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 6 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; 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: Refer to separate information sheet. 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.

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 e.g. HDR or APS1.

REFERRALS
All samples MUST 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 (rajes.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
- Targeted gene screening determined by the patient’s clinical presentation and pedigree, or analysis of all genes simultaneously.
  - Sequencing analysis of the coding region and exon/intron boundaries of the GATA3 gene (exons 2-6).
  - Sequencing analysis of the coding region and exon/intron boundaries of the AIRE gene (exons 1-14).
  - Sequencing analysis of the coding region and exon/intron boundaries of the PTH gene (exons 2-3).
  - Sequencing analysis of the coding region and exon/intron boundaries of the GCM2 gene (exons 1-5).
  - Sequencing analysis of the coding region and exon/intron boundaries of the CASR gene (exons 2-7).
  - Sequencing analysis of the coding region and exon/intron boundaries of the GNA11 gene (exons 1-7).
- When a 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: 40 days
Carrier/presymptomatic/familial mutation test: 10 days

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