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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Familial adenomatous polyposis (FAP) and attenuated FAP (AFAP)

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Familial adenomatous polyposis (FAP), adenomatous polyposis coli (APC), familial polyposis coli (FPC), attenuated adenomatous polyposis coli (AAPC); phenotypic variants: Gardner syndrome, Turcot syndrome.

1.2 OMIM# of the disease

175100.

1.3 Name of the analysed genes or DNA/chromosome segments

APC (5q22).

1.4 OMIM# of the gene(s)

611731.

1.5 Clinical diagnostic criteria

According to polyp number and age at onset, the phenotype is usually classified as classical (typical) FAP or attenuated FAP (AFAP).[1,2] However, it should be kept in mind that the formation of colorectal adenomas is a biological continuum without any clearly delineated features. In particular, AFAP is not well defined as a disease entity. Widely used clinical criteria are the following:

Classical FAP: more than 100 colorectal adenomas; early onset (polyp formation during second decade of life, gastrointestinal symptoms during third decade of life).

AFAP: a milder course of the colorectal disease with a delay in onset of adenomatosis and colorectal cancer of 10–25 years compared with classical FAP; <100 colorectal adenomas at 25 years of age or older and/or a late-onset of disease (≥ 45 years of age) irrespective of polyp number.

1.6 Mutational spectrum

Mutation detection rate: 80–93% in classical FAP.[3,4]

De novo events: 10–40%.[3,5,6]

Genomic rearrangements: large deletions <10–15% in classical FAP; large duplications are very rare. Broad spectrum of point mutations, >90% are truncating (nonsense, del/ins and splice sites).

Hot spots: codon 1309 (about 11%, 5-bp del), codon 1061 (7%, 5-bp del), codon 213 (3%, C>T transition), codon 1068 (2%, 4-bp del).

The vast majority of mutations are located in the 5′ half of the gene, mutations 3′ to codon 1700 are rare (1%).

Post-zygotic mosaicism in 10–15% of *de novo* events.[7]

1.7 Analytical methods

Stepwise analyses

1. Clinical selection: all patients with the clinical diagnosis of an attenuated or classical colorectal adenomatous polyposis (at least 10 synchronous adenomatous polyps). In AFAP and pedigrees consistent with an autosomal recessive mode of inheritance, screening for MUTYH mutations should be performed prior or after APC screening. In case of few colorectal adenomas tumour screening for microsatellite instability and immunohistochemical staining should be considered (see 3.1, differential diagnoses). A careful clinical examination including histology is a prerequisite for performing cost-effective mutation analysis.
2. Germline mutation analysis:
   - Direct sequencing of all 15 coding exons.
   - In some centres screening of exons 3 to 15J (codon 1700) in all patients and exons 1, 2, 15J-W (codons 1700-ter) in case of extra-digestive manifestation only.
   - In some centres pre-screening of the gene by protein truncation test (PTT) of exon 15 (genomic level) or of the whole gene (RNA level) and/or by DHPLC, SSCP, CSGE.
   - Screening of the whole gene including promoter region for large genomic anomalies (deletions and duplications) by MLPA or QMPSF.
   - Linkage analysis and functional tests for interpretation of unclassified APC variants.
   - Future perspective: sequencing of the coding regions or the whole gene by next generation sequencing technologies.

1.8 Analytical validation

The results of molecular genetic diagnostics can, as a rule, be definitely evaluated.

Confirmation of mutation in an independent biological sample of the index case or an affected relative to exclude mistake of samples.

In case of deletion/duplication of *one* exon, confirmation with a second technique/kit based on different primers.

Difficulties in interpreting somatic mosaicism.

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

Prevalence at birth: 0%.

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Prevalence in general population: 2.3–3.2/100 000.[5,8]
Incidence: about 1:8000–10 000.[5,8]
Prevalence in colorectal cancer patients: <1%.

1.10 If applicable, prevalence in the ethnic group of investigated person
Not applicable.

1.11 Diagnostic setting

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

Comment: Prenatal diagnosis and pre-implantation genetic diagnosis (PGD) are rarely requested. An explanation might be that FAP is a relatively late-manifesting and treatable disease. Another reason might be that some FAP patients at childbearing age are not informed about reproductive options. In general, prenatal diagnosis and PGD should be performed according to each countries law, but only after appropriate, non-directive genetic counselling.

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)
Almost 100% (by direct sequencing).

Can be distinctly less in mosaic cases, depending on degree of mosaic and analysed tissue. In these cases, pre-screening methods appear to be more sensitive than direct sequencing.[7]

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

Dependent not only on age and family history, but also on colorectal phenotype (number of adenomas).

Classic FAP: about 80–90%.

AFAP: about 20–30%.

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.

Almost 100%.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
Penetrance in proven mutation carriers is almost complete. Because of the high clinical variability, clinically mildly affected persons may not be diagnosed or will be deceased for other reasons during pre-symptomatic (sub-clinical) stage of the disease.

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 and a pathogenic germline mutation was identified: almost 100%.

Index case in that family had not been tested: very unusual situation. This is not a meaningful approach and should therefore be avoided.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: the tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

The most relevant differential diagnosis of an attenuated/late-onset FAP is the MUTYH-associated polyposis (see CUGC MAP[9]). In case of a low number of (synchronous) adenomas hereditary non-polyposis colorectal cancer (Lynch syndrome) (see CUGC Lynch syndrome[10]) should be considered.

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	☐

In sporadic attenuated cases, differentiating FAP and MUTYH-associated polyposis (MAP) can be achieved by molecular genetic analysis only.

3.1.2 Describe the burden of alternative diagnostic methods to the patient.
The diagnosis 'colorectal polyposis' in a clinically affected person can only be established by colonoscopy and subsequent histological examination of removed polyps, which is a burdensome examination. Alternative burdenless diagnostic methods are ocular fundus examination and mandibular radiography, but these methods are helpful in only a few patients.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Very cost-effective and time-saving but not useful for predictive testing.

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

No	☐	
Yes	☒	
	Therapy (please describe)	In general, the management of FAP is based on the clinical course of the disease and not on the results of mutation screening. However, in some cases the position of the mutation might be considered for the type and time of colorectal surgery (attenuated form and important risk of desmoids tumors).
	Prognosis (please describe)	
	Management (please describe)	If the position of the mutation supports the clinical diagnosis of an attenuated disease, it affects the procedure of endoscopic surveillance (age at beginning and periodicity).[11]

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*

Yes: increase compliance to participate in specific preventive check-ups (in particular colonoscopic surveillance program). In some cases the position of the mutation might affect the procedure and time of surgical management (although the decision of colectomy should be based mainly on the clinical phenotype). In some cases family planning and choice of profession.

If the test result is *negative*

Yes. Release from intensified screening program. Psychological relief.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done?
Same as for proven mutation carriers:

Close-meshed early diagnosis programs, colectomy when polyps have been detected. Yet, these measures are taken in vain in half of the persons at risk (non-carriers).

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 the mutation is known in the family).

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

By securing the primary cause of the disease, extended diagnostic investigations in other symptomatic relatives can be avoided.

By exclusion of a carrier status in predictive diagnostics, superfluous preventive investigations can be avoided and psychological relief is obtained.

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?
Technically yes, after considering specific rules and ethical aspects.

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?

Support for family life organisation.

Efficiency of subsequent clinical management.

For many patients prove of diagnosis is a value itself – irrespective of a medical benefit – because the disease and its cause can clearly be named. When a genetic cause is verified, an assumption of 'own fault' as cause of disease (exogenous poisons, 'wrong conduct') often can be lapsed with relief.

The main benefits of genetic diagnostics in FAP are the differentiation from MAP (which example do not have a risk for developing desmoid tumours), a precise recurrence risk calculation for close relatives, and relief of non-carriers during predictive testing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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