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Review Article

Medico-Genetics of Oculocutaneous Albinism; An Updated Study with Pakistani Perspective

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Abstract

Albinism is a rare genetic disease associated with reduced melanin pigment biosynthesis in eyes, skin or hair. Clinically it is categorized, based on the affected tissue, into two types i.e ocular albinism (OA); when hypopigmentation influence the retinal pigment epithelium leaving skin and hair unaffected, and oculocutaneous albinism (OCA); when hypopigmentation occur in hair, skin and eye. Various genetic studies to date identified six genes (*TYR, TYRP1, OCA2, SLC45A2, SLC24A5, C10orf11*) and a locus (OCA5) for whom the candidate gene is yet to be known. All these reported genes, at the molecular level, are involved in melanin pigment biosynthesis. Among these reported genes, *TYR* and *OCA2* are the most prevalent genetic factors of OCA in Pakistani population. The study will assist in understanding the molecular factors of OCA and melanin synthesis pathway to reduce its prevalence rate. The review aims to systematically reread and analyze the oculocutaneous albinism and its various types in the context of developed world as well as Pakistani community.

Key words: Oculocutaneous albinism, melanin, *TYR, TYRP1, OCA2, SLC45A2, SLC24A5, MC1R.*

Introduction

Albinism is a rare genetic disease with reduced melanin pigment biosynthesis in eyes, skin or hair. Clinically it is categorized, based on the affected tissue, into two types i.e ocular abinism (OA); when hypopigmentation influence the retinal pigment epithelium leaving skin and hair unaffected, and Oculo cutaneous albinism (OCA); when hypopigmentation occur in hair, skin and eye[1].

Oculocutaneous albinism

Oculocutaneous albinism (OCA) is a disordered condition of melanin pigment biosynthesis in melanocytes. The persons affected of this disease have reduced or no melanin pigment in the skin, hair and eyes, along with retinal cell deterioration. The disease segregate mostly in autosomal recessive mode with non syndromic features. The additional clinical features include congenital nystagmus, hypopigmentation, low pigmentation of retinal epithelium and permanent photophobia. In oculocutaneous albinism (OCA), biosynthesis of melanin pigment is disturbed. Lack of this pigment in dermal tissue leads to severe photosensitivity and high risk of skin cancer while lack of pigment in the eye affects optic neural tracts misrouting and results in photophobia, nystagmus and reduced visual acuity[2].

Epidemiology of OCA

Epidemiologic survey has estimated that all known forms of albinism affects one in 17000 newborns in western societies, specially north America and Europe, but this ratio may be high in Asia and Africa due to high rate of consanguineous marriages. Prevalence rate of different genetic forms of OCA, among the various world populations, has determined OCA1 as the most widespread type of loci, mapped among the Caucasian patients, followed by OCA2, OCA4 and OCA3 respectively[3].

Genetics of oculocutaneous albinism and its clinical analysis

Genetic analysis of families with inherited OCA, so far, has identified seven loci and six genes including; OCA1 (*TYR*), OCA2 (*OCA2*), OCA3 (*TYRP1*), OCA4 (*SLC45A2*), OCA5, OCA6 (*SLC24A5*), and OCA7 (*C10orf11*). The detailed information of each locus, its gene and associated phenotype is explained in Table-1.

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OCA1 (MIM# 203100)

OCA1 was the first locus reported to be associated with OCA. This locus was mapped on chromosome 11q14.3 and harbor *TYR* gene (MIM# 606933) which consist of 5 exons. *TYR* gene encodes 529 amino acid long tyrosinase enzyme. This enzyme contains tyrosine hydroxylase and DOPA oxidase catalytic domains. This enzyme mediates the initial two steps of melanin pigment synthesis by converting tyrosine to DOPA and then to DOPA quinone. It is expressed predominantly in melanocytes where it controls the biosynthesis of melanin pigment from tyrosine. Clinically it is sub-categorized into OCA1A, characterized by complete loss of tyrosinase activity and OCA1B, characterized by reduced enzyme activity[4].

The clinical spectrum of OCA1 linked patients showed whitish colour of hair, eyelashes and eyebrows and the colour of Iris ranges from light blue to almost pink. In this OCA condition pigment does not develop and amelanotic nevi may also be present. Visual acuity in patients is 1/10 or even less, and photophobic condition is severe.

In OCA1B, the hair and skin may develop some pigment with the passage of time (after 1 to 3 years). Colour of iris also changes during the life time from blue to green/brown. Being the temperature-sensitive variant, manifest the depigmented body hairs, and pigmented hairs on hands and feet. Visual acuity in these patients is normally 2/10. This phenotype was previously known as yellow albinism[5].

OCA2 (MIM# 203200)

OCA2 locus is located on human chromosome 15q11-q13 and contain *OCA2* (previously called as *P* gene) (MIM# 611409). This gene contains two non-coding and 23 coding exons which encodes a polypeptide of 838 amino acids long (~110 kDa by weight) making 12 putative transmembrane helices. As a member of the Na^+/H^+ antiporter family, the OCA2 protein is thought to play an essential role in maintaining the acid pH of the melanosomes, which regulates the tyrosinase activity.

The OCA2 protein also participates in the localization of tyrosinase (TYR) and tyrosinase-related protein 1 (TYRP1) to the plasma membrane and thus involved in biogenesis of melanosomes.

The phenotypic consequences of OCA2 mutant individuals include varied amount of cutaneous pigment in hair and skin. Nevi and ephelids are common. Iris color in these patients is same as like in OCA1A cases. Visual acuity is usually better than in OCA1, and can reach up to 3/10 [6].

OCA3 (MIM# 115501)

The third locus of oculocutaneous albinism, OCA3, is positioned on long arm of chromosome 9 (9p23). OCA3 harbors the *TYRP1* (MIM# 115501) gene, which

Table 1: Updated list of OCA gene and loci.

Gene (MIM#)	*OCA Locus*	*Chromo-somal Position*	*Total Reported Mutations*	*Protein Encoded*	*Cellular localization**	*Biologic Function**	*Molecular Function**
TYR (606933)	OCA1	11q14.3	323	Tyrosinase	Melanosome Membrane	Melanin Biosynthetic Process from Tyrosine	Monophenol Monoxygenase Activity
OCA2 (611409)	OCA2	15q12-q13.1	167	P Protein	Melanosome Membrane	Eye Pigment Biosynthetic Process	L-Tyrosine transmembrane Transporter Activity
TYRP1 (115501)	OCA3	9p23	26	Tyrosinase Related Protein 1	Melanosome Membrane Endosome Membrane	Melanocyte Differentiation, Melanosome Organization	Oxidoreductase Activity
SLC45A2 (606202)	OCA4	5p13.2	86	Solute Carrier Family 45, Member 2	Melanosome Membrane	Visual Perception, Melanin, Biosynthetic Process, Developmental Pigmentation	Transport Substances Required for Melanin Biosynthesis
Unknown	OCA5	4q24	-	-	-	-	-
SLC24A5 (609802)	OCA6	15q21.1	10	Solute Carrier Family 24 Member 5	Melanosome Membrane	Ion Transport	Ca^{+2}, K^{+}:Na^{+} Antiporter Activity, Symporter Activity
C10orf11 (614537)	OCA7	10q22.2-q22.3	6	Leucine-rich repeat-Containing Protein C10orf11	Melanoblasts and Melanocytes	Melanocyte Differentiation	Under Investigation

* Cellular Localization, Biologic Functions and Molecular Functions are enlisted from BioGPS database.

Table 2: Gene and their reported mutations mapped in Pakistani families.

TYR	p.Arg299His[13] p.Pro406Leu[13] p.Gly419Arg [13] p.Arg278* [13] p.Pro21Leu [13] p.Cys35Arg [13] p.Tyr411His [13] p.Ile198Thr [15] c. -ΔGA115 [16] p.Gln376TER [5] p.Glu328Gln [5] p.Arg278TER [5]
OCA2	p.Asp486Tyr [13] p.Leu527Arg [13] c.1045-15 T > G [13] p.Pro743Leu [13] p.Ala787Thr [13]
TYRP1	p.Glu216GlyfsX42[1] p.Leu84Pro [1] p.Ala511Val [1]
SLC45A2	c.889-6T>G [1]
MC1R	c.917G>A [14]

spans over the 17 Kb DNA fragment and consist of 8 exons. *TYRP1* encodes 536 amino acid long enzyme with tyrosinase hydroxylase activity and catalyzes the oxidation of 5,6-dihydroxyindole-2- carboxylic acid monomer to melanin pigment in the melanin synthesis pathway. Clinical features of OCA3 associated families results in Rufous or red OCA in African individuals, who have red hair and reddish brown skin (xanthism). Visual anomalies are not always detectable, may be because the hypopigmentation not sufficient to alter the development[7].

OCA4 (MIM# 606574)

Pathogenic sequence change in *SLC45A2* (MIM# 606202) gene is the cause of OCA4 condition. This gene is located on chromosome 5p13.3, consisting of seven exons. The longest transcript of *SLC45A2* encodes a solute carrier family 45, member 2 (SLC45A2) protein composed of 530 amino acids long and has a molecular weight of ~58 kDa. Its exact function is unknown, but SLC45A2 is suppose to act as a melanosomal protein and substance transporter. Phenotypic consequences of OCA4 (SLC45A2) mutant revealed absence of pigment in skin, hair and eyes. Within the family, variation in hair colour was observed from white to honey blonde or brown. Additionally; photophobia, nystagmus, foveal hypoplasia, and reduced visual acuity was also reported[1].

OCA5 (MIM# 615312)

The genetic identity of OCA5 locus on 4q24 is still unknown. OCA5 locus is mapped on chromosome 4q24. The clinical symptoms of OCA5 patients exhibited golden hair, whitish skin and reduced visual acuity. Additional ocular problems also include nystagmus, photophobia and foveal hypoplasia[8].

OCA6 (MIM# 113750)

OCA6 phenotype is caused due to mutated *SLC24A5* gene. *SLC24A5* (solute carrier family 24, member 5) consist of 9 exons and its longest transcript encodes 500 amino acid long protein. SLC24A5 is a putative K^{+}-dependent Na^{+}/Ca^{++} exchanger 5 (NCKX5),

which has been implicated in hypopigmentation. It may function in the calcium homeostasis of melanosomes or trans-Golgi network, which is required for melanin biosynthesis or melanosomal protein trafficking[9]. The clinical manifestation of OCA6 mutation exhibit blonde hair at birth but converted to dark brown at elder age. The skin was white and iris was brownish. Nystagmus and photophobic conditions were less severe. Visual acuity in OCA6 patients was 20/100. Fundus examination showed hypopigmentatio, less develop macula with central disappearance of fovea[10].

OCA7 (MIM# 609446)

OCA7 locus harbor *C10orf11* gene (MIM# 614537), which is located on long arm of chromosome 10 (10q22.2–q22.3). This gene consist of 6 exons which encodes 198 amino acid long leucine rich repeat containing protein. Although its fully validated function is unknown but it is believed that it may be required for melanocyte differentiation on the basis of its expression pattern in melanoblast and melanocyte in human fetal cells.

Clinical synopsis of OCA7 mutant revealed light pigmentation as compared to related people. Ocular feature included nystagmus, iris transillumination and sever scattered pigmentation of the peripheral fundus. Visual acuity was observed between 6/9 and 3/60[11].

OCA in Pakistan

As a corollary of the inimitable socio-cultural customs in the population of Pakistan, approximately 60% of marriages are consanguineous, of which more than 80% are between first cousins. These large consanguineous families are a powerful resource for genetic studies of recessively inherited disorders like OCA. It is generally believe that OCA2 is more prevalent in Pakistani population than OCA1 in contrast to the Indian population. Giebel et al., 1991[11] identified a single point mutation (c.1117 C>T, p. Arg373*) in *TYRP1* gene in a large consanguineous Pakistani family[12]. In an other genetic study; Thomas *et al.*, (2012)[13] enrolled 40 extended Pakistani families from Punjab province and screened various OCA loci, candidate genes and pathogenic variants. They identified different mutations in *TYR* and *OCA2* genes. They reported seven pathogenic variants in *TYR* and five mutations in *OCA2* gene (Table-2). Then Kausar et al., 2012 in a cohort study identified three new mutations in *TYRP1* and one novel mutation in *SLC45A2*[1]. In the same year 2012, Saleha and her coworkers discover a novel *MC1R* gene in a Pakistani family affected with OCA[14]. After this discovery, Kausar and her colleagues in the subsequent year identified one novel OCA5 locus in a consanguineous Pakistani family[8]. And most recently Shah et al., in 2014 identified a novel mutation in *TYR* gene in a Pakistani family (See Table-2)[15].

Discussion

Genetically inherited disorders are a big dilemma for those countries, including Pakistan, where inter familial marriages are part of custom. Furthermore; people living in the rural area never believe in inherited disorder but rather consider it be caused by spiritual power which is a serious hurdle in the research and remedy of these genetic disorders. Oculocuatenous albinism is a rare genetic disease with reduced pigmentation in skin, hair and retinal cells[1]. So far seven loci and six genes have been reported to be implicated in OCA, which are distributed along different chromosomes. Among these loci and genes, *TYR, OCA2, TYRP1, MC1R, SLC45A2* and OCA5 locus are reported in Pakistani population. Apart from these reported loci and gene, many families are still uncharacterized. Until 2010, research on OCA did not attracted the scientists because OCA is not a life threatening disorder. It was during 2012 when scientists among the globe diverted their attention towards Pakistani families for disease gene identification. Dr. Zubair Ahmad and his colleagues determined that *TYR* and *OCA2* is the most prevalent gene in Pakistani population[13]. This effort will help in genetic counseling, premarital screening and prenatal screening of families at risk. And this study will assist in understanding the molecular factors of OCA and melanin synthesis pathway to reduce its prevalence rate.

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