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Transcription Factor Pathways and Congenital Heart Disease

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Abstract

Congenital heart disease is a major cause of morbidity and mortality throughout life. Mutations in numerous transcription factors have been identified in patients and families with some of the most common forms of cardiac malformations and arrhythmias. This review discusses factor pathways known to be important for normal heart development and how abnormalities in these pathways have been linked to morphological and functional forms of congenital heart defects. A comprehensive, current list of known transcription factor mutations associated with congenital heart disease is provided, but the review focuses primarily on three key transcription factors, Nkx2-5, GATA4, and Tbx5, and their known biochemical and genetic partners. By understanding the interaction partners, transcriptional targets, and upstream activators of these core cardiac transcription factors, additional information about normal heart formation and further insight into genes and pathways affected in congenital heart disease should result.

Keywords

Transcription factors; Tbx5; Nkx2-5; GATA4; MEF2C; mouse; human; conduction system; septal defect; VSD; ASD; pediatric

Introduction

Defects in heart formation are a significant cause of neonatal morbidity and mortality in humans, while defects in the formation of the cardiac conduction system present a significant mortality risk throughout life (Hoffman et al., 2004; Rubart and Zipes, 2005). Congenital heart defects may be broadly grouped into two major categories: 1) morphological abnormalities, including developmental defects resulting in structural malformations; and 2) functional abnormalities, including cardiac rhythm disturbances and cardiomyopathies. While the underlying genetic basis for many of these defects remains elusive, mutations in genes encoding core cardiac transcription factors have emerged as major contributors to many forms of congenital heart disease.

As more has been learned about the transcriptional circuits controlling normal heart development, the number of transcription factors implicated in human congenital heart disease has grown concomitantly. In this review, we highlight transcription factor pathways known to be important for normal heart development and discuss how abnormalities in these pathways have been linked to morphological and functional forms of congenital heart defects. We focus primarily on three key transcription factors, Nkx2-5, GATA4, and Tbx5, and their known biochemical and genetic partners. All three of these transcription factors play central roles in cardiac development, and mutations in each have been implicated in congenital heart disease. We discuss the hypothesis that the important genetic or

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biochemical interactions between these transcription factors during normal development may be important causes or modifiers of congenital heart defects in humans.

Basic Heart Development

Mammalian heart development begins with the specification of cardiac progenitor cells within the anterior lateral plate mesoderm (Brand, 2003; Evans et al.,; Harvey, 2002). These progenitor cells condense into two lateral heart primordia and include both myocardial and endocardial lineage precursors around day 15 of human embryonic development and embryonic day (E) 7.5 of mouse development (Brand, 2003; Harvey, 2002; Srivastava, 2006). By E8.5 of mouse development, and 3 weeks of human development, the bilaterally paired condensations of cardiac precursors move medially to form a primitive heart tube (Harvey, 2002). The linear heart tube undergoes rightward looping as cells from the second heart field are added to both the inflow and outflow poles (Black, 2007; Vincent and Buckingham, 2010).

Following cardiac looping, endocardial cushions begin to form within the outflow tract (OFT) and at the common atrioventricular canal (AVC) during the sixth and seventh weeks of human development (Person et al., 2005). The endocardial cushions help to septate the heart into the four cardiac chambers and divide the outflow tract into the aorta and pulmonary artery (Combs and Yutzey, 2009; Person et al., 2005). The early cardiac conduction system also begins to be specified at this time, while the developing heart receives important contributions from the neural crest and proepicardium (Brand, 2003; Hutson and Kirby, 2007; Vincent and Buckingham, 2010). Toward the later stages of development, the heart undergoes extensive remodeling before it assumes the mature four-chambered structure with divided inflow and outflow, finely formed valve leaflets and functional conduction network (Combs and Yutzey, 2009; Evans et al., 2010); Figure 1).

A Group of “Core Cardiac Transcription Factors” Controls Heart Development

A group of transcription factors, including the homeodomain protein Nkx2-5, GATA family zinc finger proteins GATA4, 5, and 6, MEF2 factors and SRF (MADS box proteins), T-box factors, including Tbx1, Tbx2, Tbx3, Tbx5, Tbx18, and Tbx20, and the Lim-homeodomain protein Isl1, is critical for heart development (Black and Cripps, 2010; Greulich et al., 2011; Harvey et al., 2002; He et al., 2011; Peterkin et al., 2005). These core transcription factors interact with each other and with an array of other transcription factors to control heart development. Later, many of the same transcription factors are re-utilized to control cardiac chamber maturation, conduction system development, and endocardial cushion remodeling (Oka et al., 2007; Olson, 2006).

The core cardiac transcription factors function in a mutually reinforcing transcriptional network in which each of the factors regulate the expression of the others (Black, 2007; He et al., 2011; Olson, 2006). Several of the core factors involved in heart development also function as biochemical partners for each other, reflecting a complex molecular and genetic interplay controlling multiple stages of heart and conduction system development (Figures 2 and 3). Therefore, it is not surprising that mutations in several of the genes encoding the core cardiac transcription factors are associated with congenital heart disease (Table I). Nkx2-5, GATA4, and Tbx5 are perhaps the most studied and well characterized of the cardiac transcription factors implicated in patients with congenital heart disease, and all three are critical for normal heart development.

Nkx2-5 is a central regulator of heart development and is affected in congenital heart disease

The homeodomain protein Nkx2-5 controls many aspects of cardiac development, beginning with specification and proliferation of cardiac precursors to later events, such as the formation of the outflow tract (Harvey et al., 2002). Nkx2-5 acts near the top of a large transcriptional cascade controlling multiple cardiac genes. Expression of *Nkx2-5* is regulated by GATA factors and SMAD proteins and is also controlled by Nkx2-5 itself in an auto-regulatory loop (Liberatore et al., 2002; Lien et al., 2002; Lien et al., 1999; Searcy et al., 1998). More recently, *Nkx2-5* expression in the second heart field was shown to be dependent on the Isl1, while interactions between Nkx2-5, BMP2, and SMAD1 control cardiac progenitor specification and proliferation (Prall et al., 2007; Takeuchi et al., 2005).

Nkx2-5 acts combinatorially with other core cardiac transcription factors to promote cardiomyocyte differentiation and chamber identity. For example, Nkx2-5 and the basic helix-loop-helix protein Hand2 cooperate to activate *Irx4*, which is necessary for determining ventricular identity (Yamagishi et al., 2001). Ventricular identity is also controlled by Nkx2-5 through a direct physical interaction with the MADS box transcription factor MEF2C (Vincentz et al., 2008). Nkx2-5 interacts with another MADS box transcription factor, SRF, and GATA4 to promote cardiac sarcomeric protein gene expression (Sepulveda et al., 2002). Nkx2-5 also plays a role in outflow tract development through regulation of the transcriptional repressor *Jarid2* (Barth et al., 2010).

In mice, loss of *Nkx2-5* results in embryonic lethality with failure of cardiac looping and deficient myocardial differentiation (Lyons et al., 1995; Tanaka et al., 1999). In humans, mutations in *NKX2-5* have been found in patients with a variety of structural malformations including septation defects, alignment defects, and compaction defects, and cardiac conduction defects (Benson, 2010; Reamon-Buettner and Borlak). Patients with *NKX2-5* mutations also have cardiac rhythm abnormalities (Benson, 2010). Consistent with those observations, Nkx2-5 functions in the development and maintenance of the cardiac conduction system in the mouse in a transcriptional cascade that involves interactions with Tbx5 and Id2 (Jay et al., 2004; Moskowitz et al., 2007). *Nkx2-5* heterozygous mice have progressive atrioventricular (AV) block, a phenotype similar to part of the spectrum of congenital heart disease phenotypes described in human patients with *NKX2-5* mutations (Benson, 2010; Biben et al., 2000). In addition, mutation of *Shox2*, an upstream transcriptional repressor of *Nkx2-5* expressed in the sinoatrial node (SAN), results in mid-gestational embryonic lethality in mice with severe hypoplasia of the SAN and associated abnormal heart rate (Blaschke et al., 2007; Espinoza-Lewis et al., 2009). The essential role of Nkx2-5 in multiple distinct aspects of heart development and congenital heart disease suggests that modifiers, targets, or partners of Nkx2-5 are also likely to be associated with congenital heart disease.

GATA4 regulates cardiac morphogenesis and myocyte proliferation and is frequently associated with congenital heart disease

The zinc finger transcription factor GATA4 plays a central role in cardiac development and is critical for survival of the embryo (Peterkin et al., 2005; Pikkariainen et al., 2004). Mice that lack GATA4 have abnormal ventral folding, failure of midline fusion of the heart primordia, and extensive endoderm defects with embryonic lethality by E10.5 (Kuo et al., 1997; Molkenkin et al., 1997). Dosage of GATA4 is responsible for regulation of cardiac morphogenesis, and graded reduction of GATA4 leads to abnormal cardiac development with a common atrioventricular canal, double outlet right ventricle, and hypoplasia of the

ventricular myocardium (Pu et al., 2004). GATA4 is also an important regulator of cardiomyocyte proliferation through direct transcriptional activation of cell cycle regulators, including *cyclin D2* and *cdk4*, which may explain the lack of sufficient cardiac septation and chamber hypoplasia observed in patients with *GATA4* mutations (Rajagopal et al., 2007; Rojas et al., 2008).

Like Nkx2-5, GATA4 acts combinatorially with other core cardiac transcription factors to regulate heart development, including the previously discussed interactions with Nkx2-5 (Liberatore et al., 2002; Lien et al., 2002; Lien et al., 1999; Searcy et al., 1998). GATA4 also functions as an important partner for the T-box transcription factor Tbx5; mice doubly heterozygous for *Gata4* and *Tbx5* die at E15.5 due to insufficient development of the ventricular myocardium and have atrial septal defects (Maitra et al., 2009). Furthermore, GATA4 and Tbx5 directly interact and activate expression of *Cx30.2*, which encodes a gap-junction protein enriched in the AV node and required for normal AV node delay (Munshi et al., 2009).

In addition to interactions with Nkx2-5 and Tbx5, GATA4 also functions as a transcriptional partner or in transcriptional pathways with several other important cardiac transcription factors, including MEF2C. MEF2 physically interacts with GATA factors, including GATA4 and 6 to synergistically activate the expression of *Nppa*, *α -MHC*, *α -CA*, and *B-type natriuretic peptide (BNP)* (Morin et al., 2000). Additionally, GATA transcription factors, including GATA4, directly activate *Mef2c* transcription in the second heart field in combination with Isl1 (Dodou et al., 2004). GATA4 also interacts with the BMP signaling effector Smad4 within the developing endocardium, and importantly, *GATA4* mutations identified in human patients with septation defects were found to cause disrupted interaction between GATA4 and Smad4 (Moskowitz et al., 2011). Other patients with deletions in the *GATA4* locus have more severe forms of congenital heart disease, including septation defects, outflow tract alignment defects, dextrocardia, and pulmonary stenosis (Hirayama-Yamada et al., 2005; Okubo et al., 2004; Pehlivan et al., 1999; Sarkozy et al., 2005). Linkage analyses were used to demonstrate associations between *GATA4* mutations and multiple cardiac defects including ASD and VSD (Garg et al., 2003; Hirayama-Yamada et al., 2005; Okubo et al., 2004; Sarkozy et al., 2005). Interestingly, one of the *GATA4* mutations described in these family studies resulted in a missense mutation within the protein-protein interaction domain of GATA4. This alteration led to a disruption of the interaction of GATA4 and Tbx5, while it maintained the ability of GATA4 to interact with Nkx2-5 (Garg et al., 2003). These data suggest a cooperative role for GATA4 and Tbx5 in cardiac septation, and further support the notion that transcription factor interactions with their partners underscore congenital heart defects.

Involvement of Tbx5 in heart development and congenital heart disease

Genetic studies in mice have established that Tbx5 plays an important role in cardiac morphogenesis and development of the conduction system. Embryonic mice that lack Tbx5 have abnormal heart tube formation with hypoplastic atria, whereas over-expression of Tbx5 results in inhibition of ventricular maturation (Bruneau et al., 2001). Mice that lack one copy of *Tbx5* have ASD, occasional VSD, and AV block, similar to mice lacking a single copy of *Nkx2-5* (Bruneau et al., 2001). Like the other core cardiac transcription factors, Tbx5 is involved in multiple transcription factor pathways and combinatorial interactions involved in morphological development of the heart and in the development of the cardiac conduction system (Hatcher and Basson, 2009). Mice doubly heterozygous for *Tbx5* and *Gata4* have growth retardation and early neonatal lethality with AVSD and myocardial thinning, similar to the human *GATA4* mutant phenotype (Maitra et al., 2009). Tbx5 also physically interacts with Nkx2-5 to control gene expression in cells of the cardiac conduction system (Bruneau

et al., 2001; Hiroi et al., 2001), and Tbx5 and MEF2C physically interact and form a transcriptional complex resulting in synergistic activation of *Myh6* expression (Ghosh et al., 2009).

Given its interactions with GATA4, Nkx2-5, and other core cardiac transcription factors, and its extensive role in cardiac morphological and conduction system development, it is not surprising that *TBX5* is associated with human congenital heart disease. *TBX5* mutations were first identified in human patients with Holt-Oram syndrome (Basson et al., 1997; Li et al., 1997). These patients have defects in cardiac septation with secundum ASD and VSD as well as defects in cardiac conduction system and upper limb formation (Basson et al., 1994).

Summary and future directions

In addition to genetic, transcriptional, and biochemical interactions among themselves, Tbx5, Nkx2-5, and GATA4 each interact extensively with other cardiac transcription factors during normal heart development. In a few cases, mutations in these transcription factors have been implicated in congenital heart disease (Table I), but overall, the role that these interacting partners play in human heart malformations has remained largely undefined. Interestingly, Nkx2-5, GATA4, and Tbx5 each interact independently with MEF2C (Ghosh et al., 2009; Morin et al., 2000; Vincentz et al., 2008). MEF2C is critical for normal cardiac development in mice. Mice that lack MEF2C die early in development with severe cardiovascular defects, including failure of normal cardiac looping (Lin et al., 1997), suggesting that *MEF2C* might be associated with congenital heart disease in humans, although this has not been demonstrated to date.

An excellent example of a transcriptional partner and that has been associated with congenital heart disease is the friend of GATA (FOG) 2. FOG2 is a cofactor for GATA4, and mutations in *FOG2* have been found in a group of patients with congenital heart disease (Finelli et al., 2007; Svensson et al., 1999). *FOG2* mutations were also identified using a candidate-based approach in patients with tetralogy of Fallot (Pizzuti et al., 2003). Targeted mutation of *Fog2* in a mouse model resulted in embryonic lethality due to congestive heart failure with morphological abnormalities resembling those seen in human tetralogy of Fallot patients, and importantly, those seen in *Gata4* loss-of-function mutants (Svensson et al., 2000; Tevosian et al., 2000). Knowing the importance of GATA family members in directing normal heart formation and the function of FOG2 in modulating GATA activity, FOG2 was considered as a possible candidate and was subsequently found to be responsible for a common form of human congenital heart disease.

Using multiple model systems, combined with human genetic studies, we are gaining an increased appreciation for the intricate networks of transcriptional modifiers and partners that are required for normal heart development. Importantly this list of transcriptional modifiers, targets, and partners is very likely to contain genes with mutations that are associated with congenital heart disease. By further studying the interactions of the core cardiac transcription factors, we will more clearly understand how these transcription factors interact to promote normal heart development and how mutations affecting these transcription factor pathways result in congenital heart disease.

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Figure 1. Schematic representations of several stages of mammalian heart development with key events in mouse and human heart development denoted. Mouse development is denoted in embryonic days (E). Ao, aorta; AVC, atrioventricular canal; CCS, cardiac conduction system; CM, cardiac mesoderm; LA, left atrium; LV, left ventricle; NCC, neural crest cells; OFT, outflow tract; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SAN, sinoatrial node; SV, sinus venosus; V ventricle.

Figure 2. Transcription factor pathways discussed in this review that are involved in myocardial development and heart morphogenesis

Figure 3.

Transcription factor pathways discussed in this review that are involved in cardiac conduction system development, maturation, and function.

Table 1

Transcription factors with mutations found in human patients with congenital heart disease and reported interaction partners.

Transcription Factor	Associated CHD Phenotype	References
<i>ANKRD1</i>	TAPVR	(Cinquetti et al., 2008)
<i>CITED2</i>	TOF, ASD, VSD, AS, PS, SI, TGA, RVOTO, TAPVR	(Sperling et al., 2005)
<i>ETS1</i>	DORV, HLHS, ASD	(Ye et al., 2010)
<i>FOG2/ZFPM2</i>	TOF, DORV	(De Luca et al., 2011; Finelli et al., 2007; Pizzuti et al., 2003)
<i>FOXC1</i> (18p11.2 del)/ <i>FOXC2</i>	HLHS, PVA, PAH, VSD, OA, ASD, PDA, BSVC	(Brice et al., 2002; Finegold et al., 2001; Maclean et al., 2005; Yu et al., 2010)
<i>FOXH1</i>	TGA	(De Luca et al., 2010)
<i>GATA4</i>	ASD, AVSD, VSD, PS, AR, VPS, PDA, TOF, AF	(Butler et al., 2010; Chen et al., 2010a; Chen et al., 2010b; Chen et al., 2010c; De Luca et al., 2010; Dinesh et al., 2010b; Garg et al., 2003; Giglio et al., 2000; Guida et al., 2010; Hirayama-Yamada et al., 2005; Liu et al., 2011; Nemer et al., 2006; Pehlivan et al., 1999; Peng et al., 2010; Posch et al., 2010a; Rajagopal et al., 2007; Reamon-Buettner et al., 2007; Sarkozy et al., 2005; Schluterman et al., 2007; Tomita-Mitchell et al., 2007; Wang et al., 2010; Wang et al., 2011a; Zhang et al., 2008; Zhang et al., 2009b)
<i>GATA6</i>	PTA, TOF, ASD	(Kodo et al., 2009; Lin et al., 2010; Maitra et al., 2010)
<i>HAND1</i>	VSD, ASD, AVSD	(Cheng et al., 2011a; Goldmuntz et al., 2011; Reamon-Buettner et al., 2008; Reamon-Buettner et al., 2009; Wang et al., 2011a)
<i>HAND2</i>	TOF, DORV, PS	(Shen et al., 2010)
<i>HOXA1</i>	DORV, TOF, VSD, TAPVR, IAA, PDA	(Bosley et al., 2008)
<i>IRX4</i>	VSD	(Cheng et al., 2011b)
<i>JAG1</i>	TOF, VSD, PPS, Ao dextroposition	(Eldadah et al., 2001; Greenway et al., 2009; Heritage et al., 2002; Heritage et al., 2000; Krantz et al., 1999; Li et al., 2010; Li et al., 1997a; Oda et al., 1997; Rauch et al., 2010)
<i>MYOCD</i>	PVD	(Ransom et al., 2008)
<i>NFATC1</i>	VSD	(Yehya et al., 2006)
<i>NKX2-5</i>	ASD, VSD, AVSD, TOF, SVAS, LVNC, PA, PS, PDA, MV anomalies, conduction defects, DORV, PAPVR, TAPVR, heterotaxy, TGA	(Baekvad-Hansen et al., 2006; Benson et al., 1999; De Luca et al., 2010; Dinesh et al., 2010a; Elliott et al., 2003; Gioli-Pereira et al., 2010; Gutierrez-Roelens et al., 2002; Ikeda et al., 2002; Konig et al., 2006; McElhinney et al., 2003b; Ouyang et al., 2011; Pabst et al., 2008; Pauli et al., 1999; Rauch et al., 2010; Reamon-Buettner and Borlak, 2004a; Reamon-Buettner et al., 2004; Schott et al., 1998; Stallmeyer et al., 2010; Wang et al., 2011b; Zhang et al., 2009a; Zhu et al., 2000)
<i>NKX2-6</i>	PTA	(Heathcote et al., 2005)
<i>PITX2</i>	AF	(Franco et al., 2011)
<i>SALL4</i>	VSD, PTA, TOF	(Paradisi and Arias, 2007; Wang et al., 2010)
<i>TBX1/22q11del</i>	IAA, PTA, AAA, TOF, malaligned VSD	(Akcakus et al., 2003; Alikasifoglu et al., 2000; Beauchesne et al., 2005; Borgmann et al., 1999; Botto et al., 2003; Brunet et al., 2009; Calderon et al., 2009; Devriendt et al., 1996; Gawde et al., 2006; Gioli-Pereira et al., 2008; Goldmuntz et al., 1998; Goodship et al., 1998; Henwood et al., 2001; Hokanson et al., 2001; Hu et al., 2009; Iserin et al., 1998; Ito et al., 2002; Jiang et al., 2005; Jiang et al., 2010; Lindsay et al., 1995; Lupski et al., 1991; Matsuoka et al., 1994; McElhinney et al., 2001; McElhinney et al., 2003a; Oh et al., 2002; Poon et al., 2007; Rauch et al., 2004; Rauch et al., 2010; Raymond et al., 1997; Repetto et al., 2009; Rope et al., 2009; Ryan et al., 1997; Sorensen et al., 2010; Swaby et al., 2011; Tomita-Mitchell et al., 2010; van Engelen et al., 2010; Verhoeven et al.,

Transcription Factor	Associated CHD Phenotype	References
		2011; Wilson et al., 1992; Worthington et al., 1998; Wozniak et al., 2010; Yakut et al., 2006; Yates et al., 1996; Yong et al., 1999)
22q11dup	VSD, HLHS, TAPVR, conotruncal anomalies	(Ensenauer et al., 2003; Ou et al., 2008; Sparkes et al., 2005)
<i>TBX5</i>	ASD, VSD, AVSD, rhythm abnormalities	(Basson et al., 1997; Li et al., 1997b; Liu et al., 2009; McDermott et al., 2008; Postma et al., 2008; Reamon-Buettner and Borlak, 2004b; Zhu et al., 2008)
<i>TBX20</i>	ASD, dilated cardiomyopathy, valve defects	(Hammer et al., 2008; Kirk et al., 2007; Liu et al., 2008; Posch et al., 2010b; Qian et al., 2008)
<i>TFAP2B</i>	Char syndrome, PDA	(Chen et al., 2011; Mani et al., 2005; Satoda et al., 2000; Vaughan and Basson, 2000; Zhao et al., 2001)
<i>ZEB2</i>	Mowat-Wilson Syndrome	(Adam et al., 2006; Balasubramaniam et al., 2010; Dastot-Le Moal et al., 2007; Garavelli et al., 2009; Heinritz et al., 2006; McGaughan et al., 2005; Sasongko et al., 2007; Saunders et al., 2009; Wilson et al., 2003; Zweier et al., 2005)
<i>ZIC3</i>	TGA, DORV, PS, TAPVR, ASD, AVSD, heterotaxy	(Bedard et al., 2010; De Luca et al., 2010; Ware et al., 2004)

Abbreviations used: AAA, aortic arch anomalies; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; AVC, atrioventricular canal; AVSD atrioventricular septal defect; BAV, bicuspid aortic valve; BPV, bicuspid pulmonary valve; BSVC, bilateral superior vena cava; DORV, double outlet right ventricle; HAA, hypoplastic aortic arch; HCM, hypertrophic cardiomyopathy; HLHS, hypoplastic left heart syndrome; HOCM, hypertrophic obstructive cardiomyopathy; IAA, interrupted aortic arch; LVH, left ventricular hypertrophy; LVNC, left ventricular non-compaction; MS, mitral stenosis; MV, mitral valve; MVD, mitral valve dysplasia; MVP, mitral valve prolapse; OA, overriding aorta; PA, pulmonary atresia; PAH, pulmonary artery hypoplasia; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; PPAS, peripheral pulmonary artery stenosis; PPS, peripheral pulmonic stenosis; PS, pulmonary stenosis; PTA, persistent truncus arteriosus; PVA, pulmonary valve atresia; PVD, pulmonary valve dysplasia; PVS, pulmonary valve stenosis; RAA, right aortic arch; RVOTO, right ventricular outflow tract obstruction; SI, situs inversus; SVAS, supraaortic stenosis; SVPS, supraaortic pulmonary stenosis; SVT, supraventricular tachycardia; TAPVR, total anomalous venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TVP, tricuspid valve prolapse; VAS, valvar aortic stenosis; VPS, valvar pulmonary stenosis; VSD, ventricular septal defect.