Clinical utility gene card for WAGR syndrome

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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: WAGR syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

WAGR syndrome; Wilms tumor, aniridia, genitourinary anomalies and mental retardation syndrome; chromosome 11p13 deletion syndrome.

1.2 OMIM# of the disease

194072.

1.3 Name of the analyzed genes or DNA/chromosome segments

WT1, PAX6.

1.4 OMIM# of the gene(s)

607102 *(WT1)*, 607108 *(PAX6).*

1.5 Mutational spectrum

Breakpoints differ in individual cases, but the minimum deletion involves both *PAX6* and *WT1*, which are ~700 kb apart in the distal half of band 11p13.

1.6 Analytical methods

FISH, array CGH, MLPA, high-resolution cytogenetics may identify larger deletions and chromosomal rearrangements. Expert advice should be sought if an etiology is not identified.[1,2]

1.7 Analytical validation

Analyze known non-deleted and deleted cases in parallel as controls to show that reagents used for FISH, array CGH and MLPA are working well.

1.8 Estimated frequency of the disease

(Incidence at birth ('birth prevalence') or population prevalence):

Rare, with only a few hundred cases reported.

1.9 If applicable, prevalence in the ethnic group of the 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 negatives D: True negatives
	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)

Essentially 100% with appropriate FISH probes, MLPA or array CGH. Cytogenetic analysis is less sensitive and, if normal, one of the above methods must be used. Very rarely mosaic sub-microscopic deletions will reduce the analytical sensitivity of MLPA and array CGH but not the use of appropriate FISH probes.

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

Essentially 100% with appropriate FISH probes, MLPA or array CGH.

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.

Nearly 100% if sporadic aniridia and Wilms tumor, male genitourinary abnormalities or significant nephropathy is present. If sporadic aniridia alone is present (eg, a newborn female), then 10–30% have WAGR syndrome (data limited by small numbers).[3]

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. It is worthwhile pointing out that other 11p13 deletions that include *WT1* but do not involve *PAX6* can occur. Therefore, for patients without aniridia but for whom *WT1* deletion is suspected

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(eg, a patient with Wilms tumor, genitourinary abnormalities and cognitive impairment), genetic testing for 11p13 deletion is recommended.

Essentially 100% if aniridia is not present.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)

Essentially 100% for aniridia (which is congenital), other features due to *WT1* gene deletion are variable. In all, 42.5–77% have been shown to develop Wilms tumor depending on the deletion size. End-stage renal disease develops in 47% of WAGR patients with Wilms tumor by 20 years after diagnosis and also occurs in those without WT. Individuals with XY genotype and intra-abdominal gonads have a high risk of gonadoblastoma and should undergo gonadectomy. XY individuals with descended testes must undergo regular examination for testicular tumors. Individuals with XX genotype have also developed gonadoblastoma and should be screened by imaging.[4,5]

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:

Essentially 100% if no aniridia.

Index case in that family had not been tested:

Essentially 100% if no aniridia.

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.
Not applicable.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Not applicable.

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

No	☐	
Yes	☒	
	Therapy (please describe)	Ultrasound screening for Wilms tumor allows for early diagnosis and therefore decreased treatment toxicity. See other management below.
	Prognosis (please describe)	Good for Wilms tumor treatment. Individuals with end-stage renal disease may require transplantation. Cognitive deficits are lifelong. Visual acuity is reduced significantly in most patients and further ocular complications may be severe, including cataract, glaucoma, and corneal opacification/vascularization.
	Management (please describe)	Depends on specific manifestations. Aniridia should be managed by an expert ophthalmologist. Supportive measures for the visually impaired are required and ophthalmologists will monitor to identify and treat later-onset corneal disease, glaucoma and cataract. Early identification of nephropathy allows referral for expert management. Wilms tumor may require surgery, chemotherapy and occasionally radiotherapy. Gonadoblastoma requires surgical treatment (see 2.5 above). Obesity and its complications are common. Special education and behavioral management (including interventions for autism) are frequently required for cognitive impairment.[6,7]

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)

See 3.1.4 for management if test result is positive.

If the test result is **negative** (please describe)

If test result is negative, eg, a sporadic aniridia patient does not have a WT1 deletion, then monitoring for genitourinary complications, including Wilms tumor, is not warranted.

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)?
An individual with sporadic aniridia should undergo screening for Wilms tumor by renal ultrasound and urinalysis every 3 months until 6 years and daily caretaker abdominal examination. Renal disease should be screened for by annual blood pressure and urinalysis for proteinuria beginning in early adolescence and through adulthood. There is also risk for gonadoblastoma (see 2.5 above).[8]

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

There are rare instances of familial recurrence of WAGR syndrome due to inherited chromosomal rearrangements or submicroscopic WAGR deletions. Parents and all at-risk relatives (determined by pedigree analysis) should be evaluated for a WAGR-associated chromosomal rearrangement or sub-microscopic deletion.[9,10]

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

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

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes, for prenatal diagnosis in the event of a familial chromosomal rearrangement or inherited sub-microscopic deletion.

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

An individual with WAGR syndrome has ~50% chance of passing on the deleted chromosome to the offspring. Prenatal testing for the parental deletion or chromosome rearrangement should be offered.

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

Yes. In addition to the value of understanding the cause and recurrence risk of the disorder, many families have benefited greatly from joining the International WAGR Syndrome Association support group (http://www.wagr.org) and meeting other families. This support group has been instrumental in gathering data about the natural history of WAGR syndrome and stimulating research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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