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Review

Genetic causes of congenital diaphragmatic hernia

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SUMMARY

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.

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 hernias (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 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 genetic etiologies are increasingly 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

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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. While the isochromosome is detectible 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 to 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 mouse 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 to 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 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.