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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Williams–Beuren Syndrome [7q11.23]

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Williams–Beuren syndrome, WBS; Williams syndrome, WS.

1.2 OMIM# of the disease

#194050.

1.3 Name of the analysed genes or DNA/chromosome segments

7q11.23, 27 unique sequence genes including: *NSUN5*, *TRIM50*, *FKBP6*, *FZD9*, *BAZ1B*, *BCL7B*, *TBL2*, *MLXIPL*, *VPS37D*, *DNAJC30*, *WBSCR22*, *STX1A*, *ABHD11*, *CLDN3*, *CLDN4*, *WBSCR27*, *WBSCR28*, *ELN*, *LIMK1*, *EIF4H*, *LAT2*, *RCF2*, *CLIP2*, *GTF2IRD1*, *GTF21*, *NCF1* and *GTF2IRD2* within the Williams critical region. *NCF1* and *GTF2IRD2* are variably deleted in WBS.

microRNAs: MIR4284, MIR590; long intergenic non-protein coding RNA LINC00035.

1.4 OMIM# of the gene(s)

ELN, **130160*; *GTF2IRD1*, **604318*; *NCF1*, **608512*.

1.5 Mutational spectrum

Deletion 7q11.23 of variable size:

~1.55 Mb (~95% of cases) to ~1.84 Mb (~5% of cases).[1,2]

Karyotype of a WBS deletion according to HGVS: chr7.hg19:g.(?_72,644,269)_(74,142,297_?)del.

Rarely, smaller or larger atypical deletions are identified.[3]

Clinical phenotype of the 1.55 and 1.84 Mb deletion are similar but features of the atypical deletions vary depending on the size of deletion and the genes involved.

In non-WBS patients, point mutations within the elastin gene cause similar vascular and connective tissue features to WBS.[4]

For genomic copy number variations and genotype/phenotype correlations, see: https://decipher.sanger.ac.uk/syndrome/3;

http://www.ncbi.nlm.nih.gov/clinvar/;

https://www.iscaconsortium.org/;

http://www.ncbi.nlm.nih.gov/projects/dbvar/ISCA/index.shtml;

http://dgv.tcag.ca/dgv/app/home

All findings should be shared through these databases.

1.6 Analytical methods

FISH,[5] MLPA, qPCR, Microsatellite analysis, chromosomal microarray analysis (CMA), with FISH, MLPA and CMA most commonly employed.

1.7 Analytical validation

Parallel analysis of positive and negative controls, depending on analytical method.

1.8 Estimated frequency of the disease

(Incidence at birth ('birth prevalence') or population prevalence. If known to be variable between ethnic groups, please report):

1:7500–1:10 000.[6]

1.9 Diagnostic setting

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

Comment:

The vast majority of WBS cases arise due to a sporadic genetic event. It is, therefore, not meaningful to analyse relatives without clinical phenotype. In 25–30% of the cases, a parent carries an inversion polymorphism[7] which, however, cannot be detected by the usual WBS analytical methods (FISH, MLPA, CMA).

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positive B: False positive	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)

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2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
Nearly 100%, depending on analytical method.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Nearly 100%, depending on analytical method.

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.

No known phenocopies of WBS have been reported to date. For individuals with classic features of WBS, clinical sensitivity is high. For individuals with fewer features, especially absence of cardiovascular disease, clinical sensitivity is lower.

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.

For individuals without features of WBS, specificity is nearly 100%. However, as clinical manifestations are highly variable, clinical specificity for individuals at the mild end of the spectrum (eg, without cardiovascular abnormalities) may be low depending on the quality of the clinical assessment.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
100%, with variable expression of the phenotype.

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:
Nearly 100%.
Index case in that family had not been tested:
Cannot be assessed without testing the index case.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: 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 clinical diagnosis can be highly probable in individuals with classic features of WBS[8] (eg, supravalvular aortic stenosis, characteristic facial features/neurocognitive profile, hypercalcemia, etc); confirmation using genetic testing is, however, always needed. In individuals with a less classic presentation, the paucity of clinical features may not support clinical suspicion of the disorder so that genetic testing both suggests and confirms the diagnosis. Evaluation would include, but is not restricted to a cardiology examination with echocardiogram and EKG, laboratory evaluation for calcium abnormalities, clinical examination by a clinician experienced with WBS and neurocognitive assessment.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
As the clinical diagnosis of WBS can be suggested for only a subset of individuals, this is not a cost-effective diagnostic method.

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

No	☐	
Yes	☒	
	Therapy (please describe)	Depending on clinical symptoms: specific measures of educational and/or vocational support, surgical correction of existing cardiovascular defects, psycho-pharmacological and anti-hypertensive medication, therapy of hypercalcemia by low-calcium diet, ophthalmological treatment of hyperopia and strabismus, ear protection for avoiding exposure to high volume noise, physical therapy.
	Prognosis (please describe)	Prognosis is influenced by distribution and extent of clinical problems (eg, severity of cardiovascular disease) and therapeutic measures. Lifelong medical monitoring is needed. Formal mortality data do not yet exist.
	Management (please describe)	Regular cardiologic evaluation, measurement of blood pressure, endocrinological surveillance (for calcium, glucose and thyroid abnormalities), ultrasound examination of bladder and kidneys, determination of serum and urine calcium and of urine creatinine, vision and hearing, developmental diagnostic testing and corresponding therapeutic actions. Also see the Guidelines of the American Academy of Pediatrics for Patients with Williams–Beuren syndrome[9] and Multisystem study of 20 older adults with Williams syndrome.[10]

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) Yes, see 3.1.4.

If the test result is negative (please describe) Not specifically. The lifestyle will be, however, influenced by the underlying disease.

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)?
In the absence of genetic testing, individuals with classic features of WBS should be managed according to guidelines for health maintenance in WBS.[9,10] Such guidelines include staying active and preventing obesity (eg, to minimize risk of developing diabetes and osteopenia).

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, if no other family members are similarly affected. In the unlikely event that family members are similarly affected, genetic test results from them are needed to resolve the situation in the family.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes, if no other family members are similarly affected.

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 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. Doing this test may lessen the diagnostic odyssey that potentially includes more invasive testing. Diagnosis enables family members and caregivers to have realistic expectations about their child's growth, health and development. Diagnosis allows optimization of specific therapies (diet, preventive examinations, supportive measures such as assistance in school and therapeutic services).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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