



**Next Generation Sequencing Panel for Distal Arthrogyposes**

Arthrogyposis is a term used to describe multiple congenital contractures that affect two or more different areas of the body (1). Distal Arthrogyposes are a group of autosomal dominant disorders that are mainly characterized by the involvement of the distal parts of the limbs without primary neurological and/or muscle disease. Findings include a consistent pattern of hand and foot involvement, limited involvement of proximal joints and variable expressivity (1).

Our Distal Arthrogyposes Panel includes analysis of the 11 genes listed below.

Distal Arthrogyposes Panel		
<i>CHST14</i>	<i>MYH3</i>	<i>TNNI2</i>
<i>ECEL1</i>	<i>MYH8</i>	<i>TNNT3</i>
<i>FBN2</i>	<i>NALCN</i>	<i>TPM2</i>
<i>MYBPC1</i>	<i>PIEZO2</i>	

Genes and Associated Disorder	Inheritance	Clinical Features/Molecular Pathology
<i>CHST14</i> [OMIM#603967]  Ehlers-Danlos syndrome, musculocontractural type [OMIM#601776]	AR	Sonoda <i>et al</i> , 2000 identified two brothers with multiple distal arthrogyposis, peculiar facial appearance, cleft palate, short stature, hydronephrosis, retention testis, and normal intelligence (2). Subsequent analysis of the <i>CHST14</i> gene identified a homozygous missense mutation in these individuals. Mutations in <i>CHST14</i> are implicated in Ehlers-Danlos syndrome, musculocontractural type, which is characterized by distinctive craniofacial dysmorphism, congenital contractures of thumbs and fingers, clubfeet, severe kyphoscoliosis, muscular hypotonia, hyperextensible thin skin with easy bruisability and scarring, wrinkled palms, joint hypermobility and ocular involvement.
<i>ECEL1</i> [OMIM#605896]  Arthrogyposis, distal, type 5D [OMIM#615065]	AR	McMillin <i>et al</i> , 2013, identified mutations in <i>ECEL1</i> in five out of seven families with DA5D (3). Missense, frameshift, in-frame deletions and splicing mutations have all been reported. <i>ECEL1</i> encodes a neuronal endopeptidase and is expressed in the brain and peripheral nerves (3).
<i>FBN2</i> [OMIM#612570]  Arthrogyposis, distal, type 8 [OMIM#178110] Arthrogyposis, distal, type 9 [OMIM#121050]	AD	Park <i>et al</i> , 1998 identified mutations in <i>FBN2</i> in samples from 6/12 unrelated congenital contractural arachnodactyly (CCA) patients (4). CCA shares many phenotypic characteristics of neonatal Marfan syndrome including dolichostenomelia, arachnodactyly, scoliosis, pectus deformities and congenital contractures. In contrast to Marfan syndrome, patients with CCA do not typically have ectopia lentis or aortic root dilatation (4).
<i>MYBPC1</i> [OMIM#160794]  Arthrogyposis, distal, type 1B [OMIM#614335]	AR	Gurnett <i>et al</i> , 2010 identified two novel heterozygous missense mutations in <i>MYBPC1</i> in two families with DA1B (5). <i>MYBPC1</i> encodes for myosin binding protein and although the function of this protein has not been fully elucidated, it appears to be involved in the stabilization of sarcomere structures (5).
<i>MYH3</i> [OMIM#160720]  Arthrogyposis, distal, type 2A [OMIM#193700] Arthrogyposis, distal, type 2B [OMIM#601680]	AD	Toydemir <i>et al</i> , 2006 identified mutations in <i>MYH3</i> in 26/28 cases of patients with DA2A and 12/38 cases of patients with DA2B (6). Overall, mutations in <i>MYH3</i> may account for approximately 90% of cases of DA2A and 40% of cases of DA2B. No mutations overlap between those that cause DA2A and DA2B (1).
<i>MYH8</i> [OMIM#160741] Arthrogyposis, distal, type 6 [OMIM#108200] Arthrogyposis, distal, type 7 [OMIM#158300]	AD	Toydemir <i>et al</i> , 2006 identified a single missense mutation in <i>MYH8</i> in four families with Trismus-pseudocamptodactyly syndrome (TPS) (7). TPS is characterized by an inability to fully open the mouth and camptodactyly that is only apparent upon dorsiflexion of the wrists (7).
<i>NALCN</i> [OMIM#611549]  Congenital contractures of the limbs and face, hypotonia and developmental delay [OMIM#616266]	AD	Chong <i>et al</i> , 2015 identified fourteen different de novo heterozygous mutations in the <i>NALCN</i> gene in unrelated patients with congenital severe contractures of the limbs, abnormal facial features, hypotonia and developmental delay. All 14 mutations were missense mutations located near the S5 and S6 pore-forming regions of the <i>NALCN</i> protein. Functional studies suggest that <i>NALCN</i> mutations have a dominant-negative effect, abolishing wild-type expression of <i>NALCN</i> (8). Homozygosity for <i>NALCN</i> pathogenic variants has been reported in three families affected by hypotonia and intellectual disability (9).

<i>PIEZO2</i> [OMIM#613629] Arthrogryposis, distal, type 3 [OMIM#114300] Arthrogryposis, distal, type 5 [OMIM#108145]	AD	McMillin <i>et al</i> , 2014 identified heterozygous mutations in <i>PIEZO2</i> in 10 out of 12 patients (83%) with distal arthrogryposis type 3, a rare disorder characterized by cleft palate and multiple congenital contractures of the hands and feet (10). <i>PIEZO2</i> mutations were also found in 24 out of 29 families (83%) with distal arthrogryposis type 5, which is associated with contractures, ocular abnormalities such as ophthalmoplegia, ptosis and/or strabismus, and pulmonary hypertension (10).
<i>TNNI2</i> [OMIM#191043] Arthrogryposis multiplex congenital, distal, type 2B [OMIM#601680]	AD	Sung <i>et al</i> , 2003 identified two different missense mutations in 4/34 kindreds with DA2B (11). This protein is part of the multimeric troponin-tropomyosin-myosin complex of the sarcomere.
<i>TNNT3</i> [OMIM#600692] Arthrogryposis, distal, type 2B [OMIM#601680]	AD	Sung <i>et al</i> , 2003 sequenced <i>TNNT3</i> in 47 families with DA2B and identified a missense mutation in a woman with DA2B and her 2 affected daughters (12). <i>TNNT3</i> is involved in the process of striated muscle contraction.
<i>TPM2</i> [OMIM#190990] Arthrogryposis, distal, type 1A [OMIM#108120] Arthrogryposis, distal, type 2B [OMIM#601680]	AD	Sung <i>et al</i> , 2003 identified a heterozygous missense mutation in <i>TPM2</i> in 1/14 probands with DA1A (11). Tajsharghi <i>et al</i> , 2007 identified a heterozygous missense mutations in <i>TPM2</i> in a mother and daughter with DA2B (13). The <i>TPM2</i> gene encodes beta-tropomyosin, an isoform of tropomyosin that is mainly expressed in slow, type 1 muscle fibers.

### Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

### Distal Arthrogryposis Panel (11 genes)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2,500
CPT codes:	81406 81407
Turn-around time:	8 weeks

**Note: We cannot bill insurance for the above test.**

### Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

**For more information about our testing options, please visit our website at [dnatesting.uchicago.edu](http://dnatesting.uchicago.edu) or contact us at 773-834-0555.**

### References:

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