Fetal akinesia: review of the genetics of the neuromuscular causes

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ABSTRACT

Fetal akinesia refers to a broad spectrum of disorders in which the unifying feature is a reduction or lack of fetal movement. Fetal akinesias may be caused by defects at any point along the motor system pathway including the central and peripheral nervous system, the neuromuscular junction and the muscle, as well as by restrictive dermopathy or external restriction of the fetus in utero. The fetal akinesias are clinically and genetically heterogeneous, with causative mutations identified to date in a large number of genes encoding disparate parts of the motor system. However, for most patients, the molecular cause remains unidentified. One reason for this is because the tools are now only becoming available to efficiently and affordably identify mutations in a large panel of disease genes. Next-generation sequencing offers the promise, if sufficient cohorts of patients can be assembled, to identify the majority of the remaining genes on a research basis and facilitate efficient clinical molecular diagnosis. The benefits of identifying the causative mutation(s) for each individual patient or family include accurate genetic counselling and the options of prenatal diagnosis or preimplantation genetic diagnosis. The increasing use of second-trimester ultrasound has enabled earlier detection of these cases. Diagnosis of fetal akinesia must combine assessment of clinical features and muscle morphology with genetic testing. While a pathological hallmark of congenital myotonic dystrophy and centronuclear myopathy is central nuclei, these cases of fetal akinesia may present with weakness, respiratory insufficiency and failure to gain motor milestones during the first months of life. However, a more severe phenotype with prenatal or neonatal onset and associated contractures is increasingly recognised. A study of 12 cases diagnosed as having SMA and joint

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Table 1 Summary of disease genes associated with fetal akinesia

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Genes encoding components of the neuromuscular junction

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Genes encoding adult skeletal muscle proteins

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Genes encoding fetal-expressed myostructural proteins

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Other genes

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AD, autosomal dominant; AMC, arthrogryposis multiplex congenita; AR, autosomal recessive; CC, Carney complex; CM, congenital myopathy; CMS, congenital myasthenic syndrome; CNM, centronuclear myopathy; CRM, core-rod myopathy; D, distal arthrogryposis; DM, dystrophic dystrophy; DMPK, dystrophia myotonica protein kinase; EV, Escobar variant; FADS, fetal akinesia deformation sequence; GSD-Iv, glycogen storage disease type IV; LAAHD, lethal arthrogryposis with anterior horn cell disease; LCCS, lethal congenital contracture syndrome; LMD1B, limb-girdle muscular dystrophy type 1B; MPS, multiple pterygia syndrome; MIM, Mendelian Inheritance in Man; MTM, myotubular myopathy; SMA, spinal muscular atrophy; WWS, Walker-Warburg syndrome; XL, X linked.

Contractures in at least two regions of the body found that six were homozygous for the common deletion of SMN1. These infants died by postnatal day 25. In a report of 30 cases diagnosed in utero with FADS (MIM 208150), spinal cord pathology was identified in only one case. Subsequent molecular analysis revealed homozygous deletion of SMN1. Additional cases of SMA with fetal akinesia have been reported. Devriendt et al described a patient who presented with fetal akinesia from 32 weeks’ gestation, generalised oedema and flexion contractures were present. The patient died at the age of 25 days. The patient had a homozygous deletion of SMN1 and a single copy of SMN2. Another infant born with features of FADS including micrognathia, high arched palate and multiple joint contractures showed homozygous deletion of SMN1 with only one copy of SMN2 (MIM 601627). Thus, homozygous deletions of SMN1 can cause severe forms of SMA presenting as FADS. The severe presentation in these cases may be attributed to the concurrent low SMN2 copy number.

Epidermal growth factor receptor 3 (ERBB3)

Atrophy of the anterior horn of the spinal cord is also seen in the neonatally lethal congenital contracture syndrome type 2 (LCCS2; MIM 607592) identified in two Israeli–Bedouin kindreds. Attempted cases had diminished intrauterine movement, polyhydramnios, multiple joint contractures, severe muscle wasting, micrognathia and neurogenic bladders; fetal hydrops was not a feature. All affected individuals were homozygous for an ERBB3 mutation resulting in a frameshift and premature stop codon. ERBB3 (MIM 190151) encodes the v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 3 that is a modulator of the phosphatidylinositol-3-kinase pathway. ErbB3-null mice generally die in utero. Those that develop to term are small, are immobile, fail to breathe and die shortly after birth.

mRNA export mediator GLE1 (GLE1)

Loss of motor neurons also occurs in LCCS1 (MIM 253310). This rare autosomal recessive disorder is characterised by absence of fetal movements from ~13 weeks’ gestation, accompanied by hydrops, facial abnormalities, lung hypoplasia, pterygia, multiple joint contractures and almost absent skeletal muscle. A slightly milder phenotype designated as lethal arthrogryposis with anterior horn cell disease (LAAHD; MIM 611890) is characterised by fetal akinesia, arthrogryposis and motor neuron loss. The LCCS1 locus was mapped in Finnish families to chromosome 9q34 and mutations identified in mRNA export mediator GLE1 (MIM 605371). All except one of 52 patients with LCCS1 were homozygous for a substitution in intron 5 (LCCS1 FinMajor) that creates a cryptic splice acceptor site. The remaining individual was a compound heterozygote for the FinMajor mutation and a point mutation (p.R569H). All 12 patients with the slightly milder LAAHD were compound heterozygous for GLE1 mutations. Another individual affected with arthrogryposis but with prolonged survival and originally diagnosed as having severe SMA was also found to be compound heterozygous for GLE1 mutations. Thus, LCCS1 and LAAHD are allelic disorders with homozygosity for the FinMajor mutation that results in a more severe phenotype.

Inositol hexakisphosphate has been shown to bind directly to the yeast homologue of GLE1 (Gle1). The inositol hexakisphosphate–Gle1 complex stimulates activity of a DExd/H-box protein to mediate mRNA export.

Phosphatidylinositol-4-phosphate 5-kinase, type I, gamma (PIPS5K1C)

LCCS5 (MIM 611369), also identified in Israeli–Bedouin kindreds, is a variant of LCCS2 lacking the bladder defect. Affected newborns were small with multiple contractures and severe muscle atrophy. All died of respiratory insufficiency within hours of birth. A homozygous missense mutation was identified in PIPS5K1C (MIM 605102) in all affected individuals. This enzyme is involved in the production of phosphatidylinositol-4,5-bisphosphate. Thus, LCCS2 and LCCS3 are associated with defects in the phosphatidylinositol 3-kinase pathway, and all LCCS genes are involved in inositol pathways. PIPS5K1C null mice die on the day of birth due to immobility and an inability to feed; their neurons show defects in synaptic vesicle trafficking.

Trisomy 1q

Motor neuron loss was seen in a case that presented at 29 weeks’ gestation with absent fetal movements, camptomastody and hydrops; micro/retrognathism and posterior cleft palate
diagnosed as Pierre Robin sequence (PRS). Cytogenetic analysis revealed a rearrangement consisting of direct duplication of chromosomal region 1q25.1-q31.1. Other partial 1q trisomies have been reported in cases with PRS and campodactyly. Taken together, these studies suggest that one or more dosage-sensitive genes in the 1q25 segment cause PRS and distal arthrogyrosis.22

**Ubiquitin activating enzyme 1 (UBE1)**

The severe, lethal form of X linked SMA (MIM 301830) is characterised by AMC, hypotonia, areflexia and infantile death due to respiratory insufficiency, associated with loss of anterior horn cells.23 Mutation analysis of 125 genes within the linkage region identified mutations in the **UBE1** (MIM 314570) in five of the six affected families studied. Missense mutations, M559I and S547G, were each identified in one family, while a synonymous C-to-T substitution, found to significantly reduce UBE1 expression, occurred in three families.24

**FETAL AKINESIA DUE TO MUTATIONS IN GENES AFFECTING THE PERIPHERAL NERVES**

Severe cases of congenital hypomyelination neuropathy, involving near-total amytelination of the peripheral nerves, have been associated with AMC, respiratory distress and early infant death.25 Congenital hypomyelination neuropathy can be caused by mutations in the early growth response 2 gene (**EGR2**; MIM 129010)26 and the myelin protein zero gene (**MPZ**; MIM 159440)27 and thus may represent a severe form of Dejerine–Sottas syndrome (MIM 145900), which is an early-onset motor and sensory neuropathy. None of the described hypomyelination cases with in utero presentation underwent genetic testing, however, it is plausible that some may harbour **EGR2** and **MPZ** mutations.

**FETAL AKINESIA DUE TO MUTATIONS IN GENES ENCODING COMPONENTS OF THE NMJ**

The acetylcholine receptor (AChR)

During embryonic development, the AChR is comprised of two α1, one β1, one γ and one δ subunit. After 33 weeks’ gestation, the γ subunit is replaced by the ε subunit, and this configuration of the AChR persists into adulthood (except in denervated muscle).28

AChR: α and δ subunits (**CHRNA1** and **CHRND**)

In a study of 60 families with FADS, mutations in the genes encoding the α (**CHRNA1** (MIM 100690)) and δ (**CHRND**) subunits of the AChR were identified in two families each.29 In these cases, prenatal ultrasound detected hypokinesia and growth retardation. All affected fetuses did not survive to term. Postmortem examinations revealed contractures, cedema and pterygia. Affected fetuses from one family had a homozygous missense mutation in a completely conserved residue of **CHRNA1**. In the second family, the affected fetus carried a homozygous duplication of 17 base pairs in **CHRNA1** resulting in a frameshift mutation and a subsequent premature stop codon (H25RSX19). A homozygous nonsense mutation in **CHRND** in the third family introduced a premature stop codon (H25RSX19). A homozygous nonsense mutation in **CHRND** in the δ subunit of the AChR (**CHRND**; MIM 100720).31 Expression studies revealed that the S274del mutation was a null mutation and that AChR containing the E59K mutant had slower activation times.

AChR: γ subunit (**CHRNG**)

Mutations in the gene encoding the γ subunit of the AChR (**CHRNG**; MIM 100750) are known to cause the recessively inherited prenatal lethal (MIM 253290) and non-lethal (also known as Escobar variant32; MIM 265000) forms of MPS.33–34 Mutations were identified in individuals from seven families with Escobar syndrome; five families showed consanguinity, and three of these also had a history of spontaneous abortions. In all cases, the initial presentation was reduced fetal movement. At birth, patients presented with joint contractures, multiple pterygia and facial dysmorphism (high-arched palate, long face, small mouth and retrognathia). Three nonsense mutations, one putative splice-site and one frameshift mutation were identified. These mutations are predicted to truncate major components of the γ subunit or to result in mRNA nonsense-mediated decay.35

In a separate study, mutations in **CHRNG** were identified in affected individuals from 6 of 15 families with lethal or Escobar variant MPS. In all cases, the mutations were homozygous; four of the families were known to be consanguineous.34 **CHRNG** mutations thus appear to account for ~50% of lethal and Escobar variants of MPS.35 Mutations in **CHRNG** have also been identified in affected individuals from three families diagnosed as having recessive FADS.29

Antibodies to the γ subunit of the AChR

Approximately 20% of infants of women with myasthenia gravis (MIM 254200) have transient neonatal myasthenia. However, cases in which there are maternal antibodies specific for **CHRNG** can have antenatal onset resulting in multiple joint contractures and reduced fetal movement.36

Contactin-1 (**CNTN1**)

**CNTN1** (MIM 600016) is a neural immunoglobulin-family adhesion protein expressed in the central and peripheral nervous system and at the NMJ.37 A consanguineous Egyptian family was identified with four individuals affected by an autosomal recessive lethal congenital myopathy, associated with fetal akinesia and secondary loss of β2-syntrophin and α-dystrobrevin.38 All four affected infants were found to have a homozygous duplication (c.871dupT) in **CNTN1**, causing a frameshift and premature stop codon (S291fsX296).37 Patient muscle biopsies showed significantly reduced transcript levels and abnormal contactin-1 localisation at the sarcolemma instead of exclusively at the NMJ.

**Downstream of kinase-7/muscle intrinsic activator of MUSK** (**DOK7**)

**DOK7** (MIM 610285) binds with and phosphorylates muscle skeletal tyrosine kinase (MUSK), a crucial step for AChR clustering in synaptogenesis.39 **DOK7** mutations cause CMS with limb girdle weakness40 and a recessive proximal myopathy.41

In a study of 14 families with lethal MPS or FADS and no evidence of **CHRNG**, **CHRNA1**, **CHRNB1**, **CHRND** or **RAPS** mutations, a homozygous splice-site mutation in **DOK7** was identified in a consanguineous family with three children affected with lethal FADS.35 This is consistent with the notion that, whereas partial loss of **DOK7** function will cause a CMS phenotype, complete loss of function is lethal.42

A similar model has been suggested for **RAPS** mutations.42
Nesprin-1/synaptic nuclear envelope protein-1 (SYNE1)
In a consanguineous family, two children presented with AMC at birth, following decreased fetal movements, and showed delayed motor milestones and progressive motor decline. An unaffected brother of the two affected children married a first-degree cousin, and they had two affected fetuses that at 28 and 16 weeks’ gestation showed bilateral clubfoot and reduced fetal movement; these pregnancies were terminated. Linkage analysis and fine mapping revealed a critical linkage region on 6q25. Nesprin-1 (SYNE1; MIM 608441) was the most plausible candidate gene. Sequencing revealed a homozygous substitution of the conserved AG splice-acceptor site at the junction of intron 136 and exon 137. This mutation resulted in retention of intron 136 leading to a premature stop codon.

Nesprin-1 is involved in anchoring the specialised nuclei underneath the NMJ; it is also involved in linking the nuclear skeleton to the cytoskeleton. Mice that are homozygous null for the C-terminus of nesprin-1 exhibit 50% perinatal lethality, progressive muscle wasting, muscle weakness and kyphoscoliosis.

Mutations in SYNE1 also cause autosomal recessive adult-onset spinocerebellar ataxia 8 (MIM 610745) and Emery–Dreifuss muscular dystrophy 4 (MIM 612998).

Rapsyn (RAPSN)
Rapsyn (receptor associated protein of the synapse) is involved in assembly and localisation of the AChR to the muscle membrane. Mutations in the rapsyn gene (RAPSN; MIM 601592) are a common cause of CMS (reviewed by Milone et al).

In a study of 16 patients with RAPSN-based myasthenic syndromes, 10 had AMC. All 10 patients harboured a common founder N88K substitution.

In a study of 15 families with lethal MPS or FADS in which CHRNG mutations were excluded, a homozygous RAPSN c.1177-1178delAA frameshift mutation was detected in a consanguineous family with three pregnancies affected with lethal FADS. Akinesia was detected at 19 weeks’ (twin pregnancy) and 22 weeks’ gestation; both pregnancies were terminated. The fetuses had contractures, hydrops, absent respiratory movement and craniofacial abnormalities; pterygia were absent.

RAPSN mutations were also identified in two isolated cases of non-consanguineous infants born with contractures. The first patient had distinctive facial features and repeated apnoic events. This infant was a compound heterozygote for a missense L258F mutation and an intronic mutation. The second patient presented with AMC, generalised hypotonia and similar distinctive facial features. This patient had scoliosis, moderate contractures, mild proxi and exercise-induced weakness and was found to be homozygous for a missense mutation (R164C) in RAPSN. A third family has been reported in which one fetus was aborted and two siblings were born at term with FADS, associated with compound heterozygosity for missense mutations (F159S and A189V) in RAPSN. The symptoms included severe respiratory insufficiency, contractures and craniofacial abnormalities (tented lips, micrognathia, wide nasal bridge, low-set ears and downsloping palpebral fissures).

Fetal akinesia due to mutations in genes encoding adult skeletal muscle proteins
Actin, skeletal muscle alpha (ACTA1)
Skeletal muscle α-actin is the principal protein of the skeletal muscle thin filament. Mutations in the ACTA1 gene (MIM 102610) cause a wide spectrum of congenital myopathies characterised by muscle weakness (most often severe) and one or more of the following pathological entities: actin accumulations, caps, cores, core-like areas and rods, fibre-type disproportion, intranuclear rods, nemaline bodies and zebra bodies.

Mutations in ACTA1 have been shown to account for some cases of FADS with pathological features usually associated with the congenital myopathies. A patient diagnosed as having classic Pena–Shokeir syndrome/FADS presented with reduced fetal movement, severe hypotonia at birth and respiratory insufficiency due to lung hypoplasia, requiring mechanical ventilation. The muscle biopsy showed actin accumulations and cytoplasmic and intranuclear rods. A heterozygous missense mutation was identified in ACTA1 (D154N).

Another patient with a heterozygous missense mutation (G15N) in ACTA1 presented with fetal akinesia, lung hypoplasia, reduced intrauterine growth and polyhydramnios and died 1 h postdelivery. Postmortem analysis revealed low-set ears, bilateral pes equinovarus, dysplastic thumbs, marked hirsutism, scoliosis, fractures, hyperextended feet and flexed fingers. The muscle biopsy showed accumulations of actin filaments. Other cases of ACTA1-based nemaline myopathy with fetal akinesia have also been reported.

Amphiphysin 2 (BIN1)
Mutations in BIN1 (MIM 601248) cause autosomal recessive cenronuclear myopathy (MIM 255200), a congenital myopathy characterised by centrally nucleated myofibres. In one consanguineous family, three affected fetuses presented with reduced fetal movement and oligohydramnios, lung hypoplasia, intrauterine growth retardation, contractures and centronuclear myopathy.

Dystrophia myotonica protein kinase (DMPK)
Myotonic dystrophy is caused by a trinucleotide (CTG) repeat expansion (MIM 160900). The congenital form of the disorder is associated with maternal transmission of a markedly expanded repeat, and the clinical presentation can overlap with FADS. For example, two siblings presented with polyhydramnios, intrauterine growth retardation, pulmonary hypoplasia and short umbilical cord, and died of respiratory insufficiency at 29 and 12 h of age. Reduced fetal movements were noted in the last week of both pregnancies. Muscle biopsies revealed myopathic features with small immature fibres and an excess of central nuclei, consistent with a diagnosis of congenital myotonic dystrophy. In addition, the maternal grandmother had displayed symptoms of myotonic dystrophy. Although DNA was not available for the siblings, molecular genetic analysis of the mother revealed her to be a subclinical carrier of the disease.

A study of the incidence of FADS in Denmark identified two children with characteristic symptoms of FADS and underlying congenital myotonic dystrophy. Both children died within the first 72 h of life.

Fukutin-related protein (FKRP)
FKRP (MIM 606596) is a glycosyltransferase that glycosylates the membrane protein α-dystroglycan. Mutations in FKRP cause a spectrum of muscular dystrophy—dystroglycanopathies (MDDG): the milder, later-onset limb-girdle muscular dystrophy type 2I (LGMD2I or MDDG5; MIM 607155); a congenital form with or without mental retardation (MDDG6; MIM 606612); and a more severe congenital form with brain and eye anomalies (Walker–Warburg syndrome, muscle–eye–brain disease or MDDG5; MIM 613155). Severe cases of
FKRP-related dystroglycanopathies may be associated with fetal akinesia. Two siblings, of consanguineous parents, diagnosed as having Walker–Warburg syndrome due to a homozygous start codon mutation (Met1Val), predicted to result in a null allele in FKRP, have been reported. Reduced fetal movements were identified in the first child at 34 weeks’ gestation. After birth, he exhibited severe hydrocephalus, limited spontaneous movement, and severe eye and brain abnormalities, and died at the age of 6 days due to respiratory failure. Muscle biopsy demonstrated dystrophic features. The second affected fetus was found to have severe hydrocephalus at 17 weeks’ gestation, and the pregnancy was terminated.

Lamin A/C (LMNA)

While the vast majority of fetal akinesia cases due to LMNA mutations arise due to a restrictive dermopathy, an autosomal recessive case of myopathic fetal akinesia due to a homozygous mutation in LMNA occurred in a consanguineous family. The mutation in the heterozygous form resulted in limb-girdle muscular dystrophy type 1B (MIM 159001).

Myotubularin (MTM1)

Mutations in MTM1 (300415) cause X linked myotubular myopathy (MIM 310400). Some of these cases present with reduced in utero movements and polyhydramnios, including a manifesting carrier.

Nebulin (NEB)

Mutations in the gene for the thin filament protein nebulin (NEB; MIM 161650) cause nemaline myopathy, core-rod myopathy, and distal myopathy. In a study of severe cases of nemaline myopathy due to recessive NEB mutations, affected infants displayed features characteristic of fetal akinesia including reduced fetal movement, polyhydramnios, arthrogryposis, rocker-bottom feet, talipes, cleft palate, low-set ears and a lack of spontaneous breathing. Of the six infants that survived to term, death occurred between 30 min and 19 months postbirth.

Ryanodine receptor-1 (RYR1)

The RYR1 (MIM 180901) is the voltage-gated Ca2+-release channel of the sarcoplasmic reticulum. Mutations in RYR1 have been classically associated with dominant central core disease and malignant hyperthermia; however, recent studies have shown that recessive RYR1 mutations result in a much more severe clinical phenotype associated with multiple-minicore disease, centronuclear myopathy, congenital fibre-type disproportion and congenital muscular dystrophy. In a study of seven patients from six families that presented with fetal akinesia syndrome and polyhydramnios during pregnancy with central core disease (MIM 117000), mutations in RYR1 were identified in four cases. Two cases from one family (R614C/G215E) and a separate isolated case (I4650P/K4724Q) were compound heterozygotes, while the fourth case harboured a dominant mutation (G4899E).

An isolated case born at 39 weeks’ gestation, after an uneventful pregnancy, presented with an atypical form of lethal neonatal hypotonia. The patient showed global hypotonia and immobility, feeding difficulties and mild distal arthrogryposis, without polyhydramnios or craniofacial abnormalities; the muscle biopsy demonstrated multi-minicores (MIM 180901). The patient was a compound heterozygote for a duplication (S2279dup) and a large in-frame deletion resulting in a loss of 54 of 106 exons in RYR1.

The I4898T mutation in RYR1 has been identified in several unrelated families with central core disease. Recently, this mutation, also in the heterozygous state, was identified in monzygotic twins presenting with polyhydramnios and loss of fetal movement from 27 weeks’ gestation. Both infants required intubation and ventilator support from birth; death occurred at 27 and 40 days of life. Muscle biopsies were consistent with core-rod myopathy (MIM 180901). In a cohort study of 24 patients with centronuclear myopathy, 17 harboured RYR1 mutations; of these, 11 had reduced in utero movement.

Tropomyosin, slow beta (TPM2)

Dominant mutations in β-tropomyosin (TPM2; MIM 190990) cause two congenital myopathies: nemaline myopathy and cap disease. Homozygosity for TPM2 null mutations has been identified in affected consanguineous siblings with the Escobar variant of MFS. The proband, born at term, presented with severe hypotonia and arthrogryposis, scoliosis, pes varus, distal and proximal joint contractures and multiple pterygia; the muscle biopsy showed multiple nemaline bodies. Two affected cousins had the same clinical picture.

Mutations in TPM2 can also cause distal arthrogryposes (DAs), a group of clinically and genetically heterogeneous disorders characterised by multiple congenital contractures of the limbs. Distal arthrogryposis is divided into 10 subgroups based on clinical features. Mutations in TPM2 were first associated with DA1 (MIM 108120), which is characterised by camptodactyly and clubfoot, with occasional involvement of the shoulders and hips. A TPM2 missense mutation (R135W) was identified in a mother and daughter affected with DA2B/Sheldon–Hall/variant Freeman–Sheldon syndrome (MIM 601680), the most common DA. Both were born with predominantly distal contractures and showed proximal and distal muscle weakness.

Tropomin I, fast skeletal muscle (TNNT3)

Studies of other families with dominant DA2B mapped the disease to 1p15.5. Subsequently, two different mutations (R156X and R174Q) in the gene encoding the fast skeletal muscle isoform of troponin I (TNNT2; MIM 191045) were identified in 4 of 32 kindreds diagnosed as having DA2B. A large Chinese kindred was also identified in which some affected individuals presented with DA1 and others with DA2B. Sequencing of TNNT2 revealed a 3 bp deletion in exon 8, deleting lysine residue 175 (p.K175del). Two further studies identified 3 bp deletions in TNNT2 in two separate multi-generational families, one presenting with DA1 (p.K176del) and one presenting with DA2B (p.E167del).

Tropomin T, fast skeletal muscle (TNNT3)

A study of 47 families with classical Freeman–Sheldon syndrome, characterised by striking contractures of the orofacial muscles (DA2A, ‘whistling face syndrome’; MIM 193700) or DA2B, revealed a missense mutation (R63H) in TNNT3 (MIM 600692) in a mother with DA2B and her two affected children. A subsequent study sequencing TNNT3 in 31 patients identified the same R63H mutation in one individual with DA1.

In vitro, TPM1, TNNT2 and TNNT3 DA mutations result in increased Ca2+ sensitivity of the thin filament and hence increased contractility, leading to the hypothesis that the development of DA in these cases is due to increased tension in
developing muscles resulting in contractures and limb deformities. Thus, the development of DA, in some cases, may be an active process rather than a passive one. The distal muscle groups are predominantly fast-twitch, and thus, these are the muscle groups most affected.

**FETAL AKINESIA DUE TO MUTATIONS IN GENES ENCODING FETALLY EXPRESSED MYOSTRUCTURAL PROTEINS**

Mutations in a number of genes encoding proteins that predominate in fetal life cause disorders arising from reduced fetal movement.

**Myosin heavy chain, embryonic (MYH3)**

In a study of 28 cases of DA2A and 38 cases of DA2B, mutations in the gene encoding embryonic myosin heavy chain (MYH3; MIM 160270) were found in 26 and 12 cases, respectively. In 20 of the DA2A cases, a missense mutation was found which was predicted to cause substitution of Arg674 with either cysteine or histidine. This residue is paralogous to the Arg674 residue of MYH8 that is mutated in trismus–pseudocamptodactyly syndrome (TPS). Subsequently, three further MYH3 myosin head mutations were identified in two unrelated families with DA2B and a de novo case of DA2A.

**Myosin heavy chain, perinatal (MYH8)**

A dominant mutation (c.2021G>A, p.R674Q) in the gene encoding perinatal myosin (MYH8; MIM 160741) was identified in a large family with Carney complex (a multiple neoplasia syndrome; MIM 160980) associated with TPS (MIM 158300) and two unrelated families with TPS alone. TPS, also referred to as DA7, Dutch—Kentucky or Hecht—Beals syndrome, is a rare autosomal dominant disorder characterised by inability to fully open the mouth (trismus) and an unusual camptodactyly of the fingers that is only observed upon hyperextension of the wrists.

A subsequent study of four unrelated families with TPS, including the original TPS pedigree, found that all shared the p.R674Q MYH8 mutation, but haplotype analysis showed that the mutation arose separately in North American and European families.

**Myosin binding protein C1, skeletal muscle slow type (MYBPC1)**

A study of a family with 12 members affected with DA1 revealed linkage to a region of chromosome 12q23.2 containing more than 60 genes. A candidate gene approach identified a missense mutation, p.W236R, in MYBPC1 (MIM 160794) encoding skeletal muscle myosin binding protein C1. This variant was also present in the proband’s grandfather who had bilateral clubfoot. Subsequent sequencing of MYBPC1 in 14 other patients with DA1 identified a p.Y856H substitution in one patient.

**Utrrophin (UTRN)**

A chromosome 6q duplication was identified in a patient with hypertelorism, downsloping palpebral fissures, a tented upper lip, short neck, mental retardation and joint contractures. Comparative genomic hybridisation showed that the proximal breakpoint occurred within the gene encoding utrophin (UTRN; MIM 128240) between exons 42 and 54. The authors suggested that this should result in haploinsufficiency of UTRN and that this underlies the joint contractures. Utrrophin, the fetal homologue of dystrophin, is expressed at the sarclemma of fetal skeletal muscle but becomes confined to the NMJ in mature fibres. Another case showing a 6q23-q25.1 duplication that would have involved either disruption or an increased copy number of UTRN presented with severe arthrogryposis/FADS, while patients with 6q duplication syndrome with proximal duplications not encompassing UTRN do not show arthrogryposis. Thus, alterations involving UTRN are likely to underlie the arthrogryposis associated with some cases of 6q duplication syndrome. However, it must be noted that SYNE1 also lies within the reported 6q duplicated region. Recessive SYNE1 mutations cause arthrogryposis.

**FETAL AKINESIA ASSOCIATED WITH OTHER GENES**

**Fibroblast growth factor receptor 2 (FGFR2)**

Fibroblast growth factors have multiple roles in human morphogenesis acting via receptors including FGFR-2. FGFR-2 is expressed in mesenchymal and epithelial cells and is important in multiple phases of limb development. FGFR2 (MIM 176943) gain of function mutations cause craniosynostosis syndromes, which can manifest limb anomalies including pterygia. A fetus with features consistent with fetal akinesia, including multiple pterygia, with an FGFR2 c.1019A>G, p.Y340C mutation has been reported. There were additional dysmorphic and skeletal findings consistent with an FGFR-2 related craniosynostosis. Prenatally detected pterygia have not been otherwise reported with FGFR2 mutations; thus, ‘double trouble’ genetic and/or environmental factors are likely to have been involved in the described case.

**Glycogen branching enzyme (GBE1)**

Glycogen storage disease type IV (MIM 232500) is a clinically heterogeneous autosomal recessive disorder arising from GBE deficiency and results in the accumulation of amylopectin-like polysaccharides. The typical form involves liver disease in childhood that progresses to lethal cirrhosis. The neuromuscular form varies in age of onset and severity. The perinatal form presents as FADS characterised by AMC, hydrops and perinatal death. Compound heterozygous or homozygous mutations in GBE1 (MIM 607839) underlie the FADS form of glycogen storage disease type IV.

**CONCLUSIONS**

Despite recent identification of multiple genes for fetal akinesia, the vast majority of cases are without a molecular diagnosis. Most cases of this heterogeneous group of disorders are isolated or from small families. Whole exome sequencing of cohorts of well-characterised patients is the most promising way forward to improve diagnosis, through the identification of novel loci, and to analyse the known genes in further patients. For example, whole exome sequencing of DNA from only two isolated cases recently lead to the identification of the causative gene for Fowler syndrome (MIM 225790), a rare form of prenatally lethal fetal akinesia. Clinicians and researchers should ideally collect detailed data on all undiagnosed patients with FADS—including prenatal scans, autopsy findings (including muscle and neuropathology) and DNA—to enable and facilitate diagnosis and gene discovery for these conditions. Targeted capture and next-generation sequencing of known disease genes already offer the possibility of affordable analysis of multiple disease genes in clinical diagnosis. The potential of whole exome sequencing will be crucial to identifying the unknown genetic bases of fetal akinesia.

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