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Congenital heart defects associated with aneuploidy syndromes: New insights into familiar associations

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Abstract

The frequent occurrence of congenital heart defects (CHDs) in chromosome abnormality syndromes is well-known, and among aneuploidy syndromes, distinctive patterns have been delineated. We update the type and frequency of CHDs in the aneuploidy syndromes involving trisomy 13, 18, 21, and 22, and in several sex chromosome abnormalities (Turner syndrome, trisomy X, Klinefelter syndrome, 47,XYY, and 48,XXYY). We also discuss the impact of noninvasive prenatal screening (mainly, cell-free DNA analysis), critical CHD screening, and the growth of parental advocacy on their surgical management and natural history. We encourage clinicians to view the cardiac diagnosis as a "phenotype" which supplements the external dysmorphology examination. When detected prenatally, severe CHDs may influence decision-making, and postnatally, they are often the major determinants of survival. This review should be useful to geneticists, cardiologists, neonatologists, perinatal specialists, other pediatric specialists, and general pediatricians. As patients survive (and thrive) into adulthood, internists and related adult specialists will also need to be informed about their natural history and management.

KEYWORDS

Down syndrome, Klinefelter syndrome, trisomy 13 syndrome, trisomy 18 syndrome, trisomy 22 syndrome, Turner syndrome

1 | INTRODUCTION

Most clinicians, from trainees to medical specialists, are impressed by the common occurrence and often-distinctive pattern of congenital heart defects (CHDs) in many malformation syndromes, especially those with aneuploidy. At a personal level, many of us recall these as career-defining moments, which contributed to our decision to care for people with these syndromes. A leading pediatric cardiology textbook reported a concise review of the occurrence of CHDs in syndromes (using rounded figures) as 50–80% in trisomy 13, 95% in trisomy 18, 50% in Down syndrome and 25% in Turner syndrome (table 3.2 in Goldmuntz & Crenshaw, 2016). In contrast, CHDs are considered rare in Klinefelter syndrome, 47,XYY, and complete trisomy X. Although only a few years have elapsed since that review, an update is appropriate because of additional research and reporting. With tremendous changes in prenatal and postnatal genetic testing (e.g., prenatal chromosome microarray and cfDNA testing), critical CHD (CCHD) newborn screening programs, and the role of parental advocacy, we review these CHD syndrome associations, noting the impact on prevalence, management, and natural history. Finally, we explore whether the most robust chromosome associations can provide insights into the nonsyndromic forms of CHD, and future directions for research.

2 | METHODS

2.1 | Definitions

Aneuploidy is defined as the absence or presence of an additional complete chromosome. We include the following autosomal (trisomy

13, trisomy 18, Down syndrome, and trisomy 22) and sex chromosome abnormality syndromes (45,X; 47,XXX; 47,XXY; 47,XYY; and 48,XXYY) (Tables 1 and 2). Mosaic forms will be briefly noted for trisomy 22 which is usually lethal, but associated with survival in the mosaic form, and 47,XXX which is often associated with a slightly milder form of Turner syndrome.

We define CHDs as structural defects of the intracardiac and vascular structures. For completeness sake, we briefly mention other cardiovascular abnormalities including aortic dilation, mitral valve prolapse, and congenital coronary artery anomalies. Omitted from discussion are hypertension, lymphedema, dyslipidemia, and acquired coronary artery disease, although we recognize that these are common morbidities associated with older individuals in some of the aneuploidy syndromes.

2.2 | Literature

We present an efficient discussion of this topic, citing major review articles instead of historical articles if they included an exhaustive review of major case series and attempted evidence-based analysis.

2.3 | New patients

Limited unpublished data from the authors' individual specialty clinics was noted for specific issues.

3 | SYNDROME REVIEW

Table 1 (autosome aneuploidy) and Table 2 (sex chromosome aneuploidy) review the frequency and types of CHDs. Clinical features for each syndrome can be reviewed in a familiar textbook (Jones, Jones, & Del Campo, 2013). In general, percentages were rounded off, and ranges were used on the tables, unless a specific figure was well-validated.

4 | DISCUSSION

4.1 | Epidemiology of aneuploidy syndromes and CHDs

The population-based birth prevalence of CHDs in the United States has been estimated as approximately 68 per 10,000 livebirths (Bjornard et al., 2013). In France, this increases to 90 per 10,000 when termination of pregnancy and stillbirths are included, decreasing to 78 per 10,000 when chromosome abnormalities are excluded (Khoshnood et al., 2013). The estimated incidence of CHDs is ~2.4 million people (1 million children) (Gilboa et al., 2016).

4.2 | CHD diagnosis and management across the lifespan

Prenatal ultrasonography and fetal echocardiography have had a tremendous impact on decision- making during pregnancy. The presence of a serious CHD often influences parental decision-making to continue pregnancy. Additionally, the success of CHD surgery may be limited by comorbidities and potentially early mortality with a diagnosis of aneuploidy.

The first success in diagnosing Down syndrome in a fetus was reported over 50 years ago (Valenti, Schutta, & Kehaty, 1968). Currently, amniocentesis, chorionic villus sampling, and rarely percutaneous umbilical blood sampling can obtain fetal tissues directly for chromosome studies, metabolic testing, sequencing analyses, or utilize microarray for diagnostic testing (Carlson and Voora, 2017). All procedures to obtain samples are associated with increased risk of miscarriage (Bianchi, Crombleholme, D'Alton, & Malone, 2010).

In contrast to diagnostic testing, genetic screening tests for aneuploidy that do not incur additional pregnancy risk and are now routinely offered to pregnant women. These include early risk assessment (11–14 weeks) with ultrasound and serum markers, and noninvasive prenatal testing (NIPT). Routine first trimester prenatal ultrasound may also detect "soft markers" of aneuploidy such as increased nuchal fold, hypoplastic nasal bone, and other suspicious findings (Bianchi et al., 2019). The second trimester anatomical survey can detect many birth defects including CHDs, with further definition provided by fetal echocardiogram or fetal MRI. Characteristic CHDs may then be followed by diagnostic testing for aneuploidy.

NIPT, especially cell-free DNA (cfDNA) testing, is now recommended for genetic screening for aneuploidy as it is more accurate than the first or second trimester screening (Bianchi et al., 2014). This test screens dosage of cfDNA (fetal placental DNA plus maternal DNA) in a maternal blood sample, thus avoiding risk to the pregnancy. cfDNA screening is typically used to detect 13, 18, 21, X and Y, and usually expanded panels include the 22q11 region which can potentially detect trisomy 22. It should be noted that the positive predictive value of cfDNA screening for 45,X is low (~26%), and any positive test should be confirmed with amniocentesis or neonatal karyotype (Bianchi et al., 2010). The American College of Medical Genetics and Genomics recommends that cfDNA screening replace serum screening for aneuploidy for all pregnant women (Gregg, et al., 2016).

There is insufficient data on prenatal testing to specifically address how many of those affected with aneuploidy come to attention after prenatal echo and vice versa. Data is sparse regarding the overall ascertainment of fetal echocardiography leading to a diagnosis of aneuploidy, and there are few or no studies regarding fetuses with aneuploidy assessed by other means, and their subsequent echocardiographic findings (Pavlicek et al., 2019; Tuuli et al., 2009). In addition to the expanded prenatal diagnosis of aneuploidy syndromes with frequent CHDs, postnatal diagnosis of the most severe CHDs in CCHD newborn screening programs has grown rapidly worldwide (Bakker et al., 2019; Liberman et al., 2014; Oster et al., 2016). Among the current list of 12 CCHDs are 7 primary screening target defects (hypoplastic left heart syndrome, tetralogy of Fallot, truncus arteriosus, pulmonary atresia, tricuspid atresia,

TABLE 1 Congenital heart defects (CHDs) in autosomal aneuploidy syndromes

Syndrome	Trisomy 13	Trisomy 18	Trisomy 22	Trisomy 21 (Down syndrome)
References	Musewe, Alexander, Techima, Smallhorn, & Freedom, 1990 Wylie et al., 1994; Lin et al., 2007 Polli et al., 2014 Kosiv, Gossett, Bai, & Collins, 2017 Domingo, Carey, Eckhauser, Wilkes, & Menon, 2019	Van Praagh et al., 1989 Musewe et al., 1990 Balderston, Shaffer, Washington, & Sondheimer, 1990 Baty et al., 1994; Crider, Olney, & Cragan, 2008 Savva, Walker, & Morris, 2010 Kosiv et al., 2017	Abdelgadir, Nowaczyk, & Li, 2013; Kehinde et al., 2014	Bergstrom et al., 2016; Pfitzer et al., 2018; Freeman et al., 2008 Lange, Guenther, Busch, Hess, & Schreiber, 2007; de Graaf et al., 2015
Prevalence of syndrome per 10,000 livebirths	1.4	1.2–2.3	NA	12.6
[a]Frequency at birth of CHDs in syndrome	[b] ≥ 80%	≥ 90%	75–100%	50%
Types of CHDs				
Laterality defects	Rare	Rare	Not reported	Rare
[c]Conotruncal, all	25–50%	25–50%	5–25%	Rare
D-TGA		Rare		
Other	Rare	Rare	Not reported	Rare
L-transposed great arteries				
Single ventricle				
Single ventricle physiology	20–30%			
Septal defects, all	25–50%		50–75%	5–25%
ASD, secundum	85%	50–75%		
VSD, membranous	40–50%	≥ 90%		
VSD, muscular				
VSD, canal-type				
VSD, malalignment				
PDA	50–60%	85%		
AVSD	10%	10%	Rare	25–50%
AVSD, complete				5–25%
ASD, primum				
TAPVC	Rare	Rare	Not reported	
Valve defects	Polyvalvar dysplasia	Polyvalvar dysplasia	5–25%	Rare
	75%	75–100%		
Outcome of surgery	Decreased in-hospital mortality	Decreased in-hospital mortality	Unknown	Similar age and with similar outcome compared to those without down syndrome
Impact of CHD on life expectancy	Main determinant	Main determinant	Unknown	Main determinant
Other rare cardiac abnormalities	Cor triatriatum		Complex CHDs	Aortic arch abnormality

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; LB, livebirth; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect.

[a]Frequency of CHDs are noted as a range, unless a specific frequency has been well-established.

[b]The frequency of any birth defects in the newborn period is considered a birth prevalence.

[c]Conotruncal defects include truncus arteriosus, interrupted aortic arch, type B, tetralogy of Fallot, malalignment-type ventricular septal defect and double outlet right ventricle.

d-transposition of the great arteries, and total anomalous pulmonary venous connection), plus an additional five defects (coarctation, Ebstein anomaly, interrupted aortic arch, single ventricle, double outlet right ventricle). Ongoing research will continue to quantify the impact of CCHD screening on CHD prevalence estimates, and should note whether aneuploidy syndromes are included.

4.3 | Trisomy 13 and trisomy 18

Although there are substantial differences in the external appearance and malformations of trisomy 13 and trisomy 18, they are often discussed together because of similar challenges in prenatal and postnatal decision-making. Both are associated with multiple birth defects, severe intellectual

TABLE 2 Congenital heart defects in sex chromosome aneuploidy syndromes[a]

Syndrome	Turner syndrome (45, X and other karyotypes)	48, XXYY
References	Mortensen, 2018; Gutmark-Little, 2013; Silberbach, 2018	Tartaglia, 2008
Prevalence of syndrome per 10,000 livebirths	4.0 females	NA
[a]Frequency at birth of CHDs in syndrome	23–50%	18/93 (19.6%)
Types of CHDs		
Laterality defects	Rare	N/A
Conotruncal, all	Rare	N/A
Other (L-transposed great arteries, single ventricle)	Rare	Rare (1%)
L-transposed great arteries		
Single ventricle		
Simple shunts:		5–25%
ASD, secundum	ASD (unspecified), rare	VSD (unspecified)
VSD, membranous	VSD (unspecified), rare	ASD (unspecified)
VSD, muscular		
PDA		
AVC,/AVSD	Rare	N/A
AVC, AVSD, complete		
ASD, primum		
TAPVC	Rare	N/A
	PAPVC, 5–25%	
Valve defects	BAV 25%	Rare
	Aortic stenosis	Mitral valve prolapse
	MV stenosis	Pulmonic stenosis
	HLHS	
Outcome of surgery	Similar risk as non-TS outcomes with exception of PAPVR and HLHS (increased mortality)	N/A
Impact of CHD on life expectancy	Accounts for 50% of threefold increase in early death; life expectancy reduced by 13 years	N/A
Other cardiac abnormalities	ETA, 25–50% Aortic dilation, 25–40% Coarctation, 5–25% Congenital coronary artery anomalies, 5–25% PLSVC, 5–25%	

Abbreviations: AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; CHD, congenital heart defect; ETA, elongation of the transverse aorta; HLHS, hypoplastic left heart syndrome; LB, livebirth; PLSVC, persistent left superior vena cava; TAPVC, total anomalous pulmonary venous connection.
[a]Klinefelter syndrome and 47,XYY were omitted because of the rarity of CHDs.
[b]Frequency of CHDs are noted as a range, unless a specific frequency has been well-established.
[c]Conotruncal defects include truncus arteriosus, interrupted aortic arch, type B, tetralogy of Fallot, malalignment-type ventricular septal defect and double outlet right ventricle.

disability, and high mortality. The leading parent support group welcomes families with both trisomy syndromes (and a few related disorders) (Support of Families of Trisomy, S.O.F.T.). The type and frequency of CHDs in these aneuploidy syndromes has been well described over many decades (Lin et al., 2007; Musewe et al., 1990; Polli et al., 2014), with superior delineation of morphologic types in autopsy studies (Van Praagh et al., 1989). As noted in Table 1, simple shunts are common in both disorders. However, conotruncal CHDs, atrioventricular septal defect (AVSD), and polyvalvar dysplasia create a cardiac phenotype that can lead to clinical diagnosis when associated with various noncardiac defects, especially for trisomy 18 (Van Praagh et al., 1986). Similar to what is observed in Down syndrome, pulmonary vascular changes increase mortality (Tahara, Shimozono, Nitta, & Yamaki, 2014). The prenatal ultrasonographic detection of a complete AVSD tends to prompt reflex consideration of Down syndrome, but these trisomies must also be included. The presence of a serious CHD may contribute to the decision to terminate pregnancy; some parents who continued their pregnancies reported feeling pressure (Guon, Wilfond, Farlow, Brazg, & Janvier, 2013).

Although a conservative approach (palliative measures) has been the traditional guideline for infants with trisomy 18, more clinicians (48%) were willing to discuss surgery in one study (Kaulfus et al., 2019). There is a growing body of literature analyzing outcome, the impact of natural history, CHDs, surgery, and attitudes of parents and providers (Baty et al., 1994; Domingo et al., 2019; Kaneko et al., 2008; Kosiv et al., 2017; Lakovschek, Streubel, & Ulm, 2011; Meyer et al., 2016; Weaver, Starr, Austin, Stevenson, & Hammel, 2018). Recent outcome studies provide strong support for consideration of CHD surgery (Kosiv et al., 2017), but the impact on survival after 1 year is debated. Follow-up after cardiac surgery for trisomy 13 and 18 has focused on in-hospital mortality and survival up to two years; longer term studies are not available because of rarity of survivors. Parents responded with often emotional insights in a survey about their decision to continue pregnancy after prenatal diagnosis, and the power of a supportive social network (Guon et al., 2013; Janvier, Farlow, & Wilfond, 2012). Rather than advising a single guideline for all patients, decision-making about surgery for CHDs in trisomy 13 and trisomy 18 should take in to account numerous factors for each family (Domingo et al., 2019; Jenkins & Roberts, 2017).

Mosaicism for trisomy 13 was generally associated with a less severe outcome among almost 50 reported patients (Chen et al., 2017; Griffith et al., 2009; Hsu & Hou, 2007; Wieser, Wohlmuth, Rittinger, Fischer, & Wertaschnigg, 2015). Although some patients have a milder phenotype and favorable outcome, there is no consistent correlation between the percentage of trisomy 13 cells and the severity of defects and intellect. Long-term outcome studies with neuropsychologic evaluations have not been reported. In the most detailed review, CHDs were noted in 74%, involving mostly atrial septal defects and ventricular septal defects, and a single case with tetralogy of Fallot (Griffith et al., 2009).

4.4 | Down syndrome

There is abundant literature and ongoing research about the type and frequency of CHDs in Down syndrome (Versacci, DiCarlo, Digilio, & Marino, 2018). The American Academy of Pediatrics recommends that all patients with Down syndrome have a postnatal echocardiogram, to be read by a pediatric cardiologist regardless of whether a fetal echocardiogram was performed. Referral to a pediatric cardiologist is recommended for any infant whose results are abnormal (Bull et al., 2011). In the future this may change, as recent evidence shows that complex CHDs were not missed on fetal echocardiography performed on patients with Down syndrome, that is, postnatal echocardiography did not detect additional CHDs (Cooper et al., 2019). In adolescence and into adulthood, there is a risk for valvular disease, and echocardiography with Doppler should be considered in any patients with symptoms (such as increasing fatigue, shortness of breath, exertional dyspnea, or a new murmur or gallop) (Bull et al., 2011). Valve disease was among the mostly mild abnormalities detected on a cross-sectional study of 149 subjects ages 10–20. Nine (6%) had new echocardiographic findings, including transitional AVSD in one subject (Clauss et al., 2019). Studies of CHDs in Down syndrome have not consistently shown disparity by sex (Morales-Demori, 2017; Santoro, Coi, Spadoni, Bianchi, & Pierini, 2018), but have been shown to differ by race with higher rates of AVSD in black patients with Down syndrome (Freeman et al., 2008).

The natural history and outcome of intervention for CHDs in patients with Down syndrome varies. The presence of a CHD in Down syndrome increases the chance of pulmonary hypertension (Bush et al., 2018) and increases neonatal mortality (Cua, Haque, Santoro, Nicholson, & Backes, 2017). Patients with Down syndrome and single ventricle palliation are at high risk for procedural and long-term mortality (Peterson et al., 2019). However, many neonates with Down syndrome and CHD have surgical repair at similar age and with similar outcomes compared to those without Down syndrome (Lange et al., 2007). The median age at surgery was 3.3 months for primary AVSD repair and did not differ in patients with Down syndrome (Burstein et al., 2019). Long-term developmental outcomes at school age do not differ between those with Down syndrome and CHD and those without CHD (Morales-Demori, 2017).

4.5 | Trisomy 22

Complete, nonmosaic trisomy 22 is frequent (11–15%) among of spontaneous miscarriages with aneuploidy, and ~5% of all spontaneous miscarriage (Ford, Wilkin, Thomas, & McCarthy, 1996; Menasha, Levy, Hirschhorn, & Kardon, 2005). Live-born children with this condition are rare, primarily published as case reports. Complete trisomy 22 typically leads to neonatal death (mean survival 4 days of life), with the maximum reported age of 3 years (Heinrich et al., 2012). A review of live-born patients with complete trisomy 22 noted that 92% (24/26) had CHDs (Kehinde et al., 2014). A review of the literature identified septal defects (Kontomanolis, Pandya, & Limperis, 2010; Ma, Ouyang, Hao, Zhao, et al., 2018; McPherson & Stetka, 1990; Naicker & Aldous, 2014), conotruncal anomalies (Stratton et al., 1993; Tinkle, Walker, Blough-Pfau, Saal, & Hopkin, 2003; Xu et al., 2019), aortic arch anomalies (Bacino et al., 1995), hypoplastic right heart (Bacino et al., 1995), and complex CHDs (Bacino et al., 1995; Tonni, Ventura, Pattacini, Bonasoni, & Ferrari, 2012). This is similar to a

prenatal series of 5 patients combined with 10 from the literature (Stressig, Körtge-Jung, Hickmann, & Kozlowski, 2005).

Mosaic trisomy 22 is rare, with at least 22 cases reported. Various types of CHDs were noted in 76% of a series of 21 patients (Abdelgadir et al., 2013; Kalyina et al., 2019). It is difficult to discern the cause of early mortality in patients with complete or mosaic trisomy 22, whether it is cardiac in nature, or some other etiology. The number of published cases is small, and long term follow-up is not available.

4.6 | Turner syndrome

Turner syndrome has a major impact on a multitude of systems, and appropriate diagnosis and management of congenital and acquired cardiovascular disease is crucial. As noted on Table 1, CHDs of the left side of heart predominate, ranging from bicuspid aortic valve (BAV) and coarctation of the aorta, to hypoplastic left heart syndrome. An echocardiogram is recommended for all patients at diagnosis, even if prenatal testing (fetal echocardiography) did not detect a CHD. Thereafter, imaging should be obtained at regular intervals following evidence-based guidelines (Silberbach et al., 2018). In addition to echocardiography with Doppler, cardiac magnetic resonance imaging is necessary to image the entire arch, preferably, at an age when sedation is not needed (Guttmark-Little and Backeljauw, 2013; Silberbach et al., 2018). Aortic dilatation is common in individuals with BAV, whether they have Turner syndrome. In women with Turner syndrome, the reported range of prevalence of dilatation is wide (11–48%). This is attributable to differences in imaging (echocardiography, MRA, CTA) and attempts to adjust this measurement in light of short stature. Aortic dissection is a rare but feared complication in this patient population, occurring at greater frequency and significantly younger age than the general population, particularly during pregnancy. Those women attempting pregnancy, typically via assisted reproductive technologies, should be closely monitored with cardiac imaging, before, during, and after pregnancy (Donadille, Bernard, & Christin-Maitre, 2019). Congenital coronary artery anomalies are common in Turner syndrome women (20%), and their anatomy should be delineated in the planning of aortic surgery (Viuff et al., 2016). In all Turner syndrome patients, blood pressure screening and intervention is mandatory as hypertension prevalence increases with age and is thought to be a risk factor for aortic dilatation and dissection. Electrocardiography is necessary given that conduction defects affect 50%, including QT prolongation.

Of 226 individuals evaluated in the MGH Turner syndrome clinic, 76 (34%) had a CHD (aortic dilatation excluded), with a similar frequency in patients less than or equal to 18 years (36/96, 38%) and those older than 18 years (40/130, 31%). Among this group, 50 of 226 (22%) individuals had a BAV, with equal occurrence regardless of age.

4.7 | Trisomy X (47,XXX)

Congenital heart defects are not a typical feature of 47,XXX syndrome, and have been omitted from Table 2. In a clinical series of 16 patients with malformations (Haverty, Lin, Simpson, Spence, & Martin, 2004), and a population-based prevalence study from Europe, no CHDs were noted (Boyd et al., 2011).

However, CHDs may occur in individuals with a form of Turner syndrome mosaicism involving 47,XXX and 45,X. The phenotype varies greatly, and case series have reported hypoplastic left heart syndrome (Sybert, 2002), and regurgitant mitral and tricuspid valves (Tang, Lin, Guo, & Yu, 2019).

4.8 | Klinefelter syndrome (47,XXY and variants)

Klinefelter syndrome (47,XXY) is the most common aneuploidy syndrome, affecting ~1 in 600 males. Individuals with Klinefelter syndrome are generally not considered to be at increased risk for major structural malformations, including CHDs. Some historical studies showed a small increase in morbidity or mortality associated with CHD and other congenital anomalies (Gravholt et al., 2018). A concern about ascertainment bias is often noted, as it is estimated that up to 75% of cases of Klinefelter syndrome are undiagnosed, while those with malformations are more likely to undergo genetic diagnostic testing. In the MGH Klinefelter Syndrome Clinic, we have seen individuals with assorted CHDs in whom Klinefelter syndrome was detected because chromosomal testing was performed as part of the diagnostic evaluation. Given the fact that Klinefelter syndrome is the most common aneuploidy and that CHDs are relatively common in the general population, we hypothesize that these may be unrelated incidental findings.

Small studies have suggested a possible association between Klinefelter syndrome and a shortened QTc interval (Jørgensen et al., 2015), though the clinical relevance of this remains unclear. Overall, most clinicians do not routinely recommend screening for CHD or arrythmias in all individuals with a diagnosis of typical Klinefelter syndrome.

4.9 | 47,XYY

Similar to Klinefelter syndrome, the diagnosis of 47,XYY is not considered a risk factor for CHDs. In a population-based study in Denmark, an increased risk of "cardiovascular disease" was reported, but CHDs were not specified (Stochholm, Juul, & Gravholt, 2010). This may reflect an increased incidence of general adult-onset cardiovascular disease in this population, which is likely to be multifactorial in its etiology.

4.10 | Higher order male sex chromosome aneuploidies

The rate of CHDs and other malformations appears increased in individuals with 48,XXYY, 48,XXXY, 49,XXXXY, and other higher order male sex chromosome aneuploidies (Peet, Weaver, & Vance, 1998;

Tartaglia et al., 2008). However, given the rarity of these syndromes, large studies have not been performed. The best estimates come from studies of patients with 48,XXYY, where the incidence of CHDs has been estimated at 19%, with ventricular septal defects being the most common type (Tartaglia et al., 2008).

4.11 | Genetic basis and developmental insights

The development of the human heart is a complex process that takes place between 3 and 8 weeks of embryonic development. The different regions of the heart (atria, ventricles, atrioventricular canal, outflow tract, aortic arch) have distinct embryonic origins, and their differentiation and morphogenesis is orchestrated by a multitude of developmental signaling pathways (Epstein, 2010; Zaidi and Brueckner, 2019). Errors in these mechanisms are believed to underlie CHDs. The high incidence of CHDs in many genetic syndromes, including aneuploidies, is therefore not surprising.

The occurrence of a rare defect in a common syndrome can appear as a tantalizing signal about the chromosome location of causative genes. The association of specific subtypes of CHDs with a given genetic syndrome may reflect the relative importance of the perturbed gene(s) for that syndrome in the development of that region of the heart. Understanding such associations has the potential to provide significant insights into the mechanisms of nonsyndromic causes of CHDs. Classic examples include the interplay between the pharyngeal endoderm, the cardiac neural crest, and the secondary heart field, which is thought to underlie the cardiac outflow and aortic arch defects in 22q11 deletion syndrome, and the role of the Ras-MAPK signaling cascade in the endocardial cushions, which has been hypothesized to explain the valvular defects seen in Noonan syndrome (Calcagni et al., 2017). In the case of aneuploidy syndromes, however, making a case for such a mechanism is far more complex given the fact that so many genes have the potential to be perturbed. As discussed below, this hypothesis has been explored for Down syndrome and Turner syndrome.

Analysis of patients with partial trisomy 21 identified a candidate region for CHDs (Pelleri et al., 2017). Next-generation sequencing implicated candidate genes for CHD in patients with Down syndrome (Alharbi et al., 2018). These and other studies suggest that the prevalence of CHDs, and AVSD, in particular, in Down syndrome is likely multifactorial and related to a complex interplay between genes on chromosome 21 with variants elsewhere in the genome. Initial genome-wide association study of patients with Down syndrome and AVSD identified regions of interest, and a few common genetic variants of large effect size, but which did not account for risk for AVSD in Down syndrome (Ramachandran et al., 2015). Study of copy number variants in patients with Down syndrome and AVSD or CHD, demonstrated the complex, multifactorial nature of AVSD in Down syndrome and supported that Down syndrome-associated AVSD is likely heterogenous (Ramachandran et al., 2015; Rambo-Martin et al., 2018).

With an X aneuploidy syndrome, the hypothesis of a dosage effect can be evaluated to some degree. Women with 45,X Turner syndrome have more CHDs compared to women with Trisomy X and males with 47,XXY. Women with the lowest level of 45,X mosaicism (<20%) are generally thought to have fewer CHDs than those with complete 45,X. Whereas 70% of all patients with BAV are male, the association (~30%) with Turner syndrome is striking. These observations suggest that more than one X chromosome is protective. However, half of women with Turner do not have a CHD, which may be due to an interaction of the X chromosome with autosomal variants (Prakash et al., 2016). To this point, very recent exome sequencing studies suggest an association of aortopathy and BAV with hemizygosity of *TIMP1* (Xp11.3) and variants of its autosomal paralogue *TIMP3* (22q12.3). The products of these genes are members of the tissue inhibitor of matrix metalloproteinase family, known inhibitors of matrix metalloproteinases which themselves degrade the extracellular matrix. Their findings show a 20-fold risk of having a BAV in the setting of only having one copy of *TIMP1* (i.e., Turner syndrome) and a specific variant of *TIMP3* (Corbitt et al., 2018; Corbitt, Gutierrez, Silberbach, & Maslen, 2019).

Despite these advances, the molecular mechanisms for most CHDs in both Down syndrome and Turner syndrome, as well as other aneuploidies, remain largely unclear. More evidence is necessary to establish the contribution of autosomal genetic variants. For Turner syndrome, these exciting studies redirect prior efforts to interrogate Xp for causative genes (Bondy et al., 2013).

In conclusion, CHDs in aneuploidy syndrome are never pathognomonic as individual defects, but in the presence of noncardiac features, distinctive patterns of CHDs can assist in diagnosis, even in fetal life. Timely diagnosis of CHDs and appropriate follow up into adulthood in aneuploidy syndromes is crucial to improve outcomes in these often complex and multi-system conditions. Multidisciplinary care in both the prenatal and postnatal setting is an essential part of maternal-fetal medicine, prenatal and cardiogenetics clinics, as well as the specialty clinics dedicated to the specific aneuploidies such as Down syndrome and Turner syndrome (Lin et al., 2019). Early observations about dosage effect and chromosome locus have not yet yielded pathogenic genes, though further research will hopefully provide clues to the genetic underpinnings of both syndromic and nonsyndromic CHDs.

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CONFLICT OF INTEREST

These authors have no conflict of interest to declare.

WEBSITES

Trisomy 13, Trisomy 18

National Library of Medicine Genetics Home Reference https://ghr.nlm.nih.gov/condition/trisomy-18

Support of Families with Trisomy and Related Chromosome Disorders (SOFT) https://trisomy.org/

Trisomy 21

National Down Syndrome Society (NDSS) https://www.ndss.org/

National Down Syndrome Congress (NDSC) https://www.ndsc.org/

MGH Down Syndrome Program http://www.massgeneral.org/downsyndrome

DS-Connect (the Down Syndrome Registry hosted by the National Institutes of Health) https://dsconnect.nih.gov/

Trisomy 22

Chromosome 22 Central http://c22c.org/

Turner syndrome

MGH Turner Syndrome Clinic https://www.massgeneral.org/children/services/treatmentprograms.aspx?id=1682

Turner Syndrome Society of the United States http://www.turnersyndrome.org/

Turner Syndrome Global Alliance http://tsgalliance.org/

Turner Syndrome Foundation, Inc. www.TSFUSA.org

National Library of Medicine Genetics Home Reference https://ghr.nlm.nih.gov/condition/turner-syndrome

Turner Syndrome Society of the United States (TSSUS): Clinical Practice Guidelines for the Care of Girls and Women with Turner syndrome (Gravholt et al., 2017), and Brief Synopsis for Turner Syndrome Girls and Women and for their Parents/Caregivers/Families. http://www.turnersyndrome.org/

UpToDate. Clinical manifestations and diagnosis of Turner syndrome (Philippe Backeljauw, MD).

http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-turner-syndrome

Klinefelter syndrome (XXY and related karyotypes)

National Library of Medicine Genetics Home Reference https://ghr.nlm.nih.gov/condition/klinefelter-syndrome

AXYS: association for X and Y chromosome variations http://www.genetic.org

MGH Klinefelter syndrome clinic https://www.massgeneral.org/children/services/treatmentprograms.aspx?id=2069

DATA AVAILABLITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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