TRPV4-RELATED SKELETAL DYSPLASIAS

TRPV4 GENE SEQUENCING

Mutations have been identified in the TRPV4 gene (OMIM 605427) in individuals with spondylometaphyseal dysplasia, Kozlowski type; individuals with metatropic dysplasia (Krakow 2009); and individuals with brachyolmia type 3 (Rock 2008). More recently, mutations in TRPV4 have also been associated with parastremmatic dysplasia and spondylo-epiphyseal dysplasia, Maroteaux type (Nishimura 2010).

Spondylometaphyseal dysplasia, Koslowski type (OMIM 184252)
Spondylometaphyseal dysplasias are a group of disorders characterized by short stature with vertebral and metaphyseal abnormalities. Spondylometaphyseal dysplasia, Koslowski type (SMDK), is distinguished by postnatal short stature and progressive kyphoscoliosis, along with other specific radiologic features. Individuals are typically diagnosed after the age of two years when a waddling gait is noticed. Inheritance of SMDK is autosomal dominant.

Metatropic dysplasia (OMIM 156530)
Metatropic dysplasia is characterized by short limbs and a long narrow trunk in the newborn period. The phenotype changes over time, presenting with a severe progressive kyphoscoliosis and joint contractures. Radiologic features include platyspondyly and metaphyseal enlargement. Metatropic dysplasia was initially considered to be clinically and genetically heterogeneous, with possible autosomal dominant and autosomal recessive forms. Current data suggest that metatropic dysplasia is an autosomal dominant condition with variable expressivity.

Brachyolmia type 3 (OMIM 113500)
The brachyolmias are a group of disorders characterized by a short trunk, scoliosis, and mild short stature. Brachyolmia type 3 is autosomal dominant, whereas other types are autosomal recessive. Brachyolmia type 3 presents with severe kyphoscoliosis and flattened, irregular cervical vertebrae. There may be minimal epiphyseal and metaphyseal abnormalities.

Parastremmatic dysplasia (OMIM 168400)
Parastremmatic dysplasia is characterized by unusual deformities of the legs, with windswept appearance and severe genu valgum, scoliosis, platyspondyly, “flaky” appearance of endochondral bone, and multiple contractures of major joints. Inheritance is autosomal dominant.

Spondylo-epiphyseal dysplasia, Maroteaux type (OMIM 184095)
Spondylo-epiphyseal dysplasia, Maroteaux type, is characterized by short stature with progressive truncal shortening without significant scoliosis. Radiologic features include platyspondyly without anterior tongue formation, champagne-glass configuration of pelvic inlet, and generalized shortening of metacarpals and phalanges. It is sometimes referred to as brachyolmia type 2. Inheritance is autosomal dominant.

Testing: Testing is performed by sequencing the entire coding region of TRPV4. This will detect point mutations, small deletions, and small insertions. It will not detect a partial or whole gene deletion or duplication. Partial sequencing in regions known to carry mutations can be carried out; please note on submission form if this tiered approach is being requested.
Mutations in exons 6 and 11 through 16 have been associated with skeletal dysplasias.

Certain mutations in \textit{TRPV4} have been associated with three specific types of autosomal dominant neuromuscular disorders. One of these mutations may be identified during this test. This will be reported to the ordering provider.

**Turnaround time:** 10-14 business days

**CPT codes and cost:**

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<th>Service Description</th>
<th>CPT Code</th>
<th>Cost</th>
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<tr>
<td>Full gene sequencing</td>
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<tr>
<td>Sequencing of exons 6 &amp; 11-16 only:</td>
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<tr>
<td>Known mutation testing</td>
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**BILLING:**  
*We do not bill third party payers (insurance companies) for samples received from external sources. The person or institution (e.g., Clinical Lab; Send-out Lab; Physician Office) sending the sample is responsible for full payment of the invoices within 30 days of receipt of the invoice.*  
If the patient is on Medical assistance, please contact the lab **prior** to sample submission. Direct patient billing will be accepted **only** when a valid credit card form is received with the patient sample.

**Online resources:**

- Little People of America - [http://www.lpaonline.org](http://www.lpaonline.org)

**References:**


Facsimile Verification Form

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Name of Physician/Lab receiving Fax: ____________________________________________
Street Address: _______________________________________________________________
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Fax Number: _____________________________________
(to which lab results and /or patient information may be sent)

Phone Number: ____________________________________

By signing this Facsimile Verification Form, I validate the accuracy of the above information and assume
responsibility for assuring that the Fax machine is in a location which will maintain confidentiality of all
reports transmitted by the Molecular Diagnostics Laboratory of the
Alfred I. duPont Hospital for Children, to the above fax number.

Authorized Contact Person: ______________________________________________

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If you have any questions regarding this form please contact Susan Kirwin, Assistant Director of The Molecular
Diagnostics Laboratory, at 302.651.6777.

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For Direct Patient Billing
Prepayment for the testing services is required prior to beginning our testing. Please complete this form and include this paperwork with the shipment of the patient sample.

Billing questions can be addressed to: Denise Axsmith  
Senior Budget/Financial Analyst  
Nemours/A.I. duPont Hospital for Children  
daxsmith@nemours.org  
Phone: 302.651.6802  
Fax: 302.651.6881

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