Arthrogryposis as a Syndrome: Gene Ontology Analysis

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Abstract

Arthrogryposis by definition has multiple congenital contractures. All types of arthrogryposis have decreased in utero fetal movement. Because so many things are involved in normal fetal movement, there are many causes and processes that can go awry. In this era of molecular genetics, we have tried to place the known mutated genes seen in genetic forms of arthrogryposis into biological processes or cellular functions as defined by gene ontology. We hope this leads to better identification of all interacting pathways and processes involved in the development of fetal movement in order to improve diagnosis of the genetic forms of arthrogryposis, to lead to the development of molecular therapies, and to help better define the natural history of various types of arthrogryposis.

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Arthrogryposis is the term that has been used for the last century to describe individuals born with multiple congenital contractures (e.g., 2 or more areas in different body parts with limitation of movement present at birth) [Hall, 2014]. Multiple congenital contractures have been

recognized at birth for hundreds of years, particularly because there is often difficulty with delivery, and the contractures are obviously present in the newborn. Often in the past, severely affected individuals did not survive. During the last century, the term arthrogryposis multiplex congenita was often used for multiple congenital contractures. However, arthrogryposis and arthrogryposis multiplex congenita are both descriptive terms or signs rather than a specific diagnosis [Hall, 2012, 2014].

What makes arthrogryposis so interesting is that anything which interferes with normal fetal movement may lead to congenital contractures. In the severest form, fetal akinesia deformation sequence, secondary deformations of multiple tissues are seen (craniofacial changes, pulmonary hypoplasia, polyhydramnios, decreased gut mobility and shortened gut, short umbilical cord, skin changes, and multiple joints with limitation of movement, including limbs, jaw, and spine) [Hall, 2009].

Nowadays, the recognition of an affected infant is possible prenatally utilizing real-time ultrasound studies; however, the presence of joint contractures is most often missed [Filges and Hall, 2013]. In arthrogryposis, delivery is often breech and difficult, leading to C-section. In spite of a C-section, fractures of the long bones occur in the perinatal period in at least 10% of affected infants [Hall et al., 2014].

Arthrogryposis is not all that infrequent occurring in about 1/3,000 pregnancies [Lowry et al., 2010]. Of these children, about 1/3 will primarily have limbs affected, 1/3 will have limbs plus other body areas affected with nor-

mal intelligence, and 1/3 will have central nervous system dysfunction (in the past, half of these would die at birth or in the first year, or have such severe involvement as to be lethal) [Hall, 2012]. Amyoplasia is the most common form of arthrogryposis occurring in about 1/10,000 live births [Hall et al., 2014]. Amyoplasia is recognized by its unique clinical features. Individuals with this form usually do surprisingly well and have normal to high intelligence, but it appears to be totally sporadic (although increased in one of monozygotic twins). Most other recognizable types of arthrogryposis have a genetic basis (i.e., single gene mutation) [Michalk et al., 2008; Hall, 2014; Hunter et al., 2015; Bayram et al., 2016].

Over the last 40 years, the heterogeneity and diversity of specific disorders has begun to be recognized and delineated. Over 400 different specific conditions with arthrogryposis have been recognized and over 320 genes implicated [Michalk et al., 2008; Hall, 2014; Hunter et al., 2015; Bayram et al., 2016]. There is a need to annotate and functionally group these genes into known pathways and biological processes. Such a grouping has potential for identification and prioritization of other candidate disease genes. Additionally, it should inform the development of better molecular diagnostic techniques and specific therapeutic options. Until now, nonspecific physical therapy to loosen contractures and realign joints, casting, and surgeries to improve joint function have been the standard therapy.

It is clear that anything which limits or interferes with fetal movement may lead to congenital contractures (limitation of joint movement) [Hall, 2012, 2014]. These include myopathic processes with structural elements, ion channels, and mechanosensing elements; neuropathic processes including central and peripheral nerves, anterior horn cells, and brain organization and function; myelin deficiency; neuromotor endplate abnormalities; connective tissue disorders; limitation of space and constraint in utero; vascular compromise (decreased blood flow to the placenta or to the embryo/fetus); teratogenic exposure, and maternal illnesses. Any of the above-mentioned processes or clinical situations may lead to decreased fetal movement. Even hypotonia of the fetus may be severe enough to decrease in utero movement sufficiently, leading to contractures at birth.

We performed an enrichment analysis (EA) to identify overrepresented functional biological groupings within the list of assembled 320 genes (table 1). EA is a common bioinformatic technique to describe common biological aspects associated with a list of genes. Gene lists are often the output of high-throughput genomics experiment or, in the case here, a listing of genes associated

with a disease process. EA involves computing an enrichment statistic across a corpus of gene sets to identify over- and/or underrepresented gene sets in the gene list being interrogated. A corpus of gene sets is a collection of genes categorized together based on some biological aspect or property. The outcome of EA results in a list of statistically enriched gene sets describing the biological properties common within the given gene list. This allows for biologist interpretation of gene lists, whether it is a differential gene expression list or a list of genes associated with a disease state, such as the syndrome of arthrogryposis detailed in this review.

Popular gene set libraries used for EA include manually curated gene sets representing canonical signaling pathways, such as Reactome [Croft et al., 2014], and structured gene sets based on the Gene Ontology (GO) resource [Gene Ontology Consortium, 2015]. The GO is a resource, in the form of a structured ontology, which describes and categorizes gene product functions in distinct categories and the relationships between them. The GO functional categories are classified in 3 general categories: biological process, molecular function, and cellular component. The biological process category contains individual GO terms that describe processes associated with molecular events and pathways representing multi-protein-dependent functions. The molecular function category, in contrast, describes basic gene functions at the molecular level. Lastly, the cellular component category describes the location, environment, or part of the cell, so that the gene product can be located.

The EA for this review was performed using the software tool ClueGO [Bindea et al., 2009]. ClueGO calculates enrichment scores for selected gene sets against a user-provided gene list. Our analysis was performed using the biological process and cellular component categories of the gene ontology. The biological process category was selected because it captures functional descriptions that provide a better biological interpretation based on multicomponent signaling and functional groupings. The cellular component category was selected as it provides details on not only intracellular locations, but also higher ordered structures such as the 'synaptic membrane'. The other main benefit of performing EA with ClueGO is that it groups similar GO terms and provides a network-based view of the enriched GO terms. This is important in that it aides interpretation of results by grouping related GO terms, based on shared gene members, presenting the results as a network. Since GO has a hierarchical ontological-based structure, GO terms often have overlapping gene members. When results of enrich-

Table 1. Gene table

Gene	Entrez Gene ID	Aliases	Functions
ABCC8	6833	ABC36, HHF1, HI, HRINS, MRP8, PHHI, SUR, SUR1, SUR1delta2, TNDM2	sarcolemma, synaptic transmission
ACTA1	58	ACTA, ASMA, CFTD, CFTD1, CFTDM, MPFD, NEM1, NEM2, NEM3	striated muscle thin filament, muscle filament sliding
ACTB	60	BRWS1, PS1TP5BP1	axon guidance, regulation of body fluid levels
ACTG1	71	ACT, ACTG, BRWS2, DFNA20, DFNA26, HEL-176	striated muscle cell development, muscle cell development
ADAMTS10	81794	ADAM-TS10, ADAMTS-10, WMS, WMS1	proteinaceous extracellular matrix
ADAMTSL2	9719	GPHYS1	lung development, respiratory system development
ADCY6	112	AC6, LCCS8	sarcolemma, regulation of neurogenesis
ADGRG6	57211	APG1, DREG, GPR126, PS1TP2, VIGR	axon ensheathment
ADSL	158	AMPS, ASASE, ASL	carbohydrate derivative biosynthetic process
AIMP1	9255	EMAP2, EMAP11, HLD3, SCYE1, p43	regulation of epithelial cell proliferation, epithelial cell proliferation
AKT1	207	AKT, CWS6, PKB, PKB-ALPHA, PRKBA, RAC, RAC-ALPHA	Schwann cell development, Schwann cell differentiation
ALG2	85365	CDG1i, CMS14, CMSTA3, NET38, hALPG2	mannosylation, glycoprotein biosynthetic process
ALG3	10195	CDG1D, CDGS4, CDGS6, D16Ert436e, NOT56L, Not56, not	mannosylation, glycoprotein biosynthetic process
ANTXR2	118429	CMG-2, CMG2, HFS, ISH, JHF	endoplasmic reticulum part
AP1S2	8905	DC22, MRX59, MRXS21, MRXS5, MRXS6, PGS, SIGMA1B	neuromuscular process, connective tissue development
APLN	187	AGTRL1, APJ, APJR, HG11	heart development, embryonic morphogenesis
ARX	170302	CT121, EIEE1, ISSX, MRX29, MRX32, MRX33, MRX36, MRX38, MRX43, MRX54, MRX76, MRX87, MRXS1, PRTS	cerebral cortex cell migration, cerebral cortex development
ASXL1	171023	BOPS, MDS	bone development, lung development
ATM	472	AT1, ATA, ATC, ATD, ATDC, ATE, TEL1, TELO1	neuron apoptotic process, regulation of neuron death
ATN1	1822	B37, D12S755E, DRPLA, HRS, NOD	neuron apoptotic process, neuron death
ATP7A	538	DSMAX, MK, MNK, SMAX3	collagen fibril organization, central nervous system neuron differentiation
ATRX	546	ATR2, JMS, MRX52, MRXH1, RAD54, RAD54L, SFM1, SHS, XH2, XNP, ZNF-HX	limb morphogenesis, limb development
ATXN2	6311	ASL13, ATX2, SCA2, TNRC13	neuromuscular process, central nervous system neuron differentiation
ATXN3	4287	AT3, ATX3, JOS, MJD, MJD1, SCA3	actin filament-based process, synaptic transmission
B3GAT3	26229	GLCAT1, glcUAT-1	chondroitin sulfate metabolic process, proteoglycan metabolic process
BAG3	9531	BAG-3, BIS, CAIR-1, MFM6	spinal cord development, I band
BICD2	23299	SMALED2, ba526D8.1	organelle localization
BIN1	274	AMPH2, AMPHL, SH3P9	sarcolemma, I band
CANT1	124583	DBQD, SCAN-1, SCAN1, SHAPY	proteoglycan metabolic process, glycoprotein biosynthetic process
CAPN3	825	CANP3, CANPL3, LGMD2, LGMD2A, nCL-1, p94	muscle cell cellular homeostasis, sarcolemma
CASK	8573	CAGH39, CAMGUK, CMG, FGS4, LIN2, MICPCH, MRXSNA, TNRC8	regulation of cellular response to growth factor stimulus, synaptic membrane
CD24	100133941	CD24A	neuromuscular synaptic transmission, neuroblast proliferation
CD6	923	TP120	response to wounding
CDK5	1020	LIS7, PSSALRE	Schwann cell development, Schwann cell differentiation
CHAT	1103	CHOACTASE, CMS1A, CMS1A2, CMS6	developmental growth, synaptic transmission
CHMP1A	5119	CHMP1, PCH8, PCOLN3, PRSM1, VPS46-1, VPS46A	organelle localization
CHRNA1	1134	ACHRA, ACHRD, CHRNA, CMS1A, CMS1B, CMS2A, FCCMS, SCCMS	muscle cell cellular homeostasis, neuromuscular synaptic transmission
CHRNA1	1140	ACHRB, CHRNA, CMS1D, CMS2A, CMS2C, SCCMS	neuromuscular synaptic transmission, skeletal muscle contraction
CHRNA1	1144	ACHRD, CMS2A, CMS3A, CMS3B, CMS3C, FCCMS, SCCMS	neuromuscular synaptic transmission, skeletal muscle contraction
CHRNA1	1145	ACHRE, CMS1D, CMS1E, CMS2A, CMS4A, CMS4B, CMS4C, FCCMS, SCCMS	neuromuscular synaptic transmission, skeletal muscle contraction
CHRNA1	1146	ACHRG	neuromuscular synaptic transmission, chemical synaptic transmission, postsynaptic
CHST14	113189	ATCS, D4ST1, EDSMC1, HNK1ST	chondroitin sulfate metabolic process, proteoglycan metabolic process
CHST3	9469	C6ST, C6ST1, HSD	chondroitin sulfate metabolic process, proteoglycan metabolic process
CHUK	1147	IKBKA, IKK-alpha, IKK1, IKKA, NFKB1A, TCF16	skeletal muscle contraction, striated muscle contraction
CNTN1	1272	F3, GP135, MYPCN	positive regulation of epithelial cell proliferation, regulation of epithelial cell proliferation
CNTNAP1	8506	CASPR, CNTNAP, NRXN4, P190	axon ensheathment, neuromuscular process, regulation of membrane potential
COG7	91949	CDG2E	glycoprotein biosynthetic process, glycoprotein metabolic process
COL11A2	1302	DFNA13, DFNB53, FBCG2, HKE5, PARP, STL3	fibrillar collagen trimer, complex of collagen trimers
COL1A1	1277	EDSC, OI1, OI2, OI3, OI4	fibrillar collagen trimer, complex of collagen trimers
COL1A2	1278	OI4	fibrillar collagen trimer, complex of collagen trimers
COL2A1	1280	ANFH, AOM, COL11A3, SEDC, STL1	fibrillar collagen trimer, complex of collagen trimers
COL3A1	1281	EDS4A	fibrillar collagen trimer, complex of collagen trimers
COL6A1	1291	OPLL	complex of collagen trimers, collagen metabolic process
COL6A2	1292	PP3610	collagen metabolic process, sarcolemma
COL6A3	1293	DYT27	complex of collagen trimers, collagen metabolic process
COL7A1	1294	EBD1, EBDCT, EBRI, NDNC8	complex of collagen trimers, collagen metabolic process

Table 1 (continued)

Gene	Entrez Gene ID	Aliases	Functions
<i>CRLF1</i>	9244	<i>CISS, CISS1, CLF, CLF-1, NR6, zcytor5</i>	neuron apoptotic process, regulation of neuron death
<i>CTSA</i>	5476	<i>GLB2, GSL, NGBE, PPCA, PPGB</i>	lysosomal lumen, glycoprotein biosynthetic process
<i>CTSL</i>	1514	<i>CATL, CTSL1, MEP</i>	lysosomal lumen, collagen metabolic process
<i>DCX</i>	1641	<i>DBCN, DC, LISX, SCLH, XLIS</i>	cerebral cortex cell migration, hippocampus development
<i>DES</i>	1674	<i>CSM1, CSM2, LGMD2R</i>	muscle filament sliding, actin filament-based movement
<i>DHCR24</i>	1718	<i>DCE, Nbla03646, SELADIN1, seladin-1</i>	skin development, regulation of neuron death
<i>DHCR7</i>	1717	<i>SLOS</i>	lung development, respiratory system development
<i>DMPK</i>	1760	<i>DM, DM1, DM1PK, DMK, MDPK, MT-PK</i>	skeletal muscle contraction, chemical synaptic transmission, postsynaptic
<i>DNM2</i>	1785	<i>CMT2M, CMTD11, CMTDIB, DI-CMTB, DYN2, DYNII, LCCS5</i>	regulation of cellular response to growth factor stimulus, synaptic membrane
<i>DPAGT1</i>	1798	<i>ALG7, CDG-Ij, CDG1J, CMS13, CMSTA2, D11S366, DGPT, DPAGT, DPAGT2, G1PT, GPT, UAGT, UGAT</i>	glycoprotein biosynthetic process, glycoprotein metabolic process
<i>DPM1</i>	8813	<i>CDGIE, MPDS</i>	mannosylation, glycoprotein biosynthetic process
<i>DST</i>	667	<i>BP240, BPA, BPAG1, CATX-15, CATX15, D6S1101, DMH, DT, EBSB2, HSA6, MACF2</i>	I band, contractile fiber
<i>DYM</i>	54808	<i>DMC, SMC</i>	bone development, skeletal system development
<i>DYNC1H1</i>	1778	<i>CMT2O, DHCI1, DHC1a, DNCH1, DNCL, DNECL, DYHC, Dnchc1, HL-3, SMALED1, p22</i>	organelle localization, glycoprotein biosynthetic process
<i>DYSF</i>	8291	<i>FER1L1, LGMD2B, MMD1</i>	sarcolemma, muscle contraction
<i>EBP</i>	10682	<i>CDPX2, CHO2, CPX, CPXD, MEND</i>	skeletal system development, endoplasmic reticulum part
<i>EGR2</i>	1959	<i>AT591, CMT1D, CMT4E, KROX20</i>	Schwann cell differentiation, peripheral nervous system development
<i>EMD</i>	2010	<i>EDMD, LEMD5, STA</i>	skeletal muscle tissue development, skeletal muscle organ development
<i>ERBB3</i>	2065	<i>ErbB-3, HER3, LCCS2, MDA-BF-1, c-erbB-3, c-erbB3, erbB3-S, p180-ErbB3, p45-sErbB3, p85-sErbB3</i>	Schwann cell differentiation, peripheral nervous system development
<i>ERCC1</i>	2067	<i>COFS4, RAD10, UV20</i>	developmental growth, embryo development
<i>ERCC2</i>	2068	<i>COFS2, EM9, TFIIH, TTD, TTD1, XPD</i>	glial cell development, spinal cord development
<i>ERCC6</i>	2074	<i>ARMDS, CKN2, COFS, COFS1, CSB, RAD26, UVSSI</i>	developmental growth
<i>ERLIN2</i>	11160	<i>C8orf2, Erlin-2, NET32, SPFH2, SPG18</i>	endoplasmic reticulum part
<i>ESCO2</i>	157570	<i>2410004117Rik, EFO2, RBS</i>	animal organ development
<i>EZH2</i>	2146	<i>ENX-1, ENX1, EZH1, EZH2b, KMT6, KMT6A, WVS, WVS2</i>	hippocampus development, limbic system development
<i>FAM20C</i>	56975	<i>DMP-4, DMP4, GEF-CK, RNS</i>	bone development, osteoblast differentiation
<i>FBN1</i>	2200	<i>ACMICD, ECTOL1, FBN, GPHYS2, MASS, MFS1, OCTD, SGS, SKS, WMS, WMS2</i>	extracellular matrix disassembly, regulation of cellular response to growth factor stimulus
<i>FBN2</i>	2201	<i>CCA, DA9, EOMD</i>	embryonic limb morphogenesis, extracellular matrix disassembly
<i>FBN3</i>	84467		regulation of cellular response to growth factor stimulus, proteinaceous extracellular matrix
<i>FGD1</i>	2245	<i>AAS, FGDY, MRXS16, ZFYVE3</i>	actin filament-based process, cellular response to growth factor stimulus
<i>FGF9</i>	2254	<i>FGF-9, GAF, HBFG-9, HBGF-9, SYNS3</i>	chondrocyte differentiation, regulation of stem cell proliferation, embryonic skeletal system development
<i>FGFR1</i>	2260	<i>BFGFR, CD331, CEK, FGFR, FGFR-1, FLG, FLT-2, FLT2, HBGFR, HH2, HRTFDS, KAL2, N-SAM, OGD, bFGF-R-1</i>	cerebral cortex cell migration, neuroblast proliferation
<i>FGFR2</i>	2263	<i>BBDS, BEK, BFR-1, CD332, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25</i>	prostate gland epithelium morphogenesis, neuroblast proliferation
<i>FGFR3</i>	2261	<i>ACH, CD333, CEK2, HSGFR3EX, JTK4</i>	glial cell development, bone morphogenesis
<i>FHL1</i>	2273	<i>FHL-1, FHL1A, FHL1B, FLH1A, KYOT, SLIM, SLIM-1, SLIM1, SLIMMER, XMPMA</i>	regulation of membrane potential, muscle organ development
<i>FKBP10</i>	60681	<i>BRKS1, FKBP65, OI1, OI6, PPIASE, hFKBP65</i>	endoplasmic reticulum part
<i>FKRP</i>	79147	<i>LGMD2I, MDC1C, MDDGA5, MDDGB5, MDDGC5</i>	mannosylation, sarcolemma
<i>EKTN</i>	2218	<i>CMD1X, FCMD, LGMD2M, MDDGA4, MDDGB4, MDDGC4</i>	mannosylation, muscle organ development
<i>FLNA</i>	2316	<i>ABP-280, ABPX, CSBS, CVD1, FLN, FLN-A, FLN1, FMD, MNS, NHBP, OPD, OPD1, OPD2, XLVD, XMVD</i>	protein import, actin cytoskeleton
<i>FLNB</i>	2317	<i>ABP-278, ABP-280, AOI, FH1, FLN-B, FLN1L, LRS1, SCT, TABP, TAP</i>	hippocampus development, limbic system development
<i>FUCA1</i>	2517	<i>FUCA</i>	lysosomal lumen, glycoprotein biosynthetic process
<i>GAA</i>	2548	<i>LYAG</i>	muscle cell cellular homeostasis, skeletal muscle contraction
<i>GAD1</i>	2571	<i>CPSQ1, GAD, SCP</i>	synaptic transmission
<i>GBA</i>	2629	<i>GBA1, GCB, GLUC</i>	lysosomal lumen, skin development
<i>GBE1</i>	2632	<i>APBD, GBE, GSD4</i>	carbohydrate metabolic process
<i>GCK</i>	2645	<i>FGQTL3, GK, GLK, HHF3, HK4, HKIV, HXKP, LGLK, MODY2</i>	actin cytoskeleton, carbohydrate derivative biosynthetic process
<i>GDF5</i>	8200	<i>BDA1C, BMP-14, BMP14, CDMP1, LAP-4, LAP4, OS5, SYM1B, SYNS2</i>	chondrocyte differentiation, embryonic limb morphogenesis
<i>GJA1</i>	2697	<i>AVSD3, CMDR, CX43, EKVP, GJAL, HLHS1, HSS, ODDD, PPKCA</i>	actin filament-based movement, embryonic limb morphogenesis
<i>GLI3</i>	2737	<i>ACLS, GCPs, GLI3-190, GLI3FL, PAP-A, PAPA, PAPA1, PAPB, PHS, PPDIV</i>	cerebral cortex cell migration, neuroblast proliferation
<i>GLRA1</i>	2741	<i>HKPX1, STHE</i>	chemical synaptic transmission, postsynaptic, neuromuscular process
<i>GLRB</i>	2743	<i>HKPX2</i>	neuromuscular process, synaptic membrane
<i>GLUL</i>	2752	<i>GLNS, GS, PIG43, PIG59</i>	positive regulation of epithelial cell proliferation, regulation of epithelial cell proliferation
<i>GPC3</i>	2719	<i>DGSX, GTR2-2, MXR7, OCI-5, SDYS, SGB, SGBS, SGBS1</i>	body morphogenesis, chondroitin sulfate metabolic process
<i>GRHL3</i>	57822	<i>SOM, TFCP2L4, VWS2</i>	skin development, embryonic organ morphogenesis
<i>GRN</i>	2896	<i>CLN11, GEP, GP88, PCDGF, PEPI, PGRN</i>	neural precursor cell proliferation, positive regulation of epithelial cell proliferation
<i>GUSB</i>	2990	<i>BG, MPS7</i>	lysosomal lumen, carbohydrate metabolic process

Table 1 (continued)

Gene	Entrez Gene ID	Aliases	Functions
HEXA	3073	TSD	chondroitin sulfate metabolic process, lysosomal lumen
HEXB	3074	ENC-1AS, HEL-248, HEL-S-111	chondroitin sulfate metabolic process, lysosomal lumen
HLA-DRB1	3123	DRB1, DRw10, HLA-DR1B, HLA-DRB, SS1	negative regulation of cell proliferation, response to wounding
HOXA13	3209	HOX1, HOX1J	prostate gland epithelium morphogenesis, embryonic limb morphogenesis
HOXD13	3239	BDE, BDS, HOX41, SPD	prostate gland epithelium morphogenesis, embryonic limb morphogenesis
HRAS	3265	C-BAS/HAS, C-H-RAS, C-HA-RAS1, CTLO, H-RASIDX, HAMS, HRAS1, RASH1, p21ras	positive regulation of epithelial cell proliferation, neuron apoptotic process
HSPG2	3339	HSPG, PLC, PRCAN, SJA, SJS, SJS1	chondroitin sulfate metabolic process, bone morphogenesis
IDS	3423	MPS2, SIDS	chondroitin sulfate metabolic process, lysosomal lumen
IGF2	3481	C11orf43, GRDF, IGF-II, PP9974	digestive system development, striated muscle cell differentiation
IGHMBP2	3508	CATF1, CMT2S, HCSA, HMN6, SMARD1, SMUBP2, ZFAND7	spinal cord development, central nervous system neuron differentiation
IMPAD1	54928	GPAPP, IMP 3, IMP-3, IMPA3	chondroitin sulfate metabolic process, bone morphogenesis
INSR	3643	CD220, HHF5	digestive system development, regulation of developmental growth
IRF6	3664	LPS, OFC6, PIT, PPS, PPS1, VWS, VWS1	skin development, epithelial cell proliferation
ISP	729920	MDDGA7, MDDGC7, Nip, hCG_1745121	mannosylation, glycoprotein biosynthetic process
ITGA6	3655	CD49f, ITGA6B, VLA-6	digestive tract development, digestive system development
ITGB4	3691	CD104	digestive tract development, digestive system development
KCNA1	3736	AEMK, EA1, HBK1, HUK1, KV1.1, MBK1, MK1, RBK1	neuroblast proliferation, hippocampus development
KCNJ11	3767	BIR, HHF2, IKATP, KIR6.2, MODY13, PHH1, TNDM3	sarcolemma, regulation of membrane potential
KCNK9	51305	K2p9.1, KT3.2, TASK-3, TASK3	regulation of membrane potential, synaptic transmission
KIAA0196	9897	RTSC, SPG8	cell development
KIF14	9928	MKS12	hippocampus development, limbic system development
KIF5C	3800	CDCBM2, KINN, NKHC, NKHC-2, NKHC2	axon guidance, axonogenesis
KIF7	374654	ACLS, AGBK, HLS2, JBTS12, UNQ340	heart development, blood vessel development
KLHL40	131377	KBTBD5, NEM8, SRY, SYRP	muscle fiber development, I band
KLHL41	10324	KBTBD10, Krp1, SARCOSIN	muscle fiber development, striated muscle contraction, striated muscle cell development
KLKB1	3818	KLK3, PKK, PKKD, PPK	extracellular matrix disassembly, extracellular matrix organization
L1CAM	3897	CAMLL1, CD171, HSAS, HSAS1, MASA, MIC5, N-CAM-L1, N-CAMLL1, NCAM-L1, S10, SPG1	synaptic membrane, regulation of developmental growth
LAMA2	3908	LAMM	Schwann cell development, Schwann cell differentiation
LARGE	9215	MDC1D, MDDGA6, MDDGB6	muscle cell cellular homeostasis, mannosylation
LIFR	3977	CD118, LIF-R, SJS2, STWS, SWS	cell-type specific apoptotic process, neuron projection morphogenesis
LMBR1	64327	ACHP, C7orf2, DIF14, LSS, PPD2, THYP, TPT, ZRS	embryonic limb morphogenesis, limb morphogenesis
LMNA	4000	CD118, CDDC, CMD1A, CMT2B1, EMD2, FPL, FPLD, FPLD2, HGPS, IDC, LDP1, LFP, LGMD1B, LMN1, LMNC, LMNL1, PRO1	striated muscle cell development, muscle cell development
LMX1B	4010	LMX1.2, NPS1	chordate embryonic development, embryo development
LTBP2	4053	C14orf141, GLC3D, LTBP3, MSPKA, MSTP031, WMS3	regulation of stem cell proliferation, stem cell proliferation
MAGEL2	54551	NDNL1, PWLS, SHFYNG, nM15	actin filament-based process
MASPI	5648	3MC1, CRARF, CRARF1, MAP1, MASP, MASP3, Map44, PRSS5, RaRF	response to wounding
MED12	9968	ARC240, CAGH45, FGS1, HOPA, MED12S, OHDOX, OKS, OPA1, TNRC11, TRAP230	Schwann cell development, Schwann cell differentiation
MEGF10	84466	EMARDD	muscle cell development, skeletal muscle tissue development
MFN2	9927	CMT2A, CMT2A2, CPRP1, HSG, MARF	organelle localization, chordate embryonic development
MMP2	4313	CLG4, CLG4A, MMP-2, MMP-II, MONA, TBE-1	face development, body morphogenesis
MNX1	3110	HB9, HLXB9, HOXHB9, SCRA1	spinal cord development, neuron migration
MTM1	4534	CNM, MTMX, XLMTM	muscle cell cellular homeostasis, I band
MUSK	4593	CMS9, FADS	neuron apoptotic process, regulation of neuron death
MYBPC2	4606	MYBPC, MYBPCF	muscle filament sliding, actin filament-based movement
MYH2	4620	IBM3, MYH2A, MYHSA2, MYHas8, MYPOP, MyHC-2A, MyHC-IIa	muscle filament sliding, actin filament-based movement
MYH3	4621	HEMHC, MYHC-EMB, MYHSE1, SMHCE	muscle filament sliding, skeletal muscle contraction
MYH7B	57644	MHC14, MYH14	skeletal muscle contraction, actin filament-based movement
MYH8	4626	DA7, MyHC-peri, MyHC-pn, gtMHC-F	muscle filament sliding, skeletal muscle contraction
MYO18B	84700		muscle fiber development, I band
MYO9A	4649		actin cytoskeleton
MYOT	9499	LGMD1, LGMD1A, MFM3, TTID, TTOD	sarcolemma, I band
NALCN	259232	CLIFAHDD, Canlon, IHPRF, INNFD, VGCNL1, baA430M15.1	regulation of membrane potential
NEB	4703	NEB177D, NEM2	striated muscle thin filament, muscle filament sliding
NEFH	4744	NFH	hippocampus development, peripheral nervous system development
NEU1	4758	NANH, NEU, SIAL1	lysosomal lumen, glycoprotein biosynthetic process
NF1	4763	NFNS, VRNF, WSS	Schwann cell development, Schwann cell differentiation
NOG	9241	SYM1, SYNS1	prostate gland epithelium morphogenesis, face development
OCRL	4952	INPP5F, LOCR, NPHL2, OCRL-1, OCRL1	muscle system process, chordate embryonic development
OFD1	8481	71-7A, CXorf5, JBTS10, RP23, SGBS2	cell projection morphogenesis, cell part morphogenesis
ORC4	5000	ORC4L, ORC4P	actin cytoskeleton
ORC6	23594	ORC6L	actin cytoskeleton
PAFAH1B1	5048	LIS1, LIS2, MDCR, MDS, PAFAH	cerebral cortex cell migration, neuroblast proliferation
PANK2	80025	C20orf48, HARP, HSS, NBIA1, PKAN	regulation of membrane potential, carbohydrate derivative biosynthetic process
PAX3	5077	CDHS, HUP2, WS1, WS3	spinal cord development, central nervous system neuron differentiation

Table 1 (continued)

Gene	Entrez Gene ID	Aliases	Functions
<i>PEX1</i>	5189	<i>PBD1A, PBD1B, ZWS, ZWS1</i>	protein targeting to peroxisome, intracellular protein transmembrane import
<i>PEX10</i>	5192	<i>NALD, PBD6A, PBD6B, RNF69</i>	integral component of peroxisomal membrane, protein targeting to peroxisome
<i>PEX12</i>	5193	<i>PAF-3, PBD3A</i>	integral component of peroxisomal membrane, protein targeting to peroxisome
<i>PEX13</i>	5194	<i>NALD, PBD11A, PBD11B, ZWS</i>	integral component of peroxisomal membrane, protein targeting to peroxisome
<i>PEX14</i>	5195	<i>NAPP2, PBD13A, Pex14p, dJ734G22.2</i>	protein targeting to peroxisome, intracellular protein transmembrane import
<i>PEX2</i>	5828	<i>PAF1, PBD5A, PBD5B, PMP3, PMP35, PXMP3, RNF72, ZWS3</i>	integral component of peroxisomal membrane, protein targeting to peroxisome
<i>PEX26</i>	55670	<i>PBD7A, PBD7B, PEX26M1T, Pex26pM1T</i>	integral component of peroxisomal membrane, protein targeting to peroxisome
<i>PEX3</i>	8504	<i>PBD10A, TRG18</i>	integral component of peroxisomal membrane, protein targeting to peroxisome
<i>PEX5</i>	5830	<i>PBD2A, PBD2B, PTS1-BP, PTS1R, PXR1</i>	protein targeting to peroxisome, intracellular protein transmembrane import
<i>PEX6</i>	5190	<i>PAF-2, PAF2, PBD4A, PDB4B, PXAAA1</i>	protein targeting to peroxisome, intracellular protein transmembrane import
<i>PEX7</i>	5191	<i>PBD9B, PTS2R, RCDP1, RD</i>	protein targeting to peroxisome, intracellular protein transmembrane import
<i>PFKM</i>	5213	<i>ATP-PFK, GSD7, PFK-1, PFK1, PFKA, PFKX, PPP1R122</i>	muscle cell cellular homeostasis, carbohydrate metabolic process
<i>PIEZO2</i>	63895	<i>C18orf30, C18orf58, DA3, DA5, FAM38B, FAM38B2, HsT748, HsT771, MWKS</i>	regulation of membrane potential
<i>PIGT</i>	51604	<i>CGI-06, MCAHS3, NDAP, PNH2</i>	neuron apoptotic process, neuron death
<i>PIP5K1C</i>	23396	<i>LCSC3, PIP5K-GAMMA, PIP5K1-gamma, PIP5Kgamma</i>	organelle localization, axon guidance
<i>PITX1</i>	5307	<i>BFT, CCF, LBNBG, POTX, PTX1</i>	embryonic limb morphogenesis, limb morphogenesis
<i>PLEKHG5</i>	57449	<i>CMTRIC, DSMA4, GEF720, Syx, Tech</i>	chemotaxis, cellular response to growth factor stimulus
<i>PLOD1</i>	5351	<i>EDS6, LH, LHI, LLH, PLOD</i>	extracellular matrix organization, endoplasmic reticulum part
<i>PLOD2</i>	5352	<i>BRKS2, LH2, TLH</i>	extracellular matrix organization, endoplasmic reticulum part
<i>PLOD3</i>	8985	<i>LH3</i>	collagen fibril organization, lung development
<i>PLP1</i>	5354	<i>GPM6C, HLD1, MMPL, PLP, PLP/DM20, PMD, SPG2</i>	glial cell development, axon ensheathment
<i>PMM2</i>	5373	<i>CDG1, CDG1a, CDGS, PMI, PMI1, PMM 2</i>	glycoprotein biosynthetic process, glycoprotein metabolic process
<i>PMP22</i>	5376	<i>CMT1A, CMT1E, DSS, GAS-3, HMSNIA, HNPP, Sp110</i>	peripheral nervous system development, axon ensheathment
<i>POMGNT1</i>	55624	<i>GNTL2, Gnt L2, LGMD20, MEB, MGAT1.2, gnt-L2</i>	glycoprotein biosynthetic process, glycoprotein metabolic process
<i>POMGNT2</i>	84892	<i>AGO61, C3orf39, GTDC2, MDDGA8</i>	mannosylation, neuron migration
<i>POMT1</i>	10585	<i>LGMD2K, MDDGA1, MDDGB1, MDDGC1, RT</i>	mannosylation, extracellular matrix organization
<i>POMT2</i>	29954	<i>LGMD2N, MDDGA2, MDDGB2, MDDGC2</i>	mannosylation, glycoprotein biosynthetic process
<i>POR</i>	5447	<i>CPR, CYPOR, P450R</i>	bone morphogenesis, chondrocyte differentiation
<i>PRG4</i>	10216	<i>CACP, HAPO, JCAP, MSF, SZP</i>	stem cell proliferation, animal organ development
<i>PRKARIA</i>	5573	<i>ACRDYS1, ADOHR, CAR, CNC, CNC1, PKR1, PPNAD1, PRKARI, TSE1</i>	striated muscle cell development, muscle cell development
<i>PRX</i>	57716	<i>CMT4F</i>	axon ensheathment
<i>PSD3</i>	23362	<i>EFA6D, EFA6R, HCA67</i>	synaptic membrane
<i>PTDSS1</i>	9791	<i>LMHD, PSS1, PSSA</i>	carbohydrate derivative biosynthetic process, endoplasmic reticulum part
<i>PTH1R</i>	5745	<i>PFE, PTHR, PTHR1</i>	chondrocyte differentiation, cartilage development
<i>RAB18</i>	22931	<i>RAB18LI1, WARBM3</i>	brain development, head development
<i>RAB3GAP1</i>	22930	<i>P130, RAB3GAP, RAB3GAP130, WARBM1</i>	face development, body morphogenesis
<i>RAPSN</i>	5913	<i>CMS11, CMS4C, FADS, RAPSYN, RNF205</i>	neuromuscular synaptic transmission, neuron apoptotic process
<i>RBM10</i>	8241	<i>DXS8237E, GPATC9, GPATCH9, S1-1, TARPS, ZRANB5</i>	cell-type specific apoptotic process, negative regulation of cell proliferation
<i>RELN</i>	5649	<i>ETL7, LIS2, PRO1598, RL</i>	cerebral cortex cell migration, hippocampus development
<i>RET</i>	5979	<i>CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET-ELE1, RET51</i>	digestive tract development, digestive system development
<i>RIPK4</i>	54101	<i>ANKK2, ANKRD3, DIK, NKRD3, PKK, PPS2, RIP4</i>	morphogenesis of an epithelium, tissue morphogenesis
<i>RMRP</i>	6023	<i>CHH, NME1, RMRPR, RRP2</i>	hippocampus development, limbic system development
<i>RNASEH2A</i>	10535	<i>AGS4, JUNB, RNASEHI, RNHIA, RNHL</i>	osteoblast differentiation, ossification
<i>RNASEH2B</i>	79621	<i>AGS2, DLEU8</i>	chordate embryonic development, embryo development
<i>RYR1</i>	6261	<i>CCO, MHS, MHS1, PPP1R137, RYDR, RYR, RYR-1, SKRR</i>	muscle fiber development, sarcolemma
<i>SCN4A</i>	6329	<i>CMS16, HOKPP2, HYKPP, HYPP, NAC1A, Na(V)1.4, Nav1.4, SkM1</i>	muscle contraction, regulation of membrane potential
<i>SEPN1</i>	57190	<i>CFTD, MDRS1, RSM1, RSS, SELN</i>	muscle fiber development, striated muscle cell development
<i>SETX</i>	23064	<i>ALS4, AOA2, SCAR1, bA479K20.2</i>	regulation of neurogenesis, regulation of nervous system development
<i>SGCG</i>	6445	<i>35DAG, A4, DAGA4, DMDA, DMDA1, LGMD2C, MAM, SCARMD2, SCG3, gamma-SG</i>	sarcolemma, muscle cell development
<i>SHOX</i>	6473	<i>GCFX, PHOG, SHOXY, SS</i>	skeletal system development
<i>SKI</i>	6497	<i>SGS, SKV</i>	Schwann cell development, Schwann cell differentiation
<i>SLC12A6</i>	9990	<i>ACCPN, KCC3, KCC3A, KCC3B</i>	blood vessel development, synaptic transmission
<i>SLC26A2</i>	1836	<i>D5S1708, DTD, DTDST, EDM4, MST153, MSTP157</i>	regulation of membrane potential, ossification
<i>SLC39A13</i>	91252	<i>LZT-Hs9</i>	connective tissue development, tissue development
<i>SLC3A1</i>	6519	<i>ATRI, CSNU1, D2H, NBAT, RBAT</i>	carbohydrate metabolic process
<i>SLC9A6</i>	10479	<i>MRSA, NHE6</i>	regulation of cellular response to growth factor stimulus, developmental growth

Table 1 (continued)

Gene	Entrez Gene ID	Aliases	Functions
<i>SMN1</i>	6606	<i>BCD541, GEMIN1, SMA, SMA1, SMA2, SMA3, SMA4, SMA@, SMN, SMNT, T-BCD541, TDRD16A</i>	I band, contractile fiber
<i>SOD1</i>	6647	<i>ALS, ALS1, HEL-S-44, IPOA, SOD, hSod1, homodimer</i>	muscle cell cellular homeostasis, Schwann cell development
<i>SOX10</i>	6663	<i>DOM, PCWH, WS2E, WS4, WS4C</i>	neuroblast proliferation, peripheral nervous system development
<i>SOX9</i>	6662	<i>CMD1, CMPD1, SRA1, SRXX2, SRXY10</i>	prostate gland epithelium morphogenesis, bone morphogenesis
<i>SPG20</i>	23111	<i>SPARTIN, TAHCCP1</i>	neuromuscular process, connective tissue development
<i>SRD5A3</i>	79644	<i>CDG1P, CDG1Q, KRIZI, SRD5A2L, SRD5A2L1</i>	glycoprotein biosynthetic process, glycoprotein metabolic process
<i>STAC3</i>	246329	<i>NAM</i>	neuromuscular synaptic transmission, skeletal muscle contraction
<i>SULF1</i>	23213	<i>SULF-1</i>	prostate gland epithelium morphogenesis, proteoglycan metabolic process
<i>SYNE1</i>	23345	<i>8B, ARCA1, C6orf98, CPG2, EDMD4, MYNE1, Nesp1, SCAR8, dj45H2.2</i>	contractile fiber, synaptic membrane
<i>TARP</i>	445347	<i>CD3G, TCRG, TCRGC1, TCRGC2, TCRGV</i>	cell-type specific apoptotic process
<i>TBX15</i>	6913	<i>TBX14</i>	embryonic skeletal system development, skeletal system morphogenesis
<i>TBX5</i>	6910	<i>HOS</i>	embryonic limb morphogenesis, limb morphogenesis
<i>TGFB3</i>	7043	<i>ARVD, ARVD1, RNHF, TGF-beta3</i>	face development, body morphogenesis
<i>TNNI2</i>	7136	<i>AMCD2B, DA2B, FSSV, fsTnI</i>	striated muscle thin filament, muscle filament sliding
<i>TNNT1</i>	7138	<i>ANM, NEM5, STNT, TNT, TNTS</i>	striated muscle thin filament, muscle filament sliding
<i>TNNT3</i>	7140	<i>TNTF</i>	striated muscle thin filament, muscle filament sliding
<i>TPM2</i>	7169	<i>AMCD1, DA1, DA2B, HEL-S-273, NEM4, TMSB</i>	striated muscle thin filament, muscle filament sliding
<i>TPM3</i>	7170	<i>CAPM1, CFTD, HEL-189, HEL-S-82p, NEM1, OK/SW-cl.5, TM-5, TM3, TM30, TM30nm, TM5, TPMsk3, TRK, hscp30</i>	striated muscle thin filament, muscle filament sliding
<i>TREX1</i>	11277	<i>AGS1, CRV, DRN3, HERNS</i>	endoplasmic reticulum part
<i>TSC1</i>	7248	<i>LAM, TSC</i>	hippocampus development, limbic system development
<i>TSC2</i>	7249	<i>LAM, PPP1R160, TSC4</i>	protein import, morphogenesis of an epithelium
<i>TWIST2</i>	117581	<i>AMS, BBRSAY, Dermo1, FFDD3, SETLSS, bHLHa39</i>	face development, body morphogenesis
<i>TYMP</i>	1890	<i>ECGF, ECGF1, MEDPS1, MNGIE, MTDPS1, PDECGF, TP, hPD-ECGF</i>	blood vessel development, chemotaxis
<i>UBA1</i>	7317	<i>A1S9, A1S9T, A1ST, AMCX1, CFAP124, GXP1, POC20, SMAX2, UBA1A, UBE1, UBE1X</i>	endoplasmic reticulum part
<i>UBE3A</i>	7337	<i>ANCR, AS, E6-AP, EPVE6AP, HPVE6A</i>	developmental growth, brain development
<i>UPK3A</i>	7380	<i>UP3A, UPIII, UPIIIA, UPK3</i>	endoplasmic reticulum part, cellular component morphogenesis
<i>UTRN</i>	7402	<i>DMDL, DRP, DRP1</i>	sarcolemma, synaptic membrane
<i>VPS33B</i>	26276		bone development, organelle localization
<i>WNT5A</i>	7474	<i>hWNT5A</i>	prostate gland epithelium morphogenesis, face development
<i>WNT7A</i>	7476		chemical synaptic transmission, postsynaptic, chondrocyte differentiation
<i>ZBTB42</i>	100128927	<i>LCCS6, ZNF925</i>	muscle organ development, muscle structure development
<i>ZC4H2</i>	55906	<i>HCA127, KIAA1166, WRWF, WWS</i>	spinal cord development, central nervous system neuron differentiation
<i>ZIC3</i>	7547	<i>HTX, HTX1, VACTERLX, ZNF203</i>	digestive tract development, digestive system development
<i>ZMPSTE24</i>	10269	<i>FACE-1, FACE1, HGPS, PRO1, STE24, Ste24p</i>	endoplasmic reticulum part
<i>ZNF335</i>	63925	<i>MCPH10, NIF-1, NIF1, NIF2</i>	neuroblast proliferation, regulation of stem cell proliferation

This table lists all the genes associated with arthrogryposis used in the ClueGO enrichment analysis. Entrez Gene ID: Entrez Gene unique ID; Aliases: additional gene names; Functions: GO terms that are associated with the specific gene.

ment are presented in tabular form, this could inhibit the interpretation and summary of the results. The network visualization groups similar GO terms as nodes in the network with edges representing a measure of shared gene membership (kappa score).

The ClueGo analysis identified 145 enriched GO terms with a corrected $p < 0.001$ (online suppl. table 1; see www.karger.com/doi/10.1159/000446617 for all online suppl. material). The automatic grouping of terms, performed by ClueGO, assigned them to 22 groups based on overlapping gene membership measured by the kappa score statistic (online suppl. table 2). The number of GO terms in the groups varied from a maximum of 57 to 8 groups with just 1 term each and 9 groups with shared GO terms. The network representation is displayed in figure 1. The network is composed of nodes representing enriched GO

terms connected by kappa scores that are a measure of gene overlap between terms. The node color represents the membership in one of the ClueGO determined clusters. While ClueGo attempts to determine the most representative GO term to name the grouped terms, we have provided our own annotation grouping for greater clarity in interpretation and meaning (online suppl. table 3). This grouping is indicated by the shading overlaid on the network with an annotated group labeled with a summary title of the underlying GO terms in the group.

The purpose of this paper is to highlight the genes in which mutations have been identified to be associated with arthrogryposis in order to emphasize the importance of defining the other genes in their developmental pathways. This is in order to (1) develop a logical diagnostic approach and (2) to begin to think about specific

Fig. 1. GO enrichment network. The nodes in the network represent a specific GO term. The edges connecting the nodes are based on the kappa statistic that measures the overlap of shared genes between terms. The node colors correspond to the ClueGO-determined GO term clusters. The shadings represent author-annotated groupings with a summary title.

therapies for specific disorders. For instance, in the disorders of neuromuscular endplate related to fetal endplate receptor, they seem to respond to increased neurotransmitters (a readily available drug used to myasthenia gravis), which then seem to allow the normal adult endplate to be able to function [Michalk et al., 2008].

Perhaps the most puzzling aspect of arthrogryposis is why extra connective tissue/fibrosis is deposited around the immobile joint(s) in the fetus. Is the process related to

immobilizing that occurs with a sprain or fracture, where pain leads to an individual immobilizing the surrounding joints which then develop contractures? This process would be magnified as the fetus grows. Or is there another unique developmental process of fibrosis in young individuals? Is the process similar to tendon and ligament formation? Are connective tissue stem cells overstimulated or more susceptible in the fetus? Is this excess of connective tissue an unusual scar of some type? Is one of

the connective tissue growth factors a potential therapy for arthrogryposis contractures of the future?

In this molecular era, syndromes of congenital anomalies give insight into normal developmental processes and their secondary and tertiary effects. In the case of arthrogryposis, so many of the features are secondary deformations related to fetal non-movement [Hall, 2009]. Nevertheless, all of the features which are part of the natural history of the specific disorder are important for families to know about in order to plan effectively.

The specific gene mutation in a specific disorder is acting against the rest of the individual's genome, epigenetics, and environmental history. In the course of development, the embryo fetus goes through many physiological developmental stages. The vulnerabilities, timing of insults, involved polymorphisms along a pathway, and gene action also provide insights into the human normal and abnormal developmental processes.

The work up of affected individuals [Hall, 2012, 2014] as well as the known genes are covered elsewhere; the associated syndromes are found in OMIM (<http://www.omim.org/>) [Hall, 2012, 2014; Hunter et al., 2015; Bayram et al., 2016].

Table 1 outlines gene ontology categories and begins to suggest prime candidates for recognizing critical pathways involved in normal fetal movement. Interestingly, many candidate genes show up in several ontology categories. This may relate to different domains of the genes, to alternative splicing, or to the 'recycling' of pathways for different functions.

It is hoped that this exercise is useful to those reflecting on the many mechanisms and structures involved in the development of movement, and fetal movement in particular. The listing of all genes recognized to be involved in arthrogryposis at this time is obviously an incomplete list. Some genes are involved in several disorders which were clinically thought to be distinct (perhaps related to the specific nucleotide replacement or perhaps related to various modifiers). Once a group of families with a specific mutation has their whole genome analyzed, the variation in clinical phenotype can be elucidated and important modifiers identified.

Many specific single gene disorders have intra- and interfamilial variability as to how severe the contractures are at birth, what positioning they take, or whether contractures are even present. For instance, several forms of dominant distal arthrogryposis have completely unaffected carrier individuals [Kimber et al., 2012].

It is also hoped that this listing will point to other genes involved in ontological processes that may also result in arthrogryposis and be part of the pathways leading to normal fetal movement – thereby providing better diagnostic precision among the present quagmire of interpretation of the whole genome and even exome sequencing. Ultimately, specific therapies may involve alternative pathways and enhance the affected pathway.

Disclosure Statement

The authors declare no conflicts of interest.

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