

## Review Article

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# Oculocutaneous Albinism-A review

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### Abstract

Oculocutaneous albinism (OCA) is a group of autosomal recessive disorder characterized by hypopigmentation of the hair skin and eyes due to defect in melanin biosynthesis. These inherited disorders caused by mutation in particular genes that are required for the biosynthesis of melanin pigment in specialized cells. Clinical features include vision problems, nystagmus, photophobia and reduced pigment in skin makes the patient suffering from this type of albinism susceptible to skin cancer. Oculocutaneous albinism is classified into syndromic and non-syndromic OCA. There are seven types of OCA which occur due to the mutation in one or more genes that play role in pigment production in melanosomes. This review article contains detailed information about genetic basis, clinical description and etiology of all seven types of Oculocutaneous albinism.

**Keywords:** Albinism; Genetic mutation of OCA; Hypopigmentation; Oculocutaneous albinism; Types of OCA

### Introduction

Oculocutaneous albinism is a hereditary disease found in small group human population around the world, which are associated to the mutation of specific gene responsible for the synthesis of melanin in melanocyte cells. Like all other types of albinism oculocutaneous albinism is also attributed to the insufficient or completely ceases the production and release of melamine from the specific cells. Lack or complete absence of melanin results in hypopigmentation in hair, skin and eyes [1]. Seven different types of OCA are known and all of these are caused by the mutation in one or more genes that are linked to melanin biosynthesis in one way or another. It is also reported that some genes which are not directly linked to pigment production can

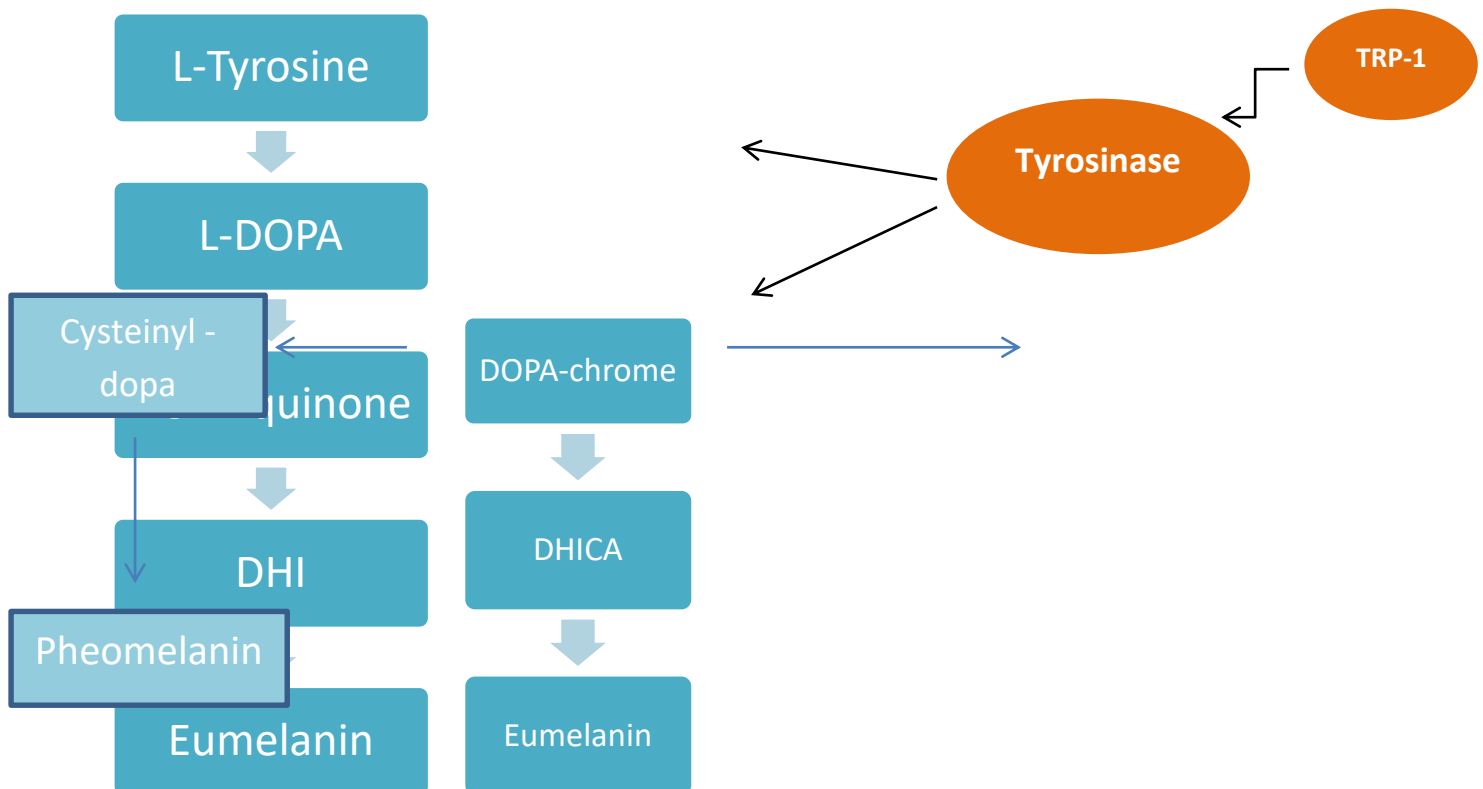
also leads to this type of albinism as mutations in these genes are regulating the expression of main genes that are involved in melanin synthesis. Reduced or absence of melanin can lead to abnormal eye development and results in decreased visual acuity, visual abnormalities including strabismus, photophobia (light sensitivity), nystagmus (side to side involuntary eye movement) and optic nerves mis-routing [2]. As melanin has a role to protect body from the harmful sun rays hypopigmentation in skin can increase the possibility of cancer because the person with oculocutaneous albinism lacks this shield against harmful sunrays [3]. Approximately 1 in 17,000 to 1 in 20,000 people are affected by albinism. As it is autosomal recessive disorder consanguineous marriages are a major cause of this type of

albinism. OCA- mutated genes can be found in one out of 70 individuals [4].

### Melanogenesis

It is a complex multistep process through which melanin is produced. Skin pigmentation is a process in which highly specialized epidermal cells called melanocytes produces melanin and then the pigment is distributed to epidermal keratinocytes. Melanin is of two types: pheomelanin which is yellow to reddish

brown and black to brown eumelanin. The ratio of these two types of melanin determines the color of eyes, skin and hair [5]. Melanin production is dependent on the activation of tyrosine which was catalyzed by the enzyme tyrosinase. The cutaneous and ocular-melanin synthesis is mainly dependent on tyrosine gene. The first two steps in melanin biosynthesis are catalyzed by enzyme tyrosinase (Fig. 1).



**Figure 1. Melanin synthesis pathway. Different form of melanin synthesized by amino acid tyrosine. First two steps the black arrows indicated that the amino acid tyrosine catalyzed by tyrosinase enzyme: while the light blue arrow indicated the hydroxylation of tyrosine into melanin biosynthesis**

This enzyme is involved in oxidation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and is then subsequently converted into dopaquinone. Formation of insoluble eumelanin is the second step and is also catalyzed by tyrosinase enzyme. An alternative pathway produces a red yellow

pigment called as phaeomelanin which gains entry into melanin biosynthesis pathway [6].

### Types of oculocutaneous albinism

Oculocutaneous albinism is an autosomal recessive disorder which means that which shows that as autosomal chromosomes are responsible for this disease thus the risk of this disease is same for both male and

females. Being a recessive disorder person having two defective genes show symptoms. If a person receives a defective gene and a normal gene this individual will not show symptoms but will be a carrier. The risk of two carriers individual to have an affected child is 25%. While the possibility of having a carrier child will be 50% in each pregnancy [7].

Seven different genes are known to be associated with different types of OCA. Each of these genes has a role in melanin biosynthesis in melanocytes which are present in hair follicles, skin, iris and retina of eye.

Oculocutaneous Albinism is subdivided into syndromic and non-syndromic OCA. Non-syndromic OCA only affects visual acuity and skin pigmentation third type only occurs with clinic symptoms affecting hair, eyes and skin while the syndromic OCA affects other parts of the body in addition to hypopigmentation and visual problems. For instance, in Hermansky Pudlack Syndrome (HPS) include bleeding problems, abnormal fat protein compound storage and Oculocutaneous Albinism [8]. Non syndromic OCA is of four types: OCA1, OCA2, OCA3 and OCA4 which results due the mutation in following four genes respectively *TYRP*, *OCA2* gene, *TYRP1* and *SLC45A2* [9].

#### **Oculocutaneous albinism type 1 / *TYR* gene mutation**

This is the most severe type of oculocutaneous albinism reason being the melanin production in this type is absent throughout the life of an individual due to mutation in tyrosine gene which negatively affects synthesis of melanin [10]. Mutation in this gene affects the functioning of tyrosinase enzyme partially or completely. This is also called as tyrosinase negative type of oculocutaneous albinism because the activity of this enzyme is disrupted in an affected individual [11].

The *TYR* gene can be found on the chromosome 11q14.3 and it starts at 88,911,039bp and ends at 89,028,926 bp. The tyrosinase gene contains 5 coding regions (axons) and code for the tyrosinase enzyme which is composed of 529 amino acids. This enzyme is present inside melanocytes and is involved in melanin synthesis pathway. Melanin gives color to skin, hair and is also found in retina which are light sensitive tissue in the back of the eye which helps in normal vision [12]. First reaction in melanin biosynthesis is catalyzed by tyrosinase enzyme. These enzymes functions by converting tyrosine amino acid into another compound called as dopaquinone. The dopaquinone moves through multiple enzymatic reactions and is converted into melanin in hair follicle, skin and eyes. 323 types of mutations have been reported in *TYR* gene in different patients suffering from OCA1. Mutations in this gene ultimately lead to hypopigmentation due to reduced production of melanin in melanocytes [13]. There are two variations of OCA1: OCA1A and OCA1B. Person suffering from OCA1A completely lack melanin pigment in epidermal keratinocytes. Any mutation in *TYR* gene results in complete absence of tyrosinase enzyme in melanocytes which leads to white skin and hair by birth and the irises of these individual don't turn dark over time. The color of iris ranges from blue to slightly pink and completely transparent in some cases. Vision in these individual's ranges from 20/200 to 20/400 [14]. Second type is OCA1B in this the patient have white to yellow skin and hair that can darken over time and the irises of these individual also changes color from blue to green or brown. Visual acuity is better in people with OCA1B than OCA1A. The main difference between these two types is that in OCA1A there is no melanin production while in OCA1B the melanin production is not completely absent

but it is produced in such a less amount that it has negative effect on individual [15].

### **Oculocutaneous albinism type 2 / *OCA2* gene mutation**

OCA type 2 individuals are linked to same vision problems as is seen in individuals with OCA1. There is wide range of skin pigmentation in individuals with OCA2 primarily depending upon the individual's genetic background and the type of mutation present [16]. Hair is not completely white, skin and hair follicles have some pigment in it but are still lighter than unaffected individual. Extensive sun exposure can lead to the pigmented lentigines and nevi (dark spots in skin). Individuals with OCA type 2 can have these dark spots in their skin after sun light exposure [17].

This type of albinism is associated with mutation in *OCA2* gene also known as *P* gene. *OCA2* gene is found on chromosome 15q11.2-q12 and consists of 25 exons out of which 2 are non-coding while the rest 23 are coding. The *OCA2* gene codes for P protein which is made up of 838 amino acids [18]. P protein has a role in normal movement of tyrosine substrate inside melanosomewhere tyrosine is metabolized and also regulates the internal environment of melanosomes and also plays role to maintain optimum pH of melanosomes [19].

In human genome mutation database 167 mutations have been reported in *OCA2* gene till now. The types of mutations which are seen in this gene include, missense, nonsense, splice site and insertion or deletion which leads to frame shift mutation. All of these mutations can disturb the functioning of P protein which will ultimately affect the melanin production in melanosomes. Mutations ranging from several kilobases to several hundred kilobases have been reported. This type of oculocutaneous albinism is most prevalent in African population and is also found in 22% of total

albino patients in German population [20, 21].

Experimental studies on human and mouse have been done to look for the molecular changes that occur due to the mutation in *OCA2* gene. It is reported that mutation on *OCA2* gene results in tyrosinase accumulation in trans Golgi system which carries tyrosinase to plasma membrane and instead of moving towards the melanosomes the tyrosinase is secreted out of the cell through this transportation pathway. Prevalence of this type of OCA is highest of all the other types 1/699 people. The risk of skin cancer due to sun exposure is higher in individuals with OCA2 [22].

### **Oculocutaneous albinism type 3/ *TYRP1* gene mutation**

This type was initially documented in African population. Individuals with this type of mutation have red to reddish brown skin with hazel to brown eyes and this type is also called as rufous albinism [23]. Recent studies have shown that this type is also found in many other populations including Asian Indian, Asian descent (Japan and Chinese population), northern European. Affected Asian individuals have blonde hair and light brown eyebrows however pigmentation increases with age. Visual acuity is less severe than in OCA1 and OCA2. In this type pigment production is not reduced to an extent that can modify the development [24]. *TYRP1* gene in humans consists of 8 exons out of which 7 are coding while 1 is non-coding. This gene is found on chromosome 9p23 [25]. This gene codes for tyrosinase related protein 1 which is made up of 537 amino acids and shows amino acid homology to tyrosine by 40-52%. This protein helps on availability of tyrosinase protein and also adjusts the catalytic activity of tyrosinase in melanin synthesis. This gene is also responsible to control the cell cycle including the cell propagation and cell death of melanosomes [26].

TYRP1 is involved in catalytic oxidation of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) into indole-5,6-quinone-2-carboxylic acid in melanogenesis. TYRP1 enzyme has a role in later stages of melanin production. Wild type *TYRP1* has a function in development of mesenchymal cells, melanin biosynthesis and pigmentation whereas biological functions of mutant *TYRP1* are protein metabolism, glycoprotein metabolism and neural crest cell development. Mutation in this gene also affects the expression of other genes that has a role in pigment production [27].

#### Oculocutaneous albinism type 4 / *SLC45A2* gene mutation

Physical features of OCA4 are very similar to OCA2. The hair color of individual with OCA4 ranges from yellow to brown. The amount of pigment in the eye decides the

visual acuity that ranges from 20/30 to 20/400.

This type of Oculocutaneous Albinism occurs due to the mutation in *SLC45A2* gene. This gene is found on human chromosome 5p13.3. it consists of 7 coding exons which translates into four alternatively spliced variants [28] The longest spliced isoform codes for solute carrier family 45, member 2 protein and is made up of 530 amino acids. This protein is found on melanosomal membranes, a membrane transporter protein with 12 transmembrane helices [29].

First case of OCA4 was reported in turkey in 2001. This form is infrequent throughout the world and there are not much cases reported. In human genome mutation database up to now 86 mutations of *SLC45A2* have been reported (Table 1)[30].

**Table 1. four major types of Oculocutaneous Albinism along with detailed information (Adopted from Shah *et al.* [31])**

Gene	Type of OCA	Size of gene	Location on chromosome	Gene product	Mutations
<i>TYR</i>	OCA1	65 kb	11q14.3	Tyrosinase	303
<i>P-gene</i> (OCA2)	OCA2	345 kb	15q11.2-q12	OCA2	152
<i>TYRP1</i>	OCA3	17 kb	9p23	Tyrosinase related protein	16
<i>MATP</i>	OCA4	40 kb	5p13.3	Membrane associated transporter protein	77

#### Oculocutaneous albinism type 5 (OCA5)

This type was identified in 1 consanguineous Pakistani family. A novel *OCA* locus is found to be linked to a gene present on chromosome 4q24. The gene responsible is not yet identified. The affected individual has golden hair, white skin due to hypopigmentation, photophobia, nystagmus and vision problems as is found in type 1 OCA. Approximately 3.8 Mb genetic linkage intervals contain 14 candidate genes. These include solute carrier protein family members (*SLC9B2*, *SLC9B1*) and proteins which are associated with lysosomes [32].

#### Oculocutaneous albinism type 6 (OCA6)

It is the rarest form of OCA which occurs due to the mutation in *SLC24A5* gene which codes for membrane transporter protein that functions for the pigment production in vertebrate's species. This gene is found on chromosome 15q [33]. The protein coded by *SLC24A5* has a role as solute carriers. They belong to a family of potassium dependent sodium/ calcium exchangers. Individuals have hair with different colors ranging from golden to dark brown. Other clinical features include irises Transillumination, visual

acuity, fovea hypoplasia and photophobia [34].

#### **Oculocutaneous albinism type 7 (OCA7)**

OCA7 is characterized by skin hypopigmented as compared to their normal parents; hair color is blonde to dark brown in this case. Affected person have irises Transillumination and nystagmus. Vision ranges from 6/18 to 3/60. OCA7 is caused by mutation in *C10orf11* gene located on human chromosome 10q22.2-q22.3. Immunohistochemistry has shown the localization of C10orf11 in melanocytes and melanoblasts in human fetal tissues and no localization is seen in retinal pigment epithelial cells [35].

Different types of OCA can be identified by clinical observation like skin pigmentation, hair color and vision. However, in some cases clinical symptoms overlap in different types of OCA so in these situations molecular diagnosis can help to identify the OCA subtype and the kind of mutation present in gene. Once the disease causing mutation status is known in a family prenatal diagnosis, carrier detection and evaluation of risk factor in each pregnancy is possible [36].

#### **Discussion and Conclusion**

This study can help to identify the main causes of OCA and can also play a role to highlight that how cousin marriages can affect the generations if any one or both the parents are carrier. Cousin marriages play a major role in onset of multiple genetic diseases. Genetic counseling can help to identify the possible risk of any genetic disorder and can help in early intervention by uncovering the hidden gene mutations.

There are seven different types of Oculocutaneous Albinism all of which occur due the mutation in one or more gene that has a role in melanin biosynthesis. Molecular prenatal analysis and genetic analysis can help in decision making and can identify the possible risks present. Those families with increased risk of having an albino child are

advised to go for prenatal testing. These types of tests can be carried out using sequencing, mutation detection and haplotype examination.

#### **Authors' contributions**

Conceived and designed the experiments: MJU Hasnain, MT Pervez & QA Shah, Wrote the paper: MJU Hasnain, QA Shah, S Ahmad & MA Arain.

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