

## RAPID COMMUNICATION

## Mutations in the MATP Gene in Five German Patients Affected by Oculocutaneous Albinism Type 4

Uta Rundshagen,<sup>1</sup> Christine Zühlke,<sup>1\*</sup> Sven Opitz,<sup>1</sup> Eberhard Schwinger,<sup>1</sup> and Barbara Käsmann-Kellner<sup>2</sup><sup>1</sup>Institut für Humangenetik der Universität Lübeck, Lübeck, Germany; <sup>2</sup>Augenklinik der Universität des Saarlandes, Homburg (Saar), Germany

Communicated by Mark H. Paalman

Oculocutaneous albinism (OCA) is caused by a deficiency of melanin synthesis and characterized by generalized hypopigmentation of skin, hair, and eyes. Due to the hypopigmentation of the retinal pigment epithelium, OCA is usually associated with congenital visual impairment, in addition to an increased risk of skin cancer. OCA is a genetically heterogeneous disease with distinct types resulting from mutations in different genes involved in the pathway which results in pigmentation. OCA1 is associated with mutations in the TYR gene encoding tyrosinase. OCA2 results from mutations in the P gene encoding the P protein and is the most common form of OCA. OCA3, also known as rufous/red albinism, is caused by mutations in the TYRP1 gene, which encodes the tyrosinase-related protein 1. Recently, OCA4 was described as a new form of OCA in a single patient with a splice site mutation in the MATP gene (or AIM1), the human ortholog of the murine underwhite gene. The similarity of MATP to transporter proteins suggests its involvement in transport functions, although its actual substrate is still unclear. We screened 176 German patients with albinism for mutations within the MATP gene and identified five individuals with OCA4. In this first report on West European patients, we describe 10 so far unpublished mutations, as well as two intronic variations, in addition to two known polymorphisms. *Hum Mutat* 23:106–110, 2004. © 2003 Wiley-Liss, Inc.

KEY WORDS: albinism; oculocutaneous albinism; OCA; MATP; AIM1; OCA4

## DATABASES:

MATP – OMIM: 606202, 606574 (OCA4); GenBank: NT\_006576.13, (genomic contig) AF172849, NM\_016180.2 (mRNA)

## INTRODUCTION

Albinism represents a group of genetically heterogeneous hereditary abnormalities of melanin pigment synthesis that result in a deficiency or complete absence of melanin in affected individuals.

A reduction of melanin causes hypopigmentation of hair and skin, leading to an increased sensitivity to ultraviolet radiation and a predisposition to skin cancer. In the visual system, the deficiency of melanin during fetal and postpartum development of the retinal and cerebral branches of the visual system results in severe alterations such as foveal dysplasia and abnormal routing of the optic nerves, which subsequently leads to a congenital visual impairment, nystagmus, and often strabismus [Creel et al., 1990]. The lack of melanin may either be restricted to the eye (ocular albinism, OA), or it can involve skin, hair, and eyes (oculocutaneous albinism, OCA).

Several genes have been found to be associated with human pigmentation. Mutations of these genes may cause at least four genetic types of recessively inherited OCA. Mutations in the tyrosinase encoding gene, the rate-limiting enzyme in melanin synthesis [Jimbow et al.,

1976], are associated with OCA1 (MIM# 203100) [Kwon et al., 1987; Giebel et al., 1991]. Mutations in the human gene encoding the P protein, which probably functions as a transporter, result in OCA2 (MIM# 203200), the most common form of OCA [Rinchik et al., 1993; Puri et al., 1997]. OCA3, also known as rufous or red albinism, is caused by mutations in the gene encoding the tyrosinase-related protein 1 (TYRP1; MIM# 115501), and is a rare form of OCA [Boissy et al., 1996; Jiménez-Cervantes et al., 1994].

In 2001, a mutation analysis of the human membrane-associated transporter protein (MATP) gene (MIM# 606202), also known as the melanoma antigen named “altered in melanoma” (AIM1) [Harada et al., 2001] was published by Newton et al. [2001]. Among more than 100 patients with albinism, a homozygous G>A

Received 15 July 2003; accepted revised manuscript 17 October 2003.

\*Correspondence to: Christine Zühlke, Institut für Humangenetik, Ratzeburger Allee 160, D – 23538 Lübeck, Germany.  
E-mail: zuehlke@uni-luebeck.de

DOI 10.1002/humu.10311

Published online in Wiley InterScience (www.interscience.wiley.com).

transition of the exon 2 splice-acceptor site was found in a single person with generalized hypopigmentation. The resulting phenotype was termed OCA type 4 (OCA4; MIM# 606574) [Newton et al., 2001]. Findings in other species point to an involvement of the encoded protein in the pigmentation pathway. For example, the murine ortholog of the human MATP gene, the “underwhite” gene, is responsible for cases of hypopigmentation in mice [Sweet et al., 1998]. Furthermore, mutations in a highly homologous gene reduce the melanin content in Japanese medaka fish [Fukamachi et al., 2001].

The human MATP gene is located on chromosome 5p and consists of seven exons spanning a region of approximately 40 kb. The protein is predicted to span a lipid bilayer 12 times and probably functions as a transporter. It shows great similarities to sucrose/proton symporters in plants [Newton et al., 2001], but the substrate in the human organism is still unknown.

To look for mutations, we performed molecular analyses for the MATP gene of 176 German patients with OCA. The frequency of OCA4 among patients with OCA has yet to be estimated in different populations. Furthermore, genotype–phenotype correlations are highly necessary for adequate counseling of patients and their families.

## MATERIALS AND METHODS

After having obtained written informed consent for genetic analyses, total genomic DNA was isolated from proteinase K/SDS digests of blood samples.

PCR primers for the specific amplification of individual exons from genomic DNA were designed (Table 1). Two overlapping fragments were synthesized for exons 1, 3, and 7. PCR was performed at an annealing temperature of 55°C in a volume of 25 µl containing 50 ng genomic DNA, 10 pmol of each primer, 5 pmol dNTP, and 0.5 units *Taq* polymerase (Eppendorf, www.eppendorf.com). Products were separated by agarose (1.5%) gel electrophoresis and visualized by ethidium bromide staining.

To search for mutations, SSCP analyses were performed. PCR products were mixed with one volume formamide and heated for 5 min to 95°C, followed by cooling on ice. Samples were resolved on 6% polyacrylamide gels containing 10% urea or glycerol at 30 W and room temperature for 2 to 4 hr [Sambrook and Russell, 2001]. For individuals with a single mutant OCA4 allele, SSCP analyses for the complete coding region were performed in parallel with both gel configurations (10% urea as well as 10% glycerol) and varying run duration. The SSCP banding pattern was detected by silver staining.

PCR products of DNA samples showing irregular patterns in the SSCP analysis were amplified twice, purified (NucleoSpin Extract 2 in 1-Kit; Macherey-Nagel, www.macherey-nagel.com), and sequenced using the dideoxy chain termination method on double-stranded DNA templates (SequiTherm EXCEL II DNA Sequencing Kit; Epicentre, www.epicentre.com) in the presence of IRD800-labeled universal (uni) or reverse (rev) M13 primers on a Licor 4200 automated sequencer (Licor, www.licor.com). Trace file analysis was performed using the Seqworks software package by Sven Opitz (www.humangenetik.uni-luebeck.de).

The sequences obtained were compared to the human MATP cDNA (NCBI AF172849). Mutation numbering is based on this sequence, with +1 corresponding to the A of the translation initiation codon ATG. Exon numbering and boundaries were obtained by alignment of cDNA NM\_016180.2 (GenBank 22-Mar-2001) and the Homo sapiens chromosome 5 genomic contig NT\_006576.13 (GenBank 28-Apr-2003).

## RESULTS

Molecular investigations of 176 patients with OCA revealed changes of single nucleotides, deletions, and insertions within the MATP gene in 11 nonrelated individuals. Using SSCP and sequencing strategies, we found 13 different DNA variations in this gene.

### Mutations

In five patients, mutations on both alleles were identified (Table 2). Patient 1 is homozygous for a T>C transition at position 1082 of the cDNA (c.1082T>C, p.L361P). Subsequent analysis of the parents' DNA

TABLE 1. PCR and Sequencing Primers

Exon	Size	No. of primer pairs	Designation	Sequence (5' → 3')
1	385 bp	2	AIM1-F1-uni	Uni –AAC ACA GAC CCT AGG ACC AC <sup>a</sup>
			AIM1-R1-rev	Rev –CAC ACA ATG CTG TAC AGG CTG <sup>b</sup>
			AIM1-F2-uni	Uni –TAT GTG ACC CCA GTC CTG CT
			AIM1-R2-rev	Rev –CTC CTG CAG AGG TAC ACA CTA
2	177 bp	1	AIM2-F-uni	Uni –CAG GAT TTA GGA GAC CAA TGT
			AIM2-R-rev	Rev –CTG AAG GAG AGA CTT TCT GGA
3	326 bp	2	AIM3-F1-uni	Uni –GGG AGT GTC TAT GCA TGA GG
			AIM3-R1-rev	Rev –GAA TGC CCT TTG CAA CCT CTG
			AIM3-F2-uni	Uni –TCT GTG CAG TAT CTC TGA AGC
			AIM3-R2-rev	Rev –CCC ATG AAA CTC TTC TCG TC
4	144 bp	1	AIM4-F-uni	Uni –GGC TGA GTT TCT GCA GTG AAG
			AIM4-R-rev	Rev –ACA GTG ATT GTG TGC ACA GAC
5	124 bp	1	AIM5-F1-uni	Uni –GTA CCT CAA CAG CCT CCA ATC
			AIM5-R1-rev	Rev –TCC AAG TTG TGC TAG ACC AGA
6	212 bp	1	AIM6-F-uni	Uni –GAG GCA CTG CCA GCT GTA ATT
			AIM6-R-rev	Rev –GTT ACC CAA GGC AGA GGT TCA
7	225 bp	2	AIM7-F1-uni	Uni –CTG ACC TGT GCC CTA AAT GAC
			AIM7-R1-rev	Rev –CTG TGA TCA CCA CGA CGA CAA
			AIM7-F2-uni	Uni –CCT GGG CTT TCT GGT CAA CAC
			AIM7-R2-rev	Rev –TCC TGC CAT GTG CTT CAC TGT

<sup>a</sup>M13-uni-sequence: 5'- TGT AAA ACG ACG GCC AGT -3'.

<sup>b</sup>M13-rev-sequence: 5'- CAG GAA ACA GCT ATG ACC -3'.

TABLE 2. DNA Alterations in the OCA4 Gene

DNA	Exon	Alteration in DNA <sup>a</sup>	Alteration in protein	Origin of the allele
Patient 1	5	c.1082T>C; c.1082T>C	p.L361P	One allele from each parent
Patient 2	1	c.172C>G	p.P58A	Mother
	6	c.1179_1203dup	p.Y401X	Father
Patient 3	3	c.661_663del	p.F221del	?
	4	c.986delC	p.T329fsX68	?
Patient 4	4	c.986delC	p.T329fsX68	Mother
	7	c.1457C>T	p.A486V	Father
Patient 5	4	c.950A>G	p.Y317C	Father
	7	c.1429G>A	p.A477T	Mother
Patient 6	4	c.986delC	p.T329fsX68	?
Patient 7	4	c.986delC	p.T329fsX68	?
Patient 8	4	c.986delC	p.T329fsX68	?
Patient 9	3	c.606G>C	p.W202C	?
Patient 10	3	c.814G>A <sup>b</sup>	p.E272K <sup>b</sup>	?
Patient 11	7	c.1567_1574dup	p.F525fsX15	?
<b>Intronic variations</b>				
3 Patients	IVS3+46C>T		?	?
4 Patients	IVS3+59_+61dup		?	?

<sup>a</sup>DNA variation numbering based on GenBank NM-016180.2, with +1 as A of the ATG start codon. Introns based on genomic contig GenBank NT\_006576.13.

<sup>b</sup>Polymorphism according to Nakayama et al. [2002].

showed the obligate heterozygosity for this allele. The mutation is localized within the luminal protein loop between transmembrane domains 7 and 8. Cutaneous hypopigmentation in the patient was marked, and the hair was white-yellowish. During life, there was no increase of pigmentation on the skin and very little increase of pigmentation in the hair (the patient had white hair as a child, and is now 42 years old). Visual acuity is 20/200 in both eyes, and there is distinct hypopigmentation of the pigment epithelia of the iris and of the retina. Macular hypoplasia, optic dysplasia, and nystagmus were found.

Four patients are compound heterozygous for different mutations in the MATP gene. Patient 2 showed a C>G transition at position 172 of the cDNA (c.172C>G, p.P58A) which affects the transmembrane domain 1 of the protein and the duplication of a 25-bp DNA fragment (c.1179\_1203dup; Table 2). The latter mutation results in the stop of translation in exon 6 (p.Y401X) and the loss of transmembrane domains 9–12 in the protein. The mutated alleles could be found either in the DNA of the mother or in the DNA of the patient's father (Table 2). Phenotypically, the patient showed white-silvery hair and severe hypopigmentation of the pigment epithelia of the eye; macular dysplasia is associated with atypical choroidal vessels spanning below the presumed macular area. There was also optic nerve dysplasia, visual acuity was 20/400 in both eyes, and additionally there was marked nystagmus. No increase in skin or hair pigmentation was observed.

Patient 3 carries the loss of a single triplet in exon 3 (c.661\_663del), which does not alter the reading frame, but causes the deletion of one amino acid in transmembrane domain 6 (p.delF221). The second mutation is caused by the deletion of a single nucleotide at position 986 of the cDNA (c.986delC) corresponding to

transmembrane domain 7 of the MATP protein. This mutation does change the reading frame and leads to a translation stop in exon 6 (p.T329fsX68). Blood samples of the parents could not be obtained, so the origin of both alleles remains unclear. As in Patient 1, this proband showed white-yellowish hair. Hypopigmentation of the ocular structures was distinct, but not as severe as in Patient 2. Optic dysplasia was present. The patient had a pendular nystagmus and visual acuity of 20/200 in both eyes. The skin was very pale. No increase of pigmentation of the skin and hairs was noted (age 11 years).

In Patient 4, we found the mutation c.986delC, as was reported in Patient 3. The second allele showed a C>T transition at position 1457 of the cDNA (c.1457C>T, p.A486V) affecting transmembrane domain 11. Analysis of the parents' DNA could clarify the origin of both mutations (Table 2). As was the case in Patients 1 and 3, the proband showed white-yellowish hair. The skin was extremely pale and over the last 8 years no increase of pigmentation was noted. The ocular hypopigmentation was comparable to that of Patients 1 and 3; there was also dysplasia of the optic nerve head. Nystagmus was present, visual acuity was 20/200 in both eyes.

We found a A>G transition at position 950 (c.950A>G, p.Y317C) in the DNA of Patient 5. The mutation concerns the intracellular protein loop between domains 6 and 7. On the second allele, this person showed a G>A transition at position 1429 (c.1429G>A, p.A477T), which affects domain 11 of the protein. We were able to prove the presence of both sequence variations either in the patient's mother or father (Table 2). This patient was distinctly different from the other four probands. Now aged 9 years, he shows dark blonde hair that has become darker since infancy (the patient had been a medium-to-light blonde,

and his hair was never white). The skin was pale, but he was able to develop a very slight tan. Compared to the other patients, ocular hypopigmentation was less. Additionally, this proband was the only one of the OCA4 patients without optic dysplasia; however the optic nerve head was unusually small and slightly pale. Macular structures could not be discriminated, including examination in red-free light. Visual acuity was surprisingly good at 20/30 and 20/40; nystagmus had a very low intensity.

Six patients were found to be heterozygous for alterations in the MATP gene. As in Patient 3 and 4, the deletion c.986delC was detected in Patients 6, 7, and 8. In Patient 9, we identified a G>C transition at position 606 of the cDNA (c.606G>C, p.W202C); Patient 10 showed the polymorphism c.814G>A (p.E272K) described by Newton et al. [2001]. Patient 11 carried a duplication of seven nucleotides between position 1567 and 1574 of the cDNA (Table 2), resulting in p.F525fsX15 with 539 amino acid residues, in contrast to the wild-type protein, which was composed of 530 amino acids.

Comparing the phenotypes, we found that differentiation between patients with a single DNA variation and individuals homozygous for the SCA4 mutation is not possible by pure clinical investigations.

### Polymorphisms

In addition to the mutations, we were able to reveal two polymorphisms described by Newton et al. [2001]. Polymorphism c.1122C>G (p.F374L) is rather common and is present heterozygously in 15 unrelated individuals (15 out of 352 alleles; 4.3%). Heterozygosity of DNA polymorphism c.987G>A (silent, affecting codon T329) was found in four individuals (four out of 352 alleles; 1.1%).

Furthermore, two sequence variations within intron 3 were detected. The insertion IVS3+60\_+61insTGT was seen in four patients and the substitution IVS3+46C>T was seen in three of our patients.

### DISCUSSION

The analysis of 176 unrelated German patients with symptoms of albinism revealed five individuals with homozygous (Patient 1) or compound heterozygous (Patients 2–5) mutations in the MATP gene. Therefore, we assume that these five patients are affected by OCA4. The frequency of 2.84% of patients with pigmentation defects investigated in this study is significantly higher than expected, according to Newton et al. [2001] (one in 102 patients). Including the five patients with single OCA4 mutations (Patients 6–9, and 11), our results suggest that patients with genetically-defined OCA4 are present in 5% to 6% of all affected persons in the Caucasian population.

Among the five individuals with OCA4, a single case was homozygous for one of the mutations, although consanguinity was not known for this family. Two of the remaining four patients carried the deletion c.986delC,

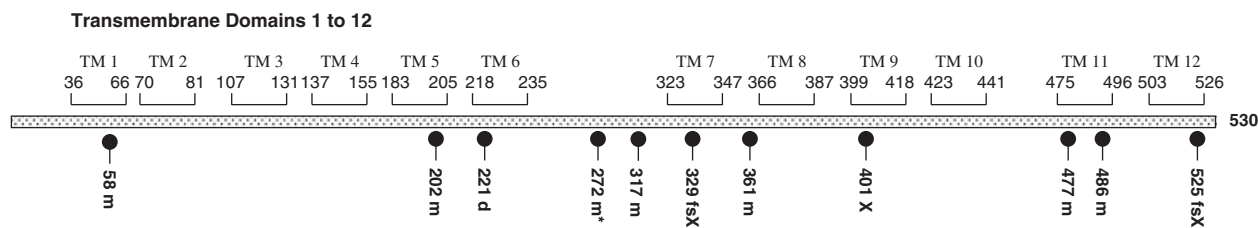
which could be identified in a total of five patients (Patients 3, 4, and 6–8). The high frequency of this mutation (5 out of 16 DNA alterations) might be caused by a founder effect in the German population. On the other hand, the presence of eight different mutations in five persons with OCA4 points to numerous origins of this disease. Overall, we detected 10 unrelated and unknown mutations: one deletion, two frameshifts, and seven missense mutations.

Clinically, four of the five probands with OCA4 showed very pale skin, and white-yellowish hair with little or no further pigmentation during life. Visual acuity was between 20/400 and 20/200, and all but one of the patients showed optic nerve head dysplasia, which is found only in 31% of all albinism patients (n = 351 patients, all types of albinism; Barbara Käsmann-Kellner, unpublished results). In one patient, cutaneous and ocular pigmentation was much better, and in spite of macular hypoplasia as confirmed by examination in red-free light, a surprisingly good visual acuity was achieved.

For the six individuals with oculocutaneous albinism (Patients 6–11), alterations have been detected in only one of the MATP alleles. Mutations within the OCA1 and OCA2 gene have been excluded by molecular analyses. It seems likely, therefore, that the second mutation was not detected by the SSCP conditions used, or it occurs in gene regions not presented in the PCR products; the promoter and extended intronic parts have not been investigated. It is well known that mutations in the splice-acceptor sequences as described by Newton et al. [2001] for a Turkish patient, are associated with the disease phenotype. This points to disease-causing DNA changes localized in untranslated regions and frequently occurring in patients. In addition, deletions or duplications of the complete gene or single exons are not seen by the SSCP procedure, but may be important in mutational analyses [Hedrich et al., 2001].

Furthermore, pathologic effects of heterozygous mutations in nonallelic genes must be discussed. Recently, in cases of OA and Waardenburg syndrome, digenic mutation types have been described [Ming and Muenke, 2002]. Thus, it seems quite possible that heterozygous mutations in nonallelic genes encoding proteins or enzymes involved in pigment synthesis and transport might produce an additional negative effect, resulting in OCA phenotypes.

The distribution of mutations in the MATP gene revealed that 10 of 11 (>90%) DNA variations are localized in the last two-thirds of the protein (Fig. 1). It is not yet known whether changes in the amino terminal part of the protein are associated with more severe or unrelated phenotypes. Patient 2 carries a missense mutation in exon 1. Her ocular findings resemble those of probands 1, 3, and 4 in all aspects apart from a slight difference in hair color. Patients 1, 3, and 4 have white-yellowish hair; Patient 2 has silvery-white hair. Hypopigmentation of the ocular structures was similar, and Patient 2 showed optic nerve head dysplasia along with the other probands. Visual acuity was slightly worse in this patient (20/400 versus 20/200), which could be



**FIGURE 1. Distribution of DNA variations within the MATP protein. Schematic presentation of the 530-amino acid protein with transmembrane domains, according Newton et al. [2001]. The first and last amino acid of each domain is given. Positions of DNA variations are marked by ●— plus the number of the affected amino acid. m: missense mutations; d: deletions; m\*: polymorphisms; X: nonsense mutations; fsX: frame shift mutations.**

correlated to age and cooperation, as Proband 2 was 4 years old—the youngest of our OCA patients.

Newton et al. [2001] identified the DNA polymorphism c.987G>A in 18 individuals (17.6% of alleles). In contrast, this polymorphism is rare, with 2.3 % in the German population (four alleles out of 352). The polymorphism p.F374L was found in 15 of our patients in the heterozygous condition (8.5%), representing the most frequent sequence variation in the study reported here. Newton et al. [2001] detected this polymorphism in 67 individuals, mainly in the heterozygous state. As the reported sample includes 102 patients as well as some control samples, the precise frequency remains uncertain, but should be higher than 50%.

The significantly higher frequency of both polymorphisms in Newton et al. [2001] may be caused by population-specific differences. In addition, polymorphism p.F374L might show a positive correlation to skin color variations among major human populations [Nakayama et al., 2002].

The detection of the 10 mutations we have described underlines the important role of the MATP protein in general pigmentation and is the first evidence for OCA4 for patients in Western Europe.

#### ACKNOWLEDGMENTS

We thank all patients and their families for providing blood samples for scientific research. We thank J. Atici and U. Gehlken for excellent technical help, and Mrs. C. Menzel-Dowling, Institut fuer Anatomie and Zellbiologie, Universitaet des Saarlandes for reading the manuscript.

#### REFERENCES

- Boissy RE, Zhao H, Oetting WS, Austin LM, Wildenberg SC, Boissy YL, Zhao Y, Sturm RA, Hearing VJ, King RA, Nordlund JJ. 1996. Mutation in and lack of expression of tyrosinase-related protein-1 (TRP-1) in melanocytes from an individual with brown oculocutaneous albinism: a new subtype of albinism classified as "OCA3". *Am J Hum Genet* 58:1145–1156.
- Creel DJ, Summer CG, King RA. 1990. Visual anomalies associated with albinism. *Ophthalmic Pediatr Genet* 11:193–200.
- Fukamachi S, Shimada A, Shima A. 2001. Mutations in the gene encoding B, a novel transporter protein, reduce melanin content in medaka. *Nat Genet* 28:381–385.
- Giebel LB, Tripathi RK, Strunk KM, Hanifin JM, Jackson CE, King RA, Spritz RA. 1991. Tyrosinase gene mutations associated with type 1B ("yellow") oculocutaneous albinism. *Am J Hum Genet* 48:1159–1167.
- Harada M, Li YF, El-Gamil M, Rosenberg SA, Robbins PF. 2001. Use of an in vitro immunoselected tumor line to identify shared melanoma antigens recognized by HLA\*0201-restricted T cells. *Cancer Res* 61:1089–1094.
- Hedrich K, Kann M, Lanthaler AJ, Dalski A, Eskelson C, Landt O, Schwinger E, Vieregge P, Lang AE, Breakefield XO, Ozelius LJ, Pramstaller PP, Klein C. 2001. The importance of gene dosage studies: mutational analysis of the parkin gene in early-onset parkinsonism. *Hum Mol Genet* 10:1649–1656.
- Jimbow K, Quevedo WC, Fitzpatrick TB, Szabo G. 1976. Some aspects of melanin biology: 1950–1975. *J Invest Dermatol* 67:72–89.
- Jiménez-Cervantes C, Solano F, Kobayashi T, Urabe K, Hearing VJ, Lozano JA, García-Borrén JC. 1994. A new enzymatic function in the melanogenic pathway: the DHICA oxidase activity of tyrosinase-related protein-1 (TRP-1). *J Biol Chem* 269:17993–18001.
- Kwon BS, Haq AK, Pomerantz SH, Halaban R. 1987. Isolation and sequence of a cDNA clone for human tyrosinase that maps at the mouse *c*-albino locus. *Proc Natl Acad Sci USA* 84:7437–7477.
- Ming JE, Muenke M. 2002. Multiple hits during early embryonic development: digenic diseases and holoprosencephaly. *Am J Hum Genet* 71:1017–1032.
- Nakayama K, Fukamachi S, Kimura H, Koda Y, Soemantri A, Ishida T. 2002. Distinctive distribution of AIM1 polymorphism among major human populations with different skin colour. *J Hum Genet* 47:92–94.
- Newton JM, Cohen-Barak O, Hagiwara N, Gardner JM, Davisson MT, King RA, Brilliant MH. 2001. Mutations in the human orthologue of the mouse underwhite gene (*uw*) underlie a new form of oculocutaneous albinism, OCA4. *Am J Hum Genet* 69:981–988.
- Puri N, Durbam-Pierre D, Aquaron R, Lund PM, King RA, Brilliant MH. 1997. Type 2 oculocutaneous albinism (OCA2) in Zimbabwe and Cameroon: distribution of the 2.7-kb deletion allele of the *P* gene. *Hum Genet* 100:651–656.
- Rinchik EM, Bultman SJ, Horsthemke B, Lee ST, Strunk KM, Spritz RA, Avidano KM, Jong MTC, Nicholls RD. 1993. A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. *Nature* 361:72–76.
- Sambrook J, Russell DW. 2001. *Molecular cloning: a laboratory manual*, Vol. 2. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.
- Sweet HO, Brilliant MH, Cook SA, Johnson KR, Davisson MT. 1998. A new allelic series for the underwhite gene on mouse chromosome 15. *J Hered* 89:546–551.