Genetic Testing for Heritable Mutations in the APC Gene

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Consent for cancer genetic testing

Link to pre test counselling information

Target Population

- a person with 10 or more adenomatous colorectal polyps (cumulative count) **before 30yrs** of age
- a person with 20 or more adenomatous colorectal polyps (cumulative count) **regardless of age**
- patients 10-60yrs age with an intra-abdominal or abdominal wall desmoid
- a known pathogenic APC mutation is identified in a relative

Genetic testing is essential for good clinical care of individuals who are suspected of having a heritable mutation in this gene.

Investigations which should be considered before germline genetic testing

Check if relatives are on the **hereditary cancer register** (HCR)

The results of the following investigations may significantly influence the likelihood of detecting a heritable mutation in the APC gene.

- the cumulative number of adenomatous colorectal polyps
- detection of a somatic mutation in the CTNNB1 (beta-catenin) gene in a desmoid tumour (available evidence indicates somatic CTNNB1 and germline APC mutations are mutually exclusive)
- where multiple colorectal adenomas are documented in an isolated family member (i.e. apparently sporadic adenomatous polyposis) consider testing for homozygous recessive mutations in MUTYH
- where multiple colorectal adenomas are documented in 2 or more full-sibs in the absence of a family history consider testing for homozygous recessive mutations in MUTYH

Factors which influence the pre-test probability of a heritable mutation

The frequency of APC germline mutations in unselected individuals with CRC is <0.2%[1].

Over 70% of patients with a typical FAP phenotype have an APC mutation identified.

Approximately 25% of patients with an atypical FAP phenotype have an APC mutation identified.

About 15-20% of APC mutations arise de novo.

Factor	Probability of detecting a heritable mutation
More than 100 adenomatous polyps	60 - 93%[2,3]
Between 20 and 100 adenomatous polyps	~30%[4]
Extra colonic manifestations (when colorectal polyp status is unknown) ■ multiple osteomas of the skull or mandible ■ intra-abdominal or abdominal wall desmoid tumour diagnosed at 10-60 yrs age ■ desmoid tumour (any location) diagnosed <10 yrs age ■ multiple and/or bilateral CHRPE at any age	 unknown 7.5[5] -16%[6] unknown unknown

Patient has a first or second degree relative with documented pathogenic mutation	25 - 50%
Abbreviation: CHRPE - congenital hypertrophy of the retinal pigment epithelium	

Circumstances in which testing is not indicated

Evidence of mismatch repair deficiency within colorectal carcinoma or polyp.

Colorectal polyposis due to non-adenomatous polyps (e.g. serrated, hamartomatous, juvenile etc).

Colorectal polyposis due to polyps of mixed histology (e.g. significant numbers of both serrated and adenomatous polyps).

Person with isolated, single CHRPE (congenital hypertrophy of the retinal pigment epithelium) after review by an opthalmologist.

Predictive testing should never be ordered when only an unclassified variant or polymorphism has been identified in a family.

Diagnostic testing

Methodology	Proportion of identified mutations detected by method %	Laboratories	Access
Direct Sequencing	up to 85%	**RCPA catalogue of genetic tests and laboratories**	Publicly funded testing depending on eligibility
Sequencing and MLPA	up to 93%[3]		

Interpretation of mutation testing results

Result	Reference databases	Considerations and advice
Mutation search		
Pathogenic mutation	**InSiGHT**	**Link to risk management of FAP guidelines**
Variant	Clinical Molecular Genetics Society Best Practice Guidelines - website currently unavailable	Review periodically Identify other genes for which a mutation search could be considered (Link to our management guidelines when available)
Inconclusive		Identify other genes for which a mutation search could be considered [Link to inconclusive management guidelines when available]
Predictive testing		
Family mutation identified		**Link to risk management of FAP guidelines**
Family mutation not found		Screening tailored based on a revised risk estimate

Counselling

Link to pre test counselling information

Websites

Centre for Genetics Education NSW Health

Link to Hereditary Cancer Registry

InSight

EuroGene Test

Clinical Molecular Genetics Society Best Practice Guidelines - website currently unavailable

Further References

For further references used to develop this protocol please see the History tab

References

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3. **Legard A., Rouleau E. and Ferrari A. Germline APC mutation spectrum derived from 863 genomic variations identified through a 15-year medical genetics service to french patients with FAP. 2010. J Med Genet. Online Aug 2010.**
4. **Nielsen, M., F. J. Hes, F. M. Nagengast, M. M. Weiss, E. M. Mathus-Vliegen, H. Morreau, M. H. Breuning, J. T. Wijnen, C. M. Tops and H. F. Vasen. 2007. "Germline mutations in APC and MUTYH are responsible for the majority of families with attenuated familial adenomatous polyposis." Clin Genet 71(5):427-433**
5. **Nieuwenhuis, M. H., M. Casparie, L. M. Mathus-Vliegen, O. M. Dekkers, P. C. Hogendoorn and H. F. Vasen. 2011. "A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses." Int J Cancer 129(1):256-261.**
6. **Fallen, T., M. Wilson, B. Morlan and N. M. Lindor. 2006. "Desmoid tumors -- a characterization of patients seen at Mayo Clinic 1976-1999." Fam Cancer 5(2):191-194.**

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