SickKids | Genome Diagnostics

Connective Tissue Disorders:
Osteopetrosis and
disorders of increased bone density

Osteopetrosis is a descriptive term that refers to a group of rare, heritable disorders of the skeleton characterized by increased bone density on radiographs. Some features are: generalized osteosclerosis, club-shaped long bones, osteosclerosis of the skull base, bone-within-bone appearance. Osteopetrotic conditions vary greatly in their presentation and severity, ranging from neonatal onset with life-threatening complications such as bone marrow failure (e.g. classic or "malignant", autosomal recessive (ARO)), to the incidental finding of osteopetrosis on radiographs. Classic ARO is characterized by fractures, short stature, compressive neuropathies, hypocalcaemia with attendant tetanic seizures, and life-threatening pancytopenia. The presence of primary neurodegeneration, intellectual disability, skin and immune system involvement, or renal tubular acidosis may point to rarer osteopetrosis variants, whereas onset of primarily skeletal manifestations such as fractures and osteomyelitis in late childhood or adolescence is typical of autosomal dominant osteopetrosis (ADO). Osteopetrosis is caused by failure of osteoclast development or function.

Genetics

Osteopetrosis syndrome can be inherited in autosomal dominant, or autosomal recessive fashion, with the autosomal recessive forms being the most severe. The targeted Next-Generation Sequencing (NGS) panel described below include genes associated with both modes of inheritance.

Who Should be Tested?

- Individuals clinically suspected of being affected with a type of osteopetrosis
- The relatives of a proband with identified pathogenic variants in an osteopetrosis-associated gene
- Pregnancies at increased risk due to a family history of osteopetrosis

Test Methods

Complete sequencing of the coding region and flanking intron/exon boundaries of the genes listed below. This is done via NGS of the osteopetrosis targeted gene panel. Please refer to our "A Guide to Next-Generation Sequencing" information sheet available on our website, for further details.

Interpretation of Test Results

Genetic testing may reveal one or more variants in the osteopetrosis genes, which should be interpreted in the context of the suspected clinical diagnosis, inheritance pattern, clinical findings, family history and other experimental data. Please refer to our "A Guide to interpreting sequence variants" information sheet available on our website, for further details.

Gene	Type of Osteopetrosis
CA2	Osteopetrosis, autosomal recessive 3, with renal tubular acidosis
CLCN7	Osteopetrosis, autosomal dominant 2 and autosomal recessive 4
LRP5	Osteopetrosis, autosomal dominant 1
OSTM1	Osteopetrosis, autosomal recessive 5
SNX10	Osteopetrosis, autosomal recessive 8
TCIRG1	Osteopetrosis, autosomal recessive 1
TNFRSF11A	Osteopetrosis, autosomal recessive 7
TNFRSF11B	Paget disease of bone 5, juvenile-onset
TNFSF11	Osteopetrosis, autosomal recessive 2

For More Information:

Osteopetrosis:
http://ghr.nlm.nih.gov/condition/osteopetrosis

To locate a genetics center near you:

Canadian Association of Genetic Counsellors (CAGC):
www.cagc-accg.ca

National Society of Genetic Counselors (NSGC):
www.nsgc.org

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1. *A negative result asfter NGS testing does not rule out the presence of a deletion or duplication. Deletion/duplication testing is available through our laboratory. If clinically indicated, please contact us to discuss this testing.*
2. *The clinical course or severity of symptoms cannot be predicted by molecular analysis.*
3. *Test results should be interpreted in the context of clinical findings, family history and other laboratory data.*
4. *Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of Osteopetrosis.*
5. *This test was developed and its performance characteristics validated by the Molecular Genetics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.*