Oxford University Hospitals
NHS Foundation Trust

OXFORD GENETICS LABORATORIES
MOLECULAR GENETICS
CURRENT DISEASE SERVICES – OCTOBER 2019

Highly specialised services (HSS) are indicated.

Achondroplasia (*FGFR3*)
Screen for common mutation

Amyotrophic lateral sclerosis (ALS) / Motor neurone disease (MND)
Direct mutation test – PCR & TP-PCR
Direct mutation test – Southern analysis

Andersen-Tawil syndrome
Testing for known mutations
KCNJ2 Mutation screening

Angelman syndrome (AS)
Deletion and Methylation analysis
Family studies for Uniparental disomy (*Parental samples are also required)*
UBE3A mutation screen
Testing for known mutations

Apert syndrome (*FGFR2*) *HSS funded service*
Screen for common mutations

Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Testing for known mutations
NGS screen of candidate genes (-11 gene panel) inc MLPA of *PKP2*

Ataxia
Testing for known mutations
NGS screen of candidate genes (98 gene panel)

Autosomal Dominant Hypocalcaemia (ADH)
Testing for known mutations
Mutation screening *CASR* (FHH1)
Mutation Screening *GNA11* (FHH2)

Beckwith-Wiedemann syndrome
Deletion and methylation analysis

Breast/Ovarian cancer (BRCA1/ BRCA2)
Testing for known mutations
BRCA1/BRCA2 Mutation screen (incl dosage)
NGS screen of panel of candidate genes
Targetted analysis (e.g Ashkenazi screen)

Brugada syndrome
Testing for known mutations
NGS screen of candidate genes (*SCN5A* only)

Calcium Sensing Receptor (FHH1, ADH1, FIHP) (R319)
Testing for known mutations
Mutation screening

CANCER:

Breast/Ovarian cancer
Testing for known mutations
BRCA1/BRCA2 R208 Mutation screen (incl. dosage)
NGS screen of panel of breast cancer candidate genes
Targeted analysis (e.g. Ashkenazi screen)

Ovarian Cancer panel (R207)

Colorectal Cancer panel (R209)

Inherited Polyposis panel (R211)

Lynch syndrome / Inherited MMR deficiency (R210)
Testing for known mutations
Mutation screening and dosage (R210.2/R210.5)
Microsatellite Instability (R210.1)
MS-MMR (promoter methylation analysis) (R210.4)

Li- Fraumeni (*TP53*)
Mutation screen incl. dosage

PTEN
Mutation screen incl. dosage

Prostate cancer
Mutation screen by small panel

Inherited Pancreatic Cancer
Mutation screen by small panel

Von Hippel Lindau syndrome (VHL)
Testing for known mutations
Mutation screening and dosage analysis

Inherited Parathyroid Cancer (*CDC73*)
Mutation screen incl. dosage

Cardiomyopathy (see Familial dilated/hypertrophic cardiomyopathy)

Carpenter syndrome (*RAB23*) *HSS funded service*
Testing for known mutations
Mutation screening of *RAB23*

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
Testing for known mutations
NGS screen of candidate genes (6 gene panel)

Cleidocranial dysplasia (*RUNX2*) *HSS funded service*
Testing for known mutations
Mutation screening (including dosage analysis)
Dosage analysis only

Congenital Myasthenic Syndromes *HSS funded service*
Testing for known mutations
Mutation screening of candidate genes:

- *CHRNE / CHRNG / RAPSN / DOK7 / COLQ/ CHAT*
- *CHRNA1 / CHRNB1 / CHRND / GFPT1 / DPAGT1*

Craniofacial disorders *HSS funded service*
Testing for known mutations
7 gene craniosynostosis panel by Sanger sequencing (*FGFR1* exon 7, *FGFR2* exons 3, 5, 8, 10, 11, 14-18, *FGFR3* exons 7 &10, *TWIST1*, *EFNB1*, *TCF12* and *ERF*) and dosage analysis

Individual gene analysis may be available on request – see list below:

Level 1 mutation screening (*FGFR1* exon 7, *FGFR2* exons 8 & 10, *FGFR3* exons 7 &10, *TWIST1*) and dosage analysis
Level 2 mutation screening (*FGFR2* exons 3, 5, 11, 14-18)
EFNB1 mutation screen and dosage analysis
ERF mutation screen
TCF12 mutation screen
IL11RA mutation screen
ZIC1 mutation screen
SMAD6 mutation screen
Boston-type Craniosynostosis
Dosage analysis only

Craniofrontonasal syndrome (*EFNB1*) *HSS funded service*
Included in the 7 gene craniosynostosis panel (listed under craniofacial disorders). Individual gene analysis may be available on request.

Cystic Fibrosis (CF)
Screen for common mutations
Dosage analysis

Duchenne & Becker Muscular Dystrophy (DMD/BMD)
Testing for known mutations
Duplication and deletion screening
Family studies by linkage
Mutation screening of *DMD* gene by NGS

Endocrine Neoplasia (R217)
Panel test *(AIP, CDC73, CDKN1B,MEN1,RET)*

Epilepsy
NGS screen of candidate genes (337 gene panel)
Testing for known mutations

Factor V Leiden and common Prothrombin mutation analysis - see Non-Malignant Haematology section

Familial Dilated Cardiomyopathy (DCM)
Testing for known mutations
NGS screen of candidate genes (33 gene panel)

Familial adenomatous polyposis coli (FAP)
Testing for known mutations
Mutation screening (including dosage analysis)

Familial Hypertrophic Cardiomyopathy (HCM)
Testing for known mutations
NGS screen of candidate genes (22 gene panel)

Familial Hypocalciuric Hypercalcaemia (FHH)
Testing for known mutations
Mutation screening *CASR* (FHH1)
Mutation screening *GNA11* (FHH2)
Mutation Screening *AP2S1* (FHH3)
Simultaneous Mutation Screening *CASR, AP2S1* & *GNA11* (R152)

Familial Isolated Pituitary adenoma
Testing for known mutations
Mutation screening *AIP*

Familial Malignant Melanoma
Testing for known mutations
Mutation screening *CDKN2A & CDK4*

***FLNA*-associated disorders – please see 'X-linked periventricular nodular heterotopia…'**

Fragile X syndrome (FRAXA)
Direct mutation test – PCR
Direct mutation test – Asuragen
Direct mutation test - Southern analysis

Frontonasal dysplasia testing – (*ALX1*, *ALX3* & *ALX4*)
Testing for known mutations
Mutation screening (including dosage analysis)

***GDF5*-associated skeletal disorders**
Testing for known mutations
Mutation screening and dosage analysis

***GLI3*-associated skeletal disorders**
Pallister-Hall syndrome, Grieg Cephalopolysyndactyly syndrome, Preaxial polydactyly type IV, Preaxial polydactyly type A1
Testing for known mutations
Targeted *GLI3* screen (PHS)
Mutation screening of *GLI3* and dosage analysis
Dosage analysis only

GLUT1 deficiency syndrome – *SLC2A1*
Testing for known mutations
Mutation screening (including dosage analysis)

***GREM1* associated mixed polyposis**
Testing for known mutation

Haemochromatosis testing / HFE genotyping / Iron overload - see Non-Malignant Haematology section

Haemophilia A&B - see Non-Malignant Haematology section

Hereditary Motor and Sensory neuropathies (X-linked CMT)
Testing for known mutations
Mutation screening of *GJB1 (Cx32)*

Hereditary papillary renal carcinoma
Testing for known mutations
Mutation screening *MET*

Huntington disease (HD)
Direct mutation test
Exclusion testing by linkage (*family members are also required*)

Hyperparathyroidism Jaw Tumour syndrome (& FIHP)
Proforma required
Testing for known mutations
Mutation screening *CDC73* (incl dosage)
Dosage analysis only

Hyperparathyroidism (R151)
Testing for known mutations
Mutation screening of candidate genes by panel
Or individual genes:
- *MEN1* screen
- *CDC73* screen
- *CASR* screen

Hypoparathyroidism (R153)
Testing for known mutations
Mutation screening of candidate genes by panel
Or individual genes:
- *AIRE* screen
- *GATA3* screen
- *CASR* screen
- *GCM2* screen
- *PTH* screen
- *GNA11* screen

Hypochondroplasia (*FGFR3*)
Testing for known mutations
Targeted *FGFR3* screen

Iron metabolism disorders - see Non-Malignant Haematology section

Joubert syndrome and related disorders
Testing for known mutations
NGS screen of candidate genes (29 gene panel) includes MLPA of *NPHP1*

Juvenile polyposis syndrome (JPS)
Testing for known mutations
Mutation screening and dosage analysis (*SMAD4* & *BMPR1A)*

LADD syndrome/ ALSG
Testing for known mutations
Mutation screening (*FGFR3* exon 13, *FGFR2* exon 13 & 16 and *FGF10*) and dosage analysis

Lebers Hereditary Optic Neuropathy (LHON)
LHON screen – 3 common mtDNA mutations

Li-Fraumeni syndrome
Testing for known mutations
Mutation screening and dosage analysis *TP53*

Long QT syndrome (LQT)
Testing for known mutations
NGS screen of candidate genes (10 gene panel)

Lynch syndrome (previously HNPCC)
Testing for known mutations
Mutation screening and dosage (*MLH1*, *MSH2, MSH6* genes)
Microsatellite Instability
Dosage only
MS-MMR (promoter methylation analysis)

Mitochondrial diseases
HSS funded service (except for LHON - see above)
Testing for known mutations
Testing for m.1555A>G only (HSS funded only if patient has hearing loss)
Screen for common mitochondrial DNA (mtDNA) mutations which may include:

- m.3243A>G (R64.1)
- m.8993T>C/G (R351.2)
- m.8344A>G (R350.1)
- m.4300A>G (R397.1)
- m.1555A>G (R65.1)
- mtDNA rearrangements (R299.1)

mtDNA whole sequencing by NGS (R300.1)
mtDNA depletion analysis (muscle or liver tissue/DNA required) (R301.1)
Mutation screening of nuclear genes associated with mitochondrial disorders:-

- *POLG* target screen (5 common mutations – R315.1)
- *POLG* sequencing (R315.2)
- *POLG* dosage analysis
- *DGUOK, MPV17, POLG & TRMU* sequencing (R317.1)
- *SURF1* sequencing
- *TMEM70* sequencing (R396.1)
- *SLC19A3* sequencing (R395.1)
- *PDHA1* sequencing & dosage analysis
- NGS nuclear gene panels:
    - Disorders of mtDNA maintenance (R352.1)
    - PDH deficiency (R361.1)
    - Extended panel of nuclear genes (R63.1)

Biochemical assay for PDH enzyme activity in fibroblasts

MEN1 & FIHP & MEN4
Testing for known mutations
Mutation screening *MEN1* gene (incl dosage)
Dosage analysis only, *MEN1* and/or *CDKN1B*
Screen *CDKN1B* (MEN4) (excl dosage as same kit as MEN1)
Endocrine Neoplasia panel test (R217)

MEN2 & FMTC (R218)
Testing for known mutations
Mutation screening in *RET* exons 10 & 11
Mutation screening in *RET* exons 5, 8, 10, 11, 13, 14, 15 & 16

MYH polyposis
Test for 2 common mutations
Testing for known mutations

MHYRE syndrome
Testing for known/common mutation

Myotonic dystrophy Type 1
Direct mutation test – PCR
Direct mutation test – Southern analysis

NGS sequencing panels – reanalysis
Re-interrogation NGS – Unmasking NGS data plus Sanger
Re-interrogation NGS – Unmasking NGS data no Sanger
Variant reclassification letter
Variant confirmation and interpretation

***NOG*-associated skeletal disorders**
Testing for known mutations
Mutation screening and dosage analysis

Non-Malignant Haematology:

Bleeding and platelet disorders panel (R90)
This panel consists of 108 genes associated with coagulation, bleeding, and platelet disorders

Single gene screens, targeted, prenatal diagnosis and dosage analysis is available:
R117 Factor VIII deficiency (Haemophilia A)
R118 Factor IX deficiency (Haemophilia B)
R121 Von Willebrand disease
R112 Factor II deficiency
R115 Factor V deficiency
R116 Factor VII deficiency
R119 Factor X deficiency
R120 Factor XI deficiency
R122 Factor XIII deficiency
R123 Combined vitamin K-dependent clotting factor deficiency
R124 Combined Factor V and VIII deficiency

Thrombophilia with a likely monogenic cause panel (R97)
This panel consists of 20 genes associated with thrombotic disorders

Factor V Leiden and common Prothrombin mutation analysis

Iron metabolism disorders – NOT common *HFE* mutations (R96)
This panel consists 26 genes associated with iron overload, hyperferritinaemia, iron deficiency, sideroblastic anaemia with iron overload, Gaucher disease, Wilson disease, Aceruloplasminemia and Neuroferritinopathy. Currently, a smaller 16 gene panel is in routine service.

Iron overload – hereditary haemochromatosis testing (*HFE* genotyping) (R95)
Screen for the common *HFE* p.His63Asp and p.Cys282Tyr variants

Painful channelopathies/neuropathies
Testing for known mutations
Mutation screening of candidate genes –
- 5 gene screen *SCN9A, SCN10A, SCN11A, TRPA1, NAGLU*

Parietal foramina (*ALX4* & *MSX2*) *HSS funded service*
Testing for known mutations
Mutation screening (*ALX4* and *MSX2)* and dosage analysis
Dosage analysis only

Pheochromocytoma / Paranganglioma
Testing for known mutations
10 gene mutation screen (*VHL, SDHB, SDHC, SDHD, SDHA, TMEM127, MAX, SDHAF2, RET* ex 10&11, *FH*)
Individual gene screens on request

Platelet Disorders (including inherited platelet disorders affecting platelets numbers, platelets function, with a syndromic phenotype, and/or associated with increased risk for haematologic malignancies) **- see Non-Malignant Haematology section**

Polymerase Proofreading-Associated Polyposis (PPAP)
Colorectal cancer (*POLD1*/*POLE*)
Testing for known mutations
Mutation screen

Prader-Willi syndrome (PWS)
Deletion and methylation analysis
Family studies for Uniparental disomy (*Parental samples are also required)*

PTEN
PTEN mutation screening and dosage analysis

Inherited Retinal Dystrophy (IRD)
NGS screen of candidate genes:_
RP and RP-like phenotypes (111 gene panel)
Syndromic retinal dystrophies (84 gene panel)
Macular phenotypes includes Stargardt disease (17 gene panel)
Non-progressive conditions, includes albinism, achromatopsia, tritanopia (17 gene panel)
Congenital Stationary Night Blindness (16 gene panel)
Optic nerve disease (11 gene panel)
Optic nerve panel plus 3 LHON common mtDNA mutations
Testing for known mutations

Rare Bleeding disorders (FV, FVII, FX, FXI, FXIII and others genes) **- see Non-Malignant Haematology section**

Robinow syndrome (autosomal dominant)
Testing for known mutations
WNT5A, DVL1, DVL2 and DVL3 mutation screen and *WNT5A* dosage analysis

Robinow syndrome (recessive) & Brachydactyly type B1
Testing for known mutations
Targeted *ROR2* mutation screen (BDB1)
ROR2 mutation screening and dosage analysis

Russell Silver syndrome
Dosage and methylation analysis (chromosome 7 and 11)

Short QT Syndrome
Testing for known mutations
NGS screen of candidate genes (4 gene panel)

Succinate dehydrogenase (SDH) / Familial Paraganglioma Syndromes
Testing for known mutations
SDHB/C/D Mutation screening

Spinal and bulbar muscular atrophy
Direct mutation test
Linkage analysis (*Family members are also required)*

Spinal muscular atrophy
SMN1 dosage analysis
Linkage analysis (*Parental samples are also required)*

Synpolydactyly type II, Brachydactyly type D & type E
Sequencing of known mutations
Dosage analysis of known mutations
HOXD13 mutation screening and dosage analysis

Thanataphoric dysplasia
Testing for known mutations
Targeted FGFR3 screen

Thrombotic Disorders (monogenic - Protein C, Protein S and Antithrombin III deficiency) **- see Non-Malignant Haematology section**

TP53
TP53 mutation screening and dosage analysis

Treacher Collins syndrome types 1-3
Testing for known mutations
TCOF1 / *POLR1D* / *POLR1C* mutation screening and dosage analysis

Timothy Syndrome
Testing for known mutations
Screen for known mutations in *CACNA1C*

Uromodulin (*UMOD*) & *REN*
Mutation screening

UPD14
Dosage for postnatal cases (incl. methylation)
Family studies for Prenatal Uniparental disomy (*Parental samples are also required)*

UPD16
Family studies for Uniparental disomy (*Parental samples are also required)*

Von Hippel Lindau syndrome (VHL)
Testing for known mutations
Mutation screening and dosage analysis

Von Willebrand Disease - see Non-Malignant Haematology section

X-linked periventricular nodular heterotopia, Otopalatodigital syndromes types 1 & 2, Melnick-Needles syndrome, Frontometaphyseal dysplasia
Testing for known mutations
FLNA mutation screening (full gene)
[Targeted screening may be available at reduced cost – call to discuss]

ZRS regulatory region of *SHH*-associated skeletal disorders
Testing for known mutations
Mutation screening and dosage analysis

Zygosity testing
To aid in the diagnosis of medical conditions only
Ideally, parental samples are also required
Microsatellite analysis