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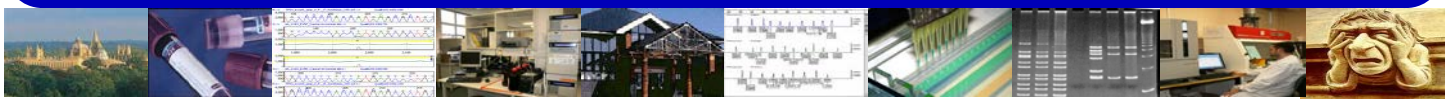

FAMILIAL BENIGN HYPOCALCIURIC HYPERCALCAEMIA (FHH)
OMIM: 145980/145981/600740

INTRODUCTION

Familial benign hypocalciuric hypercalcaemia is an autosomal dominant disorder of extracellular calcium homeostasis, characterised by lifelong hypercalcaemia with inappropriately low urinary calcium excretion (mean urinary calcium:creatinine clearance ratio <0.01)

Identification of pathogenic variants in the genes responsible for FHH can confirm the diagnosis based on clinical/biochemical presentation. This can assist in directing patient management and whether surgical intervention is required.

It is a genetically heterogeneous condition where the types are clinically indistinguishable. To date the following genes have been identified as causative of FHH:

***CASR*:** Pathogenic loss of function mutations in the *CASR* gene account for FHH type1 **(FHH1)**. ~65% of individuals with definite FHH are reported to have a pathogenic variant in this gene.

***GNA11*:** pathogenic variants in this gene are causative of FHH type 2 **(FHH2).** Nesbit *et al*, 2013, *NEJM*, identified pathogenic *GNA11* variants in >10% *CASR* & *AP2S1* negative FHH patients (although the cohort tested was small).

***AP2S1*:** The molecular basis of FHH type 3 **(FHH3)** has been identified as mutation of codon p.Arg15 of the *AP2S1* gene. >20% of *CASR* negative FHH patients have this mutation (Nesbit *et al*, Jan 2013, *Nature Genetics*).

TESTING

Diagnostic:	Patients with a consistent “Clinical/Biochemical diagnosis”.
Presymptomatic/confirmation:	Individuals at risk of developing FHH/ relatives of individuals in whom a pathogenic variant has been identified.

REFERRALS

All samples MUST be accompanied by a completed ‘Hypercalcaemia and Hyperparathyroidism’ 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.
- Familial mutation referrals should ideally be referred through/in collaboration with Clinical Genetics departments.
- Requests for familial mutation testing should either be discussed with the laboratory in advance or be accompanied by details regarding the known pathogenic mutation in the family.

STRATEGY & TECHNICAL INFORMATION

- Mutation screening in diagnostic referrals is undertaken by fluorescent sequencing of the entire coding region and intron/exon boundaries of the selected gene (*CASR* and *GNA11*), or specific analysis of codon p.Arg15 in *AP2S1*.
- Testing can be undertaken sequentially or simultaneous analysis of the 3 genes is available.
- 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:	40 days
Presymptomatic/Familial Mutation test:	10 days

N.B. Details are correct for the date of printing only – last updated 14/07/2015