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Genetic testing for ocular albinism and oculocutaneous albinism

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for ocular albinism and oculocutaneous albinism. Ocular albinism has X-linked recessive inheritance, with a prevalence that varies from 1/40000 to 1/1000000, and is caused by mutations in the *GPR143* and CACNA1F genes. Oculocutaneous albinism has autosomal recessive inheritance, with an overall prevalence of 1/17000, and is caused by mutations in the *TYR*, OCA2, *TYRP1*, *SLC45A2*, *SLC24A5* and *C10orf11* genes. Clinical diagnosis involves ophthalmological examination, testing of visually evoked potentials (VEP) and electrophysiological testing (ERG). The genetic test is useful for confirming diagnosis, differential diagnosis, for couple risk assessment and access to clinical trials.

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Ocular albinism and oculocutaneous albinism

Ocular Albinism Type 1 (other synonyms: Nettleship-Falls ocular albinism, OA1, XLOA)(1)

Aland Island eye disease (other synonyms: AIED, Forsius – Eriksson type ocular albinism) (Retrieved from OMIM.org)

Oculocutaneous Albinism (other synonyms: autosomal recessive albinism, OCA. Subtypes are OCA1 (OCA1A, OCA1B), OCA2, OCA3, OCA4, OCA5, OCA6 and OCA7)(2)

General information about the disease

Ocular albinism (type 1 acronym OA1 or XLOA and Aland Island eye disease acronym AIED) and oculocutaneous albinism (acronyms OCA1A, OCA1B, OCA2, OCA3, OCA4, OCA6, OCA7) are inherited diseases of the retina characterized by reduced visual acuity (between 20/40 and 20/400), nystagmus, foveal hypoplasia, and hypopigmentation of iris pigment epithelium and ocular fundus. Major refractive errors, reduced or absent binocular function, altered visually evoked potentials (VEP), misrouting of optic nerve fiber radiations at the chiasma resulting in reduced stereoscopic vision, strabismus and photoaversion are also common. Ocular albinism almost always presents with eye changes, while oculocutaneous albinism also presents with hypopigmentation of the hair and skin.

OA1 is a non-progressive disorder and visual acuity remains stable throughout life, often slowly improving into the mid-teens, whereas AIED presents with progressive myopia, color vision defect and defective dark adaption. The estimated prevalence is 1/60,000 to 1/150,000 (1) for OA1 and <1/1,000,000 for AIED (from http://www.orpha.net/).

Patients with OCA1A have white hair, white skin that does not tan and translucent irides, none of which darken with age. Individuals with OCA1B have hair and skin that darken slightly with age and sun exposure, and blue irides that darken to light brown/tan or green/hazel with age, although transillumination defects persist. The worldwide

prevalence of OCA1 is estimated at 1/40,000 (3).

Individuals with OCA2 have lightly pigmented hair, lashes and brows, the color ranging from pale gold to brown that may darken with age but does not vary greatly from adolescence to adulthood. The prevalence of OCA2 is estimated to be 1/38,000-1/40,000 in most world populations, except Africans (prevalence 1/3,900-1/1,500) (4).

OCA3 is considered a relatively mild subtype, and in the rare non-African cases, reddish hair has been reported. OCA3 has an estimated prevalence of 1/8,500 in Africa. It is rarely seen in other populations (2).

Individuals with OCA4 are usually recognized in the first year of life and generally have some hair pigment, the color ranging from silvery white to pale gold. Hair color may darken with age, but does not vary significantly from childhood to adulthood. This form of albinism is rarer than OCA2, with an estimated world prevalence of 1/100,000, except in the Japanese population (5).

Ocular albinism and oculocutaneous albinism are probable diagnoses in cases with typical clinical eye signs/symptoms and tests. Diagnosis is confirmed by identifying a pathogenic variant of the relevant genes by molecular genetic testing.

Differential diagnoses should include various forms of inherited and degenerative eye disorders such as X-linked congenital nystagmus, blue cone monochromacy, complete and incomplete achromatopsia, and Leber congenital amaurosis. In most of these diagnostic groups, electroretinography (ERG) is fundamental for differential diagnosis, whereas differential diagnosis with respect to the exclusively cutaneous form of albinism is only possible by genetic testing.

OA1 and AIED are rare X-linked inherited diseases involving pathogenic variants of *GPR143 (OMIM gene:* 300808*; OMIM disease: 300500) and* CACNA1F *(OMIM gene: 300110; OMIM disease:* 300600*),* respectively.

Oculocutaneous albinism is a heterogeneous group of rare autosomal recessive inherited disorders involving pathogenic variants of *TYR* (OMIM gene: 606933; OMIM disease: 203100), *TYR* (OMIM gene: 606933; OMIM disease: 606952), OCA2 (OMIM gene: 601409; OMIM disease: 203200), *TYRP1* (OMIM gene: 115501; OMIM disease: 203290), *SLC45A2* (OMIM gene: 606202; OMIM disease: 606574), *SLC24A5* (OMIM gene: 608902; OMIM disease: 113750) and *C10orf11* (OMIM gene: 614537; OMIM disease: 615179) (1-5). (Retrieved from OMIM.org). Pathogenic variants may include over 100 causative sequence variations (missense, nonsense, splice-site, small insertions and deletions). Partial or whole gene deletions/duplications are also commonly reported (6).

Aims of test

- To determine the gene defect responsible for the pathology
- To confirm the clinical diagnosis of the disease
- To determine carrier status for the disease

Test characteristics

Expert centers/ Published guidelines

This test is listed in the Orphanet database, offered by about 24 accredited medical genetic laboratories in the EU, and in the GTR database, offered by about 12 accredited medical genetic laboratories in the US.

The guideline for clinical use of this test is described in "Gene reviews"(1,3-5).

Test strategy

A multi-gene NGS panel is used for the detection of nucleotide variations in coding exons and flanking introns in the *GPR143*, CACNA1F, *TYR*, OCA2, *TYRP1*, *SLC45A2*, *SLC24A5* and *C10orf11* genes. Potentially causative variants and regions low coverage are Sanger-sequenced. MLPA is used for detection of duplications and deletions in *GPR143*, CACNA1F, *TYR*, OCA2 and *SLC45A2* (2). Sanger sequencing is also used for family segregation studies. The tests identify variations in known causative genes in patients suspected to have ocular albinism and oculocutaneous albinism. To perform molecular diagnosis, a single sample of biological material is normally sufficient. This may be 1 ml blood in a sterile tube with 0.5 ml K3EDTA, or 1 ml saliva in a sterile tube with 0.5 ml ethanol 95%. Sampling rarely has to be repeated. Gene-disease associations and the interpretation of genetic variants are rapidly developing fields. It is therefore possible that the genes mentioned in this note may change as new scientific data is acquired. It is also possible that genetic variants today defined as of "unknown or uncertain significance" may acquire clinical importance.

Genetic test results

Positive

Identification of pathogenic variants in *GPR143*, CACNA1F, *TYR*, OCA2, *TYRP1*, *SLC45A2*, *SLC24A5* and *C10orf11* confirms the clinical diagnosis and is an indication for family studies. A pathogenic variant is known to be causative for a given genetic disorder based on previous reports or predicted to be causative based on the loss of protein function or expected significant damage to protein or protein/protein interactions. In this way it is possible to obtain a molecular diagnosis in new/other subjects, establish the risk of recurrence in family members and plan preventive and/or therapeutic measures.

Inconclusive

Detection of a variant of unknown or uncertain significance: a new variation and/or without any evident pathogenic significance or with insufficient or significant conflicting evidence to indicate it is likely benign or likely pathogenic for a given genetic disorder. In these cases, it is advisable to extend testing to the patient's relatives in order to assess variant segregation and clarify its contribution. In some cases it could be necessary to perform further examinations/tests or to do a clinical reassessment of pathological signs.

Negative

The absence of variations in the genomic regions investigated does not exclude a clinical diagnosis but suggests the possibility of:

- sequence variations in gene regions not investigated by this test, such as regulatory regions (5' and 3' UTR) and deep intronic regions;
- variations in other genes not investigated by the present test;
- alterations that cannot be identified by sequencing, such as large rearrangements that cause loss (deletion) or gain (duplication) of extended gene fragments.

Unexpected

Unexpected results may come out from the test, for example information regarding consanguinity; absence of family correlation or the possibility of developing genetically based diseases.

Risk for progeny

Autosomal recessive transmission needs that both healthy carrier parents transmit their disease variant to his/her children. In this case, the probability of having an affected boy or girl is therefore 25%.

The gene has X-linked recessive transmission. Affected males only transmit the disease variant to their daughters. The probability that a female carrier transmits the pathogenic variant to her offspring is 50% in any pregnancy independently of the sex of the conceived. Females who inherit the pathogenic variant will be carriers and usually unaffected. Males who inherit the pathogenic variant will be affected.

Limits of the test

The test is limited by current scientific knowledge regarding the genes and disease.

Analytical sensitivity (proportion of positive tests when the genotype is truly present) and analytical specificity (proportion of negative tests when the genotype is not present)

NGS: Analytical sensitivity: >99% (with a minimum coverage of 10X); Analytical specificity: 99.99%.

SANGER: Analytical sensitivity: >99.99%; Analytical specificity: 99.99%.

MLPA: Analytical sensitivity: >99.99%; Analytical specificity: 99.99%.

Clinical sensitivity (proportion of positive tests if the disease is present) and clinical specificity (proportion of negative tests if the disease is not present)

Clinical sensitivity: variations in genes associated with ocular albinism and oculocutaneous albinism are not constant and vary from >75% for OCA1A to 50% for other individuals who show a degree of pigmentation (2).

Clinical specificity: is estimated at approximately 99.99% to ocular albinism; [Author's laboratory data] (7); data not available to oculocutaneous albinism.

Prescription appropriateness

The genetic test is appropriate when:

a) the patient meets the diagnostic criteria for the disease;

b) the genetic test has diagnostic sensitivity greater than or equal to other published tests.

Clinical utility

Clinical management	Utility
Confirmation of clinical diagnosis	yes
Differential diagnosis	yes
Access to clinical trial (8)	yes
Couple risk assessment	yes

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