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Heart Failure in Congenital Heart Disease: A confluence of acquired and congenital

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Abstract

Heart failure (HF) is a common cause of morbidity and mortality in congenital heart disease (CHD), with rising prevalence due to improved interventional and surgical treatment options and outcomes. The interplay between genetic factors and acquired postnatal factors in CHD might play a major role in the progression to HF. In this review, we propose three putative routes which lead to HF in CHD: rare monogenic entities that cause both CHD and HF, severe CHD lesions in which acquired hemodynamic effects of CHD or surgery result in HF, and most commonly a combined effect of complex genetics in overlapping pathways and acquired stressors caused by the primary lesion. Novel sequencing technologies have allowed a better understanding of the genomic architecture of HF and CHD with multiple overlapping pathways and hypothesized mechanisms through which pathway deficiencies that led to CHD can increase the risk of progression to HF. Through next-generation sequencing technologies and drug screening using patient-specific induced pluripotent stem cells, the coming years hold a tremendous promise of better understanding this confluence and yielding effective therapeutics.

Keywords

Heart Failure; Congenital Heart Disease; Genomics; Adult

Introduction

Congenital heart disease encompasses all malformations of the heart that occur *in utero* and exist at birth and is estimated to affect at least 8.1 per thousand live births.[1] The prevalence of complex and hemodynamically significant lesions, which result in early deaths if not addressed via surgical or percutaneous methods, is 2.3 per thousand infants.[2] The past three decades have witnessed marked progress in pediatric cardiology and cardiac surgery,

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allowing patients to survive to adulthood. As a result, the prevalence of an adult population with CHD (ACHD) outnumbers the pediatric population with CHD in the USA.[2,3] An analysis of 71,686 patients with CHD between 1987 and 2005, revealed that infant CHD mortality has decreased dramatically, but with a shifting mortality burden towards adulthood.[4] Heart failure (HF) is the major problem in ACHD, as nearly one quarter develops heart failure at 30 years.[5] The events inciting HF in ACHD patients are different than in other forms of HF, however there are limited data available to guide their management. Consensus guidelines for diagnosis and treatment of HF are often used for HF ACHD patients because adequate controlled data are lacking for this sub-population.[6]

Dramatic advances in cardiac genetics have paralleled improvements in the treatment of CHD. Over the past two decades, 50 to 70% of the genetic causes of inherited cardiomyopathies were established through increasingly powerful methods of DNA analysis. Discovery of the genetics of nonsyndromic congenital heart disease lags behind the inherited cardiomyopathies. Sequencing initially identified mutations in transcription factor genes involved in heart development in familial cases, and the large majority of sporadic CHD have remained unexplained. This is likely due to the complexity of the underlying genetic causes; multiple mutations may increase the risk of CHD, in an additive fashion, or manifest in the presence of environmental factors and result in cardiac malformation. Current research emphasizes the important role of gene-environment interactions and epigenetics in CHD.

As the molecular signatures of CHD and HF are being characterized with the use of available technology, it is increasingly appreciated that at least some disease pathways are shared. Determining the molecular basis of HF in ACHD will play a crucial role in developing treatment strategies for this growing population. This review will summarize the limited current knowledge of the genetics of HF in ACHD, and discuss how innovation may discover therapies for this population.

Routes to Heart Failure in CHD Patients

The progression to HF in patients with CHD involves proven and hypothesized mechanisms, which we classify into three routes (Figure 1). The first route is purely acquired and mechanical with no genetic element. This includes incomplete or palliative correction of a lesion leading to a chronic state of hemodynamic stress and subsequent heart failure.[6] The probability of heart failure in CHD lesions such as tetralogy of Fallot (TOF), and transposition of the great arteries (TGA) can be as high as 80% at 50 years of age, while it is around 20–30% for isolated valvular disease or defects that result in left-to-right shunt.[6] Additional myocardial insults can complicate surgery, including injury to the myocardium, coronary arteries, and conduction system.[6] Post surgical conduction disease may require permanent ventricular pacing, which can lead to progressive contractile dysfunction.[6] Since these insults often occur in the first years of life, the effects of altered hemodynamics or tissue injury accumulate over years, resulting in early development of HF.

Although the increased prevalence of HF in ACHD is primarily viewed as a result of a volume or pressure overload, whereby the starting point is an abnormal heart, an independent genetic component is also present. This second route depicted in Figure 1 delineates a purely genetic component that causes both cardiac malformation and a cardiomyopathy that result in HF, unrelated to hemodynamic stress. Many of the pathways involved in cardiac development *in utero* are also involved in myocardial structure and stability. Therefore, it is not surprising that certain molecular perturbations can cause both a cardiac defect at birth, and a cardiomyopathy that can present later in life, often in childhood. As described in greater detail in following sections, Noonan Syndrome (NS) is

the second most frequent syndromic form of CHD and can cause both CHD and cardiomyopathy. Similarly, another example of congenital cardiomyopathy is left ventricular non-compaction (LVNC), a heterogeneous disorder that often results in HF. LVNC has been associated with CHD including atrial and ventricular septal defects, Ebstein anomaly and outlflow tract lesions, and is caused by genes such as *MYH7* and the transcription factor *NKX2-5* among others.[7–10]

In a Dutch registry of 10,808 CHD patients followed for 21 years (median), the incidence of HF-admissions was 1.2 per 1000 patient years and median age at first HF-admission was 46.7 years. This incidence of HF admissions in ACHD patients is more than ten times what is reported in an age matched cohort without CHD (0.1 per 1000 person years).[11] The true prevalence of HF is thought to be higher as not all HF events in CHD patients resulted in hospital admission. Low prevalence CHD lesions such as TGA and TOF that result in HF via markedly abnormal hemodynamics do not solely account for the epidemic of HF in CHD. Moreover, gene mutations that cause both cardiomyopathy and CHD are extremely rare. Therefore, it is unlikely that these two routes alone explain the high incidence of HF in CHD. This suggests additional mechanisms through which CHD patients can develop HF. We present this as a third route in figure 1, which is a combination of congenital genetic risk and acquired hemodynamic stressors. There is significant overlap in the molecular pathways that result in CHD during development and those that are responsible for the integrity of the postnatal myocardium. This overlap suggests that molecular perturbations that result in abnormal cardiac development can increase the risk for heart failure in adulthood, especially in the presence of chronically perturbed hemodynamics. Heart failure also involves the reactivation of many fetal genes. One can expect the reactivation of a mutated pathway to exacerbate the progression to HF in the setting of CHD. With the current era of high throughput DNA, RNA, protein and metabolic analysis this hypothesis can be studied using a systems biology approach to investigate the development of HF in CHD patients, particularly those with mild phenotypes whose progression to HF might not be justified by the degree of volume or pressure overload caused by the lesion.

Monogenic Causes of Heart Failure in Cardiomyopathy and CHD

The genetic basis of HCM was first described in 1990.[12,13] Following this discovery, the principal genetic causes of hypertrophic, dilated and arrythmogenic cardiomyopathies have been identified. Depending on phenotype, a disease causing mutation can be found in 30–70% of patients. Culprit genes encode structural proteins such as those that form the sarcomere, cellular cytoskeleton, or ion channels.[14] (Table 1) Genetic testing for inherited cardiomyopathies is clinically available and improves the efficiency of family screening, enabling early diagnosis and timely clinical management in at-risk individuals.[15]

Alternatively, the clinical application of CHD genetics remains limited. Monogenic causes of CHD are estimated to account for only 5–10% of disease, usually related to loss of function mutations in transcription factor genes and other signaling molecules that disturb molecular pathways during cardiac development.[16] (Table 1) Monogenic causes have predominantly been identified in syndromic cases where CHD occurs with non-cardiac congenital malformations.[16] In only a minority of presentations is genetic testing available and useful. Genetic testing is available for most syndromic cases. To name few examples, Holt-Oram Syndrome, which causes CHD and upper limb malformations, is caused by mutations in *TBX5* and *SALL4* genes.[16] Alagille Syndrome causing CHD along with liver disease, is caused by mutations in the *JAG1* or *NOTCH2* genes.[16] Among the non-syndromic genes, *GATA4* and *Nkx2-5* are two well-established genes in familial CHD,[16] and are also available for clinical genetic testing. The genetic cause of non-syndromic CHD is less well understood, and clinical genetic testing is not routinely advised for such

patients.[17,18] However, there are several genetically characterized syndromes where CHD and HF are common morbidities; including Noonan, Williams-Beuren and 22.q11.2 deletion syndromes.

Noonan Syndrome (NS), in which HCM is the second most common cardiac manifestation, is a representative example. NS results from abnormal RAS-MAPK signaling, which normally regulates cellular proliferation, differentiation, and survival.[19] Mutations in different components of the RAS-MAPK pathway have been described, including *PTPN11, KRAS, SOS1, NRAS, RAF1*, *SHOC2* and *CBL*;[19,20] which typically result in constitutive activation.[19] The 20% of NS patients who develop HCM present with a wide phenotypic spectrum, with approximately 25% dying of heart failure in the first year of life.[19] The CHD manifestations of NS are pulmonary stenosis, present in more than 50% of cases and secundum atrial septal defect in 6–10%. Other less common malformations include ventricular septal defect, atrioventricular canal, aortic stenosis and coarctation.[19] Common extra-cardiac manifestations of NS include short stature and facial dysmorphism.[20] Adults with NS suffer from cardiac complications of the syndrome that result frequently in HF, whether due to the cardiomyopathy, the associated valvular disease, or both.[21] The limited natural history data in NS suggests that cardiovascular complications are a major cause of mortality. [22] Noonan syndrome with Multiple Lentigenes (formerly known as LEOPARD syndrome) is similar to NS, is caused by loss of function mutations inthe *PTPN11* gene and has a high frequency (>70%) of associated HCM.[23] Additional manifestations of this rare syndrome include multiple lentigines and sensorineural deafness.[24]

Williams-Beuren Syndrome (WBS) is caused by a microdeletion on chromosome 7q11.23, a region that includes 26 to 28 genes.[25] The syndrome is characterized in most cases by supravalvular aortic stenosis (SVAS), mental retardation, and distinctive facial features.[25] Loss of one allele of the *ELN* gene, which encodes elastin and resides on the 7q11.23 locus, causes familial SVAS without the other manifestations of WBS.[25] Severe SVAS in children leads to cardiac hypertrophy and heart failure unless corrected surgically. Adults with SVAS suffer from high risk of cardiovascular complications; of 113 patients with median 6 year follow up, 7.3% developed new-onset heart failure[26]

The 22q11.2 microdeletion syndrome (also known as DiGeorge or velocardiofacial syndrome) has a diverse phenotypic spectrum. Common manifestations include ventricular outflow tract defects, facial dysmorhpism, hypocalcemia and immunodeficiency.[21] The syndrome is caused by a 1.5 to 3 Mb hemizygous deletion on chromosome 22q11.2 and most clinical manifestations, especially the cardiac malformations, are explained by the loss of one allele of the *TBX1* gene.[21] The most common outflow tract defects seen in the syndrome are TOF, type B interrupted aortic arch (IAA), and truncus arteriosus (TA). Microdeletion in the same region may cause isolated CHD without obvious extra-cardiac syndromic manifestations.[21] Complications of these malformations in adulthood are common and include re-coarctation of an IAA that was previously surgically reconstructed, residual or acquired obstruction of the left ventricular outflow tract, or arrhythmias that arise after repair of TOF.[21] Genetic testing for 22q11.2 deletion is readily available and recommended for CHD lesions typical of the 22q11.2 syndrome, including aortic arch abnormalities.[27] Genetic diagnosis may have clinical implications, as in patients with isolated TOF and 22q11.2 deletion, there is evidence for an increased prevalence of aortic root dilation.[28]

Several other genes have been associated with familial forms of non-syndromic CHD. Evidence is most robust for loss of function (LOF) mutations in *GATA4*, *TBX5*, and *NKX2-5*, which are transcription factors expressed in the developing heart,[16] although other transcription factors and signaling molecules have been implicated. The transcripts of these

three genes form a complex that regulates downstream targets involved in the regulation of cardiac development. LOF mutations in these genes can be a result of nonsense or frameshift mutations that cause a truncated protein or due to CNVs, which result in loss or gain of a copy of a gene. For example, at least 10% of TOF are caused by *de novo* CNVs.[29] In addition to identifying the role of CNVs in CHD, the advent of exome sequencing is starting to yield a better understanding of novel molecular causes of CHD. A recent study showed that *de novo* LOF mutations in histone-modifying genes contribute to 10% of severe CHD, highlighting a unique role for epigenetic mechanisms involved in the molecular pathophysiology of CHD.[18] Identification of CHD as part of a genetic syndrome would allow prediction of not only cardiac but also extra-cardiac outcomes as well as interventions to modify them e.g. aggressive monitoring and treatment of hypertension and of coronary artery lesions in WBS that may contribute to cardiac hypertrophy and dysfunction. This may help personalize the care of the adult CHD patient at risk for HF.

Overlapping Pathways in CHD and HF Genetics

While the genetics of CHD and HF in humans has been studied separately, with the few directly shared disease genes described to date, there is significant evidence from model organisms and *in-vitro* studies that similar molecular pathways are involved (Table 2). Several genes involved in embryonic cardiac development continue to be expressed in the adult heart where they play a role in maintaining cardiomyocyte survival and integrity. *GATA4* and *GATA6* are two transcription factor genes that are mutated in familial cases of CHD.[16] In addition to their role in cardiac development, they are potent activators of cardiac promoters such as atrial natriuretic factor (ANF) and B-type natriuretic peptide (BNP) in the adult heart.[30] They also regulate the transcription of cardiac sarcomere genes, namely alpha- and beta-myosin heavy chain.[30] Moreover, *GATA4* is a survival factor for adult cardiomycytes as it also regulates the antiapoptotic gene *BCL-X*.[31] Myocyte apoptosis is a major element in the pathophysiology of heart failure, and it has been established that genetic or pharmacologic enhancement of *GATA4* can prevent cardiomyocyte toxicity and drug-induced cardiotoxicity such as with doxorubicin treatment, where GATA4 depletion is an early event.[31] This data collectively suggest that GATA4 is a potential target in heart failure treatment, and that CHD patients with LOF mutations in their *GATA4* or *GATA6* genes might have increased apoptosis of their cardiomyocytes predisposing them to heart failure in the setting of other insults such as volume overload caused by CHD. *GATA4* also plays a role in calcium-calcineurin signaling responsible for cardiac hypertrophy and heart failure.[32] Calcineurin dephosphorylates Nuclear Factor of Activated T Cells (NFATC), which results in its translocation to the nucleus where it binds GATA4 and activates transcription of a hypertrophic gene program.[32] NFATC transcription factor is essential for valve formation in mice,[33] and mutations in *NFATC1* have been associated with CHD in humans.[34,35] Recent murine data also suggests an important role for NFATC transcription factors in the cardiomyocyte response to stress.[36] Calcineurin also activates CaMK and results in phosphorylation of histone deacetylase (HDAC), a nuclear protein causing its dissociation from the transcription factor Myocyte Enhancer Factor (MEF2) and its externalization from the nucleus.[32] MEF2 transcription factors are the second effectors of calcineurin signaling, and also play critical roles in both cardiac development and normal postnatal myocardial survival.[37] This calcium-dependent signaling pathway constitutes an excellent potential target in heart failure and/or cardiac hypertrophy.[32]

Epigenetics, particularly the role of molecules such as HDAC responsible for DNA methylation and histone modifications represents another shared pathway in CHD and HF. The importance of increased DNA methylation of genes in cardiomyopathy hearts as compared to controls has been described, [38,39] and recently, a large exome sequencing project identified that *de novo* truncating mutations in similar histone-modifying genes is

seen in ~10% of sporadic CHD.[18] Heart failure progression involves a pattern of gene expression including re-expression of fetal genes involved in cardiac development, increased expression of genes encoding extracellular matrix proteins, altered calcium signaling, and histone modification.[40] These processes involve genes that can be mutated in the setting of CHD. Therefore, one can hypothesize that pre-existing defects in these pathways can potentially worsen the progression to heart failure in CHD patients. Addressing this hypothesis is a methodologic challenge that has only recently become possible with the advent of technologies such as next-generation sequencing. While this review does not intend to explore all potential overlapping molecular pathways in heart failure and CHD, the above examples of epigenetics, transcription factors, and calcium-dependent signaling serve as putative examples. Using IPA (Ingenuity® Systems, www.ingenuity.com), a software toolkit to model and analyze complex biological systems, we performed a rapid analysis of canonical pathways on a set of 146 literature-curated genes known to be involved in CHD in humans or in animal models. This yielded multiple pathways that are known to be involved in heart failure (Table 2). Genes involved in Hypoxia-Inducible Factor (HIF)1-alpha signaling are activated in cardiac hypertrophy,[41] while their down-regulation is associated with the development of TGA in mice.[42] Similarly, other signaling pathways such as Wnt/β-catenin, TGF-β, and JAK/Stat are involved in heart failure and at the same time harbor CHD candidate genes. Understanding the genomics of HF has crossed many milestones, but most of the work has been focused on identifying the molecular signature of ischemic and non-ischemic cardiomyopathies and trying to target the ensuing HF.[43,44] CHD patients with HF constitute a smaller niche that has not been interrogated. Studies looking at gene expression profiles through RNA sequencing of human hearts with CHD and HF and corresponding controls will be extremely valuable to understand the unique molecular causes of HF in CHD patients.

The Future of Personalized Treatment of HF in ACHD

Current treatment of HF in ACHD involves therapies which limit neurohumoral activation, and are based on extrapolation from adults with HF unrelated to CHD. While using beta-adrenergic blockers, aldosterone antagonism, and angiotensin inhibition has intuitive appeal, there are limited data to support the use of these drugs in the ACHD population with HF. Indeed, emerging data challenges the notion that we can extrapolate conventional HF therapies to ACHD patients with HF. For example, a recent trial of valsartan in patients with a systemic right ventricle failed to show any beneficial effect on the primary end point of right ventricular ejection fraction, and most secondary end points.[45] This trial suggests that the ACHD population might have unique genetic and acquired factors that would make medications used in common causes of HF ineffective. Pharmacogenomic studies have established that SNPs in adrenergic receptors could modify the response to beta-blockers.[46] Similarly in CHD patients, SNPs in HF pathways targeted by pharmacotherapy can potentially result in resistance to drug therapy. Such studies will be needed for CHD patients to have better tailored therapies. In one successful example, polymorphisms in the renin-angiotensisn-aldosterone system (RAAS) genes were used to identify a subgroup of high-risk patients with single ventricle that do not show reverse remodeling after staged surgery.[47] This high-risk subset may benefit from earlier volume unloading surgery before injury becomes irreversible. A study in surgically repaired TOF patients identified variations in HIF1-alpha genes were associated with RV dilation and dysfunction during follow-up likely related to maladaptive response to hypoxia and hemodynamic load.[48] It raised the possibility that earlier repair of TOF may limit hypoxic injury of the myocardium and promote better long-term adaptation. These studies show the power of genomics in guiding clinical decisions including surgical decisions. These studies need to be done in adult CHD patients to determine if the effect of genetic variations on adverse ventricular remodeling persists into adulthood.

Another promising aspect of how genomics can help tailor therapy in HF in ACHD is targeted therapy of particular pathways known to be involved in the progression to heart failure. While it seems early to discuss therapeutics because most of the complex genetic aspects of HF in CHD remains incompletely understood, there has been at least one example with inhibition of the pathways that leads to HCM in NS, where a clinical trial using a MEK1 inhibitor is underway (www.clinicaltrials.gov NCT01556568). Once other pathways are clearly defined, similar targeted therapy for the prevention of HF in other forms of ACHD may follow. Progress towards this goal has been enabled by high throughput sequencing technologies and with the availability of patient-specific induced pluripotent stem cells (iPS) from patients with cardiomyopathies where drug specific cardiotoxicity was demonstrated at the single-cell level.[49] These cells could be used for rapid screening of cardioactive drugs with the patient's genetic background, an approach being assesed in primary cardiomyopathy.[50,51]

Conclusions

Heart failure is a major cause of morbidity and mortality in ACHD and the current approach for its treatment is rarely evidence-based. Rare monogenic causes of CHD and HF include Noonan Syndrome, Williams-Beuren Syndrome, and 22q11 Syndrome. Overlapping molecular pathways between CHD and HF exist, and their interrogation will pave the way for a better understanding of the development of HD in CHD. HF in ACHD is most commonly a result of a confluence between inherited complex genetic factors and acquired stressors caused by the defect. Current technologies such as next-generation sequencing and iPS will contribute to the understanding of this confluence and pave the way for novel therapeutics.

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Key Points

- Heart failure is a major cause of morbidity and mortality in ACHD and the current approach for its treatment is rarely evidence-based.
- Rare monogenic causes of CHD and HF include Noonan Syndrome, Williams-Beuren Syndrome, and 22q11 Syndrome.
- Overlapping molecular pathways between CHD and HF exist, and their interrogation will pave the way for a better understanding of the development of HD in CHD.
- HF in ACHD is most commonly a result of a confluence between inherited complex genetic factors and acquired stressors caused by the defect. C
- urrent technologies such as next-generation sequencing and iPS will contribute to the understanding of this confluence and pave the way for novel therapeutics.

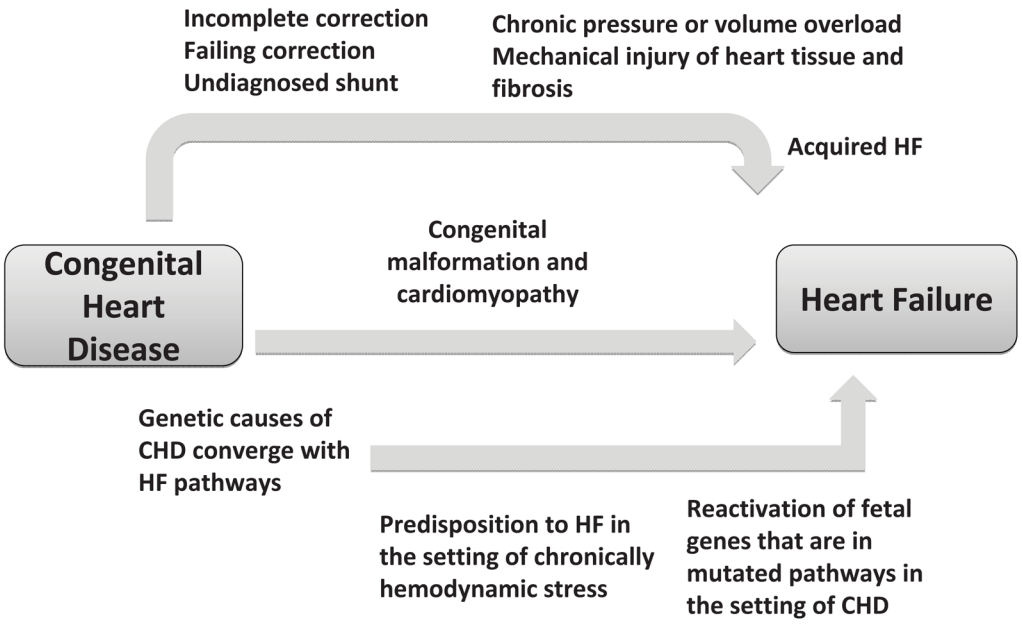

Figure 1.

Schematic of the hypothesized mechanisms linking congenital heart disease with heart failure. We propose three putative routes which lead to HF in ACHD: rare monogenic entities that cause both CHD and HF (middle arrow), severe CHD lesions in which acquired hemodynamic effects of CHD or surgery result in HF (top arrow), and most commonly a combined effect of complex genetics in overlapping pathways and acquired stressors caused by the lesion (bottom arrow).

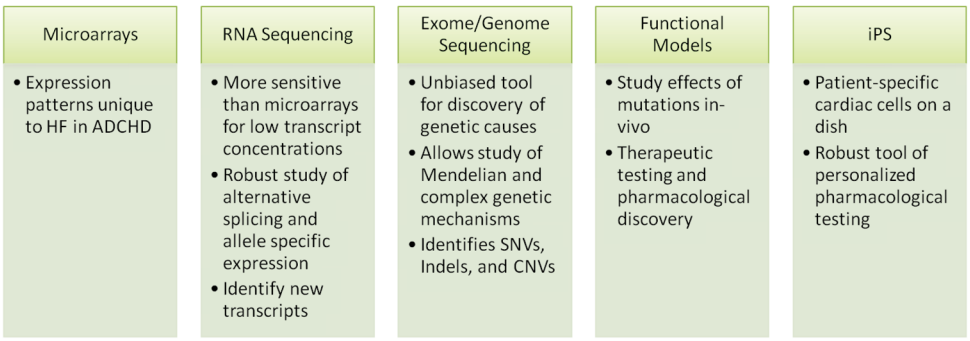

Figure 2.
Current genomic technologies and proposed mechanisms of contribution to the understanding of HF in ADCHD.

Table 1

Comparison of differences and similarities between congenital heart disease and cardiomyopathy

	Congenital Heart Disease	Cardiomyopathy
Differences		
Phenotype	Wide spectrum of cardiac malformations including the valves, septa, and great vessels	Dilation or hypertrophy of the myocardium +/− disease of the conduction system; results in HF or SCD
Expression	Present at birth by definition	Typical disease onset is in adolesence or adulthood, but can express at any age
Genetics	LoF mutations in transcription factor genes and other signaling molecules that disturb molecular pathways during cardiac development	Mutations in structural genes involving proteins of the sarcomere, cellular cytoskeleton, or ion channels
Population Attributable Risk of Genetic Causes	5–10%	50–70%
Clinical Genetic Testing	Not recommended except in rare syndromic cases	Recommended in most familial cases
Similarities		
Phenotype	Several syndromes with CHD and congenital CMP; Co-occurrence of LVNC with CHD	
Expression	Congenital cardiomyopathies occurring in the setting of CHD	
Genetics	Multiple shared pathways between heart development and myocardial disease; Few genes that cause both CHD and congenital CMP; Multiple genes that cause CHD have altered expression in the setting of heart failure	

HF Heart Failure, SCD Sudden Cardiac Death, LoF Loss of Function, CHD Congenital Heart Disease, CMP Cardiomyopathy, LVNC Left Ventricular Non-Compactum

Table 2

Canonical Pathways from IPA Analysis of CHD Candidate Genes that have major roles in HF

Pathway	Candidate Genes in CHD
Wnt/β-catenin Signaling	SOX2,GJA1,CREBBP
HIF1α Signaling	CREBBP,HRAS,NAA10
Cardiac hypertrophy signaling	NKX2-5,ADCY2,SOS1,CREBBP,HRAS,GATA4
Noonan pathway	SOS1, PTPN11
BMP Signaling Pathway	NKX2-5,SOS1,CREBBP,HRAS,PITX2
TGF-β Signaling	NKX2-5,SOS1,CREBBP,HRAS,PITX2
JAK/Stat Signaling	PTPN11,SOS1,HRAS
RAR Activation	NSD1,ADCY2,CREBBP,PML,CITED2
PPARα/RXRα Activation	ADCY2,SOS1,CREBBP,HRAS,MED12