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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Mowat–Wilson syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

1. Mowat–Wilson.[1–7]
2. Hirschsprung disease–mental retardation syndrome.[1,6,8–11]
3. Microcephaly, mental retardation and distinct facial features, with or without Hirschsprung disease.[1,6,10–12]

1.2 OMIM# of the disease

235730.[6]

1.3 Name of the analysed genes or DNA/chromosome segments

ZEB-2; chromosome 2q21–q23.[3,6–9,13]

1.4 OMIM# of the gene(s)

605802.[6]

1.5 Mutational spectrum

1. Large chromosome deletions, including the entire *ZEB-2* gene and additional contiguous genes.[2–7,13–25]
2. Exon deletions. Both, complete or partial gene, deletions account for about 20% of cases.[2–7,13–26]
3. Loss-of-function gene mutations (truncating mutations, nonsense mutations, frameshift mutations) are detected in about 70% of cases.[2–7,13–25,27]
4. Missense variants are rare.[2–7,14,28,29]
5. A small proportion of patients (about 10%), who present with a clinical phenotype, highly consistent with MWS, have a negative genetic test. Atypical mutations can be considered in these cases, and the diagnosis can be confirmed clinically.[2–7]

1.6 Analytical methods

1. Multiplex ligation-dependent probe amplification (MLPA).[2,3,5,7,13]
2. Direct gene sequencing of *ZEB-2* gene between amino acid positions 1 and 1214 (Gene Bank Accession Number NM_014795.2), by analysing exons and flanking intron sequences.[2,3,5,7,13,14]

1.7 Analytical validation

(1) If a partial or complete gene deletion is detected by MLPA by several probes or by array-CGH, with reliably sufficient probes for the given array and analysis setting, no alternative validation is necessary. If the parents are analysed for mosaicism or balanced rearrangements by FISH, confirmation of FISH with molecular probes containing ZEB-2 should be performed in the index patient. If MLPA or array-CGH results are indicated by an unreliable number of probes, alternative validation should be performed by FISH, qPCR, further MLPA probes or by higher density array-CGH.

In cases with deletions, detectable by FISH, parents are investigated by FISH to look for a balanced chromosome insertion, encompassing ZEB-2 or a mosaic deletion.

If a single exon deletion is detected by a MLPA probe, the respective exon should be sequenced to exclude a mutation or polymorphism at the probe-binding site. If the latter was excluded, confirmation can be performed by real-time PCR on genomic DNA or by phenotypic analysis, in particular by facial features evaluation.[2,3,5,7,13,14]

(2) Gene mutations are validated by (a) bidirectional direct sequencing, (b) evaluation of the expected functional impairment of the altered protein and (c) exclusion of the presumed mutation in healthy parents.

1.8 Estimated frequency of the disease

Estimated birth incidence is 1 in 50 000–100 000.[2–7]

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

Unknown.[2–7]

1.10 Diagnostic setting

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

Comment: Non-mosaic ZEB-2 mutations are fully penetrant. Parents of an affected child could be tested for a somatic mosaicism, but the detection rate is expected to be low. Healthy relatives (parents excluded) are not at risk for being mosaic for the mutation; thus, they are not eligible for the genetic test exploring a potential mosaicism. Recurrence risk in patient's siblings is about 2%, based on documented cases of gonadal mosaicism.[30,31] Accordingly, prenatal diagnosis is offered in subsequent pregnancies of the patient's parents only.

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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)
In our experience, sensitivity of the genetic test is above 90%.[2–7]

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Analytical specificity in our experience is about 100%.[2–7]

2.3 Clinical sensitivity
The reliability of a clinical diagnosis is dependent on the experience of the physician and diagnosis might be difficult in some patients, even for experts on the disorder. Moreover, a reliable prenatal diagnosis can only be offered if the underlying genetic mutation in the index case is known.[2–7,25]

2.4 Clinical specificity
Almost 100% of cases in which the clinical phenotype is not consistent with MWS have a negative genetic test.[25]

2.5 Positive clinical predictive value
Gene mutations associated with Mowat–Wilson syndrome are 100% fully penetrant with variable phenotype. For these reasons, a positive genetic test never has a predictive value.[2–7]

2.6 Negative clinical predictive value
If the index case in the family had been tested with positive results, practically 100% of relatives without symptoms will not develop the disease.[2–7]

If the index case in the family had not been tested, a low risk to develop the disease in presence of a negative genetic test is limited to siblings of the patient.[30,31]

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: the tested person is clinically affected
At a very early age, differential diagnosis could consider Pitt–Hopkins syndrome, or some chromosome deletion syndromes with an overlapping phenotype, although a detailed phenotype analysis is highly predictive for MW. Array-CGH is recommended if the genetic test for MWS is negative.[1–7]

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.
The reliability of a clinical diagnosis is dependent on the experience of the physician and diagnosis might be difficult in some patients, even for experts on the disorder. Moreover, a reliable prenatal diagnosis can only be offered if the underlying genetic mutation in the index case is known.

If the genetic test for MWS is negative, alternative diagnostic methods are strongly suggested by the constellation of clinical manifestations. In considering a slightly overlapping phenotype with either Pitt–Hopkins syndrome or different microdeletion/microduplication syndromes, additional genetic tests could include:

1. MLPA/gene sequencing of *TCF4* for differential diagnosis with Pitt–Hopkins syndrome.
2. Array-CGH for differential diagnosis with chromosome del/dup syndromes mimicking in part the MWS phenotype.[2–7]

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
No data available.

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

No	☐	
Yes	☒	
	Therapy (please describe)	Symptomatic
	Prognosis (please describe)	Variable, being because of mental retardation and congenital anomalies.
	Management (please describe)	Surveillance for Hirschsprung disease, constipation, CHD, epilepsy, urogenital anomalies, scoliosis and congenital eye anomalies. Rehabilitation therapy is important, because many patients have receptive language skills and communicate successfully using alternative methods, like sign language.
	Management	

There is no specific treatment for MWS, as the neurological defect and also other malformations, resulting from the mutation, occur in the early stage of embryonal development. The frequent presence of serious congenital malformations require clinical investigation with intervention of neonatologists, paediatricians and several specialists. Congenital heart disease and Hirschsprung disease require early surgery during the first days or months of life. Constipation may persist after HSCR surgery. Seizures are common and require standard therapy. Genitourinary anomalies such as hypospadias, cryptorchidism, bifid scrotum, vesicoureteral reflux and hydronephrosis might be present in the first years of life and may require surgery. Eye problems are frequent and require a specialized help. Musculoskeletal anomalies, such as pes planus, calcaneovalgus deformity and scoliosis, may occur, so orthopaedic evaluation is appropriate. Audiology is recommended, although deafness is rarely present. All advised vaccinations are recommended. A periodic follow-up for the different clinical problems should be carried out regularly. Psychomotor development is retarded in all patients, and speech is almost always severely limited (typically from 0 to 100 words). Rehabilitation, including physical therapy, psychomotor and speech therapy, should be started as soon as possible. Augmented communication (signing, picture exchange, Makaton) is recommended.[1–41]

3.3 Genetic risk assessment in family members of a diseased person

A slight increase of the recurrence risk in family members is limited to siblings of the diseased person, caused by a potential gonadal mosaicism in one parent. Genetic prenatal diagnosis is offered in these cases.[30,31]

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

If the diseased person had a positive genetic test, family members with a negative test, in particular parents and patient's siblings tested prenatally, are not at risk for being affected.

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

With exception of the patient's parents, each healthy family member is not eligible for the genetic test.

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

No.

3.4 Prenatal diagnosis

Prenatal diagnosis is offered to siblings of the affected person, limited to the specific gene mutation detected in the diseased person.[2–7,30,31]

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

Yes, limited to siblings.[2–7,30,31]

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

A positive genetic test is greatly useful for family members. It restricts a low recurrence risk to subsequent siblings of the diseased person. On the contrary, each healthy family member has not an increased risk of having affected children, with the only exclusion of the healthy parents of the affected person because of a possible gonadal or somatic mosaicism.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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