

# Genetic Basis of Human Congenital Heart Disease

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Congenital heart disease (CHD) is the most common major congenital anomaly with an incidence of ~1% of live births and is a significant cause of birth defect–related mortality. The genetic mechanisms underlying the development of CHD are complex and remain incompletely understood. Known genetic causes include all classes of genetic variation including chromosomal aneuploidies, copy number variants, and rare and common single-nucleotide variants, which can be either *de novo* or inherited. Among patients with CHD, ~8%–12% have a chromosomal abnormality or aneuploidy, between 3% and 25% have a copy number variation, and 3%–5% have a single-gene defect in an established CHD gene with higher likelihood of identifying a genetic cause in patients with nonisolated CHD. These genetic variants disrupt or alter genes that play an important role in normal cardiac development and in some cases have pleiotropic effects on other organs. This work reviews some of the most common genetic causes of CHD as well as what is currently known about the underlying mechanisms.

Congenital heart disease (CHD) is the most common major congenital anomaly with an incidence of ~1% of live births (Hoffman and Kaplan 2002; Calzolari et al. 2003). CHD is a significant cause of birth defect–related mortality (Hanna et al. 1994; Lee et al. 2001; Hoffman and Kaplan 2002; Calzolari et al. 2003; Centers for Disease Control and Prevention (CDC) 2007; van der Linde et al. 2011; Gilboa et al. 2016). CHD encompasses any malformation of the cardiovascular system present at birth, and there are many subtypes ranging from relatively simple lesions such as atrial and ventricular septal defects to complex lesions such as hypoplastic left heart syndrome (HLHS) in which there

are underdeveloped left-sided cardiac structures and only a single functioning ventricle. The high concordance in monozygotic twins, the increased risk of recurrence in first-degree relatives compared with the general population, and genetic syndromes associated with specific types of CHD all suggest a genetic component to CHD in at least some cases (Nora et al. 1988). The genes and genetic mechanisms underlying CHD are complex and remain incompletely understood, but our understanding has improved significantly over the past decade. All classes of genetic variation including chromosomal aneuploidies, copy number variants (CNVs), and rare and common *de novo* and inherited single-nucleo-

tide variants (SNVs) contribute to CHD (Thienpont et al. 2007; Erdogan et al. 2008; Southard et al. 2012; Gelb and Chung 2014). These genetic variants disrupt or alter genes that play an important role in normal cardiac development. Although many of the genes and mutations that increase the risk of developing CHD have been identified, only ~20%–30% of individuals with CHD have an identifiable single genetic factor, and this yield varies significantly by cardiac lesion and whether there are additional medical features besides CHD (Grech and Gatt 1999; Gelb 2004; Cowan and Ware 2015; Patel et al. 2016). This work reviews the most common genetic causes of CHD as well as the known genetic mechanisms.

## OVERVIEW OF CHD

CHD is the most common birth defect affecting ~1% of live births, or up to 3% of live births in studies that include bicuspid aortic valve (BAV) (Hoffman and Kaplan 2002; Calzolari et al. 2003; Tutar et al. 2005; van der Linde et al. 2011; Egbe et al. 2014). CHD encompasses a wide spectrum of defects, with varying physiologic consequences. More severe lesions that require multiple surgeries have an incidence of ~0.1% of live births (Bernier et al. 2010). Despite significant advances in clinical care, CHD remains the leading cause of birth defect-related mortality (Boneva et al. 2001; Lee et al. 2001; Marelli et al. 2007; Gilboa et al. 2010; Khairy et al. 2010). Data from the Metropolitan Atlanta Congenital Heart Defects Program showed a 1-yr survival of 83% for patients with critical CHD (Oster et al. 2013). For those patients who survive through infancy, there are still significant lifelong morbidities (Oster et al. 2013; Agarwal et al. 2014).

## EVIDENCE FOR THE GENETIC BASIS OF CHD

The etiology of CHD is multifactorial. A genetic or environmental cause can be identified in ~20%–30% of all cases, and that number is changing as new methods of testing become available (Grech and Gatt 1999; Gelb 2004; Cowan and Ware 2015; Patel et al. 2016).

The overall incidence of CHD is similar between males and females; however, there are differences by type of CHD with males having a slightly higher incidence of more severe lesions (Sampayo and Pinto 1994; Moons et al. 2009). There are also differences in incidence of specific lesions based on race and ethnicity. Patent ductus arteriosus (PDA) and ventricular septal defects (VSDs) are more common in Europeans, whereas atrial septal defects (ASDs) are more common in Hispanics (Fixler et al. 1990; Egbe et al. 2014). The differences observed based on gender and race suggest that genetics play an important role in the development of specific types of CHD, with certain populations having increased genetic susceptibility.

The risk of CHD recurrence in the offspring of an affected parent is between 3% and 20% depending on the lesion. Recurrence risk in the offspring of women with CHD is about twice as high as the recurrence in offspring of men with CHD (Burn et al. 1998). A study from Northern Ireland found that the risk of recurrence of CHD for siblings was 3.1%, and siblings had an increased risk of extracardiac anomalies even in the absence of CHD (Hanna et al. 1994). Other studies have shown similar risk of recurrence among siblings; more severe types of CHD have higher recurrence rates (Calcagni et al. 2006; Øyen et al. 2009; Brodwall et al. 2017). Lesions with the highest recurrence risk are heterotaxy (HTX), right ventricular outflow tract obstruction, and left ventricular outflow tract obstruction (Loffredo et al. 2004). Approximately one-half of siblings with recurrent CHD have a different lesion, supporting the theory that the etiology of CHD is multifactorial (Oyen et al. 2010). Table 1 describes the estimated recurrence risk for CHD by lesion and affected family member.

Overall, twins have an increased risk of CHD compared with singleton pregnancies, which is thought to be the result of vascular changes related to a shared placenta (Manning and Archer 2006; Herskind et al. 2013; Best and Rankin 2015). A population-based Taiwanese study calculated the adjusted risk ratio for CHD with an affected relative and found that it was 12.03 for a twin, 4.91 for a first-degree relative, and 1.21 for

**Table 1.** Risk of recurrence for common isolated congenital heart disease

Lesion	Father affected (%)	Mother affected (%)	One sibling affected (%)	Two siblings affected (%)
ASD	1.5–3.5	4–6	2.5–3	8
AVSD	1–4.5	11.5–14	3–4	10
VSD	2–3.5	6–10	3	10
AS	3–4	8–18	2	6
PS	2–3.5	4–6.5	2	6
TOF	1.5	2–2.5	2.5–3	8
CoA	2–3	4–6.5	2	6
HLHS	21	21	2–9	6
D-TGA	2	2	1.5	5

Data adapted from Cowan and Ware (2015).

See Nora et al. (1988); Nora (1994); Calcagni et al. (2006); Hinton et al. (2007).

(AS) Aortic stenosis, (ASD) atrial septal defect, (AVSD) atrioventricular septal defect, (CoA) coarctation of the aorta, (D-TGA) d-loop transposition of the great arteries, (HLHS) hypoplastic left heart syndrome, (PS) pulmonary stenosis, (TOF) tetralogy of Fallot, (VSD) ventricular septal defect.

a second-degree relative. They determined that the phenotypic variance of CHD was 37.3% for familial transmission and 62.8% for non-shared environmental factors (Kuo et al. 2018). In a large Norwegian birth cohort study, the adjusted relative risk ratio of CHD for siblings of a child with CHD was 14.0 for same-sex twins, 11.9 for opposite-sex twins, 3.6 for full siblings, and 1.5 for half siblings (Brodwall et al. 2017). These data suggest a genetic component, although there is also higher incidence of CHD in dizygotic twins compared with non-twin siblings suggesting an environmental component in addition (Caputo et al. 2005).

## GENETIC TESTING IN CONGENITAL HEART DISEASE

When a genetic cause of CHD is identified, this knowledge can assist clinical management by identifying other organ systems that should be screened for structural or functional problems and by facilitating predictions about future complications and prognosis (Pierpont et al. 2007). Identification of a genetic etiology, which may be inherited or de novo, allows for more accurate estimation of recurrence risk. Despite the importance of identifying a genetic cause in patients with CHD, current genetic testing practices are quite variable (Cowan and Ware 2015).

Genetic testing for a fetus with CHD can start in the prenatal period with either chorionic

villus sampling (CVS) at 10–11 wk gestation or amniocentesis after 15–16 wk gestation to obtain placental/fetal DNA. More recently, noninvasive prenatal testing (NIPT) has been used to obtain fetal cell-free DNA from maternal blood to screen for aneuploidies and common deletions or duplications, most notably 22q11.2 deletion syndrome (Wapner et al. 2015; Grace et al. 2016; Dugoff et al. 2017; Gil et al. 2017). NIPT is a screening test, and abnormal findings require confirmatory testing using chorionic villi, amniocytes, or postnatal testing.

Clinical genetic testing in infants with CHD using karyotyping, fluorescence in situ hybridization (FISH), and chromosome microarray analysis (CMA) has an overall clinical yield of 15%–25% with a higher likelihood of finding a genetic diagnosis in patients with dysmorphic facial features and extracardiac anomalies (Breckpot et al. 2010, 2011; Baker et al. 2012; Al Turki et al. 2014; Connor et al. 2014; Ahrens-Nicklas et al. 2016). Karyotyping is a test performed on metaphase chromosomes that allows for the identification of aneuploidies and large chromosomal rearrangements. CMA is used to detect CNVs across the genome and can reliably detect deletions or duplications as small as ~100,000 nucleotides. If a specific deletion or duplication syndrome is suspected, FISH can be used and allows for rapid turnaround and focused testing. It is most commonly used to test for 22q11.2 deletion.

Recent decreases in sequencing cost allow for more comprehensive assessment of the genome and have powered gene panel testing, whole-exome sequencing (WES), and whole-genome sequencing (WGS). For each of these tests, significant bioinformatics analysis is required after sequencing to determine the significance of the variant in each individual patient, often using data from family members to assess for the inheritance status and segregation with CHD in the family. WES targets the protein-coding regions, which comprise ~1.5% of the genome, and has been particularly useful in assessing patients with CHD and extracardiac features (Gelb et al. 2013; Glessner et al. 2014; Homsy et al. 2015; LaHaye et al. 2016; Sifrim et al. 2016). WES is used increasingly in clinical practice because CHD is so genetically heterogeneous and because our knowledge of CHD genetics is incomplete (Bamshad et al. 2011). The yield of WES for CHD in the clinical setting of a single large genetic reference laboratory was 28% (Retterer et al. 2016). The impact of having these genetic diagnoses on clinical care has not yet been elucidated. WGS sequences the entire genome including noncoding regions, but studies have not yet shown the additional clinical utility of WGS in patients with CHD, although this is an area of active investigation.

All of the tests described have limitations in terms of their detection and potential to identify variants of unknown significance, which may be difficult for both clinicians and patients to interpret. For this reason, it is important for cardiologists, medical geneticists, and genetic counselors to work together to decide the most appropriate testing and to interpret the results and explain them to the patient and their family.

## CHROMOSOMAL ANEUPLOIDIES

Aneuploidy is an abnormal number of chromosomes such as a trisomy. The risk of most aneuploidies increases with increasing maternal age. In the Baltimore–Washington Infant study, chromosomal abnormalities were identified >100 times more frequently in patients with CHD compared with normal controls with a total of 12.9% of CHD cases having chromosomal

abnormalities (Ferencz et al. 1989). The following sections review some of the most common aneuploidy syndromes associated with CHD. Additional data on prevalence, types of CHD, and associated features for each syndrome, as well as details on additional syndromes, are included in Table 2.

## Down Syndrome

Down syndrome is the most common chromosomal abnormality found in patients with CHD and is usually caused by complete trisomy 21 (Hartman et al. 2011; de Graaf et al. 2016, 2017). CHD is found in 40%–50% of patients with Down syndrome, most commonly atrioventricular septal defect (AVSD) in ~40% followed by VSD, ASD, PDA, and tetralogy of Fallot (TOF) (Freeman et al. 2008; Allen et al. 2013).

CHD is a common cause of mortality in patients with Down syndrome, contributing to 13% of deaths in childhood and 23% of deaths in adulthood (Bittles et al. 2007). Some studies suggest that individuals with Down syndrome have worse outcomes after congenital heart surgery compared with those with no chromosomal abnormalities (Reller and Morris 1998; Landis et al. 2016). More recently, studies have shown equal or decreased risk of in-hospital mortality for patients with Down syndrome undergoing repair of CHD compared with patients with normal karyotypes except among patients with single ventricle physiology (Anaclerio et al. 2004; Formigari et al. 2004; Michielon et al. 2006, 2009; Lange et al. 2007; Evans et al. 2014; St Louis et al. 2014; Tumanyan et al. 2015). Although Down syndrome does not seem to confer an increased risk of mortality for most patients undergoing CHD repair, there is increased morbidity including increased length of stay, frequency of pulmonary hypertension, and other postoperative complications (Malec et al. 1999; Ip et al. 2002; Fudge et al. 2010; Lal et al. 2013).

## Trisomy 18 and 13

Many fetuses with trisomy 13 or 18 do not survive to birth; however, among those who do, CHD is common. Ninety-five percent of pa-

**Table 2.** Common aneuploidies and copy number variants associated with syndromic congenital heart disease

Syndrome	Genetic change	Prevalence in live births	Common clinical features	Associated congenital heart disease	Patients with the condition who have CHD (%)	References
<b>Aneuploidies</b>						
Down syndrome	Trisomy 21	1 in 800	Hypotonia, flat facies, epicanthal folds, up-slanting palpebral fissures, single palmar transverse crease, small ears, skeletal anomalies, intellectual disability	AVSD, VSD, ASD, PDA (less commonly TOF, D-TGA)	40–50	Bull et al. 2011; Allen et al. 2013; de Graaf et al. 2016, 2017
Patau syndrome	Trisomy 18	1 in 8000	Glenched hands, short sternum, limb anomalies, rocker-bottom feet, micrognathia, esophageal atresia, severe intellectual disability	PDA, ASD, VSD, AVSD, polyvalvular dysplasia, TOF, DORV	80–95	Van Praagh et al. 1989; Musewe et al. 1990; Embleton et al. 1996; Springett et al. 2015
Edward syndrome	Trisomy 13	1 in 20,000	Midline facial defects, scalp defects, forebrain defects, polydactyly, hypotelorism, microcephaly, deafness, skin and nail defects, severe intellectual disability	PDA, ASD, VSD, HLHS, laterality defects	57–80	Musewe et al. 1990; Wyllie et al. 1994; Lin et al. 2007; Goldstein and Nielsen 2008; Springett et al. 2015
Turner syndrome	45, X	1 in 2500	Short stature, broad chest with wide-spaced nipples, webbed neck, congenital lymphedema, normal intelligence or mild learning disability	BAV, CoA, PAPVR, HLHS	35	Sybert and McCauley 2004; Gravholt et al. 2017
<b>Microdeletions/duplications</b>						
1p36 deletion	1p36 deletion	1 in 5000	Growth deficiency, microcephaly, deep-set eyes, low-set ears, hearing loss, hypotonia, seizures, genital anomalies, intellectual disability	ASD, VSD, PDA, BAV, PS, MR, TOF, CoA	70	Battaglia et al. 2008a
1q21.1 deletion	1q21.1 deletion	Unknown (rare)	Short stature, cataracts, mood disorders, autism spectrum disorder, hypotonia	PDA, VSD, ASD, TOF, TA	33	Bernier et al. 2016
1q21.1 duplication	1q21.1 duplication	Unknown (rare)	Autism spectrum disorder, attention deficit hyperactivity disorder, intellectual disability, scoliosis, short stature, gastric ulcers	TOF, D-TGA, PS	27	Bernier et al. 2016

*Continued*

Table 2. Continued

Syndrome	Genetic change	Prevalence in live births	Common clinical features	Associated congenital heart disease	Patients with the condition who have CHD (%)	References
1q41-q42 deletion	1q41q42 deletion	Unknown (rare)	Developmental delay, frontal bossing, deep-set eyes, broad nasal tip, cleft palate, clubfeet, seizure, short stature, congenital diaphragmatic hernia	BAV, ASD, VSD, TGA	40–50	Rosenfeld et al. 2011
2q31.1 deletion	2q31.1 deletion	Unknown (rare)	Growth retardation, microcephaly, craniosynostosis, cleft lip/palate, limb anomalies, genital anomalies	VSD, ASD, PDA, PS	38	Mitter et al. 2010; Dimitrov et al. 2011
2q37 deletion	2q37 deletion	Unknown (rare)	Short stature, obesity, intellectual disability, sparse hair, arched eyebrows, epicanthal folds, thin upper lip, small hands and feet, clinodactyly, CNS anomalies, ocular anomalies, gastrointestinal anomalies, renal anomalies, GU anomalies	CoA, ASD, VSD	14–20	Casas et al. 2004; Falk and Casas 2007
3p25 deletion	3p25 deletion	Unknown (rare)	Growth deficiency, microcephaly, hypotonia, polydactyly, renal anomalies, intellectual disability	AVSD, VSD	33	Shuib et al. 2009
Wolf-Hirschhorn syndrome	4p16.3 deletion	1 in 20,000–1 in 50,000	Feeding difficulty, seizures/epilepsy, microcephaly, wide spaced eyes, broad nasal bridge, intellectual disability	ASD, PS, VSD, PDA	50–65	Battaglia et al. 2008b
Deletion 4q	4q deletion	1 in 100,000	Growth deficiency, craniofacial anomalies, cleft palate, genitourinary defects, digital anomalies, intellectual disability	VSD, PDA, peripheral pulmonary stenosis, AS, ASD, TOF, CoA, tricuspid atresia	50	Xu et al. 2012
Cri-du-chat syndrome	5p deletion	1 in 15,000–1 in 50,000	Catlike cry, growth retardation, hypotonia, dysmorphic features, intellectual disability	PDA, VSD, ASD	15–20	Hills et al. 2006; Nguyen et al. 2015

Williams-Beuren syndrome	7q11-23 deletion ( <i>ELN</i> gene)	1 in 20,000	Dysmorphic facial features, connective tissue abnormalities, skeletal and renal anomalies, cognitive defects, mild intellectual disability, growth and endocrine abnormalities including hypercalcemia in infancy	Supravalvar AS, supravalvar PS, branch pulmonary artery stenosis	50-80	Kececioglu et al. 1993; Morris 1993; Morris and Mervis 2002
8p23.1 deletion	8p23.1 deletion (including <i>GATA4</i> )	Unknown (rare)	Microcephaly, growth retardation, congenital diaphragmatic hernia, developmental delay, neuropsychiatric problems	AVSD, ASD, VSD, PS, TOF	50-75	Wat et al. 2009
9p deletion	9p deletion	Unknown (rare)	Trigonocephaly, midface hypoplasia, long philtrum, hypertelorism, up-slanting palpebral fissures, abnormal ears, abnormal external genitalia, hypotonia, seizures, intellectual disability	PDA, VSD, ASD, CoA	45-50	Huret et al. 1988; Swinkels et al. 2008
Kleefstra syndrome	9q34.3 subtelomeric deletion (including <i>EHMT1</i> )	Unknown (rare)	Intellectual disability, delayed speech hypotonia, microcephaly, brachycephaly, hypertelorism, synophrys, midface hypoplasia, anteverted nares, prognathism, everted lips, macroglossia, behavioral problems, obesity	ASD, VSD, TOF, pulmonary arterial stenosis	30-47	Kleefstra et al. 2006, 2009
10p deletion	10p deletion	Unknown (rare)	Hypoparathyroidism, immune deficiency, deafness, renal anomalies, intellectual disability	PS, BAV, ASD, VSD	42	Lindstrand et al. 2010
Duplication 10q24-qter	10q duplication	Unknown (rare)	Growth retardation, hypotonia, microcephaly, dysmorphic facies, kidney anomalies, limb anomalies, intellectual disability	TOF, AVSD, VSD	20-50	Aglan et al. 2008; Carter et al. 2010
Jacobson syndrome	11q deletion	1 in 100,000	Growth retardation, developmental delay, thrombocytopenia, platelet dysfunction, wide-spaced eyes, strabismus, broad nasal bridge, thin upper lip, prominent forehead, intellectual disability, autism, immunodeficiency	VSD, HLHS, AS, CoA, Shone's complex	56	Grossfeld et al. 2004
15q24 deletion	15q24 deletion	Unknown (rare)	Growth retardation, intellectual disability, abnormal corpus callosum, microcephaly, abnormal ears, hearing loss, genital anomalies, digital anomalies	PDA, pulmonary arterial stenosis, PS	20-40	Mefford et al. 2012

*Continued*

Table 2. Continued

Syndrome	Genetic change	Prevalence in live births	Common clinical features	Associated congenital heart disease	Patients with the condition who have CHD (%)	References
Koolen-de Vries syndrome	17q21 deletion	1 in 16,000	Hypotonia, developmental delay, seizures, facial dysmorphisms, friendly behavior	ASD, VSD	27	Koolen et al. 2008
22q11.2 deletion syndrome (DiGeorge, velocardiofacial syndrome)	22q11.2 deletion	1 in 6000	Hypertelorism, broad nasal root, long and narrow face, long, slender fingers, hypocalcemia, immunodeficiency, behavioral problems, autism spectrum disorder, learning disability, psychiatric problems	IAA type B, TA, TOF, right aortic arch	75–80	Botto et al. 2003; Digilio et al. 2003; Peyvandi et al. 2013b
22q11.2 duplication	22q11.2 duplication	Unknown	Velopharyngeal insufficiency, cleft palate, hearing loss, facial anomalies, urogenital abnormalities, mild learning disability, hypotonia, scoliosis, frequent infections	VSD, aortic regurgitation, MVP, CoA, TOF, HLHS, IAA, TA, D-TGA	15	Portnoi 2009
Phelan-McDermid syndrome	22q13 deletion	Unknown (rare)	Developmental delay, intellectual disability, hypotonia, absent/delayed speech, autism spectrum disorder, long, narrow head, prominent ears, pointed chin, droopy eyebrows, deep-set eyes	TR, ASD, PDA, TAPVR	25	Phelan and McDermid 2012

Data adapted from Pierpont et al. (2018).

(AS) Aortic stenosis, (ASD) atrial septal defect, (AVSD) atrioventricular septal defect, (BAV) bicuspid aortic valve, (CoA) coarctation of the aorta, (DORV) double outlet right ventricle, (D-TGA) d-loop transposition of the great arteries, (HLHS) hypoplastic left heart syndrome, (IAA) interrupted aortic arch, (MIR) mitral regurgitation, (PAPVR) partial anomalous pulmonary venous return, (PDA) patent ductus arteriosus, (PS) pulmonary stenosis, (TA) truncus arteriosus, (TOF) tetralogy of Fallot, (TR) tricuspid regurgitation, (VSD) ventricular septal defect.



tients with trisomy 18 have CHD with PDA and VSD being the most common diagnoses. Most patients show polyvalvar dysplasia with two or more valves showing thickened, myxomatous, or dysplastic leaflets, although regurgitation and stenosis are uncommon (Van Praagh et al. 1989; Musewe et al. 1990). The majority of trisomy 13 patients have cardiac defects with PDA, ASD, and VSD being the most common lesions (Musewe et al. 1990; Lin et al. 2007). Life expectancy is limited in both trisomy 18 and 13, and most individuals die within the first year of life. Therefore, there has been significant debate as to whether repair of CHD should be offered in these patients (Embleton et al. 1996; Rasmussen et al. 2003; Yates et al. 2011).

### Turner Syndrome

Turner syndrome is a sex chromosome disorder that results from a complete or partial loss of an X chromosome resulting in 45, X karyotype. Those with mosaicism or structural abnormalities of the X chromosome tend to have less severe phenotypes compared with those with complete loss (Gøtzsche et al. 1994; Bucerzan et al. 2017). The most common cardiac lesions associated with Turner syndrome are left-sided lesions including BAV in 30% of patients and coarctation of the aorta (CoA) in 10% of patients. More serious lesions such as partial anomalous pulmonary venous return (PAPVR) and HLHS are less common (Mazzanti and Cacciari 1998; Sybert and McCauley 2004). Individuals with Turner syndrome can have hypertension in the absence of CHD and can develop aortic root dilation; it is therefore recommended that all patients have a baseline echocardiogram and be followed with serial imaging (Lacro et al. 1988; Gravholt et al. 2017).

### COPY NUMBER VARIATION

CNVs consist of deletions or duplications of contiguous regions of DNA that affect ~12% of the genome and can impact either a single gene or multiple contiguous genes (Redon et al. 2006). Pathogenic CNVs tend to be de novo and large and disrupt coding portions of

genes. These are found more frequently in patients with CHD compared with controls. There is wide variation in the reported prevalence of CNVs between 3% and 25% depending on the method of detection. CNVs are observed more frequently in patients with CHD and extracardiac features compared with those with isolated CHD (Goldmuntz et al. 2011; Soemedi et al. 2012; Southard et al. 2012; Zhu et al. 2016). Thienpont et al. (2007) used array-comparative genomic hybridization (CGH) in patients with CHD and associated extracardiac anomalies and identified likely pathogenic CNVs in 17% of patients. Glessner et al. (2014) performed WES in 538 patients with CHD and found that 9.8% of patients without a previous genetic diagnosis had a rare de novo CNV.

Recent data have shown that CNVs are not only causative of CHD, but they also impact clinical outcomes. Carey et al. (2013) compared neurocognitive and growth outcomes in patients with single ventricle physiology and found that patients with pathogenic CNVs had decreased linear growth and those with CNVs associated with known genomic disorders had the poorest neurocognitive and growth outcomes. Kim et al. (2016) examined CNVs in 422 cases of nonsyndromic CHD and found that the presence of a likely pathogenic CNV was associated with a significantly lower transplant-free survival after surgery. The increased risk of morbidity in patients with large CNVs may be due to additional genes that are impacted or due to pleiotropic effects of single genes within the region. Some of the most common syndromes caused by CNVs and associated with CHD are described in this section. Additional details are included in Table 2.

### 22q11.2 Deletion Syndrome

22q11.2 deletion syndrome is the most common microdeletion syndrome associated with CHD. The majority of patients clinically diagnosed with DiGeorge or velocardiofacial syndrome have a microdeletion of 22q11.2. Seventy-five to eighty percent of patients with 22q11.2 deletion have CHD, with conotruncal defects being the most common lesions (Marino et al. 2001).

The prevalence of 22q11.2 deletion in patients with CHD is highest in patients with type B interrupted aortic arch (IAA), truncus arteriosus, TOF, and isolated aortic arch anomalies (Nielsen and Wohler 1991; McElhinney et al. 2001; Agergaard et al. 2012; Peyvandi et al. 2013a; Donofrio et al. 2014). Among patients with conotruncal lesions, up to 50% have a 22q11 deletion (Goldmuntz et al. 1998).

22q11.2 deletion is a syndrome that involves a contiguous deletion, most commonly involving more than 40 genes. Efforts to determine which gene within this region is responsible for the cardiovascular phenotype initially focused on *TBX1* (Jerome and Papaioannou 2001; Merscher et al. 2001). Mutations in *TBX1* have been identified in patients with clinical features of DiGeorge syndrome without a deletion, supporting the role of *TBX1* in the development of CHD (Yagi et al. 2003). There are some shared clinical features between 22q11.2 duplication syndrome and the deletion syndrome, and experimental evidence suggests that both overexpression and underexpression of *TBX1* in the developing outflow tract can lead to CHD (Chen et al. 2014; Hasten et al. 2018). Some individuals with conotruncal defects and features of DiGeorge syndrome have a deletion in 22q11 that does not encompass the *TBX1* gene, and two other genes in this region, *CRKL* and *MAPK1*, have been associated with the CHD phenotype (Breckpot et al. 2012; Thorsson et al. 2015).

### Williams–Beuren Syndrome

Williams–Beuren syndrome, or Williams syndrome, is caused by a contiguous gene deletion at 7q11.23 that encompasses the elastin gene *ELN* (Ewart et al. 1993; Morris and Mervis 2002). Similar to 22q11 deletion syndrome, deletions are often sporadic but can be inherited. Between 50% and 80% of patients with Williams syndrome have CHD, most commonly supravalvar aortic stenosis (AS), supravalvar pulmonary stenosis (PS), and branch pulmonary artery stenosis (Kececioglu et al. 1993). Whereas the supravalvar AS tends to progress in childhood, the PS can improve (Wren et al. 1990; Eronen et al. 2002). Patients with Williams syndrome

are at increased risk of sudden cardiac death and anesthesia-related complications (Conway et al. 1990; Latham et al. 2016). These complications are thought to arise from abnormalities in the coronary arteries and ventricular hypertrophy secondary to outflow obstruction, but the precise mechanisms are not known.

Mutations in *ELN*, a critical component of vascular tissue, are observed in patients with autosomal dominant isolated supravalvar AS, leading to the conclusion that haploinsufficiency of this gene is the etiology of CHD in patients with Williams syndrome (Curran et al. 1993; Ewart et al. 1993; Li et al. 1997a). Mutations in *ELN* lead to a vasculopathy that can cause arterial narrowing with thickened arterial walls. Narrowing of the aorta, coronary arteries, and renal arteries often lead to complications in these patients. It is recommended that all patients with supravalvar AS and patients with peripheral PS that does not resolve in the first few years of life undergo genetic testing (Pierpont et al. 2018).

### SINGLE-GENE DEFECTS

In addition to CNVs, de novo sequence variants in single genes have been identified using WES in patients with CHD, both in syndromic and nonsyndromic cases. Patients with CHD have an excess burden of de novo protein altering variants in genes that are expressed during cardiac development (Zaidi et al. 2013). A European study using WES in 1891 patients found that in patients with nonisolated CHD, there were an increased number of de novo protein-truncating variants and deleterious missense variants in known autosomal dominant CHD-associated genes as well as in non-CHD genes associated with developmental delay. In isolated CHD patients, there was a much lower frequency of de novo deleterious variants, but there was an increase in rare, inherited protein-truncating variants in CHD-associated genes likely representing mutations that are incompletely penetrant (Sifrim et al. 2016).

If there is family history of a syndrome that involves CHD, testing for single-gene defects can be targeted based on family member test

results or clinical suspicion. With the exception of Noonan syndrome panels, gene panels have not been routinely incorporated into testing for CHD because of the large number of genes involved. Therefore, in patients with a strong suspicion for a genetic cause of CHD, WES can be used effectively to identify single-gene defects.

### Monogenic Conditions Causing Syndromic CHD

As sequencing techniques have improved, the genetic causes of several well-characterized clinical syndromes have been discovered. The following section describes examples of the most common monogenic syndromes associated with CHD. These syndromes are inherited in an autosomal dominant manner. Some are caused by variants in one gene and others are genetically heterogeneous. Table 3 contains additional details for selected syndromes.

#### Alagille Syndrome

Alagille syndrome is a condition consisting of CHD, hepatic complications including bile duct paucity and cholestasis, and skeletal and ophthalmologic anomalies. There is significant variability in the expression even within the same family, with some individuals displaying very mild features and others with severe CHD or liver disease leading to transplant or death (Quiros-Tejeira et al. 1999; Kamath et al. 2003; Izumi et al. 2016; Ziesenitz et al. 2016). More than 90% of patients with Alagille syndrome have cardiovascular involvement. The most common lesion is branch pulmonary artery stenosis. More complex lesions include TOF with or without pulmonary atresia (Emerick et al. 1999; McElhinney et al. 2002). Other vascular anomalies are frequently found in patients with Alagille syndrome and are a significant cause of mortality (Kamath et al. 2004).

Alagille syndrome is genetically heterogeneous; the two most commonly associated genes are *JAG1*, which encodes a ligand in the Notch signaling pathway, and *NOTCH2*, a Notch receptor (Li et al. 1997b; Oda et al. 1997; McDaniell et al. 2006; Kamath et al. 2012). The Notch

signaling pathway is important for controlling cell fate during development, and mutations in this pathway are also associated with other cardiac diseases (Niessen and Karsan 2008). *JAG1* mutations are found in ~90% of individuals with clinical Alagille syndrome, and these are usually loss-of-function mutations, suggesting haploinsufficiency as the mechanism (Warthen et al. 2006). In addition, 3%–7% of patients have deletions of chromosome 20p12, which contains *JAG1*. In a large family with cardiac defects typical of Alagille syndrome but no hepatic phenotype, a missense mutation that leads to slightly decreased *JAG1* was identified suggesting that the variable expression may be associated with the amount of *JAG1* (Lu et al. 2003). *NOTCH2* mutations are found in 1%–2% of individuals with Alagille syndrome (Spinner et al. 1993; McDaniell et al. 2006).

#### Holt–Oram Syndrome

The two most common features of Holt–Oram syndrome are CHD and upper extremity malformations (Holt and Oram 1960). All patients with Holt–Oram syndrome have some upper limb anomaly ranging from mild abnormalities of the carpal bone to complete phocomelia (McDermott et al. 1993). Among patients with Holt–Oram syndrome, 75% have CHD, and the most common types are ASDs and VSDs. More complex forms of CHD occur in ~15%–25% of patients (Sletten and Pierpont 1996; Baban et al. 2014; Barisic et al. 2014). Patients are also at risk for cardiac conduction disease, which can be progressive and lead to complete heart block (McDermott et al. 1993; Basson et al. 1994).

About 75% of cases of Holt–Oram syndrome are caused by mutations in *TBX5*, a member of the T-box family of transcription factors, which plays a role in regulation of gene expression during embryogenesis (Basson et al. 1997; Li et al. 1997c; McDermott et al. 2005). *TBX5* is expressed in the developing heart and limb and has been shown to be involved in the development of the cardiac septum and conduction system, consistent with the clinical findings in Holt–Oram syndrome (Steimle and Moskowitz 2017). Most of the variants in *TBX5* are

**Table 3.** Common monogenic conditions associated with syndromic congenital heart disease (CHD)

Syndrome	Genes	Chromosome location	Live birth prevalence	Common clinical features	Associated congenital heart disease	Patients with the genetic condition who have CHD (%)	References
Adams–Oliver	<i>DLL4</i> <i>DOCK6</i> <i>EOGT</i> <i>NOTCH1</i>	15q15.1 19p13.2 3p14.1 9q34.3	Unknown (rare)	Aplasia cutis congenital, transverse terminal limb defects	BAV, PDA, PS, VSD, ASD, TOF	20	Hassed et al. 2017
Alagille	<i>JAG1</i> <i>NOTCH2</i>	20p12.2 1p12-p11	1 in 100,000	Bile duct paucity, cholestasis, posterior embryotoxin, butterfly vertebrae, renal defects	Branch pulmonary artery stenosis, TOF, PA	90–95	Emerick et al. 1999; McElhinney et al. 2002; McDaniel et al. 2006; Turpenny and Ellard 2012
Axenfeld–Rieger	<i>FOXC1</i>	6p25.3	1 in 200,000	Ocular anomalies including glaucoma, dental anomalies, redundant periumbilical skin	ASD, AS, PS, TOF, BAV, TA	Unknown	Gripp et al. 2013
Baller–Gerold and Rothmund–Thomson	<i>RECQL4</i>	8q24.3	Unknown (rare)	Radial hypoplasia, craniosynostosis, poikiloderma, growth deficiency, malignancy	VSD, TOF, subaortic stenosis	25	Van Maldergem et al. 2006; Fradin et al. 2013
Bardet–Biedl	<i>BBS2</i> <i>BBS6</i>	16q13 20p12.2	1 in 100,000–1 in 160,000	Retinal dystrophy, polydactyly, obesity, genital anomalies, renal dysfunction, learning difficulties	AS, PS, PDA, cardiomyopathies	7–50	Forsythe and Beales 2013; Suspitsin and Imyanitov 2016
Cantu	<i>ABCC9</i>	12p12.1	Unknown (rare)	Congenital hypertrichosis, osteochondroplasia, macrocephaly, coarse facial features	Cardiomegaly, ventricular hypertrophy, PDA, BAV	60–75	Grange et al. 2006; Scurr et al. 2011

Carpenter	<i>RAB23</i>	6p11.2	Unknown (rare)	Craniosynostosis, polysyndactyly, obesity	ASD, VSD, TOF, PDA, PS	18–50	Jenkins et al. 2007; Kadakia et al. 2014
Cardiofaciocutaneous	<i>BRAF</i> <i>KRAS</i> <i>MAP2K1</i> <i>MAP2K2</i>	7q34 12p12.1 15q22.31 19p13.3	1 in 810,000	Curly hair, sparse eyebrows, feeding difficulty, developmental delay	PS, ASD, VSD, HCM	75	Pierpont et al. 2014; Jhang et al. 2016
Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder	<i>CDK13</i>	7p14.1	Unknown (rare)	Intellectual disability, hypertelorism, upslanted palpebral fissures, wide nasal bridge and narrow mouth, seizures	ASD, VSD, PS	56	Sifrim et al. 2016; Bostwick et al. 2017; Hamilton et al. 2018
Char	<i>TFAP2B</i>	6p12.3	Unknown (rare)	Dysmorphic facies, abnormal fifth digit, strabismus, hearing anomalies	PDA, VSD	26–75	Satoda et al. 1999, 2000
CHARGE	<i>CHD7</i>	8q12	1 in 10,000– 1 in 15,000	Coloboma, choanal atresia, growth retardation, genital hypoplasia, ear anomalies, intellectual disability	TOF, PDA, DORV, AVSD, VSD	75–85	Corsten-Janssen et al. 2013; Trider et al. 2017
Coffin–Siris	<i>ARID1B</i> <i>SMARCA4</i>	6q25 22q11	Unknown (rare)	Intellectual disability, feeding difficulty, coarse facies, hypoplastic distal phalanges, hypertrichosis	ASD, VSD, PS, AS, dextrocardia, CoA, PDA, TOF	44	Kosho et al. 2014; Nemani et al. 2014
Cornelia de Lange	<i>NIPBL</i>	5p13	1 in 10,000– 1 in 30,000	Growth retardation, dysmorphic facies, hirsutism, limb deficiency	VSD, ASD, PS, PDA	13–70	Selcorni et al. 2009
Costello	<i>HRAS</i>	11p15.5	1 in 300,000– 1 in 1,250,000	Short stature, feeding difficulties, coarse facial features, skin abnormalities, intellectual disability	PS, ASD, VSD, HCM, arrhythmias	50–60	Lin et al. 2011; Abe et al. 2012

*Continued*

Table 3. Continued

Syndrome	Genes	Chromosome location	Live birth prevalence	Common clinical features	Associated congenital heart disease	Patients with the genetic condition who have CHD (%)	References
Ellis-van Creveld	<i>EVC</i> <i>EVC2</i>	4p16.2 4p16.2	1 in 60,000– 1 in 200,000	Short limbs, short ribs, postaxial polydactyly, dysplastic nails and teeth	Common atrium	60–75	Ruiz-Perez et al. 2000, 2003; O'Connor et al. 2015
Fragile X	<i>FMR1</i>	Xq27.3	1 in 4000 males, 1 in 8000 females	Intellectual disability, autism spectrum disorder, macrocephaly, macro- orchidism, seizures, prominent forehead, large ears, hyperflexibility	MVP, aortic dilation	10–20	Kidd et al. 2014
Genitopatellar or Ohdo/ Say-Barber-Biesecker-Young-Simpson	<i>KAT6B</i>	10q22.2	Unknown (rare)	Intellectual disability, genital and patellar anomalies	ASD, VSD, PFO	50	Campeau et al. 2012
Heterotaxy	<i>GDF1</i> <i>NODAL</i> <i>ZIC3</i>	19p13.11 10q22.1 Xq26.3	1 in 10,000	Biliary atresia, abdominal situs abnormality, spleen abnormality, isomerism of lungs and bronchi, systemic venous anomalies	Pulmonary venous anomalies, atrial anomalies, AVSD, PS, AS, conotruncal anomalies	>90	Belmont et al. 2004; Lin et al. 2014; Jin et al. 2017
Holt-Oram	<i>TBX5</i>	12q24.1	1 in 100,000	Upper limb anomalies	ASD, VSD, AVSD, conduction defects	75	McDermott et al. 1993; Basson et al. 1994
Johanson-Blizzard	<i>UBR1</i>	15q15.2	Unknown (rare)	Pancreatic insufficiency, Hypoplastic/aplastic nasal alae, cutis aplasia, developmental delay, intellectual disability	Dysplastic mitral valve, PDA, VSD, ASD, dextrocardia	10	Alpay et al. 2000; Almashraki et al. 2011

Kabuki	<i>KDM6A</i> <i>KMT2D</i>	Xp11.3 12q13	1 in 32,000	Growth deficiency, wide palpebral fissures, arched eyebrows, protruding ears, clinodactyly, intellectual disability	CoA, BAV, VSD	30–50	Wessels et al. 2001; Hannibal et al. 2011
Kleefstra	<i>EHMT1</i>	9q34.3	Unknown (rare)	Microcephaly, hypotonia, neuropsychiatric anomalies, broad forehead, synophrys, midface hypoplasia, depressed nasal bridge, short nose, ear anomalies, intellectual disability	ASD, VSD, TOF, PDA, CoA, BAV	40–45	Kleefstra et al. 2009; Ciaccio et al. 2019
Koolen-de Vries	<i>KANSL1</i>	17q21.31	1 in 16,000	Hypotonia, friendly behavior, long face, upslanting palpebral fissures, narrow/short palpebral fissures, ptosis, epicanthal folds, bulbous nasal tip (88%), everted lower lip, and large prominent ears intellectual disability, epilepsy, kidney anomalies	ASD, VSD, PDA, BAV, PS	39	Koolen et al. 2008, 2016
Loeys-Dietz	<i>TGFBR1</i> <i>TGFBR2</i> <i>SMAD3</i>	9q22.33 3p24.1 15q22.33	Unknown (rare)	Aortic and peripheral arterial aneurysms, pectus excavatum, scoliosis, talipes equinovarus, hypertelorism, cleft palate/bifid uvula	BAV, PDA, ASD, MVP	30–50	MacCarrick et al. 2014; Loughborough et al. 2018
Mandibulofacial dysostosis, Guion-Almeida type	<i>EFTUD2</i>	17q21.31	Unknown (rare)	Microcephaly, midface hypoplasia, micrognathia, choanal atresia, hearing loss, cleft palate, intellectual disability	ASD, VSD, PDA	30–60	Lines et al. 2012; Lehalle et al. 2014

*Continued*

Table 3. Continued

Syndrome	Genes	Chromosome location	Live birth prevalence	Common clinical features	Associated congenital heart disease	Patients with the genetic condition who have CHD (%)	References
Marfan	<i>FBNI</i>	15q21.1	1 in 5000	Ocular anomalies (ectopia lentis), skeletal anomalies (arachnodactyly, loose joints), vascular anomalies	AR, MVP	80	Thacoor 2017
Mental retardation, autosomal dominant	<i>KAT6A</i>	8p11.21	Unknown (rare)	Microcephaly, global developmental delay, craniofacial dysmorphism, hypotonia, feeding difficulty, ocular anomalies	PDA, ASD, VSD	Unknown	Arboleda et al. 2015; Tham et al. 2015
Mowat–Wilson	<i>ZEB2</i>	2q22.3	Unknown (rare)	Short stature, Microcephaly, hypertelorism, pointed chin, Hirschsprung disease, intellectual disability, seizures	VSD, CoA, ASD, PDA, PS	50	Zweier et al. 2005; Garavelli et al. 2009
Myhre	<i>SMAD4</i>	18q21.2	Unknown (rare)	Short stature, dysmorphic facies, hearing loss, laryngeal anomalies, arthropathy, intellectual disability	ASD, VSD, PDA, PS, AS, CoA	60	Lin et al. 2016
Nephronophthisis and Meckel–Gruber-like syndrome	<i>NPHP3</i>	3q22.1	Unknown (rare)	Nephronophthisis, CNS malformations, cystic kidneys, polydactyly, situs inversus	AS, ASD, PDA	20	Salonen and Paavola 1998; Bergmann et al. 2008; Tory et al. 2009
Neurofibromatosis	<i>NFI</i>	17q11.2	1 in 3000–1 in 4000	Changes in skin pigmentation, tumor growth, macrocephaly, scoliosis, hypertension	PS, CoA, MR, PDA, VSD, AS, AR, ASD	2–15	Lin et al. 2000; Incecik et al. 2015; Leppävirta et al. 2018



Noonan	<i>PTPN11</i> <i>SOS1</i> <i>RAF1</i> <i>KRAS</i> <i>NRAS</i> <i>RIT1</i> <i>SHOC2</i> <i>SOS2</i> <i>BRAF</i> <i>LZTR1</i> <i>BCOR</i>	12q24.13 2p22.1 3p25.2 12p12.1 1p13.2 1q22 10q25.2 14q21.3 7q34 22q11.21 Xp11.4	1 in 1000– 1 in 2500	Dysmorphic facies, short stature, chest deformities, lymphatic anomalies, skeletal anomalies, hematologic defects	PS, HCM, ASD, TOF, AVSD, VSD, PDA	75–90	Marino et al. 1999; Romano et al. 2010; Jhang et al. 2016
Oculofaciocardiodental (OFCD)			Unknown (rare)	Congenital cataracts, microphthalmia, dysmorphic features, dental anomalies, syndactyly, flexion deformities, intellectual disability	ASD, VSD, PS, AS, PDA, dextrocardia, DORV	66–74	Horn et al. 2005; Hilton et al. 2009
Orofaciodigital	<i>OFD1</i>	Xp22.2	Unknown (rare)	Ciliary defects, facial anomalies, abnormal digits, brain and kidney anomalies	ASD, AVSD, HLHS	33–100	Bouman et al. 2017
Peters plus	<i>B3GLCT1</i> <i>B3GALT1</i>	13q12.3	Unknown (rare)	Anterior eye anomalies, developmental delay, cleft lip and palate, short stature, broad hands and feet	ASD, VSD, PS, subvalvar AS	25–30	Maillette de Buy Wenniger-Prick and Hennekam 2002; Lesnik Oberstein et al. 2006
Polycystic kidney disease, autosomal dominant	<i>PKD1</i>	16p13.3	1 in 1000	Polycystic kidneys, hypertension, extrarenal cysts	MVP, ASD, PDA	10–20	Ivy et al. 1995; Dell 2011
Renal–hepatic–pancreatic dysplasia/nephronophthisis	<i>NEK8</i>	17q11.2	Unknown (rare)	Ciliary dysfunction, renal, hepatic and pancreatic anomalies	Cardiomegaly, HCM, septal defects, PDA	Unknown	Grampa et al. 2016; Rajagopalan et al. 2016

*Continued*

Table 3. Continued

Syndrome	Genes	Chromosome location	Live birth prevalence	Common clinical features	Associated congenital heart disease	Patients with the genetic condition who have CHD (%)	References
Roberts	<i>ESCO2</i>	8p21.1	Unknown (rare)	Growth retardation, cleft lip/palate, hypertelorism, sparse hair, symmetrical limb reduction, cryptorchidism, intellectual disability	ASD, AS	20–50	Van Den Berg and Francke 1993; Goh et al. 2010
Robinow	<i>ROR2</i>	9q22.31	Unknown (rare)	Mesomelic limb shortening, hypertelorism, nasal anomalies, midface hypoplasia, brachydactyly, clinodactyly, micropenis, short stature, scoliosis	PS, VSD, ASD, DORV, TOF, CoA, TA	15–30	Al-Ata et al. 1998; Mazzeu et al. 2007
Rubinstein-Taybi	<i>CBP</i> <i>EP300</i>	16p13.3 22q13.2	1 in 100,000 to 1 in 125,000	Growth retardation, microcephaly, highly arched eyebrows, long eyelashes, down-slanting palpebral fissures, broad nasal bridge, beaked nose, highly arched palate, broad thumbs, large toes, intellectual disability	PDA, VSD, ASD	30	Stevens and Bhakta 1995; Hennekam 2006
Sifrim-Hitz-Weiss	<i>CHD4</i>	12p13.31	Unknown (rare)	Developmental delay, hearing loss, macrocephaly, palate abnormalities, ventriculomegaly, hypogonadism, intellectual disability	PDA, ASD, VSD, BAV, TOF, CoA	Unknown	Sifrim et al. 2016; Weiss et al. 2016

Smith–Lemli–Opitz	<i>DHCR7</i>	11q12–13	1 in 15,000– 1 in 60,000	Growth retardation, dysmorphic facial features, genital anomalies, limb anomalies, intellectual disability	AVSD, ASD, VSD	50	Lin et al. 1997; Digilio et al. 2003; Waterham and Hennekam 2012
Sotos	<i>NSD1</i>	5p35.3	1 in 10,000– 1 in 50,000	Tall stature, macrocephaly, high-anterior hairline, frontal bossing, thin face, downslanting palpebral fissures, advanced bone age, developmental delay	ASD, PDA, VSD	8–50	Leventopoulos et al. 2009
Syndromic microphthalmia/ pulmonary hypoplasia- diaphragmatic hernia- anophthalmia-cardiac defect (PDAC)	<i>STRA6</i>	15q24.1	Unknown (rare)	Pulmonary hypoplasia, diaphragmatic defects, bilateral anophthalmia, contractures, camptodactyly	ASD, VSD, PS, PDA, PA, TOF, CoA, TA	50	Marcadier et al. 2016
Townes–Brocks	<i>SALL1</i>	16p12.1	1 in 250,000	Imperforate anus, dysplastic ears, thumb malformations, renal agenesis, multicystic kidneys, microphthalmia	VSD, ASD, PA, TA	20–30	Miller et al. 2012; Liberalesso et al. 2017
Weill–Marchesani	<i>ADAMTS10</i>	19p13.2	Unknown (rare)	Short stature, brachydactyly, joint stiffness, microspherophakia, ectopia lentis	MVP, AS, PS	50	Dagoneau et al. 2004; Kojuri et al. 2007

(AR) Aortic regurgitation, (AS) aortic stenosis, (ASD) atrial septal defect, (AVSD) atrioventricular septal defect, (BAV) bicuspid aortic valve, (CoA) coarctation of the aorta, (DORV) double outlet right ventricle, (HCM) hypertrophic cardiomyopathy, (HLHS) hypoplastic left heart syndrome, (MR) mitral regurgitation, (MVP) mitral valve prolapse, (PA) pulmonary atresia, (PDA) patent ductus arteriosus, (PFO) patent foramen ovale, (PS) pulmonary stenosis, (TA) truncus arteriosus, (TOF) tetralogy of Fallot, (TR) tricuspid regurgitation, (VSD) ventricular septal defect.

S.N. Nees and W.K. Chung

truncating variants, and the mechanism of disease is suspected to be haploinsufficiency. However, some variants that cause gain of function have similar phenotypes (Basson et al. 1997, 1999; Fan et al. 2003; Böhm et al. 2008; Muru et al. 2011). In the remaining 25% of cases of Holt–Oram syndrome, no genetic etiology has been identified, although it is hypothesized that these patients may have mutations in regulatory domains of *TBX5* not included in routine sequencing.

### Noonan Syndrome and RASopathies

Noonan syndrome and the RASopathies are a group of disorders with overlapping phenotypes including CHD, short stature, dysmorphic facial features, and abnormal neurodevelopment. These disorders are caused by mutations in genes that encode proteins involved in the RAS/MAPK pathway, a signal-transduction pathway important for cell growth, differentiation, senescence, and death (Allanson 2016). Other than Noonan syndrome, disorders include cardiofaciocutaneous syndrome (CFC), Costello syndrome (CS), and Noonan syndrome with multiple lentigines.

Noonan syndrome is a disorder with both clinical and genetic heterogeneity consisting of characteristic facial features, short stature, CHD, cardiomyopathy, and chest deformities (Romano et al. 2010; Allanson and Roberts 2016). Cardiac involvement is present in 80%–90% of individuals. The most common cardiovascular findings are PS in 50%–60% and hypertrophic cardiomyopathy (HCM) in 20% (Marino et al. 1999; El Bouchikhi et al. 2016; Jhang et al. 2016). The presence of HCM contributes to significant mortality and tends to be earlier-onset and more rapidly progressive than other types of pediatric HCM (Wilkinson et al. 2012; Gelb et al. 2015).

About one-half of the patients with Noonan syndrome have missense variants in *PTPN11*, which lead to activation of SHP2 and increased RAS/MAPK signaling (Tartaglia et al. 2001, 2002). Among those without *PTPN11* variants, 20% have variants in *SOS1* (Roberts et al. 2007). The cardiovascular manifestations of Noonan syndrome vary depending on the mutation. Mutations in *PTPN11* are more commonly associ-

ated with PS, whereas mutations in *RAF1* or *RIT1* are associated with a high risk of HCM (Tartaglia et al. 2002; Aoki et al. 2016; Jhang et al. 2016; Kouz et al. 2016).

The other RASopathies share some common features, including developmental delays, short stature, ptosis, hypertelorism, and macrocephaly. Individuals with CFC and CS tend to have more severe cognitive impairment compared with individuals with Noonan syndrome (Abe et al. 2012). Cardiac defects are found in ~75% of individuals with CFC, and, similar to Noonan syndrome, the most common findings are PS and HCM (Pierpont et al. 2014; Jhang et al. 2016). HCM is found in the majority of individuals with Noonan syndrome with multiple lentigines and is much more frequent than in individuals with Noonan syndrome (Limongelli et al. 2007; Aoki et al. 2016).

Given the clinical and genetic overlap between the RASopathies, gene panels have been developed that allow for sequencing the most commonly affected genes. These are useful in evaluation of patients with CHD in whom a RASopathy is suspected, because it may be difficult to distinguish between the syndromes based on clinical features alone, especially in infancy. An accurate diagnosis can assist with screening for other systemic involvement and providing prognostic information.

The majority of mutations causing RASopathies are gain-of-function mutations leading to increased signaling in the Ras/MAPK pathway (Carta et al. 2006; Pandit et al. 2007; Roberts et al. 2007, 2013; Cordeddu et al. 2009; Martignelli et al. 2010; Tartaglia et al. 2011; El Bouchikhi et al. 2016; Kouz et al. 2016). This provides a potential therapeutic target for inhibitors of RAS/MAPK signaling cascade (Chen et al. 2010; Marin et al. 2011; Rauen et al. 2011; Wu et al. 2011; Inoue et al. 2014). In one case report, a rapamycin analog was used to inhibit mTOR activity as palliative therapy in an individual with Noonan syndrome with multiple lentigines (NSML) and severe HCM, but further research is needed to determine if these therapies can improve the neurodevelopmental or cardiovascular outcomes in patients with these disorders (Hahn et al. 2015; Aoki et al. 2016).

## Heterotaxy and Ciliopathies

The heart is an asymmetric organ, and left–right patterning is critical for normal cardiac development. Disorders of left–right patterning include heterotaxy syndrome (HTX), in which there is abnormal sidedness of multiple organs, and situs inversus totalis (SIT), in which the organs are in a mirror-image pattern. Data from the National Birth Defects Prevention study showed that among patients with laterality defects, 68% had complex CHD and another 9% had simple CHD. Those with HTX were much more likely to have complex CHD compared with those with SIT (Lin et al. 2014). The association between CHD and laterality defects suggests a common developmental mechanism, perhaps because of defects in cilia as the primary cause of these abnormalities.

Cilia are organelles that have a crucial role in cellular signaling during development, particularly in the proper formation of the left–right axis in the developing embryo (Yoshida and Hamada 2014). Abnormal ciliary structure or function is associated with syndromic ciliopathies, which include primary ciliary dyskinesia (PCD) and HTX, both of which are associated with CHD (Sutherland and Ware 2009).

A study examining chemically mutagenized fetal mice identified more than 200 mouse lines with various forms of CHD, 30% of which were consistent with HTX. WES in the fetal mice identified recessive CHD mutations in 61 genes, more than one-half of which were cilia-related (Li et al. 2015). In a study of WES in a large cohort of individuals with CHD, among 28 de novo mutations, 13 were in genes that were also identified in the mouse screen (Zaidi et al. 2013; Klena et al. 2017).

HTX is associated with CHD in the majority of individuals. Individuals with HTX are classified into two categories: left atrial isomerism (polysplenia syndrome) and right atrial isomerism (asplenia syndrome). In left atrial isomerism, common types of CHD include interruption of the inferior vena cava, PAPVR, and heart block. In right atrial isomerism, the most common defects are AVSDs, total anomalous pulmonary venous return (TAPVR), and cono-

truncal defects. Extracardiac manifestations include spleen abnormalities, gut malrotation, biliary atresia, and CNS abnormalities (Sutherland and Ware 2009; Lin et al. 2014). HTX has a high risk of familial recurrence (Oyen et al. 2010). All types of inheritance including X-linked, autosomal dominant, and autosomal recessive have been described with multiple implicated genes including *LEFTYA*, *CRYPTIC*, and *ACVR2B* (Belmont et al. 2004). Pathogenic variants in *ZIC3*, a zinc-finger transcription factor involved in heart looping, are thought to contribute to ~5% of HTX cases in males (Cowan et al. 2014; Paulussen et al. 2016).

PCD is a disorder characterized by abnormal ciliary motility in the airway tract that leads to frequent respiratory infections and complications (Mirra et al. 2017; Dalrymple and Kenia 2018). HTX and associated CHDs are found in ~6% of patients with PCD showing the overlapping phenotypes and genetic etiologies of these conditions (Kennedy et al. 2007).

There is evidence that mutations in cilia genes are also involved in isolated CHD—especially AVSDs and D-transposition of the great arteries (D-TGA) (Versacci et al. 2018). In patients with CHD but no HTX, there is a high incidence of ciliary motion defects—up to 51% in one study (Garrod et al. 2014).

Given the significant genetic heterogeneity seen in HTX and PCD, genetic testing can be difficult. All patients should have CMA first because some CNVs and chromosomal abnormalities can be associated with HTX (Cowan et al. 2016). Gene panels are available for PCD, which include the most commonly associated genes (Pierpont et al. 2018).

## GDF1 and Founder Ashkenazi Mutation

Given the heterogeneity of CHD, there are likely to be genes involved in the pathogenesis of CHD in specific populations. One such gene is *GDF1*, which is associated with CHD in the Ashkenazi Jewish population. A study screening 375 unrelated patients with CHD identified loss-of-function mutations in *GDF1* among cases with various types of CHD including conotruncal defects and atrioventricular canal defects. These

were heterozygous mutations, and they hypothesized that *GDF1* represented a susceptibility gene (Karkera et al. 2007). Linkage analysis in a family with right atrial isomerism led to the identification of compound heterozygous recessively inherited truncating mutations in *GDF1* (Kaasinen et al. 2010). A large study using WES data for 2871 CHD cases showed an increase in homozygous mutations in *GDF1* among cases with evidence of Ashkenazim based on PCA analysis. One specific mutation, c.1091T>C, accounted for ~5% of severe CHD cases among those with Ashkenazi descent (Jin et al. 2017). Although the overall contribution to CHD is likely low, *GDF1* is an important contributor in certain populations (Sun et al. 2013).

### Monogenic Causes of Isolated CHD

In addition to the syndromes described above, variants in an increasing number of genes have been identified in individuals with isolated CHD, initially through studies of familial CHD and later through the use of NGS. Among the genes that have been identified, most fall into one of the following functional categories and play an important role in normal cardiac development: transcription factors, signaling molecules, and structural proteins (Fahed et al. 2013). Select examples in each of these functional categories are described below. Table 4 contains additional genes associated with isolated CHD. The list of genes associated with isolated CHD is rapidly expanding but it is often difficult to prove the pathogenicity of rare variants, especially in the setting of phenotypic heterogeneity.

### Transcription Factors

There is a set of highly conserved transcription factors that are critical for cardiac development (Olson 2006; Kodo et al. 2012). Mutations in the homeobox transcription factor *NKX2-5* were reported in both familial and sporadic cases of CHD associated with conduction defects in 1998 (Schott et al. 1998). The most common phenotype in individuals with *NKX2-5* mutations is ASD with conduction delay (Benson et al. 1999; Stallmeyer et al. 2010). Identification

of *NKX2-5* mutations in individuals with these cardiac findings is clinically relevant because they are at increased risk of progressive conduction disease and sudden cardiac death, and the genetic information is considered in decision-making regarding pacemakers and implantable cardiac defibrillators (Perera et al. 2014; Ellesøe et al. 2016).

Other transcription factors that have been associated with structural heart disease in both human and mouse models include members of the GATA family (Garg et al. 2003; Rajagopal et al. 2007; Kodo et al. 2009; Wei et al. 2013; Qian et al. 2017) and members of the Tbox family that have been implicated in both syndromic and isolated forms of CHD (Kirk et al. 2007; Griffin et al. 2010; Smemo et al. 2012; Huang et al. 2017). Recent work has identified *SOX17* as a contributor to CHD associated with pulmonary hypertension as well as isolated and familial pulmonary hypertension (Zhu et al. 2018). *SOX17* is a transcriptional target of GATA4, and it inhibits signaling in the WNT/B-catenin pathway involved in cardiac development (Zorn et al. 1999; Holtzinger et al. 2010).

### Cell Signaling and Adhesion Models

Many signaling pathways are involved in cardiac development, and genes in these pathways are frequently disrupted in patients with CHD. Notch signaling is important for cellular differentiation and is involved in the pathogenesis of both isolated and syndromic CHD (Li et al. 1997b; McDaniell et al. 2006; Kamath et al. 2012; Stittrich et al. 2014; Meester et al. 2019). Mutations in *NOTCH1* have been identified in autosomal dominantly inherited CHD consisting primarily of BAV and are associated with abnormalities of the outflow tracts and semilunar valves (Garg et al. 2005; Kerstjens-Frederikse et al. 2016; Preuss et al. 2016). In patients with isolated TOF, *NOTCH1* was noted to be the most frequent site of genetic variants accounting for 4.5% of patients (Page et al. 2019).

Another cell signaling family that is crucial for cardiac development is the TGF- $\beta$  cytokine superfamily. Several genes in this family are im-

**Table 4.** Selected monogenic causes of isolated congenital heart disease

Gene	Chromosome location	Mode of inheritance	Cardiac disease	References
<i>ACTC1</i>	15q14	AD	ASD, HCM, DCM, LVNC	Matsson et al. 2008
<i>CITED2</i>	6q24.1	AD	ASD, VSD	Sperling et al. 2005
<i>CRELD1</i>	3p25.3	AD	ASD, AVSD	Guo et al. 2010
<i>GATA4</i>	8p23.1	AD	ASD, VSD, AVSD, PS, TOF	Zhang et al. 2017
<i>GATA5</i>	20q13.33	AD, AR	ASD, BAV, TOF, VSD, DORV	Jiang et al. 2013; Shan et al. 2014
<i>GATA6</i>	18q11.2	AD	TA, TOF	Kodo et al. 2009; Xu et al. 2018; Zhang et al. 2018
<i>HAND1</i>	5q33.2	AD	SV, VSD	Reamon-Buettner et al. 2008, 2009
<i>HAND2</i>	4q34.1	AD	PS, TOF, VSD	Shen et al. 2010; Topf et al. 2014; Sun et al. 2016
<i>MEIS2</i>	15q14	AD	ASD, VSD, CoA	Verheije et al. 2019
<i>MYBPC3</i>	11p11.2	AD	ASD, PDA, VSD, MR	Wells et al. 2011; Wessels et al. 2015
<i>MYH6</i>	14q11.2	AD, AR	ASD, HCM, DCM, HLHS	Theis et al. 2015; Jin et al. 2017
<i>MYH7</i>	14q11.2	AD for CM	EA, LVNC, HCM, DCM	Postma et al. 2011; Hanchard et al. 2016
<i>NODAL</i>	10q22.1	AD	D-TGA, DORV, TOF, VSD	Roessler et al. 2008; Mohapatra et al. 2009
<i>NOTCH1</i>	9q34.3	AD	ASD, VSD, CoA, HLHS, DORV	Garg et al. 2005; Kerstjens-Frederikse et al. 2016
<i>NKX2-5</i>	5q35.1	AD	ASD, TOF, HLHS	Schott et al. 1998; Benson et al. 1999; Stallmeyer et al. 2010
<i>NR2F2</i>	15q26.2	AD	AVSD, AS, CoA, VSD, HLHS, TOF, DORV	Al Turki et al. 2014; Bashamboo et al. 2018; Qiao et al. 2018
<i>SMAD2</i>	18q21.1	AD	HTX, DORV, ASD, VSD, PDA	Zaidi et al. 2013; Granadillo et al. 2018
<i>SMAD6</i>	15q22.31	AD	BAV, CoA, AS	Gillis et al. 2017
<i>TAB2</i>	6q25.1	AD	BAV, AS, TOF	Thienpont et al. 2010
<i>TBX1</i>	22q11.2	AD	Conotruncal defects, VSD, IAA, ASD	Yagi et al. 2003
<i>TBX5</i>	12q24.1	AD	VSD, ASD, AVSD, conduction defects	Basson et al. 1999
<i>TBX20</i>	7p14.2	Unknown	ASD, VSD, MS, DCM	Kirk et al. 2007

Genes in this table are associated with congenital heart disease based on criteria established by The Clinical Genome Resource Gene Curation Working Group (2018).

(AS) Aortic stenosis, (ASD) atrial septal defect, (AVSD) atrioventricular septal defect, (BAV) bicuspid aortic valve, (CM) cardiomyopathy, (CoA) coarctation of the aorta, (DCM) dilated cardiomyopathy, (DORV) double outlet right ventricle, (D-TGA) d-loop transposition of the great arteries, (EA) Ebstein's anomaly of the tricuspid valve, (HCM) hypertrophic cardiomyopathy, (HLHS) hypoplastic left heart syndrome, (HTX) heterotaxy syndrome, (IAA) interrupted aortic arch, (LVNC) left ventricular noncompaction, (MR) mitral regurgitation, (PDA) patent ductus arteriosus, (PS) pulmonary stenosis, (SV) single ventricle, (TA) truncus arteriosus, (TOF) tetralogy of Fallot, (VSD) ventricular septal defect.

plicated in heart development including *BMP-2*, *BMP-4*, *TGF- $\beta$ 2*, and *TGF- $\beta$ 3* (Nakajima et al. 2000; Armstrong and Bischoff 2004). The TGF- $\beta$  superfamily also includes Nodal, a secreted signaling ligand that has been implicated in laterality defects including HTX as well as isolated CHD (Roessler et al. 2008; Mohapatra

et al. 2009). Isolated CHD lesions associated with *NODAL* mutations include D-TGA, double outlet right ventricle (DORV), TOF, and isolated VSDs. Overexpression of TGF- $\beta$ 1 seems to play a role in the development of pulmonary hypertension in patients with CHD, suggesting that alterations in this pathway may have pleo-

S.N. Nees and W.K. Chung

tropic effects on the heart as well as the pulmonary vasculature (Gao et al. 2005; Yuan 2018).

### Structural Proteins

Mutations in structural cardiac proteins also contribute to CHD in some patients. Mutations in cardiac sarcomere proteins are associated with cardiomyopathies and recently have been reported in some types of CHD. *MYH6* encodes myosin heavy chain 6, and dominant mutations have been associated with ASDs in addition to dilated cardiomyopathy (Granados-Riveron et al. 2010; Posch et al. 2011). Recently, recessive *MYH6* missense mutations were identified in two patients with HLHS and decreased ventricular function, suggesting a role in the development of the normal ventricular myocardium (Theis et al. 2015). Mutations in *MYH7*, another sarcomeric protein, have been associated with Ebstein's anomaly of the tricuspid valve and left ventricular noncompaction (Postma et al. 2011). *ACTC1* encodes a cardiac actin and mutations have been identified in familial cases of ASDs without cardiac dysfunction (Matsson et al. 2008).

### Histone Modifiers

WES has identified several monogenic causes of isolated and nonisolated CHD. Zaidi et al. (2013) used WES in 362 severe cases of CHD and showed an excess of likely damaging de novo variants in genes expressed during cardiac development. This study showed significant enrichment of genes involved in the modification of histone 3 lysine 4 (H34K). Methylated H34K is an important regulator of developmental genes. Other genes in this pathway, including *MLL2*, *KDM6A*, and *CHD7*, have been previously associated with CHD (Vissers et al. 2004; Lederer et al. 2012). Histone modifications are important regulators of gene expression. These data suggest that the H34K pathway is important for appropriate gene regulation during cardiac development and that other epigenetic mechanisms may play a role in the pathogenesis of CHD. In addition, this shows the utility of

using WES to identify new genes and mechanisms in cases of CHD of unknown etiology.

### COMMON VARIANTS AND CHD

Given that the majority of CHD cases do not yet have a known genetic cause, several investigators have hypothesized that common variants may play a role in the risk of CHD. Genome wide association studies (GWASs) have been used to identify common variants associated with specific types of CHD. A large study of CHD found a region on chromosome 4p16 that was associated with risk of ASD, and genotype at this locus accounted for ~9% of the population-attributable risk (Cordell et al. 2013a). A GWAS in the Han Chinese population identified two loci, 1p12 and 4q13.1, associated with CHD. Another study in the Han Chinese using a compound heterozygous model identified four additional loci that explained 7.8% of the CHD variance in the population, suggesting that multiple modes of inheritance are contributing (Jiang et al. 2018). Several studies have examined specific groups of CHD including left-sided lesions and TOF and have identified susceptibility loci that account for a small proportion of the genetic variation in each case (Cordell et al. 2013b; Mitchell et al. 2015; Hanchard et al. 2016). Although common variants likely have a role in CHD susceptibility, these account for only a small proportion of the genetic risk, and large studies of individuals with similar CHD lesions are needed to identify additional susceptibility loci.

### RECOMMENDATIONS FOR CLINICAL GENETIC TESTING

Recommendations for clinical genetic testing in CHD are evolving. Any individual with features suggestive of a recognizable chromosomal condition should undergo focused testing. Because many syndromic forms of CHD have variable presentations, patients with CHD with any extracardiac finding including dysmorphic features, growth deficiency, developmental delay, or another congenital anomaly should be offered genetic testing. If there is a family history of congenital anomalies or multiple miscarriages



es, genetic testing should also be offered (Pierpont et al. 2007, 2018). In neonates and young infants, it can be difficult to appreciate dysmorphic features, cognitive delays, and extracardiac anomalies. Testing should be considered for these patients if they have a type of CHD that is frequently associated with genetic syndromes including TOF, IAA, truncus arteriosus, and left-sided obstructive lesions, even in the absence of other features (Ito et al. 2017). For fetuses diagnosed with CHD, there is a much higher chance of identifying genetic abnormalities, possibly because of high rates of intrauterine demise with certain conditions. For this reason, genetic testing and counseling should be offered in all cases of prenatally diagnosed CHD because a positive test may help identify additional anomalies and affect pregnancy management (Donofrio et al. 2014; Bensemlali et al. 2016; Lazier et al. 2016).

CMA is the appropriate first-line test for most individuals and has been shown to be cost-effective (Manning and Hudgins 2010; Geddes et al. 2017). In cases in which rapid results will have a clinical benefit, FISH for aneuploidy or 22q11.2 deletion can be considered. The limitation of CMA is that balanced chromosomal rearrangements cannot be detected, and if this is suspected, karyotype is needed. If CMA is negative and a genetic cause of CHD is strongly suspected, WES can be considered.

## CONCLUDING REMARKS

Congenital heart disease is a broad phenotype that encompasses many different cardiac structures and many genetic variants. Among patients with CHD, 8%–12% have an aneuploidy or large chromosomal abnormality, and 3%–5% have a single-gene defect. The frequency of detection of CNVs in CHD patients varies widely between 3% and 25% with increased frequency among those with nonisolated CHD. Recent evidence suggests that heterozygous de novo predicted deleterious SNVs can be identified in 8% of CHD patients and inherited autosomal recessive SNVs in 2% (Jin et al. 2017). A given syndrome or genetic variant can cause different types of CHD in different patients because of

genetic modifiers. In addition, for each type of CHD, there is a long list of possible genetic causes. As sequencing becomes more cost-effective, additional causes will certainly be identified, and we are just beginning to understand how genetics impact outcomes among patients with CHD.

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S.N. Nees and W.K. Chung

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S.N. Nees and W.K. Chung

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