Review

The Role of De Novo Variants in Patients with Congenital Diaphragmatic Hernia

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Abstract: 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. This review gives an overview of the known de novo disease-causing variants in CDH patients.

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 patients present syndromic. These patients present with additional anomalies of other organ systems (“non-isolated”), 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 patients 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 patients 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 patients 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 [11–16]. Furthermore, it 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 patients.

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 FGFR1 [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 patients 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 haploinsufficiency 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: 25,428,263–25,597,992       | 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    | 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 | WTI           | 11p13                | chr11: 32,389,058–32,435,360     | Male pseudohermaphroditism, cardiac abnormalities                                         | [51,52]   |
| 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 valvarular 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 patients have been identified, most of them by whole exome (WES)/whole genome (WGS) sequencing techniques. Among these are some well-known CDH-associated genes. de 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 patients 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 patients, also showing cardiac and genitourinary malformations [12,17,61–63].

Other genes with described de novo variants in non-isolated CDH patients are listed in Table 2. Clinical features of patients are available in Table S1. In very few genes, variants in more than one patient 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 patients.

| Gene    | Chromosomal Location | Genomic Coordinates (GRCh38/hg38) | Number of Patients 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            |
| 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                |
| Gene   | Chromosomal Location | Genomic Coordinates (GRCh38/hg38) | Number of Patients with de novo Variants | References | Design/Method of Studies |
|--------|----------------------|-----------------------------------|-----------------------------------------|------------|--------------------------|
| 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                                      | [12,17,61–63] | 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                 |
| 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: 44,357,484–44,561,262      | 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             |
Table 2. Cont.

| Gene     | Chromosomal Location | Genomic Coordinates (GRCh38/hg38) | Number of Patients with de novo Variants | References | Design/Method of Studies |
|----------|----------------------|------------------------------------|-----------------------------------------|------------|--------------------------|
| 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: 41,085,445–41,256,579        | 1 o                                     | [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             |
| STAG2    | Xq25                 | chrX: 123,961,314–124,102,656     | 1                                       | [14]       | trio WES                 |

* Variants reported in the same patient, additionally de novo CNV deletion 8p23. ◦ Variants reported in the same patient.

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 patient. 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 patients.
Table 3. Genes with de novo variants in isolated CDH patients.

| Gene   | Chromosomal Location | Genomic Coordinates (GRCh38/hg38) | Number of Patients 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 | 1q4                   | 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             |
| WTI    | 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             |
| TXK    | 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                 |
| APIG1  | 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 sequencing |
| 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: 62,877,738–62,937,992     | 1                                       | [12]       | trio WES/WGS             |
| HSDB1B10| 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                 |

3. Discussion

Based on the current knowledge, we have to assume that de novo events play a major role in CDH etiology. In up to 30% of CDH cases a genetic cause can be established, more often in non-isolated than in isolated CDH. For the estimation of the fraction of causal CNVs/variants being de novo, large family trio studies are needed. However, in these, often only de novo events are reported. By looking at subsets of two large CNV studies [8,10] the fraction of causal CNVs being de novo can be estimated up to 80%. Similarly, the fraction of causal variants being de novo could be estimated around 50% [15]. However, these estimations are based on small sample sizes only. Most likely, the fraction of de novo events is currently underestimated due to restricted genetic testing for newborns with (especially sporadic isolated) CDH in clinical practice.

The contribution of de novo variants to a disease depends on several factors. (i) It is higher in sporadic than in familial diseases; (ii) it is higher when the impact on fitness of the disease is higher; (iii) it is higher in monogenic than in complex diseases [69]. On the other hand, the incidence of a disease caused by de novo events increases with (i) mutational...
target size; (ii) target mutability and (iii) paternal age at conception [69]. When conferring this to CDH, CDH is a mostly sporadic disease with high impact on fitness with not fully understood genetics, but monogenic forms being reported. The mutational target size is most likely large due to the heterogeneity of CDH. Paternal age at conception has not been reported to be a risk factor for CDH.

A well-studied example of a condition with reduced reproductive fitness is developmental delay/intellectual disability (DD/ID). Here it could be shown that de novo variants account for ~50% of the genetic background of DD/ID [70]. For CDH, a similar or even higher proportion can be hypothesized. Larger whole genome/whole exome sequencing studies on case-parent-trios will most likely reveal additional de novo variants. The pathogenicity of the many rare de novo variants reported in CDH patients could also be further supported by larger resequencing studies which would identify additional patients harboring the same variant.

Genetic counseling for affected families with the sporadic occurrence of non-syndromic CDH should however, imply the recurrence risk of about 1% in future pregnancies. This, however, changes accordingly, when a genetic diagnosis has been established. Regardless of the establishment of a genetic diagnosis, affected families should be referred to a prenatal medicine center during the first and second trimester of subsequent pregnancies.

4. Conclusions

Among rare and severe birth defects, CDH is one of the more common ones. The current knowledge on the genetics of CDH suggests that a substantial fraction of CDH is due to underlying genetic de novo events. However, it is conceivable that several common variants form a “risk haplotype” that predisposes to non-syndromic CDH.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/genes12091405/s1, Table S1: Additional clinical features of non-isolated CDH patients from Table 2.

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