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A new type of syndromic albinism associated with mutations in *AP3D1*

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Albinism is a rare genetic condition affecting approximately 1:17,000 newborns in Europe and North America. The disease is mainly characterized by poor vision, which is most often (but not always) presented with variable hypopigmentation of the hair, skin and eyes. Visual abnormalities include foveal hypoplasia and retinal axon misrouting at the optic chiasm, resulting in reduced visual acuity and altered stereoscopic vision, respectively (Montoliu et al. 2014). Albinism can exist in isolation (non-syndromic) or in combination with additional system abnormalities (syndromic). Until relatively recently, the gene loci associated with albinism were limited to only a handful of genes encoding components of either the melanogenic pathway in pigment cells (for non-syndromic albinism) or the machinery responsible for the biogenesis of melanosomes – the organelles within which melanins are synthesized (for syndromic albinism). However, our understanding of the molecular causes of albinism has greatly expanded over the last few years to as many as 20 different gene loci (Table 1), including newly reported types of **o**culo**c**utaneous **a**lbinism (OCA) (Montoliu et al. 2014) and some apparently unrelated syndromes such as **f**oveal **h**ypoplasia, **o**ptic **n**erve **d**ecussation defects and **a**nterior segment dysgenesis (FHONDA; Montoliu and Kelsh, 2014). Earlier this year, Ammann and colleagues added a new gene to the list by describing a new type of syndromic albinism associated with mutations in the *AP3D1* and assigned to Hermansky-Pudlak syndrome (HPS) type 10 (HPS10).

Syndromic types of albinism, such as HPS, result from defects in the formation of melanosomes and other lysosome-related organelles (LROs). LROs comprise a group of cell-type specific subcellular organelles that share some features with classical lysosomes but have unique components and morphological features that confer distinctive physiological functions. These functions include pigmentation, immunity, hemostasis, and lung plasticity among others (Marks et al., 2013). Thus, in addition to the visual and pigmentation alterations due to defects in melanosome formation, HPS patients suffer from a complex

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disorder that always includes a tendency to bleed and/or bruise excessively (due to defects in the formation of platelet dense granules), and depending on the HPS subtype may also include lung fibrosis (due at least in part to defective lamellar bodies in lung epithelial cells), recurrent infections (due to a number of LRO defects in lymphocytes and dendritic cells and to neutropenia), granulomatous colitis, hemophagocytic lymphohistiocytosis (HLH) and/or cardiomyopathy (Wei and Li, 2013). Chediak-Higashi syndrome (CHS) is another type of syndromic albinism with a milder bleeding tendency but more severe immunodeficiency and lymphoproliferation, as well as neurological dysfunction. Both HPS and CHS are caused by mutations in genes encoding proteins that regulate intracellular trafficking steps common to the formation of multiple LROs. The genes affected in HPS encode subunits of four major cytoplasmic protein complexes: adaptor protein (AP)-3 and biogenesis of lysosome-related organelles complex (BLOC)-1, -2 and -3. Work in skin melanocytes indicate that AP-3, BLOC-1 and BLOC-2 function in the delivery of components from the biosynthetic pathway to melanosomes, whereas BLOC-3 functions mainly in a recycling pathway from melanosomes required to “re-arm” the forward pathways (Marks et al, 2013; Dennis et al., 2016). Mouse models corresponding to each of the known HPS variants exist and have been instrumental in better understanding these disorders.

AP-3 is a heterotetrameric adaptor protein complex that reversibly associates with early endosomal membranes, and recognizes transmembrane proteins destined for lysosomes or LROs via exposed cytoplasmic sorting signals; it then packages these proteins into clathrin-coated transport vesicles for delivery to their destination (Marks et al. 2013). AP-3 exists in two forms, all of which include a single δ and either the o3A or σ3B subunits. A ubiquitous AP-3A isoform additionally incorporates the β3A and μ3A subunits, whereas a neuronal-specific AP-3B isoform incorporates the β3B and μ3B subunits. Mutations in the *AP3B1* gene, encoding the ubiquitously expressed β3A subunit, are associated with HPS2 and result in immunodeficiencies and lung fibrosis in addition to albinism and bleeding. A small subset of HPS2 patients also present with HLH due to defects in cytotoxic T cell function, but in mouse models and most patients the HLH is transient (Jessen et al., 2013). Mutations in the *Ap3d1* gene encoding the δ subunit were known in mice (mouse mutant *mocha*, listed in the IFPCS-ESPCR database *color genes:* http://www.espcr.org/micemut/), and result in neurological phenotypes in addition to those phenotypes seen in HPS2. However, the homologous mutation in the human *AP3D1* gene had not been detected.

The publication by Ammann and collaborators (2016) now reports a patient, a child born from consanguineous parents of Turkish origin, with a mutation in the *AP3D1* locus. Like HPS2 patients, this patient displayed albinism, neutropenia and immunodeficiency characterized by defects in cell-mediated cytolysis. An overt tendency for bleeding was not observed, but platelet function tests were not performed and a bleeding tendency was likely missed due to the severity of the other complications. Additionally, and like the *mocha* mouse, the patient presented with neurodevelopmental delay, generalized seizures and impaired hearing. Through exome sequencing the authors identified a mutation in the *AP3D1* locus and proposed the new HPS type to be named HPS10. The severe neurological phenotype observed in this first HPS10 patient, in contrast to what has been reported in HPS2 patients, can be explained by the fact that the same AP3D1 subunit is shared by the ubiquitous and neuronal AP-3 complexes, and thus the patient lacks AP-3 in all tissues. By

contrast, the neuron-specific β3B subunit can compensate for the loss of the *AP3B1* gene in neurons of HPS2 patients. Although this was only a single patient and a bleeding tendency was not confirmed, the similarity of the patient's symptoms to those of the *mocha* mouse and the rescue of the cytolytic phenotype by expression of a wild-type AP-3δ subunit makes it highly likely that the mutation in the *AP3D1* locus was, in fact, responsible for the disease. The patient unfortunately died at the age of three and half years as a result of a septic pneumonia. HLH was not detected, but this was not surprising given the low frequency of HLH in HPS2 patients (Jessen et al., 2013).

The identification of a new genetic target for syndromic albinism corresponding to a known mouse coat color gene raises the likelihood that additional HPS-related genes will be identified in the future (see Table 1). For example, mutations encoding additional subunits of AP-3 and BLOC-1 have not yet been associated with HPS-like pathologies in humans, even though mice with known mutations at some of the orthologous loci (e.g. *cappuccino/ Bloc1s4* and *muted/Bloc1s5)* have a clear HPS-like phenotype (Wei and Li, 2013). Moreover, a point mutation in the *Vps33a* gene, encoding a subunit of the HOPS/ VPS-C complex that functions in endolysosomal fusion events, is found in a mouse HPS model (Wei and Li, 2013), and yet no corresponding mutation in a subunit gene for the corresponding human HOPS/ VPS-C complex has been identified among syndromic albinism patients. More potential targets for disease will emerge from our increasing understanding of how these complexes function within cells. Therefore, the list of syndromic types of albinism will surely continue to grow in the forthcoming years.

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Table 1

Current loci associated with different types of albinism and their corresponding mouse mutant models

Gene	Albinism	Mouse model	Complex/Function
TYR	OCA1	*albino*	melanogenic enzyme
OCA2	OCA2	*pink-eyed dilute*	chloride channel in melanogenesis
TYRP1	OCA3	*brown*	melanogenic enzyme
SLC45A2	OCA4	*underwhite*	melanogenesis
4q24	OCA5		unknown
SLC24A5	OCA6		K^+-dependent Na^+/Ca^{2+} exchanger in melanogenesis
C10ORF11	OCA7		less pigment cells/melanocyte differentiation?
GPR143	OA1	*oa1*	GPCR in melanogenesis
SLC38A8	FHONDA		solute carrier/unknown
LYST	CHS	*beige*	organelle fusion or fission
HPS1	HPS1	*pale ear*	BLOC-3 subunit – membrane transport
AP3B1	HPS2	*pearl*	AP-3 subunit – membrane transport
HPS3	HPS3	*cocoa*	BLOC-2 subunit – membrane transport
HPS4	HPS4	*light ear*	BLOC-3 subunit – membrane transport
HPS5	HPS5	*ruby eye-2*	BLOC-2 subunit – membrane transport
HPS6	HPS6	*ruby eye*	BLOC-2 subunit – membrane transport
DTNBP1	HPS7	*sandy*	BLOC-1 subunit – membrane transport
BLOC1S3	HPS8	*reduced pigmentation*	BLOC-1 subunit – membrane transport
BLOC1S6	HPS9	*pallid*	BLOC-1 subunit – membrane transport
AP3D1	HPS10	*mocha*	AP-3 subunit – membrane transport
Bloc1s5		*muted*	BLOC-1 subunit – membrane transport
Bloc1s4		*cappuccino*	BLOC-1 subunit – membrane transport
Vps33a		*buff*	HOPS subunit – membrane transport
Rab38		*chocolate*	membrane transport regulator
Rabggta		*gunmetal*	membrane transport regulator
Slc7a11		*subtle gray*	cysteine transporter in melanogenesis