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REVIEW ARTICLE

Albinism in Europe

Mónica MÁRTINEZ-GARCÍA,[1,2] Lluís MONTOLIU[1,2]

[1]*Department of Molecular and Cellular Biology, National Centre for Biotechnology (CNB-CSIC), and* [2]*Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), ISCIII, Madrid, Spain*

ABSTRACT

Albinism is a rare genetic condition associated with a variable hypopigmentation phenotype, which can affect the pigmentation of only the eyes or both the eyes and the skin/hair, resulting in ocular (OA) or oculocutaneous albinism (OCA), respectively. At least four forms of OCA and one of OA are known, associated with *TYR* (OCA1), *OCA2* (OCA2), *TYRP1* (OCA3), *SLC45A2* (OCA4) and *GPR143* (OA1) loci, respectively. Additionally, the rarest syndromic forms of albinism, affecting the normal function of other organs, can be grouped in Hermansky–Pudlak syndrome (HPS1–9) and the Chediak–Higashi syndrome (CHS1). In summary, a total of 15 genes are currently associated with various types of albinism. However, new genes have been recently described, associated with autosomal recessive oculocutaneous albinism with highly similar phenotypes but diverse molecular origin, indicating that there are likely to be more than 15 genes whose mutations will be associated with albinism. In this review, we will describe the different types of albinism and comment on its prevalence in European countries. Some preclinical attempts for innovative therapeutic approaches of different types of albinism will be also discussed.

Key words: genetic, mutations, ocular albinism, oculocutaneous albinism, retina, tyrosinase.

INTRODUCTION

Albinism is a generic clinical term describing an heterogeneous group of several types of rare congenital diseases globally characterized by decreased pigmentation in skin, hair and/or eyes, and associated with retinal and, hence, visual alterations. Eye abnormalities, the most important and handicapping traits for persons with albinism (besides the obvious hypopigmentation), include fovea hypoplasia, reduced pigmentation of retinal pigment epithelium cells, photoreceptor rod cell deficit, misrouting of the optic nerves at the chiasm, reduced pigmentation in the iris, photophobia and nystagmus.[1,2] Several studies suggest that all known forms of albinism affect 1:17 000 newborns in Western societies, mostly North America and Europe, although frequencies ranging from 1:10 000–20 000 have been also reported[2,3] and other prevalences apply in Asia.[4,5] In some countries in Africa, due to consanguinity issues, the prevalence of albinism can be much higher.[6]

The characteristic retinal alterations result in visual abnormalities commonly associated with persons with albinism, including reduced visual acuity, impaired stereoscopic vision, photophobia, iris transillumination and poor night vision. In addition, strabismus, refractive errors and alterations in color perception are also frequent among persons with albinism. Skin hypopigmentation must be protected from sun exposure and sunburns, hence, the adequate use of clothes, hats and efficient sunscreens is strongly recommended. The effects of iris transillumination and photophobia may be avoided with the use dark glasses. The poor visual acuity and refractive errors can be corrected with glasses or contact lenses. Nystagmus can be fixed with eye muscle surgery and strabismus can be also solved by patching one eye.[3]

Most of these retinal alterations have been well reproduced in animal models, primarily genetically modified rodents, transgenic mice, where the relationships between genetic modifications and phenotype alterations have been investigated and produced a substantial increase in our current understanding of the albinism genetic condition.[7,8]

TYPES OF ALBINISM

Albinism may be classified according to the hypopigmentation trait being associated with skin, hair and eyes, or eyes only. The former case corresponds to the so-called oculocutaneous albinism (OCA), whereas the latter, when the hypopigmentation affects primarily the retinal pigment epithelium cells and the skin and hair remain pigmented, is described as ocular albinism (OA). In OCA, irrespective of the observed pigmentation level, the number and structure of melanocytes remain largely unaltered, whereas in OA the appearance of altered large melanosomes within melanocytes is characteristic.[2,9,10]

Recessive mutations in at least four autosomal genes have been associated with OCA (see Table 1), namely, *TYR* (OCA1), *OCA2* (OCA2), *TYRP1* (OCA3) and *SLC45A2* (OCA4),[11] of

Correspondence: Lluis Montoliu, Ph.D., Centro Nacional de Biotecnologia (CNB-CSIC), Campus de Cantoblanco, Darwin 3, Madrid 28049, Spain. Email: montoliu@cnb.csic.es
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Table 1. Mutations detected in genes associated with albinism

Gene	Chromosomal location	Albinism	Mutations
TYR	11q14–q21	OCA1	303
OCA2	15q11.2–q12	OCA2	152
TYRP1	9p23	OCA3	16
SLC45A2	5p13.3	OCA4	77
GPR143	Xp22.3	OA1	114
LYST	1q42.1–q42.2	CHS1	50
HPS1	10q23.1–q23.3	HPS1	31
AP3B1	5q14.1	HPS2	11
HPS3	3q24	HPS3	7
HPS4	22cen–q12.3	HPS4	13
HPS5	11p14	HPS5	11
HPS6	10q24.32	HPS6	9
DTNBP1	6p22.3	HPS7	2
BLOC1S3	19q13.32	HPS8	2
BLOC1S6	15q21.1	HPS9	1

Source: Human Gene Mutation Database, 14 December 2012.

which OCA1 (Figs 1,2) is the commonest type of OCA and the commonest type of albinism among Caucasian patients, followed by OCA2, OCA4 and OCA3, the rarest type of OCA.[12] Similarly, molecular diagnosis approaches among albino subjects reported in Europe, confirmed these observations, with OCA1 being recognized as the most frequent type of OCA in German,[13] French,[14] Danish[15] and Italian[16] European populations, with somewhat diverse percentages, normally not altering the prevalence among different types of OCA, and also associated with the size of the series of patients studied and reported for each country. A variable percentage of cases regularly remain unresolved in all those studies reported above, where only one mutation (or none) is detected, suggesting the presence of genetic alterations in non-coding genomic regions, which may be located far away from the locus and be associated with relevant regulatory transcriptional regulators[17,18] or the existence of additional loci, associated with OCA, yet to be identified. One of these new OCA loci has been recently identified, the C10orf11 gene, whose mutations have been associated with a new type of autosomal recessive OCA[19] OCA1, associated with mutations in the *TYR* gene, has also been subdivided into two types, OCA1A, where no pigmentation is produced, and OCA1B, where some pigmentation levels (variable, normally developing postnatally) are observed,[17] related to the amino acid residues affected and their impact on the enzymatic biochemical oxidative reaction.[20] Based on the residual enzymatic activity characteristic of some TYR mutations,[21] Brooks *et al.* has suggested the use of a drug, nitisinone, commonly used to treat patients with hereditary tyrosinemia type I, as a potential therapeutic approach, aiming to benefit from the expected increased enzymatic activity resulting from the higher accumulation of the amino acid L-tyrosine in the blood, as a side-effect associated with this drug treatment.[22]

Oculocutaneous albinism type 2 is the commonest OCA in Africa and some mutations in the *OCA2* locus have a clearly defined African origin.[23–25] However, due to the regular and historic immigration from Africa to Europe, OCA2 cases are not

Figure 1. Young Spanish boy with oculocutaneous albinism. Picture taken and kindly provided by Ana Yturralde. Included in the book: "Albinismo, una condición genética, dos realidades: España y Senegal", published by ALBA (2009), the Spanish Association in support of people with albinism (www.albinismo.es).

Figure 2. Young Spanish girl with oculocutaneous albinism. Picture taken and kindly provided by Ana Yturralde. Included in the book: "Albinismo, una condición genética, dos realidades: España y Senegal", published by ALBA (2009), the Spanish Association in support of people with albinism (www.albinismo.es).

rare among Europeans, and, as such, *OCA2* mutations are routinely detected in genetic studies on albinism conducted in European countries, although logically, with lower prevalence, as compared to Africa.[14–16]

Oculocutaneous albinism type 3, associated with recessive mutations in the *TYRP1* gene, is the less frequent type of OCA. It is also referred to as red/rufous albinism[2] and is rarely detected[13,14,16] or absent[15] in genetic studies in Europe.

Oculocutaneous albinism type 4, associated with recessive mutations in the *SLC45A2* gene, was initially described among the Japanese population, where it is frequently detected[26] but was also rapidly reported in Europe[27] and, since then, regularly found in genetic studies of albino subjects in different European countries, usually as the third most common type of OCA, after OCA1 and OCA2.[14–16]

The clinical manifestations (hypopigmentation and visual phenotypes) of all four OCA types are highly similar, and often it is very difficult to differentiate patients affected by mutations in any of these four genes: *TYR*, *OCA2*, *TYRP1* and *SLC45A2*. Therefore, proper diagnosis of OCA human subjects requires precise molecular analysis of mutations in these four genes.

In addition to OCA1–4, additional and relatively uncommon syndromic types of OCA, with additional phenotypic alterations beyond hypopigmentation and visual alterations, have been described, including as many as nine different types of Hermansky–Pudlak syndrome (HPS1–9) and Chediak–Higashi syndrome (CHS), which are altogether relatively rare and presenting an altered biogenesis of lysosomal-derived organelles, including melanosomes.[3,28,29] HPS is very rare, except in some countries, such as Puerto Rico. In addition to oculocutaneous hypopigmentation, HPS is characterized by hypopigmentation and the accumulation of ceroid material in the body. These patients also suffer from severe immunological deficiency, interstitial lung fibrosis, granulomatous colitis and mild bleeding alterations associated with altered platelet function.[5] HPS, although a rare type of albinism in Europe, has been regularly described and identified.[30–33]

Chediak–Higashi syndrome is also uncommon, and CHS patients, besides the hypopigmented phenotype, are prone to bacterial infections, bleeding, bruisability and peripheral neuropathy.[34] Some CHS cases have been reported seldom in Europe.[35] All these types of syndromic albinism are detailed in Table 1.

In addition to autosomal recessive OCA, the other type of albinism, primarily affecting the pigmentation of retinal pigment epithelium cells, is OA type 1 (OA1), associated with mutations in the X-linked *GPR143* locus, a gene encoding an intracellular G protein-coupled receptor involved in melanosome biogenesis,[36,37] proposed to regulate melanosome transport in pigment cells[38] and, whose apparent ligand is L-dihydroxy-phenylalanine (L-DOPA),[39] hence suggesting a link between a metabolite intermediate in melanin biosynthesis, altered melanosome biogenesis and visual alterations, suggested by the innovative rescue experiments reported in transgenic mice.[40] OA1 cases have been regularly reported in Europe by several laboratories.[15,16,41,42] In OA1 cases, unlike OCA individuals, female heterozygous carriers already show alterations in ocular pigmentation,[2] whereas males inheriting the mutated X-chromosome will inevitably display the classical OA1 phenotype. In the absence of molecular studies, the difficulties in the correct diagnosis of some related cases of autosomal ocular albinism must be also noted. When these genetic tests have been conducted, most of these patients have been reassigned to mild forms of OCA, the majority of which, again, correspond to OCA1 cases.[43]

Altogether, and according to the latest release (14 December 2012) of the Human Gene Mutation Database,[44] as many as 729 mutations have been reported in any of the 15 loci associated with all known different types of albinism (Table 1). Unfortunately, most persons with albinism remain genetically undiagnosed and, hence, efforts still need to be developed to aim for the universal genetic analysis, efficient and affordable to all interested families, of all known mutations and types of albinism. Some attempts have been already reported involving technical optimization of current or novel methods.[15,45–49] The use and popularization of next-generation sequencing approaches and related technical advances are expected to boost and ease these genetic tests, while providing the basis for addressing a pending and most relevant task in albinism, namely, the systematic correlation of genotypes and phenotypes, with a variety of mutations in various genes, not always resulting in identical phenotypes. Such correlation studies will be essential for our proper understanding of the pathological mechanisms underlying the observed clinical traits of hypopigmentation and visual alterations.

NEW GENES WITH MUTATIONS ASSOCIATED WITH ALBINISM

As indicated in Table 1, mutations in at least 15 genes in the human genome are associated with different types of albinism. However, a substantial number of cases of albinism remain unresolved, suggesting that there will be additional genes associated with albinism. Therefore, we already know that these 15 are not the only genes in the human genome whose mutations will be also associated with albinism. Several additional genes must be associated with this rare genetic condition, although to date, we mostly ignore them. Approximately 400 genes appear to be associated with pigmentation in mammals, according to the Coat Color Genes database (http://www.espcr.org/micemut/); therefore, there is room for several additional genes in the genome potentially associated with albinism. The use of next-generation sequencing approaches will greatly facilitate the discovery of these new genes. Or, alternatively, the discovery of new mutated alleles of known genes in intergenic gene-regulatory regions, surrounding the coding region of the loci, will also increase our understanding of loci involved, as already envisaged by King *et al.* several years ago, before these modern sequencing techniques became a reality.[17] In fact, some potential candidates for these far-upstream DNA-regulatory regions have been already identified in the human *TYR* locus by two groups, independently.[18,50]

Regarding the characterization of new genes whose mutations are associated with albinism, at least three additional loci

have been reported, totally or partially, to date. First, in 2012, a new OCA gene (named *OCA5*) was found in a consanguineous Pakistani family, and mapped on chromosome 4q24.[51] The clinical manifestation of the affected individuals was that of a classical non-syndromic OCA, with depigmented iris, golden hair color, albinotic retina fundus and fovea hypoplasia, resulting in 6/60 visual acuity, yet however did not correspond to any of the four other known loci associated with OCA (*TYR*, *OCA2*, *TYRP1* or *SLC45A2*). The chromosomal region contains 14 genes and the authors of this study are trying to identify the locus associated with this new OCA type.

Another gene associated with albinism was found in families from the Faroe Islands and Denmark. Using homozygosity mapping, the authors located a 3.5-Mb homozygous region (located at 10q22.2–q22.3) containing five genes. One of them, *C10orf11*, carried a nonsense mutation in the affected individuals.[19] The same team demonstrated that this gene was indeed associated with a new form of albinism when they reproduced the phenotype in an animal model, zebrafish, with an induced target in the same homologous locus. This gene encodes a protein with a relevant role in melanocyte differentiation and would constitute the sixth OCA gene (or *OCA6*).

Finally, a third gene is on its way to being uncovered and associated with albinism, also. However, in this case pigmentation does not seem to be affected, rather, all three patients investigated with mutations in this new locus (one Dutch, two from Afghan origin) were pigmented, tanned normally and did not show any hypopigmentation, yet they displayed the classical chiasmal misrouting and fovea hypoplasia characteristic visual abnormalities associated with albinism.[52] The molecular identity of this gene has not yet been revealed, but it is expected to be released soon. If confirmed, it may represent a new category of albinism, where the visual abnormalities are present but the pigmentation remains unaltered. It is still too early to assess the relevance of this finding but it may have a strong impact in the field, and perhaps trigger a new nomenclature for all these mutations and genetic conditions, where the common and important traits would be the visual alterations, and where most loci (but not all) would, in addition, show hypopigmentation as a secondary trait.[53]

THERAPEUTIC PROPOSALS FOR ALBINISM, PRE-CLINICAL ATTEMPTS

Albinism has been studied for many years as an example of a congenital rare disease without cure, where a person born with albinism will eventually die with the same albinism. However, the situation may change in the next years, thanks to innovative research developments that have been devised and explored in animal models of albinism, mostly rodents. Two of these proposals originated in Europe, whereas one proposal comes from the USA and one from Japan.

Our group demonstrated, using transgenic mice, that the main cause of visual and hearing alterations associated with a mouse model of OCA1 was the deficit of an intermediate metabolite, L-DOPA, not the absence of the end product, the pigment melanin.[40,54] These experiments suggested that the experimental addition of L-DOPA, provided at the right time during embryo development, was sufficient to overcome the visual abnormalities associated with albinism, even in the absence of pigmentation.[40] The critical role of L-DOPA in a variety of cellular functions, beyond its crucial role in the pigmentation pathway, was also illustrated by an article proposing it to be the endogenous ligand of the GR143 receptor, whose mutations lead to OA1[39] and has been also recently recognized in the field.[55] A clinical trial has been launched in the USA to explore the treatment of adults with L-DOPA and investigate its therapeutic potential (http://clinicaltrials.gov/show/NCT01176435).

The use of adeno-associated viral vectors (AAV) has been also explored, with success, by the group of Surace, at TIGEM in Naples (Italy) to deliver the correct and functional versions of the mutated genes locally, at the retina of mouse models of OCA1[56] and OA1.[57] These proof-of-principle experiments, suggested that similar approaches could be explored in human subjects in the future.

A third therapeutic proposal came from the innovative use of an approved drug, nitisinone, originally devised to treat patients with hereditary tyrosinemia type 1. The new application of nitisinone was suggested by the group of Brooks, from the National Institutes of Health (Bethesda, MD, USA).[22] This drug has a useful side-effect, because it triggers the anomalous accumulation of tyrosine in the blood, thus increasing the concentration of the reagent used by the enzyme tyrosinase (TYR) and resulting in an increased oxidation and improved pigmentation in eyes and skin of mouse models of OCA1B, with some residual tyrosinase activity. These very promising results soon will be also explored in humans, in tentative clinical trials.[58]

Finally, the group of Fukai (Osaka, Japan) has suggested the use of aminoglycosides, known to allow the read-through effect over certain nonsense mutations, as a potential therapeutic intervention for some mutations commonly found in albinism.[59]

Additional studies and validations are still required before transferring any of these therapeutic proposals, here listed, to routine treatment for human subjects. However, over the last few years several therapeutic interventions have been devised and, as we progress into our understanding of the cellular and molecular mechanisms underlying the alterations associated with albinism, we shall be able to envisage potentially new treatments for a rare genetic condition whose patients, until recently, had lost hope for any type of cure. The situation has now changed and will continue improving in the near future.

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