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J. G. R. Kromberg, BA(Social work)MA, PhD, Associate professor, Division of Human Genetics, School of Pathology, National Health Laboratory Service and University of the Witwatersrand, P. O. Box 1038, Johannesburg 2000, South Africa, J. Bothwell, MBBch, FFDerm, MMed, FRCP, Consultant Dermatologist, Bamsley Hospital, Gawber Road, Bamsley 575 2EP), S. H. Kidson, BSc, MSc, PhD, Professor and Deputy Dean, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Observatory 7925, Cape Town, South Africa, P. Manga, PhD, Assistant Professor, The Ronald O Perelman, Department of Dermatology, New York University School of Medicine, Smilow Research Center, RM 407, 522 First Ave, New York, 10016, USA. R. Kerr, PhD, Lecturer, and T. Jenkins, MD, Emeritus Professor, Division of Human Genetics, School of Pathology, National Health Laboratory Service and University of the Witwatersrand, P. O. Box 1038, Johannesburg 2000, South Africa

TYPES OF ALBINISM IN THE BLACK SOUTHERN AFRICA POPULATION

J. G. R. KROMBERG, J. BOTHWELL, S. H. KIDSON, P. MANGA, R. KERR, and T. JENKINS

ABSTRACT

***Background*: Oculocutaneous albinism (OCA) is the most common inherited disorder in Southern African blacks and several types have been described. Molecular techniques, where available, can be used to confirm a clinical diagnosis and the type of OCA, if necessary, and for prenatal diagnosis.**
***Objectives*: To investigate and classify the different types of albinism commonly found and to determine the clinical implications for each type.**
***Design*: A descriptive survey.**
***Setting*: Gauteng province, South Africa, and Lesotho.**
***Subjects*: Three groups of subjects with OCA (96 from a genetics clinic, 62 from a dermatology clinic, and 31 from community surveys) from the black African population participated.**
***Main outcome measures*: Subjects underwent clinical and/or dermatological examinations and were then classified according to type of OCA.**
***Results*: Four forms of OCA were identified: most (82%) subjects had OCA2 (a tyrosinase-positive type) with three sub-types: those without large freckles (ephelides) on exposed areas (named OCA 2a in this study), those with such freckles (named OCA 2b), and those with brown albinism (BOCA); the remainder had red/ rufous albinism, ROCA (OCA 3). The four forms could be distinguished from each other clinically without using molecular genetic testing.**
***Conclusion*: The most common types of albinism found in the black population of Southern Africa are OCA 2 and OCA 3. Given the high prevalence of the disorder, together with the high risk of skin cancer, and the recent persecution of affected individuals in certain East African countries, these findings and their clinical implications have significance in terms of both education and awareness for health professionals and lay people caring for those with albinism.**

INTRODUCTION

The term albinism includes a number of inherited disorders affecting normal pigmentation. Lack of pigmentation may be localised to the eye (ocular albinism, OA) or may be seen in the eye, skin and hair (oculocutaneous albinism, OCA). While albinism was initially thought to be caused by different mutations at one genetic locus, it is now apparent that the genetics of albinism is complex and the disorder shows locus heterogeneity. To date, nine types of OCA have been described (the genetic characteristics of the common types, are summarised in Table 1). With the elucidation of the molecular aetiology of OCA, molecular testing is the method of choice to confirm a clinical diagnosis and to categorise the type of OCA. Following a molecular work-up, prenatal diagnosis can usually be offered, should this be requested by the family. However, where molecular testing is not available, clinical characteristics may be used in determining the type of albinism in an affected individual.

Table 1
Genetic characteristics of 4 types of albinism

Type of Albinism	Inheritance	Locus	Chromosome	Omim* No
OCA1	Autosomal recessive	TYR	11q14-21	203100
OCA2 (tyrosinase-positive)	Autosomal recessive	P	15q11-13	203200
OCA2-BOCA		P	l5q11-13	203200
OCA3-ROCA	Autosomal recessive	*TYRP1*	9p23	203290
OCA4	Autosomal recessive	*MATP*	5pl3	606574

*Online Mendelian Inheritance in Man (OMIM)

OCA2 is by far the most common form of albinism worldwide, due essentially to its high frequency in Sub-Saharan Africa, and it is the most common autosomal recessive genetic condition in black populations in this area. In other parts of Africa, sickle cell anaemia is the most common recessively inherited disorder, carrier numbers having reached high frequencies due to heterozygote advantage in the presence of endemic malaria. The frequency of OCA2 is at least 1 in 3900 black individuals in South Africa (1) and some geographic regions have frequencies as high as 1 in 1900 (Swaziland) and 1 in 1300 (Botswana) (2), while in Zimbabwe the figure is 1 in 4000 (3). In West and Central Africa, respectively, frequencies of 1 in 1100 in the Ibo in Nigeria (4), and 1 in 7900 in the Bamileke in Cameroon (5), have been reported.

Type 1 OCA (Online Mendelian Inheritance in Man (OMIM) 203100), comprises disorders involving mutations in the *tyrosinase* gene *(TYR)* on chromosome 11 p, rendering *TYR* non-functional and, therefore, this type of albinism was initially referred to as *tyrosinase*-negative OCA. Sub-types of OCA 1 have been described, but will not be discussed here. Type 2 OCA (OMIM 203200) has a slightly milder phenotype and *tyrosinase* activity is normal to high (*tyrosinase*-positive OCA). OCA2 results from mutations in the *P* gene on chromosome 15q. Brown OCA (BOCA) is also linked to the *P* locus, and is, therefore, a subtype of OCA2. Red or rufous OCA (ROCA), OCA type 3 (OMIM 203290), is caused by mutations in the *TYRPJ* gene on chromosome 9p. More recently, a new form of human OCA has been described, OCA type 4 (OMIM 606574); the gene involved is *MATP* (human chromosome 5p), the human homologue of the mouse *underwhite* gene (6).

Individuals with OCA 1 present at birth with marked hypo-pigmentation, the skin is *milkywhite*, the hair white and the eyes light blue. There is foveal hypoplasia, nystagmus, photophobia, and the optic tract shows abnormal decussation of the optic nerve fibres at the chiasma. The eyes may darken and the skin may appear to gain colour over time, but it never confers the ability to tan and will burn on exposure to the sun. Pigmented lesions like moles (naevi), freckles (ephelides) or lentigines are rarely observed on the skin. This type of albinism is extremely rare in black Africans, with only three cases having been reported in African Americans (7-9), and one case having been reported in a black African from the Cameroon (10). Interestingly, the latter patient presented with "darkly pigmented patches" on his face.

The molecular locus associated with OCA2 was mapped for Southern Africa subjects by Ramsay *et al* (13). OCA2 is a somewhat milder phenotype than OCAl: the eyes are usually pigmented (blue-grey or light brown in colour) and pigment accumulates in the hair over time (pheomelanin) giving it a straw-coloured appearance. The skin is creamy white and does not tan. Black individuals in sub-Saharan Africa affected with OCA2 may present with an unusual phenotype. Certain individuals will develop pigmented patches which are dendritic in conformation, with a central area of pigmentation and finger-like projections (11). Although they are similar to large freckles or lentigines, histologically they show increased pigment but no increase in the number of melanocytes, which is more consistent with freckles (11). These freckles are not present at birth, but develop from the second or third year of life. They usually only appear on the sun-exposed regions of the skin (the face, neck, forearms and hands), suggesting that they develop in reaction to UV light exposure. Individuals who develop freckles seem to be protected, to some extent, against radiation damage caused by the sun, since they have fewer skin cancers early in life (12). Other skin conditions include round pink or brown macules or papules, with the histology of moles (naevi), which can be found on sun exposed or non-sun exposed sites (11).

Brown oculocutaneous albinism (BOCA) was originally presumed to occur only in black Africans and African-Americans, but Caucasoid individuals

with this form of albinism have been described (14). Amounts of eumelanin in the skin and eyes are reduced but not absent. The phenotype in affected individuals from the black population is one of light brown skin, darker coloured hair and light brown or grey eyes. Affected individuals present with the same ocular defects seen in other types of albinism. The Caucasian phenotype was described as being essentially similar to OCA2, with white skin and golden blond hair. The brown locus has been identified in humans, and BOCA is linked to the *P* locus on chromosome 15q (15). Thus OCA2 and BOCA are allelic, with BOCA possibly being caused by milder mutations in the OCA2 gene. As these conditions are caused by mutations at the same locus, it is possible to have individuals affected with either BOCA or OCA2 in the same family. Molecular OCA2 gene mutation analysis in ten black subjects affected with BOCA showed nine to be compound heterozygotes for the severe 2.7 *kb P.* gene deletion mutation and another unidentified mutation (15). It is proposed that the second mutation in these individuals is likely to be a milder, 'leaky', mutation.

Rufous oculocutaneous albinism (ROCA), oculocutaneous albinism type 3, has been described in black Africans (16). Individuals with ROCA have a reddish-bronze skin colour, ginger coloured hair (which is lighter in colour than the skin) and the eyes are blue or brown. Both eumelanosomes and pheomelanosomes at various stages of melanisation are present in the skin, as well as many aberrant melanosomes (17). The visual anomalies of ROCA are often mild but nystagmus and misrouting of the optic tract have been described in certain individuals (16), lending support to the delineation of this phenotype as a form of OCA. The prevalence of ROCA in southern Africa is approximately 1 in 8500 (16). ROCA is caused by mutations at the tyrosinase-related protein 1 (TYRP1) locus, and two common mutations have been reported (18). The nonsense mutation, S166X, and a second mutation, 368delA, account for 45 and 50% respectively, of ROCA chromosomes in Southern Africa.

A fourth type of albinism, OCA4, has been described. The human gene, *MATP* (also called *SLC45A2*), is located on chromosome 5p13. Mutations in this gene account for a significant percentage (24%) of albinism in Japan (6), but are not thought to playa major role in the aetiology of albinism in African populations.

The focus of this paper is on OCA2 (including BOCA) and OCA3 (the rufous type), which have been observed most frequently in Africa. The aim of the study, therefore, was to identify, describe and classify the most common types of albinism found in the black population of Southern Africa, to describe the sub-types occurring, and to determine the clinical implications associated with the findings.

MATERIALS AND METHODS

Subjects for our long-term continuing studies on oculocutaneous albinism have been ascertained over the past 30 years by various means. These methods have included community surveys and field-work, in South Africa and the neighbouring countries (specifically Lesotho, Botswana and Swaziland), and visits to schools, health centres, clinics and hospitals to inform them about albinism, the local research projects and the services available for affected people. When subjects were ascertained they received genetic counselling, health education, leaflets on albinism, free anti-actinic cream and referral to a dermatology clinic. Also, they could participate in the current research project, if they wished to do so.

Accessible families were approached and many volunteered to participate in various of our studies, some of which have been reported previously (1,2,11-13,15,16). The three groups of subjects, all from the black African population, who presented with albinism and were included in the present study were: (1) Subjects (96) ascertained in community surveys in Soweto and Johannesburg, who were classified by means of clinical examinations (in some cases classification was confirmed by molecular studies); (2) Subjects (62) ascertained from greater Johannesburg who presented at a hospital dermatology clinic where they were examined by a dermatologist for skin problems; (3) Subjects ascertained from the greater Johannesburg area, as well as during a community survey in Lesotho, specifically for studies on the brown (11) and rufous (20) types of albinism (a few of whom are included in group 1 and 2 above).

Data were collected on these three groups of subjects for the purposes of describing and classifying (initially using the criteria of Witkop *et al* 1983 (19)) the common types of albinism found locally. The clinical examinations were undertaken, using a standard form compiled especially for the purpose, by several different medical practitioners over the years, including one of us (TJ), and the dermatological examinations were carried out by a dermatologist (JB). When subjects were willing, and a phlebotomist was available, a blood sample was collected from them for molecular studies and the results of these studies have been reported elsewhere (13,15,18). Statistical analysis was used where necessary to identify the significance of differences between groups of data (a p-value of <0.05 was considered significant).

Ethics clearance (protocol M940711) for the study was granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.

RESULTS

Classification: The clinical examination of the first group of subjects (N=96), showed that the majority (82%) could be classified into the OCA2 group. No subjects appeared to have the OCA 1 type and all had some form of pigmentation (Table 2). This sample of subjects cannot be said to be representative of the total group of people with albinism as they were volunteers who happened to present to our research team, but the results indicate a trend, and suggest that OCA2 occurs more frequently than either brown or rufous albinism.

Table 2
Types of albinism found in 96 subjects

Type	No	%
OCA1	0	0
OCA2	79	82
OCA2 Brown (BOCA)	11	12
OCA3 Rufous (ROCA)	6	6
Total	96	100

OCA2: clinical features and sub-types: During the clinical examinations it became apparent that there were two distinct sub-types in the OCA2 group: those subjects who presented with large dendritic freckles, and those who did not. In the 79 subjects classified as being affected with OCA2 (Table 2), six were not examined for these lesions, but of the 73 examined, 41 (56%) had no freckles and 32 (44%) had freckles on the exposed areas of their skin. In order to assess whether these freckles developed in all affected members of a family the data for 22 sibships were examined and the results are presented in Table 3. Since freckles were noted to be generally absent in children under the age of ten years this group of subjects was excluded from the analysis. From the data it was apparent that sibs were generally concordant for freckles. When the data were submitted to statistical analysis a significant difference was found, concordance for freckling occurring far more often than discordance ($X2 = 6.6$, $p<0.01$). For convenience, in the present study, these sub-groups were labelled OCA2a (those without freckles) and OCA2b (those with freckles), the former type occurring slightly more frequently than the latter.

Table 3
Freckles in sibships with OCA2

Freckles	Sibships	
	No	%
Present in all sibs	8	36
Absent in all sibs	9	41
Present in some, absent in some	5*	23
Total	22	100

*includes one 3 child sibship in which 2 sibs have freckles and one does not.

In order to assess the nature of the skin and eye problems in these two sub-types of OCA2, the dermatologist's (JB) data were analysed and the findings appear in Table 4. In general those with OCA2a had more skin and eye problems of every sort, than OCA2b subjects. From our experience and reports from the mothers we have noted that the presence of freckles is generally disliked by the mother, as well as by the individuals with albinism themselves. They, therefore, try to make them fade, and to stop them enlarging and increasing in number, by using various creams, without success.

Table 4
Skin and eye defects in albinos without (N=33) and with freckles (N~23)

Defect	Subjects without freckles		Subjects with freckles		No Info*	TOTAL	
	No	%	No	%	No	No	%
Naevi present	31	94	18	78		49	87
Elastosis	32	97	23	100	1	55	98
Keratosis	28	85	14	61		42	75
Carcinomas	3	9	2	9	1	5	9
Keloids	1	3	0	0	1	1	2
Nystagmus	33	100	23	100		56	100
Translucency	11	33	3	13	1	14	25

* No Info =No information

Brown albinism: Altogether 11 individuals with brown albinism were identified and examined at various stages of the study (some have been included in a previous paper in which comparisons between rufous and brown albinism were made (16). These individuals with albinism were distinct because of their light cream skin colour and ability to tan without too much resulting skin damage. They also had ginger to brown hair which darkened as they grew older and most had hazel to brown eyes. The characteristics of 11 subjects appear in Table 5. In comparison with OCA2a and b individuals, they had a darker skin colour, fewer visual problems, such as nystagmus, and many of them had brown eyes.

Table 5
Skin pigment, hair and eye colour and visual defects in 11 individuals with brown albinism (BOCA)

Characteristic	No	%	Total examined
Skin			
Light tan	11	100	11
Freckles present	7	60	
Hair colour			
Ginger	8	73	11
Light brown	3	27	11
Iris colour			
Blue	2	18	11
Hazel	3	27	11
Brown	6	55	11
Nystemus	5	55	9
Strabismus	2	22	9

Rufous/red albinism: This type of albinism is very striking and generally when a verbal message is sent around the community for all people with albinism to report to a specific place, individuals with the rufous type also present themselves (some of the subjects in this study have been included in a previous more detailed paper on rufous albinism (16)). Evidently, the community members see such individuals as different and reports have reached us of rejection at birth in cases where the mother was unhappy at the sight of her unusually pigmented infant.

The affected individuals usually have a light brick red skin and gold hair which often darken with age to red-brown and ginger, respectively. Some also have reduced visual acuity, and/or photophobia, and some have nystagmus and/or strabismus, but none has blue eyes. The characteristics of the 20 rufous albinos examined appear in Table 6.

Table 6
Skin pigment, hair and eye colour and visual defects in 20 individuals with rufous albinism (ROCA)

Characteristic	No	%	Total examined
Skin			
Red	19	100	19
Naevi	3	33	10
Freckles	0	0	18
Hair colour			
Ginger	17	94	18
Reddish	2	11	18
Iris colour			
Blue	0	0	20
Hazel	6	30	20
Brown	14	70	20
Nystagmus	8	42	19
Strabismus	1	10	10

Differentiating between the types: Due to the differences in clinical characteristics presented above, for the four (including the three OCA2 sub-types) types of albinism commonly found in Southem Africa, it was possible to distinguish between them on clinical grounds. Although we did not confirm the classification for every subject with molecular tests, when those in the rufous category were subsequently tested for *TYRP 1* mutations, our classification of the subjects in that category was verified 100% (18), providing credibility to our clinical assessment in the field. For the purpose of clinical classification, therefore, a table has been drawn up (Table 7) giving all the characteristics presently known for each type, including the molecular findings, in a way similar to that presented by Witkop *et al* in 1983 (19) and King *et al* in 1995 (20) .

Table 7
Characteristics of the types of albinism found among the Bantu speaking peoples of Southern Africa

Characteristic	OCA 2a	OCA 2b	BROWN (BOCA)	RUFOUS(OCA3)
Hair colour	Light yellow-gold, darkens with age	Yellow-gold darkens with age	Light brown to dark brown, darkens with age	Gold, ginger or reddish - darkens with age
Skin colour	White to cream	White to cream	Cream to light tan	Reddish brown
Freckles	Absent	Present ++	May be present	Absent
Susceptibility to skin cancer	+++	++	+	May be present
Reflectance spectrophotometry	Lighter skin colour than Causoids	Lighter skin than than Caucasoids		?No characteristic spectnun Eye
colour	Blue to light brown	Blue to brown	Blue (few) to hazel or brown	Hazel to brown
Translucency	++	+	+	Unusual
Red reflex	May be present	May be present	May be present	Absent
Fundal pigment	Little	Little	Little?	Normal to reddish
Nystagmus	+++	++	+	May be present
Pholophobia	+++	++	+	May be present
Visual acuity	Infants severe Adults better, but still poor	Infants severe Adults better, but still poor	Maybe defective	Defective to normal
Strabismus	May be present	May be present	Occasional	Rare
Tyrosinase assays	Normal levels	Normal levels	Normal levels	Normal to high levels
EM studies	Present	Present	Present	Present
Melanosomes	Type I-III	Types I-III (type IV present in freckles)	Types I-Ill	Types I-IV
Visual evoked potential	Decussation defect present	Decussation defect present	Decussation defect may be presentmay	Decussation defect be present in some
Genetics	AR*, *P* gene mutations on chromosome 15q11	AR*, *P* gene mutations on chromosome 15q11	AR *, *P* gene mutations on chromosome 15q11	AR*, *TYRPI* gene mutations on chromosome 9p23
Other	In all population groups	Recognised only in black Africans	Recognised only in Africans? ??	Found in Africa, Papua New Guinea, Pacific Islands ++

* AR = Autosomal Recessive

DISCUSSION

The findings from this study suggest that amongst the black population of Southern Africa there are four common types of albinism which may be distinguished clinically from each other (with little overlap), using a few simple guide-lines. This finding is similar to that of Stannus (21), who described individuals with various grades of albinism, nearly 100 years ago, in Nyasaland, now Malawi. The most common type found, in the present study, was OCA2. Molecular results on OCA2 subjects from Southem Africa show that the 2.7kb deletion is common, accounting for 78% of OCA2 chromosomes (22). The remaining mutations remain elusive, and no further common mutation/s have been identified (23).

The classification of albinism in Southern Africa should include the two common types: OCA2 and OCA3 (rufous). The OCA2 group, however, could be subdivided into those without freckles (OCA2a), those with them (OCA2b), and those with brown albinism (BOCA). This sub-division is clinically relevant since the group without freckles have more keratoses and also a significantly higher rate of skin cancer (12). However, on a molecular level types OCA2a and 2b cannot be differentiated, at

present. Nevertheless, people with all forms of OCA2 should be targeted for more health education and emphasis on the prevention of sun damage by care of the skin, avoidance of sunshine, and the use of sun screens, long sleeved cotton clothing, and wide-brimmed hats. Although the brown individuals have more pigment, we have seen cases of skin cancer amongst them too. We, therefore, recommend the use of sun screen creams, with a high sun protection factor, for all individuals with albinism, especially while they live in Southern Africa with its high rate of sunny days, minimal sky cover and high risk from exposure to harmful ultraviolet rays.

Another important aspect of the management of OCA to consider is the fact that affected individuals have poor to very poor eye-sight. Children with OCA have been found to be slower to sit and to crawl than their pigmented peers (24). However, it is now appreciated that this delay is associated with poor visual acuity and affected infants need a little extra stimulation, while school children need a seat at the front of the classroom in order to see the black-board and the teacher, as well as extra time for writing tests and examinations. Visual aids, such as magnifying glasses, monocular telescopes and prescription spectacles, are also available and helpful. Scholastic potential, which is within the normal range, should then be achievable.

Our classification shows that the vast majority of black African individuals with albinism have OCA2 (classic or BOCA), with the remaining individuals affected with ROCA. Although the sample used was not a random one, our observations on over 600 families (enrolled in our research projects) suggest that this is the situation in the total group. The proportion of individuals with BOCA and ROCA cannot be estimated, at present, more reliably than that of 12 and 6%, respectively, of the group presented here. These figures could be underestimates as individuals with these types of albinism are probably less likely to present for research purposes, since they have fewer problems than OCA2a and OCA2b individuals and are unlikely to be similarly motivated. Also, due to the heterogeneous nature of the local population and the wide range of skin colour, associated with both San and Caucasoid admixture, people with brown or rufous albinism are not as easily detected in the general population as OCA2a and OCA2b individuals. However our studies suggest that although albinism in general occurs in 1 in 3900 people (1), the rufous type occurs in about 1 in 8500 (16), so in fact our present estimate, in this study, that only 6% of the total group of people with albinism have this type is very likely to be an underestimate.

Bamicot (25) in his study in Nigeria in 1952 suggested that rufous albinism occurred quite frequently there and the condition has also been described in Cameroon (26). The situation with individuals with BOCA is equally problematic and there is some confusion in the early years with children of mixed ancestry and those with depigmentation due to malnutrition. Although we do not have further data, we suggest that the 12% proportion of the group presented here for brown albinism is also likely to be an underestimate. From the results on the characteristics of brown and rufous albinism it is obvious, in most cases, that the individuals with the rufous type have more pigment than those with the brown type. A few of the BOCA subjects (2/11) had blue eyes, but none (0/20) of the ROCA subjects did. Also, half (55%) of these with brown albinism had nystagmus, while slightly fewer (42%) of those with rufous albinism did.

In cases where individuals present with an uncharacteristic or intermediate phenotype, the possibility of interplay between different proteins involved in pigment production should not be ignored. Such a situation has been described in Southern African siblings, presenting with an unusual phenotype - OCA2 but reddish skin and hair (15). At the molecular level these siblings were found to be homozygous for *TYRP I* mutations and, therefore, affected with ROCA, but were found, in addition, to be heterozygous for the 2.7kb *P* gene deletion mutation. The genetic basis of OCA types 1-4 has been reviewed recently by Rooryk *et al* (27) and a comprehensive description of the types appear in the *On Line Mendelian Inheritance of Man* (28).

We hope that, for practical purposes, the findings from this study will assist those working in the field (many of whom do not have access to molecular diagnostics), in Africa, to understand the characteristics of people with different types of albinism. We hope, too, that the superstitions surrounding albinism (29) and the recently promoted erroneous beliefs (that albino body parts make a most powerful medicine), that have had tragic consequences for people with albinism living in East and Central Africa, will be negated by the fact that affected people have been studied in many ways and found to be normal in every way, apart from their unusual pigmentation and visual problems. Furthermore, the information presented here should lead to a better understanding of the types of albinism, to more informed health education and targeted services, improved counselling, and consequently, improved quality of life for all affected individuals.

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