Blueprint Genetics

Arthrogryposes Panel

Test code: MA0501

Is a 78 gene panel that includes assessment of non-coding variants.

Is ideal for patients with a clinical suspicion of arthrogryposis or fetal akinesia.

Arthrogryposes are a group of disorders that involve congenital joint contractures. This comprihensive panel includes Fetal Akinesia Deformation Sequence / LMPS / Related Disorder Panel and covers, but is not limited to the disrders covered by the subpanels. This panel enables effective differential diagnostics of arthrogryposes and associated diseases. The Panel is also part of Comprehensive Skeletal / Malformation Syndrome Panel.

About Arthrogryposes

Arthrogryposis (also known as arthrogryposis multiplex congenita, AMC) is characterized by congenital contractures of 2 or more different body areas without a primary neurologic or muscle disease. Children born with joint contractures have abnormal fibrosis of the muscle tissue causing muscle shortening, and therefore are unable to perform passive extension and flexion in the affected joints. Arthrogryposis has been divided into three groups: amyoplasia, distal arthrogryposis, and syndromic. Amyoplasia is characterized by severe joint contractures and muscle weakness while distal arthrogryposis mainly involves the hands and feet. Syndromic arthrogryposis consists with a primary neurological or muscle disease. 70-80% of arthrogryposes are caused by neurological abnormalities and most types that have primary neurological or muscle disease result from an underlying genetic syndrome. More than 35 specific genetic disorders associated with arthrogryposis have been described. Fetal akinesia deformation sequence syndrome (FADS) is characterised by decreased fetal movement (fetal akinesia) as well as intrauterine growth restriction, arthrogryposis, and developmental anomalies.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Arthrogryposes Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ACTA1	Myopathy	AD/AR	68	212
ADGRG6	Lethal congenital contracture syndrome 9	AR	4	4
AGRN	Myasthenic syndrome, congenital	AR	14	16
BIN1	Myopathy, centronuclear	AD/AR	9	15
CACNA1E	Epileptic encephalopathy	AD	8	6
CASK	Mental retardation and microcephaly with pontine and cerebellar hypoplasia, FG syndrome, Mental retardation	XL	87	112
CFL2	Nemaline myopathy	AR	2	9
CHAT	Myasthenic syndrome, congenital	AR	24	73
CHRNA1	Myasthenic syndrome, congenital	AD/AR	28	35
CHRNB1	Myasthenic syndrome	AD/AR	11	11

CHRND	Myasthenic syndrome	AD/AR	18	26
CHRNE	Myasthenic syndrome	AD/AR	48	134
CHRNG	Multiple pterygium syndrome, Escobar syndrome	AR	17	34
CHST14	Ehlers-Danlos syndrome, musculocontractural	AR	15	21
CHUK	Cocoon syndrome	AR	2	5
CNTNAP1	Lethal congenital contracture syndrome 7	AR	10	21
COL6A2	Epilepsy, progressive myoclonic, Bethlem myopathy, Myosclerosis, congenital, Ullrich congenital muscular dystrophy	AD/AR	101	182
COLQ	Myasthenic syndrome, congenital	AR	23	67
DHCR24	Desmosterolosis	AR	6	9
DOK7	Myasthenic syndrome, congenital	AR	28	75
DPAGT1	Congenital disorder of glycosylation, Myasthenic syndrome, congenital	AR	16	32
ECEL1	Arthrogryposis	AR	25	31
EGR2	Neuropathy, Dejerine-Sottas disease, Charcot-Marie-Tooth disease	AD/AR	13	21
ERBB3	Lethal congenital contractural syndrome 2	AR	11	4
ERCC5	Xeroderma pigmentosum, Xeroderma pigmentosum/Cockayne syndrome	AR	21	54
ERCC6*	Xeroderma Pigmentosum-Cockayne Syndrome, De Sanctis-Cacchione syndrome	AD/AR	87	135
EXOSC3	Pontocerebellar hypoplasia	AR	11	19
FBN2	Congenital contractural arachnodactyly (Beals syndrome)	AD	50	97
FHL1*	Myopathy with postural muscle atrophy, Emery-Dreifuss muscular dystrophy, Reducing bod myopathy	XL	26	62
FKBP10	Bruck syndrome 1, Osteogenesis imperfecta, type XI	AR	20	44
FKTN	Muscular dystrophy-dystroglycanopathy, Dilated cardiomyopathy (DCM), Muscular dystrophy-dystroglycanopathy (limb-girdle)	AD/AR	45	58
FLVCR2	Proliferative vasculopathy and hydraencephaly-hydrocephaly syndrome	AR	9	17
GBA*	Gaucher disease	AR	84	488
GBE1	Glycogen storage disease	AR	36	70
GFPT1	Myasthenic syndrome, congenital	AR	13	42
GLDN	Lethal congenital contracture syndrome 11	AR	11	11
GLE1	Lethal congenital contracture syndrome, Arthrogryposis, lethal, with anterior horn cell disease	AR	7	17
KAT6B	Ohdo syndrome, SBBYS variant, Genitopatellar syndrome	AD	47	73

KIAA1109	Craniofacial dysmorphism, skeletal anomalies, and mental retardation syndrome	AR	7	16
KLHL40	Nemaline myopathy	AR	11	26
LGI4	Arthrogryposis multiplex congenita, neurogenic, with myelin defect	AR	9	7
LMNA	Heart-hand syndrome, Slovenian, Limb-girdle muscular dystrophy, Muscular dystrophy, congenital, LMNA-related, Lipodystrophy (Dunnigan), Emery-Dreiffus muscular dystrophy, Malouf syndrome, Dilated cardiomyopathy (DCM), Mandibuloacral dysplasia type A, Progeria Hutchinson-Gilford type	AD/AR	250	564
MPZ	Neuropathy, Roussy-Levy syndrome, Dejerine-Sottas disease, Charcot-Marie-Tooth disease	AD	108	241
MTM1	Myopathy, centronuclear	XL	158	301
MUSK	Myasthenic syndrome, congenital	AR	17	22
MYBPC1	Arthrogryposis, Lethal congenital contractural syndrome	AD/AR	7	7
MYH2	Inclusion body myopathy	AD	24	24
MYH3	Arthrogryposis	AD	21	45
MYH8	Carney complex variant, Arthrogryposis, distal, type 7, Trismus-pseudocamptodactyly syndrome	AD	1	2
NALCN	Neuroaxonal neurodegeneration, infantile, with facial dysmophism, Congenital contractures of the limbs and face, hypotonia, and developmental delay	AD/AR	47	50
NEB*	Nemaline myopathy	AR	305	309
PIEZO2*	Marden-Walker syndrome, Distal arthrogryposis	AD	30	28
PLOD2	Bruck syndrome, Osteogenesis imperfecta type 3	AR	8	23
PMM2	Congenital disorder of glycosylation	AR	76	128
PPP3CA	Epilepitic encephalopathy	AD	8	11
RAPSN	Myasthenic syndrome, congenital	AR	26	58
RARS2#	Pontocerebellar hypoplasia	AR	23	37
RIPK4	Popliteal pterygium syndrome, lethal type, Bartsocas-Papas syndrome	AR	4	15
SCO2	Leigh syndrome, Hypertrophic cardiomyopathy (HCM), Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency, Myopia	AR	42	37
SELENON	Muscular dystrophy, rigid spine, Myopathy, congenital, with fiber-disproportion	AR	38	63
SMN1*,#	Spinal muscular atrophy	AR	29	111
SMN2*,#	Spinal muscular atrophy	AD	1	9

TGFB3	Loeys-Dietz syndrome (Reinhoff syndrome), Arrhythmogenic right ventricular dysplasia	AD	19	26
TK2	Mitochondrial DNA depletion syndrome	AR	38	52
TNNI2	Arthrogryposis multiplex congenita	AD	5	11
TNNT1	Nemaline myopathy	AR	6	8
TNNT3	Arthyrgryposis, distal, type 2B	AD	3	4
TPM2	CAP myopathy, Nemaline myopathy, Arthrogryposis, distal	AD	18	38
TPM3*	CAP myopathy, Nemaline myopathy, Myopathy, congenital, with fiber-disproportion	AD	21	27
TRPV4	Metatropic dysplasia, Spondyloepiphyseal dysplasia Maroteaux type, Parastremmatic dwarfism, Hereditary motor and sensory neuropathy, Spondylometaphyseal dysplasia Kozlowski type, Spinal muscular atrophy, Charcot-Marie-Tooth disease, Brachyolmia (autosomal dominant type), Familial Digital arthropathy with brachydactyly	AD	61	78
TSEN2	Pontocerebellar hypoplasia	AR	8	5
TSEN54	Pontocerebellar hypoplasia	AR	23	21
UBA1	Spinal muscular atrophy, infantile	XL	3	5
VIPAS39	Arthrogryposis, renal dysfunction, and cholestasis 2	AR	8	13
VPS33B	Arthrogryposis - renal dysfunction - cholestasis	AD/AR	17	58
VRK1	Pontocerebellar hypoplasia	AR	9	9
ZBTB42	Lethal congenital contracture syndrome	AR	2	1
ZC4H2	Wieacker-Wolff syndrome	XL	20	16

*Some regions of the gene are duplicated in the genome. Read more.

The gene has suboptimal coverage (means <90% of the gene's target nucleotides are covered at >20x with mapping quality score (MQ>20) reads), and/or the gene has exons listed under Test limitations section that are not included in the panel as they are not sufficiently covered with high quality sequence reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#)

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database (ClinVar); HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD). The list of associated, gene specific phenotypes are generated from CGD or Mitomap databases.

Non-coding disease causing variants covered by the panel

Gene	Genomic location HG19	HGVS	RefSeq	RS-number
CHRNE	Chr17:4804936	c.501-16G>A	NM_000080.3	
CHRNE	Chr17:4806452	c.-94G>A	NM_000080.3	

CHRNE	Chr17:4806453	c.-95G>A	NM_000080.3	
CHRNE	Chr17:4806454	c.-96C>T	NM_000080.3	rs748144899
COL6A2	Chr21:47538492	c.1117-35_1118dupAAAAGACGTGAGGCTGATTCTGCAAACCCTTCCAGGG	NM_001849.3	
COL6A2	Chr21:47541407	c.1459-63G>A	NM_001849.3	
ERCC5	Chr13:103514354	c.881-26T>G	NM_000123.3	
ERCC6	Chr10:50681659	c.2599-26A>G	NM_000124.3	rs4253196
EXOSC3	Chr9:37782146	c.475-12A>G	NM_016042.3	rs370087266
FBN2	Chr5:127670560	c.3974-24A>C	NM_001999.3	
FBN2	Chr5:127670562	c.3974-26T>G	NM_001999.3	
FBN2	Chr5:127671284	c.3725-15A>G	NM_001999.3	
FKTN	Chr9:108368857	c.648-1243G>T	NM_006731.2	
GBA	Chr1:155205646	c.1225-14_1225-11delTGTCinsAGT	NM_000157.3	
GBA	Chr1:155208109	c.589-12C>G	NM_000157.3	
GBA	Chr1:155211053	c.-150A>G	NM_000157.3	rs1232943445
GBE1	Chr3:81542964	c.2053-3358_2053-3350delGTGTGGTGGinsTGTTTTTTACATGACAGGT	NM_000158.3	rs869320698
LMNA	Chr1:156100609	c.513+45T>G	NM_170707.3	
LMNA	Chr1:156105681	c.937-11C>G	NM_170707.3	rs267607645
LMNA	Chr1:156107037	c.1608+14G>A	NM_170707.3	
LMNA	Chr1:156107433	c.1609-12T>G	NM_170707.3	rs267607582
MTM1	ChrX:149767035	c.137-19_137-16delACTT	NM_000252.2	
MTM1	ChrX:149767045	c.137-11T>A	NM_000252.2	
MTM1	ChrX:149783032	c.232-26_232-23delGACT	NM_000252.2	
MTM1	ChrX:149808833	c.529-909A>G	NM_000252.2	
MTM1	ChrX:149818176	c.868-13T>A	NM_000252.2	
NEB	Chr2:152355017	c.24220-151C>A	NM_001271208.1	
NEB	Chr2:152410918	c.19429-381_19429-379delTTTinsA	NM_001271208.1	
PMM2	Chr16:8891573		NM_000303.2	
PMM2	Chr16:8898599	c.179-25A>G	NM_000303.2	rs760689221
PMM2	Chr16:8926102	c.640-15479C>T	NM_000303.2	rs1258107584
PMM2	Chr16:8941558	c.640-23A>G	NM_000303.2	
RAPSN	Chr11:47469717	c.193-15C>A	NM_005055.4	
RAPSN	Chr11:47470715	c.-199C>G	NM_005055.4	
RAPSN	Chr11:47470726	c.-210A>G	NM_005055.4	rs786200905
RARS2	Chr6:88244587	c.613-3927C>T	NM_020320.3	
SELENON	Chr1:26143316	c.*1107T>C	NM_020451.2	
TGFB3	Chr14:76425035	c.*495C>T	NM_003239.2	rs387906514

TGFB3	Chr14:76447266	c.-30G>A	NM_003239.2	rs770828281
VPS33B	Chr15:91550814	c.499-11G>A	NM_018668.3	

Test Strengths

All exons of the *GBA* gene have segmentally duplicated pseudogenes that reduce sensitivity of NGS diagnostics in general. However, Blueprint Genetics custom assay has good coverage (>20x) with high mapping rates (mapping quality >40) for 100.0% of the target regions in *GBA* gene. Our validation showed high mean coverage of 184X for the *GBA* gene. Thus, our NGS Panel is not expected to have major limitations in detecting variants in *GBA* gene although clinical validation has not been performed at large scale for Gaucher disease.

Deletion / duplication analysis (either in isolation or as part of Plus analysis including sequencing) testing can detect the copy number of *SMN1* exon 7, which is commonly used as a marker for copy number of the *SMN1* gene. In individuals identified to have homozygous *SMN1* deletions, we include reporting of *SMN2* copy number.

The strengths of this test include:

- CAP accredited laboratory
- CLIA-certified personnel performing clinical testing in a CLIA-certified laboratory
- Powerful sequencing technologies, advanced target enrichment methods and precision bioinformatics pipelines ensure superior analytical performance
- Careful construction of clinically effective and scientifically justified gene panels
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Our Nucleus online portal providing transparent and easy access to quality and performance data at the patient level
- Our publicly available analytic validation demonstrating complete details of test performance
- ~2,000 non-coding disease causing variants in our clinical grade NGS assay for panels (please see 'Non-coding disease causing variants covered by this panel' in the Panel Content section)
- Our rigorous variant classification scheme
- Our systematic clinical interpretation workflow using proprietary software enabling accurate and traceable processing of NGS data
- Our comprehensive clinical statements

Test Limitations

Due to high sequence homology between *SMN1* and *SMN2*, this panel has not been validated to detect single nucleotide variants or small insertions and deletions in *SMN1* which are associated with spinal muscular atrophy in a small number of patients (<5%). The following exons are not included in the panel as they are not sufficiently covered with high quality sequence reads: *SELENON* (NM_020451:3), *TK2* (NM_001271934:3), *TSEN2* (NM_001321278:12). Genes with suboptimal coverage in our assay are marked with number sign (#) and genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. Gene is considered to have suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (please see the Panel Content section)
- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

- Low level mosaicism in nuclear genes (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Low level heteroplasmy in mtDNA (>90% are detected at 5% level)
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments
- Some disease causing variants present in mtDNA are not detectable from blood, thus post-mitotic tissue such as skeletal muscle may be required for establishing molecular diagnosis.

The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics.

For additional information, please refer to the Test performance section and see our Analytic Validation.

Test performance

The Blueprint Genetics arthrogryposes panel covers classical genes associated with arthrogryposis. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sliced from our high-quality whole exome sequencing data. Please see our sequencing and detection performance table for different types of alterations at the whole exome level (Table).

Assays have been validated for different starting materials including EDTA-blood, isolated DNA (no FFPE), saliva and dry blood spots (filter card) and all provide high-quality results. The diagnostic yield varies substantially depending on the assay used, referring healthcare professional, hospital and country. Blueprint Genetics' Plus Analysis (Seq+Del/Dup) maximizes the chance to find a molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be a cost-effective first line test if your patient's phenotype is suggestive of a specific mutation type.

The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sectioned from our high-quality, clinical grade NGS assay. Please see our sequencing and detection performance table for details regarding our ability to detect different types of alterations (Table).

	Sensitivity % (TP/(TP+FN)	Specificity %
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		
1-10 bps	96.9% (7,563/7,806)	>99.9999%
11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA
Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%

Microdeletion/-duplication sdrs (large CNVs, n=37))	
Size range (0.1-47 Mb)	100% (37/37)
The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics	
Mean sequencing depth	143X
Nucleotides with >20x sequencing coverage (%)	99.86%

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

	Sensitivity %	**Specificity %**
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%
Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		
Single nucleotide variants n=2026 SNVs		
Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.3% (12/13)	99.98%
Heteroplasmic (<5%)	88.9% (48/54)	99.93%
Insertions and deletions by sequence analysis n=40 indels		
Heteroplasmic (45-100%) 1-10bp	100.0% (32/32)	100.0%

Heteroplasmic (5-45%) 1-10bp	100.0% (3/3)	100.0%
Heteroplasmic (<5%) 1-10bp	100.0% (5/5)	99,997%
SIMULATION DATA /(mitomap mutations)		
Insertions, and deletions 1-24 bps by sequence analysis; n=17		
Homoplasmic (100%) 1-24bp	100.0% (17/17)	99.98%
Heteroplasmic (50%)	100.0% (17/17)	99.99%
Heteroplasmic (25%)	100.0% (17/17)	100.0%
Heteroplasmic (20%)	100.0% (17/17)	100.0%
Heteroplasmic (15%)	100.0% (17/17)	100.0%
Heteroplasmic (10%)	94.1% (16/17)	100.0%
Heteroplasmic (5%)	94.1% (16/17)	100.0%
Copy number variants (separate artifical mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%
The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X
Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%	
rho zero cell line (=no mtDNA), mean sequencing depth	12X	

Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the 'Test limitations" section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases such as, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, the customer has an access to details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with inadequate coverage if present. This reflects our mission to build fully transparent

diagnostics where customers have easy access to crucial details of the analysis process.

Clinical interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis of sequence variants is confirmation of variants classified as pathogenic or likely pathogenic using bi-directional Sanger sequencing. Variant(s) fulfilling the following criteria are not Sanger confirmed: the variant quality score is above the internal threshold for a true positive call, and visual check-up of the variant at IGV is in-line with the variant call. Reported variants of uncertain significance are confirmed with bi-directional Sanger sequencing only if the quality score is below our internally defined quality score for true positive call. Reported copy number variations with a size <10 exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in population cohorts and detailed information about related phenotypes. We also provide links to the references used, congress abstracts and mutation variant databases used to help our customers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification within the family. In the case of variants of uncertain significance (VUS), we do not recommend family member risk stratification based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD codes

Commonly used ICD-10 codes when ordering the Arthrogryposes Panel

ICD-10	Disease
Q74.3	Arthrogryposis

Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3µg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient's name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- American Association of Neuromuscular & Electrodiagnostic Medicine
- Arthrogryposis Multiplex Congenita Support
- Bamshad M et al. Arthrogryposis: a review and update. J Bone Joint Surg Am. 2009 Jul;91 Suppl 4:40-6.
- European Alliance for Arthrogryposis
- GeneReviews
- GeneReviews - Congenital Contractural Arachnodactyly
- GeneReviews - Congenital Myasthenic Syndromes
- GeneReviews - Spinal Muscular Atrophy
- Genetic and Rare Disease Information Center
- Kowalczyk B et al. Arthrogryposis: an update on clinical aspects, etiology, and treatment strategies. Arch Med Sci. 2016 Feb 1;12(1):10-24.
- Muscular Dystrophy Association
- NORD - Arthrogryposis
- NORD - Arthrogryposis Multiplex Congenita
- National Organization for Rare Disorders
- The Arthrogryposis Group