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REVIEW PAPER

Albinism – symptomatology, aetiology, and therapy

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ABSTRACT

Albinism is a rare, genetically determined disorder of melanogenesis resulting in a reduction or complete absence of melanin in tissues of ectodermal origin, especially skin, hair, and irises of the eyes. It may occur in isolated form as oculocutaneous albinism inherited in an autosomal recessive manner or ocular albinism inherited in an X-linked recessive manner. Syndromic forms of albinism may additionally include involvement of other systems with various combination of symptoms and signs. The paper presents the classification, clinical characteristics, pathogenesis, and genetic basis of various forms of isolated and syndromic albinism. The diagnostic approach and available therapeutic interventions have been discussed.

KEY WORDS:

melanogenesis, hypopigmentation, ocular albinism, oculocutaneous albinism.

INTRODUCTION

Albinism (from the Latin "albus", meaning "white") is a rare, genetically determined disorder of the melanogenesis resulting in a reduction or complete absence of melanin in tissues of ectodermal origin, especially skin, hair, and irises of the eyes [1]. Melanin is a biopolymer produced in brown-black (eumelanin) and red-yellow (pheomelanin). Biosynthesis of both eumelanin and pheomelanin begins the same way. Tyrosine is converted into dihydroxyphenylalanine (DOPA), which requires tyrosine hydroxylase and tetrahydrobiopterin as a cofactor. The enzyme tyrosinase then converts DOPA into dopaquinone, which can form the eumelanin or pheomelanin. Eumelanin, rich in nitrogen, plays a role in protecting the skin against damage caused by ultraviolet radiation. Complete lack of eumelanin production deprives of natural protection against UV, which results in an increased risk of skin diseases. Pheomelanin, however, is rich in sulphur and does not have photoprotective properties. Although it does not have a protective function against external factors, it gives minimal colour [2]. Melanogenesis in lighter forms of albinism is directed at the production of pheomelanin. The phenotypic variability of albinism is wide and ranges from complete absence of pigmentation of the hair, skin, and/or irises to mild depigmentation. In more severe forms of albinism, the melanogenesis process is blocked.

CLASSIFICATION

There are 2 main groups of albinism: syndromic and isolated (with its 2 forms, oculocutaneous albinism – OCA, and ocular albinism – OA). In OCA features such as colour/degree of hypopigmentation of the skin, hair, and/or irises of the eyes coexist with ocular abnormalities/vision disorders, while OA primarily affects the eyes. Oculocutaneous albinism is inherited in an autosomal recessive manner, while OA is typically inherited in an X-linked recessive manner. Oculocutaneous albinism may take on 8 different types (OCA1-8). All are caused by a pathogenic variant in one of the genes involved in the melanin biosynthesis process, with the exception of OCA5 associated with the chromosomal region 4q24 with no causative gene identified so far [1, 3–6]. Moreover, OCA type 1 albinism is divided into subtypes OCA1A and OCA1B – both caused by molecular variants

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TABLE 1. Isolated albinism

Type	Gene locus	Phenotype
OCA 1A	*TYR* 11q14.3	The most severe form due to the complete lack of tyrosinase activity and therefore the complete lack of melanin; hair and skin, regardless of age, are white, and the irises are light blue, pink or red due to the translucency of blood vessels; the skin is very sensitive to UV radiation; there is severe impairment of visual function, nystagmus, foveal hypoplasia, iris transillumination, photophobia, visual acuity range 0.2– 0.05 [7, 29]
OCA 1B		A slightly milder form, because the enzyme tyrosinase is active, although only to a small extent; the melanogenesis process is focused on the biosynthesis of yellow-red pheomelanin (hence the other name "yellow OCA"); the phenotype of patients with this subtype is initially identical to that of subtype A, but by the age of 3 years they will show some melanisation of the skin (from cream to tan with light moles and freckles) and hair (from yellow to light brown); the irises are blue, green, hazel or light brown, foveal hypoplasia occurs, nystagmus, visual acuity ranges 0.2–0.1 [8, 29, 30]
OCA 2	*OCA2* 15q12-q13	Classic OCA 2: the skin is creamy white or tanned, often with moles and freckles, the hair, eyebrows and eyelashes are yellow, blond or light brown, the irises are blue, hazel, brown or grey. Visual acuity range 0.8–0.1, usually 0.32–0.2; there is nystagmus and photophobia. Brown OCA 2: people look "normal", have brown skin, hair, and eyes, but are relatively less pigmented compared to healthy family members. Red OCA 2: this variant occurs with an associated MC1R gene mutation, patients have light eyes, red hair, and vision problems [12, 30]
OCA 3	*TYRP1* 9p23	Melanocytes of people affected by OCA 3 show only about 7% of normal activity; 2 varieties of skin colour - the so-called "brown albinism", characterised by light brown skin prone to tanning and light brown hair and Rufous type, in which skin is red-brown, the hair is red, and the irises are coloured nut or light brown; sometimes visual disturbances are undetectable [30]
OCA 4	*SLC45A2* 5p13.2	Pheomelanin predominance, cream-colored skin, silver-white to light brown/yellow hair, blue, hazel to light brown irises, visual acuity range 0.63–0.05, usually 0.2–0.1 [12, 30]
OCA 5	Gene not identified 4q24	White skin and golden hair, iris hypopigmentation, nystagmus, foveal hypoplasia, photophobia, impaired visual acuity [6, 29]
OCA 6	*SLC24A5* 15q21.1	Decreased eumelanin content, fair skin, light hair that darkens with age, blue, green or light brown irises, mild nystagmus, foveal hypoplasia, mild photophobia, decreased visual acuity (0.2) [30]
OCA 7	*LRMDA* (c10orf11) 10q22.2-q22.3	Lighter skin colour compared to healthy relatives, blond to dark brown hair, nystagmus, foveal hypoplasia, iris transillumination, mild photophobia, visual acuity range 0.63–0.05; very rare, in a related family from the Faroe Islands [30]
OCA 8	DCT 13q32.1	Mild oculocutaneous albinism with congenital nystagmus and photophobia. Reduced visual acuity, mild to moderate; iris transillumination; hypopigmentation of the retina; moderate foveal hypoplasia (grade I); mild hypopigmentation of skin; mild hypopigmentation of hair [31, 32]
OA	*GPR143* Xp22.2	A rare disease limited to the organ of vision, which mainly affects men; they have eye symptoms, but the colour of their skin and hair does not deviate from the norm; nystagmus, photophobia, strabismus (in approximately 60% of patients), foveal hypoplasia and refractive errors occur; vision disorders are the result of improper development of the visual pathway (melanin deficiency prevents the normal development of neural connections between the retina of the eyes and the visual centres in the brain); due to eye fundus abnormalities spatial vision is impaired and visual acuity decreases (it ranges 0.2–0.1); female carriers of OA are generally asymptomatic; however, some may have a mild form of OA with hypopigmentation of the retinal pigment epithelium and slightly transparent iris, but no visual impairment [14]

OA – ocular albinism, OCA – oculocutaneous albinism

in *TYR* gene encoding tyrosinase [7, 8]. Isolated forms of albinism with its genetic background and clinical characteristics are presented in Table 1. Oculocutaneous albinism and/or hypopigmentation of skin/hair/irises may be one of the clinical manifestations in some complex syndromes with involvement of various systems, in which concomitant hearing loss, peripheral neuropathy, immunodeficiency, cardiomyopathy, brain defects, platelet dysfunction, or dysmorphia in various constellations may occur. Table 2 presents selected syndromes with albinism, divided into types according to genetic background.

EPIDEMIOLOGY

The worldwide prevalence of albinism is estimated at 1 : 17,000 to 1 : 20,000 [1, 9]. The most common form of isolated albinism (1 : 39,000) is OCA2 with a prevalence in African Americans of 1 : 10,000), in all Americans at 36,000, and in Sub-Saharan Africans at 1 : 3900 [10]. OCA1, with a prevalence of 1 : 40,000, occurs the most frequently among Europeans, and it is one of the most common forms of OCA in America and China, accounting for 70% of cases [3]. OCA3 with an

TABLE 2. Selected syndromes associated with albinism

Disorder (mode of inheritance)	Gene locus	Phenotype
Chediak-Higashi syndrome (AR)	*LYST* 1q42.3	Oculocutaneous albinism, nystagmus, foveal hypoplasia, photophobia, peripheral neuropathy, presence of inclusion bodies in myeloblasts and promyelocytes of the bone marrow, neutropenia, increased susceptibility to pyogenic infections, tendency of excessive bleeding and bruising, occurrence of lymphomas [33]
Griscelli syndrome type 1 (AR)	*MYO5A* 15q21.2	Hypopigmentation of skin and hair, decreased visual acuity, immunodeficiency, pancytopenia, hemophagocytic syndrome, brain demyelination [34]
Griscelli syndrome type 2 (AR)	*RAB27A* 15q21.3	
Griscelli syndrome type 3 (AR)	*MLPH* 2q37.3	
Hermansky-Pudlak syndrome type 1 (AR)	*HPS1* 10q24.2	Oculocutaneous albinism, iris hypopigmentation, nystagmus, foveal hypoplasia, accumulation of ceroid deposits in tissues, especially kidneys and lungs, haemorrhagic diathesis due to platelet dysfunction; some forms (HPS2, HPS10) present immunodeficiency (neutropenia) and haemophagocytic syndrome; the most severe forms (HPS1, HPS4) are associated with interstitial lung fibrosis and granulomatous colitis [35]
Hermansky-Pudlak syndrome type 2 (AR)	*AP3B1* 5q14.1	
Hermansky-Pudlak syndrome type 3 (AR)	*HPS3* 3q24	
Hermansky-Pudlak syndrome type 4 (AR)	HPS4 22q12.1	
Hermansky-Pudlak syndrome type 5 (AR)	*HPS5* 11p15.1	
Hermansky-Pudlak syndrome type 6 (AR)	*HPS6* 10q24.32	
Hermansky-Pudlak syndrome type 7	*DTNBP1* 6p22.3	
Hermansky-Pudlak syndrome type 8 (AR)	*BLOC1S3* 19q13.32	
Hermansky-Pudlak syndrome type 9 (AR)	*BLOC1S6* 15q21.1	
Hermansky-Pudlak syndrome type 10 (AR)	*AP3D1* 19p13.3	
Hermansky-Pudlak syndrome type 11 (AR)	*BLOC1S5* 6p24.3	
Tietz syndrome (AD)	*MITF* 3p13	Hypopigmentation of eyebrows and eyelashes, hypopigmentation of the iris, sensorineural hearing loss [36]
Vici syndrome (AR)	*EPG5* 18q12.3-q21.1	Agenesis of the corpus callosum, delayed psychomotor development, muscle hypotonia, hypopigmentation of the skin and hair, cleft lip and palate, immunodeficiency, cardiomyopathy, cataract [37]
Waardenburg syndrome type 1 (AD)	*PAX3* 2q36.1	Hypopigmentation of skin and hair, iris heterochromia, sensorineural deafness (type 2), with additional features, namely dysmorphia: telecanthus, dystopia canthorum in type 1, hands malformation in type 3 and Hirschsprung disease in type 4 [38]
Waardenburg syndrome type 2A (AD)	*MITF* 3p13	
Waardenburg syndrome type 2E (AR)	*SOX10* 22q13.1	
Waardenburg syndrome type 2F	*KITLG* 12q21.32	
Waardenburg syndrome type 3 (AD, AR)	*PAX3* 2q36.1	
Waardenburg syndrome type 4A (AD, AR)	*EDNRB* 13q22.3	
Waardenburg syndrome type 4B (AD, AR)	*EDN3* 20q13.32	
Waardenburg syndrome type 4C (AD)	*SOX10* 22q13.1	

overall prevalence of 1 : 8500, occurs mainly in southern Africa [10, 11]. The prevalence of OCA4 is 1 : 100,000, but it accounts for 24% of OCA in the Japanese population [12, 13]. The very rare OCA5 has been described in a Pakistani family [5], while OCA6 was reported in single Chinese and East Indian families. The overall prevalence of OA is estimated at 1 : 60,000 [14]. According to Orphanet, the prevalence of selected syndromes associated with albinism is as follows: Hermansky-Pudlak 1–9 : 1,000,000, Waardenburg 1 : 40,000, Tietz, Griscelli, and Vici < 1 : 1,000,000. Only 500 cases with Chediak-Higasi have been described so far.

AETIOLOGY AND GENETIC BACKGROUND

Pigmentation genes in humans (approximately 120) as a result of regulatory processes control the number and size of melanosomes, as well as the amount and type of melanin synthesised and its distribution. The *TYR* gene encodes tyrosinase, which plays a key role in the melanin biosynthesis process. Mutations of the *TYR* gene (*TYR*), which cause OCA1, may cause complete or partial inactivation of tyrosinase, leading to the most severe or the milder form of albinism, where in the latter form biosynthesis of the yellow-red pheomelanin predominates [7, 8, 15, 16]. The *OCA2* gene, responsible for OCA2, encodes the melanosome transmembrane protein P. Its exact functions are not fully understood, but it appears to be involved in transporting proteins into melanosomes, stabilising the melanosomal protein complex, and regulating pH within the melanosome, which are crucial in the process of melanin biosynthesis [17]. The *TYPR1* gene (OCA3) encodes a protein related to tyrosinase, which stabilises and modulates its activity, supporting the process of melanin biosynthesis and contributing to maintaining the integrity of the melanosome [18, 19]. The product of *SLC45A2* (OCA4) is a melanosomal membrane transporter protein that transports substances needed for melanin biosynthesis to the melanosome [12]. The *SLC24A5* (OCA5) gene encodes protein that is important for the maturation and architecture of melanosomes [20], and *LRMDA* (c*10orf11)* (OCA7) – for melanocyte differentiation, regulating early stages of melanosome biogenesis [21]. Tyrosinase-related protein 2 encoded by the *DCT* gene (OCA8) is one of the 3 key enzymes in the biosynthesis of eumelanin [22, 23]. And finally, the *GPR143* gene encodes an intracellular G-protein-coupled receptor involved in melanosome biogenesis and is responsible for OA [24].

CLINICAL CHARACTERISTICS

Skin manifestations of OCA include hypopigmentation, which may vary individually and is subject to change with age. Consequences of skin exposure to sunlight may help to assess the severity of hypopigmentation – the greater the degree of depigmentation, the higher risk of skin burning instead of tanning [1, 3–5]. Due to the reduction or lack of eumelanin, individuals with albinism have an increased risk of sun damage to the skin: lentigines, actinic keratosis, solar erythema, as well as an increased risk of skin cancer, e.g. squamous cell, basal cell carcinoma, or melanoma. The first is the most common malignant tumour found in people with albinism (over 75% of cases), developing already in teenage years. Basal cell carcinoma accounts for approximately 24%, and melanoma – only 1% of all skin cancers in patients with albinism [5, 25]. An impaired process of melanin biosynthesis may cause various eye abnormalities. The most common include the following: early-onset nystagmus mainly in the horizontal plane, seen in the first weeks of life, refractive errors, including hypermetropia/myopia and astigmatism, strabismus, and decreased visual acuity. Loss of retinal pigment epithelium with transillumination, observed in the majority of patients with albinism, is associated with photophobia. On fundus examination, reduced pigmentation retinal epithelium and choroid, foveal hypoplasia and optic nerve abnormalities are present. Chiasmal misrouting was also reported [1, 3–5].

Psychological issues may be associated both with visual impairment and with general appearance, because albinism is a disease with characteristic presentation, which is easy to notice. Visual problems may influence early neurodevelopment in many aspects, i.e. acquisition of motor skills, hand-eye coordination, language and communication, social abilities, and cognition; however, some improvement in school performance is seen with age, and problems in reading are observed only in some patients with OCA/OA. Anxiety and depressive disorders are much more frequent in this group in comparison to the general paediatric population, and more than half of OCA/OA patients present at least one feature characteristic of autism spectrum disorders or attention deficit hyperactivity disorder (ADHD) [26, 27]. A significant problem for people suffering from albinism is their unusual appearance, which arouses interest in others or causes ridicule and lack of social acceptance. In some cultures, the fate of people with albinism is particularly dramatic. They are subject to harassment, persecution, and even murder due to the prevailing superstition that their body parts have magical powers and ensure the success of their purchasers [28].

More detailed clinical characteristics of various forms of isolated OCA and OA are presented in Table 1, while a clinical description of syndromes associated with albinism is presented in Table 2.

DIAGNOSIS

Clinical findings may not accurately predict a molecular diagnosis, and the spectrum of clinical disease varies widely as many patients with OCA are compound hetero-

zygotes. The diagnostic yield of whole-genome sequencing or targeted gene panels for albinism with positive yields ranges 28–91%. The presence or absence of cutaneous involvement of albinism significantly affects genetic diagnostic yield. The overall initial genetic diagnostic yield of OA/OCA in the paediatric population is 66% [39–41]. There is no significant difference between race and ethnicities; however, the diagnostic yield of OA (33%) is significantly lower ($p = 0.007$) than OCA (76%). Causative variants in *OCA2* (28%) and *TYR* (20%) are most common [39]. Among missense variants in the *TYR* gene, which are predominant, there are pathogenic mutations and functional polymorphisms – the most common are c.575A > C, p.Tyr92Ser and c.1205G > A, p.Arg402Gln [42–45]. Furthermore, Hermansky-Pudlak syndrome variants were identified in 9% of patients [39]. Re-classification of variants of uncertain significance (VUS) in non-diagnostic cases resulted in genetic diagnoses for 29% of individuals and increased the overall diagnostic yield to 70% of all subjects [39, 40].

TREATMENT

Albinism is an incurable disorder. It is only possible to prevent its negative effects and treat complications caused by the lack of melanin. Albinism significantly limits the normal existence of people affected by it – permanent protection of the body against solar radiation is required. In patients with visual acuity reduction some daily activities like reading, writing, and working with a computer may be difficult, which in turn has a major impact on the professional life of these people. To provide eye protection using special filtering glasses is recommended. To improve visual acuity appropriate correction of refractive errors is helpful, and where appropriate, surgical correction of abnormal head posture in selected cases of nystagmus [46, 47]. Novel strategies for systemic treatment of subtypes of albinism are in preclinical testing. Currently, novel therapies that aim to directly address the molecular errors of albinism, such as l-DOPA and nitisinone [48], are being developed and have entered human trials though with limited success. Experimental gene-based strategies for editing the genetic errors in albinism have also met early success in animal models [49]. The emergence of these new therapeutic modalities represents a new era in the management of albinism [46].

DISCLOSURES

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