Distal Arthrogryposis Panel

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Arthrogryposis multiplex congenita (AMC), or arthrogryposis, is a descriptive term for a group of disorders involving congenital contractures affecting two or more joints in different areas of the body. Arthrogryposis is a consequence of decreased or absent fetal movement (fetal hypokinesia or akinesia). Nongenetic etiologies include fetal crowding, uterine abnormalities, decreased amniotic fluid, and maternal illnesses such as myasthenia gravis or Zika infection. Genetic etiologies account for >50% of cases and include chromosome abnormalities and single gene disorders which affect the central nervous system, muscles, nerves, connective tissue, etc.[1] This group of disorders exhibits both clinical and genetic heterogeneity, making classification and diagnosis difficult, especially in prenatal cases with only approximately 25% of prenatal arthrogryposis diagnosed by ultrasound prior to 24 weeks gestation.[2]

Featured ARUP Testing

Distal Arthrogryposis Panel, Sequencing 3003917

Method: Massively Parallel Sequencing

- Use for the molecular confirmation of a diagnosis of distal arthrogryposis (DA).
- Do not order for the diagnosis of amyoplasia.
- Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary.

Disease Overview

Distal arthrogryposes (DAs) are a subset of genetic AMCs that involve contractures of the distal parts of the limbs. The contractures are congenital but occur in the absence of primary neurologic and/or muscle disease. The shared findings among DA include a consistent pattern of hand and foot involvement, limited involvement of the proximal joints, and variable expressivity. There are multiple types of DA caused by different genes (genetic heterogeneity).[3]

Symptoms of Arthrogryposis

- Multiple congenital contractures
- Decreased fetal movement/akinesia
- Abnormal position of hands/feet
- Central nervous system (CNS) anomalies
- Developmental delay/intellectual disability
- Seizures

Prevalence

Approximately 1/3,000 births[4]

Genetics

Genes

ECEL1, *FBN2*, *MYBPC1*, *MYH3*, *MYH8*,[a] *NALCN*,[a] *PIEZO2*,[a] *TNNI2*, *TNNT3*, *TPM2*

[a]One or more exons are not covered by sequencing for the indicated gene (see Limitations).

Inheritance

Variable: dependent on condition (see Genes Tested table)

Test Interpretation

Clinical Sensitivity

Variable: dependent on phenotype/condition

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One or more pathogenic variants detected	Diagnosis of heritable DA confirmed
Negative	No pathogenic variants detected	Diagnosis of heritable DA is less likely but not excluded
Uncertain	Variant of uncertain clinical significance	Unknown if variant is disease causing or benign

Limitations

- A negative result does not exclude a heritable form of arthrogryposis.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants
  - Large deletions/duplications in any of the tested genes
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - MYH8 (NM_002472) exon 5
    - NALCN (NM_001350748) exon 19
    - PIEZO2 (NM_022068) exon 4
- The following may not be detected:

- Deletions/duplications/insertions of any size by massively parallel sequencing
- Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
- Low-level somatic variants

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ECEL1	605065	Distal arthrogryposis, type 5D (DA5D)	AR
FBN2	121050	Distal arthrogryposis, type 9 (DA9) (Contractural arachnodactyly, congenital; CCA)	AD
MYBPC1	614335	Distal arthrogryposis, type 1B (DA1B)	AD
	614915	Lethal congenital contracture syndrome 4 (LCCS4)	AR
MYH3	193700	Distal arthrogryposis, type 2A (DA2A)	AD
	618436	Distal arthrogryposis type 2B (DA2B)	AD
	618469	Contractures, pterygia, and spondylocarpotarsal fusion syndrome 1B	AR
	178110	Contractures, pterygia, and spondylocarpostarsal fusion syndrome 1A (multiple pterygium syndrome)	AD
MYH8	158300	Distal arthrogryposis, type 7 (DA7) (trismus-pseudocamptodactyly syndrome)	AD
NALCN	616266	Congenital contractures of the limbs and face, hypotonia, and developmental delay (CLIFAHDD)	AD
	615419	Hypotonia, infantile, with psychomotor retardation and characteristic facies 1 (IHPRF1)	AR
PIEZO2	114300	Distal arthrogryposis, type 3 (DA3)	AD
	108145	Distal arthrogryposis, type 5 (DA5)	AD
	617146	Distal arthrogryposis with impaired proprioception and touch (DAIPT)	AR
	248700	Marden-Walker syndrome (MWKS)	AD
TNNI2	601680	Distal arthrogryposis, type 2B (DA2B1)	AD
TNNT3	618435	Distal arthrogryposis, type 2B2	AD
TPM2	108120	Distal arthrogryposis, type 1A (DA1A)	AD
	108120	Distal arthrogryposis, type 2B (DA2B4)	AD
	609285	Nemaline myopathy 4, autosomal dominant (NEM4)	AD

References

1. Niles KM, Blaser S, Shannon P, et al. Fetal arthrogryposis multiplex congenita/fetal akinesia deformation sequence (FADS)-aetiology, diagnosis, and management. *Prenat Diagn*. 2019;39(9):720-731.

2. Dieterich K, Le Tanno P, Kimber E, et al. The diagnostic workup in a patient with AMC: overview of the clinical evaluation and paraclinical analyses with review of the literature. *Am J Med Genet C Semin Med Genet*. 2019;181(3):337-344.

3. Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. *J Bone Joint Surg Am*. 2009;91 Suppl 4(Suppl 4):40-46.

4. Desai D, Stiene D, Song T, et al. Distal arthrogryposis and lethal congenital contracture syndrome - an overview. *Front Physiol*. 2020;11:689.

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com

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