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Genetic causes of congenital diaphragmatic hernia

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Abstract

Congenital diaphragmatic hernia (CDH) is a moderately prevalent birth defect that, despite advances in neonatal care, is still a significant cause of infant death, and surviving patients have significant morbidity. The goal of ongoing research to elucidate the genetic causes of CDH is to develop better treatment and ultimately prevention. CDH is a complex developmental defect that is etiologically heterogeneous. This review summarizes the recurrent genetic causes of CDH including aneuploidies, chromosome copy number variants, and single gene mutations. It also discusses strategies for genetic evaluation and genetic counseling in an era of rapidly evolving technologies in clinical genetic diagnostics.

Keywords

Congenital diaphragmatic hernia; Copy number variants; Gene; Genomics; Syndromes

1. Introduction

Congenital diaphragmatic hernia (CDH) occurs in 1 in 3000 live births, accounting for 8% of all birth defects and 1–2% of infant mortality, making it one of the most prevalent and lethal congenital anomalies [1–3]. The diaphragm develops during the 4th–8th week of gestation, and the hernia is thought to occur when the pleuroperitoneal folds and septum transversum fail to converge and fuse. Posterior lateral hernias (Bodaleck) account for >95% of neonatal diagnoses with 85% occurring on the left side [1,4]. Anterior retrosternal or parasternal CDHs (Morgagni) account for ~2% of all CDH cases. Other rare types of hernias include an anterior hernia often associated with Pentalogy of Cantrell and a central hernia which involves a defect in the central tendon. Diaphragm eventration resulting from incomplete muscularization of the diaphragm is also included within the spectrum of CDH. Approximately 50–80% of CDHs are diagnosed in the prenatal period when the liver and intestines are visualized in the chest with a malpositioned heart. CDH may occur as an

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isolated defect, but ~40% of CDH cases are non-isolated and have at least one additional anomaly [5,6]. The most frequent co-occurring defect is congenital heart disease (CHD) which is present in ~20% of patients [4,6]. Birth defects of all other systems have also been described in CDH cases. In some cases, the constellation of birth defects is associated with a specific syndrome and may provide insight into the genetic etiology. More than 50 different genetic causes have been associated with CDH, most in non-isolated cases, but, increasingly, genetic etiologies are being identified in isolated CDH cases. We review the most widespread chromosomal and monogenetic causes with CDH as a recognized feature.

2. Genetics

2.1. Chromosomal

Complete or mosaic chromosome aneuploidies, large chromosome deletions/duplications, and complex chromosome rearrangements identifiable by karyotype are present in 10–35% of CDH cases and occur at greatest frequency in non-isolated, prenatally diagnosed cases [2,6–11]. An additional 3.5–13% of cases without identifiable karyotype abnormalities have copy number variants (CNVs) including microdeletions or microduplications identifiable by chromosome microarray analysis, which offers higher resolution over a standard karyotype [12–20]. Aneuploidies and CNVs are associated with increased neonatal mortality [12,18].

Aneuploidies, CNVs and cytogenetic rearrangements involving almost all chromosomes have been described with CDH. Holder et al. published an exhaustive review of all reported cases of chromosome anomalies in CDH [21], and chromosome microarray analysis has expanded our understanding of recurrent CNVs associated with CDH. We briefly review the aneuploidies associated with CDH and provide a more detailed discussion of recurrent CNVs. A complete list of all recurrent and newly reported CNVs is available in Supplementary Table S1.

2.2. Aneuploidies

The most prevalent aneuploidy associated with CDH, trisomy 18, occurs in ~2–5% of CDH cases [2,7]. CDH has also been infrequently described in trisomy 13, which accounts for <1% of CDH cases [2,7,10]. Down syndrome is the most frequently occurring aneuploidy identified in children with a Morgagni hernia [22]. Other aneuploidies infrequently described with CDH include trisomy 9 [23], trisomy 16 [24], trisomy 22 [25], mosaic trisomy 2 [15], and mosaic trisomy 8 [7]. Sex aneuploidies including Turner syndrome (45,X) [10] and trisomy X (46,XXX) [6] have also rarely been described with CDH. With the exception of the sex aneuploidies, complete aneuploidies are often diagnosed prenatally or in the neonatal period by the presence of associated birth defects and dysmorphic features.

2.3. Copy number variants

2.3.1. Tetrasomy 12p, Pallister–Killian syndrome (OMIM: 601803)—Pallister–Killian syndrome (PKS), or mosaic tetrasomy 12p, is one of the more widespread chromosome disorders associated with CDH. PKS is caused by mosaic isochromosome 12p. Whereas the isochromosome is detectable by karyotype, PKS can be a difficult molecular

diagnosis to make as the isochromosome 12p does not culture in standard blood (lymphocytes) and is usually only found in a karyotype of cells from amniocentesis, buccal swab, or skin biopsy [26]. Up to 50% of PKS cases have a CDH, and PKS accounts for ~2–5% of CDH cases [27]. Other common features of PKS include central nervous system (CNS) anomalies, shortened limbs, coarse facial features, and some degree of intellectual disability.

2.3.2. 8p23.1 deletion syndrome (OMIM: 222400)—The 8p23.1 deletion syndrome accounts for 3–5% of CDH cases [12,16,28]. A CDH is present in ~50% of cases and almost all cases have CHD. Additional anomalies include CNS anomalies, dysmorphic facial features, intellectual disability, and autism. The critical region for CDH is 3.7 Mb encompassing base pairs 8,079,861–11,860,569 (hg19) [28]. This region includes two genes, *GATA4* and *SOX7*, which have been implicated in the development of the diaphragm. *GATA4* is a transcription factor important in heart and diaphragm development. Heterozygous knockout mice have diaphragm defects [29]. The activation and expression of *GATA4* is influenced by retinoids [30], and the retinoid signaling pathway is well known to be involved in diaphragm development [31]. Both inherited and de-novo mutations in *GATA4* have been identified in isolated cases of CDH and of CDH with CHD [32]. *SOX7* is also a transcription factor, and *SOX7* knockout mice have anterior CDH [28,33].

2.3.3. 15q26.1 deletion syndrome (OMIM: 142340)—The 15q26.1 deletion syndrome is associated with CDH and accounts for 1–2% of CDH cases [12,17,19]. This syndrome is associated with a broad spectrum of features including dysmorphic facial features, intrauterine growth restriction (IUGR), skeletal and digit anomalies, genitourinary abnormalities, imperforated anus, CHD, CNS anomalies, hypotonia, and behavior problems. CDH is estimated to occur in ~10–30% of cases [34,35]. The critical region for CDH is a 1.8 Mb deletion encompassing base pairs 97,898,996 to 99,682,477 (hg19) [35]. *COUP-TFII* is a CDH candidate gene in this region. *COUP-TFII* encodes a transcriptional factor of the steroid/thyroid hormone receptor superfamily and is a downstream target of retinoid signaling [36]. Conditional knockout *COUP-TFII* in the gastric mesenchyme in mice results in CDH [37].

2.3.4. 1q41–42 deletion syndrome (OMIM: 612530)—The 1q41–42 deletion syndrome is associated with CDH in 30% of cases [38]. Other associated anomalies include CNS anomalies, seizures, intellectual disability, cleft palate, dysmorphic features, hypoplastic nails, club feet, and contractures of the limbs [38]. It accounts for ~1–3% of CDH cases [14,16,19]. A 4.7 Mb deletion encompassing base pairs 219,914,853 to 224,637,114 (hg19) [39] is the critical region for CDH. *DISP1* and *HLX* are candidate CDH genes. A de-novo mutation in *DISP1* was recently described in a child with CDH, VSD, cleft lip and palate, tethered cord, and hypotonia [40]. *HLX* knockout mice have CDH [41]. Missense variants in *HLX* have been described in four cases of isolated CDH [39].

2.3.5. 8q23.1 deletions—Large (>30 Mb) de-novo deletions as well as small inherited microdeletions (0.7–1 Mb) of 8q23.1 have been described in association with CDH [8,16,42]. The smallest microdeletion was a 700 kb deletion from base pairs 106,800,200–

107,511,467 (hg19) [16] associated with IUGR and neonatal death, inherited from an apparently healthy mother. A paternally inherited 1 Mb deletion at 8p23.1 was associated with eventration and intestinal malrotation [16]. Patients with larger deletions have additional anomalies including IUGR, shortened limbs with contractures, and dysmorphic facial features [8,42]. The *ZFPM2/FOG2* gene is located at 8q23.1 and encodes a multi-zinc-finger transcriptional protein that regulates the expression of the GATA target genes [43]. It is a co-repressor for both *COUP-TFII* and *GATA4* in the retinoid signaling pathway [44]. A mouse model with a hypomorphic *ZFPM2/FOG2* allele has diaphragmatic defects [45]. De-novo and inherited autosomal dominant mutations in *ZFPM2/FOG2* have been associated with isolated CDH, and CDH with CHD, and may account for up to 5% of the genetic causes of CDH [45–47].

2.3.6. 4p16 deletion, Wolf–Hirschhorn syndrome (OMIM: 194190)—The 4p16 deletion which causes Wolf–Hirschhorn syndrome (WHS) is infrequently reported with CDH. Structural birth defects including CNS, cardiac, renal, or limb defects and CDH typically occur only in children with 4p16 deletions >5 Mb [48]. Other features of WHS include characteristic facial features of a ‘Greek warrior helmet’ with high forehead, hypertelorism, high arched eyebrows, micrognathia with downturned corners of the mouth, intellectual disabilities, and growth delay.

2.3.7. 11q23.2 duplications—Partial trisomy 11, resulting from the unbalanced translocations 11;22(q23.3;q11.2) [49], 11;12 (q23.3;q24.3) [50], and less frequently 11;13(q23.2;q12.3) [51], has been associated with CDH. Additional anomalies include CNS anomalies, polydactyly, growth retardation and dysmorphic facial features.

2.3.8. Other recurrent CNVs—Several other microdeletion/microduplication syndromes have rarely been associated with CDH. The 16p11.2 deletion/duplication is an autism susceptibility locus associated with a wide spectrum of neurocognitive manifestations. There have been several cases of CDH reported with the 16p11.2 deletion [16,17,52]. The 17q12 deletion was first identified to be associated with renal cysts, maturity onset diabetes of the young, and variable developmental delay. It has also been identified in several isolated CDH cases [12,16].

2.4. Single gene mutations

Mutations in >20 different genes have been described in both syndromic and non-syndromic CDH. This review will focus on syndromes with defined genetic bases. A complete list of all reported monogenetic etiologies associated with CDH is available in Supplementary Table S2.

2.5. Autosomal recessive

2.5.1. Donnai–Barrow syndrome (OMIM: 600073)—Donnai–Barrow syndrome (DBS)/facio-oculo-acoustico-renal (FOAR) is due to autosomal recessively inherited mutations in *LRP2* [53]. CDH occurs in >50% of DBS/FOAR cases [54]. Other features of DBS/FOAR syndrome include agenesis of the corpus callosum, developmental delay, enlarged anterior fontanel, myopia, hypertelorism, sensorineural hearing loss, and

omphalocele. Low molecular weight proteinuria with elevated levels of retinol binding (RBP) and vitamin-D-binding proteins (DBP) is a cardinal feature [53]. *LRP2* encodes megalin which is an endocytic transmembrane receptor that interacts with the sonic hedgehog (SHH) signaling pathway [55].

2.5.2. Matthew–Wood syndrome (OMIM: 6011186)—Matthew–Wood syndrome (MWS) is an autosomal recessive condition caused by mutations in *STRA6* [56] and *RARB* [57]. MWS is associated with microphthalmia to anophthalmia, IUGR, cardiac and renal anomalies. Many cases of MWS have a diaphragm defect which ranges from complete agenesis to eventration of the diaphragm [56,58,59]. *STRA6* belongs to a novel group of retinoic-acid-inducible genes [60]. Patients with MWS have also been found to have homozygous mutations in *RARB* [57]. *RARB* is one of a family of transcriptional transducers of the retinoid signaling pathway, and compound knockout mice of the *RARB* and *RARA* genes have diaphragm defects [61].

2.5.3. Cutis laxa (OMIM: 219100 and 613177)—Cutis laxa is a group of disorders characterized by loose and/or wrinkled skin. Some cases involve other body systems including the pulmonary, gastrointestinal, urinary, muscular and skeletal systems. Two cases of cutis laxa with CDH and other features including pulmonary artery stenosis, diverticulosis with tortuosity of the intestinal tract, joint laxity, hypotonia, and dysmorphic features were caused by autosomal recessive mutations in *LTBP4* [62]. A patient with cutis laxa and CDH associated with a homozygous mutation in *EFEMP2/FBLN4* has also been described [63].

2.5.4. Spondylocostal dysostosis (OMIM: 277300)—Spondylocostal dysostosis is within the spectrum of Jarcho–Levin syndrome and is characterized by multiple segmental defects of the vertebrae with additional features including short stature, kyphoscoliosis, respiratory compromise due to small chest size and infrequently CDH. One patient with spondylocostal dysostosis with CDH and homozygous *DLL3* mutations has been described [64].

2.5.5. Other rare autosomal recessive conditions associated with CDH—There is a single case of isolated CDH with an 86 kb deletion at 9p22.3 encompassing *FREMI* and a splice mutation in the other copy of *FREMI* [65]. This child had no features of the FREM1-related syndromes, which include bifid nose with anorectal and renal anomalies.

2.6. Autosomal dominant

2.6.1. WT1-opathies (OMIM: 194080)—Autosomal dominant mutations in *WT1* are associated with a spectrum of syndromes referred to as WT1-opathies. Denys–Drash syndrome (DDS) is the most common WT1-opathy associated with CDH [66]. DDS is associated with disorder of sexual development including retention of Müllerian structures and undervirilization of external genitalia in males and duplicated uterus and cervix in females as well as structural defects of the kidneys, progressive glomerulopathy, and predisposition to Wilms tumors. Up to 30% of DDS patients have CDH [66]. DDS is associated with mutations in the DNA binding sites of *WT1* [67,68]. CDH has also been infrequently described in association with other WT1-opathies including Meacham [69],

Frasier syndrome [70], and WAGR (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation) [71]. *WT1* encodes for a zinc-finger-containing protein which is involved in the retinoic acid signaling pathway. *WT1* knockout mice have defects of the diaphragm [72].

2.6.2. Cornelia de Lang syndrome (OMIM: 122470)—Cornelia de Lang syndrome (CdLS) is characterized by specific dysmorphic facial features including microbrachycephaly, highly arched eyebrows with synophrys and long eyelashes, anteverted nose with a long philtrum and thin upper lip with downturned corners of the mouth. Associated defects may include CHD, limb defects, IUGR, intellectual disability as well as CDH. Mutations in *NIPBL* are the most common known cause of CdLS, and several cases of CdLS with CDH have been described with *NIPBL* mutations [73,74]. The *NIPBL* gene encodes a protein that is essential for segregation of homologous chromosomes during meiosis I and for repair of DNA double-strand breaks during G2 phase of mitosis [75].

2.6.3. Marfan syndrome (OMIM: 154700)—Marfan syndrome is an autosomal dominant connective tissue disorder caused by mutations in *FBN1*. CDH is not a feature of the classic presentation of Marfan syndrome, but several rare cases of severe neonatal Marfan syndrome have been associated with CDH [76–78]. Whereas classic Marfan syndrome is often inherited from an affected parent, neonatal Marfan syndrome is caused by de-novo mutations, typically in exons 24 and 25 of *FBN1* [79].

2.6.4. Other rare autosomal dominant conditions associated with CDH—One or more cases of the following autosomal dominant conditions have all been described with CDH: Kabuki syndrome with a mutation in *KMT2D/MLL2* [80], Baller–Gerold/Saethre–Chötzen with a mutation in *TWIST* [81], Apert syndrome with craniosynostosis and an *FGFR2* mutation [82], SHORT syndrome with a *BMP4* mutation [83], tuberous sclerosis type 2 with a *TSC2* mutation [84], Beckwith–Wiedemann syndrome with a paternally inherited der(4)t(4;11)(q33;p14) [85], C-trigonocephaly [86], and multiple pterygium syndrome [87] without identified causes.

2.7. X-linked

2.7.1. Craniofrontonasal syndrome (OMIM: 304110)—Craniofrontonasal syndrome (CNFS) is an X-linked condition caused by mutations in *EFNB1* characterized by coronal craniosynostosis, hypertelorism, bifid nasal tip, frontal bossing, scoliosis, and skeletal anomalies of the thorax and clavicles. Paradoxically, females are typically more severely affected than males. Several cases of CNFS with CDH have been described [88–90]. Both affected males and females have been reported with CDH. *EFNB1* encodes a member of the ephrin family of ligands. The eight ephrins are involved in cell migration and motility by interacting with adhesion proteins or altering cytoskeletal organization [91–93].

2.7.2. Simpson–Golabi–Behmel (OMIM: 312870)—Simpson–Golabi–Behmel (SGB) is an X-linked condition caused by mutations in *GDS* characterized by pre- and postnatal macrosomia, syndactyly and polydactyly, pectus excavatum, club feet, vertebral anomalies, CHD and cardiac arrhythmias, renal anomalies, developmental delay and a predisposition to

the development of embryonal tumors including Wilms tumor and hepatoblastoma. Several cases of SGB with *GPC3* mutations have been described, and in one series CDH occurred in 18% (5/28) [94,95]. The GPC3 protein is one of six glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycans that function as cell surface receptors and modulate cellular responses to growth factors and other morphogens including fibroblast growth factors, bone morphogenetic proteins, and members of the SHH and Wnt gene families [96].

2.7.3. Focal dermal hypoplasia (OMIM: 305600)—The X-linked recessive condition focal dermal hypoplasia, also called Goltz–Gorlin, is caused by mutations in *PORCN* and is characterized by dermal linear pigmentation, fat herniation through skin, and ocular, digit, and teeth abnormalities. Several cases with CDH have been described [97–99]. *PORCN* encodes an endoplasmic reticulum transmembrane protein involved in processing of Wnt proteins [100]. A single case of Lowe syndrome caused by a mutation in *OCRL1* was associated with CDH, cataracts, learning difficulties, rickets, poor growth, and seizures [101].

2.7.4. Syndromes with unknown genetic etiologies—Fryns syndrome (OMIM: 229850) is a common clinical diagnosis for CDH cases associated with multiple congenital anomalies usually including dysmorphic features and limb defects. Some cases have been associated with CNVs associated with CDH (15q26.2, 1q41, 1q25). All modes of inheritance have been described, but no genes have been associated with Fryns syndrome, suggesting that it may be genetically heterogeneous. Gershoni–Baruch [102] and X-linked thoracoabdominal syndrome [103] have also been described to include CDH, but the molecular etiology of these conditions is unknown.

2.8. Non-syndromic single gene mutations

In addition to single gene mutations in *GAT4*, *ZFPM2/FOG2*, and *DIPS1*, other rare single gene mutations have also been reported with CDH. *GATA6* mutations have been described in CDH cases with and without CHD [104]. *MYH10* mutations have been identified in two children with CDH. One child had an apparently isolated CDH and passed away in the neonatal period, and the other child had multiple congenital anomalies and intellectual disability [105]. It is anticipated that, with recent advances in comprehensive genomic sequencing technology, additional genes will be identified in both isolated and non-isolated CDH, providing further insight into this genetically heterogeneous condition.

2.9. Multifactorial

Currently the cause of ~80% of CDH cases remains unknown, demonstrating our limited understanding of the genetic etiologies of CDH as well as suggesting non-genetic, non-Mendelian, or multifactorial etiologies for CDH. A multifactorial inheritance and the possibility of epigenetic influences in CDH is supported by monozygotic twin studies showing, in one case series, 100% (5/5) discordance for CDH [7]. Studies of other birth defects such as CHD have suggested an oligogenic etiology [106] whereby multiple genetic variants all contribute to a developmental defect. Finally, although no specific environmental factor has clearly been associated with CDH, the well-described involvement of retinol signaling pathway in diaphragm development raises the question of whether

maternal retinol may affect the risk of CDH. One study of nine CDH cases found lower levels of retinol and retinol-binding protein (RBP) in cases compared to their unaffected siblings, and the mothers of affected children had significantly higher levels of retinol and RBP than mothers of children without CDH [107].

2.10. Genetic evaluation and counseling

The identification of a genetic cause for the CDH provides important information about prognosis, management, and recurrence risk, and therefore a complete genetic evaluation including a physical examination, family history, and chromosome microarray is warranted for all cases of CDH. A karyotype in fibroblasts should be completed if PKS is suspected. Prenatally, families should be offered an amniocentesis since non-invasive methods such as cell-free fetal DNA do not provide a comprehensive genetic characterization.

Single gene analysis should be completed as indicated by the associated birth defects, dysmorphic features or family history. Presently, there is no laboratory offering testing for a panel of genes associated with CDH, though this may be available in the future. An alternative to the gene-by-gene genetic evaluation is whole exome sequencing (WES). Recent studies have demonstrated the effectiveness of WES to detect genetic causes in CDH [104]. WES analyses should include the affected individual and both parents to increase the probability of identifying de-novo genetic events. As the turnaround time for clinical WES improves, this may provide an important part of the evaluation of newborns with CDH.

In addition to providing information about the prognosis and care of the affected fetus/child, identification of the genetic etiology provides definitive information about the recurrence risk for the family. Recurrence risk is estimated to be ~2% in families with no known family history in whom the genetic etiology is unknown [108,109]. When an inherited genetic cause is identified, the recurrence is dependent on the specific pattern of inheritance of the condition. A de-novo genetic cause has a <1% recurrence risk. It is important to note that several of the autosomal dominant forms of CDH have been associated with reduced penetrance [32,47,104]. When the molecular etiology is identified, families can pursue prenatal testing or preimplantation genetic diagnosis for future pregnancies.

Even with a complete genetic evaluation, a cause will not be identified for the majority of CDH cases. A negative genetic evaluation in the absence of a family history of CDH is reassuring. Although we do not yet know all the monogenetic causes of CDH, a negative evaluation decreases the risk of recurrence.

3. Conclusion

It is clear that there is significant heterogeneity in the cause of CDH and that we are in a period of rapid expansion of our knowledge of the genetic causes of CDH. As we define the spectrum of genes associated with CDH, we will be able to define common molecular causes of CDH and define the clinical syndromes associated with these genes to inform prognosis and guide treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Practice points

- Aneuploidies and chromosome copy number variants are present in 10–35% of CDH cases and are more frequent in non-isolated cases.
- More than 20 different monogenetic disorders are associated with CDH.
- A complete genetic evaluation is appropriate for all CDH cases and has the potential to provide information about prognosis, management, and recurrence risk.

Research directions

- Comprehensive genomic characterization of large numbers of patients with both isolated and non-isolated cases of CDH will be necessary to identify the full spectrum of genes and mutations causing CDH to facilitate future clinical genetic testing.