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Oculocutaneous Albinism in Pakistan: A Review

Sajjad Ali Shah[1], **Masroor Ellahi Babar**[2], **Tanveer Hussain**[2], **Anwar Saeed**[1], **Abdul Wajid** [3], **Muhammad Irshad**[1], **Nazakat H Memon**[4] **and Muhammad Idrees**[5,6*]

[1]*Department of Biotechnology, Bacha Khan University Charsadda, Pakistan*

[2]*Department of Molecular Biology, Virtual University Lahore, Pakistan*

[3]*Institute of Molecular Biology and Biotechnology, University of Veterinary and Animal Sciences, Lahore, Pakistan*

[4]*Department of Biochemistry and Molecular Biology, West China School of Basic Medical Science and Forensic Medicine, Sichuan University, Chengdu, P.R. China*

[5]*CAS Key Laboratory of Mountain Ecological Restoration and Bioresource Utilization & Ecological Restoration and Biodiversity Conservation Key Laboratory of Sichuan Province, Chengdu Institute of Biology, P.R. China*

[6]*The University of Chinese Academy of Science, Beijing, P.R. China*

[*]**Corresponding author:** Muhammad Idrees, CAS Key Laboratory of Mountain Ecological Restoration and Bioresource Utilization and Ecological Restoration and Biodiversity Conservation Key Laboratory of Sichuan Province, Chengdu Institute of Biology, Chinese Academy of Science, P.O Box 416, Chengdu 61004, P.R. China, Tel: + 86-10-68597521; E-mail: idreesbiotech@yahoo.com

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Abstract

Oculocutaneous albinism (OCA) is an autosomal recessive disorder of abnormal melanin biosynthesis characterized by hypopigmentation of skin, hair and eyes. The patients with OCA have high risk of skin cancer, actinic injury and nystagmus. Oculocutaneous albinism is further classified into non-syndromic OCA and syndromic OCA. Autosomal recessive disorders like oculocutaneous albinism are more common in Pakistani population due to cousin marriages and large consanguineous families. This review paper includes updated data on the different research work done in Pakistani population on the four types OCA1, OCA2, OCA3 and OCA4 of oculocutaneous albinism and the mutations reported, also little information about the new forms OCA5, OCA6 and OCA7of oculocutaneous albinism.

Keywords: Albinism; Oculocutaneous albinism; Types of OCA; Risk; Genetic mutations

Introduction

Albinism is an autosomal disorder mainly by ophthalmic features with or without complete symptoms. It is not a single genetic disease but a collection of inherited disorders which shows a range of diverse phenotypes, and dependent on the patient's genetic background. The color of the hair and skin of ocular albinism patient might be a petite differs from normal to vary pale, while that of oculocutaneous albinism (OCA) patients have slight or complete absence of pigment in their skin, hair and eyes.15 genes are presently linked with different forms of albinism; still new genes were recently identified linked with the autosomal recessive OCA with extremely parallel phenotypes but different molecular source, which indicated that there are more than fifteen genes which are linked with albinism [1].

Literature Review

Oculocutaneous albinism (OCA) is an autosomal recessive disorder of abnormal melanin formation which results into the hypo pigmentation of skin, hair plus eyes. They also have a high possibility of skin cancer. The biosynthesis of melanin is directly or indirectly controlled by genes mutation and is accountable for the different type of albinism [2].

Individuals affected with OCA obvious a broad diversity of phenotypes with restricted number of genotypes. Current molecular genetics has expectant new methods for understanding and sorting of the subtypes of OCA. In addition to the systemic and ocular symptom, ophthalmologists should be well-known to the precise visual requirements and psychosomatic challenges of the affected persons [3].

OCA is linked with melanin biosynthesis that leads to congenital hypo-pigmentation of cutaneous and ocular tissues as well as linked with ordinary developmental deviation of eye. The mutation in the OCA is specific to population [4].

Types of Oculocutaneous Albinism

Oculocutaneous albinism is further classified into Non-syndromic OCA and Syndromic OCA. Four types of non-syndromic OCA: *OCA1*, *OCA2*, *OCA3* and *OCA4* are caused by mutation in four genes respectively *TYRP*, *TYRP1* and *SLC45A2* [5]. Syndromic forms of OCA having more phenotypic symptoms along with visual and hypo pigmentation problems. It includes nine different types of Hermansky-Pudlak syndrome *(HPS1-9)* and Chedaik-Higashi syndrome (CHS). The Hermansky-Pudlak syndrome is caused due to mutation in one of the genes *HPS1* to *HPS9*. All of these genes encoded protein which is responsible for endosomal channels [6].

At least 16 genes are responsible for causing oculocutaneous albinism in humans. Among them four are responsible for causing non-syndromic oculocutaneous albinism while the rest 12 genes are responsible for causing syndromic oculocutaneous [7].

Type 1 (OCA1/TYR) gene mutation

OCA type 1 is the most severe form of albinism in which the production of melanin is completely absent throughout life and mutation in *TYR* gene is responsible for this type of albinism [8]. The TYR gene is present on the chromosome 11q14.3 starting from

88,911,039 bp and ends at 89,028,926 bp. The *TYR* gene is composed of 5 coding regions (exons) and codes for tyrosinase enzyme which is composed of 529 amino-acid. The tyrosinase enzyme is present inside the melanocytes cells which are responsible for the production of melanin. The melanin gives color to eye, skin and hair (Figure 1). At the back of the eye in the light sensitive tissue (retina) melanin is also found where it plays a role normal vision [9].

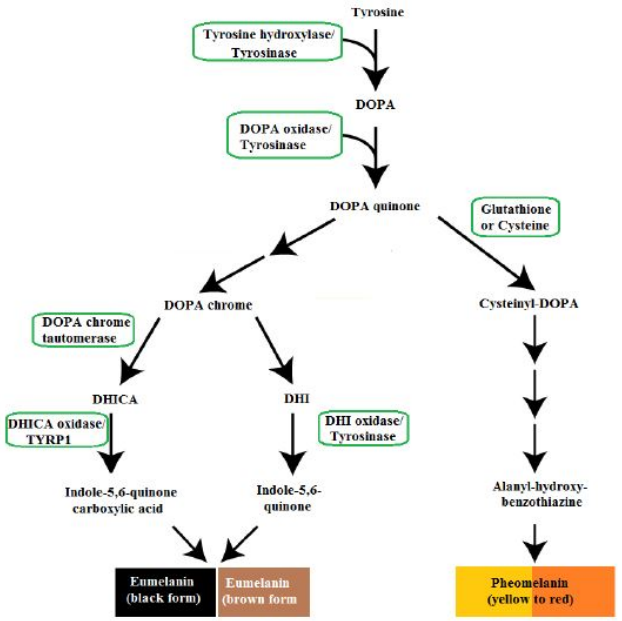

Figure 1: Pathway showing the synthesis of different forms of melanin from amino acid tyrosine by the enzymes tyrosinase and *TYRP1* involved in OCA1 and OCA3 respectively.

In the synthesis of melanin, tyrosinase enzyme catalyzes the first reaction. It changes the amino acid tyrosine to another compound called dopaquinone. The dopaquinone is then changed to pigment melanin within the retina, iris, skin and hair follicles by a sequence of further reactions are listed in Figure 2. In the *TYR* gene approximately 323 mutations have been identified in patients having the *OCA1* phenotype in the human genome mutation database [10]. Mutations in this gene results in the abnormal production of melanin ultimately leads to the hypo pigmentation of the skin, hair and eyes results in abnormal vision. There are two subtypes of *OCA1* which are *OCA1A* and *OCA1B*. In *OCA1A* the enzymatic activity of tyrosinase is completely missing, while in that of *OCA1B* the enzymatic activity is not completely absent but reduced greatly which has negative effect on the individual [11].

In *OCA1A* the eyebrows, hair, skin and eyelashes are white. Irises are slightly blue to approximately pink, and entirely transparent. The visual perspicacity is 1/10 or even less, while in *OCA1B*, the skin and hair may build up a few pigments with age (after one to three years), and irises might change from blue to brown/green. In this case the visual perspicacity is 2/10. This phenotype was formerly recognized as yellow albinism [12]. Null mutations in *TYR* gene is the main cause of the harshest type of albinism *OCA1* [13].

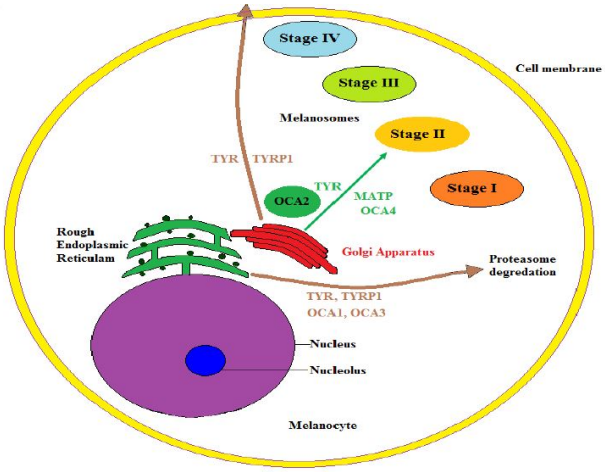

Figure 2: Diagrammatic representation of melanosome biogenesis in the melanocyte and transport of *TYR* and *TYRP1* from the endoplasmic reticulum (ER) via Golgi apparatus to the developing melanosome. Places are indicated by brown arrows where the transport or sorting of *TYR* and *TYRP1* from the synthesis in the ER to the melanosomes is abolished caused by mutations in the four genes found to be responsible for OCA (OCA1 to OCA4, respectively [10]. In the *TYR* gene approximately 323 mutations have been identified in patients having the OCA1 phenotype in the human genome mutation database. Mutations in this gene results in the abnormal production of melanin ultimately leads to the hypo pigmentation of the skin, hair and eyes results in abnormal vision.

Type 2 (OCA2) gene mutations

OCA type 2 is autosomal-recessive disorder linked due to mutation in *OCA2* gene. The *OCA2* (*MIM# 203200*) gene contains 25 exons (two non-coding and 23 coding) covers 345 kb of genomic DNA located on chromosome 15q11.2-q12 (Contig Accession No. NT_010280.17). The *OCA2* gene is translated into an 838 amino- acid plays an important role in the sorting and carrying of tyrosinase and tyrosine-related protein 1(*TYRP1*) toward the plasma, and maintains the pH of the melanosomes [14,15]. To date, 167 mutations have been found in the *OCA2* gene in the human genome mutation database. These mutations include splice site, nonsense, missense mutation and deletion or insertions leading to frame shift mutation. Large deletions from several kilo base pairs to several hundreds of kilo base pairs have also been identified. It is believed to exist most widespread in Black Africans and explains 22% of albino patient of the Germans [16,17]. Within Asians, in Japan, the occurrence of *OCA2* is reported to be approximately 8% in albino patients [18]. Experiments on humans and mouse melanocytes have revealed that fault in OCA2 gene leads to the accumulation of tyrosinase in trans-Golgi system which lead to the transportation of peptide plasma membrane and then finally concealed from the cells [19]. The recorded rate of this mutation is one of the highest estimated rates of OCA which is approximately 1/669 people. The patients affected with OCA type 2 normally have pale skin, red hair and blue or green eyes since birth [20]. The risk of sun induced skin cancers is considerable high in patients having mutation in *OCA2* gene. The association between melanoma and *OCA2* was reviewed using pedigree which shows that the mutation in *OCA2* gene have

harmful effects on pigmentation, supports offered GWAS information on the significance of the *OCA2* gene in melanoma tendency, and might eventually aid in the establishment of molecular remedy in the cure of melanoma and OCA [21].

OCA3/TYRP1 gene mutation

Type III OCA, an autosomal recessive disease linked with mutations in *TYRP1* gene. OCA 3 is also known as rufous/red albinism2 is the less common type of OCA [1]. OCA3 normally affect 1 out of 8,500 individuals in Africa, while it is very unusual in Asiatic and Caucasians populations. OCA3 is described by the reduction in melanin production or completely lack of melanin in hairs, eye and skin. OCA3 consequences in red or Rufous OCA in African population, who have reddish brown skin and red hair. Optical incongruities are not constantly noticeable, maybe due to the hypopigmentation is not enough to modify the development [13].

The human *TYRP1*(*MIM 115501*) gene comprises of 8 exons (seven coding and one non-coding) and 7 introns, straddling nearly 15–18 kb of genomic DNA in 9p23. The gene *TYPR1* code protein known as tyrosinase related protein-1 which has a molecular weight of ~75 kDa. *Tyrp1* is consist of 537 amino acid and shares 40–52% of amino acid homology to tyrosinase. This protein is involved in sustaining the constancy of tyrosinase protein and adjusting its catalytic action in the synthesis of melanin. This gene is also involved in preservation of melanosome arrangement and influence melanocytes propagation and cell death [8]. *TYRP1* catalyzes the oxidation of 5, 6-dihydroxyindole-2-carboxylic acid (DHICA) into indole-5, 6-quinone-2-carboxylic acid during melanogenesis. A genetic approach system is used to analyze and construct the co-expression networks, which are probably associated with *TYRP1* gene mutations which play a vital role in pigmentation. Biologic processes linked with wild type *TYRP1* are melanin biosynthesis, development of mesenchymal cells and pigmentation, while those biological processes which are linked with mutant *TYRP1* are protein metabolism, development of neural crest cell and glycoprotein metabolism. The mutation in *TYRP1* gene reduces the activity of gene to control the expression of other genes that play an important role in pigmentation metabolism [22]. Till 2014, only 26 mutations in the *TYRP1*gene have been added in the human genome mutation database. In African blacks the most common type of OCA is OCA3.

OCA4/ SLC45A2 gene mutation

Oculocutaneous albinism type 4 is an autosomal recessive disease which is caused by mutation in *SLC45A2* gene [12]and caused by mutations in Solute carrier family 45, member 2 *(SLC45A2)* also called *MATP* gene. It is located on human chromosome 5p13.3. It consists of seven coding exons which codes for four alternatively spliced variants. The solute carrier family 45, member 2 protein is coded through the longest spliced isoform (Gene Bank NM_016180) and has a molecular weight of ~58 kDa and is composed of 530 amino acids. The established solute carrier family 45, member 2 protein exhibits structural homology to plant sucrose-proton symporters and contain 12 putative transmembrane domains. Human *SLC45A2* function like a membrane carrier for melanosomal proteins and other substances to the melanosomes and is present in the melanosomal membrane [23,24], even though the exact function of this gene is not clear. First of all, it is reported in 2001 in a Turkish OCA patient, categorizing *SLC45A2* as the 4th gene accomplished of causing OCA [25]. Clinical phenotypes of OCA4 differ from whole depigmentation to fractional pigmentation with brown irises and hair and some affected individuals show upgrading during the first period of life [26]. Type 4 seems to be the infrequent form of OCA through the world since only 1 individual is affected with *OCA4*, of Turkish descent, was noticed amongst 102 albinos within varied inhabitants from Asia, North America, Africa and Europe [27], and only 5affected individuals were recognized among 176 German patients but, OCA4 is one of the most conjoint type in the Japanese population [26]. Mutations in this gene results in the fourth type of OCA called oculocutaneous albinism type 4 (OCA4), the second most prevalent type of OCA in Japan after OCA1. In the human genome mutation database, 86mutations of *SLC45A2* have been reported up to now. A comprehensive detailed of the four OCA genes and their mutations are listed in the Table 1.

Gene Name	Albinism	Size of gene	Chromosome location	Gene product	Prevalence	Mutations
TYR	OCA1	65kb	11q14.3	Tyrosinase	1:40,000	303
p- gene	OCA2	345kb	15q11.2-q12	OCA2	1:36,000(Europeans) 1:3,900–10,000 (Africans)	152
TYRP1	OCA3	17 kb	9p23	Tyrosinase-related protein	Rare (Europeans) 1:8,500 (Africans)	16
MATP	OCA4	40 kb	5p13.3	Membrane-associated transporter protein	Rare (Europeans, Asians) 1:85.000 in Japanese	77

Table 1: Detail of the four known OCA genes and their reported mutations.

Oculocutaneous albinism in Pakistani populations

Research work on OCA in Pakistani families shows different pathogenic mutations including novels as well as reported mutations of genes (*TYR*), *p.Pro21Leu, p.Cys35Arg, p.Ser44Arg, p.Arg77Gln, p.Ser192Tyr, p.Ile198Thr, p.Arg239Trp, p.Arg278*, c.344delGA, p.Gln328Glu, p.Glu376*, p.Ser315_a316del, p.Pro431Thr, p.Glu453*, p.Gly419Arg, p.Pro431Leu, p.Pro21Leu, p.Tyr411His, p.Cys35Arg, Arg299His, p.Pro406Leu, (OCA2) p.Met318Ile, p.Asp486Tyr, p.Leu527Arg, p.Pro743Leu, p.Ala787Thr* and (*SLC45A2*) *p.Gln272Lys*. The missense substitution (*p.Arg77Gln*) in *TYR* was found more frequent in families from different geographical areas of Azad Kashmir, Pakistan [28-30].

OCA5

A novel locus for non-syndromic oculocutaneous albinism was found linked to gene on human chromosome 4q24in a consanguineous Pakistani family [31]. Clinical symptoms of the affected individuals from this family shows golden-colored hair, white skin, nystagmus, photophobia, foveal hypoplasia, and impaired visual acuity, regardless of their sex and age. The approximate 3.84 Mb genetic linkage interval contain 14 candidate genes which are flanked by markers D4S421 and D4S2913. These genes included members of the solute carrier protein family (i.e., *SLC9B1*, *SLC9B2*, and *SLC39A8*) and proteins known to be associated with lysosomes (i.e., MANBA), among other putative candidates [32].

New types of OCA

OCA 6: By using exome sequencing approach it was found that mutations in *SLC24A5* (15q21.1) resulted in a new form of OCA, named as OCA6. *SLC24A5* is a well-known gene in the pigment cell arena which codes for solute carrier protein. Clinical features of the patients with OCA6 are; lighter hair color that darkened with age, iris transillumination, photophobia, fovea hypoplasia, reduced visual acuity, and nystagmus, with no defects in platelet dense granules. OCA6 is found in different ethnic groups [33].

OCA 7: This type of OCA is caused by mutation in *C10orf11* gene (10q22.2-q22.3), identified in a consanguineous Faroese family through homozygosity mapping. Clinical features of the patients with OCA7 presented lighter pigmentation, as compared to unaffected relatives, as well as nystagmus, iris transillumination, reduced visual acuity, and chiasm misrouting of their optical tracts. Localization of C10ORF11 in melan oblasts and melanocytes in human fetal tissue and no localization in retinal pigment epithelial cells were showed by Immunohistochemistry [34]. All forms of OCA are diagnosed by the clinical observation such as hypopigmentation of the skin, hair and characteristic ocular symptoms. But there is a clinical overlap between the subtypes, so it can be difficult to differentiate from one another. Molecular diagnosis can help us to identify gene mutations and OCA subtype. As soon as the disease-causing mutations have been known within the family then carrier detection plus prenatal diagnosis are possible. Patients having reduced visual activity and photophobia can use spectacles (probably bifocals) and sunglasses or phototrophic lenses that will give him sufficient help. Patients having nystagmus and strabismus must be treated well and sunscreens are recommended for them. For premature finding of skin malignancy, regular skin checks ought to be obtainable. OCA patients have normal natural life, maturity, aptitude and productiveness. Recessively inherited diseases are more common in populations where cousin marriages are common, like Pakistan [35]. These big consanguineous families are an invaluable repository for study of recessively inborn disorders similar to oculocutaneous albinism.

Discussion and Conclusion

This study may play a role in creating awareness about the effect of cousin marriages that is the first step towards decreasing socio-economic burden of the country by genetic counseling and also to prevent oculocutaneous albinism in Pakistan due to inbreeding.

Albinism consists of different phenotypes, but families expected to give birth to severely handicapped albino baby and wish to abort such fetus are appropriate for prenatal testing, otherwise prenatal test is not offered. Genetic analysis and molecular prenatal testing were carried out using mutation detection, sequencing and haplotype exanimation. Families having increased risk of an albino baby wish to carry out prenatal tests to prevent the affected babies. This molecular testing enables an approach to prevent the albinism. This can also be used in other individuals affected with albinism.

Declarations

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interest

The authors declare that they have no conflicts of interest.

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