

Cytogenomic Aberrations in Congenital Cardiovascular Malformations

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Key Words

Aneuploidies · Congenital cardiovascular malformations · Cytogenomic aberrations

Abstract

Congenital cardiovascular malformations are the most common birth defects, with a complex multifactorial etiology. Genetic factors play an important role, illuminated by numerous cytogenetically visible abnormalities, as well as sub-microscopic genomic imbalances affecting critical genomic regions in the affected individuals. Study of rare families with Mendelian forms, as well as emerging next-generation sequencing technologies have uncovered a multitude of genes relevant for human congenital cardiac diseases. It is clear that the complex embryology of human cardiac development, with an orchestrated interplay of transcription factors, chromatin regulators, and signal transduction pathway molecules can be easily perturbed by genomic imbalances affecting dosage-sensitive regions. This review focuses on chromosomal abnormalities contributing to congenital heart diseases and underscores several genomic disorders linked to human cardiac malformations in the last few decades.

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Congenital heart diseases (CHDs) are a leading cause of infant mortality around the world, affecting 0.5–0.7% of all liveborn infants [Mitchell et al., 1971; Hoffman and Kaplan, 2002; Hoffman et al., 2004]. This estimate excludes bicuspid aortic valve (BAV), a common anomaly with a prevalence of ~1% in healthy adults [Roger et al., 2011] and an important risk factor for subacute bacterial endocarditis, aortic valve calcification/stenosis, and aortic aneurysm and dissection [Michelena et al., 2008; Tzemos et al., 2008]. It is anticipated that over three-fourths of children with CHD who survive the first year of life will live to adulthood [Pierpont et al., 2007]. As these children reach adulthood, increasing concerns have emerged related to disease transmission and the risk to future progeny. It is crucial that genetic risk factors be determined for this rising number of individuals for appropriate counseling.

Several studies have elucidated the genetic underpinnings of susceptibility to this major birth defect, both related to single gene etiology and large cytogenetically visible chromosomal aberrations. CHD can occur as an isolated birth defect or in conjunction with extracardiac anomalies, including abnormal craniofacial features, other congenital anomalies, developmental abnormalities,

and/or growth deficits. Indeed, the overall frequency of extracardiac anomalies including neurocognitive delay has been estimated to range from 20 to 44% in individuals with CHD [Greenwood et al., 1975; Wallgren et al., 1978; Marino et al., 2012]. Defects in single genes have traditionally been estimated to account for 3–5% of all children with CHD [van der Bom et al., 2011]. However, genome-wide exome sequencing studies indicate a higher burden of de novo mutations in severe CHD, accounting for ~10% of the cases [Zaidi et al., 2013].

Conventional karyotyping detects chromosomal abnormalities that are responsible for 10–12% of all CHDs in liveborn infants [Hartman et al., 2011]. Within this group, trisomy 21 is the most common cause, constituting about half of the cases [Hartman et al., 2011] (table 1). The frequency of cytogenetically visible karyotype abnormalities in fetuses with abnormal cardiac ultrasound findings is even higher, estimated to be around 17–22% [Chaoui et al., 1999; Song et al., 2009; Mademont-Soler et al., 2013], with the most common being trisomies 21, 18, and 13, and monosomy X. Additionally, about 8% of fetuses with CHD with normal karyotype studies have submicroscopic aberrations including 22q11.2 deletion and other segmental aneusomies [Mademont-Soler et al., 2013]. The characterization of DNA copy number variations (CNVs) by chromosomal microarray analysis has indeed been revolutionary in the field of cardiovascular genetics. The most frequent genomic disorder responsible for CHD is the 22q11 deletion syndrome which occurs in about 1 in 4,000 live births [Burn and Goodship, 1996]. Other important disorders known to cause CHD include 1p36 monosomy, Williams-Beuren syndrome (7q11.23 deletion), 8p23.1 deletion including *GATA4*, and 9q34 deletion encompassing *EHMT1* (Kleefstra syndrome). It is evident that the probability of determining an underlying genetic perturbation in those with CHD plus extracardiac anomalies (i.e. syndromic CHD) is significantly higher in comparison to those with isolated CHD defects [Thienpont et al., 2007; Breckpot et al., 2011; Derwińska et al., 2012; Geng et al., 2014]. In syndromic CHD, the burden of genomic imbalance may be as high as ~30%, combining the frequency of large cytogenetically visible aberrations and submicroscopic events in the published reports. This assessment may still be underestimated, as detection of smaller exonic deletions in cardiac specific genes has traditionally been below the detection threshold for many commercially available array platforms. This review focuses on frequently observed cytogenetic and submicroscopic genomic imbalances that are major players in human CHDs.

Aneuploidies and CHD

Karyotype studies detect abnormalities in about one-tenth of all liveborn infants with CHD [Hartman et al., 2011]. Within this group, trisomy 21 is the most common cause, constituting about half of the cases [Hartman et al., 2011]. Indeed, Down syndrome (DS; MIM 190685) is categorically the most common cause of syndromic CHD diagnosed in 1 in 730 live births. Typically diagnosed prenatally or at birth, the syndrome is easily recognized in the presence of characteristic dysmorphic facial features and hypotonia. The prevalence of CHD in DS is ~50% [Jaiyesimi and Baichoo, 2007]. Atrioventricular septal defect (AVSD) is the most common cardiac defect, observed in 30–40% of infants [Tubman et al., 1991; Frid et al., 1999], followed by ventricular septal defect (VSD), atrial septal defect (ASD), and tetralogy of Fallot (TOF) [Källén et al., 1996]. Coarctation of the aorta (CoA), pulmonary valve stenosis (PS), vascular ring, and defects of single ventricle physiology are seen less frequently [Lin et al., 2008; Irving and Chaudhari, 2012]. Persistent pulmonary hypertension of the neonate, even in the absence of structural heart disease, occurs more frequently in DS as compared to the general population [Suzuki et al., 2000; Weijerman et al., 2010]. It is recommended that all children with DS have an echocardiogram and consultation with a cardiologist as needed in the newborn period [Bull, 2011].

Sex chromosome abnormalities including Turner syndrome (TS) make up ~3% of G-banded cytogenetic abnormalities observed in CHD. TS (45,X) occurs in 1 in 2,500 live births and is the most commonly encountered sex chromosome abnormality in females. CoA is found in up to 12–17% of females with TS, compared to 0.04% in the general population [Sachdev et al., 2008; Kim et al., 2011]. Hypoplastic left heart syndrome (HLHS) is noted in association with TS in about 2% of the cases [Tan and Yeo, 2009]. BAV is observed in 30% of individuals with TS [Sachdev et al., 2008], in sharp contrast to the 1.3% prevalence observed in healthy adults [van Egmond et al., 1988; Korpál-Szczyrska et al., 2005; Völkl et al., 2005; Roger et al., 2011]. Aortopathy including dilatation of the ascending aorta, aortic aneurysms, and aortic dissection has been exemplified in several studies [Carlson and Silberbach, 2007; Bondy, 2008]. Aortic dissection occurs in 1–2 of 100 affected females and is observed ~6 times more frequently in TS than in healthy females [Gravholt et al., 2006]. Although it usually occurs in the third to fifth decades of life, it can happen as early as in the first decade [Sybert, 1998].

Table 1. Chromosomal abnormalities and genomic disorders associated with CHD

Categories	Syndromes	Type of defects	Frequency of heart defects, %	Extracardiac congenital abnormalities
Aneuploidies	trisomy 21 Down syndrome	AVSD, VSD, ASD, TOF	45–50	characteristic facial features, hypothyroidism, intellectual disability, hypotonia, duodenal atresia, Hirschsprung disease
	45,X Turner syndrome	BAV, CoA, HLHS	30–32	short stature, gonadal dysgenesis, webbed neck, renal anomalies
	trisomy 18 Edwards syndrome	polyvalvular disease, VSD, ASD, PDA, endocardial cushion defects, left-sided lesions, DORV	80–100	growth retardation, clenched hands, rocker-bottom feet, omphalocele, severe intellectual disability
	trisomy 13 Patau syndrome	ASD, VSD, PDA, DORV, TOF, CoA	80	cleft lip/palate, microphthalmia, scalp defects, holoprosencephaly, postaxial polydactyly, growth retardation, severe intellectual disability
Large cytogenetic abnormalities	4p16.3 deletion Wolf-Hirschhorn syndrome	ASD, PS, TOF, VSD, PDA	50	Greek warrior helmet craniofacial dysmorphism, intellectual disability, feeding difficulties, seizures, urinary tract malformations, structural brain anomalies
	5p monosomy Cri-du-chat syndrome	PDA, VSD, ASD, TOF, pulmonary atresia	29	high-pitched cat-like cry, round face, hypertelorism, micrognathia, microcephaly, intellectual disability
	11q deletion Jacobsen syndrome	VSD, ASD, TA, DORV, BAV, AS, HLHS, MS, CoA	56	dysmorphic features, thrombocytopenia, pyloric stenosis, anal atresia/stenosis, annular pancreas, gut malrotation, growth retardation, intellectual disability
	chromosome 22 partial tetrasomy Inv dup (22)(q11) Cat eye syndrome	TAPVR, TOF, PS, tricuspid atresia, HLHS	50–67	coloboma, anal atresia, biliary atresia, malrotation of the gut, preauricular tags or pits, renal malformation
Genomic disorders	22q11.2 deletion DiGeorge syndrome	IAA type B, aortic arch anomalies, TA, TOF	75	thymic and parathyroid hypoplasia, hypocalcemia, immunodeficiency, dysmorphic features, palatal insufficiency, renal anomalies, learning difficulties, and psychiatric disorders
	7q11.23 deletion Williams-Beuren syndrome	SVAS, PPS	75	social personality, hypercalcemia dysmorphic features, intellectual disability
	8p23.1 deletion	AVSD, ASD, PS, TOF	75–94	congenital diaphragmatic hernia
	1p36 deletion	septal defects, PDA, CoA, TOF, cardiomyopathy	70	dysmorphic features, sensorineural hearing loss, seizures, intellectual disability, brain abnormalities
	1q21.1 deletion	CoA, IAA-type A, IAA-type B, BAV, aortopathy, VSD, TA, TGA, CoA, PDA	10–25	microcephaly, developmental delay
	1q21.1 duplication	TOF	20	macrocephaly, developmental delay

Table 1 (continued)

Categories	Syndromes	Type of defects	Frequency of heart defects, %	Extracardiac congenital abnormalities
	17p11.2 deletion Smith-Magenis syndrome	septal defects, TOF, PS, PA, TAPVR	~30	dysmorphic features, failure to thrive, hypotonia, intellectual disability, sleep disturbance, self-injurious behaviors
	17p11.2 duplication Potocki-Lupski syndrome	dilated aortic root, septal defects, conduction abnormalities, BAV, HLHS	40	dysmorphic features, hypotonia, intellectual disability, autism spectrum disorder
	17p13.3 deletion Miller-Dieker syndrome	septal defects, TOF, PDA	20	cerebral agyria/pachygyria, type I lissencephaly, corpus callosum dysgenesis/agenesis, microcephaly, seizures, dysmorphic features, intellectual disability
	9q34.3 deletion Kleefstra syndrome	septal defects, PS, BAV, PDA	40	brachycephaly, synophrys, cupid-bowed upper lip, prominent jaw, hypotonia, intellectual disability, epilepsy, behavior abnormalities
	15q26qter deletion	VSD, ASD, CoA, HLHS, AS	~66	growth retardation, microcephaly, intellectual disability, congenital diaphragmatic hernia
	17q21.31 deletion	septal defects, PS, BAV	39	long face, upslanting palpebral fissures, epicanthic folds, tubular nose, large prominent ears, intellectual disability

AS = Aortic valve stenosis; DORV = double-outlet right ventricle; IAA-A/IAA-B = interruption of the aortic arch type A/B; MS = mitral stenosis; PA = pulmonary atresia; PPS = peripheral pulmonary stenosis; SVAS = supra-aortic stenosis; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; TS = truncus arteriosus.

Moreover, with pregnancies resulting from the increasing use of assisted reproductive techniques in TS, the risk of aortic dissection is significantly higher during pregnancy, with a mortality rate exceeding more than 100 times the population risk. The growing evidence of aortic disease in TS and the high risk of acquired heart diseases calls for vigilant cardiac follow-up well into adulthood, even in the absence of CHD [Carlson and Silberbach, 2007; Bondy, 2008].

Other frequent cytogenetic abnormalities associated with CHD in the presence of multiple congenital anomalies include trisomy 18 and trisomy 13, both with significantly shortened lifespans. CHD is present in more than 90% of all infants with trisomy 18, including VSD and patent ductus arteriosus (PDA). Karyotype analysis is necessary for a definitive diagnosis; however, the presence of polyvalvular disease is a useful adjunct to other clinical assessments [Balderston et al., 1990]. CHD is present in almost 80% of infants with trisomy 13 [Polli et al., 2014]. Although septal defects are the most com-

mon abnormalities, double outlet right ventricle, TOF, and CoA are frequently reported as well [Maeda et al., 2011].

Large Cytogenetic Abnormalities and CHD

Cat eye syndrome (CES) (MIM 115470) is a rare chromosomal disorder with an estimated prevalence of 1/50,000–150,000 live births. The majority of the affected individuals carry a small supernumerary bisatellited marker chromosome which results in tetrasomy of the p arm and part of the 22q11.1q11.21 region. It has been observed that even interstitial duplications (i.e. 3 copies) of part of the 22q11.2 region can be associated with clinical features of CES [Meins et al., 2003]. Individuals with CES frequently have CHD, particularly observed as total anomalous pulmonary return [Rosias et al., 2001] or TOF. Abnormalities such as PS, tricuspid atresia, HLHS, and single ventricle are rarely reported [Berends et al.,

2001; Rosias et al., 2001]. Infants with CHD in the presence of preauricular pits and/or tags, anal atresia, iris coloboma, biliary atresia, malrotation of the gut, and/or renal malformations should be evaluated for this syndrome.

Wolf-Hirschhorn syndrome (WHS) (MIM 194190), with an estimated frequency of 1/20,000–50,000 live births [Maas et al., 2008] is caused by a partial deletion of the short arm of chromosome 4. Individuals with WHS have characteristic ‘Greek warrior helmet’ craniofacial dysmorphism, intellectual disability, feeding difficulties, seizures, urinary tract malformations, and structural brain anomalies. Approximately half of the affected individuals have structural heart defects. Septal defects are common. Other lesions that are reported include PS, TOF, VSD, and PDA [Battaglia et al., 2008a]. An important role of *FGFR1* has been identified by candidate gene analysis of phenotypic-specific defects in WHS [Catela et al., 2009].

Cri-du-chat syndrome (5p– syndrome; MIM 123450) affecting 1/15,000–45,000 live births is characterized by high-pitched monochromatic cry, significant intellectual disability, growth retardation, and distinct craniofacial features including a round face, microcephaly, and hypertelorism. The clinical manifestations become less striking over time [Van Buggenhout et al., 2000]. About 29% of all affected individuals have CHDs [Wilkins et al., 1983], including PDA, VSD, and ASD. Right ventricular outflow tract obstructive anomalies including TOF and pulmonary atresia have also been described [Hills et al., 2006].

Jacobsen syndrome (JS; MIM 147791), caused by distal deletions of the long arm of chromosome 11, is associated with CHD in more than half of the affected individuals. The estimated prevalence of JS is about 1/100,000 births [Penny et al., 1995]. Severe congenital heart defects, including HLHS (in 5–10% of all 11q– patients), CoA, type B truncus arteriosus, and double outlet right ventricle have been described. *ETS-1*, a transcription factor within this region, has been implicated in cardiac defects [Ye et al., 2010]. *Ets1* has an important role in formation of the interventricular septum, and is required for the migration and differentiation of a subset of the cardiac neural crest [Gao et al., 2010]. Other features of JS include intellectual disability, growth retardation, characteristic facial dysmorphism, thrombocytopenia, and multiple congenital anomalies [Grossfeld et al., 2004; Mattina et al., 2009]. *FLI-1*, which is important for megakaryocytes differentiation, is responsible for platelet abnormalities of JS [Hart et al., 2000]. Approximately 18–25% of the affected children have gastrointestinal tract malformations, in-

cluding pyloric stenosis, anal atresia/stenosis, annular pancreas, or gut malrotation [Mattina et al., 2009]. Screening studies include an echocardiogram, renal ultrasound, neurodevelopmental evaluations, and monitoring of platelet and coagulation function.

CHD and the Microdeletion/Microduplication Syndromes

Genomic disorders resulting from instability of regional genomic architecture are an important cause of CHD [Greenway et al., 2009; Breckpot et al., 2010; Lalani et al., 2013a; Syrmou et al., 2013]. These CNVs are often below the detection threshold of G-banded karyotype analysis and are often ascertained by array-comparative genomic hybridization (array-CGH) studies and SNP genotyping. The burden of CNVs is significantly higher in syndromic cardiac malformations in comparison to isolated CHD. Nonallelic homologous recombination (NAHR) or crossing-over in meiosis between low copy repeats can result in recurrent deletions or duplications. Genomic disorders resulting from such rearrangements of the human genome play an important role in human cardiac malformations [Liu et al., 2012]. Frequently, the altered gene dosage of functionally relevant gene(s) within the deleted or duplicated intervals causes the cardiac malformation. Genome-wide studies have shown that obtaining chromosomal microarray analysis in the evaluation of children with CHD (syndromic and nonsyndromic) can be immensely valuable. CNVs are reported between 3 and 20% of all CHD cases, depending on the classification of nonsyndromic or syndromic cardiac malformations, respectively [Thienpont et al., 2007; Breckpot et al., 2011; Derwińska et al., 2012]. The segmental aneusomies have significant contributions in several important cardiac lesions including TOF [Greenway et al., 2009], heterotaxy [Fakhro et al., 2011], left-sided heart defects [Hitz et al., 2012; Iascone et al., 2012; Warburton et al., 2014], single ventricle heart defects [Carey et al., 2013; Lalani et al., 2013a], and AVSD [Priest et al., 2012].

DiGeorge/Velocardiofacial Syndrome

DiGeorge syndrome (DGS; MIM 188400) or velocardiofacial syndrome, caused by a 22q11.2 deletion is the most frequent genomic disorder associated with CHD. It is estimated that ~1.5% of all CHDs at birth are caused by a 22q11.2 deletion [Botto et al., 2003]. Meiotic nonallelic recombination events mediate the typical ~3-Mb

deletion, with a smaller 1.5-Mb deletion within the typical interval implicated in a subset of individuals. The extracardiac features of DGS include thymus and parathyroid gland aplasia/hypoplasia, craniofacial anomalies, palatal insufficiency, renal anomalies, learning difficulties, and psychiatric disorders. DGS classically presents with distinctive facies and conotruncal cardiac anomalies in the neonatal period. Most cardiac malformations observed in this syndrome are caused by haploinsufficiency of *TBX1* [Lin et al., 2008]. About 75% of individuals with DGS have cardiac defects, which include TOF, truncus arteriosus, and interrupted aortic arch type B. HLHS, PS, heterotaxy, isolated right pulmonary artery atresia, and aberrant subclavian arteries are also described [McDonald-McGinn et al., 1999]. In some instances, defects such as double outlet right ventricle and D-transposition of the great vessels have also been observed.

Williams-Beuren Syndrome and Reciprocal 7q11.23 Reciprocal Duplication Syndrome

Williams-Beuren syndrome (WBS; MIM 194050) is a multisystem genetic disorder caused by heterozygous deletion of about 1.55 to 1.83 Mb on the long arm of chromosome 7 (7q11.23). The estimated prevalence of this disorder is 1 in 7,500–10,000 births [Strømme et al., 2002]. Individuals with WBS have distinctive facial characteristics, including periorbital fullness, upturned nose, wide mouth, and full cheeks. Other features include hypercalcemia, failure to thrive, intellectual disability and an overly sociable personality. Supravalvular aortic stenosis is present in ~75% of the cases [Keating, 1995; Eronen et al., 2002]. Other defects include pulmonary artery stenosis and, less often, mitral valve prolapse, aortic arch hypoplasia, aortic insufficiency and VSD. CoA and total anomalous pulmonary return are rarely seen in WBS [Ferrero et al., 2007]. Stenosis of other medium-sized arteries such as renal arteries, coronary arteries, and abdominal and thoracic aorta has also been described. Haploinsufficiency of the elastin gene (*ELN*) within the common deleted interval causes stenosis of medium and large arteries [Merla et al., 2012].

The 7q11.23 microduplication syndrome is caused by the reciprocal duplication of the WBS region. Mild to moderate aortic dilatation has been reported in a significant number of individuals [Parrott et al., 2015]. The ascending aorta is notably more commonly involved, while the aortic root and sinotubular junction are less affected.

1p36 Deletion

Deletions of chromosome 1p36 (MIM 607872) are one of the most frequent subtelomeric rearrangements, observed in 1 in 5,000 live births [Heilstedt et al., 2003; Rosenfeld et al., 2010]. The syndrome is characterized by moderate to severe intellectual disability and craniofacial dysmorphisms (microcephaly, brachycephaly, large and persistently open anterior fontanelle, deep-set eyes, straight eyebrows, and midface hypoplasia) [Heilstedt et al., 2003; Rosenfeld et al., 2010]. Approximately 70% of individuals have cardiac abnormalities [Gajecka et al., 2007; Battaglia et al., 2008b] including septal defects, PDA, valvular abnormalities, CoA, and TOF. Within the 1p36 region, at least 5 critical regions for structural defects and 2 characterizing the left ventricular noncompaction (LVNC) phenotype have been identified by using fine breakpoint mapping [Zaveri et al., 2014]. Approximately 23–27% of individuals have noncompaction cardiomyopathy (LVNC) [Battaglia et al., 2008b].

1q21.1 Deletion and Duplication

Class I deletion or recurrent 1q21.1 distal deletion (~1.35-Mb; MIM 612474) is associated with CHD with incomplete penetrance (10–25% of individuals). Mild to moderate intellectual disability, microcephaly, and a broad spectrum of cardiac defects including CoA, IAA-type A, IAA-type B [Christiansen et al., 2004], BAV, aortopathy, PDA, truncus arteriosus, and transposition of the great vessels [Mefford et al., 2008] have been described. Class II deletion is a larger deletion (~2.7 Mb) and includes the thrombocytopenia absent radius syndrome region. Within the ~1.35 Mb interval, the gap junction alpha-5 protein (*GJA5*), also known as connexin 40 (Cx40), has been implicated in cardiac defects. Several studies have shown that reciprocal duplication 1q21.1 (MIM 612475) is strongly associated with TOF [Greenway et al., 2009; Silversides et al., 2012; Dolcetti et al., 2013].

8p23.1 Deletion Including GATA4

Recurrent deletions of 8p23.1 mediated by NAHR by local low copy repeats are associated with CHD with high penetrance [Wat et al., 2009; Lalani et al., 2013a]. At least 2 dosage-sensitive genes (*GATA4* and *SOX7*) are located in this region. *GATA4* mutations cause isolated ASD, TOF, and AVSD in rare families [Garg et al., 2003; Nemer et al., 2006]. The reciprocal duplication syndrome 8p23.1 is linked to conotruncal abnormalities with incomplete penetrance. Other cardiac defects such as TOF, septal defects, PS, and AVSD have also been reported [Barber et al., 2010, 2013; Zhang et al., 2013].

Smith-Magenis Syndrome

Smith-Magenis syndrome (SMS; MIM 182290) is caused by an interstitial deletion of 17p11.2, involving the retinoic acid-induced 1 (*RAI1*) gene. SMS is characterized by brachycephaly, significant behavior disorder, sleep disturbance, craniofacial abnormalities (midface hypoplasia, prognathism), hoarse voice, speech delay with or without hearing loss, psychomotor and growth retardation, and skeletal anomalies. CHDs such as septal defects and TOF are present in about one-third of individuals with SMS [Smith et al., 1986; Greenberg et al., 1996; Sweeney et al., 1999; Thomas et al., 2000]. Other defects include pulmonary atresia, PS, and total anomalous pulmonary return.

Potocki-Lupski Syndrome

Potocki-Lupski syndrome (MIM 610883) is caused by a reciprocal duplication of the SMS region in 17p11.2 [Bi et al., 2003; Potocki et al., 2007], spanning about 3.7 Mb. Infantile hypotonia, failure to thrive, intellectual disability, poor feeding, oropharyngeal dysplasia, and sleep apnea are some of the characteristic features [Potocki et al., 2007; Soler-Alfonso et al., 2011]. Approximately 40% of individuals with Potocki-Lupski syndrome have CHD [Jefferies et al., 2012]. Dilated aortic root, septal defects, PFO, conduction abnormalities, BAV, and HLHS have been described [Sanchez-Valle et al., 2011; Yusupov et al., 2011; Jefferies et al., 2012].

Miller-Dieker Syndrome

Miller-Dieker syndrome (MIM 247200) is a rare disorder, characterized by cerebral agyria/pachygyria or type I lissencephaly, corpus callosum dysgenesis/agenesis, microcephaly, seizures, and distinctive facies (prominent forehead, midface hypoplasia, a small, upturned nose, and low-set and abnormally shaped ears). It is caused by a terminal deletion in 17p13.3 encompassing *PFAH1B1*. Septal defects and TOF are reported in both prenatal and postnatal cases in various studies [Kowase et al., 1997; Chen et al., 2010; Lalani et al., 2013a]. Most individuals with this condition do not survive beyond childhood.

Kleefstra Syndrome

A subtelomeric deletion in chromosome 9q34.3 or a point mutation in the euchromatin histone methyltransferase 1 (*EHMT1*) gene cause Kleefstra syndrome (MIM 610253), characterized by intellectual disability, hypotonia, and facial dysmorphism. Craniofacial features include microcephaly and/or brachycephaly, synophrys, and/or arched eyebrows, midface hypoplasia, a short nose with

upturned nares, and downturned corners of the mouth [Harada et al., 2004]. Approximately 40–50% of individuals with Kleefstra syndrome have CHD, primarily ASD or VSD, TOF, aortic coarctation, BAV, and pulmonic stenosis [Kleefstra et al., 2009; Willemsen et al., 2012]. Hypoplastic left heart is rarely reported [Campbell et al., 2014].

Deletions of 15q26 Syndrome

Left-sided outflow tract lesions including CoA, aortic stenosis, and HLHS have been frequently reported in terminal deletions of 15q26 [Tumer et al., 2004; Slavotinek et al., 2006; Klaassens et al., 2007; Scott et al., 2007; Baptista et al., 2008; Davidsson et al., 2008; Choi et al., 2011]. Within this region, at least 2 genes, *MCTP2* and *NR2F2*, have been shown to be important for cardiogenesis. *NR2F2* plays an important role in angiogenesis, atrial malformations, and lymphatic development in animal models [Aranguren et al., 2011; Pereira et al., 1999]. While *NR2F2* has been implicated in AVSD in some families [Al Turki et al., 2014], *MCTP2* has been shown to be important for left-sided outflow tract development [Lalani et al., 2013b]. It is plausible that there are other dosage-sensitive genes important for human cardiac morphogenesis within this 15q26 interval.

17q21.31 Microdeletion Syndrome

A 500–650-kb heterozygous deletion in chromosome 17q21.31 that includes *KANSL1* or a heterozygous intragenic pathogenic variant in *KANSL1* can cause Koolen-De Vries syndrome (MIM 610443) [Boettger et al., 2012; Koolen et al., 2006, 2012; Steinberg et al., 2012; Zollino et al., 2012]. Approximately 30–40% of individuals are diagnosed with cardiac septal defects [Koolen et al., 2008]. Other cardiac defects such as PS and BAV are also reported [Tan et al., 2009]. The extracardiac features include distinctive facial features such as a long face, upslanting palpebral fissures, epicanthal folds, tubular nose, and large prominent ears. Developmental delay and mild to moderate intellectual disability is frequently observed.

16q24.3 Microdeletion Syndrome

Submicroscopic deletions of 16q24.3 have been reported frequently in individuals with neurodevelopmental concerns [Willemsen et al., 2010, 2012; Sacharow et al., 2012; Lalani et al., 2013a]. The *ANKRD11* gene within the deletion interval has been linked to KBG syndrome (MIM 148050), with common features of intellectual disability, macrodontia, and short stature [Sirmaci et al., 2011; Ockeloen et al., 2015]. In a subset of these individuals, cardiac abnormalities have been reported, including VSD, cleft

mitral valve, aortic root dilatation, and supravalvular pulmonary stenosis [Devriendt et al., 1998; Brancati et al., 2004; Nicolini et al., 2009; Sacharow et al., 2012; Lalani et al., 2013a; Ockeloen et al., 2015]. Although the penetrance of heart defects is uncertain in 16q24.3 deletion at present, cardiac evaluation has now been recommended in young children diagnosed with KBG syndrome [Ockeloen et al., 2015]. The risk of aortic root dilatation has also been shown in at least a few reports [Nicolini et al., 2009; Lalani et al., 2013a], indicating the need for careful echocardiographic evaluation of individuals with *ANKRD11* deletions or point mutations.

Conclusion

In conclusion, cytogenomic abnormalities clearly play an important role in cardiovascular malformations, particularly when associated with extracardiac defects. It is

reasonable to estimate that large cytogenetic and segmental aneusomies of genomic disorders, together account for about 25–30% of all syndromic forms of CHDs in live-born infants. The pervasive use of chromosomal microarray analysis with ever increasing resolution promises to identify much smaller genomic imbalances at the exonic level in genes related to cardiogenesis. Furthermore, the increasing use of exome sequencing and whole genome sequencing will be pivotal in delineating not only rare sequence variants, but also small copy number alterations of coding exons relevant for human cardiac malformations.

Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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