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Rufous Oculocutaneous Albinism in Southern African Blacks Is Caused by Mutations in the *TYRP1* Gene

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Summary

Oculocutaneous albinism (OCA) is the most common autosomal recessive disorder among southern African Blacks. There are three forms that account for almost all OCA types in this region. Tyrosinase-positive OCA (OCA2), which is the most common, affects ~1/3,900 newborns and has a carrier frequency of ~1/33. It is caused by mutations in the *P* gene on chromosome 15. Brown OCA (BOCA) and rufous OCA (ROCA) account for the majority of the remaining phenotypes. The prevalence of BOCA is unknown, but for ROCA it is ~1/8,500. Linkage analysis performed on nine ROCA families showed that ROCA was linked to an intragenic marker at the *TYRP1* locus (maximum LOD score = 3.80 at $\theta = .00$). Mutation analysis of 19 unrelated ROCA individuals revealed a nonsense mutation at codon 166 (S166X) in 17 (45%) of 38 ROCA chromosomes, and a second mutation (368delA) was found in an additional 19 (50%) of 38 chromosomes; mutations were not identified in the remaining 2 ROCA chromosomes. In one family, two siblings with a phenotypically unclassified form of albinism were found to be compound heterozygotes for mutations (S166X/368delA) at the *TYRP1* locus and were heterozygous for a common 2.7-kb deletion in the *P* gene. These findings have highlighted the influence of genetic background on phenotype, in which the genotype at one locus can be influenced by the genotype at a second locus, leading to a modified phenotype. ROCA, which in southern African Blacks is caused by mutations in the *TYRP1* gene, therefore should be referred to as "OCA3," since this is the third locus that has been shown to cause an OCA phenotype in humans.

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Introduction

Oculocutaneous albinism (OCA) is the most common autosomal recessive disorder in southern African Blacks. Tyrosinase-positive OCA (OCA2, or ty-pos OCA) is by far the most common and affects ~1/3,900 individuals (Kromberg and Jenkins 1982). Together with two rarer forms of OCA, brown OCA (BOCA) and rufous OCA (ROCA), almost all cases of OCA in southern Africa have been accounted for. Tyrosinase-negative OCA (OCA1, or ty-neg OCA), caused by mutations in the tyrosinase gene (*TYR*), does not appear to occur in this population. OCA2 has been mapped to chromosome 15q11.2-12 in southern African Blacks (Ramsay et al. 1992). Unlike the situation in European populations, the condition shows locus homogeneity in this African population (Kedda et al. 1994). The most common mutation is a 2.7-kb deletion (Durham-Pierre et al. 1994), which accounts for 78% of OCA2 mutations in southern Africa (Stevens et al. 1995). BOCA and ROCA have been reported numerous times in Africa. They originally were reported together as so-called xanthism, which may have been due to the lack of an early formal distinction between and definition of these types (Pearson et al. 1911; Stannus 1913). BOCA and ROCA are physically distinguishable primarily on the basis of skin and hair color (Kromberg et al. 1990). BOCA initially was defined in the Nigerian population (King et al. 1980) and only has been found to occur in the Black, or Negroid, populations of Africa and America (King et al. 1985). ROCA principally has been reported in the Black populations of Africa and Papua New Guinea (Stannus 1913; Walsh 1971; Kromberg et al. 1990). In southern Africa, ROCA occurs at a prevalence of ~1/8,500 individuals (Kromberg et al. 1990). The condition results in a red-bronze skin color, ginger-red hair, and blue or brown irides. The visual anomalies associated with albinism are often very mild in ROCA individuals, with ~76% having nystagmus. A previous report (Kromberg et al. 1990) showed the absence of misrouting of the optic tract, a common feature of albinism, in four individuals. This led to the suggestion that ROCA, in fact, may not be a true form of albinism but, instead, is an extreme in the normal pigmentation range. One individual, tested subsequently,

Table 1

Criteria for the Definition of ROCA and BOCA

Characteristic	ROCA	BOCA
Skin Color	Brick-red, mahogany, or bronze	Tan or light brown
Hair Color	Ginger or reddish-ginger	Light brown
Nystagmus	Mild or absent	Mild or absent

has been shown to have abnormal visually evoked potentials, confirming misrouting (J. G. R. Kromberg, P. Manga, and E. Zwane, unpublished data) and supporting classification of ROCA as a form of OCA. Ultrastructural analysis of the hair bulbs and skin showed both eumelanosomes and pheomelanosomes, in various stages of melanization. There were a normal number of melanosomes in the skin keratinocytes, but they were packaged into clusters, instead of being dispersed singly as in the skin of normally pigmented Black individuals (Kidson et al. 1993).

In this study, the aim was to identify the gene responsible for ROCA. A linkage study was undertaken by use of polymorphic markers linked to candidate loci known to be involved in the melanin biosynthetic pathway. These loci included those for tyrosinase (*TYR;* 11q14-q21) (Barton et al. 1988), the human homologue of the mouse pink-eyed dilute gene (*P;* 15q11.2-q12) (Rinchik et al. 1993), and tyrosinase-related protein 1 (*TYRP1;* 9p23) (Chintamaneni et al. 1991; Murty et al. 1992) and protein 2 (*TYRP2;* 13q31-q32) (Bouchard et al. 1994; Sturm et al. 1994). When the candidate gene had been identified, mutation detection was performed by the screening of exons, by use of PCR, SSCP analysis, and sequencing.

Figure 1 Two sibs (*front*) affected with an atypical form of OCA and their normally pigmented father (*back left*). Their mother was not available, although she was reported as being normally pigmented. Seen with the sibs and their father is an unrelated individual affected with ROCA. She is a compound heterozygote for the *TYRP1* mutations (S166X/368delA). The sibs also are compound heterozygotes for the same *TYRP1* mutations (S166X/368delA) but, in addition, are heterozygous for the 2.7-kb deletion at the *P* locus. The 368delA mutation was inherited from the sibs' father; therefore, the remaining two mutations (S166X and the 2.7-kb deletion) must have been inherited from their mother.

Subjects, Material, and Methods

Subjects

The clinical criteria used in the classification of types of albinism are shown in table 1. The features were selected on the basis of the descriptions of Kromberg et al. (1990) and King et al. (1994). Any individuals found not to match the criteria exactly were excluded from the linkage study but were included in the mutation-detection studies.

Nineteen families, comprising 73 individuals, were included in this study. Of the 19 unrelated affected individuals, 16 were classified unambiguously as having ROCA, whereas 3 had unusual phenotypes that were neither strictly ROCA nor strictly BOCA. The initial 16 ROCA individuals had red-bronze skin and ginger hair, but visual anomalies were not always detectable; 76% of these individuals had nystagmus, and only 14% had strabismus. Of the three remaining individuals, two did not show the typical ginger scalp hair, but the hair on the forearms was ginger. These two individuals also had a skin color that was darker than expected for ROCA individuals. The third family was atypical in that the hair on the affected individuals was similar to that of individuals with OCA2 but was slightly red, whereas the skin was a much lighter, red-yellow color than is typical of the ROCA tinge (fig. 1).

Of the 19 families, only 9 were used in the linkage study. The probands in each of these 9 families had typical ROCA. Of the remaining 10 families, 4 were excluded because DNA samples were available only from the affected individuals (these included two individuals with unusual phenotypes); 3 were not suitable for linkage, owing to DNA being available only from the af-

Table 2

Markers Used in the Linkage-Analysis Study

Pigment Locus	Chromosomal Localization	Marker	Reference
P	15q11-q13	*GABRB3*	Mutirangura et al. (1992)
TYR	11q14-q21	*TYR*	Morris et al. (1991)
TYRP1	9p23	*D9S43*	Weber and May (1990)
		AC1	Box and Sturm (1994*b*)
		AC2	Sturm et al. (1995)
TYRP2	13q31-q32	*TYRP2*	Box and Sturm (1994*a*)

fected individuals and from one parent (including 1 family with an unusual phenotype); and 3 were collected after the conclusion of the linkage study.

Included in the *TYRP1* mutation-analysis studies were 126 normally pigmented, Black, southern African individuals, as well as 46 individuals from the Central African Republic (CAR), of whom 7 had an unclassified form of OCA and 39 were normally pigmented.

Linkage Analysis

Polymorphic markers linked to candidate pigment loci were used for linkage analysis. These markers are shown in table 2. Alleles for microsatellite markers were determined after PCR products had been separated, by PAGE, on standard 6% sequencing gels. The MLINK package of the computer program LINKAGE was used to perform two-point linkage analysis. Since the alleles detected in the microsatellite systems were too numerous to be analyzed by use of a personal computer, marker alleles were recoded for individual families, to minimize the number of alleles defined, without loss of linkage information. The frequencies of alleles were calculated from unaffected chromosomes in the families used for the study. For males and females, an equal recombination rate was assumed, together with 100% penetrance for OCA.

Detection of the Common P *Gene Deletion Mutation*

Screening of all OCA subjects for the 2.7-kb deletion mutation, identified by Durham-Pierre et al. (1994), was performed. The PCR detection method described by Durham-Pierre et al. (1994) was used. PCR using three oligonucleotide primers was performed, and the products were electrophoresed on a 3% composite gel (2 Nusieve:1 high-gelling-temperature agarose). An 820-bp fragment indicated the presence of the deletion, and a 240-bp fragment indicated the presence of a nondeleted *P* gene.

SSCP and Heteroduplex Analysis of the TYRP1 *Gene*

Each of the exons was amplified individually from genomic DNA. The primers used in the amplification of the *TYRP1* exons are shown in table 3. PCR was performed in either a Cetus or a Hybaid thermocycler for 30 cycles, for 1 min at 94°C, for 1 min at the appropriate annealing temperature, and for 1 min at 72°C. The annealing temperatures for exons 1, 2, 3, 4, 5, 6, 7, and 8 were 50°C, 55°C, 57°C, 47°C, 50°C, 51°C, 45°C, and 51°C, respectively.

The products were separated on mutation detection–enhancement gels (FMC Bioproducts), to detect either single-strand conformational or heteroduplex variants. The gels were run under the conditions suggested by the manufacturer. The products were separated on gels with 10% glycerol as well as with no glycerol, under identical conditions.

Sequencing

Each SSCP and heteroduplex variant was sequenced by use of either the Sequenase (United States Biochemical) sequencing kit with 6% PAGE or the ABI *Taq* FS sequencing kit (dye terminator; Perkin Elmer) with 4% PAGE, by use of an ABI377 automated sequencer. The entire coding region of the *TYRP1* gene was sequenced for three ROCA individuals.

Detection of Polymorphisms in the TYRP1 *Gene*

The *Tsp*509I polymorphism was detected as described by Wildenberg et al. (1995). The L500L *Hinf*I polymorphism was detected by amplification of exon 8, di-

Table 3

Primers Used in the Amplification of *TYRP1* Exons

Exon	Primer
1	5′-AGAAGTTCATCAGAGACATC-3′
	5′-TCACCATCATTAATTACATT-3′
2	5′-CGTGCTTCAGTCTTCTCTACA-3′
	5′-GCAAGGACTTATGAACTCATTC-3′
3	5′-CGCAAGGCAGATGTTTTCATG-3′
	5′-AAGGCATCTTGTCTGTAAAGA-3′
4	5′-AGACCAAACGAAAATGAATA-3′
	5′-AAATTCTGACTCCAAGCTATC-3′
5	5′-AAAGAGCGACAATAAGAACTC-3′
	5′-AAAGCCTTCTCAAAGAAACTT-3′
6	5′-TTGCTATTACCTGGAAAAGTG-3′
	5′-TGCAAAAAGCATATGAAAATG-3′
7	5′-ATACGTTGTCTTTGGAATAAT-3′
	5′-ATACCGTGATTACTCTACTTG-3′
8	5′-TGTCCACTTTTTGGTGATAAC-3′
	5′-ATTCAACCAGGTGGTTTTGTG-3′

Table 4

LOD Scores Indicating Linkage of ROCA to *TYRP1*

		LOD Score at θ =				
Phenotype	Locus	.00	.10	.20	.30	.40
ROCA	*TYRP1 AC1*	3.49	2.68	1.70	.85	.26

gestion with *Hinf*I, and separation on a 3% agarose gel. All other mutations were identified by sequencing.

Results

Linkage In ROCA Families

Linkage to the loci *TYR* (LOD score [Z] = −2 at θ = .02), *P* (Z = −2 at θ = .08, with *GABRB3*), and *TYRP2* (Z = −2 at θ = .002) was excluded in nine ROCA families. Linkage to the *TYRP1* locus could not be excluded by use of either the extragenic marker *D9S43* (maximum Z [Z_{max}] = 0.15 at θ = .00) (Weber and May 1990) or the intragenic marker *AC2* (Z_{max} = 0.48 at θ = .00) (Sturm et al. 1995). Linkage to the locus was confirmed (Z_{max} = 3.49 at θ = .00) by use of a second intragenic microsatellite marker, *AC1* (Box and Sturm 1994*b*) (table 4).

Mutation Detection in the TYRP1 *Gene*

Two mutations were identified in the *TYRP1* gene. The first is a base substitution (C→G) at codon 166 of exon 3, which alters a serine to a stop codon (S166X) and accounts for 45% (17/38) of ROCA mutations. S166X results in the loss of an *Mbo*I restriction site, which was used to detect the mutation. One hundred twenty-six normally pigmented Black southern African individuals (n = 252) were screened, but none were found to carry the mutation. The second mutation is a deletion of an A at codon 368 of exon 6 (368delA), which results in a stop codon being generated downstream, at codon 384 (Boissy et al. 1996). This mutation accounts for 50% (19/38) of ROCA mutations. Of the individuals carrying these mutations, 3 were homozygous for the S166X mutation, 4 were homozygous for the 368delA mutation, 10 were compound heterozygotes for these two mutations, and the remaining 2 individuals were compound heterozygotes for an unknown mutation and for one of the known mutations.

The two mutations were found to be in linkage disequilibrium with alleles of the *TYRP1* intragenic microsatellite markers (Box and Sturm 1994*b;* Sturm et al. 1995). The S166X mutation appears to be associated exclusively with the 166-bp (*AC1*) and 225-bp (*AC2*) alleles, whereas 368delA appears to be associated exclusively with the 158-bp (*AC1*) and 229-bp (*AC2*) alleles (table 5).

Despite sequencing of all exonic regions of the *TYRP1* gene, the mutations in the two remaining ROCA chromosomes could not be identified. No pathogenic mutations were identified in the seven individuals from the CAR who had OCA; however, a number of apparently nonpathogenic sequence variants were found both in the CAR and in the ROCA individuals (table 6).

Characterization of an OCA Family with an Atypical Phenotype

Two sibs with an unusual OCA phenotype were identified (fig. 1). Their skin color was compatible with that of ROCA individuals, although it was somewhat lighter. Their hair, however, was an almost straw-yellow color, which is much lighter than the reddish-ginger color that is common in ROCA individuals and which is similar to the hair color of OCA2 individuals. The family structure was too small for linkage analysis to be performed, but mutation analysis of both the *P* and the *TYRP1* genes was undertaken. The sibs were found to be compound heterozygotes for the two *TYRP1* mutations (S166X/368delA), which normally would result in the ROCA phenotype. This phenotype evidently had been modified by the presence of at least one mutation, the common 2.7-kb deletion at the *P* gene locus, although the presence of another mutation at this locus could not be ruled out.

Discussion

The aim of this study was to identify the gene locus responsible for causing the ROCA phenotype. In order to accomplish this, it was necessary to establish that the ROCA phenotype could be distinguished from that of BOCA. The distinction between BOCA and ROCA can be made on the basis of strict clinical features. There are, however, various forms of OCA that fall into a spectrum between the two types. Individuals falling into this spectrum were excluded from the linkage study but

Table 5

Association of Mutations, in the *TYRP1* Gene, with Alleles of the Intragenic Microsatellites

Mutation	*AC1* Allele[a] (bp)	*AC2* Allele (bp)	No. of Chromosomes
S166X	166	225	9
S166X	NR	225	2
368delA	158	229	16
368delA	NR	229	1
Unknown	NR	227	1
Unknown	164	225	1

Note.—The phase of the alleles could not be determined in three individuals. In these cases, the expected alleles were present, and, therefore, the haplotypes were assumed to be the same as those that were determined conclusively. Data for these individuals have been included in the table.

[a] NR = no results.

Table 6

Apparently Nonpathogenic Variants Identified in Three ROCA and Seven CAR OCA Individuals in Whom Each *TYRP1* Exon Was Sequenced

Sequence Variant	Detection[a]	Method of Detection
IVS1+99 (T→C)	1 in 3 ROCA individuals	Sequencing
G209G (T→A)	1 in 3 ROCA individuals	Sequencing
IVS7−20 (delT)	1 in 7 CAR OCA individuals	Sequencing
L500L (G→A)	1 in 52 southern African NPB individuals	Loss of *Hinf*I site
	2 in 7 CAR OCA individuals	Loss of *Hinf*I site
	2 in 39 CAR NPB individuals	Loss of *Hinf*I site
*Tsp*509I (A→C)	96 in 104 southern African NPB individuals	Loss of *Tsp*509I site[b]

NOTE.—If the sequence variant resulted in the alteration of a recognition site for a restriction enzyme, the no. of individuals screened was increased.

[a] Detection was in the heterozygous state, for each individual. NPB = normally pigmented Black.

[b] Described by Wildenberg et al. (1995).

were included in the mutation-detection study. The establishment of linkage to the *TYRP1* gene, in a group of individuals classified as having ROCA, and the subsequent identification of mutations in the gene, in all individuals in this group, confirms the existence of a unique OCA phenotype.

ROCA, in southern African Blacks, is caused by mutations in the *TYRP1* gene. The *TYRP1* locus is the human homologue of the mouse *brown* locus, *b* (Jackson 1988), and has been mapped to human chromosome 9p23 (Chintamaneni et al. 1991; Murty et al. 1992). It encodes a 537-amino-acid protein, and the mature gene product is a transmembrane melanosomal glycoprotein of 75 kD (gp75). The gene consists of eight exons, the first of which is not translated (Sturm et al. 1994). The exact function of the protein is not known, but it is thought to act as a 5,6-dihydroxyindole-2-carboxylic acid oxidase (Jiménez-Cervantes et al. 1994), although it also can employ 5,6-dihydroxyindole for its oxidase activity or can act as a catalase (Halaban and Moellmann 1990; Jiménez et al. 1991; Jiménez-Cervantes et al. 1993; Winder et al. 1993). Two mutations, S166X and 368delA, account for 95% of the ROCA mutations found in this study. Both mutations result in the generation of stop codons, and, therefore, truncated proteins are produced, leading to the ROCA phenotype.

In contrast to the findings of this study, it has been reported that a condition referred to as "BOCA" was caused by the lack of TYRP1 in an African American neonate (Boissy et al. 1996). The fraternal twin of this patient was normally pigmented and was found to have normal levels of TYRP1, whereas the protein was not detected in melanocyte cultures from the affected twin, who had a 368delA/368delA genotype. Although this assignment appears appropriate, with the *tyrp1* gene in mouse being responsible for the *brown* phenotype, linkage analysis between BOCA and a *TYRP1* intragenic microsatellite marker, in six southern African BOCA families, indicated nonlinkage (Manga et al. 1994). There are two possible explanations for the discrepancy in phenotypes assigned to the homozygous 368delA genotype. It is possible that the phenotype of the patient seen by Boissy et al. (1996) resembled BOCA as seen in Africa and as first delineated by King et al. (1980), but their patient was "evaluated" at the age of 1 d and at the age of 1 year. The phenotype may change with age and, in this case, may have come to resemble ROCA. An alternative explanation is that different phenotypes may result from mutations in the same gene: for example, both ty-pos OCA and ocular OCA result from mutations in the *P* gene (Spritz and Hearing 1994). In these situations, however, the mutations usually are different, in contrast to the present situation in which the single case with BOCA in the study by Boissy et al. (1996) and four of the ROCA patients in this study had identical genotypes (368delA/368delA). If the phenotypic difference is verified, it may be due to the different genetic backgrounds of these individuals.

The influence of genetic background on phenotype is illustrated by one family that shows an atypical OCA phenotype, in which the affected individuals were shown to be homozygous for mutations at the *TYRP1* locus but apparently were heterozygous for a mutation at the *P* locus (although a second so-called mild mutation at the *P* locus cannot be ruled out with certainty). This suggests that the *P* gene acts as a modifier of the phenotype. The phenomenon of phenotypic modification involving the *P* and the *TYRP1* genes has been reported in mice. It was found that mice homozygous for mutations at the *brown* (*TYRP1*) locus showed different hair colors and that the difference in hair color could be explained by the genotype at the *p* locus. Homozygous mutant *brown* mice that were wild-type homozygous at the *p* locus were darker than those with one mutated *p* allele. In fact, six shades of color were distinguishable, with the hair being lighter as the number of mutations at each locus increased, with the lightest hair color found in mice homozygous for mutations at both the *p* and *brown* loci (Wallace 1953).

A molecular-nomenclature system for albinism has been proposed by King et al. (1994), in which phenotypes can be classified according to the genes that are mutated in the affected individuals. To date, OCA1 refers to phenotypes caused by mutations at the *TYR* lo-

cus, whereas the subtypes are referred to as "OCA1A" (typical tyrosinase-negative albinism), "OCA1B" (yellow-mutant OCA), and "OCA1MP" (minimal-pigment OCA). Mutations at the *P* gene locus are responsible for OCA2, and the phenotype resulting from mutations in the *TYRP1* gene was designated "OCA3" (Boissy et al. 1996). Therefore, the ROCA patients reported in this study also should be classified as having OCA3, even though their phenotype differs from that described by Boissy et al. (1996). However, this neat form of classification does become complicated when an individual has mutations at more than one locus and an indeterminate phenotype.

There are >50 genes that are known to play a role in mouse pigmentation, and it is likely that there will be at least that many in humans. It is remarkable that two loci, *P* and *TYRP1,* should account for almost all forms of albinism in southern African Black populations, whereas the *TYR* gene, which appears to be involved in roughly one-half of OCA phenotypes in populations of European origin, has not been associated with OCA in Africa. The interaction of the gene products is obviously an important factor in pigment phenotype, as was shown by the phenotype variation in the family reported in this study, with mutations at both the *P* and the *TYRP1* loci; therefore, allelic variation at one locus will be influenced by variation at other loci.

The interaction of gene products involved in pigment biosynthesis provides a rational explanation for different phenotypes, despite identical genotypes at a particular locus. These interactions may determine the extent of eye involvement in OCA phenotypes. The visual anomalies may result from a threshold effect involving altered interactions between mutated *TYRP1* gene products and other optic-development genes. The extent of the alteration would be determined by the genotypes at all the loci; thus, individuals such as those seen in this study, with identical genotypes at the *TYRP1* locus, present either with or without nystagmus and strabismus, the most visible evidence of eye involvement. As has been done for the mouse, a hierarchy of dominance and epistasis of alleles and loci eventually will be determined for human pigmentation phenotypes.

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