mutation in individual 2 is a deletion of a thymidine-guanidine basepair within a series of GTGTG at codon 244 in exon I. This deletion creates a termination codon (TGA) at this location (fig. 4*B*). It should be noted that the sequence showing the mutation at codon 244 does not exhibit a sequence for both alleles for the proband. This occurs because the mutation at codon 191 of the maternal allele interferes with the binding of the sequencing primer that hybridizes at this location. The paternal DNA can be sequenced, but the sequencing reaction showing the normal maternal sequences at codon 244 cannot proceed. The father of individual 2 was heterozygous for the codon 192 polymorphism (TAT/TCT), and both the mother and individual 2 were homozygous for the TCT (serine) codon.

Analysis of individual 3 revealed a frameshift mutation and a missense mutation (fig. 3, *bottom*). The paternally inherited mutation is a single base insertion of an adenine at codon 96, producing a premature termination codon (TAA) at codon 168 (fig. 4*C*). The maternally inherited mutation is a base substitution of C→A, causing a missense mutation of threonine to leucine at codon 373 in exon III (fig. 4*C*). Individual 3 is heterozygous for the codon 192 polymorphism.

Electron Microscopy

Electron micrographs of hairbulb melanocytes of individual 2 showed numerous stage I and stage II premelanosomes (fig. 5). Premelanosomal matrix architecture was normal, and there was no pigment deposition within the cell.

Discussion

We have found three unrelated individuals with type IA OCA who have frameshift mutations within the gene coding for tyrosinase. A fourth frameshift mutation has been reported by Tomita et al. (1989) in two unrelated Japanese patients who were homozygous for this mutation. The Japanese frameshift mutation consisted of a single base insertion (cytosine) within a series of four cytosines located at codon 310 in exon II, which produced a premature termination codon at 316 (TGA).

Three of the four frameshift mutations found in type IA OCA reside within repetitive base sequences. Kunkel (1985), using purified DNA polymerases, has shown that a substantial number of frameshift mutations occur at repetitive base sequences, and Streisinger et al. (1966; also see Streisinger and Owen 1985) have suggested a model showing how repetitive base sequences will produce frameshift mutations with

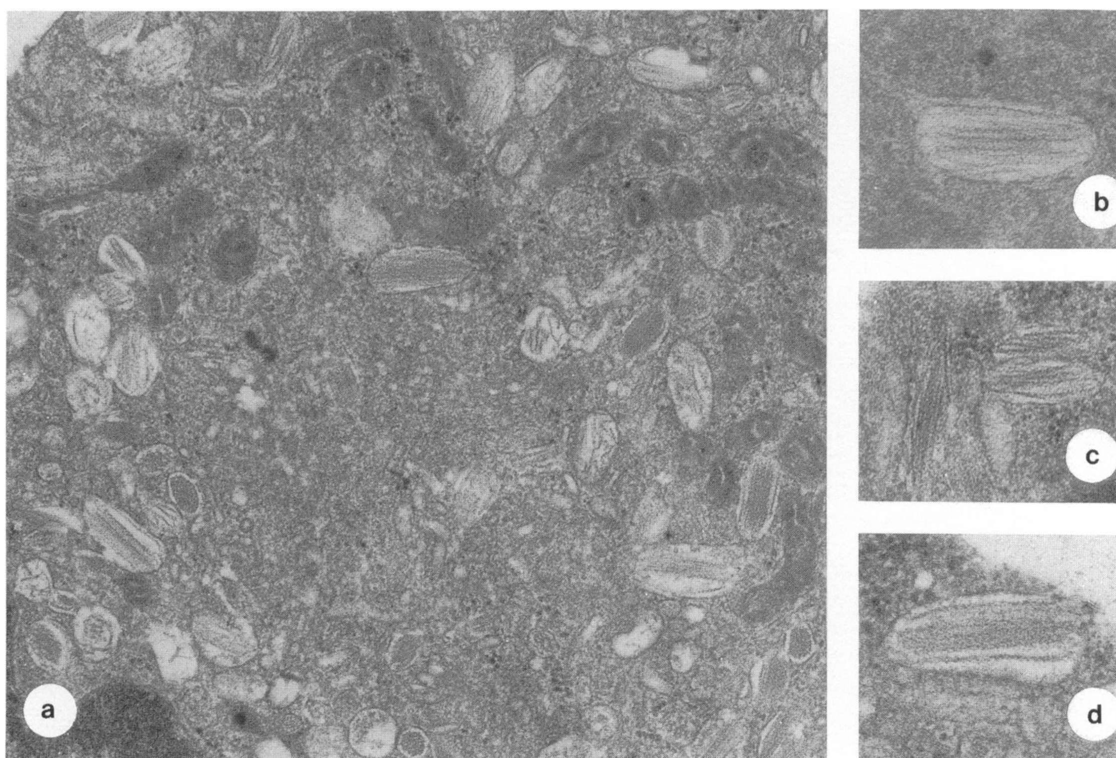


Figure 5 Electron micrograph of hairbulb melanocytes of individual 2. *a*, Stage I and stage II premelanosomes within a hairbulb melanocyte (magnification × 33,600). *b–d*, Detail of premelanosomal matrix (magnification × 55,000 in *b* and *d* and × 42,000 in *c*).

an especially high frequency. According to the model, the repetitive sequence allows slippage and misalignment of the two DNA strands, with a looping out of one or more bases. Subsequent DNA synthesis would then either omit or add a nucleotide or nucleotide pair. The mutation at codon 191 found in individuals 1 and 2 is within a string of five guanidines which is an especially active repetitive sequence for single base–deletion frameshift mutations (Fuchs et al. 1988).

The missense mutation found in individual 1 (codon 382) is adjacent to a missense mutation reported by Spritz et al. (1990) at codon 383. As is the case with their mutation, this location is a potential N-glycosylation site (Asn-X-Thy/Ser). Imokawa and Mishima (1982, 1986) have shown the importance of glycosylation in tyrosinase maturation and intracellular translocation; however, the absence of glycosylation should not affect the catalytic properties of the enzyme and would not be expected to result in the absence of tyrosinase activity in the melanocyte. Of more importance is the fact that both this mutation and the mutation of individual 3 at codon 373 are in the location of the proposed copper B region of tyrosinase and that interference with copper binding would inhibit catalytic function of the enzyme (Hearing and Jimenez 1989).

This missense mutation at codon 382 also occurs at a CpG dinucleotide. This mutation hot spot is caused by methylation-mediated deamination and is responsible for 35% of all single basepair substitutions causing human genetic disease (Abadie et al. 1989; Cooper and Krawczak 1990). The highest percentage of mutations at the CpG dinucleotide are CG→TG or CG→CA substitutions, depending on which cytosine is methylated. In individual 1, however, a C→A substitution [or G→T on the (–) strand] has occurred. It has been shown that, even when mutations caused by methylation-mediated deamination are excluded, the CpG dinucleotide still mutates at a frequency higher than expected, compared with other dinucleotides (Copper and Krawczak 1990). The mutation found by Spritz et al. at codon 383 does show a base substitution (CG→CA) and is consistent with methylation-mediated deamination.

One additional point can be made about these stud-

ies. Individual 2 has two frameshift mutations, producing premature termination in exon I, and little if any tyrosinase protein should be present in the melanocyte. This offers the opportunity to analyze melanosomal development in the absence of tyrosinase. It has been postulated that tyrosinase may play a structural as well as an enzymatic role in the formation of the premelanosome (Seiji 1967; Seiji et al. 1972), but we find no evidence for this. The electron micrographs of hairbulb melanocytes from individual 2 showed normal premelanosomal matrix architecture. No structural change related to an absence of tyrosinase could be detected. From this we can conclude that tyrosinase molecules are not necessary for normal premelanosomal development.

Currently, several different mutations of the tyrosinase gene have been reported in type I OCA, and it is expected that additional mutations will be found. We are continuing to sequence DNA from other individuals, to identify other mutations within the tyrosinase gene and to understand the genetic heterogeneity of type I OCA.

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