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The Tyrosinase-positive Oculocutaneous Albinism Locus Maps to Chromosome 15q11.2-q12

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Summary

Tyrosinase-positive oculocutaneous albinism (ty-pos OCA), an autosomal recessive disorder of the melanin biosynthetic pathway, is the most common type of albinism occurring worldwide. In southern African Bantu-speaking negroids it has an overall prevalence of about 1/3,900. Since the basic biochemical defect is unknown, a linkage study with candidate loci, candidate chromosomal regions, and random loci was undertaken. The ty-pos OCA locus was found to be linked to two arbitrary loci, D15S10 and D15S13, in the Prader-Willi/Angelman chromosomal region on chromosome 15q11.2-q12. The pink-eyed dilute locus, *p*, on mouse chromosome 7, maps close to a region of homology on human chromosome 15q, and we postulate that the ty-pos OCA and *p* loci are homologous.

Introduction

Tyrosinase-positive oculocutaneous albinism (ty-pos OCA) (type II) is the most prevalent type of albinism in caucasoids, Africans, and Native Americans (Witkop et al. 1989) and in peoples of the Pacific region (Walsh 1971). In Africa the prevalence ranges from 1/1,100 in the Ibo of Nigeria (Okoro 1975) to 1/4,459 in the Zulu of South Africa (Kromberg and Jenkins 1982). The overall rate of about 1/3,900 in South Africa makes it the most common recessive genetic disorder of negroids in the country. In other parts of sub-Saharan Africa where the hereditary hemolytic anemias, including sickle cell disease, are prevalent, it would, of course, not be more common than these. Throughout sub-Saharan Africa it is responsible for a great deal of morbidity, with skin cancer and gross visual impairment being important sequelae.

In ty-pos OCA the brown/black pigment, or eumelanin, is virtually absent from the skin, hair, and eyes, though the yellow/orange, or pheomelanin, pigment is present in these tissues and accumulates with age. Malignant skin lesions (squamous and basal cell carcinomas) are present in 62% of albinos of age 30–49 years and in virtually all albinos over the age of 50 years (Kromberg et al. 1989). Affected individuals have irides that are diaphanous on illumination; the foveal reflex is usually diminished or absent; and esotropic stabismus, horizontal nystagmus, and photophobia occur as a result of misrouting of the optic tracts (Creel 1980).

Tyrosinase-negative (ty-neg) OCA (type IA) is the next most common type of albinism in caucasoids, though it is virtually absent in negroid peoples. This locus has been identified as that coding for tyrosinase and has been designated "TYR" (Kwon et al. 1987); several different mutations cause this disorder, and there are specific mutations causing the "yellow mutant" and "temperature sensitive" types of OCA (Chintamaneni et al. 1991; Giebel et al. 1991; King et al. 1991).

The basic biochemical defect in ty-pos OCA is unknown, so a classical linkage study has been used to localize the disease locus. In the search for the locus, we used random polymorphic markers and reported on the exclusion of 57% of the genome (Jenkins et al. 1990), as calculated by the computer program EXCLUDE (Edwards 1987). Since then we have, however, concentrated on candidate loci which had

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been cloned and on candidate chromosomal regions showing homology to mouse syntenic groups containing pigment loci. Deleted chromosomal regions causing syndromes including disorders of pigmentation and the occasional coexistence with albinism or albinoid features were also investigated. The Prader-Willi/Angelman chromosomal region (PWCR/ANCR) maps to 15q11.2-q12, and the clinical features of the two syndromes often include hypopigmentation and ocular abnormalities which are typical of OCA (Creel et al. 1986). Recent studies show that about 60% of both Prader-Willi syndrome (PWS) and Angelman syndrome (AS) individuals have a cytogenetically visible deletion within 15q11.2-q13 (Butler 1989; Pembrey et al. 1989; Magenis et al. 1990; Fryburg et al. 1991; Hamabe et al. 1991*a*, 1991*b*). There is a positive correlation between hypopigmentation and 15q deletions (Wiesner et al. 1987; Butler 1989).

OCA has been found in at least three patients with PWS: in a black infant with a del 15q11.2 and no family history of albinism (Phelan et al. 1988), in a Chinese girl with a cytogenetically normal karyotype (Wallis and Beighton 1989), and in a child from a family with three other OCA siblings (Wiesner et al. 1987). None of these cases was investigated for tyrosinase status, and the last family may well indicate the chance coexistence of albinism and PWS. A single case of coexistent OCA and AS has been reported; a deletion of 15q11.2-q13 was present, and there was low hairbulb tyrosinase activity (Fryburg et al. 1991).

The PWCR/ANCR was initially tested for linkage to the ty-pos OCA locus by using two probes, pTD3-21 (D15S10) (Donlon et al. 1986) and pTD189-1 (D15S13) (Tantravahi et al. 1989), both of which map to chromosome 15q11.2-q12. When a positive lod score (Z) value was obtained, we tested two highly informative AC-repeat polymorphisms in this region, one of which mapped at the D15S10 locus (Lindeman et al. 1991) and the other of which mapped at the thrombospondin-1 locus (THBS-1) on chromosome 15q15 (Jaffe et al. 1990; Polymeropoulos et al. 1990). A Z value of 6.88 at a recombination fraction (θ) of .108 with the D15S10 locus confirmed linkage of the ty-pos OCA locus to markers mapped to chromosome 15q11.2-q12.

Subjects and Methods

Families

The subjects of this study included 79 affected individuals and 190 normal individuals from 42 families. The affected individuals were diagnosed on the basis of the clinical features outlined by Witkop et al. (1989). Families were classified into two groups: 13 families having ephelides or eumelanin-pigmented patches and 24 families in which there were affected individuals of age 10 years or older who did not possess ephelides. Five families were unclassified with regard to their ephelides status.

DNA Studies

Genomic DNA was digested with *Taq*I restriction enzyme, run on 0.8% agarose gels, and blotted onto Hybond-N membranes by the method of Southern (1975). The ^{32}P-labeled probes pTD3-21 and pTD189-1 (Donlon et al. 1986; Tantravahi et al. 1989) were hybridized at 42°C for 18–36 h. Membranes were washed in 2 × SSPE, 0.1% SDS twice for 15 min at room temperature and twice in 1 × SSPE, 0.1% SDS for 30 min at 65°C. The membranes were rinsed in 0.1 × SSPE and were exposed to CURIX film at −70°C for 1–7 d.

PCR was carried out in 25-μl volumes containing 250 ng of genomic DNA; 100 ng of each primer; 200 μM each of dATP, dGTP, and dTTP; 3–5 μCi of α-[^{32}P]dCTP; and 1 unit of *Taq* polymerase (Promega). Thirty cycles of amplification were performed in a Perkin Elmer Cetus DNA Thermal Cycler with denaturation for 1 min at 94°C, annealing for 1 min at 55°C, and primer extension for 1 min 30 s at 72°C. A 2-μl aliquot of each amplified sample was run in a 6% polyacrylamide gel at 1,200 V and 20–25 mA. Samples were loaded in four consecutive loadings 40 min apart. The final loading was run for 2–3 h at room temperature. Gels were dried and autoradiographed for 2–24 hours with CURIX film at room temperature.

DNA Markers

The DNA probes pTD3-21 (D15S10) and pTD189-1 (D15S13) detect *Taq*I RFLPs (Donlon et al. 1986; Tantravahi et al. 1989). Probe pTD3-21 detects polymorphic fragments of 9 kb, 8.2 kb, and 3 kb (Colman et al. 1991), whereas pTD189-1 detects polymorphic fragments of 3.5 kb and 2.1 kb. PCR primers amplifying the AC-repeat polymorphisms at the D15S10 locus (Lindeman et al. 1991) and the THBS1 locus (Polymeropoulos et al. 1990) were used.

Linkage Analysis

Two-point linkage analysis was carried out using the MLINK package of the LINKAGE Computer program (Lathrop et al. 1984). A test for locus heteroge-

Table 1

Pairwise Z Values between Chromosome 15q11-q15 Markers and ty-pos OCA at Various Combined Male and Female θ Values

Locus	Polymorphism	Chromosome Location	No. of Informative Families	Z at θ of						
				.01	.05	.10	.15	.20	.30	.40
D15S10 ...	$(AC)_n$;p3-21/*Taq*I	15q11.2-q13	39	−2.09	5.47	6.86	6.53	5.56	3.05	.88
D15S13 ...	p189-1/*Taq*I	15q11.2-q13	19	−.76	1.47	1.93	1.89	1.64	.94	.28
THBS1	$(AC)_n$	15q15	38	−16.38	−3.56	.41	1.75	2.06	1.44	.45

neity was done by using the HOMOG program (Ott 1985).

Results

Linkage results are presented in table 1 and show that the D15S10, D15S13, and THBS1 loci are linked to ty-pos OCA. There were no significant sex differences. The D15S10 locus is identified in this study by a haplotype of two polymorphisms, pTD3-21/*Taq*I and an AC repeat (Lindeman et al. 1991). Both markers are contained within a single phage clone and are tightly linked to one another ($Z = 15.85$ at $\theta = .0$). The pTD189-1 polymorphism is the result of an insertion/deletion and was scored using both *Taq*I and *Bgl*II (Nicholls et al. 1989); results were completely concordant. THBS1, which maps to 15q15, also showed linkage to ty-pos OCA ($Z = 2.06$ at $\theta = .201$).

The polymorphic AC-repeat markers D15S10 and THBS-1 have been reported as two-allele (Lindeman et al. 1991) and nine-allele (Polymeropoulos et al. 1990) systems, respectively. However, in the southern African negroid population additional alleles were identified. The D15S10 marker revealed nine alleles, including one allele of 161 bp and eight alleles of size 173–187 bp, giving a heterozygosity of .79. The THBS-1 marker revealed 15 alleles in southern African negroids, and their size range was 161–189 bp, with a heterozygosity of .87.

Z values were assessed separately for families with ephelides and families without ephelides. There was no evidence for locus heterogeneity between the two groups as evaluated by the HOMOG program.

A multipoint location map indicating the most likely position of ty-pos OCA with regard to the loci D15S10 and D15S13 is shown in figure 1. THBS1 was omitted from the location map because, with available data, it is impossible to determine the marker-marker order unambiguously. The location map was computed with the D15S10 haplotype (shown as "S10") and D15S13 (shown as "S13") at a fixed distance (10.3 cM) apart. In order to facilitate multipoint linkage analysis, the nine-allele system of the D15S10 AC-repeat polymorphism was reduced to five alleles while maintaining the same linkage information. D15S10 is fixed at location .5, D15S13 at location .603. There is no sex difference. The loci D15S10 and D15S13 are situated on the same side of the ty-pos OCA locus, but it is not clear which is the closer (if D15S10 is the closer, then $Z = 6.94$; if D15S13 is the closer, then $Z = 6.33$). The ty-pos OCA locus does not map between the two markers ($Z = 3.11$).

Discussion

With a prevalance of 1/3,900, the carrier frequency of ty-pos OCA in southern Africa is about 1/32. The reason for this high carrier rate is not apparent, but some selective advantage cannot be ruled out. If the gene or genes responsible for the condition could be cloned and studied at the DNA level, the functional properties could be elucidated and a clearer under-

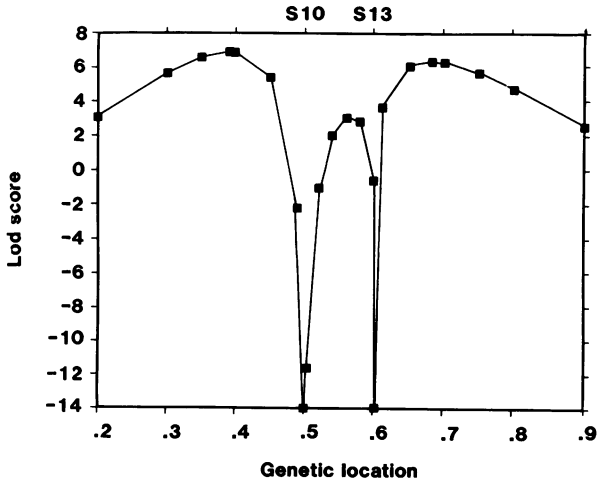

Figure 1 Location map of ty-pos OCA, computed with the D15S10 haplotype (S10) and D15S13 (S13) at a fixed distance (i.e., 10.3 cM) apart.

standing of the population genetics could be obtained. Treatment of the condition may become possible, and, eventually, gene therapy might be feasible. The assignment of the locus for ty-pos OCA to chromosome 15q11.2-q12 represents the first step in this process.

PWCR/ANCR on Chromosome 15q11.2-q12

PWS and AS are often associated with hypopigmentation and the visual disturbances characteristic of albinism. The proportion of individuals with strabismus and/or nystagmus varies from 40% to as high as 90% in different studies (Creel et al. 1986). Two cases of coexistent PWS and OCA had normal karyotypes, whereas one PWS case with OCA and one AS case with OCA showed cytogenetically visible deletions of chromosome 15q11.2-q13. Linkage of two loci, D15S10 and D15S13, situated within the PWCR/ANCR on 15q11.2-q12 support the theory that there is a pigment locus within the region (Wiesner et al. 1987).

It is generally accepted that heterozygotes and homozygotes for ty-pos OCA have normal hairbulb tyrosinase levels, although some variation occurs (Witkop et al. 1989). In PWS and AS patients tyrosinase levels were decreased (Hittner et al. 1982; Wiesner et al. 1987; Fryburg et al. 1991), irrespective of whether hypopigmentation was present (Wiesner et al. 1987). This is a puzzling observation, but it could be due to allelic heterogeneity. Alternatively, it is possible that there are two pigment loci in the PWCR/ANCR: the ty-pos OCA locus and another locus which influences tyrosinase levels.

Several studies have shown that the hypopigmentation correlates with the DNA deletion in the 15q11.2-q12 region (Wiesner et al. 1987; Butler 1989). The present studies place the ty-pos OCA locus 10.8 cM from the locus D15S10, which maps proximal to D15S12 (Hamabe et al. 1991*a*, 1991*b*). Linkage analyses with D15S12 are in progress in order to determine whether this marker is closer to ty-pos OCA.

Mouse/Human Comparative Studies

The mouse/human comparative map shows regions of homology between markers flanking several mouse pigment loci and their syntenic human homologues (Searle et al. 1989; Nadeau et al. 1991). Three mouse chromosomes—2, 7, and 9—contain genes with homologues on human chromosome 15. Each of these mouse chromosomes contains a pigment locus: chromosome 2 bears the agouti locus, *a;* chromosome 7 contains the pink-eyed dilute locus, *p,* as well as the albinism/tyrosinase locus, c; and chromosome 9 contains the dilute locus, *d*. The syntenic region including the *c,* or Tyr, locus on mouse chromosome 7 maps to human chromosome 11q. The TYR locus at 11q14-q21 (Kwon et al. 1987) has been excluded as the ty-pos OCA locus, by linkage analysis (Colman et al., in press).

The *p* locus is flanked distally by a region containing the homologous genes gamma-aminobutyric acid receptor beta-3 subunit (Wagstaff et al. 1991), insulin-like growth factor 1 receptor, and the feline sarcoma oncogene, which map to human chromosome 15. However, only the human gamma-aminobutyric acid receptor beta-3 subunit gene maps close to the PWCR/ANCR, whereas the other two map to 15q25-qter. More recently, three markers—MN7, DN34, and DN10—have been shown to have mouse homologous sequences close to and distal to the *p* locus (fig. 2) (Chaillet et al. 1991; Knoll et al. 1991). It has been suggested that the hypopigmentation observed in PWS and AS could be related to the altered function of a human homologue of the *p* locus in the mouse (Nicholls et al. 1991). Strong evidence in support of this hypothesis was presented by Nakatsu et al. (1992). The 28RN fragment (unique-sequence subclone of p28) (Brilliant et al. 1991) which is associated with a duplication at the *p* locus in the *p*-unstable (p^{un}) mutant allele has been shown to be tightly linked to D7Nic1. D7Nic1 is the mouse homologue of the human brain cDNA, DN10, which maps within the PWCR (Nakatsu et al. 1992). Since linkage was found between ty-pos OCA and markers at 15q11.2-q12, the *p* locus appears to be the best candidate for this form of albinism.

The p Locus as a Homologue of ty-pos OCA

Thirteen alleles have been identified at the *p* locus, and they all result in the production of decreased eumelanin pigment in both coat and eyes; the size of the melanosomes is reduced, and some investigators have reported aberrant internal matrix structures. Neurological and sperm abnormalities are associated with some of the mutant *p* alleles. Misrouting of the optic tracts, as seen in ty-pos OCA, has not been noted, but it is not clear whether it was specifically investigated. One allele, p^{un}, produces a phenotype consisting of areas of dilute and intense pigmentation, the latter due to a spontaneous somatic reversion to the wild-type form at a relatively high frequency (Silvers 1979). There appears to be a duplication within or near the region of the p^{un} DNA, and loss of this duplication is said to result in the reversion of the p^{un} phenotype to the wild-type form (Brilliant et al. 1991). The pigment phenotype of p^{un}/p^{un} mice with somatic reversions giving areas of normal pigmentation bears a resemblance

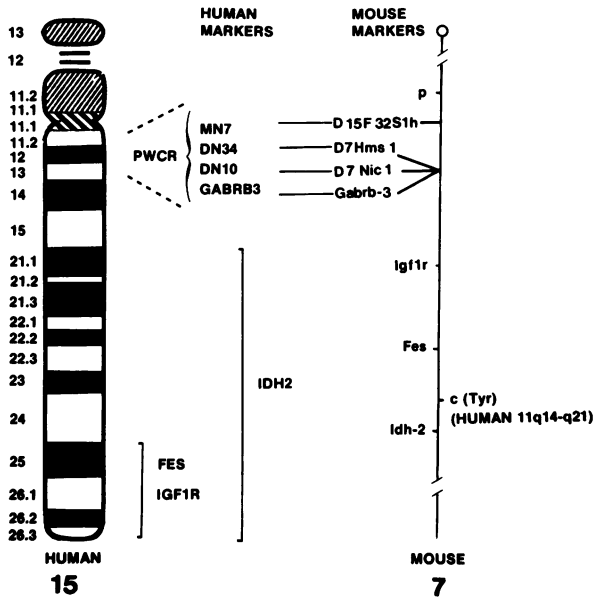

Figure 2 Comparative genetic maps showing homologous regions between human chromosome 15 and mouse chromosome 7. The pigment loci depicted are the *p* locus and the *c* locus. The following genes are shown (mouse gene first, human gene second): insulin-like growth factor 1 receptor (Igf1r, IGF1R), feline sarcoma oncogene (Fes, FES), and isocitrate dehydrogenase 2, mitochondrial (Idh-2, IDH2) (Searle et al. 1989; Nadeau et al. 1991). Markers in the PWCR on human chromosome 15q11.2-q12 have been mapped distal to the *p* locus on mouse chromosome 7 (Nadeau et al. 1991). Human cDNA probes DN34 and DN10 were used to detect the mouse loci D7Hms1 and D7Nic1. A human genomic probe, MN7, was used to detect the mouse locus designated "D15F32S1h" (Chaillet et al. 1991), and the human gamma-aminobutyric acid receptor beta-3 subunit (GABRB3) gene was used to localize the mouse homologue, Gabrb-3 (Wagstaff et al. 1991). The position of the *p* locus relative to the D15F32S1h, D7Hms1, D7Nic1, and Gabrb-3 loci is not certain, although recent evidence shows that the *p* and D7Nic1 loci are 0–1.67 cM apart (95% confidence limits) (Nakatsu et al. 1992). The probes—pTD3-21 and pTD189-1—and the AC-repeat polymorphism at D15S10 (Lindeman et al. 1991) used in the present study map to the PWCR (Donlon et al. 1986; Tantravahi et al. 1989). The AC-repeat polymorphism at the THSB1 locus (Polymeropoulos et al. 1990) maps to band 15q15 (Jaffe et al. 1990).

to that of ty-pos OCA individuals with ephelides, suggesting that spontaneous somatic reversion in some ty-pos albinos may give rise to the ephelides. Cloning of the mouse *p*-locus gene would greatly facilitate the isolation of the human homologue.

In summary, close linkage between ty-pos OCA and two loci on 15q11.2-q12, as well as the conservation of a syntenic linkage group between mouse chromosome 7 and human chromosome 15, indicate that the locus for ty-pos OCA is on human chromosome 15q11.2-q12 and that it may be the human homologue of the mouse *p* locus. We propose that the locus be called "OCA2."

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References

Brilliant MH, Gondo Y, Eicher EM (1991) Direct molecular identification of the mouse pink-eyed unstable mutation by genome scanning. Science 252:566–569

Butler MG (1989) Hypopigmentation: a common feature of the Prader-Labhart-Willi syndrome. Am J Med Genet 45: 140–146

Chaillet JR, Knoll JHM, Horsthemke B, Lalande M (1991) The syntenic relationship between the critical deletion region for the Prader-Willi/Angelman syndromes and proximal mouse chromosome 7. Genomics 11:773–776

Chintamaneni CD, Halaban R, Kobayashi Y, Witkop CJ, Kwon BS (1991) A single base insertion in the putative transmembrane domain of the tyrosinase gene as a cause for tyrosinase-negative oculocutaneous albinism. Proc Natl Acad Sci USA 88:5272–5276

Colman MA, Segalo P, Ramsay M, Jenkins T (1991) A third allele is detected by the probe pTD3-21 (D15S10) in southern African chromosomes. Nucleic Acids Res 19: 5097

Colman MA, Stevens G, Ramsay M, Kwon B, Jenkins T. Exclusion of two candidate pigment loci, *c* and *b*, a chromosomal region, part of 11p, and 33 random polymorphic markers as the locus for tyrosinase-positive oculocutaneous albinism. Hum Genet (in press)

Creel D (1980) Inappropriate use of albino animals as models in research. Pharmacol Biochem Behav 12:969–977

Creel DJ, Bendel CM, Wiesner GL, Wirtschafter JD, Arthur DC, King RA (1986) Abnormalities of the central visual pathways in Prader-Willi syndrome associated with hypopigmentation. N Engl J Med 314:1606–1609

Donlon TA, Lalande M, Wyman A, Bruns G, Latt SA (1986) Isolation of molecular probes associated with the chromosome 15 instability in the Prader-Willi syndrome. Proc Natl Acad Sci USA 83:4408–4412

Edwards JH (1987) Exclusion mapping. J Med Genet 24: 539–543

Fryburg JS, Breg WR, Lindgren V (1991) Diagnosis of Angelman syndrome in infants. Am J Med Genet 38:58–64

Giebel LB, Tripathi RK, King RA, Spritz RA (1991) A tyrosinase gene missense mutation in temperature-sensitive

type I oculocutaneous albinism. J Clin Invest 87:1119–1122

Hamabe J, Fukushima Y, Harada N, Abe K, Matsuo N, Nagai T, Yoshioka A, et al (1991*a*) Molecular study of the Prader-Willi syndrome: deletion, RFLP and phenotype analyses of 50 patients. Am J Med Genet 41:54–63

Hamabe J, Kuroki Y, Imaizumi K, Sugimoto T, Fukushima Y, Yamaguchi A, Izumikawa Y, et al (1991*b*) DNA deletion and its parental origin in Angelman syndrome patients. Am J Med Genet 41:64–68

Hittner HM, King RA, Riccardi VM, Ledbetter DH, Borda RP, Ferrell RE, Kretzer FL (1982) Oculocutaneous albinoidism as a manifestation of reduced neural crest derivatives in the Prader-Willi syndrome. Am J Ophthalmol 94: 328–337

Jaffe E, Bornstein P, Disteche CM (1990) Mapping of the thrombospondin gene to human chromosome 15 and mouse chromosome 2 by *in situ* hybridisation. Genomics 7:123–126

Jenkins T, Heim RA, Dunn DS, Zwane E, Colman MA, Ramsay M, Kromberg JGR (1990) In quest of the tyrosinase-positive oculocutaneous albinism gene. Ophthal Paediatr Genet 11:251–254

King RA, Townsend D, Oetting W, Summers CG, Olds DP, White JG, Spritz RA (1991) Temperature-sensitive tyrosinase associated with peripheral pigmentation in oculocutaneous albinism. J Clin Invest 87:1046–1053

Knoll JHM, Wagstaff J, Glatt K, Graham JM, Greenberg F, Horsthemke B, Lalande M (1991) Molecular analysis of distal 15q11-q13: A difference between Angelman and Prader-Willi syndromes. Am J Hum Genet 49 [Suppl]: A87

Kromberg JGR, Castle D, Zwane E, Jenkins T (1989) Albinism and skin cancer in southern Africa. Clin Genet 36: 43–52

Kromberg JGR, Jenkins T (1982) Prevalence of albinism in the South African Negro. S Afr Med J 61:383–386

Kwon BS, Haq AK, Pomerantz SH, Halaban R (1987) Isolation and sequence of a cDNA clone for human tyrosinase that maps to the mouse *c*-albino locus. Proc Natl Acad Sci USA 84:7473–7477

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Lindeman R, Kouts S, Woodage T, Smith A, Trent RJ (1991) Dinucleotide repeat polymorphism of D15S10 in the Prader-Willi chromosome region (PWCR). Nucleic Acids Res 19:5449

Magenis RE, Toth-Fejel S, Allen LJ, Black M, Brown MG, Budden S, Cohen R, et al (1990) Comparison of the 15q deletions in Prader-Willi and Angelman syndromes: specific regions, extent of deletions, parental origin, and clinical consequences. Am J Med Genet 35:333–349

Nadeau J, Grant P, Kosowsky M (1991) Mouse on human homology map. Mouse Genome 89:31–37

Nakatsu Y, Gondo Y, Brilliant MH (1992) The *p* locus is closely linked to the mouse homolog of a gene from the Prader-Willi chromosomal region. Mammalian Genome 2:69–71

Nicholls RD, Knoll JH, Glatt K, Hersh JH, Brewster TD, Graham JM, Wurster-Hill D, et al (1989) Restriction fragment length polymorphisms within proximal 15q and their use in molecular cytogenetics and the Prader-Willi syndrome. Am J Med Genet 33:66–77

Nicholls RD, Neumann PE, Horsthemke B, Rinchik G (1991) Mapping of loci deleted in Angelman and Prader-Willi syndromes identifies conservation of synteny in mice and possible animal models. Am J Hum Genet 49 [Suppl]: A334

Okoro AN (1975) Albinism in Nigeria. Br J Dermatol 92: 485–492

Ott J (1985) Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore

Pembrey M, Fennell SJ, Van den Berghe J, Fitchett M, Summers D, Butler L, Clarke C, et al (1989) The association of Angelman's syndrome with deletions within 15q11-13. J Med Genet 26:73–77

Phelan MC, Albiez KL, Flannery DB, Stevenson RE (1988) The Prader-Willi syndrome and albinism in a black infant. Proc Greenwood Genet Cent 7:27–29

Polymeropoulos MH, Xiao H, Rath DS, Merrill CR (1990) Dinucleotide repeat polymorphism at the human thrombospondin gene (THBS1). Nucleic Acids Res 18:7467

Searle AG, Peters J, Lyon MF, Hall JG, Evans EP, Edwards JH, Buckle VJ (1989) Chromosome maps of man and mouse IV. Ann Hum Genet 53:89–140

Silvers WK (1979) The coat colors of mice. Springer, New York

Southern EM (1975) Detection of specific sequences among DNA fragments separated by gel electrophoresis. J Mol Biol 98:503–517

Tantravahi U, Nicholls RD, Stroh H, Ringer S, Neve RL, Kaplan L, Wharton R, et al (1989) Quantitative calibration and use of DNA probes for investigating chromosome abnormalities in the Prader-Willi syndrome. Am J Med Genet 33:78–87

Wagstaff J, Chaillet JR, Lalande M (1991) The $GABA_A$ receptor β3 subunit gene: characterisation of a human cDNA from chromosome 15q11q13 and mapping to a region of conserved synteny on mouse chromosome 7. Genomics 11:1071–1078

Wallis CE, Beighton PH (1989) Synchrony of oculocutaneous albinism, the Prader-Willi syndrome, and a normal karyotype. J Med Genet 26:337–339

Walsh RJ (1971) A distinctive pigment of the skin in New Guinea indigenes. Ann Hum Genet 34:379–388

Wiesner GL, Bendel CM, Olds DP, White JG, Arthur DC, Ball DW, King RA (1987) Hypopigmentation in the Prader-Willi syndrome. Am J Hum Genet 40:431–442

Witkop CJ, Quevedo WC, Fitzpatrick TB, King RA (1989) Albinism. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic basis of inherited disease, 6th ed. McGraw-Hill, New York, pp 2905–2947