

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

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Eur J Pediatr Surg 2021;31:472–481.

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 intra-thoracic 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

received
October 25, 2021
accepted
November 1, 2021

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Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/s-0041-1740337>.
ISSN 0939-7248.

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 cells¹³ 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 of 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 non-specific 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* variants⁵⁷ 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	<i>HLX</i> , ⁸¹ <i>DISP1</i> 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	<i>CHRMG</i> , ⁹⁵ <i>ECEL1</i> 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	<i>FGFR1</i> , <i>CTBP1</i> , <i>NSD2</i> , <i>FGFR3</i> , <i>CPLX1</i> , <i>MAEA</i> , <i>CTBP1-AS2</i> and <i>ZNF141</i> ^{42,100,101}	32,44,50,100,102–105
4q31q34		Loss	Vertebrae/rib anomalies, dysmorphic features, cleft palate, sacral dimple, polydactyly	<i>GAB1</i> , ¹⁰⁶ <i>NAA15</i> 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	<i>GATA4</i> , ⁷⁶ <i>SOX7</i> , ¹⁰⁹ <i>NEL2</i> ¹¹⁰	32,44,110–118
8q22q23	chr8:98,943,820–105,387,943	Loss	Facial dysmorphism, developmental delay, intrauterine growth restriction	<i>ZFPM2</i> ^{77,78,119}	52,104,120,121
11q23	chr11:116,811,535–135,076,622	Gain	CNS malformations, polydactyly, growth retardation, dysmorphic features	<i>BARX2</i> 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	<i>NR2F2</i> ¹³⁴	32,44,50,114,117 135–141
16p11.2	chr16:29641039–30184133	Gain/loss	Limb and skeletal defects, cleft palate, autism	<i>TBX6</i> 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	<i>TBX1</i> , ¹⁴⁷ <i>HIRA</i> 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	<i>HCCS</i> , ⁵⁸ <i>CLCN4</i> , ⁴¹ <i>MID1</i> ¹⁵⁴	44,155–157

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

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
<i>HLX</i>	chr1:220,879,443-220,885,059	Isolated and Complex CDH	5	42,81
<i>LBR</i>	chr1:225,401,503-225,428,855	Isolated CDH	12	147
<i>GLI2</i>	chr2:120,797,321-120,990,675	Isolated and Complex CDH	6	42
<i>LRP2</i>	chr2:169,127,109-169,362,534	Complex CDH, Donnai-Barrow syndrome (# 222448)	10	158
<i>RARB</i>	chr3:25,428,263-25,597,932	Complex CDH with MCOPS12 (# 615524)	5	69
<i>FGFR1</i>	chr4:1,009,979-1,026,891	Isolated and Complex CDH with Wolf-Hirschhorn syndrome (# 194190)	5	42,102,105,159
<i>PPARGC1A</i>	chr4:23,792,021-23,890,047	Isolated CDH	7	147
<i>PDGFRA</i>	chr4:54,229,293-54,298,245	Isolated and Complex CDH	9	42,160
<i>SLIT3</i>	chr5:168,661,740-169,301,139	Isolated and Complex CDH	5	42,161
<i>NIPBL</i>	chr5:36,876,769-37,066,413	Complex CDH, Cornelia de Lange syndrome (# 122470)	4	59,162-164
<i>MET</i>	chr7:116,672,196-116,798,377	Isolated and Complex CDH	6	42
<i>SOX7</i>	chr8:10,723,768-10,730,511	Isolated and Complex CDH	8	109
<i>ZFPM2</i>	chr8:105,318,438-105,804,539	Isolated CDH	23	52,56,57,77,110,117,119,147,160
<i>GATA4</i>	chr8:11,704,202-11,760,002	Isolated and Complex CDH	21	42,57,76,109,117,147
<i>NSD1</i>	chr8:38,269,704-38,382,271	Isolated CDH	12	147
<i>CHD7</i>	chr8:60,678,740-60,868,028	Complex CDH, CHARGE Syndrome (# 214800)	8	42,165
<i>EYA1</i>	chr8:71,197,511-71,548,061	Isolated and Complex CDH	11	42,147
<i>PBX3</i>	chr9:125,747,373-125,967,377	Isolated and Complex CDH	6	42
<i>CTBP2</i>	chr10:124,984,317-125,160,513	Isolated and Complex CDH	20	42,147
<i>MYO1D</i>	chr11:17,719,571-17,722,136	Isolated CDH	8	42,147
<i>WTT1</i>	chr11:32,389,058-32,435,360	Complex CDH with Denys-Drash syndrome (# 194080), Meacham syndrome (# 608978)	12	56,57,60-64
<i>MYRF</i>	chr11:61,752,636-61,788,518	Complex CDH	12	32,56,57,166-168
<i>KMT2D</i>	chr12:49,018,978-49,060,794	Complex CDH, Kabuki syndrome (# 147920)	8	58,169-171
<i>FREM2</i>	chr13:38,687,077-38,887,131	Complex CDH	5	172
<i>MMP14</i>	chr14:22,836,585-22,847,758	Isolated and Complex CDH	11	42,147
<i>FBN1</i>	chr15:48,408,313-48,645,709	Complex CDH with Marfan syndrome (# 154700)	8	58,65-68
<i>STRA6</i>	chr15:74,179,975-74,202,858	Complex CDH with MCOPS9 (# 601186)	12	42,173-177
<i>NR2F2</i>	chr15:96,330,700-96,340,258	Isolated and Complex CDH	5	32,64,134,147,178
<i>PIGN</i>	chr18:61,905,255-62,154,623	Complex CDH, MCAH1 (# 614080)	7	179-181
<i>LONP1</i>	chr19:5,691,835-5,720,572	Isolated and Complex CDH	23	57
<i>GPC3</i>	chrX:133,535,745-133,985,594	Complex CDH, X-linked Simpson-Golabi-Behmel syndrome (# 312870)	20	71,182-186
<i>EFNB1</i>	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 (*ZFPF2*), 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 consortium⁸⁰ 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.

Funding

Rheinische Friedrich-Wilhelms-Universität Bonn. Bonfor grant number O-112.0062

Conflict of Interest

None declared.

References

- McGivern MR, Best KE, Rankin J, et al. Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study. *Arch Dis Child Fetal Neonatal Ed* 2015;100(02): F137–F144
- Gupta VS, Harting MT, Lally PA, et al; Congenital Diaphragmatic Hernia Study Group. Mortality in congenital diaphragmatic hernia: a multicenter registry study of over 5000 patients over 25 years. *Ann Surg* 2021 (e-pub ahead of print)
- Pickering M, Jones JF. The diaphragm: two physiological muscles in one. *J Anat* 2002;201(04):305–312
- Kardon G, Ackerman KG, McCulley DJ, et al. Congenital diaphragmatic hernias: from genes to mechanisms to therapies. *Dis Model Mech* 2017;10(08):955–970
- Longoni M, Pober BR, High FA. Congenital Diaphragmatic Hernia Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*(®). Seattle (WA): University of Washington Seattle Copyright © 1993–2020, University of Washington, Seattle. *GeneReviews* is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993
- Stoll C, Alembik Y, Dott B, Roth MP. Associated malformations in cases with congenital diaphragmatic hernia. *Genet Couns* 2008; 19(03):331–339
- Pober BR. Overview of epidemiology, genetics, birth defects, and chromosome abnormalities associated with CDH. *Am J Med Genet C Semin Med Genet* 2007;145C(02):158–171
- Zaiss I, Kehl S, Link K, et al. Associated malformations in congenital diaphragmatic hernia. *Am J Perinatol* 2011;28(03): 211–218
- Chiu PP, Ijsselstijn H. Morbidity and long-term follow-up in CDH patients. *Eur J Pediatr Surg* 2012;22(05):384–392
- Amoils M, Crisham Janik M, Lustig LR. Patterns and predictors of sensorineural hearing loss in children with congenital diaphragmatic hernia. *JAMA Otolaryngol Head Neck Surg* 2015;141(10): 923–926
- Masumoto K, Nagata K, Uesugi T, Yamada T, Taguchi T. Risk factors for sensorineural hearing loss in survivors with severe congenital diaphragmatic hernia. *Eur J Pediatr* 2007;166(06): 607–612
- Merrell AJ, Ellis BJ, Fox ZD, Lawson JA, Weiss JA, Kardon G. Muscle connective tissue controls development of the diaphragm and is a source of congenital diaphragmatic hernias. *Nat Genet* 2015;47 (05):496–504
- Cleal L, McHaffie SL, Lee M, Hastie N, Martínez-Estrada OM, Chau YY. Resolving the heterogeneity of diaphragmatic mesenchyme: a novel mouse model of congenital diaphragmatic hernia. *Dis Model Mech* 2021;14(01):14
- Carmona R, Cañete A, Cano E, Ariza L, Rojas A, Muñoz-Chápuli R. Conditional deletion of WT1 in the septum transversum mesenchyme causes congenital diaphragmatic hernia in mice. *eLife* 2016;5:5
- Sefton EM, Gallardo M, Kardon G. Developmental origin and morphogenesis of the diaphragm, an essential mammalian muscle. *Dev Biol* 2018;440(02):64–73
- Sefton EM, Kardon G. Connecting muscle development, birth defects, and evolution: an essential role for muscle connective tissue. *Curr Top Dev Biol* 2019;132:137–176
- Paris ND, Coles GL, Ackerman KG. Wt1 and β -catenin cooperatively regulate diaphragm development in the mouse. *Dev Biol* 2015;407(01):40–56
- Coles GL, Ackerman KG. Kif7 is required for the patterning and differentiation of the diaphragm in a model of syndromic congenital diaphragmatic hernia. *Proc Natl Acad Sci U S A* 2013;110(21):E1898–E1905
- Clugston RD, Zhang W, Greer JJ. Early development of the primordial mammalian diaphragm and cellular mechanisms of nitrofen-induced congenital diaphragmatic hernia. *Birth Defects Res A Clin Mol Teratol* 2010;88(01):15–24
- Noda K, Kitagawa K, Miki T, et al. A matricellular protein fibulin-4 is essential for the activation of lysyl oxidase. *Sci Adv* 2020;6 (48):eabc1404
- Nakamura H, Doi T, Puri P, Friedmacher F. Transgenic animal models of congenital diaphragmatic hernia: a comprehensive overview of candidate genes and signaling pathways. *Pediatr Surg Int* 2020;36(09):991–997
- Beurskens N, Klaassens M, Rottier R, de Klein A, Tibboel D. Linking animal models to human congenital diaphragmatic hernia. *Birth Defects Res A Clin Mol Teratol* 2007;79(08): 565–572
- Hornstra IK, Birge S, Starcher B, Bailey AJ, Mecham RP, Shapiro SD. Lysyl oxidase is required for vascular and diaphragmatic development in mice. *J Biol Chem* 2003;278(16):14387–14393

- 24 Garne E, Haeusler M, Barisic I, Gjergja R, Stoll C, Clementi MEuroscan Study Group. Congenital diaphragmatic hernia: evaluation of prenatal diagnosis in 20 European regions. *Ultrasound Obstet Gynecol* 2002;19(04):329–333
- 25 Cordier AG, Jani JC, Cannie MM, et al. Stomach position in prediction of survival in left-sided congenital diaphragmatic hernia with or without fetoscopic endoluminal tracheal occlusion. *Ultrasound Obstet Gynecol* 2015;46(02):155–161
- 26 Basta AM, Lusk LA, Keller RL, Filly RA. Fetal stomach position predicts neonatal outcomes in isolated left-sided congenital diaphragmatic hernia. *Fetal Diagn Ther* 2016;39(04):248–255
- 27 Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictors of survival in fetal diaphragmatic hernia. *J Pediatr Surg* 1996;31(01):148–151, discussion 151–152
- 28 Burgos CM, Frenckner B, Luco M, Harting MT, Lally PA, Lally KP Congenital Diaphragmatic Hernia Study Group. Prenatally versus postnatally diagnosed congenital diaphragmatic hernia - Side, stage, and outcome. *J Pediatr Surg* 2019;54(04):651–655
- 29 Kilian AK, Büsing KA, Schuetz EM, Schaible T, Neff KW. Fetal MR lung volumetry in congenital diaphragmatic hernia (CDH): prediction of clinical outcome and the need for extracorporeal membrane oxygenation (ECMO). *Klin Padiatr* 2009;221(05):295–301
- 30 Deprest JA, Flemmer AW, Gratacos E, Nicolaides K. Antenatal prediction of lung volume and in-utero treatment by fetal endoscopic tracheal occlusion in severe isolated congenital diaphragmatic hernia. *Semin Fetal Neonatal Med* 2009;14(01):8–13
- 31 Snoek KG, Peters NCJ, van Rosmalen J, et al. The validity of the observed-to-expected lung-to-head ratio in congenital diaphragmatic hernia in an era of standardized neonatal treatment; a multicenter study. *Prenat Diagn* 2017;37(07):658–665
- 32 Qiao L, Wynn J, Yu L, et al. Likely damaging *de novo* variants in congenital diaphragmatic hernia patients are associated with worse clinical outcomes. *Genet Med* 2020;22(12):2020–2028
- 33 Coughlin MA, Gupta VS, Ebanks AH, Harting MT, Lally KP Congenital Diaphragmatic Hernia Study Group. Incidence and outcomes of patients with congenital diaphragmatic hernia and pulmonary sequestration. *J Pediatr Surg* 2021;56(06):1126–1129
- 34 Coughlin MA, Werner NL, Gajarski R, et al. Prenatally diagnosed severe CDH: mortality and morbidity remain high. *J Pediatr Surg* 2016;51(07):1091–1095
- 35 Jancelewicz T, Brindle ME. Prediction tools in congenital diaphragmatic hernia. *Semin Perinatol* 2020;44(01):151165
- 36 Ferguson DM, Gupta VS, Lally PA, et al; Congenital Diaphragmatic Hernia Study Group. Early, postnatal pulmonary hypertension severity predicts inpatient outcomes in congenital diaphragmatic hernia. *Neonatology* 2021;118(02):147–154
- 37 Brindle ME, Cook EF, Tibboel D, Lally PA, Lally KP Congenital Diaphragmatic Hernia Study Group. A clinical prediction rule for the severity of congenital diaphragmatic hernias in newborns. *Pediatrics* 2014;134(02):e413–e419
- 38 Cochiussen-den Otter SCM, Erdem Ö, van Rosmalen J, et al. Validation of a prediction rule for mortality in congenital diaphragmatic hernia. *Pediatrics* 2020;145(04):145
- 39 Yu L, Wynn J, Ma L, et al. *De novo* copy number variants are associated with congenital diaphragmatic hernia. *J Med Genet* 2012;49(10):650–659
- 40 Russo FM, Debeer A, De Coppi P, et al. What should we tell parents? Congenital diaphragmatic hernia. *Prenat Diagn* 2020. Doi: 10.1002/pd.5880
- 41 Yu L, Sawle AD, Wynn J, et al. Increased burden of *de novo* predicted deleterious variants in complex congenital diaphragmatic hernia. *Hum Mol Genet* 2015;24(16):4764–4773
- 42 Longoni M, High FA, Russell MK, et al. Molecular pathogenesis of congenital diaphragmatic hernia revealed by exome sequencing, developmental data, and bioinformatics. *Proc Natl Acad Sci U S A* 2014;111(34):12450–12455
- 43 Bendixen C, Reutter H. The role of *de novo* variants in patients with congenital diaphragmatic hernia. *Genes (Basel)* 2021;12(09):1405
- 44 Pober BR, Lin A, Russell M, et al. Infants with Bochdalek diaphragmatic hernia: sibling recurrence and monozygotic twin discordance in a hospital-based malformation surveillance program. *Am J Med Genet A* 2005;138A(02):81–88
- 45 Wang W, Pan W, Chen J, Xie W, Liu M, Wang J. Outcomes of congenital diaphragmatic hernia in one of the twins. *Am J Perinatol* 2019;36(12):1304–1309
- 46 Sahin S, Kutman KH, Bozkurt O, et al. A trisomy 13 case presenting with congenital diaphragmatic hernia and microphthalmia. *Genet Couns* 2015;26(02):263–265
- 47 Jain A, Kumar P, Jindal A, et al. Congenital diaphragmatic hernia in a case of patau syndrome: a rare association. *J Neonat Surg* 2015;4:20
- 48 Tonks A, Wyldes M, Somerset DA, et al. Congenital malformations of the diaphragm: findings of the West Midlands Congenital Anomaly Register 1995 to 2000. *Prenat Diagn* 2004;24(08):596–604
- 49 Holder AM, Klaassens M, Tibboel D, de Klein A, Lee B, Scott DA. Genetic factors in congenital diaphragmatic hernia. *Am J Hum Genet* 2007;80(05):825–845
- 50 Zhu Q, High FA, Zhang C, et al. Systematic analysis of copy number variation associated with congenital diaphragmatic hernia. *Proc Natl Acad Sci U S A* 2018;115(20):5247–5252
- 51 Scott DA, Klaassens M, Holder AM, et al. Genome-wide oligonucleotide-based array comparative genome hybridization analysis of non-isolated congenital diaphragmatic hernia. *Hum Mol Genet* 2007;16(04):424–430
- 52 Wat MJ, Veenma D, Hogue J, et al. Genomic alterations that contribute to the development of isolated and non-isolated congenital diaphragmatic hernia. *J Med Genet* 2011;48(05):299–307
- 53 Yu L, Hernan RR, Wynn J, Chung WK. The influence of genetics in congenital diaphragmatic hernia. *Semin Perinatol* 2020;44(01):151169
- 54 Matsunami N, Shanmugam H, Baird L, et al. Germline but not somatic *de novo* mutations are common in human congenital diaphragmatic hernia. *Birth Defects Res* 2018;110(07):610–617
- 55 Bogenschutz EL, Fox ZD, Farrell A, et al. Deep whole-genome sequencing of multiple proband tissues and parental blood reveals the complex genetic etiology of congenital diaphragmatic hernias. *HGG Adv* 2020;1(01):100008
- 56 Qi H, Yu L, Zhou X, et al. *De novo* variants in congenital diaphragmatic hernia identify MYRF as a new syndrome and reveal genetic overlaps with other developmental disorders. *PLoS Genet* 2018;14(12):e1007822
- 57 Qiao L, Xu L, Yu L, et al. Rare and *de novo* variants in 827 congenital diaphragmatic hernia probands implicate LONP1 as candidate risk gene. *Am J Hum Genet* 2021;108(10):1964–1980
- 58 Scott TM, Campbell IM, Hernandez-García A, et al. Clinical exome sequencing data reveal high diagnostic yields for congenital diaphragmatic hernia plus (CDH+) and new phenotypic expansions involving CDH. *J Med Genet* 2021;jmedgenet-2020-107317
- 59 Hosokawa S, Takahashi N, Kitajima H, Nakayama M, Kosaki K, Okamoto N. Brachmann-de Lange syndrome with congenital diaphragmatic hernia and NIPBL gene mutation. *Congenit Anom (Kyoto)* 2010;50(02):129–132
- 60 Devriendt K, Deloof E, Moerman P, et al. Diaphragmatic hernia in Denys-Drash syndrome. *Am J Med Genet* 1995;57(01):97–101
- 61 Antonius T, van Bon B, Eggink A, van der Burgt I, Noordam K, van Heijst A. Denys-Drash syndrome and congenital diaphragmatic hernia: another case with the 1097G > A(Arg366His) mutation. *Am J Med Genet A* 2008;146A(04):496–499
- 62 Suri M, Kelehan P, O'neill D, et al. WT1 mutations in Meacham syndrome suggest a coelomic mesothelial origin of the cardiac

- and diaphragmatic malformations. *Am J Med Genet A* 2007;143A(19):2312–2320
- 63 Denamur E, Bocquet N, Baudouin V, et al. WT1 splice-site mutations are rarely associated with primary steroid-resistant focal and segmental glomerulosclerosis. *Kidney Int* 2000;57(05):1868–1872
 - 64 Schwab ME, Dong S, Lianoglou BR, et al. Exome sequencing of fetuses with congenital diaphragmatic hernia supports a causal role for NR2F2, PTPN11, and WT1 variants. *Am J Surg* 2021;S0002-9610(21)00396-2
 - 65 Jacobs AM, Toudjarska I, Racine A, Tsiouras P, Kilpatrick MW, Shanske A. A recurring FBN1 gene mutation in neonatal Marfan syndrome. *Arch Pediatr Adolesc Med* 2002;156(11):1081–1085
 - 66 Revenu N, Quenum G, Detaille T, Verellen G, De Paepe A, Verellen-Dumoulin C. Congenital diaphragmatic eventration and bilateral uretero-hydronephrosis in a patient with neonatal Marfan syndrome caused by a mutation in exon 25 of the FBN1 gene and review of the literature. *Eur J Pediatr* 2004;163(01):33–37
 - 67 Stheneur C, Faivre L, Collod-Bérout G, et al. Prognosis factors in probands with an FBN1 mutation diagnosed before the age of 1 year. *Pediatr Res* 2011;69(03):265–270
 - 68 Beck TF, Campeau PM, Jhangiani SN, et al. FBN1 contributing to familial congenital diaphragmatic hernia. *Am J Med Genet A* 2015;167A(04):831–836
 - 69 Srour M, Chitayat D, Caron V, et al. Recessive and dominant mutations in retinoic acid receptor beta in cases with microphthalmia and diaphragmatic hernia. *Am J Hum Genet* 2013;93(04):765–772
 - 70 Donnai D, Barrow M. Diaphragmatic hernia, exomphalos, absent corpus callosum, hypertelorism, myopia, and sensorineural deafness: a newly recognized autosomal recessive disorder? *Am J Med Genet* 1993;47(05):679–682
 - 71 Yano S, Baskin B, Bagheri A, et al. Familial Simpson-Golabi-Behmel syndrome: studies of X-chromosome inactivation and clinical phenotypes in two female individuals with GPC3 mutations. *Clin Genet* 2011;80(05):466–471
 - 72 Hogue J, Shankar S, Perry H, Patel R, Vargervik K, Slavotinek A. A novel EFN1 mutation (c.712delG) in a family with craniofrontonasal syndrome and diaphragmatic hernia. *Am J Med Genet A* 2010;152A(10):2574–2577
 - 73 Maas SM, Lombardi MP, van Essen AJ, et al. Phenotype and genotype in 17 patients with Goltz-Gorlin syndrome. *J Med Genet* 2009;46(10):716–720
 - 74 Russell MK, Longoni M, Wells J, et al. Congenital diaphragmatic hernia candidate genes derived from embryonic transcriptomes. *Proc Natl Acad Sci U S A* 2012;109(08):2978–2983
 - 75 Longoni M, High FA, Qi H, et al. Genome-wide enrichment of damaging de novo variants in patients with isolated and complex congenital diaphragmatic hernia. *Hum Genet* 2017;136(06):679–691
 - 76 Yu L, Wynn J, Cheung YH, et al. Variants in GATA4 are a rare cause of familial and sporadic congenital diaphragmatic hernia. *Hum Genet* 2013;132(03):285–292
 - 77 Longoni M, Russell MK, High FA, et al. Prevalence and penetrance of ZFPM2 mutations and deletions causing congenital diaphragmatic hernia. *Clin Genet* 2015;87(04):362–367
 - 78 Brady PD, Van Houdt J, Callewaert B, Deprest J, Devriendt K, Vermeesch JR. Exome sequencing identifies ZFPM2 as a cause of familial isolated congenital diaphragmatic hernia and possibly cardiovascular malformations. *Eur J Med Genet* 2014;57(06):247–252
 - 79 Beck TF, Veenma D, Shchelochkov OA, et al. Deficiency of FRAS1-related extracellular matrix 1 (FREM1) causes congenital diaphragmatic hernia in humans and mice. *Hum Mol Genet* 2013;22(05):1026–1038
 - 80 Reiss I, Schaible T, van den Hout L, et al; CDH EURO Consortium. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. *Neonatology* 2010;98(04):354–364
 - 81 Slavotinek AM, Moshrefi A, Lopez Jimenez N, et al. Sequence variants in the HLX gene at chromosome 1q41-1q42 in patients with diaphragmatic hernia. *Clin Genet* 2009;75(05):429–439
 - 82 Kantarci S, Ackerman KG, Russell MK, et al. Characterization of the chromosome 1q41q42.12 region, and the candidate gene DISP1, in patients with CDH. *Am J Med Genet A* 2010;152A(10):2493–2504
 - 83 Youssoufian H, Chance P, Tuck-Muller CM, Jabs EW. Association of a new chromosomal deletion [del(1)(q32q42)] with diaphragmatic hernia: assignment of a human ferritin gene. *Hum Genet* 1988;78(03):267–270
 - 84 Kantarci S, Casavant D, Prada C, et al. Findings from aCGH in patients with congenital diaphragmatic hernia (CDH): a possible locus for Fryns syndrome. *Am J Med Genet A* 2006;140(01):17–23
 - 85 Rosenfeld JA, Lacassie Y, El-Khechen D, et al. New cases and refinement of the critical region in the 1q41q42 microdeletion syndrome. *Eur J Med Genet* 2011;54(01):42–49
 - 86 Shaffer LG, Theisen A, Bejjani BA, et al. The discovery of microdeletion syndromes in the post-genomic era: review of the methodology and characterization of a new 1q41q42 microdeletion syndrome. *Genet Med* 2007;9(09):607–616
 - 87 Slavotinek AM, Moshrefi A, Davis R, et al. Array comparative genomic hybridization in patients with congenital diaphragmatic hernia: mapping of four CDH-critical regions and sequencing of candidate genes at 15q26.1-15q26.2. *Eur J Hum Genet* 2006;14(09):999–1008
 - 88 Zeng S, Patil SR, Yankowitz J. Prenatal detection of mosaic trisomy 1q due to an unbalanced translocation in one fetus of a twin pregnancy following in vitro fertilization: a postzygotic error. *Am J Med Genet A* 2003;120A(04):464–469
 - 89 Ahmed AA, Gilbert-Barness E. A Fryns syndrome-like phenotype with mosaic t(1;22)(q12;p12) chromosomal translocation. *Clin Dysmorphol* 2004;13(02):111–112
 - 90 Ahn HY, Shin JC, Kim YH, et al. Prenatal diagnosis of congenital diaphragmatic hernia in a fetus with 46,XY/46,X,-Y,+der(Y)t(Y;1)(q12;q12) mosaicism: a case report. *J Korean Med Sci* 2005;20(05):895–898
 - 91 Otake K, Uchida K, Inoue M, et al. Congenital diaphragmatic hernia with a pure duplication of chromosome 1q: report of the first surviving case. *Pediatr Surg Int* 2009;25(09):827–831
 - 92 Clark RD, Fenner-Gonzales M. Apparent Fryns syndrome in a boy with a tandem duplication of 1q24-31.2. *Am J Med Genet* 1989;34(03):422–426
 - 93 Li C. A prenatally recognizable malformation syndrome associated with a recurrent post-zygotic chromosome rearrangement der(Y)t(Y;1)(q12;q21). *Am J Med Genet A* 2010;152A(09):2339–2341
 - 94 Christiansen LR, Lage JM, Wolff DJ, Pai GS, Harley RA. Mosaic duplication 1(q11q44) in an infant with nephroblastomatosis and mineralization of extraplacental membranes. *Pediatr Dev Pathol* 2005;8(01):115–123
 - 95 Pacifici PG, Peter C, Yampolsky P, Koenen M, McArdle JJ, Witzemann V. Novel mouse model reveals distinct activity-dependent and -independent contributions to synapse development. *PLoS One* 2011;6(01):e16469
 - 96 Nagata K, Kiryu-Seo S, Maeda M, Yoshida K, Morita T, Kiyama H. Damage-induced neuronal endopeptidase is critical for presynaptic formation of neuromuscular junctions. *J Neurosci* 2010;30(20):6954–6962
 - 97 Casas KA, Mononen TK, Mikail CN, et al. Chromosome 2q terminal deletion: report of 6 new patients and review of phenotype-breakpoint correlations in 66 individuals. *Am J Med Genet A* 2004;130A(04):331–339
 - 98 Brackley KJ, Kilby MD, Morton J, Whittle MJ, Knight SJ, Flint J. A case of recurrent congenital fetal anomalies associated with a

- familial subtelomeric translocation. *Prenat Diagn* 1999;19(06): 570–574
- 99 Reddy KS, Flannery D, Farrer RJ. Microdeletion of chromosome sub-band 2q37.3 in two patients with abnormal situs viscerum. *Am J Med Genet* 1999;84(05):460–468
- 100 Callaway DA, Campbell IM, Stover SR, et al. Prioritization of candidate genes for congenital diaphragmatic hernia in a critical region on chromosome 4p16 using a machine-learning algorithm. *J Pediatr Genet* 2018;7(04):164–173
- 101 Hildebrand JD, Soriano P. Overlapping and unique roles for C-terminal binding protein 1 (CtBP1) and CtBP2 during mouse development. *Mol Cell Biol* 2002;22(15):5296–5307
- 102 Tautz J, Veenma D, Eussen B, et al. Congenital diaphragmatic hernia and a complex heart defect in association with Wolf-Hirschhorn syndrome. *Am J Med Genet A* 2010;152A(11): 2891–2894
- 103 Basgul A, Kavak ZN, Akman I, Basgul A, Gokaslan H, Elcioglu N. Prenatal diagnosis of Wolf-Hirschhorn syndrome (4p-) in association with congenital diaphragmatic hernia, cystic hygroma and IUGR. *Clin Exp Obstet Gynecol* 2006;33(02):105–106
- 104 Howe DT, Kilby MD, Sirry H, et al. Structural chromosome anomalies in congenital diaphragmatic hernia. *Prenat Diagn* 1996;16(11):1003–1009
- 105 van Dooren MF, Brooks AS, Hoozeboom AJ, et al. Early diagnosis of Wolf-Hirschhorn syndrome triggered by a life-threatening event: congenital diaphragmatic hernia. *Am J Med Genet A* 2004; 127A(02):194–196
- 106 Sachs M, Brohmann H, Zechner D, et al. Essential role of Gab1 for signaling by the c-Met receptor in vivo. *J Cell Biol* 2000;150(06): 1375–1384
- 107 Young RS, Palmer CG, Bender HA, Weaver DD, Hodes ME. Brief cytogenetic case report: a 4.5-year-old girl with deletion 4q syndrome—de novo, 46,XX, del(4) (pter leads to q31:). *Am J Med Genet* 1982;12(01):103–107
- 108 Park Y, Gong G, Choe G, Yu E, Kim KS, Lee I. Jarcho-Levin syndrome—a report of an autopsy case with cytogenetic analysis. *J Korean Med Sci* 1993;8(06):471–475
- 109 Wat MJ, Beck TF, Hernández-García A, et al. Mouse model reveals the role of SOX7 in the development of congenital diaphragmatic hernia associated with recurrent deletions of 8p23.1. *Hum Mol Genet* 2012;21(18):4115–4125
- 110 Longoni M, Lage K, Russell MK, et al. Congenital diaphragmatic hernia interval on chromosome 8p23.1 characterized by genetics and protein interaction networks. *Am J Med Genet A* 2012; 158A(12):3148–3158
- 111 Pecile V, Petroni MG, Fertz MC, Filippi G. Deficiency of distal 8p—report of two cases and review of the literature. *Clin Genet* 1990; 37(04):271–278
- 112 Borys D, Taxy JB. Congenital diaphragmatic hernia and chromosomal anomalies: autopsy study. *Pediatr Dev Pathol* 2004;7(01): 35–38
- 113 Shimokawa O, Miyake N, Yoshimura T, et al. Molecular characterization of del(8)(p23.1p23.1) in a case of congenital diaphragmatic hernia. *Am J Med Genet A* 2005;136(01):49–51
- 114 Slavotinek A, Lee SS, Davis R, et al. Fryns syndrome phenotype caused by chromosome microdeletions at 15q26.2 and 8p23.1. *J Med Genet* 2005;42(09):730–736
- 115 López I, Bafalliu JA, Bernabé MC, García F, Costa M, Guillén-Navarro E. Prenatal diagnosis of de novo deletions of 8p23.1 or 15q26.1 in two fetuses with diaphragmatic hernia and congenital heart defects. *Prenat Diagn* 2006;26(06):577–580
- 116 Wat MJ, Shchelochkov OA, Holder AM, et al. Chromosome 8p23.1 deletions as a cause of complex congenital heart defects and diaphragmatic hernia. *Am J Med Genet A* 2009;149A(08): 1661–1677
- 117 Arrington CB, Bleyl SB, Matsunami N, et al. A family-based paradigm to identify candidate chromosomal regions for isolated congenital diaphragmatic hernia. *Am J Med Genet A* 2012; 158A(12):3137–3147
- 118 Keitges EA, Pasion R, Burnside RD, et al. Prenatal diagnosis of two fetuses with deletions of 8p23.1, critical region for congenital diaphragmatic hernia and heart defects. *Am J Med Genet A* 2013; 161A(07):1755–1758
- 119 Ackerman KG, Herron BJ, Vargas SO, et al. Fog2 is required for normal diaphragm and lung development in mice and humans. *PLoS Genet* 2005;1(01):58–65
- 120 Kuechler A, Buysse K, Clayton-Smith J, et al. Five patients with novel overlapping interstitial deletions in 8q22.2q22.3. *Am J Med Genet A* 2011;155A(08):1857–1864
- 121 Temple IK, Barber JC, James RS, Burge D. Diaphragmatic herniae and translocations involving 8q22 in two patients. *J Med Genet* 1994;31(09):735–737
- 122 Meech R, Gonzalez KN, Barro M, et al. Barx2 is expressed in satellite cells and is required for normal muscle growth and regeneration. *Stem Cells* 2012;30(02):253–265
- 123 Klaassens M, Scott DA, van Dooren M, et al. Congenital diaphragmatic hernia associated with duplication of 11q23-qter. *Am J Med Genet A* 2006;140(14):1580–1586
- 124 Fernández-Perea Y, García-Díaz L, Sánchez J, Antiñolo G, Borrego S. Ultrasound, echocardiography, MRI, and genetic analysis of a fetus with congenital diaphragmatic hernia and partial 11q trisomy. *Case Rep Obstet Gynecol* 2017;2017:1471704
- 125 Park JP, McDermet MK, Doody AM, Marin-Padilla JM, Moeschler JB, Wurster-Hill DH. Familial t(11;13)(q21;q14) and the duplication 11q, 13q phenotype. *Am J Med Genet* 1993;45(01):46–48
- 126 Zakowski MF, Wright Y, Ricci A Jr. Pericardial agenesis and focal aplasia cutis in tetrasomy 12p (Pallister-Killian syndrome). *Am J Med Genet* 1992;42(03):323–325
- 127 Wilkens A, Liu H, Park K, et al. Novel clinical manifestations in Pallister-Killian syndrome: comprehensive evaluation of 59 affected individuals and review of previously reported cases. *Am J Med Genet A* 2012;158A(12):3002–3017
- 128 Ozlü T, Ocak Z, Ozyurt O. Prenatal diagnosis of Pallister Killian Syndrome in a fetus with congenital diaphragmatic hernia, short limbs, and increased nuchal translucency. *Taiwan J Obstet Gynecol* 2014;53(03):404–405
- 129 Jamuar S, Lai A, Unger S, Nishimura G. Clinical and radiological findings in Pallister-Killian syndrome. *Eur J Med Genet* 2012;55(03):167–172
- 130 Tidrenczel Z, P Tardy E, Sarkadi E, Simon J, Beke A, Demeter J. [Prenatally diagnosed case of Pallister-Killian syndrome]. *Orv Hetil* 2018;159(21):847–852
- 131 Libotte F, Bizzoco D, Gabrielli I, et al. Pallister-Killian syndrome: cytogenetics and molecular investigations of mosaic tetrasomy 12p in prenatal chorionic villus and in amniocytes. Strategy of prenatal diagnosis. *Taiwan J Obstet Gynecol* 2016;55(06): 863–866
- 132 Karaman B, Kayserili H, Ghanbari A, et al. Pallister-Killian syndrome: clinical, cytogenetic and molecular findings in 15 cases. *Mol Cytogenet* 2018;11:45
- 133 Enns GM, Cox VA, Goldstein RB, Gibbs DL, Harrison MR, Golabi M. Congenital diaphragmatic defects and associated syndromes, malformations, and chromosome anomalies: a retrospective study of 60 patients and literature review. *Am J Med Genet* 1998;79(03):215–225
- 134 High FA, Bhayani P, Wilson JM, Bult CJ, Donahoe PK, Longoni M. De novo frameshift mutation in COUP-TFII (NR2F2) in human congenital diaphragmatic hernia. *Am J Med Genet A* 2016;170(09):2457–2461
- 135 Klaassens M, van Dooren M, Eussen HJ, et al. Congenital diaphragmatic hernia and chromosome 15q26: determination of a candidate region by use of fluorescent in situ hybridization and array-based comparative genomic hybridization. *Am J Hum Genet* 2005;76(05):877–882

- 136 Bettelheim D, Hengstschläger M, Drahoňský R, Eppel W, Bernaschek G. Two cases of prenatally diagnosed diaphragmatic hernia accompanied by the same undescribed chromosomal deletion (15q24 de novo). *Clin Genet* 1998;53(04):319–320
- 137 Mosca AL, Pinson L, Andrieux J, et al. Refining the critical region for congenital diaphragmatic hernia on chromosome 15q26 from the study of four fetuses. *Prenat Diagn* 2011;31(09):912–914
- 138 Jaillard S, Loget P, Lucas J, et al. Terminal 6.9Mb deletion of chromosome 15q, associated with a structurally abnormal X chromosome in a patient with congenital diaphragmatic hernia and heart defect. *Eur J Med Genet* 2011;54(02):186–188
- 139 Biggio JR Jr, Descartes MD, Carroll AJ, Holt RL. Congenital diaphragmatic hernia: is 15q26.1–26.2 a candidate locus? *Am J Med Genet A* 2004;126A(02):183–185
- 140 Brady PD, DeKoning P, Fryns JP, Devriendt K, Deprest JA, Vermeesch JR. Identification of dosage-sensitive genes in fetuses referred with severe isolated congenital diaphragmatic hernia. *Prenat Diagn* 2013;33(13):1283–1292
- 141 Castiglia L, Fichera M, Romano C, et al. Narrowing the candidate region for congenital diaphragmatic hernia in chromosome 15q26: contradictory results. *Am J Hum Genet* 2005;77(05):892–894, author reply 894–895
- 142 Fernandez BA, Roberts W, Chung B, et al. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11.2 in individuals ascertained for diagnosis of autism spectrum disorder. *J Med Genet* 2010;47(03):195–203
- 143 Strong M, Garabedian M, Pettigrew A, Barron N, Hansen W. Prenatal diagnosis of partial trisomy 16p and its association with congenital diaphragmatic hernia. *Prenat Diagn* 2013;33(08):797–799
- 144 Yap P, McGillivray G, Norris F, Said JM, Kornman L, Stark Z. Fetal phenotype of 17q12 microdeletion syndrome: renal echogenicity and congenital diaphragmatic hernia in 2 cases. *Prenat Diagn* 2015;35(12):1265–1267
- 145 Goumy C, Laffargue F, Eymard-Pierre E, et al. Congenital diaphragmatic hernia may be associated with 17q12 microdeletion syndrome. *Am J Med Genet A* 2015;167A(01):250–253
- 146 Hendrix NW, Clemens M, Canavan TP, Surti U, Rajkovic A. Prenatally diagnosed 17q12 microdeletion syndrome with a novel association with congenital diaphragmatic hernia. *Fetal Diagn Ther* 2012;31(02):129–133
- 147 Kammoun M, Souche E, Brady P, et al. Genetic profile of isolated congenital diaphragmatic hernia revealed by targeted next-generation sequencing. *Prenat Diagn* 2018;38(09):654–663
- 148 Gupta N, Shastri S, Singh PK, et al. Nasopharyngeal teratoma, congenital diaphragmatic hernia and Dandy-Walker malformation - a yet uncharacterized syndrome. *Clin Genet* 2016;90(05):470–471
- 149 Tan TY, Collins A, James PA, et al. Phenotypic variability of distal 22q11.2 copy number abnormalities. *Am J Med Genet A* 2011;155A(07):1623–1633
- 150 Unolt M, DiCairano L, Schlechtweg K, et al. Congenital diaphragmatic hernia in 22q11.2 deletion syndrome. *Am J Med Genet A* 2017;173(01):135–142
- 151 Bétrémieux P, Lionnais S, Beuchée A, et al. Perinatal management and outcome of prenatally diagnosed congenital diaphragmatic hernia: a 1995–2000 series in Rennes University Hospital. *Prenat Diagn* 2002;22(11):988–994
- 152 Oskarsdóttir S, Persson C, Eriksson BO, Fasth A. Presenting phenotype in 100 children with the 22q11 deletion syndrome. *Eur J Pediatr* 2005;164(03):146–153
- 153 Stark Z, Behrsin J, Burgess T, et al. SNP microarray abnormalities in a cohort of 28 infants with congenital diaphragmatic hernia. *Am J Med Genet A* 2015;167A(10):2319–2326
- 154 Taylor J, Aftimos S. Congenital diaphragmatic hernia is a feature of Opitz G/BBB syndrome. *Clin Dysmorphol* 2010;19(04):225–226
- 155 Plaja A, Vendrell T, Sarret E, Torán N, Mediano C. Terminal deletion of Xp in a dysmorphic anencephalic fetus. *Prenat Diagn* 1994;14(05):410–412
- 156 Qidwai K, Pearson DM, Patel GS, et al. Deletions of Xp provide evidence for the role of holocytochrome C-type synthase (HCCS) in congenital diaphragmatic hernia. *Am J Med Genet A* 2010;152A(06):1588–1590
- 157 Allanson J, Richter S. Linear skin defects and congenital microphthalmia: a new syndrome at Xp22.2. *J Med Genet* 1991;28(02):143–144
- 158 Kantarci S, Al-Gazali L, Hill RS, et al. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. *Nat Genet* 2007;39(08):957–959
- 159 Gofin Y, Mackay LP, Machol K, et al. Evidence that FGFR1 contributes to congenital diaphragmatic hernia development in humans. *Am J Med Genet A* 2021;185(03):836–840
- 160 Bleyl SB, Moshrefi A, Shaw GM, et al. Candidate genes for congenital diaphragmatic hernia from animal models: sequencing of FOG2 and PDGFRalpha reveals rare variants in diaphragmatic hernia patients. *Eur J Hum Genet* 2007;15(09):950–958
- 161 Kaya TB, Aydemir O, Ceylaner S, Ceylaner G, Tekin AN. Isolated congenital diaphragm hernia associated with homozygous SLIT3 gene variant in dizygous twins. *Eur J Med Genet* 2021;64(07):104215
- 162 Wilmink FA, Papatsonis DN, Grijseels EW, Wessels MW. Cornelia de Lange syndrome: a recognizable fetal phenotype. *Fetal Diagn Ther* 2009;26(01):50–53
- 163 Banait N, Fenton A, Splitt M. Cornelia de Lange syndrome due to mosaic NIPBL mutation: antenatal presentation with sacrococcygeal teratoma. *BMJ Case Rep* 2015;2015:bcr2015211006
- 164 Hague J, Twiss P, Mead Z, Park SM. Clinical diagnosis of classical Cornelia De Lange syndrome made from postmortem examination of second trimester fetus with novel NIPBL pathogenic variant. *Pediatr Dev Pathol* 2019;22(05):475–479
- 165 Jongmans MC, Admiraal RJ, van der Donk KP, et al. CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. *J Med Genet* 2006;43(04):306–314
- 166 Rossetti LZ, Grinton K, Yuan B, et al. Review of the phenotypic spectrum associated with haploinsufficiency of MYRF. *Am J Med Genet A* 2019;179(07):1376–1382
- 167 Jin SC, Homsy J, Zaidi S, et al. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nat Genet* 2017;49(11):1593–1601
- 168 Pinz H, Pyle LC, Li D, et al. De novo variants in Myelin regulatory factor (MYRF) as candidates of a new syndrome of cardiac and urogenital anomalies. *Am J Med Genet A* 2018;176(04):969–972
- 169 McVeigh TP, Banka S, Reardon W. Kabuki syndrome: expanding the phenotype to include microphthalmia and anophthalmia. *Clin Dysmorphol* 2015;24(04):135–139
- 170 Li Y, Bögershausen N, Alanay Y, et al. A mutation screen in patients with Kabuki syndrome. *Hum Genet* 2011;130(06):715–724
- 171 Zarate YA, Zhan H, Jones JR. Infrequent manifestations of Kabuki syndrome in a patient with novel MLL2 mutation. *Mol Syndromol* 2012;3(04):180–184
- 172 Jordan VK, Beck TF, Hernandez-Garcia A, et al. The role of FREM2 and FRAS1 in the development of congenital diaphragmatic hernia. *Hum Mol Genet* 2018;27(12):2064–2075
- 173 Chassaing N, Ragge N, Kariminejad A, et al. Mutation analysis of the STRA6 gene in isolated and non-isolated anophthalmia/microphthalmia. *Clin Genet* 2013;83(03):244–250
- 174 Pasutto F, Sticht H, Hammersen G, et al. Mutations in STRA6 cause a broad spectrum of malformations including anophthalmia, congenital heart defects, diaphragmatic hernia, alveolar capillary dysplasia, lung hypoplasia, and mental retardation. *Am J Hum Genet* 2007;80(03):550–560

- 175 Chassaing N, Golzio C, Odent S, et al. Phenotypic spectrum of STRA6 mutations: from Matthew-Wood syndrome to non-lethal anophthalmia. *Hum Mutat* 2009;30(05):E673–E681
- 176 Golzio C, Martinovic-Bouriel J, Thomas S, et al. Matthew-Wood syndrome is caused by truncating mutations in the retinol-binding protein receptor gene STRA6. *Am J Hum Genet* 2007;80(06):1179–1187
- 177 West B, Bove KE, Slavotinek AM. Two novel STRA6 mutations in a patient with anophthalmia and diaphragmatic eventration. *Am J Med Genet A* 2009;149A(03):539–542
- 178 Bashamboo A, Eozenou C, Jorgensen A, et al. Loss of function of the nuclear receptor NR2F2, encoding COUP-TF2, causes testis development and cardiac defects in 46,XX children. *Am J Hum Genet* 2018;102(03):487–493
- 179 McInerney-Leo AM, Harris JE, Gattas M, et al. Fryns syndrome associated with recessive mutations in PIGN in two separate families. *Hum Mutat* 2016;37(07):695–702
- 180 Alessandri JL, Gordon CT, Jacquemont ML, et al. Recessive loss of function PIGN alleles, including an intragenic deletion with founder effect in La Réunion Island, in patients with Fryns syndrome. *Eur J Hum Genet* 2018;26(03):340–349
- 181 Brady PD, Delle Chiaie B, Christenhusz G, et al. A prospective study of the clinical utility of prenatal chromosomal microarray analysis in fetuses with ultrasound abnormalities and an exploration of a framework for reporting unclassified variants and risk factors. *Genet Med* 2014;16(06):469–476
- 182 Hughes-Benzie RM, Pilia G, Xuan JY, et al. Simpson-Golabi-Behmel syndrome: genotype/phenotype analysis of 18 affected males from 7 unrelated families. *Am J Med Genet* 1996;66(02):227–234
- 183 Veugelers M, Cat BD, Muyltermans SY, et al. Mutational analysis of the GPC3/GPC4 glypican gene cluster on Xq26 in patients with Simpson-Golabi-Behmel syndrome: identification of loss-of-function mutations in the GPC3 gene. *Hum Mol Genet* 2000;9(09):1321–1328
- 184 Li M, Shuman C, Fei YL, et al. GPC3 mutation analysis in a spectrum of patients with overgrowth expands the phenotype of Simpson-Golabi-Behmel syndrome. *Am J Med Genet* 2001;102(02):161–168
- 185 Cottreau E, Mortemousque I, Moizard MP, et al. Phenotypic spectrum of Simpson-Golabi-Behmel syndrome in a series of 42 cases with a mutation in GPC3 and review of the literature. *Am J Med Genet C Semin Med Genet* 2013;163C(02):92–105
- 186 Slavotinek AM. Single gene disorders associated with congenital diaphragmatic hernia. *Am J Med Genet C Semin Med Genet* 2007;145C(02):172–183
- 187 Twigg SR, Kan R, Babbs C, et al. Mutations of ephrin-B1 (EFNB1), a marker of tissue boundary formation, cause craniofrontonasal syndrome. *Proc Natl Acad Sci U S A* 2004;101(23):8652–8657
- 188 Twigg SR, Matsumoto K, Kidd AM, et al. The origin of EFNB1 mutations in craniofrontonasal syndrome: frequent somatic mosaicism and explanation of the paucity of carrier males. *Am J Hum Genet* 2006;78(06):999–1010
- 189 Vasudevan PC, Twigg SR, Mulliken JB, Cook JA, Quarrell OW, Wilkie AO. Expanding the phenotype of craniofrontonasal syndrome: two unrelated boys with EFNB1 mutations and congenital diaphragmatic hernia. *Eur J Hum Genet* 2006;14(07):884–887