MEDICAL REVIEW

More Than Skin Deep: Genetics, Clinical Manifestations, and Diagnosis of Albinism

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Although albinism may be considered a simple diagnosis, its clinical manifestations, which include hypopigmentation of the skin, hair, and eyes and ocular abnormalities such as nystagmus and reduced visual acuity, are often subtle and initially missed. In oculocutaneous albinism, there is wide phenotypic variability, which correlates with specific mutations in genes with roles in melanin biosynthesis. Additionally, syndromic forms of albinism such as Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Griscelli syndrome are associated with serious complications such as bleeding abnormalities, lysosomal storage defects, immunodeficient states, and progressive neurologic defects, which all can result in mortality. It is critical to confirm a suspicion of albinism and perform an appropriate workup involving molecular testing in order to establish a diagnosis. Given the various subtypes of oculocutaneous albinism and the life-threatening complications in syndromic forms of albinism, a diagnosis permits proper genetic counseling and timely implementation of necessary screenings and treatments. Recommendations regarding sun exposure and treatment of ocular abnormalities are imperative in oculocutaneous albinism, and preventive therapies should be implemented in syndromic forms. With knowledge of the differential in conjunction with the execution of simple diagnostic tests, many of these complications can be predicted and consequently ameliorated or prevented.

INTRODUCTION

Albinism is an inherited condition affecting approximately one in 17,000 persons and is characterized by absent or reduced pigmentation in the skin, hair, and eyes (oculocutaneous albinism [OCA]), or only the eyes (ocular albinism) (C. J. Witkop, 1979). There are various associated manifestations, including systemic pathologies in syndromic albinism. Hypopigmentation may be subtle and missed in neonates and become apparent only with age and sun exposure, and ocular abnormalities and systemic complications may not develop for years, leading to delayed diagnoses and treatment (Torres-Serrant, Ramirez, Cadilla, Ramos-Valencia, & Santiago-Borrero, 2010). Therefore, it is imperative to confirm a diagnosis of albinism and to be aware of the systemic symptoms of associated syndromes. Although most persons with albinism have a presentation limited to OCA, in the face of additional symptoms, one must consider syndromes such as Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome (CHS), and Griscelli syndrome (GS).

PATHOGENESIS OF PIGMENTATION

Melanocytes are derived from neural crest precursors known as melanoblasts, which are guided by signaling pathways toward destinations including the basal epithelium of the epidermis, the hair bulbs of the skin, and the uveal tract of the eye (Dessinioti, Stratigos, Rigopoulos, & Katsambas, 2009). Once in target sites, melanoblasts differentiate into functional melanocytes by synthesizing melanin within lysosome-like organelles called melanosomes, within which tyrosine is converted to melanin. Melanosomes are then transferred via melanocytic dendrites to surrounding keratinocytes (Dessinioti et al., 2009).

Melanin is derived from tyrosine and its synthesis is primarily regulated by tyrosinase, *P* gene, tyrosinase-related protein 1 (TYRP1), and membrane-associated transporter protein (MATP), which are each mutated in the OCA subtypes (Figure 1). Tyrosinase catalyzes the hydroxylation of tyrosine to dopaquinone in the bottleneck step of melanin synthesis. Diversion to two pathways then occurs, with one synthesizing the eumelanin that composes brown and black pigments, and the other synthesizing pheomelanin, which is responsible for blonde and reddish pigments (Levin & Stroh, 2011). Pigmentation is therefore affected by several factors: host cell presence, melanosome formation, and the quantity of melanin within melanosomes. Of note: while OCA is associated with defects in melanin production, syndromic albinism is attributed to defective formation and transport of melanosomes (Scheinfeld, 2003).

OCULOCUTANEOUS ALBINISM

OCA is a group of autosomal recessive (AR) disorders caused by absent or deficient melanin biosynthesis, manifesting as generalized hypopigmentation of the hair, skin, and eyes and ocular abnormalities. It is attributed to defects in four genes (*OCA1–4*), with much of the phenotypic variation attributed to compound heterozygosity (Gronskov, Ek, & Brondum-Nielsen, 2007).

The degree of skin and hair pigmentation varies according to the type of OCA. Iris hypopigmentation is associated with reduced visual acuity, nystagmus, photophobia, foveal hypoplasia, strabismus, refractive error, color-vision impairment, and amblyopia. These defects may be related to abnormal misrouting of the optic nerves (Creel, Summers, & King, 1990). Visual evoked potentials reveal characteristic patterns representing abnormal decussation and can confirm OCA (Moss, 2000). Nystagmus, which is typically the most clinically apparent ocular abnormality, may not appear
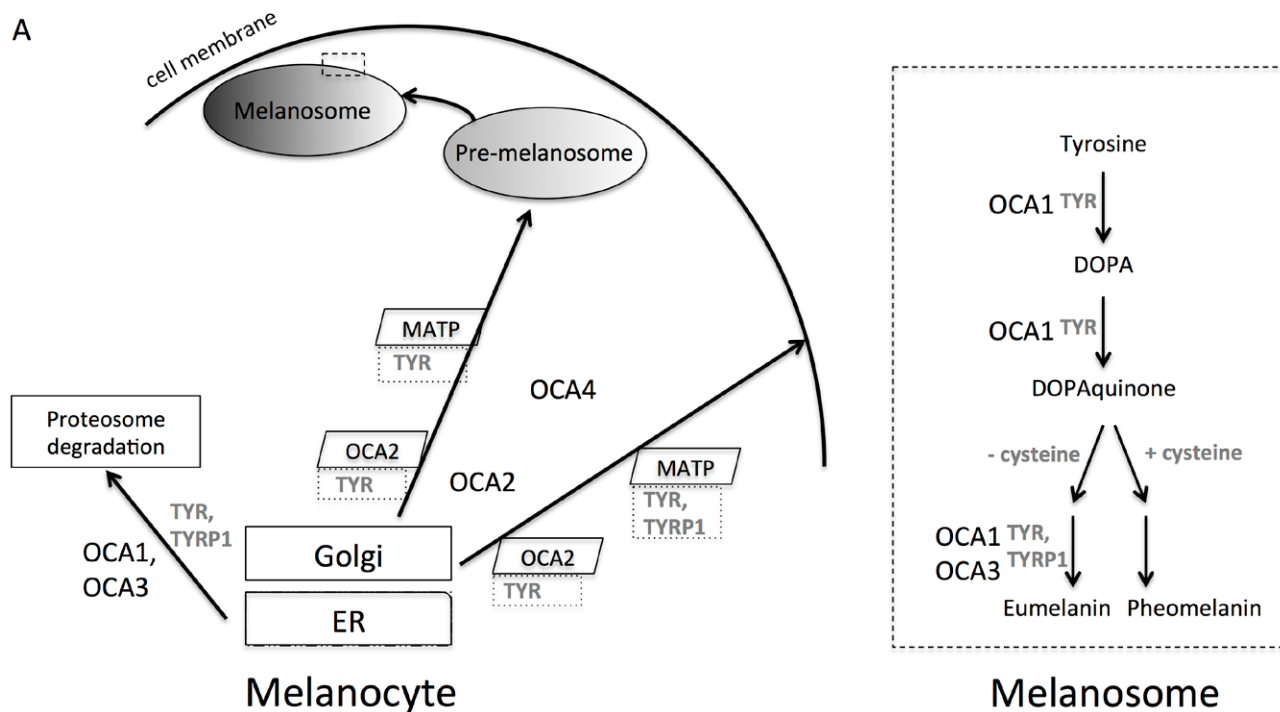
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Figure 1 │ Melanosome formation and melanin biosynthesis in the melanocyte and melanosome, respectively. (A) Melanosome biogenesis within the melanocyte and sorting of melanosome proteins TYR and TYRP1 from the endoplasmic reticulum and golgi to the developing melanosome via OCA2 and MATP proteins. Minor TYR or TYRP1 mutations lead to proteasome degradation, causing disease. Mutations in TYR, OCA2, TYRP1, and MATP cause OCA1, OCA2, OCA3, and OCA4, respectively. (B) Melanin biosynthesis may be disrupted by TYR or TYRP1 mutations, causing OCA1 and OCA3, respectively. Adapted from Grosnkov, Ek, & Brondum-Nielsen, 2007. TYR: tyrosinase, TYRP1: tyrosinase-related protein 1.

until the patient is 2 to 3 months old. Parents may initially think that the infant is unable to fixate on targets, as the nystagmus manifests in a large-amplitude and low-frequency pattern (Levin & Stroh, 2011; Moss, 2000). With age, the nystagmus becomes pendular, followed by development of the typical jerk nystagmus (Levin & Stroh, 2011).

Type 1 OCA (OCA1) is itself divided into four subtypes, all bearing mutations in the tyrosinase gene (*TYR*), which is mapped to chromosome 11q14-2. Phenotypic manifestations of each subtype are directly related to the type of *TYR* mutation.

Type 1A OCA is the most clinically severe, as tyrosinase activity is absent secondary to a null mutation in each copy of *TYR* (Giebel, Musarella, & Spritz, 1991). Individuals with this mutation are born with white skin and hair and light-blue to pink irises; they later manifest nystagmus, poor visual acuity, and prominent photophobia. Their skin cannot tan and can develop only amelanotic nevi.

Type 1B OCA is caused by a point mutation in *TYR* that changes the conformation of tyrosinase or causes new splicing sites (Matsunaga et al., 1999). Decreased tyrosinase activity permits some melanin accumulation over time. Although at birth the phenotype may be indistinguishable from that of type 1A, pigment may rapidly accumulate. Hair

may grow with a white-tipped pattern and appear blonde or light brown, due to preferential shunting to the pheomelanin pathway, and iris color may change from blue to green or brown (Giebel et al., 1991; Gronskov et al., 2007). As in type 1A, vision is moderately to severely reduced, with prominent nystagmus developing soon after birth.

Type 1MP OCA, the "minimal pigment" form of OCA1, has decreased tyrosinase activity, permitting some pigment, with blonde hair color and pigmented nevi developing. Type 1 TS OCA is the "temperature-sensitive" form resulting from a *TYR* missense mutation that produces tyrosinase with activity that varies according to temperature (Giebel et al., 1991). While its initial presentation may also be indistinguishable from that of type 1A, during puberty tyrosinase function becomes normal in the cooler areas of the body, producing dark hair on the arms, legs, and chest; white hair remains in the warmer areas, including the axilla, pubic region, and scalp (Levin & Stroh, 2011).

The molecular genetic defect in Type 2 OCA (OCA2) is in the *P* gene, now known as *OCA2*, mapped to 15q11.2–11.3 (Ramsay et al., 1992). It encodes a melanosomal membrane protein that regulates the influx of proteins such as TYR and TYRP1 (Levin & Stroh, 2011). Manifesting with some pigment production, skin and hair color range from white to fair and yellow to black, and eyes are typically

light blue with improved ocular function compared to the 1A phenotype. Newborns usually have pigmented hair and irises, with typical nevi and ephileds (Gronskov et al., 2007). Clinically, OCA2 is most comparable to types 1B and 1MP and it is the most prevalent form worldwide, affecting about one in 10,000 African Americans (Oetting & King, 1999). Approximately one in 100 patients with Prader-Willi or Angelman syndromes also manifest OCA2, as *OCA2* is located in the region of chromosome 15 between the genes responsible for these syndromes (Lee et al., 1994).

Type 3 OCA (OCA3) is caused by mutations in *TYRP1,* which encodes an enzyme that catalyzes eumelanin formation and stabilizes TYR (Toyofuku et al., 2001). As this type presents with a minimally hypopigmented phenotype, it is almost exclusively described in South African blacks, although it has recently been described in other populations (Tomita & Suzuki, 2004; K. H. Zhang et al., 2011). Mutations in *TYRP1* are responsible for brown or rufous albinism; brown albinism presents with light-brown skin pigment, beige to light-brown hair, and blue-green to brown irises, while the rufous phenotype is characterized by a red-bronze skin with nevi, ginger-red hair, and blue or brown irises (Kromberg et al., 1990). In one Caucasian patient with *TYRP1* mutation, hair was yellow-gold with orange highlights. Otherwise, the phenotype was indistinguishable from types 1B and OCA2 (Rooryck, Roudaut, Robine, Musebeck, & Arveiler, 2006).

Type 4 OCA is caused by mutations in *MATP*, which has suggested roles in protein transport and melanosome function. The clinical phenotype is similar to type 1A OCA but is most common in Japan (Tomita & Suzuki, 2004).

There are increasing numbers of OCA subtypes due to digenic inheritance. For example, a mutation in the microphthalmia-associated transcription factor (*MITF*) gene combined with a *TYR* mutation produces ocular albinism with deafness, which may be attributed to melanin's role within the stria vasculosa of the ear (Chiang, Spector, & McGregor, 2009). Due to clinical overlap among the various types of OCA and increasing subtypes, molecular diagnosis permits proper counseling, implementation of appropriate precautions and interventions, and differentiation from subtypes with defined morbidities and mortality.

SYNDROMIC OCULOCUTANEOUS ALBINISM
Hermansky-Pudlak Syndrome
HPS is a rare AR disease, affecting one in 500,000 to 1,000,000 persons, but it is quite common in Switzerland and Puerto Rico, affecting one in 1,800 northwestern Puerto Ricans (C. J. Witkop et al., 1990). This syndrome is attributed to at least nine distinct genetic defects causing subtypes HPS1–9 and is characterized by OCA, bleeding abnormalities, and lysosomal ceroid storage defects in some subtypes (Krisp, Hoffman, Happle, Konig, & Freyschmidt-Paul, 2001). HPS gene products were identified as subunits of at least three multiprotein complexes named biogenesis of lysosome-related organelle complex (BLOC) -1, -2, and -3, with roles in intracellular protein trafficking and newly defined interactions with the actin cytoskeleton (Dell'Angelica,

2004; Ryder et al., 2013). The symptoms are attributed to abnormalities in the function and formation of intracellular vesicles, such as melanosomes in melanocytes, dense bodies in platelets, and lytic granules in T cells, neutrophils, and lung type II epithelial cells (Dessinioti et al., 2009; Wei, 2006). Albinism results from protein mistrafficking that disables melanosome production, forming macromelanosomes that can be observed on skin biopsy (Levin & Stroh, 2011). The platelet dysfunction is attributed to deficiency of dense bodies, which normally trigger the secondary aggregation response. This leads to a prolonged bleeding time with normal platelet counts and normal coagulation factor activity (Torres-Serrant et al., 2010). The lysosomal storage defect is demonstrated by a yellow, autofluorescent, amorphous lipid-protein complex, called ceroid lipofuscin, in urinary sediment and parenchymal cells; it predisposes patients to the development of granulomatous colitis, renal failure, cardiomyopathy, and pulmonary fibrosis.

The *HPS1* gene, located on chromosome 10q23.1–q23.3, encodes a transmembrane protein that regulates protein traffic targeted to melanosomes. It is the most frequently presenting HPS mutation and is phenotypically very similar to HPS4 (Wei, 2006). HPS1 and HPS4 are the most severely affected of the subtypes, with prominent OCA, prolonged bleeding, complications from granulomatous colitis, and early death from pulmonary fibrosis. The *HPS4* gene is mapped on chromosome 22q11.2–q12.2, and intracellular HPS1 and HPS4 proteins associate together in BLOC-3 (Wei, 2006).

HPS2 can be clinically distinguished, as it causes immunodeficiency and manifests with congenital neutropenia and recurrent respiratory illness (Jung et al., 2006). It is attributed to mutations in the *AP3B1* gene, which encodes the Beta3A subunit of the heterotetrameric adaptor protein complex known as adaptor protein-3 (AP-3), which acts in mediating cargo-protein selection in transport vesicles and in sorting proteins to lysosomes (Dell'Angelica, 2004; Wei, 2006). The immunodeficiency is caused by a deficient AP3-dependent antigen presentation pathway and loss of microtubule-mediated movement of enlarged lytic granules in cytotoxic T-lymphocytes, among other innate immunity defects (Fontana et al., 2006; Sugita et al., 2002).

The *HPS3* gene is mapped to chromosome 3q24 and contains sorting signals for targeting to vesicles (Anikster et al., 2001). It is commonly associated with central Puerto Rican or Ashkenazi Jewish ancestry and is clinically similar to HPS5 and HPS6, presenting with very mild skin hypopigmentation, ocular albinism, visual acuity of approximately 20/100 or better, and mild bruising, without colitis or pulmonary fibrosis. The defective proteins in HPS3, HPS5, and HPS 6 interact with one another in BLOC-2 and regulate organelle biosynthesis (Huizing et al., 2009; Q. Zhang et al., 2003). HPS5, however, is uniquely reported to have elevated cholesterol levels (Dessinioti et al., 2009; Wei, 2006).

There is a single report of a patient with HPS7, with a mutation in the dysbindin gene, *DTNBP1* on chromosome

Disease	Gene	Symptoms
Table 1 | Subtypes of oculocutaneous albinism and syndromic albinism with associated genes and symptoms.		

OCA
  OCA1
  OCA2
  OCA3
  OCA4
	TYR
	P gene/OCA2
	TYRP1
	MATP
		OCA

HPS
  HPS1-6
  HPS7
  HPS8
  HPS9
	HPS1-6
	DTNBP1
	BLOC1S3
	PLDN
		OCA, bleeding abnormalities, and lysosomal ceroid storage defects such as granulomatous colitis, pulmonary fibrosis
		
		Immunodeficiency in HPS2

CHS	LYST	OCA with silvery hair, bleeding tendency, peripheral neuropathy, immune deficiency

GS
  GS1
  GS2
  GS3
	MYO5A1
	RAB27A
	MLPH
		OCA with silvery hair
		Neurologic impairment in GS1
		Hemophagocytic syndrome in GS2

Abbreviations: BLOC1S3, biogenesis of lysosomal organelles complex-1, subunit 3; CHS, Chediak-Higashi syndrome; DTNBP1, dystrobrevin-binding protein 1; GS, Griscelli syndrome; HPS, Hermansky-Pudlak syndrome; LYST, lysosomal trafficking regulator; MATP, membrane-associated transport protein; MLPH, melanophilin; MY05A, myosin VA; PLDN, pallidin; OCA, oculocutaneous albinism; RAB27A, Ras-related protein 27A; TYR, tyrosinase; TYRP1 tyrosinase-related protein 1.

6p22.3, which encodes a component of BLOC-1; the patient presented with OCA, bleeding tendency, and decreased lung compliance (Li et al., 2003). HPS8 and HPS9 are also caused by mutations in BLOC-1. HPS8 is attributed to a mutated BLOC-3 gene (*BLOC1S3*) and is detected in a large consanguineous Pakistani family with incomplete OCA and platelet dysfunction. The proband was born with silvery hair that later darkened, hazel eyes, and pale skin that reddened in the sun (Morgan et al., 2006). HPS9 is associated with a mutation in the pallidin gene (*PLDN*), and clinically manifested with albinism and immunodeficiency in one patient (Cullinane et al., 2011).

A delay in diagnosis of HPS can be attributed to clinical variability (Torres-Serrant et al., 2010). Although hypopigmentation can be subtle at birth, nearly all patients with HPS have nystagmus (Gradstein et al., 2005). Early on, nystagmus is very fast and later slows as additional ocular abnormalities, such as wandering eye movements, become prominent. Typically, bleeding abnormalities initially present with bruising upon ambulation, but they may occur earlier with circumcision or trauma. One report detailed an infant who had a complicated delivery necessitating forceps and presented at 7 weeks old with seizures and associated subdural hematomas and retinal hemorrhages. The infant was found to have abnormal platelet function and was later diagnosed with HPS (Russell-Eggitt, Thompson, Khair, Liesner, & Hann, 2000). Epistaxis usually occurs in childhood, and prolonged bleeding with menses or after tooth extraction or any surgical procedure is typical. As ceroid accumulation increases with age, granulomatous colitis resembling Crohn's disease presents on average at 15 years old and occurs in 15 percent of cases, while pulmonary fibrosis typically does not become symptomatic until the patient's thirties and is usually fatal (Avila et al., 2002).

The diagnosis of HPS is established both clinically and via demonstration of absent dense bodies on whole-mount electron microscopy of platelets. Bleeding-time or platelet-aggregation abnormalities and tissue biopsy showing ceroid deposition may assist in diagnosis (Levin & Stroh, 2011). Sequence analyses for HPS1-8 mutations are available on a clinical basis and for HPS9 on a research basis only.

Given the bleeding risks in HPS, the platelet function of individuals with suspected albinism should be evaluated prior to surgical procedures. Although the bleeding diathesis is usually mild, death from hemorrhage has been reported (Theuring & Fiedler, 1973). In addition, bleeding in HPS has been controlled by administering desmopressin prior to surgery (Zatik, Poka, Borsos, & Pfliegler, 2002) and by making platelet concentrates available during surgery. It is important to be aware that aspirin and indomethacin are contraindicated in patients with HPS, as they exacerbate the platelet abnormality (Witkop, White, Gerritsen, Townsend, & King, 1973).

Chediak-Higashi Syndrome

CHS is a rare AR disease that is characterized by partial OCA with characteristic silvery hair and bleeding tendency, peripheral neuropathy, and immune deficiency (Dessinioti et al., 2009). This syndrome arises due to mutations in the CHS1/lysosomal trafficking regulator (*LYST*) gene, located on chromosome 1q42–43, which has roles in membrane identification and intravesicular sorting. Various vesicles are affected, and diagnosis is via visualization of pathognomonic giant peroxidase-positive cytoplasmic granules in neutrophils on a peripheral blood smear (Tomita & Suzuki, 2004). Abnormal granules can also be found in melanocytes, fibroblasts, endothelial cells, neurons, and Schwann cells, and

are formed through fusion, cytoplasmic injury, and phagocytosis (Nargund et al., 2010). CHS is distinguished by neutrophils defective in chemotaxis, mobilization, and bactericidal activity, and functionally defective cytotoxic T and natural killer cells. This results in recurrent pyogenic infections and uncontrolled T-cell and macrophage activation associated with a typically fatal hemophagocytic lymphoproliferative syndrome, considered the accelerated phase of CHS.

Most patients with CHS have a functionally null mutant CHS1 allele and manifest severe disease in childhood. At birth, patients may manifest OCA, exhibiting silvery hair and skin hypopigmentation, with cutaneous slate-gray patches and tanning capacity after sun exposure. Affected children may then develop recurrent infections of the skin, lung, and respiratory tract. The accelerated phase may occur soon after birth and is characterized by generalized lymphohistiocytic infiltrates, fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, and bleeding (Nargund et al., 2010). Ten to 15 percent of patients manifest adolescent and adult forms associated with missense-mutant alleles that encode proteins with partial function (Karim et al., 2002). These patients may survive to adulthood but develop progressive, often fatal neurologic dysfunction with intellectual decline, tremor, ataxia, peripheral neuropathy, and white-matter deterioration (Scheinfeld, 2003).

Although treatment of CHS is controversial, further investigation is critical in an individual with OCA and recurrent infections. Blood-smear examination leads to diagnosis and implementation of the only curative treatment, bone-marrow transplant, as fatality is within 30 months of the accelerated phase without treatment (Nargund et al., 2010). Other modes of therapy are controversial and include parenteral vitamin C administration during the stable phase in order to normalize neutrophils' bactericidal activity and high-dose methylprednisolone with or without splenectomy (Kanjanapongkul, 2006; Nargund et al., 2010).

Griscelli Syndrome
GS is another rare AR disorder that manifests as partial OCA with characteristically silver hair, large pigment conglomerates in hair shafts, and accumulation of mature melanosomes within melanocytes (Mancini, Chan, & Paller, 1998). Defects in MYO5A1 and RAB27A cause GS type 1 (GS1) and GS type 2 (GS2), respectively, and both map to 15q21.1. GS type 3 (GS3) is attributed to mutations in melanophilin (MLPH). RAB27A encodes a small GTPase protein, Rab27a, which targets the melanosome membrane and binds to melanophilin in melanocytes. Molecular motor myosin-Va, which is encoded by MYO5A1, is then recruited and permits movement of melanosomes along the actin cytoskeleton.
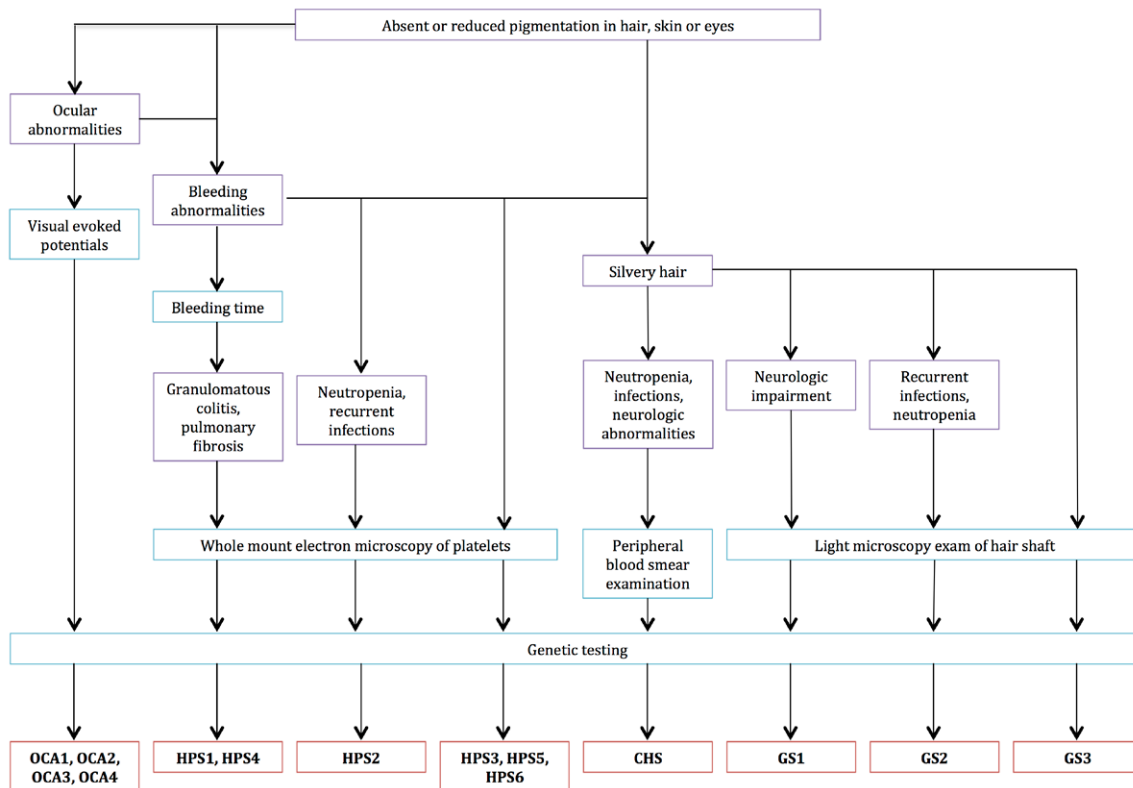

Figure 2 | Diagnostic algorithm for albinism. Based on clinical signs and symptoms and subsequent clinical and histologic studies and genetic testing, OCA, HPS, CHS, and GS can be diagnosed. Abbreviations: CHS, Chediak-Higashi syndrome; GS, Griscelli syndrome; HPS, Hermansky-Pudlak syndrome; OCA, oculocutaneous albinism.

The tripartite myosin-Va-melanophilin-Rab27a complex enables mature melanosomes to migrate to the dendritic tips of melanocytes, permitting delivery of melanin to adjacent keratinocytes (Al-Idrissi et al., 2010).

Patients with GS1 develop primary neurologic impairment that manifests as muscle hypotonia and intellectual disability, as myosin-Va has a critical role in neuron function (Sanal et al., 2002). In GS2, however, Rab27a is necessary in lymphocyte lytic granule release and lymphocyte homeostasis. Correspondingly, there is an uncontrolled T-lymphocyte and macrophage activation syndrome known as hemophagocytic syndrome (HS), which is associated with lymphocytic infiltration of organs and high mortality unless treated with hematopoietic stem cell transplantation (Al-Idrissi et al., 2010; Scheinfeld, 2003). HS may present in the neonatal period and is associated with preterm delivery (Lipton, Westra, Haverty, Roberts, & Harris, 2004). In contrast, GS3 is phenotypically restricted to characteristic hypopigmentation of the skin and hair.

Rapid diagnosis of GS can occur via light microscopy examination of a hair shaft demonstrating abnormal aggregates of pigment, permitting implementation of appropriate counseling and interventions according to the subtype. GS2 requires early diagnosis and preemptive treatment in order to prevent its severe complications (Wong & Yano, 2012).

CONCLUSION

There is a limited differential of albinism, including few genetic syndromes with life-threatening consequences (Table 1). Diagnosis can be determined based on pedigree, review of systems, physical exam of skin, hair, and eyes, visual evoked potentials, and if indicated, skin biopsy, whole-mount platelet electron microscopy studies, blood smear, or hair shaft microscopy (Figure 2). Further, genetic testing via methods such as RT-PCR and genomic sequencing can confirm a diagnosis, as well as allow for prenatal testing and carrier detection (Falik-Borenstein et al., 1995; Santiago Borrero et al., 2006). With diagnosis, appropriate recommendations regarding ophthalmologic screening frequency, necessity for ocular muscle surgery, degree of sun exposure, and expectations related to systemic complications can be delineated. Delayed genetic counseling has been associated with poor academic performance in OCA, hemorrhage in HPS, and mortality in both CHS and GS (Torres-Serrant et al., 2010). With knowledge of the differential in conjunction with the execution of simple diagnostic tests, many of these complications can be predicted and consequently ameliorated or prevented.

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