De-novo disease-causing variants in CDH

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The genetic etiology of congenital diaphragmatic hernia (CDH), a common and severe birth defect, is still incompletely understood. Chromosomal aneuploidies, copy number variations (CNVs), and variants in a large panel of CDH-associated genes, both de novo and inherited, have been described. Due to impaired reproductive fitness, especially of syndromic CDH patients, and still significant mortality rates, the contribution of de novo variants to the genetic background of CDH is assumed to be high. This assumption is supported by the relatively low recurrence rate among siblings. Advantages in high-throughput genome-wide genotyping and sequencing methods have recently facilitated the detection of de novo variants in CDH.

Keywords: congenital diaphragmatic hernia ; de novo variants ; impaired reproductive fitness ; mortality

1. Introduction

Congenital diaphragmatic hernia (CDH) is a relatively common birth defect reported to affect 2–3 per 10,000 live births [1]. Due to a high early neonatal and prenatal mortality, the hidden prevalence might be even higher [2]. The term CDH comprises a variety of defects in the diaphragm, ranging from diaphragmatic eventration to localized defects of variable size and locations to diaphragmatic agenesis. The most common type is the so-called “Bochdalek hernia” (dorsolateral) on the left side. CDH leads to herniation of abdominal viscera into the thorax during early embryonic development. Newborn patients typically present with respiratory distress which is, in short, due to hypoplasia of the lungs accompanied by abnormal structure of pulmonary vessels and alveolar septa, and pulmonary hypertension. Advancements in the prenatal diagnosis and postnatal management of CDH have led to reduced but still high mortality rates of 20–30% [3][4]. Surviving patients often exhibit significant long-term morbidity [5].

The etiology of CDH is incompletely understood. It is suggested that both genetic and environmental factors contribute to CDH, and although associations with different environmental factors have been described, no finding could be replicated to date [6]. From a medical genetics point of view, about 40% of CDH cases present syndromic or non-isolated. These patients present with additional anomalies of other organ systems, mostly cardiac defects, malformations of the central nervous system, urinary tract, and gastrointestinal system [7]. In these cases, a genetic diagnosis can be established more likely than in cases of isolated or non-syndromic CDH. Overall, in about 30% of CDH cases disease-causing genetic aberrations can be identified by chromosomal analysis, molecular karyotyping, and exome/or genome sequencing. Here, it has been shown that about 6% of CDH cases present with chromosomal imbalances detectable by routine chromosomal analysis or molecular karyotyping [8]. Earlier reports describe detection rates of up to 10% [9]. Using a customized array comparative genomic hybridization assay, Zhu et al. reported likely causative CNVs in 13% of a mixed CDH cohort [10]. An additional 3–10% of cases present with known monogenic syndromes. More recent sequencing studies have identified *de novo* damaging variants in known and novel CDH-associated genes in 10–30% of CDH patients [11][12][13][14][15][16]. Furthermore, is has been shown that the presence of a likely damaging *de novo* variant in a patient is associated with higher mortality and overall worse clinical outcome [17].

To establish a genetic diagnosis is increasingly important for affected families to provide proper counseling, especially as more CDH survivors reach reproductive age. This review focuses on the role of *de novo* events in CDH cases.

2. Known Genetic Factors

2.1. Associated Microscopic and Submicroscopic Anomalies

Except for the theoretical possibility of a trisomy 21 due to parental balanced translocation of chromosome 21 (not reported/investigated by most papers), all aneuploidies associated with CDH to date have been described to occur *de novo*. Aneuploidies (rarely) associated with CDH include trisomy 13, 18, 21, and triple X [17]. Furthermore it has been

described in females with 45,X karyotype [18]. More frequently CDH has been described in patients with mosaic tetrasomy 12p (Pallister-Killian syndrome) [19], which always occurs *de novo*.

Other frequently detected CNVs include 15q26 deletion [20], comprising the CDH-associated gene *NR2F2* [21]; 8p23.1 deletion [22], comprising the CDH-associated gene *ZFPM2* [23]; 11q23 duplication typically resulting from parental balanced translocations [24], and 1q41–42 deletion [25], which includes the CDH-associated genes *HLX* and *DISP1* [26][27].

Less frequently described in association with CDH 4p16 deletions (Wolf-Hirschhorn syndrome) [28][29], comprising the CDH-associated gene *FGFRL1* [30]; 22q11.2 deletion [31]; deletion and duplication of 17q12 [32][33], and 1q12 duplication [34]. Very rare CNVs in CDH patients have been described and comprehensively been reviewed by Wynn et al. [18].

Among the CNVs found in CDH cases are, as expected, many *de novo* events. Other CNVs are caused by unbalanced translocations from a parental balanced translocation. Few CNVs are reported to be inherited [32][35]. The genome-wide *de novo* CNV rate in general is estimated to be 0.5–3% [36][37], about 2–12 times lower than the rate of *de novo* CNVs in CDH patients. CNVs are more likely to be detected in non-isolated cases of CDH than in isolated cases [8] and in general, more deletions (with a pathomechanism of haploinsufficency for CDH-associated genes) have been reported. Overall, *de novo* CNVs have been shown to be a major contributor to the formation of CDH.

2.2. *de novo* Variants in Monogenic CDH Syndromes

More than 20 syndromes with known genetic causes have been associated with the occurrence of CDH. Among these are dominant, recessive, and X-linked inherited syndromes. *de novo* events commonly play a role in autosomal dominant or X-linked syndromes. The rare occurrence of *de novo* events leading to a recessive CDH-associated syndrome is described for Cutis laxa Type 1C [38]. Some well-known monogenic syndromes caused by *de novo* events and featuring CDH are Cornelia de Lange syndrome (*NIPBL*) [39][40]; Craniofrontonasal syndrome (*EFNB1*) [41]; Focal dermal hypoplasia (*PORCN*) [42]; and Kabuki syndrome (*KMT2D*; *MLL2*) [14][43][44]. A full list of monogenic syndromes in which *de novo* events are reported is provided in **Table 1**. It has to be noted that for many described variants in other CDH-related autosomal dominant inherited syndromes, the inheritance pattern is not investigated or reported, but appears to be likely dominant *de novo*.

Table 1. Monogenic syndromes with associated CDH caused by *de novo* events.

Syndrome	OMIM	Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Additional Malformations	References
PDAC syndrome	#615524	*RARB*	3p24.3	chr3: 25,428,263–25,597,932	Micro-/Anophtalmia, pulmonary hypoplasia, cardiac abnormalities	[45]
Cornelia de Lange syndrome	#122470	*NIPBL*	5p13.2	chr5: 36,876,769–37,066,413	Hypertelorism, synophrys, low anterior hairline, upper limb malformations	[40][46][47]
Coffin-Siris syndrome	#135900, #614609	*ARID1B, SMARCA4*	6q25.3	chr6: 156,776,020–157,210,779 chr19: 10,961,001–11,062,256	Growth retardation, long eyelashes, frequent respiratory tract infections, hypotonia, developmental delay	[14][48]
Congenital heart defects and skeletal malformations syndrome (CHDSKM)	#617602	*ABL1*	9q34.12	chr9: 130,713,016–130,885,683	Dysmorphic facial features, congenital heart disease, skeletal abnormalities, joint laxity, failure to thrive, gastrointestinal problems, male genital anomalies	[14][49]
Apert syndrome	#101200	*FGFR2*	10q26.13	chr10: 121,479,857–121,598,403	Acrocephaly, micrognathia, limb malformations	[50]
Denys-Drash syndrome, Meacham syndrome	#194080, #608978	*WT1*	11p13	chr11: 32,389,058–32,435,360	Male pseudohermaphroditism, cardiac abnormalities	[51][52]

Syndrome	OMIM	Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Additional Malformations	References
Kabuki syndrome	**#147920**	***KMT2D***	**12q13.12**	**chr12: 49,018,978–49,060,794**	**Mental retardation, short stature, eversion of eyelids, finger pads**	[14][43][44][53]
Marfan syndrome Type 1	**#154700**	***FBN1***	**15q21.1**	**chr15: 48,408,313–48,645,709**	**Congenital contractures, arachnodactyly, aortic dilatation, cardiac valve insufficiency**	[14][54]
Geleophysic dysplasia 2	**#614185**	***FBN1***	**15q21.1**	**chr15: 48,408,313–48,645,709**	**Short stature, cardiac valvular thickening, skin thickening, joint problems**	[17]
Rubinstein-Taybi syndrome 2	**#613684**	***EP300***	**22q13.2**	**chr22: 41,092,592–41,180,077**	**Failure to thrive, cardiovascular abnormalities, motor and speech delays, dysmorphic facial features**	[14][55]
Focal dermal hypoplasia	**#305600**	***PORCN***	**Xp11.23**	**chrX: 48,508,992–48,520,808**	**Sparse hair, anophtalmia, limb malformations, Pentalogy of Cantrell**	[42]
Craniofrontonasal syndrome	**#304110**	***EFNB1***	**Xq13.1**	**chrX: 68,829,021–68,842,160**	**Coronal craniosynostosis, duplex thumb, partial agenesis of corpus callosum**	[41]

2.3. *de novo* Variants in Non-Isolated CDH

Several genes harboring *de novo* variants in non-isolated CDH cases have been identified, most of them by whole exome (WES)/whole genome (WGS) sequencing techniques. Among these are some well-known CDH-associated genes. D*e novo* variants in *GATA4* have been described in non-isolated [17][22][56] and isolated CDH [57]. *GATA4* is known to be associated with congenital heart defects in humans and is further supported by a mouse model [58]. It encodes a transcription factor that is part of the retinoic acid signaling pathway, which has been implicated in diaphragm development [59].

Repeatedly, non-isolated CDH cases were found to carry *de novo* variants in *NR2F2* [16][17][21][57], an interaction partner of *ZFPM2*, a gene commonly affected by the deletion of 8p23.1 observed in CDH patients. The role of *NR2F2* in diaphragm development is further supported by its expression pattern and a mouse model [60]. More recently, *de novo* variants in *MYRF*, a membrane associated transcription factor, have been described in non-isolated CDH cases, also showing cardiac and genitourinary malformations [12][17][61][62][63].

Other genes with described *de novo* variants in non-isolated CDH cases are listed in **Table 2**. Clinical features of patients are available in Table S1. In very few genes, variants in more than one case could be detected. This illustrates the heterogeneity of the genetic background of CDH. The largest WES/WGS study on family trios could identify *de novo* likely gene-disrupting (LGD) or deleterious missense (D-mis) variants in 21% of non-isolated CDH cases [12]. Another family trio study also showed an increased burden of *de novo* D-mis and LGD variants in a mixed cohort of isolated and non-isolated CDH [13]. Recently a WES study established a genetic diagnosis in 28/76 (37%) non-isolated CDH patients, of which 15/76 (20%) were attributable to *de novo* variants [14]. These findings further strongly support a major role of *de novo* variants in CDH.

Table 2. Genes with *de novo* variants in non-isolated CDH cases.

Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Number of Cases with *de novo* Variants	References	Design/Method of Studies
PRKACB	**1p31.1**	**chr1: 84,078,062–84,238,498**	**1**	[14]	**trio WES**
SLC5A9	**1p33**	**chr1: 48,222,716–48,248,638**	**1**	[14]	**trio WES**
ZNF362	**1p35.1**	**chr1: 33,256,492–33,300,719**	**1**	[17]	**trio WES/WGS**

Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Number of Cases with *de novo* Variants	References	Design/Method of Studies
HSPG2	1p36.12	chr1: 21,822,244–21,937,310	1 °	[17]	trio WES
UBAP2L	1q21.3	chr1: 154,220,955–154,270,847	1	[17]	trio WGS
POGZ	1q21.3	chr1: 151,402,724–151,459,494	1	[12]	clinical WES
DISP1	1q41	chr1: 222,815,039–223,005,995	1	[27]	targeted sanger sequencing
INHBB	2q14.2	chr2: 120,346,136–120,351,803	1	[14]	trio WES
TTC21B	2q24.3	chr2: 165,873,362–165,953,776	1	[17]	trio WGS
ROBO1	3p12.3	chr3: 78,598,688–79,019,015	1	[17]	targeted panel sequencing
FOXP1	3p13	chr3: 70,954,708–71,583,978	1	[15]	clinical WES
RAF1	3p25.2	chr3: 12,583,601–12,664,117	1	[12]	trio WES/WGS
FAT4	4q28.1	chr4: 125,314,955–125,492,932	1	[17]	trio WGS
CDO1	5q22.3	chr5: 115,804,733–115,816,659	1	[14]	trio WES
FOXP4	6p21.1	chr6: 41,546,426–41,602,384	1	[12]	trio WES/WGS
PTPN12	7q11.23	chr7: 77,537,295–77,640,069	1	[14]	trio WES
BRAF	7q34	chr7: 140,719,327–140,924,810	1	[12]	trio WES/WGS
GATA4	8p23.1	chr8: 11,704,202–11,760,002	3	[17][22][56]	targeted sanger sequencing, trio WGS
EYA1	8q13.3	chr8: 71,197,511–71,548,061	1	[11][57]	WES, targeted panel sequencing
TLN1	9p13.3	chr9: 35,696,948–35,732,195	1 °	[17]	trio WES
PLPP6	9p24.1	chr9: 4,662,294–4,665,258	1	[14]	trio WES
NOTCH1	9q34.3	chr9: 136,494,433–136,546,048	1	[17]	trio WGS
CTR9	11p15.3	chr11: 10,751,246–10,779,746	1 *	[16]	trio WES
MYRF	11q12.2	chr11: 61,752,636–61,788,518	11	[12][17][61][62][63]	trio WES/WGS, clinical WES, trio WGS
PTPN11	12q24.13	chr12: 112,419,112–112,504,764	1	[12]	trio WES/WGS
HNRNPC	14q11.2	chr14: 21,210,613–21,269,421	1	[17]	trio WGS
BMP4	14q22.2	chr14: 53,949,736–53,956,825	1	[64]	targeted sanger sequencing
DLST	14q24.3	chr14: 74,881,916–74,903,743	1	[14]	trio WES

Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Number of Cases with *de novo* Variants	References	Design/Method of Studies
TCF12	15q21.3	chr15: 56,918,644–57,289,853	1	[15]	clinical WES
SIN3A	15q24.2	chr15: 75,370,933–75,455,783	1	[14]	trio WES
NR2F2	15q26.2	chr15: 96,330,700–96,340,258	4	[16][17][21][57][65]	clinical WES, targeted panel sequencing, trio WES, trio WGS
TRAF7	16p13.3	chr16: 2,155,782–2,178,129	1	[15]	clinical WES
ANKRD11	16q24.3	chr16: 89,285,175–89,490,318	1	[17]	trio WGS
MYH10	17p13.1	chr17: 8,474,207–8,630,761	1	[66]	clinical WES
TP53	17p13.1	chr17: 7,668,421–7,687,490	1 *	[16]	trio WES
NLK	17q11.2	chr17: 28,042,677–28,196,381	1	[17]	trio WGS
FZD2	17q21.31	chr17: 44,557,484–44,561,262	1	[32]	aCGH
ATXN7L3	17q21.31	chr17: 44,191,805–44,198,070	1	[17]	trio WGS
ALYREF	17q25.3	chr17: 81,887,835–81,891,586	1	[12]	trio WES/WGS
GATA6	18q11.2	chr18: 22,169,589–22,202,528	1	[67]	trio WES
NACC1	19p13.13	chr19: 13,118,264–13,141,147	1	[12]	trio WES/WGS
LONP1	19p13.3	chr19: 5,691,835–5,720,572	1	[14]	trio WES
LTBP4	19q13.2	chr19: 40,601,369–40,629,818	1	[38]	targeted sanger sequencing
ZC3H4	19q13.32	chr19: 47,064,187–47,113,776	1	[12]	trio WES/WGS
PCNA	20p12.3	chr20: 5,114,953–5,126,626	1	[12]	trio WES/WGS
EPB41L1	20q11.23	chr20: 36,092,712–36,230,343	1	[12]	trio WES/WGS
ARFGEF2	20q13.13	chr20: 48,921,711–49,036,693	1	[14]	trio WES
ADNP	20q13.13	chr20: 50,888,918–50,931,437	1	[17]	trio WGS
SCAF4	21q22.11	chr21: 31,671,000–31,732,118	1	[17]	trio WGS
DDX3X	Xp11.4	chrX: 41,333,348–41,350,287	1	[15]	clinical WES
USP9X	Xp11.4	chrX: 41,085,445–41,236,579	1 °	[17]	trio WES/WGS
CLCN4	Xp22.2	chrX: 10,156,975–10,237,660	1	[14]	trio WES
HCCS	Xp22.2	chrX: 11,111,301–11,123,078	1	[15]	clinical WES

Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Number of Cases with *de novo* Variants	References	Design/Method of Studies
STAG2	**Xq25**	**chrX: 123,961,314–124,102,656**	**1**	[14]	**trio WES**

2.4. *de novo* Variants in Isolated CDH

In patients with isolated CDH a genetic cause is less likely to be established by current genotyping or sequencing techniques. The above-mentioned study on case-parent-trios could identify *de novo* likely gene-disrupting or deleterious missense variants in only 12% of isolated CDH cases [12]. Among the described *de novo* variants in isolated CDH are variants in the already mentioned genes *ZFPM2* [12][23][68], *GATA4* [57], and *PTPN11* [12][16][17]. As in non-isolated CDH, variants in very few genes could be implicated in more than one case. A list of genes with *de novo* variants in isolated CDH is provided in **Table 3**. Notably, some genes are reported to carry *de novo* variants in non-isolated and isolated CDH cases.

Table 3. Genes with *de novo* variants in isolated CDH cases.

Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Number of Cases with *de novo* Variants	References	Design/Method of Studies
HSPG2	**1p36.12**	**chr1: 21,822,244–21,937,310**	**2**	[13][14]	**trio WES**
ATAD3A	**1p36.33**	**chr1: 1,512,175–1,534,685**	**1**	[12]	**trio WES/WGS**
POGZ	**1q21.3**	**chr1: 151,402,724–151,459,494**	**1**	[12]	**trio WES/WGS**
KDM5B	**1q32.1**	**chr1: 202,724,495–202,808,421**	**1**	[12]	**trio WES/WGS**
ZBTB18	**1q44**	**chr1: 244,051,283–244,057,476**	**1**	[12]	**trio WES/WGS**
MYT1L	**2p25.3**	**chr2: 1,789,124–2,331,348**	**1**	[12]	**trio WES/WGS**
FOXP1	**3p13**	**chr3: 70,954,708–71,583,978**	**1**	[12]	**trio WES/WGS**
SRGAP3	**3p25.3**	**chr3: 8,980,594–9,249,213**	**1**	[12]	**trio WES/WGS**
KPNA1	**3q21.1**	**chr3: 122,421,902–122,514,939**	**1**	[17]	**trio WGS**
NAA15	**4q31.1**	**chr4: 139,301,505–139,391,384**	**1**	[12]	**trio WES/WGS**
SMO	**7q32.1**	**chr7: 129,188,633–129,213,545**	**1**	[12]	**trio WES/WGS**
GATA4	**8p23.1**	**chr8: 11,704,202–11,760,002**	**1**	[57]	**targeted panel sequencing**
ZFPM2	**8q23.1**	**chr8: 105,318,438–105,804,539**	**3**	[12][23][68]	**WES, trio WES/WGS, targeted sanger sequencing**
EMX2	**10q26.11**	**chr10: 117,542,746–117,549,546**	**1**	[12]	**trio WES/WGS**
WT1	**11p13**	**chr11: 32,389,058–32,435,360**	**3**	[12][16]	**trio WES/WGS**
PTPN11	**12q24.13**	**chr12: 112,419,112–112,504,764**	**3**	[12][16][17]	**trio WES/WGS**
MEIS2	**15q14**	**chr15: 36,889,204–37,100,549**	**1**	[12]	**trio WES/WGS**

Gene	Chromosomal Location	Genomic Coordinates (GRCh38/hg38)	Number of Cases with *de novo* Variants	References	Design/Method of Studies
TBX6	**16p11.2**	**chr16: 30,085,793–30,091,924**	**1**	[11]	**WES**
CTCF	**16q22.1**	**chr16: 67,562,467–67,639,176**	**1**	[17]	**trio WGS**
AP1G1	**16q22.2**	**chr16: 71,729,000–71,808,834**	**1**	[12]	**trio WES/WGS**
MYH10	**17p13.1**	**chr17: 8,474,207–8,630,761**	**1**	[17]	**targeted panel sequencxing**
SRSF1	**17q22**	**chr17: 58,000,919–58,007,246**	**1**	[17]	**trio WGS**
LONP1	**19p13.3**	**chr19: 5,691,835–5,720,572**	**2**	[17]	**trio WGS**
CIC	**19q13.2**	**chr19: 42,268,537–42,295,796**	**1**	[12]	**trio WES/WGS**
LAMA5	**20q13.33**	**chr20: 62,309,065–62,367,312**	**1**	[12]	**trio WES/WGS**
DIDO1	**20q13.33**	**chr20: 62,877,738–62,937,952**	**1**	[12]	**trio WES/WGS**
HSD17B10	**Xp11.22**	**chrX: 53,431,261–53,434,370**	**1**	[12]	**trio WES/WGS**
FLNA	**Xq28**	**chrX: 154,348,529–154,371,283**	**1**	[17]	**trio WGS**

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