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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Wolf–Hirschhorn (4p-) syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Wolf–Hirschhorn syndrome (4p- syndrome, monosomy 4p. Includes Pitt–Rogers–Danks syndrome).

1.2 OMIM# of the disease
194190.

1.3 Name of the analysed genes or DNA/chromosome segments
4p16.3.

1.4 OMIM# of the gene(s)
WHSC1 602952.
LETM1 604407.

1.5 Mutational spectrum
Not applicable.

1.6 Analytical methods
Not applicable.

1.7 Analytical validation
Not applicable.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
1:50 000 births with a 2:1 female/male ratio.

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	☒	☐

Comment:

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)
The technology utilized for testing should be designed to detect deletion of the critical region for WHS, which includes at least portions of the *LETM1* and *WHSC1* genes. Therefore, either fluorescence *in situ* hybridization (FISH) with a probe covering this region or genomic microarray with coverage of this region should yield greater than 99% clinical sensitivity. Standard chromosome studies may not identify microdeletions of this region and would be predicated to have only a 50–60% clinical and analytical sensitivity. Also, as unbalanced translocations are frequently identified in this syndrome, genomic microarray or FISH with the subtelomeric probes should be considered to identify any concurrent duplications with the 4p deletion.

As the phenotype and genotype are interrelated for the diagnosis, then the analytical and clinical sensitivity and specificity should all be greater than 99% if the appropriate testing technology is utilized.

2.2 Analytical specificity (proportion of negative tests if the genotype is not present)
$>99\%$.

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.
$>99\%$.

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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.
>99%.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
Not applicable.

2.6 Negative clinical predictive value
(probability of not developing 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:
Not applicable.
Index case in that family had not been tested:
Not applicable.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically ffected
(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)	Rehabilitation therapy with enrolment in a personalised rehabilitation program, covering motor aspects, cognition, communication, and socialisation. Early intervention followed by appropriate school placement are recommended. Anti-epileptic therapy: in the authors' experience, the atypical absences are well controlled by valproic acid, alone or associated with ethosuccimide, whereas carbamazepine may worsen the electroclinical picture. Other medical therapies as requested by the clinical condition. Having a diagnosis prevents the performance of unnecessary testing on the common diagnostic odyssey.
Prognosis (please describe)	Depends on the presence or absence of major malformations, and type and severity of seizures and their management. Larger deletions can be associated with the risk of major malformations and a more severe phenotype.
Management (please describe)	Physical, neurological and functional evaluations (cognitive, language, and motor development and social skills) are mandatory. Proper waking/sleeping video-EEG-polygraphic studies in infancy and childhood to detect type of seizures (particularly atypical absences that may be clinically missed in such children) are highly recommended. Evaluation for feeding problems and gastroesophageal reflux as needed. Search for skeletal anomalies, with referral for orthopaedic and physical therapy evaluation, is essential. Heart examination, ophthalmology consultation; otolaryngological evaluation and audiological screening should be performed in each individual at diagnosis, even in the absence of overt anomalies. Renal function testing and renal ultrasonography are mandatory, to detect structural renal anomalies and/or vesicoureteral reflux. Planning for transition to adulthood should begin in adolescence.

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)
Not applicable.

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test result is positive (please describe):
Not applicable.

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 1.10 'C' was marked)
Risk to family members depends on the mechanism of origin of the deletion. If the deletion is a simple deletion and the parents are phenotypically normal, they are very unlikely to carry a deletion. If the deletion is part of an unbalanced translocation, then there is a significant risk (greater than 50%) that either parent would carry a balanced version of the translocation.

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes, as it will likely determine the aetiology of the disease and the recurrence risk.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
It will likely result in more genetic testing within other family members if an unbalanced translocation is identified.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
For certain types of genetic results (eg, unbalanced translocation) this would increase the likelihood of an abnormal genetic test in either parent

3.4 Prenatal diagnosis

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

Prenatal testing is available to families in which one parent is known to be a carrier of a chromosome rearrangement.

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

Not necessarily, parental testing should be done first to determine recurrence risk.[1–21]

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)

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