EDITOR'S CHOICE

Double outlet right ventricle: aetiologies and associations

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ABSTRACT

Background: Double outlet right ventricle (DORV), a clinically significant congenital heart defect, occurs in 1–3% of individuals with congenital heart defects. In contrast to other major congenital heart defects, there are no systematic or comprehensive data regarding associations, aetiologies, and pathogenesis of DORV. We analysed reported cases in the medical literature to address these issues.

Methods: We queried the PubMed database using key words "double outlet right ventricle" and "DORV" for case reports, epidemiologic analyses and animal studies with this cardiac anomaly. The anatomic subtype of DORV was classified according to criteria of Van Praagh.

Results: Chromosomal abnormalities were present in 61 of the 149 cases of DORV. Trisomies 13 and 18, and del 22q11 were the most commonly associated cytogenetic lesions; different anatomic subtypes of DORV were noted in trisomies 13 and 18 versus del 22q11. DORV was reported in many uncommon or rare non-chromosomal syndromes. Mutations and non-synonymous sequence variants in the *CFC1* and *CSX* genes were the most commonly reported monogenic loci associated with DORV in humans; numerous genes are reported in murine models of DORV. Animal studies implicate maternal diabetes and prenatal exposure to ethanol, retinoids, theophylline, and valproate in DORV teratogenesis.

Conclusions: The large number of genes associated with DORV in both humans and animal models and the different anatomic subtypes seen in specific aetiologies indicate the likelihood of several distinct pathogenetic mechanisms for DORV, including impairment of neural crest derivative migration and impairment of normal cardiac situs and looping.

Congenital cardiovascular malformations are found in approximately 4–8/1000 newborns and represent a common cause of paediatric morbidity and mortality.[1–5] The incidence may be as much as 10-fold greater in fetuses, due to the high frequency of fetal demise in the setting of severe malformations.[6] Recent reports indicate an increasing prevalence of congenital heart defects, but acknowledge that the increase is likely due to improvements in ascertainment and reporting, inclusion of broader categories of defects, and advances in pregnancy management and subsequent repair/palliation of complex congenital malformations.[3 7]

Congenital heart defects (CHDs) represent a major proportion of clinically significant birth defects.[1 6] While most CHDs occur as isolated malformations, a substantial minority occurs in combination with abnormalities of other organ systems.[5 8 9] Aetiologic categories of congenital heart disease include chromosomal abnormalities, teratogenic exposures, single gene disorders, and multifactorial determination.[5 10–15] The underlying basis for most cases of non-syndromic CHD is currently unexplained. However, there has been substantial recent progress in knowledge of genetic factors involved in the development of cardiac structural abnormalities for both isolated and syndromic CHD.[16–22]

Combined cytogenetic–epidemiologic analyses have identified discrete chromosomal regions involved in the pathogenesis of many congenital cardiac lesions.[23–27] Elucidation of the molecular genetic basis of numerous single and contiguous gene syndromes associated with cardiac lesions[14 15 28–30] also adds to our current understanding. Despite these recent advances, double outlet right ventricle (DORV) remains one of the least understood categories of CHD.

A key issue in any analysis of DORV concerns its definition. In general, the term "double outlet right ventricle" refers to a family of anatomically related complex congenital cardiac lesions involving the outflow tracts. During the development of the heart, the outflow tract initially connects exclusively with the primitive right ventricle and must undergo extensive remodelling to divide into a separate pulmonary artery and aorta; subsequently, there is continued remodelling to establish direct continuity from the left ventricle to the aorta. The endocardial cushions in the outflow tract are responsible for formation of the semilunar valves as well as for the development of the conal septum, the portion of the ventricular septum between the distal ventricular outflow tracts.

DORV anatomy was first described by Mery in 1703.[31] More than 200 years later, the term "double-outlet ventricle" was employed by Braun *et al*[32] in 1952. Shortly thereafter Witham described "double outlet right ventricle" as a specific cardiac diagnosis.[33] In 1972, Lev *et al*[34] used the relationship of the VSD to the great arteries as the basis for his classification, which remains one of the most widely used clinical classification schemes applied to DORV.

As reviewed in Walters *et al*,[35] some authors used the degree of aortic override as a defining criterion for the diagnosis of DORV such that if the aorta is more than 50% over the right ventricle, it is labelled DORV. This "50% rule" becomes problematic in cases of tetralogy of Fallot with extreme override of the aorta. Alternatively, the absence or loss of normal fibrous continuity between the mitral and aortic valves (that is, presence of subaortic conus) has been proposed as a definition of DORV. This, too, is problematic as the presence

Table 1 Chromosomal associations of double outlet right ventricle (see table 2 for key to abbreviations)

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
1	Trisomy 13	I	DORV PS	Microcephaly, CL/CP, microphthalmia, CFD, malrotation of gut, kyphoscoliosis, MR	127
2–3	Trisomy 13	Unk	DORV		45
4	Trisomy 13	II	DORV MA AoV atresia LSVC	Fetus (18 weeks), holoprosencephaly, CL/CP, retinal dysplasia, MD	128
5	Trisomy 13 phenotype	II	DORV MA Absent AoV Absent PV LSVC	Fetus (14 weeks), cystic hygroma, CL/CP, SUA	128
6	Trisomy 13 phenotype	II	DORV Absent AoV Absent PV	Fetus (21 weeks), cystic hygroma, SUA	128
7–9	Trisomy 13	II	DORV LV hypo	Fetus (25, 30, 30 weeks)	129
10	Trisomy 13	II	DORV LV hypo	Olfactory agenesis, CL/CP, malrotation of gut, polydactyly	130
11	Trisomy 18	II	DORV MA LV hypo PS		131
12–13	Trisomy 18	II	DORV MA LV hypo		131
14	Trisomy 18	II	DORV ASD MA LV hypo Bilat. PDA	Accessory spleen	131
15	Trisomy 18	II	DORV CAVC	Fetus (30 weeks)	129
16–19	Trisomy 18	Unk	DORV	Fetus (25, 27, 29, 32 weeks)	129
20	Trisomy 18	II	DORV MA AoV atresia LV hypo	Fetus (31 weeks), IUGR, vascular mass of abdominal wall, horseshoe kidney, MD, SUA	132
21	Trisomy 18	II	DORV MA LV hypo PS Absent CS	Fetus (22 weeks), malrotation of gut, Dandy–Walker malformation	133
22–24	Trisomy 18	Unk	DORV		45
25	Trisomy 18	II	DORV LSVC	CDH	57
26	Trisomy 21	II	DORV PS		134
27	Trisomy 21	Unk	DORV		36
28	Trisomy 21	II	DORV Bilat SVC		135
29	Trisomy 21	I	DORV PS		135
30	Trisomy 21	II	DORV MV abnl		135
31	Trisomy 21	II	DORV MV abnl		135
32	47, XYY	II	DORV LV hypo TGA MA	Ileal atresia, volvulus	130

Continued

Table 1 Continued

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
33	Mosaic 8p tetrasomy	II	DORV ASD MA	Limb reduction, intestinal malrotation	136
34–40	Recombinant 8 rec 8, dup q, inv(8)(p23q22)	Unk	DORV		137
41	Duplication 8q	Unk	DORV		137
42–43	Deletion 8p	Unk	DORV		137
44	Deletion 8p del(8) (p23.1→pter)	II	DORV CAVC LV hypo PS	CFD, micrognathia, fetal bradycardia, arrhythmias	138
45	Duplication 8p add (8)(p23; ?)	II	DORV MA	CFD, developmental delay	25
46	Mosaic tetrasomy 8p	II	DORV ASD	Agenesis corpus callosum, CFD, seizures, growth and developmental delays, skeletal abnl	139
47	Deletion 8p del (8) (p21.3→ pter)	III	DORV AVSD L isomerism RV hypo PS	IUGR, microcephaly, hypospadias, growth and developmental delays	140, 141
48	Deletion 17p13	II	DORV ASD MA LV hypo PS	Fetus (34 weeks), IUGR, malrotation of colon, hypoplastic thymus, absent parathyroid	142
49	Isochromosome 18q	II	DORV VSD (mult) MV & TV dysplastic LV & LA hypo IAA Dextrocardia	Fetus (29 weeks), alobar holoprosencephaly, microcephaly, CFD, micrognathia, joint contractures, hypoplastic thymus, absent parathyroid, MD, partial malrotation of gut, streak ovaries	143
50–51	Deletion 22q11	I	DORV	CFD	144
52	Deletion 22q11	II	DORV PS LPA absent Aberrant RSCA	Fetus (23 weeks), CFD, absent thymus, renal cysts, short humeri and femurs	145
53	Deletion 22q11	II	DORV ASD PS	CFD, VPI	146
54	Deletion 22q11	III	DORV CAVC L isomerism Interrupted IVC	Fetus (20 weeks), polysplenia, bowel malrotation, absent thymus, multicystic kidney	147
55	Deletion 22q11	I	DORV PS	CFD, MR	148
56	Deletion 22q11	I	DORV PS	CFD, pulmonary HTN, MR	148
57	Deletion 22q11	I	DORV R AoA Isolated LPA		47
58	Deletion 22q11	I	DORV R AoA PS	CFD, absent thymus, seizures, T cell deficiency	149
59	Deletion 22q11	I	DORV PS Dextrocardia	CFD, vertebral fusion, growth delay	150
60	Deletion 22q11	I	DORV PS Major Ao-Pulm collaterals	CFD, growth delay	150
61	Derivative 6 der (6) t(3;6) (q27;p21)	II	DORV VSD (mult) ASD	Bilat microphthalmia and blepharophimosis, R choanal atresia, CFD, hydrocephalus	151

See table 2 for footnotes.

of subaortic conus is a continuous variable in DORV and one that does not lend itself to a binary or dichotomous definition.[35]

The Congenital Heart Surgery Nomenclature and Database Project was developed to provide a more unified and inclusive framework for classification of congenital heart disease and assessment of surgical repair.[35] The consensus definition of DORV was made deliberately broad by stating "DORV is a type of ventriculoarterial connection in which both great vessels arise either entirely or predominantly from the right ventricle".

Consistent with other complex CHDs, DORV may occur as an isolated cardiac defect, together with other cardiac lesions, or in association with extracardiac anomalies.[31 36–42] It occurs in approximately 3–9/100 000 live births,[1 4 43] although at least one report noted rates of between 15–24/100 000.[3] Conservative estimates project DORV accounting for about 1–3% of all congenital heart defects.[1 44]

Unlike other major congenital heart lesions, there has been little systematic study of the aetiologic bases of DORV. To date, no comprehensive investigations—retrospective or prospective—have been performed to evaluate potential developmental anomalies and genetic associations with DORV. We report here a comprehensive analysis of genetic disorders and teratogenic agents associated with DORV organised by distinct anatomic subtypes whenever possible, in an effort to identify relevant developmental processes underlying this disorder.

METHODS

The medical literature was reviewed for cases of DORV. Cases were ascertained in the English language literature using PubMed literature searches with "double outlet right ventricle" and "DORV" as key words, as well as review of references in articles describing cases of DORV. Both epidemiologic analyses of congenital heart disease and case reports were used.

We defined a congenital heart lesion as DORV if both great arteries (that is, the aorta and pulmonary artery) are related to the morphologically right ventricle either by (1) both arising from the conus (infundibulum) or (2) one great artery arises from the conus and the other great artery has fibrous continuity with only the right ventricle (RV) portion of the atrioventricular (AV) canal (tricuspid valve, right ventricular portion of a common AV valve or RV portion of a straddling mitral valve).

We excluded cases with preserved mitral valve to semilunar valve fibrous continuity. And although forms of tetralogy of Fallot with extreme override sometimes have been classified as cases of DORV, this was not included in our definition of DORV phenotypes because of arbitrariness of the "50% rule".

When sufficient anatomic detail was provided, cases from the literature were further sub-categorised into three types: type I DORV as an isolated conotruncal anomaly; type II DORV with conotruncal anomalies and associated malformations of the AV valves and ventricles; and type III DORV associated with heterotaxy (polysplenia, asplenia, atrial isomerism).[31] Documentation of either cardiac isomerism or a combination of characteristic cardiac/vascular malformations in association with visceral situs was necessary to be included in the heterotaxy category. This classification scheme provides a detailed anatomic framework by which to examine the heterogeneous group of DORV malformations.

Each case was reviewed for: pregnancy history and family history, if available; cardiac anatomy; major physical findings noted on examination and/or autopsy; and results of diagnostic testing (including cytogenetic, biochemical, and molecular genetic analyses). Only cases with a definitive genetic diagnosis or those without a definitive diagnosis but with adequate clinical or pathologic detail were included. Cases of DORV reported in experimental animals were also reviewed.

RESULTS

Chromosomal abnormalities associated with DORV

A variety of chromosomal abnormalities were noted in 61 of the 149 cases of DORV included in this analysis (table 1), comprising slightly less than 41% of reported cases. DORV was observed in conjunction with aneuploidies, as well as cytogenetic duplications, deletions and rearrangements.

DORV is a relatively rare diagnosis in the common autosomal trisomies. Nonetheless, the common trisomies comprise a substantial fraction of the reported chromosomal associations with DORV (31/61 cases), with 15 and 10 cases of definite or presumed trisomies 18 and 13, respectively. In contrast to the overall frequency of trisomy 21 in children and fetuses, only six cases of DORV were reported in association with this cytogenetic abnormality. One necropsy study examining CHDs associated with chromosomal abnormalities found a 12% (15/129) prevalence of DORV, but no cases of DORV associated with trisomy 21.[45] Epidemiologic data support an increased risk of DORV in trisomies 13 and 18 but no comparable heightened risk in trisomy 21.[46]

Seven of the 10 cases (70%) of trisomy 13 had DORV with abnormal left heart development. At least six of 15 cases (40%) of trisomy 18 also demonstrated hypoplastic left heart development; insufficient anatomic detail was provided for seven of the other trisomy 18 cases, precluding classification of DORV subtype in those cases. Thus, DORV can occur in individuals with trisomy 13 and trisomy 18, with the majority of these cases occurring in conjunction with hypoplasia of left heart structures.

Cytogenetic abnormalities involving chromosome 8 were reported in 15 cases of DORV (14/15 involving abnormal dosage of 8p), comprising 10% of cases. Most of these cases showed type II DORV (for example, mitral atresia, ventricular hypoplasia, and complete AV canal).

Eleven cases (7%) of DORV were reported in association with deletion of chromosome 22q11. Of these cases, eight of 11 demonstrated a type I DORV cardiac phenotype (that is, with conotruncal abnormalities only); no cases of hypoplastic left heart development were reported. In all postnatal cases where non-cardiac phenotypic data were reported, craniofacial dysmorphism was also noted. While cases of DORV and 22q11 deletion have been reported, DORV appears to be an uncommon or rare finding within the 22q11 deletion syndrome populations previously studied.[47–49]

Non-chromosomal disorders associated with DORV

A variety of non-chromosomal conditions have been associated with DORV and comprised over 56% (84/149) of the cases in this analysis (table 2). DORV has been reported in the following syndromes: Adams–Oliver, Ellis–van Creveld, Gardner–Silengo–Wachtel, Kabuki, Kalmann, Melnick–Needles, Noonan, Opitz, Ritscher–Schinzel, and Robinow syndromes.

Eight cases (~5%) of DORV (five with heterotaxy) were associated with a mutation or non-synonymous sequence variant(s) in the *CFC1* gene; current data support the sequence variants in causation or predisposition to DORV in some populations.[50–52] Although the *CFC*1 gene has been implicated in establishment of left-right asymmetry in vertebrates,[50 52] it has been noted in cases of DORV both with and without laterality defects.[51 52] The *EGF-CFC* gene family, of which *CFC1* is a

Table 2 Non-chromosomal disorders associated with double outlet right ventricle

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
62	Melnick–Needles syndrome	Unk	DORV	CFD, skeletal dysplasia, motor delay, phosphate reabsorption low	152
63	Melnick–Needles syndrome or ter Haar syndrome	I	DORV	Brachycephaly, congenital glaucoma, CFD, hypo nails, skeletal abnl, absent distal phalanges of toes, SUA	153
64	Gardner–Silengo–Wachtel syndrome or genito–palato-cardiac syndrome	I	DORV	Fetus (21 weeks), micrognathia, CFD, flexion deform digits Gonadal dysgenesis: 46, XY with NL female genitalia Family history of CHD	154
65	Noonan syndrome	II	DORV ASD MA AoV atresia LV hypo	Pigmented nevus, ptosis, hypertelorism, micrognathia, low set ears, short/webbed neck, widely spaced nipples, hypotonia	155
66	Kalmann syndrome	II	DORV ASD Pulm art: hypo R AoA Anomalous CA	IUGR, microcephaly, sensory neural hearing loss, micropenis, cryptorchidism, MR, absent olfaction, undetectable LH and FSH	156
67	Ritscher–Schinzel syndrome	II	DORV ASD Abnl SVC	CFD, Bilat iris and retinal colobomas, macrocephaly, partial syndactyly, developmental delay	157
68	Ritscher–Schinzel syndrome	I	DORV	CFD, Dandy–Walker malformation, bilat iris and L optic nerve colobomas, large fontanels, proximal thumb Family history CHD	157
69	Robinow syndrome	III	DORV ASD R isomerism TA, PS	Microcephaly, CFD, blue sclerae, pre/postnatal short stature, delayed skeletal maturation, growth delay	158
70	Opitz syndrome	I	DORV PA R AoA	Closed bladder exstrophy, bilat double collecting system, CFD, cryptorchidism	159
71	Ellis–van Creveld (EVC) syndrome	III	DORV CAVC Common atrium R isomerism Unroofed CS LSVC	Short limb dwarfism, thoracic defect, polydactyly, ectodermal defects, visceral heterotaxia, asplenia	160
72	Adams–Oliver syndrome	II	DORV PS Polyvalvular dysplasia Pulmonary artery: hypo	Microcephaly, CFD, scalp defect, encephalocele, skeletal abnl, hepatoportal sclerosis, pulmonary HTN, growth delay	161
73	Kabuki syndrome	Unk	DORV	CFD	162
74	Kabuki syndrome	II	DORV Ao coarctation	FTT, submucous CP, ear pit, CFD, MR	163
75	VACTERL	I	DORV PS	Single lobed R lung, tracheal agenesis, imperforate anus	164
76	Rhabdo-myomatous dysplasia	III	DORV ASD PDA Multiple Ao–pulmonary collaterals Anom drainage pulmonary veins	R lung hypo, bilobar R and L lung, rhabdomyomatosis	165
77	*CFC1* sequence variant	III	DORV CAVC PA TAPVR R AoA Dextrocardia	R isomerism of lungs, intestinal malrotation, asplenia	50
78	*CFC1* mutation	II	DORV Subpulmonary VSD AoA: hypo		51

Continued

Table 2 Continued

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
79	*CFC1* sequence variant	II	DORV DIRV PA Single ventricle		51
80	*CFC1* sequence variant	III	DORV AVSD PS TAVPR L IVC	Transverse liver, R sided stomach, asplenia	52
81	*CFC1* sequence variant	III	DORV Interrupted IVC Hepatic venous drainage to L sided atrium Bilat SVC PS Bilat/sym PVR	Malrotation	52
82	*CFC1* sequence variants	III	DORV AVSD PA Interrupted IVC Hepatic venous drainage to R sided atrium		52
83	*CFC1* sequence variants	III	DORV AVSD MA TAPVR Absent LSVC Hepatic venous drainage to RA	Transverse liver, asplenia, malrotation	52
84	*CFC1* sequence variants	II	DORV AVSD PS Interrupted IVC		52
85	*CRX* mutation	II	DORV ASD		54
86	*CRX* mutation	Unk	DORV		55
87	*Cn43* mutations	I	DORV		166
88	Unk	III	DORV PS TAPVC Dextrocardia	Situs inversus	167
89	Unk	III	DORV PS TAPVC Dextrocardia		167
90	Unk	I	DORV Major Ao–pulmonary collaterals	Total situs inversus	146
91	Unk	III	DORV CAVC PS TAPVC L SVC IVC drains to LA	Asplenia, visceral heterotaxia, symmetrical liver	168
92	Unk	I	DORV TGA	Partial situs inversus	169
93	Unk	I	DORV PS	Total situs inversus	169
94	Unk	I	DORV AVSD PS Common atrium	Total situs inversus	169
95	Unk	III	DORV TGA	Total situs inversus	130

Continued

Table 2 Continued

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
96	Unk	III	DORV RV hypo AVSD L isomerism		130
97	Unk	III	DORV AVSD TAPVR R isomerism		130
98	Unk	III	DORV AVSD TGA CoA IAA L isomerism	Malrotation of gut	130
99	Unk	III	DORV AVSD TGA LVNC L isomerism		130
100	Unk	III	DORV	Fetus (29 weeks), IUGR, holoprosencephaly, fused eyes, absent nose, Abnl facial bones, omphalocele, 2/3 R syndactyly, bilat radial aplasia, hypoplastic L thumb, aplastic R thumb, polysplenia, incomplete lobation R lung, kyphosis	170
101	Unk	II	DORV ASD MS AoV atresia TV dysplasia	Accessory spleen	171
102	Unk	III	DORV CAVC AoV atresia MS (cleft) LV hypo AoA hypo Double AoA Interrupted IVC LSVC	Polyhydramnios, ascites, hepatomegaly, non-immune hydrops, polysplenia, midgut malrotation	172
103	Unk	III	DORV ASD PS R isomerism IVC drains to LA TAPVD	Bilat R bronchial isomerism, undersized spleen, midline liver	173
104	Unk	Unk	DORV	Ectopia cordis	174
105	Unk	I	DORV Dextrocardia LV diverticulum	Ectopia cordis, CL/CP, encephalocele, hydrocephalus, CDH, ventral hernia	175
106	Unk	I	DORV	Ectopia cordis	130
107	Unk	I	DORV PS Dextrocardia	Premature, ectopia cordis, omphalocele, CDH	175
108	Unk	I	DORV PS	Pentalogy of Cantrell (omphalocele, short sternum with defective formation lower third, CDH, CHD), hydronephrosis, sensory neural hearing loss, cryptorchidism, asthma, growth and developmental delay	176
109	Unk	II	DORV ASD Ao coarct LSVC	Ectopia cordis, sternal cleft, diastasis recti, pericardial defect	177
110	Unk	II	DORV ASD LV hypo LSVC	Ectopia cordis, incomplete split sternum, pericardium absent	177

Continued

Table 2 Continued

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
111	Unk	III	DORV ASD LV hypo	CDH, polysplenia	57
112	Unk	I	DORV	CDH	178
113	Unk	Unk	DORV	CDH	179
114	Unk	Unk	DORV	CDH	180
115–123	Unk	Unk	DORV	CDH	181
124	Unk	II	DORV MS, AS LV hypo	Renal–hepatic–pancreatic dysplasia	169
125	Unk	II	DORV TGA LV hypo	Micrognathia, SUA	169
126	Unk	I	DORV PS TGA	Omphalocele, SUA	169
127	Unk	I	DORV	Bilat renal agenesis, oligohydramnios	169
128	? new AR syndrome	II	DORV CAVC ASD LV hypo PS		182
129	? new AR syndrome	II	DORV ASD PS	Growth delay Family history CHD, consanguinity	183
130	? new AR syndrome	II	DORV ASD PS LSVC	CFD, microcephaly, growth delay, micrognathia Family history CHD, consanguinity	183
131	Unk	Unk	DORV	Absent testes, communicating hydrocephalus, peroxisomal dysfunction per Robinow and Beemer (1990) Family history CHD, consanguinity	184
132	Unk	II	DORV MS AoV atresia LV hypo PA TV dysplasia	Fetus (17 weeks), IUGR, hydraencephaly, hypoplastic L forearm w/abs L hand, R radial aplasia, hydrocephaly, hydrops	185
133	Unk	Unk	DORV	CFD, psychomotor retardation, ataxia	146
134	Unk	I	DORV PS	Unilateral otic hypoplasia/hemifacial microsomia, spinal abnl, absent sacrum, bilat hypoplastic lungs, single cystic/dyspl kidney	186
135	Unk	II	DORV ASD Ventricular inversion PS	Unilateral otic hypoplasia/hemifacial microsomia, unilobed lungs	186
136	Unk	I	DORV PDA	CFD, sacral dimple, growth and motor delay	150
137	Unk	I	DORV TGA PS	CFD	150
138	Unk	II	DORV ASD PS	Anal atresia, thumb contractures, growth delay	150
139	Unk	III	DORV PA R isomerism Atypical ductus LV hypo	CFD, renal agenesis, Bilat syndactyly fingers and toes, bifid uvula, MR	150

Continued

Table 2 Continued

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
140	Unk	III	DORV CAVSD, ASD R isomerism Atypical ductus	Sacral dimple, bilat camptodactyly fingers	150
141	Unk	II	DORV MA AoV atresia LA hypo PA Abnl CA LSVC	Fetus (14 weeks), cystic hygroma, CL/CP, SUA, bilat hypoplastic thymus	187
142	Unk.	II	DORV AoV atresia PA	Fetus (21 weeks), cystic hygroma, SUA, absent thymus	187
143	Unk	II	DORV AVSD Absent PV	Polydactlyly, webbed neck	130
144	Unk	I	DORV TGA Overriding TV	CL, hemivertebrae	130
145	Unk	II	DORV AVSD TGA PA	Inguinal hernia, hydronephrosis	130

Abnl, abnormal; Ao, aorta; AoA, aortic arch; AoV, aortic valve; ASD, atrial septal defect; AVSD, atrioventricular septal defect; Bilat, bilateral; CA, coronary artery; CAVC, complete atrioventricular canal; CDH, congenital diaphragmatic hernia; CFD, craniofacial dysmorphism; CL/CP, cleft lip/cleft palate; Coarct, coarctation; CS, coronary sinus; DILV, double inlet left ventricle; DORV, double outlet right ventricle; dyspl, dysplastic; ECA, extracardiac anomalies; FTT, failure to thrive; HTN, hypertension; Hypo, hypoplastic; IAA, interrupted aortic arch; IVC, inferior vena cava; IUGR, intrauterine growth retardation; LA, left atrium; LPA, left pulmonary artery; LSVC, persistent left superior vena cava; LV, left ventricle; LVNC, left ventricular non-compaction; MA, mitral atresia; Malrot, malrotation; MD, Meckel's diverticulum; MV, mitral valve; NL, normal; PA, pulmonary atresia; PS, pulmonary stenosis; Pulm art, pulmonary artery; PV, pulmonary valve; RA, right atrium; RSCA, right subclavian artery; RV, right ventricle; SUA, single umbilical artery; TAPVC, total anomalous pulmonary venous connection; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; Unk, unknown; VCFS, velocardiofacial syndrome; VPI, velopharyngeal insufficiency; VSD, ventricular septal defect.

member, codes for extracellular proteins that are thought to be essential in intercellular signalling pathways active in lateral plate mesoderm during development.[53]

Mutations of the *CRX* gene were associated with two cases of DORV.[54 55] This cardiac specific homeobox gene encodes the transcription factor Nkx2.5, and has been implicated in both first and secondary heart field development and has been reported in atrial and ventricular septal defects as well as in electrical conduction abnormalities.[56]

Several types of extracardiac anomalies occurred with substantial frequency in cases of DORV. As noted above, heterotaxy was present in 24/149 (16%) of all cases, occurring in 22/149 (almost 15%) of non-chromosomal cases versus 2/149 (1%) of cytogenetic cases. Both right and left isomerism was reported, as were four cases of complete situs inversus. Five cases were identified with abnormal lung lobation. Six cases of DORV were seen in association with ectopia cordis, with or without additional midline defects.

Two other types of extracardiac anomalies were frequently observed in association with DORV: congenital diaphragmatic hernia, and urogenital malformations. Nine cases (6%) were seen in association with congenital diaphragmatic hernia including one case of trisomy 18 (table 1); this was noted earlier in epidemiologic and experimental animal studies.[57] Fourteen cases of DORV (9%) were seen with urogenital malformations. Four of these 14 cases included either a proband and/or family member with gonadal dysgenesis or other urogenital malformation.

Familial recurrence of CHD was reported in seven cases (~5%) of DORV. Three of seven cases demonstrated multiple consanguineous unions within the pedigree. A recent study of parental consanguinity and congenital heart malformations also found a significant association between parental consanguinity and DORV.[58]

Human teratogenic exposures and DORV

While a number of environmental risk factors have been associated with CHD, there are few data associating human DORV with teratogenic exposures; only about 3% of the cases reported in the literature appeared to have a possible teratogenic association based on the reported information (table 3). An association of maternal diabetes and DORV has been reported in several epidemiologic studies and case reports.[42 59 60] Prenatal exposures to ethanol, retinoic acid or theophylline with adrenergic agonists have been reported in humans with DORV.[61 62] Of note, similar teratogens have been associated with TOF[63–65] and may influence pathways unique to type I DORV.

Animal models of DORV

Studies using experimental animals reveal diverse single gene, multigenic, and teratogenic aetiologies of DORV (tables 4 and 5). The wide variety of genetic defects resulting in a DORV phenotype lends support to the hypothesis that DORV represents a "final common pathway" phenotype for multiple perturbations in cardiac outflow tract development.

Simple and complex DORV phenotypes were observed in 78% of *TGF-β_2* (transforming growth factor-β2) knockout mouse embryos,[66] 50% of transgenic chicks with misexpression

Table 3 Teratogenic associations

Case	Diagnosis	Segmental type	Cardiac anatomy	Significant extracardiac findings	Reference
146	Fetal alcohol syndrome (FAS)	I	DORV PA	Facial features of FAS Teratogenic exposures: ethanol	188
147	Unk	I	DORV VSDs R AoA AoA hypo	Fetus (22 weeks) Teratogenic exposures: maternal diabetes mellitus	60
148	Unk	II	DORV LV hypo R AoA PS	Teratogenic exposure: Carbamazepine	189
149	Unk	II	DORV VSD MS LV hypo PS	Kidney dysplasia, rudimentary spleen Teratogenic exposures: theophylline, albuterol, terbutaline, aminophylline	62

AoA, aortic arch; DORV, double outlet right ventricle; LV, left ventricle; MS, mitral stenosis; PS, pulmonary stenosis; PA, pulmonary atresia; PS, pulmonary stenosis; Unk, unknown; VSD, ventricular septal defect.

of *Noggin* and associated loss of function of bone morphogenetic proteins 2 and 4,[67] and 38% of *Dvl2* (dishevelled) knockout mouse embryos.[68] Additional members of the *TGF-β_2* superfamily of growth factors have also been implicated in aberrant neural crest development,[69] though their precise role in human DORV is unclear.

Not surprisingly, genes previously recognised in left-right axis determination have been associated with the development of DORV. DORV has been identified in a subset (12–35%) of iv/iv (inversus viscerum) mouse embryos; these studies implicate the homeobox gene *Pitx2* in the pathogenesis of DORV.[70–77]

DORV has also been associated with mutations of the murine *Pax3* (*splotch*) and *Folbp1* genes.[70 78 79] DORV was also noted in mice with homozygous *Lp* genotype, with the *Vangl2* gene implicated in subsequent analyses; these mice also displayed incomplete axial rotation, defective rostral neural tube closure, and a variety of arch abnormalities.[80 81] Mutations of the *Pax3* gene are reported to affect proper neural crest cell migration[70] and a deficiency of the folic acid binding protein 1 promotes cell death during organogenesis, particularly of the presumptive migrating cardiac neural crest.[79] Mutations in the *Vangl2* gene, a member of the non-canonical Wnt signalling pathway regulating cell polarity, have been shown to result in outflow tract remodelling and alignment abnormalities.[81]

Multigenic causation of DORV has been described. In murine models, homozygous null mutations of *RXR-alpha* resulted in DORV in 17% of progeny.[82] Conotruncal malformations of varying severity, including DORV, were observed in mice bred with combined retinoic acid receptor gene deficiencies (*RAR alpha1* and *RXR alpha*). This may reflect overlapping roles for individual retinoic acid receptor genes and their localised expression in the developing heart. Combining mutations in both receptors synergistically increased the frequency and severity of conal malformations.[83]

Similarly, DORV may occur in animals with targeted mutations in the endothelin converting enzyme genes *ECE-1* and *ECE-2*. DORV was seen in homozygous null mutants of *ECE-1*. There was a notable increase in the frequency and severity of conotruncal abnormalities in double knockout embryos for both *ECE-1* and *ECE-2*. These findings highlight the importance of endothelins in cardiac outflow tract development and suggest functional redundancy of these related metalloproteases.[84]

There are additional autosomal recessive animal models with DORV. Relevant genes include mutations of: *non-muscle myosin II-B*,[85] platelet derived growth factor receptor genes,[86] *Cx40* (a gap junction protein),[87] *AP-2alpha*,[88] *Gata4*/cofactor *Fog*,[89 90] *Cited2* (*Tfap2* co-activator),[91] *Trapα*/*Ssrl*,[92] *Ptdsr*,[93] *Sox11*,[94] *Sox4/NF-ATC*,[95] *Presenilin1* (*PS1*),[96] and *Fgf12-IIIb*.[97] These genetic animal models of DORV indicate that disruption of any of the multiple pathways can result in a DORV phenotype.

Studies in animals also implicate diverse teratogens in causing or enhancing susceptibility for the development of DORV phenotypes. DORV was observed in animals receiving commonly used medications such as ephedrine,[98] theophylline,[99] Tedral (combination of theophylline, ephedrine, and phenobarbital),[99] sodium valproate,[100] and retinoic acid/vitamin A.[101–103] The incidence of DORV in these animal studies ranged from 15–62%, depending on the timing and duration of exposure. Other agents implicated in causing DORV in animals include bisdiamine,[104] nimustine hydrochloride,[105] copper citrate,[106] and bromodeoxyuridine.[107] Murine maternal diabetes, as in humans, is implicated in the pathogenesis of congenital heart defects, including DORV.[108] Supplementation of diabetic pregnant mice with vitamin E results in a notable reduction of the severity of cardiac malformations, presumably due to its antioxidant effects.[109] Finally, the application of localised electrical shock to the conotruncal area of the chick embryonic heart was associated with different forms of DORV; ectopia cordis was also variably present.[110]

DISCUSSION

In pronounced contrast to other major congenital heart defects, little attention has been paid to defining the aetiologic bases of DORV. The wide range of cardiac morphology historically labelled as DORV has made the understanding of DORV challenging. The most commonly used classification system[34 35] is based on the anatomy of both great arteries and VSD and on the resultant physiology of the cardiac lesions; it does not consider other possible coexisting cardiac malformations.

The classification system proposed by Van Praagh and colleagues describes primary malformations of the ventricular outflow portion of the heart (type I DORV), malformations of the ventricular outflow tract with additional malformations of the AV canal, AV valves, ventricles, venous and arterial pathways (type II), and lastly, defects in cardiac lateralisation

Table 4 Genetic disorders with double outlet right ventricle in animal models

Gene	Inheritance	Cardiac anatomy	Species	Reference
iv	AR	DORV (12%) CAVC (24%) Common atrium (17%) Sinus venosus (9%)	Mouse	72
Platelet-derived growth factor receptor alpha subunit	AR	DORV TA Facial cleft	Mouse	86
RXR alpha	AR	DORV (17%) Hypo compact zone (94%) VSD (94%)	Mouse	82
RXR alpha/RAR alpha 1 [RXR$\alpha -/-$*, RAR*$\alpha -/+$*]* double mutant embryo	Multigene	DORV	Mouse	83
Non-muscle myosin II-B	AR	DORV VSD	Mouse	85
TGFβ_2	AR	DORV (19%) VSD (94%) DILV (25%)	Mouse	190
TGFβ_2	AR	DORV (78%) VSD (38%) TV/MV abnormal (33%) Overriding TV (25%) AoA hypo (21%)	Mouse	66
ECE-1/ECE-2 [ECE-1 $-/-$*; ECE-2* $-/-$*, ECE-1* $-/-$*; ECE-2* $+/+$*]* double mutant embryo	Multigene	DORV (42%) VSD (100%) Overriding aorta (29%) AV valve displaced (33%) Aorticopulmonary septation defects (42%) Great vessel malalignment (33%)	Mouse	84
Noggin	Transgenic	DORV (50%) Truncus arteriosus (27%)	Chick	67
Splotch (Pax3)	AR	DORV (6–8%) Truncus arteriosus (50–53%)	Mouse	78
Splotch (Pax3)	AR	DORV (58%) Truncus arteriosus (42%)	Mouse	70
Folbp1 (Pax3)	AR	DORV (10%) Truncus arteriosus VSD	Mouse	79
Cited2 (Tfap2 co-activator)	AR	DORV	Mouse	91
Pitx2δ*c*	AR	DORV (28%) TGA/TGA and PS (65%) Truncus arteriosus (7%)	Mouse	70
Pitx2δ*c*	AR	DORV (100%)	Mouse	75
Pitx2δ*abc*	AR	DORV (majority) CAVC	Mouse	74
Pitx2	AR	DORV	Mouse	73, 76
Pitx2 (iv/iv)	AR	DORV (35%)	Mouse	71
TBX1/Pitx2	Multigene	DORV (17%) ASD (50%) Valve defects (50%) Pulmonary trunk and vein malformations (50%) VSD (25%) Others (50%)	Mouse	77
Lp/Lp	AR	DORV (100%) Double AoA (66%) Right AoA (33%)	Mouse	80
Cx40 ($-/-$*)*	AR	DORV (17%) Endocardial cushion defects (17%)	Mouse	87
AP-2alpha (AP-2α $-/-$*)*	AR	DORV (87%) Truncus arteriosus (13%)	Mouse	88
Gata4 (Gata4 ki/ki) transgenic	AR	DORV (100%)	Mouse	89
Gata4 (H/H)	AR	DORV CAVC Ventricular myocardium hypo	Mouse	90

Continued

Table 4 Continued

Gene	Inheritance	Cardiac anatomy	Species	Reference
ES(#21)-11	Chimeric chromosome 21	DORV (29%)	Mouse	191
Trapα/Ssr1	AR	DORV	Mouse	92
Ptdsr	AR	DORV VSD PA: hypo Thymus: hypo	Mouse	93
AP-2alpha	AR	DORV (majority)	Mouse	88
Sox11	AR	DORV VSD Spectrum of outflow tract malformations	Mouse	94
Sox4/NF-Atc	Multigene	DORV Truncus arteriosus TOF	Mouse	95
Presenilin 1 (PS1)	AR	DORV VSD PS	Mouse	96
Fgf12-IIIb	AR	DORV (minority)	Mouse	97
Vang-like 2 (Wnt signalling pathway)	AR	DORV (remodelling of cardiac outflow tract)	Mouse	81
Dishevelled 2 (Dvl2) (Wnt signalling pathway)	AR	DORV (38%) TGA Truncus arteriosus	Mouse	68
Ara9	AR	DORV (57%)	Mouse	192

AoA, aortic arch; AR, autosomal recessive; AV, atrioventricular; ASD, atrial septal defect; CAVC, complete atrioventricular canal; DILV, double inlet left ventricle; DORV, double outlet right ventricle; MV, mitral valve; PA, pulmonary atresia; PS, pulmonary stenosis; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

associated with DORV (type III).[31] Defining DORV anatomic subtypes affords additional insights into potential developmental mechanisms leading to DORV seen here as the clustering of specific anatomic subtypes of DORV with distinct genetic or chromosomal abnormalities.

Two general themes have become apparent with progress in definition of the molecular genetic bases underlying some of the common structural anomalies of the heart.[5 10–15] First, it is clear that a single genetic lesion can be associated with a spectrum of structural anomalies.[14 23 24 27 30 111] Second, apparently similar cardiac anomalies have been identified with lesions of disparate chromosomal regions or genes.[23 24 27 112 113] The data assembled here show that both of these themes apply to DORV as well.

Much of the most rigorous genetic and developmental study of normal cardiac development and of the genesis of DORV has come from recent animal studies.[56] There are, however, two important limitations of the animal studies that must be considered in the context of using them to understand human DORV. First, the DORV phenotypes in the many animal models are structurally heterogeneous and sometimes loosely defined anatomically. Second, an abundance of experience with animal models has provided us with the insight that those models do not always faithfully reflect the pathogenesis of human disease. To date, the limited information regarding aetiologies and developmental processes of DORV from medical case reports and epidemiologic studies has been consistent with insights from studies on animal models.

The precise mechanisms by which specific genetic lesions or teratogenic exposures result in maldevelopment from normal anatomy to DORV phenotypes are largely unknown. Two different types of data from this study support the concept that disruptions in distinct developmental pathways are involved in the pathogenesis of DORV in animals and humans. First, specific chromosomal lesions appear to be associated with distinct anatomic subtypes of DORV. Thus, type II DORV is observed in individuals with trisomy 13 or trisomy 18. In contrast, type I DORV is noted in individuals with chromosome 22q11 deletions. Second, different developmental pathways are implicated in the pathogenesis of DORV based on the catalogue of genes and teratogens noted in this analysis. These include, for example, genes and teratogens influencing neural crest development,[66 67 70 79 82–84 95 101] abnormalities of key structural or contractile proteins such as *myosin II-D*,[85] and genetically or teratogen induced cell death at key developmental periods.[105 114]

In addition to the likelihood that perturbation of distinct developmental pathways can lead to DORV, the data here reveal an additional key aspect of the pathophysiology of DORV. Similar to other major congenital cardiac lesions, the chromosomal abnormalities, mutated genes or teratogenic exposures that are associated with DORV are not necessarily solely determinative of that cardiac phenotype; sometimes, there is even no demonstrable cardiac abnormality despite a chromosomal anomaly or mutated gene. This, in turn, means that there must be a multifactorial mode of determination in many instances of DORV, with some environmental contribution for many of the genetic lesions described here to be associated with DORV.

Mechanistic explanations of DORV predated the discovery of genes of cardiac morphogenesis. Morphological models of DORV have included abnormalities of cardiac septation, rotation, remodelling and haemodynamics.[38 115–119] The current challenge is to couple what is valid from the mechanistic models with the insights of developmental genetics.

There are various approaches to conceptualise the developmental genetics of heart formation. One recent review organised the diverse pathways implicated in cardiac development into heart region specific pathways.[56] Transcription factors *Nkx2.5*, *Gata4* and *Tbx 20* are postulated to influence right ventricular development via pathways that include *Isl1, Mef2c*, and *Hand2*, while *Shh, Tbx1*, members of the forkhead family, *Pitx2, Fgf8* and *Fgf 10* appear essential for development of the great arteries.[56] Interactions between these and other pathways are

Table 5 Teratogens associated with double outlet right ventricle in animal studies

Exposure	Cardiac anatomy	Species	Reference
Copper citrate	DORV	Hamster	106
	VSD		
Retinoic acid	DORV	Hamster	103
	VSD		
	TGA		
	Overriding aorta w/VSD		
Retinoic acid	DORV	Chick	101
	VSD		
Vitamin A	DORV	Mouse	102
	TGA		
	VSD		
Ephedrine	DORV	Chick	98
	Truncus arteriosus		
	VSD w/overriding aorta		
Ethanol	DORV	Mouse	193
	VSD		
	TOF		
	TGA		
	Endocardial cushion defect		
	Overriding PA		
	Overriding Ao		
Bromodeoxyuridine	DORV	Chick	107
	VSD		
	PDA		
Nimustine hydrochloride	DORV	Quail–chick chimeras	105
	VSD		
	Truncus arteriosus		
Bis-diamine	DORV	Chick	104
	VSD		
	Truncus arteriosus		
Tedral (theophylline, ephedrine and phenobarbital)	DORV	Chick	99
	VSD		
	DORV with DILV		
	Truncus arteriosus		
	TGA		
Theophylline	DORV	Chick	99
	VSD		
	DORV with DILV		
Sodium valproate	DORV	Mouse	100
	VSD		
Maternal diabetes	DORV	Mouse	108
	Endocardial cushion defect		
	TGA		
	AS		
	VSD		
Electrical shock	DORV	Chick	110
	Ectopia cordis		
Bay 11-7085 *NF-κB* signalling pathway	DORV	Chick	194
	VSDs		
	Great arteries stenosis		

Ao, aorta; AS, aortic stenosis; DILV, double inlet left ventricle; DORV, double outlet right ventricle; PDA, patent ductus arteriosus; PA, pulmonary atresia; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

presently a subject of intense investigation. Also relevant is the determination of the contribution of somatic mutation present during embryonic development to the construction of abnormal cardiac phenotypes, including DORV.[120]

The genetic and metabolic complexity of the morphological remodelling of the developing outflow tract offers a basis for the anatomic variability of DORV such that different anatomic subtypes could be based on distinct underlying mechanisms. For example, one could hypothesise that type I DORV might reflect abnormalities of cells (neural crest or anterior heart field) necessary for normal outflow tract development. Genes belonging to or regulating members of the *TGFβ* superfamily (*activin type IIB receptor*, *noggin*, *TGFβ2*) and other genes or teratogens influencing neural crest development (*Sox-4*,[121] *NF-1*, *RAR* genes, *ECE-1*, *ECE-2*, *Pax-3*, maternal diabetes) have been associated with defects in cardiac outflow anatomy, including DORV. Type II DORV might reflect abnormal genetically programmed or teratogen induced maldevelopment of the endocardial cushions crucial in atrioventricular and semilunar valve formation, also affecting portions of the conal and ventricular septum of the heart. Mutations of *Gata4* appear potential candidates for type II DORV; mutations and sequence variants in highly conserved regions of *Gata4* have been reported in association with septation and endocardial cushion defects, including CAVC. To date, however, abnormalities of *Gata4* have only rarely been noted in association with DORV, although data from patients with DORV are limited.[18 122] DORV seen in association with defects in laterality (type III) would be predicted to occur in models with altered left-right axis determination. Genes implicated in determining body plans such as *Pitx2, CFC1, Cx43* (left-right axis determination), *Hox 1.5* (rostral-caudal specification) and abnormalities of situs and looping (*lefty-1, inversin*) are reasonable candidates for type III DORV; mutations in several of these genes have already been noted in a few cases of human DORV and pertinent animal models.[50 51 53 70 72 77 123–126]

In summary, this analysis indicates the considerable aetiologic heterogeneity of DORV, with multiple chromosomal, monogenic and teratogenic causes, and reveals the likelihood of at least several pathogenetic processes. Additional human and animal studies are needed to further define genetic and non-genetic aetiologies and pathogenetic mechanisms of DORV. This information will be important to define the natural histories of the diverse causes of DORV with their varied cardiac and extracardiac pathologies, and to accurately define the associated reproductive recurrence risks. Such information may also prove helpful in advancing surgical therapies and, potentially, prenatal preventive strategies as well.

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