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

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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

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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.

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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

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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

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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

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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

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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

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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

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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

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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 [RXRα−/−, RARα−/+] 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
Pitx2δc	AR	DORV (28%) TGA/TGA and PS (65%) Truncus arteriosus (7%)	Mouse	70
Pitx2δc	AR	DORV (100%)	Mouse	75
Pitx2δabc	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

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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

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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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REFERENCES

1. **Botto LD,** Correa A. Decreasing the burden of congenital heart anomalies: an epidemiologic evaluation of risk factors and survival. *Prog Pediatr Cardiol* 2003;**18**:111–21.
2. **Ferencz C,** Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, Hepner SI, Downing JW. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. *Am J Epidemiol* 1985;**121**:31–6.
3. **Hoffman JI,** Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002;**39**:1890–900.
4. **Loffredo CA.** Epidemiology of cardiovascular malformations: prevalence and risk factors. *Am J Med Genet* 2000;**97**:319–25.
5. **Pierpont ME,** Basson CT, Benson DW Jr, Gelb BD, Giglia TM, Goldmuntz E, McGee G, Sable CA, Srivastava D, Webb CL. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* 2007;**115**:3015–38.

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6. **Hoffman JI.** Incidence of congenital heart disease: I. Postnatal incidence. *Pediatr Cardiol* 1995;**16**:103–13.
7. **Botto LD,** Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. *Pediatrics* 2001;**107**:E32.
8. **Fixler DE.** Epidemiology of congenital heart disease. *Oski's pediatrics: principles and practice*. Philadelphia: Lippincott, Williams, and Wilkins, 1999:277–81.
9. **Greenwood RD.** Cardiovascular malformations associated with extracardiac anomalies and malformation syndromes. Patterns for diagnosis. *Clin Pediatr* 1984;**23**:145–51.
10. **Ferencz C,** Neill CA, Boughman JA, Rubin JD, Brenner JI, Perry LW. Congenital cardiovascular malformations associated with chromosome abnormalities: an epidemiologic study. *J Pediatr* 1989;**114**:79–86.
11. **Marino B,** Digilio MC. Congenital heart disease and genetic syndromes: specific correlation between cardiac phenotype and genotype. *Cardiovasc Pathol* 2000;**9**:303–15.
12. **Nora JJ,** Berg K, Nora AH. Congenital heart disease: genetics. *Cardiovascular diseases: genetics, epidemiology and prevention*. New York: Oxford University Press, 1991:53–80.
13. **Opitz JM,** Clark EB. Heart development: an introduction. *Am J Med Genet* 2000;**97**:238–47.
14. **Srivastava D.** Genetic assembly of the heart: implications for congenital heart disease. *Annu Rev Physiol* 2001;**63**:451–69.
15. **Weismann CG,** Gelb BD. The genetics of congenital heart disease: a review of recent developments. *Curr Opin Cardiol* 2007;**22**:200–6.
16. **Kirk EP,** Sunde M, Costa MW, Rankin SA, Wolstein O, Castro ML, Butler TL, Hyun C, Guo G, Otway R, Mackay JP, Waddell LB, Cole AD, Hayward C, Keogh A, Macdonald P, Griffiths L, Fatkin D, Sholler GF, Zorn AM, Feneley MP, Winlaw DS, Harvey RP. Mutations in cardiac T-box factor gene TBX20 are associated with diverse cardiac pathologies, including defects of septation and valvulogenesis and cardiomyopathy. *Am J Hum Genet* 2007;**81**:280–91.
17. **Konig K,** Will JC, Berger F, Muller D, Benson DW. Familial congenital heart disease, progressive atrioventricular block and the cardiac homeobox transcription factor gene NKX2.5: identification of a novel mutation. *Clin Res Cardiol* 2006;**95**:499–503.
18. **Rajagopal SK,** Ma Q, Obler D, Shen J, Manichaikul A, Tomita-Mitchell A, Boardman K, Briggs C, Garg V, Srivastava D, Goldmuntz E, Broman KW, Woodrow Benson D, Smoot LB, Pu WT. Spectrum of heart disease associated with murine and human GATA4 mutation. *J Mol Cell Cardiol* 2007;**43**:677–85.
19. **Sarkozy A,** Conti E, Neri C, D'Agostino R, Digilio MC, Esposito G, Toscano A, Marino B, Pizzuti A, Dallapiccola B. Spectrum of atrial septal defects associated with mutations of NKX2.5 and GATA4 transcription factors. *J Med Genet* 2005;**42**:e16.
20. **Schluterman MK,** Krysiak AE, Kathiriya IS, Abate N, Chandalia M, Srivastava D, Garg V. Screening and biochemical analysis of GATA4 sequence variations identified in patients with congenital heart disease. *Am J Med Genet A* 2007;**143**:817–23.
21. **Sun G,** Lewis LE, Huang X, Nguyen Q, Price C, Huang T. TBX5, a gene mutated in Holt-Oram syndrome, is regulated through a GC box and T-box binding elements (TBEs). *J Cell Biochem* 2004;**92**:189–99.
22. **Xu H,** Morishima M, Wylie JN, Schwartz RJ, Bruneau BG, Lindsay EA, Baldini A. Tbx1 has a dual role in the morphogenesis of the cardiac outflow tract. *Development* 2004;**131**:3217–27.
23. **Brewer C,** Holloway S, Zawalnyski P, Schinzel A, FitzPatrick D. A chromosomal deletion map of human malformations. *Am J Hum Genet* 1998;**63**:1153–9.
24. **Brewer C,** Holloway S, Zawalnyski P, Schinzel A, FitzPatrick D. A chromosomal duplication map of malformations: regions of suspected haplo- and triplolethality – and tolerance of segmental aneuploidy – in humans. *Am J Hum Genet* 1999;**64**:1702–8.
25. **Johnson MC,** Hing A, Wood MK, Watson MS. Chromosome abnormalities in congenital heart disease. *Am J Med Genet* 1997;**70**:292–8.
26. **Storch TG,** Mannick EE. Epidemiology of congenital heart disease in Louisiana: an association between race and sex and the prevalence of specific cardiac malformations. *Teratology* 1992;**46**:271–6.
27. **van Karnebeek CD,** Hennekam RC. Associations between chromosomal anomalies and congenital heart defects: a database search. *Am J Med Genet* 1999;**84**:158–66.
28. **Gelb BD.** Molecular genetics of congenital heart disease. *Curr Opin Cardiol* 1997;**12**:321–8.
29. **Gelb BD.** Genetic basis of congenital heart disease. *Curr Opin Cardiol* 2004;**19**:110–5.
30. **Mah CS,** Vaughan CJ, Basson CT. Advances in the molecular genetics of congenital structural heart disease. *Genetic Testing* 1999;**3**:157–72.
31. **Van Praagh S,** Davidoff A, Chin A, Shiel FS, Reynolds J, Van Praagh R. Double outlet right ventricle: anatomic types and developmental implications based on a study of 101 autopsied cases. *Coeur* 1982;**XIII**:389–440.
32. **Braun K,** De Vries A, Feingold DS, Ehrenfeld NE, Feldman J, Schorr S. Complete dextroposition of the aorta, pulmonary stenosis, interventricular septal defect, and patent foramen ovale. *Am Heart J* 1952;**43**:773–80.
33. **Witham AC.** Double outlet right ventricle; a partial transposition complex. *Am Heart J* 1957;**53**:928–39.
34. **Lev M,** Bharati S, Meng CC, Liberthson RR, Paul MH, Idriss F. A concept of double-outlet right ventricle. *J Thorac Cardiovasc Surg* 1972;**64**:271–81.
35. **Walters HL,** Mavroudis C, Tchervenkov CI, Jacobs JP, Lacour-Gayet F, Jacobs ML. Congenital Heart Surgery Nomenclature and Database Project: double outlet right ventricle. *Ann Thorac Surg* 2000;**69**:249–63.
36. **Baciewicz FA Jr,** Melvin WS, Basilius D, Davis JT. Congenital heart disease in Down's syndrome patients: a decade of surgical experience. *Thorac Cardiovasc Surg* 1989;**37**:369–71.
37. **Brown DL,** Emerson DS, Shulman LP, Doubilet PM, Felker RE, Van Praagh S. Predicting aneuploidy in fetuses with cardiac anomalies: significance of visceral situs and noncardiac anomalies. *J Ultrasound Med* 1993;**12**:153–61.
38. **Bruyere HJ,** Kargas SA, Levy JM. The causes and underlying developmental mechanisms of congenital cardiovascular malformations: a critical review. *Am J Med Genet Suppl* 1987;**3**:411–31.
39. **Fyler DC.** Double-outlet right ventricle. *Nadas' pediatric cardiology*. Philadelphia: Hanley and Belfus, 1992:643–8.
40. **Hagler DJ.** Double outlet right ventricle. In: Allen, Driscoll, Shaddy, Feltes, eds. *Moss and Adams heart disease in infants, children, and adolescents including the fetus and young adult,* 7 ed. Philadelphia: Lippincott, Williams and Wilkins, 2008:1100–27.
41. **Jones KL.** *Smith's recognizable patterns of human malformations*, 5 ed. Philadelphia: WB Saunders Co, 1997.
42. **Lin AE.** Congenital heart defects in malformation syndromes. *Clin Perinatol* 1990;**17**:641–73.
43. **Pradat P,** Francannet C, Harris JA, Robert E. The epidemiology of cardiovascular defects, part I: a study based on data from three large registries of congenital malformations. *Pediatr Cardiol* 2003;**24**:195–221.
44. **Silka MJ.** Double-outlet right ventricle. *Oski's pediatrics: principles and practice*. Philadelphia: Lippincott, Williams, and Wilkins, 1999:1332–4.
45. **Tennstedt C,** Chaoui R, Korner H, Dietel M. Spectrum of congenital heart defects and extracardiac malformations associated with chromosomal abnormalities: results of a seven year necropsy study. *Heart* 1999;**82**:34–9.
46. **Harris JA,** Francannet C, Pradat P, Robert E. The epidemiology of cardiovascular defects, part 2: a study based on data from three large registries of congenital malformations. *Pediatr Cardiol* 2003;**24**:222–35.
47. **Goldmuntz E,** Clark BJ, Mitchell LE, Jawad AF, Cuneo BF, Reed L, McDonald-McGinn D, Chien P, Feuer J, Zackai EH, Emanuel BS, Driscoll DA. Frequency of 22q11 deletions in patients with conotruncal defects. *J Am Coll Cardiol* 1998;**32**:492–8.
48. **Takahashi K,** Kido S, Hoshino K, Ogawa K, Ohashi H, Fukushima Y. Frequency of a 22q11 deletion in patients with conotruncal cardiac malformations: a prospective study. *Eur J Pediatr* 1995;**154**:878–81.
49. **Voigt R,** Maier-Weidmann M, Lange PE, Haaf T. Chromosome 10p13-14 and 22q11 deletion screening in 100 patients with isolated and syndromic conotruncal heart defects. *J Med Genet* 2002;**39**:e16.
50. **Bamford RN,** Roessler E, Burdine RD, Saplakoglu U, dela Cruz J, Splitt M, Goodship JA, Towbin J, Bowers P, Ferrero GB, Marino B, Schier AF, Shen MM, Muenke M, Casey B. Loss-of-function mutations in the EGF-CFC gene CFC1 are associated with human left-right laterality defects. *Nat Genet* 2000;**26**:365–9.
51. **Goldmuntz E,** Bamford R, Karkera JD, dela Cruz J, Roessler E, Muenke M. CFC1 mutations in patients with transposition of the great arteries and double-outlet right ventricle. *Am J Hum Genet* 2002;**70**:776–80.
52. **Selamet Tierney ES,** Marans Z, Rutkin MB, Chung WK. Variants of the CFC1 gene in patients with laterality defects associated with congenital cardiac disease. *Cardiol Young* 2007;**17**:268–74.
53. **Saijoh Y,** Adachi H, Sakuma R, Yeo CY, Yashiro K, Watanabe M, Hashiguchi H, Mochida K, Ohishi S, Kawabata M, Miyazono K, Whitman M, Hamada H. Left-right asymmetric expression of lefty2 and nodal is induced by a signaling pathway that includes the transcription factor FAST2. *Mol Cell* 2000;**5**:35–47.
54. **Benson DW,** Silberbach GM, Kavanaugh-McHugh A, Cottrill C, Zhang Y, Riggs S, Smalls O, Johnson MC, Watson MS, Seidman JG, Seidman CE, Plowden J, Kugler JD. Mutations in the cardiac transcription factor NKX2.5 affect diverse cardiac developmental pathways. *J Clin Invest* 1999;**104**:1567–73.
55. **McElhinney DB,** Geiger E, Blinder J, Benson DW, Goldmuntz E. NKX2.5 mutations in patients with congenital heart disease. *J Am Coll Cardiol* 2003;**42**:1650–5.
56. **Srivastava D.** Making or breaking the heart: from lineage determination to morphogenesis. *Cell* 2006;**126**:1037–48.
57. **Migliazza L,** Otten C, Xia H, Rodriguez JI, Diez-Pardo JA, Tovar JA. Cardiovascular malformations in congenital diaphragmatic hernia: human and experimental studies. *J Pediatr Surg* 1999;**34**:1352–8.
58. **Nabulsi MM,** Tamim H, Sabbagh M, Obeid MY, Yunis KA, Bitar FF. Parental consanguinity and congenital heart malformations in a developing country. *Am J Med Genet* 2003;**116A**:342–7.
59. **Ferencz C,** Rubin JD, McCarter RJ, Clark EB. Maternal diabetes and cardiovascular malformations: predominance of double outlet right ventricle and truncus arteriosus. *Teratology* 1990;**41**:319–26.
60. **Stewart PA,** Wladimiroff JW, Becker AE. Early prenatal detection of double outlet right ventricle by echocardiography. *Br Heart J* 1985;**54**:340–2.
61. **Lammer EJ,** Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix AW Jr, Lott IT. Retinoic acid embryopathy. *N Engl J Med* 1985;**313**:837–41.
62. **Park JM,** Schmer V, Myers TL. Cardiovascular anomalies associated with prenatal exposure to theophylline. *South Med J* 1990;**83**:1487–8.
63. **Adams MM,** Mulinare J, Dooley K. Risk factors for conotruncal cardiac defects in Atlanta. *J Am Coll Cardiol* 1989;**14**:432–42.
64. **Tikkanen J,** Heinonen OP. Risk factors for conal malformations of the heart. *Eur J Epidemiol* 1992;**8**:48–57.
65. **Vergara P,** Digilio MC, Zorzi AD, Carlo DD, Capolino R, Rimini A, Pelegrini M, Calabro R, Marino B. Genetic heterogeneity and phenotypic anomalies in children

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with atrioventricular canal defect and tetralogy of Fallot. *Clin Dysmorphol* 2006;**15**:65–70.
66. **Bartram U,** Molin DG, Wisse LJ, Mohamad A, Sanford LP, Doetschman T, Speer CP, Poelmann RE, Gittenberger-de Groot AC. Double-outlet right ventricle and overriding tricuspid valve reflect disturbances of looping, myocardialization, endocardial cushion differentiation, and apoptosis in TGF-beta(2)-knockout mice. *Circulation* 2001;**103**:2745–52.
67. **Allen SP,** Bogardi JP, Barlow AJ, Mir SA, Qayyum SR, Verbeek FJ, Anderson RH, Francis-West PH, Brown NA, Richardson MK. Misexpression of noggin leads to septal defects in the outflow tract of the chick heart. *Dev Biol* 2001;**235**:98–109.
68. **Hamblet NS,** Lijam N, Ruiz-Lozano P, Wang J, Yang Y, Luo Z, Mei L, Chien KR, Sussman DJ, Wynshaw-Boris A. Dishevelled 2 is essential for cardiac outflow tract development, somite segmentation and neural tube closure. *Development* 2002;**129**:5827–38.
69. **Stoller JZ,** Epstein JA. Cardiac neural crest. *Semin Cell Dev Biol* 2005;**16**:704–15.
70. **Bajolle F,** Zaffran S, Kelly RG, Hadchouel J, Bonnet D, Brown NA, Buckingham ME. Rotation of the myocardial wall of the outflow tract is implicated in the normal positioning of the great arteries. *Circ Res* 2006;**98**:421–8.
71. **Campione M,** Ros MA, Icardo JM, Piedra E, Christoffels VM, Schweickert A, Blum M, Franco D, Moorman AF. Pitx2 expression defines a left cardiac lineage of cells: evidence for atrial and ventricular molecular isomerism in the iv/iv mice. *Dev Biol* 2001;**231**:252–64.
72. **Icardo JM,** Sanchez de Vega MJ. Spectrum of heart malformations in mice with situs solitus, situs inversus, and associated visceral heterotaxy. *Circulation* 1991;**84**:2547–58.
73. **Kitamura K,** Miura H, Miyagawa-Tomita S, Yanazawa M, Katoh-Fukui Y, Suzuki R, Ohuchi H, Suehiro A, Motegi Y, Nakahara Y, Kondo S, Yokoyama M. Mouse Pitx2 deficiency leads to anomalies of the ventral body wall, heart, extra- and periocular mesoderm and right pulmonary isomerism. *Development* 1999;**126**:5749–58.
74. **Liu C,** Liu W, Lu MF, Brown NA, Martin JF. Regulation of left-right asymmetry by thresholds of Pitx2c activity. *Development* 2001;**128**:2039–48.
75. **Liu C,** Liu W, Palie J, Lu MF, Brown NA, Martin JF. Pitx2c patterns anterior myocardium and aortic arch vessels and is required for local cell movement into atrioventricular cushions. *Development* 2002;**129**:5081–91.
76. **Lu MF,** Pressman C, Dyer R, Johnson RL, Martin JF. Function of Rieger syndrome gene in left-right asymmetry and craniofacial development. *Nature* 1999;**401**:276–8.
77. **Nowotschin S,** Liao J, Gage PJ, Epstein JA, Campione M, Morrow BE. Tbx1 affects asymmetric cardiac morphogenesis by regulating Pitx2 in the secondary heart field. *Development* 2006;**133**:1565–73.
78. **Conway SJ,** Henderson DJ, Kirby ML, Anderson RH, Copp AJ. Development of a lethal congenital heart defect in the splotch (Pax3) mutant mouse. *Cardiovasc Res* 1997;**36**:163–73.
79. **Tang LS,** Wlodarczyk BJ, Santillano DR, Miranda RC, Finnell RH. Developmental consequences of abnormal folate transport during murine heart morphogenesis. *Birth Defects Res A Clin Mol Teratol* 2004;**70**:449–58.
80. **Henderson DJ,** Conway SJ, Greene ND, Gerrelli D, Murdoch JN, Anderson RH, Copp AJ. Cardiovascular defects associated with abnormalities in midline development in the loop-tail mouse mutant. *Circ Res* 2001;**89**:6–12.
81. **Henderson DJ,** Phillips HM, Chaudhry B. Vang-like 2 and noncanonical Wnt signaling in outflow tract development. *Trends Cardiovasc Med* 2006;**16**:38–45.
82. **Gruber PJ,** Kubalak SW, Pexieder T, Sucov HM, Evans RM, Chien KR. RXR alpha deficiency confers genetic susceptibility for aortic sac, conotruncal, atrioventricular cushion, and ventricular muscle defects in mice. *J Clin Invest* 1996;**98**:1332–43.
83. **Lee RY,** Luo J, Evans RM, Giguere V, Sucov HM. Compartment-selective sensitivity of cardiovascular morphogenesis to combinations of retinoic acid receptor gene mutations. *Circ Res* 1997;**80**:757–64.
84. **Yanagisawa H,** Hammer RE, Richardson JA, Emoto N, Williams SC, Takeda S, Clouthier DE, Yanagisawa M. Disruption of ECE-1 and ECE-2 reveals a role for endothelin-converting enzyme-2 in murine cardiac development. *J Clin Invest* 2000;**105**:1373–82.
85. **Tullio AN,** Accili D, Ferrans VJ, Yu ZX, Takeda K, Grinberg A, Westphal H, Preston YA, Adelstein RS. Nonmuscle myosin II-B is required for normal development of the mouse heart. *Proc Natl Acad Sci U S A* 1997;**94**:12407–12.
86. **Schatteman GC,** Motley ST, Effmann EL, Bowen-Pope DF. Platelet-derived growth factor receptor alpha subunit deleted Patch mouse exhibits severe cardiovascular dysmorphogenesis. *Teratology* 1995;**51**:351–66.
87. **Gu H,** Smith FC, Taffet SM, Delmar M. High incidence of cardiac malformations in connexin40-deficient mice. *Circ Res* 2003;**93**:201–6.
88. **Brewer S,** Jiang X, Donaldson S, Williams T, Sucov HM. Requirement for AP-2alpha in cardiac outflow tract morphogenesis. *Mech Dev* 2002;**110**:139–49.
89. **Crispino JD,** Lodish MB, Thurberg BL, Litovsky SH, Collins T, Molkentin JD, Orkin SH. Proper coronary vascular development and heart morphogenesis depend on interaction of GATA-4 with FOG cofactors. *Genes Dev* 2001;**15**:839–44.
90. **Pu WT,** Ishiwata T, Juraszek AL, Ma Q, Izumo S. GATA4 is a dosage-sensitive regulator of cardiac morphogenesis. *Dev Biol* 2004;**275**:235–44.
91. **Bamforth SD,** Braganca J, Eloranta JJ, Murdoch JN, Marques FI, Kranc KR, Farza H, Henderson DJ, Hurst HC, Bhattacharya S. Cardiac malformations, adrenal agenesis, neural crest defects and exencephaly in mice lacking Cited2, a new Tfap2 co-activator. *Nat Genet* 2001;**29**:469–74.
92. **Mesbah K,** Camus A, Babinet C, Barra J. Mutation in the Trapalpha/Ssr1 gene, encoding translocon-associated protein alpha, results in outflow tract morphogenetic defects. *Mol Cell Biol* 2006;**26**:7760–71.
93. **Schneider JE,** Bose J, Bamforth SD, Gruber AD, Broadbent C, Clarke K, Neubauer S, Lengeling A, Bhattacharya S. Identification of cardiac malformations in mice lacking Ptdsr using a novel high-throughput magnetic resonance imaging technique. *BMC Dev Biol* 2004;**4**:16.
94. **Sock E,** Rettig SD, Enderich J, Bosl MR, Tamm ER, Wegner M. Gene targeting reveals a widespread role for the high-mobility-group transcription factor Sox11 in tissue remodeling. *Mol Cell Biol* 2004;**24**:6635–44.
95. **Restivo A,** Piacentini G, Placidi S, Saffirio C, Marino B. Cardiac outflow tract: a review of some embryogenetic aspects of the conotruncal region of the heart. *Anat Rec A Discov Mol Cell Evol Biol* 2006;**288**:936–43.
96. **Nakajima M,** Moriizumi E, Koseki H, Shirasawa T. Presenilin 1 is essential for cardiac morphogenesis. *Dev Dyn* 2004;**230**:795–9.
97. **Marguerie A,** Bajolle F, Zaffran S, Brown NA, Dickson C, Buckingham ME, Kelly RG. Congenital heart defects in Fgfr2-IIIb and Fgf10 mutant mice. *Cardiovasc Res* 2006;**71**:50–60.
98. **Nishikawa T,** Bruyere HJ Jr, Takagi Y, Gilbert EF, Uno H. Cardiovascular teratogenicity of ephedrine in chick embryos. *Toxicol Lett* 1985;**29**:59–63.
99. **Matsuoka R,** Nishikawa T, Bruyere HJ Jr, Gilbert EF. Teratogenic effect of tedral (theophylline, ephedrine, and phenobarbital) on cardiac development in chick embryos. *Congenit Anom* 1992;**31**:65–75.
100. **Sonoda T,** Ohdo S, Ohba K, Okishima T, Hayakawa K. Sodium valproate-induced cardiovascular abnormalities in the Jcl:ICR mouse fetus: peak sensitivity of gestational day and dose-dependent effect. *Teratology* 1993;**48**:127–32.
101. **Bouman HG,** Broekhuizen ML, Baasten AM, Gittenberger-de Groot AC, Wenink AC. Spectrum of looping disturbances in stage 34 chicken hearts after retinoic acid treatment. *Anat Rec* 1995;**243**:101–8.
102. **Davis LA,** Sadler TW. Effects of vitamin A on endocardial cushion development in the mouse heart. *Teratology* 1981;**24**:139–48.
103. **Taylor IM,** Wiley MJ, Agur A. Retinoic acid-induced heart malformations in the hamster. *Teratology* 1980;**21**:193–7.
104. **Okishima T,** Takamura K, Matsuoka Y, Ohdo S, Hayakawa K. Cardiovascular anomalies in chick embryos produced by bis-diamine in dimethylsulfoxide. *Teratology* 1992;**45**:155–62.
105. **Miyagawa S,** Kirby ML. Pathogenesis of persistent truncus arteriosus induced by nimustine hydrochloride in chick embryos. *Teratology* 1989;**39**:287–94.
106. **DiCarlo FJ Jr.** Syndromes of cardiovascular malformations induced by copper citrate in hamsters. *Teratology* 1980;**21**:89–101.
107. **Nishibatake M,** Kargas SA, Bruyere HJ Jr, Gilbert EF. Cardiovascular malformations induced by bromodeoxyuridine in the chick embryo. *Teratology* 1987;**36**:125–32.
108. **Morishima M,** Yasui H, Ando M, Nakazawa M, Takao A. Influence of genetic and maternal diabetes in the pathogenesis of visceroatrial heterotaxy in mice. *Teratology* 1996;**54**:183–90.
109. **Siman CM,** Gittenberger-de Groot AC, Wisse B, Eriksson UJ. Malformations in offspring of diabetic rats: morphometric analysis of neural crest-derived organs and effects of maternal vitamin E treatment. *Teratology* 2000;**61**:355–67.
110. **Ishikawa S,** Inaba Y, Masuda H, Okuyama K, Park DS, Kanda M. Spectrum of double outlet right ventricle induced by electrical shock at the conotruncus of the embryonic chick heart: emphasis on cellular changes and evaluation of hemodynamics using Doppler. *Am J Med Genet Suppl* 1987;**3**:445–58.
111. **Rosenthal N,** Harvey RP. Single allele mutations at the heart of congenital disease. *J Clin Invest* 1999;**104**:1483–4.
112. **Budarf ML,** Emanuel BS. Progress in the autosomal segmental aneusomy syndromes (SASs): single or multi-locus disorders? *Hum Mol Genet* 1997;**6**:1657–65.
113. **Roberts AE,** Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, Kucherlapati RS. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. *Nat Genet* 2007;**39**:70–4.
114. **Sugishita Y,** Watanabe M, Fisher SA. The development of the embryonic outflow tract provides novel insights into cardiac differentiation and remodeling. *Trends Cardiovasc Med* 2004;**14**:235–41.
115. **Anderson RH,** McCarthy K, Cook AC. Double outlet right ventricle. *Cardiol Young* 2001;**11**:329–44.
116. **Bartelings MM,** Gittenberger-de Groot AC. Morphologic considerations on congenital malformations of the outflow tract part 2: complete transposition of the great ateries and double outlet right ventricle. *Int J Cardiol* 1991;**33**:5–26.
117. **Bostrom MP,** Hutchins GM. Arrested rotation of the outflow tract may explain double-outlet right ventricle. *Circulation* 1988;**77**:1258–65.
118. **Clark EB.** Pathogenetic mechanisms of congenital cardiovascular malformations revisited. *Semin Perinatol* 1996;**20**:465–72.
119. **Hartwig NG,** Vermeij-Keers C, De Vries HE, Gittenberger-de Groot AC. Aplasia of semilunar valve leaflets: two case reports and developmental aspects. *Pediatr Cardiol* 1991;**12**:114–7.
120. **Reamon-Buettner SM,** Borlak J. Somatic NKX2-5 mutations as a novel mechanism of disease in complex congenital heart disease. *J Med Genet* 2004;**41**:684–90.
121. **Schilham MW,** Oosterwegel MA, Moerer P, Ya J, de Boer PA, van de Wetering M, Verbeek S, Lamers WH, Kruisbeek AM, Cumano A, Clevers H. Defects in cardiac outflow tract formation and pro-B-lymphocyte expansion in mice lacking Sox-4. *Nature* 1996;**380**:711–4.
122. **Tomita-Mitchell A,** Maslen CL, Morris CD, Garg V, Goldmuntz E. GATA4 sequence variants in patients with congenital heart disease. *J Med Genet* 2007;**44**:779–83.

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123. **Chisaka O,** Capecchi MR. Regionally restricted developmental defects resulting from targeted disruption of the mouse homeobox gene hox-1.5. *Nature* 1991;**350**:473–9.
124. **Huang GY,** Wessels A, Smith BR, Linask KK, Ewart JL, Lo CW. Alteration in connexin 43 gap junction gene dosage impairs conotruncal heart development. *Dev Biol* 1998;**198**:32–44.
125. **Kathiriya IS,** Srivastava D. Left-right asymmetry and cardiac looping: implications for cardiac development and congenital heart disease. *Am J Med Genet* 2000;**97**:271–9.
126. **Schneider H,** Brueckner M. Of mice and men: dissecting the genetic pathway that controls left- right asymmetry in mice and humans. *Am J Med Genet* 2000;**97**:258–70.
127. **Martlew RA,** Sharples A. Anaesthesia in a child with Patau's syndrome. *Anaesthesia* 1995;**50**:980–2.
128. **Miyabara S,** Sugihara H, Maehara N, Shouno H, Tasaki H, Yoshida K, Saito N, Kayama F, Ibara S, Suzumori K. Significance of cardiovascular malformations in cystic hygroma: a new interpretation of the pathogenesis. *Am J Med Genet* 1989;**34**:489–501.
129. **Wladimiroff JW,** Stewart PA, Reuss A, Sachs ES. Cardiac and extra-cardiac anomalies as indicators for trisomies 13 and 18: a prenatal ultrasound study. *Prenat Diagn* 1989;**9**:515–20.
130. **Kim N,** Friedberg MK, Silverman NH. Diagnosis and prognosis of fetuses with double outlet right ventricle. *Prenat Diagn* 2006;**26**:740–5.
131. **Van Praagh S,** Truman T, Firpo A, Bano-Rodrigo A, Fried R, McManus B, Engle MA, Van Praagh R. Cardiac malformations in trisomy-18: a study of 41 postmortem cases. *J Am Coll Cardiol* 1989;**13**:1586–97.
132. **Duncan WJ,** George D, Ezzat W, Wallace K, Van den Beuken B. Double-outlet single ventricle and an abdominal vascular mass: in utero diagnosis with pathological confirmation. *Pediatr Cardiol* 1993;**14**:37–9.
133. **Patel CR,** Muise KL, Redline RW. Double-outlet right ventricle with intact ventricular septum in a foetus with trisomy-18. *Cardiol Young* 1999;**9**:419–22.
134. **Parvathy U,** Balakrishnan KR, Ranjith MS, Saldanha R, Sai S, Vakamudi M. Surgical experience with congenital heart disease in Down's syndrome. *Indian Heart J* 2000;**52**:438–41.
135. **Oshima Y,** Yamaguchi M, Yoshimura N, Oka S, Ootaki Y. Anatomically corrective repair of complete atrioventricular septal defects and major cardiac anomalies. *Ann Thorac Surg* 2001;**72**:424–9.
136. **Roskes EJ,** Boughman JA, Schwartz S, Cohen MM. Congenital cardiovascular malformations (CCVM) and structural chromosome abnormalities: a report of 9 cases and literature review. *Clin Genet* 1990;**38**:198–210.
137. **Gelb BD,** Towbin JA, McCabe ER, Sujansky E. San Luis Valley recombinant chromosome 8 and tetralogy of Fallot: a review of chromosome 8 anomalies and congenital heart disease. *Am J Med Genet* 1991;**40**:471–6.
138. **Hutchinson R,** Wilson M, Voullaire L. Distal 8p deletion (8p23.1----8pter): a common deletion? *J Med Genet* 1992;**29**:407–11.
139. **Napoleone RM,** Varela M, Andersson HC. Complex congenital heart malformations in mosaic tetrasomy 8p: case report and review of the literature. *Am J Med Genet* 1997;**73**:330–3.
140. **Devriendt K,** Matthijs G, Van Dael R, Gewillig M, Eyskens B, Hjalgrim H, Dolmer B, McGaughran J, Brondum-Nielsen K, Marynen P, Fryns JP, Vermeesch JR. Delineation of the critical deletion region for congenital heart defects, on chromosome 8p23.1. *Am J Hum Genet* 1999;**64**:1119–26
141. **Devriendt K,** Van Schoubroeck D, Eyskens B, Gewillig M, Vandenberghe K, Fryns JP. Prenatal diagnosis of a terminal short arm deletion of chromosome 8 in a fetus with an atrioventricular septal defect. *Prenat Diagn* 1998;**18**:65–7.
142. **Greenberg F,** Courtney KB, Wessels RA, Huhta J, Carpenter RJ, Rich DC, Ledbetter DH. Prenatal diagnosis of deletion 17p13 associated with DiGeorge anomaly. *Am J Med Genet* 1988;**31**:1–4.
143. **van Essen AJ,** Schoots CJ, van Lingen RA, Mourits MJ, Tuerlings JH, Leegte B. Isochromosome 18q in a girl with holoprosencephaly, DiGeorge anomaly, and streak ovaries. *Am J Med Genet* 1993;**47**:85–8.
144. **Momma K,** Kondo C, Matsuoka R, Takao A. Cardiac anomalies associated with a chromosome 22q11 deletion in patients with conotruncal anomaly face syndrome. *Am J Cardiol* 1996;**78**:591–4.
145. **Goodship J,** Robson SC, Sturgiss S, Cross IE, Wright C. Renal abnormalities on obstetric ultrasound as a presentation of DiGeorge syndrome. *Prenat Diagn* 1997;**17**:867–70.
146. **Mehraein Y,** Wippermann CF, Michel-Behnke I, Nhan Ngo TK, Hillig U, Giersberg M, Aulepp U, Barth H, Fritz B, Rehder H. Microdeletion 22q11 in complex cardiovascular malformations. *Hum Genet* 1997;**99**:433–42.
147. **Raymond FL,** Simpson JM, Mackie CM, Sharland GK. Prenatal diagnosis of 22q11 deletions: a series of five cases with congenital heart defects. *J Med Genet* 1997;**34**:679–82.
148. **Matsuoka R,** Kimura M, Scambler PJ, Morrow BE, Imamura S, Minoshima S, Shimizu N, Yamagishi H, Joh-o K, Watanabe S, Oyama K, Saji T, Ando M, Takao A, Momma K. Molecular and clinical study of 183 patients with conotruncal anomaly face syndrome. *Hum Genet* 1998;**103**:70–80.
149. **Sergi C,** Serpi M, Muller-Navia J, Schnabel PA, Hagl S, Otto HF, Ulmer HE. CATCH 22 syndrome: report of 7 infants with follow-up data and review of the recent advancements in the genetic knowledge of the locus 22q11. *Pathologica* 1999;**91**:166–72.
150. **Derbent M,** Yilmaz Z, Baltaci V, Saygili A, Varan B, Tokel K. Chromosome 22q11.2 deletion and phenotypic features in 30 patients with conotruncal heart defects. *Am J Med Genet* 2003;**116A**:129–35.
151. **Braga S,** Schmidt A. Clinical and cytogenetic spectrum of duplication 3p. *Eur J Pediatr* 1982;**138**:195–7.
152. **ter Haar B,** Hamel B, Hendriks J, de Jager J. Melnick-Needles syndrome: indication for an autosomal recessive form. *Am J Med Genet* 1982;**13**:469–77.
153. **Hamel BC,** Draaisma JM, Pinckers AJ, Boetes C, Hoppe RL, Ropers HH, Brunner HG. Autosomal recessive Melnick-Needles syndrome or ter Haar syndrome? Report of a patient and reappraisal of an earlier report. *Am J Med Genet* 1995;**56**:312–6.
154. **Greenberg F,** Gresik MV, Carpenter RJ, Law SW, Hoffman LP, Ledbetter DH. The Gardner-Silengo-Wachtel or genito-palato-cardiac syndrome: male pseudohermaphroditism with micrognathia, cleft palate, and conotruncal cardiac defect. *Am J Med Genet* 1987;**26**:59–64.
155. **Antonelli D,** Antonelli J, Rosenfeld T. Noonan's syndrome associated with hypoplastic left heart. *Cardiology* 1990;**77**:62–5.
156. **Cortez AB,** Galindo A, Arensman FW, Van Dop C. Congenital heart disease associated with sporadic Kallmann syndrome. *Am J Med Genet* 1993;**46**:551–4.
157. **Marles SL,** Chodirker BN, Greenberg CR, Chudley AE. Evidence for Ritscher-Schinzel syndrome in Canadian Native Indians. *Am J Med Genet* 1995;**56**:343–50.
158. **Sabry MA,** Ismail EA, al-Naggar RL, al-Torki NA, Farah S, al-Awadi SA, Obenbergerova D, Bastaki L. Unusual traits associated with Robinow syndrome. *J Med Genet* 1997;**34**:736–40.
159. **Jacobson Z,** Glickstein J, Hensle T, Marion RW. Further delineation of the Opitz G/BBB syndrome: report of an infant with complex congenital heart disease and bladder exstrophy, and review of the literature. *Am J Med Genet* 1998;**78**:294–9.
160. **Digilio MC,** Marino B, Ammirati A, Borzaga U, Giannotti A, Dallapiccola B. Cardiac malformations in patients with oral-facial-skeletal syndromes: clinical similarities with heterotaxia. *Am J Med Genet* 1999;**84**:350–6.
161. **Swartz EN,** Sanatani S, Sandor GG, Schreiber RA. Vascular abnormalities in Adams-Oliver syndrome: cause or effect? *Am J Med Genet* 1999;**82**:49–52.
162. **Digilio MC,** Marino B, Toscano A, Giannotti A, Dallapiccola B. Congenital heart defects in Kabuki syndrome. *Am J Med Genet* 2001;**100**:269–74.
163. **Ohdo S,** Madokoro H, Sonoda T, Nishiguchi T, Kawaguchi K, Hayakawa K. Kabuki make-up syndrome (Niikawa-Kuroki syndrome) associated with congenital heart disease. *J Med Genet* 1985;**22**:126–7.
164. **Wang CM,** Chen SJ, Lu JH, Hwang BT. Tracheal agenesis with multiple congenital anomalies: a case report. *Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal* 1998;**61**:48–52.
165. **Lienicke U,** Hammer H, Schneider M, Heling K, Wauer RR, Mau H, Vogel M. Rhabdomyomatous dysplasia of the newborn lung associated with multiple congenital malformations of the heart and great vessels. *Pediatr Pulmonol* 2002;**34**:222–5.
166. **Chen P,** Xie LJ, Huang GY, Zhao XQ, Chang C. Mutations of connexin43 in fetuses with congenital heart malformations. *Chin Med J (Engl)* 2005;**118**:971–6.
167. **Pacifico AD,** Ricchi A, Bargeron LM Jr, Colvin EC, Kirklin JW, Kirklin JK. Corrective repair of complete atrioventricular canal defects and major associated cardiac anomalies. *Ann Thorac Surg* 1988;**46**:645–51.
168. **Ando F,** Shirotani H, Kawai J, Kanzaki Y, Setsuie N. Successful total repair of complicated cardiac anomalies with asplenia syndrome. *J Thorac Cardiovasc Surg* 1976;**72**:33–8.
169. **Smith RS,** Comstock CH, Kirk JS, Lee W, Riggs T, Weinhouse E. Double-outlet right ventricle: an antenatal diagnostic dilemma. *Ultrasound Obstet Gynecol* 1999;**14**:315–9.
170. **Bollmann VR,** Schilling H, Abet L, Reinhold-Richter L, Zienert A. Ultrasonographic diagnosis of severe fetal malformation. *Zentralblatt fur Gynakologic* 1989;**111**:1185–8.
171. **Toews WH,** Lortscher RH, Kelminson LL. Double outlet right ventricle with absent aortic valve. *Chest* 1975;**68**:381–2.
172. **Bierman FZ,** Yeh MN, Swersky S, Martin E, Wigger JH, Fox H. Absence of the aortic valve: antenatal and postnatal two-dimensional and Doppler echocardiographic features. *J Am Coll Cardiol* 1984;**3**:833–7.
173. **Gunal N,** Bilgic A, Lenk MK, Yurdakul Y, Sarigul A, Ispir S. Abnormal connection of the inferior vena cava to the left atrium with double outlet right ventricle and heterotaxia: a case report. *Cathet Cardiovasc Diagn* 1996;**37**:287–9.
174. **Alphonso N,** Venugopal PS, Deshpande R, Anderson D. Complete thoracic ectopia cordis. *Eur J Cardiothorac Surg* 2003;**23**:426–8.
175. **Morales JM,** Patel SG, Duff JA, Villareal RL, Simpson JW. Ectopia cordis and other midline defects. *Ann Thorac Surg* 2000;**70**:111–4.
176. **Takaya J,** Kitamura N, Tsuji K, Watanabe K, Kinoshita Y, Hattori Y, Teraguchi M, Taniuchi S, Takada K, Hamada Y, Kaneko K. Pentalogy of Cantrell with a double-outlet right ventricle: 3.5-year follow-up in a prenatally diagnosed patient. *Eur J Pediatr* 2008;**167**:103–5.
177. **Leca F,** Thibert M, Khoury W, Fermont L, Laborde F, Dumez Y. Extrathoracic heart (ectopia cordis). Report of two cases and review of the literature. *Int J Cardiol* 1989;**22**:221–8.
178. **Reyes C,** Chang LK, Waffarn F, Mir H, Warden MJ, Sills J. Delayed repair of congenital diaphragmatic hernia with early high-frequency oscillatory ventilation during preoperative stabilization. *J Pediatr Surg* 1998;**33**:1010–4; discussion 4–6.
179. **Benjamin DR,** Juul S, Siebert JR. Congenital posterolateral diaphragmatic hernia: associated malformations. *J Pediatr Surg* 1988;**23**:899–903.
180. **Fauza DO,** Wilson JM. Congenital diaphragmatic hernia and associated anomalies: their incidence, identification, and impact on prognosis. *J Pediatr Surg* 1994;**29**:1113–7.
181. **Graziano JN.** Cardiac anomalies in patients with congenital diaphragmatic hernia and their prognosis: a report from the Congenital Diaphragmatic Hernia Study Group. *J Pediatr Surg* 2005;**40**:1045–9; discussion 9–50.

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182. **Rein AJ,** Dollberg S, Gale R. Genetics of conotruncal malformations: review of the literature and report of a consanguineous kindred with various conotruncal malformations. *Am J Med Genet* 1990;**36**:353–5.
183. **Bindewald B,** Ulmer H, Muller U. Fallot complex, severe mental, and growth retardation: a new autosomal recessive syndrome? *Am J Med Genet* 1994;**50**:173–6.
184. **Beemer FA,** von Ertbruggen I. Peculiar facial appearance, hydrocephalus, double-outlet right ventricle, genital anomalies and dense bones with lethal outcome. *Am J Med Genet* 1984;**19**:391–4.
185. **Marek J,** Skovranek J, Povysilova V. Congenital absence of aortic and pulmonary valve in a fetus with severe heart failure. *Heart* 1996; **75**:98–100.
186. **Kumar A,** Friedman JM, Taylor GP, Patterson MW. Pattern of cardiac malformation in oculoauriculovertebral spectrum. *Am J Med Genet* 1993; **46**:423–6.
187. **Miyabara S,** Ando M, Yoshida K, Saito N, Sugihara H. Absent aortic and pulmonary valves: investigation of three fetal cases with cystic hygroma and review of the literature. *Heart Vessels* 1994;**9**:49–55.
188. **Smith DF,** Sandor GG, MacLeod PM, Tredwell S, Wood B, Newman DE. Intrinsic defects in the fetal alcohol syndrome: studies on 76 cases from British Columbia and the Yukon Territory. *Neurobehav Toxicol Teratol* 1981;**3**:145–52.
189. **Nir A,** Weintraub Z, Oliven A, Kelener J, Lurie M. Anatomic evidence of spontaneous intrauterine closure of a ventricular septal defect. *Pediatr Cardiol* 1990;**11**:208–10.
190. **Sanford LP,** Ormsby I, Gittenberger-de Groot AC, Sariola H, Friedman R, Boivin GP, Cardell EL, Doetschman T. TGFbeta2 knockout mice have multiple developmental defects that are non-overlapping with other TGFbeta knockout phenotypes. *Development* 1997;**124**:2659–70.
191. **Shinohara T,** Tomizuka K, Miyabara S, Takehara S, Kazuki Y, Inoue J, Katoh M, Nakane H, Iino A, Ohguma A, Ikegami S, Inokuchi K, Ishida I, Reeves RH, Oshimura M. Mice containing a human chromosome 21 model behavioral impairment and cardiac anomalies of Down's syndrome. *Hum Mol Genet* 2001;**10**:1163–75.
192. **Lin BC,** Sullivan R, Lee Y, Moran S, Glover E, Bradfield CA. Deletion of the aryl hydrocarbon receptor-associated protein 9 leads to cardiac malformation and embryonic lethality. *J Biol Chem* 2007;**282**:35924–32.
193. **Daft PA,** Johnston MC, Sulik KK. Abnormal heart and great vessel development following acute ethanol exposure in mice. *Teratology* 1986;**33**:93–104.
194. **Hernandez-Gutierrez S,** Garcia-Pelaez I, Zentella-Dehesa A, Ramos-Kuri M, Hernandez-Franco P, Hernandez-Sanchez F, Rojas E. NF-kappaB signaling blockade by Bay 11-7085 during early cardiac morphogenesis induces alterations of the outflow tract in chicken heart. *Apoptosis* 2006;**11**:1101–9.

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