

Oxford Molecular Genetics Laboratory

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Polymerase Proofreading-Associated Polyposis (PPAP) – OMIM 612591, 615083 174761 (*POLD1*), 174762 (*POLE*)

INTRODUCTION

Polymerase proofreading associated polyposis (PPAP) is the suggested name for the condition predisposed by pathogenic mutations in the exonuclease/proof reading domain of the *POLE* and *POLD1* genes. This leads to a heritable susceptibility to developing multiple adenomas and / or early onset colorectal cancer. The phenotype of PPAP is similar to that seen with MutYH associated polyposis (multiple adenomas) or Lynch syndrome (large adenomas or early onset carcinoma). Mutations in *POLD1* are also associated with development of endometrial carcinoma. Tumours tend to be microsatellite stable.

TESTING AND REFERRALS

Diagnostic:

- Clinically affected patients. Usually these patients will have tested negative for mutations in *MutYH*, *APC* and / or Lynch syndrome associated genes.
- UK referrals must be made through Clinical Genetics departments.

Presymptomatic/confirmation test for a familial mutation:

- Individuals at risk of inheriting a pathogenic mutation in *POLD1* or *POLE*.
- Referrals from Clinical Genetics only.
- Requests for presymptomatic testing should either be accompanied by details of the known pathogenic mutation in the family or discussed with the laboratory in advance.

Prenatal:

- Prenatal testing is not usually requested.
- Prenatal requests would only be accepted from Clinical Genetics and must be discussed with the laboratory and arranged in advance.

STRATEGY & TECHNICAL INFORMATION

- Mutation screening in diagnostic referrals is undertaken by fluorescent sequencing analysis of exons 8-13 of *POLD1* and exons 9-14 of *POLE* (including exon/intron boundaries).
- 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.

TARGET REPORTING TIMES

Diagnostic test (2 gene screen):	8 weeks
Presymptomatic/Familial Mutation test:	10 days

CLINICAL SENSITIVITY

The proportion of colorectal cancers accounted for by mutations in *POLD1* and *POLE* is still to be determined. However Palles *et al*, 2013, reported variants in 3/15 and 3/469 patients in the studies which originally implicated involvement of these two genes in colorectal cancer susceptibility.

Ref: Palles *et al*, Nature Genetics, 45, 136-144; 2013.

N.B. Details are correct for the date of printing only – last updated 29/06/2015