SYNDROMES AND DISORDERS ASSOCIATED WITH OMPHALOCELE (III): SINGLE GENE DISORDERS, NEURAL TUBE DEFECTS, DIAPHRAGMATIC DEFECTS AND OTHERS

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SUMMARY
Omphalocele can be associated with single gene disorders, neural tube defects, diaphragmatic defects, fetal valproate syndrome, and syndromes of unknown etiology. This article provides a comprehensive review of omphalocele-related disorders: otopalatodigital syndrome type II; Melnick-Needles syndrome; Rieger syndrome; neural tube defects; Meckel syndrome; Shprintzen-Goldberg omphalocele syndrome; lethal omphalocele-cleft palate syndrome; cerebro-costo-mandibular syndrome; fetal valproate syndrome; Marshall-Smith syndrome; fibrochondrogenesis; hydrocephalus syndrome; Fryns syndrome; omphalocele, diaphragmatic defects, radial anomalies and various internal malformations; diaphragmatic defects, limb deficiencies and ossification defects of skull; Donnai-Barrow syndrome; CHARGE syndrome; Goltz syndrome; Carpenter syndrome; Toriello-Carey syndrome; familial omphalocele; Cornelia de Lange syndrome; C syndrome; Elejalde syndrome; Malpuech syndrome; cervical ribs; Sprengel anomaly, anal atresia and urethral obstruction; hydrocephalus with associated malformations; Kennerknecht syndrome; lymphedema, atrial septal defect and facial changes; and craniosynostosis-mental retardation syndrome of Lin and Gettig. Perinatal identification of omphalocele should alert one to the possibility of omphalocele-related disorders and familial inheritance and prompt a thorough genetic counseling for these disorders. [Taiwan J Obstet Gynecol 2007;46(2):111–120]

Key Words: congenital malformation, diaphragmatic hernia, genetics, neural tube defect, omphalocele, single gene disorder

Introduction
Omphalocele can be associated with single gene disorders, neural tube defects, diaphragmatic defects, fetal valproate syndrome, and syndromes of unknown etiology. A comprehensive review is provided as follows.

Otopalatodigital Syndrome-Spectrum Disorders
Otopalatodigital (OPD) syndrome-spectrum disorders include four phenotypically related conditions: OPD type I, OPD type II (OPD2), frontometaphyseal dysplasia, and Melnick-Needles syndrome (MNS). These conditions are characterized by anomalous ossification, and skeletal patterning of the axial and appendicular skeleton [1]. The extra skeletal malformations of OPD syndrome-spectrum disorders include hydrocephalus, encephalocele, cleft palate, cardiac defects,
omphalocele, and obstructive uropathy. Of note, omphalocele most commonly occurs in males with OPD2 and MNS. Typical OPD2 and MNS have mutations in the FLNA gene [1]. OPD-spectrum disorders are X-linked, with more severe expression in males [1]. Prenatal diagnosis of male fetuses with omphalocele and multiple malformations involving the bones, palate, heart, brain, urinary tracts and digits should be accompanied by genetic counseling of maternal and fetal OPD-spectrum disorders.

**OPD2**

OPD2 (OMIM 304120) is characterized by craniofacial, skeletal, visceral, brain, auditory and palatal defects. The skeletal dysplasia includes hypomineralized calvaria, pronounced skull base sclerosis, thoracic hypoplasia, campomelia, and patterning anomalies of the hands and feet [1]. The extraskelatal anomalies include hydrocephalus, hearing loss, craniofacial dysmorphism, cerebellar hypoplasia, obstructive uropathy, cardiac defects, and omphalocele [1]. Most affected males die in the perinatal period or infancy, and the survivors suffer from neurodevelopmental delay [1]. The female carriers usually manifest a subclinical bony dysplasia and facial dysmorphism and may occasionally manifest more severe phenotype [1]. OPD2 is caused by gain-of-function mutations in the FLNA gene [2]. FLNA (OMIM 300017) encodes filamin A, which is an actin-binding protein that regulates reorganization of the actin cytoskeleton by interacting with integrins, transmembrane receptor complexes, and second messengers. Loss-of-function mutations in FLNA result in embryonic death in males and periventricular nodular heterotopia (OMIM 300049), a localized neuronal migration disorder, in females. Omphalocele can be a major identifiable defect in cases with OPD2. Stillman et al first described the association of omphalocele with OPD in a male infant [3]. Riconda et al reported of a mother with mild expression of OPD2 and her two sons with fetal OPD2 and omphalocele that led to neonatal death [4]. The first pregnancy had abnormal prenatal sonographic findings, and the male fetus had cleft lip and palate, omphalocele, and abnormal positioned fingers. In the second pregnancy, prenatal ultrasound at 22 gestational weeks revealed a male fetus with marked bowing of the long bones, marked frontal bossing with micrognathia, and omphalocele. Young et al reported the prenatal sonographic diagnosis of omphalocele in three male fetuses with OPD2 [5]. Of these three fetuses with OPD2 and omphalocele, two were associated with polyhydramnios. Blanchet et al reported a male fetus with OPD2 and multiple congenital anomalies reported in MNS, such as omphalocele, hypospadias, thoracic dysplasia, skeletal abnormalities, and pulmonary hypoplasia [6]. They suggested that OPD2 and MNS belong to the same spectrum of malformations due to mutations in the same X-linked gene. Eccles et al reported the prenatal ultrasound findings of shortening and bowing of the lower legs and forearms, a large midline palate, micrognathia, and an anterior abdominal wall defect in a male fetus with OPD2 [7]. Robertson et al found that four in four patients with both OPD2 and omphalocele had a missense mutation occurring in exon S of FLNA [2]. Katz et al, however, did not find any mutations in exon S of FLNA in 179 omphalocele cases and suggested that mutations in FLNA are not common causes of isolated omphalocele and omphalocele associated with multiple anomalies [8].

**Melnick–Needles syndrome**

Melnick–Needles syndrome (MNS; OMIM 309350) is characterized by widely spaced and prominent eyes, severe micrognathia, omphalocele, urethral obstruction, hypoplastic kidneys, bowing of long bones, positional deformities of the hands and feet, long digits, cervicothoracic kyphosis, thoracolumbar lordosis, ribbon-like ribs, and thoracic hypoplasia. Embryonic or perinatal lethality occurs in affected males, and affected females have facial dysmorphism, thoracic hypoplasia, pronounced irregularity of the long bones, short stature, and long digits [1,9]. MNS is caused by gain-of-function mutations in the FLNA gene [2]. Theander and Ekberg first described the association of omphalocele with MNS and reported a male infant with omphalocele and skeletal changes of MNS born to a 27-year-old mother with osteodysplasty and MNS [10]. von Oeyen et al reported that a woman with MNS gave birth to a male infant with MNS, omphalocele, hypoplastic kidneys, and skeletal dysplasia [11]. Donnenfeld et al reported a male fetus with MNS, decreased calvarial mineralization, omphalocele, oligohydramnios, prune belly sequence, urethral atresia, megacystis, tetralogy of Fallot, atrophicventricular canal defects, complete malrotation of the gut, mandibular hypoplasia, bowed irregular long bones and ribs who was born to a woman with MNS [9].

**Rieger Syndrome**

Rieger syndrome (OMIM 180500) is an autosomal dominant disorder characterized by craniofacial abnormalities, malformation of the anterior chamber of the eye, hypodontia (partial anodontia), and abdominal wall defects (including a spectrum ranging from an elongated umbilical stump to omphalocele). Both haploinsufficiency and gain-of-function mutations in...
a homeobox transcription factor gene, PITX2 (OMIM 601542), cause Rieger syndrome [12,13]. PITX2 is a member of the Pitx family of genes that encode paired-type bicoid-related homeobox-containing proteins which are transcription factors that play an important role in development [14]. Studies in mice revealed that Pitx2 knockout mice manifested failure of ventral wall closure, and the heterozygotes demonstrated variable findings of patent umbilical rings, failure of ventral body wall closure, and evisceration of abdominal wall defects [14–17]. Reddihough et al first reported the association of omphalocele with Rieger syndrome [18]. They described a family in which the father and two sons had characteristic ocular and dental findings of Rieger syndrome, and two affected members, the father and the older son, had a history of omphalocele being repaired shortly after birth. The birth prevalence of omphalocele is significantly higher in Rieger syndrome than in the general population (4.3% vs. 0.03%) [8]. Katz et al suggested that mutations in PITX2 may be rare causes of omphalocele [8]. Perinatal identification of omphalocele in association with craniofacial abnormalities, anterior chamber anomalies, and dental anomalies should be considered in the diagnosis of Rieger syndrome.

**Omphalocele and Neural Tube Defects**

Calzolari et al proposed that omphalocele and neural tube defects (NTDs) are related congenital anomalies by the findings of a tendency for omphalocele to be associated with anencephaly and/or spinal bifida [19]. Folate-related genes play an important part in the susceptibility to NTDs. In particular, the thermolabile variant of methylenetetrafolate reductase, MTHFR 677C → T, has been shown to be a risk factor of NTDs. Mills et al found a significant association between MTHFR 677C → T and omphalocele [20]. They hypothesized that folate-related genes play a role in the etiology of omphalocele and suggested that folic acid-containing multivitamins may prevent omphalocele.

**Meckel Syndrome**

Meckel syndrome (MKS) is a lethal, autosomal recessive disorder characterized by occipital encephalocele, bilateral renal cystic dysplasia, hepatic ductal proliferation, fibrosis and cysts, and polydactyly. There are three types of MKS: MKS1 (OMIM 249000), MKS2 (OMIM 603194), and MKS3 (OMIM 607361). Genetic heterogeneity of MKS has been established by three reported MKS loci, i.e. MKS1 on 17q23, MKS2 on 11q13, and MKS3 on 8q21.13–q22.1. MKS1 (OMIM 609883) encodes a component of flagellar apparatus basal body proteome which is associated with ciliary function [21]. MKS3 (OMIM 609884) encodes meckelin (OMIM 609884), a seven-transmembrane receptor protein [22]. The identification of the MKS1 and MKS3 genes makes molecular genetic testing possible for at-risk families and allows for accurate genetic counseling, carrier testing, and prenatal diagnosis. The MKS triad of occipital encephalocele, postaxial polydactyly, and bilateral enlarged multicystic kidneys can be diagnosed before the 14th gestational week by ultrasonography [23,24]. But later in pregnancy, severe oligohydramnios may make the diagnosis of polydactyly and encephalocele difficult. Omphalocele may occasionally be associated with MKS. Su et al reported prenatal sonographic findings of omphalocele, encephalocele, bilateral renal cystic dysplasia, polydactyly, microcephaly, intrauterine growth restriction, and oligohydramnios at 23 gestational weeks in a fetus with MKS [25].

**Shprintzen–Goldberg Omphalocele Syndrome**

Shprintzen–Goldberg omphalocele syndrome (OMIM 182210) is an autosomal dominant disorder characterized by dysmorphic faces, omphalocele, laryngeal and pharyngeal hypoplasia, spinal anomalies, and learning disabilities. Shprintzen and Goldberg first described this condition in a father and three daughters [26]. Zelante et al reported another case of Shprintzen–Goldberg omphalocele syndrome in a 6-year-old boy with omphalocele, imperforate anus, feeding impairment, scoliosis, and abnormal facial appearance [27]. Strenge et al observed that a microdeletion at 22q11.2 can produce a phenotype resembling Shprintzen–Goldberg omphalocele syndrome [28].

**Lethal Omphalocele-Cleft Palate Syndrome**

Lethal omphalocele-cleft palate syndrome (OMIM 258320) was first described by Czeizel in three children of normal unrelated parents [29]. The first daughter died at the age of 2 months with omphalocele, posterior cleft palate, and uterus bicornis. The second daughter died at the age of 4 months with omphalocele, uvula duplex, and hydrocephalus internus. The third daughter died at the age of 1 year with omphalocele, and cleft palate.
Cerebro-Costo-Mandibular Syndrome

Cerebro-costo-mandibular syndrome (CCMS; OMIM 117650) is characterized by Pierre Robin anomaly, speech difficulties, severe micrognathia with glossoptosis, a small thorax with rib-gap defect, and the occasional occurrence of intellectual impairment. CCMS has an autosomal recessive pattern, and in some cases there is parent-to-child transmission, suggesting an autosomal dominant inheritance of this disorder. James and Afitos reported an infant and her father with typical features of CCMS [30]. The child was diagnosed on prenatal ultrasound with the findings of omphalocele, cystic hygroma, cleft palate, and micrognathia. Early prenatal diagnosis of CCMS is possible by the sonographic detection of increased nuchal translucency, cystic hygroma, severe micrognathia, polyhydramnios, a narrow chest with rib abnormalities and/or omphalocele [30–34]. Postnatal confirmatory diagnosis of CCMS can be made by skeletal X-rays, autopsy or a positive family history.

Fetal Valproate Syndrome

Prenatal valproic acid exposure is known to be associated with myelomeningocele, open spina bifida (i.e. sacral or lumbo-sacral spina bifida), congenital heart defects, preaxial ray reduction defects, myopia, limb deformities, and occasionally, umbilical hernias and omphalocele [35]. Ong et al reported omphalocele in rats exposed to calcium valproate in utero [36]. Boussemart et al reported typical dysmorphic features of the fetal valproate syndrome and omphalocele in a newborn baby who was exposed to valproic acid in utero [37].

Marshall–Smith Syndrome

Marshall–Smith syndrome (OMIM 602535) is a disorder of unknown etiology characterized by accelerated skeletal maturation, relative failure to thrive, respiratory difficulties, mental retardation, a prominent forehead, shallow orbits, blue sclerae, a depressed nasal bridge, and micrognathia. Omphalocele has been noted to be an occasional anomaly associated with Marshall–Smith syndrome [38].

Fibrochondrogenesis

Fibrochondrogenesis (OMIM 228520) is a lethal autosomal recessive disorder characterized by rhizomelic chondrodysplasia, broad long-bone metaphyses, pear-shaped vertebral bodies, microscopic changes of cartilage with unique interwoven fibrous septa, and fibroblastic dysplasia of chondrocytes. Omphalocele and hydrops have been noted to be associated with fibrochondrogenesis [39].

Hydrolethalus Syndrome

Hydrolethalus syndrome (OMIM 236680) is an autosomal recessive disorder caused by mutations in the HYLS1 gene [40]. Hydrolethalus syndrome is characterized by polyhydramnios, lethality, postaxial polydactyly of the hands, preaxial polydactyly of the feet, micrognathia, cleft lip and palate, cardiac septal defects, and hydrocephaly with absent midline structure of the brain, but without cystic kidneys, hepatic ductal plate malformations or encephalocele [40,41]. Omphalocele has been noted to be occasionally associated with hydrolethalus syndrome [41]. Christensen et al reported two sibs (one male and one female) with anencephaly, median cleft lip, omphalocele, and preaxial polydactyly, suggesting the diagnosis of the acrocallosal syndrome or hydrolethalus [42]. The family history was consistent with autosomal recessive inheritance.

Fryns Syndrome

Fryns syndrome (OMIM 229850) is associated with congenital diaphragmatic hernia (CDH), pulmonary hypoplasia, brachytelephalangy, craniofacial dysmorphism, orofacial clefting, and malformations of internal organs [43]. Fryns syndrome has an autosomal recessive inheritance pattern. However, Slavotinek et al performed array-based comparative genomic hybridization in 29 probands with CDH and mapped four CDH-critical regions on chromosomes 15q26.2, 8p23.1, 4p16.3, and 1q41–q42 [44,45]. Arnold et al reported omphalocele in a case with Fryns syndrome [46]. Omphalocele has been noted to be an occasional anomaly associated with Fryns syndrome [47].

Omphalocele, Diaphragmatic Defects, Radial Anomalies and Various Internal Malformations

Gershoni-Baruch et al first reported a syndrome with radial ray defects, omphalocele, and diaphragmatic hernia [48]. Bird et al reported the recurrence of diaphragmatic agenesis in association with multiple midline defects in two sibs [49]. The first sib had CDH, absent left radius and digits 1 and 2, abnormal pulmonary sequestration, and vascular and renal malformations.
The second sib had omphalocele, left diaphragmatic defect, abnormal lung lobulation, and an accessory spleen. Winter suggested a syndrome of diaphragmatic defects and multiple midline defects [50]. Lin et al reported omphalocele, absence of radii, hypoplasia of one humerus, a hemivertebra, and syndactyly in a stillborn male with diploid-triploid mixoploidy at 22 gestational weeks [51]. Devriendt et al reported omphalocele, scoliosis, and radial ray defect of the right arm in a newborn girl and suggested a syndrome with key manifestations including omphalocele, radial anomalies, diaphragmatic defects, and various internal malformations [52]. Pivnick et al reported an infant with a midline thoracoabdominal syndrome, a deficiency of the right lower limb, and ectrodactyly [53]. Uygur et al reported pentalogy of Cantrell, and limb defects [54]. Chen et al reported a fetus with pentalogy of Cantrell, hypoplasia of the right upper limb, and ectrodactyly [55]. The cases reported by Pivnick et al [53], Uygur et al [54] and Chen et al [55] provide evidence for the concurrence of pentalogy of Cantrell and limb defects and imply a syndrome with involvement of the genes responsible for limb morphogenesis and fusion of the sternum in the syndrome.

Diaphragmatic Defects, Limb Deficiencies and Ossification Defects of Skull

The syndrome of diaphragmatic defects, limb deficiencies, and ossification defects of skull (OMIM 601163) is an autosomal recessive disorder with malformations including diaphragmatic defects, hypoplastic lungs, omphalocele, limb deficiencies, syndactyly of toes, and ossification defects of the skull [56].

Donnai–Barrow Syndrome

Donnai–Barrow syndrome (OMIM 222448) is an autosomal recessive disorder characterized by diaphragmatic defects, omphalocele, absence of corpus callosum, hypertelorism, myopia, and sensorineural deafness [57]. Omphalocele is a frequent clinical feature of Donnai–Barrow syndrome [57–60].

CHARGE Syndrome

CHARGE syndrome (OMIM 214800) is an autosomal dominant disorder. The mnemonic term CHARGE describes the features of this syndrome:
- C—coloboma of the eye;
- H—heart defects;
- A—atresia of the choanae;
- R—retardation of mental and somatic development;
- G—genital anomalies; and
- E—ear anomalies with abnormal pinnae or hearing loss.

Mutations involving the chromodomain helicase DNA-binding protein-7 (CHD7) (OMIM 608892) are found in two of three cases with CHARGE syndrome [61]. CHARGE syndrome can also be caused by mutations in the semaphorin-3E gene (SEMA3E) (OMIM 608166). Omphalocele has been noted to be an occasional anomaly associated with CHARGE syndrome [62].

Goltz Syndrome

Goltz syndrome or focal dermal hypoplasia (OMIM 305600) is an X-linked dominant disorder with in utero lethality in hemizygous males. Goltz syndrome is characterized by poikiloderma with focal dermal hypoplasia, syndactyly, and dental anomalies. There may be ocular anomalies such as coloboma of the iris and choroids, strabismus and microphthalmia, and mental retardation. Omphalocele has been noted to be an occasional anomaly associated with Goltz syndrome [63].

Carpenter Syndrome

Carpenter syndrome or acrocephalopolysyndactyly type II (OMIM 201000) is an autosomal recessive disorder characterized by acrocephaly, syndactyly, polydactyly, congenital heart defects, mental retardation, hypogenitalism, cryptorchidism, obesity, umbilical hernia, omphalocele, and bony abnormalities [64].

Toriello–Carey Syndrome

Toriello–Carey syndrome (OMIM 217980) is likely an autosomal recessive disorder characterized by agenesis of corpus callosum, Pierre Robin sequence, and short palpebral fissures. Various hernias, such as inguinal hernia, umbilical hernia, hiatal hernia and gaping umbilicus, have been reported to be associated with Toriello–Carey syndrome [65].

Familial Omphalocele

Cases with familial omphalocele (OMIM 164750, 310980) have been reported. Kanagawa et al presented a family with nine subjects affected with omphalocele.
in three generations and concluded that an autosomal dominant gene was responsible for omphalocele [66]. Pryde et al described a woman with five consecutive pregnancies complicated by omphalocele as an isolated defect and emphasized the heterogeneity of omphalocele [67]. In a genetic-epidemiologic study of omphalocele and gastroschisis, Yang et al concluded that non-syndromic omphalocele best fits an autosomal recessive model [68]. Havalad et al reported the familial occurrence of omphalocele in a family with four affected males in two generations and suggested an X-linked inheritance of this disorder [69].

**Cornelia de Lange Syndrome**

Cornelia de Lange syndrome (OMIM 122470) is characterized by a distinctive facial appearance, malformation of the upper limbs, physical and mental retardation, gastroesophageal dysfunction, cardiac, ophthalmologic and genitourinary anomalies, and hirsutism. Most cases occur as a new autosomal dominant mutation in the NIPBL gene [70,71]. However, X-linked Cornelia de Lange syndrome caused by mutations in the SMC1L1 gene has been reported [72]. Lemire first described omphalocele in a fetus with Cornelia de Lange syndrome and the prenatal sonographic findings of an abdominal wall defect, intrauterine growth restriction, pleural effusions, a two-vessel umbilical cord, and bilateral clubfeet [73]. He suggested that omphalocele may be an associated feature of Cornelia de Lange syndrome.

**C Syndrome**

C syndrome or Opitz trigonocephaly syndrome (OMIM 211750) is characterized by trigonocephaly, mental retardation, a typical facial appearance, redundant skin, joint and limb abnormalities, and visceral abnormalities [74]. C syndrome has been assumed to be an autosomal recessive disorder. However, various reports suggest that C syndrome is a heterogeneous condition with a chromosomal imbalance, e.g. del(3)(q27–qter) [75], dup(3)(q23–qter)/del(3)(p25–pter) [76], trisomy of 3pter [77], de novo balanced reciprocal translocation t(3;18)(q13.13;q12.1) [78], del(2)(p25–pter)/dup(17)(q24–qter) [79], partial trisomy and tetrasomy 13 [80], and del(9)(q34.3) [81]. Omphalocele has been reported to be a clinical manifestation of C syndrome [82–84]. Interestingly, omphalocele can also be associated with dup(3q) [85–91]. The phenotypic overlap between C syndrome and dup(3q) syndrome suggests a role of chromosome 3 in the pathogenesis of omphalocele and trigonocephaly.

**Elejalde Syndrome**

Elejalde syndrome or acrocephalopolydactylous dysplasia (OMIM 200995) is an autosomal recessive disorder characterized by a high birth weight, a swollen globular body with thick skin, short limbs, craniosynostosis, acrocephaly, a short neck with redundant skin folds, postaxial polydactyly, omphalocele, an abnormal face, enlarged liver and kidneys, ascites, and cystic renal dysplasia. Omphalocele has been reported to be associated with Elejalde syndrome, organomegaly, and ascites [92,93]. Sihlanova et al postulated that Elejalde syndrome is related to an inactivating FGFR gene mutation [94].

**Malpuech Syndrome**

Malpuech syndrome or Malpuech facial clefting syndrome (OMIM 248340) is an autosomal recessive disorder characterized by growth and mental retardation, cleft lip and palate, hypertelorism, ptosis of eyelids, caudal appendage, renal agenesis, undescended testes, and micropenis. Omphalocele and umbilical hernia have been reported to be associated with Malpuech syndrome. Guion-Almeida reported omphalocele or umbilical hernia in patients with Malpuech syndrome [95]. Crisponi et al reported umbilical hernia in a boy with Malpuech syndrome [96]. Reardon et al reported umbilical hernia or omphalocele in two sibs with clinical features of Malpuech syndrome and Juberg-Hayward syndrome [97].

**Cervical Ribs, Sprengel Anomaly, Anal Atresia and Urethral Obstruction**

Frydman et al described omphalocele in a male infant born of first-cousin parents in a family with the syndrome of cervical ribs, Sprengel anomaly, anal atresia and urethral obstruction (OMIM 601389) and suggested X-linked dominant transmission in some affected males with severe manifestations [98].

**Hydrocephalus with Associated Malformations**

As described by Game et al, four fetuses, from a family with hydrocephalus and associated malformations, had
growth retardation, hydrocephalus, micrognathia, hypoplastic multilobed lungs, intestinal malrotation, omphalocele, shortness of lower limbs, bowed tibias, foot deformities, and other defects (OMIM 236640) [99]. The authors suggested autosomal recessive inheritance of this disorder.

Kennerknecht Syndrome

Kennerknecht et al first reported the syndrome of agonadism associated with multiple internal malformations (OMIM 202660) in two phenotypic sisters with the karyotypes of 46,XY and 46,XX [100]. The two phenotypic sisters had similar internal malformations including agonadism, hypoplasia of the right pulmonary artery, hypoplasia of the right lung, isolated dextrocardia with complex cardiac malformation, and either diaphragmatic hernia or omphalocele. Kennerknecht et al further reported the syndrome of agonadism, XY chromosomal constitution, mental retardation, short stature, retarded bone age, and multiple extragenital malformations (OMIM 600908) in two phenotypic sisters with a karyotype of 46,XY [101]. The older sister had omphalocele, right renal agenesis, and malrotation of the colon. Kennerknecht et al suggested autosomal recessive inheritance of these disorders [101]. In addition, Silengo et al reported the Kennerknecht syndrome in a 46,XX girl and her 46,XY sister with agonadism [102].

Lymphedema, Atrial Septal Defect and Facial Changes

Irons et al reported the syndrome of lymphedema, atrial septal defect, and facial changes (OMIM 601927) in a family and suggested autosomal recessive inheritance of this disorder [103]. The two brothers had congenital lymphedema of the lower limbs, atrial septal defect, and a similar facial appearance, and the sister had hydrops fetalis, atrial septal defect, omphalocele, and other anomalies.

Craniosynostosis-Mental Retardation Syndrome of Lin and Gettig

Lin and Gettig reported the craniosynostosis-mental retardation syndrome of Lin and Gettig (OMIM 218649) in two brothers born to non-consanguineous parents [104]. The malformations of the syndrome include midline craniosynostosis, agenesis of the corpus callosum, severe mental retardation, an unusual facial appearance of small downsllanting palpebral fissures, ptosis, strabismus, a long hypoplastic philtrum, short columella and thin lips, contractures, camptodactyly, hypoplasia, hypogonadism, small omphalocele, and multiple small bowel atresias. Hedera and Innis reported a third case of the craniosynostosis-mental retardation syndrome of Lin and Gettig in a boy with a small umbilical hernia and suggested autosomal recessive inheritance of this disorder [105].

Conclusion

This article provides a comprehensive review of omphalocele-related disorders. Perinatal identification of omphalocele should alert one to the possibility of omphalocele-related disorders and familial inheritance and prompt a thorough genetic counseling for these disorders.

References


