Oxford Molecular Genetics Laboratory
Genetics Laboratories, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
www.ouh.nhs.uk/geneticslab

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).

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