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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: achromatopsia

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Complete or incomplete achromatopsia, rod monochromatism, rod monochromacy, complete or incomplete colour blindness, and Pingelapese blindness.

1.2 OMIM# of the disease

ACHM2 216900, ACHM3 262300, ACHM4 139340, and ACHM5 613093.

1.3 Name of the analysed genes or DNA/chromosome segments

Gene: *CNGB3*, chr. 8q21–q22.
Gene: *CNGA3*, chr. 2q11.
Gene: *GNAT2*, chr. 1p13.
Gene: *PDE6C*, chr. 10q24.

1.4 OMIM# of the gene(s)

CNGA3 [600053], protein: cyclic nucleotide-gated cation channel, α3.
CNGB3 [605080], protein: cyclic nucleotide-gated cation channel, β3.
GNAT2 [139340], protein: guanine nucleotide-binding protein, α-transducing activity polypeptide 2.
PDE6C [600827], protein: phosphodiesterase 6C, cGMP-specific, cone α-prime.

1.5 Mutational spectrum

Missense mutations, nonsense mutations, splice mutations, and small deletions and insertions.

1.6 Analytical methods

Genomic sequencing of coding exons and flanking intronic sequences. dHPLC and HRM may also apply.

1.7 Analytical validation

Confirmation of mutation in an independent biological sample of the index case and/or in an affected subject; segregation analysis in the parents of the index patient.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

1:30 000–1:50 000.[1]

1.9 If applicable, prevalence in the ethnic group of investigated person

Unknown.

1.10 Diagnostic setting

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

Comment:
As penetrance is 100% and since disease is present from birth, the test is not used for predictive testing.

2. TEST CHARACTERISTICS

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

2.1 Analytical sensitivity (proportion of positive tests if the genotype is present)

Nearly 100%.

2.2 Analytical specificity (proportion of negative tests if the genotype is not present)

Above 95%.
Assuming a complete screening of all genes.
Variants of unknown significance might be re-classified as deleterious *a posteriori*.

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.

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It is 75–90%[2–4] depending on population – there is evidence for further genetic heterogeneity.

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.

Above 95%.

2.5 Positive clinical predictive value
(**life-time risk to develop the disease if the test is positive**)
Although clinical expression can vary (complete and incomplete achromatopsia, rarely cone dystrophy and macular degeneration), the condition is expected to be 100% penetrant.

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:

Although mutations in CNGA3, CNGB3, GNAT2, and PDE6C are responsible for the majority of ACHM cases, further genetic heterogeneity is expected. Yet as achromatopsia is a congenital disorder, disease is evident early.

Index case in that family had not been tested:

This approach cannot be supported.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: the tested person is clinically affected
(To be answered if in 1.10 '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):	☒	Standard clinical ophthalmological evaluation and testing Electrophysiological examination (Electroretinography) Psychophysical testings (colour vision, dark adaptometry)

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Initial clinical and electrophysiological investigations are always necessary before molecular genetic analysis is prescribed. However, clinical investigations are sometimes incomplete in young children (approximate visual acuity, ERG recorded with skin electrodes and/or handheld non-Ganzfeld stimulator). Complete clinical investigations and ERG recording may require general anaesthesia.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Clinical and electrophysiological testing in young children may require anaesthesia and hospitalisation.

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

No.	☐	
Yes.	☒	
	Therapy (please describe)	There is no specific therapy available, although gene therapy in relevant models is progressing.
	Prognosis (please describe)	The genetic diagnosis essentially contributes to the classification of cases with similar clinical features. This is the basis for prognostic statements. Achromatopsia is expected to be a stationary disease, yet in rare cases progression and macular degeneration have been observed.[2,5]
	Management (please describe)	Genetic testing has considerable consequence on clinical management as the condition is usually stationary. Consequently, learning Braille and education in specialized schools is not required, as opposed to cases with either Leber congenital amaurosis or certain cases of cone dystrophy. Both these latter conditions are differential diagnoses of achromatopsia, in which patients become progressively blind. Patients should be informed about the possibilities of filtering glasses or contact lenses (red tinted or brown) to reduce photophobia and improve contrast sensitivity. Low-vision aids include high-powered magnifiers for reading.

3.2 Predictive setting: the tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.10 '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):

Genetic analysis can guide potential parents concerned about the risk of having affected children and will help in management of the disease in affected patients (see 3.1.4).

If the test result is negative (please describe):

This will lead to reconsider the clinical diagnosis. The diagnosis of achromatopsia will therefore be either confirmed, suggesting a rare genetic form (genetic heterogeneity) for which the causative gene remains unknown, or excluded and redirected to for example, blue cone monochromacy.

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)?
Regular ophthalmological follow-up examination.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes, autosomal recessive inheritance if genotype defined.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
No.

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

3.4 Prenatal diagnosis
(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?
Genetic counselling is mandatory. Prenatal diagnosis is increasingly asked by at-risk couples and the use of prenatal diagnostic test varies with national/ethical customs.

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)?

Correct diagnosis has implications on education and professional career choices (low vision).

Parents are given accurate information on the cause of the disease, progression and recurrence risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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