Received: 5 March 2019 | Revised: 13 June 2019 | Accepted: 17 July 2019

DOI: 10.1002/ajmg.c.31733

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics WILEY

Gene ontology analysis of arthrogryposis (multiple congenital contractures)

Jeff Kiefer[1] | Judith G. Hall[2,3]

[1]Systems Oncology, Scottsdale, Arizona

[2]Department of Medical Genetics, University of British Columbia and BC Children's Hospital, Vancouver, British Columbia, Canada

[3]Department of Pediatrics, University of British Columbia and BC Children's Hospital, Vancouver, British Columbia, Canada

Correspondence
Judith G. Hall, Department of Medical Genetics, BC Children's Hospital, 4500 Oak Street, Room C234, Vancouver, British Columbia V6H 3N1, Canada.
Email: jhall@cw.bc.ca

Abstract

In 2016, we published an article applying Gene Ontology Analysis to the genes that had been reported to be associated with arthrogryposis (multiple congenital contractures) (Hall & Kiefer, 2016). At that time, 320 genes had been reported to have mutations associated with arthrogryposis. All were associated with decreased fetal movement. These 320 genes were analyzed by biological process and cellular component categories, and yielded 22 distinct groupings. Since that time, another 82 additional genes have been reported, now totaling 402 genes, which when mutated, are associated with arthrogryposis (arthrogryposis multiplex congenita). So, we decided to update the analysis in order to stimulate further research and possible treatment. Now, 29 groupings can be identified, but only 19 groups have more than one gene.

KEYWORDS

arthrogryposis, developmental pathways, enrichment analysis, gene ontology, multiple congenital contractures

1 | INTRODUCTION

Arthrogryposis is the term that has been used for the last century to describe individuals born with multiple congenital contractures (e.g., limitation of movement of joints in two or more different body areas present at birth; Hall, 2014). Arthrogryposis and arthrogryposis multiplex congenita are both descriptive terms or signs rather than a specific diagnosis. After the pattern of embryonic structures have been laid out, the fetus normally begins to move—first its jaw and trunk, then the upper limbs, and a little later, the lower limbs. Many things can lead to a failure of normal fetal movement, including myopathic processes due to nuclear structural elements, ion channels, and mechanosensing elements; neuropathic processes including abnormalities of central or peripheral nerves, anterior horn cells, and brain organization and function; myelin structural abnormalities or deficiency; neuromotor endplate abnormalities; connective tissue disorders; limitation of space and constraint in utero; vascular compromise (decreased blood flow to the placenta and/or to the embryo/fetus); teratogenic exposure, and maternal illnesses. When there is decreased fetal movement, extra connective tissue is laid down around the joints of limbs, spine, and jaw (Hall, 2009). That mechanism of this contracture formation is poorly understood, but leads to a variety of secondary deformations (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).

Insight into the mechanism(s) underlying arthrogryposis should help lead to improved recognition, prevention, and therapies. For these reasons, we believe including the additional genes and their groupings may be useful and promote basic research into the underlying mechanisms and causes. It is also hoped that this model of gene ontology (GO) will be used for other heterogeneous congenital anomalies.

2 | METHODS

Over many years, one of the authors has accumulated a list of disorders with multiple congenital contractures (arthrogryposis) by regularly doing Medline, PubMed, and OMIM searches using appropriate search terms. Those where a gene mutation had been identified make up this publication list. Only full publications with the clinical features of affected individuals are included. If contractures were in only one body area, they were excluded. If not congenital, they were excluded. If the report included a clinical description of multiple congenital contractures, it was accepted.

TABLE 1 Gene table

NAME	EntrezGeneID	Aliases	Functions
ABCA7	10347	[ABCA-SSN, ABCX, AD9]	Glycoprotein biosynthetic process| glycoprotein metabolic process
ABCC8	6833	[ABC36, HHF1, HI, HRINS, MRP8, PHHI, SUR, SUR1, SUR1delta2, TNDM2]	Glial cell development | sarcolemma
ACTA1	58	[ACTA, ASMA, CFTD, CFTD1, CFTDM, MPFD, NEM1, NEM2, NEM3, SHPM]	Skeletal muscle thin filament assembly | striated muscle thin filament
ACTB	60	[BRWS1, PS1TP5BP1]	L1CAM interactions | distal axon
ACTG1	71	[ACT, ACTG, DFNA20, DFNA26, HEL-176]	Striated muscle contraction | sarcomere organization
ACTG1P10	83	[ACTGP10, ACTL1, ACTP1]	Not mapped
ADAMTS10	81794	[ADAM-TS10, ADAMTS-10, WMS, WMS1]	Diseases of glycosylation | disease
ADAMTSL2	9719	[GPHYSD1]	Diseases of glycosylation | respiratory system development
ADCY6	112	[AC6, LCCS8]	Negative regulation of neurogenesis | negative regulation of cell development
ADGRG6	57211	[APG1, DREG, GPR126, LCCS9, PR126, PS1TP2, VIGR]	Schwann cell development | Schwann cell differentiation
ADSL	158	[AMPS, ASASE, ASL]	Protein complex oligomerization
AIMP1	9255	[EMAP2, EMAPII, HLD3, SCYE1, p43]	Regulation of epithelial cell proliferation | blood vessel development
AK9	221264	[AK 9, AKD1, AKD2, C6orf199, C6orf224, dJ70A9.1]	Not mapped
AKT1	207	[AKT, CWS6, PKB, PKB-ALPHA, PRKBA, RAC, RAC-ALPHA]	Schwann cell development | Schwann cell differentiation
ALG2	85365	[CDG1I, CDGIi, CMS14, CMSTA3, NET38, hALPG2]	Diseases of glycosylation | positive regulation of epithelial cell proliferation
ALG3	10195	[CDG1D, CDGS4, CDGS6, D16Ertd36e, NOT56L, Not56, NOT]	Diseases of glycosylation | protein glycosylation
ANTXR2	118429	[CMG-2, CMG2, HFS, ISH, JHF]	Disease | endoplasmic reticulum part
AP1S2	8905	[DC22, MRX59, MRXS21, MRXS5, MRXSF, PGS, SIGMA1B]	Vesicle-mediated transport | Golgi subcompartment
APLNR	187	[AGTRL1, APJ, APJR, HG11]	Positive regulation of epithelial cell proliferation | regulation of epithelial cell proliferation
ARX	170302	[CT121, EIEE1, ISSX, MRX29, MRX32, MRX33, MRX36, MRX38, MRX43, MRX54, MRX76, MRX87, MRXS1, PRTS]	Cell proliferation in forebrain | cerebral cortex development
ASAH1	427	[AC, ACDase, ASAH, PHP, PHP32, SMAPME]	Lysosomal lumen
ASCC1	51008	[ASC1p50, CGI-18, SMABF2, p50]	Not mapped
ASXL1	171023	[BOPS, MDS]	Neuroblast proliferation | cellular component assembly involved in morphogenesis
ASXL3	80816	[BRPS, KIAA1713]	Animal organ morphogenesis | animal organ development
ATAD3A	55210	[HAYOS]	Not mapped
ATM	472	[AT1, ATA, ATC, ATD, ATDC, ATE, TEL1, TELO1]	Positive regulation of cellular component movement | cellular response to growth factor stimulus
ATN1	1822	[B37, D12S755E, DRPLA, HRS, NOD]	Regulation of cellular response to growth factor stimulus | gland development
ATP7A	538	[DSMAX, MK, MNK, SMAX3]	Respiratory system development | central nervous system neuron differentiation
ATR	545	[FCTCS, FRP1, MEC1, SCKL, SCKL1]	Gland morphogenesis | digestive tract development
ATRX	546	[JMS, MRX52, RAD54, RAD54L, XH2, XNP, ZNF-HX]	Limb morphogenesis | limb development
ATXN2	6311	[ATX2, SCA2, TNRC13]	Negative regulation of cellular component organization | Golgi subcompartment

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
ATXN3	4287	[AT3, ATX3, JOS, MJD, MJD1, SCA3]	Gland development | Actin cytoskeleton organization
AUTS2	26053	[FBRSL2, MRD26]	Neuron migration | growth cone
B3GAT3	26229	[GLCATI, JDSCD, glcUAT-I]	Diseases associated with glycosaminoglycan metabolism | proteoglycan metabolic process
BAG3	9531	[BAG-3, BIS, CAIR-1, MFM6]	Z disc | I band
BICD2	23299	[SMALED2, bA526D8.1]	COPI-independent Golgi-to-ER retrograde traffic | vesicle-mediated transport
BIN1	274	[AMPH2, AMPHL, CNM2, SH3P9]	Sarcolemma | Z disc
CANT1	124583	[DBQD, DBQD1, EDM7, SCAN-1, SCAN1, SHAPY]	Proteoglycan metabolic process | glycoprotein biosynthetic process
CAPN3	825	[CANP3, CANPL3, LGMD2, LGMD2A, nCL-1, p94]	Sarcomere organization | myofibril assembly
CASK	8573	[CAGH39, CAMGUK, CMG, FGS4, LIN2, MICPCH, MRXSNA, TNRC8, hCASK]	Non-integrin membrane-ECM interactions | extracellular matrix organization
CAVIN1	284119	[CAVIN, CGL4, FKSG13, PTRF, CAVIN-1]	Positive regulation of cellular component movement | regulation of cell motility
CBL	867	[C-CBL, CBL2, FRA11B, NSLL, RNF55]	Growth cone | cellular response to transforming growth factor beta stimulus
CCDC22	28952	[CXorf37, JM1, RTSC2]	Not mapped
CD24	100133941	[CD24A]	L1CAM interactions | kidney development
CD6	923	[TP120]	Not mapped
CD96	10225	[tactile]	Not mapped
CDK5	1020	[LIS7, PSSALRE]	Schwann cell development | Schwann cell differentiation
CDON	50937	[CDO, CDON1, HPE11, ORCAM]	Myotube differentiation | cerebral cortex development
CFL2	1073	[NEM7]	Sarcomere organization | myofibril assembly
CHAT	1103	[CHOACTASE, CMS1A, CMS1A2, CMS6]	Neuromuscular synaptic transmission | chemical synaptic transmission
CHMP1A	5119	[CHMP1, PCH8, PCOLN3, PRSM1, VPS46-1, VPS46A]	Not mapped
CHRNA1	1134	[ACHRA, ACHRD, CHRNA, CMS1A, CMS1B, CMS2A, FCCMS, SCCMS]	Synaptic transmission, cholinergic | neuromuscular synaptic transmission
CHRNB1	1140	[ACHRB, CHRNB, CMS1D, CMS2A, CMS2C, SCCMS]	Synaptic transmission, cholinergic | neuromuscular synaptic transmission
CHRND	1144	[ACHRD, CMS2A, CMS3A, CMS3B, CMS3C, FCCMS, SCCMS]	Synaptic transmission, cholinergic | neuromuscular synaptic transmission
CHRNE	1145	[ACHRE, CMS1D, CMS1E, CMS2A, CMS4A, CMS4B, CMS4C, FCCMS, SCCMS]	Synaptic transmission, cholinergic | neuromuscular synaptic transmission
CHRNG	1146	[ACHRG]	Synaptic transmission, cholinergic | neuromuscular synaptic transmission
CHST14	113189	[ATCS, D4ST1, EDSMC1, HNK1ST]	Diseases associated with glycosaminoglycan metabolism | proteoglycan metabolic process
CHST3	9469	[C6ST, C6ST1, HSD]	Diseases associated with glycosaminoglycan metabolism | proteoglycan metabolic process
CHUK	1147	[IKBKA, IKK-alpha, IKK1, IKKA, NFKBIKA, TCF16]	Skeletal muscle contraction | striated muscle contraction
CLIC3	9022	[]	Ion transmembrane transport
CNTN1	1272	[F3, GP135, MYPCN]	L1CAM interactions | positive regulation of epithelial cell proliferation
CNTNAP1	8506	[CASPR, CNTNAP, NRXN4, P190]	Schwann cell development | Schwann cell differentiation
COASY	80347	[DPCK, NBIA6, NBP, PPAT, UKR1, pOV-2]	Kidney development | renal system development

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
COG6	57511	[CDG2L, COD2, SHNS]	Vesicle-mediated transport | Golgi subcompartment
COG7	91949	[CDG2E]	Protein glycosylation | glycoprotein biosynthetic process
COL11A2	1302	[DFNA13, DFNB53, FBCG2, HKE5, OSMEDA, OSMEDB, PARP, STL3]	Fibrillar collagen trimer | complex of collagen trimers
COL13A1	1305	[CMS19, COLXIIIA1]	Collagen chain trimerization | collagen degradation
COL1A1	1277	[EDSARTH1, EDSC, OI1, OI2, OI3, OI4]	Fibrillar collagen trimer | complex of collagen trimers
COL1A2	1278	[EDSARTH2, EDSCV, 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, EDSVASC]	Fibrillar collagen trimer | complex of collagen trimers
COL6A1	1291	[BTHLM1, OPLL, UCHMD1]	Collagen chain trimerization | endochondral bone growth
COL6A2	1292	[BTHLM1, PP3610, UCMD1]	Collagen chain trimerization | endochondral bone growth
COL6A3	1293	[BTHLM1, DYT27, UCMD1]	Collagen chain trimerization | endochondral bone growth
COL7A1	1294	[EBD1, EBDCT, EBR1, NDNC8]	Complex of collagen trimers | collagen chain trimerization
COLEC11	78989	[3MC2, CL-K1-I, CL-K1-II, CL-K1-IIa, CL-K1-IIb, CLK1]	Vesicle-mediated transport | peptidyl-amino acid modification
CPT2	1376	[CPT1, CPTASE, IIAE4]	Integral component of organelle membrane | protein complex oligomerization
CRLF1	9244	[CISS, CISS1, CLF, CLF-1, NR6, zcytor5]	Kidney development | renal system development
CRTAP	10491	[CASP, LEPREL3, OI7, P3H5]	Protein hydroxylation | collagen biosynthesis and modifying enzymes
CTSA	5476	[GLB2, GSL, NGBE, PPCA, PPGB]	Lysosomal lumen | endoplasmic reticulum
CTSL	1514	[CATL, CTSL1, MEP]	Assembly of collagen fibrils and other multimeric structures | collagen degradation
DCHS1	8642	[CDH19, CDH25, CDHR6, FIB1, MVP2, PCDH16, VMLDS1]	Digestive tract development | digestive system development
DCX	1641	[DBCN, DC, LISX, SCLH, XLIS]	L1CAM interactions | limbic system development
DES	1674	[CDCD3, CMD1F, CSM1, CSM2, LGMD1D, LGMD1E, LGMD2R]	Striated muscle contraction | striated muscle contraction
DHCR24	1718	[DCE, Nbla03646, SELADIN1, SELADIN-1]	Golgi subcompartment | Golgi apparatus part
DHCR7	1717	[SLOS]	Respiratory system development | blood vessel development
DMPK	1760	[DM, DM1, DM1PK, DMK, MDPK, MT-PK]	Skeletal muscle contraction | excitatory postsynaptic potential
DNM2	1785	[CMT2M, CMTDI1, CMTDIB, DI-CMTB, DYN2, DYNII, LCCS5]	L1CAM interactions | growth cone
DOCK7	85440	[EIEE23, ZIR2]	Cell proliferation in forebrain | neuroblast proliferation
DOK7	285489	[C4orf25, CMS10, CMS1B]	Peptidyl-amino acid modification
DPAGT1	1798	[ALG7, CDG-Ij, CDG1J, CMS13, CMSTA2, D11S366, DGPT, DPAGT, DPAGT2, G1PT, GPT, UAGT, UGAT]	Diseases of glycosylation | protein glycosylation
DPM1	8813	[CDGIE, MPDS]	Protein O-linked mannosylation | diseases of glycosylation
DRG2	1819	[]	Not mapped
DST	667	[BP240, BPA, BPAG1, CATX-15, CATX15, D6S1101, DMH, DT, EBSB2, HSAN6, MACF2]	Assembly of collagen fibrils and other multimeric structures | collagen formation
DYM	54808	[DMC, SMC]	Bone development | skeletal system development

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
DYNC1H1	1778	[CMT2O, DHC1, DHC1a, DNCH1, DNCL, DNECL, DYHC, Dnchc1, HL-3, SMALED1, p22]	COPI-independent Golgi-to-ER retrograde traffic | vesicle-mediated transport
DYSF	8291	[FER1L1, LGMD2B, MMD1]	Muscle fiber development | sarcolemma
EBP	10682	[CDPX2, CHO2, CPX, CPXD, MEND]	Skeletal system development | endoplasmic reticulum part
ECEL1	9427	[DA5D, DINE, ECEX, XCE]	Not mapped
EGFLAM	133584	[AGRINL, AGRNL, PIKA]	Proteoglycan metabolic process | glycosaminoglycan metabolic process
EGR2	1959	[AT591, CMT1D, CMT4E, KROX20]	Schwann cell differentiation | peripheral nervous system development
EIF2AK4	440275	[GCN2, PVOD2]	Negative regulation of neurogenesis | negative regulation of cell development
EIF2S3	1968	[EIF2, EIF2G, EIF2gamma, MEHMO, MRXSBRK, eIF-2gA]	Not mapped
EMD	2010	[EDMD, LEMD5, STA]	Skeletal muscle tissue development | skeletal muscle organ development
EMG1	10436	[C2F, Grcc2f, NEP1]	Chordate embryonic 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]	Embryonic organ development | negative regulation of cellular component organization
ERCC2	2068	[COFS2, EM9, TFIIH, TTD, TTD1, XPD]	Cellular component assembly involved in morphogenesis | glial cell development
ERCC5	2073	[COFS3, ERCC5-201, ERCM2, UVDR, XPG, XPGC]	Positive regulation of cellular component organization
ERCC6	2074	[ARMD5, CKN2, COFS, COFS1, CSB, CSB-PGBD3, POF11, RAD26, UVSS1]	Peptidyl-amino acid modification
ERGIC1	57222	[AMCN, ERGIC-32, ERGIC32, NET24]	Golgi subcompartment | Golgi apparatus part
ERLIN2	11160	[C8orf2, Erlin-2, NET32, SPFH2, SPG18]	Disease | peptidyl-amino acid modification
ESCO2	157570	[2410004I17Rik, EFO2, RBS]	Animal organ development
EXOSC3	51010	[CGI-102, PCH1B, RRP40, Rrp40p, bA3J10.7, hRrp-40, p10]	Not mapped
EXOSC8	11340	[CIP3, EAP2, OIP2, PCH1C, RRP43, Rrp43p, bA421P11.3, p9]	Neuron development | neuron differentiation
EXTL3	2137	[BOTV, EXTL1L, EXTR1, ISDNA, REGR, RPR]	Proteoglycan metabolic process | protein glycosylation
EZH2	2146	[ENX-1, ENX1, EZH2b, KMT6, KMT6A, WVS, WVS2]	Limbic system development | pallium development
FAM20C	56975	[DMP-4, DMP4, G-CK, GEF-CK, RNS]	Bone development | regulation of cellular response to growth factor stimulus
FBN1	2200	[ACMICD, ECTOL1, FBN, GPHYSD2, MASS, MFLS, MFS1, OCTD, SGS, SSKS, WMS, WMS2]	Integrin cell surface interactions | degradation of the extracellular matrix
FBN2	2201	[CCA, DA9, EOMD]	Degradation of the extracellular matrix | embryonic limb morphogenesis
FBN3	84467	[]	Degradation of the extracellular matrix | extracellular matrix organization
FBXL4	26235	[FBL4, FBL5, MTDPS13]	Not mapped
FGD1	2245	[AAS, FGDY, MRXS16, ZFYVE3]	Actin cytoskeleton organization | animal organ morphogenesis
FGF9	2254	[FGF-9, GAF, HBFG-9, HBGF-9, SYNS3]	Chondrocyte differentiation | embryonic limb morphogenesis
FGFR1	2260	[BFGFR, CD331, CEK, ECCL, FGFBR, FGFR-1, FLG, FLT-2, FLT2, HBGFR, HH2, HRTFDS, KAL2, N-SAM, OGD, bFGF-R-1]	Cell proliferation in forebrain | Endochondral ossification

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
FGFR2	2263	[BBDS, BEK, BFR-1, CD332, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25]	Cell proliferation in forebrain | endochondral bone growth
FGFR3	2261	[ACH, CD333, CEK2, HSFGFR3EX, JTK4]	Endochondral bone growth | Endochondral ossification
FHL1	2273	[FCMSU, FHL-1, FHL1A, FHL1B, FLH1A, KYOT, RBMX1A, RBMX1B, SLIM, SLIM-1, SLIM1, SLIMMER, XMPMA]	Muscle organ development | animal organ morphogenesis
FKBP10	60681	[BRKS1, FKBP65, OI11, OI6, PPIASE, hFKBP65]	Peptidyl-amino acid modification | endoplasmic reticulum part
FKRP	79147	[LGMD2I, MDC1C, MDDGA5, MDDGB5, MDDGC5]	Protein O-linked mannosylation | sarcolemma
FKTN	2218	[CMD1X, FCMD, LGMD2M, MDDGA4, MDDGB4, MDDGC4]	Protein O-linked mannosylation | integral component of organelle membrane
FLNA	2316	[ABP-280, ABPX, CSBS, CVD1, FGS2, FLN, FLN-A, FLN1, FMD, MNS, NHBP, OPD, OPD1, OPD2, XLVD, XMVD]	Cerebral cortex development | Z disc
FLNB	2317	[ABP-278, ABP-280, AOI, FH1, FLN-B, FLN1L, LRS1, SCT, TABP, TAP]	Digestive tract development | digestive system development
FLVCR2	55640	[C14orf58, CCT, EPV, FLVCRL14q, MFSD7C, PVHH]	Not mapped
FOXP3	50943	[AIID, DIETER, IPEX, JM2, PIDX, XPID]	Cell surface receptor signaling pathway involved in cell–cell signaling | negative regulation of cell proliferation
FUCA1	2517	[FUCA]	Lysosomal lumen | glycosaminoglycan metabolic process
GAA	2548	[LYAG]	Skeletal muscle contraction | lysosomal lumen
GAD1	2571	[CPSQ1, GAD, SCP]	Distal axon | axon part
GBA	2629	[GBA1, GCB, GLUC]	Lysosomal lumen | protein complex oligomerization
GBE1	2632	[APBD, GBE, GSD4]	Disease
GCK	2645	[FGQTL3, GK, GLK, HHF3, HK4, HKIV, HXKP, LGLK, MODY2]	Cellular response to organonitrogen compound | Golgi subcompartment
GDAP1	54332	[CMT4, CMT4A, CMTRIA]	Integral component of organelle membrane
GDF5	8200	[BDA1C, BMP-14, BMP14, CDMP1, LAP-4, LAP4, OS5, SYM1B, SYNS2]	Chondrocyte differentiation | gland morphogenesis
GFM2	84340	[EF-G2mt, EFG2, MRRF2, MST027, MSTP027, RRF2, RRF2mt, hEFG2, mEF-G 2]	Not mapped
GFPT1	2673	[CMS12, CMSTA1, GFA, GFAT, GFAT 1, GFAT1, GFAT1m, GFPT, GFPT1L, MSLG]	Diseases of glycosylation | protein glycosylation
GJA1	2697	[AVSD3, CMDR, CX43, EKVP, EKVP3, GJAL, HLHS1, HSS, ODDD, PPKCA]	Proteoglycan metabolic process | lysosomal lumen
GLDN	342035	[CLOM, COLM, CRG-L2, CRGL2, LCCS11, UNC-112]	Axon | neuron development
GLE1	2733	[GLE1L, LCCS, LCCS1, hGLE1]	Not mapped
GLI1	2735	[GLI]	Gland morphogenesis | digestive tract development
GLI3	2737	[ACLS, GCPS, GLI3-190, GLI3FL, PAP-A, PAPA, PAPA1, PAPB, PHS, PPDIV]	Cell proliferation in forebrain | Endochondral ossification
GLRA1	2741	[HKPX1, STHE]	Excitatory postsynaptic potential | distal axon
GLRB	2743	[HKPX2]	Excitatory postsynaptic potential | cell surface receptor signaling pathway involved in cell–cell signaling
GLUL	2752	[GLNS, GS, PIG43, PIG59]	Positive regulation of epithelial cell proliferation | distal axon
GPC3	2719	[DGSX, GTR2-2, MXR7, OCI-5, SDYS, SGB, SGBS, SGBS1]	Diseases associated with glycosaminoglycan metabolism | lysosomal lumen
GRHL3	57822	[SOM, TFCP2L4, VWS2]	Embryonic organ morphogenesis | embryonic organ development

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
GRN	2896	[CLN11, GEP, GP88, PCDGF, PEPI, PGRN]	Positive regulation of cellular component movement | regulation of cell motility
GUSB	2990	[BG, MPS7]	Lysosomal lumen | glycosaminoglycan metabolic process
GZF1	64412	[JLSM, ZBTB23, ZNF336]	Kidney development | renal system development
HEXA	3073	[TSD]	Diseases associated with glycosaminoglycan metabolism | proteoglycan metabolic process
HEXB	3074	[ENC-1AS, HEL-248, HEL-S-111]	Diseases associated with glycosaminoglycan metabolism | proteoglycan metabolic process
HLA-DRB1	3123	[DRB1, HLA-DR1B, HLA-DRB, SS1]	Protein complex oligomerization | negative regulation of cell proliferation
HOGA1	112817	[C10orf65, DHDPS2, DHDPSL, HP3, NPL2]	Not mapped
HOXA13	3209	[HOX1, HOX1J]	Skeletal system development
HOXD13	3239	[BDE, BDSD, HOX4I, SPD, SPD1]	Gland 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 | regulation of epithelial cell proliferation
HSPG2	3339	[HSPG, PLC, PRCAN, SJA, SJS, SJS1]	Diseases associated with glycosaminoglycan metabolism | non-integrin membrane-ECM interactions
HWE1	100415903	[]	Not mapped
IBA57	200205	[C1orf69, MMDS3, SPG74]	Not mapped
IDS	3423	[MPS2, SIDS]	Proteoglycan metabolic process | lysosomal lumen
IFIH1	64135	[AGS7, Hlcd, IDDM19, MDA-5, MDA5, RLR-2, SGMRT1]	Peptidyl-amino acid modification
IGF2	3481	[C11orf43, GRDF, IGF-II, PP9974]	Endochondral ossification | digestive system development
IGHMBP2	3508	[CATF1, CMT2S, HCSA, HMN6, SMARD1, SMUBP2, ZFAND7]	Growth cone | distal axon
IMPAD1	54928	[GPAPP, IMP 3, IMP-3, IMPA3]	Chondrocyte development | endochondral bone morphogenesis
INPP5K	51763	[MDCCAID, PPS, SKIP]	Skeletal muscle fiber development | muscle fiber development
INSR	3643	[CD220, HHF5]	Digestive system development | positive regulation of developmental growth
IRF6	3664	[LPS, OFC6, PIT, PPS, PPS1, VWS, VWS1]	Skeletal muscle fiber development | muscle fiber development
ISLR2	57611	[LINX]	Positive regulation of developmental growth | axonogenesis
ISPD	729920	[MDDGA7, MDDGC7, nip, hCG_1745121, hISPD]	Protein O-linked mannosylation | protein glycosylation
ITGA6	3655	[CD49f, ITGA6B, VLA-6]	Non-integrin membrane-ECM interactions | assembly of collagen fibrils and other multimeric structures
ITGB4	3691	[CD104, GP150]	Non-integrin membrane-ECM interactions | assembly of collagen fibrils and other multimeric structures
KAT6B	23522	[GTPTS, MORF, MOZ2, MYST4, ZC2HC6B, qkf, querkopf]	Peptidyl-amino acid modification
KBTBD13	390594	[HCG1645727, NEM6]	Not mapped
KCNA1	3736	[AEMK, EA1, HBK1, HUK1, KV1.1, MBK1, MK1, RBK1]	Neuroblast proliferation | limbic system development
KCNH1	3756	[EAG, EAG1, Kv10.1, TMBTS, ZLS1, h-EAG, hEAG1]	Myotube differentiation | striated muscle cell differentiation
KCNJ11	3767	[BIR, HHF2, IKATP, KIR6.2, MODY13, PHHI, TNDM3]	Sarcolemma | muscle contraction

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
KCNK9	51305	[K2p9.1, KT3.2, TASK-3, TASK3]	Muscle contraction | ion transmembrane transport
KIAA0586	9786	[JBTS23, SRTD14, Talpid3]	Plasma membrane bounded cell projection part
KIAA1109	84162	[ALKKUCS, FSA, Tweek]	Not mapped
KIF14	9928	[MCPH20, MKS12]	Cell proliferation in forebrain | limbic system development
KIF1A	547	[ATSV, C2orf20, HSN2C, MRD9, SPG30, UNC104]	Cell proliferation in forebrain | axon part
KIF5C	3800	[CDCBM2, KINN, NKHC, NKHC-2, NKHC2]	Growth cone | axon guidance
KIF7	374654	[ACLS, AGBK, HLS2, JBTS12, UNQ340]	Plasma membrane bounded cell projection part
KLHL3	26249	[PHA2D]	Kidney development | renal system development
KLHL40	131377	[KBTBD5, NEM8, SRYP, SYRP]	Skeletal muscle fiber development | muscle fiber development
KLHL41	10324	[KBTBD10, Krp1, SARCOSIN]	Skeletal muscle fiber development | sarcomere organization
KLKB1	3818	[KLK3, PKK, PKKD, PPK]	Degradation of the extracellular matrix | extracellular matrix organization
L1CAM	3897	[CAML1, CD171, HSAS, HSAS1, MASA, MIC5, N-CAM-L1, N-CAML1, NCAM-L1, S10, SPG1]	L1CAM interactions | positive regulation of developmental growth
LAMA2	3908	[LAMM]	Synaptic transmission, cholinergic | Schwann cell differentiation
LARGE1	9215	[LARGE, MDC1D, MDDGA6, MDDGB6]	Protein O-linked mannosylation | diseases of glycosylation
LGI4	163175	[AMCNMY, LGIL3]	Schwann cell development | Schwann cell differentiation
LIFR	3977	[CD118, LIF-R, SJS2, STWS, SWS]	Enzyme linked receptor protein signaling pathway
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, MADA, PRO1]	Striated muscle cell development | muscle cell development
LMOD3	56203	[NEM10]	Skeletal muscle thin filament assembly | striated muscle thin filament
LMX1B	4010	[LMX1.2, NPS1]	Chordate embryonic development | neuron differentiation
LTBP2	4053	[C14orf141, GLC3D, LTBP3, MSPKA, MSTP031, WMS3]	Extracellular matrix organization | cellular response to transforming growth factor beta stimulus
MAGEL2	54551	[NDNL1, PWLS, SHFYNG, nM15]	Actin cytoskeleton organization | positive regulation of cellular component organization
MAP3K7	6885	[CSCF, FMD2, MEKK7, TAK1, TGF1a]	Cellular response to transforming growth factor beta stimulus | cell surface receptor signaling pathway involved in cell–cell signaling
MASP1	5648	[3MC1, CRARF, CRARF1, MAP1, MASP, MASP3, MAp44, PRSS5, RaRF]	Vesicle-mediated transport
MECOM	2122	[AML1-EVI-1, EVI1, KMT8E, MDS1, MDS1-EVI1, PRDM3, RUSAT2]	Protein kinase B signaling | glycoprotein biosynthetic process
MED12	9968	[ARC240, CAGH45, FGS1, HOPA, MED12S, OHDOX, OKS, OPA1, TNRC11, TRAP230]	Schwann cell development | Schwann cell differentiation
MEGF10	84466	[EMARDD]	Skeletal muscle tissue development | muscle cell development
MFN2	9927	[CMT2A, CMT2A2, CMT2A2A, CMT2A2B, CPRP1, HMSN6A, HSG, MARF]	Chordate embryonic development | negative regulation of cell proliferation
MGP	4256	[GIG36, MGLAP, NTI]	Endochondral ossification | cartilage development
MHS3	7977	[]	Sarcolemma | striated muscle contraction

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
MMP2	4313	[CLG4, CLG4A, MMP-2, MMP-II, MONA, TBE-1]	Face morphogenesis | collagen degradation
MNX1	3110	[HB9, HLXB9, HOXHB9, SCRA1]	Central nervous system neuron differentiation | neuron projection morphogenesis
MTM1	4534	[CNM, MTMX, XLMTM]	I band | positive regulation of developmental growth
MUSK	4593	[CMS9, FADS]	ECM proteoglycans | extracellular matrix organization
MYBPC1	4604	[LCCS4, MYBPCC, MYBPCS]	Skeletal muscle thin filament assembly | myosin filament
MYBPC2	4606	[MYBPC, MYBPCF]	Skeletal muscle thin filament assembly | myosin filament
MYH14	79784	[DFNA4, DFNA4A, FP17425, MHC16, MYH17, NMHC II-C, NMHC-II-C, PNMHH, myosin]	Myosin filament | skeletal muscle contraction
MYH2	4620	[IBM3, MYH2A, MYHSA2, MYHas8, MYPOP, MyHC-2A, MyHC-IIa]	Myosin filament | muscle filament sliding
MYH3	4621	[DA2A, DA2B, DA8, HEMHC, MYHC-EMB, MYHSE1, SMHCE]	Myosin filament | face morphogenesis
MYH7B	57644	[MHC14, MYH14]	Myosin filament | skeletal muscle contraction
MYH8	4626	[DA7, MyHC-peri, MyHC-pn, gtMHC-F]	Myosin filament | striated muscle contraction
MYMK	389827	[MYOMAKER, TMEM226, TMEM8C]	Myotube differentiation | striated muscle cell differentiation
MYO18B	84700	[KFS4]	Cardiac muscle fiber development | myosin complex
MYO3A	53904	[DFNB30]	Myosin complex | embryonic organ morphogenesis
MYO9A	4649	[]	Myosin complex | morphogenesis of an epithelium
MYOD1	4654	[MYF3, MYOD, PUM, bHLHc1]	Skeletal muscle fiber development | muscle fiber development
MYOM2	9172	[TTNAP]	Skeletal muscle thin filament assembly | myosin filament
MYOT	9499	[LGMD1, LGMD1A, MFM3, TTID, TTOD]	Sarcolemma | Z disc
MYPN	84665	[CMD1DD, CMH22, MYOP, NEM11, RCM4]	Sarcomere organization | myofibril assembly
NAA10	8260	[ARD1, ARD1A, ARD1P, DXS707, MCOPS1, NATD, OGDNS, TE2, hARD1]	Negative regulation of cellular component organization | Golgi subcompartment
NALCN	259232	[CLIFAHDD, CanIon, IHPRF, IHPRF1, INNFD, VGCNL1, bA430M15.1]	Ion transmembrane transport | cation transport
NEB	4703	[NEB177D, NEM2]	Striated muscle contraction | striated muscle contraction
NEFH	4744	[CMT2CC, NFH]	Peripheral nervous system development | axonogenesis
NEU1	4758	[NANH, NEU, SIAL1]	Peripheral nervous system development | lysosomal lumen
NF1	4763	[NFNS, VRNF, WSS]	Schwann cell development | Schwann cell differentiation
NOG	9241	[SYM1, SYNS1, SYNS1A]	Face morphogenesis | gland morphogenesis
NRXN1	9378	[Hs.22998, PTHSL2, SCZD17]	Non-integrin membrane-ECM interactions | excitatory postsynaptic potential
NSD1	64324	[ARA267, KMT3B, SOTOS, SOTOS1, STO]	Peptidyl-amino acid modification
OCRL	4952	[INPP5F, LOCR, NPHL2, OCRL-1, OCRL1]	Protein kinase B signaling | negative regulation of neurogenesis
OFD1	8481	[71-7A, CXorf5, JBTS10, RP23, SGBS2]	Plasma membrane bounded cell projection part
ORC4	5000	[ORC4L, ORC4P]	Not mapped
ORC6	23594	[ORC6L]	Not mapped
P3H1	64175	[GROS1, LEPRE1, OI8]	Protein hydroxylation | collagen biosynthesis and modifying enzymes

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
PAFAH1B1	5048	[LIS1, LIS2, MDCR, MDS, NudF, PAFAH]	COPI-independent Golgi-to-ER retrograde traffic | neuroblast proliferation
PANK2	80025	[C20orf48, HARP, HSS, NBIA1, PKAN]	Proteoglycan metabolic process | lysosomal lumen
PAX3	5077	[CDHS, HUP2, WS1, WS3]	Muscle organ development | Actin cytoskeleton
PDHA1	5160	[PDHA, PDHAD, PDHCE1A, PHE1A]	Not mapped
PEX1	5189	[HMLR1, PBD1A, PBD1B, ZWS, ZWS1]	Peroxisomal membrane transport | Peroxisomal protein import
PEX10	5192	[NALD, PBD6A, PBD6B, RNF69]	Integral component of peroxisomal membrane | peroxisomal membrane transport
PEX12	5193	[PAF-3, PBD3A]	Integral component of peroxisomal membrane | peroxisomal membrane transport
PEX13	5194	[NALD, PBD11A, PBD11B, ZWS]	Integral component of peroxisomal membrane | peroxisomal membrane transport
PEX14	5195	[NAPP2, PBD13A, Pex14p, dJ734G22.2]	Peroxisomal membrane transport | Peroxisomal protein import
PEX2	5828	[PAF1, PBD5A, PBD5B, PMP3, PMP35, PXMP3, RNF72, ZWS3]	Integral component of peroxisomal membrane | peroxisomal membrane transport
PEX26	55670	[PBD7A, PBD7B, PEX26M1T, Pex26pM1T]	Integral component of peroxisomal membrane | peroxisomal membrane transport
PEX3	8504	[PBD10A, PBD10B, TRG18]	Integral component of peroxisomal membrane | peroxisomal membrane transport
PEX5	5830	[PBD2A, PBD2B, PTS1-BP, PTS1R, PXR1, RCDP5]	Peroxisomal membrane transport | Peroxisomal protein import
PEX6	5190	[HMLR2, PAF-2, PAF2, PBD4A, PDB4B, PXAAA1]	Peroxisomal membrane transport | Peroxisomal protein import
PEX7	5191	[PBD9B, PTS2R, RCDP1, RD]	Peroxisomal membrane transport | Peroxisomal protein import
PFKM	5213	[ATP-PFK, GSD7, PFK-1, PFK-A, PFK1, PFKA, PFKX, PPP1R122]	Protein complex oligomerization | plasma membrane bounded cell projection part
PI4KA	5297	[PI4K-ALPHA, PIK4CA, PMGYCHA, pi4K230]	Not mapped
PIEZO2	63895	[C18orf30, C18orf58, DA3, DA5, DAIPT, FAM38B, FAM38B2, HsT748, HsT771, MWKS]	Ion transmembrane transport | cation transport
PIGS	94005	[]	Endoplasmic reticulum part | organelle subcompartment
PIGT	51604	[CGI-06, MCAHS3, NDAP, PNH2]	Endoplasmic reticulum part | neuron differentiation
PIP5K1C	23396	[LCCS3, PIP5K-GAMMA, PIP5K1-gamma, PIP5Kgamma]	Vesicle-mediated transport | Actin cytoskeleton organization
PITX1	5307	[BFT, CCF, LBNBG, POTX, PTX1]	Embryonic limb morphogenesis | limb morphogenesis
PLEKHG5	57449	[CMTRIC, DSMA4, GEF720, Syx, tech]	Chemical synaptic transmission
PLOD1	5351	[EDS6, EDSKCL1, LH, LH1, LLH, PLOD]	Peptidyl-lysine hydroxylation | protein hydroxylation
PLOD2	5352	[BRKS2, LH2, TLH]	Peptidyl-lysine hydroxylation | protein hydroxylation
PLOD3	8985	[LH3]	Peptidyl-lysine hydroxylation | protein hydroxylation
PLP1	5354	[GPM6C, HLD1, MMPL, PLP, PLP/DM20, PMD, SPG2]	Glial cell development | axon ensheathment
PMM2	5373	[CDG1, CDG1a, CDGS, PMI, PMI1, PMM 2]	Diseases of glycosylation | protein glycosylation
PMP22	5376	[CIDP, CMT1A, CMT1E, DSS, GAS-3, GAS3, HMSNIA, HNPP, Sp110]	Peroxisomal membrane | peripheral nervous system development
POLR3A	11128	[ADDH, HLD7, RPC1, RPC155, hRPC155]	Not mapped
POLR3D	661	[BN51T, RPC4, RPC53, TSBN51]	Not mapped
POMGNT1	55624	[GNTI.2, GnT I.2, LGMD2O, MEB, MGAT1.2, RP76, gnT-I.2]	Diseases of glycosylation | integral component of organelle membrane

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
POMGNT2	84892	[AGO61, C3orf39, GTDC2, MDDGA8]	Protein O-linked mannosylation | neuron migration
POMT1	10585	[LGMD2K, MDDGA1, MDDGB1, MDDGC1, RT]	Protein O-linked mannosylation | diseases of glycosylation
POMT2	29954	[LGMD2N, MDDGA2, MDDGB2, MDDGC2]	Protein O-linked mannosylation | diseases of glycosylation
POR	5447	[CPR, CYPOR, P450R]	Endochondral bone growth | cartilage development involved in endochondral bone morphogenesis
PPIB	5479	[B, CYP-S1, CYPB, HEL-S-39, OI9, SCYLP]	Collagen biosynthesis and modifying enzymes | collagen formation
PRG4	10216	[CACP, HAPO, JCAP, MSF, SZP]	Actin cytoskeleton | protein complex oligomerization
PRKAR1A	5573	[ACRDYS1, ADOHR, CAR, CNC, CNC1, PKR1, PPNAD1, PRKAR1, TSE1]	Cardiac muscle fiber development | sarcomere organization
PRPH	5630	[NEF4, PRPH1]	Neuron projection | plasma membrane bounded cell projection part
PRX	57716	[CMT4F]	Axon ensheathment | sarcolemma
PSD3	23362	[EFA6D, EFA6R, HCA67]	Plasma membrane bounded cell projection part
PTDSS1	9791	[LMHD, PSS1, PSSA]	Endoplasmic reticulum part | organelle subcompartment
PTH1R	5745	[PFE, PTHR, PTHR1]	Endochondral ossification | chondrocyte differentiation
PTHLH	5744	[BDE2, HHM, PLP, PTHR, PTHRP]	Chondrocyte development | Endochondral ossification
PTLAH	8830	[FPAH]	Not mapped
RAB18	22931	[RAB18LI1, WARBM3]	COPI-independent Golgi-to-ER retrograde traffic | vesicle-mediated transport
RAB3GAP1	22930	[P130, RAB3GAP, RAB3GAP130, WARBM1]	Face morphogenesis | COPI-independent Golgi-to-ER retrograde traffic
RAB3GAP2	25782	[RAB3-GAP150, RAB3GAP150, SPG69, WARBM2, p150]	COPI-independent Golgi-to-ER retrograde traffic | vesicle-mediated transport
RAPSN	5913	[CMS11, CMS4C, FADS, RAPSYN, RNF205]	Synaptic transmission, cholinergic | neuromuscular synaptic transmission
RBM10	8241	[DXS8237E, GPATC9, GPATCH9, S1-1, TARPS, ZRANB5]	Negative regulation of cell proliferation
RELN	5649	[ETL7, LIS2, PRO1598, RL]	Excitatory postsynaptic potential | limbic system development
RET	5979	[CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET-ELE1]	Digestive tract development | digestive system development
RIPK4	54101	[ANKK2, ANKRD3, DIK, NKRD3, PKK, PPS2, RIP4]	Morphogenesis of an epithelium
RMND1	55005	[C6orf96, COXPD11, RMD1, bA351K16, bA351K16.3]	Not mapped
RMRP	6023	[CHH, NME1, RMRPR, RRP2]	Limbic system development | pallium development
RNASEH2A	10535	[AGS4, JUNB, RNASEHI, RNHIA, RNHL, THSD8]	Embryonic organ development | positive regulation of cellular component movement
RNASEH2B	79621	[AGS2, DLEU8]	Chordate embryonic development
RNASEH2C	84153	[AGS3, AYP1]	Golgi subcompartment | Golgi apparatus part
RYR1	6261	[CCO, MHS, MHS1, PPP1R137, RYDR, RYR, RYR-1, SKRR]	Skeletal muscle fiber development | muscle fiber development
RYR3	6263	[RYR-3]	Sarcolemma | Z disc
SAMHD1	25939	[CHBL2, DCIP, HDDC1, MOP-5, SBBI88, hSAMHD1]	Protein complex oligomerization
SCARF2	91179	[NSR1, SREC-II, SREC2, SRECRP-1, VDEGS]	Not mapped
SCN4A	6329	[CMS16, HOKPP2, HYKPP, HYPP, NAC1A, Na(V)1.4, Nav1.4, SkM1]	Skeletal muscle contraction | L1CAM interactions
SELENON	57190	[CFTD, MDRS1, RSMD1, RSS, SELN, SEPN1]	Skeletal muscle fiber development | muscle fiber development

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
SEMA3A	10371	[COLL1, HH16, Hsema-I, Hsema-III, SEMA1, SEMAD, SEMAIII, SEMAL, SemD, COLL-1]	Limbic system development | gland morphogenesis
SEPSECS	51091	[LP, PCH2D, SLA, SLA/LP]	Peptidyl-amino acid modification
SETBP1	26040	[MRD29, SEB]	Not mapped
SETX	23064	[ALS4, AOA2, SCAR1, Sen1, bA479K20.2]	Growth cone | protein kinase B signaling
SGCG	6445	[35DAG, A4, DAGA4, DMDA, DMDA1, LGMD2C, MAM, SCARMD2, SCG3, gamma-SG]	Excitatory postsynaptic potential | glial cell development
SHOX	6473	[GCFX, PHOG, SHOXY, SS]	Skeletal system development
SIM1	6492	[bHLHe14]	Kidney development | renal system development
SKI	6497	[SGS, SKV]	Face morphogenesis | Schwann cell development
SLC12A6	9990	[ACCPN, KCC3, KCC3A, KCC3B]	Blood vessel development | chemical synaptic transmission
SLC25A19	60386	[DNC, MCPHA, MUP1, THMD3, THMD4, TPC]	Integral component of organelle membrane | ion transmembrane transport
SLC26A2	1836	[D5S1708, DTD, DTDST, EDM4, MST153, MSTP157]	Diseases associated with glycosaminoglycan metabolism | diseases of glycosylation
SLC2A10	81031	[ATS, GLUT10]	Disease | ion transmembrane transport
SLC35A3	23443	[AMRS]	Integral component of organelle membrane | Golgi subcompartment
SLC39A13	91252	[EDSSPD3, LZT-Hs9, SCDEDS, ZIP13]	Integral component of organelle membrane | Golgi subcompartment
SLC3A1	6519	[ATR1, CSNU1, D2H, NBAT, RBAT]	Disease | ion transmembrane transport
SLC5A7	60482	[CHT, CHT1, CMS20, HMN7A]	Synaptic transmission, cholinergic | neuromuscular synaptic transmission
SLC6A5	9152	[GLYT-2, GLYT2, HKPX3, NET1]	Chemical synaptic transmission | disease
SLC6A9	6536	[GCENSG, GLYT1]	Integral component of organelle membrane | protein glycosylation
SLC9A6	10479	[MRSA, NHE6]	Regulation of cellular response to growth factor stimulus | distal axon
SLCO5A1	81796	[OATP-J, OATP-RP4, OATP5A1, OATPJ, OATPRP4, SLC21A15]	Not mapped
SMARCAD1	56916	[ADERM, BASNS, ETL1, HEL1]	Protein complex oligomerization
SMN1	6606	[BCD541, GEMIN1, SMA, SMA1, SMA2, SMA3, SMA4, SMA@, SMN, SMNT, T-BCD541, TDRD16A]	Z disc | I band
SMN2	6607	[BCD541, C-BCD541, GEMIN1, SMNC, TDRD16B]	Z disc | I band
SNAP25	6616	[CMS18, RIC-4, RIC4, SEC9, SNAP, SNAP-25, SUP, bA416N4.2, dJ1068F16.2]	Growth cone | distal axon
SOD1	6647	[ALS, ALS1, HEL-S-44, IPOA, SOD, hSod1, homodimer]	Schwann cell development | Schwann cell differentiation
SOX10	6663	[DOM, PCWH, WS2E, WS4, WS4C]	Neuroblast proliferation | peripheral nervous system development
SOX9	6662	[CMD1, CMPD1, SRA1, SRXX2, SRXY10]	Chondrocyte development | cartilage development involved in endochondral bone morphogenesis | Endochondral ossification
SPART	23111	[SPG20, TAHCCP1]	Regulation of cellular response to growth factor stimulus | negative regulation of neurogenesis
SPTBN4	57731	[CMND, QV, SPNB4, SPTBN3]	L1CAM interactions | positive regulation of developmental growth
SRD5A3	79644	[CDG1P, CDG1Q, KRIZI, SRD5A2L, SRD5A2L1]	Diseases of glycosylation | protein glycosylation

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
STAC3	246329	[MYPBB, NAM]	Neuromuscular synaptic transmission | skeletal muscle fiber development
STRA6	64220	[MCOPCB8, MCOPS9, PP14296]	Face morphogenesis | digestive tract development
SULF1	23213	[SULF-1]	Chondrocyte development | proteoglycan metabolic process
SYNE1	23345	[8B, ARCA1, C6orf98, CPG2, EDMD4, KASH1, MYNE1, Nesp1, SCAR8, dJ45H2.2]	Sarcomere | myofibril
SZT2	23334	[C1orf84, EIEE18, KIAA0467, SZT2A, SZT2B]	Peroxisome | central nervous system neuron differentiation
TAF8	129685	[II, TAF, TAF(II)43, TAFII-43, TAFII43, TBN]	Glycosaminoglycan metabolic process | protein glycosylation
TARP	445347	[CD3G, TCRG, TCRGC1, TCRGC2, TCRGV]	Protein complex oligomerization | animal organ development
TBX15	6913	[TBX14]	Skeletal system morphogenesis | embryonic organ morphogenesis
TBX22	50945	[ABERS, CLPA, CPX, TBXX, dJ795G23.1]	Not mapped
TBX3	6926	[TBX3-ISO, UMS, XHL]	Limbic system development | gland morphogenesis
TBX5	6910	[hos]	Embryonic limb morphogenesis | limb morphogenesis
TGFB3	7043	[ARVD, ARVD1, LDS5, RNHF, TGF-beta3]	Face morphogenesis | ECM proteoglycans
TGFBR2	7048	[AAT3, FAA3, LDS1B, LDS2, LDS2B, MFS2, RIIC, TAAD2, TBR-ii, TBRII, TGFR-2, TGFbeta-RII]	Endochondral bone growth | chondrocyte development | cartilage development involved in endochondral bone morphogenesis
TNN	63923	[TN-W]	ECM proteoglycans | neuron migration
TNNI2	7136	[AMCD2B, DA2B, FSSV, fsTnI]	Striated muscle thin filament | striated muscle contraction
TNNT1	7138	[ANM, NEM5, STNT, TNT, TNTS]	Striated muscle thin filament | striated muscle contraction
TNNT3	7140	[TNTF, beta-TnTF]	Striated muscle thin filament | striated muscle contraction
TOE1	114034	[PCH7, hCaf1z]	Not mapped
TOR1A	1861	[DQ2, DYT1]	Growth cone | distal axon
TPM2	7169	[AMCD1, DA1, DA2B, HEL-S-273, NEM4, TMSB]	Striated muscle thin filament | striated muscle contraction
TPM3	7170	[CAPM1, CFTD, HEL-189, HEL-S-82p, NEM1, OK/SW-cl.5, TM-5, TM3, TM30, TM30nm, TM5, TPM3nu, TPMsk3, TRK, hscp30]	Striated muscle thin filament | striated muscle contraction
TREX1	11277	[AGS1, CRV, DRN3, HERNS]	Heart morphogenesis | kidney development
TRIP4	9325	[ASC-1, ASC1, HsT17391, MDCDC, SMABF1, ZC2HC5]	Ion transmembrane transport | cation transport
TRPV4	59341	[BCYM3, CMT2C, HMSN2C, OTRPC4, SMAL, SPSMA, SSQTL1, TRP12, VRL2, VROAC]	Cartilage development involved in endochondral bone morphogenesis | endochondral bone morphogenesis
TRPV5	56302	[CAT2, ECAC1, OTRPC3]	Protein complex oligomerization | ion transmembrane transport
TSC1	7248	[LAM, TSC]	Limbic system development | cerebral cortex development
TSC2	7249	[LAM, PPP1R160, TSC4]	Protein kinase B signaling | morphogenesis of an epithelium
TSEN2	80746	[PCH2B, SEN2, SEN2L]	Not mapped
TSEN34	79042	[LENG5, PCH2C, SEN34, SEN34L]	Not mapped
TSEN54	283989	[PCH2A, PCH4, PCH5, SEN54L, sen54]	Not mapped

(Continues)

TABLE 1 (Continued)

NAME	EntrezGeneID	Aliases	Functions
TSPAN7	7102	[A15, CCG-B7, CD231, DXS1692E, MRX58, MXS1, TALLA-1, TM4SF2, TM4SF2b]	Not mapped
TTN	7273	[CMD1G, CMH9, CMPD4, EOMFC, HMERF, LGMD2J, MYLK5, SALMY, TMD]	Skeletal muscle thin filament assembly | cardiac muscle fiber development
TUBA1A	7846	[B-ALPHA-1, LIS3, TUBA3]	COPI-independent Golgi-to-ER retrograde traffic | L1CAM interactions
TUBB2A	7280	[CDCBM5, TUBB, TUBB2]	COPI-independent Golgi-to-ER retrograde traffic | L1CAM interactions
TUBB2B	347733	[CDCBM7, PMGYSA, bA506K6.1]	COPI-independent Golgi-to-ER retrograde traffic | L1CAM interactions
TWIST2	117581	[AMS, BBRSAY, DERMO1, FFDD3, SETLSS, bHLHa39]	Positive regulation of cellular component movement | regulation of cell motility
TYMP	1890	[ECGF, ECGF1, MEDPS1, MNGIE, MTDPS1, PDECGF, TP, hPD-ECGF]	Axon ensheathment | blood vessel development
UBA1	7317	[A1S9, A1S9T, A1ST, AMCX1, CFAP124, GXP1, POC20, SMAX2, UBA1A, UBE1, UBE1X]	Endoplasmic reticulum part | organelle subcompartment
UBE3A	7337	[ANCR, AS, E6-AP, EPVE6AP, HPVE6A]	Brain development | central nervous system development
UNC50	25972	[GMH1, HSD23, PDLs22, UNCL, URP]	Integral component of organelle membrane | Golgi subcompartment
UPK3A	7380	[UP3A, UPIII, UPIIIA, UPK3]	Kidney development | renal system development
USP16	10600	[UBP-M, UBPM]	Protein complex oligomerization
UTRN	7402	[DMDL, DRP, DRP1]	Peroxisome | sarcolemma
VIPAS39	63894	[C14orf133, SPE-39, SPE39, VIPAR, VPS16B, hSPE-39]	Peptidyl-lysine hydroxylation | protein hydroxylation
VMA21	203547	[MEAX, XMEA]	Endoplasmic reticulum part | organelle subcompartment
VPS16	64601	[hVPS16]	Axon | neuron projection
VPS33B	26276	[]	Peptidyl-lysine hydroxylation | protein hydroxylation
VPS53	55275	[HCCS1, PCH2E, hVps53L, pp13624]	Vesicle-mediated transport | Golgi subcompartment
VPS8	23355	[KIAA0804]	Not mapped
VRK1	7443	[PCH1, PCH1A]	Golgi subcompartment | Golgi apparatus part
WASHC5	9897	[KIAA0196, RTSC, RTSC1, SPG8]	Regulation of neuron projection development | regulation of neuron differentiation
WNT5A	7474	[hWNT5A]	Gland morphogenesis | embryonic limb morphogenesis
WNT7A	7476	[]	Cell proliferation in forebrain | excitatory postsynaptic potential
ZBTB42	100128927	[LCCS6, ZNF925]	Muscle organ development | animal organ development
ZC4H2	55906	[HCA127, KIAA1166, WRWF, WWS]	Central nervous system neuron differentiation | regulation of neuron differentiation
ZIC2	7546	[HPE5]	Brain development | central nervous system development
ZIC3	7547	[HTX, HTX1, VACTERLX, ZNF203]	Digestive tract development | digestive system development
ZMPSTE24	10269	[FACE-1, FACE1, HGPS, PRO1, STE24, Ste24p]	Cardiac muscle fiber development | endochondral bone growth
ZNF335	63925	[MCPH10, NIF-1, NIF1, NIF2]	Neuroblast proliferation | central nervous system neuron differentiation

Note: Lists all the genes in the arthrogryposis syndrome lists; NAME = The HGNC gene symbol; EntrezGeneID = The entrez gene unique id; Aliases = Additional gene names; Functions = GO terms that are associated with that gene.

The definition of arthrogryposis used over the years has been multiple congenital contractures in multiple body areas. An article in this volume provides a systematic approach to the definition.

Then, we performed an enrichment analysis (EA) to identify over-represented functional biological groupings within the list of assembled 402 genes. EA is a common bioinformatic technique to describe common biological aspects associated with a list of genes. The biological processes are outlined in Supporting Information Tables S1–S3. 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 (Table 1). EA involves computing an enrichment statistic across a corpus of genes sets to identify over- and/or under-represented 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 a given gene list. This allows for biologist interpretation of gene lists, whether it be a differential gene expression list or a list of genes associated with a disease state, such as the arthrogryposis syndromes detailed in this review.

Popular gene set libraries used for EA include manually curated gene sets represented canonical signaling pathways, such as Reactome (Croft et al., 2011) and structured genes sets based on the GO resource (The Gene Ontology Consortium, 2018). The GO is a resource, in the form of a structured ontology, describes and categorizes gene product functions in distinct categories and the relationships between them. The GO functional categories are classified in three 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 cell that the gene product can be located within.

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 GO, the pathway database, Reactome and Wiki Pathway (Kelder et al., 2012), and the CORUM database of protein complexes (Giurgiu et al., 2018). 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 "synaptic membrane." The two pathway resources represent canonical signaling pathways covering numerous cellular signaling mechanisms that are manually annotated. The CORUM database of protein complexes provides information on molecular interactions at the protein level. The 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 aids interpretation of results by grouping related GO terms, based on shared gene members, and presenting the results as a network. Since the GO has a hierarchical ontological based structure, GO terms often have overlapping gene members. When results of enrichment are presented in tabular form, this could inhibit interpretation and summary of the results. The network visualization groups similar GO terms as nodes in the network with edges representing a measure of share gene membership (kappa score).

3 | RESULTS

The ClueGo analysis identified 217 enriched gene sets with a corrected *p*-value <.001. The automatic grouping of terms, performed by ClueGO, assigned them to 29 groups based on overlapping gene membership measured by the kappa score statistic. The number of gene sets in the groups varied from a maximum of 36 to 10 groups with just one term each. 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 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. This grouping is indicated by the shading overlaid on the network with annotated group labeled with a summary title of the underlying GO terms in the group.

The results are tabulated in Figure 1 and Table 1 (gene table) and Supporting Information Tables S1–S3.

Table 1 is straightforward with genes listed that have had full published reports indicating clinical descriptions of individuals with arthrogryposis (multiple congenital contractures). Supporting Information Tables S1–S3 divide these genes into functional groups.

4 | DISCUSSION

The purpose of this article 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 (appropriate gene panels when needed) and (2) to begin to think about specific 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 the 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 or target for therapy for arthrogryposis contractures in the future?

In this molecular era, syndromes of congenital anomalies give insight into normal developmental processes and their secondary and

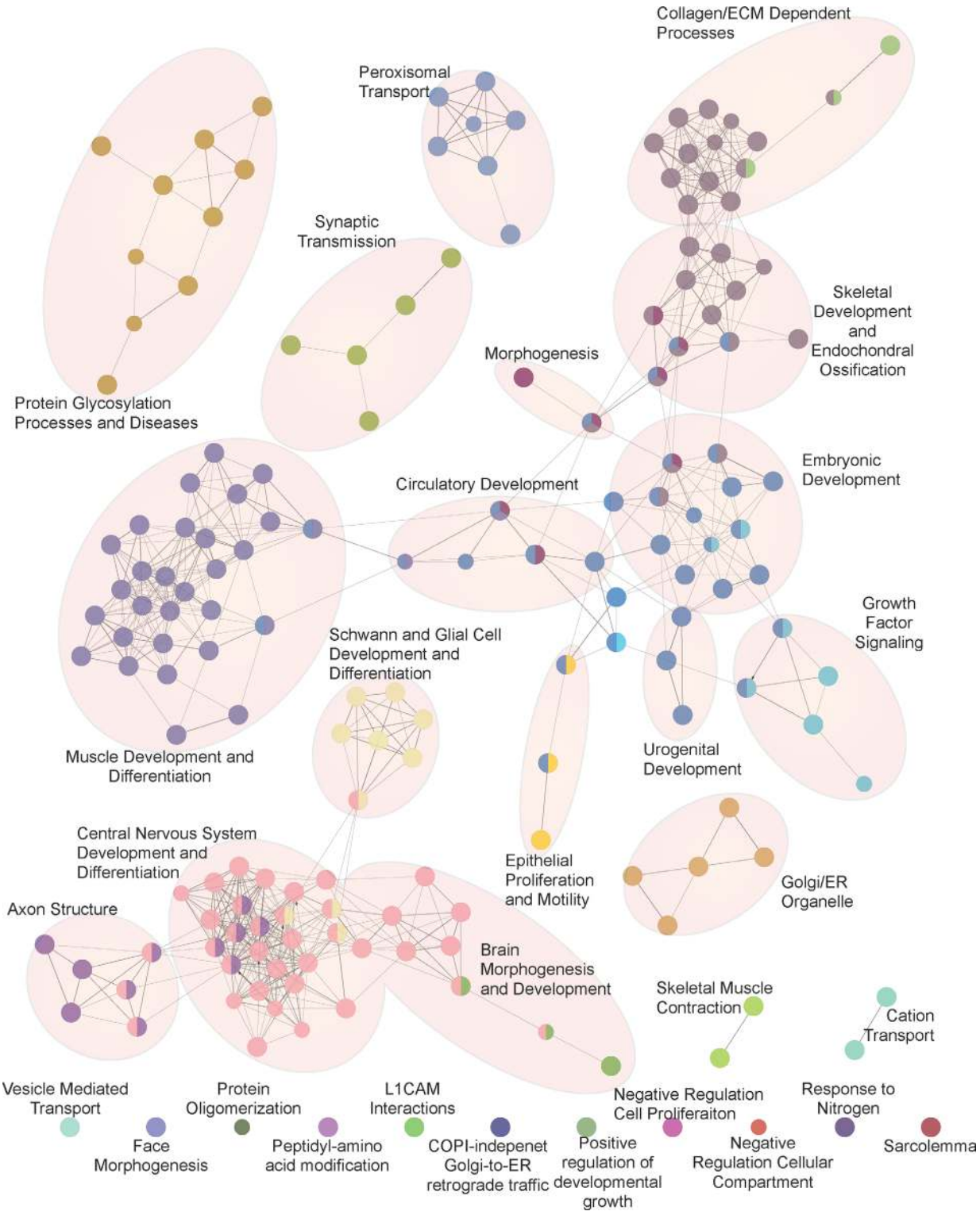

FIGURE 1 Gene ontology and pathway enrichment analysis of arthrogryposis associated genes. The assembled list of arthrogryposis associated genes were analyzed using the ClueGO software and enrichment results visualized in network form. Each node represents a statistically significantly enriched ontology or pathway with larger nodes being more significant. The node color represents membership is a ClueGO annotated functional grouping of terms. Nodes with more than one color represent those nodes with membership in additional ClueGO grouping. The larger shaded groupings represent author annotated grouping of individual nodes into expert curated biological groupings. Edges connect genes to associated functional clusters, where size indicates the degree of enrichment for each cluster

tertiary effects. In the case of arthrogryposis, so many of the features are secondary deformations related to fetal nonmovement (Hall, 2009). Nevertheless, all of the features which are part of the natural history of the specific disorder are important for families and their healthcare providers 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 and timing of insults involve polymorphisms or other variations affecting a pathway. Abnormal gene actions also provide insights into 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 syndromes associated with these mutations are also found in OMIM (http://www.omim.org/) (Hall, 2012, 2014; Hunter et al., 2015; Bayram et al., 2016).

The tables in the supplement outline GO categories and begins to suggest prime candidates for recognizing critical pathways involved in normal fetal movement. Interestingly, many of these 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 at different stages of development and in different tissues.

It is hoped that this exercise is useful to those reflecting on the many mechanisms, structures, and tissues involved in the development of movement, and human 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 or domains). Once a group of families with a specific arthrogryposis mutation has their whole genome analyzed, the variation in clinical phenotype can be elucidated and important modifiers of that gene's function identified.

Many specific single gene disorders in arthrogryposis have intra- and interfamilial variability as to how severe the contractures are at birth, what positioning the contractures take, or whether contractures are even present. For instance, several forms of dominant distal arthrogryposis have completely unaffected carrier individuals (Kimber, Tajsharghi, Kroksmark, Oldfors, & Tulinius, 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/or enhance the affected pathway.

ACKNOWLEDGEMENT

The authors wish to acknowledge the expert assistance of Amy Ho.

ORCID

Judith G. Hall https://orcid.org/0000-0001-5062-491X

REFERENCES

Bayram, Y., Karaca, E., Coban Akdemir, Z., Yilmaz, E. O., Tayfun, G. A., Aydin, H., … Lupski, J. R. (2016). Molecular etiology of arthrogryposis in multiple families of mostly Turkish origin. *The Journal of Clinical Investigation*, *126*, 762–778.

Bindea, G., Mlecnik, B., Hackl, H., Charoentong, P., Tosolini, M., Kirilovsky, A., … Galon, J. (2009). ClueGO: A Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks. *Bioinformatics*, *25*, 1091–1093. https://doi.org/10.1093/bioinformatics/btp101

Croft, D., O'Kelly, G., Wu, G., Haw, R., Gillespie, M., Matthews, L., … Stein, L. (2011). Reactome: A database of reactions, pathways and biological processes. *Nucleic Acids Research*, *39*, D691–D697. https://doi.org/10.1093/nar/gkq1018

Giurgiu, M., Reinhard, J., Brauner, B., Dunger-Kaltenbach, I., Fobo, G., Frishman, G., Montrone, C., Ruepp, A., 2018. CORUM: The comprehensive resource of mammalian protein complexes-2019. *Nucleic Acids Research 33*, D364. doi:10.1093/nar/gky973

Hall, J. G. (2009). Pena Shokeir phenotype (fetal akinesia deformation sequence) revisited. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *85*, 677–694.

Hall, J. G. (2012). Arthrogryposes (multiple congenital contractures). In D. L. Rimoin, R. E. Pyeritz, & B. R. Korf (Eds.), *Emery and Rimoin's principle and practice of medical genetics* (6th ed.). New York, NY: Churchill Livingstone.

Hall, J. G. (2014). Arthrogryposis (multiple congenital contractures): Diagnostic approach to etiology, classification, genetics, and general principles. *European Journal of Medical Genetics*, *57*, 464–472.

Hall, J. G., & Kiefer, J. (2016). Arthrogryposis as a syndrome: Gene ontology analysis. *Mol Syndromol*, *7*, 101–109.

Hunter, J. M., Kiefer, J., Balak, C. D., Jooma, S., Ahearn, M. E., Hall, J. G., & Baumbach-Reardon, L. (2015). Review of X-linked syndromes with arthrogryposis or early contractures—Aid to diagnosis and pathway identification. *American Journal of Medical Genetics. Part A*, *167A*, 931–973.

Kelder, T., van Iersel, M. P., Hanspers, K., Kutmon, M., Conklin, B. R., Evelo, C. T., & Pico, A. R. (2012). WikiPathways: Building research communities on biological pathways. *Nucleic Acids Research*, *40*, D1301–D1307. https://doi.org/10.1093/nar/gkr1074

Kimber, E., Tajsharghi, H., Kroksmark, A. K., Oldfors, A., & Tulinius, M. (2012). Distal arthrogryposis: Clinical and genetic findings. *Acta Paediatrica*, *101*, 877–887.

Michalk, A., Stricker, S., Becker, J., Rupps, R., Pantzar, T., Miertus, J., … Hoffmann, K. (2008). Acetylcholine receptor pathway mutations explain various fetal akinesia deformation sequence disorders. *American Journal of Human Genetics*, *82*, 464–476.

The Gene Ontology Consortium. (2018). The gene ontology resource: 20 years and still going strong. *Nucleic Acids Research*, *45*, D331–D338. https://doi.org/10.1093/nar/gky1055

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Kiefer J, Hall JG. Gene ontology analysis of arthrogryposis (multiple congenital contractures). *Am J Med Genet Part C*. 2019;181C:310–326. https://doi.org/10.1002/ajmg.c.31733