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HPS11 and OCA8: Two new types of albinism associated with mutations in *BLOC1S5* and *DCT* genes

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Albinism is a rare genetic condition associated with profound visual alterations and a variable hypopigmentation phenotype. The impairment of the visual system includes diagnostic foveal hypoplasia along with misrouting of retinal axons at the optic chiasm, whose consequences are a reduced visual acuity and altered stereoscopic vision, respectively. It is assumed that between 1:10,000 and 1:20,000 newborns can be a person with albinism, with great variations depending on world areas. Historically, albinism has been categorized into oculocutaneous (OCA) or ocular (OA) types, depending on the organs affected by the hypopigmentation, but, currently, it is recommended to refer the different types of albinism according to the gene that is mutated. Albinism is genetically heterogeneous, with an increasing number of genes that have been reported whose mutations appear to be associated with albinism. There are non-syndromic and syndromic types of albinism. The latter can be more severe because their complex phenotype might include bleeding, lung fibrosis, abnormal susceptibility to infections, and immunodeficiency. There are two types of syndromic albinism: Chediak–Higashi syndrome (CHS) and Hermansky–Pudlak syndrome (HPS), with many HPS subtypes. Our knowledge of the genetic alterations underlying the different types of albinism has substantially evolved during the last 30 years, progressively increasing the list of genes that are known to be associated with this rare disease (Montoliu et al., 2014; Montoliu & Marks, 2017).

Two new publications from Benoit Arveiler's laboratory at the CHU Hospital in Bordeaux (France) have added two more genes whose mutations cause two new types of albinism: a new syndromic HPS type (HPS11), associated with mutations in the *BLOC1S5* gene (Pennamen et al., 2020a), and a new oculocutaneous albinism (OCA8), associated with mutations in the gene encoding the melanogenic enzyme dopachrome tautomerase *DCT* (Pennamen et al., 2020b). Including these two new types, the current list of genes causing albinism expands up to 22 types of albinism associated with mutations in 21 genes and a chromosomal region containing a gene that remains to be identified (Table 1).

HPS patients are extremely rare. The occurrence of HPS (OMIM #203300; Orphanet #79430) globally is estimated at 1–9/1,000,000, except for some areas, like in Puerto Rico, where the frequency can raise more than 500 times (1/1,800). Considering their biological function, all genes whose mutations result in any of the known types of HPS (or the single type of CHS) encode different subunits of multiprotein complexes that are known to participate in the maturation, trafficking, and functional specification of lysosome-related organelles, such as the melanosomes. A comparison of the human and mouse mutations in genes associated with HPS, along with the existence of additional protein subunits contributing to the formation of lysosomes/melanosomes, already suggests that new HPS types of albinism and genes could be identified (Montoliu & Marks, 2017). The coat color mouse mutants *muted* and *cappuccino* is associated with mutations in *Bloc1s5* and *Bloc1s4* genes, respectively, two additional BLOC-1 (biogenesis of lysosome-related organelles complex-1) subunits for which no patients had been reported before. Pennamen et al. (2020a) have now reported two unrelated individuals from a cohort of 230 patients undiagnosed, with lighter hair color than their parents, the typical retinal alterations, and variable signs of excessive bleeding and other HPS-related phenotypes. These two patients carried distinct homozygous deletions, of ~19 kb or just 1 bp, in the *BLOC1S5* gene, both resulting in non-functional BLOC1S5 protein and therefore impairing the stability of the BLOC-1 complex. The proposed name for this new type of syndromic albinism HPS is HPS11.

Dopachrome tautomerase (DCT) is a melanogenic enzyme that catalyzes the conversion of dopachrome, an intermediate in melanin biosynthesis, to dihydroxyindole-2-carboxylic acid (DHICA). In mice, Dct is encoded by the *Tyrp2* locus (now renamed to *Dct*) and *Dct* mutant mice are hypopigmented, such as *slaty*, whose name already indicates the reduced coat color pigmentation (Guyonneau et al., 2004). Genes encoding other melanogenic enzymes, such as TYR or TYRP1, had been already associated with albinism, OCA1 and OCA3, respectively. The remaining OCA- or OA-related genes

Coverage on: Pennamen, P., et al. BLOC1S5 pathogenic variants cause a new type of Hermansky-Pudlak syndrome. Genet Med. 2020a Jun 22. https://doi.org/10.1038/s41436-020-0867-5; and, Pennamen, P., et al. Dopachrome tautomerase variants in patients with oculocutaneous albinism. Deposited in bioRxiv on 27 June 2020; https://doi.org/10.1101/2020.06.26.171223. Genet Med. (2020b) in press.

TABLE 1 Updated list of genes whose mutations cause different types of albinism

Albinism Type	Human gene	Human chromosome	Mouse gene	Mouse chromosome
OCA1	*TYR*	11q14.3	*Tyr*	7
OCA2	*OCA2*	15q12-q13.1	*Oca2*	7
OCA3	*TYRP1*	9p23	*Tyrp1*	4
OCA4	*SLC45A2*	5p13.2	*Slc45a2*	15
OCA5	*n.d.*	4q24	*n.d.*	3
OCA6	*SLC24A5*	15q21.1	*Slc24a5*	2
OCA7	*LRMDA*	10q22.2-q22.3	*Lrmda*	14
OCA8	*DCT*	13q32.1	*Dct*	14
OA1	*GPR143*	Xp22.2	*Gpr143*	X
FHONDA	*SLC38A8*	16q23.3	*Slc38a8*	8
CHS	*LYST*	1q42.3	*Lyst*	13
HPS1	*HPS1*	10q24.2	*Hps1*	19
HPS2	*AP3B1*	5q14.1	*Ap3b1*	13
HPS3	*HPS3*	3q24	*Hps3*	3
HPS4	*HPS4*	22q12.1	*Hps4*	5
HPS5	*HPS5*	11p15.1	*Hps5*	7
HPS6	*HPS6*	10q24.32	*Hps6*	19
HPS7	*DTNBP1*	6p22.3	*Dtnbp1*	13
HPS8	*BLOC1S3*	19q13.32	*Bloc1s3*	7
HPS9	*BLOC1S6*	15q21.1	*Bloc1s6*	2
HPS10	*AP3D1*	19P13.3	*Ap3d1*	10
HPS11	*BLOC1S5*	6p24.3	*Bloc1s5*	13

Abbreviations: CHS, Chediak–Higashi syndrome; FHONDA, foveal hypoplasia, optic nerve decussation defects, and anterior segment dysgenesis; HPS, Hermansky–Pudlak syndrome; n.d., not determined; OA, ocular albinism; OCA, oculocutaneous albinism.

FIGURE 1 Adult man genetically diagnosed with OCA1. Photography by Ana Yturralde

(*OCA2*, *SLC45A2*, and *SLC24A5*) were related to the biosynthesis of melanin, or its regulation, or involved in melanocyte differentiation or melanosome-specific functions (*GPR143*, *SLC38A8*, and *LMRDA*). But this was not the case of *DCT*, since no mutations had been described in humans associated with albinism. Pennamen et al. (2020b) found two unrelated individuals, from the same cohort of undiagnosed patients, carrying distinct mutations in the *DCT* gene and presenting mild hypopigmentation and moderate ocular features characteristic of albinism, hence suggesting that mutations in this locus could also cause a mild form of this genetic condition. Furthermore, they tested the effect of the same mutations in mice, at the *Dct* locus, using CRISPR-Cas9 genome editing tools, and the resulting animals were also hypopigmented. Similarly, the inactivation of the *Dct* gene in zebrafish also resulted in hypopigmentation in the skin and the retina. Hence, they concluded that *DCT* mutations are the genetic cause of a new type of OCA whose proposed name is OCA8.

Since the identification of mutations in *TYR*, as the genetic cause of OCA1, reported in 1989 by Richard A. King and Shigeki Shibahara groups, our knowledge on the genes associated with albinism has increased enormously (Figure 1), from one single type and one gene to the current 22 types of albinism associated with mutations in 21 genes and a chromosomal region. Moreover, the current understanding in the field is that we have not yet saturated the human genome. Probably, there are additional genes in the human genome whose mutations will result in new types of albinism. Some gene candidates have been proposed in the literature (e.g., *GNAI3*, reported by Debora Farber's laboratory at UCLA in 2016 in PLoS ONE). However, additional scientific evidence is still needed before these candidates can be formally considered associated with albinism.

Describing new genes associated with albinism will also help to reduce the significant number (~30%) of clinically diagnosed people with albinism, where we fail to detect the responsible molecular lesion (Lasseaux et al., 2018; Montoliu et al., 2014). An additional source for detecting new mutations is the non-coding DNA regulatory elements, which might also contribute to the missing mutations in these undiagnosed patients (Seruggia et al., 2020).

This has been an exciting journey, from a rare genetic condition that was originally known for mutations in a single gene (*TYR*) to a most genetically heterogeneous landscape, with a minimum of 21 loci whose mutations correlate with, at least, 22 different types of albinism. As a pigment cell scientific community, we need to stay alert and open to accept further additional genes, yet to be isolated. Benoit Arveiler's group just brought us two more genes. Research on albinism is still a very active field. Waiting already for the next gene.

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