Increasing the complexity: new genes and new types of albinism

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KEYWORDS albinism/vision/melanin/genes/diagnosis

PUBLICATION DATA Received 6 August 2013, revised and accepted for publication 17 September 2013, published online 21 September 2013

doi: 10.1111/pcmr.12167

Summary

Albinism is a rare genetic condition globally characterized by a number of specific deficits in the visual system, resulting in poor vision, in association with a variable hypopigmentation phenotype. This lack or reduction in pigment might affect the eyes, skin, and hair (oculocutaneous albinism, OCA), or only the eyes (ocular albinism, OA). In addition, there are several syndromic forms of albinism (e.g. Hermansky–Pudlak and Chediak–Higashi syndromes, HPS and CHS, respectively) in which the described hypopigmented and visual phenotypes coexist with more severe pathological alterations. Recently, a locus has been mapped to the 4q24 human chromosomal region and thus represents an additional genetic cause of OCA, termed OCA5, while the gene is eventually identified. In addition, two new genes have been identified as causing OCA when mutated: *SLC24A5* and *C10orf11*, and hence designated as OCA6 and OCA7, respectively. This consensus review, involving all laboratories that have reported these new genes, aims to update and agree upon the current gene nomenclature and types of albinism, while providing additional insights from the function of these new genes in pigment cells.

Introduction

Albinism refers to a group of rare congenital diseases globally characterized by poor vision and a variable hypopigmentation phenotype. The absence or decrease in pigmentation can occur in the skin, hair, and the eyes (oculocutaneous albinism, OCA) or only impair pigmentation in the eyes (ocular albinism, OA). Until very recent, there were four genes known to be associated with OCA, namely: *TYR* (OCA1), *OCA2* (OCA2), *TYRP1* (OCA3), and *SLC45A2* (OCA4), and one single gene associated with OA: *GPR143* (OA1) (Grønskov et al., 2007; Innamorati et al., 2006; King and Oetting, 2006; King et al., 2001; Schiaffino and Tacchetti, 2005; Suzuki and Tomita, 2008). Moreover, there are also syndromic forms of albinism, such as Hermansky–Pudlak Syndrome (HPS) and Chediak–Higashi Syndrome (CHS), which are characterized by more severe phenotypes affecting a range of additional cell types, beyond pigment cells, and are less common than OCA and OA types of albinism (Huizing et al., 2008; Ito et al., 2005; Wei and Li, 2013). As many as nine different types of HPS and one form of CHS are currently known and are caused by mutations in their corresponding genes, namely: *HPS1* (HPS1), *AP3B1* (HPS2), *HPS3* (HPS3), *HPS4* (HPS4), *HPS5* (HPS5), *HPS6* (HPS6), *DTNBP1* (HPS7), *BLOC1S3* (HPS8), *BLOC1S6* (HPS9), and *LYST* (CHS1) (see Table 1).

Table 1. Current list of human genes associated with albinism

Gene	Chromosomal location[a]	Albinism type[b]	OMIM[c]	ORPHANET[d]	HGNC[e]
TYR	11q14.3	OCA1[f]	#203100	ORPHA352731	HGNC:12442
OCA2	15q12-q13.1	OCA2	#203200	ORPHA79432	HGNC:8101
TYRP1	9p23	OCA3	#203290	ORPHA79433	HGNC:12450
SLC45A2	5p13.2	OCA4	#696574	ORPHA79435	HGNC:16472
n.d.	4q24	OCA5	#615312	n.d.	HGNC:44139
SLC24A5	15q21.1	OCA6	#609802	n.d.	HGNC:20611
C10orf11	10q22.2-q22.3	OCA7	#615179	ORPHA352745	HGNC:23405
GPR143	Xp22.2	OA1	#300500	ORPHA54	HGNC:20145
LYST	1q42.3	CHS1	#214500	ORPHA167	HGNC:1968
HPS1	10q24.2	HPS1	#203300	ORPHA231500	HGNC:5163
AP3B1	5q14.1	HPS2	#608233	ORPHA183678	HGNC:566
HPS3	3q24	HPS3	#614072	ORPHA231512	HGNC:15597
HPS4	22q12.1	HPS4	#614073	ORPHA231500	HGNC:15844
HPS5	11p15.1	HPS5	#614074	ORPHA231512	HGNC:17022
HPS6	10q24.32	HPS6	#614075	ORPHA231512	HGNC:18817
DTNBP1	6p22.3	HPS7	#614076	ORPHA231531	HGNC:17328
BLOC1S3	19q13.32	HPS8	#614077	ORPHA231537	HGNC:20914
BLOC1S6	15q21.1	HPS9	#614171	ORPHA280663	HGNC:8549

[a]According to Ensembl release 72, June 2013: GRCh37 (GCA_000001405.12) (http://www.ensembl.org).
[b]Oculocutaneous albinism (OCA); ocular albinism (OA); Hermansky–Pudlak Syndrome (HPS); Chediak–Higashi Syndrome (CHS).
[c]OMIM: Online Mendelian Inheritance of Man database (http://omim.org).
[d]ORPHANET: The portal for rare diseases and orphan drugs (http://www.orpha.net).
[e]HGNC: HUGO Gene Nomenclature Committee (http://www.genenames.org/).
[f]OCA1 is usually subdivided in two subtypes: OCA1A (OMIM #203100, ORPHA79431) and OCA1B (OMIM #606952, ORPHA79434) associated with the total or partial absence of melanin, respectively (King et al., 2003).
n.d. = not defined.
Note: OCA5, OCA6, and OCA7 types of albinism, reported within a short period of time, have been previously described in recent publications under alternative names (Grønskov et al., 2013; Kausar et al., 2013; Martínez-García and Montoliu, 2013; Wei et al., 2013b). However, this table reflects the consensus current view of all co-authors of this review (including the authors associated with OCA5, OCA6, and OCA7), and its use will be disseminated and promoted elsewhere.

While the impact of the absence of melanin in the skin, and, hence, the reduced protection against the sun can be potentially overcome with adequate protection, the visual alterations are the most handicapping traits for persons with albinism. Visual deficits include foveal hypoplasia, reduced pigmentation of retinal pigment epithelium cells, misrouting of the optic nerves at the chiasm, reduced pigmentation in the iris, photophobia, and nystagmus (Grønskov et al., 2007; Martínez-García and Montoliu, 2013; Summers, 2009). Photoreceptor rod cell deficit, observed in all other albino mammals investigated so far (Grant et al., 2001; Jeffery et al., 1994, 1997), although suggested in old studies (Elschnig, 1913), has not yet been properly demonstrated in primates.

The prevalence of all known forms of albinism in the best-studied Western populations, mostly in North America and Europe, appears to be 1:17 000 newborns (within a range of 1:10 000–20 000) (Gargiulo et al., 2011; Grønskov et al., 2007, 2009; Hutton and Spritz, 2008a,b; King and Oetting, 2006; Oetting and King, 1999; Rooryck et al., 2008; Rundshagen et al., 2004; Zühlke et al., 2007). Different frequencies of several types of albinism have been also reported from Asia (Inagaki et al., 2004; Lin et al., 2006; Suzuki and Tomita, 2008; Wei and Li, 2013; Wei et al., 2010, 2011), whereas the highest prevalence is found in some countries in Africa, mostly due to consanguinity issues and founder effects (Aquaron et al., 2007; Cruz-Inigo et al., 2011; Spritz et al., 1995) (Figure 1).

Our knowledge on the biology and physiology of pigment cells, where melanin is produced, has greatly advanced thanks to the knowledge of the genes, which when mutated cause albinism. Among these genes, there are some encoding key melanogenic enzymes (i.e., *TYR*, *TYRP1*) (García-Borrón and Solano, 2002; Jimbow et al., 2000; Oetting, 2000; Sarangarajan and Boissy, 2001) , specific receptor/solute carrier/integral proteins found in melanosomes, the subcellular compartments where melanin is synthesized (i.e., *OCA2*, *SLC45A2*, *GPR143*) (Lopez et al., 2008; Newton et al., 2001; Palmisano et al., 2008; Rosemblat et al., 1994; Schiaffino and Tacchetti, 2005; Toyofuku et al., 2002), and a large family of proteins involved in the biogenesis of lysosome-related organelles (Huizing et al., 2002; Wei and Li, 2013) such as the melanosomes (i.e., *HPS1*, *AP3B1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1*, *BLOC1S3*, *BLOC1S6*, *LYST*). For example, HPS1 and HPS4 form a lysosomal trafficking complex termed BLOC-3 (biogenesis of lysosome-related organelles complex-3) (Martina et al., 2003; Oh et al.,

Figure 1. Young boy from Senegal with oculocutaneous albinism and his mother. 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). This book has been translated to French by Genespoir (2012), the French Organization for albinism (www.genespoir.org).

1996; Suzuki et al., 2002). *AP3B1* encodes the large β1 subunit of the adaptor-related protein complex-3 (AP-3), involved in protein trafficking to specialized endosomal-lysosomal organelles such as melanosomes (Dell'Angelica et al., 1998). HPS3, HPS5, and HPS6 form the BLOC-2 complex (biogenesis of lysosome-related organelles complex-2), also involved in lysosomal trafficking (Anikster et al., 2001; Gautam et al., 2004; Zhang et al., 2003). *DTNBP1* and *BLOC1S3* encode two subunits of the ubiquitously expressed BLOC-1 (biogenesis of lysosome-related organelles complex-1) multisubunit protein complex, required for the normal biogenesis of melanosomes (Li et al., 2003; Morgan et al., 2006; Starcevic and Dell'Angelica, 2004). Finally, *BLOC1S6* encodes yet another subunit of BLOC-1 (Cullinane et al., 2011).

Recently, mutations in *C10orf11* and *SLC24A5* have been described to cause OCA (Grønskov et al., 2013; Wei et al., 2013b), and an additional OCA locus, whose associated gene is not yet known, has been reported (Kausar et al., 2013), thereby increasing the complexity, the number of genes/loci (from 15 to 18, see Table 1), and the current types of albinism that should be considered in any genetic diagnostic attempt of albinism. Therefore, it is important to establish a consensus nomenclature to name and refer to these new types of albinism, which is one of the objectives of this review. We will describe the three new types of OCA (OCA5, OCA6, and OCA7) and the two genes (*SLC24A5* and *C10orf11*) in which mutations have been recently uncovered to cause albinism.

OCA5: a new genetic cause of non-syndromic OCA mapped to chromosome 4q24

In 2012, a group of researchers, led by Dr. Zubair M. Ahmed, investigating the cause of albinism in a consanguineous Pakistani family, concluded that the OCA phenotype presented by these individuals was linked to a gene on human chromosome 4q24 (Kausar et al., 2013). Affected individuals from this family presented clinical symptoms of OCA, including golden-colored hair, white skin, nystagmus, photophobia, foveal hypoplasia, and impaired visual acuity, regardless of their sex and age (Figure 2). The genetic linkage interval of approximate 3.84 Mb harbored 14 genes, flanked by markers *D4S421* and *D4S2913*. Candidate genes within the linkage interval included members of the solute carrier protein family (i.e., *SLC9B1*, *SLC9B2,* and *SLC39A8*) and proteins known to be associated with lysosomes (i.e., *MANBA*), among other putative candidates. However, sequencing of these candidate genes did not reveal any pathogenic variant. Further experiments are required to eventually identify the gene associated with OCA5, including the (i) identification of additional OCA5 families; (ii) massive parallel sequencing of genomic DNA enriched for the entire *OCA5* critical interval; and (iii) systematic correlation with the orthologous loci in related mammalian species (i.e., mice), where perhaps one of these genes had been already associated with impairing pigmentation and/or visual function.

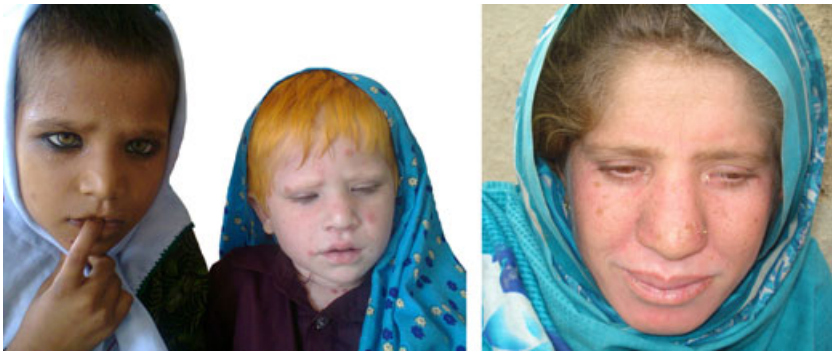

Figure 2. OCA5 affected (right, middle) and normal individuals (left). Affected individuals have golden color hair and commonly use hair dyes. These pictures were taken by Tasleem Kausar. The subjects in the photographs provided written, informed consent for publication of their photographs.

The *SLC24A5* gene is associated with OCA6 type of albinism

Earlier this year, a Chinese team of researchers, led by Wei Li, reported the use of a massive exome sequencing approach to reveal the molecular basis of albinism in an OCA-affected family. They found that mutations in *SLC24A5,* encoding another solute carrier protein, and a well-known gene in the pigment cell arena, were also associated with a new form of OCA, named as OCA6 (Wei et al., 2013b). The few patients with OCA6 detected, explored (this is one of the rarest form of OCA), and presented the following clinical features: lighter hair color, that darkened with age, iris transillumination, photophobia, fovea hypoplasia, reduced visual acuity, and nystagmus, with no defects in platelet dense granules, which are all characteristic traits of non-syndromic autosomal recessive OCA (Figure 3). *SLC24A5* mutations have been detected in patients of diverse ethnic origins, thus indicating that OCA6 is not restricted to the Chinese population. It is noteworthy that the cutaneous phenotype was heterogeneous, with hair color varying from white to blond and dark brown (Morice-Picard et al., 2013).

Mutations in *SLC24A5* had been associated with pigment variants in zebrafish, mouse, and human subjects (Lamason et al., 2005; Vogel et al., 2008). In zebrafish, *slc24A5* mutants have been known as the *golden* mutants, where the number, size, and density of the melanosomes were diminished (Lamason et al., 2005). In *Slc24a5*-knockout mice, ocular albinism and hypopigmentation features have been reported, which may result from milder reductions in melanosome size and pigmentation (Vogel et al., 2008). A SNP in *SLC24A5* (rs1426654) encoding an alanine or threonine at position 111 was detected; strikingly, Thr111 is present in almost all individuals of European American origin, while Ala111 is present in African Asian populations. Thr111 is associated with lighter pigmented skin, thus suggesting an important role of this SNP in the establishment of human pigmentation (Lamason et al., 2005). Recent results indicate a role of SLC24A5 in the maturation of melanosomes (Wei et al., 2013b). The assembly of SLC24A5 into melanosomes seems to be pivotal for the melanosomal architecture and to ensure that melanin is synthesized properly. Therefore, the lack of SLC24A5 may impair or disrupt melanosomal maturation, and, as a consequence, the normal melanin biosynthesis. From the other side, deficiencies of HPS proteins, involved in the melanosome (and other related lysosomal-related organelles) biogenesis, would result in the alteration of specific protein complexes, such as BLOC-1 and BLOC-2, which, in turn, would imply the interruption of the targeting of SLC24A5 into melanosomes, thereby providing a possible explanation for the presence of OCA symptoms in patients with HPS (Wei et al., 2013b).

Similarly, TYR and TYRP1 are transported into melanosomes mediated by BLOC-1 and BLOC-2 (reviewed by Wei et al., 2013a). However, the detailed mechanism of how BLOC-1 and BLOC-2 are involved in the trafficking of SLC24A5 to melanosomes is unknown. These melanosomal proteins are important for the architecture of mature melanosomes and proper melanin biosynthesis. Mistargeting of these proteins encoded by several OCA genes may affect the maturation of melanosomes and melanin biosynthesis, resulting in the OCA symptoms in patients with HPS. These findings provide new information on the molecular and cellular basis of the pathogenesis of non-syndromic OCA and HPS.

During melanosomal biogenesis, it has been known that different melanosomal proteins are transported into immature or mature melanosomes via different transporting machineries (Wei et al., 2013a). It requires further investigation into the transport mechanism to learn how SLC24A5 is sorted from Golgi apparatus or endosomes and transported into melanosomes. Interestingly, OCA2, SLC45A2, and SLC24A5 function as ion transporters on melanosomal membranes (Ito and Wakamatsu, 2011). How these ion exchangers are coupled to maintain the homeostasis of melanosomes which is required for melanin biosynthesis remains unclear.

The *c10 orf11* gene is associated with OCA7 type of albinism

In 2013, a collaborative research effort led by Karen Grønskov and Thomas Rosenberg found a new gene associated with albinism among OCA individuals from the Faroe Islands (Denmark). The gene, *C10orf11*, was identified through homozygosity mapping in a consanguineous Faroese family. The initial genomic homozygous interval extended up to 3.5 Mb on chromosome 10 and

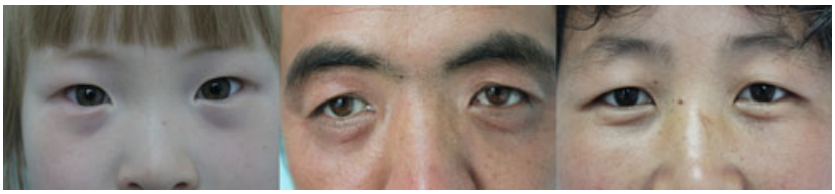

Figure 3. An OCA6 family with mutations in the *SLC24A5* gene. The girl (proband, 5 yr old, left) inherits the c.1361insT frameshift mutation from her father (OCA6 carrier, 35 yr old, middle) and the c.591G>A non-sense mutation from her mother (OCA6 carrier, 36 yr old, right). These pictures were taken by Dr. Aihua Wei. The subjects in the photographs provided written, informed consent for publication of their photographs.

contained five genes. Sequencing one of these genes, *C10orf11*, identified a non-sense mutation co-segregating with the OCA phenotype. In addition, a 1-bp insertion in the same *C10orf11* gene was found in a patient originating from Lithuania (Grønskov et al., 2013). Affected individuals presented lighter pigmentation, as compared to unaffected relatives, but eye symptoms were predominant with nystagmus, iris transillumination, reduced visual acuity, and chiasm misrouting of their optical tracts. This new type of OCA has been termed OCA7 (Figure 4).

C10orf11 encodes a 198 amino acid protein containing three leucine-rich repeats (LRRs) and one LRR C-terminal (LRRCT) domain. The family of LRRs-containing proteins encompasses members with a variety of functions, including cell adhesion and signaling, extracellular-matrix assembly, neuronal development, and RNA processing (Bella et al., 2008). Immunohistochemistry showed localization of C10orf11 in human fetal tissue in melanoblasts and melanocytes migrating from dermis to the basal membrane and eventually to hair bulbs and the basal layer of epidermis. No localization was seen in the retinal pigment cells neither in the developing eye nor in the adult eye (Grønskov et al., 2013). Expression at other developmental stages cannot be excluded. These data strongly suggested a role of this new gene in melanocyte differentiation and prompted the investigators to explore the function of *C10orf11* using the zebrafish as a model organism. A single zebrafish homolog, *c10orf11*, is known. In situ hybridization showed *c10orf11* expression (mRNA) in the migrating neural crest cells. Knock down of *c10orf11* using morpholino antisense oligonucleotides resulted in a reduction in pigmentation and in the apparent number of pigmented melanocytes. Only wild-type *c10orf11* but not mutant *c10orf11* could revert the morphant phenotype. These findings strongly suggested an evolutionary functional conservation of *C10orf11* in melanocyte differentiation, from fish to mammals (Grønskov et al., 2013).

Perspectives

A substantial fraction of individuals with albinism (approximately 20% of patients investigated) routinely remain molecularly unresolved at all genetic diagnostic centers, because only one mutation is found, or no mutations are found in any of the known genes (Suzuki and Tomita, 2008; Rooryck et al., 2008, 2009; BA and FMP, unpublished data). Therefore, in addition to the possibility of mutations in intergenic sequences, the next most likely scenario is the existence of additional genes in which mutations will cause new forms of albinism. The list of genes whose functions are directly or indirectly related to pigmentation rapidly approaches the number of 400 (Coat Color Genes: http://www.espcr.org/micemut), nearly 2% of the total number of genes we have in the human and mouse genomes (approximately 25 000 genes; i.e., ENSEMBL: http://www.ensembl.org). However, just a bit more than 4% of those 400 genes are causative of albinism when mutated (currently, 18 genes, as presented in this review). Therefore, there is still ample room for searching and testing additional potential candidates. The new genomic and massive sequencing approaches might soon lead to the discovery of more genes and novel mutations in known genes associated with albinism (Wei et al., 2013b).

In addition to these 18 genes, Griscelli Syndrome (GS) (and its three known forms, namely: GS1, GS2, and GS3, associated with mutations in the *MYO5A*, *RAB27A,* and *MLPH* genes, respectively) is listed sometimes as an additional type of syndromic albinism (Scheinfeld, 2003). However, the GS is not associated with the visual alterations that are characteristic of albinism, even though its complex phenotype includes hypopigmentation in skin and hair, due to defects involving melanosome transport in melanocytes (Van Gele et al., 2009). Therefore, we have not considered the three GS genes in the list of genes associated with albinism (Table 1).

As the list of genes associated with albinism expands, it might get also more complex, challenging the long-standing definitions and traits that have been used, instrumentally and robustly, over the past few decades to describe the albinism phenotype. The wide phenotypic heterogeneity presented by the affected individuals raises the question of the definition of the word 'albinism'. What trait or group of traits is really diagnostic of albinism? The virtual absence of pigmentation is normally only observed with some OCA1 (i.e., OCA1A; King et al., 2003) and OCA4 individuals. The phenotype of OCA4 is very variable, from just similar to OCA1A to near normal, among Japanese patients (Inagaki et al., 2004; Suzuki and Tomita, 2008). The other OCA types (OCA2, OCA3,

Figure 4. Examples of two pigmentation extremes among OCA7 individuals with identical mutation in the *C10orf11* gene (left/middle and right). Left and middle pictures correspond to the same affected individual at 10 months and 3 yr of age, respectively. The parents of the subjects in the photographs provided written, informed consent for publication of their photographs.

OCA5, OCA6, and OCA7) and the syndromic forms of albinism (HPS1-9 and CHS1) display a highly variable phenotype regarding pigmentation. One of the most extreme phenotypes is the ocular albinism form (OA1), which usually displays almost wild-type pigmentation in the skin and hair, making the diagnosis very difficult, unless a careful eye examination is performed.

In spite of all the genetic diversity, all known forms of albinism show, with some variability, the same characteristic visual alterations, namely: foveal hypoplasia, chiasmal misrouting of the optical pathways, iris transillumination, photophobia, and nystagmus (Grønskov et al., 2007; Martínez-García and Montoliu, 2013; Summers, 2009). The combined effects of these alterations of the visual system result in individuals with reduced visual acuity and impaired depth perception. Some years ago, the relationships between pigmentation and vision were uncovered, using transgenic mice, and the experiments concluded that L-DOPA, an intermediate early metabolite of the synthesis of melanin (or one of its derivatives), was the only requirement to allow the retinal and visual development to proceed normally (Lavado et al., 2006). Therefore, the alterations in the visual system associated with albinism are a consequence of lack of L-DOPA and not of melanin. L-DOPA was subsequently described to be the ligand for the GPR143 receptor, which is associated with OA1 (Lopez et al., 2008). L-DOPA has also been implicated in a growing list of tasks, illustrating the pleiotropic role of this metabolite in melanocyte and overall cellular function (Slominski et al., 2012).

Altogether it is therefore conceivable to consider the hypopigmented phenotype as a secondary trait and as a feature that is rather the consequence than the actual cause of albinism. Therefore, albinism could be primarily defined by the alterations in the visual system, and, facultatively, the additional phenotypic traits (i.e., hypopigmentation). Hence, we might envisage new forthcoming genes associated with albinism whose mutations would result in the classic visual symptoms and signs but without an obvious alteration in the pigmentation patterns. The existence of one such genes was suggested several years ago (van Genderen et al., 2006). Therefore, let us be prepared for more complexity, more genes, and more forms of albinism yet to come.

Acknowledgements

The authors wish to thank ALBA (www.albinismo.es) and Genespoir (www.genespoir.org), the Spanish and French Associations, respectively, for their work in support of people with albinism and for their commitment in support of research in albinism; the Union Nationale des Aveugles et Déficients Visuels (France); Ana Yturralde, photographer, for her excellent picture of an African boy with albinism, and the following institutions for grant support: CIBERER-ISCIII, Biomedicine project 'VISIONANIMAL', Comunidad de Madrid, S2010/BMD-2439 (to L.M.); RPB Career Development Award (to Z.M.A), National Natural Science Foundation of China (Nos. 31230046 and 81101182) (to W.L. and A.W.), Health and Labor Sciences Research Grants; Research on intractable diseases; H24-039 (to T.S.) and Ministry of Health (France) (to B.A.). Financial support for the OCA7 studies was provided by The Danish Society of the Blind.

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