Familial Adenomatous Polyposis (FAP) – OMIM +175100

INTRODUCTION
Classic FAP is a colon cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps develop. Age related penetrance is seen in FAP mutation carriers however, by age 35 years ~95% of individuals with \( APC \) mutations have polyps; without surgery there is a very high lifetime risk of developing colon cancer. Extracolonic manifestations are variably present and include polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumours, desmoid tumours, and associated cancers.

Attenuated FAP (AFAP) is still associated with an increased risk for colon cancer, but there are fewer colonic polyps (average of 30) which are usually more proximally located. Age of onset is generally later than for Classic FAP. FAP & AFAP are both autosomal dominant conditions caused by mutations of the \( APC \) tumour suppressor gene (5q21).

Approximately 20% of affected individuals have no family history of FAP/AFAP and present as new cases due to de novo \( APC \) mutations. The majority of mutations in the \( APC \) gene cause premature termination of translation, either through a frameshift or nonsense mutation. The different presentations of FAP can be associated with mutations in particular parts of the \( APC \) gene (e.g. AFAP tend to be associated with mutations at either end of the gene and in exon 9) but this correlation is not absolute.

TESTING
- Diagnostic: Clinically affected patients
- Presymptomatic: Individuals at risk of developing FAP/AFAP. Clinically unaffected relatives of individuals in whom an \( APC \) pathogenic mutation has been identified.
- Prenatal: Prenatal testing is not usually requested.

REFERRALS
- All diagnostic & presymptomatic referrals must be referred through Clinical Genetics departments.
- Requests for presymptomatic testing should either be discussed with the laboratory in advance or be accompanied by details regarding the known pathogenic mutation in the family
- Prenatal requests are only accepted from Clinical Genetics and must be discussed with the laboratory and arranged in advance.

STRATEGY & TECHNICAL INFORMATION
- Mutation screening of diagnostic referrals is undertaken by fluorescent sequencing of the entire coding region and intron/exon boundaries of the \( APC \) gene (exons 1-15) and dosage analysis by MLPA (multiplex ligation-dependant probe amplification) for large scale rearrangements of the \( APC \) gene.
- When a pathogenic mutation has been identified in an individual, subsequent testing of family members (presymptomatic or diagnostic confirmation) involves testing for the familial mutation only.

CLINICAL SENSITIVITY
Germline pathogenic \( APC \) variants may be found in 80-93% of patients with a clinical diagnosis of classical FAP and 20-30% of patients with AFAP, Aretz et al, Eur J Hum Genet. 2015 23.

TARGET REPORTING TIMES
- Diagnostic test: 40 working days
- Presymptomatic/Familial Mutation test: 10 working days

N.B. Details are correct for the date of printing only – last updated 11/06/2015