Genetic Factors in Congenital Diaphragmatic Hernia

A. M. Holder,* M. Klaassens,* D. Tibboel, A. de Klein, B. Lee, and D. A. Scott

Congenital diaphragmatic hernia (CDH) is a relatively common birth defect associated with high mortality and morbidity. Although the exact etiology of most cases of CDH remains unknown, there is a growing body of evidence that genetic factors play an important role in the development of CDH. In this review, we examine key findings that are likely to form the basis for future research in this field. Specific topics include a short overview of normal and abnormal diaphragm development, a discussion of syndromic forms of CDH, a detailed review of chromosomal regions recurrently altered in CDH, a description of the retinoid hypothesis of CDH, and evidence of the roles of specific genes in the development of CDH.

Congenital diaphragmatic hernia (CDH [MIM 142340, 222400, 610187, and 306950]) is defined as a protrusion of abdominal viscera into the thorax through an abnormal opening or defect that is present at birth. In some cases, this protrusion is covered by a membranous sac. In contrast, diaphragmatic eventrations are extreme elevations, rather than protrusions, of part of the diaphragm that is often atrophic and abnormally thin. CDH is a relatively common birth defect, with an incidence of ~1 in every 3,000 live births.[1,2] CDH is often associated with potentially lethal lung hypoplasia and pulmonary hypertension. Despite advances in therapy, mortality remains high, especially among severely affected infants, and long-term morbidity among survivors is common.[3]

The most common type of CDH is the posterolateral, or Bochdalek-type, hernia, which accounts for 90%–95% of CDH cases.[1] Other types of CDH include anterior retrosternal or peristernal Morgagni hernias, central (septum transversum) hernias, and pars sternalis hernias, which are found in the pentalogy of Cantrell—a rare association involving abnormalities of the anterior diaphragm, sternum, heart, and abdominal wall.

Although there are multiple examples of familial cases of CDH in the literature, the recurrence risk for isolated cases of CDH is often reported to be <2% on the basis of a mathematical model of multifactorial inheritance risk.[1,4,5] Empiric data also suggest a relatively low recurrence risk for CDH.[6–8] Although multifactorial inheritance may best explain most cases of CDH in humans, much has been learned about the genetic factors that play a role in the development of CDH by studies of patients with CDH caused by specific genetic syndromes and chromosome anomalies. Our understanding of CDH has also been aided by basic research with the use of dietary, teratogen-induced, and knockout models of CDH.

Overview of Normal and Abnormal Diaphragm Development

The development of the human diaphragm occurs between the 4th and 12th wk of gestation. Traditional views of diaphragm development suggest that the diaphragm arises from four different structures.[9] The septum transversum gives rise to the central portion of the diaphragm, the pleuroperitoneal folds (PPFs) give rise to the posterolateral section of the diaphragm, the dorsal (esophageal) mesentery gives rise to a portion of the diaphragm posterior to the esophagus, and elements from the thoracic body wall contribute to a rim of musculature around the diaphragm's periphery. In contrast to this traditional view, systematic examinations of diaphragm development in rodents have failed to identify contributions to the diaphragm musculature from the lateral body wall, the septum transversum, or the esophageal mesenchyme.[10] Rather, myogenic cells and axons were shown to coalesce within the PPF and then to expand to form the neuromuscular component of the diaphragm.[10] If further investigation shows that this model provides an accurate depiction of diaphragm development in humans, the classic view of diaphragm development will need to be revised.[11]

Several theories have been proposed concerning the primary embryologic events that lead to the development of CDH. Events implicated in these theories have included (1) abnormalities in (ipsilateral) lung development, (2) failure of closure of the pleuroperitoneal canals, (3) defective myoblast formation, and (4) abnormal phrenic nerve innervation.[12–14]

Although it is possible that each of these abnormalities may play a role in the development of some cases of CDH, there is growing evidence from animal models that CDH

From the Department of Molecular and Human Genetics, Baylor College of Medicine (A.M.H.; B.L.; D.A.S.), and Howard Hughes Medical Institute (A.M.H.; B.L.), Houston; and Departments of Pediatric Surgery (M.K.; D.T.) and Clinical Genetics (M.K.; A.d.K.), Erasmus Medical Centre, Rotterdam, The Netherlands

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Address for correspondence and reprints: Dr. Brendan Lee, 635E, One Baylor Plaza, Houston, TX 77030. E-mail: blee@bcm.tmc.edu

* These two authors contributed equally to this work.

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Table 1. Examples of Genetic Syndromes Associated with CDH

Syndrome Name	Chromosome(s)	Gene(s)	Brief Description
Beckwith-Wiedemann (MIM 130650)	11p15, 5q35	*CDKN1C* (MIM 600856), *NSD1* (MIM 606681)	Autosomal dominant inheritance, macroglossia, hypoglycemia, visceromegaly, abdominal-wall defects, and overgrowth
CHARGE (MIM 214800)	8q12.1	*CHD7* (MIM 608892)	Autosomal dominant inheritance, coloboma, cardiac abnormalities, choanal atresia, growth retardation, genital abnormalities, ear abnormalities, and hearing loss
Cornelia de Lange (MIM 122470 and 300590)	5p13.1, Xp11.22-p11.21	*NIPBL* (MIM 608667), *SMC1A* (MIM 300040)	Autosomal dominant inheritance, distinctive facial features, microcephaly, hirsutism, malformations of the upper limbs, and growth retardation
Craniofrontonasal (MIM 304110)	Xq12	*EFNB1* (MIM 300035)	X-linked dominant inheritance, females more severely affected, craniosynostosis, hypertelorism, broad nasal tip, grooved nails of the hallux and thumb, syndactyly, and skeletal abnormalities
Denys-Drash (MIM 194080)	11p13	*WT1* (MIM 607102)	Autosomal dominant inheritance, male pseudohermaphroditism, genital abnormalities, and increased risk of Wilms tumor
Donnai-Barrow (MIM 222448)	2q23-q31[30]	...	Autosomal recessive inheritance, CDH, omphalocele, agenesis of the corpus callosum, hypertelorism, and hearing loss
Fryns (MIM 229850)	Fryns-like phenotype has been seen with duplication of 1q24-q31.2; deletion of the terminal portion of 6q, 8p23.1, and 15q26; and partial trisomy 22[24,26–29]	...	Autosomal recessive inheritance, CDH, coarse facial features, cleft lip/palate, cardiac malformations, cerebral abnormalities, and hypoplastic finger/toenails
Pallister-Killian (MIM 601803)	Mosaic tetrasomy 12p	...	Coarse facial features with broad forehead and hypertelorism, sparse temporal hair, hypopigmentations, and mental retardation
Simpson-Golabi-Behmel (MIM 312870 and 300209)	Xq26, Xp22.3-p22.2	*GPC3* (MIM 300037), *CXORF5* (MIM 300170)	X-linked recessive inheritance, macrosomia, coarse facial features, hypertelorism, macroglossia, skeletal abnormalities, abdominal-wall defects, and renal abnormalities
Thoracoabdominal (MIM 313850)	Xq25-q26.1	...	X-linked dominant inheritance, diaphragmatic and ventral hernias, hypoplastic lungs, and cardiac anomalies
Wolf-Hirschhorn (MIM 194190)	4p16	...	"Greek helmet" facial appearance, mental and growth retardation, cleft lip/palate, cardiac defects, and epilepsy

arises from malformation of the amuscular mesenchymal substratum of the PPF before pleuroperitoneal canal closure.[10,15,16] Critical findings that support this model include the normal formation of the primordial diaphragm in *Fgf10*$^{-/-}$ mouse embryos that have complete lung agenesis and the ability to induce defects characteristic of CDH in *c-met*$^{-/-}$ mouse embryos that do not form diaphragm muscle fibers because of a defect in muscle precursor migration.[16]

Pulmonary hypoplasia is one of the most serious clinical complications accompanying CDH. The role of physical compression on the development of pulmonary hypoplasia in CDH was effectively demonstrated in studies of surgically produced CDH in fetal lambs and is consistent with the observation that pulmonary hypoplasia is usually more severe on the side of the diaphragmatic defect.[17,18] However, studies of lung development in rodents with CDH caused by in utero exposure to the herbicide nitrofen suggested that pulmonary hypoplasia was present before development of a diaphragmatic defect.[12,19] This observation led to the development of the dual-hit hypothesis, which states that pulmonary hypoplasia can be caused by the combined effect of an early insult that directly affects lung development followed by further restriction in lung growth, later in gestation, secondary to diminished fetal breathing movements and competition for space as a result of the herniation of the abdominal contents into the thoracic cavity.[19]

It is possible that these two hits may be caused by defects within a single gene that affects both lung and diaphragm development. Examples of genes that are known to affect both lung and diaphragm development include *Friend of GATA2* (*FOG2* [MIM 603693]) and *GATA-binding protein 4* (*GATA4* [MIM 600576]).[20–22] In the future, it may be possible to formally test the dual-hit hypothesis by generating conditional knockout mice in which the lungs and the primordial diaphragm are targeted separately. These studies may also provide another means of testing whether diaphragmatic defects can be induced or altered by a primary pulmonary insult.

Syndromic Forms of CDH

CDH may occur either as an isolated birth defect or in association with other non–hernia-related anomalies (known as "nonisolated CDH" or "CDH+"). Some anomalies—including lung hypoplasia, abnormalities in cardiac position, intestinal malrotation, and patent ductus arteriosus—are typically considered secondary effects of CDH and are not considered grounds for classification as nonisolated CDH. Common findings associated with CDH include cardiovascular abnormalities, abnormalities of the CNS, and genitourinary and/or renal anomalies.

Some individuals with nonisolated CDH have patterns of anomalies that are strongly suggestive of a specific genetic syndrome. In patients with CDH for whom a syndromic diagnosis can be provided, the most frequently diagnosed syndrome is Fryns syndrome (MIM 229850).[23–25] However, reports of individuals with Fryns-like phenotypes associated with chromosomal anomalies—including duplication of 1q24-q31.2; deletion of the terminal portion of 6q, 8p23.1, and 15q26; and partial trisomy 22—suggests that some cases of CDH attributed to this autosomal recessive syndrome are likely to represent genocopies of this disorder.[24,26–29]

Many of the syndromes associated with CDH have specific Mendelian inheritance patterns and, in some cases, the location and/or the identity of the causative gene(s) is known. Examples of CDH syndromes associated with a particular chromosomal locus or causative gene(s) are shown in table 1. CDH is a cardinal feature of some of these syndromes, whereas, for others, the rates of CDH are lower but probably exceed the level seen in the general population.

The existence of genetic syndromes associated with CDH provides one of the strongest lines of evidence that genetic factors play a role in the development of CDH. It is likely that much of our understanding of CDH will be shaped by studies that focus on understanding the molecular mechanisms by which changes in these genes result in diaphragmatic defects. These studies may, in turn, help us identify interacting genes that are involved in the development of other forms of CDH.

Chromosomal Abnormalities Described in Patients with CDH

Chromosomal anomalies have been identified as an important etiology for nonisolated CDH.[31] In the majority of published cases, chromosome anomalies were identified using a combination of G-banded chromosome analysis and/or FISH. The use of new genomic technologies—like array-based comparative genomic hybridization (array CGH)—is likely to increase the number of chromosomal anomalies identified in individuals with CDH and may aid in the identification of CDH-related genes.[23,24,32]

Trisomy 13, 18, and 21 and 45,X are the most common aneuploidies described in association with CDH.[31] Structural abnormalities—including deletions, duplications, inversions, and translocations—of nearly all chromosomes have also been described in association with CDH.[33,34] Both Lurie[33] and Enns et al.[34] have published useful reviews of chromosomal anomalies associated with CDH. Using these reviews as a foundation, we have compiled an updated list of the CDH-associated chromosomal anomalies (table 2).

Chromosomal regions that are involved in balanced translocation or are recurrently deleted or duplicated in patients with CDH are of particular interest to researchers, because they are more likely to harbor genes that cause or predispose to the development of CDH than are less commonly affected regions of the genome. It is important to note that many of the deletions and duplications described in the literature are the product of unbalanced

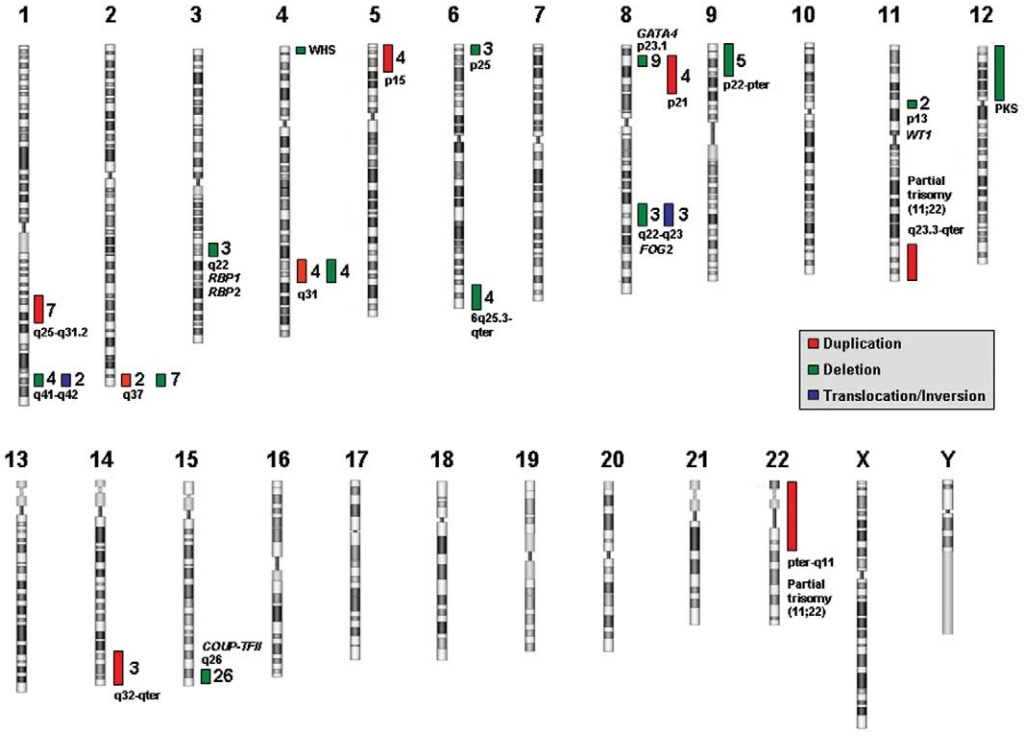

Figure 1. Chromosomal regions and selected candidate genes for CDH. Recurrent chromosomal abnormalities associated with patients with CDH are represented by colored bars. For each region, the number of patients described with that duplication (*red bar*), deletion (*green bar*), or translocation/inversion (*blue bar*) is given. Selected candidate genes and genetic syndromes are included beside their respective regions. PKS = Pallister-Killian syndrome; WHS = Wolf-Hirschorn syndrome.

translocations, and it is possible that the diaphragmatic defects seen in these cases are caused by two or more genes located in nonadjacent chromosomal regions. It should also be noted that, in most instances, CDH occurs in only a fraction of individuals with a particular chromosomal abnormality. This suggests that genetic background, environmental factors, and/or stochastic events may also play a role in determining whether an individual develops CDH.

Chromosomal regions that have been associated with CDH in three or more individuals are shown in figure 1 and are described individually below. Several of these intervals overlap the position of genes that are involved in the retinoic-acid signaling pathway—which has been hypothesized to play a role in the development of CDH—or genes that have been implicated in the development of CDH because of studies involving animal models and/or human subjects. In most cases, the chromosomal region described represents a minimally affected region defined by G-banded chromosome analysis and/or FISH. In instances where the minimal affected region has been defined using high-resolution techniques, such as array CGH, we have made specific mention of these results.

Duplication of 1q25q31.2

Duplication of this region has been described in at least seven patients with CDH.[26,40–42,44–46] At least three of these cases of CDH were also associated with cleft palate.

Deletion of 1q41-q42

Deletions of this region have been reported in four cases of CDH.[23,49–51] Three cases involve a larger deletion, identified by standard cytogenetics techniques. The smallest deletion was determined by Kantarci et al.[23] using high-resolution array CGH that refined the interval to an ~5-Mb region bounded by BACs RP11-553F10 and RP11-275O4. One individual with balanced translocation and one individual with an inversion involving 1q41 have also been described.[36,39]

Deletion or Duplication of 2q37

CDH has been described in seven patients with deletions of 2q37and in two patients with 2q37 duplications.[39,45,56–61] Interestingly, in almost all these patients, the duplication or deletion starts at band q37. Of the patients in whom

Table 2. Structural Chromosomal Anomalies Described in Patients with CDH

Chromosome, Type of Anomaly, and Patient Karyotype	Study Author(s)
Chromosome 1:	
Balanced translocation:	
46,X,t(X;1)(q26;q12)	Punnett[35]
46,XY,t(1;15)(q41;q21.2) de novo	Smith et al.[36]
46,XY,t(1;21)(q32;q22)pat	Howe et al.[37]
46,XY,t(1;14)(p22;q13),inv(6)(p25q22),del(15)(q26.1q26.2)	Klaassens et al.[38]
Inversion:	
46,XY,inv(1)(q41q44)mat	Tonks et al.[39]
Duplication:	
46,XY/46,X,der(Y)t(Y;1)(q12;q12)	Ahn et al.[40]
46,XY[9]/46,X,der(Y),t(Y;1)(q12;q12)[12]	Zeng et al.[41]
46,XX,der(22)t(1;22)(q12;p12)[11]/46,XX[9]	Ahmed et al.[42]
der(9)t(1;9)(q32.3;p24.1)	Kousseff[43]
dup(1)(q22q32)	Schneider et al.[44]
dup(1)(q22q32)mosaicism	van Dooren[45]
46,XY/46,XY,dup(1)(q24.2q31.2)	Clark and Fenner-Gonzalez[26]
dup(1)(q25q31.2)	Mehraein et al.[46]
Deletion:	
der(1)t(1;21)mosaicism	Philip et al.[47]
46,XX,del(1)(p)	Benjamin et al.[48]
46,XX,del(1)(q32.3q42.3)	Youssoufian et al.[49]
46,XY,del(1)(q41q42.12)	Kantarci et al.[23]
46,XY,del(1)(q32.3q42.2)	Slavotinek et al.[50]
46,XX,del(1)(q42.11q42.3)	Rogers et al.[51]
Chromosome 2:	
Duplication:	
46,XX/47,XX,der(2)del(2)(p13)del(2)(q12)	Grevengood et al.[52]
der(X)t(X;2)(q27;p13)mat	Sarda et al.[53]
dup(2)(p13p25)	van Dooren[45]
dup(2)(p21p25)	van Dooren[45]
der(6)t(2;6)(p23;p25)	Bender et al.[54]
46,XY,dup(2)(p21p25)	Heathcote et al.[55]
46,XY,der(7)t(2;7)(p25.3;q34)mat	Enns et al.[34]
dup(2)(q33q37)	Johnson et al.[56]
46,XY,der(15)t(2;15)(q37.2;q26.2)	Scott et al.[57]
Deletion:	
46,XX,der(2)t(2;7)(q36;q37)pat	Brackley et al.[58]
46,XY,del(2)(q33q35 or q35q37) de novo	Tonks et al.[39]
46,XY,der(2)t(2;8)(q37;p11.2)pat	Tonks et al.[39]
46,XX,der(2)t(2;14)(q37.1;q31.2)	van Dooren[45]
der(2)t(2;14)(q37;q31.2)	De La Fuente et al.[59]
46,XX,del(2)(q37.1)	Casas et al.[60]
46,XY,del(2)(q37.3)	Reddy et al.[61]
Chromosome 3:	
Balanced translocation:	
46,XY,t(3;12)(p21.1;p13.3) de novo	Tonks et al.[39]
Duplication:	
der(21)t(3;21)(p24.3;q11.2)mat	Pettigrew[62]
46,XX,der(15)t(3;15)(q29;q26.1)mat	Rosenberg et al.[63]
Deletion:	
del(3)(p)	Steinhorn et al.[64]
del(3)(p12p21)	Pfeiffer et al.[65]
46,XY,del(3)(q11.1q13.2)/47,XY,del(3)(q11.2q13.2),+r(3)	Brennan et al.[66]
46,XY,del(3)(q21q23)	Wolstenholme et al.[67]
del(3)(q22); two patients	Dillon et al.[68]
der(3)t(3;5)(q27;q31)	Kristeshavilli et al.[69]
Miscellaneous:	
46,XY,der,t(3;8)(p23;p23.1)	Tibboel and Gaag[31]
Chromosome 4:	
Ring chromosome[a]:	
45,XX,−4/46,XX,r(4)(p1?6;q3?3)	Kocks et al.[70]

(*continued*)

Table 2. (continued)

Chromosome, Type of Anomaly, and Patient Karyotype	Study Author(s)
Duplication:	
46,XY,rec(4),dup(4)(q),inv(4)(p15.2q25)pat	Kobori et al.[71]
46,XY,inv dup(4)(q32q26),del(4)(q32)	Frints et al.[72]
46,XX,der(22)t(4;22)(q28.3;p13)	Celle et al.[73]
46,XY,der(18)t(4;18)(q31;q23)	Yunis et al.[74]
dup(4)(q25q31)	van Dooren[45]
Deletion:	
46,XY,del(4)(p16)	van Dooren et al.[75]
del(4)(p16); two patients	Howe et al.[37]
46,XY,del(4)(p16)	Tachdjian et al.[76]
del(4)(p16)	Pober et al.[8]
del(4)(p16.3)	Casaccia et al.[77]
46,XY,rec(4),dup(4)(q),inv(4)(p15.2q25)pat	Kobori et al.[71]
del(4)(p16); two patients	Laziuk et al.[78]
46,XX,del(4)(p13)	Sergi et al.[79]
del(4)(p16.3)	Van Buggenhout et al.[80]
del(4)(p16.3)	Slavotinek et al.[50]
46,XX,der(4)t(4;13)(p16;q32)	Tapper et al.[81]
del(4)(q31.3)	Del Campo et al.[82]
46,XX,del(4)(qter)	Park et al.[83]
del(4)(q31)	van Dooren[45]
del(4)(q31.1q31.3 or q31.3q32.2)	Wakui et al.[84]
del(4)(q31)	Young et al.[85]
46,XY,inv dup(4)(q32q26),del(4)(q32)	Frints et al.[72]
der(4)t(4;20)(q34.2;q13.1)pat	Pober et al.[8]
der(4)t(4;20)(q34.2;q13.1)pat	Reiss et al.[86]
Chromosome 5:	
Duplication:	
Partial trisomy 5	Bollmann et al.[87]
dup(5)(q33)	Korner et al.[88]
46,XY,−9,+t(5q;9p)	Torfs et al.[1]
der(15)t(5;15)(p15.3;q24), two cases	Aviram-Goldring et al.[89]
der(9)t(5;9)(p13;p22)	Liberfarb et al.[90]
47,XY,t(5;13)(p15;q21)+der(13)t(5;13)(p15;q21)mat	Masuno et al.[91]
der(3)t(3;5)(q27;q31)	Kristeshavilli et al.[69]
Deletion:	
del(5)(q13q22)	Kousseff[43]
Chromosome 6:	
Balanced translocation:	
46,XY,t(6;8)(q24;q23)	Howe et al.[37]
Inversion:	
46,XY,t(1;14)(p22;q13),inv(6)(p25q22),del(15)(q26.1q26.2)	Klaassens et al.[38]
Duplication:	
47,XY,+der(22)t(6;22)(p25;q11.2)	Scarbrough et al.[92]
46,XY,der(15)t(6;15)(p25;q24)mat	Kristofferson et al.[93]
der(15)t(6;15)(p25;q24)mat	Kristofferson et al.[93]
46,XX, inv dup(6)(p25.2p22.2)	Scott et al.[57]
Deletion:	
der(6)t(2;6)(p23;p25)	Bender et al.[54]
46,XY,der(6)t(X;6)(p21.2;p25)	Batanian et al.[94]
46,XY,der(6)t(6;8)(p25.1;q24.23)	Baruch and Erickson[95]
del(6)(q15q21)	Yu and Bock[96]
46,XY,del(6)(q23)	Shen-Schwarz et al.[97]
del(6)(q23)	van Dooren[45]
46,XX,del(6)(q25.3)	Krassikoff and Sekhon[27]
del(6)(qter)mat	Le Caignec et al.[32]
Miscellaneous:	
46,XX,add(6)(q23 or q25)	Tonks et al.[39]
Chromosome 7:	
Duplication:	
dup(7)(p15p22)	Herrmann et al.[98]
46,XX,der(2)t(2;7)(q36;q37)pat	Brackley et al.[58]
46,XY,der(18)t(7;18)(qter;p11.1)	Habedank and Trost-Binkhues[99]

(*continued*)

Table 2. (continued)

Chromosome, Type of Anomaly, and Patient Karyotype	Study Author(s)
Deletion:	
del(7)(p21)	van Dooren[45]
del(7)(q)	Fauza and Wilson[100]
del(7)(q11q22)	Klep-de Pater et al.[101]
46,XY,del(7)(q32)	Torfs et al.[1]
46,XX,del(7)(q32)	Dott et al.[102]
der(7)t(7;20)(q33.2;p13)	Kjaer et al.[103]
46,XY,der(7)t(2;7)(p25.3;q34)mat	Enns et al.[34]
Miscellaneous:	
chtb(7)(q31.1)	Bonneau et al.[104]
Chromosome 8:	
Balanced translocation:	
46,XY,t(6;8)(q24;q23)	Howe et al.[37]
t(8;14)(q24;q21)	Philip et al.[47]
46,XX,t(8;13)(q22.3q22)mat	Temple et al.[105]
46,XX,t(8;15)(q22.3q15) de novo	Temple et al.[105]
Duplication:	
Trisomy 8 mosaicism	Pober et al.[8]
46,XY,der(2)t(2;8)(q37;p11.2)pat	Tonks et al.[39]
46,XY, inv dup(8)(p23.1p11.22)	Ringer et al.[106]
dup(8)(p21)	van Dooren[45]
46,XY,der(12)t(8;12)(p21;p13)	Moreno Fuenmayor et al.[107]
46,XX,der(15)t(8;15)(q24.1;q26.1)	Chen et al.[108]
46,XY,dup(8)(q)	Hilfiker et al.[109]
46,XY,der(6)t(6;8)(p25.1;q24.23)	Baruch and Erickson[95]
Deletion:	
46,XY,del(8)	Thorpe-Beeston et al.[110]
del(8)(p)	Pober et al.[8]
del(8)(p22)	Kousseff[43]
46,XY,del(8)(p23.1)	Howe et al.[37]
del(8)(p23.1)	Faivre et al.[111]
46,XY,del(8)(p23.1p23.1)	Shimokawa et al.[112]
46,XX,del(8)(p23.1)	Borys and Taxy[113]
46,XY,del(8)(p23.1)	Lopez et al.[114]
46,XX,del(8)(p23.1)	Pecile et al.[115]
46,XY,del(8)(p23.1)	Fraer et al.[116]
46,XY,del(8)(p23.1:p23.1)	Slavotinek et al.[24]
del(8)(q21.2q22)	Maerzke et al.[117]
del(8)(q22q24.1)	Harnsberger et al.[118]
del(8)(q22q24.1)	Capellini et al.[119]
Miscellaneous:	
46,XX,add(8)(p?)	Betremieux et al.[120]
46,XY,der,t(3;8)(p23;p23.1)	Tibboel and Gaag[31]
Chromosome 9:	
Ring chromosome[a]:	
r(9)	Dillon et al.[68]
Duplication:	
47,XX,+9	Chen et al.[121]
47,XY,+9	Suzumori et al.[122]
47,XX,+9	Sepulveda et al.[123]
Trisomy 9	Frohlich[124]
Trisomy 9	Robert et al.[125]
Trisomy 9	Dott et al.[102]
47,XX,+i(9p)	Henriques-Coelho et al.[126]
Deletion:	
46,XX,der(9)t(9;16)(p22;q24)	Alfi et al.[127,128]
der(9)t(5;9)(p13;p22); two patients	Liberfarb et al.[90]
46,XY,der(9)t(9;11)(p24;p13)pat	Donnenfeld et al.[129]
46,XY,−9,+t(5q;9p)	Torfs et al.[1]
46,XY,der(9)t(9;16)(q34.3;q24.3)	Ferrero et al.[130]
der(9)t(1;9)(q32.3;p24.1)	Kousseff[43]
Chromosome 10:	
Balanced translocation:	
t(X,10) de novo	Cunniff et al.[131]

(*continued*)

Table 2. (continued)

Chromosome, Type of Anomaly, and Patient Karyotype	Study Author(s)
Duplication:	
46,XY,der(21)t(10;21)(p11;p11)	Yunis et al.[132]
46,XY,der(20)t(10;20)(p12;p12)	Lurie et al.[133]
Miscellaneous:	
46,XY,add(10)(q?q24) de novo	Tonks et al.[39]
Chromosome 11:	
Duplication:	
46,XY,der(9)t(9;11)(p24;p13)pat	Donnenfeld et al.[129]
47,XX or XY,+der(22)t(11;22)(q23;q11)	Iselius et al.,[134] Fraccaro et al.,[135] Phelan et al.,[136] Azancot et al.,[137] de Beaufort et al.,[138] Aurias et al.,[139] Noel et al.,[140] Dean et al.,[29] Kousseff,[43] Hickmann et al.,[141] van Dooren,[45] Tonks et al.,[39] Dott et al.,[102] Borys and Taxy,[113] and Kadir et al.[142]
47,XY,+der(13)t(11;13)(q21;q14)	Park et al.[143]
46,XY,der(12)t(11;12)(q23.3;q24.3)mat	Klaassens et al.[144]
Deletion:	
46,XY,del(11)(p12p15.1)	Scott et al.[145]
del(11)(p13)	Gustavson et al.[146]
46,XY,?del(11)(q23),9qh+	Dott et al.[102]
46,XX,der(11)t(11;12)(q24;p11.2)	Decker-Philips et al.[147]
Chromosome 12:	
Balanced translocation:	
t(12;15)	Fauza and Wilson[100]
46,XY,t(3;12)(q21.1;p13.3) de novo	Tonks et al.[39]
Duplication:	
Mosaic tetrasomy 12p	Bergoffen et al.,[148] Corning et al.,[149] Rodriguez et al.,[150] Donnenfeld et al.,[129,151] Dott et al.,[102] Betremieux et al.,[152] Veldman et al.,[153] Witters et al.,[154] Tonks et al.,[39] Borys and Taxy,[113] Takakuwa et al.,[155] and Pober et al.[8]
46,XX,der(11)t(11;12)(q24;p11.2)	Decker-Philips et al.[147]
der(15)t(12;15)	Pober et al.[8]
Deletion:	
46,XY,der(12)t(8;12)(p21;p13)	Moreno Fuenmayor et al.[107]
46,XY,del(12)	Howe et al.[37]
46,XY,der(12)t(11;12)(q23.3;q24.3)mat	Klaassens et al.[144]
Chromosome 13:	
Balanced translocation:	
46,XX,t(8;13)(q22.3q22)mat	Temple et al.[105]
Ring chromosome[a]:	
r(13)	van Dooren[45]
Duplication:	
47,XY,+der(13)(qter→q31::q31→neo→qter)	Warburton et al.[156] and Tohma et al.[157]
46,XX,der(4)t(4;13)(p16;q32)	Tapper et al.[81]
47,XY,+der(13)t(11;13)(q21;q14)	Park et al.[143]
47,XY,t(5;13)(p15;q21)+der(13)t(5;13)(p15;q21)mat	Masuno et al.[91]
Deletion:	
46,XX,13q-	Benjamin et al.[48]
Chromosome 14:	
Balanced translocation:	
t(8;14)(q24;q21)	Philip et al.[47]
46,XY,t(1;14)(p22;q13),inv(6)(p25q22),del(15)(q26.1q26.2)	Klaassens et al.[38]
Duplication:	
dup(14)(q24q32)	van Dooren[45]
46,XX,dup(14)(q32.1)	Masada et al.[158]
der(2)t(2;14)(q37;q31.2)	De La Fuente et al.[59]
46,XY/47,XY,+14	Howe et al.[37]
46,XX/46,XX,i(14)(q10)	Scott et al.[57]
Deletion:	
46,XY,del(14)(q32.11qter), bilateral eventration	Masada et al.[158]
Chromosome 15:	
Balanced translocation:	
46,XY,t(1;15)(q41;q21.2) de novo	Smith et al.[36]
46,XX,t(8;15)(q22.3q15) de novo	Temple et al.[105]
t(12;15)	Fauza and Wilson[100]

(*continued*)

Table 2. (continued)

Chromosome, Type of Anomaly, and Patient Karyotype	Study Author(s)
Duplication:	
inv dup(15)	van Dooren[45]
46,XY,dup(15)(q11q13)mat	Boyar et al.[159]
47,XX,+dic(15)(q11.2)	Howe et al.[37]
dup(15)(q15q26)	van Dooren[45]
dup(15)(q15q26) + del(X)(p22)	van Dooren[45]
der(X)t(X;15)(p22;q15)mat	Zabel and Baumann[160]
Deletion:	
46,XY,r(15)(p11q26)	de Jong et al.[28]
46,XY,r(15)(p11q26.1), two cases	Klaassens et al.[38]
r(15)(q25.3)	Elghezal et al.[161]
46,XY,der(15)t(6;15)(p25;q24)mat	Kristofferson et al.[93]
der(15)t(6;15)(p25;q24)mat	Kristofferson et al.[93]
46,XX,der(15)t(3;15)(q29;q26.1)mat	Rosenberg et al.[63]
46,XX,der(15)t(15;17)(q24.3;q23.3)	Howe et al.[37]
46,XY,del(15)(q24) 46,XX,del(15)(q24)	Bettelheim et al.[162]
46,XX,der(15)t(8;15)(q24.1;q26.1)	Chen et al.[108]
46,XY,der(15)t(15;20)(q26.3;q13.1)	Reiss et al.[86]
der(15)t(5;15)(p15.3;q24), two cases	Aviram-Goldring et al.[89]
46,XX,del(15)(q25q26.2)	Schlembach et al.[163]
46,XX,del(15)(q26.1)	Biggio et al.[164]
46,XX,del(15)(q26.1) de novo	Hengstschlager et al.[165]
46,XY,del(15)(q26.1) de novo	Tonks et al.[39]
46,XY,r(15)(q26.2)	Tumer et al.[166]
46,XY,t(1;14)(p22;q13),inv(6)(p25q22),del(15)(q26.1q26.2)	Klaassens et al.[38]
del(15)(q26)	Pober et al.[8]
der(15)t(12;15)	Pober et al.[8]
46,XX,del(15)(q26.2)	Slavotinek et al.[24]
46,XX,del(15)(q26.2;26.2)	Slavotinek et al.[24]
46,XY,der(15)t(8;15)(q24.2;q26.2)	Slavotinek et al.[50]
del(15)(q26.1)	Lopez et al.[114]
46,XY,der(15)t(2;15)(q37.2;q26.2)	Scott et al.[57]
Chromosome 16:	
Duplication:	
47,XY+ mar 16	Howe et al.[37]
46,XX,der(9)t(9;16)(p22;q24)	Alfi et al.[127,128]
46,XY,der(9)t(9;16)(q34.3;q24.3)	Ferrero et al.[130]
47,XX,+16[3]/46,XX[15]	Chen et al.[167]
47,XX,+16	Johnson et al.[168]
Chromosome 17:	
Ring chromosome[a]:	
46,XX,r(17)/45,XX,−17	Baldermann et al.[169]
Duplication:	
45,XX,der(15)t(15;17)(q24.3;q23.3)	Howe et al.[37]
Chromosome 18:	
Duplication:	
46,XX/46,XX,del(18)(ptel)/46,XX,−18, +i(18q)	Le Caignec et al.[32]
46,XY,idic(18)(p11)[15]/45,XY,−18[6]/46,XY,del(18)(p11.7)[6]/ spurious cells[3]	Dott et al.[102]
iso(18)(q)	Hayashi et al.[170]
Deletion:	
46,XX/46,XX,del(18)(ptel)/46,XX,−18, +i(18q)	Le Caignec et al.[32]
46,XY,idic(18)(p11)[15]/45,XY,−18[6]/46,XY,del(18)(p11.7)[6]/ spurious cells[3]	Dott et al.[102]
iso(18)q	Hayashi et al.[170]
46,XY,der(18)t(7;18)(qter;p11.1)	Habedank and Trost-Binkhues[99]
46,XY,der(18)t(4;18)(q31;q23)	Yunis et al.[74]
45,XX,der(18)t(18;22)(qter;q11),−22	Geneix et al.[171]
Chromosome 20:	
Duplication:	
der(4)t(4;20)(q34.2;q13.1)pat	Reiss et al.[86]
der(7)t(7;20)(q33.2;p13)	Kjaer et al.[103]
46,XY,der(15)t(15;20)(q26.3;q13.1)	Reiss et al.[86]
der(4)t(4;20)(q34.2;q13.1)pat	Pober et al.[8]
Deletion:	
46,XY,der(20)t(10;20)(p12;p12)	Lurie et al.[133]

(*continued*)

Table 2. (continued)

Chromosome, Type of Anomaly, and Patient Karyotype	Study Author(s)
Chromosome 21:	
Translocation:	
46,XY,t(1;21)(q32;q22)pat	Howe et al.[37]
Duplication:	
der(1)t(1;21)mosaicism	Philip et al.[47]
Tetrasomy 21	Pober et al.[8]
Deletion:	
46,XY,der(21)t(10;21)(p11;p11)	Yunis et al.[132]
46,XY,+X,dic(X;21)(p11.1;p11.1)	Smith et al.[172]
der(21)t(3;21)(p24.3;q11.2)mat	Pettigrew[62]
Chromosome 22:	
Duplication:	
47,XY,+der(22)t(6;22)(6p25;q11.2)	Scarbrough et al.[92]
47,XX or XY,+der(22)t(11;22)(q23;q11)	Iselius et al.,[134] Fraccaro et al.,[135] Phelan et al.,[136] Azancot et al.,[137] de Beaufort et al.,[138] Aurias et al.,[139] Noel et al.,[140] Dean et al.,[29] Kousseff,[43] Hickmann et al.,[141] van Dooren,[45] Tonks et al.,[39] Dott et al.,[102] Borys and Taxy,[113] and Kadir et al.[142]
Trisomy 22	Kim et al.,[173] Ladonne et al.,[174] Phillipson et al.,[175] Dean et al.,[29] Golombek and Shaw,[176] Ramsing et al.,[177] and Van Voss et al.[178]
Deletion:	
45,XX,der(18)t(18;22)(qter;q11),−22	Geneix et al.[171]
46,XX,der(22)t(1;22)(q12;p12)[11]/46,XX[9]	Ahmed et al.[42]
del(22)(q11q11)	Betremieux et al.[152]
46,XX,der(22)t(4;22)(q28.3;p13)	Celle et al.[73]
Chromosome X:	
Balanced translocation:	
46,X,t(X;1)(q26;q12)	Punnett[35]
Monosomy:	
45,X	David and Illingworth,[6] Benjamin et al.,[48] Bollmann et al.,[87] Tibboel and Gaag,[31] Cunniff et al.,[131] Robert et al.,[125] Dawani et al.,[180] and Scott et al.[57]
Diploid/tetraploid mosaicism:	
92,XXXX/46,XX	Witters et al.[154]
Duplication:	
46,XY,der(6)t(X;6)(p21.2;p25)	Batanian et al.[94]
Deletion:	
46,X,del(X)(p22.1)	Plaja et al.[179]
der(X)t(X;2)(q27;p13)mat	Sarda et al.[53]
der(X)t(X;15)(p22;q15)mat	Zabel and Baumann[160]
dup(15)(q15q26) + del(X)(p22)	van Dooren[45]
der(X)t(X;Y)(p22.3;q11.2)	Pober et al.[8]
46,XY,+X,dic(X;21)(p11.1;p11.1)	Smith et al.[172]
Chromosome Y:	
Duplication:	
der(X)t(X;Y)(p22.3;q11.2)	Pober et al.[8]
Deletion:	
46,XY/46,X,der(Y)t(Y;1)(q12;q12)	Ahn et al.[40]
46,XY[9]/46,X,der(Y),t(Y;1)(q12;q12)[12]	Zeng et al.[41]

[a] Always with deletion.

this region is deleted, two also have duplications of the distal portion of 14q, which is discussed below.[45,59]

Deletion of 3q22

Deletions of this region have been described in three individuals with CDH.[67,68] Two of these patients had blepharophimosis and facial dysmorphism most likely attributable to deletions of *FOXL2,* which is known to cause blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES [MIM 110100]).[67,68] The most-promising CDH candidate genes located in this region are the genes for cellular retinol binding protein 1 (*RBP1* [MIM 180260]) and cellular retinol binding protein 2 (*RBP2* [MIM 180280]). These genes are part of the retinol signaling pathway and have been shown to play a role in vitamin A homeostasis and lung maturation in mice.[181,182] No mutations in *RBP1* or *RBP2* have been described in patients with CDH to date.

Deletion of 4p16

Wolf-Hirschhorn syndrome (MIM 194190) is associated with deletions of 4p16 and is characterized by a "Greek helmet" facial appearance, growth retardation, mental retardation, seizures and/or epilepsy, cleft lip and/or palate, and cardiac abnormalities. Although not a common finding in Wolf-Hirschhorn syndrome, CDH has been described in association with at least 14 cases of 4p16 deletion.[8,37,50,71,75–77,79–81,183] The patient described by Casaccia et al.[77] has the smallest known deletion of 4q16 associated with CDH (2.6 Mb), with the deletion extending from locus *D4S43* to the telomere.

Duplication or Deletion of 4q31

CDH has been described in four individuals with 4q31 duplications.[45,71,73,74] Deletions of this region have also been seen in four individuals with CDH.[45,82,84,85]

Duplication of 5p15

Duplications of 5p15 have been described in at least four patients with CDH.[89–91] All these cases were accompanied by an additional chromosomal anomaly, such as deletion 9p22-pter or deletion 15q26-qter, both of which are discussed below.

Deletion of 6p25

Deletions of this region have been seen in at least three individuals with CDH, all of whom have an additional chromosomal duplication.[54,94,95]

Deletion of 6q25.3-qter

Deletions involving this region have been seen in four cases of CDH.[27,32,45,97] Le Caignec et al.[32] used array CGH to identify a <5-Mb subtelomeric deletion of 6q in a patient with CDH and other anomalies. It should be noted, however, that this same deletion was found in the patient's mother, who presented with only learning disabilities.

Deletion of 8p23.1

Deletions involving 8p23.1 have been described in >30 individuals with abnormal phenotypes, including nine patients with CDH.[24,37,43,111–116] More-distal deletions of 8p23.1-p23.2 have also been found in unaffected individuals, suggesting that more-telomeric deletions may be a normal variant in the white population.[184] Shimokawa et al. used array CGH to define an ~6-Mb deletion of 8p23.1 in a patient with CDH.[112] This deletion was flanked by low-copy repeats and was bounded by BACs RP11-143D15 and RP11-252C15. *GATA4* resides within this region and has been proposed as a candidate gene for CDH. Of note, deletions and loss-of-function mutations of *GATA4* have been seen in individuals with cardiac defects involving the cardiac septum, and the majority of patients with CDH with deletion of 8p23.1 also have cardiac anomalies (atrial, ventricular, or atrioventricular septal defect).[115,184–187] *Gata4* heterozygous-null mice also display diaphragm defects in association with pulmonary and cardiac abnormalities.[22] This animal model is discussed in greater detail below.

Duplication of 8p21-p23.1

Duplication of 8p21-p23.1 has been described four times in patients with CDH.[39,45,106,107] The patient described by Moreno Fuenmayor et al.[107] had a phenotype consistent with that of other patients with duplication 8p21.[188] The patient described by Ringer et al.[106] had an inverted duplication of 8p11.22-p23.1. In some instances, patients with an inverted duplication of 8p also have a small deletion of 8p23.1, a region recurrently deleted in CDH. Unfortunately, it is unclear whether the patient described by Ringer et al.[106] also carried this deletion.

Deletion of 8q22-q23

Three patients with CDH with 8q deletions have been described.[117–119] Each of these deletions included bands 8q22-q23, and all these patients had dysmorphic features similar to those of other patients with similar deletions.[189] There are also three affected individuals with balanced translocations that involve this region.[37,105] *FOG2* resides within this region, and data supporting its role in diaphragm development are described below.

Deletion of 9p24-pter

Deletions of this region have been described in five patients with nonisolated CDH.[43,90,127,129] All these deletions were terminal deletions as part of unbalanced translocation with another autosome.

Deletion of 11p13

Although only two patients with CDH have been described with a deletion of 11p13, this region is of particular interest because it harbors the Wilms tumor 1 gene (*WT1*).[145,146] Data supporting a role for *WT1* in the development of CDH is described below.

Duplication of 11q23.3-qter

This duplication has been described numerous times in patients with CDH. In most cases, this duplication is the result of the more common chromosomal anomaly 47,XX, or XY,+der(22)t(11;22), resulting from 3:1 meiotic segregation.[144] Two patients have been described in whom the duplication of 11q23-qter is the result of an unbalanced translocation with another autosome.[143,144]

Duplication of 12p

Mosaic tetrasomy 12p, or Pallister-Killian syndrome, is characterized by coarse facial features, sparse temporal

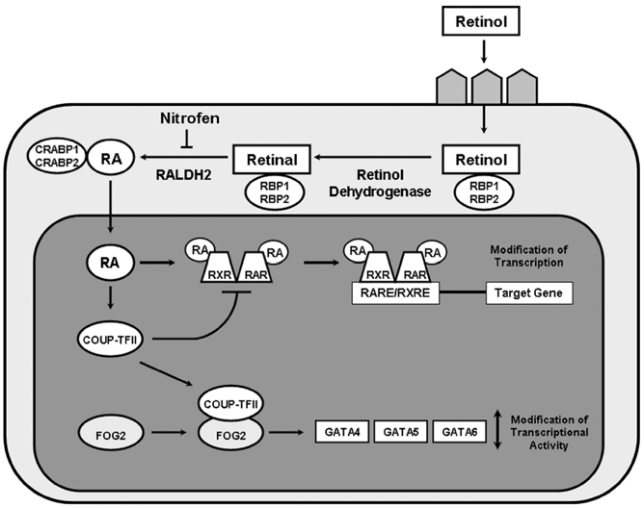

Figure 2. Retinoic acid (RA) signaling pathway and CDH candidate genes. Retinol travels to target cells via the blood and is taken up by receptors on the cell surface. Once in the cytoplasm, retinol is converted to retinal by retinol dehydrogenases and then to RA by retinal dehydrogenases, of which RALDH2 is the predominant enzyme. The action of RALDH2 can be inhibited by teratogens, such as nitrofen. Several binding proteins are present in the cytoplasm, including retinol-binding proteins 1 and 2 (RBP1 and RBP2), which bind retinol and retinal, and cellular RA-binding proteins 1 and 2 (CRABP1 and CRABP2). When RA enters the nucleus, it mediates its effects by binding to RA receptors (RARs) and retinoid X receptors (RXRs). RARs and RXRs dimerize and regulate gene expression by binding to short DNA sequences—RA-responsive elements (RAREs) and retinoid X–responsive elements (RXREs)—located in the vicinity of target genes. *COUP-TFII* expression is upregulated by RA. COUP-TFII can act as a repressor of this pathway by directly sequestering RXR, thereby preventing heterodimerization to RAR and inhibiting gene transcription. This process may be a negative feedback system that precisely balances the transcription of certain genes during diaphragm development. COUP-TFII has been shown to interact physically with FOG2, which, in turn, modulates the transcriptional activity of *GATA4*, *GATA5*, and *GATA6*.

hair, skin abnormalities, mental retardation, and a high rate of CDH.[190] This syndrome usually results from mosaicism for an isochromosome: i(12)(p10).[191] Also, one patient with CDH and a balanced translocation involving 12p13.1 has been described.[39]

Duplication of 14q32

Mosaic trisomy 14 has been described in at least two patients with nonisolated CDH, and duplications of 14q32 have been described three times in association with CDH.[37,45,57,59,158]

Deletion of 15q26

Deletions of the distal part of the long arm of chromosome 15 have been described in at least 26 patients with nonisolated CDH, making this anomaly one of the most reported structural chromosomal anomalies in CDH.[33,38] The majority of patients with deletions of the long arm of 15q have a severe phenotype that can include cardiac abnormalities, limb abnormalities, and dysmorphic features. *Chick ovalbumin upstream promoter-transcription factor II* (*COUP-TFII*) resides within this region, and data supporting its role in the development of CDH is described below.

Duplication of 22pter-q11

Duplications of this region have been described numerous times in patients with CDH. This duplication usually is seen as part of the common chromosomal anomaly 47,XX, or XY,+der(22)t(11;22), resulting from 3:1 meiotic segregation.[144] Although no patients with isolated duplications of this region have been described, CHD is also a recurrent finding in individuals with trisomy 22.[33]

Candidate Pathways and Genes

Although the etiology of most cases of CDH remains unknown, there is increasing evidence that specific pathways and genes play a role in the development of CDH. These data are derived from the identification of candidate genes in regions commonly deleted and/or duplicated in CDH and from several genetic animal models. In this section, we review evidence for involvement of the retinoid signaling pathway and genes *COUP-TFII, FOG2, GATA4, WT1,* and *SLIT3* in the development of CDH.

Retinoid Signaling Pathway

Vitamin A (retinol) and its derivatives (retinoids) are essential for embryonic development. Abnormalities in the retinoid signaling pathway and its downstream targets have long been hypothesized to lead to the development of CDH.[192] The first connection between retinoids and CDH resulted from the observation that 25%–40% of the offspring of rat dams that were fed a diet deficient in vitamin A developed CDH and that the proportion of affected pups diminished when vitamin A was reintroduced into the diet in midgestation.[193–195]

Subsequently, in utero exposure to the herbicide nitrofen, bisdiamine (a spermatogenesis inhibitor), SB-210661 (a 5-lipoxygenase inhibitor), and BPCA (a thromboxane-A_2 receptor antagonist) was shown to cause CDH in rodents.[196] The diaphragmatic defects caused by these substances closely mimicked the characteristics of human posterolateral CDH, including the intermittent incidence of associated cardiac anomalies.[197] The connection between these defects and the retinoid signaling pathway became clear when vitamin A was found to decrease the incidence and severity of nitrofen-induced CDH.[13] Later, it was shown that nitrofen, bisdiamine, SB210661, and BPCA inhibit RALDH2, a key enzyme responsible for the conversion of retinal to retinoic acid.[196]

Two knockout mouse models also suggest a role for re-

tinoid signaling in the development of CDH. A proportion of RARα/RARβ receptor double-knockout mice have posterolateral diaphragmatic defects similar to those seen both in humans and in teratogen-induced mouse models of CDH.[198] Targeted ablation of *Coup-TFII,* a gene encoding a transcription factor regulated by the retinoid signaling pathway, has also been shown to cause posterolateral CDH similar to Bochdalek-type CDH seen in humans.[199]

Preliminary evidence that retinoids may play a role in the development of CDH in human comes from a small study in which the levels of plasma retinol and retinol-binding protein in the cord blood of infants with CDH was found to be 50% lower than those in age-matched controls.[200]

COUP-TFII

COUP-TFII (also known as NR2F2) is a transcription factor in the steroid/thyroid hormone receptor superfamily. The *COUP-TFII* gene is located on chromosome 15q26 in a region recurrently deleted in individuals with CDH.[33,38] Klaassens et al.[38] defined a minimally deleted region for CDH on chromosome 15q26 by use of FISH and array CGH data from patients with nonisolated CDH. Of the genes within this region, *COUP-TFII* was thought to be the strongest candidate because its expression had been shown previously to be regulated by retinoids and because COUP-TFII regulates gene transcription by influencing retinoic acid receptor or retinoid X receptor heterodimerization (fig. 2).[201,202] This region has since been reduced to include *COUP-TFII* and only eight other known genes.[57] As mentioned above in the discussion of the retinoid signaling pathway, homozygous tissue-specific ablation of *Coup-TFII* in mice causes posterolateral CDH similar to Bochdalek-type CDH seen most commonly in humans.[199]

Together, these data suggest that deletion of *COUP-TFII* is likely to play a key role in the development of CDH in individuals with 15q26 deletions. It has not yet been determined whether abnormalities in *COUP-TFII* are responsible for cases of CDH not associated with 15q26 deletions. Although several research groups are actively screening *COUP-TFII* in patient cohorts, to date, no CDH-causing mutations in this gene have been published.

FOG2

FOG2 (also known as ZFPM2) is a zinc finger–containing protein that modulates the transcriptional activity of GATA proteins, which, in turn, play important roles in early embryogenesis. The first indication that *FOG2* might play a role in normal diaphragm development came with the discovery of an N-ethyl-N-nitrosourea mouse mutant with pulmonary hypoplasia and an abnormal diaphragm that lacked muscularization of the posterolateral and peripheral regions. Sequencing of the *Fog2* gene in this mouse revealed a hypomorphic splice-donor mutation.[21] A de novo R112X heterozygous mutation was subsequently found in an infant who died shortly after birth with diaphragmatic eventration and severe pulmonary hypoplasia.[21]

Although no mutations in *FOG2* have been found in individuals with CDH, it is interesting to note that *FOG2* is located on chromosome 8q23 in a region commonly deleted in individuals with CDH and that FOG2 interacts physically with COUP-TFII.[203] It is possible that these proteins work together to regulate downstream target genes that play a role in the development of CDH.

GATA4

GATA4 is a member of a family of DNA-binding proteins that recognize a consensus sequence (the GATA motif), which is found in the promotor regions of many genes.[204] *GATA4* encodes a transcription factor that interacts with FOG2 during the morphogenesis of the heart.[205] *GATA4* is located on chromosome 8p23.1, a region recurrently deleted in individuals with CDH.

Recently, Jay et al.[22] showed that 70% of heterozygous *Gata4*$^{+/\Delta ex2}$ mice on a C57BL/6 background displayed cardiac, lung, or diaphragm defects. The diaphragmatic defects, which affected ~30% of mice, were located in the ventral midline and were covered by a sac that was continuous with the diaphragm. Together with the occurrence of 8p23.1 deletions in human patients, this research provides additional evidence that GATA4 is important for lung and diaphragm development in humans. To date, no CDH-causing mutations in *GATA4* have been identified.

WT1

WT1 is located on chromosome 11p13, a region recurrently deleted in individuals with CDH, and encodes a zinc-finger transcription factor that is expressed in the pleural and abdominal mesothelium that help to form the diaphragm.[145,146,206] Mutations in *WT1* associated with CDH have been described in two patients with Denys-Drash syndrome (MIM 194080)—characterized by male pseudohermaphroditism, nephropathy, and Wilms tumor—and one patient with Frasier syndrome (MIM 136680)—characterized by focal and segmental glomerulosclerosis, male pseudohermaphroditism, and gonadoblastoma.[207–209] A child with Meacham syndrome (MIM 608978)—characterized by CDH, double vagina, sex reversal, and cardiac malformations—was also found to have a de novo *WT1* mutation.[210] Further evidence of the role of *WT1* in CDH comes from homozygous *Wt1*-null mouse embryos that develop diaphragmatic hernias.[211]

Recently, Clugston et al.[11] compared the *Wt1*$^{-/-}$ mutant with other CDH animal models—namely, the nitrofen rat model and the vitamin A–deficient rat model. They found that the *Wt1* null mutants have defects in the PPF as do the two other models, suggesting that there is a common pathogenic mechanism in dietary, teratogenic, and genetic models of CDH.

Homolog of Drosophila Slit 3 *(*SLIT3*)*

SLIT3 is located on chromosome 5q35.1 and is one of three human homologs of the *Drosophila Slit* gene. In mice, *Slit3* is expressed predominantly in the mesothelium of the diaphragm during embryonic development.[212] Homozygous *Slit3*-deficient mice have CDH on or near the ventral midline portion of the central tendon that is similar to the central (septum transversum) type of diaphragmatic hernia seen in humans.[212,213] Although *SLIT3* seems to be a strong candidate gene for this relatively rare type of CDH, no *SLIT3* mutations have been identified in humans with CDH to date.

Discussion

The existence of specific CDH-associated genetic syndromes, recurrently deleted and/or duplicated chromosomal regions, and transgenic mouse models of CDH provide evidence of the important role that genetic factors play in the development of CDH. Future research efforts in each of these areas will provide information that will help us to better understand the etiology of many cases of CDH. Although the genes for several CDH-related syndromes are known, many have not yet been discovered. Additional efforts must also be made to determine the role that these genes play in diaphragm development. The increased use of high-resolution cytogenetic techniques—such as array CGH—in both the clinical and research settings are likely to aid in the discovery of new CDH-related genes as new chromosomal regions associated with CDH are identified and as previously identified regions are refined. Transgenic models have proven to be a valuable resource not only as a way to begin to understand the role that specific genes play in diaphragm development but also as a tool for the discovery of new CDH-related genes. The current emphasis on development of improved resources for transgenic mouse studies will make it easier for researchers to rapidly test hypotheses regarding the involvement of particular genes or gene combinations in diaphragm development. The increasing availability of new technologies, such as micro–magnetic resonance imaging scanners, may also make it easier to screen existing mouse strains for diaphragm defects.

Although several genes have been clearly shown to underlie abnormal diaphragm development in mice, few CDH-related mutations have been identified in corresponding genes in humans. One possible explanation is that the genes and pathways that underlie CDH development in mice are different than those that commonly cause CDH in humans. This, however, seems less likely when one considers that many of these genes are located in chromosomal regions recurrently deleted in individuals with CDH and, therefore, represent excellent candidates for CDH in humans.

Another possibility is that de novo mutations in individual genes are responsible for only a fraction of human CDH cases. The chance of identifying such an event may be particularly low when one considers that this fraction would likely represent a heterogeneous population in which de novo mutations in many different genes can result in the same basic phenotype. If this is the case, identifying de novo mutations in individual genes may require both the recruitment and screening of relatively large numbers of patients with CDH. Such efforts may still be worthwhile because the identification of de novo changes provides valuable evidence that a particular gene is involved in the development of human CDH. Such discoveries could also prove clinically significant if phenotype and/or genotype analysis suggests that a particular subgroup of patients with CDH is more likely to carry de novo mutations in a particular gene. It is important, however, that such screening efforts do not overlook subtle inherited changes that may be important for understanding the complex inheritance pattern that likely underlies the majority of CDH cases.

The assumption that the majority of CDH cases results from a complex inheritance pattern, in which a combination of genetic and environmental factors affect the final phenotype, is consistent with the sporadic nature of the disease and the relatively few instances of familial cases described in the literature.[1,4,5] Indeed, it seems reasonable to hypothesize that relatively small inherited changes in the function of two or more genes within the same CDH-related pathway could cause diaphragmatic defects in the offspring of otherwise-normal carrier parents. An additional level of variation may also be added by environmental stressors—such as toxins or nutritional factors such as vitamin A—acting on genetically susceptible individuals. The combined effects of several genes and the environment may also underlie the association of CDH with some chromosomal abnormalities.

Research into the underlying causes of CDH has the potential to positively effect the clinical management of CDH in affected individuals and their families. The description of multiple genetic syndromes associated with CDH highlights the importance of a careful evaluation of patients with CDH. In cases in which CDH is diagnosed prenatally, such an evaluation may have an influence on medical decision making, including decisions made about the possible termination of the pregnancy. It has also become clear that a significant proportion of nonisolated CDH cases are attributable to chromosomal anomalies.[30] Since recent studies suggest that some causal chromosomal anomalies can be missed on routine G-banded chromosome analysis, it seems prudent to consider obtaining a higher-resolution cytogenetic study, such array CGH, to look for cryptic deletions and duplications in patients with nonisolated CDH with normal chromosome analyses.[23,24,61] Storage of DNA samples from patients with CDH and their parents should also be considered becauase access to such material may ultimately allow a diagnosis to be made, which, in turn, would form the foundation for improved genetics counseling for all family members.

Our understanding of the genetic factors associated with CDH may make it possible to devise preventative strategies or to improve therapeutic interventions for patients with CDH. It is important to keep in mind that measures aimed at improving clinical outcome may not require the prevention or correction of the diaphragmatic defect itself. Instead, these strategies may focus on improvement in postnatal lung function, and, eventually, prenatal modulation (such as tracheal occlusion procedures), since pulmonary hypoplasia and pulmonary hypertension are major contributors to both the morbidity and the mortality associated with CDH. With this in mind, it will be important to identify which CDH-related genes and pathways have direct affects on normal diaphragm and lung development, because they may be particularly good therapeutic targets.

Addendum

After submission of this manuscript, Pasutto et al.[214] reported that homozygous mutations in the *stimulated by retinoic acid gene 6 homolog* (*STRA6* [MIM 610745]) cause a broad spectrum of malformations, including CDH, anophthalmia, congenital heart defects, alveolar capillary dysplasia, lung hypoplasia, and mental retardation. In a separate report, Kawaguchi et al.[215] showed that STRA6 acts as a membrane receptor for retinol binding protein and mediates cellular uptake of vitamin A.

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Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CDH, *FOG2, GATA4,* Fryns syndrome, Beckwith-Wiedemann syndrome, *CDKN1C, NDS1,* CHARGE syndrome, *CHD7,* Cornelia de Lange syndrome, *NIPBL, SMC1A,* craniofrontonasal syndrome, *EFNB1,* Denys-Drash syndrome, *WT1,* Donnai-Barrow syndrome, Palister-Killian syndrome, Simpson-Golabi-Behmel syndrome, *GPC3, CXORF5,* thoracoabdominal syndrome, Wolf-Hirschhorn syndrome, BPES, *RBP1, RBP2,* Frasier syndrome, Meacham syndrome, and *STRA6*)

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