Genetic Diagnostic Strategies and Counseling for Families Affected by Congenital Diaphragmatic Hernia

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Abstract

Congenital diaphragmatic hernia (CDH) is a relatively common and severe birth defect with variable clinical outcome and associated malformations in up to 60% of patients. Mortality and morbidity remain high despite advances in pre-, intra-, and postnatal management. We review the current literature and give an overview about the genetics of CDH to provide guidelines for clinicians with respect to genetic diagnostics and counseling for families. Until recently, the common practice was (molecular) karyotyping or chromosome microarray if the CDH diagnosis is made prenatally with a 10% diagnostic yield. Undiagnosed patients can be reflexed to trio exome/genome sequencing with an additional diagnostic yield of 10 to 20%. Even with a genetic diagnosis, there can be a range of clinical outcomes. All families with a child with CDH with or without additional malformations should be offered genetic counseling and testing in a family-based trio approach.

Keywords
- CDH
- genetic counseling
- genetic testing
- variant
- recurrence risk

Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly affecting 2 to 3 per 10,000 live births.[1] There has been a slight increase in CDH prevalence over time,[1] and mortality has been decreasing with advancements in clinical management but still remains as high as 20%.[2] CDH is a developmental defect of the diaphragm, the skeletal muscle involved in respiration and gastrointestinal transit that divides the thoracic and the abdominal cavity.[3] Its main tissue components are myofibers and connective tissue.[4] The phenotypic spectrum of CDH is variable, ranging from diaphragmatic eventration to localized defects to complete agenesis of a hemidiaphragm. Most defects (~80%) occur on the left side, fewer on the right side and rarely bilateral.[5] The pathophysiology of CDH includes compression of intrathoracic organs during fetal development by herniated abdominal viscera that leads to lung hypoplasia with abnormalities of pulmonary structures and pulmonary hypertension. This results in dilatation and insufficiency of the right ventricle and subsequent respiratory and cardiac failure.[5] CDH can present as the only structural anomaly or in association with one or more anomalies.[6,7] Associated anomalies can be diverse and affect different organ systems. Most frequent are cardiac defects, malformations of the urogenital system, the central nervous system, musculoskeletal system, limb malformations, and gastrointestinal anomalies.[1,8] CDH is also a feature of some distinct clinical

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syndromes with known monogenic causes. Patients with associated malformations are referred to as "complex CDH" or "non-isolated CDH" in contrast to patients without associated anomalies, referred to as "isolated CDH." Long-term morbidity of surviving CDH patients can be related to the developmental defect itself or to the required treatment and includes poor growth, feeding problems, developmental delay, behavioral problems, chronic lung disease, gastroesophageal reflux, chest asymmetry, and sensorineural hearing loss.[9–11]

Diaphragm Development and CDH

Animal models have been instrumental for our understanding of diaphragm development. Around E8.5 in mice, myoblast progenitors from the cervical somites (C3 to C5) migrate to transient mesenchymal structures called pleuroperitoneal folds. They are guided to the pleuroperitoneal folds by muscle connective tissue fibroblasts.[12] Next, myoblast and other mesenchymal cells[13] migrate to and from the posthepatic mesenchymal plate and subsequently these structures fuse with the septum transversum between E12.5 and E13.5[13,14] forming a primordial diaphragm around E14.5. In CDH patients, this process is disturbed, and the diaphragm does not fully close.[15,16] Decreased proliferation, increased apoptosis as well as migration and differentiation defects of progenitor cells are proposed mechanisms underlying CDH.[12,17–19] Implicated biological processes include retinoic acid signaling and muscle connective tissue formation.[12,20–23]

Diagnostic Course, Morbidity, and Mortality

In approximately 50% of patients, the diagnosis of CDH is made prenatally, and in countries with prenatal ultrasound screening programs in up to 74%.[24] As soon as the diagnosis CDH in a fetus is suspected, the expecting mother should be referred to a center with expertise for further evaluation. This typically includes a comprehensive ultrasound examination and/or fetal magnetic resonance imaging to detect additional anomalies and determine the size of the diaphragmatic defect and lung volume.

Prenatal predictors for survival and clinical outcome can be determined and include organ position,[25–27] defect size,[28] lung volume,[29] lung-to-head ratio,[30,31] and the presence of associated malformations.[1,32] Postnatal predictors are birth weight and Apgar score. Survival is also decreased in patients with persistent pulmonary hypertension and bronchopulmonary sequestration.[33,34] Clinical predictors can be combined in several prediction tools.[35–38]

Genetic counseling with careful evaluation of the family history is strongly recommended. Asymptomatic small diaphragm defects or eventration may be present in family members. Prenatal assessment also includes an amniocentesis to screen for genetic anomalies, mostly by karyotype or, superior in diagnostic yield, chromosome microarray analysis. In 6 to 10% of cases, chromosomal anomalies can be detected.[24,39] A detectable chromosomal anomaly is more commonly associated with nonisolated CDH and/or an underlying genetic syndrome, and sometimes leads to the detection of associated anomalies which have been overlooked. If a typical combination of associated malformations suggests a specific syndrome, gene panel testing can also be performed. The results of all prenatal investigations are integrated for families to make a decision about expectant management, fetal intervention, or pregnancy termination.[40]

However, not all anomalies can be diagnosed prenatally, so a diagnosis of isolated CDH can only be confirmed after birth and only after several months for neurodevelopmental disorders. Syndromic clinical characteristics that are nonspecific are described in 7.7% of patients.[8] Often, these are not major associated malformations and require meticulous evaluation by a dysmorphologist or clinical geneticist. If the chromosomal analysis is nondiagnostic, further genetic testing can be offered. This can be targeted panel sequencing of known CDH-associated genes or exome/genome sequencing, preferably a parent/child trio approach to identify de novo genetic alterations. Damaging de novo genetic alterations in isolated and complex CDH are associated with higher mortality, persistent pulmonary hypertension, and worse neurodevelopmental outcome.[32] These de novo pathogenic changes are seen more often in complex CDH.[41–43] However, determining the contribution of individual de novo genetic alterations not previously implicated in CDH and the predicted phenotype remains a challenge.

Most Frequent Genetic Alterations Associated with CDH

The exact contribution of genetic factors to the etiology of CDH is challenging to determine. CDH has been described to segregate within families, although most cases are sporadic.[7,44] Further complicating heritability estimates are the historically impaired reproductive fitness and the relatively low disease incidence.[44,45] Different types of genetic variants are associated with CDH. These include aneuploidies,[32,39,46–49] copy number variations (CNVs), and single nucleotide variants.[39,50–52] There are many (over 150) genes and over 80 CNVs associated with CDH, mostly from animal models or monogenic syndromes.[4,49,50,53] However, not many patients share the same affected gene or locus.[41–43] These genes and loci have been comprehensively reviewed elsewhere,[43,53] and the more frequent findings are summarized below in ►Tables 1 and 2. Somatic mosaicism is not a major contributor.[54,55] In contrast, de novo variants in the germline can usually be detected in blood.[32,54–56] Constrained coding regions are enriched for de novo variants[57] and diagnostic yields of at least 20% are feasible depending on the technology used to determine the genetic variation.

Recurrence Risk

The overall recurrence risk for subsequent pregnancies after a sporadic case of CDH with unknown etiology is low, approximately 1%.[44] This is due to the high prevalence of

Table 1 Selected high prevalence copy number variations

Chromosomal location	Critical region, if reported (GRCh38/hg38)	Type	Clinical features other than CDH	CDH (candidate) genes	References
1q41–42	chr1:219,741,511–224,449,412	Loss	Dysmorphic facial features, cleft palate, CNS malformations, limb defects, seizures, intellectual disability, Fryns syndrome	*HLX*,[81] *DISP1*[82]	39,50,52,81–87
1q12	chr1:144,041,370–248,938,897	Gain	Cleft palate, genitourinary anomalies, limb defects, optic hypoplasia		39,88–91
1q24q31		Gain	Microretrognathia, microtia, kyphoscoliosis, oligodactyly, syndactyly, joint contractures, CNS malformation, omphalocele, cardiac anomalies, genitourinary anomalies		39,92–94
2q37	chr2:234,749,515–234,778,436	Loss	Congenital heart disease, CNS malformations, renal anomalies, developmental delay, anophthalmia, short stature	*CHRNG*,[95] *ECEL1*[96]	48,51,97–99
4p16	chr4:1–2,334,901	Loss	Wolf–Hirschhorn syndrome: dysmorphic facial features (broad, flat nasal bridge and a high forehead), congenital heart disease, CNS malformations, renal anomalies, limb defects, intellectual disabilities	*FGFRL1*, *CTBP1*, *NSD2*, *FGFR3*, *CPLX1*, *MAEA*, *CTBP1-AS2*, and *ZNF141*[42,100,101]	32,44,50,100,102–105
4q31q34		Loss	Vertebrae/rib anomalies, dysmorphic features, cleft palate, sacral dimple, polydactyly	*GAB1*,[106] *NAA15*[56]	44,107,108
5p15.2	chr5:12674655–12754065	Loss	microcephaly, intellectual disability, brain malformation, dysmorphic features		50
8p23.1	chr8:8,222,339–12,003,060	Loss	CNS anomalies, congenital heart disease, dysmorphic facial features, intellectual disability, autism; Fryns syndrome	*GATA4*,[76] *SOX7*,[109] *NEIL2*[110]	32,44,110–118
8q22q23	chr8:98,943,820–105,387,943	Loss	Facial dysmorphism, developmental delay, intrauterine growth restriction	*ZFPM2*[77,78,119]	52,104,120,121
11q23	chr11:116,811,535–135,076,622	Gain	CNS malformations, polydactyly, growth retardation, dysmorphic features	*BARX2*[122]	50,123–125
12p		Gain	Pallister–Killian syndrome: CNS malformations, short limbs, dysmorphic features, intellectual disability		32,126–133
15q26	chr15:97,355,766–99,142,272	Loss	Dysmorphic features, intrauterine growth restriction, genitourinary anomalies, CNS malformations, skeletal and digit anomalies, behavioral abnormalities, intellectual disability; Fryns syndrome	*NR2F2*[134]	32,44,50,114,117 135–141
16p11.2	chr16:29641039–30184133	Gain/loss	Limb and skeletal defects, cleft palate, autism	*TBX6*[42]	32,50,52,140,142,143
17q12	chr17:36,627,644–37,848,064	Loss	Renal anomalies, skeletal anomalies, minor facial dysmorphic features, hydrocephalus		39,50,52,57,144–146
22q11.2	chr22:21,446,813–22,623,395	Loss	22q11.2 syndrome: congenital heart disease, genitourinary anomalies	*TBX1*,[147] *HIRA*[148]	39,44,57,112,149–153
Xp22		Loss	CNS malformations, microphthalmia, renal anomalies, dysmorphic features, developmental delay; microphthalmia with linear skin defects (MLS) and MIDAS syndrome	*HCCS*,[58] *CLCN4*,[41] *MID1*[154]	44,155–157

Abbreviations: CDH, congenital diaphragmatic hernia; CNS, central nervous system.

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Table 2 Most frequently reported genes with variants in CDH patients

Gene	Genomic coordinates (GRCh38/hg38)	Phenotype/associated syndrome (# OMIM)	Minimal number of reported CDH cases	References
HLX	chr1:220,879,443–220,885,059	Isolated and Complex CDH	5	42,81
LBR	chr1:225,401,503–225,428,855	Isolated CDH	12	147
GLI2	chr2:120,797,321–120,990,675	Isolated and Complex CDH	6	42
LRP2	chr2:169,127,109–169,362,534	Complex CDH, Donnai-Barrow syndrome (# 222448)	10	158
RARB	chr3:25,428,263–25,597,932	Complex CDH with MCOPS12 (# 615524)	5	69
FGFRL1	chr4:1,009,979–1,026,891	Isolated and Complex CDH with Wolf-Hirschhorn syndrome (# 194190)	5	42,102,105,159
PPARGC1A	chr4:23,792,021–23,890,047	Isolated CDH	7	147
PDGFRA	chr4:54,229,293–54,298,245	Isolated and Complex CDH	9	42,160
SLIT3	chr5:168,661,740–169,301,139	Isolated and Complex CDH	5	42,161
NIPBL	chr5:36,876,769–37,066,413	Complex CDH, Cornelia de Lange syndrome (# 122470)	4	59,162–164
MET	chr7:116,672,196–116,798,377	Isolated and Complex CDH	6	42
SOX7	chr8:10,723,768–10,730,511	Isolated and Complex CDH	8	109
ZFPM2	chr8:105,318,438–105,804,539	Isolated CDH	23	52,56,57,77,110,117,119,147,160
GATA4	chr8:11,704,202–11,760,002	Isolated and Complex CDH	21	42,57,76,109,117,147
NSD1	chr8:38,269,704–38,382,271	Isolated CDH	12	147
CHD7	chr8:60,678,740–60,868,028	Complex CDH, CHARGE Syndrome (# 214800)	8	42,165
EYA1	chr8:71,197,511–71,548,061	Isolated and Complex CDH	11	42,147
PBX3	chr9:125,747,373–125,967,377	Isolated and Complex CDH	6	42
CTBP2	chr10:124,984,317–125,160,513	Isolated and Complex CDH	20	42,147
MYOD1	chr11:17,719,571–17,722,136	Isolated CDH	8	42,147
WT1	chr11:32,389,058–32,435,360	Complex CDH with Denys–Drash syndrome (# 194080), Meacham syndrome (# 608978)	12	56,57,60–64
MYRF	chr11:61,752,636–61,788,518	Complex CDH	12	32,56,57,166–168
KMT2D	chr12:49,018,978–49,060,794	Complex CDH, Kabuki syndrome (# 147920)	8	58,169–171
FREM2	chr13:38,687,077–38,887,131	Complex CDH	5	172
MMP14	chr14:22,836,585–22,847,758	Isolated and Complex CDH	11	42,147
FBN1	chr15:48,408,313–48,645,709	Complex CDH with Marfan syndrome (# 154700)	8	58,65–68
STRA6	chr15:74,179,975–74,202,858	Complex CDH with MCOPS9 (# 601186)	12	42,173–177
NR2F2	chr15:96,330,700–96,340,258	Isolated and Complex CDH	5	32,64,134,147,178
PIGN	chr18:61,905,255–62,154,623	Complex CDH, MCAHS1 (# 614080)	7	179–181
LONP1	chr19:5,691,835–5,720,572	Isolated and Complex CDH	23	57
GPC3	chrX:133,535,745–133,985,594	Complex CDH, X-linked Simpson-Golabi-Behmel syndrome (# 312870)	20	71,182–186
EFNB1	chrX:68,829,021–68,842,160	Complex CDH with X-linked Craniofrontonasal syndrome (# 304110)	5	72,187–189

Abbreviation: CDH, congenital diaphragmatic hernia.

de novo genetic alterations in sporadic CDH cases. It has been noted that the recurrence risk might be underestimated as parents with affected children might decide to have fewer children. Chromosomal imbalances due to balanced parental translocations have been described in CDH. For example, for the 2q37 deletion and 4p16 deletion, the recurrence risk has to be estimated for each individual case based upon the parental karyotype. On the other hand, autosomal-dominant,[56–68] autosomal recessive,[69,70] and X-linked[71–73] inheritance patterns for monogenic syndromes associated with CDH have been described. CDH survivors carrying a confirmed causal variant can have up to 50% risk for their offspring assuming complete penetrance. So, parents of an affected child and CDH survivors have to be counseled differently.

Conclusion and Outlook

Bioinformatics and multiomics are increasingly valuable and have been instrumental in identifying new disease genes.[42,74] Combining disease cohorts to increase sample sizes revealed that damaging de novo variants are associated with complex phenotypes and worse clinical outcome.[32,75] The relative contributions and discovery of CDH disease genes including GATA binding protein 4 (*GATA4*), FRAS1-related extracellular matrix 1 (*FREM1*), myelin regulatory factor (MYRF), zinc finger protein, FOG family member 2 (*ZFPM2*), and lon peptidase 1, mitochondrial (*LONP1*) [56,57,75–79] were all identified by combining cohorts. This highlights the value of collaborations such as the CDH-EURO consortium[80] and the DHREAMS consortium (http://www.cdhgenetics.com). Detecting de novo alterations is important for genetic counseling of CDH due to the association with clinical outcome, associated comorbidities, and recurrence risk. It is therefore strongly recommended to include parents in genetic analyses of exome/genome sequencing using a trio approach.

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Conflict of Interest

None declared.

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