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ORIGINAL INVESTIGATION

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Type 2 oculocutaneous albinism (OCA2) in Zimbabwe and Cameroon: distribution of the 2.7-kb deletion allele of the P gene

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Abstract In previous studies, we characterized a 2.7-kb interstitial deletion allele of the P gene associated with tyrosinase-positive oculocutaneous albinism (OCA2) in African Americans and Africans. In this study, we investigated the frequency of this allele among OCA2 subjects in two African countries, Zimbabwe and Cameroon. The deletion allele was most common in Zimbabwe, comprising nearly all (92%) mutant alleles, which is the highest incidence reported so far. In addition, the deletion allele was widespread but less common among OCA2 Camerooni-ans and accounted for 65% of the mutant alleles.

Introduction

Oculocutaneous albinism (OCA) is a heterogeneous genetic disorder characterized by hypopigmentation of the hair, skin, and eyes and is associated with the ocular features of nystagmus, reduced visual acuity and misrouting of the optic fibers at the chiasm (Witkop et al. 1989). Witkop and coworkers (Witkop et al. 1970, 1972, 1973) first separated OCA into two major types, known as tyrosinase-negative OCA and tyrosinase-positive OCA, through clinical, family, and hairbulb biochemical analyses. Subsequent work has identified the genes involved in these types of OCA and has demonstrated phenotypic variation in hypopigmentation for each. OCA1 or tyrosinase-negative OCA results from mutations of the tyrosinase gene on chromosome 11q (Witkop et al. 1970; Oetting and King 1993). OCA2 or P-related OCA results from mutations of the P gene on chromosome 15q (Gardner et al. 1992; Ramsay et al. 1992; Rinchik et al. 1993; Durham-Pierre et al. 1994; Lee et al. 1994) that encodes a 110-kDa protein integral to the melanosomal membrane (Rosemblat et al. 1994). A variety of diverse mutations in the P gene have been described (reviewed in Oetting et al. 1996). Consistent with its cellular localization, its predicted structure of 12 membrane-spanning domains, and sequence similarity to anion transport channels in bacteria, the P protein may be a transport or pore-type protein (Gardner et al. 1992; Lee et al. 1995). However, recent biochemical evidence suggests that the P protein does not transport tyrosine, the critical substrate for melanin biosynthesis (Gahl et al. 1995).

OCA2 is the most common form of albinism, especially among Africans and African Americans. There is a high incidence of OCA2 among specific African populations: 1 in 7900 among the Bamileke of Cameroon (Aquaron 1980, 1990), 1 in 3900 in South Africans (Kromberg and Jenkins 1982), and 1 in 1100 among the Ibo of Nigeria (Okoro 1975; Witkop et al. 1989). The frequency of OCA2 is also high in Zimbabwe, with an overall occurrence of 1 in 4182 (Lund 1996), with a higher prevalence in the capital city of Harare (1 in 2833) (Kagore and Lund 1995). OCA2 in equatorial and in southern Africa is associated with skin carcinomas (Luande et al. 1985; Kromberg et al. 1989). The frequency of OCA2 among African Americans is 1 in 10 000. This is in contrast to a frequency of 1 in 36 000 among Caucasian Americans (Witkop et al. 1989). The higher OCA2 frequency among African Americans is thought to reflect the frequency of the original (enslaved) African population in the United States (Durham-Pierre et al. 1994, 1996).

In a previous study (Durham-Pierre et al. 1994), we found a 2.7-kb deletion allele that included a single exon (exon 7; Lee et al. 1995) of the P gene. This deletion al-

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lele was found in five out of five unrelated OCA2 African Americans, in an obligate heterozygote from Haiti, and in two Africans with OCA2 from Cameroon and Zaire, all but one of whom were heterozygous for the 2.7-kb deletion allele. This same deletion allele accounts for a significant fraction of the mutant P alleles in African Americans with typical OCA2 (Durham-Pierre et al. 1994; Lee et al. 1994) and is carried at a frequency of 1 in 200 to 1 in 500 in African Americans (Durham-Pierre et al. 1996). The 2.7-kb allele has an African origin (Durham-Pierre et al. 1994) and is associated with a common haplotype, suggesting a common founder (Stevens et al. 1995, 1997). The deletion allele accounts for 78% and 77%, respectively, of the mutant P alleles among South African and Tanzanian OCA2 subjects (Stevens et al. 1995; Spritz et al. 1995). We recently studied five OCA2 individuals from the Tonga group in Zimbabwe; all were found to be homozygous for the 2.7-kb deletion allele (Lund et al. 1997).

To extend our knowledge about the frequency of this deletion allele in Africa, we analyzed genomic DNA from 26 OCA2 individuals from Zimbabwe and 36 from Cameroon.

Materials and methods

Subjects

The subjects in this study included Africans with typical OCA2 from several ethnic groups in Zimbabwe and Cameroon, as well as one member of the Senga group of Zambia, currently living in Zimbabwe. Controls included CE, an OCA2 individual from a family from Brandywine, MD., USA, homozygous for the 2.7-kb mutation allele; DT, an OCA2 African American, heterozygous for this same deletion allele; DP, a normally pigmented African American; and LH, a normally pigmented Caucasian (Durham-Pierre et al. 1994, 1996). All human studies were done following ethical standards laid down in the 1964 Declaration of Helsinki, with either written or verbal consent obtained from subjects or their guardians.

Analysis of DNA by PCR

Blood samples from Zimbabwe were collected on 3MM filter paper (Whatman). Those from Cameroon were collected and dried on NBS filter paper (903; Schleicher and Schuell). Controls included blood collected from DT blotted on NBS filter paper and processed in parallel with the African samples as well as purified (aqueous) DNA samples from CE, DP, and LH. Three oligonucleotide primers (MHB 71, MHB 72, and MHB 107, obtained from the DNA Synthesis Facility, Fox Chase Cancer Center) were based on the sequences of clone pDDP24 (a wild-type genomic clone spanning the 2.7-kb deletion). A restriction map of pDDP24 with the positions of the primers used in this study has been presented in previous studies (Durham-Pierre et al. 1994, 1996). MHB 72 (5′-GCGGTGGCTGTCATGGC-3′) and MHB 107 (5′-CATAGTCTTGGTTTTTGTAGTCCT-3′) are forward primers. MHB 71 (5′-GGAGGGTGCATTCATTCTTCAG-3′) is a reverse primer. For PCR amplification from purified DNA, reactions included 0.5 μM of each primer (MHB 71, MHB 72, and MHB 107), 30 ng genomic DNA, 1.2 U of AmpliTaq (Perkin Elmer Cetus) in a total volume of 60 μl. For PCR amplification uisng filter paper, 20 μl of Gene Releaser (Bioventures) was added to 1 mm^2 of filter paper, mixed by vortexing, and allowed to stand for 10 min. After 10 min, the sample was treated following the Gene Releaser protocol: 65° C for 30 s; 8° C for 30 s; 65° C for 90 s; 97° C for 180 s; 8° C for 60 s; 65° C for 180 s; 97° C for 60 s; 65° C for 60 s; hold at 80° C. Following this procedure, 0.5 μM of each primer (MHB 107, MHB 71, and MHB 72) and 1.2 U of AmpliTaq were added to the 20 μl of Gene Releaser per filter paper per tube to a total final volume of 60 μl. The following conditions were used for PCR: denaturation at 94° C for 1 min; annealing at 60° C for 1 min; synthesis at 72° C for 1 min; repeated 35 times. PCR products were separated in a 2% agarose gel (1% GTG/1% NuSieve; FMC) and visualized by ethidium bromide staining. For enhanced accuracy and sensitivity in determining the allele status, most sets of PCR products were subsequently transferred to Hybond N^+ (Amersham) filter paper and subjected to hybridization with a 2.4-kb *Sst*I–*Sph*I genomic fragment (Probe II; Durham-Pierre et al. 1994) that corresponds to portions of the specific PCR products.

Results

In a previous study (Durham-Pierre et al. 1994), we detected this identical 2.7-kb deletion allele in two Africans with OCA2 (one from Cameroon and another from Zaire). We have also found five OCA2 individuals of the distinct Tonga ethnic group in Zimbabwe to be homozygous for the 2.7-kb deletion allele of the P gene (Lund et al. 1997). To extend these data and to determine the frequency of the 2.7-kb deletion among other ethnic groups in Zimbabwe and Cameroon, we examined 26 non-Tonga OCA2 individuals from Zimbabwe and 36 new OCA2 Cameroonians using a PCR-based assay (Fig. 1). These results, summarized in Table 1, showed that 48/52 P alleles in OCA2 individuals from Zimbabwe were the 2.7-kb deletion, accounting for 92% of mutant P alleles. If we include the five Tonga OCA2 individuals from our other study (Lund et al. 1997), the 2.7-kb deletion allele of the P gene allele accounts for 94% of the mutant P alleles among 31 OCA2

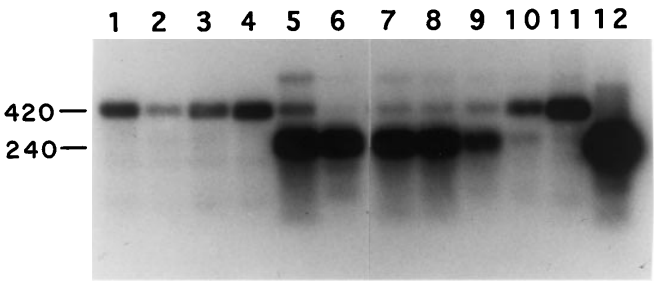

Fig. 1 PCR analysis of DNA from ten Africans and two control subjects. *Lanes 1–5* Subjects A1, A2, A3, M2 (Table 1), and a carrier for the deletion allele from Zimbabwe. *Lanes 6–10* Subjects 80, 95, 96, 97, and 98 (Table 1) from Cameroon. *Lane 11* CE, previously found to be homozygous for the deletion allele; *lane 12* LH, a normally pigmented Caucasian (Durham-Pierre et al. 1994, 1996). Blood samples from various subjects were amplified by PCR and separated by gel electrophoresis. In this assay, the common deletion allele produces a 420-bp upper fragment and non-deletion alleles produce a 240-bp lower fragment. The size of the fragments was determined by comparison with molecular marker fragments. To visualize the PCR products more readily and more specifically, the resolved fragments in the gels were blotted onto Hybond N^+ filters and hybridized to a genomic fragment from the P gene that overlaps all specific products of the PCR reaction. After washing at high stringency (0.5 × SSC at 65° C) the specific products were visualized by autoradiography. Both filter paper-spotted blood and aqueous control samples were used

Table 1 Summary of PCR analyses of subjects from Zimbabwe and Cameroon. Karange, Ndau, Zezuru, Korekore, and Manyika are all dialect sub-groups of the Shona. Results for the Tonga individuals have been reported elsewhere (Lund et al. 1997). (*S* Sibs, *FID* Father of N2 and N3, *MID* mother of N2 and N3, *C* cousins)

Country	Group	Subject code		Deletion allele status		
				2	1	0
Zimbabwe	Shona	C1		+		
Zimbabwe	Shona	C2		+		
Zimbabwe	Karanga	C3		+		
Zimbabwe	Ndau	C5		+		
Zimbabwe	Zezuru	C6			+	
Zimbabwe	Korekore	C7		+		
Zimbabwe	Karanga/Zezuru	C8		+		
Zimbabwe	Ndau	Ndau I		+		
Zimbabwe	Zezuru	Z1			+	
Zimbabwe	Zezuru	Z2	S	+		
Zimbabwe	Zezuru	Z3		+		
Zimbabwe	Zezuru	Z4		+		
Zimbabwe	Zezuru	Z5		+		
Zimbabwe	Zezuru	Z6		+		
Zimbabwe	Zezuru	Z7	S	+		
Zimbabwe	Zezuru	Z8		+		
Zimbabwe	Zezuru/Ndau	Z9		+		
Zimbabwe	Ndebele	N1	FID		+	
Zimbabwe	Shona/Ndebele	N2	S		+	
Zimbabwe	Shona/Ndebele	N3		+		
Zimbabwe	Shona	N4	MID	+		
Zimbabwe	Manyika	M1		+		
Zimbabwe	Manyika	M2		+		
Zimbabwe	Zezuru	A1	S	+		
Zimbabwe	Zezuru	A2		+		
Zimbabwe	Zezuru	A3		+		
Zimbabwe	Tonga	T1	S	+		
Zimbabwe	Tonga	T2		+		
Zimbabwe	Tonga	T3		+		
Zimbabwe	Tonga	T4	S	+		
Zimbabwe	Tonga	T5		+		
Zambia[a]	Senga	C9		+		
Cameroon	Bamileke	79				+
Cameroon	Bamileke	80				+
Cameroon	Bamileke	94				+
Cameroon	Bamileke	36	S		+	
Cameroon	Bamileke	64			+	
Cameroon	Bamileke	71	S	+		
Cameroon	Bamileke	72		+		
Cameroon	Bamileke	75		+		
Cameroon	Bamileke	76	S	+		
Cameroon	Bamileke	77		+		
Cameroon	Bamileke	81	S		+	
Cameroon	Bamileke	82			+	
Cameroon	Bamileke	83	S		+	
Cameroon	Bamileke	84			+	
Cameroon	Bamileke	86	S		+	
Cameroon	Bamileke	87			+	
Cameroon	Bamileke	88			+	
Cameroon	Bamileke	90	S		+	
Cameroon	Bamileke	91			+	
Cameroon	Bamileke	95	S		+	
Cameroon	Bamileke	96			+	
Cameroon	Bamileke	96′			+	
Cameroon	Bamileke	97	S		+	
Cameroon	Bamileke	98		+		
Cameroon	Banem	31		+		

[a] Living in Zimbabwe, originating in Zambia

Table 1 (continued)

Country	Group	Subject code		Deletion allele status		
				2	1	0
Cameroon	Bamoun	85		+		
Cameroon	Bamoun	89		+		
Cameroon	Bassa	30		+		
Cameroon	Bassa	73	C	+		
Cameroon	Bassa	74		+		
Cameroon	Beti	32		+		
Cameroon	Beti	38			+	
Cameroon	Beti	62				+
Cameroon	Beti	78			+	
Cameroon	Beti	92	S	+		
Cameroon	Beti	93		+		

individuals from Zimbabwe. In Cameroon, 47/72 P alleles in OCA2 individuals carried the 2.7-kb deletion, accounting for 65% of mutant P alleles. The 2.7-kb deletion allele was less common among the Bamileke ethnic group (27/48 alleles, i.e., 56%), than in the four other ethnic groups combined, namely Banem, Bamoun, Bassa, and Beti (20/24 P alleles, i.e., 83%).

Discussion

Tyrosinase-positive OCA is one of the most common forms of albinism in the world (Witkop et al. 1989). Although OCA2 occurs worldwide, it has a relatively high frequency in sub-Sahara African populations, including Zimbabwe (Lund 1996) and Cameroon (Aquaron 1990). Recent molecular genetic studies have identified a 2.7-kb deletion that eliminates exon 7 (161 nucleotides) of the P gene resulting in the formation of a premature stop codon and premature truncation of the predicted polypeptide product (Durham-Pierre et al. 1994; Lee et al. 1995). It is estimated that this single gene mutation is associated with 17–50% of all mutant alleles in African Americans (Durham-Pierre et al. 1994; Lee et al. 1994) and close to 80% of mutant P alleles in South Africa (Stevens et al. 1995, 1997) and Tanzania (Spritz et al. 1995). Durham-Pierre et al. (1994) postulated an African origin of the 2.7-kb deletion allele. Stevens et al. (1995, 1997) found that the 2.7-kb deletion allele was associated with a common haplotype, which confirmed the African origin of this allele and suggested a common founder. Further studies have been conducted by us to determine if this allele is also as widespread among OCA2 individuals belonging to different ethnic groups in Zimbabwe and Cameroon as it is in other parts of Africa.

This study has shown that the 2.7-kb deletion allele is also widespread among OCA2 individuals belonging to different ethnic groups in Zimbabwe and Cameroon, as well as being found in one OCA2 member of the Senga group from Zambia living in Zimbabwe. In Zimbabwe, OCA2 members of the Karanga, Ndau, Zezuru, Korekore, and Manyika sub-groups of the Shona have been tested, in addition to one member of the Ndebele, the next most populous ethnic group in Zimbabwe after the Shona. These sub-groups of the Shona are distinguished by dialect and geographical location. The results show that, in OCA2 individuals from Zimbabwe, the 2.7-kb deletion allele accounts for 92% of the mutant P alleles. There is, therefore, remarkable homogeneity in the mutation of the P gene among OCA2 individuals from different parts of the country. This is the highest global incidence reported so far for this mutation.

Among the subjects studied from Zimbabwe (Table 1), only four individuals were found to be heterozygous. These individuals stand out for two reasons: Z1 is the only subject with pigmented patches on sun-exposed parts and C6 had a very unusual phenotype, being covered with brown freckles on the skin in exposed parts of the body. The finding of pigmented patches, freckles, or ephelides among OCA2 individuals who are heterozygous for the 2.7-kb deletion was also noted by Stevens et al. (1995). They found OCA2 individuals with and without ephelides who were homozygous for the deletion allele, but there was a significant excess of individuals homozygous for the deletion allele in the group without ephelides. Of the other two heterozygous individuals from Zimbabwe, N1 comes from a different ethnic group, Ndebele, and has passed his non-deletion mutant allele to his son, N2.

Around 2000 years ago, Negro people in west Africa migrated across the center of the continent (McEvedy 1980). The Bantu speakers were one of the groups that settled in equatorial Africa. From there they spread east, south, and west, driven by a population explosion, reaching Zimbabwe around 300 A.D.. The widespread distribution of the deletion allele that has been observed among OCA2 individuals in west, east, central, and southern Africa suggests that this mutation originated more than 2000 years ago, before the initial exodus from west Africa occurred. The results reported here show a significant difference between the incidence of the deletion P allele in OCA2 individuals from Zimbabwe and Cameroon. The differences in the frequency of the deletion allele observed in present-day populations in this region may be explained by genetic drift due to a founder effect.

Differences in marriage patterns among different groups of Bantu speakers (some actively encourage consanguineous marriages, while others strictly prohibit such liaisons) influences the frequency of OCA2 and its mutant alleles in different populations. Among the Shona of Zimbabwe, marriage traditions discourage alliances between kin and the prevalence of OCA2 (about 1 in 4000) is not as high as among other groups in southern Africa that promote cousin marriages, such as the Sotho of South Africa, where the prevalence is around 1 in 2000 (Kromberg and Jenkins 1982). The results reported here reveal a remarkable degree of allele homogeneity among the Shona OCA2 population in Zimbabwe, suggesting that the mutation can be traced to one common ancestral founder.

Cameroon encompasses 136 ethnic groups. It was found that the highest proportion of albinism occurred in the Bamileke group (70%) (Aquaron and Kandem 1986; Aquaron 1990); therefore, most of our studies were conducted on these subjects (24/36). Our results indicate that in the Bamileke tribe, the 2.7-kb deletion allele accounted for 56% of P mutation alleles. In the Bamileke tribe, marriages tend to occur within the same clan or town; the greater inbreeding tendency of the Bamileke group may account for the high prevalence of this mutant allele in this population. In addition, Bamileke society is organized as small kingdoms headed by a king or fon. A total of 131 kingdoms has been recognized. The kingdoms vary in size and in population from 500 to 66 000 inhabitants (Bandjoun). A founder effect is illustrated in the Balengou kingdom where the eighth and ninth kings at the beginning of this century had albinism. They were polygamist, with 80–100 wives and 200–300 children. The Bamileke are the predominant ethnic group in Cameroon, with approximately 2 million in a population of 10 million, and are located mainly in the west province with the highest density of inhabitants 74.5/km^2 and in two main cities of Cameroon, Yaounde, the administrative capital, and Douala, the economic harbor. Even though OCA2 occurs in the Bamileke tribe with a higher frequency than among other tribes in Cameroon, the 2.7-kb deletion allele represents only 56% of mutant P alleles. The 44% remaining mutations are unknown at this time. The two albinos from the Balengou kingdom (subjects 36 and 64) are heterozygous for the 2.7-kb deletion allele and the two albinos from Bandjoun kingdom (subjects 71 and 72) are homozygous.

In the four other ethnic groups studied (Bamoun, Banem, Bassa, Beti), the study was conducted on 12 subjects, with the 2.7-kb deletion allele accounting for 83% (20/24) mutant alleles. The Bamoun are located in the west province near the Bamileke and the other three ethnic groups are in the south of Cameroon.

Stevens et al. (1997) did not find any carriers of the P gene deletion allele among 80 non-OCA2 Cameroonians studied. Because they did not report the ethnicity of their Cameroonian subjects, we cannot directly compare our data with theirs. However, among the predominant Bamileke group, we would expect 1 in 78 non-OCA2 individuals to carry the P gene deletion allele. This is based on a prevalence of OCA2 of 1 in 7900 (Aquaron 1990) and the percentage of P gene deletion alleles in OCA2 individuals in this population (56%, this study). However, not finding the deletion allele in 80 non-OCA2 Cameroonians (Stevens et al. 1997) is not statistically different from the calculated expectation of 1 in 78.

Due to the lack of protective melanin pigment in the skin of OCA2 subjects from Africa, there is a frequent occurrence of UV-induced skin cancers, principally squamous cell carcinoma (Luande et al. 1985). Cameroon is located 2–12° above the equator and is sunny throughout the year. The death of albinos in this area is mainly due to solar radiation-induced cancer, occurs during the second to fourth decade of life, and constitutes a major public health problem. OCA2 individuals from Zimbabwe have frequent sunburns and sun-induced lesions, with a high risk of skin cancers (Kagore and Lund 1995; Lund 1996). Registering all albinos early in life, educating them to prevent the damaging effects of the sun (protective clothing, sun-screening agents, and indoor occupations), and treating premalignant and malignant lesions are of great importance to OCA2 individuals in these countries.

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