Oxford Molecular Genetics Laboratory

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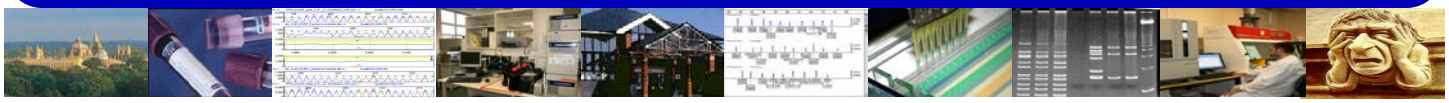

FAMILIAL ISOLATED HYPERPARATHYROIDISM (FIHP) – OMIM +145000

INTRODUCTION

Primary hyperparathyroidism (PHPT) is characterised by hypercalcaemia and inappropriately high levels of parathyroid hormone (PTH). It is most commonly associated with sporadic parathyroid adenomas but can be seen in association with hereditary conditions.
Hereditary PHPT may occur either as part of a syndrome, for example multiple endocrine neoplasia type I (MEN1) or as an isolated endocrinopathy with similarly affected family members - familial isolated hyperparathyroidism (FIHP).

To date the following key genes have been identified as causative of FIHP:
MEN1**:** 20-57% (average frequency ~22%) of individuals with FIHP (Cardinal *et al*, 2005, *JMG*, **42**:69-74, Miedlich *et al*, 2001, *Eur J Endocrinol*, **145**:155-60; Villablanca *et al*, 2002, *Eur J Endocrinol*, **147**:313-22; Pannett *et al*, 2003, *Clin Endocrinol*, **58**:639-46.
CDC73**:** 0-33% (combined frequency 14%) of individuals with FIHP (Newey *et al*, 2010, *Hum Mut*, **31**:295-307).
CASR**:** 18-25% of individuals with familial isolated hyperparathyroidism (FIHP) (Warner *et al*, 2004, *JMG*, **41**:155-60 & own data)
GCM2: Activating mutations have been reported in the CCID region of *GCM2* (codons p.379_395), penetrance has not been determined (Guan *et al* 2016 Am J Hum Genet 99:1-11)
Other much rarer causes include ***CDKN1B*** (Argawal *et al*, JCEM, 2009, 94(5)) & codon p.Arg15 of ***AP2S1***.
RET is associated with hyperparathyroidism but generally in the syndromic context (MEN2).

Identification of a pathogenic mutation in one of these genes indicates that although it may have only been seen in the context of FIHP in the family, clinical screening for the relevant syndromic feature may be warranted.

TESTING

Diagnostic:	Clinically affected patients.
Presymptomatic:	Individuals at risk of developing FIHP/ clinically unaffected relatives of individuals in whom a pathogenic variant has been identified.
Prenatal:	Prenatal testing is not usually requested

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).
- UK diagnostic referrals are accepted from Clinical Genetics, Endocrinology and consultants from other relevant specialties.
- Presymptomatic referrals should ideally be referred through/in collaboration with 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 in diagnostic referrals is undertaken by fluorescent sequencing of the entire coding region and exon intron boundaries of the listed genes, and dosage analysis by multiplex ligation-dependent probe amplification (MLPA) for large scale rearrangements (*MEN1*, *CDC73* & *CDKN1B* only).
- Testing is undertaken simultaneously as a panel test comprising: *MEN1*, *CDC73*, *CASR*, *CDKN1B* (including analysis of uORF in the 5' UTR), *RET* (exons 5, 8, 10, 11, 13-16 only), *AP2S1* (codon p.Arg15) and *GCM2* (codons p.379_395).

TARGET REPORTING TIMES

Diagnostic test:	42 days
Presymptomatic/familial mutation test:	14 days

N.B. Details are correct for the date of printing only – last updated 07/11/2019