Review Article

Prenatal diagnosis and genetic analysis of fetal akinesia deformation sequence and multiple pterygium syndrome associated with neuromuscular junction disorders: A review

Chih-Ping Chen a,b,c,d,e,f,g,*

a Department of Medicine, Mackay Medical College, New Taipei City, Taiwan
b Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
c Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan
d Department of Biotechnology, Asia University, Taichung, Taiwan
e School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
f Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
g Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan

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Abstract

Fetal akinesia deformation sequence is a clinically and genetically heterogeneous disorder characterized by a variable combination of arthrogryposis, fetal akinesia, intrauterine growth restriction, developmental abnormalities such as cystic hygroma, pulmonary hypoplasia, cleft palate, cryptorchidism, cardiac defects and intestinal malrotation, and occasional pterygia of the limbs. Multiple pterygium syndrome is a clinically and genetically heterogeneous disorder characterized by pterygia of the neck, elbows and/or knees, arthrogryposis, and other phenotypic features such as short stature, genital abnormalities, craniofacial abnormalities, clubfoot, kyphoscoliosis, and cardiac abnormalities. Fetal akinesia deformation sequence may phenotypically overlap with the lethal type of multiple pterygium syndrome. This article provides a comprehensive review of prenatal diagnosis and genetic analysis of fetal akinesia deformation sequence and multiple pterygium syndrome associated with neuromuscular junction disorders. Prenatal diagnosis of fetal akinesia along with cystic hygroma, increased nuchal translucency, nuchal edema, hydrops fetalis, arthrogryposis, pterygia, and other structural abnormalities should include a differential diagnosis of neuromuscular junction disorders. Genetic analysis of mutations in the neuromuscular junction genes such as CHRNA1, CHRND, CHRNG, CNTN1, DOK7, RAPSN, and SYNE1 may unveil the pathogenetic cause of fetal akinesia deformation sequence and multiple pterygium syndrome, and the information acquired is helpful for genetic counseling and clinical management.

Keywords: CHRNA1; CHRND; CHRNG; CNTN1; DOK7; fetal akinesia deformation sequence; multiple pterygium syndrome; prenatal diagnosis; RAPSN; SYNE1

Introduction

Fetal akinesia deformation sequence (FADS; OMIM 208150) is a clinically and genetically heterogeneous disorder characterized by a variable combination of arthrogryposis, fetal akinesia, intrauterine growth restriction (IUGR), developmental abnormalities such as cystic hygroma, pulmonary hypoplasia, cleft palate, cryptorchidism, cardiac defects and intestinal malrotation, and occasional pterygia of the limbs [1–5]. In a retrospective population-based study in Denmark, Bayat et al [6] reported that the incidence of FADS was 1:15,000. FADS was originally reported by Pena and Shokeir [1] and Lindhout et al [3] to describe a disorder called Pena–Shokeir syndrome consisting of the symptoms of IUGR, polyhydramnios, facial dysmorphism, pulmonary hypoplasia,
a short umbilical cord, and supplementary symptoms of cleft or high-arched palate and bell-shaped chest. The pathogenetic mechanisms of FADS include neuropathy, muscular disorders, neuromuscular junction (NMJ) disorders, maternal myasthenia gravis, restrictive dermopathy, and others [5,7–12]. FADS may phenotypically overlap with the lethal type of multiple pterygium syndrome (LMPS; OMIM 253290). Multiple pterygium syndrome (MPS) is a clinically and genetically heterogeneous disorder characterized by pterygia (webbing) of the neck, elbows and/or knees, arthrogryposis (joint contractures), and other phenotypic features such as short stature, genital abnormalities, craniofacial abnormalities, clubfoot, kyphoscoliosis, and cardiac abnormalities [13–15]. MPS can occur in autosomal-recessive [12,16–18], autosomal-dominant [19], or X-linked-dominant [20] transmission.

**Genetic analysis of mutations in the genes associated with NMJ in fetuses with FADS/MPS**

FADS and/or MPS have been reported to be caused by mutations in the genes associated with NMJ such as CHRNA1 (OMIM 100690), CHRN* (OMIM 100720), CHRNA (OMIM 100730), RAPSN (OMIM 601592), DOK7 (OMIM 610285), CNTN1 (OMIM 600016), and SYNE1 (OMIM 608441).

**CHRNA1**

CHRNA1, CHRNB1 (OMIM 100710), CHRN* D, CHRNA, and CHRND (OMIM 100725) encode the acetylcholine receptor (AChR) subunits of α1, β1, δ, γ, and ε, respectively. The AChR of fetal type consists of α1 (two) subunits and one of each β1, δ, and γ subunits, whereas the AChR of adult type consists of two α1, β1, δ, and ε subunits because of replacement of the fetal γ subunit by the adult ε subunit after 33 weeks of gestation [21–23]. Heterozygous mutations of CHRNA1 can cause autosomal dominant congenital slow-channel myasthenic syndrome (OMIM 601462) and congenital fast-channel myasthenic syndrome (OMIM 608930). Homozygous mutations of CHRNA1 have been reported to cause autosomal-recessive LMPS [12]. Michalk et al [12] reported two male sib fetuses in a consanguineous German family with LMPS and compound heterozygous mutations of c.234 G→A in CHRNA that predicts W57X in mature protein or W78X in precursor. Both fetuses were terminated at 15 weeks of gestation and manifested IUGR, edema, cystic hygroma, decreased movements, and joint contractures. One fetus additionally showed cystic hygroma, muscle hypoplasia, scoliosis, contractures, pectus excavatum, broad ribs and clavicles, and pterygia. Michalk et al [12] also reported five sib fetuses in a non-consanguineous German family with LMPS and compound heterozygous mutations of c.283 T→C or c.1390C→T in CHRNA that predict F74L/R443X in mature protein or F95L/R464X in precursor. The first female fetus was delivered at 23 gestational weeks with neonatal death, generalized edema, a depressed nasal bridge, low-set ears, a big atrial septal defect, lung hypoplasia, hydrothorax, and ascites. The second female fetus was terminated at 19 gestational weeks with cystic hygroma, joint contractures, faciocranial dysmorphism, hypertelorism, a depressed nasal bridge, micrognathia, low-set ears, contractures, pterygia, rocker-bottom feet, lung hypoplasia, hydrothorax, pericardial effusion, and shortened ribs. The third male fetus was terminated at 12 gestational weeks with cystic hygroma, decreased movements, joint contractures, contractures, and pterygia. The fourth male fetus was terminated at 13 gestational weeks with IUGR, cystic hygroma, decreased movements, joint contractures, micrognathia, low-set ears, contractures, and pterygia. The fifth male fetus was terminated at 19 gestational weeks with IUGR, edema, cystic hygroma, joint contractures, faciocranial dysmorphism, down-slanting palpebral fissures, a depressed nasal bridge, micrognathia, low-set ears, contractures, and pterygia.

**CHRNG**

Homozgyous and compound heterozygous mutations in CHRNG have been reported to cause autosomal-recessive Escobar syndrome (OMIM 265000) and LMPS [18,24]. Morgan et al [18] reported two sibs of different sex in a consanguineous Arab family with LMPS and a homozygous missense mutation of c.320 T→G in CHRNG that predicts p.Val107Gly. The sister died at age 3 months because of congenital heart disease, and the brother died at age 3 days because of lung hypoplasia. Morgan et al [18] also reported a male fetus in a consanguineous Turkish family with LMPS and a homozygous frameshift mutation of c.753_754delICT in...

RAPSN

The RAPSN gene encodes a postsynaptic protein that functions as a link between AchR and the agrin-binding dystrophin-associated glycoprotein complex to stabilize AchR at the NMJ [25]. Homozygous or compound heterozygous mutations in RAPSN can cause autosomal recessive FADS and congenital myasthenic syndrome associated with AchR deficiency (OMIM 608931). Michalk et al [12] reported two sibs of different sex with FADS in a non-consanguineous Pakistani family. The sibs were born at term with severe respiratory problems, inborn contractures, down-slanting palpebral fissures, mild hypertelorism, a wide nasal bridge, low-set ears, micrognathia, a small mouth, tented lips, a short broad neck, subcutaneous edema, hypoplastic lungs, abnormal posture, hyperextension of the extremities, a small thorax, no respiratory movements, hypotonia, delayed motor milestones, and progressive motor decline after the first decade. In that family, a brother of affected children married his first cousin who had two pregnancies that manifested bilateral clubfeet and decreased fetal movements at 28 and 16 weeks of gestation in the first and second fetuses, respectively.

CNTN1

The CNTN1 gene encodes a neural adhesion and NMJ protein that is restricted to the NMJ and function for NMJ adhesion [27]. Homozygous mutations in CNTN1 can cause severe fetal akinesia and Compton—North congenital myopathy (OMIM 612540). Compton et al [27] identified a homozygous 1-bp duplication (c.871dupT) in exon 8 of CNTN1 that results in a frameshift and premature truncation (S291fsX296) within the third Ig domain and predicts a nonsense-mediated mRNA decay.

SYNE1

The SYNE1 gene encodes a synaptic nuclear envelope protein 1 or nesprin 1. Nesprin 1 anchors specialized myonuclei underneath NMJ, binds lamin A and emerin, and interacts with the cytoplasmic domain of MuSK [28–31]. Mutations in SYNE1 can cause autosomal-recessive spinocerebellar ataxia 8 (OMIM 610743), autosomal-dominant Emery—Dreifuss muscular dystrophy 4 (OMIM 612998), and autosomal-recessive myogenic arthrogryposis multiplex congenita [32]. Attali et al [32] identified homoygosity for an acceptor site mutation 2-bp 5’ to exon 137 in SYNE1 (IVS136-2 A > G) that predicts retention of intron 136 in mRNA and generates a premature stop codon and loss of the C-terminal transmembrane KASH domain in a two-generation consanguineous family with arthrogryposis, decreased fetal movements, hypotonia, delayed motor milestones, and progressive motor decline after the first decade. In that family, a brother of affected children married his first cousin who had two pregnancies that manifested bilateral clubfeet and decreased fetal movements at 28 and 16 weeks of gestation in the first and second fetuses, respectively.

Prenatal diagnosis of FADS/MPS by ultrasound and magnetic resonance imaging

Prenatal diagnosis of reduced or absent fetal movements in association with abnormal fetal posture should include
a differential diagnosis of spina bifida, trisomy 18, arthrogryposis, FADS, fetal constraint, body stalk anomaly, caudal regression sequence, fetal hypoxia/severe hypotonia, amniotic bands, fetal neck masses, joint dislocations, vertebral segmentation abnormalities, iniencephaly, and MPS [33]. Fetal akinesia/arthrogryposis can result from primary defects of brain, spinal cord, peripheral nerves, NMJ, skeletal musculature and connective tissues, vascular compromise, restricted intruterine space, teratogenic exposures, ischemia, maternal illness, and circulating maternal antibodies to neurotransmitters, myelin, and muscle proteins [34,35]. Fetal akinesia can be detected by prenatal ultrasound as early as 12 weeks of gestation [36]. Prenatal ultrasound findings of fetal akinesia/arthrogryposis include lack of extremity motions, persistent abnormal posture of the limbs, lack of facial movements, polyhydramnios due to decreased fetal swallowing, pulmonary hypoplasia, a short umbilical cord due to decreased fetal movements, IUGR, increased nuchal translucency, nuchal edema or cystic hygroma in the first trimester, and hydrops fetalis [36–65]. Fetal magnetic resonance imaging can be a useful adjunct to prenatal ultrasound in evaluating central nervous system findings [62,65]. The abnormal neurological magnetic resonance imaging findings include agenesis of the corpus callosum, lissencephaly, hydrocephalus, and spinal cord abnormalities [37]. Prenatal ultrasound findings of Escobar MPS include small stature, multiple pterygia of neck, axillae, elbows and knees, micrognathia, digital hypoplasia, camptodactyly, syndactyly, and scoliosis [66]. Prenatal ultrasound findings with LMPS include IUGR, flexion contractures of the limbs, multiple extensive pterygia, cystic hygroma, hydrops, and hydroplastic lungs [67–77].

In summary, this article provides a comprehensive review of prenatal diagnosis and genetic analysis of FADS/MPS associated with NMJ disorders. Prenatal diagnosis of fetal akinesia along with cystic hygroma, increased nuchal translucency, nuchal edema, hydrops fetalis, arthrogryposis, pterygia, and other structural abnormalities should include a differential diagnosis of NMJ disorders. Genetic analysis of mutations in the genes associated with NMJ may unveil the pathogenetic cause of FADS/MPS, and the information acquired is helpful for genetic counseling and clinical management.

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References


