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 PHP1a and PPHP are caused by inactivating mutations in the GNAS1 gene. PHP1a is usually caused by mutations in maternal GNAS1, PPHP in paternal allele.

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.

Mutations in the PRKAR1A and PDE4D genes are associated with Acrodysostosis type 1 and 2 respectively. Acrodysostosis is a type of skeletal dysplasia and is a differential diagnosis of AHO. Clinical symptoms include facial dysostosis, short stature, nasal hypoplasia and severe brachydactyly. Patients may also have advanced bone age, obesity and hormone resistance. PDE4D (5q11.2-q12.1) encodes a cAMP-specific phosphodiesterase (PDE). PRKAR1A (17q24.2) encodes a cAMP-dependent regulatory subunit of protein kinase A.

We also offer testing for GNAS1 somatic mutations for two codons associated with McCune Albright syndrome. For further information, please refer to the McCune Albright syndrome service pack sheet.

Referrals
- Patients with clinical symptoms as above.
- Familial mutation testing for family members.

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.

Service offered
Analysis of GNAS1, PDE4D & PRKAR1A genes by next generation sequencing (Agilent SureSelect and Illumina NextSeq). A minimum coverage of 30 reads is required to call a variant. In-house validation attributes a minimum sensitivity of 97.5% (with 95% confidence) for regions covered ≥30x. This assay is not currently validated to detect large deletions / duplications. All clinically relevant variants are confirmed by Sanger sequence analysis. Known benign polymorphisms and sequence variants which are unlikely to be pathogenic are not reported.

Target reporting time
The target reporting time is 8 weeks for a diagnostic screen and 2 weeks for familial mutation testing. Please contact the laboratory for urgent cases.