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Arthrogryposis as a Syndrome: Gene Ontology Analysis

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Arthrogryposis · ClueGO · Connective tissue · Cytoscape · Enrichment analysis · Fetal movement · Gene ontology · Molecular pathways · Multiple congenital contractures · Reactome

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.

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-

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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 multiprotein-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	*GPHYSD1*	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, EMAPII, 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	*CDGIi, CMS14, CMSTA3, NET38, hALPG2*	mannosylation, glycoprotein biosynthetic process
ALG3	10195	*CDG1D, CDGS4, CDGS6, D16Ertd36e, NOT56L, Not56, not*	mannosylation, glycoprotein biosynthetic process
ANTXR2	118429	*CMG-2, CMG2, HFS, ISH, JHF*	endoplasmic reticulum part
AP1S2	8905	*DC22, MRX59, MRXS21, MRXS5, MRXSF, PGS, SIGMA1B*	neuromuscular process, connective tissue development
APLNR	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, MRXHF1, 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	*GLCATI, glcUAT-I*	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
CHRNB1	1140	*ACHRB, CHRNB, CMS1D, CMS2A, CMS2C, SCCMS*	neuromuscular synaptic transmission, skeletal muscle contraction
CHRND	1144	*ACHRD, CMS2A, CMS3A, CMS3B, CMS3C, FCCMS, SCCMS*	neuromuscular synaptic transmission, skeletal muscle contraction
CHRNE	1145	*ACHRE, CMS1D, CMS1E, CMS2A, CMS4A, CMS4B, CMS4C, FCCMS, SCCMS*	neuromuscular synaptic transmission, skeletal muscle contraction
CHRNG	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, NFKBIKA, 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, EBR1, NDNC8*	complex of collagen trimers, collagen metabolic process

Table 1 (continued)

Gene	Entrez Gene ID	Aliases	Functions
CRLF1	9244	*CISS, CISS1, CLF, CLF-1, NR6, zcytor5*	neuron apoptotic process, regulation of neuron death
CTSA	5476	*GLB2, GSL, NGBE, PPCA, PPGB*	lysosomal lumen, glycoprotein biosynthetic process
CTSL	1514	*CATL, CTSL1, MEP*	lysosomal lumen, collagen metabolic process
DCX	1641	*DBCN, DC, LISX, SCLH, XLIS*	cerebral cortex cell migration, hippocampus development
DES	1674	*CSM1, CSM2, LGMD2R*	muscle filament sliding, actin filament-based movement
DHCR24	1718	*DCE, Nbla03646, SELADIN1, seladin-1*	skin development, regulation of neuron death
DHCR7	1717	*SLOS*	lung development, respiratory system development
DMPK	1760	*DM, DM1, DM1PK, DMK, MDPK, MT-PK*	skeletal muscle contraction, chemical synaptic transmission, postsynaptic
DNM2	1785	*CMT2M, CMTDI1, CMTDIB, DI-CMTB, DYN2, DYNII, LCCS5*	regulation of cellular response to growth factor stimulus, synaptic membrane
DPAGT1	1798	*ALG7, CDG-Ij, CDG1J, CMS13, CMSTA2, D11S366, DGPT, DPAGT, DPAGT2, G1PT, GPT, UAGT, UGAT*	glycoprotein biosynthetic process, glycoprotein metabolic process
DPM1	8813	*CDGIE, MPDS*	mannosylation, glycoprotein biosynthetic process
DST	667	*BP240, BPA, BPAG1, CATX-15, CATX15, D6S1101, DMH, DT, EBSB2, HSAN6, MACF2*	I band, contractile fiber
DYM	54808	*DMC, SMC*	bone development, skeletal system development
DYNC1H1	1778	*CMT2O, DHC1, DHC1a, DNCH1, DNCL, DNECL, DYHC, Dnchc1, HL-3, SMALED1, p22*	organelle localization, glycoprotein biosynthetic process
DYSF	8291	*FER1L1, LGMD2B, MMD1*	sarcolemma, muscle contraction
EBP	10682	*CDPX2, CHO2, CPX, CPXD, MEND*	skeletal system development, endoplasmic reticulum part
EGR2	1959	*AT591, CMT1D, CMT4E, KROX20*	Schwann cell differentiation, peripheral nervous system development
EMD	2010	*EDMD, LEMD5, STA*	skeletal muscle tissue development, skeletal muscle organ development
ERBB3	2065	*ErbB-3, HER3, LCCS2, MDA-BF-1, c-erbB-3, c-erbB3, erbB3-S, p180-ErbB3, p45-sErbB3, p85-sErbB3*	Schwann cell differentiation, peripheral nervous system development
ERCC1	2067	*COFS4, RAD10, UV20*	developmental growth, embryo development
ERCC2	2068	*COFS2, EM9, TFIIH, TTD, TTD1, XPD*	glial cell development, spinal cord development
ERCC6	2074	*ARMD5, CKN2, COFS, COFS1, CSB, RAD26, UVSS1*	developmental growth
ERLIN2	11160	*C8orf2, Erlin-2, NET32, SPFH2, SPG18*	endoplasmic reticulum part
ESCO2	157570	*2410004I17Rik, EFO2, RBS*	animal organ development
EZH2	2146	*ENX-1, ENX1, EZH1, EZH2b, KMT6, KMT6A, WVS, WVS2*	hippocampus development, limbic system development
FAM20C	56975	*DMP-4, DMP4, GEF-CK, RNS*	bone development, osteoblast differentiation
FBN1	2200	*ACMICD, ECTOL1, FBN, GPHYSD2, MASS, MFS1, OCTD, SGS, SSKS, WMS, WMS2*	extracellular matrix disassembly, regulation of cellular response to growth factor stimulus
FBN2	2201	*CCA, DA9, EOMD*	embryonic limb morphogenesis, extracellular matrix disassembly
FBN3	84467		regulation of cellular response to growth factor stimulus, proteinaceous extracellular matrix
FGD1	2245	*AAS, FGDY, MRXS16, ZFYVE3*	actin filament-based process, cellular response to growth factor stimulus
FGF9	2254	*FGF-9, GAF, HBFG-9, HBGF-9, SYNS3*	chondrocyte differentiation, regulation of stem cell proliferation, embryonic skeletal system development
FGFR1	2260	*BFGFR, CD331, CEK, FGFBR, FGFR-1, FLG, FLT-2, FLT2, HBGFR, HH2, HRTFDS, KAL2, N-SAM, OGD, bFGF-R-1*	cerebral cortex cell migration, neuroblast proliferation
FGFR2	2263	*BBDS, BEK, BFR-1, CD332, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25*	prostate gland epithelium morphogenesis, neuroblast proliferation
FGFR3	2261	*ACH, CD333, CEK2, HSFGFR3EX, JTK4*	glial cell development, bone morphogenesis
FHL1	2273	*FHL-1, FHL1A, FHL1B, FLH1A, KYOT, SLIM, SLIM-1, SLIM1, SLIMMER, XMPMA*	regulation of membrane potential, muscle organ development
FKBP10	60681	*BRKS1, FKBP65, OI11, OI6, PPIASE, hFKBP65*	endoplasmic reticulum part
FKRP	79147	*LGMD2I, MDC1C, MDDGA5, MDDGB5, MDDGC5*	mannosylation, sarcolemma
FKTN	2218	*CMD1X, FCMD, LGMD2M, MDDGA4, MDDGB4, MDDGC4*	mannosylation, muscle organ development
FLNA	2316	*ABP-280, ABPX, CSBS, CVD1, FLN, FLN-A, FLN1, FMD, MNS, NHBP, OPD, OPD1, OPD2, XLVD, XMVD*	protein import, actin cytoskeleton
FLNB	2317	*ABP-278, ABP-280, AOI, FH1, FLN-B, FLN1L, LRS1, SCT, TABP, TAP*	hippocampus development, limbic system development
FUCA1	2517	*FUCA*	lysosomal lumen, glycoprotein biosynthetic process
GAA	2548	*LYAG*	muscle cell cellular homeostasis, skeletal muscle contraction
GAD1	2571	*CPSQ1, GAD, SCP*	synaptic transmission
GBA	2629	*GBA1, GCB, GLUC*	lysosomal lumen, skin development
GBE1	2632	*APBD, GBE, GSD4*	carbohydrate metabolic process
GCK	2645	*FGQTL3, GK, GLK, HHF3, HK4, HKIV, HXKP, LGLK, MODY2*	actin cytoskeleton, carbohydrate derivative biosynthetic process
GDF5	8200	*BDA1C, BMP-14, BMP14, CDMP1, LAP-4, LAP4, OS5, SYM1B, SYNS2*	chondrocyte differentiation, embryonic limb morphogenesis
GJA1	2697	*AVSD3, CMDR, CX43, EKVP, GJAL, HLHS1, HSS, ODDD, PPKCA*	actin filament-based movement, embryonic limb morphogenesis
GLI3	2737	*ACLS, GCPS, GLI3-190, GLI3FL, PAP-A, PAPA, PAPA1, PAPB, PHS, PPDIV*	cerebral cortex cell migration, neuroblast proliferation
GLRA1	2741	*HKPX1, STHE*	chemical synaptic transmission, postsynaptic, neuromuscular process
GLRB	2743	*HKPX2*	neuromuscular process, synaptic membrane
GLUL	2752	*GLNS, GS, PIG43, PIG59*	positive regulation of epithelial cell proliferation, regulation of epithelial cell proliferation
GPC3	2719	*DGSX, GTR2-2, MXR7, OCI-5, SDYS, SGB, SGBS, SGBS1*	body morphogenesis, chondroitin sulfate metabolic process
GRHL3	57822	*SOM, TFCP2L4, VWS2*	skin development, embryonic organ morphogenesis
GRN	2896	*CLN11, GEP, GP88, PCDGF, PEPI, PGRN*	neural precursor cell proliferation, positive regulation of epithelial cell proliferation
GUSB	2990	*BG, MPS7*	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, BDSD, HOX4I, SPD*	prostate gland epithelium morphogenesis, embryonic limb morphogenesis
HRAS	3265	*C-BAS/HAS, C-H-RAS, C-HA-RAS1, CTLO, H-RASIDX, HAMSV, 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
ISPD	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, PHHI, 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, SRYP, 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	*CAML1, CD171, HSAS, HSAS1, MASA, MIC5, N-CAM-L1, N-CAML1, 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	*CDCD1, 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
MASP1	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, CanIon, IHPRF, INNFD, VGCNL1, bA430M15.1*	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
PEX1	5189	*PBD1A, PBD1B, ZWS, ZWS1*	protein targeting to peroxisome, intracellular protein transmembrane import
PEX10	5192	*NALD, PBD6A, PBD6B, RNF69*	integral component of peroxisomal membrane, protein targeting to peroxisome
PEX12	5193	*PAF-3, PBD3A*	integral component of peroxisomal membrane, protein targeting to peroxisome
PEX13	5194	*NALD, PBD11A, PBD11B, ZWS*	integral component of peroxisomal membrane, protein targeting to peroxisome
PEX14	5195	*NAPP2, PBD13A, Pex14p, dJ734G22.2*	protein targeting to peroxisome, intracellular protein transmembrane import
PEX2	5828	*PAF1, PBD5A, PBD5B, PMP3, PMP35, PXMP3, RNF72, ZWS3*	integral component of peroxisomal membrane, protein targeting to peroxisome
PEX26	55670	*PBD7A, PBD7B, PEX26M1T, Pex26pM1T*	integral component of peroxisomal membrane, protein targeting to peroxisome
PEX3	8504	*PBD10A, TRG18*	integral component of peroxisomal membrane, protein targeting to peroxisome
PEX5	5830	*PBD2A, PBD2B, PTS1-BP, PTS1R, PXR1*	protein targeting to peroxisome, intracellular protein transmembrane import
PEX6	5190	*PAF-2, PAF2, PBD4A, PDB4B, PXAAA1*	protein targeting to peroxisome, intracellular protein transmembrane import
PEX7	5191	*PBD9B, PTS2R, RCDP1, RD*	protein targeting to peroxisome, intracellular protein transmembrane import
PFKM	5213	*ATP-PFK, GSD7, PFK-1, PFK1, PFKA, PFKX, PPP1R122*	muscle cell cellular homeostasis, carbohydrate metabolic process
PIEZO2	63895	*C18orf30, C18orf58, DA3, DA5, FAM38B, FAM38B2, HsT748, HsT771, MWKS*	regulation of membrane potential
PIGT	51604	*CGI-06, MCAHS3, NDAP, PNH2*	neuron apoptotic process, neuron death
PIP5K1C	23396	*LCCS3, PIP5K-GAMMA, PIP5K1-gamma, PIP5Kgamma*	organelle localization, axon guidance
PITX1	5307	*BFT, CCF, LBNBG, POTX, PTX1*	embryonic limb morphogenesis, limb morphogenesis
PLEKHG5	57449	*CMTRIC, DSMA4, GEF720, Syx, Tech*	chemotaxis, cellular response to growth factor stimulus
PLOD1	5351	*EDS6, LH, LH1, LLH, PLOD*	extracellular matrix organization, endoplasmic reticulum part
PLOD2	5352	*BRKS2, LH2, TLH*	extracellular matrix organization, endoplasmic reticulum part
PLOD3	8985	*LH3*	collagen fibril organization, lung development
PLP1	5354	*GPM6C, HLD1, MMPL, PLP, PLP/DM20, PMD, SPG2*	glial cell development, axon ensheathment
PMM2	5373	*CDG1, CDG1a, CDGS, PMI, PMI1, PMM 2*	glycoprotein biosynthetic process, glycoprotein metabolic process
PMP22	5376	*CMT1A, CMT1E, DSS, GAS-3, HMSNIA, HNPP, Sp110*	peripheral nervous system development, axon ensheathment
POMGNT1	55624	*GNTI.2, GnT I.2, LGMD2O, MEB, MGAT1.2, gnT-I.2*	glycoprotein biosynthetic process, glycoprotein metabolic process
POMGNT2	84892	*AGO61, C3orf39, GTDC2, MDDGA8*	mannosylation, neuron migration
POMT1	10585	*LGMD2K, MDDGA1, MDDGB1, MDDGC1, RT*	mannosylation, extracellular matrix organization
POMT2	29954	*LGMD2N, MDDGA2, MDDGB2, MDDGC2*	mannosylation, glycoprotein biosynthetic process
POR	5447	*CPR, CYPOR, P450R*	bone morphogenesis, chondrocyte differentiation
PRG4	10216	*CACP, HAPO, JCAP, MSF, SZP*	stem cell proliferation, animal organ development
PRKAR1A	5573	*ACRDYS1, ADOHR, CAR, CNC, CNC1, PKR1, PPNAD1, PRKAR1, TSE1*	striated muscle cell development, muscle cell development
PRX	57716	*CMT4F*	axon ensheathment
PSD3	23362	*EFA6D, EFA6R, HCA67*	synaptic membrane
PTDSS1	9791	*LMHD, PSS1, PSSA*	carbohydrate derivative biosynthetic process, endoplasmic reticulum part
PTH1R	5745	*PFE, PTHR, PTHR1*	chondrocyte differentiation, cartilage development
RAB18	22931	*RAB18LI1, WARBM3*	brain development, head development
RAB3GAP1	22930	*P130, RAB3GAP, RAB3GAP130, WARBM1*	face development, body morphogenesis
RAPSN	5913	*CMS11, CMS4C, FADS, RAPSYN, RNF205*	neuromuscular synaptic transmission, neuron apoptotic process
RBM10	8241	*DXS8237E, GPATC9, GPATCH9, S1-1, TARPS, ZRANB5*	cell-type specific apoptotic process, negative regulation of cell proliferation
RELN	5649	*ETL7, LIS2, PRO1598, RL*	cerebral cortex cell migration, hippocampus development
RET	5979	*CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET-ELE1, RET51*	digestive tract development, digestive system development
RIPK4	54101	*ANKK2, ANKRD3, DIK, NKRD3, PKK, PPS2, RIP4*	morphogenesis of an epithelium, tissue morphogenesis
RMRP	6023	*CHH, NME1, RMRPR, RRP2*	hippocampus development, limbic system development
RNASEH2A	10535	*AGS4, JUNB, RNASEHI, RNHIA, RNHL*	osteoblast differentiation, ossification
RNASEH2B	79621	*AGS2, DLEU8*	chordate embryonic development, embryo development
RYR1	6261	*CCO, MHS, MHS1, PPP1R137, RYDR, RYR, RYR-1, SKRR*	muscle fiber development, sarcolemma
SCN4A	6329	*CMS16, HOKPP2, HYKPP, HYPP, NAC1A, Na(V)1.4, Nav1.4, SkM1*	muscle contraction, regulation of membrane potential
SEPN1	57190	*CFTD, MDRS1, RSMD1, RSS, SELN*	muscle fiber development, striated muscle cell development
SETX	23064	*ALS4, AOA2, SCAR1, bA479K20.2*	regulation of neurogenesis, regulation of nervous system development
SGCG	6445	*35DAG, A4, DAGA4, DMDA, DMDA1, LGMD2C, MAM, SCARMD2, SCG3, gamma-SG*	sarcolemma, muscle cell development
SHOX	6473	*GCFX, PHOG, SHOXY, SS*	skeletal system development
SKI	6497	*SGS, SKV*	Schwann cell development, Schwann cell differentiation
SLC12A6	9990	*ACCPN, KCC3, KCC3A, KCC3B*	blood vessel development, synaptic transmission
SLC26A2	1836	*D5S1708, DTD, DTDST, EDM4, MST153, MSTP157*	regulation of membrane potential, ossification
SLC39A13	91252	*LZT-Hs9*	connective tissue development, tissue development
SLC3A1	6519	*ATR1, CSNU1, D2H, NBAT, RBAT*	carbohydrate metabolic process
SLC9A6	10479	*MRSA, NHE6*	regulation of cellular response to growth factor stimulus, developmental growth

Table 1 (continued)

Gene	Entrez Gene ID	Aliases	Functions
SMN1	6606	*BCD541, GEMIN1, SMA, SMA1, SMA2, SMA3, SMA4, SMA@, SMN, SMNT, T-BCD541, TDRD16A*	I band, contractile fiber
SOD1	6647	*ALS, ALS1, HEL-S-44, IPOA, SOD, hSod1, homodimer*	muscle cell cellular homeostasis, Schwann cell development
SOX10	6663	*DOM, PCWH, WS2E, WS4, WS4C*	neuroblast proliferation, peripheral nervous system development
SOX9	6662	*CMD1, CMPD1, SRA1, SRXX2, SRXY10*	prostate gland epithelium morphogenesis, bone morphogenesis
SPG20	23111	*SPARTIN, TAHCCP1*	neuromuscular process, connective tissue development
SRD5A3	79644	*CDG1P, CDG1Q, KRIZI, SRD5A2L, SRD5A2L1*	glycoprotein biosynthetic process, glycoprotein metabolic process
STAC3	246329	*NAM*	neuromuscular synaptic transmission, skeletal muscle contraction
SULF1	23213	*SULF-1*	prostate gland epithelium morphogenesis, proteoglycan metabolic process
SYNE1	23345	*8B, ARCA1, C6orf98, CPG2, EDMD4, MYNE1, Nesp1, SCAR8, dJ45H2.2*	contractile fiber, synaptic membrane
TARP	445347	*CD3G, TCRG, TCRGC1, TCRGC2, TCRGV*	cell-type specific apoptotic process
TBX15	6913	*TBX14*	embryonic skeletal system development, skeletal system morphogenesis
TBX5	6910	*HOS*	embryonic limb morphogenesis, limb morphogenesis
TGFB3	7043	*ARVD, ARVD1, RNHF, TGF-beta3*	face development, body morphogenesis
TNNI2	7136	*AMCD2B, DA2B, FSSV, fsTnI*	striated muscle thin filament, muscle filament sliding
TNNT1	7138	*ANM, NEM5, STNT, TNT, TNTS*	striated muscle thin filament, muscle filament sliding
TNNT3	7140	*TNTF*	striated muscle thin filament, muscle filament sliding
TPM2	7169	*AMCD1, DA1, DA2B, HEL-S-273, NEM4, TMSB*	striated muscle thin filament, muscle filament sliding
TPM3	7170	*CAPM1, CFTD, HEL-189, HEL-S-82p, NEM1, OK/SW-cl.5, TM-5, TM3, TM30, TM30nm, TM5, TPMsk3, TRK, hscp30*	striated muscle thin filament, muscle filament sliding
TREX1	11277	*AGS1, CRV, DRN3, HERNS*	endoplasmic reticulum part
TSC1	7248	*LAM, TSC*	hippocampus development, limbic system development
TSC2	7249	*LAM, PPP1R160, TSC4*	protein import, morphogenesis of an epithelium
TWIST2	117581	*AMS, BBRSAY, DERMO1, FFDD3, SETLSS, bHLHa39*	face development, body morphogenesis
TYMP	1890	*ECGF, ECGF1, MEDPS1, MNGIE, MTDPS1, PDECGF, TP, hPD-ECGF*	blood vessel development, chemotaxis
UBA1	7317	*A1S9, A1S9T, A1ST, AMCX1, CFAP124, GXP1, POC20, SMAX2, UBA1A, UBE1, UBE1X*	endoplasmic reticulum part
UBE3A	7337	*ANCR, AS, E6-AP, EPVE6AP, HPVE6A*	developmental growth, brain development
UPK3A	7380	*UP3A, UPIII, UPIIIA, UPK3*	endoplasmic reticulum part, cellular component morphogenesis
UTRN	7402	*DMDL, DRP, DRP1*	sarcolemma, synaptic membrane
VPS33B	26276		bone development, organelle localization
WNT5A	7474	*hWNT5A*	prostate gland epithelium morphogenesis, face development
WNT7A	7476		chemical synaptic transmission, postsynaptic, chondrocyte differentiation
ZBTB42	100128927	*LCCS6, ZNF925*	muscle organ development, muscle structure development
ZC4H2	55906	*HCA127, KIAA1166, WRWF, WWS*	spinal cord development, central nervous system neuron differentiation
ZIC3	7547	*HTX, HTX1, VACTERLX, ZNF203*	digestive tract development, digestive system development
ZMPSTE24	10269	*FACE-1, FACE1, HGPS, PRO1, STE24, Ste24p*	endoplasmic reticulum part
ZNF335	63925	*MCPH10, NIF-1, NIF1, NIF2*	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

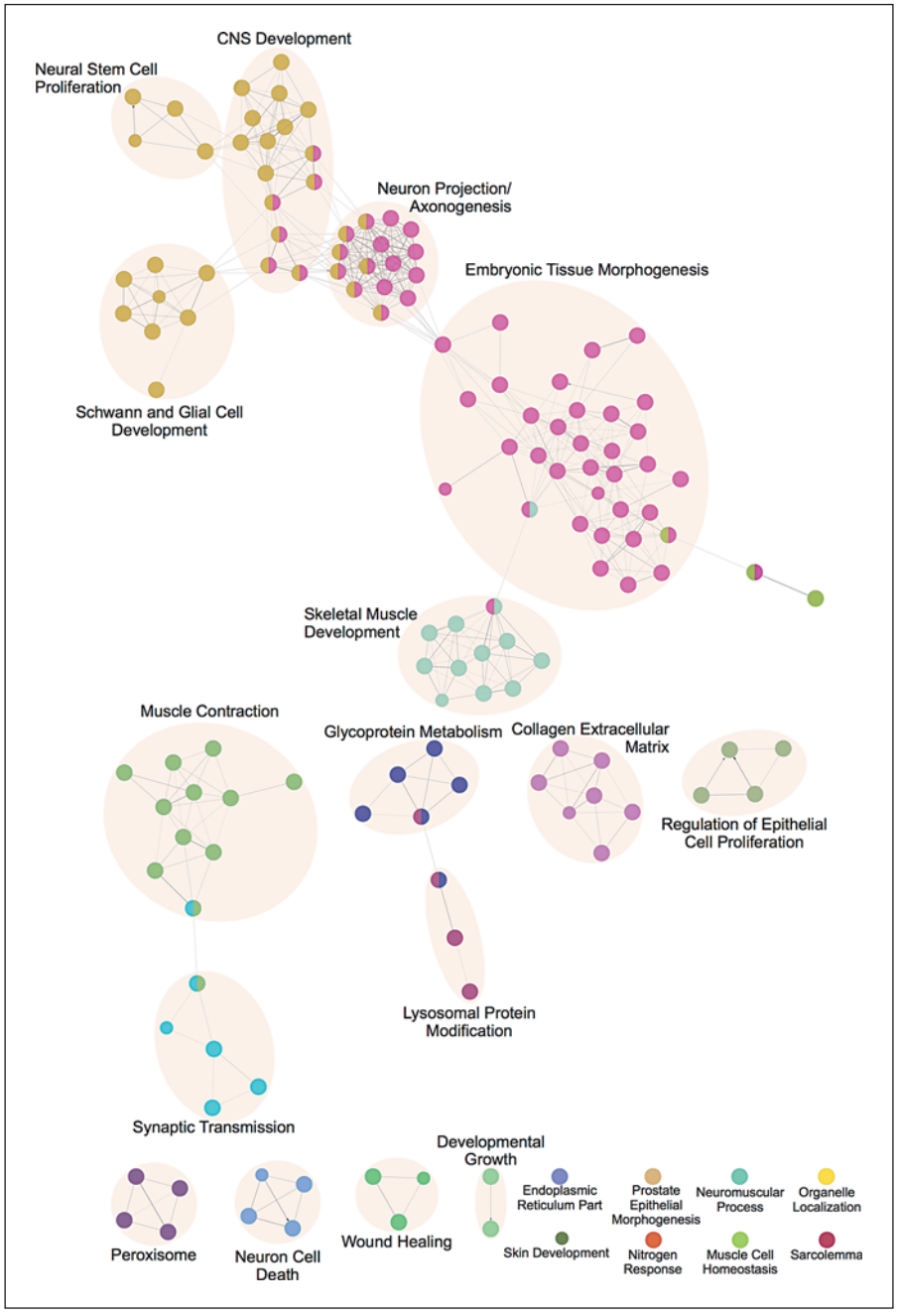

Fig. 1. GO enrichment network. The nodes in the network represent a specific GO term. The edges connecting the nodes are based on the kappa statistic that measures the overlap of shared genes between terms. The node colors correspond to the ClueGO-determined GO term clusters. The shadings represent author-annotated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