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Congenital heart diseases and cardiovascular abnormalities in 22q11.2 deletion syndrome: From well-established knowledge to new frontiers

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Abstract

Congenital heart diseases (CHDs) and cardiovascular abnormalities are one of the pillars of clinical diagnosis of 22q11.2 deletion syndrome (22q11.2DS) and still represent the main cause of mortality in the affected children. In the past 30 years, much progress has been made in describing the anatomical patterns of CHD, in improving their diagnosis, medical treatment, and surgical procedures for these conditions, as well as in understanding the underlying genetic and developmental mechanisms. However, further studies are still needed to better determine the true prevalence of CHDs in 22q11.2DS, including data from prenatal studies and on the adult population, to further clarify the genetic mechanisms behind the high variability of phenotypic expression of 22q11.2DS, and to fully understand the mechanism responsible for the increased postoperative morbidity and for the premature death of these patients. Moreover, the increased life expectancy of persons with 22q11.2DS allowed the expansion of the adult population that poses new challenges for clinicians such as acquired cardiovascular problems and complexity related to multisystemic comorbidity. In this review, we provide a comprehensive review of the existing literature about 22q11.2DS in order to summarize the knowledge gained in the past years of clinical experience and research, as well as to identify the remaining gaps in comprehension of this syndrome and the possible future research directions.

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CONFLICT OF INTEREST

None.

Keywords

22q11.2 deletion syndrome; cardiac surgery; cardiology follow-up; cardiovascular abnormalities; congenital heart diseases; CRKL; miRNA; prenatal counseling; single nucleotide polymorphisms; TBX1

1 | INTRODUCTION

The association between congenital heart disease (CHDs), thymic hypoplasia/aplasia, and hypoparathyroidism has been noticed since the first cases of DiGeorge syndrome (DGS) reported in the mid-1960s. In patients with clinical DGS, most of whom were diagnosed at necropsy, the “major cause of death was severe cardiac malformation usually involving the aortic arch or conotruncus” (DiGeorge, 1965; Freedom, Rosen, & Nadas, 1972; Moerman, Goddeeris, Lauwerijns, & Van der Hauwaert, 1980). Conotruncal defects (CTDs) were also the main feature of Conotruncal Anomaly Face syndrome, described in the 1970s in Japan (Kinouchi, Mori, Ando, & Takao, 1976), which explains why velo-cardio-facial syndrome, having been associated with ventricular septal defect (VSD) as the most frequent CHD, was thought to be a novel condition (McDonald-McGinn, Zackai, & Low, 1997; Shprintzen et al., 1978).

Only when progress in genetic diagnostic methods allowed the identification of the 22q11.2 deletion in the 90s, unifying all those eponymous syndromes as phenotypic variations on a theme, it became evident that CHDs were one of the pillars of clinical diagnosis of 22q11.2 deletion syndrome (22q11.2DS) (Kelly et al., 1993; Lindsay, Halford, Wadey, Scambler, & Baldini, 1993; Matsuoka et al., 1994). Indeed, since then different studies have reported CHD in 75–80% of patients with 22q11.2DS, in most cases CTDs (Marino et al., 2001; Matsuoka et al., 1998; McDonald-McGinn et al., 1999; Ryan et al., 1997). However, it is possible that the prevalence of CHDs in the 22q11.2 deletion population is overestimated, since children and adults without a significant CHD may escape diagnosis. In fact, publications focusing on adult populations, often diagnosed following psychiatric problems, report a prevalence of CHD in one third of patients with the deletion (Bassett et al., 2005; Cohen, Chow, Weksberg, & Bassett, 1999; Vogels et al., 2014). On the other hand, minor defects, such as asymptomatic aortic arch anomalies (AAA), often go unrecognized and thus the prevalence of cardiovascular manifestations may instead go underestimated (Beauchesne et al., 2005; Cohen et al., 1999; McElhinney et al., 2001).

In the past 30 years, much progress has been made in describing the anatomical patterns of CHD, in improving their diagnosis, medical treatment, and surgical procedures for these conditions, as well as in understanding the underlying genetic and developmental mechanisms (Carotti et al., 2008; Marino et al., 2001; McDonald-McGinn et al., 2015; Momma, 2010). However, cardiac defects, in particular some specific malformations, are still the main cause of mortality (~87%) in children with 22q11.2DS, with a median age at death of 3–4 months (Marino et al., 2001; McDonald-McGinn et al., 1999; Repetto et al., 2014; Unolt, Crowley, et al., 2016). In addition, adults with 22q11.2DS die prematurely, with sudden death and heart failure being the most common causes of death, even in patients without CHD (Bassett et al., 2009).

2 | CONGENITAL HEART DISEASES

2.1 | Prevalent anatomic patterns and their frequencies in the 22q11.2 population

It is already well known that the most common cardiac defects seen in patients with 22q11.2DS are CTDs, including tetralogy of Fallot (TOF), pulmonary atresia with ventricular septal defect (PA-VSD), interrupted aortic arch (IAA), mainly type B, truncus arteriosus (TA), and conoventricular VSD (Marino et al., 2001; McElhinney, Driscoll, Levin, et al., 2003; Momma, 2010; Toscano et al., 2002). AAA, either in association with intracardiac anomalies or isolated, are also commonly seen: cervical aortic arch (CAA), double aortic arch (DAA), right-sided aortic arch (RAA), and abnormal origin of the subclavian arteries (Kazuma, Murakami, Suzuki, Umezu, & Murata, 1997; Momma, Matsuoka, & Takao, 1999; McElhinney et al., 2001). Less often, other cardiovascular anomalies have been reported in patients with 22q11.2DS including, hypoplastic left heart syndrome (HLHS), transposition of great arteries, double outlet right ventricle, total anomalous pulmonary venous connection, atrial septal defect, tricuspid atresia, pulmonary valve stenosis, bicuspid aortic valve or aortic valve stenosis, aortic origin of a pulmonary artery (PA) (hemitruncus arteriosus), crossing PAs or malposition of the branch PAs (Babaoğlu et al., 2013; Consevage et al., 1996; Lee et al., 2014; Marble, Morava, Lopez, Pierce, & Pierce, 1998; Marino, Digilio, Giannotti, & Dallapiccola, 1996; Marino, Digilio, Novelli, Giannotti, & Dallapiccola, 1997; McDonald-McGinn et al., 2001; Melchionda et al., 1995; Momma, 2010; Recto, Parness, Gelb, Lopez, & Lai, 1997; J. Zhang et al., 2015).

The prevalence of each CTD in 22q11.2 patients, listed in Table 1, are based on a review of the largest population studies reported in the literature and have already been reported in a review by Momma in 2010 (Momma, 2010). Some of those studies were multicenter (Botto et al., 2003; Park et al., 2007; Ryan et al., 1997) while others were single-institution studies from different countries (Marino et al., 2001; Matsuoka et al., 1998; McDonald-McGinn et al., 1999; Oskarsdottir, Vujic, & Fasth, 2004). In each study, TOF was the most prevalent heart disease, followed by PA with VSD. The different frequencies of the individual CHD were due probably to patient selection.

Notably, these prevalence rates were based on studies conducted mainly on pediatric populations. As Momma already noted in 2010, data from the adult population are different and since then further studies confirmed this finding. Indeed, in adults with 22q11.2DS the frequency of CHD is lower, ranging from 25 to 35% and the most recurrent malformations are usually VSD and TOF (Bassett et al., 2005; Fung et al., 2015; Poirsier et al., 2016; Vogels et al., 2014). This may reflect the poorer long-term prognosis of 22q11.2 patients with CHD, as compared to those without CHD. However, these studies were conducted retrospectively and the adult patients described belonged mainly to the generation with low survival of CHD. The surgical and medical treatment of CHDs has enormously improved in the last 30 years and the population of the so-called GUCHs (grown-up congenital hearts) is now expanding (Lin et al., 2008; Warnes et al., 2008); thus we can speculate that also the 22q11.2-GUCH population will increase in the next 10 years.

Another interesting update concerns frequency of CHDs in fetuses with the 22q11.2 deletion. Thanks to the advances of prenatal genetic testing more and more often the

diagnosis of 22q11.2DS is made prenatally. The most relevant studies, investigating clinical features of fetuses with 22q11.2DS (Besseau-Ayasse et al., 2014; Noel et al., 2014), were conducted in France and both reported a very high frequency of CHD, respectively 84% (228/272) and 91% (68/74) of fetuses, as well as both identified a higher prevalence of TA (respectively 15% and 27% of all CHDs). Moreover, Noel reported 2 fetuses with HLHS (3% of all CHDs) (Noel et al., 2014). These data suggest that the prevalence of CHDs, especially that of the most severe CHDs, may be even higher in 22q11.2DS but they may also reflect a bias of ascertainment of those patients noted on ultrasound to have CHD (Bretelle et al., 2010; Lee et al., 2014; J. Zhang et al., 2015). It is possible that with the increasing use of population-based prenatal genetic screening, applying ever more accurate and less invasive methodologies, and with the enhancement of fetal echocardiography, future studies will better define the fetal cardiovascular phenotype of 22q11.2DS also in populations not biased by inclusion criteria (e.g., indication for prenatal screening).

Finally, several studies have recently reported a correlation between the type of 22q11.2 deletion and phenotype. In fact, the atypical nested deletions (LCR22-B to LCR22-D or LCR22-C to LCR22-D) were found to have a milder phenotype. In regard to the cardiovascular features (Burnside, 2015; Racedo et al., 2015; Rump et al., 2014), all studies agreed that while the types of CHDs described in individuals with nested deletions are not different from those in individuals with the standard (LCR22A-LCR22D) or proximal (LCR22A-LCR22B) deletion (both of which include the important developmental cardiac gene *TBX1*), the prevalence tends to be much lower (approximately 20%). The most frequent CHD was VSD, followed by TOF. Other CTDs were found occasionally.

Importantly, CTDs in patients with 22q11.2DS are frequently associated with additional cardiovascular anomalies as a distinctive recognizable pattern (Table 2) (Marino et al., 2001; Momma, 2010). This is very important for correct differential diagnosis between syndromic and nonsyndromic CTDs, as well as for cardiac surgery management. In particular, the TOF associated anomalies may include hypoplasia or absence of the infundibular septum, absent pulmonary valve, discontinuity, diffuse hypoplasia or crossing of the PAs and RAA or CAA with or without aberrant left subclavian artery (Babaoğlu et al., 2013; Chessa et al., 1998; Galindo et al., 2006; M. C. Johnson et al., 1995; Marino et al., 2001; Momma, Kondo, Ando, Matsuoka, & Takao, 1995). In PA-VSD, major aortopulmonary collateral arteries (MAPCAs) are common, with hypoplasia and, sometimes, discontinuity of the PAs (Anaclerio et al., 2001; Momma, Kondo, & Matsuoka, 1996). Typical characteristics of TA in patients with 22q11.2DS include type A3 of Van Praagh with discontinuity of PAs and AAA (i.e., IAA type B, RAA or DAA) and severe dysplasia with stenosis of the truncal valve (Marino, Digilio, & Dallapiccola, 1998; McElhinney, Driscoll, Emanuel, & Goldmuntz, 2003; Momma, Ando, & Matsuoka, 1997). Finally in IAA type B, associated subarterial VSD with hypoplasia of infundibular septum and aberrant right subclavian artery are evocative for 22q11.2DS (Marino, Digilio, Toscano, & Dallapiccola, 2000; Marino et al., 1999; Momma, Ando, Matsuoka, & Joo, 1999).

2.2 | Cardiac surgery: Mortality and morbidity

Owing to the aforementioned anatomical complexity, surgical repair of CTDs in patients with 22q11.2DS requires special perioperative care (Table 3) while the surgical technique does not require any modification (Anaclerio et al., 2004; Carotti et al., 2008; Formigari et al., 2009; Jatana, Gillis, Webster, & Ades, 2007). Several studies reported that, if appropriate treatment is provided following specific protocols for perioperative management of these patients, the surgical prognosis is not worse in patients with TOF, TA, and with VSD, when compared to their non-deleted counterparts (Alsoufi et al., 2017; Carotti et al., 2008; Michielon et al., 2006, 2009). Conversely, 22q11.2DS is reported as a risk factor for increased surgical mortality in patients with PA-VSD with MAPCAs. Possible explanations include the anatomical complexity of pulmonary vascular patterns, vasomotor instability, airway hyperresponsiveness, increased frequency of airway bleeding and of infectious complications (mainly fungal), and coexisting airway anomalies (Table 3) (Ackerman et al., 2001; Anaclerio et al., 2001, 2004; Carotti, Albanese, Minniti, Guccione, & Di Donato, 2003; Carotti, Marino, & Di Donato, 2003; Mahle et al., 2003; Michielon et al., 2009; Yamagishi et al., 2002). Also in IAA, the anatomic features typically associated with 22q11.2DS (i.e., type B anatomy, subaortic narrowing, hypoplasia and posteriorly deviated infundibular septum, coexistence of TA) strongly influence the surgical procedure and may represent a risk factor for immediate surgical mortality (Alsoufi et al., 2016; Anaclerio et al., 2004; Carotti et al., 2008; McCrindle et al., 2005; Michielon et al., 2009). The specific morphology of subaortic obstruction may suggest surgical options alternative to the resection of the infundibular septum (Backer, 2016).

Subsequent studies focused in greater detail on postoperative morbidity of patients with 22q11.2DS, pointing out that the microdeletion affects early operative outcomes in terms of need for prolonged intubation/tracheostomy and/or reintubation, as well as in terms of wound and systemic infections (Table 3). These complications resulted, according to the authors, in a significantly longer stay in the intensive care unit (ICU) (Alsoufi et al., 2017; McDonald et al., 2013; Mercer-Rosa, Pinto, Yang, Tanel, & Goldmuntz, 2013; O'Byrne et al., 2014; Yeoh et al., 2014; Ziolkowska et al., 2008). These findings are particularly important, since longer ICU and hospital stays are associated with worse cognitive and neuropsychiatric outcome (Forbess et al., 2002; Marelli, Miller, Marino, Jefferson, & Newburger, 2016; Marino et al., 2012). To date, studies in 22q11DS have not consistently found a correlation between the CHD status and neurodevelopmental measures, suggesting that the genetic anomaly itself contributes substantially to neurodevelopmental delays and perhaps to neuropsychiatric vulnerability (Atallah et al., 2007; Carotti et al., 2008; Maharasingam, Ostman-Smith, & Pike, 2003; Mercer-Rosa et al., 2015; Swillen et al., 2005; Unolt, Gaynor, et al., 2016; Yi et al., 2014). However, it is possible that the samples are just not large enough to determine if neurodevelopmental outcomes in 22q11.2DS vary by severity and type of CHD: further studies in the future may help answer univocally this question. Meanwhile, healthcare providers must do their utmost in order to reduce the postoperative morbidity and thus try to improve the neurodevelopmental outcome of these patients.

3 | OTHER CARDIOVASCULAR PROBLEMS

Besides congenital cardiovascular malformations, a subset of patients with 22q11.2DS develops aortic root dilation. This may be isolated, associated with minor cardiovascular anomalies or with CTDs. In several patients, the dilation progressed (John, McDonald-McGinn, Zackai, & Goldmuntz, 2009; John, Rychik, Khan, Yang, & Goldmuntz, 2014; Niwa, Siu, Webb, & Gatzoulis, 2002). Further studies are needed to determine if this association between 22q11.2DS and aortic root dilation becomes significant over time/in adults. The clinical importance of these findings remains to be determined, since so far there has been no report of aortic root dissection. However, these findings may provide novel insight into genetic mechanisms underlying aortic root dilatation (Kay, 2016).

Moreover, as reported by Bassett et al., cardiovascular causes, including sudden death, heart failure, and stroke, remain the most common causes of premature death in adults with 22q11.2DS (median age at death 41.5 year) (Bassett et al., 2009). In this study, even when features associated with possible arrhythmogenicity (e.g., atrial flutter, prolonged QT interval, major CHDs) were taken into account, they were not a sufficient explanation for sudden death in this cohort. Thus, further studies including postmortem data and genetic investigations are required to better define the mechanism responsible for sudden death in 22q11.2DS and the possible roles of major associated conditions. Indeed, besides CHDs, patients with 22q11.2DS may have many other conditions that increase their risk for cardiovascular diseases (CVDs). Some of these are secondary to other systemic conditions associated with 22q11.2DS, such as hypocalcemia, or to thyroid disorders that may cause arrhythmias, autoimmune disorders, chronic kidney disease that may cause hypertension and electrolytes imbalance (Cheung et al., 2014; Choi et al., 2005; Devriendt, Swillen, Fryns, Proesmans, & Gewillig, 1996; McDonald-McGinn et al., 2015; McLean-Tooke, Spickett, & Gennery, 2007; Shugar et al., 2015). Some of these conditions predisposing to CVDs have a multifactorial basis including genetic predisposition and psychiatric and behavioral problems associated with the 22q11.2 deletion, low physical activity due to fatigue/ hypotonia/ developmental delay, as well as side effects of some pharmacological therapies (e.g., antipsychotic and antiepileptic treatment) resulting in obesity, impaired lipid metabolism, and diabetes mellitus (Choi et al., 2005; Fung et al., 2015; Kennedy et al., 2014; Lin et al., 2008; Mercer-Rosa et al., 2015; Philip & Bassett, 2011; Voll et al., 2017).

4 | CARDIOLOGY FOLLOW-UP RECOMMENDATIONS

Considering the importance of both congenital and acquired cardiovascular anomalies in patients with 22q11.2DS, regular cardiology followup is highly recommended in all age groups (Bassett et al., 2011; Fung et al., 2015). Electrocardiography, transthoracic echocardiography, and relevant laboratory tests (e.g., calcium levels, electrolytes, thyroid studies) are mandatory in baseline workup at diagnosis, even in adults and asymptomatic patients. Owing to the frequency of AAA in this population, routine assessment of the laterality and branching pattern of the aortic arch is indicated, with particular attention to patients with respiratory or feeding disorders. This may be sometimes difficult to achieve with echocardiography alone, and MRI may be necessary, especially in older children, adolescents, and adults (McElhinney et al., 2001).

When a CHD is diagnosed it represents a chronic disease that requires lesion specific management and patient-tailored follow-up, especially when surgical repair is needed. Even following corrective surgery, lifetime surveillance is mandatory in order to monitor possible residual valve lesions and outflow obstruction, ventricular function, arrhythmias, heart failure, aortic root dilatation, and bacterial endocarditis. In fact, a significant proportion of these patients require cardiac catheterization, interventional procedures, and repeated cardiac interventions (Carotti et al., 2008; Lin et al., 2008; Warnes et al., 2008). Further studies on the GUCH population will provide answers to the question whether adults with 22q11.2DS are at higher risk for long-term complications and for need of reintervention, compared to non-syndromic counterparts. However, in the interim, it seems prudent that even patients with normal cardiac anatomy, electrocardiography, and echocardiography should still be followed periodically and these studies should be repeated in adolescence, at initial assessment during transition from pediatric care, and during the annual/biennial follow-up in children and in adults with 22q11.2DS, especially in the presence of other major conditions associated with increased CVD risk (Bassett et al., 2011; Fung et al., 2015).

5 | PREGNANCY AND PRENATAL COUNSELING

For women with CHD and 22q11.2DS, specific pregnancy and contraception education is required taking into account the specific defect and the presence of additional risk factors (such as smoking, obesity, or bleeding disorders). Counseling regarding recurrence risk of the chromosome 22q11.2 deletion and increased risks of maternal, fetal, and neonatal complications should be given by healthcare providers, who have experience with both the heart anomaly and the genetic condition. Patients should be encouraged to access tertiary care facilities with access to specialized pregnancy and postnatal care (Chan et al., 2015; Grewal, Silversides, & Colman, 2014). Regarding prenatal diagnosis, given that there is a 50% recurrence risk for the 22q11.2 deletion, noninvasive options can include monitoring by means of level II ultrasounds beginning at approximately 16 weeks gestational age (GA), followed by fetal echocardiography that may be repeated serially when a CHD is detected from 18 through 22 weeks GA. If a CHD or any other malformation is found, amniocentesis or other sampling techniques are necessary for genetic confirmation of the diagnosis (McDonald-McGinn & Zackai, 2008). However, given the 50% recurrence risk, in order to provide a definitive diagnosis, couples will benefit from counseling regarding the availability of chorionic villus sampling and amniocentesis, as well as options of pursuing pre-implantation genetic diagnosis using in vitro fertilization, donor gametes, or adoption.

In the general population, when a CHD is identified on fetal ultrasonography or echocardiography, deletion studies should be considered in any fetus with the associated CTDs, especially in IAA type B (≈50% of cases associated with 22q11.2DS), in TA (≈35% associated with 22q11.2DS), and in TOF (≈16% associated with 22q11.2DS) (Digilio et al., 1996; Goldmuntz et al., 1998; Marino et al., 2001; Peyvandi et al., 2013) (Table 4). Prenatal diagnosis is highly recommended also when other CHD are found in combination with other sonographic findings (such as cleft lip/palate, renal anomalies, polyhydramnios, congenital diaphragmatic hernia, polydactyly, vertebral anomalies, or club foot) or when significant findings are identified in a parent following a careful family history (Besseau-Ayasse et al., 2014; McDonald-McGinn & Zackai, 2008; Ming et al., 1997; Noel et al., 2014; Unolt et al.,

2017). Finally, thymic hypoplasia or aplasia may reliably be diagnosed during fetal echocardiography, giving information that may be useful in deciding which fetus needs 22q11.2 testing, as well as in counseling women/couples who decline amniocentesis or who are awaiting amniocentesis results (Barrea et al., 2003; Chaoui et al., 2002; Volpe et al., 2003). With reference to women/couples who decline amniocentesis, noninvasive prenatal testing (NIPT) for fetal aneuploidy detection is an increasingly offered service, with the ability to detect smaller fetal (and sometimes maternal) segmental aneuploidies, including 22q11.2 deletion (Gross et al., 2016; Wapner et al., 2015). Further technological advances are likely to improve its accuracy. NIPT may identify previously undiagnosed mothers as well as it may lead to a discordant positive result (e.g., due to mosaicism) (Bunnell, Zhang, Lee, Bianchi, & Wilkins-Haug, 2017). Thus, a thorough pre- and post-NIPT counseling is essential.

6 | GENES AND PATHOGENESIS OF THE CARDIOVASCULAR PHENOTYPE

6.1 | TBX1

Of the protein-coding genes located within the DiGeorge critical region (DGCR), TBX1 is thought to be the most important gene for the cardiovascular phenotype of 22q11.2DS, based on multiple mouse model approaches (Baldini, Fulcoli, & Illingworth, 2017; Jerome & Papaioannou, 2001; Lindsay et al., 1999, 2001) and mutational analysis in patients (Yagi et al., 2003). Indeed, *Tbx1* plays a dual role in outflow tract (OFT) morphogenesis: Its expression in the embryonic pharyngeal endoderm is necessary for the separation of the aorta and PAs, while its function in the secondary heart field is required for the proper OFT alignment and truncal valve septation, as well as for the cardiac neural crest cells migration and patterning (Maeda, Yamagishi, McAnally, Yamagishi, & Srivastava, 2006; Vitelli et al., 2002; Ward, Stadt, Hutson, & Kirby, 2005; Xu et al., 2004; Z. Zhang & Baldini, 2008). Moreover, *Tbx1* is required in a gene dosage-dependent manner for formation of the caudal pharyngeal arch arteries. When all those functions of TBX1 are compromised, the cardiac phenotype of patients with 22q11.2DS may include both TA and type B IAA and associated AAA (Momma et al., 1997).

On the other hand, lineage-tracing experiments suggested that *Tbx1* is not expressed in the entire secondary heart field, but only in the right-sided OFT, which might give rise to the subpulmonary infundibulum and proximal PA. Thus the subpulmonary myocardial region is particularly *Tbx1* dependent (Maeda et al., 2006). These findings explain why TOF and PA-VSD are the most frequent CHDs in 22q11.2DS, as well as support the hypothesis that "from anatomic and developmental standpoints, TOF is basically a monology, that is an underdevelopment of the subpulmonary infundibulum (conus) while the other anatomic features of the classical tetrad are its sequelae" (Van Praagh et al., 1970).

It is noteworthy that a recent study showed that vitamin B12 treatment up-regulated the *Tbx1* gene expression in the haploinsufficient mouse model, significantly ameliorating the phenotype. In particular, it demonstrated that vitamin B12 treatment partially rescued pharyngeal arch artery defects. These findings aroused hope for potential pharmacological

strategies that could compensate for developmental defects in patients with 22q11.2DS (Lania et al., 2016).

6.2 | Other genes and other possible genetic mechanisms

Human and mouse model data suggest that haploinsufficiency of *CRKL* (v-crk avian sarcoma virus CT10 oncogene homologue-like) located in the DGCR LCR22C-LCR22D region could be responsible for the cardiac outflow tract and AAA in individuals with nested distal deletions (Moon et al., 2006; Racedo et al., 2015).

Another interesting gene within the 22q11.2 locus is *DGCR8*, which plays an important role in microRNAs (miRNA) biogenesis. As recent studies demonstrated, *DGCR8* haploinsufficiency causes miRNA dysregulation in 22q11.2 deletion mouse models and in peripheral blood leukocytes derived from individuals with 22q11.2DS (Sellier et al., 2014; Shiohama, Sasaki, Noda, Minoshima, & Shimizu, 2003). Given the important role of miRNA in cardiac development (van Rooij & Olson, 2007), it is legitimate to think that miRNA-related mechanisms may contribute to the cardiovascular phenotype of 22q11.2DS.

Considering the high variability of phenotypic expression of 22q11.2DS, besides hemizygosity of the genes within the deleted region, other genetic mechanisms have been proposed. One of the most compelling theories considers the influence of the anomalies in genes from the intact 22q11.2 region, as well as additional modifying variants located outside the 22q11.2 region, involving both proteincoding genes and regulatory mechanisms (Goldmuntz et al., 2009). For example, studies evaluating common and rare copy number variants and single nucleotide polymorphisms (SNPs), found that duplications of the glucose transporter gene *SLC2A3* have been demonstrated to increase the risk of CHD in patients with 22q11.2DS (Mlynarski et al., 2015, 2016). Another study suggested that rare deleterious SNPs in histone modification-related genes might modify the cardiovascular phenotype in 22q11.2DS (Guo et al., 2015). Conversely, there is increasing evidence that hemizygosity of the 22q11.2 region disrupts some crucial signaling pathways, such as Sonic hedgehog homolog, mitogen-activated protein kinase 1 or non-canonical Wnt signaling (Chen et al., 2012; Maynard et al., 2013; Newbern et al., 2008). Studies investigating interactions between genes mapping within and outside of the 22q11.2 critical region may elucidate the increased susceptibility to CHDs in some families of probands with 22q11.2DS and in relatives without the 22q11.2 deletion (Digilio et al., 2005; Peyvandi et al., 2014; Swaby et al., 2011).

The new frontier in cardiovascular genetics in patients with 22q11.2DS is to identify also the genetic basis of the other above-mentioned cardiovascular problems, which may affect long-term outcome.

7 | CONCLUSIONS

22q11.2DS represents a paradigm of clinical genetics and anticipatory care, showing how the identification of a genotype-phenotype correlation can reduce morbidity and mortality in patients with CHDs, by adopting specific diagnostic and surgical protocols of perioperative care.

Moreover, research on 22q11.2DS led to the identification of genes essential in the cardiac morphogenesis and thus to a better understanding of the genetic mechanisms that control cardiovascular development also in non-syndromic patients.

Now, one of the greatest challenges is to find the missing link between the genotype and the phenotype in order to identify genome and molecular pathways we will, hopefully, be able to manipulate one day looking forward to novel therapeutic strategies. A joint effort of pediatric cardiologists, clinical and molecular geneticists, and developmental biologists from multiple institutions and countries has already started to overcome this challenge.

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TABLE 1

Most commonly seen cardiovascular abnormalities associated with chromosome 22q11.2DS

Congenital heart defect	% in patients with 22q11.2DS[a]
Tetralogy of Fallot	20–45%
Pulmonary atresia + ventricular septal defect	10–25%
Interrupted aortic arch	5–20%
Truncus arteriosus	5–10%
Ventricular septal defects (conoventricular)	10–50%
Isolated aortic arch anomalies	10%

[a]Prevalence of conotruncal anomalies in patients with 22q11.2DS based on a review of publications with large sample sizes (Botto et al., 2003; Marino et al., 2001; Matsuoka et al., 1998; McDonald-McGinn et al., 1999; Oskarsdottir et al., 2004; Park et al., 2007; Ryan et al., 1997).

TABLE 2

Additional cardiovascular anomalies that may be associated with conotruncal defects in patients with 22q11.2DS

Congenital heart defect	Associated cardiovascular anomalies
Tetralogy of Fallot[a]	• Hypoplasia/absence of infundibular septum • Absent pulmonary valve • Discontinuity/diffuse hypoplasia of PAs • Crossing PAs • Right/cervical AA with or without ALSA • ARSA
Pulmonary atresia + ventricular septal defectb	• MAPCAs • Hypoplasia/discontinuity of PAs • Absent ductus arteriosus • Right/cervical AA with or without ALSA • ARSA
Interrupted aortic archc	• Subarterial VSD with hypoplasia of infundibular septum • ARSA • TA • Crossing PAs
Truncus arteriosusd	• Severe dysplasia of the truncal valve • Discontinuity of PAs • Crossing PAs • Double AA • Right AA with or without ALSA • IAA type B
Ventricular septal defectse	• Cervical AA • Right AA with or without ALSA • ARSA

AA = Aortic arch; ALSA = Aberrant left subclavian artery; ARSA = Aberrant right subclavian artery; IAA = Interrupted aortic arch; MAPCAs = Major aorto-pulmonary collaterals; PAs = Pulmonary arteries; TA = Truncus arteriosus; VSD = Ventricular septal defect.

[a](Babaoğlu et al., 2013; Chessa et al., 1998; Galindo et al., 2006; M. C. Johnson et al., 1995; Marino et al., 2001; Momma et al., 1995).

[b](Anaclerio et al., 2001; Momma et al., 1996).

[c](Marino et al., 1999, 2000; Momma, Ando, et al., 1999).

[d](Marino et al., 1998; McElhinney, Driscoll, Emanuel, et al., 2003; Momma et al., 1997).

[e](McElhinney, Driscoll, Levin, et al., 2003; Peyvandi et al., 2013; Toscano et al., 2002).

TABLE 3

Extracardiac issues that potentially increase perioperative morbidity in patients with 22q11.2DS

Issue	Management
Immune dysfunction (mostly T-cell dysfunction, immunoglobulin, and humoral deficits)[a]	• Check immune status at diagnosis (complete blood cell count with differential, T cells analysis using a flow cytometry panel, immunoglobulins; immunology consult) • Use irradiated and CMV-seronegative blood products (mandatory in neonates and recommended in the first 6 months of life) • Antibiotic and antifungal coverage prior to surgery and for 48 hours postoperatively • Aggressive treatment of postoperative infections • In severely immunocompromised patients evaluate need for *Pneumocystis jiroveci* prophylaxis
Thrombocytopenia[b]	• Check platelet count regularly and transfuse if needed • Consider possible anaphylactic shock following platelets transfusion in patients with severe IgA deficiency
Hypocalcemia[c]	• Check calcium levels regularly including following discharge • Treat even when subclinical
Velopharyngeal and airway anomalies[d] (e.g. cleft palate, VPI, laryngeal web, vascular ring, etc.)	• Clinical assessment by ENT and plastic surgery before surgery (possible need for fiberoptic intubation) and before extubation • If vascular ring suspected, MRI is indicated
Pulmonary hyper-responsiveness[e]	• Treat bronchospasm
Vasomotor instability[f]	• Vasopressor therapy
Upper cervical spine and craniovertebral junction anomalies[g] (e.g. fusion of one or more cervical vertebrae, hypoplastic Cl, nonunion of spinal elements with possible spinal canal encroachment or spinal cord impingement)	• May cause injury, particularly when the positioning of the head and neck in a prolonged extension is required for the duration of the surgery • MRI to evaluate cervical spine and spinal canal and dynamic MRI when significant instability is observed • Spinal precautions during surgery, if anomalies are detected
GI anomalies[h] (e.g. GERD, intestinal malrotation, feeding problems, Hirschsprung's disease, imperforate anus)	• Abdominal ultrasound preoperatively • GI consult as needed • Treat GERD, if needed • Tube feeding, if needed • Feeding and swallowing rehabilitation • UGI with small bowel follow through if needed

Issue	Management
	• Treat constipation
Kidney anomalies[i]	• Abdominal ultrasound preoperatively
Neurological anomalies[j]	• Seizure prophylaxis

CMV = cytomegalovirus; ENT = ear-nose-throat; GERD = gastroesophageal reflux; GI = gastrointestinal; MRI = magnetic resonance imagining; VPI = velopharyngeal insufficiency.

[a-j](Carotti et al., 2008; Jatana et al., 2007; Yeoh et al., 2014).

[a](Gennery, 2012; McLean-Tooke et al., 2007).

[b](Kato et al., 2003; Lawrence, McDonald-McGinn, Zackai, & Sullivan, 2003; McLean-Tooke et al., 2007).

[c](Cheung et al., 2014; Choi et al., 2005).

[d](Dyce et al., 2002; T. R. Johnson, Goldmuntz, McDonald-McGinn, Zackai, & Fogel, 2005; Kennedy et al., 2014; Momma, Matsuoka, et al., 1999; McElhinney, Jacobs, McDonald-McGinn, Zackai, & Goldmuntz, 2002; McElhinney et al., 2001; Repetto et al., 2014; Sacca et al., 2017; Stransky et al., 2015).

[e](Ackerman et al., 2001; Yamagishi et al., 2002).

[f](Hamidi et al., 2014; Shashi, Berry, & Hines, 2003; Stransky et al., 2015).

[g](Hamidi et al., 2014; Kolman et al., 2017; Stransky et al., 2015).

[h](Giardino et al., 2014; McDonald-McGinn et al., 2015).

[i](Devriendt et al., 1996; Fung et al., 2015).

[j]Andropoulos, Stayer, Diaz, & Ramamoorthy, 2004; Bassett et al., 2011; McDonald-McGinn et al., 2015; Noel et al., 2014).

TABLE 4

Cardiovascular abnormalities specifically associated with chromosome 22q11.2DS that should prompt prenatal testing

Congenital heart defect	% of cases associated with 22q11.2DS[a]
Tetralogy of Fallot	10–15%
Pulmonary atresia + ventricular septal defect + MAPCAs	30–45%
Interrupted aortic arch type B	50–80%
Truncus arteriosus	30–50%
Isolated aortic arch anomalies	25%
Conoventricular ventricular septal defect (particularly if associated with an aortic arch anomaly)	5%

[a](Digilio et al., 1996; Goldmuntz et al., 1998; Marino et al., 2001; Peyvandi et al., 2013).