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Treat Oculocutaneous Albinism with Gene Therapy

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Author's contribution

Author MLN designed the study, performed the literature searches, wrote the first draft of the manuscript and involved in revising the manuscript critically for significant intellectual need. The author read and approved the final manuscript.

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Review Article

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ABSTRACT

Oculocutaneous albinism (OCA) is a group of hereditary recessive disorder recognized as a loss of pigmentation. OCA can derive from mutations in different genes that produce melanin. These mutations cause disturbances to get a standard melanin synthesis. There are 7 types of oculocutaneous albinism. These include OCA1, OCA2, OCA3, OCA4, OCA5, OCA6, and OCA7. To help OCA patients, it may include management of such as hats with brims and sunscreens. An effective therapy is unavailable for albinism at present. However, to fight OCA in the future, gene therapy can be used. Gene therapy can include use of such as retrovirus vectors, adenovirus vectors, and CRISPR/Cas9 system. Research results in animal models have shown remarkable advances. It means that the gene therapy will be helpful to treat people with albinism.

Keywords: Albinism; albino; oculocutaneous albinism; gene therapy.

1. INTRODUCTION

Oculocutaneous albinism (OCA) is a heterogeneous group of monogenic recessive disorder. It is a reduction of pigmentation resulting in hypopigmentation in the eyes, hair and skin. Characteristic eye features include reduced visual acuity, nystagmus, strabismus, photophobia, foveal, and reduced iris [1,2,3], Tomita and Miyamura reported that the

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dissimilarity of skin color in human normally relies on the quantity of melanin pigment in the epidermis [4]. Clinically, two types of albinism exist; that is, OCA and ocular albinism (OA1). Based on the occurrence of mutations, OCA genes include non-syndromic OCA genes and syndromic OCA genes. The non-syndromic OCA genes include *TYR*, *OCA2*, *MC1R, TYRP1*, *SLC45A2*, *OCA5*, *SLC24A5*, and *C10orf11 (LRMDA)*. HGNC approved *OCA5* as a gene symbol [5]. *MC1R* gene alters the look of OCA2 patients [6]. The syndromic OCA genes may comprise *CHS1, HPS1, HPS2, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3,* and *BLOC1S6.*

All ethnic backgrounds have the opportunity to have albinism disorder. About 1 in 17,000 [3,7] to 20,000 people have one of the albinism types [8,9]. The carrier frequency is 1 in 70 people [3, 7]. Albinism is widespread in areas of the globe nearer to the equator. Equator area has greater infiltration of the sun's ultraviolet radiation [9]. OCA1 is the greatest common subtype discovered in Caucasian [10]. It influences 1 in 40,000 people worldwide. It is extremely rare in African-American [7]. The carrier frequency of OCA1 is 1 in 100 people [11]. OCA2 is most common in Africa [7]. It influences around 1 in 39,000 people. Predominance in African population is around 1 in 1,500 to 1 in 3,900 people. OCA2 influences 1 in 10,000 African-American [12]. It can influence as many as 1 in 1,000 in particular African [10]. The carrier frequency is around 1 in 50 to 1 in 100 people [12]. OCA3 affects around 1 in 8,500 people in Southern Africa [7,10,13]. OCA3 or ROCA (Rufous OCA) [14] is extremely rare in Caucasians and Asiatic people [7]. OCA4 is rare among Caucasians as well as Africans [10]. It is the majority common in Japanese [10,15] and Korean. In Japan, OCA4 influences 1 in 4 people [10]. OCA4 influences 1 in 100,000 people worldwide [15]. OCA5 has seemed in a Pakistani family. OCA6 has arisen in a Chinese family and a man from eastern India. Finally, OCA7 has seemed in a consanguineous Faroese family, and Lithuanian patients in Denmark [2].

Currently, there is no treatment for the fundamental molecular error in albinism. Present treatments are helpful for patients with albinism. Therapeutic for OCA and OA1 are under improvement. However, an effective therapy for any of the fundamental molecular error has not yet achieved clinical practice. Current management focuses on improvement of any refractive mistakes, management of strabismus, and efficient sun shield. Genetic counseling is another crucial aspect in the management of albinism. Therefore, to verify a hereditary detection of patients with albinism is crucial [1].

To treat albinism disorders, four methods can be used. These include the following: nitisinone, aminoglycosides, L-DOPA, and adeno-associated viruses (AAV) vectors. Nitisinone triggers the anomalous accumulation of tyrosine in the blood. Aminoglycosides are a potential therapeutic intervention in some mutations commonly found in albinism [10]. L-DOPA can improve the vision of OCA1 and OA1. Finally, AAV is a gene therapy technique for curing OCA1 and OA1. Other virus vectors for gene therapy are retrovirus, adenovirus, Sendai virus, and herpes simplex virus type 1 (HSV-1). In addition, to fight albinism, genome editing techniques can be used. These techniques can comprise meganucleases (MNs), zinc finger nucleases (ZFNs) system, transcription activator-like effectors nucleases (TALENs) system, and clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system.

In this article, the author describes progress in the study of OCA. The author focuses on the genetic aspects. These comprise genes in the disorder, and gene therapy for oculocutaneous albinism.

2. GENES IN OCULOCUTANEOUS ALBINISM

A gene is the basic bodily and functional unit of inheritance. Genes work as directives to create proteins. Mutations are able to rise in a gene. A gene mutation is a stable alteration in the DNA. It can result in the protein destruction. A genetic disorder, such as alkaptonuria and albinism, derived from a condition caused by mutations in one or more genes [16,17]. In albinism, mutations can occur in genes such as *TYR* and *LRMDA*. Mutations in oculocutaneous albinism can include such as missense and non-sense, Table 1.

2.1 *TYR* Gene

The official name of the *TYR* gene is "tyrosinase." *TYR* is the gene's official symbol. Other symbols for the *TYR* gene comprise LB24-AB, Monophenol monooxygenase, OCA1A, OCAIA, SK29-AB, Tumor Rejection Antigen AB, and TYRO_HUMAN. Human *TYR* gene occupies

chromosome 11q14.3 in the chromosome map [5,18]. The cytogenetic location of *TYR* gene is on the chromosome q arm at position 14.3 [18]. *TYR* gene includes base pair 89,177,565 to base pair 89,295,759 [19]; Table 2.

The *TYR* gene supplies directives for making tyrosinase. Tyrosinase plays a crucial role in the standard vision [18]. *TYR* gene comprises 5 exons spanning about 65 kb of genomic DNA [7, 10,20,21]. The *TYR* gene encodes a protein of 529 amino acids [7,10]. It is a copper-containing enzyme catalyzing the first two steps in the melanin biosynthesis pathway. The *TYR* gene converts tyrosine to L-dihydroxy-phenylalanine (DOPA), and then to DOPAquinone [7,21,22]. Mutations entirely eliminating tyrosinase activity trigger OCA1A. Mutations rendering some enzyme activity trigger OCA1B. It allows some deposit of melanin pigment eventually [7,10]. Mutations in the *TYR* gene can comprise frameshift, missense, non-sense [3,5], insertion, and gross deletion [3]; Table 1.

Temperature-sensitive OCA1 (OCA1-TS) is a very uncommon type of OCA1. OCA1-TS typifies the construction of the TS tyrosinase proteins. It leads to dark hair on the legs, arms, and chest in the cooler body areas. In the warmer body areas, TS tyrosinase proteins lead to white hair on the scalp, axilla, and pubic area [4,10]. A mutation in TS tyrosinase protein is inactive at 37℃ [10].

OCA1A patients have white hair, light-colored eyes, and extremely whitish skin [8,18] that do not light brown [11,18]. They have completely transparent irides, none of which lessens over time [11]; Fig. 1. Photophobia, nystagmus, and foveal hypoplasia escort this pigmentation [4]. Visual acuity is 1/10 or less [7], between 20/100 and 20/400 [11]. Visual acuity has refractive errors, and sometimes an extent of color vision harm [7]; Fig. 2. OCA1B patients have white hair, light-colored eyes, and whitish skin at birth. However, OCA1B has hair and eye color often darken over time and skin may be light brown [18]. OCA1B patients can have visual acuity around 2/10 [7] or between 20/100 and 20/200 [11].

2.2 *OCA2* Gene

The official name of the *OCA2* gene is "oculocutaneous albinism II." *OCA2* is the gene's official symbol. Other symbols for the *OCA2* gene comprise BOCA, Melanocyte-specific transporter protein, oculocutaneous albinism II (pinkeye dilution homolog, mouse), PED, P gene, P_HUMAN, and Pink-eyed dilution homolog. Human *OCA2* gene occupies chromosome 15q12-q13.1 in the chromosome map. The cytogenetic location of *OCA2* gene is on the q arm of chromosome 15 between 12 and 13.1 [23]. *OCA2* gene includes base pair 27,719,008 to base pair 28,099,342 [24]; Table 2.

The *OCA2* gene supplies directives for making the P protein. This protein exists in melanocytes, which may function in the production of melanin. It may also help control the melanosomes

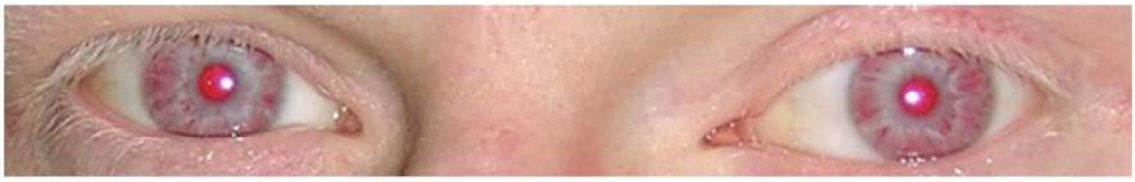

Fig. 1. Eyes of an OCA1 patient (from reference [7])

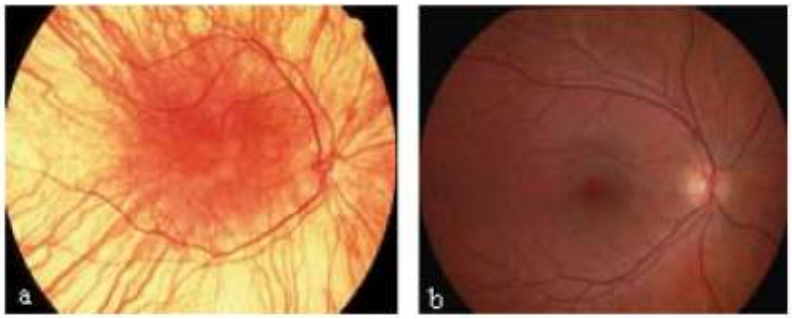

Fig. 2. An albinism eye (a) and a normal eye (b) (from reference [7])

relative pH. The pH is essential for the majority biological procedures [23]. *OCA2* gene comprises 24 exons [7,10,25] spanning almost 345 kb of genomic DNA [7,10,25]. It is extremely polymorphic [10,25]. The *OCA2* gene encodes a protein of 838 amino acids [7,10]. OCA2 protein is a 110-kDa integral melanosomes with 12 predictable transmembrane domains [7,10]. Mutations in the *OCA2* gene result in OCA2 disorder [7,10,12]. Mutations can comprise gross deletion, insertion, missense, non-sense, splice site [3], frameshift, small-in-frame deletions, and point mutations [26]; Table 1.

OCA2 patients have a minimum to modest degree of pigmentation in the eyes, hair, and skin [10,12]. It may include nystagmus, foveal hypoplasia, and strabismus [12]. The skin is generally a milky white color and hair may be light yellow, blond or light brown [23]. The amount of cutaneous pigmentation in OCA2 may vary from minimum to near-standard [12]. Visual acuity in OCA2 is generally superior to OCA1 [7, 12], though overlap occur. Visual acuity may reach 20/25 and 20/200 and is generally within the scope of 20/60 to 20/100 [12].

2.3 *MC1R* Gene

The official name of the *MC1R* gene is "melanocortin 1 receptor." *MC1R* is the gene's official symbol. Other names for the *MC1R* gene comprise MC1-R, the melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor), melanocyte stimulating hormone receptor, melanotropin receptor, MSH-R, and MSHR_HUMAN. Human *MC1R* gene occupies chromosome 16q24.3 in the chromosome map. The cytogenetic location of *MC1R* gene is on the q arm of chromosome 16 at position 24.3 [6]. *MC1R* gene includes base pair 89,917,879 to base pair 89,920,977 [27]; Table 2.

The *MC1R* gene supplies directives for making the melanocortin 1 receptor. This receptor plays a key role in standard pigmentation [6]. It mainly occupies the surface of melanocytes and regulates melanin production [6,28]. The melanocortin 1 receptor is also active in cells other than melanocytes. These include such as cells for the immunity and inflammatory responses. The receptor's role in these cells is unclear [6]. *MC1R* gene contains 4 exons. It yields several transcripts, namely, MC1R-001, MC1R-002, and MC1R-003. MCR1-001 contains a 951 nucleotide. It encodes for a 317 amino acids protein. MC1R-001 contains exons 2, 3, and 4. MC1R-002 contains exons 1-4. It contains a 1,149 nucleotide. MC1R-002 encodes for a 382 amino acids protein. Finally, the MC1R-003 is mainly possible a non-coding transcript [28]. Mutations in the *MC1R* gene can be a missense mutation [29].

This form of albinism has fair hair, light-colored eyes, milky white skin, and vision troubles. People with mutations in both the *OCA2* and *MC1R* genes have numerous of the common characteristics of OCA2. However, they characteristically have red hair instead of the typical yellow, fair-haired, or bright brown hair [6].

2.4 *TYRP1* Gene

The official name of the *TYRP1* gene is "tyrosinase-related protein 1." *TYRP1* is the gene's official symbol. Other names for the *TYRP1* gene comprise b-PROTEIN, CAS2, Catalase B, CATB, DHICA oxidase, Glycoprotein 75, GP 75, TRP, TRP-1, TYRP, and TYRP1_HUMAN. The human *TYRP1* gene occupies chromosome 9p23 in the chromosome map. The cytogenetic location of *TYRP1* gene is on the p arm of chromosome 9 at position 23 [30]. *TYRP1* gene includes base pair 12,693,385 to base pair 12,710,266 [31]; Table 2.

The *TYRP1* gene supplies directives for making the tyrosinase-related protein 1. This enzyme functions for making the melanin pigment [30], although the precise function of the protein is unknown [13,30]. It may help stabilize tyrosinase [30]. *TYRP1* gene consists of 8 exons [7,10,13] and 7 introns [10], spanning almost 17 kb of genomic DNA [7]. The gene encodes tyrosinase-related protein 1. It has a molecular weight of 75 kDa. The gene seems to be the majority plentiful melanosomes protein of the melanocyte [10,13]. Tyrosinase-related protein 1 contains a 537 amino acid protein [7,13]. Human tyrosinase-related protein 1 also has a role in the change of L-tyrosine to low quantities of DOPA. It is a vital cofactor in tyrosinase activity [10]. Mutations in the *TYRP1* gene result in OCA3 disorder. These mutations can comprise a missense mutation [32], and a non-sense mutation [13,32].

OCA3 results in Rufous OCA (ROCA) in Southern Africa [7,9,32]. OCA3 patients have red hair, reddish brown skin [7], and brown irises. This condition arises mostly in dark-skinned people from Southern Africa [30]. Visual anomalies are not always detectable, perhaps

because the pigmentation is not sufficient to change the improvement [7].

2.5 *SLC45A2* Gene

The official name of the *SLC45A2* gene is "solute carrier 45, member." *SLC45A2* is the gene's official symbol. Other symbols for the *SLC45A2* gene include AIM1, AIM-1, MATP, melanoma antigen AIM1, membrane-associated transporter protein, S45A2_HUMAN, and solute carrier family 45, member 2. Human *SLC45A2* gene occupies chromosome 15p13.2 in the chromosome map. The cytogenetic location of *SLC45A2* gene is on the p arm of chromosome 5 at position 13.2 [33]. The *SLC45A2* gene includes base pair 33,944,616 to base pair 33,984,675 [34]; Table 2.

Certain polymorphisms in the *SLC45A2* gene may refer to standard variations in skin, hair, and eye dye [33]. *SLC45A2* gene comprises 7 exons spanning around 40 kb of genomic DNA [7,10]. The SLC45A2 protein consists of 530 amino acids, which comprises 12 putative transmembrane domains. It displays sequence and structural resemblance to plant sucrose transporters. The melanoma cell lines express the SLC45A2 protein [7,10]. The function of the SLC45A2 likely refers to the melanin establishment. This protein possibly delivers molecules essential for the standard function of melanosomes [33]. Mutations in the *SLC45A2* gene result in OCA4 disorder [35]. These mutations can comprise, missense, small deletions/insertions [15], splice site [2,15], non-sense [2,15,35] and frameshift [36]; Table 1.

OCA4 patients usually have hypopigmentation of the skin and hair, iris translucency nystagmus, strabismus, and foveal hypoplasia. The amount of cutaneous pigmentation varies from minimum to close standard. Hair color may darken over time. However, it does not change drastically from childhood to adult. Visual acuity may get to 20/30 to 20/400. It is generally in the scope of 20/100 to 20/200 [15].

2.6 *OCA5* Gene

The name of the *OCA5* gene is "oculocutaneous albinism 5 (autosomal recessive)." The Hugo Gene Nomenclature Committee (HGNC) approves *OCA5* as the gene's symbol. Human *OCA5* gene occupies 4q24 in the chromosome map. The cytogenetic location of *OCA5* gene is on the q arm of chromosome 4 at position 24 [37]. The *OCA5* gene includes base pair 101,100,000 to base pair 107,700,000 [38]; Table 2. Mutations in the *OCA5* gene have not been identified [37].

PKAB80 had golden-colored hair, white skin, nystagmus, photopobia, foveal hyploplasia, and impaired visual acuity. Bodily, clinical, and hematologic assessments of OCA5 patients disclosed no extra visible clinical phenotypes [37].

2.7 *SLC24A5* Gene

The name of the *SLC24A5* gene is "solute carrier family 24 (sodium/potassium/calcium exchanger), member 5." The HGNC approves *SLC24A5* as the gene's symbol. Other symbols of the *SLC24A5* gene comprise JSX, NCKX5, OCA6, and SHEP4. Human *SLC24A5* gene occupies chromosome 15q21.1 in the chromosome map. The cytogenic location of *SLC24A5* gene is on the q arm of chromosome 15 at position 21.1 [39]. The *SLC24A5* gene includes base pair 48,120,972 to base pair 48,142,392 [40]; Table 2. Mutations in the *SLC45A2* gene result in OCA6 disorder. Mutations in the *SLC24A5* gene can include a frameshift mutation and a non-sense mutation [41].

OCA6 patients display pinkish-white skin, dark brown hair, brown irides, mild nystagmus and photophobia. Visual acuity is 20/100 [41].

2.8 *LRMDA* Gene

The name of the *LRMDA* gene is "leucine rich melanocyte differentiation associated." The HGNC approves *LMRDA* as the gene's symbol. Other symbols for the *LRMDA* or *C10orf11* gene include CDAO7, and OCA7. Human *LRMDA* gene occupies chromosome 10q22.3 in the chromosome map. The cytogenetic location of *LRMDA1* gene is on the q arm of chromosome at position 22.3 [42]. The *LRMDA* gene includes base pair 75,431,646 to base pair 76,559,220 [43]; Table 2. Homozygous mutation in the *LRMDA* gene results in OCA7. *LRMDA* gene encodes a leucine-rich repeat protein. It plays a role in melanocyte differentiation. Mutations in this gene result in OCA7 disorder [42]. A mutation in the *LRMDA* gene can be a non-sense mutation [44].

OCA7 patients display decreased pigmentation associated with classic albinism ocular

abnormalities. These comprise reduced visual acuity, macular hypoplasia, optic dysplasia, atypical choroidal vessels, nystagmus [42], and iris transillumination. The hair color variation may be pale blond to shade brown [44].

3. OTHER ALBINISM DISORDERS

OA1 is a form of albinism that affects the eye and melanocytes [45]. OA1 derived from pathogenic variants in the *GPR143* gene [11]. The gene location is on the X chromosome (Table 2). OA1 has nystagmus, strabismus, reduced visual acuity, foveal hyploplasia, and abnormal crossing of the optic fibers [7,11]. Pigment of the skin and hair is standard [10]. OA1 affects about 1 in 50,000 people [46].

The Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder [11]. It shows hypopigmentation and the accumulation of a material called ceroid in tissues during the body. HPS is a very rare disorder. However, it may affect approximately 1 in 1,800 people in Puerto Rico [7]. Visual acuity can reach 20/50 to 20/400 [11]. The disease can affect the dysfunctions of lungs, intestine, kidneys, or heart. The main stern shape of HPS is pulmonary fibrosis. It is normally observed in patient's ages of 40-50 years [10]. It has a connection with biallelic pathogenic variants in *HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOCK1S3,* or *BLOCK1S6* [11].

Chediak-Higashi syndrome (CHS1) is an autosomal recessive disorder [10,11]. It shows easy bruisability, peripheral neuropathy [7], incomplete OCA, immunodeficiency, and a gentle bleeding trend [11]. CHS typifies pigment reduction on the eye, skin, and hair. Mutations in the *CHS1* gene have a relationship to CHS1 (Table 2). The *CHS1* gene supplies directives for making the lysosomal delivery regulator. This protein plays a main role in the delivery of materials into lysosomes. Lysosomes operate for reprocess centers within cells. Digestive enzymes act to stop working poisonous materials. It also digests bacteria that damage the cell, and reprocess worn-out cell components [10]. Biallelic pathogenic variants in *LYST* are causative [11].

4. GENE THERAPY

To treat certain inherited disorders such as OCA and alkaptonuria, gene augmentation therapy (GAT) can be used. Nelwan and Strachan and Reap showed that GAT aim is clinically reversible disorders. It also helps to get no exact for expression levels of the introduced gene and a clinical outcome at low expression levels [17].

4.1 Gene Delivery Vehicles

The patient's cells manipulated, namely, the edited genes, gene segments or oligonucleotides

Table 1. Mutations in Oculocutaneous Albinism

Genes	Mutations	References
TYR	Insertion, gross deletion	[3]
	Splice site	[3]
	Frameshift, missense,	[3, 5]
	Non-sense,	[3, 5]
OCA2	Gross deletion	[3]
	Insertion, missense,	[3]
	Non-sense, splice site	[3]
	Frameshift	[26]
	Small-in-frame deletion	[26]
	Point mutations	[26]
MC1R	Missense	[29]
TYRP1	Non-sense	[13, 32]
	Missense	[32]
SLC45A2	Small deletions/insertions	[15]
	Splice site	[2, 15]
	Missense, non-sense	[2, 15, 35]
	Frameshift	[36]
OCA5	No mutation	[37]
SLC24A5	Frameshift, non-sense	[41]
LRMDA	Non-sense	[44]

Table 2. Locations for albinism associated Genes

OCA	Gene	Chromosome location	Base pair location*
OCA1	*TYR*	11q14.3	89,177,565 to 89,295,759
OCA2	*OCA2*	15q11.2-q12	27.719,008 to 28,099,342
OCA3	*TYRP1*	9p23	12,693,385 to 12,710,266
OCA4	*SLC45A2*	5p13.2	33,944,616 to 33,984,675
OCA5	*OCA5*	4q24	101,100,000 to 107,700,000
OCA6	*SLC24A5*	15q21.1	48,120,972 to 48,142,392
OCA7	*LRMDA*	10q22.3	75,431,646 to 76,559,220
OA1	*GPR143*	Xp22.2	9,725,413 to 9,765,965
CHS1	*LYST*	1q42.3	235,661,031 to 235,883,708
HPS1	*HPS1*	10q24.2	98,415,068 to 98,446,963
HPS2	*AP3B1*	5q14.1	78,002,326 to 78,294,755
HPS3	*HPS3*	3q24	149,129,584 to 149,173,196
HPS4	*HPS4*	22q12.1	26,443,613 to 26,483,863
HPS5	*HPS5*	11p15.1	18,278,670 to 18,322,498
HPS6	*HPS6*	10q24.32	102,065,367 to 102,068,038
HPS7	*DTNBP1*	6p22.3	15,522,801 to 15,663,058
HPS8	*BLOC1S3*	19q13.32	45,178,745 to 45,202,715
HPS9	*BLOC1S6*	15q21.1	45,587,123 to 45,609,716

**Taken from Genetics Home Reference for: GPR143 [47] LYST [48], HPS1 [49], AP3B1 [50], HPS3 [51], HPS4 [52], HPS5 [53], HPS6 [54], DTNBP1 [55], BLOC1S3 [56], and BLOC1S6 [57].*

must be transmitted into the DNA molecule; e.g. bacterial plasmid. This plasmid possesses edited sequences needed for gene expression in aim cells. To help the sufficient cellular uptake of molecules, the edited materials must be put within gene delivery vehicles [17].

A wide array of delivery vehicles has been tested. These include safety, integrating vectors as adenoviruses to non-integrating vectors as Sendai virus. Delivery vehicles also comprise non-viral vectors such as transposing-base and episomes delivery methods. Viral vectors can bring the corrected hereditary information into a patient to replace incorrect genes in the patient. There are obtainable some types of vectors in gene therapy. These vectors can include retroviruses, adenoviruses, AAV, Sendai virus, and HSV-1 [16,17]. To treat OCA in the animal models, these vectors such as retroviruses and AAV have been used.

Gene delivery vectors can deliver gene editing tools. Gene editing tools can comprise the MNs, ZFNs system, TALENs system, and the CRISPR/Cas9 system. MNs as a gene editing tool have not been widely used. Both ZFNs and TALENs have the same techniques [16]. These two techniques use different DNA binding arrays. Those are zinc finger arrays, and TAL effector repeats. Finally, the CRISPR/Cas9 system uses sgRNA to produce site-specific gene editing in aim cells with great frequency [58].

The CRISPR/Cas9 system needs RNA-DNA identification. The tracRNA and crRNA lead Cas9 to a specific string. A mixture of the tracRNA/crRNA into a sgRNA has led to the gene-editing procedure development. It is specific for any aim within the genome. The endonuclease requires a protospacer adjacent motif (PAM). PAM is an invariant fraction of the DNA aim. It is unobtainable in the sgRNA. The CRISPR/Cas9 system operates sgRNA to find the matching string in the DNA and later construct DSBs. DSBs are double-strand breaks. Error-prone non-homologous end joining (NHEJ) fixes DSBs through homology-directed repair (HDR). NHEJ generates indel mutations, guiding to knock-out the role of gene [16].

4.2 Therapy for OCA

OCA is a high-quality contestant for a cure with gene therapy. It is an autosomal recessive disorder. OCA is suitable with GAT technique. In this technique, moderate demonstration levels of an injected gene may result in a significant difference. In animal models, research results have shown important advances to treat OCA disorder (Table 3).

To combat OCA, lentivirus, adenoviruses, AAV, ZFNs, TALENs, and CRISPR/Cas9 have been used. Ikawa et al. introduced a potential primary attempt toward the progress of *in vivo* gene therapy approaches for Hermansky-Pudlak

syndrome. The authors showed that lentiviral-mediated gene transfer corrected *HPS1* gene expression and role. It is the *HPS1* gene expression and role in human epidermal melanocytes [59]. HPS1 is one of the syndromic oculocutaneous albinisms.

Kawaguchi et al. examined the demonstration levels of the various diacylglycerol kinase (DGK) isoforms. The authors examined these in pigmented human melanocytic cells. In their study, Kawaguchi et al. used adenovirus-mediated gene transfer. The authors showed that DGKζ is mainly plentiful isoforms displayed in human melonocytic cells. A DGKζ inhibitor drastically reduced levels of melanin, tyrosinase activity and tyrosinase protein. The inhibition did not alter levels tyrosinase and MITF mRNA. Isoform-particular siRNA demonstrated that knockdown of DGKζ reduced melanin and tyrosinase manifestation. Over-expression of DGKζ improved tyrosinase protein levels. However, it is without an important improvement in tyrosinase mRNA levels. It shows that DGKζ controls tyrosinase at the posttranscriptional level [60]. It means that DGKζ with an adenovirus vector may be useful to get a standard melanin synthesis.

Among vector-based delivery vehicle, AAV is very promising for gene therapy protocols. AAV-mediated retinal gene delivery of the human *Tyrosinase* gene can activate melanosome biogenesis and melanin production. Gargiulo *et al.* stated that AAV 2/1-CMV-hTYR-mediated can trigger *ex novo* melanin biosynthesis in retinal pigment epithelium. Also, it can trigger *ex novo* melanin biosynthesis in the choroid. The authors injected sub retinal of AAV 2/1-CMV-hTYR-mediated delivery at birth and adult^{c2j} in mice. Histological investigation confirmed that melanin pigmentation in the retinal pigment epithelium is present. The ultra structural analysis demonstrated that pigmented stage III and fully mature stage IV melanosomes are obtainable. It suggests that deposition of melanin and consecutive pigmentation of the eye is reversible when treated. This study result provides proof-of-principle of an effective approach for future application in albino patients [61].

Ishibashi et al. examined the effectiveness of TALENs in making mutations in genes in *Xenopus tropicalis.* The authors targeted the tyrosinase (*tyr*) gene in their investigation. Ishibashi et al. injected mRNA encoding TALENs targeting the first exon of the *tyr* gene into two-cell-stage embryos. PCR-amplified embryos demonstrated 70% carrier deletion mutations and 30% normal at the targeted loci. Injected embryos with TALENs RNAs comprise 300 pg each RNA, 400 pg each RNA, and 600 pg. Treatments with 600 pg consist of L-RNA and R-RNA. Treatments with 300 pg and 400 pg resulted in three phenotypes. These form full albinism, partial albinism, and wild type. Phenotype analysis showed that treatment with 300 pg each RNA produced 68% full albinism, 27% partial albinism, and 5% wild type, Treatment with 400 pg each RNA resulted in 74% full albinism, 21% partial albinism, and 5% wild type. Mutations in *tyr* gene were efficiently transmitted into the F_1 progeny. These findings are far-reaching implications to develop efficient reverse genetic approaches in this emerging amphibian model [62]. In the hemophilia A case, Park et al. reversed the incorrect sequences of the *F8* gene to the wild type situation. The authors used TALENs in combination with induced pluripotent stem cells (iPSCs) in their study [16]. Thus, to reverse the incorrect segments in the *tyr* gene in *Xenopus tropicalis,* it is possible. It seems TALENs system may be useful to treat albinism in human.

Song et al. showed that a *Tyr* 3' UTR mutation caused decreased melanin production and graying in rabbits. Moreover, functional analysis of the 3' UTR in animal models can be accomplished by double sgRNA directed CRISPR/Cas9 system. This animal model will be beneficial to comprehend the link between the 3' UTR area and gene manifestation, as well as the fundamental mechanism of hereditary diseases [63]. Yoshimi et al. built CRISPR/Cas9 constructions in rats. The authors used albino F344 rats and agouti DA rats (wild type) in their study. To target F344 and DA rats, Yoshimi et al. used Cas9/gRNA:Tyr^{c} and Cas9/gRNA:Tyr^{C}, respectively. When the crossing was established between F_1, and F_1, the progeny were agouti-colored, albino-colored or mosaic-colored coats. To recover the albino rats, Yoshimi *et al.* co-injected the created elements into F344 rat embryos. These elements include gRNA:Tyr^{c}, Cas9 mRNA, 80-bp ssODN. The authors obtained 7.7% pup with a retrieval of the coat-color for albino without agouti, hooded phenotype. Sequence analysis showed indel mutations in 23.1% pups, and 7.7% accurate SNP exchange in one pup [64]. These research results show that CRISPR/Cas9 can be beneficial to fight OCA disorder.

Table 3. Vehicles in Gene Therapy Researches for OCA

Vehicles	Targeted genes	Results	References
Lentiviruses	*HPS1*	Corrected *HPS1*	[59]
Adenovirus	*TYR*	Improved melanin	[60]
AAV	*TYR*	Improved melanin	[61]
TALENs	*tyr*	Caused albino	[62]
CRISPR/Cas9	*Tyr*	Reduced melanin	[63]
CRISPR/Cas9	*Tyr*	Treated albino	[64]

It seems that gene therapy will be beneficial to treat OCA. This method can edit incorrect segments in the albinism genes, for example. For this purpose, viral vectors such as lentiviruses and AAV can deliver these incorrect segments for treatment of OCA. These vectors can also deliver gene editing tools such as TALENs and CRISPR/Cas9 to repair albinism genes. In addition, use gene editing tools in combination with iPSCs are possible. For example, in the hemophilia A case, the CRISPR/Cas9 system in combination with iPSCs is possible. Nelwan showed that this combination has shown crucial improvements to fight hemophilia A [16]. It is reasonable to state that this combination may be useful to overcome albinism disorder.

5. CONCLUSIONS

Oculocutaneous albinism is one of the Mendelian disorders identified as a reduced pigmentation that inherited recessively. OCA is a monogenic recessive disorder. There are no efficient treatments for OCA patients at present. Current treatments such as the use of sunscreens and dark glasses are helpful. Animal models for the study of disease mechanisms and cure for OCA are obtainable. To treat OCA, gene therapy has shown important improvements in animal models. This technique can increase melanin production in the OCA. For this purpose, gene correction techniques are already available. These comprise techniques to edit erroneous segments in the genes such as *TYR* gene and *LRMDA* gene. This technique can include gene delivery vectors and gene editing tools. Gene delivery vectors may include such as retrovirus, adenovirus and AAV. Gene editing tools may comprise such as TALENs system and CRISPR/Cas9 system. For example, CRISPR/Cas9 system can correct albinism phenotype in rats. Either TALENs or CRISPR/Cas9 system in combination with iPSCs can be useful to fight albinism. It seems that gene therapy would be very beneficial for treating OCA disorder.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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