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Thanatophoric Dysplasia (Type I & II)

Thanatophoric dysplasia (TD) is one of the most common lethal skeletal dysplasias. TD is characterized by extremely short ribs, narrow thorax, tubular bones, hypotonia, brachydactyly, distinctive facial features, macrocephaly, a small chest which crowds the respiratory system, and compression of the brain due to deformations of the skull. Two types of TD exist: Type I based on the absence of cloverleaf skull and a curved femur, and Type II based on the presence of a cloverleaf skull and a straight femur.

Genetics

Thanatophoric dysplasia is an autosomal dominant condition caused by mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*), located on chromosome 4 (4p16.3). TD is present when an individual has one copy of the defective *FGFR3* gene. Majority of probands have a *de novo* mutation in *FGFR3*. Risk of recurrence for parents who have one affected child is not significantly increased over the general population. A slightly increased risk of germline mosaicism is theoretically possible, however this has not previously been reported in the literature.

Twelve different mutations in the *FGFR3* gene which cause TD Type I have been identified, and are listed in the chart below. TD Type II is caused almost entirely by one type of mutation in the *FGFR3* gene: a substitution (A>G) at nucleotide 1948 (p.Lys650Glu).

c.742C>T (p.Arg248Cys)	c.1111A>T (p.Ser371Cys)	c.2419T>A (p.X 807Argext141)	c.2421A>T (p.X 807Cysext141)
c.746C>G (p.Ser249Cys)	c.1118A>G (p.Tyr373Cys)	c.2420G>T (p.X 807Leuext141)	c.2421A>C (p.X 807Cysext141)
c.1108G>T (p.Gly370Cys)	c.2419T>G (p.X 807Glyext141)	c.2420G>C (p.X 807Serext141)	c.2421A>G(p.X 807Trpext141)

Who Should be Tested?

- Individuals clinically suspected of being affected with Thanatophoric dysplasia
- Pregnancies at risk due to abnormal ultrasound findings or a family history of TD
- Individuals with a family history of Thanatophoric dysplasia

Test Methods

- Direct sequencing of the *FGFR3* gene to identify the mutations listed above for TD Type I testing.
- Direct mutation detection assay using PCR to test for the most common *FGFR3* gene mutation associated with the TD Type II: c.1948A>G (p.Lys650Glu) and full *FGFR3* gene sequencing..

Potential Outcomes & Interpretation of Test Results

***FGFR3* Gene Mutations**	**Explanation**
None detected	This result does not support a diagnosis of TD
Mutation detected	This result supports a diagnosis of TD

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/ Item # 187600

GeneReviews online clinical information resource http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=td#td

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Current molecular testing may not detect all possible mutations causing TD. A negative test does not rule out the possibility that the individual has a rare mutation not included in this assay.

2. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

3. This test was developed and its performance characteristics validated by the Genome Diagnostics 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.