Oculocutaneous Albinism

Kunal Ray, Mainak Sengupta

Molecular and Human Genetics Division, CSIR-Indian Institute of Chemical Biology, Kolkata - 700 032, India (KR, MS)

Published in Atlas Database: August 2012
Online updated version: http://AtlasGeneticsOncology.org/Kprones/OculocutaneousAlbinismID10022.html
DOI: 10.4267/2042/48475

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2013 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names
Albinism, Oculocutaneous Albinism type 1 (OCA1)
Oculocutaneous Albinism type 2 (OCA2)
Oculocutaneous Albinism type 3 (OCA3)
Oculocutaneous Albinism type 4 (OCA4)
Tyrosinase-Negative Albinism
Tyrosinase-Positive Albinism

Note
Oculocutaneous Albinism (OCA) is a group of congenital developmental disorder characterized by complete or partial loss of melanin in skin, hair and eye. OCA is caused due to defects in genes associated with melanin biosynthetic pathway. Depending on the gene mutated, OCA can be classified into Oculocutaneous Albinism type 1 (OCA1), Oculocutaneous Albinism type 2 (OCA2), Oculocutaneous Albinism type 3 (OCA3) and Oculocutaneous Albinism type 4 (OCA4). OCA1 affects 1 per 40000 individuals in most populations (King et al., 2001) but is very uncommon among African-Americans. The overall prevalence of OCA2 is estimated to be 1:36000 in USA, but it is a lot more common among the African Americans with a prevalence of 1:10000 (Okoro, 1975). In fact, OCA2 affects 1 in 3900 of the population in the southern parts of Africa. OCA3 or Rufous oculocutaneous albinism has been estimated to affect 1:8500 individuals in Africa; however, it is very rare in any other populations as per published literature. OCA4 has been found to be the second largest rare form of albinism after OCA1 in Japan. It is worth mentioning that in countries like India where endogamy prevails, the incidence of OCA would be higher than the world average. In fact, in India, a preponderance of homozygous mutations is found and OCA1 is caused majorly because of founder mutations (Chaki et al., 2005; Chaki et al. 2006).

Inheritance
OCA is inherited in an autosomal recessive mode. However, recently, it has been hypothesized that the clinical spectrum of OCA depends on the pigmentation threshold of the patient. In genotypically darker complexion individuals such as in Africans, two mutations are needed to completely shut off the high pigmentation background; whereas in individuals with lighter complexion such as Caucasians, OCA can be manifested by the presence of one mutation and one hypomorphic allele (Chiang et al., 2008).

Clinics

Note
OCA is characterized by partial or total absence of melanin in the skin, hair and eyes at birth. The absence of optimum content of melanin during embryogenesis acts as a cue to trigger defects in eye development that cannot be corrected. A portion of the retinal ganglion cell (RGC) axons, originally destined to the ipsilateral hemisphere of the dorsal lateral geniculate nuclei (dLGN) of the midbrain, misproject to the contralateral side, thereby resulting in the disruption of binocular vision (Lund, 1965; Guillery, 1971; Cooper and Pettigrew, 1979; Drager and Olsen, 1980; Lavado and Montoliu, 2006). The developmental defect concerned with abnormal nerve fibre projection has been discussed in details in a review by Ray et al., 2007 (Ray et al., 2007).

Phenotype and clinics

The reduction of melanin in peripheral retina results in a stereoscopic set of developmental defects in neuronal migration in the visual pathways leading to foveal hypoplasia, abnormal routing of the nerve fibers from the eye to brain with consequent low vision (reduced visual acuity usually in the range 20/60 to 20/400 and refractive errors), photophobia, iris transillumination,
nystagmus and strabismus. An OCA affected person is considered legally blind if he/she has a visual acuity of 20/200 (6/60) or less. The degree of severity of the eye features as well as skin pigmentation varies with the different subtypes of albinism. Due to loss of pigmentation, the iris looks hazel or light blue or in extreme cases as in OCA1, it is translucent to such an extent that it appears pink or red in ambient light. The skin remains white or only become slightly pigmented with time in case of OCA1 whereas the patients suffering from the other 3 types of albinism have residual pigmentation and look pinkish or yellowish. If unprotected from sun rays, hypopigmented skin in the albinistic individuals may develop erythema. Moreover, the reduction in melanin pigment in the skin results in an increased sensitivity to UV induced skin damage and subsequently non-melanotic skin cancers. It must be stated here that based on the severity of pigment loss, the most severe form of OCA viz. OCA1 can be sub-classified into two categories - (a) OCA1A: when the tyrosinase enzyme activity is completely lacking, and (b) OCA1B: when some residual activity is retained. The visual acuity of the OCA1A patients is greatly reduced; the degree of nystagmus, strabismus, photophobia are usually severe and the translucent iris that appear pink early in life, often become gray-blue with age. In case of OCA1A there is an absence of pigmentation throughout the patient's life. In contrast, in OCA1B, although there is little or no apparent melanin at birth, progressive melanization might occur with time. The range of pigmentation in OCA1B varies from little cutaneous pigment to nearly normal skin color and the phenotype is often influenced by ethnicity. OCA1B is called 'yellow OCA' due to the color of the hair, produced by pheomelanin synthesis.

**Neoplastic risk**

The loss of pigment often leads to non-melanotic skin cancers in form of Squamous Cell Carcinoma (SCC) and Basal Cell Carcinoma (BCC) (Mabula et al., 2012). Melanoma is rare in albino patients (Pehamberger et al., 1984).

**Treatment**

No specific treatment is available for OCA1. Attention must be paid to avoidance of direct sun exposure.

**Evolution**

OCA1B patients although are born with almost no pigmentation, show a progressive melanization with age.

**Prognosis**

With proper protection from direct exposure from sun and visual aids like dome magnifiers, reading glasses, hand-held and stand magnifiers, patients should be able to lead a normal life.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Specific symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYR</td>
<td>OCA1 (A and B)</td>
<td>OCA1A: The skin, hair, eyelashes and eyebrows are white, irises completely translucent. Visual acuity is 1/10 or less with intense photophobia. OCA1 symptoms do not vary with age or race. Amelanotic nevi may be present. <strong>OCA1B:</strong> In OCA1B, the hair and skin may develop some pigment with time and the irises may appear to green/brown. Visual acuity is 2/10.</td>
</tr>
<tr>
<td>OCA2</td>
<td>OCA2</td>
<td>While the degree of cutaneous pigment and iris color may vary, the newborn with OCA2 nearly always have pigmented hair. Nevi and freckles are commonly found in the skin. Visual acuity is better than in OCA1, and can reach 3/10. Africans with OCA2 appear with light brown hair and skin, and gray irises.</td>
</tr>
<tr>
<td>TYRP1</td>
<td>OCA3</td>
<td>Among Africans OCA3 affected individuals have red hair and reddish brown skin (xanthosis). Visual anomalies are less severe and often not detectable.</td>
</tr>
<tr>
<td>SLC45A2</td>
<td>OCA4</td>
<td>The clinical findings of OCA are very similar to that of OCA2</td>
</tr>
</tbody>
</table>

Table 1: Causal genes and specific symptoms for 4 classical OCA syndromes.
Oculocutaneous Albinism Ray K, Sengupta M

Genes involved and proteins

Note
OCA can be classified into four major types viz. Oculocutaneous Albinism type 1 (OCA1), Oculocutaneous Albinism type 2 (OCA2), Oculocutaneous Albinism type 3 (OCA3) and Oculocutaneous Albinism type 4 (OCA4). Each of the classical subtypes is caused due to defects in 4 different genes independently. Table 1 shows the genes involved in OCA:

### TYR

**Location**
11q14.3

**Note**
TYR codes for Tyrosinase protein, the rate limiting enzyme of melanin biosynthetic pathway.

**DNA/RNA Description**
The human tyrosinase gene consists of 5 exons and spans about 65 kb of the genome.

**Transcription**
It encodes a 2082 bp transcript (Accession No: NM_000372.4).

**Pseudogene**
TYR-like segment (TYRL, 11p11.2, MIM 191270) is a pseudogene of TYR, which contains sequences very similar to exons IV and V of TYR gene. It is hypothesized that duplication of TYR exons IV and V regions followed by 11q:11p translocation has given rise to the TYRL segment.

**Protein Description**
TYR (monophenol monoxygenase EC 1.14.18.1) encodes a ~80 kDa glycoprotein (Accession No: NP_000363.1) composed of 529 amino acids. TYR is a melanosomal membrane bound glycoenzyme with a type-3 copper active site. The mature TYR polypeptide includes an 18-amino acid long N-terminal signal peptide, six N-glycosylation sites, two copper binding sites (CuA and CuB) and one transmembrane (TM) domain followed by a relatively short carboxyl tail.

**Expression**
TYR is mainly expressed in two cell types: (a) Melanocytes that are derived from neural crest cells colonizing within iris, cochlea, skin and choroids, and (b) Retinal pigment epithelial (RPE) cells that are derived from the optic cup. During mouse embryogenesis, the expression of TYR could be first detected from +16.5 days post coitum onwards in the skin melanocytes and from +10.5 days postcoitum onwards in the RPE cells (Beermann et al., 1992).

**Localisation**
TYR is a melanosomal membrane protein and the TM region anchors the bulk of the protein inside the melanosomal lumen.

**Function**
TYR catalyzes the rate limiting steps of melanin biosynthesis viz. hydroxylation of L-tyrosine to L-DOPA and oxidation of L-DOPA to DOPAquinone. It also catalyzes the conversion of 5,6 dihydroxyindole to Indole 5,6 Quinone and 5,6,dihydroxyindole carboxylic acid to Indole 5,6 quinone carboxylic acid.

**Homology**
TYR, Tyrosinase Related Protein 1 (TYRP1) and Tyrosinase Related Protein 2 (TYRP2/DCT) represent a family of closely related gene products (with almost 40% amino acid identity) that share a common tertiary structure (Jimenez-Cervantes et al., 1998; Kobayashi et al., 1998).
These have been grouped together to form the TYRP family of genes.

**Mutations**

**Germinal**
TYR mutations are responsible for OCA1. A few OCA2 mutations have been associated with autosomal recessive ocular albinism (AROA). OCA1 is an endoplasmic reticulum retention (ER) disorder and all the missense mutations that have been functionally characterized have yielded ER -retained proteins.

### OCA2

**Location**
15q12

**Note**
OCA2 codes for OCA2 protein, hypothesized to be involved in the transport of tyrosine, the precursor to melanin synthesis, within the melanocyte.

**DNA/RNA Description**
The human OCA2 gene consists of 24 exons and spans ~344.5 kb of the genome.

**Transcription**
It encodes a 3154 bp transcript (Accession No: NM_000275.2).

**Protein Description**
OCA2 encodes a ~110 kDa protein (Accession No: NP_000266.2) composed of 838 amino acids. The OCA2 protein is thought to be a melanosomal multipass integral membrane protein (with 12 predicted transmembrane domains) involved in small molecule transport, specifically tyrosine - a precursor of melanin.
Expression
Due to its localization in the melanosomal membrane, OCA2 is thought to be expressed in the melanocytes.

Localisation
OCA2 is hypothesized to be present in the melanosomal membrane of the melanocytes.

Function
The precise function of OCA2 has not been elucidated till date. However, the potential functions include: a) normal biogenesis of melanosomes (Rosemblat et al., 1998; Orlov and Brilliant et al., 1999); b) for normal processing and transport of tyrosinase and other melanosomal proteins (Puri et al., 2000; Manga et al., 2001; Toyofuku et al., 2002; Chen et al., 2002); and c) maintenance of an acidic pH in melanosomes (Nikomatsu and Orlov, 2006).

Homology
Its sequence predicts that OCA2 has a homology to a superfamily of permeases (Rinchik et al., 1993; Lee et al., 1995).

Mutations
Germinal
OCA2 mutations are responsible for OCA2. A few OCA2 mutations have been associated with autosomal recessive ocular albinism (AROA) too.

TYRP1
Location
9p23

Note
TYRP1 codes for TYRP1 protein, hypothesized to be involved in melanin synthesis, stabilization of tyrosinase and modulating its catalytic activity, maintenance of melanosome structure and affects melanocyte proliferation and melanocyte cell death. Defects in this gene are the cause of rufous oculocutaneous albinism and oculocutaneous albinism type III.

DNA/RNA
Description
The human TYRP1 gene consists of 8 exons and spans ~24.8 kb of the genome.

Transcription
It encodes a 2876 bp transcript (Accession No: NM_000550.2).

Protein
Description
TYRP1 encodes a ~60.7 kDa protein (Accession No: NP_000541.1) composed of 537 amino acids. The TYRP1 protein is thought to be a melanosomal membrane single-pass type I membrane protein.

Expression
TYRP1, similar to TYR, is mainly expressed in two cell types: (a) Melanocytes that are derived from neural crest cells colonizing within iris, cochlea, skin and choroids, and (b) Retinal pigment epithelial (RPE) cells that are derived from the optic cup.

Localisation
TYRP1 is hypothesized to be localized in melanosome membrane.

Function
Oxidation of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) into indole-5,6-quinone-2-carboxylic acid. May regulate or influence the type of melanin synthesized.

Homology
Belongs to the tyrosinase family. Homologous to murine brown locus.

Mutations
Germinal
TYRP1 mutations are responsible for OCA3.

SLC45A2
Location
5p13.2

Note
SLC45A2 codes for SLC45A2 protein, hypothesized to be involved in the transport of substances required for melanin biosynthesis within the melanocyte.

DNA/RNA
Description
The human SLC45A2 gene consists of 7 exons and spans 40.1 kb of the genome.

Transcription
It encodes a 1734 bp transcript (Accession No: NM_016180.3).

Protein
Description
SLC45A2 encodes a ~58 kDa protein (Accession No: NP_057264.3) and composed of 530 amino acids. The protein is thought to be a melanosomal multipass membrane protein (contains 12 putative transmembrane domains) involved in small molecule transport.

Expression
Expressed in most melanoma cell lines and melanocytes.

Localisation
SLC45A2 is hypothesized to be present in the melanosomal membrane of the melanocytes.

Function
The precise function of SLC45A2 has not been elucidated till date. Studies on Medaka fish show that the SLC45A2/MATP plays an important role in pigmentation and probably functions as a membrane transporter in melanosomes (Fukamachi et al., 2001).

Homology
Belongs to the glycoside-pentoside-hexuronide (GPH) cation symporter transporter (TC 2.A.2) family.
Mutations

Germinal

SLC45A2 mutations are responsible for OCA4.

References


Lavado A, Montoliu L.. New animal models to study the role of tyrosinase in normal retinal development. Front Biosci. 2006 Jan 1;11:743-52. (REVIEW)


This article should be referenced as such: