Review Paper

Treat Oculocutaneous Albinism with Gene Therapy

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 comprise 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 comprise reduced visual acuity, nystagmus, strabismus, photophobia, foveal, and reduced iris [1, 2, 3]. Tomita and Miyamura reported that the 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 comprise non-syndromic OCA genes and syndromic OCA genes. The non-syndromic OCA genes comprise TYR, OCA2, MC1R, TYRP1, SLC45A2, OCA5, SLC24A5, and C10orf11 (LRMDA). HGNC approved OCA5 as a gene symbol [5]. The 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. Approximately 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. The equator area has greater infiltration of the sun’s ultraviolet radiation [9]. OCA1 is the majority common subtype discovered in Caucasian [10]. It influences 1 in 40,000 people in the majority populates. It is extremely rare in African-American [7]. The carrier frequency of OCA1 is 1 in 100 people in the majority populates [11]. OCA2 is the majority common in Africa [7]. It influences around 1 in 39,000 people in the majority populates. Predominance in African population is around 1 in 1,500 to 1 in 3,900 people. OCA2 influences 1 in 10,000 African-American people [12]. It can influence as many as 1 in 1,000 people in particular Africa populates [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 populates [7]. OCA4 is rare among Caucasians as well as Africans [10]. It is the majority common in Japanese [10, 15] and Korean populates. In Japan, OCA4 influences 1 in 4 people [10]. OCA4 influences 1 in 100,000 people worldwide [15]. OCA 5 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. Currents 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 monoxygenase, OCA1A, OCAIA, SK29-AB, Tumor Rejection Antigen AB, and TYRO_HUMAN. The 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]. The TYR gene includes base pair 89,177,565 to base pair 89,295,759 [19]; Table 2.

The TYR gene has a crucial function for making tyrosinase. This enzyme exists in the melanocytes that produce melanin. It is the substance that gives color to skin, hair, and eyes. Melanin also exists in the light-sensitive tissue in the retina. Tyrosinase plays a role in the standard vision [18]. The 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°C [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].

Fig. 1. Eyes of an OCA1A patient (from Reference [7]).

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

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. The 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]. The OCA2 gene includes base pair 27,719,008 to base pair 28,099,342 [24]; Table 2.

The OCA2 gene has an important function 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 relative pH. Tight control of pH is essential for the majority biological procedures [23]. The 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]. The OCA2 gene comprises 24 exons [7, 10, 25] spanning almost 345 kb of genomic DNA [7, 10, 25].

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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. The 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]. The MC1R gene includes base pair 89,917,879 to base pair 89,920,977 [27]; Table 2.

The MC1R gene has a crucial function of making the melanocortin 1 receptor. This receptor plays a key role in standard pigmentation [6]. The receptor 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 comprise such as cells for the immunity and inflammatory responses. The receptor’s role in these cells is unclear [6]. The MC1R gene contains 4 exons. It yields
several transcripts, namely, MC1R-001, MC1R-002, and MC1R-003. MC1R-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 possesses fair hair, light-colored eyes, milky white skin, and vision troubles. People with mutations in both the OCA2 and MC1R genes possess numerous of the common characteristics of OCA2. However, they characteristically possess 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]. The TYRP1 gene includes base pair 12,693,385 to base pair 12,710,266 [31]; Table 2.

The TYRP1 gene has a crucial function of making the tyrosinase-related protein 1. The location of this enzyme is in melanocytes. This enzyme functions for making the melanin pigment [30], although the precise function of the protein is unknown [13, 30]. This enzyme may help stabilize tyrosinase [30]. The 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 missense mutation [32], and 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. The 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.

The exact function of the SLC45A2 is still unclear. It likely refers to the melanin establishment. This protein possibly delivers molecules essential for the standard function of melanosomes. 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]. 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. The 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, photophobia, foveal hypoplasia, 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. The 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 comprise 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. The 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].

Table 1. Mutations in Oculocutaneous Albinism

<table>
<thead>
<tr>
<th>Genes</th>
<th>Mutations</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>TYR</td>
<td>Insertion, gross deletion</td>
<td>[3]</td>
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<tr>
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<td>Splice site</td>
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<td></td>
<td>Non-sense, splice site</td>
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<tr>
<td></td>
<td>Frameshift</td>
<td>[26]</td>
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</table>
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]

### 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 hypoplasia, and abnormal crossing of the optic fibers [7, 11]. The pigment of the skin and hair is standard [10]. OA1 affects approximately 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, DTNB1, BLOCK1S3, or BLOCK1S6** [11].

<table>
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<tr>
<th>OCA</th>
<th>Gene</th>
<th>Chromosome location</th>
<th>Base pair location*</th>
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<td>TYRP1</td>
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<td>OCA4</td>
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*Base pair location is given in human genome assembly GRCh37/hg19.*
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<th>Gene</th>
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<td>45,587,123 to 45,609,716</td>
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</tr>
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</table>

*Taken from Genetics Home Reference for: GPR143 [47] LYST [48], HPS1 [49], AP3B1 [50], HPS3 [51], HPS4 [52], HPS5 [53], HPS6 [54], DTNB1P [55], BLOC1S3 [56], and BLOC1S6 [57].

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 has a crucial function of 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 reprocesses 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 hereditarily influenced, namely, the edited genes, gene segments or oligonucleotides must be launched 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 wrapped within appropriate gene delivery vehicles [17].

A wide array of delivery vehicles has been tested. These comprise 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 comprise 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). The PAM is an invariant fraction of the DNA aim. It is unobtainable

in the sgRNA. The CRISPR/Cas9 system operates sgRNA to identify 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 normal human epidermal melanocytes, human melanoma cells, and mouse melanoma cells. DGKζ is mainly plentiful isoforms displayed in human epidermal melanocytes, human melanoma cells, and mouse melanoma cells. Kawaguchi et al found that DGKζ adenovirus-mediated overexpression of DGKζ increased tyrosinase protein levels. The authors used Western blot analysis to validate the adenovirus-mediated demonstration of DGKζ. Overexpression of DGKζ affects tyrosinase expression in human epidermal melanocytes. The adenovirus-mediated overexpression of DGKζ is the only isoform that improve tyrosinase protein levels in human epidermal melanocytes. However, it is without a significant improvement in tyrosinase mRNA levels. It shows that DGKζ controls tyrosinase at the posttranscriptional level [60]. It means that adenovirus-mediated overexpression of DGKζ may be useful to get a normal melanin synthesis for the albinism cases.

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 adult25 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 comprise 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 F₁
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) [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]. Yoshiimi 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, Yoshiimi et
al used Cas9/gRNA:Tyr⁺ and Cas9/gRNA:Tyr⁻, respectively. When the crossing was established
between F₁, and F₁, the progeny were agouti-colored, albino-colored or mosaic-colored coats. To
recover the albino rats, Yoshiimi et al co-injected the created elements into F344 rat embryos. These
elements comprise gRNA:Tyr⁺, 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.

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.

Table 3. Vehicles in Gene Therapy Researches for OCA

<table>
<thead>
<tr>
<th>Vehicles</th>
<th>Targeted Genes</th>
<th>Results</th>
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<tr>
<td>Lentiviruses</td>
<td>HPS1</td>
<td>Corrected HPS1</td>
<td>[59]</td>
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</table>
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]

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 comprise gene delivery vectors and gene editing tools. Gene delivery vectors may comprise 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

There is no conflict of interest to disclose.

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