Double outlet right ventricle: aetiologies and associations

D Obler,1 A L Juraszek,2 L B Smoot,2 M R Natowicz3

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.7–9

Congenital heart defects (CHDs) represent a major proportion of clinically significant birth defects.10 While most CHDs occur as isolated malformations, a substantial minority occurs in combination with abnormalities of other organ systems.11–13 Aetiological categories of congenital heart disease include chromosomal abnormalities, teratogen exposures, single gene disorders, and multifactorial determination.14–19 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.20–22

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 lesions28–30 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...
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<th>Case</th>
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### Table 1

**Case** | **Diagnosis** | **Segmental type** | **Cardiac anatomy** | **Significant extracardiac findings** | **Reference**
---|---|---|---|---|---
33 | Mosaic 8p tetrasomy | II | DORV | Limb reduction, intestinal malrotation | 136
34–40 | Recombinant 8q | 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, hypoplasias, 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 | 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 PS | 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 | 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 | Bilateral 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.38

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.39 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 births4;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 atroventricular (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 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).45 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 (51/61 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 15 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, Kalman, 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.46–49 Although the CFC1 gene has been implicated in establishment of left-right asymmetry in vertebrates,46,50 it has been noted in cases of DORV both with and without laterality defects.51–53 The EGF-CFC gene family, of which CFC1 is a
Table 2  Non-chromosomal disorders associated with double outlet right ventricle

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<th>Case</th>
<th>Diagnosis</th>
<th>Segmental type</th>
<th>Cardiac anatomy</th>
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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; Coarc, 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; LVC, 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; TGF, tetralogy of Fallot; TV, tricuspid valve; Unk, unknown; VCFS, velocardiofacial syndrome; VPI, velopharyngeal insufficiency; VSD, ventricular septal defect.

Mutations of the CRX gene were associated with two cases of DORV.54 55 This cardiac specific homebox 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.62 65 67 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 TOF65 66 and may influence pathways unique to type I DORV.

Animal models of DORV
Studies using experimental animals reveal diverse single gene, multigenic, and teratogenic aetologies 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-β2 (transforming growth factor-β2) knockout mouse embryos,59 50% of transgenic chicks with misexpression
Table 3 Teratogenic associations

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

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

there are additional autosomal recessive animal models with DORV. Relevant genes include mutations of: non-muscle myosin II-B, platelet derived growth factor receptor genes, Cx40 (a gap junction protein), AP-2alpha, Gap43/cofactor Fog, Cited2 (Tap2 co-activator), Trau/Ssz1, Pdx4, Sox4, Sox4/NF-ATC, Presenilin1 (PS1), and Fgf12-Illb. 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, theophylline, Tedral (combination of theophylline, ephedrine, and phenobarbital), sodium valproate, and retinoic acid/vitamin A. 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 bis-diamine, nimustine hydrochloride, copper citrate, and bromodeoxyuridine. Murine maternal diabetes, as in humans, is implicated in the pathogenesis of congenital heart defects, including DORV. 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. 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.

**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 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>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Cardiac anatomy</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>iv</td>
<td>AR</td>
<td>DORV (12%)</td>
<td>Mouse</td>
<td>72</td>
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<td></td>
<td></td>
<td>CAVC (24%)</td>
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<td>Common atrium (17%)</td>
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<td></td>
<td>Sinus venosus (9%)</td>
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<tr>
<td>Platelet-derived growth factor receptor alpha subunit</td>
<td>AR</td>
<td>DORV</td>
<td>Mouse</td>
<td>86</td>
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<td>TA</td>
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<td></td>
<td>Facial cleft</td>
<td></td>
<td></td>
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<td>AR</td>
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<tr>
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<td></td>
<td>Hypo compact zone (94%)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>VSD (94%)</td>
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</tr>
<tr>
<td>RXR alpha/RAR alpha 1 [RXRα−/−, RARα−/+] double mutant embryo</td>
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<td>DORV</td>
<td>Mouse</td>
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<td>Mouse</td>
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<td>VSD</td>
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<td>(94%)</td>
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<td></td>
<td>VSD (94%)</td>
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<tr>
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<td>DILV (25%)</td>
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<td>AR</td>
<td>DORV (78%)</td>
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<td>VSD (38%)</td>
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<td>TV/MV abnormal (33%)</td>
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<td>Overriding TV (25%)</td>
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<td>ECE-1/ECE-2 [ECE-1 −/−; ECE-2 −/−, ECE-1 −/−; ECE-2 +/+] double mutant embryo</td>
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<td>DORV (42%)</td>
<td>Mouse</td>
<td>84</td>
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<td>VSD (100%)</td>
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<td>Overriding aorta (29%)</td>
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<td>AV valve displaced (33%)</td>
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<td>Chick</td>
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<td>DORV (58%)</td>
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<td>Truncus arteriosus (42%)</td>
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<td>Folbp1 (Pax3)</td>
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<tr>
<td></td>
<td></td>
<td>VSD</td>
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<tr>
<td>Cited2 (Tlasp2 co-activator)</td>
<td>AR</td>
<td>DORV</td>
<td>Mouse</td>
<td>91</td>
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<tr>
<td>Ptx2/1c</td>
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<td>DORV (28%)</td>
<td>Mouse</td>
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<td>TGA/TGA and PS (65%)</td>
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<td>Ptx2/abc</td>
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<td>AR</td>
<td>DORV</td>
<td>Mouse</td>
<td>73, 76</td>
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<td>DORV (35%)</td>
<td>Mouse</td>
<td>71</td>
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<td>DORV (17%)</td>
<td>Mouse</td>
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<td>ASD (50%)</td>
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<td>Valve defects (50%)</td>
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<td>Pulmonary trunk and vein malformations (50%)</td>
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<td>VSD (25%)</td>
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<td>Others (50%)</td>
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<tr>
<td>Cx40 (−/−)</td>
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<td>DORV (17%)</td>
<td>Mouse</td>
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<td></td>
<td></td>
<td>Endocardial cushion defects (17%)</td>
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<td></td>
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<td>AP-2alpha [AP-2α−/−]</td>
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<td>DORV (87%)</td>
<td>Mouse</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Truncus arteriosus (13%)</td>
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<td></td>
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<tr>
<td>Gata4 (Gata4 ki/ki) transgenic</td>
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<td>DORV (100%)</td>
<td>Mouse</td>
<td>89</td>
</tr>
<tr>
<td>Gata4 (H/H)</td>
<td>AR</td>
<td>DORV</td>
<td>Mouse</td>
<td>90</td>
</tr>
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<td></td>
<td>CAVC</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular myocardium hypo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
associated with DORV (type III).11 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.10–15 First, it is clear that a single genetic lesion can be associated with a spectrum of structural anomalies.14 23 27 30 112 Second, apparently similar cardiac anomalies have been identified with lesions of disparate chromosomal regions or genes.23 24 27 113 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 models do not always faithfully reflect the pathogenesis of many instances of DORV, with some environmental contributions that there must be a multifactorial mode of determination in many instances of DORV, with some environmental contributions that there must be a multifactorial mode of determination in many instances of DORV, with some environmental contributions.

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.58 115–119 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 Tbx5 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.69 Interactions between these and other pathways are

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Cardiac anatomy</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES(21)-11</td>
<td>Chimeric chromosome 21</td>
<td>DORV (29%)</td>
<td>Mouse</td>
<td>191</td>
</tr>
<tr>
<td>Trapx/Ssr1</td>
<td>AR</td>
<td>DORV</td>
<td>Mouse</td>
<td>92</td>
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<tr>
<td>Ptdsr</td>
<td>AR</td>
<td>DORV</td>
<td>Mouse</td>
<td>93</td>
</tr>
<tr>
<td>Sox11</td>
<td>AR</td>
<td>DORV (majority)</td>
<td>Mouse</td>
<td>88</td>
</tr>
<tr>
<td>Sox4/NF-Atc</td>
<td>Multigenic</td>
<td>Spectrum of outflow tract malformations</td>
<td>Mouse</td>
<td>95</td>
</tr>
<tr>
<td>Presenilin 1 (PS1)</td>
<td>AR</td>
<td>DORV</td>
<td>Mouse</td>
<td>96</td>
</tr>
<tr>
<td>Fgf12-lllb</td>
<td>AR</td>
<td>DORV (minority)</td>
<td>Mouse</td>
<td>97</td>
</tr>
<tr>
<td>Vang-like 2 (Wnt signalling pathway)</td>
<td>AR</td>
<td>DORV (remodelling of cardiac outflow tract)</td>
<td>Mouse</td>
<td>81</td>
</tr>
<tr>
<td>Dishevelled 2 (Dvl2) (Wnt signalling pathway)</td>
<td>AR</td>
<td>DORV (38%)</td>
<td>Mouse</td>
<td>68</td>
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<td>Ax49</td>
<td>AR</td>
<td>DORV (57%)</td>
<td>Mouse</td>
<td>192</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cardiac anatomy</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper citrate</td>
<td>DORV</td>
<td>Hamster</td>
<td>106</td>
</tr>
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<td>Retinoic acid</td>
<td>DORV</td>
<td>Hamster</td>
<td>103</td>
</tr>
<tr>
<td>Retinoic acid</td>
<td>VSD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td>DORV</td>
<td>Mouse</td>
<td>102</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Truncus arteriosus</td>
<td>Chick</td>
<td>98</td>
</tr>
<tr>
<td>Ethanol</td>
<td>VSD</td>
<td>Mouse</td>
<td>193</td>
</tr>
<tr>
<td>Bromodeoxyuridine</td>
<td>VSD</td>
<td>Chick</td>
<td>107</td>
</tr>
<tr>
<td>Nimustine hydrochloride</td>
<td>VSD</td>
<td>Quail–chick chimeras</td>
<td>105</td>
</tr>
<tr>
<td>Bis-diamine</td>
<td>VSD</td>
<td>Chick</td>
<td>104</td>
</tr>
<tr>
<td>Terald (theophylline, ephedrine and phenobarbital)</td>
<td>VSD</td>
<td>Chick</td>
<td>99</td>
</tr>
<tr>
<td>Theophylline</td>
<td>VSD</td>
<td>Chick</td>
<td>99</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>DORV</td>
<td>Mouse</td>
<td>100</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>DORV</td>
<td>Mouse</td>
<td>108</td>
</tr>
<tr>
<td>Electrical shock</td>
<td>DORV</td>
<td>Chick</td>
<td>110</td>
</tr>
<tr>
<td>Bay 11-7085 NF-κB signalling pathway</td>
<td>VSDs</td>
<td>Chick</td>
<td>194</td>
</tr>
</tbody>
</table>

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.

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 II receptor, noggin, TGFβ2) and other genes or teratogens influencing neural crest development (Six-4, 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. DOOR 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 Ptx2, CFC1, Csx3 (left-right axis determination), Hox t.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.

In summary, this analysis indicates the considerable aetiological heterogeneity of DORV, with multiple chromosomal, mono- 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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