GNAS1 gene mutation disorders
(AHO/PHP1a/PPHP/ McCune Albright’s disease)

Introduction:
Albright’s hereditary osteodystrophy (AHO) is an autosomal dominant disorder characterised by short stature, obesity, brachydactyly, subcutaneous ossifications and mental defects. There is a 2:1 ratio of affected females to males. AHO can present in one of two ways: with the somatic features of AHO alone (pseudopseudohypoparathyroidism, PPHP); or with AHO plus resistance to multiple hormones which increase cAMP in their target organs (pseudohypoparathyroidism type 1a, PHP 1a). Both PHP 1a and PPHP are caused by inactivating mutations in the GNAS1 gene. PHP1a is usually caused by mutations in maternal GNAS1, PPHP in paternal allele.

McCune Albright syndrome (MAS) is characterised by precocious puberty, café au lait spots and polyostotic fibrous dysplasia of bone where the normal interior of bone is replaced by fibro-osseous connective tissue. McCune Albright syndrome is caused by somatic activating mutations in exons 8 and 9 of GNAS1. All MAS patients are mosaics.

GNAS1 encodes the α subunit of the G protein Gs. The G proteins are a family of guanine nucleotide binding proteins involved in transmembrane signalling. They form heterotrimers of α, β and γ. GNAS1 (located on 20q13.3) has 13 exons, 6 polyadenylation sites 3' and 4 isoforms (due to differential splicing of exons 3 and 4). There are two alternatively spliced transcripts using exons upstream of GNAS1 (termed XLαs and NESP55) spliced to GNAS1 ex2-13 (+/- exon 3) expressed in most fetal tissue. Although the gene is biallelically expressed in most fetal tissue, XLαs is only expressed from the paternal chromosome and NESP55 only expressed from the maternal chromosome.

Samples required
- 5ml venous blood in plastic EDTA bottles (>1ml from neonates)
- Prenatals must be arranged in advance, through a Clinical Genetics department if possible. Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis
- A completed DNA request card should accompany all samples.

Referrals
- Patients with clinical symptoms as above.
- Carrier testing for family members for the familial mutation

Service offered
AHO: Sequencing analysis of all 13 exons. Approximately 80% of inactivating mutations will be detected by this method.

MAS: Sequencing of exons 8 and 9 plus restriction digest analysis to detect the c.602G>A mutation. Restriction digest analysis is a more sensitive assay for detecting low level mosaicism. DNA from an affected tissue such as bone has given more successful results than DNA extracted from lymphocytes.

Target reporting time
The target reporting time is 2 months for a GNAS1 mutation screen and 2 weeks for carrier testing. For urgent samples please contact the laboratory.

Prenatal testing
Prenatal testing is available for families in whom specific mutations have been identified or in whom appropriate family studies have been undertaken- please contact the laboratory to discuss.

Patient details
To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, address and ethnic origin), details of any relevant family history and full contact details for the referring clinician.