

An Intragenic Deletion of the *P* Gene Is the Common Mutation Causing Tyrosinase-Positive Oculocutaneous Albinism in Southern African Negroids

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Summary

Tyrosinase-positive oculocutaneous albinism (OCA2), an autosomal recessive disorder of the melanin biosynthetic pathway, is the most common recessive disorder occurring in southern African Bantu-speaking Negroids, with an overall prevalence of 1/3,900. The OCA2 gene, *P*, has been mapped to chromosome 15q11-q13, and recently alterations in the *P* gene have been identified in OCA2 individuals. An intragenic deletion has been described and proposed to be of African origin because of its occurrence in four unrelated African American OCA2 individuals and in two individuals, one from Zaire and the other from Cameroon. This study shows that the intragenic deletion is a common cause of OCA2 in southern African Negroids (114/146 [.78]; OCA2 chromosomes) and is associated with one common haplotype (43/55 [.78]; OCA2 chromosomes), confirming the African origin of this allele. On the basis of haplotype data, it would appear that at least seven additional, less frequent OCA2 mutations occur in this population.

Introduction

Albinism comprises a heterogeneous group of heritable disorders of the melanin pigmentary system. The most common forms of autosomal recessive albinism in humans are tyrosinase-negative oculocutaneous albinism (OCA1) and tyrosinase-positive OCA (OCA2) (Witkop et al. 1989). OCA2 is the most prevalent type of albinism in Caucasoids, Africans, Native Americans (Witkop et al. 1989), and the peoples of the Pacific region (Walsh 1971). In Africa, prevalences range from 1/1,100 in the Ibo of Nigeria (Okoro 1975) to 1/7,900 in the Bamileke tribe of Cameroon

(Aquaron 1990). Prevalences vary between the different Negroid ethnic groups in South Africa, being most prevalent in the South Sotho (1/2,041), Swazi (1/2,716), and Tswana (1/3,481) chiefdoms and less prevalent among the Pedi (1/9,700) and Shangaan (1/28,614) groups (Kromberg and Jenkins 1982). The overall rate of 1/3,900 in the Negroid people of southern Africa makes it the most common recessive genetic disorder of Negroids in the region. Observations over the past 20 years on >600 families indicate that OCA2 is by far the commonest type of albinism occurring in the Negroid peoples of southern Africa.

OCA2 is characterized by a virtual absence of the eumelanins, from the skin, hair, and eyes. Pheomelanin is present in reduced quantity and accumulates with age. Affected individuals are susceptible to squamous and basal cell carcinomas (Kromberg et al. 1989). Abnormal routing of the optic tracts leads to nystagmus and strabismus, and poor visual acuity is caused by hypoplasia of the fovea (Witkop et al. 1989), as has also been shown in southern African OCA2 patients (Castle et al. 1988).

OCA1 results from mutations at the tyrosinase locus (*TYR*) (Spritz 1993) on 11q14-21 (Kwon et al. 1987; Barton et al. 1988). Mutations at the *TYR* locus have also been found in a group of clinically defined OCA2 Caucasoids, showing that OCA2 in Caucasoids is characterized by locus heterogeneity (Tripathi et al. 1993). This contrasts with studies undertaken in the southern African Negroid population, where locus homogeneity is reported to occur at the OCA2 locus (Kedda et al. 1994).

Linkage has been demonstrated between markers on 15q11-q13 and OCA2 among the Bantu-speaking Negroid families in southern Africa, and it was postulated that the human homologue of the mouse *pink-eyed dilution* locus (*p*) was in fact the OCA2 gene (Ramsay et al. 1992). OCA2 individuals in southern Africa present with two distinct phenotypes: affected individuals are characterized by the presence or absence of pigmented patches (ephelides) containing both eumelanin and pheomelanin, on sun-exposed areas of the skin. Ephelus status is concordant within families (Kromberg et al. 1989). Studies employing electron microscopy show that OCA2 is not due to a decrease in the number of melanocytes per square millimeter and that ephelides are not due to an increase in melanocyte number,

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but to increased melanization of the melanosomes (S. Kidson, personal communication).

Mutations in the mouse *p* gene cause hypopigmentation in the eyes and coat, and one mutation in particular, pink-eyed unstable (*p^{un}*), may be of interest in the context of discussing OCA2 in humans. The *p^{un}* allele produces a phenotype of areas of dilute and intense pigmentation on the coat (Silvers 1979; Brilliant et al. 1991; Gondo et al. 1993). This phenotype bears a striking resemblance to OCA2 individuals with ephelides (Ramsay et al. 1992). Examination of the *p* melanocytes indicates a reduction in eumelanin pigment and morphological changes in melanosomes (Russell 1949), suggesting that the *p* locus encodes a structural melanosomal protein. The human *P* gene on chromosome 15q11-q13 has been cloned, and the cDNA has been sequenced (Gardner et al. 1992; Rinchik et al. 1993). The *P* gene is >150 kb and has 24 coding exons (Lee et al. 1994). It encodes an integral membrane protein with 12 transmembrane domains, and although the exact function of the 838-amino-acid *P* polypeptide is not yet known, it is postulated to be a component of the melanosomal membrane, involved in transporting the melanin precursor, tyrosine (Gardner et al. 1992; Rinchik et al. 1993).

Rinchik et al. (1993) described a de novo deletion of 15q11-q13, including the *P* locus, in the paternal chromosome, consistent with the Prader-Willi syndrome (PWS) phenotype, and a partial deletion of the *P* locus in the maternally inherited chromosome 15 in a PWS/OCA2 patient. Lee et al. (1994) have described defects in the *P* gene of four Caucasoid OCA2 patients, one of whom also has PWS, and in a patient with autosomal recessive ocular albinism. Durham-Pierre et al. (1994) have described an OCA2-causing mutation in the *P* gene, where a 2.7-kb interstitial deletion removes a single exon of the *P* gene (amino acids 216–270) and which was first detected in a large family from an inbred population of triracial (Black, Caucasoid, and American Indian) origin. This mutant *P* allele was also detected, in the heterozygous state, in four unrelated African American OCA2 individuals and in a Zairean patient and a Cameroonian patient, but not in any Caucasoids with OCA2, indicating a possible African origin for this allele. This deletion mutation results in a frameshift mutation in the first luminal loop of the *P* polypeptide, producing a truncated and nonfunctional gene product (Durham-Pierre et al. 1994).

A total of 39 southern African Negroid families, including 74 OCA2 individuals, were studied. A further 35 unrelated affected Negroid individuals were also included in the study.

Subjects, Material, and Methods

Subjects

The subjects of this study were 245 Negroid individuals from 39 families, including 74 with OCA2. In addition to

the nuclear families, a further 35 unrelated OCA2 Negroid individuals were studied. The families are resident in and around Johannesburg, and the unrelated OCA2 individuals are southern Sothos from ThabaNchu, in the Orange Free State, and Lesotho.

Southern Hybridization

Genomic DNA was extracted from peripheral blood leukocytes, by standard procedures (Miller et al. 1988). DNA samples from all the affected individuals and their available family members, including unaffected siblings, were analyzed. Genomic DNAs were digested with *Hind*III, *Taq*I, *Sca*I, *Xba*I, and *Hinc*II, according to conditions recommended by the suppliers. The DNA fragments were separated on 0.8% agarose gels and transferred to Hybond-N (Amersham) nylon membranes over two nights. Probes were radiolabeled using a Multiprime oligolabeling kit prepared by Amersham. Hybridization to the blots was at 42°C over two nights. Blots were washed twice with 2 × SSC/0.1% SDS at room temperature for 15 min; a further wash at 65°C in 1 × SSC/0.1% SDS was carried out for 30 min. The blots were rinsed three times in 0.1 × SSC. Autoradiography proceeded at –70°C for 4–7 d.

PCR Analysis

Three oligonucleotide primers designed by Durham-Pierre et al. (1994) were synthesized. PCR amplification reactions included 2 μl 10 × PCR buffer, 1.25 mM of each dNTP, 50 pmol of each primer, 1 μl of genomic DNA (20 ng), 0.2 U of Perfect Match (Stratagene), and 0.5 U of *Taq* DNA polymerase in a total volume of 20 μl. PCR conditions used were denaturation at 94°C for 1 min, annealing at 60°C for 1 min, and extension at 72°C for 1 min, repeated 30 times, followed by a final 10-min extension at 72°C. Products were separated on a 3% composite agarose gel (1.5% NuSieve/1.5% high-gelling temperature).

Results

Screening for the Deletion Mutation in Southern African Negroid Individuals

The PCR assay developed by Durham-Pierre et al. (1994) was used to detect the deletion allele in 73 unrelated affected subjects. Two PCR products are generated by the assay; the larger (820 bp) fragment is indicative of the deletion, and the smaller (240 bp) fragment is amplified from the normal, nondeleted chromosome. Results (table 1) show that the deletion is by far the commonest *P* mutant allele occurring in the Bantu-speaking OCA2 Negroids of southern Africa, accounting for 78% of the mutations and confirming the proposed African origin of this deletion. It was previously postulated that different mutations in the pigment gene may give rise to the different phenotypes, with respect to ephelus status, in OCA2 families (Ramsay et

Table 1

Genotype and Allele Frequencies of the *P* Gene Intragenic 2.7-kb Deletion in Unrelated Southern African OCA2 Individuals Classified According to the Presence (Eph +), Absence (Eph -), or Unknown (Eph 0) Status of Ephelides

EPHELUS STATUS	GENOTYPE FREQUENCIES ^a (N ^b)			TOTAL	ALLELE FREQUENCIES		SE ^c
	D/D	D/U	U/U		D	U	
Eph +25 (6)	.58 (14)	.17 (4)	(24)	.54	.46	.07
Eph -84 (32)	.11 (4)	.05 (2)	(38)	.89	.11	.03
Eph 082 (9)	.18 (2)	...	(11)	.91	.09	.06
Overall64 (47)	.27 (20)	.09 (6)	(73)	.78	.22	.03

^a D = deletion mutation; U = unknown mutation.

^b N = no. of individuals.

^c Standard error = $\sqrt{(pq/n)}$, where *n* = no. of chromosomes.

al. 1992). The deletion status in each family was, therefore, correlated with the different phenotypes, to determine whether this is the case. Homozygotes for the deletion occurred in individuals with or without ephelides, illustrating that the same mutation occurs in both phenotypes. There did, however, appear to be a significant difference in mutation distribution, between the groups. The χ^2 test was used to assess whether the genotype frequencies were significantly different between the groups. The difference was highly significant ($P < .0001$), with an excess of the deletion in individuals without ephelides (.89), compared with those with ephelides (.54). The *P* gene mutations remain unknown in 32 of 146 OCA2 chromosomes.

Haplotype Analysis

The cDNA of the *P* gene has been sequenced and subcloned (Rinchik et al. 1993). The probes used to generate haplotypes in the southern African Negroid families include IR10.1, a genomic clone that maps to D15S12, forming part of the *P* gene, and the cDNA subclones of DN10 (Rinchik et al. 1993), 912 and 1412. The subclone 680 was not used, as no polymorphisms were detected with it, using a number of enzymes. All three probes (IR10.1, 912, and 1412) were used to probe Southern blots of genomic DNA from the 39 families used in the linkage study. The DNA samples were digested with numerous restriction enzymes in the search for DNA polymorphisms. The schematic diagram of the cDNA sequence is shown in figure 1, and the positions of the subclones are indicated. Seven marker/enzyme systems were shown to detect polymorphisms (table 2), and these polymorphic marker/enzyme systems were used to construct intragenic haplotypes for OCA and non-OCA chromosomes in family groups. The OCA chromosomes were divided into deletion and nondeletion chromosome groups. The three probes detected RFLPs with the enzymes *ScaI*, *XbaI*, *HincII*, *TaqI*, and *HindIII* (table 2). Haplotype results are shown in table 3.

Haplotypes could not be determined in individuals whose family members had not been typed, and in some cases the OCA haplotypes could not be distinguished from one another. Haplotype A is commonly (43/55 chromosomes; .78) associated with the deletion chromosomes in the families. It is thus considered to be the ancestral chromosome on which the deletion mutation occurred. Haplotype A has not been found on non-OCA chromosomes. Fifteen different haplotypes are associated with non-OCA chromosomes, and one common haplotype (O), accounts for 46% (35/78) of the chromosomes. There are six (B-G) haplotypes, in addition to A, associated with the deletion.

Eight different haplotypes were identified on the OCA chromosomes, carrying a mutation or mutations other than the common deletion (table 3). Haplotypes A, H, J, and L all occurred on three OCA2 chromosomes (.18), whereas haplotype N occurred on two (.12) chromosomes, and the remaining three haplotypes (I, L, and M) each occurred on a single chromosome (.06). The haplotype data suggest that there is not a single common second OCA2 mutation, but multiple mutations, each occurring at low frequency. It is interesting to note that three nondeletion OCA chromosomes occur on the ancestral deletion-associated OCA haplotype, A.

Discussion

This study confirms that the deletion mutation is indeed of African origin. It is very common, accounting for 114 of 146 OCA2 chromosomes in southern African Negroids. The deletion allele could have attained this high frequency because of the selective advantage enjoyed by the heterozygotes over both homozygotes, or it could have done so as a result of random genetic drift in the form of founder effect.

The χ^2 test revealed a significant difference between OCA2 individuals with and without ephelides, with respect

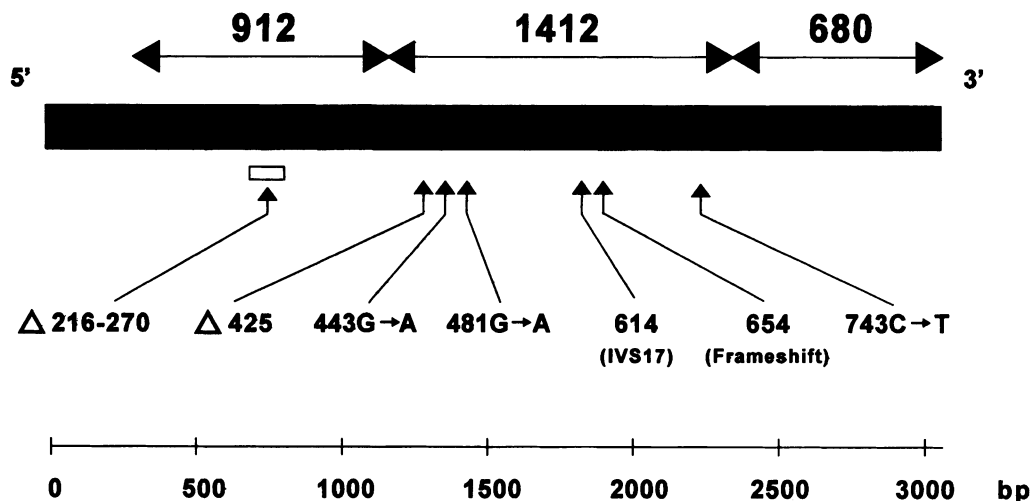


Figure 1 Schematic diagram of the DN10 clone, showing the positions of the subclones, 912 and 1412, used to generate haplotypes, and the positions of reported mutations $\Delta 216-270$ (Durham-Pierre et al. 1994); $\Delta 425$ (Lee et al. 1993); and $443G \rightarrow A$, $481G \rightarrow A$, 614, 654, and $743C \rightarrow T$ (Lee et al. 1994). IVS17 is a splice-junction mutation within the 17th intervening sequence, and 680 is a hybrid subclone (481 bp form part of the *P* gene sequence, and the remaining 199 bp are part of a co-ligated sequence that does not map to human chromosome 15).

to the distribution of the deletion allele. This could point to the fact that the different phenotypes are caused by different subsets of mutations in the *P* gene. Homozygote deletion patients occur in the groups with and without

epheles, and it is therefore unlikely that different *P* gene mutations are solely responsible for the formation of epheles. The postulate that the same mechanism that produces areas of dilute and intense pigmentation in mice, the p^{un} allele, is responsible for the phenotype with epheles in OCA2 individuals (Ramsay et al. 1992) is, therefore, no longer tenable. It seems that epheles status is produced by a different mechanism and may involve changes at loci other than *P*.

The deletion is predominantly associated with one common haplotype (A), although it is also associated with other less frequent haplotypes (table 3). Haplotypes B (five chromosomes), E (one chromosome), F (three chromosomes), and G (one chromosome), occurring on deletion OCA chromosomes, differ from the ancestral haplotype A by at least a single site, suggesting that these differences may result from intragenic point mutations in the ancestral chromosome. Haplotypes C (one chromosome) and D (one chromosome), however, differ from A by more than one site, suggesting that crossovers are more likely to be responsible for their occurrence. Three nondeletion OCA chromosomes occur on the ancestral deletion OCA haplotype (A), indicating that different mutations occur on the same chromosome background. The ancestral haplotype has not been found on 78 non-OCA chromosomes, and the non-OCA haplotypes differ from the common deletion-associated haplotype by at least two sites. The presence of the deletion mutation in Negroids of central African origin and in the Bantu-speaking Negroids of southern Africa suggests that the mutation arose before the divergence of these groups, estimated to be 2,000–3,000 years ago.

Chromosomes carrying a mutation(s) other than the de-

Table 2

Probe/Enzyme Combinations Used to Generate Intragenic Haplotypes

Haplotype Site	Probe	Enzyme	Allele ^a	Size (kb)
1	pIR10	<i>ScaI</i>	{ 1 2 3 4	17.5 16.0 12.5 19.0
2	912	<i>XbaI</i>	{ 1 2	16.0 12.0
3	912	<i>HincII</i>	{ + -	3.3
4	912	<i>TaqI</i>	{ 1 2	6.8 6.5
5	1412	<i>TaqI</i>	{ 1 2	6.8 5.2
6	1412	<i>TaqI</i>	{ + -	3.0
7	1412	<i>HindIII</i>	{ 1 2 3	2.7 2.6 2.5

^a + and - indicate presence and absence of an allele, respectively.

Table 3

Haplotype Distribution on OCA2 Chromosomes, With and Without the Deletion, in the Three Phenotypic Groups Classified According to the Presence (Eph +), Absence (Eph -), or Unknown (Eph 0) Status of Ephelides

HAPLOTYPE ^a	HAPLOTYPE SITE ^b							DELETION OCA CHROMOSOME				UNKNOWN OCA CHROMOSOME ^c			NO. OF NON-OCA CHROMOSOMES ^d
	1	2	3	4	5	6	7	Eph +	Eph -	Eph 0	No. ^d	Eph +	Eph -	No. ^d	
A	1	2	-	2	2	-	2	10	27	6	43	1	2	3	
B	1	2	-	2	2	+		1	4		5				
C		1	+					1			1				
D			+	1	2	-	3	1			1				
E	1	2	+	2					1		1				
F	1	1	-	2	2		2		2	1	3				
G		2		1						1	1				
H	1	2	+	2	2	+	2					3		3	
I	2	1	+	1	2	+	2					1		1	
J	3	1		1	2	-	3					3		3	
K	3	2	+	1	1	-	3	3			3				
L	3	1	+	2	2	-	2					1		1	
M	1	2	+	2	2	-	2						1	1	
N	1	2	+	1	2	-	1						2	1	
O	1	1	+	1	2	+									35
P	3	1	+	1	2	-	1								12
Q	2	1	+	1	2	+									11
R	1	1	+		2	-	2								4
S	3	2	+	1	2	+									3
T	1	2	+	1	2	-	2								2
U	3	1	+	1	2	+									2
V	2	2	-	1	2	+									2
W	2	1		2											1
X	2	1	+	1	1	+									1
Y	1	1	-	1	2										1
Z	3	1		1	2	-	2								1
AA	2	1	-	1	2	-									1
AB	1	1	+	1	1	+	2								1
AC	1	1	+	1	1	-	2								1
Total								13	34	8	55	12	5	17	78

^a Haplotypes designated A-Z, AA, AB, and AC.

^b Haplotypes that were incomplete but compatible with more extensive haplotypes were pooled to reduce the number of haplotypes; however, where haplotypes were not compatible they were shown separately. Numbers refer to the haplotype sites shown in table 2.

^c No Eph 0 individuals with unknown OCA mutations were observed.

^d Total number of chromosomes in each haplotype category.

letion are associated with eight haplotypes. All the haplotypes except A and M differ by at least two sites, suggesting that there are at least seven additional, rare, OCA2-causing mutations, none occurring at frequencies >.18, in southern African Negroid individuals.

There is now conclusive evidence that mutations in the *P* gene are responsible for OCA2 in southern African Negroids. It is interesting to note that the same gene is defective, and that the common deletion mutation occurs, in Negroids from Cameroon, described by Aquaron et al. (1990).

Since the deletion was found in 67 of 73 unrelated OCA2 individuals, it is likely that there is a single OCA2 locus in southern African Negroids, confirming the proposed locus

homogeneity at the *P* gene (Kedda et al. 1994). A number of different mutations have been described in the *P* gene (Lee et al. 1994; Durham-Pierre et al. 1994), the majority occurring in the transmembrane domains of the *P* polypeptide. Since the critical functional domains of the *P* protein are yet to be determined, it is difficult to predict the phenotypic effect different mutations will have on the basis of their positioning in the gene.

A search is in progress for the other less common mutations occurring in southern African OCA2 Negroid individuals. More individuals with OCA2 from west, east, and central Africa will have to be tested for their specific *P* gene mutations before the molecular epidemiology of the deletion and of other mutations is known with certainty.

The data presented in this study and those presented by Durham-Pierre et al. (1994) suggest that the deletion mutation is widely distributed in Africa and is of high frequency. Natural selection may be responsible for the occurrence of one mutation of high frequency (~80% of the mutants), together with other rarer mutations. This is similar to the pattern that has been observed in other disorders: for example, cystic fibrosis in Europe (Morral et al. 1994) and Gaucher disease among the Ashkenazi Jews (Beutler 1993).

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