CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Ehlers–Danlos syndrome types I–VII

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Ehlers–Danlos syndrome types I/II, III, IV, VI, VIIA/B, and VIIC; or according to the Villefranche nosology: classical type (EDS I and II), hypermobile type (EDS III), vascular type (EDS IV), kyphoscoliotic type (EDS VI), arthrochalasic types (EDS VIIA and EDS VIIB), dermatosparactic type (EDS VIIC), unspecified types, and varia.^{1,2}

1.2 OMIM# of the disease

130000, 130010, 130020, 130050, 225400, 130060, 225410, and 612350.

1.3 Name of the analysed genes or DNA/chromosome segments

COL5A1, COL5A2, TNXB, COL3A1, PLOD1, ZNF469, COL1A1, COL1A2, ADAMTS2, and SLC39A13.

1.4 OMIM# of the gene(s)

120215, 120190, 600985, 120180, 153454, 229200, 120150, 120160, 604539, and 608735.

1.5 Mutational spectrum

Missense mutations, nonsense mutations, splice mutations, insertions, deletions, genomic rearrangements.

Presently, more than 270 mutations are known for all 10 genes together. The majority of them (about 170) are in the COL3A1 gene.

1.6 Analytical methods

Genomic sequencing of coding regions, eventually multiple ligation-dependent analysis (MLPA) for detection of genomic rearrangements and large deletions.

1.7 Analytical validation

Direct sequencing of both DNA strands; verification of sequence and MLPA results with second DNA extraction or second PCR or hybridisation (MLPA).

1.8 Estimated frequency of the disease

(incidence at birth ('birth prevalence') or population prevalence)

Prevalence about 1:5000–1:100 000 depending on EDS type.^{1,2}

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

Not applicable for most EDS types except for EDS type VIA which is most prevalent in the Middle East.

1.10 Diagnostic setting

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

Comment:

Prenatal diagnosis is rarely requested for Ehlers–Danlos syndrome.

2. TEST CHARACTERISTICS

Genotype or disease		A: true positives	C: false negative
		B: false positives	D: true negative
	Present	Absent	
Test			
Pos.	A	B	Sensitivity: A/(A+C)
			Specificity: D/(D+B)
Neg.	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)

Nearly 100%, if a deletion/duplication diagnostic test has been made for genes with the possibility of a rearrangement.

2.2 Analytical specificity

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

Nearly 100%.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependant on variable factors such as age or family history. In such cases a general statement should be given, even if only a quantification can be made case by case.

It is 50% for EDS type I/II (COL5A1 and COL5A2 genes) which is genetically heterogeneous with additional, still unknown gene loci.

It is 95% for EDS type IV (COL3A1 gene), EDS types VIIA and VIIB (COL1A1 and COL1A genes, respectively) as well as EDS type VIA (PLOD1 gene).

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Not known in EDS type VIB (*ZNF469* gene) and EDS type VIIC (*ADAMTS2* gene).

Highly dependant on fulfilment of the clinical criteria as well as of the biochemical and ultrastructural dermal findings documented in the Villefranche nosology.^{1,2}

2.4 Clinical specificity

(proportion of negative tests if the disease is not present)

The clinical specificity can be dependant on variable factors such as age or family history. In such cases a general statement should be given, even if only a quantification can be made case by case.

Nearly 100%.

2.5 Positive clinical predictive value

(lifetime risk to develop the disease if the test is positive)

100% penetrance with, depending on EDS type, variable clinical expressivity.

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:

5%–95%, corresponding to the detection rate in the genes of the different EDS types. This question arises quite often in EDS type IV if the index patient has died already.

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) Ultrastructural analysis of dermis

Biochemically Collagen electrophoresis (electrophoretic mobility of collagen chains from cell culture), analysis of urinary pyridinolines (abnormal ratio of lysyl pyridinoline (LP) and hydroxylysyl pyridinoline (HP) cross-links)

EDS type	Clinical	Ultrastructural analysis	Collagen electrophoresis	Urinary LP/HP
I/II	++	++	(+)	—
III	+	—	—	—
IV	++	(+)	+	—
VIA	+++	—	++	+++
VIIA	+++	++	+	—
VIIIB	++	+	+++	—
VIIC	+++	+++	+++	—

Because EDS comprises a group of different entities, each with highly variable clinical expressivity, a primary molecular genetic analysis for differential diagnostics is indicated in only exceptional cases with classical clinical features and known associated mutations. Histological/ultrastructural and biochemical/biophysical investigations should be performed initially, if ever possible. The significance of different collagen diagnostic approaches in different EDS types is illustrated in the table.

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Initial clinical, biochemical, and ultrastructural investigations complement the molecular genetic analysis that, however, cannot replace the former.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Unknown.

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

No ☐

Yes ☒

Therapy (please describe) Specific supportive therapy of joints and musculature in patients with EDS type I/II, III, VI. Scrutiny for eventually developing aneurysms, special caution during surgery, scrutiny of pregnancy in EDS type IV. Early surgical-orthopaedic measures in EDS types VIIA/B.

Prognosis (please describe) The genetic diagnosis essentially contributes to classification of cases with indistinct clinical, biochemical, or ultrastructural features. This is the basis for prognostic statements.

Management (please describe) Frequent interdisciplinary clinical follow-up, depending on EDS type.

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?

Yes.

If the test result is positive (please describe):

Frequent interdisciplinary follow-up, depending on EDS type.

Specific therapeutic support of joints and musculature. Avoidance of sports with physical contacts in EDS types with predominant involvement of joints.

Scrutiny for eventually developing aneurysms, special caution during surgery, tight follow-up of pregnancy, emergency card in EDS types with vascular involvement. Wound protection in EDS types with involvement of skin and a tendency to haematomas.

If the test result is negative (please describe):

Follow-up dispensable, if a familial mutation can be excluded.

3.2.2 Which option 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 EDS types if the index patient had not been analysed genetically.

Regular and specific follow-up if the index patient's EDS type is known.

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.

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

No.

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 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)

Yes. In many cases, the genetic diagnostics contribute substantially to classification of EDS type if clinical, biochemical, and ultrastructural

findings are not fully informative. Recognising clinical symptoms as belonging to the Ehlers–Danlos syndrome and classifying them as a given EDS type is prerequisite for clinical prognosis, specific therapy, and official acceptance as severe handicap. In children with a tendency to haematomas, a suspicion of child abuse may be alleviated through the correct diagnosis of EDS type. The correct diagnosis will end a diagnostic odyssey and the unwarranted suspicion of hypochondria, and the appropriate patient organisation can now be approached.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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