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).

<table>
<thead>
<tr>
<th>FGFR3 Gene Mutations</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>None detected</td>
<td>This result does not support a diagnosis of TD</td>
</tr>
<tr>
<td>Mutation detected</td>
<td>This result supports a diagnosis of TD</td>
</tr>
</tbody>
</table>

**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**

- [Online Mendelian Inheritance in Man](http://www.ncbi.nlm.nih.gov/omim/ Item # 187600)
- To locate a genetics centre near you, please visit the [Canadian Association of Genetic Counsellors website at www.cagc-accg.ca](http://www.cagc-accg.ca) or the [National Society of Genetic Counsellors website at www.nsgc.org](http://www.nsgc.org).

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.