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Report

MC1R Mutations Modify the Classic Phenotype of Oculocutaneous Albinism Type 2 (OCA2)

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The heterogeneous group of disorders known as oculocutaneous albinism (OCA) shares cutaneous and ocular hypopigmentation associated with common developmental abnormalities of the eye. Mutations of at least 11 loci produce this phenotype. The majority of affected individuals develop some cutaneous melanin; this is predominantly seen as yellow/blond hair, whereas fewer have brown hair. The OCA phenotype is dependent on the constitutional pigmentation background of the family, with more OCA pigmentation found in families with darker constitutional pigmentation, which indicates that other genes may modify the OCA phenotype. Sequence variation in the melanocortin-1 receptor (*MC1R*) gene is associated with red hair in the normal population, but red hair is unusual in OCA. We identified eight probands with OCA who had red hair at birth. Mutations in the *P* gene were responsible for classic phenotype of oculocutaneous albinism type 2 (OCA2) in all eight, and mutations in the *MC1R* gene were responsible for the red (rather than yellow/blond) hair in the six of eight who continued to have red hair after birth. This is the first demonstration of a gene modifying the OCA phenotype in humans.

Melanins are biological polymers that are synthesized by the melanocyte in the skin and hair follicle, the iris stroma and retinal pigment epithelium (RPE), and the inner ear. The cutaneous and iridial melanocytes can make two general types of melanin, brown/black eumelanin and yellow/red pheomelanin (Prota 1992). The type that is synthesized is dependent on protein and enzyme components of the melanin pathway that are delivered to the pigment granule (melanosome) during its development (Hearing 2000; Toyofuku et al. 2001). Tyrosinase is the major enzyme in melanin synthesis, and no melanin forms in the absence of activity of this key enzyme (Silvers 1979; Oetting and King 1999). Other proteins play a role in melanin formation, but the essential nature of their function in melanin synthesis has not been established (Hearing 2000). Melanin serves as a photoprotective pigment in the skin and eye and plays an unknown role in the developing mammalian eye, where it is found long before light exposure (Sturm et al. 2001; Sturm 2002).

The switch between the synthesis of eumelanin or pheomelanin is controlled, to a large extent, by the melanocortin-1 receptor (*MC1R*) on the melanocyte (Sturm et al. 2001). Stimulation of this receptor by the melanocyte-stimulating hormone (MSH) induces the cell to make black/brown eumelanin. The antagonist to the receptor is the agouti-signaling protein, which seems to block the effect of MSH and results in a cell that makes yellow/red pheomelanin. Recent interest in the *MC1R* gene has led to the identification of a number of common mutations or variants that are associated with red hair and light skin that tans poorly or not at all (Valverde et al. 1995; Box et al. 1997; Koppula et al. 1997; Schioth et al. 1999; Flanagan et al. 2000; Palmer et al. 2000; Grimes et al. 2001; Healy et al. 2001; Schaffer and Bolognia 2001; Smith et al. 2001; Sturm et al. 2001; Sturm 2002). Mutations in this gene have also been found in animals with red coats (Robbins et al. 1993; Newton et al. 2000). Although the association of *MC1R* and red hair has been intriguing to human geneticists, the potential association of *MC1R* mutations with susceptibility to melanoma and skin cancer has been important in increasing our understanding of the epidemiology of these

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Table 1

Probands with OCA2 and Red Hair: Results of *P* and *MC1R* Gene Analysis

Individual	Age (years)	Sex	Ethnic Origin[b]	Hair Color at Birth	Hair Color at Time of Study	*P* Mutation[a]		MC1R Mutations[c]
						Maternal	Paternal	
1	18.0	F	NE	Red	Red	W679C	N489D	R151C R160W
2	.33	M	NE, AA, NA	Orange red	Orange red	V443I	P743L	R151C R160W
3	.75	F	AA	Red	Red	delEx7	V443I	0
4	.83	F	Ash	Blond/red	Blond/red	V443I	0	V60L M92V T314T
5	1.00	M	Ash	Red	Red	0	V443I	D84E R151C
6	2.00	M	NE	Blond/red	Blond/red	R290G	0	V60L
7	9.00	M	AA, WI, PR	Red	Blond/brown	0	IVS12+5g→a	0
8	17.0	F	AA	Red	Dark Blond	NW273KV	0	0

[a] Maternal and paternal *P* gene mutations identified. 0 = no mutation identified. Analysis included the entire coding region and part of the flanking intron sequences for each of the 24 exons by use of the dideoxy method of Sanger with automated fluorescent DNA sequencing (Oetting et al. 1994).

[b] Self-reported maternal and paternal ethnic background: AA = African American, Ash = Ashkenazi Jew, NA = Native American, NE = Northern European, PR = Puerto Rican, WI = West Indian.

[c] *MC1R* mutations identified in proband. Sequence analysis included the entire coding region and part of the flanking sequences of the exon by use of the dideoxy method of Sanger with automated fluorescent DNA sequencing (Oetting et al. 1994).

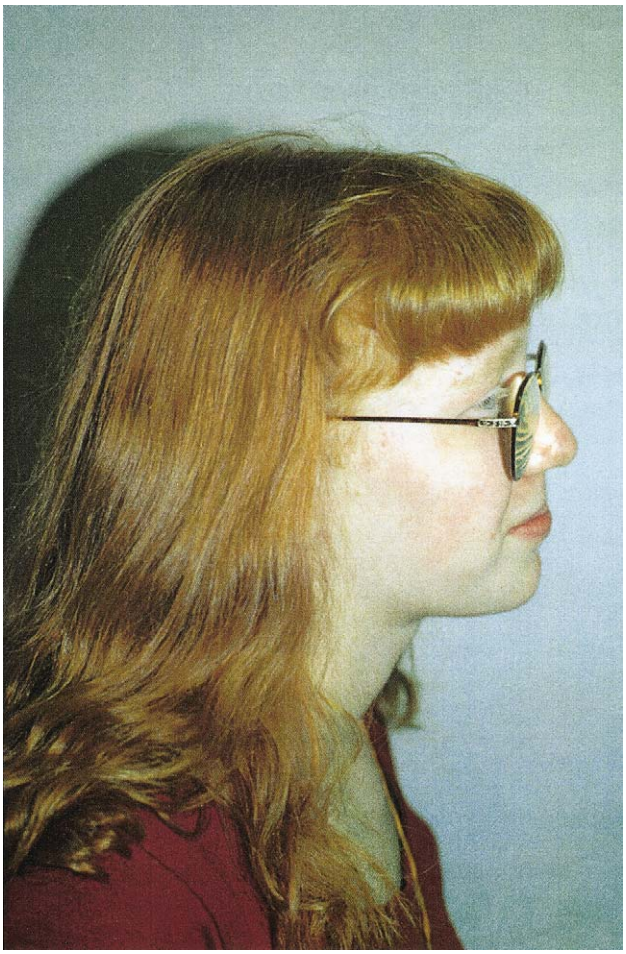

Figure 1 Proband at age 18 years, showing red hair and light skin

cancers (Valverde et al. 1996; Palmer et al. 2000; Box et al. 2001*a*, 2001*b*; Kennedy et al. 2001). Of most importance, the development of red hair cannot be solely explained by variation in the *MC1R* gene, and other genes are likely to be involved in the regulation of the amount and type of melanins that are produced by the melanocyte (Box et al. 1997; Akey et al. 2001).

Oculocutaneous albinism (OCA) is the result of a reduction in the amount of melanin synthesized in the melanocyte. Cutaneous hypopigmentation produces light hair and sun-sensitive skin. Reduction of melanin in the RPE is associated with foveal hypoplasia (which results in reduced visual acuity) and abnormal projections of the optic nerves to the brain (which usually results in strabismus) (King et al. 2001). At least 11 genes have been associated with an oculocutaneous phenotype in humans. The two most common types are type 1 (OCA1 [MIM 203100]), which results from mutations in the tyrosinase gene on chromosome 11p, and type 2 (OCA2 [MIM 203200]), which results from mutations in the *P* gene on chromosome 15q. Type 3 (OCA3 [MIM 278400]) is described as "rufous or red OCA with brick-red bronze or mahogany skin and ginger or reddish hair" and is associated with mutations in the *TYRP1* gene on chromosome 9p (Manga et al. 1997). This phenotype has been recognized only in the African population; the white equivalent is unknown. Type 4 (OCA4 [MIM 606574]) has been associated with the *MATP* gene on chromosome 5p, and one affected individual has been described with a phenotype similar to that of OCA2 (Newton et al. 2001). There are six types of Hermansky-Pudlak syndrome that have OCA associated with storage-pool–deficient platelets. (Shotelersuk and Gahl 1998;

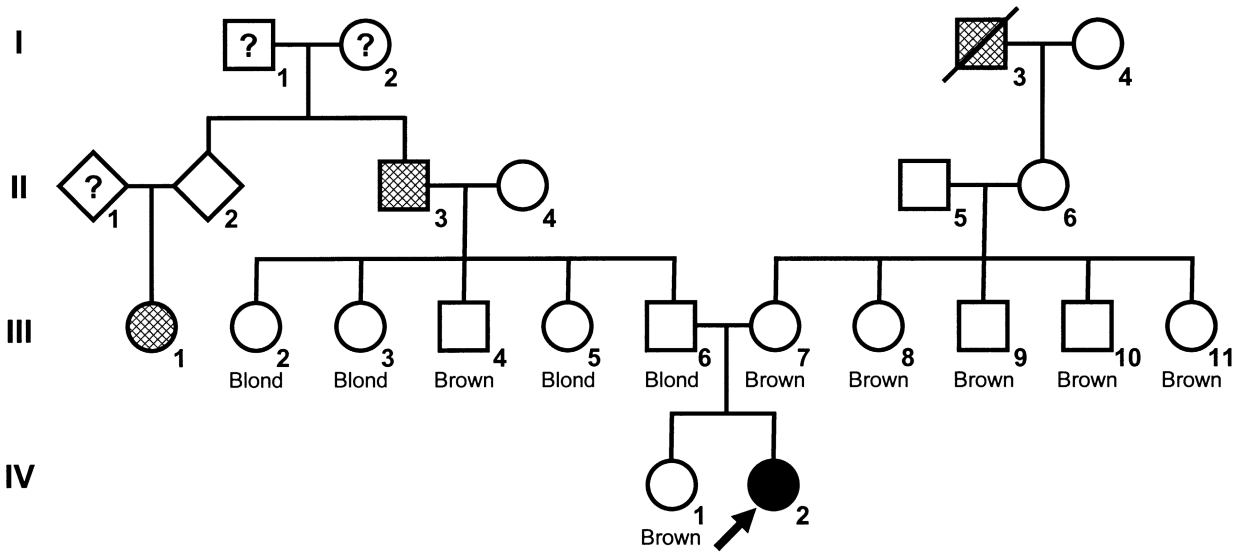

Figure 2 Family pedigree. Proband marked with arrow. Hair color indicated for parental generation and sibling. Hatched family members have red hair.

Dell'Angelica et al. 1999; Anikster et al. 2001; Huizing et al. 2001; Suzuki et al. 2002; Zhang et al. 2003). The final type of OCA is Chediak-Higashi syndrome (CHS [MIM 214500]), and albinism is a minor component of this complex phenotype (Introne et al. 1999).

The phenotype of OCA usually ranges from white hair and skin to various shades of light brown or light-to-dark-blond hair and minimal to moderate amounts of generalized skin pigmentation. Many individuals with OCA do form some cutaneous and iridial pigment, but this is usually yellow pheomelanin pigment or pigment that evolves, with time, through a yellow pheomelanin phase to a light-brown eumelanin phase. We now describe an unusual pigmentation phenotype that involves red rather than yellow hair in individuals with OCA2 rather than rufous "red" OCA. Our studies of the *P* gene (OCA2) and the *MC1R* gene (red hair) clearly identify this latter gene as a major modifier of the OCA2 phenotype.

We identified eight probands who presented with OCA associated with red hair at birth and obtained clinical information and peripheral blood for DNA after obtaining informed consent (table 1). The initial proband (individual 1) was a female who had reddish-blond hair, white skin, blue irides, and nystagmus at birth. She was diagnosed with OCA at age 2 years because of nystagmus, blue irides that had minimal transillumination, reduced retinal pigment, foveal hypoplasia, and reduced visual acuity. Corrected visual acuity was measured at 20/100 at 3.5 years and 20/60 at age 10 years. Examination at age 18 years showed red scalp hair, yellow eyebrow and eyelash hair, white skin that did not tan, light freckles, and scattered amelanotic nevi (fig. 1). The irides were light blue and showed grade-1 transillumination (on a scale of 1 [minimal] to 4 [complete]) (Summers et al. 1988). Coarse gray-black melanin pigment was absent by ophthalmoscopy, and only a rudimentary reflex was noted in the hypoplastic but opaque macula. Corrected acuity was 20/60. The diagnosis was probable OCA2, on the basis of the presence of pigmented hair at birth, but the red color of the hair was unusual and had not been described in the literature associated with this type of OCA. There was no family history of OCA, but her mother and father had relatives with red hair (fig. 2).

We first analyzed the *P* gene to establish the cause of each proband's OCA. Mutations of the 24-exon *P* gene, mapping to chromosome 15q11–13, are responsible for OCA2 (Gardner et al. 1992; Lee et al. 1994*a*; Spritz et al. 1997; Oetting and King 1999; Passmore et al. 1999). The gene is also highly polymorphic, with >30 nonpathologic sequence variants reported (Lee et al. 1995; Albinism Database). The *P* gene encodes a melanosomal protein with 12 membrane-spanning regions (Rosemblat et al. 1994). The precise function of the protein remains unknown, but studies suggest that it is involved in regulation of the intraorganelle pH or structure (Orlow and Brilliant 1999; Puri et al. 2000).

The sequence of the *P* gene was determined in DNA from each proband and the parents, by use of methods established in our laboratory (Oetting et al. 1998; Oetting and King 1999). All case subjects were compound heterozygotes with different maternal and paternal mutations (table 1). Both mutations were identified in individuals 1–3, and only one of the two mutations was

identified in individuals 4–8. For individual 1, the paternal mutation (N489D) was a base change at base 1465 (A→G), which resulted in an asparagine→aspartic acid substitution at codon 489 in the third intracellular loop (fig. 3*a*). This mutation has been shown to produce OCA2 when homozygous or allelic with another *P* gene mutation (Spritz et al. 1997; Oetting and King 1999). The maternal mutation (W679C) was a base change at base 2037 (G→C), which resulted in a tryptophan→cysteine substitution at codon 679 (fig. 3*b*). A change at amino acid 679, near the transmembrane region of extracellular loop 4, was previously proven deleterious and associated with OCA2 (Lee et al. 1994*b*; Passmore et al. 1999). The mutations in individuals 2–8 are listed in table 1. The V443I is a common *P* gene mutation associated with the typical OCA2 phenotype, and the exon 7 deletion is the common *P* gene mutation in the sub-Saharan African population. R290G, NW273KV, and P743L have been reported with a typical OCA2 phenotype (Lee et al. 1994*b*; Passmore et al. 1999; Kerr et al. 2000), and IVS12+5g→a is novel and, to our knowledge, has not been reported in OCA2 to date.

Once the diagnosis of OCA2 was established, the *MC1R* gene was analyzed to determine if mutations in this gene were modifying the typical OCA2 phenotype by the development of red rather than the typical yellow/blond hair. The *MC1R* gene encodes a 7-transmembrane G-protein-coupled receptor with two alternatively spliced variants, and, in melanocytes, the proportion of pheomelanin to eumelanin is regulated, in part, by the MSH through the MC1R (Mountjoy et al. 1992). The *MC1R* gene was analyzed in DNA from each proband, and six of the eight were found to have known *MC1R* variants (table 1) (Harding et al. 2000).

Individual 1 was a compound heterozygote: the paternal change (R151C) was a base change at base 451 (C→T) that resulted in an arginine→cysteine substitution at codon 151 in the second intracellular loop of the protein (fig. 4*a*), and the maternal change (R160W) was a base change at base 478 (C→T) that resulted in an arginine→tryptophan substitution at codon 160 in the transmembrane boundary of the second intracellular loop of the protein (fig. 4*b*). Loss-of-function variants of MC1R are unable to stimulate cAMP after stimulation with MSH, which results in a reduction of eumelanin synthesis in the melanocyte (Frandberg et al. 1998; Schioth et al. 1999; Healy et al. 2001). Furthermore, there is a strong statistical correlation between red hair and the mutations that have been described (Flanagan et al. 2000; Harding et al. 2000; Sturm et al. 2001). Individual 4 had three *MC1R* gene mutations, as has been reported elsewhere in studies of red hair (Valverde et al. 1995;

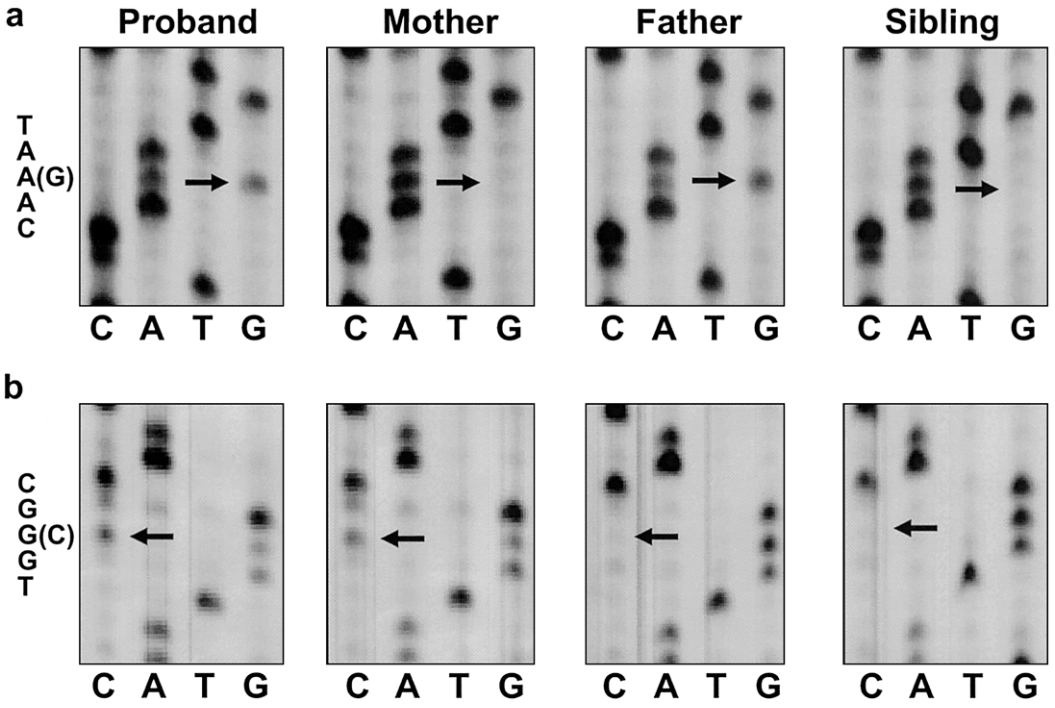

Figure 3 *P* gene sequencing results. *a*, Proband heterozygous at exon 14, codon 489, with a change from asparagine (AAT) to an aspartic acid (GAT). Mutation N489D is paternal in origin. *b*, Proband heterozygous at exon 19, codon 679, with a change from tryptophan (TGG) to cysteine (TGC). Mutation W679C is maternal in origin.

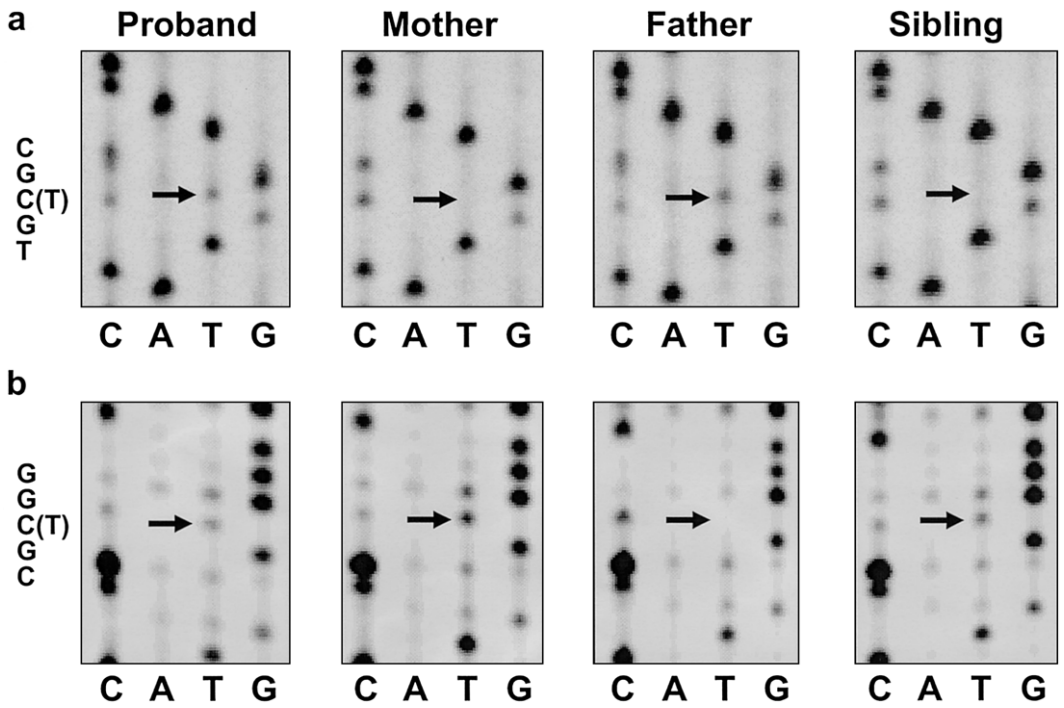

Figure 4 *MC1R* gene sequencing results. *a,* Proband heterozygous at codon 151, with a change from arginine (CGC) to cysteine (TGC). Mutation R151C is paternal in origin. *b,* Proband heterozygous at codon 160, with a change from arginine (CGG) to tryptophan (TGG). Mutation R160W is maternal in origin. The sibling is also heterozygous for the maternal mutation.

Box et al. 1997; Palmer et al. 2000; Healy et al. 2001). Individuals 7 and 8 did not have *MC1R* gene mutations; both were reported to have red hair at birth that did not persist as they developed (table 1). This suggests that *MC1R* mutations may not be responsible for red hair that is present at birth but not later in life.

The only other type of OCA that is associated with red hair is rufous or "red" albinism (OCA3), identified only in the African population and caused by mutations of the tyrosinase-related protein-1 (*TYRP1*) gene (Kromberg et al. 1990; Manga et al. 1997). Affected individuals have reddish or ginger-colored hair and skin and visual problems that are less severe than in other forms of OCA, but they do not have bright red hair.

One additional observation is suggested with these individuals. The albinism phenotype, by definition, includes abnormal ganglion cell development of the retina, clinically recognized as foveal hypoplasia, and reduced visual acuity. Visual acuity in OCA is usually in the range of 20/100–20/200, but a moderate number of affected individuals have visual acuity better than 20/100 (Summers et al. 1991, 1996; Summers 1996). This phenotype, common to all types of OCA, is produced by mutations in genes that affect the ability of melanocyte to synthesize melanin through different mechanisms, which suggests that the melanin itself plays an important role in retinal development (Schraermeyer 1990; Raymond and Jackson 1995; Ilia and Jeffery 1996; Schraermeyer and Heimann 1999; Grant et al. 2001; Donatien and Jeffery 2002). The RPE is thought to make predominantly eumelanin, but perhaps pheomelanin may also be made in the retina and have some role in retinal development. The visual acuity of individual 1 was 20/60, and this better acuity could possibly be explained by the presence of some pheomelanin in her RPE.

Our study characterizes the association of OCA2 with red hair in humans, which is the result of mutations in the *P* gene and in the *MC1R* gene. To our knowledge, this study is the first description of a gene that can modify the typical OCA2 phenotype in humans and demonstrates the complexity of pigment genetics through the action/interaction of two genes. This finding is not unexpected, however, as Silvers has reviewed the interaction of many loci on coat color in the mouse and has noted that the agouti and the extension (*MC1R*) loci can modify the phenotype produced by mutations in the murine *p* gene (Silvers 1979). Human OCA is a complex model system that can be used to reflect the many studies

of coat color in the mouse, and it is expected that additional loci that modify the human phenotype will be described in future studies.

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Electronic-Database Information

URLs for data presented herein are as follows:

Albinism Database, http://www.cbc.umn.edu/tad/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for OCA1, OCA2, OCA3, OCA4, and CHS)

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