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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Axenfeld–Rieger syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

The general term Axenfeld–Rieger syndrome is used as an umbrella term for the conditions Axenfeld anomaly, Axenfeld syndrome, Rieger anomaly and Rieger syndrome.

1.2 OMIM of the disease

602482, 601631, 180500.

1.3 Name of the analysed genes or DNA/chromosome segments

FOXC1, *PITX2*.

1.4 OMIM of the gene(s)

601542 (pituitary homeobox transcription factor-2, *PITX2*); 601090 (forkhead box transcription factor C1, *FOXC1*).

1.5 Mutational spectrum

The *PITX2* gene: intragenic mutations, microscopic and submicroscopic deletions, chromosome rearrangements such as translocations.

The *FOXC1* gene: intragenic mutations, microscopic and submicroscopic deletions and duplications.[1,2]

1.6 Analytical methods

Genomic sequencing of the coding exons for detection of intragenic mutations. FISH, MLPA, Q-PCR or high-resolution microarrays for detection of submicroscopic deletions/duplications. Conventional cytogenetic analysis for detection of chromosome rearrangements.[1,2]

1.7 Analytical validation

Confirmation of mutation in an independent biological sample of the index case or an affected relative. In case of large deletions/duplications, confirmation with a second technique.

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

1:200.000.[3]

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

Not applicable.

1.10 Diagnostic setting

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

2. TEST CHARACTERISTICS

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

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

Depends on analytical method:

Intragenic mutations in *FOXC1* and *PITX2* (sequencing): nearly 100%.[1,2]

Microscopic or submicroscopic deletions or duplications encompassing the *FOXC1* and *PITX2* genes (MLPA): nearly 100%.[2] No comprehensive data available for FISH, Q-PCR, microarrays.

Microscopic or submicroscopic deletions or duplications outside the *FOXC1* and *PITX2* genes (microarrays, conventional cytogenetics): no comprehensive data available.

Chromosomal rearrangements (conventional cytogenetics): no comprehensive data available.

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

See section 'Analytical sensitivity'.

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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.

The reported clinical sensitivity rates largely depend on the inclusion criteria of cohorts tested, and screening protocols, mainly confined to Sanger sequencing of coding regions of the *FOXC1* and *PITX2* genes, thereby missing gene deletions, duplications and chromosome rearrangements.[1]

In patients who show both ocular and systemic manifestations, the sensitivity is up to 35% in a first study.[4] In a recent study applying a screening protocol consisting of sequencing and copy number screening (MLPA), the clinical sensitivity is up to 40%.[2]

In general, this might be an underestimation as most screening protocols only apply sequencing. In addition, clinical sensitivity rates might be far higher than 40% in more selected patient populations. However, no comprehensive clinical data are available.

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%. *FOXC1* mutations have been rarely reported in aniridia,[5] primary congenital glaucoma[6] and Peters' anomaly.[7,8]

2.5 Positive clinical predictive value
(life-time risk to develop the disease if the test is positive)
Although clinical expressivity varies, ARS is thought to be fully 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:
Unclear. Although mutations in *FOXC1* and *PITX2* are responsible for the majority of typical ARS cases, genetic heterogeneity has been reported. There is at least one more locus associated with ARS, but the gene involved is yet to be identified.[9]

Index case in that family had not been tested:
Unclear.

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)	

3.1.2 Describe the burden of alternative diagnostic methods to the patient
A detailed clinical examination will precede molecular genetic testing in most cases. As ARS is a congenital disorder, the patient may be very young raising problems in ophthalmological examinations and may necessitate application of general anaesthesia.

3.1.3 How is the cost-effectiveness of alternative diagnostic methods to be judged?
Clinical diagnosis of ARS can be routinely performed by residential ophthalmologists in older patients. Diagnosis in children might involve anaesthesia and therefore requires hospitalization. Observation of systemic changes, such as dental anomalies, redundant periumbilical skin and mild craniofacial dysmorphism, might rather direct towards *PITX2* as the causal gene.

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

No	☐	
Yes	☒	
	Therapy (please describe)	
	Prognosis (please describe)	Systemic anomalies (mild craniofacial dysmorphism, dental anomalies, redundant periumbilical skin and so on) besides ocular abnormalities are often associated with *PITX2* mutations.
	Management (please describe)	Frequent interdisciplinary follow-up (ophthalmologist, paediatrician, dentist, orthodontist) if a genetic diagnosis has been made in early childhood.

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 prospective parents concerned about the risk of having affected children. Although genotype–phenotype correlations are difficult to make in ARS, knowledge of the genetic cause might facilitate disease management in terms of interdisciplinary follow-up.

If the test result is **negative** (please describe):
Follow-up dispensable, if a familial mutation can be excluded.

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)?
Interdisciplinary follow-up considering all possible ocular and systemic symptoms of ARS.

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?
Only if other affected relatives are tested as well.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
This is not a recommended approach.

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)

Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation in the family has been identified.

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?
Yes.

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)

Prospective parents might consider genetic counselling for risk calculation. Clinical management might be facilitated as genotype–phenotype correlations can be made to some extent.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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