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Insight into the Genetic Relevance of Congenital Heart Defects

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Abstract Congenital heart disease is the most common type of birth defect in the newborn—occurring in 1 % of neonates. In addition, cardiac defects account for nearly half of the neonatal deaths resulting from congenital malformations. Due to recent advances in spatial resolution of ultrasound machines and improvements in sonographic techniques, the clinician is increasingly able to detect cardiac anomalies in utero. At the same time, advances in cardiovascular surgery have improved the overall survival of the affected neonates. Due to the combination of advances in prenatal diagnosis and postnatal intervention, parents with fetuses affected by congenital cardiac defects have become the largest group who seek prenatal counseling on the risks of associated anomalies, risks for subsequent pregnancies, and the risks to the offspring of a successfully treated patient. Although most congenital heart defects are not familiarly clustered, genetic factors are still involved in most cases. In this review, we summarize recent evidence of chromosomal and genetic defects associated with congenital heart diseases to provide the optimal counseling and management for the parents with affected neonates.

Keywords Congenital heart disease · Congenital heart defects · Genetics · Chromosome · Microdeletion · Single gene disorder · Association · Neonatal deaths · Birth defect · Cardiac anomalies in utero · Prenatal medicine

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Introduction

Congenital heart disease (CHD) is the most common type of birth defect and is the leading cause of neonatal deaths [1–4]. CHD affects millions of children worldwide, and there are approximately 36,000 new cases each year in the United States alone [5]. The cause of CHD is multifactorial and generally is attributed to the environmental and genetic factors [6]. Environmental insults during embryogenesis have been shown to increase the risk of CHD [7•] and may include viral infections, such as rubella, exposure to chemical teratogens, such as retinoic acid and lithium, and maternal diseases, including diabetes and systemic lupus erythematous [8–10]. However, recent evidence suggests that the overall contribution of teratogens to CHD is small [10]. Although most congenital heart defects are not familiarly clustered, it seems likely that genetic factors are involved in most cases. The contribution of genetic factors to the development of CHD is recognized by the common association of CHD with chromosomal abnormalities, such as fetal aneuploidy and the microdeletion at the region of chromosome 22q11.2 [11•, 12, 13].

Most perinatal cardiologists are probably familiar with the prevalence of individual congenital heart diseases. For example, the prevalence for tetralogy of Fallot (TOF) is reported to be 0.62 per 1,000 live births, and the prevalence rate for transposition of great arteries (TGA) is 0.21 per 1,000 births [6]. However, they are seldom aware of occurrences of congenital heart disease related to the chance of aneuploidy or genetic defects. For instance, a review of the literature shows that the chance of chromosomal anomaly is 10 % in TOF, whereas in TGA, it is less than 1 % [14••]. Perinatal cardiologists should have an understanding of the potential risk of associated aneuploidy and the possible pattern of extracardiac malformations that may accompany a diagnosis of congenital cardiac defect. Currently, there are

763 syndromes listed on the London Dysmorphology Database where cardiac abnormalities can exist as a part of the syndrome [15]. Each of the syndromes has its distinct clinical features and related genetic errors. The appropriate genetic tests should be provided, and the expectant parents should be well-informed about the outcome of the entire syndrome and not just the outcome of the specific cardiac anomaly.

Molecular Mechanisms of Congenital Cardiac Defects

The human heart development starts on day 15–16 embryonic age with the migration of cardiogenic stem cells and consists of five major steps: 1) migration of precardiac cells from the primitive streak and assembly of the paired cardiac crescents at the myocardial plate; 2) coalescence of the cardiac crescents to form the primitive heart tube and establishment of the definitive heart; 3) cardiac looping and assurance of proper alignment of the future cardiac chambers; 4) septation and heart chamber formation; and 5) development of the cardiac conduction system and coronary vasculature [16–19]. The establishment of left-right asymmetry also is crucial for the developing embryonic heart. The establishment of these processes involves a great deal of genetic pathways, disruption of which may manifest as a heart defect [12, 20]. This can be seen by the fact that approximately one in eight infants with CHD has a combined chromosomal abnormality. Therefore, clinicians should have a low threshold for obtaining chromosomal tests in infants with CHDs, especially certain types of CHD known to be high risk for genetic disorders [21••].

Congenital Heart Defects and Aneuploidy

The frequency of aneuploidy in neonates with CHD has been estimated to be 5 % to 15 % from postnatal series [6, 8, 14••, 22, 23]. However, the incidence of chromosomal anomalies amongst fetuses with prenatally diagnosed CHD is significantly higher and varies from 33 % to 42 % [24, 25]. Atrioventricular septal defects (AVSD) and ventricular septal defects (VSD) most often are associated with abnormal karyotypes [26]. CHDs that are least likely to have an associated chromosomal abnormality are heterotaxy (2.2 %), Ebstein anomaly (2.6 %), and pulmonary valve stenosis (3.3 %) [21••].

Trisomy 21

Trisomy 21, or Down syndrome, is the most common aneuploidy, occurring with an incidence of approximately 1 in 800 births [27]. The risk of fetal trisomy 21 increases with advanced maternal age. The four-chamber view seen at 20 weeks of gestation is essential for detection of fetal cardiac anomaly. It is useful for identification of septal defects or atrioventricular valve abnormalities, such as VSD and AVSD. For AVSD, overall aneuploidy rate is approximately 46 % [13]. When AVSD is associated with aneuploidy, the type most often noted is Down syndrome, which represents 79 % of aneuploidy cases with AVSD. On the other hand, virtually 15 % cases of Down syndrome have AVSD.

Using fluorescence in situ hybridization (FISH) and Southern blot dosage analysis of 32 markers unique to human chromosome 21, Korenberg et al. constructed a phenotypic map that includes 25 features and assigned regions of 2-20 megabases as likely to contain the responsible genes [28]. Mapping of these patients with AVSD has led to the identification of a 5.5 megabase cardiac minimal region that contains at least 28 known genes. One gene within this region, DSCAM (Down syndrome cell adhesion molecule) is a novel gene that is expressed in the heart and is postulated to function as a cell adhesion molecule during cardiac development.

The other common cardiac defect seen in Down syndrome is VSD, which is reported with a prevalence of 11 % to 40 % [29, 30]. The type of VSD most commonly associated with trisomy 21 is usually the inlet perimembranous type and is likely to be an isolated cardiac defect [31–33].

Trisomy 18

Trisomy 18 (Edward syndrome) is the second common form of autosomal trisomy, with an incidence of 1 in 8,000 births [27]. Most fetuses with trisomy 18 have multiple abnormalities, and nearly 97 % of cases could be detected sonographically by an expert examiner [34]. Congenital cardiac defects could be found in more than 80 % of fetuses of trisomy 18 [14••], but the detection rate for these cardiac anomalies in the second trimester was only 36 % [35], reflecting the subtle nature of these cardiac defects. Notably, the cardiac manifestations, more than any other noncardiac markers, contribute to the high detection rate of trisomy 18. The combination of markers, including the abnormal nuchal skin fold, VSD, outflow tract abnormalities of the heart, right-to-left chamber disproportion of the heart significantly contribute to the identification of 93 % of fetuses with trisomy 18 [34]. Based on the necropsy series, the most common cardiac defects seen in trisomy 18 are VSDs (100 %), subpulmonary infundibulum (conus) (98 %), and polyvalvular disease (malformations more than one valve) (93 %). Conotruncal anomalies, such as tetralogy of Fallot and double outlet of right ventricles, are occasionally seen, with an incidence of 15 % and 10 % respectively [36].

However, there is a striking absence of TGA and situs inversus, findings that appear to be characteristic of all trisomies [22, 36].

Trisomy 13

In comparison with trisomy 21 and 18, the occurrence of trisomy 13 is rare, with an incidence of 1 in 25,000 births [27]. CHD have been found in nearly 90 % of fetuses with trisomy 13 [14••]. The three most common forms of CHD seen in trisomy 13 fetuses are patent ductus arteriosus (68 %), VSD (50 %), and atrial septal defect (50 %). One third of patients may present with complex congenital heart defects, including tetralogy of Fallot, double outlet right ventricle, hypoplastic left ventricle, and partial anomaly of pulmonary venous return [37, 38].

Turner Syndrome

Turner syndrome is the most common numerical abnormality of the sex chromosome, with an incidence of 1 in 2,000 births [39]. The prevalence rate of cardiovascular malformations ranges from 17 % to 26 % in postnatal series [40], but reaches 62 % in the fetal group [41]. Among the congenital cardiac lesions associated with Turner syndrome, coarctation of the aorta and hypoplastic left heart syndrome (HLHS) are the most common diagnoses, occurring in 45 % and 13 % of fetuses, respectively. The patterns of malformation and prevalence rates differ from postnatal series in which bicuspid aortic valve and coarctation of the aorta are the two most common diagnoses, each with an incidence of 15 % and 11 % respectively [40]. This discrepancy reflects a higher rate for spontaneous or induced abortion in fetuses with Turner syndrome complicated by cardiac defects.

Congenital Heart Defects and Constitutional Change of Chromosome

Routine G-banding technique can detect not only whole chromosomes that are extra or missing (aneuploidy), but also deletions, duplications, and translocations at the microscopic level. Microdeletion syndromes are defined as a group of clinically recognizable disorders characterized by small (<5 megabase [Mb]) deletions of chromosomal segments spanning variable number of disease genes, with each deleted gene potentially contributing to the phenotype independently [42]. These microdeletion syndromes cannot be detected by routine G-banding technique, but could be detected by array comparative genomic hybridization (aCGH) and fluorescence in-situ hybridization (FISH).

22q11.2 Deletion Syndrome

The most common chromosomal cause of significant congenital heart disease is trisomy 21, and the second most common is chromosome band 22q11 deletion [43]. The prevalence of chromosome band 22q11 microdeletions is approximately 1 per 4,000 births [14••]. Approximately 80 % cases of 22q11.2 deletion syndrome have cardiac manifestations [44].

In 1968, DiGeorge and associates first described a group of patients with unique facies, heart defects, parathyroid malfunction, and congenital absence of thymus [45]. During the same year, velopharyngeal insufficiency, conotruncal defects with unique facies were described in another set of patients as velocardiofacial syndrome [46]. It was not until advances in modern molecular genetics that researchers realized that these are the same group of patients with different names, including velo-cardio-facial syndrome (VCFS), Shprintzen syndrome, DiGeorge sequence/syndrome, CATCH22 syndrome, Sedlackova syndrome, and conotruncal anomaly face syndrome. Although the phenotype may be variable, the pathological mechanism is a microdeletion in the 22q11.2 region [42, 47–49]. The microdeletion of 22q11.2 deletion is relatively large compared with other forms of microdeletion, approximately in the 3-5 Mb range. There are four duplicated DNA sequences with 25 to 30 genes in the specific region known as the DiGeorge critical region (DGCR). These genes are currently thought to involve migration of neural crest-derived tissues, and dysfunction is associated with developmental defects, particularly that of the third and fourth branchial pouches. This affects the thymus gland, which is a mediastinal organ largely responsible for differentiation and induction of tolerance in T cells, and the parathyroid glands [47]. Approximately 7 % of cases are familial; frequently, one of the parents is diagnosed with the 22q11.2 deletion only after a more severely affected child is diagnosed.

Due to the different size of chromosomal microdeletion, the clinical phenotype of the 22q11.2 deletion syndrome is highly variable among related and unrelated individuals. Cardiac anomalies, immunodeficiency, and speech delay appear to be the most frequent phenotypic manifestations of 22q 11.2 deletion syndrome [43]. The congenital heart defects may be seen in as high as 80 % patients in the hospital-based population of 22q 11.2 deletion syndrome [44, 50]. The association of abnormal facies, hypocalcemia, and thymic abnormalities associated with the cardiac defect, namely the complete DiGeorge syndrome, has a 100 % positive predictive value for the presence of 22q11.2 microdeletion; the rate decreases to less than 50 % when only one feature of the 22q11.2 deletion syndrome is seen along with the heart defect. With an isolated conotruncal lesion was seen, microdeletions are seldom detected [51].

For a single cardiac lesion, the interrupted aortic arch has the highest risk of 22q 11.2 deletion syndrome. It is estimated that 50–89 % of patients with interrupted aortic arch will be associate with microdeletion in the chromosome 22q11 region [14••, 51]. But the most common complex cardiac lesion seen in 22q 11.2 deletion syndrome is the tetralogy of Fallot [42]. In a large collaborative study of 545 patients showing a 22q11.2 microdeletion [44], TOF (including pulmonary atresia and VSD) was encountered in 27 % of these neonates, followed by interrupted aortic arch and VSD (14 % and 14 %, respectively). Among all conotruncal defects, transposition of great arteries is most unlikely to be associated with 22q11.2 deletion syndrome (<1 %).

Wolf-Hirschhorn Syndrome (4p Deletion)

Wolf-Hirschhorn syndrome (WHS) is a well-known congenital malformation syndrome caused by deletion of the short arm of chromosome 4. A deletion of a 200 kilobase in the critical region of the terminal band (4p15.32 to 16.3) is crucial for full expression of the syndrome. The incidence of WHS is approximately 1 in 50,000 births, and approximately 200 cases have been reported in the literature [52]. Similar to 22q 11.2 deletion syndrome, three phenotypic categories have been defined based on the extent of the microdeletion. Three to five megabase deletions are associated with a mild form of the disease, 5–18 Mb deletions are associated with the classic WHS phenotype, and deletions greater than 22–25 Mb are associated with severe phenotypes [53]. In general, 50 % of WHS have cardiac lesions [54]. Nearly 50 % of WHS patients associated with congenital heart defects, including VSD, atrial septal defect (ASD), coarctation, and pulmonary stenosis [54–56].

Cry du Chat Syndrome (Cat Cry Syndrome)

The Cry du Chat Syndrome (CdCS) was first described by Lejeune et al. in 1963 [57]. CdCS results from a deletion of chromatin from the short arm of chromosome 5 (5p) with an incidence of 1 in 50,000 live births [58]. A de novo deletion is present in 85 % of cases. The remaining cases are inherited with the majority due to parental translocations [59]. The main clinical features are a high-pitched monochromatic cry, microcephaly, broad nasal bridge, epicanthal folds, micrognathia, abnormal dermatoglyphics, and severe psychomotor and mental retardation [60]. Cardiac anomalies are seen in 20 % of patients, and the spectrum of manifestations includes VSD, ASD, and TOF [58, 61].

Williams-Beuren Syndrome (WBS)

The Williams-Beuren syndrome is a genomic disorder caused by a hemizygous contiguous gene deletion of approximately 1.5–1.8 Mb pairs of DNA from chromosome 7q11.23. The prevalence is approximately 1 in 7,500–20,000 births [62]. The microdeletion of this critical region encompasses approximately 28 genes. In contrast to 22q 11.2 deletion syndrome and WHS, the size of microdeletion is rather uniform, because they arise spontaneously by inter- or intrachromosomal crossovers [63]. Patients with WBS have a characteristic constellation of medical and cognitive findings, with a hallmark feature of generalized arteriopathy presenting as stenoses of elastic arteries and hypertension [62, 64]. Congenital heart defects often seen in Williams-Beuren syndrome include supravalvular aortic stenosis, pulmonary valvular stenosis, peripheral pulmonary artery stenosis, and ventricular and atrial septal defects. The prevalence of these cardiac defects may as high as 80–90 % [14••, 61]. The characteristic facie for Williams-Beuren syndrome includes broad forehead with bitemporal narrowing, low nasal root, bulbous nasal tip, periorbital fullness, stellate iris pattern, malar flattening, full cheeks, long philtrum, full lips, wide mouth, and dental malocclusion with small and widely spaced teeth [65].

Single Gene Disorders

Noonan Syndrome

Noonan syndrome (NS) is a relatively common congenital genetic disorder with an estimated prevalence of 1 in 1,000 to 1 in 2,500 live births [66]. It is an autosomal dominant disorder with complete penetrance but variable expressivity. Until recently, diagnosis was based solely on clinical findings, but genetic studies are able to identify genetic mutations in nearly 60 % of the patients [67]. The clinical hallmarks of NS are facial dysmorphism, short stature, and cardiac defects. Burch et al. evaluated 118 clinically well-defined cases of NS with echocardiography and found that the prevalence of cardiac defects is approximately 71 % [68]. Of these individuals, approximately 30 % had pulmonary valve stenosis, 30 % had hypertrophic cardiomyopathy, and 15 % had an atrial septum defect. In a multicenter study, Sznajer et al. reported a prevalence of PTPN11 mutations of 38 % individuals with NS. Prevalence of cardiac defects was 85 % in individuals with mutations in PTPN11 and 68 % in individuals without a mutation in PTPN11. In individuals with mutations in PTPN11, pulmonary valve stenosis most often was seen [69].

Holt-Oram Syndrome

Holt-Oram syndrome (HOS) was first described in 1960 when a family with atrial septal defects and congenital anomalies of the thumbs was reported [70]. The prevalence of HOS is 1 in 100,000 live births. Haploinsufficiency of

TBX5 causes HOS and was the first single gene mutation described to cause human septation defects [71]. The cardiac defects existed in approximately 85 % of patients, with predominately secundum ASD (60 %) and VSD (18 %) [72, 73]. TBX5 missense mutations can lead to defects of the limbs or the heart, depending on the domains affected [71, 74].

Alagille Syndrome

Alagille syndrome is a rare embryopathy due to mutations in the genes JAG1 and NOTCH 2. The estimated incidence is 1 in 100,000 births [75]. Neonatal cholestasis is the main clinical feature and is due to the paucity of intrahepatic bile ducts. Cardiac abnormalities are present in 85–97 % of patients. The most common diagnose is peripheral pulmonary artery stenosis, but pulmonary atresia, ASD, VSD, and TOF also are noted [76].

Association of Multiple Anomalies with Cardiac Defects

With major advances in human genetics in recent decades, the molecular bases of many of these syndromic CHDs have been identified. The molecular etiologies of these syndromic CHD can help to understand the clinical features and prognosis of these syndromes [77]. However, the etiology of certain clinical spectrums, such as VACTERL and CHARGE association, is still largely unknown and is likely to be multifactorial [78•, 79]. The definition of "association" is different from "syndrome." Associations represent the idiopathic occurrence of multiple congenital anomalies during blastogenesis. The key concept is the implication that different causal factors acting at particular stages in development give rise to similar patterns of malformations [80]. In contrast, "syndrome" indicates an identified etiology of a spectrum of malformation (for example, deletion 22q11 syndrome). These clinical spectrums have a combination of clinical features, but most of them exhibit cardiac manifestations. The diagnosis of these associations are important for a variety of reasons, including the facilitation of care for other problems that may not be structure in nature and thus not easily identified before birth. The correct diagnosis may result in the clinician providing the appropriate counseling for the potential risks associated with these associations.

VACTERL Association

The most well-known "association" of congenital anomalies is the VACTERL association. The incidence is estimated at approximately 1 in 10,000 to 1 in 40,000 live-born infants [78•]. The VACTERL association refers to the combination of anomalies of the vertebra (V), imperforated anus (A), cardiac anomalies (C), tracheoesophageal fistula (TE), renal anomalies (R), and limb (or lung) lesions (L). The association was first proposed by Quan and Smith in 1972 [81]. The wide spectrum of defects that comprise the VACTREL anomaly suggests that the alternations occur early in the blastogenesis, thereby result in polytopic birth defects affecting multiple organ systems. Some conditions may contribute to the pathogenesis of VACTERL association, including chromosomal aberrations and teratogen exposure. More than ten single gene disorders have been described, which have phenotypic overlap with VACTERL association. Some of these include Fanconia anemia, Feingold syndrome, and Opitz G/BBB syndrome [79–83].

The principle element of VACTERL is tracheoesophageal fistula, which occurs in more than 95 % of the patients [82]. Cardiac malformations have been reported in approximately 40–80 % of patients with the VACTERL association [78•]. The cardiac lesions that most often are seen in the VACTERL association include VSD (69 %), ASD (36 %), TOF (14 %), and dextrocardia (11 %) [82].

Individuals with the VACTERL association do not typically have facial dysmorphic features, learning disability, or growth abnormalities. The surgical outcome has improved in recent decades [82, 84].

CHARGE Association

CHARGE association (or Hall-Hittner syndrome) was originally described by Bryan Hall and H.M. Hittner independently in two groups of children with multiple congenital anomalies, including choanal atresia and coloboma [83, 84]. In a later review, R. Pagon authored the term "CHARGE," which is an acronym that summarizes the six principal features: ocular Coloboma, Heart defects, Atresia of the choanae, Retardation (of growth and/or development), Genital anomalies, and Ear anomalies (abnormal pinnae or hearing loss) [85]. The incidence is approximately 1 in 10,000 births. The etiology of CHARGE association is heterogeneous. Chromosome aberrations, single gene disorders, and teratogen exposure have been shown to result in CHARGE association [79]. Recently, the CHD7 (chromodomain helicase DNA-binding protein-7) gene has been shown to be the most important gene linked to the CHARGE association. In approximately two thirds of cases, the CHD7 genes are found to be deleted. The cardiac defects of the CHARGE association can be of any type and are present in 70 % of cases of CHARGE association [86].

Nonsyndromic Congenital Heart Diseases

Congenital cardiac defects occur as a part of spectrum (syndromic CHD) in 30 % of cases and as isolated lesions

Table 1 The relevance of genetic factors and fetal cardiac defects

Disease	Incidence	Genetic origin	Percentage with cardiac defects	Principle cardiac lesions	Extracardiac anomalies
Aneuploidy					
Trisomy 21	1:800	Chromosome 21	50 %	AVSD, VSD, ASD, TOF	Mental and growth deficiency, epicanthal fold and low-set ear, shortened long bones, bowel obstruction
Trisomy 18	1:8,000	Chromosome 18	80 %	VSD, ASD, TOF, DORV, CoA polyvalvular diseases	Strawberry head, low-set ear and microtia, micrognathia, omphalocele, clenched hands, club feet or Rocker-bottom feet, renal malformations, esophageal atresia
Trisomy 13	1:25,000	Chromosome 13	90 %	VSD, ASD, HLHS, CoA	Microcephaly, holoprosencephaly, cleft lip and palate, low-set ear and microtia, micrognathia, renal malformations,
Turner syndrome	1:2,000	X chromosome	17–26 % (postnatal)		
62 % (prenatal)	CoA, HLHS	Short stature, lymphedema, shield chest, web neck, low-set ear			
Constitutional change of chromosome					
Del 22q11.2 syndrome	1:4,000	22q11.2 deletion	80 %	TOF, interrupted aortic arch, VSD, truncus arteriosus	Facial dysmorphism (hooded eyelids, auricular anomalies, hypoplastic nasal alae, a small mouth, micrognathia), palate anomaly, thymic dysgenesis, renal anomalies
Wolf–Hirschhorn syndrome	1:50,000	4p deletion	50 %	VSD	Microcephaly, micrognathia, short philtrum, prominent glabella ("Greece Helmet" appearance), ocular hypertelorism, dysplastic auricle, and periauricular tags
Cry du Chat syndrome	1:50,000	5p deletion	20 %	VSD. ASD, TOF	Microcephaly, broad nasal bridge, epicanthal folds, micrognathia, abnormal dermatoglyphics,
Williams-Beuren syndrome (WBS)	1:7,500 to 20,000	7q11.23 deletion	80–90 %	Supravalvular aortic stenosis, pulmonary valvular stenosis, VSD, ASD	broad forehead, periorbital fullness, short nose with flat bridge, wide mouth, and full lips and cheeks
Single gene disorders					
Noonan syndrome	1:1,000 to 2,500	PTPN11 (38 %)	71 %	Pulmonary valve stenosis, hypertrophic cardiomyopathy, ASD	Facial dysmorphism, short stature, web neck
Holt-Oram syndrome	1:100,000	TBX5	85 %	ASD, VSD	Limb defects
Alagille syndrome	1:100,000	JAG1, NOTCH2	85–97 %	Peripheral pulmonary artery stenosis	Neonatal cholestasis
Association of multiple anomalies with cardiac defects					
VACTERL	1:10,000 to 40,000	Heterogeneous etiology	40–80 %	VSD, ASD, TOF	Anomalies of the vertebra (V), imperforated anus (A), tracheoesophageal fistula (TE), renal anomalies (R) and limb (or lung) lesions (L)
CHARGE	1:10,000	Heterogeneous etiology			
		CHD7	70 %	Any type	Ocular coloboma (C), atresia of the choanae (A), retardation (of growth and/or development), genital anomalies (G), and ear anomalies (E; abnormal pinnae or hearing loss)

AVSD, atrioventricular septal defect; VSD, ventricular septal defect; ASD, atrial septal defect; TOF, tetralogy of Fallot; CoA, Coarctation of aorta; HLHS: hypoplastic left heart syndrome

in nearly 70 % of cases [14••]. In higher vertebrates, heart formation is a complex process that needs the orchestrations involving multiple genes and signaling pathways. It starts in the early stages of embryogenesis, before the end of gastrulation, with commitment of anterior lateral plate mesoderm cells to the cardiogenic lineage and their migration and organization into the cardiac crescent [12, 87]. If the impact of mutated genes is limited to cardiovascular system, an isolated (or nonsyndromic) CHD occurred. During the past decade, several genes responsible for embryonic cardiac development have been identified [88, 89••]. For example, the genes TbX5 and Nkx2-5 are involved in the formation and septation of cardiac chambers. Mutation of TbX5 may result in ASD and VSD, whereas mutation in Nkx2-5 may result in a broader spectrum of cardiac defects, including ASD, VSD, atrioventricular block, TOF, TGA, DORV, tricuspid atresia, and Ebstein anomaly [12, 74, 90].

Conclusions

This review summarizes the known associations between congenital cardiac defects and their corresponding genetic factors, such as aneuploidy, constitutional changes of chromosome, and single gene disorders (Table 1). Of all congenital cardiac defects, one third of all patients show an association with extracardiac malformations or part of a genetic syndrome, which should prompt further clinical and molecular investigations [14••]. Perinatal cardiologists should be familiar with these associations, because the outcome of fetuses with CHD is not only dependent on the types of cardiac lesions but also on the associated genetic errors and coexisting extracardiac anomalies [78•, 82, 91–93]. Despite significant improvement of surgical repair of even the most challenging CHDs, patients with genetic syndromes or extracardiac anomalies may show an increased risk for death or major complications, which would require dedicated care in the postoperative period [29, 94]. At the same time, whereas the cardiac defects can potentially be corrected with the appropriate cardiac surgery, the underlying genetic disorder may not be amendable to cure with current technologies. Even if karyotyping and array comparative genomic hybridization results are normal, the perinatal cardiologist should still be aware of the potential associations with other extracardiac lesions as in syndromic CHDs, such as TE fistula and imperforated anus, which most often are associated with TOF. These extracardiac lesions would further complicate the treatment course and may impact the outcome negatively.

The additional knowledge acquired from the genetic tests may benefit the clinician in facilitating the differential diagnosis of CHD. For example, right ventricle hypoplasia is rarely associated with aneuploidy, but hypoplastic left heart syndrome can sometimes occur as a part of trisomy 18 or 13 syndrome [14••].

Genetic studies, such as karyotyping, array comparative genome hybridization, and mutation analysis, have an important role in counseling families about the outcome of CHD [95]. We summarize the genotype-phenotype correlation in several well-known syndromes, including Down syndrome, DiGeorge syndrome with chromosome 22q11.2 deletion, Williams syndrome, and Holt-Oram syndrome. Although karyotyping should be offered to all the fetuses with CHD, the perinatal cardiologist should still have a priority in mind so as to choose the most appropriate genetic test for the specific cardiac anomaly. This is especially important when resources are limited.

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- •• Of major importance

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