North Bristol NHS Trust

Autosomal Recessive/Infantile/Malignant Osteopetrosis (ARO)
Autosomal Dominant/late-onset Osteopetrosis (ADO) (Albers-Schonberg disease)

Contact details:
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Sample Required:
Adult: 5mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)

Samples should be accompanied by a FULLY completed request form (available as download at www.nbt.nhs.uk/genetics or from the laboratory).

Please include details of the test required, family history, address and POSTCODE, NHS number, referring clinician and centre.

Consent and Storage:
All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question

Clinical Background and Genetics

- The osteopetroses are a heterogeneous group of disorders characterized by an increased bone density due to impaired bone resorption.
- AR malignant infantile osteopetrosis (ARO) typically results in severe disease in infancy (OMIM 259700), patients may present with generalized increase in bone density, predisposition to bone fractures, osteomyelitis, macrocephaly, frontal bossing, progressive deafness and blindness, hepatosplenomegaly, and severe anaemia/pancytopenia. Incidence is 1:250,000 in UK
- ADO presents primarily with skeletal fractures and osteomyelitis from late childhood to adulthood. Hearing/visual loss may affect around 5% of individuals. Non-penetrance of ADO has long been recognized, with an estimated 1/3 of individuals inheriting a *CLCN7* pathogenic variant NOT manifesting the ADO phenotype. Members of the same family carrying the same gene variant can therefore have extremely variable presentation. This may be due to modifier genes
- At least 10 genes are thought to account for 70% of all osteopetrosis cases, with 7 accounting for 80% of ARO cases. *TNFSF11* (*RANKL*) and *TNFRSF11A* (*RANK*) pathogenic variants are associated with reduced numbers of osteoclasts. A proportion of cases remain unidentified, implying further as yet unknown genes are involved in the disease. Rapid genetic diagnosis is crucial to inform decision making about curative stem cell transplantation (some subtypes are unresponsive) and to predict prognosis.

Service offered

- 21 genes are analysed as virtual panels from a 6000+ gene panel (custom clinical exome), NextSeq (Illumina) sequencing, GATK best practice variant pipeline. Copy number variation is assessed for the targeted genes.
- Familial testing is available for known variants (Sanger sequencing).

Referrals

- **Diagnostic Testing**: Please provide clinical details of affected patient and family history.
- **Carrier Testing:** Please provide details of affected patient and familial variant
- **Prenatal diagnosis:** Only offered where clearly pathogenic variants have been identified with known parental genotypes. Please discuss with the laboratory on a case by case basis.

Quality

BGL participates in the appropriate technical EQA schemes for Sanger and next generation sequencing.

Target reporting Times

Diagnostic screen:	12 weeks
Urgent	3 weeks
Known Familial Variant	6 weeks (routine), 2 weeks (urgent)
Prenatal:	3 days

Please contact the laboratory for up to date pricing

Clinical Advice:
Sarah Smithson Consultant Clinical Geneticist, Level B St Michael's Hospital, Bristol BS2 8EG (Tel: 0117 928 5318)

Reference:
Osteopetrosis:genetics, treatment and new insights into osteoclast function. Sobacchi et al (2013) Nat. Rev.Endocrinol.9, 522-536

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DETAILS CORRECT AT DATE OF PRINTING ONLY.
Approved by: Maggie Williams

HGNC standard name and symbol of the gene	HGNC number	OMIM Gene Number	OMIM standard name of condition and symbol	Inheritance	OMIM Disease number
ANKH	HGNC: 15492	605145	Craniometaphyseal dysplasia Chondrocalcinosis 2	AD AD	123000 118600
CA2	HGNC: 1373	611492	Osteopetrosis autosomal recessive 3 OPTB3	AR	259730
CLCN7	HGNC: 2025		Osteopetrosis autosomal recessive 4 OPTB4 Osteopetrosis autosomal dominant OPTA2	AR AD	611490 166600
CTSK	HGNC: 2536	601105	Pycnodysostosis	AR	265800
FAM123B	HGNC: 26837	300647	Osteopathia striata with cranial sclerosis	XD	300737
FAM20C	HGNC: 22140	611061	Raine syndrome (RNS)	AR	259775
FERMT3	HGNC: 23151	607901	Leukocyte adhesion deficiency Type III	AR	612840
IKBKG*	HGNC: 5961	300248	Ectodermal dysplasia, anhidrotic with immunodeficiency, osteopetrosis and lymphedema	XD	300301
LEMD3	HGNC: 28887	607884	Buschke-Ollendorff syndrome, osteopoikilosis	AD	166700
LRP5	HGNC: 6697	603506	Osteopetrosis autosomal dominant 1	AD	607634
OSTM1	HGNC: 21652	607649	Osteopetrosis autosomal recessive 5 OPT5	AR	259720
PLEKHM1	HGNC: 29017	611492	Osteopetrosis autosomal recessive 6	AR	611497
PTH1R	HGNC: 9608	168468	Metaphyseal chondrodysplasia, Murk Jansen type Blomstrand's Lethal chondrodysplasia Ollier disease/enchondromatosis Eiken Familial skeletal dysplasia	AR AR AD AR	156400 215045 166000 600002
RASGRP2	HGNC: 9879	605577	Leukocyte adhesion deficiency Type III	AR	612840
SNX10	HGNC: 14974	614780	Osteopetrosis autosomal recessive 8 OPT8	AR	615085
SOST	HGNC: 13771	605740	Sclerosteosis	AR	269500
TCIRG1	HGNC: 11647		Osteopetrosis, autosomal recessive 1, OPTB1	AR	259700
TGFB1	HGNC: 11766	190180	Camurati – Engelmann Disease	AD	131300
TNFRSF11A (RANK)	HGNC: 11908	603499	Osteopetrosis autosomal recessive 7 OPT7	AR	612301
TNFSF11 (RANKL)	HGNC: 11926	603499	Osteopetrosis autosomal recessive 2 OPT2	AR	259710
TYROBP	HGNC: 12449	604142	Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) (Nasu-Hakola disease)	AR	221770

*IKBKG Coverage is suboptimal on the clinical exome panel in use. Please contact the laboratory if there is a specific clinical interest in this gene.