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CLINICAL UTILITY GENE CARD

Clinical Utility Gene Card for: Fibrodysplasia ossificans progressiva

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Fibrodysplasia ossificans progressiva (FOP), Myositis ossificans progressiva.

1.2 OMIM# of the disease

135100.

1.3 Name of the analysed genes or DNA/chromosome segments

Activin A type I receptor/activin-like kinase 2 (ACVR1/ALK2) a bone morphogenetic protein (BMP) type I receptor, chromosome 2q23-24.[1–3]

1.4 OMIM# of the gene(s)

102576.

1.5 Mutational spectrum

The spectrum described in this paragraph is based on RefSeq NM_001105.4.

All patients have heterozygous ACVR1 missense mutations in conserved amino acids. This disease-causing variant is a *de novo* mutation and therefore referred to as a mutation.

Patients with classic clinical features of FOP (great toe malformations and progressive heterotopic ossification) have previously been found to carry the same heterozygous mutation (c.617G>A; p.(Arg206His)) in the *ACVR1* gene leading to an over-activation of the BMP signalling pathway. Only recently a new heterozygous *ACVR1* mutation at codon 207 (c.619C>G, p.(Gln207Glu)) located in a codon adjacent to the c.617G>A, p.(Arg206His) of the ACVR1 was reported in two FOP patients with the classical phenotype.[4] Among patients with FOP-like heterotopic ossification and/or toe malformation, there are patients with clinical features unusual for FOP. These atypical FOP patients form two classes: FOP-plus (classic defining features of FOP plus one or more atypical features, predominantly associated with the classical p.(Arg206His) mutation) and FOP variants (major variations in one or both of the two classic defining features of FOP, associated with non-Arg206His mutations within the ACVR1 receptor). Novel *ACVR1* mutations occur mainly in FOP variants and some cases of FOP plus.[4–6] A public list of disease causing variants is not available yet.

1.6 Analytical methods

DNA sequence analysis of protein-coding exons and splice junctions.[2]

1.7 Analytical validation

When a new mutation is found, functional testing will be necessary, like a BMP reporter assay.

1.8 Estimated frequency of the disease (incidence disease at birth ('birth prevalence') or population prevalence)

1:2 000 000.[5]

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

No ethical, racial, gender or geographic prediliction.[5]

1.10 Diagnostic setting:

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

Comment: ad A: To differentiate from other forms of heterotopic ossification (different forms of myositis ossificans (MO), progressive osseous heteroplasia (POH) or other forms that might be confused with atypical FOP).[6–8] There are at least three other forms of MO of

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which the pathology is largely unknown, including MO Circumscripta, characterized by dystrophic calcification generally following severe trauma leading to heterotopic ossifications of a single intramuscular connective tissue, MO pseudo-malignant, which is limited to soft tissue and is not associated to any trauma, and a MO associated with paraplegia, closed head injury or severe trauma (non-hereditary heterotopic ossification).[7,9] POH is characterized by progressive ossification of cutaneous, subcutaneous, and deep connective tissues and caused by an inactivation of GNAS in most cases.[10] In early stages misdiagnosis, aggressive fibromatosis or sarcoma may be suspected.

Comment: ad C: Risk assessment in first generation relatives, including brothers and sisters, could be considered due to a so-called 'variant FOP' presenting with normal great toes and late-onset heterotopic ossification[11] or when one of the parents has a germ line mosaicism.[12]

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)
100%.[2]

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
100%.[2,13]

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.
100%.[2]

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.
100%.[2]

2.5 Positive clinical predictive value
(life-time risk to develop the disease if the test is positive)
100%, although we are aware of few rare cases of FOP with negligible progression.

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative).
If the index case in the family has been tested positive for a causative mutation:
100%.
If the index case in the family has not been tested:
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The tested person is clinically affected (To be answered if in 1.10 'A' was marked)
100% in the classical mutation, although there is a clinical variability/expressivity.[1]

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):	

A diagnosis based on clinical findings (malformed great toes in association with either soft tissue swelling or heterotopic ossification in characteristic anatomic patterns could be made by very experienced doctors,[14] but in approximately 87% there is a long delay before awareness or before the appropriate diagnosis has been established.[11,15]

3.1.2 Describe the burden of alternative diagnostic methods to the patient
No alternative affirmative methods are available.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
No alternative affirmative methods are available.
On the basis of the clinical and radiologic findings the diagnosis of FOP can be highly suspected, even prior to heterotopic ossifications. Characteristic toe malformations and cervical spine fusions may be diagnosed by X-ray. However, because FOP is infrequently seen by most clinicians and onset of progressive heterotopic ossification may be variable in the first decade of life, clinical misdiagnosis is common.[14,15]

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

No	☐	
Yes	☒	
	Therapy (please describe)	None at the moment, but in the future some drugs might have different effects on the classical mutation or the other ACVR1 mutations. Current treatment options are only palliative and symptom-modifying. Prevention of soft tissue injury and protection against the influenza virus remain a hallmark of FOP management.[16]
	Prognosis (please describe)	The prognosis varies largely and depends on clinical course and severity. FOP is not only an extremely disabling disease but also a condition of shortened lifespan. The median age of the time of death is 40 years. The most common cause of death is cardiorespiratory failure (54%) from thoracic insufficiency

	syndrome, followed by pneumonia (15%), and complications of falls due to head injuries (11%).[17–19]
Management (please describe)	Paediatricians should be aware of the early diagnostic features of fibrodysplasia ossificans progressiva, even before the appearance of heterotopic ossification. This awareness should prompt early genetic consultation and testing and the institution of assiduous precautions to prevent iatrogenic harm.[14,15] Intramuscular injections, biopsies, and surgical procedures as well as injuries with soft tissue trauma can also result in exacerbation and should be avoided.

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 prognosis.

If the test result is **negative** (please describe): based on current knowledge no risk.

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)?
The lifestyle and prevention will be the same in patients with a clinical diagnosis, but with or without a genetic diagnosis.

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?
Yes (if negative).

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)

Prenatal diagnosis should only be done for FOP patients (they have 50% risk to transmit the disease) or for parents of FOP patients, if they expect new children (risk of mosaicism in an unaffected parent).[12]

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes, although rare, up to three successive generations of transmissions of FOP have been described.[20]

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)

NA.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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