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Congenital heart defects in CHARGE: The molecular role of CHD7 and effects on cardiac phenotype and clinical outcomes

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Abstract

CHARGE syndrome is characterized by a pattern of congenital anomalies (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth, Genital abnormalities, and Ear abnormalities). De novo mutations of chromodomain helicase DNA binding protein 7 (*CHD7*) are the primary cause of CHARGE syndrome. The clinical phenotype is highly variable including a wide spectrum of congenital heart defects. Here, we review the range of congenital heart defects and the molecular effects of CHD7 on cardiovascular development that lead to an over-representation of atrioventricular septal, conotruncal, and aortic arch defects in CHARGE syndrome. Further, we review the overlap of cardiovascular and noncardiovascular comorbidities present in CHARGE and their impact on the peri-operative morbidity and mortality in individuals with CHARGE syndrome.

KEYWORDS
CHARGE, CHD7, congenital heart defects

1 | INTRODUCTION

CHARGE syndrome is a rare genetic disorder (OMIM 214800) with an estimated incidence of approximately 1 in 10,000 (Issekutz, Graham, Prasad, Smith, & Blake, 2005). CHARGE syndrome was initially described as a pattern of anomalies by Hall (1979) and Hittner, Hirsch, Kreh, and Rudolph (1979) that was formally defined as an association by (Pagon, Graham, Zonana, & Yong, 1981). The primary features of CHARGE—ocular coloboma (C), heart malformations (H), atresia of the choanae (A), retardation of growth (R), genital hypoplasia (G), and ear abnormalities (E)—form an acronym that serves as the name of the condition. CHARGE was subsequently defined as a syndrome with the identification of autosomal dominant pathogenic variants in the *CHD7* gene in 2004 (Vissers et al., 2004), which occurs in 58–90% of patients with CHARGE syndrome (Jongmans et al., 2006; Lalani et al., 2006; Legendre et al., 2017; Zentner, Layman, Martin, & Scacheri, 2010). An additional spectrum of single gene pathogenic variants have been identified in individuals with the clinical features of CHARGE (Moccia et al., 2018).

Since the identification of *CHD7* and further refinement of specific features of inner ear formation, diagnostic criteria for the syndrome have undergone multiple revisions (Blake et al., 1998; Hale, Niederriter, Green, & Martin, 2016; Sanlaville & Verloes, 2007; Verloes, 2005). Heart malformations remain a key criterion for the definitions of the syndrome. While there is a highly variable cardiac phenotype, cardiac defects convey significant implications for the clinical course of individuals with CHARGE syndrome. In this review, we will discuss the spectrum of congenital heart disease in CHARGE syndrome, the clinical impact of CHARGE syndrome on outcomes in congenital heart disease, and our current understanding of the mechanisms of action of CHARGE syndrome in cardiac development.

2 | PATTERNS OF CONGENITAL HEART DISEASE IN CHARGE

2.1 | Types of congenital heart disease in CHARGE

The spectrum of congenital heart disease is highly variable in CHARGE syndrome and encompasses mild cardiac malformations (e.g., patent ductus arteriosus [PDA] and atrial septal defects) that may not require intervention to more severe malformations

(e.g., Tetralogy of Fallot) that require cardiothoracic surgery in infancy. Conotruncal defects (31–42%) and atrioventricular septal defects (AVSDs; 13–17%) with associated or isolated PDA and aortic arch abnormalities are seen more frequently in individuals with CHARGE than the full population of patients with congenital heart disease (Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Corsten-Janssen, van Ravenswaaij-Arts, & Kapusta, 2016; Lin, Chin, Devine, Park, & Zackai, 1987; Vissers et al., 2004; Wyse, Al-Mahdawi, Burn, & Blake, 1993).

We characterized this further by compiling all large case series/cohort studies (>4 patients) with published detail sufficient for classification of congenital heart disease types and compared these to the largest meta-analysis to date of all congenital cardiac defects (Table 1; Liu, Chen, et al., 2019). The cardiac phenotypes across these studies were arranged according to the large classifications based off embryologic development using a modified classification system from Botto et al. (2007). The largest single study of individuals with CHARGE syndrome examining the spectrum of congenital heart defects included 299 individuals with CHARGE syndrome (Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013). This large study aligns well with the data found in the composite of the additional studies (Table 1) and demonstrates the over-representation of conotruncal defects and AVSDs (Figure 1). Often overlapping within these larger classification categories is a high incidence of aortic arch abnormalities (e.g., right aortic arch and aberrant right subclavian arteries) and additional presence of a PDA (Corsten-Janssen et al., 2016). Despite this bias toward conotruncal and AVSD defects, the incidence of CHARGE syndrome remains rare enough that specifically screening for CHARGE in patients with heart defects plus an additionally involved organ system is not cost-effective (Corsten-Janssen et al., 2014; Corsten-Janssen & Scambler, 2017).

Given the range of pathogenic variants seen in CHARGE syndrome (Moccia et al., 2018; Zentner et al., 2010), it is important to understand the impact of causative *CHD7* variants on the CHARGE syndrome

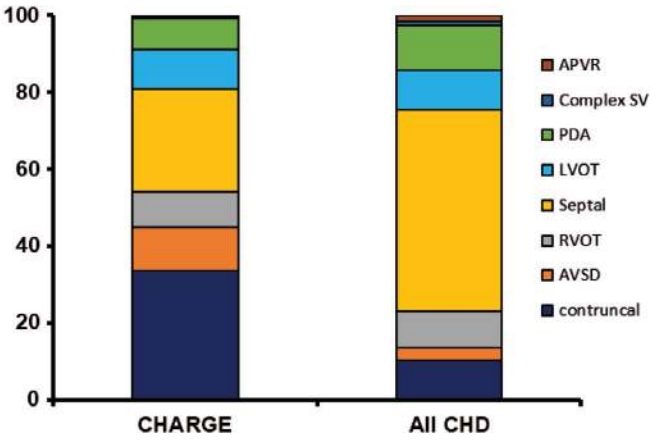

FIGURE 1 Spectrum of congenital heart disease in CHARGE syndrome compared to all congenital heart disease. Conotruncal defects and atrioventricular septal defects (AVSDs) are over-represented in CHARGE compared to all congenital heart disease from Table 1. There are fewer isolated septal defects, similar degree right ventricular outflow tract (RVOT), left ventricular outflow tract (LVOT), isolated patent ductus arteriosus (PDA), complex single ventricles (SV), and anomalous pulmonary venous return (APVR)

TABLE 1 Spectrum of congenital heart disease in CHARGE syndrome versus all congenital heart disease

	CHARGE syndrome				All CHD	
Primary classification (modified from Botto, Lin, Riehle-Colarusso, Malik, & Correa, 2007)	**Literature review (# patients)**	**Corsten-Janssen et al., 2013 (# patients)**	**Total (# patients)**	**% of all CHD**	**Prevalence per 1,000**	**% of all CHD**
Conotruncal	88	54	142	33.6	0.876	10.2
Atrioventricular Septal defect	22	26	48	11.3	0.290	3.4
Right ventricular outflow tract malformation	19	20	39	9.2	0.805	9.3
Septal defect	55	58	113	26.7	4.512	52.4
Left ventricular outflow tract malformation	20	23	43	10.2	0.886	10.3
PDA	15	19	34	8.0	1.004	11.7
Complex single ventricle	2	1	3	0.7	0.093	1.1
Abnormal pulmonary venous return	0	1	1	0.2	0.144	1.7
Number with congenital heart disease	221	202	423	100	Adapted from Liu, Chen, et al. (2019)	

Note. All congenital heart disease data adapted from Liu, Chen, et al. (2019) with meta-analysis across nations and time eras, encompassing 130,758,851 births with congenital heart disease from 1970 to 2017. Congenital heart disease from literature review of all studies >4 CHARGE patients with sufficient congenital heart disease description to enable classification and with comparison of largest single study by Corsten-Janssen, Kerstjens-Frederikse, et al. (2013) and Corsten-Janssen, Saitta, et al. (2013). (Aramaki et al., 2006; Blake, Russell-Eggitt, Morgan, Ratcliffe, & Wyse, 1990; Busa et al., 2016; Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Cyran, Martinez, Daniels, Dignan, & Kaplan, 1987; Gennery et al., 2008; Jongmans et al., 2006; Jongmans et al., 2008; Legendre et al., 2012; Lin et al., 1987; Oley, Baraitser, & Grant, 1988; Strömland et al., 2005; Wyse et al., 1993).

cardiac phenotype. Within the spectrum of CHD in CHARGE syndrome, there appears to be no significant difference in presence of CHD in patients with or without a *CHD7* pathogenic variant (Bergman et al., 2011; Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Hale et al., 2016; Legendre et al., 2017; Vissers et al., 2004; Zentner et al., 2010). However, some larger series suggest an increase in congenital heart disease in *CHD7*-positive patients (66–92%) compared to 71% of *CHD7*-negative patients (Jongmans et al., 2006; Jyonouchi, McDonald-McGinn, Bale, Zackai, & Sullivan, 2009; Lalani et al., 2006). Lanali et al. also suggests a higher incidence of AVSD and PDA in isolation or associated with other lesions in CHARGE patients with *CHD7* pathogenic variants.

For individuals with *CHD7*-related CHARGE syndrome, the type of variant in *CHD7* had a genotype–phenotype relationship with more severe phenotypes being associated with truncating variants (Bergman et al., 2011; Legendre et al., 2017). This includes an increased burden of congenital heart disease in CHARGE syndrome which occurs in 70–82% of individuals with a truncating *CHD7* variant compared to 22–64% in individuals with nontruncating variants (Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Legendre et al., 2017). The primary limitation of these data to detect more detailed genotype–phenotype relationships is the sample size in individual studies. The growing repository of large cohort studies that collect the cardiac phenotype and presence of *CHD7* variant or *CHD7* variant type (truncating or nontruncating; Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Jongmans et al., 2006; Lalani et al., 2006; Legendre et al., 2017; Vissers et al., 2004; Wincent et al., 2008) should allow for pooling of these large datasets for more detailed meta-analysis. However, the overlap of pathogenic variant data and congenital heart defect phenotype is not routinely presented in most studies, which prevents data aggregation and meta-analysis and argues for publication of supplemental datasets including this information.

2.2 | Mechanisms of cardiac malformations in CHARGE syndrome

2.2.1 | Cardiac development

The heart is the first organ to develop during embryogenesis. It proceeds primarily from the splanchnic mesoderm, though the endoderm and ectoderm also play important contributions. The mesoderm forms the first recognizable heart structure, the primitive heart tube, during gastrulation. The primitive heart tube forms the first and second heart fields, with the first heart field forming the inlets (atrioventricular valves and atria), left ventricle, and connections to the systemic and pulmonary venous pathways (Figure 2a). The second heart field forms the right ventricle and outflow tract which is initially a single vessel that then septates into the great arteries with formation of the conal septum (Verzi, McCulley, De Val, Dodou, & Black, 2005). The outflow (truncus arteriosus) connects to the dorsal aortae through the

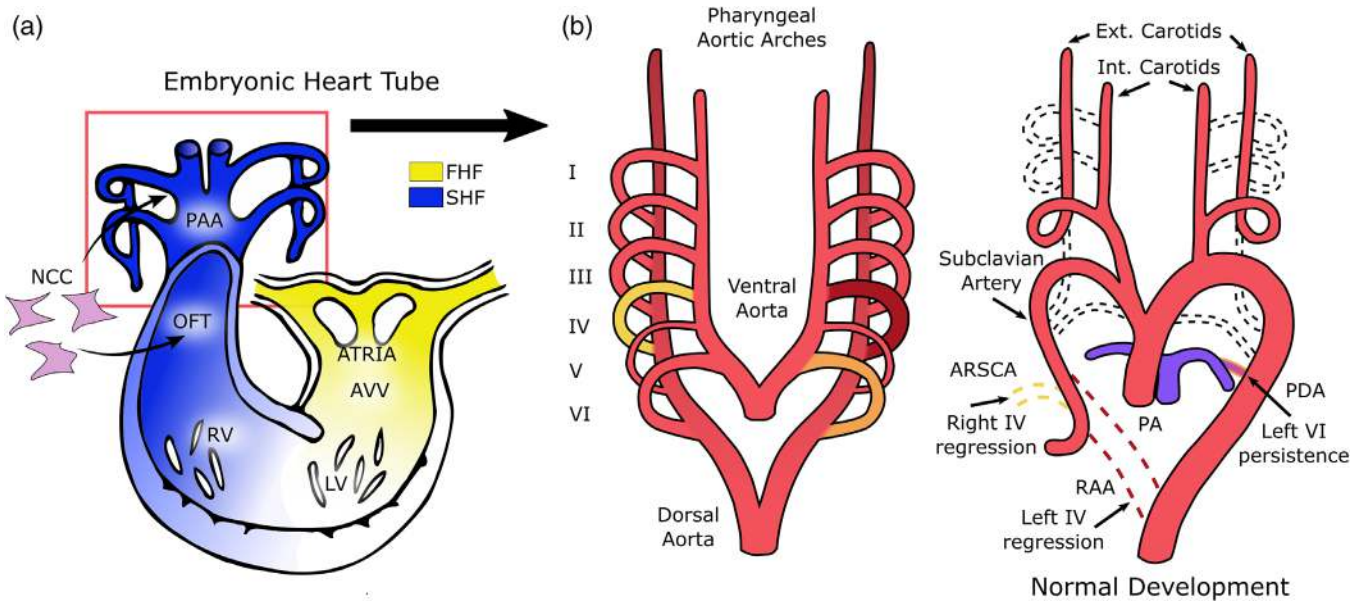

FIGURE 2 Stages of cardiac development. (a) Looping of first and second heart fields demonstrating migration of neural crest cells (NCC) to the conotruncal out flow tract (OFT) and pharyngeal aortic arches (PAA). Incomplete looping in the right ventricle (RV) or septation of the outflow tracts results in double outlet right ventricle or other conotruncal defects (e.g., Tetralology of Fallot, transposition of the great arteries). Incomplete left ventricular (LV) looping results in a double inlet left ventricle and is less common in CHARGE. Atrioventricular valve formation (AVV) begins in the first heart field (FHF) with additional components from the secondary heart field (SHF). (b) Aortic arch development. Regression in the aortic arches is heavily influenced by NCCs. Abnormal arch regression can lead to aortic arch defects typically seen in CHARGE. Examples include persistence of the left VI arch (i.e., patent ductus arteriosus (PDA), regression of the left IV arch leading to development of the right IV arch and a right aortic arch, and regression of the right IV arch leading to an aberrant right subclavian artery (ARSCA)

pharyngeal arch arteries (Figure 2b). The heart fields rotate and expand in size to establish heart looping with the second heart field moving anterior and rightward.

A complex series of events orchestrates the septation of the looped heart into four chambers with parts of both the first and second heart field contributing to the intraventricular septum. As the first and second heart field loop, the atria and ventricles are brought together at the crux of the heart, where the endocardium undergoes endothelial to mesenchymal transition, resulting in swelling and formation of the endocardial cushions. The cushions then remodel to form the atrioventricular valves. Incomplete anterior–posterior cushion union results in lack of septation of the atrioventricular valves (i.e., AVSD).

A similar process of cushion formation and rotation occurs at the level of the outlet to form the great arteries and aortic and pulmonary valves. Outflow tract cushion formation is dependent on migration of neuroectodermally derived cells called cardiac neural crest cells (see reviews [Plein, Fantin, & Ruhrberg, 2015; Stoller & Epstein, 2005]). Alteration of cardiac neural crest cell function can result in abnormal rotation (i.e., transposition of the great arteries), lack of outflow tract cushion development (i.e., truncus arteriosus), or abnormal positioning (e.g., anterior mal-alignment which results in Tetralogy of Fallot) and lead to specific patterns of congenital heart defects. Neural crest cells similarly play a critical role in regression and development of the pharyngeal arches and arch arteries (see review [Plein et al., 2015]).

It is useful to consider the spectrum of congenital heart disease as arising from patterns of altered migration (e.g., malalignment of the conal septum leading to Tetralogy of Fallot), incomplete growth (e.g., AVSD, VSD, or ASD), inappropriate regression (e.g., aberrant subclavian arteries or right aortic arch), or lack of appropriate regression (e.g., PDA) (Figure 2b). As such, impaired development within the first and second heart fields leads to the association of right sided heart lesions with conoventricular (outlets and conal septum) defects (e.g., Tetralogy of Fallot, truncus arteriosus, double outlet right ventricle) and association of the left ventricle with inlet abnormalities (e.g., double inlet left ventricle) (Figure 2a).

Given the increased frequency of conoventricular and arch vessel defects in CHARGE syndrome and the critical role in neural crest cells in septation of the outflow tract and conal septum and the pharyngeal arches, there has been long-standing focus of the involvement of neural crest cells in CHARGE syndrome (Siebert, Graham, & MacDonald, 1985). However, as demonstrated by the overrepresentation of AVSD in CHARGE syndrome and nonessential role of neural crest cells in endocardial cushion formation, additional mechanisms are likely involved in congenital heart defects associated with CHARGE syndrome.

2.2.2 | *CHD7* and associated genes in cardiac development

Chromodomain helicase DNA binding protein 7 (*CHD7*, OMIM 608892) and downstream genes are the primary causes of CHARGE syndrome. *CHD7* encodes an ATP-dependent chromatin modifier that associates with all three forms of methylated H3K4 (Schnetz et al., 2009). As with chromatin modifiers and epigenetic mechanisms of cardiac development, *CHD7* is broadly expressed in tissues, which helps to explain its pleiotropic effects.

As suggested by the pattern of cardiac defects and embryology, there are multiple lines of evidence showing that CHD7 plays a critical role in neural crest cell development and presents a stereotypic example of a neurocristopathy (Pauli, Bajpai, & Borchers, 2017). CHD7 is known to cooperate with PBAF to control formation of neural crest cells (Bajpai et al., 2010) and partially regulates Sox10 deregulation in the neural crest cells (Asad et al., 2016) leading to the CHARGE phenotype. Downstream Semaphorin and Robo pathways are critical to neural crest development and migration and may be involved in *CHD7*-negative CHARGE syndrome (S R Lalani et al., 2004; Liu, Guo, et al., 2019; Schulz et al., 2014; Ufartes et al., 2018). Additionally, there is also evidence that the disruption of Fam172a, which interacts with CHD7 and Argo2, can affect alternative splicing in neural crest cells and lead to a CHARGE phenotype (Bélanger et al., 2018), with neural crest cells being particularly sensitive to disruption of splicing machinery (Bérubé-Simard & Pilon, 2019). However, not all aspects of CHARGE can be related to the role of CHD7 on neural crest development. *CHD7* is additionally expressed in the mesoderm of the developing heart. Mesoderm lineage-specific ablation (*Mesp1*) of *CHD7* leads to disruption of endocardial cushion formation, which may explain the overrepresentation of AVSD defects in CHARGE syndrome (Payne et al., 2015).

It has been long recognized that there is a clinical overlap between individuals with CHARGE syndrome and DiGeorge Sequence/22q11.2 microdeletion syndrome (22q11.2 DS) (Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Randall et al., 2009; Sanka, Tangsinmankong, Loscalzo, Sleasman, & Dorsey, 2007). *CHD7* and *TBX1* (the locus associated with 22q11.2 DS specific cardiac defects [Lindsay et al., 2001; Merscher et al., 2001]) are synergistic in cardiac phenotypes of CHARGE (Randall et al., 2009) and both are partially mediated through effects on p53 (Caprio & Baldini, 2014; Van Nostrand et al., 2014). There is also an overlap of Kabuki syndrome, which is caused with pathogenic variations in lysine-specific chromatin modifiers (*KMT2D*, OMIM 602113 and *KDM6A*, OMIM 300128), which operate through the same chromatin remodeling machinery as CHD7 and can lead to *CHD7*-negative CHARGE syndrome (Butcher et al., 2017; Moccia et al., 2018; Sakata et al., 2017; Schulz et al., 2014). Chromatin and abnormal methylation patterning are also implicated in multifactorial causes of conotruncal defects (Radhakrishna et al., 2018). Together, these data suggest multiple common pathways in chromatin biology are necessary for neural crest cell differentiation and migration.

3 | CLINICAL IMPACT OF CHARGE ON CHD OUTCOME

Advances in congenital cardiac surgery, preoperative evaluation with catheterization, and advancing imaging have reduced mortality with surgical repair of congenital heart disease, but there remains significant morbidity and mortality associated with congenital heart disease

(Gilboa, Salemi, Nembhard, Fixler, & Correa, 2010). Multiple preoperative risk factors contribute to postoperative outcomes; prominent among these risk factors is extra-cardiac organ system involvement (Landis, Cooper, & Hinton, 2016). Abnormal development of multiple organ systems is common in many genetic syndromes and associations, with cardiac development being the most common (Fahed, Gelb, Seidman, & Seidman, 2013). As such, individuals with genetic syndromes and associations represent 20–30% of all congenital heart disease and have a higher incidence of AVSD, conotruncal defects, and aortic arch abnormalities that require surgical repair (Patel et al., 2016).

Individuals with congenital heart disease and a genetic syndrome or association have increased risk of poorer outcomes compared to nonsyndromic individuals with congenital heart disease (Alsoufi et al., 2016; Formigari et al., 2009; Landis et al., 2016; Patel et al., 2010). However, of the limited studies that dissect the effect of specific genetic syndromes and associations on outcomes after congenital heart disease repair, there are large variations in associated morbidity and mortality ranging from markedly increase risk to relative protection in surgical outcomes depending on the syndrome (Landis et al., 2016; Michielon et al., 2009). In CHARGE syndrome, the type of congenital heart defects are hemodynamically significant enough to require surgery in 63–79% of individuals with a congenital heart defect and often required multiple, staged surgical repairs (Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Husu et al., 2013; Wyse et al., 1993). The high incidence of surgical repair, high frequency of staged repair, and multiple organ systems frequently affected in individuals with CHARGE syndrome belies the importance of understanding surgical outcomes and factors to account for in the peri-operative management of individuals of CHARGE syndrome.

The wide spectrum of congenital heart disease in individuals with CHARGE syndrome and the rarity of the disease has led to limited data that specifically isolates the impact of CHARGE on postoperative outcomes. The limited data that does exist suggests that postsurgical outcomes in individuals with CHARGE syndrome are suboptimal (Michielon et al., 2009; Wyse et al., 1993), and the highest morbidity and mortality occurs within the neonatal period (<6 months; Blake et al., 1990; Tellier et al., 1998). The few identified risks factors for increased morbidity and mortality for individuals with CHARGE are predominantly airway and feeding abnormalities (Bergman et al., 2010; Blake et al., 1990; Issekutz et al., 2005; Tellier et al., 1998; Wyse et al., 1993) but there is additional increased risk of death with congenital heart disease particularly after the neonatal period (Bergman et al., 2010; Issekutz et al., 2005). The limited outcomes data in CHARGE, however, may be insufficient to assess the impact of the other associated organ system abnormalities that occur in CHARGE syndrome.

It is important to consider the role of immunodeficiency with the aforementioned airway and gastrointestinal anomalies on postsurgical outcomes in CHARGE syndrome. With increased prevalence and available outcomes data for individuals with 22q11.2, assessing the impact of 22q11.2 DS on peri-operative outcomes can provide some insight into CHARGE syndrome given the clinical overlap of cardiac defects (i.e., conotruncal and aortic arch abnormalities), airway anomalies (i.e., cleft lip and palate), and immunodeficiencies between the two syndromes (Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Hsu et al., 2016; Jyonouchi et al., 2009; Randall et al., 2009; Sanka et al., 2007). Outcomes data from 22q11.2 DS suggest mildly increased perioperative morbidity and increased length of stay, but overall similar long-term outcomes compared to nonsyndromic repair of matched congenital heart disease (Alsoufi et al., 2017; McDonald et al., 2013; Mercer-Rosa, Elci, Pinto, Tanel, & Goldmuntz, 2018; Michielon et al., 2009; Woolman et al., 2019). Part of this mild increase in perioperative morbidity and mortality in 22q11.2 DS is related to the associated immunodeficiency and increased risk of postoperative infection (Naimo et al., 2016). CHARGE and 22q11.2 DS show clinical overlap in immunodeficiency (Chopra, Baretto, Duddridge, & Browning, 2009; Hsu et al., 2016; Jyonouchi et al., 2009; Wong et al., 2015), though immune deficits tend to be less severe in CHARGE syndrome (Hsu et al., 2016). Together, these data suggest only minor contribution of immunodeficiency to peri-operative and long-term outcomes in CHARGE syndrome.

Outcomes for individuals with CHARGE syndrome are typically significantly worse than for those with 22q11.2 DS (Michielon et al., 2009), suggesting additional factors that separate these syndromes likely influence the clinical course. There are key differences between CHARGE and 22q11.2 DS in terms of the types of airway malformations (e.g., choanal atresia, vascular rings, and tracheobronchomalacia), feeding difficulties, and involvement of cranial nerves IX and X which can impart particular morbidity and mortality among CHARGE patients (K. Blake et al., 2009; Corsten-Janssen, Kerstjens-Frederikse, et al., 2013; Corsten-Janssen, Saitta, et al., 2013; Corsten-Janssen et al., 2016; Hudson, Macdonald, Friedman, & Blake, 2017; Stack & Wyse, 1991). In combination, these create a particularly high risk of postoperative airway events and aspiration, especially after cardiac surgery (Blake et al., 2009). Such events are a primary cause of death cited in the limited studies of postsurgical and long term outcomes in individuals with CHARGE (Bergman et al., 2010; Blake et al., 1990; Tellier et al., 1998; Wyse et al., 1993). Additionally, there is evidence that CHD7 plays a role in response to ischemia as evidence in negative regulation of angiogenesis in the peri-necrotic regions of glioblastoma (Boyd et al., 2019), which may play a role in cardiac recovery and remodeling after cardiac surgery. Therefore, pre- and postoperative management should include a focus on prevention of aspiration as a primary means of decreasing mortality in CHARGE patients, particularly after cardiac surgery.

4 | CONCLUSION

CHARGE syndrome has widely variable phenotypes in congenital heart disease. The spectrum of congenital heart defects appears to be secondary to chromatin signaling altering the migration and development of the neural crest cell lineage and cardiac mesoderm. However

due to the rarity of CHARGE syndrome and spectrum of pathogenic variants, understanding the full genotype–phenotype association within congenital heart disease and the other systems affected by CHARGE syndrome requires a coordinated effort to pool data across large cohort and case series studies. This effort would be enhanced by publication of descriptive datasets in supporting Information to allow for meta-analysis. Despite the wide variation in congenital heart defects in CHARGE syndrome, there is a bias toward complex congenital heart disease (e.g., conotruncal defects and AVSDs) that require major and often repeated cardiac surgical repair, which can impart considerable morbidity and mortality to individuals with CHARGE syndrome. However, poor postoperative outcomes from neonatal cardiac repair appear to be primarily driven by noncardiac risk factors. Understanding these risk factors can be critical for minimize the postoperative risk for these individuals, particularly the risk of aspiration and airway complications.

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