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CLINICAL UTILITY GENE CARD

CUGC for hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP)

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP; hereditary sclerosing poikiloderma with tendon, muscle and pulmonary involvement).

1.2 OMIM# of the disease

#615704.

1.3 Name of the analysed genes or DNA/chromosome segments

FAM111B.

1.4 OMIM# of the gene(s)

*615584.

1.5 Mutational spectrum

POIKTMP is an exceedingly rare syndromic form of autosomal dominant poikiloderma associated with tendon contractures, myopathy and pulmonary fibrosis. Its mode of inheritance and its main clinical features were inferred from observations made in a two-generation multiplex South African family,[1] the study of which contributed to the identification of causative variants in *FAM111B*.[2] Three *FAM111B* (NM_198947.3) missense variants, c.1861T>G (p.(Tyr621Asp)), c.1879A>G (p.Arg627Gly), and c.1883G>A (p.(Ser628Asn)), and one in-frame deletion, c.1262_1264delAAG (p.(Lys421del)), have been reported so far in individuals with POIKTMP.[2,3] All four variants are located in the region encoding the putative trypsin-like cysteine/serine peptidase domain of the protein. All published variants will be available soon in the public LOVD database under construction that is dedicated to *FAM111*B (www.LOVD.nl/FAM111B).

1.6 Analytical methods

Single nucleotide variants and indels are detected by bi-directional sequencing of the two coding exons of *FAM111B* and their flanking intronic sequences, using either Sanger sequencing of polymerase chain reaction products or high-throughput sequencing (HTS) targeting the regions of interest with a recommended minimal read depth of 30× and preferably of at least 100×. Whole-exome[2,3] or even whole-genome sequencing may also be used for variant detection, provided the sequence quality meets diagnostic requirements. Larger deletions or duplications involving at least one exon can be found by analysis of HTS data or they can be screened by a quantitative method such as quantitative multiplex PCR of short fluorescent fragments or multiplex ligation-dependent probe amplification.

1.7 Analytical validation

Any suspected new variant found in a patient is submitted to an internal validation through analysis of variants found in previous patients; it is also compared with public variant databases (eg, dbSNP (http://www.ncbi.nlm.nih.gov/SNP/), Exome Variant Server (http://evs.gs.washington.edu/niehsExome/), 1000 genomes (http://www.1000genomes.org/), or ExAC Browser (http://exac.broadinstitute.org/), LOVD (www.LOVD.nl/FAM111B)) and its potential pathogenic effect is searched through prediction by bioinformatic tools. Single nucleotide variants or copy number variations identified through HTS in the proband have to be confirmed respectively by Sanger sequencing of both strands or by a quantitative method, preferably in an independent venous blood sample. Finally, a segregation analysis is performed by testing samples from the proband's relatives; in multiplex families, the presence of the variant is expected in all affected members, whereas, in sporadic cases, the *de novo* nature of the variant would rather be confirmed by its absence in the proband' parents.

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):

POIKTMP is an extremely rare disorder. Its prevalence is therefore unknown. To date, only six families have been officially reported,[2,3] even though a few other cases reported in literature may be suspected of having the same disease.[4,5]

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All the POIKTMP cases reported to date have been found in individuals first diagnosed with Rothmund–Thomson syndrome (RTS), which is already a very rare form of poikiloderma suspected to be under-diagnosed precisely because of its rarity.[6] The same assumption of under-diagnosis might therefore be made for POIKTMP.

1.9 Diagnostic setting

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

Comment: POIKTMP is a congenital multisystemic disorder due to *FAM111B* dominant variants. It occurs in early childhood, where it manifests by poikiloderma, hypotrichosis, and hypohidrosis. Multiple contractures follow later on, involving more especially triceps surae muscle contractures. Myopathy can develop progressively from infancy to adulthood, and progressive pulmonary fibrosis is noted at adulthood, sometimes accompanied by other features like growth retardation, liver impairment, exocrine pancreatic insufficiency, and cataract.[2,3] Muscle MRI and histological examination are helpful for diagnosis, as they show atrophy and extensive fatty infiltration of the muscle regardless of age. Microscopic analyses of skin biopsies reveal a scleroderma-like aspect of the lesions with fibrosis and alterations of the elastic network.[2,7]

The identification of a molecular anomaly in *FAM111B* gives definitive proof of POIKTMP and enables its distinction from other types of hereditary poikiloderma, such as RTS (MIM#268400), hereditary sclerosing poikiloderma of Weary (MIM#173700), poikiloderma with neutropenia (PN; MIM#604173) or Kindler syndrome (MIM#173650).[6,8–11] Above all, the main differential diagnosis of POIKTMP is RTS as all patients were initially misdiagnosed with RTS in childhood. These two entities share indeed common characteristics, such as early-onset poikiloderma, ectodermal dysplasia features, palmoplantar hyperkeratotic lesions, growth delay.[10] Cataract observed in some of the POIKTMP cases is also characteristic of individuals negative for *RECQL4*-mutations presenting the sub-type I of RTS.[10] It is noteworthy that POIKTMP may also be misdiagnosed with other rare genodermatoses such as acrodermatitis enteropathica, more especially in the early infancy (Mercier *et al.*, in review).

Predictive testing—it is not applicable in most cases, because early POIKTMP symptoms and signs occurs in the early infancy. The value of the genetic test would therefore rather be considered diagnostic than predictive. *Prenatal*—according to our current knowledge based on a few cases only, prenatal testing would be proposed, given the unfavourable evolution of the disease and the poor prognosis inherent to the absence of any efficient treatment.

2. TEST CHARACTERISTICS

			A: True positives	C: False negative
	Genotype or disease		B: False positives	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)

Theoretically 100% of variants are localised within exons or flanking intronic sequences.

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

100%.

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.

The number of cases tested to date is still insufficient to make a precise estimation. Yet, when the three symptoms of poikiloderma/ectodermal dysplasia—typically developed in the first months of life-, tendon contractures and myopathy with fatty infiltration are present at the same time, we expect clinical sensitivity to be about 100%. The absence of one of these symptoms, and more especially the poikiloderma, makes the positivity of the testing far less likely. Failure to identify a heterozygous variant in the *FAM111B* gene may be explained by its location in unexplored regions (introns, 5'- and 3'-untranslated regions, or upstream regulating regions).

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%.

2.5 Positive clinical predictive value
(life time risk to develop the disease if the test is positive)

Referring to our relatively limited experience because of the rarity of the disease, the risk to develop POIKTMP is 100% if a pathogenic variant of *FAM111B* has been detected. On the other hand, it seems still premature to predict the severity of the disease, which is variable between the families. We suspect that symptoms are less severe or occur later in multiplex families where a *FAM111B* variant has been transmitted across generations.

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:

When a pathogenic *FAM111B* variant has been identified in the index case, the negative predictive value is 100%.

Index case in that family had not been tested:

Given the early onset of the disease, the negative predictive value is 100% in asymptomatic adults. In infant, the predictive value depends on the age of the individual. The interpretation of the test may be different in toddlers, as we cannot exclude the possibility of later onset of symptoms than the one inferred from the small series of patients known to date. Considering the clinical similarities with RTS, we assume that like for this other form of poikiloderma, a negative result in an asymptomatic infant under 2-year-old should

be taken with much caution.[6] Indeed, even though most POIKTMP variants can be expected to lie within *FAM111B* coding region, the existence of pathogenic variants located in intronic, untranslated, promoting or regulating regions cannot be definitively ruled out. Above 2-year-old, the negative predictive value raise to almost 100% in a non-affected child.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The tested person is clinically affected
(To be answered if in 1.9 '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):	Histological analysis of muscle and skin biopsies

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Diagnosis can be established by the concomitant presence of characteristic clinical features and histological findings signs. The presence of congenital poikiloderma, hypotrichosis and hypohidrosis, together with multiple contractures, in particular triceps surae muscle contractures, is suggestive of POIKTMP. Later on, these symptoms can be accompanied by a diffuse progressive muscular weakness. Muscle atrophy and fatty infiltration can be assessed by MRI and/or muscle biopsy. In adults, a progressive pulmonary fibrosis may be noted, along with other less consistent features like growth retardation, liver impairment, exocrine pancreatic insufficiency, and cataract. Histological analyses of muscle biopsies reveal a partial loss of muscle tissue associated with a characteristic extensive fibrofatty tissue infiltration. Microscopy of the skin shows a scleroderma-like aspect with fibrosis and alterations of the elastic network.

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)	There is currently no treatment available for POIKTMP, as the precise function of *FAM111B* remains unknown. As for Rothmund–Thomson, pulsed dye laser photocoagulation might however be used to treat facial telangiectasia.
	Prognosis (please describe)	Most of the patients identified to date are still young and current knowledge about the evolution of the disease is based on the seven adult patients reported to date (living affected individuals are aged from 3 to 40 years, including 5, ones aged from 23 to 40 years, two affected members from the multiplex South African family died at 30- and 56-years of age, respectively). Prognosis would rather be quite poor, more especially because of a progressive impairment of lung function by pulmonary fibrosis which, in the South African family, was observed as early as during the second decade of life and caused a premature death in two individuals. Moreover, the myopathic component of POIKTMP is also progressive and could induce a severe gait disturbance or even a loss of ambulation. Contrary to other types of hereditary poikiloderma, including RTS, PN and Kindler syndrome, where an increased risk of cancer is observed[9,10,12], no tumour of any kind was observed in any of the patients; given the relative youth of most patients with POIKTMP reported to date, this does not rule out any cancer-predisposing effect of *FAM111B* deleterious variants later in life.
	Management (please describe)	The result of the genetic test will necessarily influence disease management. Given the progression and the multisystemic involvement expected in POIKTMP, patient care should be received from a multidisciplinary team composed notably of dermatologists for poikiloderma follow-up, myologists, orthopaedic surgeons and physiatrists for myopathy follow-up, pulmonologists for evaluation of restrictive pulmonary syndrome and geneticists for genetic counselling. Regular examinations are recommended, as well as the systematic use of sunscreens to prevent sunburns favoured by their poikiloderma-induced photosensitivity.

3.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.9 '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)	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 1.9 'C' was marked)

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

Yes, if a causative variant has been identified, which allows to propose prenatal diagnosis in at risk pregnancies. Except a two-generation multiplex family in which the variant was transmitted, all affected individuals identified to date had a *de novo FAM111B* variant. The risk of recurrence in siblings is therefore very low, even if probably a bit higher than in general population when considering the possibility of germline mosaicism.

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

As almost all variants have been found *de novo*, incomplete penetrance cannot be definitively ruled out for every *FAM111B* variant. Thus, in an affected patient's family, the risk of having a variant is extremely low in asymptomatic relatives aged two years and over, but a test might be considered in younger children.

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

Theoretically, yes, but it is actually very unlikely, since, owing to our current knowledge on POIKTMP, it would rather be a very early-onset disease.

3.4 Prenatal diagnosis

(To be answered if in 1.9 'D' was marked).

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

Yes, provided the causative *FAM111B* variant has been identified.

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)

Results of *FAM111B* genetic testing may have no immediate medical consequence, because in most cases the patient has been diagnosed for a poikiloderma, which is treated accordingly. Yet, the identification of a causative variant has much impact on disease-management and long-term follow-up. As a matter of fact, the most immediate impact of the genetic test result is likely psychological, as it allows the patient and his/her family to name the disease, which may already have a positive effect on their morale. As regards the family, genetic diagnosis opens the path to genetic counselling, offering notably the possibility of prenatal testing for pregnancies to come.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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