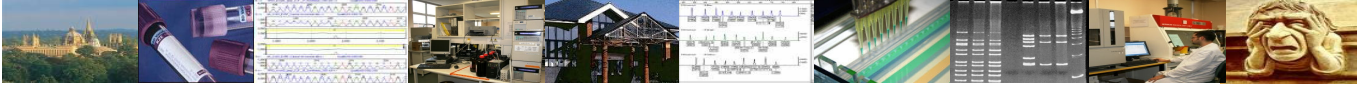


# Oxford Molecular Genetics Laboratory

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## MULTIPLE ENDOCRINE NEOPLASIA TYPE 4 (MEN4) & MULTIPLE ENDOCRINE NEOPLASIA TYPE 1- LIKE PHENOTYPE (MEN1-like) OMIM: 610755, 116899, 600778, 600431, 603369

### INTRODUCTION

Mutations in the cyclin dependent kinase inhibitor genes; *CDKN1A*, *CDKN1B*, *CDKN2B* and *CDKN2C* have been identified in a few patients with an MEN1-like phenotype and no mutation identified in the *MEN1* gene. They are therefore implicated in an inherited susceptibility to endocrine neoplasia. Clinical overlap with HPT-JT syndrome is also seen in these patients. The symptoms seen include primary hyperparathyroidism, pituitary tumour, parathyroid tumour, prolactinoma, gastrinoma, and acromegaly.

Germline mutations in *CDKN1A*, *CDKN2B* and *CDKN2C* cause an MEN1-like phenotype.

Mutations in *CDKN1B* cause MEN4; a novel form of MEN characterised by parathyroid involvement, and less typically with pituitary adenomas and other endocrine features.

### TESTING AND REFERRALS

All samples should be accompanied by a completed pre-referral form ([click here](#))

Clinical guidance is available from Professor Rajesh Thakker, Professor of Medicine, OCDEM, Churchill Hospital ([rajesh.thakker@ndm.ox.ac.uk](mailto:rajesh.thakker@ndm.ox.ac.uk)).

#### Diagnostic:

- Clinically affected patients.
- UK diagnostic referrals are accepted from Clinical Genetics, Endocrinology and consultants from other relevant specialties.

#### Carrier/presymptomatic/test for familial mutation:

- Individuals at risk of developing the condition. Relatives of clinically affected patients in whom a pathogenic mutation has been identified.
- Presymptomatic referrals should ideally be referred through/in collaboration with Clinical Genetics departments.

#### Prenatal:

- Prenatal testing is not generally requested but if required must be discussed with the laboratory and arranged in advance, and referrals are only accepted from Clinical Genetics.

### STRATEGY

Molecular analysis of *CDKN1A*, *CDKN1B*, *CDKN2B* and *CDKN2C* is recommended for patients who have previously tested negative for *MEN1* mutations or as part of the familial isolated hyperparathyroidism panel (FIHP).

Once a pathogenic mutation has been identified in an individual, molecular testing for that variant is available to at-risk or affected family members.

### TECHNICAL INFORMATION

Sanger sequencing analysis of the coding regions and exon intron boundaries of:

- *CDKN1A* (p21) (exons 2-3)
- *CDKN1B* (p27) (exons 1-2 and also analysis of a uORF in the 5' UTR)
- *CDKN2B* (p15) (exons 1-2)
- *CDKN2C* (p18) (exons 2-3)

Clinical Sensitivity: Intragenic mutations in the *CDKN1A*, *CDKN1B*, *CDKN2B* and *CDKN2C* genes have so far been reported in only a few patients and the number of cases accounted for by these mutations is as yet unknown.

Literature to date suggests that these genes may account for 2-4% of MEN1 like phenotypes in patients who have screened negative for mutations in *MEN1*.

### TARGET REPORTING TIMES

Diagnostic: 40days  
Carrier/presymptomatic/familial mutation test: 10 days

**N.B. Details are correct for the date of printing only – last updated 15/07/2015**