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Oculocutaneous Albinism Type 4

Synonym: OCA4

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Summary

Clinical characteristics

Oculocutaneous albinism type 4 (OCA4) is characterized by hypopigmentation of the hair and skin plus the characteristic ocular changes found in all other types of albinism, including: nystagmus; reduced iris pigment with iris translucency; reduced retinal pigment with visualization of the choroidal blood vessels on ophthalmoscopic examination; foveal hypoplasia associated with reduction in visual acuity; and misrouting of the optic nerves at the chiasm associated with alternating strabismus, reduced stereoscopic vision, and an altered visual evoked potential (VEP). Individuals with OCA4 are usually recognized within the first year of life because of hypopigmentation of the hair and skin and the ocular features of nystagmus and strabismus. Vision is likely to be stable after early childhood. The amount of cutaneous pigmentation in OCA4 ranges from minimal to near normal. Newborns with OCA4 usually have some pigment in their hair, with color ranging from silvery white to light yellow. Hair color may darken with time, but does not vary significantly from childhood to adulthood.

Diagnosis/testing

Because the phenotype of OCA4 overlaps that of the other genetic forms of albinism (oculocutaneous and ocular), the diagnosis of OCA4 is established by molecular genetic testing with the identification of biallelic pathogenic variants in *SLC45A2*. A multigene panel or comprehensive genomic testing is the preferred molecular genetic testing method for this disorder.

Management

Treatment of manifestations: Correction of refractive errors with spectacles or contact lenses to improve visual acuity. Strabismus surgery may be considered for cosmetic reasons. Dark glasses may alleviate photophobia but may reduce vision; a hat with a brim or visor best achieves reduction in photophobia. Protection from the sun, through the wearing of protective clothing and the regular application of sunscreen, is essential.

Prevention of secondary complications: Individuals with OCA4 should stay out of the sun from an early age, because cumulative ultraviolet exposure is a major risk factor for skin cancers.

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Surveillance: Annual ophthalmologic examination and reassessment for accurate correction of refractive error. Evaluation of the skin for cancer screening every six months is recommended.

Agents/circumstances to avoid: Prolonged exposure to sun.

Genetic counseling

OCA4 is typically inherited in an autosomal recessive manner. The parents of a proband are obligate heterozygotes and thus carriers of one *SLC45A2* pathogenic variant. Heterozygotes (carriers) are asymptomatic and not at risk of developing the disorder, but may be light in pigmentation for their ethnic group. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

Suggestive Findings

Oculocutaneous albinism type 4 (OCA4) **should be suspected** in individuals with the following clinical features:

- **Hypopigmentation** of the skin and hair varying from complete depigmentation to partial depigmentation with brown hair. In some individuals pigmentation increases during the first decade of life [Suzuki & Tomita 2008].
- **Characteristic ocular changes** found in all types of albinism, including the following findings detected on routine ophthalmologic examination:
  - Nystagmus
  - Reduced iris pigment with iris translucency
  - Reduced retinal pigment with visualization of the choroidal blood vessels on ophthalmoscopic examination
  - Foveal hypoplasia associated with reduction in visual acuity
- **Vision abnormalities** (due to misrouting of the optic nerves at the chiasm) including:
  - Alternating strabismus
  - Reduced stereoscopic vision
  - Altered visual evoked potential (VEP)

    Note: (1) A VEP is not necessary for the routine diagnosis of albinism; misrouting is implied by the finding of strabismus and reduced stereoscopic vision. (2) In some individuals, particularly those who have moderate amounts of cutaneous and retinal pigment, or those who have foveal hypoplasia and no obvious nystagmus, a VEP may be necessary to demonstrate misrouting of the optic nerves. (3) The VEP is performed with a technique specifically developed for demonstration of the misrouting and a regular VEP will not demonstrate this. (4) Normal routing of the optic nerves, demonstrated with a VEP, indicates that the diagnosis is not albinism/OCA.

Establishing the Diagnosis

The diagnosis of OCA4 **is established** in a proband with characteristic clinical findings and/or by identification of biallelic pathogenic (or likely pathogenic) variants in *SLC45A2* on molecular genetic testing (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SLC45A2* variants of uncertain significance (or identification of one known *SLC45A2* pathogenic variant and one *SLC45A2* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include the use of a **multigene panel** or **comprehensive genomic testing**.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of OCA4 overlaps that of the other genetic forms of albinism (oculocutaneous and ocular), a multigene panel or comprehensive genomic testing (when available) is the preferred molecular genetic testing method for this disorder. Single-gene testing (sequence analysis of *SLC45A2,* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A multigene panel** that includes *SLC45A2* and other genes of interest associated with albinism (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

For this disorder a multigene panel that also includes deletion/duplication analysis or exome array is recommended if no or only one pathogenic variant is identified.

Table 1. Molecular Genetic Testing Used in OCA4

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC45A2	Sequence analysis [3]	75%-85% [4]
	Gene-targeted deletion/duplication analysis [5]	Rare [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Inagaki et al [2004], Sengupta et al [2007], Hutton & Spritz [2008], Wei et al [2011], Mauri et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Rooryck et al [2008] identified deletion of exon 4 in *SLC45A2* in an individual who was described as having a severe phenotype at birth which became milder with age.

Note: Oki et al [2017] reported a multigenerational family in which OCA4 appeared to be inherited as an autosomal dominant condition associated with a heterozygous pathogenic variant in *SLC45A2*. The authors of this *GeneReview* feel that this may represent a rare occurrence, but note that no functional assay for the specific variant was performed and that concomitant heterozygous pathogenic variant(s) in a regulatory region or in other (unknown) OCA-related genes cannot be ruled out.

Clinical Characteristics

Clinical Description

A wide range of clinical phenotypes has been recognized to date [Suzuki & Tomita 2008]. The amount of cutaneous pigmentation in OCA4 is a continuum from minimal to near normal [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005]. The amount of iris and retinal pigment varies and visual acuity covers a wide range; however, no subtypes of OCA4 are recognized.

Individuals with albinism (including OCA4) are usually recognized within the first year of life because of the ocular features of nystagmus and strabismus. In many families, particularly in those with darker constitutional pigmentation, the cutaneous hypopigmentation is also obvious at birth and suggests the diagnosis.

Eye

Nystagmus. Some children with albinism have nystagmus that is noticed by the parents and the examining physician in the delivery room. Many children with albinism do not have nystagmus at birth and the parents note slow wandering eye movements and a lack of visual attention. The parents may become concerned because the child does not seem to "focus well," but the absence of nystagmus may delay the diagnosis. Most children with albinism develop nystagmus by age three to four months, and the diagnosis is often considered at the four-to-six month well-baby check-up. The nystagmus can be rapid early in life and generally slows with time; however, nearly all individuals with albinism have nystagmus throughout their lives. Nystagmus is more noticeable when individuals are tired, angry, or anxious, and less marked when they are well rested and feeling well [Summers 2009].

Iris color ranges from blue to brown. In one individual with OCA4, who had been misdiagnosed at birth as having OCA1 because of complete iris transillumination, the amount of iris pigment increased in the first ten years, resulting in blue iris color [Suzuki et al 2005].

Visual acuity in individuals with OCA4 ranges from 20/30 to 20/400 and is usually in the range of 20/100 to 20/200 [Rundshagen et al 2004, Suzuki et al 2005]. Vision is likely to be stable after early childhood and no major change or further reduction in vision should occur; loss of vision later in life is generally not related to the albinism.

Hair/Skin

The range of hair and skin pigment in individuals with OCA4 is broad [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005].

Hair. Individuals with OCA4 are often born with some pigment in their hair that ranges in color from silvery white to light yellow.

- Scalp hair may be very light, but it is usually not completely white (not as white as a sheet of paper or fresh snow); some parents may refer to light yellow/blond hair color as "white" or "nearly white" if it is very lightly pigmented or is much lighter than the hair color of other family members at a similar age.
- Furthermore, the definition of "white" scalp hair is not easy in some young children because the hair may be sparse and short and because some shampoos discolor hair.
- It is helpful to hold a piece of white paper next to the hair to determine if it is truly white.
- Hair color may darken with time, but usually the hair color does not change dramatically between childhood and adulthood [Inagaki et al 2004].

Skin. When hair color is blond or yellow, the skin is usually creamy white with little or no pigmentation. When hair color is somewhat darker, the skin is usually similar to that seen in unaffected individuals [Thody et al 1991].

Skin color in individuals with OCA4 is not usually as white as that in individuals with the OCA1A subtype of oculocutaneous albinism type 1, reflecting the fact that skin melanocytes in individuals with OCA4 can still synthesize some melanin; however, the majority of the melanin is yellow pheomelanin rather than black-brown eumelanin.

Skin cancer risk. Over many years, exposure of lightly pigmented skin to the sun can result in coarse, rough, thickened skin (pachydermia), solar keratoses (premalignant lesions), and skin cancer. Both basal cell carcinoma and squamous cell carcinoma can develop. The incidence rate of melanoma in individuals with OCA is unknown; however, the risk for melanoma in this population is generally considered to be higher than in unaffected individuals [Streutker et al 2000, Asuquo et al 2009].

Skin cancer is unusual in individuals with OCA4 in the US because of the availability of sunscreens, the social acceptability of wearing clothes that cover most of the exposed skin, and the fact that individuals with albinism often do not spend a great deal of time outside in the sun. Skin cancer in an individual with any type of OCA is very rare in northern areas of the US. Skin cancer in individuals with albinism is common particularly in some parts of Africa because of the increased amount of sun exposure throughout the year, the cultural differences in protective dress, and lack of skin-protective agents such as sunscreens. In addition, African individuals with albinism tend to have poorer prognosis with skin cancer because of late presentation to care and failure to complete treatment for economic reasons [Mabula et al 2012].

Genotype-Phenotype Correlations

The lack of a functional assay for the *SLC45A2* protein and the limited data from *SLC45A2* molecular genetic testing make genotype-phenotype correlations difficult [Newton et al 2001, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005, Konno et al 2009].

Two common pathogenic alleles, p.Asp157Asn and p.Gly188Val, have been reported in Japanese individuals. The p.Asp157Asn allele may have very low functional activity in melanogenesis; p.Gly188Val may have some residual functional activity [Inagaki et al 2004].

Recently, a family with autosomal dominant OCA4 has been reported [Oki et al 2017], with a novel heterozygous pathogenic variant: c.208T>C (p.Tyr70His). Family members with the variant demonstrate a relatively mild phenotype, with a slightly creamy complexion, brown to black hair, and mild iris hypopigmentation.

The degree of cutaneous pigmentation, ocular pigmentation, and visual development resulting from particular *SLC45A2* pathogenic variants cannot be predicted at this time.

Nomenclature

The ocular features of all types of oculocutaneous albinism (OCA) and X-linked ocular albinism (OA1) are similar and the terms "oculocutaneous albinism" and "albinism" can be used interchangeably when referring to these clinical features.

Prevalence

Prevalence of OCA4 is thought to be on the order of 1:100,000 in most populations throughout the world. It is likely to be more common in Japan, where it accounts for 24% of individuals with OCA [Inagaki et al 2004, Inagaki et al 2005].

OCA4 has also been described in individuals of German, Turkish, Korean, Indian, Chinese, Danish, and Moroccan descent [Newton et al 2001, Rundshagen et al 2004, Ikinciogullari et al 2005, Suzuki et al 2005, Sengupta et al 2007, Grønskov et al 2009, Konno et al 2009].

Genetically Related (Allelic) Disorders

OCA4 is the only phenotype known to be associated with pathogenic variants in *SLC45A2*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of OCA4

Differential Disorder	Gene(s)	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/OCA4	Distinguishing from OCA4
OCA1 (OMIM 203100, 606952)	*TYR*	AR	Oculocutaneous albinism	May have poorer visual acuity
OCA2 (OMIM 203200)	*OCA2*	AR		NA
OCA3 (OMIM 203290)	*TYRP1*	AR		Reddish hair & freckled skin; only seen in individuals of African, Pakistani, German, Indian, & Japanese heritage
OCA5 (OMIM 615312)	Unknown (candidate region is on 4q24)	AR		Golden hair
OCA6 (OMIM 113750)	*SLC24A5*	AR		Indistinguishable due to functional similarity of *SLC45A2* (OCA4) & *SLC24A5*
OCA7 (OMIM 615179)	*LRMDA* (formerly *C10orf11*)	AR		Relatively severe impaired visual acuity

Table 2. continued from previous page.

Differential Disorder	Gene(s)	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/OCA4	Distinguishing from OCA4
Hermansky-Pudlak syndrome (HPS)	*HPS1* *AP3B1* (*HPS2*) *HPS3* *HPS4* *HPS5* *HPS6* *DTNBP1* (*HPS7*) *BLOC1S3* (*HPS8*) *BLOC1S6* *AP3D1* (HPS10)	AR		Bleeding tendency, platelet dense granules; granulomatous colitis & interstitial pneumonia in HPS1 & HPS4; immunodeficiency & hemophagocytic syndrome in HPS2 & HPS10
OA1 (OMIM 300500)	*GPR143*	XL	Ocular albinism	Coloring may appear normal but some may have mild hypopigmentation of skin & hair compared to family members.
FRMD7-related infantile nystagmus	*FRMD7*	XL	Nystagmus	Absence of oculocutaneous albinism

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with oculocutaneous albinism type 4 (OCA4), the following evaluations are recommended if they have not already been completed:

- Complete ophthalmologic evaluation including measurement of visual acuity and refractive error
- Assessment for strabismus
- Assessment by dermatologist to instruct parents regarding use of sun-protective clothing, lotions, and formulas
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Ophthalmologic care is the most important part of the ongoing care for most individuals with OCA4.

The majority of individuals with albinism have significant hyperopia or myopia and astigmatism. Correction of these refractive errors with spectacles or contact lenses can improve visual acuity. Except in the very unusual individual, correction of refractive errors cannot restore visual acuity to normal because of the foveal hypoplasia.

The alternating strabismus found in most individuals with albinism is generally not associated with the development of amblyopia. Strabismus surgery is usually not required, but can be considered for cosmetic reasons if the strabismus is marked or fixed.

Photophobia is common in individuals with OCA4, but the degree of discomfort varies and does not depend entirely on the amount of melanin pigment present in the iris or skin. In general, opaque contact lenses or darkly tinted lenses do not improve visual function. Dark glasses may be helpful for individuals with albinism, but many prefer to go without dark glasses because of the reduction in vision from the dark lenses. A hat with a brim (e.g., a baseball hat with a visor) is often the best way to achieve reduction in photophobia and sun protection.

Protection from the sun through the wearing of protective clothing and the regular application of sunscreen is essential to prevent sunburn and secondary skin changes, and to decrease the risk of skin cancer in later life. Regular skin check-ups for skin cancer are recommended for adult individuals with OCA4, especially in cases of severe hypopigmentation.

Prevention of Secondary Complications

Individuals with OCA4 should stay out of the sun from an early age, as cumulative ultraviolet exposure is a major risk factor for skin cancers (see Hair/Skin, **Skin cancer risk**).

Prolonged periods in the sun require skin protection with clothing (hats with brims, long sleeves and pants, socks) and sunscreen with a high SPF number (total blocks with SPF 45-50+). There is no scientific evidence to indicate how high an SPF value is enough; individuals with OCA4 should use sunscreen with higher SPF values (45-50+) to lessen as much as possible the cumulative effect of ultraviolet to their skin.

Surveillance

Annual ophthalmologic examination and reassessment for accurate correction of refractive error are appropriate.

There is no definitive guideline supported by scientific evidence as to how often an individual should be evaluated by a dermatologist, though an evaluation of the skin for cancer screening every six months is recommended.

Agents/Circumstances to Avoid

Avoid prolonged exposure of the skin to the sun.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

OCA4 is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *SLC45A2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and not at risk of developing the disorder; they may be light in pigmentation for their ethnic group.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder, although they may be light in pigmentation for their ethnic group.

Offspring of a proband. Unless an affected individual's reproductive partner also has OCA4 or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SLC45A2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SLC45A2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC45A2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA of probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC45A2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

A fetal skin biopsy will not provide an accurate diagnosis and is not appropriate for prenatal diagnosis of OCA4.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Albinism Database**

University of Minnesota
MN
albinismdb.med.umn.edu

- **National Organization for Albinism and Hypopigmentation (NOAH)**
  Phone: 800-473-2310 (US and Canada); 603-887-2310
  Fax: 603-887-6049
  Email: info@albinism.org
  www.albinism.org
- **MedlinePlus**
  Oculocutaneous albinism
- **PanAmerican Society for Pigment Cell Research (PASPCR)**
  www.paspcr.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Oculocutaneous Albinism Type 4: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC45A2	5p13.2	Membrane-associated transporter protein	Albinism Database Mutations of the Membrane Associated Transporter Protein (MATP) Gene (aka SLC45A2)	SLC45A2	SLC45A2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Oculocutaneous Albinism Type 4 (View All in OMIM)

606202	SOLUTE CARRIER FAMILY 45, MEMBER 2; SLC45A2
606574	ALBINISM, OCULOCUTANEOUS, TYPE IV; OCA4

Molecular Pathogenesis

The phenotype resulting from heterozygosity of a single *Slc45a2* pathogenic variant in mice results in hypopigmentation that may be analogous to some of the autosomal dominant forms of albinism reported in humans. Apparent autosomal dominant inheritance of OCA4 has been recently reported in a single Japanese family [Oki et al 2017].

Gene structure. *SLC45A2* has seven exons and spans 40 kb at chromosome 5p13.3 (NM_016180.3).

Pathogenic variants. See International Albinism home page. Fifty-three pathogenic variants of *SLC45A2* have been reported. Most are missense variants, but deletions of one or a small number of bases and base changes have been detected [Newton et al 2001, Inagaki et al 2004, Rundshagen et al 2004, Ikinciogullari et al 2005, Inagaki et al 2005, Suzuki et al 2005, Sengupta et al 2007, Grønskov et al 2009, Konno et al 2009]. The most common *SLC45A2* pathogenic variant in Japanese individuals, accounting for 39% of pathogenic alleles, is the p.Asp157Asn missense variant [Inagaki et al 2004].

Most individuals with OCA4 are compound heterozygotes for *SLC45A2* pathogenic variants. Approximately 17% of reported Japanese individuals and a cohort from India have only one identifiable pathogenic variant; the

second variant could not be detected with the methods used [Inagaki et al 2004, Sengupta et al 2007]. (For more information, see Table A.).

Table 3. *SLC45A2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.208T>C	p.Tyr70His	NM_016180.3 NP_057264.3
c.469G>A	p.Asp157Asn	
c.563G>T	p.Gly188Val	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. Membrane-associated transporter protein (MATP) consists of 530 amino acids, contains 12 transmembrane domains, and is only expressed in mealocytes (NP_057264.3) [Newton et al 2001]. The precise function of MATP is yet to be elucidated, although it appears to play a role in tyrosinase processing, intracellular trafficking of tyrosinase to melanosome, and regulating tyrosinase activity through controlling melanomal pH [Costin et al 2003, Bin et al 2015].

Abnormal gene product. The mechanisms by which the abnormal protein alters the ability of the cell to synthesize melanin are unknown. However, tyrosinase, the rate-limiting enzyme in the biosynthesis of melanin that is associated with OCA1, appears to be mislocalized in mouse melanocytes that are homozygous for pathogenic *SLC45A2* alleles [Costin et al 2003]. This phenotype is shared with melanocytes that contain pathogenic variants in *OCA2*, the gene associated with OCA2 [Toyofuku et al 2002].

Chapter Notes

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- 7 September 2017 (ha) Comprehensive update posted live
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