Arthrogryposis, Distal, Type 2B: \( TNNi2 \) Gene Sequencing

**Condition Description**

Distal arthrogryposis type 2B is an autosomal dominant congenital contracture syndrome. Characteristics include contractures primarily in the distal joints of the limb, a triangular face, downsloping palpebral fissures, small mouth, and high arched palate. Other common clinical features can include prominent nasolabial folds, attached earlobes, mild cervical webbing, short stature, severe campodactyly, ulnar deviation, and vertical talus and/or talipes equinovarus. Primary neurological defects and muscle abnormalities are absent.

Contractures tend to be most severe at birth and are non-progressive. While distal joints are primarily affected, more proximal joints may also be affected. The severity of the contractures can vary between the upper and lower limbs and between the left and right sides of the body. Growth, development, cognitive abilities, and life expectancy are in the normal range. Clinical presentation is highly variable both between and within families.

Approximately half of the reported cases of distal arthrogryposis type 2B are inherited, and half are sporadic. Gene mutations can be identified in about 50% of individuals with a clinical diagnosis. Germline mosaicism has been reported. Three genes are currently known to be involved: \( TNNi2 \), \( TNNi3 \), and \( MYH3 \). While diagnosis is based on clinical criteria, mutation analysis can help distinguish distal arthrogryposis type 2B from other arthrogryposis syndromes.

This testing is for mutations in the \( TNNi2 \) gene (11p15.5) only.

For patients with suspected distal arthrogryposis type 2B, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References:**
- OMIM #601680 [Arthrogryposis, Distal, Type 2B](https://www.omim.org/entry/601680)

**Genes**

\( TNNi2 \)

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of distal arthrogryposis type 2B

**Methodology**

PCR amplification of 7 exons contained in the \( TNNi2 \) gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**Detection**

Clinical Sensitivity: Gene mutations can be identified in about 50% of individuals with a clinical diagnosis. Three genes are currently known to be involved: \( TNNi2 \), \( TNNi3 \), and \( MYH3 \). This testing is for mutations in the \( TNNi2 \) gene (11p15.5) only. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types
- Preferred specimen type: Whole Blood

**Type:** Whole Blood
Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Deletion/duplication analysis of the TNNI2 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- **Custom diagnostic mutation analysis (KM)** is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available for known familial mutations only. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.