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SLC24A5 Mutations Are Associated with Non-Syndromic Oculocutaneous Albinism

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TO THE EDITOR

Oculocutaneous albinism (OCA) is an autosomal recessive disorder characterized by hypomelanosis of the skin, hair, and eyes, associated with reduced visual acuity, nystagmus, and photophobia (Tomita and Suzuki, 2004). Its worldwide prevalence is approximately 1:17,000 (Witkop, 1979). Hypopigmentation or complete lack of pigmentation is caused by a deficiency involving the production, metabolism, or distribution of melanin, the main pigment responsible for skin coloration. Diagnosis is based on clinical findings of hypopigmentation of the skin and hair, in addition to the characteristic ocular symptoms. OCA can be isolated or associated with other anomalies in syndromic forms (Tomita and Suzuki, 2004).

Mutations of the *TYR, OCA2, TYRP1,* and *SLC45A2* genes have been associated with non-syndromic forms of OCA (OCA1–4, respectively). As these four genes do not account for all non-syndromic OCA, it has long been hypothesized that other genes might be involved. To date, more than 125 genes have been involved in pigmentation regulation, and many of them (at least 25) affect the biogenesis or function of melanosomes. Several genes encoding melanosomal proteins including *TYRP2, SLC24A5, SILV, RAB7,* and *RAB38* have been considered as good candidates for OCA. However, until recently, no pathological mutations of these genes had been reported in human OCA patients (Suzuki *et al.*, 2003, Hutton and Spritz, 2008, Grønskov *et al.*, 2009, Mondal *et al.*, 2012). Very recently, two new OCA genes were uncovered. Mutations of *C10orf11* were identified in a family from the Faroe Islands and in a Lithuanian patient (Grønskov *et al.*, 2013), and mutations of *SLC24A5* were found in a Chinese patient presenting with non-syndromic OCA (Wei *et al.*, 2013). In addition, an OCA locus was mapped to 4q24 in a consanguineous Pakistani family, but the gene has not yet been described (Kausar *et al.*, 2012).

We analyzed 399 patients with non-syndromic OCA and found that 36% were OCA1, 25% had mutations in *OCA2*, 2% were OCA3, and 11% were caused by mutations in *SLC45A2* (OCA4). An additional 6% of patients had mutations in *GPR143* (OA1) and 1% in *HPS1*. Six percent of patients had a single heterozygous mutation in one gene, and in 13% no mutation in the known genes was identified (our unpublished data). Subsequently, we sequenced the nine exons of the *SLC24A5* gene in 22 OCA patients without mutations in any of the known genes (*OCA1–4, OA1,* and *HPS1* genes) and found

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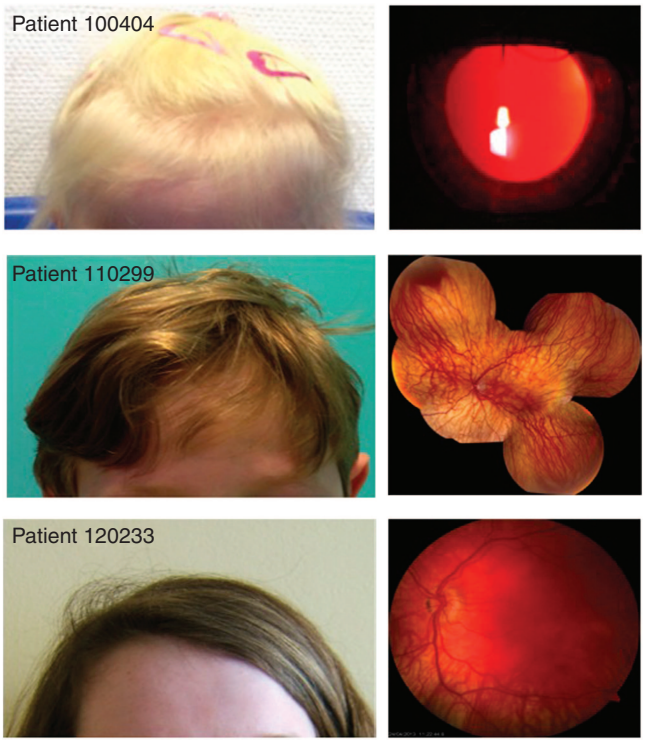

Figure 1. Phenotype of patients 100404, 110299, and 120233. Hair color is shown on the left, illustrating the phenotypic heterogeneity in patients with OCA6. Ocular phenotype is objectivized by iris transillumination (patient 100404) or eye fundus (patients 110299 and 120233) on the right.

5 index patients with biallelic mutations (Table 1). No intragenic rearrangement (deletions, duplications) was identified.

Patients 060854, 070126, and 110299 were homozygous for mutations c.590+4A>G, c.641delT/p.Leu214ArgfsX12, and c.546T>A/p.Ser182Arg, respectively. The affected brother (131242) and first cousin (0710127) of patient 070126 were also homozygous for the c.641delT/p.Leu214ArgfsX12 mutation. His unaffected brother was heterozygous for the mutation.

Compound heterozygosity was found in patients 100404 (c.344C>A/p.Ala115Glu and c.989G>A/p.Trp330X) and 120233 (c.216T>A/p.Tyr72X and a c.344C>A/p.Ala115Glu). All the identified mutations were inherited from heterozygous parents and were absent from single-nucleotide polymorphism databases (HapMap, 1000 Genomes). The two missense mutations c.546T>A/p.Ser182Arg and c.344C>A/p.Ala115Glu were predicted to be probably damaging by the prediction software Polyphen2. Moreover they affected highly conserved amino acids.

We observed a heterogeneous phenotype among the seven OCA patients with *SLC24A5* mutations reported herein (Table 1 and Figure 1). Severe hypopigmentation similar to that observed in OCA1 (white platinum golden hair and complete iris transillumination) was observed in patient 100404, whereas a milder skin phenotype with light brown hair was observed in four patients. Patient 110299 had light brown hair, but no skin pigmentation, revealing subcutaneous vascular structures. No ocular pigmentation was observed, with complete iris transillumination and absent pigmentation of the retinal pigment epithelium and choroid on fundoscopy. However, patient 120233, who had darker hair, displayed some degree of ocular pigmentation. The patient published by Wei *et al.* (2013) also had blond/light brown hair. Obviously, solid genotype–phenotype correlations cannot yet be established because of the small number of OCA6 patients identified to date. Ophthalmologic anomalies were always present and included reduced best-corrected visual acuity, nystagmus, pronounced iris transillumination, severe retinal hypopigmentation, and foveal hypoplasia. No other findings evocative of syndromic OCA, including bleeding, granulomatous colitis, pulmonary involvement, or propensity to infections, were recorded.

SLC24A5 encodes a trans-Golgi network protein with potassium-dependent sodium–calcium exchange activity that regulates human epidermal melanogenesis (Ginger *et al.*, 2008). Slc24a5-null mice have been reported to have albinotic features (Vogel *et al.*, 2008). *Slc24a5* mutations are responsible for the golden mutant in the zebrafish, in which melanosomal changes have been identified. Slc24a5 was considered to be a putative cation exchanger (nckx5) that localizes to an intracellular membrane, likely the melanosome or its precursor, in golden. The human ortholog of slc24a5 is highly conserved (68% at the mRNA level; 69% at the protein level) and was shown to be functional in the zebrafish (Lamason *et al.*, 2005). A genome-wide association study performed in a South Asian population showed that *SLC24A5* single-nucleotide polymorphism rs1426654 (Ala111Thr) was associated with lighter skin in Thr111-positive individuals, and might be a natural regulator of human skin color variation (Stokowski *et al.*, 2007). Wei *et al.* (2013) reported less mature and more immature melanosomes in epidermal melanocytes of their OCA6 patient, supporting the involvement of *SLC24A5* in the maturation of melanosomes or in the production of pigment in mature melanosomes. It was shown that HPS protein–associated complexes such as AP-3, BLOC-1, and BLOC-2 mediated the transport of melanosomal proteins such as Tyrosinase, TYRP1, OCA2, and ATP7A into mature melanosomes (Wei and Li, 2013). It was also suggested that BLOC-1 and BLOC-2, involved in Hermanski–Pudlak syndrome, could mediate the melanosomal targeting of SLC24A5, but this requires further investigations.

Our finding of mutations in *SLC24A5* in five unrelated families strengthens the importance of screening this gene in OCA, and indicates that OCA6 is not restricted to the Chinese population and accounts for 1.25% of OCA patients in

Table 1. Phenotype and *SLC24A5* mutations identified in patients with OCA6

Patients	060854	070126	131242	070127	100404	110299	120233	Patient (Wei *et al.*, 2013)
Age at presentation (years)	16	20	16	23	1	4	19	3
Sex	Male	Male	Male	Male	Female	Male	Female	Male
Clinic	Vannes	Toulouse	Toulouse	Toulouse	Angers	Ghent	Brussels	ND
Ethnic and geographic origin	French	Portuguese	Portuguese	Portuguese	French	Syrian	Belgian	Asian
Parental consanguinity	No	Yes	Yes	Yes	No	Yes	No	No
Hair color	Blond	Light brown	Light brown	Light brown	Platinum blond	Light brown	Light brown	Light brown
Skin color	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair
Tendancy to tan	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Pigmented nevus	ND	Yes	Yes	Yes	No	No	Yes	ND
Reduced visual acuity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Best-corrected visual acuity	ND	0.30 RE/0.40 LE	0.25 RE/0.40 LE	0.40 RE/0.30 LE	0.125 RE/0.125 LE	0.15 RE/ 0.20 LE	0.20 RE/0.30 LE	0.20 RE/0.20 LE
Nystagmus	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Iris color	Blue	Green	Green	Green	Blue	Blue	Green	Brownish
Iris transillumination	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Foveal hypoplasia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Retinal hypopigmentation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hearing loss	Yes	No	No	No	No	No	ND	ND
Associated findings (bleeding, granulomatous colitis, pulmonary involvement, recurrent infectious diseases)	No	No	No	No	No	No	No	No
Mutations	Hmz mutation	Hmz mutation	Hmz mutation	Hmz mutation	Mutation 1	Mutation 2	Hmz mutation	Mutation1	Mutation 2	Mutation1	Mutation 2
	c.590+4A>G	c.641delT	c.641delT	c.641delT	c.344C>A	c.989G>A	c.546T>A	c.216T>A	c.344C>A	c.591G>A	c.1361insT
AA nomenclature	p.?	p.Leu214ArgfsX12	p.Leu214ArgfsX12	p.Leu214ArgfsX12	p.Ala115Glu	p.Trp330X	p.Ser182Arg	p.Tyr72X	p.Ala115Glu	p.Trp197X	p.Cys46LeufxX43
Variant type	Splice	Truncating	Truncating	Truncating	Missense	Truncating	Missense	Truncating	Missense	Nonsense	Truncating
Exon	5	6	6	6	2	7	5	2	2	5	9
Polyphen	—	—	—	—	Probably damaging	—	Probably damaging	/	Probably damaging	Probably damaging	—
Conservation	—	—	—	—	AA highly conserved	—	AA highly conserved	/	AA highly conserved	AA highly conserved	—
Frequency (%), HapMap/ 1000 Genomes	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

Abbreviations: Hmz, homozygous; LE, left eye; ND, not determined; RE, right eye.
p.? corresponds to the common nomenclature for mutations the effect of which is not known at the protein level.

our series. Still, 11.5% of patients have no mutation after extensive analysis of the *OCA1–4*, *OCA6*, *OA1*, and *HPS1* genes, thus suggesting that other genes involved in OCA still remain to be identified.

Written informed consent was received from the patients. The authors adhere to the Declaration of Helsinki Principles. Experiments were approved by the Comité de protection des Personnes Bordeaux—Outre Mer III.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Long-Term Survival of Type XVII Collagen Revertant Cells in an Animal Model of Revertant Cell Therapy

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TO THE EDITOR

Revertant mosaicism is the coexistence of mutant cells carrying germline mutations and revertant cells that have spontaneously corrected the germline mutation by a somatic reverse mutation. Revertant mosaicism has been reported for a number of genetic diseases (Pasmooij and Jonkman, 2012), including epidermolysis bullosa. Moreover, the first case of revertant mosaicism in skin was found in a Dutch patient 026-01 with junctional epidermolysis bullosa caused by mutations in *COL17A1*. The patient was compound heterozygous for a maternal deletion in exon 18, c.1601delA, and paternal nonsense mutation in exon 51, c.3676C>T (Jonkman *et al*, 1997). Owing to gene conversion, the c.1601delA mutation was corrected and the patient presented a clinically healthy skin patch on her forearm (Figure 1a), where affected (mutant) and corrected (revertant) keratinocytes coexisted (Figure 1b). Recently, we found revertant mosaicism to occur in all Dutch patients with junctional epidermolysis bullosa (Jonkman and Pasmooij, 2009; Pasmooij *et al*, 2012).

Naturally corrected keratinocytes expressing type XVII collagen (C17) harvested from a revertant patch can be used for autologous cell therapy.

Abbreviation: C17, type XVII collagen

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