Oxford Molecular Genetics Laboratory

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HYPOPARATHYROIDISM
OMIM: 607358 / 146255 / 131320 / 168450 / 240300 / 601199/146200

INTRODUCTION

Primary hypoparathyroidism is caused by a group of heterogeneous conditions in which hypocalcaemia and hyperphosphatemia occur as a result of deficient PTH secretion. It may occur as part of a syndrome (*GATA3/AIRE*) or in isolation. A number of genes are implicated in the development of hereditary hypoparathyroidism. Mutation screening is currently available for 7 of these genes:

***GATA3*:** Pathogenic mutations cause the autosomal dominant condition HDR syndrome. Patients typically present with hypoparathyroidism, deafness and/or renal dysplasia. A significant proportion of cases arise *de novo*.

***AIRE*:** Pathogenic mutations cause the autosomal recessive condition autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) or APS1. Clinical presentation can be highly variable, including isolated hypoparathyroidism; however, a typical presentation would be hypoparathyroidism, primary adrenocortical failure and chronic mucocutaneous candidiasis.

***PTH*:** Very rare, autosomal recessive & dominant in literature. Isolated primary hypoparathyroidism.

***GCM2*:** Usually autosomal recessive isolated primary hypoparathyroidism (rare reports of dominant inheritance).

***CASR*:** Pathogenic gain of function mutations associated with autosomal dominant hypoparathyroidism/ hypocalcaemia (ADH1). *CASR* mutations may account for ~40-50% of ADH cases and ~55% of patients referrals with isolated hypoparathyroidism/ hypocalcaemia (data from our cohort).

***GNA11*:** Pathogenic gain of function mutations associated with autosomal dominant Hypocalcaemia type 2 (ADH2). Nesbit *et al*, 2013, *NEJM*, report a *GNA11* mutation in ~25% of hypocalcaemic (ADH) patients who did not have a *CASR* mutation.

***TBCE*:** Autosomal recessive. Allelic disorders HRDS (Hypoparathyroidism-retardation-dysmorphism syndrome; Sanjad-Sakati syndrome), and KCS1 (Kenny-Caffey syndrome). Presenting complaint is typically hypocalcaemic tetany or convulsions, usually neonatal, (although delayed onset up to 7 months is known), with prenatal and postnatal growth failure. There is a Middle Eastern founder variant that accounts for all but one published case.

TESTING

Diagnostic:	Clinically affected patients.
Presymptomatic/ Predictive:	Individuals at risk of developing one of the hypoparathyroidism conditions; relatives of individuals in whom a pathogenic mutation has been identified.
Carrier:	Relatives of clinically affected patients with an autosomal recessive condition (mutation known).
Prenatal:	Prenatal testing may be considered appropriate for certain conditions.

REFERRALS

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

- Clinical guidance and advice to direct appropriate gene screening is available from Professor Raj Thakker, Professor of Medicine, OCDEM, Churchill Hospital (rajesh.thakker@ndm.ox.ac.uk).
- Diagnostic referrals are accepted from Clinical Genetics, Endocrinology and consultants from other relevant specialties.
- Presymptomatic referrals and carrier tests should ideally be referred through/in collaboration with Clinical Genetics departments. Requests for presymptomatic / carrier testing should either be discussed with the laboratory in advance or be accompanied by details regarding the known pathogenic mutation(s) 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 (*GATA3* & *GCM2* only).
- Testing is undertaken simultaneously as a panel test comprising: *GATA3, AIRE, PTH, GCM2, CASR, GNA11, TBCE* (exon 3; full gene screening may be available following discussion). Analysis of single genes is also available.
- pathogenic mutation(s) has been identified in an individual, subsequent testing of family members (presymptomatic, carrier or diagnostic confirmation) involves testing for the familial mutation only.

TARGET REPORTING TIMES

Diagnostic:	42 days
Carrier/presymptomatic/familial mutation test:	14 days

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