CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Oculocutaneous albinism

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European Journal of Human Genetics (2014) 22, doi:10.1038/ejhg.2013.307; published online 12 February 2014

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Oculocutaneous albinism, autosomal recessive albinism, OCA. Subtypes include OCA1 (OCA1A and OCA1B), OCA2, OCA3, OCA4, OCA5, OCA6 and OCA7.

1.2 OMIM# of the disease

203100 (OCA1A), 606952 (OCA1B), 203200 (OCA2), 203290 (OCA3), 606574 (OCA4), 615312 (OCA5), 113750 (OCA6) and 615179 (OCA7).

1.3 Name of the analysed genes or DNA/chromosome segments

TYR, *OCA2*, *TYRP1*, *SLC45A2*, *C10orf11* and *SLC24A5*.

1.4 OMIM# of the gene(s)

606933 (*TYR*), protein: Tyrosinase. RefSeq: NG_008748.1. Transcript: NM_000372.4

611409 (*OCA2*), protein: OCA2. RefSeq: NG_009846.1. Transcript: NM_000275.2

115501 (*TYRP1*), protein: Tyrosine related protein 1. RefSeq: NG_011705.1. Transcript: NM_000550.2

606202 (*SLC45A2*), protein: Solute carrier family 45, member 2. RefSeq: NG_011691.1. Transcript: NM_016180.3

614537 (*C10orf11*), protein: C10orf11. RefSeq: not available. Transcript: NM_032024.3

609802 (*SLC24A5*), protein: Solute carrier family 24, member 5. RefSeq: NG_011500.1. Transcript: NM_205850.2.

1.5 Mutational spectrum

TYR: intragenic mutations (missense, nonsense, splice, deletions and insertions), exon and whole gene deletions.¹ Null mutations in *TYR* cause the most severe form of albinism OCA1A, where no pigmentation of skin, hair and eyes is found. The c.1205G>A (p.Arg402Gln) variant has been subject to much debate. The variant is temperature sensitive and reduced activity at physiological temperature (37 °C) was reported. Some studies find this variant more frequently in OCA individuals with one additional *TYR* mutation than with two *TYR* mutations.^{2,3} However, other studies find the same distribution of genotypes (A/A, A/G, G/G) in OCA individuals as in a HapMap population.⁴

OCA2: intragenic mutations (missense, nonsense, splice, deletions and insertions), exon and whole gene deletions and duplications.⁵ In African populations a founder mutation (a 2.7 kb deletion in the *OCA2* gene) accounts for the high frequency.⁶

TYRP1: intragenic mutations (missense, nonsense, deletions and insertions).⁷

SLC45A2: intragenic mutations (missense, nonsense, splice, deletions and insertions), exon and whole gene deletions and duplications.⁸

C10orf11: intragenic mutations (nonsense and insertion).⁹

SLC24A5: intragenic mutations (nonsense and insertions).^{10,11}

There is no evidence for digenic inheritance. Given the genetic heterogeneity in OCA the incidental non-causative finding of heterozygous carrier state of one or more OCA genes can occur.

A public database of mutations in *TYR*, *OCA2*, *TYRP1* and *SLC45A2* can be found at <http://www.retina-international.org/sci-news/databases/disease-database/albinism/>.

1.6 Analytical methods

Genomic sequencing of coding exons and flanking intron sequences for detection of intragenic mutations. MLPA or qPCR for detection of deletions and duplications. Sequencing of *TYR* is complicated by the presence of a pseudogene harbouring sequences highly similar to exon 4 and 5 of *TYR*. Mutations in *TYR* and *OCA2* account for the majority of OCA cases, and it is reasonable to start mutational analysis with these genes. In the first year of life the clinical phenotypes of OCA1A and other types of OCA may be difficult to distinguish. Recently, array-CGH analysis showed deletions in *TYR*, *OCA2* and *SLC45A2* and complex rearrangements in *OCA2*.¹²

1.7 Analytical validation

Confirmation on an independent biological sample of the index case or an affected relative may be desirable; segregation analysis in the parents of the index case to ensure that the mutations are located in trans (on separate alleles). In cases with novel mutations family studies of both affected and non-affected can be helpful.

1.8 Estimated frequency of the disease

(Incidence at birth ('birth prevalence') or population prevalence. If known to be variable between ethnic groups, please report):

Overall frequency is estimated to	1:17.000
OCA1	1:40.000
OCA2 (including Brown OCA in Africans)	1:36.000 (Europeans)
	1:3.900–10.000 (Africans)
OCA3 (Rufous OCA)	Rare in Europeans
	1:8.500 (Africans)
OCA4	Rare in Europeans
	1:85.000 in Japanese

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Received 2 May 2013; revised 21 November 2013; accepted 12 December 2013

References for frequencies can be found in Gronskov *et al.*¹³

Mutations in *C10orf11* have been found in OCA individuals from the Faroe Islands and in an OCA individual from Lithuania.⁹ Mutations in *SLC24A5* have been found in OCA individuals from India and China.^{10,11} The 4q24 locus has been mapped in individuals from Pakistan.¹⁴ These forms of OCA have only recently been described. The prevalence of these types is thus not yet known. A recent review summarizes the findings of OCA5, OCA6 and OCA7.¹⁵

1.9 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☐	☒
C. Risk assessment in relatives	☐	☐
D. Prenatal	☒	☐

Comment:

Prenatal diagnosis may vary with national settings.

2. TEST CHARACTERISTICS

Genotype or disease		A: True positives	C: False negatives
		B: False positives	D: True negatives
		Present	Absent
Test			
Positive	A	B	Sensitivity: Specificity: Positive predictive value: Negative predictive value:
Negative	C	D	A/(A + C) D/(D + B) A/(A + B) D/(C + D)

2.1 Analytical sensitivity

(proportion of positive tests if the genotype is present)

Some individuals present with only one mutation in either *TYR* or *OCA2*; the number varies between studies, but exceeds the carrier frequency. Also, in some individuals no mutations in any of the aforementioned annotated genes are found. These findings can be due to mutations left undetected in regulatory regions or intron regions; mutations missed due to allele dropout or mutations in other genes than *TYR*, *OCA2*, *TYRP1* and *SLC45A2*. Recently, mutations in two genes (*C10orf11*⁹ and *SLC24A5*¹⁰) have been established as causes of albinism. The contribution of mutations in these genes in various populations needs to be determined. Novel mutations are evaluated as to predicted pathogenicity with appropriate tools. As for all molecular genetic investigations a non-classifiable sequence variant may sometimes be found.

2.2 Analytical specificity

(proportion of negative tests if the genotype is not present)
100%.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

For individuals with OCA1A the detection rate is 75–90%. For other OCA individuals who display a degree of pigmentation the detection rate can be as low as 50% when *TYR*, *OCA2*, *TYRP1* and *SLC45A2* are investigated, however, the detection rate varies between populations.

2.4 Clinical specificity

(proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

If two pathogenic mutations are found on separate alleles the individual will display OCA. Many polymorphisms and variants of unknown significance are present in the genes. Some influence the pigmentation and contribute to the natural variance in pigmentation.

2.5 Positive clinical predictive value

(life time risk to develop the disease if the test is positive)

The disease is thought to be fully penetrant, although expressivity varies.

2.6 Negative clinical predictive value

(Probability not to develop the disease if the test is negative)

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:

Mutations in *TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *C10orf11* and *SLC24A5* cannot explain all OCA cases and further genetic heterogeneity is expected. Furthermore, several differential diagnoses exist. Yet, as OCA is a congenital disorder, disease is evident early in life.

Index case in that family had not been tested:

This approach cannot be supported.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: the tested person is clinically affected
(To be answered if in 1.9 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☒
	Other (please describe):	

In a lightly pigmented population, such as the Northern European, it can be difficult to clinically distinguish between OCA and ocular albinism (OA), especially in young boys. OA1 (OMIM 300500) is X-linked and caused by mutations in *GPR143* (OMIM 300808). Albinism can also be part of rare syndromes such as Hermansky–Pudlak syndrome (HPS) (OMIM 203300) (mutations in nine genes, *HPS1*, *AP3B1*, *HPS3–HPS6*, *DTNBP1*, *BLOC1S3* and *BLOC1S6* are known as causative), Chediak–Higashi syndrome (CHS) (OMIM 214500) (mutations in *LYST* is a known cause) and Griscelli syndrome (OMIM 214450) (*MLPH*, *RAB27A* and *MYO5A* are known as causative). Usually hypopigmentation in these syndromes is accompanied by severe systemic pathologies including immunodeficiency, bleeding diathesis of variable severity and later organ manifestations. As symptoms of albinism are present at birth these precede other symptoms. Heightened suspicion of these severe conditions is required in patients with OCA or partial albinism. A general molecular genetic screening using high throughput methods for all known genes of hypopigmentation disorders may become the approach of choice in the near future with increasing genetic heterogeneity by the identification of underlying additional genes.

3.1.2 Describe the burden of alternative diagnostic methods to the patient

A detailed clinical and ophthalmological examination will precede molecular testing. This includes ophthalmoscopic examination and fundus photography and in some cases visual evoked potential (VEP) recording. Cooperation by the patient is mandatory for the VEP and therefore sedation may be required in young patients.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Initial suspicion will be made in paediatric wards and patients should be referred for further detailed evaluation. Clinical diagnosis can be made reliably by experienced ophthalmologists at ophthalmological departments. Symptoms and signs of systemic disease (as in HPS and CHS) should be considered and excluded.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☒
Yes	☐
	Therapy (please describe)
	Prognosis (please describe)
	Management (please describe)

3.2 Predictive setting: the tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.9 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe)

If the test result is negative (please describe)

Not applicable.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?

Not applicable.

3.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 1.9 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Not applicable.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

Not applicable.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Not applicable.

3.4 Prenatal diagnosis

(To be answered if in 1.9 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?

Yes.

Provided that two disease causing mutations are identified, and that each parent is a carrier of one mutation, prenatal diagnosis will be possible in future pregnancies.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

A specific molecular diagnosis can be helpful for prognosis, that is, as to degree of hypopigmentation and risk of visual impairment.

In families with high frequency of consanguinity, carrier diagnosis can be extended and genetic counselling improved. Prospective parents might consider genetic counselling for risk calculation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by EuroGentest2 (Unit 2: 'Genetic testing as part of health care'), a Coordination Action under FP7 (Grant Agreement Number 261469) and the European Society of Human Genetics.

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