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Review of X-Linked Syndromes with Arthrogryposis or Early Contractures—Aid to Diagnosis and Pathway Identification

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The following is a review of 50 X-linked syndromes and conditions associated with either arthrogryposis or other types of early contractures. These entities are categorized as those with known responsible gene mutations, those which are definitely X-linked, but the responsible gene has not been identified, and those suspected from family history to be X-linked. Several important ontology pathways for known disease genes have been identified and are discussed in relevance to clinical characteristics. Tables are included which help to identify distinguishing clinical features of each of the conditions.

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Key words: arthrogryposis; multiple congenital contractures; arthrogryposis multiplex congenita; contractures; X-linked; myopathy; spinal muscular atrophy

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INTRODUCTION

There are over 400 specific disorders that are, or can be, associated with multiple contractures in the newborn [Hall, 2013; Hall, 2014]. A better understanding of disorders with contractures and their associated genetics is critical for accurate diagnosis and optimal treatment. Contractures are defined as joints that have reduced range of motion due to stiffening of normally flexible tissues. Proper central and peripheral nervous system development and function are required for stimulation of muscle movement. Muscle tissue, ligaments, tendons, and skin require movement for normal development and function, without which, joints develop contractures. Reduced fetal movement in utero due to myopathic processes, motor neuron degeneration, vascular compromise, abnormal skeletal or connective tissue development, limited space in the uterus, maternal illness, or toxin exposure can lead to multiple congenital contractures [Hall, 2013]. Contractures can develop at any age as a result of neuromuscular dysfunction or limitation of movement, but muscle innervation and movement in utero is particularly critical for normal joint development. The terms arthrogryposis, or arthrogryposis multiplex congenital (AMC), are generally used to describe two congenital contractures of more than one body area [Bamshad et al., 2009; Hall, 2013]. Contractures or arthrogryposis are important, often under-recognized, clinical signs rather than diagnoses.

In 1982, Hall et al. described three distinct types of X-linked arthrogryposis. Since that time, many X-linked syndromes have been described with congenital or acquired contractures as part of the phenotype. These conditions appear to be distinguishable on the basis of natural history, clinical findings and/or identified genetic cause. While it is not possible to fully describe all X-linked syndromes with contractures, 50 of these entities are reviewed here

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with an emphasis on syndromes with early contractures or arthrogryposis. Contractures have been described in patients of each of these syndromes, but contractures are not necessarily present in all patients of the syndrome. The temporal and clinical presentation of contractures can vary widely from one patient to the next for many reasons including different mutations within the same gene, epigenetic factors, variable X-inactivation, modifying variants, and environmental factors. Thus, within a given syndrome, the age of onset of contractures (congenital or acquired), severity of contractures (localized or generalized), and body areas affected by contractures can differ dramatically between affected individuals, even within the same family. The timing and specifics of arthrogryposis and contractures are often not fully described in reports, but are obvious from photographs. We describe contractures from the text and photographs in published literature, and draw from the considerable clinical experience of Dr. Judith Hall.

The first section of this review describes 23 X-linked syndromes with known genetic causes and reported contractures. Brief descriptions of the contractures and accompanying signs and symptoms are given followed by an overview of the genetics and biology of the associated gene (Tables I and II). Additionally, we have performed gene ontology (GO) analysis to further the understanding of underlying mechanisms and pathways that lead to contractures (Figs. 1 and 2). Next, seven syndromes are described for which there is evidence of X-linkage. However, responsible mutations are yet to be identified (Table III). Last, reviewed are an additional 20 syndromes suspected of being X-linked, but have not been demonstrated to show specific localization to a portion of the X-chromosome nor has a responsible genetic mutation been identified (Table IV).

It seemed timely to review these 50 conditions as genetic exome and whole genome sequencing become more commonplace. Summarizing and combining information on phenotypes, genotypes, and the underlying biological pathways will enable better diagnosis and development of more effective treatments. We have made an effort to compile information in a format beneficial to a broad audience ranging from the clinician to the bench scientist.

METHODS

We have compiled a list of genes and syndromes associated with X-linked syndromes with which contractures have been associated. We complemented that knowledge base by searching for terms in Online Mendelian Inheritance in Man (OMIM) (http://www.omim.org) and Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) to identify other X-linked genes and conditions in order to gather information about them. While a substantial list of genes and syndromes are reviewed here, it is not possible to include every gene, syndrome, or pathway related to early contractures or arthrogryposis. Rather, we have concentrated on X-linked conditions in hopes this will help with identification of responsible genes for males with contractures and families with apparently X-linked conditions with contractures. Standard nomenclature and formatting for gene and protein symbols for human and mouse were used. In order to assimilate available information of these contracture syndromes with known genetic cause, we also performed a GO analysis. The analysis was performed using the ToppGene (https://toppgene.cchmc.org/) [Chen et al., 2009] analysis tool. While we did not review autosomal arthrogryposis and contracture genes, we wanted to identify overlap between X-linked and autosomal genes associated with contractures [Hall, 2013; Hall, 2014]. Therefore, autosomal genes were also analyzed with ToppGene and comparisons between autosomal and X-linked genes were made. Significantly enriched X-linked gene ontologies associated with contractures are reported as well as ontologies that overlap with autosomal contracture genes.

RESULTS

Category I. X-linked early contracture syndromes with known genetic cause

Dandy-Walker malformation with mental retardation, basal ganglia disease, and seizures (Pettigrew syndrome); OMIM# 304340; Xp22.2; AP1S2. Pettigrew et al. [1991] reported a disorder with multiple contractures, intellectual disability (ID), Dandy-Walker malformation, basal ganglion calcifications and seizures. The affected males have a long narrow face, long thin hands, and generalized flexion contractures with cerebellar hypoplasia. Saillour et al. [2007] suggest that distinctive basal ganglia calcification is an essential parameter in this disorder and provides a biomarker for this disease.

In 1991, Huang et al. mapped the original Pettigrew syndrome family to Xq26 and suggested it was related to a hypervariable repeat motif within the hypoxanthine phosphoribosyltransferase (HPRT) locus. However, Cacciagli et al. [2013] determined that mutations in the Adaptor-Related Protein Complex 1, Sigma 2 Subunit (*AP1S2*) gene were responsible for this syndrome in the original four generation Pettigrew family. Mutations in *AP1S2* were described as early as 2006 [Tarpey et al., 2006; Saillour et al., 2007; Borck et al., 2008; Ballarati et al., 2012], but the link to Pettigrew syndrome was not made until Cacciagli's report [Cacciagli et al., 2013]. OMIM lists mutations in *AP1S2* as the cause of ID, X-linked syndromic, Fried type (OMIM 300630) because one of five families originally diagnosed with Fried syndrome was also found to have *AP1S2* mutations [Fried 1972; Saillour et al., 2007]. To date, only eight mutations in *AP1S2* have been described [HGMD] including missense, splicing, and nonsense mutations. Most of these mutations result in truncation of the protein. Mutations in this gene have been found in families of Dutch, French, and Scottish descent [Pettigrew et al., 1991; Saillour et al., 2007; Cacciagli et al., 2013]. Skewed X-inactivation was reported in at least one female [Saillour et al., 2007]; however, females are usually unaffected.

The *AP1S2* gene has five exons that encode a 157 amino acid (a.a.) protein which co-localizes at the Golgi apparatus. The 20.7 kiloDalton (kDa) protein consists mainly of a clathrin adaptor complex small-chain domain [Saillour et al., 2007]. Ap1s2 is a subunit of the heterotetramer adapter protein complex 1 (AP-1). Clathrin and AP complexes are the main components of clathrin-coated vesicles in the cell. AP-1 complexes are associated with the trans-golgi network (TGN) and are involved in the transport of proteins to the cell surface and the endosomal/lysosomal system. Cargo membrane proteins with tyrosine or dileucine-based sorting signals are selected for transport by AP-1. The C-terminal tail of the

vesicular acetylcholine transporter (VAChT) interacts with AP-1 and AP-2 [Kim and Hersh, 2004]. Altered VAChT trafficking presumably contributes to the early hypotonia seen in patients with *AP1S2* mutations as VAChT deficiencies in mice result in myasthenic phenotypes, but have not yet been reported in humans. While clinical studies are yet to be done, this suggests that acetylcholine esterase inhibitors may be of value in treating early hypotonia in individuals with *AP1S2* mutations [Prado et al., 2006; de Castro et al., 2009].

Proud syndrome; OMIM# 300004; Part of ARX Spectrum; Xp21.3; ARX. In 1992, Proud et al. described a family with corpus callosum agenesis and abnormal genitalia. Seizures and severe ID were present. Surviving males have severe microcephaly, ID, limb contractures, scoliosis, tapering fingers and hyperconvex nails. Proud et al. [1992] also established linkage of the disease to Xp21.3–Xp11.3 [Kato et al., 2004]. The Aristaless-related homeobox (*ARX*) gene is found in this region. In 2002, multiple groups reported disease causing mutations in *ARX* and in [2004], Kato et al. identified an *ARX* mutation in the original family described by Proud et al., [Bienvenu et al., 2002; Kitamura et al., 2002; Scheffer et al., 2002; Stromme et al., 2002a; Stromme et al., 2002b]. Mutations in *ARX* can result in a broad range of phenotypes ranging from males that succumb to the syndrome within the first days of life to mildly or unaffected obligate female carriers (OMIM# 300382). There have been 65 different mutations identified in *ARX* in over 100 families resulting in at least 10 well-defined but related clinical disorders including Proud Syndrome, Partington syndrome, X-linked ID (XLID), and X-linked lissencephaly with abnormal genitalia (XLAG) [HGMD]. Nearly half of the *ARX* mutations are expansions of a GCG trinucleotide repeat that is translated into a polyalanine tract in the protein [Shoubridge et al., 2010]. Other mutations include splice, nonsense, missense, and insertion/deletions. The *ARX* gene is mutated in approximately 9.5% of XLID [Vos et al., 2010].

Arx is a homeobox transcriptional repressor and contains a highly conserved 60 residue DNA-binding homeodomain. *ARX* consists of five exons that code for a 562 a.a. protein expressed predominantly in fetal and adult brain and skeletal muscle. Arx is required for normal brain development. Recently, targets of transcriptional repression by Arx have been identified and include *LMO1*, *EBF3*, and *SHOX2*. Mutations that result in complete loss of Arx expression and mutations in the homeodomain result in severe brain malformation phenotypes [Colasante et al., 2008; Fulp et al., 2008; Shoubridge et al., 2010]. Specifically, the T333N mutation immediately adjacent to the nuclear localization signal 2 within the homeodomain of the Arx protein results in Proud Syndrome [Kato et al., 2004]. This mutation results in reduced target DNA binding affinity. As a result, the repression of the Arx targets *LMO1*, *EBF3*, and *SHOX2* is incomplete [Cho et al., 2012]. The *ARX* gene is subject to X-inactivation, thus females generally have a milder phenotype. Currently, evidence suggests that *ARX* undergoes random X-inactivation rather than skewed by mutation [Shoubridge et al., 2010].

Mental retardation-hypotonic facies syndrome, X-linked (Juberg-Marsidi syndrome); OMIM# 309580; Xq21.1; ATRX. Juberg-Marsidi syndrome is an *ATRX* spectrum disorder [Gibbons and Higgs, 2000] and is characterized by microcephaly, intrauterine growth restriction (IUGR), bifrontal narrowing, blepharophimosis, cupped ears, a bulbous nose, and a small mouth. The eyes appear deep-set, with short palpebral fissures. Overall, the lower face appears triangular, the neck is short, and there is a posterior hairline. Generalized flexion contractures are present, as well as flexion contractures of the hips, elbows, knees, and 5th fingers. Seizures, deafness, and hypotonia are often seen and may progress to spasticity. The cerebral ventricle appears enlarged and dysgenesis of the corpus callosum is seen on brain imaging. Variable ID is present. These features are common to syndromes caused by mutations in *ATRX* but not always present. Mild alpha thalassemia is present in 87% of patients [Gibbons and Higgs, 2000]. *ATRX* usually shows skewed inactivation of the defective X chromosome and most female carriers are unaffected [Gibbons and Higgs 2000; De La Fuente et al., 2011].

To date, 126 mutations in *ATRX* have been reported [HGMD]. The *ATRX* gene spans 300 kb, has 36 exons and produces a large protein of ~280 kDa. Atrx is a member of the SWI2/SNF2 (SWItch/Sucrose NonFermentable) helicase/ATPase family and is expressed in the nucleus. The Atrx protein contains several domains including an N-terminal plant homeodomain zinc finger, a stretch of glutamic acid residues, coil-coil motif, several helicase domains, and a c-terminal ATPase domain. Atrx, in conjunction with its binding partner death-associated protein 6 (DAXX), functions as a histone chaperone complex and is involved in the deposition of H3.3 histones to pericentric, telomeric, and ribosomal repeat regions [De La Fuente et al., 2011; Clynes et al., 2013]. Disruption of Atrx function results in perturbation of many cellular processes including defective chromatid cohesion, telomere dysfunction, and aberrant DNA methylation [Clynes et al., 2013]. Mutations have been identified in all domains of Atrx, but mutations in the zinc finger and the helicase domains are much more prevalent. There is no clear correlation with the location or type of mutation within *ATRX* and phenotype. While not correlated with the *ATRX* mutation, evidence demonstrates that Atrx binds to a variable number tandem repeat (VNTR) near a grouping of globin genes on chromosome 16. Increasing length of the VNTR is associated with more severe alpha thalassemia with *ATRX* mutations. Furthermore, those genes closer to the VNTR are transcriptionally repressed most by *ATRX* mutations [Clynes and Gibbons, 2013; Clynes et al., 2013].

FG syndrome 4; OMIM# 300422; Xp11.4; CASK. FG syndrome 4 (FG4) includes ID, post-natal microcephaly and pontocerebellar hypoplasia [Moog et al., 2011]. Affected individuals have mild facial dysmorphism, including prominent or broad bridge of the nose and tip, a small chin, large ears, hypertelorism, and a long philtrum. The face is usually round. Magnetic resonance imaging (MRI) shows hypoplasia and flattened cerebellar hemispheres with disproportionate reduced size of the vermis [Najm et al., 2008]. In addition, there is an intact corpus callosum, but pontine hypoplasia. Central nervous system (CNS) changes are usually diffuse with dilation of the 4th ventricle [Moog et al., 2011]. Often there is growth restriction postnatally with hypo or hypertonia, optic nerve hypoplasia and other eye abnormalities. There may be electroencephalogram (EEG) changes with slowing and occasionally seizures. Other investigations seem to be normal. About 20% have congenital contractures apparently related to in utero hypotonia [Burglen et al., 2012]. Many affected individuals have chromosomal

deletions and duplications involving Xp11.4. Female carriers are generally unaffected.

FG4 is caused by mutations in Calcium/Calmodulin-dependent Serine Protein Kinase (*CASK*). Cask is a highly-conserved, multi-domain scaffolding protein highly expressed in the mammalian nervous system. The protein is a member of the membrane-associated guanylate kinase (MAGUK) family of proteins which generally co-localize with neuronal synapses and regulate trafficking, targeting, and signaling of ion channels. Synaptic function is crucially dependent on the spatial organization of the presynaptic and postsynaptic apparatuses, and the precise arrangement is achieved by a protein network at the sub-membrane level of each cell that is built around scaffolding proteins, including Cask. Cask is a unique member of the MAGUK protein family in the fact that it not only plays a role in synaptic protein targeting, but also contributes to neural development and regulation of gene expression [Hsueh, 2006]. It is a mid to large protein of 897 a.a. consisting of 27 exons. It contains a calmodulin-dependent kinase-like domain, two L27 domains, a PDZ domain, a SH3 domain, a protein 4.1 binding domain, and a guanylate kinase-like domain [Hsueh, 2009]. The Cask protein is thought to have three major functions based on interaction studies: synaptic interaction and synaptogenesis, protein trafficking and targeting, and regulation of gene expression and neural development [Hsueh, 2006].

In 2006, Hsueh established models demonstrating both insertional mutations as well as targeted knock-out (KO) of the *Cask* gene in mouse models result in lethality in mice within 24–48 hr after birth. It was found that neural apoptosis was increased in CASK deficient mice. The exact mechanism behind mouse lethality is not clear, but cleft palate occurs in both types of mutant mice. These findings suggest that Cask is important in development [Hsueh, 2006]. Multiple mutation studies have been performed on *CASK*. A missense mutation in *CASK*, which partially skips exon two, has been found to participate in FG syndrome in an Italian family [Piluso et al., 2009]. Oliva et al. [2012] concluded that these conditions are likely to involve defects in synaptogenesis, where Cask plays an important role. Skewed X-inactivation of *CASK* has been reported [Hackett et al., 2010]. Recently, mutations highly likely to cause the loss of function of the Cask protein have been seen in male patients with Ohtahara syndrome; thus expanding the clinical spectrum of *CASK* mutations [Saitsu et al., 2012].

Lissencephaly, X-linked; OMIM# 300067; Xq23; DCX. There are many forms of lissencephaly, but X-linked lissencephaly is characterized by subcortical band heterotopia [Ross et al., 1997; Toyama et al., 1998]. Affected males have lissencephaly with arrest of cortical neurons in their ascent during development [Gleeson et al., 1998]. Female carriers may just have subcortical lamin heterotopia, and can usually be recognized by an abnormal MRI [Seidahmed et al., 1996] although some female carriers are completely asymptomatic [Bahi-Buisson et al., 2013]. If they do have clinical features, they are usually mild. The males have intractable seizures, severe ID, growth failure, microphallus, and usually die during infancy. Patients may or may not be born with contractures; however management should include physical therapy to prevent contractures [Hehr et al., 1993]. They demonstrate pachygyri and agenesis of the corpus callosum on MRI. X-linked lissencephaly can be distinguished by its gyral pattern from the chromosome 17 deletion lissencephaly disorder [Ross et al., 1997; Haverfield et al., 2009].

X-linked Lissencephaly is caused by mutations in the Doublecortin gene (*DCX*). The Human Gene Mutation database (HGMD) (http://www.hgmd.org/) lists 132 disease causing mutations dispersed throughout the coding sequence of *DCX* [HGMD]. Gross deletions, duplications and complex rearrangements affecting *DCX* have been reported to cause disease as well [Ross et al., 1997; Bahi-Buisson et al., 2013]. Dcx is a mid-sized protein containing 441 a.a. coded from seven exons and two evolutionary conserved doublecortin domains. The majority of lissencephaly-causing missense mutations in *DCX* cluster in the doublecortin domains, while nonsense mutations are scattered throughout the gene. A large portion of sporadic patients are of de novo origin and are often the most severe, while inherited mutations are usually less severe. Skewed X-inactivation can account for some variability in phenotype in females [des Portes et al., 1998; Bahi-Buisson et al., 2013]. For more detailed genotype–phenotype correlations see Bahi-Buisson et al. [2013]. Doublecortin domains have been shown to bind microtubules and enhance microtubule polymerization. Dcx is expressed in migrating and differentiating neurons throughout the central and peripheral nervous system during embryonic and postnatal development [Gleeson et al., 1999]. More specifically, Dcx is highly expressed in the majority of cells of the cortical plate, intermediate zone and ventricular zone [Boekhoorn et al., 2008]. Dcx stabilization of microtubules is essential for normal neuronal migration during human brain development. Since mutations in *DCX* result in severe disease, this implies that none of the other numerous microtubule stabilizing proteins can fully compensate for loss of Dcx function [Bahi-Buisson et al., 2013; Fourniol et al., 2013].

Chondrodysplasia punctata, X-linked dominant (Conradi-Hunermann-Happle syndrome); OMIM# 302960; Xp11.23; EBP. Chondrodysplasia punctata, X-linked dominant (CDPX2) is an X-linked dominant disorder characterized by punctiform calcifications of bones and patchy defects in skin, which include linear atrophic and pigmentary lesions and striated hyperkeratosis. The hair is coarse and lusterless. Alopecia, cataracts, and patchy skeletal abnormalities are also seen [Tasker et al., 1970; Savarirayan et al., 2004]. Cardiac and dental abnormalities can also be seen. There is variable severity and changes in skin may occur over time [Traupe, 1999]. Once the bones have finished growing, they almost always are asymmetric with chondrodysplasia punctata in the epiphyseal area. Contractures of the joints, especially affecting hips, but also hands and feet are common [Happle, 1979; Canueto et al., 2012; Canueto et al., 2013]. The patchy pathology distribution reflects X-linked inactivation patterns. Syndrome severity is a reflection of both X-linked inactivation patterns and the specific mutation [Derry et al., 1999; Herman et al., 2002; Ausavarat et al., 2008]. CDPX2 is predominately seen in females as it is usually lethal in males; although a few affected males have been reported [Kozlowski et al., 2002; Shirahama et al., 2003; Arnold et al., 2012]. An affected XXY male has also been reported [Sutphen et al., 1995]. In familial patients, anticipation, phenotypic variation and incomplete penetrance are typical features in CDPX2 [Canueto et al., 2013].

In 1999, Braverman et al. and Derry et al., reported increased 8 (9)-cholesterol and 8-dehydrocholesterol in tissue samples from female probands with CDPX2. This suggested a deficiency of 3β-hydroxysteroid-δ8, δ7-isomerase activity which catalyzes an intermediate step in the conversion of lanosterol to cholesterol. Both groups identified disease causing mutations in phenylalkylamine Ca^{2+} antagonist (emopamil) binding protein (*EBP*) [Derry et al., 1999]. The *EBP* gene has five exons and codes for a small protein containing 230 a.a. which localizes to the endoplasmic reticulum membrane. Importantly, it catalyzes the conversion of δ8-sterols to their corresponding δ7-isomers. Missense, splice, nonsense, and insertion/deletion mutations in *EBP* are scattered throughout the gene, but exon 2 has the greatest proportion of mutations. Mutations occur in regions that either disrupt Ebp's isomerase activity and impair cholesterol biosynthesis [Moebius et al., 2003], or are essential for binding emopamil. Many familial and sporadic mutations have been reported. Cholesterol biosynthesis and cholesterol homeostasis is critical for many biological systems and plays a role in many processes including cellular growth, proliferation and signaling. The malformations of embryogenesis and morphogenesis seen in CDPX2 are thought to be related to cholesterol's involvement in hedgehog protein signaling pathways [Porter and Herman, 2011; Canueto et al., 2013].

MEHMO; OMIM# 300148; Xp22.11; EIF2S3. The first description of MEHMO syndrome was reported in 1989 by Delozier-Blanchet et al. Individuals with MEHMO syndrome have mental retardation, epileptic seizures, hypogonadism, microcephaly, and obesity [Steinmuller et al., 1998; DeLozier-Blanchet et al., 1999]. Many die in early childhood. Hypotonia or hypertonia is present. Thick ear helices and upturned lobules, thick alae nasi, and a tented upper lip with puffy cheeks are usually present. Profound developmental failure occurs. While overt seizures may not be present, EEG may be highly abnormal [DeLozier-Blanchet et al., 1999]. Speech can range from absent to speaking in sentences. Excessive drooling has also been reported. Short stature is common. Talipes and camptodactyly are usually present together with edematous hands and feet [Steinmuller et al., 1998]. Children often display extremely agitated and irritable behavior [DeLozier-Blanchet et al., 1999; Borck et al., 2012]. Female carriers are apparently spared.

Very recently, a report of a single family with a phenotype like MEHMO syndrome was reported to have a mutation in Eukaryotic Translation Initiation Factor 2, Subunit 3 Gamma (*EIF2S3*). *EIF2S3* is located at Xp22.11 and MEHMO syndrome had been mapped to this locus [Steinmuller et al., 1998; Borck et al., 2012]. While no individual had all the signs of MEHMO, all symptoms were displayed in at least one affected child. One family with a MEHMO-like phenotype with a mutation in a gene at the same X-chromosome locus to which MEMHO has been mapped provides evidence that *EIF2S3* mutations cause MEHMO syndrome, but further sequencing of patients are needed to confirm this finding [Borck et al., 2012]. A recent review also lists *EIF2S3* as the cause of MEHMO syndrome [Lubs et al., 2012].

Eif2s3 (Eif2γ), the protein product of *EIF2S3*, is a 472 a.a. 53 kDa protein critical for translation initiation. Eif2s3 forms the catalytic core of the heterotrimeric eukaryotic translation initiation factor 2 (eIF2). Upon binding guanosine-5'-triphosphate (GTP) and initiator methionyl-tRNA, eIF2 then binds to the 40S ribosomal subunit forming a pre-initiation complex. After binding the 5' end of an mRNA to form a 43S complex, the pre-initiation complex scans the mRNA until an AUG start codon is encountered, at which time GTP is hydrolyzed to guanosine-5'-diphosphate (GDP), eIF2 is inactivated and released, the 60S ribosomal subunit binds to form the 80S complex, and translation is initiated. Eif2s3 contains the GTP binding and hydrolysis site of eIF2 [Lorsch and Dever, 2010; Stolboushkina and Garber, 2011; Borck et al., 2012]. Interestingly, the Ile222Thr mutation identified by Borck et al. [2012] is located in the GTP-binding domain of Eif2s3. Mutation of the cognate residue in the yeast homolog of Eif2s3 resulted in growth defects in the yeast demonstrating the deleterious effect of this mutation. Furthermore, this mutation decreases the integrity of the eIF2 heterotrimeric complex by disrupting binding to the Eif2β subunit. Mutations in Eif2s3 likely alter translation of numerous proteins as it participates in such a fundamental process, but the exact mechanisms of disease are not known. Before mutations in *EIF2S3* were linked to MEHMO syndrome, defects in the mitochondrial respiratory chain were reported in one patient of MEHMO [Leshinsky-Silver et al., 2002] and may be one of many ways in which mutations in *EIF2S3* contribute to disease.

Aarskog-Scott syndrome; OMIM# 305400; Xp11.22; FGD1. Aarskog [1970] described a familial syndrome of short stature, facial dysplasia, and genital anomalies. All of the affected individuals had a round face, hypertelorism, short inverted nose, thin upper lip and full lower lip, widow's peak, mild syndactyly, hyperextension of the proximal interphalangeal joints, inguinal hernias, cryptorchidism, and shawl scrotum. Many subsequent families have been described to involve arthrogryposis [Scott, 1971; Porteous and Goudie, 1991; Stevenson, 2005]. However, generalized congenital contractures are not a consistent feature, occurring in only 15–20% of patients, with variability within a family [Hurst, 1983; Lebel et al., 2002]. Facial features can be striking because of broad forehead and hypertelorism (as well as telecanthus) and anteverted nostrils. Ears often appear low. There can be a V-shaped indentation in the upper lip with a pouty lower lip. Some families are described as having eye involvement with esotropia, latent nystagmus, and inferior oblique over action, and amblyopia. Ptosis has been described as well as hyperopia, esotropia, blue sclera, and posterior embryotoxin. Camptodactyly is frequently present. Osteochondritis dissecans has also been described [Hanley et al., 1967]. There is often metatarsus adductus at birth requiring physical therapy and/or casting. Short stature is usually in the 3rd–10th centile range; however, limbs may have rhizomelic shortening, giving the trunk a long appearance. Some joints are hyperextensible. Additional anatomical features include: pulmonary stenosis and ventricular septal defect (VSD) [Fernandez et al., 1994]; lax abdomen and the umbilicus are said to have a deep depression [Teebi et al., 1993; Tsukahara and Fernandez, 1994]. Abnormalities of the CNS including polymicrogyri and seizures have been reported [Fryns and Descheemaeker, 1995; Kaname et al., 2006]. Attention deficit hyperactivity disorder is often present.

Aarskog-Scott syndrome was mapped to Xp11.22 by Bawle et al., [1984]; and the first mutations in *FGD1* responsible for the syndrome were identified by Pasteris et al. [2000] and Orrico et al. [2004]. The *FGD1* gene has 18 exons coding for a 961 residue protein. Fgd1 is made up of a FYVE domain, N-terminal proline

rich domain (PRD) domain, two putative SRC homology 3 (SH3) -binding domains, a Rho guanine nucleotide exchange factor (GEF) domain, a Dbl homology domain (DH), a and a C-terminal pleckstrin homology (PH) domain. To date, 35 mutations in *FGD1* have been identified, about half of which are missense and nonsense mutations. Other mutations include large and small insertions/deletions, splice changes, and gross alterations [HGMD]. Notably, many of the missense mutations are found in the GEF catalytic domain. However, mutations have also been found in the PH, PRD and FYVE domains. The specifics of how mutations in each domain affect Fgd1 function and phenotype have not been determined fully [Genot et al., 2012].

Fgd1 is a member of the DH GEF family. GEFs promote the catalysis of GDP for GTP and promote Rho family GTPase activity. Fgd1's GEF activity is specific for the cell division cycle 42 (Cdc42) Rho GTPase. Cdc42 controls numerous key functions in the cell. Therefore, through its activation of Cdc42, Fgd1 participates in control of cytoskeletal membrane rearrangements, transcriptional activation, secretory membrane-trafficking, transition through G1 during the cell cycle, and tumorigenic transformation [Olson et al., 1996]. While all of the functions of Fgd1 are not yet fully understood, it is clear that it participates in regulation of bone development due to mutations resulting in Aarskog-Scott syndrome. Fgd1 is almost exclusively expressed in pre-cartilaginous mesenchymal condensations, the perichondrium and periosteum, and proliferating chondrocytes and osteoblasts. The observed pattern of Fgd1 expression correlates with Aarskog-Scott syndrome skeletal manifestations [Gorski et al., 2000]. Fgd1 may regulate the differentiation of mesenchymal cells into osteoblasts where Fgd1 is highly expressed. Furthermore, Fgd1 is not expressed during early phases of skeletogenesis but is expressed in ossifying skeletal components. Recent studies in mice provide evidence that Fgd1 regulates bone development by its direct GEF activity on Cdc42 which then signals through the MLK3/p38/ERK/RUNX2 pathway [Zou et al., 2011]. Fgd1 is also involved in podosome regulation and extracellular matrix remodeling [Ayala et al., 2009; Daubon et al., 2011].

Myopathy, reducing body, X-linked, severe early-onset; OMIM# 300717; Xq26.3; FHL1. Reducing Body Myopathy (RBM) involves females and is usually lethal in utero in males. Females have been reported to have striking asymmetric pathology possibly suggesting variable X-inactivation patterns result in asymmetric disease. Affected females have hypotonia with contractures and respiratory weakness at birth. There is a progressive myopathy with decreased deep tendon reflexes [Schessl et al., 2008], as well as progressive hypotonia and proximal weakness of all muscles. Serum creatine kinase levels are elevated. The progressive muscle weakness leads to spinal rigidity, scoliosis, frequent falls, and abnormal gait. Progressive weakness leads to death from respiratory failure at approximately five years of age [Schessl et al., 2009].

RBM is caused by mutations in the Four-and-a-Half LIM Domains 1 (*FHL1*) gene. Mutations in *FHL1* result in several other closely related myopathies including: X-linked myopathy with postural muscle atrophy (XMPMA), X-linked scapuloperoneal myopathy (X-SM), rigid spine syndrome. These myopathies all have overlapping features but are still clinically distinguishable. While *FHL1* mutations are usually dominant, some mutations do not result any discernible phenotype in females. Males that do survive are usually much more severely affected than females. *FHL1* mutation disease phenotypes range from early onset and fatality to mild late onset features [Schessl et al., 2011].

RBM is named for its unique muscle biopsy pathology which shows fiber variation without inflammation and intracytoplasmic dark inclusion bodies, called reducing bodies [Kiyomoto et al., 1995]. Muscle biopsy histopathology shows similarities and differences between various syndromes depending on the *FHL1* mutation, but most of these syndromes show some form of perinuclear intracytoplasmic aggregates. With some mutations, these aggregates can be identified by menadione- nitro blue tetrazolium (NBT) staining. Electron microscopy of muscle demonstrates the abnormal presence of highly osmiophilic granula material emanating from the muscle fiber I-band. Muscle pathology is not always uniform, so selection of a biopsy from an affected muscle is important to capture RBs and inclusion bodies. Ultrastructural analysis indicates that pathology begins where Fhl1 is normally localized, but with more severe pathology, RBs and cytoplasmic inclusions invade and displace all of the muscle fiber components [Malfatti et al., 2013].

The *FHL1* gene has seven exons and codes for a small 32 kDa protein of 280 a.a. As the name of the protein indicates, it contains contains Four-and-a-Half LIM domains. LIM domains are homeodomain cysteine and histidine-rich tandem zinc-finger protein interaction motifs. LIM domains are involved in protein-protein interactions during transcriptional regulation. LIM containing proteins are suggested to play critical roles in development of several systems and organs such as the nervous system, pancreas, and heart [Li et al., 2007]. There are 41 mutations listed in HGMD, the vast majority of which are missense mutations at conserved cysteine and histidine residues in the different LIM domains [HGMD]. *FHL1* has several splicing variants and it appears that mutations that alter all transcripts generally result in more severe phenotypes [Schessl et al., 2011]. The roles of Fhl1 and its other Fhl family members are not completely understood, but they are thought to be involved in regulation of transcription factors, cytoskeletal scaffolding, and biomedical stress response. Data suggests Fhl1 participates in muscle growth and differentiation, sarcomere assembly, and regulation of skeletal muscle mass. Fhl1 localizes to the myofibrillar sarcomere and sarcolemma in skeletal muscle. Fhl1 is known to interact with myosin binding protein C, Erk2, Hpc2, Ring1, Kbp1. Fhl1 interacts with a complex that also contains PDZ and LIM domain protein 1, gelsolin, and α-actinin 1 [Schessl et al., 2011]. *Fhl1* KO mice develop age-dependent myopathy, myofibril and intermyofibril disorganization, and have shortened life-span [Domenighetti et al., 2013].

FLNA spectrum disorders; OMIM# 300017; Xp28; FLNA. There are numerous disorders with a broad and diverse phenotypic range that result from Filamin-A (*FLNA*) mutations (Tables I and II). Here we highlight two most closely associated with contractures; FG syndrome 2 and Otopalatodigital syndrome II.

FG syndrome 2; OMIM# 300321. FG syndrome 2 (FG being the initials of the first patient), is characterized by agenesis of the corpus callosum, high broad forehead with frontal colic, ocular hypertelorism, downslanted palpebral fissures, and small cupped ears [Graham et al., 1999]. Patients will usually have relative

microcephaly. Broad thumbs and prominent fetal fingertip pads are often present [Clark et al., 2009]. Most affected individuals have hypotonia [Romano et al., 1994]. In addition, there may be joint hyperlaxity and even spasticity; however, many patients are born with congenital contractures. Joint dislocations have also been reported. Severe constipation is present in infancy and usually resolves during mid-childhood [Clark et al., 2009]. Additional features include developmental delay, particularly in speech; hyperactivity and talkativeness when speech is accomplished [Unger et al., 2007].

Otopalatodigital syndrome, type II; OMIM# 304120. Otopalatodigital syndrome, type II (OPD2) is characterized by microcephaly, small mouth, cleft palate, flexed overlapping fingers, and syndactyly. It presents as an X-linked semi-dominant, thus females are mildly affected. Males have short limb dwarfism and specific skeletal changes. Clinical features often include large anterior fontanelle, downslanting palpebral fissures, hypertelorism, exophthalmos, corneal opacities, short nose, downturned mouth, severe micrognathia, high palate, and sometimes cleft palate [Verloes et al., 2000; Murphy-Ryan et al., 2011]. Generalized flexion contractures are present at birth with broad upper limbs with bulbous tips to the fingers [Stevenson et al., 1980]. Occasionally, omphalocele is seen [Murphy-Ryan et al., 2011]. Hearing loss is common. Abnormalities of the CNS may be seen with cerebellar hypoplasia. Specific skeletal abnormalities are always present in the hands and feet. Cardiac anomalies can be seen, as well as urinary tract obstruction [Robertson, 2007].

FLNA is one of 3 filamins (A, B, C), mutations in all of which cause disease. The *FLNA* gene is fairly large spanning 26 Kb and contains 48 exons. It codes for a 280 kDa protein that functions as an actin filament cross-linking scaffold protein. Flna protein forms a rod-like structure. At one end it has a primary spectrin related F-actin binding domain followed by 15 β-pleated sheet repeats, a hinge region, a second rod structure domain consisting of 8 more β-pleated sheet repeats, a second hinge, and a final dimerization β-pleated sheet domain. The hinge regions are sensitive to inactivation by Calpain cleavage. Two 280 kDA subunits self-associate to form a 160 nm long semi-flexible strand. Flna has numerous binding partners and mutations in different domains leads to very diverse phenotypes ranging from those with moderate affects to those that are lethal. Periventricular Heterotopia is the most common syndrome caused by *FLNA* mutations followed by Frontometaphyseal dysplasia and OPD2. Most OPD2 mutations cluster in the actin binding domain. Only one mutation in *FLNA* has been reported to cause FG syndrome 2. Human null mutations in *FLNA* disrupt long range directed neuronal migration with the cerebral cortex resulting in X-linked periventricular heterotopia. Mutations that reduce expression lead to a wide range of congenital anomalies. In cells, deficiency of Flna results in polarization and motility defects. Overexpression of Flna can also prevent migration of cells. *Flna* KO is embryonic lethal in mice with severe defects in cardiovascular formation and bone development. [Robertson, 2005; Nakamura et al., 2011].

Simpson-Golabi-Behmel syndrome, Type 1; OMIM# 312870; Xq26.2; GPC3. Simpson-Golabi-Behmel syndrome, type 1 (SGBS1) is an overgrowth syndrome and results in overgrowth of the entire body, with both pre-and post-natal overgrowth. SGBS1 individuals are described as having a "bull dog like facies" with large tongues [Neri et al., 1988]. They may have pectus excavatum, VSD, clefting of the lower lip, and alveolar ridge abnormalities. Many patients have 13 ribs. Ears are unusual. Voice is low pitched. Cataracts frequently develop. Gastrointestinal (GI) abnormalities include Meckel's diverticulum and intestinal rotation. Some have coccygeal skin tags and boney appendages. Hands and feet are relatively short and broad and may have various deformities such as metatarsus varus, clubfoot, fingernail hypoplasia (especially of the index finger), cutaneous syndactyly, and postaxial polydactyly [Neri et al., 1998]. Variable congenital contractures are seen. Severe ID is a constant feature [Veugelers et al., 1998]. Interestingly, some SGBS1 patients also have hepatocellular carcinoma and embryonal tumors [Lapunzina et al., 1998]. Carrier females may have a mild expression of disease [Neri et al., 1998]. SGBS1 shows phenotypic similarity to Beckwith-Wiedemann syndrome, another overgrowth syndrome (OMIM#130650).

Pilia et al. [1996] discovered the first mutations in glipican 3 (*GPC3*) that cause SGBS1. Thus far, there are 52 reported mutations in *GPC3*, the majority of which are gross deletions, but also include missense and other types of mutations. The *GPC3* gene spans more than 500 kb and has eight exons with multiple splice variants, with the longest transcript identified coding for a 603 a.a. protein [Pilia et al., 1996]. Gpc3 is a glycosylphosphatidylinositol (GPI) membrane anchored protein thought to play an important role in cell division and growth regulation. The role of Gpc3 is not fully understood, but drosophila and mice with mutations in *GPC3* display some similar dysmorphisms to humans with SGBS1 [Jakubovic and Jothy, 2007]. Gpc3 is not only involved in embryonal tumors, but somatic mutations are associated with a specific type of cancer (Wilms tumor [White et al., 2002]). Furthermore, Gpc3 is upregulated in a large number of hepatocellular carcinomas (HCC) [Hsu et al., 1997] and is critical for HCC development [Capurro et al., 2005]. Since Gpc3 is involved in cancer and mutations lead to overgrowth in SGBS1, Gpc3 must play an important role in tumor suppression and controlling cell growth. While the proliferation and growth pathways in which Gpc3 participates are unknown, there is evidence that glypicans participate in Wnt signaling [Jakubovic and Jothy, 2007]. Gpc3 can also bind to and inhibit the dipeptidyl peptidase activity of CD26, and it can induce apoptosis in certain cell types [Gonzalez et al., 1998; Davoodi et al., 2007]. The specific embryological and developmental expression pattern of Gpc3 is consistent with the abnormalities seen in SGBS1, including homogeneous hepatocyte expression [Iglesias et al., 2008].

MASA syndrome or CRASH syndrome; OMIM# 303350; Xq28; L1CAM. L1 syndrome is a group of X-linked disorders caused by mutations in the the L1 cell adhesion molecule (*L1CAM*) gene. The most common characteristics of L1 syndrome are spasticity of the lower limbs, ID, hydrocephalus, and adducted thumbs [Schrander-Stumpel and Vos, 1993]. L1 syndromes include MASA syndrome (Mental retardation, Aphasia, Shuffling gait, and Adducted thumbs) [Schrander-Stumpel and Vos, 1993; Jouet et al., 1994] and CRASH syndrome (Corpus callosum agenesis, ID, Adducted thumbs, Spastic paraplegia (SPG), and Hydrocephalus) [Fransen et al., 1995; Sztriha et al., 2000; Zhang, 2010]. Hydro-

cephalus is characterized by aqueductal stenosis, but occasionally aqueductal stenosis is missing. Hydrocephalus may become arrested such that only ID and SPG are present. Prenatal hydrocephalus may be severe. There is often interfamilial and intrafamilial variability. Frequently, hypoplasia and contracture of the thumbs are seen. Severely adducted thumbs have been associated with the hydrocephaly, ventricular dilation, and severe ID [Finckh et al., 2000]. Some rare families, in addition to aqueductal stenosis and hydrocephalus, have congenital idiopathic intestinal pseudo obstruction [Fransen et al., 1995]. Contractures of the feet and generalized contractures may be seen [Wilson et al., 2009] and were reported in a patient prenatally diagnosed with a novel R937P *L1CAM* missense mutation.

Mutations in the *L1CAM* gene were first associated with X-linked hydrocephalus by Rosenthal et al. [1992]. Since then, 276 mutations in *L1CAM* have been reported [HGMD]. While phenotypes vary widely with *L1CAM* mutations, truncating mutations (approximately 60% of causal mutations) are generally more severe and typically result in death before the age of 3 [Basel-Vanagaite et al., 2006; Vos et al., 2010]. *L1CAM* is comprised of 28 coding exons spanning about 16 kb and produces a protein of 1257 a.a. L1cam is a transmembrane glycoprotein of the immunoglobulin superfamily of neural cell adhesion molecules expressed primarily in neurons [Kallunki et al., 1997]. L1cam contains a large extracellular domain containing repetitive immunoglobulin-like and fibronectin type III modules, a transmembrane domain, and a small cytoplasmic domain that mediates linkage to the actin cytoskeleton and the endosomal membrane system [Bateman et al., 1996]. L1cam has a myriad of functions and plays a critical role in all steps during establishment of neuronal connectivity including neuronal migration, axon growth, pathfinding, synapse formation, and plasticity [Burden-Gulley et al., 1997; Kenwrick et al., 2000; Schafer and Frotscher, 2012]. In rodents, L1CAM is expressed in cell bodies of migrating neurons beginning at embryonic stage 9.5 and onward. L1CAM is strongly expressed later in development in growing axons. Expression is more moderate in postnatal stages and in the adult L1CAM localizes to presynaptic terminals in the hippocampus. Myelinating Schwann cells express L1CAM only during embryonic and postnatal development, but non-myelinating Schwann cells express L1CAM through adulthood. L1CAM-deficient mice have phenotypes similar to those observed in human disease [Kallunki et al., 1997; Akopians et al., 2003; Schafer and Frotscher, 2012].

MED12 spectrum disorders (Opitz-Kaveggia, Ohdo syndrome, Lujan-Fryns syndrome and Lesca syndrome). All have *MED12* Mutations. Thus far, only Opitz-Kaveggia and Ohdo have reported contractures.

Ohdo syndrome; OMIM# 300895; Xq13.1; MED12. In 2006, Verloes et al. subdivided the syndromes with the blepharophimosis and ID into four categories. They identified a variety seen only in males with coarse triangular facies, multiple congenital contractures, and blepharophimosis. Dental hypoplasia and deafness may also be seen [Maat-Kievit et al., 1993]. These reports may represent examples of microdeletion/duplication syndromes. The Nowaczyk and Sutcliffe [1999] report may represent the same condition. *MED12* has recently been identified as the responsible gene [Vulto-van Silfhout et al., 2013]. The blepharophimosis is striking. They apparently do not have the adult behavioral abnormalities as Opitz-Kaveggia syndrome.

Opitz-Kaveggia syndrome (FG syndrome 1); OMIM# 305450; Xq13.1; MED12. Opitz and Kaveggia [1974] first described three brothers and two of their male first cousins with relative macrocephaly, broad flat thumbs, imperforate anus, hypotonia and moderately severe ID [Graham and Schwartz, 2013]. The syndrome was lethal during early childhood in some patients. Distinct facial features included a prominent forehead, upswept frontal hairline, downslanted palpebral fissures, ocular hypertelorism and small simple prominent ears. The corpus callosum was deficient or absent. Other defects included malformations of the intestinal tract and heart, anal stenosis, hernias, and craniosynostosis. Stature was in the lower range of normal. Flat halluces, partial syndactyly, pectus excavatum, joint contractures and spinal curvature were also features. Surviving males had congenital hypotonia with constipation. During early childhood, boys were friendly, inquisitive, and hyperactive with a very short attention span. Older males were noted to have temper tantrums with attacks of screaming and aggressive or self-abusive behavior. Female carriers were unaffected. These phenotypic characteristics were later confirmed in other reports [McCardle and Wilson, 1993; Graham et al., 1999; Risheg et al., 2007; Clark et al., 2009; Lyons et al., 2009; Graham et al., 2010; Rump et al., 2011].

Opitz-Kaveggia syndrome was linked to Xq12-q22.31 [Briault et al., 1997; Graham et al., 1998] and later found to be caused by mutations in Mediator of RNA polymerase II transcription subunit 12 (*MED12*) [Risheg et al., 2007]. Risheg et al. [2007] reported a recurrent R961W mutation in the original family described by Opitz and Kaveggia as well as in five other families. Only 12 mutations have been identified in *MED12* thus far, the most common being the recurrent Opitz-Kaveggia syndrome mutation recently reported in 10 families [Graham and Schwartz, 2013].

MED12 has one primary transcript highly expressed throughout the soma and the CNS during early fetal development [Philibert et al., 1999]. Med12 is a 2177 a.a. protein that is part of the macromolecular complex known as "Mediator". Mediator serves as a scaffold for the assembly of the pre-initiation complex and functions as a bridge to convey information from gene-specific regulatory proteins to the basal RNA polymerase II transcription machinery and general transcription factors [Rocha et al., 2010]. Med12 is part of a Mediator subcomplex referred to as the *Srb8–11* or *Cdk8* module thought to give specificity to Mediator [Vogl et al., 2013]. As a critical component of Mediator, *MED12* mutations could affect expression of numerous genes and have diverse and far reaching consequences. Early fetal expression of Med12 fits well with evidence that it is important for the development of neural crest, nervous system, cartilage, kidney, and endodermal organs [Rau et al., 2006; Shin et al., 2008; Zhou et al., 2012; Wu et al., 2013]. In mice, MED12 interacts with SOX10 to drive myelination in glial cells and may explain corpus callosum defects [Vogl et al., 2013]. Hypomorphic *Med12* mice demonstrate that MED12 is required for proper Wnt/β-catenin and Wnt/planar cell polarity signaling [Rocha et al., 2010]. MED12 mutations also disrupt Sonic Hedgehog signaling [Zhou et al., 2012]. Med12 also plays a role in regulating non-coding RNA target genes. As well, the Mediator complex harboring disease-causing *Med12* mutations displayed

diminished ability to associate with activating ncRNAs [Lai et al., 2013].

It is important to note that at least two other syndromes caused by mutations in *MED12* have strongly overlapping features and phenotypes. These syndromes include Lujan-Fryns syndrome (OMIM 309520) [Schwartz et al., 2007], and a syndrome named only thus far by its mutation p.S1967Qfsx84 [Lesca et al., 2013]. The phenotypes are so similar that the original Lujan-Fryns syndrome was initially considered to have Opitz-Kaveggia syndrome. While contractures were not reported for these two syndromes, it would not be surprising if contractures are found as a feature of these other syndromes as the phenotypes, especially hypotonia, overlap significantly. The p.S1967Qfsx84 syndrome reported by Lesca et al. [2013] resulted in variable cognitive impairment in heterozygous female obligate carriers. X-inactivation studies did not reveal a correlation between cognitive impairment and inactivation profiles in blood cells of the affected females [Lesca et al., 2013].

Myotubular myopathy, X-linked; OMIM# 310400; Xq28; MTM1. X-linked myotubular myopathy (XL-MTM) is one of the more common forms of MTM and is the most severe. There is often polyhydramnios and reduced fetal movements prior to birth. Affected individuals usually die within days or weeks of birth with generalized muscular weakness and asphyxia. Extraocular, facial and neck muscles are always affected. Diplegia, external ophthalmoplegia, and congenital myotonic dystrophy are features of MTM. Congenital eventration of the diaphragm and generalized flexion contractures can be seen [Braga et al., 1990]. Body length is usually greater than the 90th centile; enlarged head circumference without hydrocephaly is seen in 70% of patients; elongated face in 80%; and slender long digits is seen in 60% of patients. Cognitive development is apparently normal in the absence of hypoxia [Bradley et al., 1970; Herman et al., 1999]. Survivors have had pyloric stenosis, spherocytosis, gall stones, kidney stones, and nephrocalcinosis with rapidly advancing bone age [Laporte et al., 1997; Buj-Bello et al., 1999; Herman et al., 1999; Laporte et al., 2000].

XL-MTM is considered a centronuclear myopathy (CNM), a group of disorders where muscle biopsy histology reveals that the nucleus is found at the center of many rod-shaped muscle cells instead of at either end where it is normally located. Reduced nicotinamide adenine dinucleotide - tetrazolium reductase (NADH-TR) staining reveals fibers with a dark central region usually surrounded by a paler peripheral halo [Romero, 2010]. Autopsies reveal variation in the involvement in different muscles, but spinal cord is normal [Hammans et al., 2000]. Females are generally not affected, however, several reports of affected females exist [Grogan et al., 2005; Jungbluth et al., 2008; Hedberg et al., 2012]. While no effective treatment is available for XL-MTM, newer studies in mice suggest that enzyme replacement therapy may provide hope in the future [Lawlor et al., 2013].

XL-MTM was linked to Xq28 in 1990 [Thomas et al., 1990] and the first mutations in the myotubularin gene (*MTM1*) were identified by Laporte et al. [1996]. Disease-causing mutations include roughly equal proportions of deletions/insertions, nonsense, missense and splice mutations scattered across the gene [HGMD]. *MTM1* codes for the 603 a.a. lipid phosphatase Mtm1, which dephosphorylates phosphatidylinositol 3-monophosphate (PI3P) and phosphatidylinositol 3, 5-bisphosphate (PI(3, 5)P2). These two phospholipids are second messengers with many critical roles in diverse biological functions [Di Paolo and De Camilli, 2006]. Mtm1 is required for skeletal muscle maintenance, but not for myogenesis. Myotubularin has been shown to play a role in endosomal trafficking, desmin intermediate filament organization, and apoptosis [Lawlor et al., 2013]. In recent studies in *Mtm1* KO mice, key findings relating to how MTM1 deficiency leads to disease were elucidated. MTM1 deficiency results in a decreased number of triads and abnormal longitudinally oriented T-tubules in muscle fibers, structures critical for excitation-contraction coupling. MTM1 deficiency also resulted in a 3 fold reduction in Ryr1 protein level and strongly suggests defective Ryr1-mediated sarcoplasmic reticulum Ca^{2+} release and failure of muscle function. This structural and function disruption leads to loss of excitation-contraction coupling [Al-Qusairi et al., 2009; Gonzalez Rodriguez et al., 2013]. Interestingly, *RYR1* mutations can cause various forms of myopathy including CNM [Jungbluth et al., 2007].

MTMR1 and *MTM1* are adjacent to each other on the X chromosome and are thought to have arisen from a gene duplication event. It has long been suspected the *MTMR1* mutations can cause XL-MTM, but after screening 14 patients with XL-MTM that did not have mutations in *MTM1*, no mutations in *MTMR1* were identified [Copley et al., 2002]. While no mutations in *MTMR1* have been reported to date, several papers suggest a loss of expression due to splicing alterations may play a role in other myopathies [Buj-Bello et al., 2002; Santoro et al., 2010].

Oral-facial-digital syndrome 1; OMIM# 311200; Xp22.2; OFD1. The predominant clinical features of individuals with Oral-facial-digital syndrome 1 (OFD1) are oral cavity, facial, and digital malformations [Gorlin and Psaume, 1962; Juric-Sekhar et al., 2012; Bisschoff et al., 2013]. These include frontal bossing, ocular hypertelorism, macrocephaly, a short nose and averted nares with a large funnel, cleft or pseudo-cleft in the upper lip, hyperplastic frenulae, supernumerary or malpositioned teeth, and abnormalities of the digits including brachydactyly, syndactyly, clinodactyly, camptodactyly, polydactyly, and hypoplastic thumbs. Other signs include hydrops, hypotonia, a short neck, and redundant skin [Brzustowicz et al., 1999]. OFD1 patients often develop polycystic kidney disease [Feather et al., 1997a; Thauvin-Robinet et al., 2006; Gurrieri et al., 2007] renal failure, require dialysis, and renal transplantation in late childhood or adulthood [Stapleton et al., 1982; Odent et al., 1998]. Involvement of the CNS occurs in as many as 50% of patients [Gorlin and Psaume, 1962; Towfighi et al., 1985; Connacher et al., 1987]. This syndrome is usually dominantly inherited in females which produce a broad range of phenotypes [Bisschoff et al., 2013]. In males, OFD1 is usually embryonic lethal in the first or second trimester [Toriello and Franco, 1993; Thauvin-Robinet et al., 2013]. However, a few male patients with OFD1 mutations have been diagnosed with Simpson–Golabi–Behmel syndrome Type 2 (SGBS2) with macrocephaly, severe ID, and ciliary dyskinesia [Budny et al., 2006], or Joubert syndrome 10 (JBTS10) with the molar tooth sign on brain imaging [Coene et al., 2009; Field et al., 2012; Juric-Sekhar et al., 2012; Thauvin-Robinet et al., 2013]. In both SGBS2 and JBTS10 families, the female carriers have not been reported to be affected. OFD1, SGBS2, and JBST10

are ciliopathies [Toriello and Goldenberg, 2009; Toriello and Parisi, 2009; Juric-Sekhar et al., 2012].

Mutations causing *OFD1* were first mapped to Xp22.2–22.3 [Feather et al., 1997b] and subsequently mutations in the *OFD1* gene were detected [Ferrante et al., 2001]. The *OFD1* gene has 23 exons and codes for a protein of 1012 a.a. in length. To date, 136 mutations in this gene have been listed in HGMD and are spread out across the entire gene with all types of mutations including missense, frameshift, small insertion, and splice variants, however, nearly half of *OFD1* mutations are small deletions [HGMD]. *OFD1* escapes X-inactivation and shows widespread expression in pancreas, kidney, skeletal muscle, liver, lung, placenta, brain, and heart [de Conciliis et al., 1998]. Ofd1 protein is predicted to have five coil-coil domains and a LisH domain [Bisschoff et al., 2013], and is a centrosomal protein localized at the base of the primary cilia [Romio et al., 2003; Romio et al., 2004]. Ofd1 plays a critical role in primary cilia function and is required for primary cilia formation and left–right symmetry [Ferrante et al., 2006]. Correct cilia function is critical to neural patterning, progenitor proliferation, cell migration, and axon guidance in the developing human brain and spinal cord [Juric-Sekhar et al., 2012]. The phenotype of patients with OFD1 is in keeping with other ciliopathies in which midline defects and cystic kidney disease are recurrent features [Macca and Franco, 2009]. Mouse models faithfully replicate features of the disease seen in humans. Ofd1 mutation is also associated with defective sonic hedgehog and canonical Wnt signaling pathway defects. [Ferrante et al., 2006; Macca and Franco, 2009]. Besides its role in primary cilia function, Ofd1 also interacts with RuvBl1 and the Tip60 histone acetyltransferase complex suggesting a role in chromatin-remodeling [Giorgio et al., 2007].

TARP syndrome; OMIM#311900 Xp11.23; RBM10. TARP syndrome consists of talipes equinovarus deformity, atrial septal defect (ASD), Pierre Robin anomaly, and persistence of left superior vena cava [Johnston et al., 2010]. The combination of Pierre Robin anomaly, congenital heart disease and multiple congenital contractures is rather striking. Clubfeet are severe and require extensive therapy. Many other contractures are present. Liver and kidney failure, athetoid movements, and seizures have been seen. Most affected males die pre- or postnatally but one child has survived to at least age 3.5 years due to intensive medical intervention [Gorlin et al., 1970; Gripp et al., 2011]. No phenotype has been reported in carrier females.

Mutations in the RNA Binding Motif Protein 10 (*RBM10*) have been identified as the cause of TARP syndrome [Johnston et al., 2010]. To date, only four reports describing six different mutations in five unrelated families have been reported. These mutations include two nonsense mutations, a deletion spanning six exons of *RBM10*, a frameshift mutation [Johnston et al., 2010] and three de novo mutations [Johnston et al., 2014]. All of these mutations would likely induce nonsense-mediated mRNA decay and/or cause truncation or drastically destabilize the overall structure of the Rbm10 protein. The loss of function of Rbm10 in TARP syndrome demonstrates that this gene is critical for normal mammalian development [Johnston et al., 2010; Gripp et al., 2011; Wang et al., 2013; Johnston et al., 2014].

RBM10 spans about 40 Kb, has 24 exons, and undergoes typical X-inactivation, but no inactivation studies have been reported in carrier females to determine if X-inactivation is skewed. The Rbm10 protein is large nuclear protein consisting of 930 a.a., and contains two zinc finger motifs, a G patch, two RNA recognition motifs (RRM), and nuclear localization signals [Wang et al., 2013; Xiao et al., 2013]. Rbm10 has been shown to be part of splicing complexes and regulates alternative splicing [Wang et al., 2013]. Mouse models have shown expression of RBM10 in mid-gestational embryos. Whole-mount *in situ* expression analysis of murine RBM10 at E9.5 and E10.5 of development showed a similar pattern of expression, with the most robust staining observed in the first branchial arch (which gives rise to the mandible), second branchial arch, developing limb buds, and tailbud. Robust expression remained for E11.5 embryos in both the limb and tail bud regions, whereas expression in branchial arches one and two decreased at this stage. This pattern of expression correlated well with the human malformations observed in TARP syndrome, which include severe micrognathia and limb defects and likely alters expression of many genes critical for development [Johnston et al., 2010; Wang et al., 2013].

Mental retardation, X-linked syndromic, christianson type; OMIM# 300243; Xq26.3; SLC9A6. Christianson syndrome generally presents in infancy with microcephaly or acquired microcephaly, undergrowth, and global neurodevelopmental delay with ataxia [Christianson et al., 1999; Gilfillan et al., 2008; Schroer et al., 2010]. Some affected individuals die in childhood and most have shortened lifespan [Schroer et al., 2010]. Motor development is limited and is associated with mild to moderate generalized hypotonia. Affected males have severe ID and speech development problems. Hypoplasia of the cerebellum and brain stem are often present with severe loss of Purkinje cells and Tau deposition [Garbern et al., 2010]. Affected males may develop some ambulation abilities, but lose these abilities, usually by the end of the first decade of life along with regression of any other skills obtained. Affected children often have a cheery disposition and smile and laugh frequently, but this Angelman-like demeanor often becomes less apparent in adults. Seizures are common and often refractory to treatment. Contractures can be present at birth and include flexion of elbows, adduction of thumbs, and camptodactyly. However, contractures can also develop later [Christianson et al., 1999; Schroer et al., 2010]. Facial features have been described as long narrow face, large ears, long straight nose, open mouth, and prominent mandible. Heterozygous females may have mild ID or behavioral problems [Christianson et al., 1999; Garbern et al., 2010]. Older female obligate carriers have been reported to have Parkinsonism that may be related to carrier status [Riess et al., 2013]. Several Christianson syndrome reports indicate significant phenotypic overlap with Angelman syndrome caused by mutations in *UBE3A* [Gilfillan et al., 2008; Schroer et al., 2010].

Christianson's original publication linked disease in a large family to Xq24-q27 [Christianson et al., 1999] and subsequently mutations in Solute Carrier Family 9, Subfamily A member 6 (*SLC9A6*) were found to be the cause of disease [Gilfillan et al., 2008]. A total of 14 unique mutations in *SLC9A6* have been reported to date. Some mutations result in rapid degradation of Slc9a6 protein [Ohgaki et al., 2011]. The *SLC9A6* gene is ~62 Kb in length and codes for the 669 a.a. protein, often referred to as Sodium/Hydrogen Exchanger 6 (NHE6). Slc9a6 is defined as an

electroneutral organellar ion exchanger (resides in organelle membrane rather than plasma membrane). Its N-terminus has 12 transmembrane helices that are highly conserved among *Slc* family members that constitute the ion translocation domain. The C-terminus is thought to be important for binding various regulatory proteins.

Slc9a6 is expressed in many tissues, but has particularly high expression in skeletal muscle and brain, and it colocalizes, at least to some extent, to sorting and recycling endosomes. Slc9a6 binds receptor for activated protein kinase C-1 (Rack1) which dictates the distribution of Slc9a6 between the plasma membrane and endosomes [Ohgaki et al., 2008; Ohgaki et al., 2011]. *Slc9a6* KO mice recapitulate many features of human disease. *Slc9a6* KO mice have been reported to have abnormal accumulation of GM2 ganglioside and unesterified cholesterol within late endosomes and lysosomes was found in the basolateral nuclei of the amygdala, the dentate gyrus, the CA3 and CA4 hippocampal layers, and some areas of the cerebral cortex. These specific neuronal populations were also devoid of β-hexosaminidase activity, an enzyme critical for degradation of GM2 ganglioside. Cerebellar neuroaxonal dystrophy similar to that observed in lysosomal disease was also seen in *Slc9a6* KO mice and resulted in marked and progressive loss of Purkinje cells. It has therefore been suggested that disease caused by *SLC9A6* mutations be classified as a lysosomal storage disease [Stromme et al., 2011]. Interestingly there have been reports that *SCL9A6* mutations result in accumulation of Tau protein in brain neurons [Garbern et al., 2010]. Tau is a key player in Parkinson disease, fronto-temporal dementia, and Alzheimer disease and other tauopathies and several grandmothers in families with affected males were reported to have Parkinsonism [Riess et al., 2013]. Slc9a6 may also have several other roles including fine regulation of luminal pH, and regulation of clathrin-dependent endocytosis of transferrin via pH regulation [Xinhan et al., 2011].

Abruzzo-Erickson syndrome; OMIM# 302905; Xq21.1; TBX22. Abruzzo and Erickson reported a family in [1977] with apparent X-linkage and congenital contractures. The affected individuals had cleft palate or uvula, coloboma of the iris and retina, hypospadias, neurosensory deafness, short overall stature, and congenital contractures in the form of radioulnar synostosis in the male affected members and limited expression in females. ASD, cryptorchidism, flat face, micrognathia, larger of ears and esotropia were also described in the affected males. Affected males and some carrier women also had wide spacing between the second and third fingers, ulnar deviation of the second digit, and the hands appeared short for body size. Additionally, syndactyly was present in the feet of at least one affected boy. No abnormal bones were seen on X-ray of the hands.

It was recognized that the original family described by Abruzzo and Erickson had significant phenotypic overlap with CHARGE syndrome (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness) [Abruzzo and Erickson, 1989]. The majority of CHARGE syndrome patients (~70%) are due to mutations in chromeodomain helicase DNA binding protein 7 (*CHD7*). However, this original family did not have *CHD7* mutations. They also had phenotypic overlap with X-linked cleft palate (CPX), but with the additional CHARGE-like phenotypic characteristics. CPX has been demonstrated to be caused by mutations in T-Box 22 (*TBX22*) [Braybrook et al., 2001; Andreou et al., 2007] It was hypothesized and found that this family had a mutation in *TBX22* [Pauws et al., 2013].

TBX22 is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box. T-box genes encode transcription factors involved in the regulation of developmental processes, and it is believed that *TBX22* plays a major role in human palate formation [Pauws et al., 2013]. Inheritance has been seen in a Mendelian X-linked semi-dominant pattern [Braybrook et al., 2001; Kohli and Kohli, 2012]. Tbx22 is a mid-sized protein consisting of 520 a.a. and eight exons. Andreou et al. [2007] stated that the eighth exon is a novel noncoding exon, which is referred to as "exon 0", located approximately 10 kb upstream of exon 1. The transcriptional start site for exon 0 lies downstream of an active promoter that drives a *TBX22* transcript preferentially expressed in human embryonal tissue. Andreou et al. [2007] suggested that Tbx22 acts as a transcriptional repressor and is capable of autoregulating its expression through the distal *TBX22* promoter. *TBX22* missense mutations result in impaired repression activity of the protein [Andreou et al., 2007].

Spinal muscular atrophy, X-linked 2, infantile; OMIM# 301830 Xp11.23; UBA1. This syndrome is contemporarily referred to as X-linked infantile spinal muscular atrophy (XL-SMA). It is clinically very similar to classical autosomal SMA (OMIM #253300) characterized by neonatal onset of severe hypotonia, areflexia, with loss of anterior horn cells, and infant death, except with the additional features of X-linked inheritance and arthrogryposis. Although the syndrome had been reported episodically since the 1930's, it was really a review by Hall et al. [1982] that distinguished at least 3 clinical varieties of X-linked arthrogryposis. One family had a severe lethal form with severe contractures, scoliosis, chest deformities, hypotonia, micrognathia, and death from respiratory insufficiency by age 3 months associated with progressive loss of anterior horn cells. This family typifies classical XL-SMA. The Hall review was followed by an important paper by Greenberg et al., [1988]; which described under the label 'X-*linked infantile spinal muscular atrophy*' a familial disorder which appeared to be X-linked and was associated with contractures and anterior horn cell loss, confirming the syndrome of XL-SMA.

This condition is also characterized by myopathic facies, kyphosis, chest deformity, and severe muscle mass loss. Several patients experienced fractures at birth. Death is due to respiratory insufficiency, however, a few patients have survived with intense medical care and these have usually developed kyphosis and scoliosis and apparently normal intellect. Other clinical features include: generalized weakness, severely short feet with deep dimpling, clenched hands with overlapping fingers [Hall et al., 1982; Greenberg et al., 1988; Hennekam et al., 1991; Dressman et al., 2007]. Muscle biopsy and electromyogram (EMG) are consistent with neurogenic atrophy and denervation, hence the appropriate designation as a spinal muscular atrophy. Autopsies show anterior horn cell loss in the spinal cord.

Kobayashi et al. [1995] and Dressman et al. [2007] established a linkage to the short arm of Xp and in [2008] Ramser et al. reported

mutations in ubiquitin-activating enzyme 1 (*UBA1)* [Baumbach Reardon et al., 2008 [Updated 2012 Sep 13]]. Four mutations in *UBA1* in six unrelated families have been identified thus far and all are found in exon 15 of *UBA1* [Ramser et al., 2008; Dlamini et al., 2013]. The *UBA1* gene is a large 22Kbp gene with 26 exons. It contains several putative CPG islands and has an inactivation escape element 1 (INE1) adjacent to exon 15. Since *UBA1* escapes X inactivation [Carrel et al., 1996], females have two active copies of the gene and thus far, no phenotype has been observed in females heterozygous for *UBA1* mutations [Ramser et al., 2008].

Uba1 is the pinnacle enzyme in the ubiquitin proteasome pathway (UPP) [Ciechanover et al., 1982; Schulman and Harper, 2009]. Uba1 activates ubiquitin (Ub) for transfer to target proteins that are degraded by the proteasome. The first step in this process is adenylation of Ub. Exon 15 of *UBA1* is predicted to be part of the adenylation domain of Uba1 [Lee and Schindelin, 2008] and thus mutations are thought to alter the adenylation activity of Uba1. Uba1 is an essential and non-redundant gene expressed and required for survival of all cell types from yeast to man [McGrath et al., 1991]. Due to its non-redundant essential function, it is anticipated that complete inactivation of Uba1 would not be at all viable in humans. Indeed, mutations identified so far suggest only a partial loss of function. Studies demonstrate that loss or reduction of adenylation activity does not completely eliminate the ability of Uba1 to activate and transfer Ub [Tokgoz et al., 2006; Lao et al., 2012].

Wieacker-Wolf syndrome; OMIM# 314580; Xq11.2; ZC4H2. Wieacker-Wolff et al. [1985] first reported a family with multiple congenital contractures including contractures of the feet, progressive distal muscular atrophy, oculomotor apraxia, dysarthria, and mild ID. Muscle biopsy revealed that muscle atrophy was likely neurogenic. Subsequently, this constellation of findings has been recognized as a X-linked recessive neurodevelopmental disorder affecting the central and peripheral nervous system, characterized by onset of muscle weakness in utero (fetal akinesia), severe contractures at birth, skeletal abnormalities (i.e., hip dislocation, scoliosis, and pes equinovarus). Those that survive infancy show ID. Carrier females may have mild features of the disorder [Hirata et al., 2013].

The condition was originally mapped to Xp11.3–11.23 by Kloos et al. [1997]. Interestingly, before actual disease–causing mutations in zinc finger, C4H2 domain containing (*ZC4H2*) were identified as the cause of Wieacker-Wolf syndrome, Lombard et al. [2011] identified *ZC4H2* as a putative XLID gene based on computational approaches, thus demonstrating the increasing usefulness of *in silico* analysis and modeling of disease. Recently, seven different mutations in eight families were reported in *ZC4H2* to be the cause of Wieaker-Wolf syndrome [Hirata et al., 2013]. Mutations include four missense mutations, a chromosomal inversion, and two de novo deletions encompassing *ZC4H2*. This report also expanded the range of phenotypes caused by *ZC4H2* mutations.

The *ZC4H2* gene has seven exons with multiple transcript variants and codes for a 224 a.a. protein containing a c-terminal zinc finger domains characterized by four cysteine and two histidine residues. Zc4h2 also contains a coiled-coil region. Expression patterns indicate that it is transcribed in human fetal brain and other tissues. In mice and zebrafish, homologues are strongly expressed throughout the brain and spinal cord. Expression is highest during embryonic development and declines postnatally. In mouse primary hippocampal neurons, ZC4H2 localized to excitatory postsynaptic sites predominantly with postsynaptic density protein 95 (PSD95) colocalization, but not in inhibitory synapses. Mutations did not alter localization, but reduced synapse number and density. In a zc4h2 zebrafish knockdown model, gross morphology changes were not observed, but abnormal swimming and impaired α-motorneuron development was observed. Morpholinos had shorter and less branched motorneurons projecting from the spinal cord and neuromuscular endplates were reduced in number and disorganized. These findings are consistent with a developmental and neuromuscular disorder as seen in Wieacker-Wolff syndrome patients [Hirata et al., 2013].

VACTERL association, X-Linked; OMIM# 314390; Xq26.3; ZIC3. Vertebral defects, anal atresia tracheoesophageal fistula with esophageal atresia, radial and renal dysplasia was first designated VATER association in 1973 [Quan and Smith, 1973]. Cardiac and limb abnormalities are also seen and VATER was changed to VACTERL. Patients with VACTERL and hydrocephaly, however, were noted to have an X-linked pattern of inheritance [Hunter, 1987]. Hypertelorism, prominent philtrum with retrognathia, and short broad neck are typical. Abnormalities of the ear may include atresia of the external auditory canal and cleft palate. Radial ray aplasia and reduction of radial digits can be seen. Anal atresia and stenosis, as well as anteriorly placed anus are common [Solomon, 2011]. Malrotation of the bowel has been described [Lukusa et al., 1996]. Incomplete lung lobation together with esophageal hiatus of the diaphragm and agenesis of the pancreas may be seen. In the X-linked form, radial ray abnormalities and cardiac abnormalities seem to be particularly frequent. Severe atrophy of the atrial septum, abnormal position of the great arteries, persistence of the vena cava is seen, as well as ASD, heterotaxia, and double ventricle [Hunter, 1987]. GI abnormalities can be extensive including duplication of descending colon. The condition is hard to misdiagnose because all of the associated anomalies, but important to note that multiple contractures are also often present.

VACTERL and X-linked heterotaxy can be caused by mutations in Zinc finger protein of the Cerebellum 3 (*ZIC3*). The first mutations in *ZIC3* were identified in 1997 and were associated with abnormalities in left-right body axis formation during development [Gebbia et al., 1997; Purandare et al., 2002]. Further studies demonstrate that mutations in *ZIC3* cause cardiac malformations, midline abnormalities, defects in gastrulation, lack of neural tube closure, and convergent extension defects [Purandare et al., 2002; Cast et al., 2012]. Mutations in *ZIC3* were first associated with VACTERL in 2010 by Wessels et al. [2010]. To date, 31 mutations in *ZIC3* have been identified associated with Cardiac malformation and situs abnormality [HGMD].

Zic3 is a member of the GLI superfamily of transcription factors. There are five ZIC genes all containing high conserved five tandem C2H2 zinc finger motifs, with *ZIC3* being the only ZIC gene on the X chromosome. Several of the mutations in *ZIC3* disrupt the conserved C2H2 zinc finger motif while other mutations are proposed to alter its nuclear retention. Nuclear retention of Zic3, and thus its transcriptional activities, is regulated at least in part by sumoylation

TABLE I. X-Linked Genes With Mutations Associated with Contractures

Gene	Gene MIM #	Genomic coordinates (GRCh37)	Cytogenetic location	# of mutations*	Entities listed in OMIM associated with gene	Phenotype MIM #
AP1S2	300629	X:15,843,928–15,873,136	Xp22.2	8	Mental retardation, X-linked syndromic, Fried type	300630
					Dandy-Walker malformation with mental retardation, basal ganglia disease, and seizures (Pettigrew syndrome)	
ARX	300382	X:25,021,810–25,034,064	Xp21.3	65	Epileptic encephalopathy, early infantile, 1	308350
					Hydranencephaly with abnormal genitalia	300215
					Lissencephaly, X-linked 2	300215
					Mental retardation, X-linked 29 and others	300419
					Partington syndrome	309510
					Proud syndrome	300004
ATRX	300032	X:76,760,355–77,041,718	Xq21.1	126	Alpha-thalassemia myelodysplasia syndrome, somatic	300448
					Alpha-thalassemia/mental retardation syndrome	301040
					Mental retardation-hypotonic facies syndrome, X-linked (Juberg-Marsidi syndrome)	309580
CASK	300172	X:41,374,186–41,782,286	Xp11.4	62	FG syndrome 4	300422
					Mental retardation and microcephaly with pontine and cerebellar hypoplasia	300749
					Mental retardation, with or without nystagmus	300422
DCX	300121	X:110,537,006–110,655,459	Xq23	132	Lissencephaly, X-linked	300067
					Subcortical laminal heteropia, X-linked	300067
EBP	300205	X:48,380,163–48,387,103	Xp11.23	75	Chondrodysplasia punctata, X-linked dominant (Conradi-Hunermann-Happle syndrome)	302960
EIF2S3	300161	X:24,073,064–24,096,926	Xp22.11	1	MEHMO syndrome	300148
FGD1	300546	X:54,471,886–54,522,598	Xp11.22	35	Aarskog-Scott syndrome	305400
					Mental retardation, X-linked syndromic 16	305400
FHL1	300163	X:135,228,860–135,293,517	Xq26.3	41	Emery-Dreifuss muscular dystrophy 6, X-linked	300696
					Myopathy, reducing body, X-linked, childhood-onset	300718
					Myopathy, reducing body, X-linked, severe early-onset	300717
					Myopathy, X-linked, with postural muscle atrophy	300696
					Scapuloperoneal myopathy, X-linked dominant	300695
FLNA	300017	X:153,576,899–153,603,005	Xq28	138	Cardiac valvular dysplasia, X-linked	314400
					Congenital short bowel syndrome	300048
					FG syndrome 2	300321
					Frontometaphyseal dysplasia	305620
					Heterotopia, periventricular	300049
					Heterotopia, periventricular, ED variant	300537
					Intestinal pseudoobstruction, neuronal	300048
					Melnick-Needles syndrome	309350
					Otopalatodigital syndrome, type I	311300
					Otopalatodigital syndrome, type II	304120
					Terminal osseous dysplasia	300244

(*Continued*)

TABLE I. (*Continued*)

Gene	Gene MIM #	Genomic coordinates (GRCh37)	Cytogenetic location	# of mutations*	Entities listed in OMIM associated with gene	Phenotype MIM #
GPC3	300037	X:132,669,772–133,119,672	Xq26.2	52	Simpson-Golabi-Behmel syndrome, type 1	312870
					Wilms tumor, somatic	194070
L1CAM	308840	X:153,126,970–153,141,398	Xq28	276	Corpus callosum, partial agenesis of	304100
					CRASH syndrome	303350
					Hydrocephalus due to aqueductal stenosis	307000
					Hydrocephalus with congenital idiopathic intestinal pseudoobstruction	307000
					Hydrocephalus with Hirschsprung disease	307000
					MASA syndrome	303350
MED12	300188	X:70,338,405–70,362,303	Xq13.1	12	Lujan-Fryns syndrome	309520
					Ohdo syndrome, X-linked	300895
					Opitz-Kaveggia syndrome (FG syndrome 1)	305450
MTM1		X:149,737,046–149,841,615	Xq28	266	Myotubular myopathy, X-linked	310400
OFD1	300170	X:13,752,831–13,787,479	Xp22.2	136	Joubert syndrome 10	300804
					Oral-facial-digital syndrome 1	311200
					Simpson-Golabi-Behmel syndrome, type 2	300209
RBM10	300080	X:47,004,616–47,046,213	Xp11.23	6	TARP syndrome	311900
SLC9A6	300231	X:135,067,582–135,129,427	Xq26.3	14	Mental retardation, X-linked syndromic, Christianson type	300243
TBX22	300307	X:79,270,254 – 79,287,267	Xq21.1	26	Abruzzo-Erickson syndrome	302905
					Cleft palate with ankyloglossia	303400
UBA1	314370	X:47,050,198–47,074,526	Xp11.23	4	Spinal muscular atrophy, X-linked 2, infantile (XL-SMA)	301830
ZC4H2	300897	X:64,135,681 – 64,254,623	Xq11.2	7	Wieacker-Wolf syndrome	314580
ZIC3	300265	X:136,648,345–136,654,258	Xq26.3	31	Congenital heart defects, nonsyndromic, 1, X-linked	306955
					Heterotaxy, visceral, 1, X-linked	306955
					VACTERL association, X-linked	314390

Gene is HGNC Approved Gene Symbol.
*Number of unique mutations identified (HGMD Aug. 15, 2014).

TABLE II. Summary of X-Linked Contracture Syndromes with Known Genetic Cause

Entity	Phenotype MIM#	Gene	Gene Function
Aarskog-Scott syndrome- A syndrome of short stature, facial dysmorphism, and genital anomalies. Many families have been described involving multiple congenital contractures. However, congenital contractures are not a consistent feature, occurring in 15%-20% of cases, with variability within a family. Females have limited expression.	305400	*FGD1*	Fgd1 is a GEF in the DH GEF family. GEFs promote the catalysis of GDP for GTP and promote Rho family GTPase activity. Fgd1's GEF activity is specific for the Cdc42 Rho GTPase. Cdc42 controls numerous key functions in the cell. Therefore, through its activation of Cdc42, Fgd1 participates in control of cytoskeletal membrane rearrangements, transcriptional activation, secretory membrane-trafficking, transition through G1 during the cell cycle, and tumorigenic transformation.
Abruzzo-Erickson syndrome- A family was reported in 1977 with X-linkage and congenital contractures. The affected individuals had cleft palate or uvula, coloboma of the iris and retina, hypospadias, neurosensory deafness, overall short stature, and congenital contractures in the form of radioulnar synostosis in the male affected members and limited expression in the females.	302905	*TBX22*	*TBX22* is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box. T-box genes encode transcription factors involved in the regulation of developmental processes, and it is believed that *TBX22* plays a major role in human palatogenesis.
Chondrodysplasia punctata, X-linked dominant (Conradi-Hunermann-Happle syndrome)- Punctiform calcifications of bones and patchy defects in skin. Once the bones have finished growing, they are almost always asymmetric with stippled epiphyses. Contractures of the joints, especially affecting hips, but also hands and feet are common. Lethal in males.	302960	*EBP*	Identified disease causing mutations in *EBP*. Small protein which localizes to the endoplasmic reticulum membrane. Importantly, it catalyzes the conversion of δ8-sterols to their corresponding δ7-isomers. Mutations occur in regions that either disrupt Ebp's isomerase activity or impair ligand binding. The malformations of embryogenesis and morphogenesis seen in CDPX2 are thought to be related to cholesterol's involvement in hedgehog protein signaling pathways.
Dandy-Walker malformation with mental retardation, basal ganglia disease, and seizures (Pettigrew syndrome)- Multiple congenital contractures, brain malformations, and severe ID. Female carriers are usually unaffected.	304340	*AP1S2*	Protein which co-localizes at the Golgi apparatus- subunit of AP-1. Clathrin and AP complexes are the main components of clathrin-coated vesicles in the cell. AP-1 complexes are associated with the TGN and are involved in the transport of proteins to the cell surface and endosomal/lysosomal system
FG syndrome 2- Characterized by agenesis of the corpus callosum, high broad forehead with frontal colic, ocular hypertelorism, downslanted palpebral fissures, and small cupped ears. In addition, there may be joint hyperlaxity and even spasticity; however, many patients are born with congenital contractures. Female carriers are usually unaffected. Otopalatodigital syndrome, type II- Characterized by microcephaly, small mouth, cleft palate, flexed overlapping fingers, bulbous ends of the fingers and usually, syndactyly. It presents as an X-linked semi-dominant, thus females are usually affected, and males are often severely affected.	300321 304120	*FLNA*	Actin filament cross-linking scaffold protein. Flna protein forms a rod-like structure. OPD2 mutations cluster in the actin binding domain.
FG syndrome 4- Includes ID, mild facial dysmorphism, post-natal microcephaly and pontocerebellar hypoplasia; About 20% have congenital contractures apparently related to in utero hypotonia. Female carriers are usually unaffected.	300422	*CASK*	Cask is a highly-conserved, multi-domain scaffolding protein highly expressed in the mammalian nervous system. Three major functions -synaptic interaction and synaptogenesis, protein trafficking and targeting, and regulation of gene expression and neural development.
Lissencephaly, X-linked- Characterized by subcortical band heterotopia, intractable seizures, severe ID, and growth failure. Males may or may not be born with contractures. Female carriers have subcortical lamin heterotopias and can usually be recognized on MRI.	300067	*DCX*	Doublecortin (Dcx)domains have been shown to bind microtubules and enhance microtubule polymerization. Dcx is expressed in migrating and differentiating neurons throughout the central and peripheral nervous system during embryonic and postnatal development.

(*Continued*)

TABLE II. (*Continued*)

Entity	Phenotype MIM#	Gene	Gene Function
MASA syndrome or CRASH syndrome - X-linked aqueductal stenosis- L1 syndromes include MASA syndrome (mental retardation, aphasia, shuffling gait, and adducted thumbs) and CRASH syndrome (corpus callosum agenesis, retardation, adducted thumbs, SPG, and hydrocephalus); Frequently, hypoplasia and contracture of the thumbs is seen. Severely adducted thumbs have been associated with the hydrocephaly, ventricular dilation, and severe ID. Contractures are variable. Contractures of the feet were frequently seen. Female carriers are usually unaffected.	303350	*L1CAM*	L1cam is a transmembrane glycoprotein of the immunoglobulin superfamily of neural cell adhesion molecules expressed primarily in neurons. L1cam contains a large extracellular domain containing repetitive immunoglobulin-like and fibronectin type III modules, a transmembrane domain, and a small cytoplasmic domain that mediates linkage to the actin cytoskeleton and the endosomal membrane system. L1cam has a myriad of functions and plays a critical role in all steps during establishment of neuronal connectivity including neuronal migration, axon growth, pathfinding, synapse formation, and plasticity.
MEHMO syndrome- Characterized by mental retardation, epileptic seizures, hypogonadism, microcephaly, and obesity. Generalized flexion contractures are usually seen. Female carriers are apparently spared.	300148	*EIF2S3*	The protein product of *EIF2S3*, is a 472 a.a. 53 kDa protein critical for translation initiation. Eif2s3 forms the catalytic core of the heterotrimeric eIF2. Upon binding GTP and initiator methionyl-tRNA, eIF2 then binds to the 40S ribosomal subunit forming a pre-initiation complex.
Mental retardation, X-linked syndromic, Christianson type- Christianson syndrome generally presents in infancy with microcephaly or acquired microcephaly, undergrowth, and global neurodevelopmental delay with ataxia. Contractures can be present at birth and include flexion of elbows, adduction of thumbs, camptodactyly and long thin fingers. However, contractures can also develop later. Female carriers may be mildly affected and develop Parkinson's symptoms.	300243	*SLC9A6*	The *SLC9A6* gene is ~62Kb in length and codes for the 669 a.a. protein, often referred to as NHE6. Slc9a6 is defined as an electroneutral organellar ion exchanger.
Mental retardation- X-linked, intellectual disability and hypotonic facies syndrome (Juberg-Marsidi syndrome)- ATRX spectrum disorder; characterized by ID, microcephaly, IUGR, and distinct hypotonic and dysmorphic facies. Generalized flexion contractures may be present, as well as flexion contractures of the hips, elbows, knees, and 5th fingers. Variable ID. Female carriers are usually unaffected.	309580	*ATRX*	Atrx is a member of the SWI2/SNF2 helicase/ATPase family and is expressed in the nucleus. Atrx, in conjunction with its binding partner DAXX, functions as a histone chaperone complex and is involved in the deposition of H3.3 histones to pericentric, telomeric, and ribosomal repeat regions. Disruption of Atrx function results in perturbation of many cellular processes including defective chromatid cohesion, telomere dysfunction, and aberrant DNA methylation.
Myopathy, reducing body, X-linked, severe early-onset- RBM involves females and is usually lethal in utero in males. Affected females have hypotonia with contractures and respiratory weakness at birth, with progressive myopathy leading to early death around age 5 years.	300717	*FHL1*	Mutations in *FHL1* result in several closely related myopathies. Contains Four-and-a-Half LIM domains. LIM domains are homeodomain cysteine and histidine-rich tandem zinc-finger protein interaction motifs. LIM domains are involved in protein-protein interactions during transcriptional regulation. LIM containing proteins are suggested to play critical roles in development of several systems and organs such as the nervous system, pancreas, and heart.
Myotubular myopathy, X-linked- One of the more common forms of MTM and the most severe. There is often polyhydramnios and reduced fetal movements prior to birth. Generalized flexion contractures can be seen. XL-MTM is considered a centronuclear myopathy. Female carriers are spared.	310400	*MTM1*	Mtm1 dephosphorylates PI3P and PI(3, 5)P2. These two phospholipids are second messengers with many critical roles in diverse biological functions. Mtm1 is required for skeletal muscle maintenance, but not for myogenesis.
Ohdo syndrome, X-linked- Characterized by blepharophimosis, generalized flexion contractures, coarse facies, dental hypoplasia, and deafness. Female carriers are apparently spared. Moderate ID. Opitz-Kaveggia syndrome (FG syndrome 1)- Opitz-Kaveggia first described three brothers and two of their male first cousins with relative macrocephaly, broad flat thumbs, imperforate anus, hypotonia, moderately severe ID, flat halluces, partial syndactyly, and pectus	300895 305450	*MED12*	*MED12* has one primary transcript highly expressed throughout the soma and the CNS during early fetal development. Med12 is a 2177 a.a. protein that is part of the macromolecular complex known as "Mediator". Mediator serves as a scaffold for the assembly of the pre-initiation complex and functions as a bridge to convey information from gene-specific regulatory proteins to the basal RNA polymerase II transcription machinery and general transcription factors.

(*Continued*)

TABLE II. (*Continued*)

Entity	Phenotype MIM#	Gene	Gene Function
excavatum. Joint contractures and spinal curvature were also features. Female carriers are unaffected.			
Oral-facial-digital syndrome 1- Oral cavity anomalies, facial clefting, and digital malformations; including camptodactyly, and occasionally generalized contractures. CNS anomalies are seen in ~50%. X-linked dominant occurring mainly in females, lethal in males. However, a few affected males with different mutations have been reported.	311200	*OFD1*	*OFD1* escapes X-inactivation and shows widespread expression in pancreas, kidney, skeletal muscle, liver, lung, placenta, brain, and heart. It is made up of five coil-coil domains and a LisH domain. Ofd1 is a centrosomal protein localized at the base of the primary cilia. Ofd1 plays a critical role in primary cilia function and is required for primary cilia formation and left–right symmetry.
Proud syndrome- Characterized by limb contractures and ID. Part of the ARX spectrum. Agenesis of the corpus callosum, seizures, abnormal genitalia, and microcephaly. Females are mildly affected.	300004	*ARX*	Homeobox transcriptional repressor expressed in fetal and adult brain and skeletal muscle. Arx is required for normal brain development.
Simpson-Golabi-Behmel syndrome, type 1 - An overgrowth syndrome which results in overgrowth of the entire body, with both pre- and post-natal overgrowth. Multiple organ abnormalities may be present including coccygeal tags and appendages, deep voice and cleft lower lip. Clubfeet are common, other contractures are variable. Female carriers are usually spared.	312870	*GPC3*	A GPI membrane anchored protein thought to play an important role in cell division and growth regulation.
Spinal muscular atrophy, X-linked 2, infantile- SMA-like phenotype, congenital contractures, kyphosis and scoliosis, chest deformity and respiratory insufficiency, leading to early death. Progressive loss of anterior horn cells and marked hypotonia are present. No phenotypic features are seen in female carriers.	301830	*UBA1*	Uba1 expression is normally high in the spinal cord, and Uba1 is the first step in ubiquitination. Uba1 escapes X-inactivation and is a highly conserved non-redundant gene required for UPP activity in all cells.
TARP syndrome- Talipes equinovarus deformity, ASD, Robin sequence, and persistence of left superior vena cava. The combination of Pierre-Robin anomaly, congenital heart disease and multiple congenital contractures is rather striking. Clubfeet are severe and require extensive therapy. Many other contractures are present. Carrier females are apparently unaffected.	311900	*RBM10*	The Rbm10 protein is large nuclear protein consisting of 930 a.a., and contains two zinc finger motifs, a G patch, two RRMs, and nuclear localization signals; Rbm10 has been shown to be part of splicing complexes and regulates alternative splicing.
VACTERL association, X-linked- Vertebral defects, anal atresia, tracheoesophageal atresia, renal and radial dysplasia, and limb defects are recognized to be associated. The presence of cardiac and limb anomalies changed the association to VACTERAL. Affected individuals with hydrocephaly were noted to be X-linked and had associated congenital contractures.	314390	*ZIC3*	Z1C3 is a member of the GLI superfamily of transcription factors. Z1C3 is highly expressed in neuroectodermal and mesoderm tissue during gastrulation.
Wieacker-Wolf syndrome- Wieacker-Wolff et al. (1985) first reported a family with multiple congenital contractures including contractures of the feet, progressive distal muscular atrophy, oculomotor apraxia, dysarthria, and mild ID. Characterized by onset of muscle weakness in utero, fetal akinesia, and severe contractures at birth.	314580	*ZC4H2*	The *ZC4H2* gene has 7 exons with multiple transcript variants and codes for a 224 a.a. protein containing a c-terminal zinc finger domain characterized by four cysteine and two histidine residues. Zc4h2 also contains a coiled-coil region. Expression patterns indicate that it is transcribed in human fetal brain and other tissues. In mice and zebrafish, homologues are strongly expressed throughout the brain and spinal cord

at residue K248 and individuals with congenital anomalies caused by *ZIC3* mutations have aberrant sumoylation [Chen et al., 2013]. Mutations in mouse, *Xenopus laevis* and zebrafish ZIC3 homologues all show axial defects. Consistent with a role in early development, ZIC3 is highly expressed in neuroectoderm and mesoderm during gastrulation of mouse, chick, Xenopus and zebrafish embryos [Purandare et al., 2002; Cast et al., 2012; Chen et al., 2013].

Summary of syndromes with known genetic cause and gene ontology analyses

As the phenotype of all of these syndromes overlaps at least at the level of contractures, and often much more, it is likely that there are functional relationships between genes. Furthermore, the function of these X-linked genes should have some overlap with autosomal genes associated with contractures. In an effort to characterize this functional overlap, a GO analysis was performed to functionally describe both X-linked and autosomal genes associated with contractures [Hall, 2013, 2014]. The analysis was performed using the ToppGene [Chen et al., 2009] analysis tool. The two lists of genes were analyzed separately. The enrichment analysis of X-linked genes revealed 60 GO categories significant at a *P*-value $\leq$0.01 and 37 of these categories contained more than one X-linked gene (Fig. 1A). At a more generous *P*-value $\leq$0.05, there are 206 categories with 122 of them containing more than one gene. The categories, with more than one gene at a *P*-value $\leq$0.01, are plotted in Figure 1A with the genes in those categories presented also. These ontology terms represent the summarized biological processes as more than one gene shares membership in this process. In order to highlight enriched terms, we created a word cloud summarization of the 37 GO terms (Fig. 1B). Inspection of that word cloud [Feinberg, 2013], reveals a number of interesting terms representing biological processes related to the X-linked genes (Fig. 1B). For example, the most representative term is morphogenesis, suggesting that X-linked genes are associated with processes controlling developmental pathways. Additionally, interesting ontology categories associated with nervous system development are also present which link back to system-wide defects observed with contractures. Lastly, other terms of interest describing contracture associated biology represent migratory processes, spindle biology and tissue polarization.

In addition to the X-linked analysis, we extended the GO enrichment to the autosomal list of genes associated with contractures. The autosomal enrichment analysis list resulted in 291 enriched GO categories significant at a *P*-value $\leq$0.01, of which, 259 contain more than one autosomal gene. The number of categories with a *P*-value $\leq$0.05 was 682, with 478 categories containing more than one gene. Comparing the X-linked GO categories (*P*-value $\leq$0.05) with the autosomal lists resulted in 37 common ontology categories displayed graphically in Figure 2 (see also Supplementary Table I). These 37 GO terms represents common biological themes associated with contractures. Biological processes associated with morphogenesis, neuronal differentiation and development, cytoskeletal organization, and cellular movement appear to be the main overall categories.

Category II. Arthrogryposis syndromes with X-linkage established; however, the disease gene is unknown

The following disorders have been mapped to the X chromosome and have family histories compatible with X-linkage; however, no gene has been identified as yet (Table III).

Aicardi syndrome; OMIM# 304050; Xp22. Aicardi syndrome is a triad of agenesis of the corpus callosum, infantile spasm, chorioretinal abnormalities [Aicardi, 2005]. The syndrome was first described as X-linked dominant, lethal in males. It represents a progressive encephalopathy and was initially mistaken for an intrauterine viral infection because of the intracranial calcifications. Affected girls have been described as having choroid plexus papillomas and apparent microphthalmia. Neuronal and CNS abnormalities have been described including nodular heterotopia and polymicrogyri representing a malmigration disorder. Palpebral fissures are usually upslanted and there is usually an upturned nasal tip. Deep philtrum and relatively large ears have also been described. Over time, intracranial cysts and cerebellar abnormalities have additionally been observed in affected individuals, as well as enlargement of cistern magnum and cerebellar cysts. Spasticity, dystonia, intracranial calcifications and profound psychomotor development appear relatively early. Short stature and microcephaly are common. The contractures that are observed appear to be part of an autoimmune type reaction; however, they are also seen congenitally [Dale et al., 2010]. The gene has not been identified for the X-linked form in spite of striking X-inactivation studies [Eble et al., 2009]. An affected 47XXY male was reported by [Hopkins et al., 1979] However, non-X-linked forms of the disorder have been reported and the genes are part of a cyclin-dependent kinase-like 5 (Cdkl5) signaling cascade [Crow et al., 2006a; Crow et al., 2006b; Rice et al., 2007; Nemos et al., 2009].

Arthrogryposis, congenital, lower limb, X-linked (Zori); OMIM# 300158; Xq23-q27. This condition was reported in a five generation family with a mild form of non-progressive arthrogryposis, affecting only the lower limbs by Zori et al. [1998]. About half of the affected individuals had hip involvement with occasional dislocated hips. All had knee involvement (which could be in flexion or extension) and most had ankle and foot involvement. The leg contractures resulted in impaired gait; however, all were ambulatory. Thin tendons were reported at surgery. Muscle biopsy and nerve conduction were normal. Mapping localized the family to Xq23–q27; however, the responsible gene has not been identified [Zori et al., 1998]. Female carriers were spared.

Mental retardation with optic atrophy, deafness, and seizures (Gustavson); OMIM# 309555; Xq23–q27.3. Gustavson et al. [1993] described a single family with multiple flexion contractures at birth, IUGR, congenital blindness and deafness, severe ID, seizures, microcephaly and early death. Optic atrophy, large ears, vertical talus, enlarged ventricles, underdeveloped brain with cerebellar hypoplasia, and linkage to Xq23–q27.3 was reported [Malmgren et al., 1993]. One affected female and one male with aqueductal stenosis were observed in this large family. Microscopic subependymal gliotic nodules were seen in one affected male.

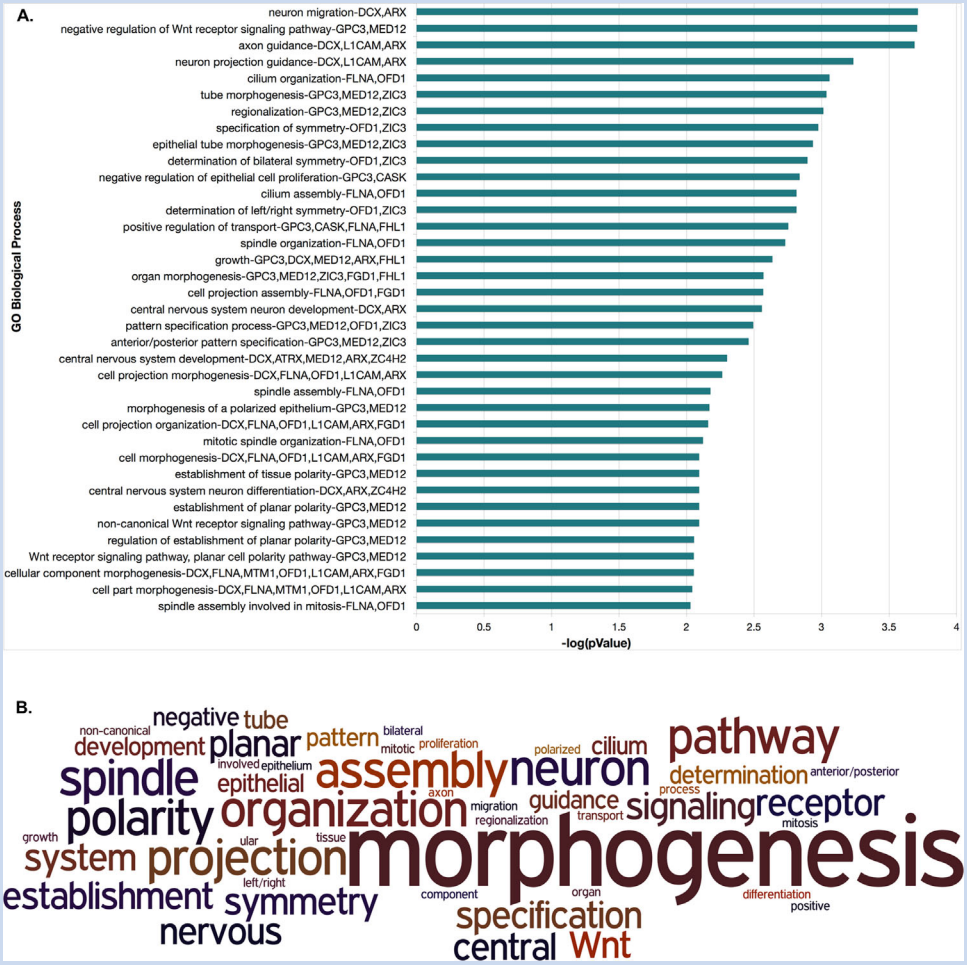

Figure 1. Enriched GO terms in X-linked contracture genes. A. *P*-values of GO enrichment for X-linked genes. The enrichment significance of each GO term is presented in the graph as a negative log 10 *P*-value; the larger the bar in the graph the more significant that term. The GO terms plotted are those with a *P*-value $\leq$0.01 and containing more than one gene. In addition, the X-linked genes mapped to each category are also presented. B. Word cloud summarization of enriched GO terms for X-linked genes. The individual ontology categories in Figure 1A were submitted to www.wordle.net for generation of a word cloud. A word cloud visualizes text by increasing the size of individual words based on occurrence. The most common word is in the largest font.

Miles-Carpenter X-linked mental retardation syndrome; OMIM# 309605; Xq13–q22. Miles and Carpenter [1991] reported a four-generation family with ID compatible with X-linkage. Males were more severely affected than females. Linkage to Xq21.31 was established. Microcephaly, asymmetric face, ptosis, strabismus, short palpebral fissures, hypogonadism, and joint hypermobility were reported. Camptodactyly of the fingers and rocker bottom feet were the major congenital contractures. Fingerprints included primarily arches.

Myopathy, congenital, with fiber-type disproportion, X-linked (Clarke); OMIM# 300580; Xq13.1–q22.1. In 2005, Clarke et al. reported a family with four generations of congenital fiber type disproportion. All have bilateral ptosis, facial weakness, poor suck, week cry, generalized hypotonia, respiratory insufficiency. One surviving child developed cardiomyopathy. Female carriers showed weakness. Linkage to Xq13.1–q22.1 has been established.

Nasodigitoacoustic syndrome (Keipert); OMIM# 255980; Xq22.2–Xq28. In 1973, Keipert et al. reported male siblings with neurosensory deafness and unusual coarse facies, including prominent tented upper lip, large mouth, depressed nasal bridge, and mild hypertelorism. Ptosis may also be present and broad distal digits with contractures [Reardon and Hall, 2003; Dumic et al., 2006]. Intelligence appears to be normal [Cappon and Khalifa, 2000]. Mild pulmonary stenosis has been reported in another family [Balci and Dagli, 1996]. Female carriers appear to be spared. The condition has been mapped to Xq22.2–Xq28 [Amor et al., 2007].

Polymicrogyria, bilateral perisylvian; OMIM# 300388; Xq27.2–q28. Affected individuals present with pseudo cerebral palsy, cognitive deficiency, and bilateral perisylvian abnormalities on CNS imaging [Jansen and Andermann, 2005]. They may have diplegia of the face. Phalangeal and mastatory muscles are variably involved

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