Arthrogryposis Panel
Sequence Analysis and Exon-Level Deletion/Duplication Testing

PANEL GENE LIST

*ACTA1, AGRN, ALG14, ALG2, ALG3, ANTXR2, BICD2, BIN1, CHAT, CHMP1A**, CHRNA1, CHRNB1, CHRND, CHRNE, CHRNG, CHST14, CNTN1, CNTNAP1, COL6A1, COL6A2, COL6A3, COLQ, DHCR24, DNM2, DOK7, DPAGT1, ECEL1, EGR2, ERCC1, ERCC5, ERCC6, EXOSC3, FBN1, FBN2, FKBP10, FKRP*, FKTN, FLVCR2, GBA*, GBE1, GFPT1, GLE1, GMPPB, IGHMBP2, KAT6B, KLHL40, KLHL41, LMNA, LMOD3, LRP4, MAGEL2, MPZ, MTM1, MUSK, MYBPC1, MYH2, MYH3, MYH8, NALCN, NEB, PIEZO2, PIP5K1C, PLOD2, RAPSN, RIPK4, RYR1, SCARF2, SCN4A, SELENON, SKI, SLC35A3, SLC39A13, SLC5A7, SOX10, SYNE1, SYT2, TGFB3, TNNI2**, TNNT1**, TNNT3, TPM2, TPM3, TRIP4, TRPV4, TSEN54, TTN, UBA1, VIPAS39, VPS33B, ZC4H2*

*Sequence analysis only for *FKRP* and *GBA*

** Only whole gene deletions and duplications may be detected for *CHMP1A, TNNI2, and TNNT1*.

CLINICAL FEATURES

Arthrogryposis, also known as arthrogryposis multiplex congenita (AMC), describes the presence of multiple non-progressive congenital joint contractures in at least two different areas of the body, leading to restricted movement of the affected joints.[1,2] It generally results from fetal akinesia and has been noted as a clinical finding in more than 400 disorders. Fetal akinesia presents prenatally as abnormal joint positioning and/or lack of fetal movement on ultrasound. [3,4] Fetal akinesia, and therefore arthrogryposis, can be caused by a variety of primary defects including disorders of the central or peripheral nervous systems, neuromuscular junction, musculature, connective tissue, or metabolic pathways.[1,5] While the most common manifestations include talipes equinovarus (club foot) and flexion deformities of the wrists, involvement of the jaw, neck, or spine may be observed.[1]

Arthrogryposis subtypes are classified by clinical features and the presence or absence of neurogenic factors that result in diminished mobility in utero.[6,7] Amyoplasia and distal arthrogryposis (DA) are not associated with neurological dysfunction.[1] Amyoplasia is characterized by hypoplastic muscles and joint contractures and is the most common type of arthrogryposis, representing ~30% of all cases.[8] DA typically involves the distal limb joints.[6] Syndromic arthrogryposis results from disorders of the central nervous system and neuromuscular junction with common forms including fetal akinesia deformation sequence/Pena-Shokeir syndrome (FADS/PSP), lethal form multiple pterygium syndrome (LMPS), and lethal congenital contracture syndromes (LCCSs).[6] Clinical features of these disorders may include fetal hydrops, intrauterine growth restriction (IUGR), polyhydramnios, craniofacial anomalies (micrognathia, retrognathia, cleft palate), pulmonary hypoplasia, or a short umbilical cord.[9,10] Affected infants usually die in utero or very shortly after birth due to respiratory insufficiency.[10,11.]

GENETICS

Fetal akinesia and arthrogryposis can be due to genetic or environmental causes. Genetic forms of arthrogryposis can be inherited or de novo and follow autosomal dominant, autosomal recessive, and X-linked inheritance patterns. Pathogenic variants have been identified in genes that function in the central or peripheral nervous system, neuromuscular junction, skeletal muscle, or connective tissue.[1,6] Autosomal recessive forms of arthrogryposis are frequently associated with FADS, with many of the associated genes encoding components of the neuromuscular junction.[5] Autosomal dominant inheritance is frequently observed in the DA syndromes.

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: FKRP and GBA genes, no copy number testing, CHMP1A, TNNI2, and TNNT1 genes only whole gene deletions or duplications may be detected

CLINICAL SENSITIVITY

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype. A molecular diagnosis can be identified in more than half of (58-65%) individuals with arthrogryposis.[7,12] Specific information about the diagnostic yield for each gene in selected populations is summarized in the table below.

DIAGNOSTIC YIELD OF ARTHROGRYPOSIS PANEL GENES IN SELECTED POPULATIONS

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)a
ACTA1	AD/AR	Congenital fiber-type disproportion myopathy; Nemaline myopathy (NM)	15-25% of NM;[13] rare for AMC[7,14]
AGRN	AR	Congenital myasthenic syndrome(CMS)/Argrin deficiency	Rare for CMS[15,16]
ALG14	AR	ALG14-related CMS	Rare for CMS[17]
ALG2	AR	ALG2- related CMS	Rare for CMS;[17,18] rare for AMC[7]
ALG3	AR	Congenital disorder of glycosylation (CDG) 1d	Rare for CDG and AMC[7,19]
ANTXR2	AR	Hyaline fibromatosis syndrome	Rare for AMC[7,20]
BICD2	AD	Autosomal domianant congenital spinal muscular atrophy (DCSMA)	Unknown[7]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)a
BIN1	AD/AR	Centronuclear myopathy 2	~2% for AMC[7]
CHAT	AR	CMS	Rare for CMS;[21] rare for AMC[7]
CHMP1A	AR	Pontocerebellar hypoplasia, type 8	Rare for AMC[7]
CHRNA1	AD/AR	CMS; Lethal multiple pterygium syndromes (LMPS)	<1% for CMS;[22] ~3% for FADS[23]
CHRNB1	AD/AR	CMS	<1% for CMS;[22] rare for AMC[23]
CHRND	AD/AR	CMS; LMPS	<1% for CMS;[22] ~3% for FADS[23]
CHRNE	AD/AR	CMS	49% for CMS;[22] rare for AMC[7]
CHRNG	AR	LMPS; Escobar syndrome (EVMPS)	~27% of EVMPS;[24] 5-8% patients with LMPS/FADS;[23,24] 7-10% for AMC[12,25]
CHST14	AR	Ehlers-Danlos syndrome,musculocontractural type 1(MC-EDS)	90% for MC-EDS[26]
CNTN1	AR	Compton-North congenital myopathy	Rare for AMC[7]
CNTNAP1	AR	Congenital hypomyelinating neuropathy;Lethal congenital contracture syndrome 7 (LCCS7)	~13% for AMC[25]
COL6A1	AD/AR	Ullrich congenital muscular dystrophy(UCMD)	~62% of patients with Ullrich or Bethlem myopathy have been found to have a mutation in one of the three collagen VI genes (*COL6A1, COL6A2, COL6A3*);[27] rare for AMC[7]
COL6A2	AD/AR	CMS	Rare for CMS[21]
DHCR24	AR	Desmosterolosis	Rare for AMC[7,28]
DNM2	AD/AR	Centronuclear myopathy; Charcot-Marie-Tooth disease(CMT); LCCS5	3% for CMT;[29] rare for AMC[7]
DOK7	AR	DOK7-related CMS; Fetal akinesia deformation sequence (FADS)	10-21% of CMS;[21,30] ~7% for lethal MPS/FADS without *CHRNG*,

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)a
			CHRNA1,CHRNB1,CHRND, or *RAPSN*[31]
DPAGT1	AR	DPAGT1-related CMS	<1% CMS;[32] rare for AMC[7,33]
ECEL1	AR	DA 5D	~70% DA5D;[34] ~3-6% for AMC[12,25]
EGR2	AD/AR	CMS type 1D; Congenital hypomyelinating neuropathy; Dejerine-Sottas disease	Rare for AMC[7]
ERCC1	AR	Cerebrooculofacioskeletal syndrome 4 (COFS4)	Rare for AMC[7,35]
ERCC5	AR	COFS3; Cockayne syndrome; Xeroderma pigmentosum, group G	Rare for AMC[7,36]
ERCC6	AR	COFS1; Cockayne syndrome; Xeroderma pigmentosum, group G	Rare for AMC[7,37]
EXOSC3	AR	Pontocerebellar hypoplasia, type 1B	Rare for AMC[7,38]
FBN1	AD	Marfan syndrome	Rare for AMC[7,39]
FBN2	AD	DA9/Congenital contractural arachnodactyly	>75% for CCA[40]
FKBP10	AR	Bruck syndrome; Osteogenesis imperfecta, type XI	Rare for AMC[7,41]
FKRP	AR	Walker–Warburg syndrome; CMD with/without intellectual disability and microcephaly; LGMD type 2	~6% of LGMD;[42] ~9% of the alphadystroglycanopathies;[43] Rare for AMC[7]
FKTN	AR	Fukuyama congenital muscular dystrophy; LGMD type 2M	~7% of th alpha-dystroglycanopathies;[44] rare for AMC[7]
FLVCR2	AR	Proliferative vasculopathy and hydranencephaly-hydrocephaly syndrome	Rare for AMC[7,45]
GBA	AR	Gaucher disease	Rare for AMC[7,46]
GBE1	AR	Glycogen storage disease IV	3% of glycogen storage disease;[47] ~2% for AMC[7]
GFPT1	AR	GFPT1-related CMS	Unknown[22]
GLE1	AR	LCSS1/Lethal arthrogryposis with anterior horn cell disease	Unknown[48]
GMPPB	AR	GMPPB-related CMS	Rare[49]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)a
IGHMBP2	AR	Spinal muscular atrophy with respiratory distress 1 (SMARD)	~33% of patients with SMARD;[50] rare for AMC[7,51]
KAT6B	AD	Genitopatellar syndrome; Say-Barber-Biesecker syndrome	Rare[7,52]
KLHL40	AR	NM	~20% of severe NM;[53] rare for AMC[7]
KLHL41	AR	NM	Rare for AMC[7]
LMNA	AD/AR	Emery-Dreifuss muscular dystrophy (EDMD); LGMD type 1B; Congenital laminopathy; Restrictive dermopathy	~25% for restrictive dermopathy[54]
LMOD3	AR	NM	Unknown[3,55]
LRP4	AD/AR	Cenani-Lenz syndrome (CLS); CMS; Sclerosteosis	Rare for CMS[56]
MAGEL2	AD	Schaaf-Yang syndrome	Unknown[57]
MPZ	AD	Charcot-Marie-Tooth disease; Congenital hypomyelinating neuropathy; Dejerine-Sottas disease	Rare[7,58]
MTM1	XLR	Myotubular myopathy	Rare for AMC[5,7]
MUSK	AR	CMS;FADS	Rare for CMS;[21] unknown for AMC, founder mutation (p.Ile575Thr) causing FADS among the Dutch[59]
MYBPC1	AD/AR	DA1; LCCS 4	~13% for DA1[60]
MYH2	AD/AR	DA5; Proximal myopathy and ophthalmoplegia	Rare for DA5[6]
MYH3	AD	DA1; DA2A/FSS;DA2B/SHS;DA8	~8% for DA1; 62 90% for DA2A/FSS;[62,63] 11-32% for DA2B/SHS;[61,62] rare for DA8;[64] ~3% for all AMC[25]
MYH8	AD	DA7/Trismus-pseudocamptodactyly syndrome	Rare, single mutation reported: R674Q[65]
NALCN	AD/AR	Congenital contractures of the limbs and face with hypotonia, and developmental delay; Infantile hypotonia with psychomotor retardation and characteristic facies (IHPRF)	De novo,~4% individuals affected with DA[66]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)a
NEB	AR	NM	~50% of NM;[67] ~6% for AMC[25]
PIEZO2	AD/AR	DA 3/Gordon syndrome & DA 5	~83% for DA3 and ~82% for DA5[68]
PIP5K1C	AR	LCCS3	Rare for AMC[7,69]
PLOD2	AR	Bruck syndrome 2	Rare for AMC [7,70]
RAPSN	AR	CMS;FADS	~1.5% for FADS;[23] ~3% for AMC[25]
RIPK4	AR	Lethal popliteal pterygium syndrome/Bartsocas-Papas type	Rare[7,71]
RYR1	AD/AR	Central core disease; Minicore myopathy with external ophthalmoplegia	~89% of central core disease;[72] ~16% for AMC[25]
SCARF2	AR	Van den Ende-Gupta syndrome	Rare[7,73]
SCN4A	AR	CMS; Paramyotonia congenita; Hyperkalemic periodic paralysis type 2; Hypokalemic periodic paralysis type 2	Rare[5,21,22]
SELENON	AD/AR	Rigid spine muscular dystrophy 1; Congenital fiber type disproportion myopathy	Unknown[74]
SKI	AD	Shprintzen-Goldberg syndrome	Rare for AMC[7,75]
SLC35A3	AR	Arthrogryposis, mental retardation, and seizures	Rare for AMC[7,76]
SLC39A13	AR	Ehlers-Danlos syndrome, spondylodysplastic type, 3	Rare for AMC[7]
SLC5A7	AD/AR	CMS; Distal hereditary motor neuropathy, type VIIA	Unknown[77]
SOX10	AD	Waardenburg syndrome	Rare for AMC[7,78]
SYNE1	AD/AR	Cerebellar ataxia type 1;Emery-Dreifuss muscular dystrophy 4	3% for AMC[25]
SYT2	AD	SYT2-related CMS	Rare[79,80]
TGFB3	AD	Loeys-Dietz syndrome 5; Arrhythmogenic right ventricular dysplasia 1	Rare for AMC[7,81]
TNNI2	AD	DA1&2B	~10% of DA2B and~6% for DA1[61]
TNNT1	AR	NM	Rare (NMD) overall;[82] rare for AMC[7]
TNNT3	AD	DA1&2B	~8% for DA1 and ~7% for DA2B;[61] ~3% for AMC[25]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)a
TPM2	AD	DA 1&2B; NM	~6% for DA1 and ~10% for DA2B;[61] ~2% for AMC[7]
TPM3	AD/AR	NM	2-3% of NM;[83] rare [7,84]
TRIP4	AR	SMA	Rare for AMC[7]
TRPV4	AD	Scapuloperoneal SMA	~3% for AMC[25]
TSEN54	AR	Pontocerebellar hypoplasia	Rare[7,85]
TTN	AD/AR	Salih Myopathy	~100% of Salih myopathy[90]
UBA1	XLR	X-linked-SMA	Rare for AMC[7,86]
VIPAS39	AR	Arthrogryposis, renal dysfunction, and cholestasis-2 (ARCS2) syndrome	Rare for AMC[7,87]
VPS33B	AR	Arthrogryposis, renal dysfunction, and cholestasis 1 (ARC-1) syndrome	Rare for AMC[7,88]
ZC4H2	XLR	Wieacker-Wolff syndrome	Rare[89]

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