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The Tyrosinase-positive Oculocutaneous Albinism Gene Shows Locus Homogeneity on Chromosome 15q11-q13 and Evidence of Multiple Mutations in Southern African Negroids

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Summary

Tyrosinase-positive oculocutaneous albinism (ty-pos OCA) is an autosomal recessive disorder of the melanin pigmentary system. South African ty-pos OCA individuals occur with two distinct phenotypes, with or without darkly pigmented patches (ephelides, or dendritic freckles) on exposed areas of the skin. These phenotypes are concordant within families, suggesting that there may be more than one mutation at the ty-pos OCA locus. Linkage studies carried out in 41 families have shown linkage between markers in the Prader-Willi/Angelman syndrome (PWS/AS) region on chromosome 15q11-q13 and ty-pos OCA. Analysis showed no obligatory crossovers between the alleles at the D15S12 locus and ty-pos OCA, suggesting that the D15S12 locus is very close to or part of the disease locus, which is postulated to be the human homologue, *P*, of the mouse *pink-eyed dilution* gene, *p*. Unlike caucasoid "ty-pos OCA" individuals, negroid ty-pos OCA individuals do not show any evidence of locus heterogeneity. Studies of allelic association between the polymorphic alleles detected at the D15S12 locus and ephelus status suggest that there was a single major mutation giving rise to ty-pos OCA without ephelides. There may, however, be two major mutations causing ty-pos OCA with ephelides, one associated with D15S12 allele 1 and the other associated with D15S12 allele 2. The two loci, GABRA5 and D15S24, flanking D15S12, are both hypervariable, and many different haplotypes were observed with the alleles at the three loci on both ty-pos OCA-associated chromosomes and "normal" chromosomes. No haplotype showed statistically significant association with ty-pos OCA, and thus none could be used to predict the origins of the ty-pos OCA mutations. On the basis of the D15S12 results, there is evidence for multiple ty-pos OCA mutations in southern African negroids.

Introduction

Tyrosinase-positive oculocutaneous albinism (ty-pos OCA) is the commonest type of OCA in Africa, with an overall prevalence of ~1 in 3,900 in southern African negroids (Kromberg and Jenkins 1982). Individuals with ty-pos OCA are characterized by an accumulation of pheomelanic (yellow/red) pigments with age, esotropic strabismus, nystagmus and photophobia, a high risk of developing skin cancer (Witkop et al. 1989), and, possibly, auditory anomalies (Creel 1980). In southern Africa, ty-pos OCA individuals present with two distinctly different phenotypes. Within a family, affected individuals are characterized by the presence or absence of clearly demarcated, pigmented patches, or ephelides, particularly on sun-exposed areas (Kromberg et al. 1989). The presence of ephelides has been correlated with a lower risk of developing skin cancer, possibly as a result of the presence of some melanin pigments offering photoprotection (Kromberg et al. 1989).

Ty-pos OCA is inherited as an autosomal recessive trait. The gene has been mapped to chromosome 15q11-q13 (Ramsay et al. 1992), within the Prader-Willi/Angelman syndrome (PWS/AS) chromosomal region. Many PWS/AS patients have hypopigmenta-

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tion and optical misrouting, similar to individuals with ty-pos OCA (Wiesner et al. 1987). Comparative mapping studies in mice showed synteny between gene markers closely linked to the *pink-eyed dilution* (*p*) locus on mouse chromosome 7 and to the PWS/AS region on human chromosome 15q11-q13 (Nakatsu et al. 1992). A mutation at this locus, the *pink-eyed unstable* mutation (p^{un}), is associated with a duplication within the *p* gene. The p^{un} phenotype is characterized by areas of light and dark pigmentation, which are due to spontaneous loss of the duplication, resulting in a reversion to wild-type (Brilliant et al. 1991; Gardner et al. 1992; Nakatsu et al. 1992). This phenotype is similar to that of the ty-pos OCA individuals with ephelides.

Once it had been established that the ty-pos OCA locus maps to 15q11-q13, additional markers in this chromosomal region were studied, in order to further define the position of the locus. This region of chromosome 15q had already been well characterized, with both genetic and physical maps having been constructed (Buiting et al. 1990; Kuwano et al. 1992; Sinnett et al. 1993). The aim of the present study was to assess locus homogeneity and to use both allelic association and haplotype analysis to determine whether the mutation(s) at the ty-pos OCA locus in southern African negroids had single or multiple origins.

Subjects, Material, and Methods

The subjects of this study were 245 southern African negroids from 41 families, each containing at least one affected ty-pos albino, identified on the basis of clinical features described by Witkop et al. (1989). All affected individuals from each family were carefully examined, and the presence or absence of ephelides was noted. The affected individuals in 13 of the families had ephelides; those in 23 families did not have ephelides; and those in 5 families were of unknown ephelus status, with 100% concordance with respect to ephelus status in all 36 families.

Linkage analysis was carried out using the MLINK program of the LINKAGE package (Lathrop et al. 1984), under the assumptions of 100% penetrance in both sexes and an allele frequency of .001 for the disease trait. The tyrosinase-negative OCA (ty-neg OCA) locus (the tyrosinase gene at 11q14-q21) was excluded as a candidate in all families by calculating the lod score (*Z*) at a recombination fraction (θ) of .01, when the *Bgl*II RFLP detected with the tyrosinase cDNA, Pmel34, was used (Spritz and Strunk 1990).

Two-point linkage analysis was carried out between 12 markers on chromosome 15q and ty-pos OCA. These markers included six polymorphic loci detected by Southern blotting: pTD3-21 (D15S10)/*Taq*I (Nicholls et al. 1989; Colman et al. 1991), pTD189-1 (D15S13)/*Taq*I (Nicholls et al. 1989), pML34 (D15S9)/*Sca*I (Nicholls et al. 1989), pIR4-3R (D15S11)/*Rsa*I (Nicholls et al. 1989), pIR10-1 (D15S12)/*Sca*I (Nicholls et al. 1989), and CMW-1 (D15S24)/*Eco*RI (Rich et al. 1988). It should be noted that the pIR10-1 probe is a cDNA sequence derived from the *P* gene (Nicholls et al. 1989; Rinchik et al. 1993). The markers also included six loci detected by PCR amplification showing variation in the number of CA repeats: D15S10 (Lindeman et al. 1991), GABRB3 (Mutirangura et al. 1992*b*), GABRA5 (Glatt et al. 1992), D15S11 (Mutirangura et al. 1992*a*), MS14 (D15S97) (A. M. Bowcock, personal communication), and 635/636 (ACTC) (Litt and Luty 1989). The two polymorphic markers at each of the D15S10 and D15S11 loci were analyzed as haplotypes in order to increase the information at each locus.

The pIR10-1 (D15S12)/*Sca*I RFLP was used to test for locus heterogeneity at the ty-pos OCA locus. The χ^2 test was then used to determine whether there was allelic association between the possible ephelus-determining alleles at the ty-pos OCA locus and the polymorphic alleles at each of the loci D15S12, D15S24, and GABRA5.

Since linkage analysis revealed no obligate crossovers between ty-pos OCA and the D15S12 locus (see Results), D15S12 was considered to be at or very close to the disease locus. Haplotypes were constructed by allele segregation studies in nuclear families by using D15S12 (at the ty-pos OCA locus) and the closest flanking markers, GABRA5 (proximal) and CMW-1 (D15S24) (distal) (Kuwano et al. 1992). The haplotype patterns for affected individuals with and without ephelides were analyzed separately in order to test for conserved patterns and to distinguish any obvious differences between the two groups.

Results

Two-Point Linkage Analysis

Table 1 summarizes the results of two-point linkage analysis between ty-pos OCA and a total of 10 marker loci on the long arm of chromosome 15. Significantly positive *Z* values were obtained between ty-pos OCA and all markers, with the exception of ACTC and D15S9, confirming that the locus for ty-pos OCA is in

Table 1

Two-Point Linkage Analysis between ty-pos OCA and 10 Markers on 15q

Marker	Locus	Chromosome Position	No. of Families[a]	Z at θ = .01	.05	.1	.2	.3	.4	Z_{max}	θ_{max}
pIR10-1	D15S12	15q11-q12	23	7.87	6.98	5.86	3.72	1.85	.50	8.09	.00
CMW-1	D15S24	15q13	38	13.88	12.45	10.58	6.85	3.54	.95	14.18	.001
GABRB3	GABRB3	15q11.2-q12	41	10.71	12.17	11.12	7.60	3.94	1.13	12.20	.04
GABRA5	GABRA5	15q11-q13	28	4.47	5.11	4.63	3.02	1.46	.38	5.12	.04
MS14	D15S97	15q11-q13	35	5.57	7.65	7.38	5.33	2.87	.81	7.70	.06
D15S11[b]	D15S11	15q11-q13	32	1.52	5.46	5.85	4.38	2.33	.66	5.90	.08
D15S10[c]	D15S10	15q11-q13	32	3.62	7.39	7.60	5.73	3.14	.92	7.70	.07
pTD189-1	D15S13	15q11-q12	20	−.79	1.46	1.96	1.70	.98	.29	1.98	.07
635/636	ACTC	15q11-qter	40	−4.24	1.05	2.36	2.18	1.18	.33	2.51	.13
pML34	D15S9	15q11-q12	24	−1.75	.77	1.41	1.33	.78	.25	1.49	.14

[a] No. of informative families.
[b] Represents D15S11 CA repeat/pIR4-3R RFLP haplotype.
[c] D15S10 represents D15S10 CA repeat/pTD3-21 RFLP haplotype.

or very near to this region. The closest marker was shown to be pIR10-1 ($Z = 8.09$; $\theta = .00$), and the linkage study failed to reveal any obligatory crossovers between ty-pos OCA and this locus; and it has been postulated that the D15S12 locus (close to the PWS/AS region on chromosome 15q11-q13) lies very close to or forms part of the gene for ty-pos OCA (Ramsay et al. 1992; Rinchik et al. 1993).

On the basis of phenotypes alone, one may postulate that at least three different alleles or mutations exist at the ty-pos OCA locus: the "normal" allele, an allele associated with ty-pos OCA presenting with ephelides, and an allele associated with ty-pos OCA without ephelides. The frequencies with which particular alleles of the closest markers segregated with the two ty-pos OCA phenotypes were calculated, in order to determine whether there was allelic association (Edwards 1980).

Locus Heterogeneity

In the test for locus heterogeneity, Z values were examined in each family, and the summated Z values between ty-pos OCA and pIR10-1 (D15S12) for each group of families (i.e., those with and those without ephelides) were positive (results not shown), suggesting that there is no locus heterogeneity in these families. The summated Z values obtained between ty-pos OCA and the tyrosinase cDNA, Pmel34, for all the families with and without ephelides, were negative at $\chi = .01$ (results not shown), indicating that in no family was linkage to the tyrosinase locus demonstrated.

Allelic Association

Table 2 shows the numbers and frequencies of the alleles detected by the pIR10-1/*Sca*I RFLP in the three different phenotypes. Allele 1 is the commonest in all groups. The χ^2 test was used to assess allelic association between the pIR10-1 alleles and each of the three groups. Significant allele differences occurred between the normal and the affected group as a whole ($P = .01$), between the normal and affected group without ephelides ($P = .009$), and between the two types of OCA, that with and that without ephelides ($P = .011$). There was no significant difference between the normal group and the disease locus in the group with ephelides ($P = .92$).

The occurrence of multiple polymorphic alleles at both the GABRA5 locus and the D15S24 locus resulted in a large spread of alleles observed in the normal group and in both the affected group with ephelides and the affected group without ephelides. No clear differences could be seen between any of the groups, on inspection of the data; and no differences were shown to be statistically significant (results not shown).

Haplotype Analysis

Haplotypes constructed using the alleles at the D15S12, D15S24, and GABRA5 loci revealed 53 different haplotypes (17 occurring on chromosomes associated with the presence of ephelides, 32 on chromosomes associated with an absence of ephelides, and 37 on normal chromosomes, with some overlap between groups) (haplotypes not shown). None of these haplo-

Table 2

pIR10-1/*Sca*I (D15S12) Alleles and Their Frequencies in Normal Individuals, in OCA Individuals without Ephelides and in OCA Individuals with Ephelides

A. Distribution of Alleles

Phenotype	No. of Alleles (frequency)			Total
	1	2	3	
Non-OCA	36 (.54)	13 (.19)	18 (.27)	67
Total OCA (with and without ephelides):	54 (.78)	7 (.10)	8 (.12)	69
OCA without ephelides	40 (.89)	4 (.09)	1 (.02)	45
OCA with ephelides	14 (.58)	3 (.13)	7 (.29)	24

B. Comparison of Groups

	χ^2	P
Non-OCA vs. Total OCA (with and without ephelides)	9.22	.01
Non-OCA vs. OCA with ephelides	.18	.92
Non-OCA vs. OCA without ephelides	13.97	.009
OCA with ephelides vs. OCA without ephelides	9.12	.011

types occurred at high frequency, nor did they differ significantly between groups. The haplotypes constructed using the alleles of the D15S12 locus and those of the flanking marker CMW-1 (D15S24) are shown in table 3. Allele 1 of the pIR10-1 (D15S12)/*Sca*I RFLP occurred with the highest frequency, in all the chromosomal groups (table 2) but is associated with all eight CMW-1 alleles. The pIR10-1 CMW-1 haplotype 1 2 appears to be relatively common in all groups, whereas the haplotype 1 7 is the most common on non-OCA chromosomes. The distribution of haplotypes is not significantly different between groups ($P > .95$).

Two-Point Mapping

Markers were ordered according to the known physical map (Kuwano et al. 1992), with the exception of D15S97 and ACTC, which have not yet been physically mapped. These markers have been positioned in accordance with the linkage results. The assumption was made that pIR10-1 (D15S12) maps close to or at the ty-pos OCA locus, and a genetic map was generated from two-point linkage analysis between ty-pos OCA and each marker, as illustrated in figure 1.

Discussion

Linkage analysis between ty-pos OCA and 10 loci on chromosome 15q11-q13, in the PWS/AS chromosomal region, confirms that the ty-pos OCA locus is in this region. Two-point linkage analysis showed no obligatory crossovers between the D15S12 locus and the disease locus; thus the D15S12 locus is likely be very close to or part of the ty-pos OCA locus (Ramsay et al. 1992). D15S12 detects the human homologue, *P*, of the mouse *p* locus (Gardner et al. 1992) and has been shown to harbor mutations causing ty-pos OCA in a variety of different ethnic groups (Lee et al. 1993; Rinchik et al. 1993).

In the absence of identified mutations, two questions can be addressed: (1) Is there locus homogeneity at the ty-pos OCA locus in southern African negroids; and (2) Is there a single mutation, or are there multiple mutations that give rise to this disorder? In a group of clinically defined "ty-pos" OCA caucasoids, Indo-Pakistanis, Middle Eastern Arabs, and Jews, 6 of 17 individuals had mutations in the tyrosinase gene, on chromosome 11q14-q21 (Barton et al. 1988; Giebel et al. 1991). It was postulated that the "ty-pos" OCA phenotype in these individuals arose from homozygosity or compound heterozygosity of two relatively mild tyrosinase allele mutations (Tripathi et al. 1992), and not from a mutation in the ty-pos OCA gene. It has been suggested that "ty-pos" OCA in caucasoids is characterized by locus heterogeneity and may be associated with mutations in the tyrosinase gene, as well as with mutations in other genes. Results of the present study suggest locus homogeneity at the ty-pos OCA locus in southern African negroid families. If it is assumed that a single locus is responsible for the ty-pos OCA pheno-

Table 3

Normal and ty-pos OCA-associated Haplotypes Generated from the pIR10-1/*Sca*I (D15S12) and CMW-1/EcoRI (D15S24) Loci

A. Distribution of Haplotypes

Haplotype		ty-pos OCA Status		
pIR10-1	CMW-1	Normal	With Ephelides	Without Ephelides
1	1	3	1	1
1	2	7	4	10
1	3	2	1	3
1	4	2	1	7
1	5	3	1	2
1	6	2	3	5
1	7	11	2	6
1	8	1	...	2
2	1	2	...	...
2	2	2	1	1
2	3	...	...	2
2	4	2	1	1
2	5	1	...	...
2	6	2	1	...
2	7	2	...	...
2	8	2	...	...
3	2	4	1	...
3	3	3	1	...
3	4	1	1	...
3	5	2	1	...
3	6	2	...	1
3	7	1	2	...
	Total	57	22	41

B. Comparison of Groups

	χ^2 (df)	*P*
Non-OCA vs. Total OCA (with and without ephelides)	10.23 (21)	.98
Non-OCA vs. OCA with ephelides	4.74 (20)	1.00
Non-OCA vs. OCA without ephelides	11.31 (21)	.95
OCA with ephelides vs. OCA without ephelides	3.82 (17)	1.00

type, then different mutations at this locus are likely to give rise to the different phenotypic manifestations—in particular, to the presence or absence of ephelides. Ephelides are genetically determined, as they may be present or absent irrespective of the amount of sun exposure.

In an attempt to answer the question of a single origin (as opposed to multiple origins) of the ty-pos OCA phenotype, allelic and haplotype associations have been examined. Allelic association was found between the alleles at the D15S12 locus and ty-pos OCA status. Allele 1 at D15S12 was significantly associated with ty-pos OCA without ephelides (.89, compared with .54 on non-OCA chromosomes). The association was less marked when the OCA families were pooled (.78, compared with .54). In the group of families with ty-pos OCA with ephelides, allele 1 had the highest frequency (.58), but there was a significantly increased frequency of allele 3 (.29, compared with .02 on ty-pos OCA chromosomes without ephelides). The association with allele 3 may represent a second mutation, which occurred more recently and which is associated with ephelides. These results may be accounted for, in part, by the occurrence of fewer families in the group with ephelides. Since allele 1 is most commonly associated with the absence of ephelides (40/45 chromosomes), a

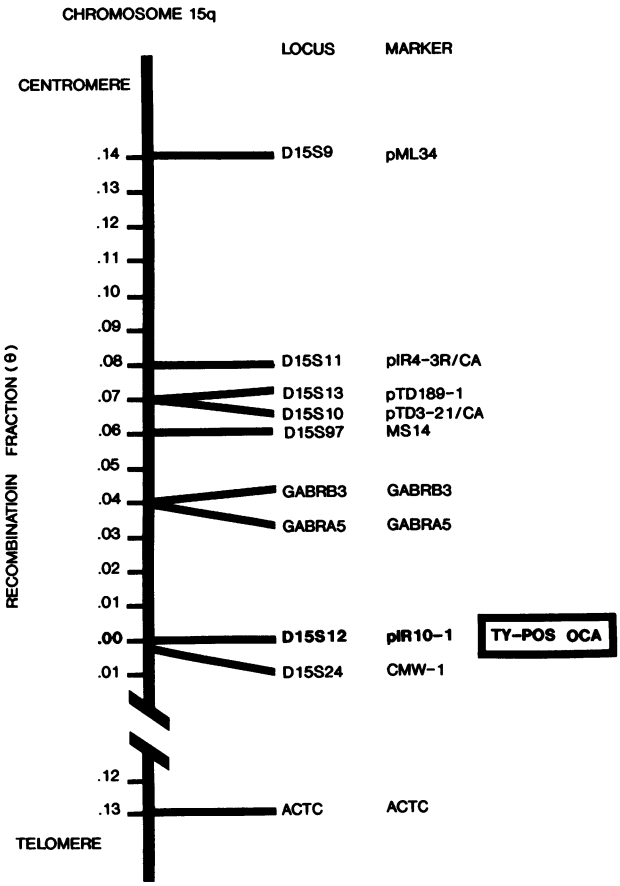

Figure 1 Linkage map of chromosome 15q, showing relative genetic distances, calculated by two-point linkage analysis, between the ty-pos OCA locus and each marker. The D15S10 and D15S11 loci have been analyzed as haplotypes (RFLP/CA repeat). GABRB3 and GABRA5 are genetically equidistant from ty-pos OCA but have been physically mapped in the order shown (Knoll et al. 1993). Marker positions are in concordance with the physical map by Kuwano et al. (1992). Two markers, ACTC and D15S97, had not previously been mapped but are shown in their most likely positions. ACTC is assumed to be distal to the OCA locus and has been positioned at $\theta = .13$. The D15S97 locus is likely to be proximal to ty-pos OCA, and two-point linkage analysis suggests that it is situated between GABRB3 and D15S10.

single major mutation may have given rise to ty-pos OCA without ephelides. The significant difference ($P = .011$), between the alleles occurring in the affected group with ephelides and those occurring in the affected group without ephelides, suggests that these phenotypes are associated with different mutations.

No significant allelic association was observed with GABRA5 (4 cM away from ty-pos OCA) or with D15S24 (0.1 cM away from ty-pos OCA). Since the rate of mutation at hypervariable loci ranges from 10^{-4} to 10^{-2} per locus per gamete per generation (Jeffreys et al. 1988; Weber and Wong 1993), the lack of allelic association even between ty-pos OCA and D15S24 may mean that there have been multiple mutations at this hypervariable locus since the major ty-pos OCA mutation arose.

Haplotypes using the closest flanking markers around the ty-pos OCA locus (represented by the D15S12 locus) were generated for normal and "affected" chromosomes, in an attempt to test whether the major mutation at this locus arose in a relatively recent common ancestor. The occurrence of numerous haplotypes associated with all three different types of chromosome (i.e., normal, OCA not associated with ephelides, and OCA associated with ephelides) made the use of these haplotypes as predictors of the origins of the mutation(s) at the disease locus impossible. The association of ty-pos OCA with many different haplotypes is likely to have occurred as a result of both the hypervariable nature of the loci (GABRA5 and D15S24) flanking the D15S12 locus and the relatively large distance of these loci (particularly GABRA5) from the disease locus. Allelic association between allele 1 at the D15S12 locus and affected chromosomes associated with an absence of ephelides suggests that a single major mutation gave rise to ty-pos OCA without ephelides.

In conclusion, there is no evidence for locus heterogeneity at the ty-pos OCA locus in southern African negroids, and data suggest that the ty-pos OCA phenotypes are caused by multiple mutations at this locus. The identification of mutations within the *P* gene of affected individuals would confirm that this locus is the ty-pos OCA locus and would shed light on the evolution of this region of chromosome 15q11-q12.

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