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82 *Current Genomics,* 2015, *16,* 82-87

Common Variants for Heart Failure

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Abstract: Heart failure (HF) is a common disease with high morbidity and mortality; however, none of the drugs available are now entirely optimal for the treatment of HF. In addition to various clinical diseases and environment influences, genetic factors also contribute to the development and progression of HF. Identifying the common variants for HF by genome-wide association studies will facilitate the understanding of pathophysiological mechanisms underlying HF. This review summarizes the recently identified common variants for HF risk and outcome and discusses their implications for the clinic therapy.

Keywords: Common variants, Dilated cardiomyopathy, Genome-wide association studies, Heart failure, Mortality, Risk.

INTRODUCTION

Heart Failure (HF) is a clinical outcome of various cardiovascular diseases, characterized by the impairment of the contractile function of the heart [1]. HF may be resulted from disorders of the myocardium, pericardium, heart valves or endocardium, or due to other causes. Most HF patients have symptoms due to left ventricular dysfunction. According to the ejection fraction of the heart, HF can be divided into 2 types: HF with preserved ejection fraction and HF with reduced ejection fraction [2].

HF incidence increases with age, rising from 20 per 1000 individuals 65–69 years of age to 80 per 1000 individuals among those 85 years of age [2]. Indeed, the pathophysiology of HF is complex, being characterized by a wide range of disease processes, with various components such as genetics factors, clinical manifestations, structure morphology, and environment influences. Although much progress has been published for the pathological mechanisms underlying HF in recent 10 years, the genetics research for the risk of HF is still a great challenge faced by the world.

Many single nucleotide polymorphisms such as CLCNKA (p.Arg83Gly) [3] and KCNE(S38G) [4] are reported to be associated with the risk of HF. However, these risk variants only explain a small proportion of HF heritability and additional predisposing variants to HF remain to be discovered. With the emergence of genome-wide association studies (GWAS), the candidate gene approach is being replaced by a more unbiased approach to search for genes controlling risk to complex diseases. In GWAS, DNA microarrays to genotype millions of single nucleotide polymorphisms (SNPs) across the human genome theoretically allow for the detection of associations to potentially causal variants, and have successfully broadened the scope of gene discovery for many complex diseases, including heart failure. Since the first HF GWAS was published in 2007 [5], several GWASs have been performed to delineate genomic loci within which are common variants of HF. We have highlighted and discussed recent advances in identifying common variants associated with HF development and outcome in this review. Since dilated cardiomyopathy(DCM) is the most common cardiac disease leading to heart failure, GWASs about the DCM are also reviewed here.

1. Common Variants Associated with HF Risk (Table 1)

Larson *et al.*, for the first time, performed a genomewide association study by the Affymetrix 100K GeneChip in 1345 Framingham Heart Study participants from the largest 310 pedigrees. They analyzed associations of 70987 qualifying SNPs to four major CVD outcomes including HF. No polymorphisms with genome-wide levels of significance ($P<5*10(-7)$) were identified, although rs740363 showed a trend for association with HF($P=8.8*10(-6)$) [5].

Later on, the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortium investigated the association of 2478304 single SNPs with incident HF by meta analyzing data in 24000 participants (21000 of European ancestry and 3000 of African ancestry) from 4 community-based prospective cohorts (the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study, and the Rotterdam Study) and firstly identified two loci with genomic significance associated with HF: rs10519210 at chromosomal position 15q22 and rs11172782 at 12q14. The above 2 loci are within 60kb of known genes: *USP3* and *CA12* in European-ancestry participants and *LRIG3* in African-ancestry [6]. This meta-analysis firstly supported the hypothesis that common genetic variation, regardless of the clinical mechanism responsible for reduced cardiac output in HF, contributes to HF risk. However, these findings lacked the replication in other community-based settings of incident HF.

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1875-5488/15 $58.00+.00

Table 1. Common variants associated with heart failure risk.

Common Variants	Locus	Genes	Races	References
rs10519210	15q22	*USP3*	European	[Smith *et al.*; 2010]
rs11172782	12q14	*LRIG3*	African	
rs1739843	Chr 1	*HSPB7*	European	[Cappola *et al.*; 2010] [Stark *et al.*; 2010]
rs6787362	Chr 3	*FRMD4B*	European	[Cappola *et al.*; 2010]
rs945416		*HSPB7*	European	[Matkovich *et al.*; 2010]
rs732286		*HSPB7*	European	
rs1763596		*HSPB7*	European	
rs1739844		*HSPB7*	European	
rs1763597		*HSPB7*	European	
rs1739843		*HSPB7*	European	
rs1739842		*HSPB7*	European	
rs1739841		*HSPB7*	European	
rs1763599		*HSPB7*	European	
rs761760		*HSPB7*	European	
rs761759		*HSPB7*	European	
rs1739840		*HSPB7*	European	

Although the *USP3* gene is known to have a role in genome stability [7] and the gene product from CA12 is known to be a membrane protein highly expressed in many tissue beds and may have a role in cancer Prognosis [8], there is litttle knowledge about the role of these genes in cardiovascular system.

Faced with the above situation, it is most implicated that the identification of common variants in specific genes that may contribute to heart failure pathogenesis would be more meaningful. The ITMAT/Broad/CARe (IBC) cardiovascular SNP-array was then utilized to analyze about 2,000 candidate genes of predicted importance to cardiovascular biology in a two-stage case-control study [9]. In stage 1, genotypes in 1590 Caucasian heart failure patients were compared to those in 577 unaffected controls, unraveling two intronic SNPs associated with all-cause heart failure: rs1739843 and rs6787362. And these results were replicated in an independent Caucasian replication population in stage 2 with 308 cases and 2314 controls of HF. It's worth noting that rs1739843 were genome-wide associated with both ischemic and nonischemic heart failure, indicating that this SNP is a marker for heart failure but not simply coronary disease or myocardial infarction. The SNP rs1738943 are located in a 5'intronic region of the *HSPB7* gene. *HSPB7* encodes the heat shock protein B7 (HSPB7), which is a member of the small heat shock protein family and is expressed almost exclusively in cardiac and skeletal muscle [10], HSPB7 preserves contractile integrity by binding to and stabilizing sarcomeric proteins [11, 12]. Mutations in HSPB5, another small heat shock protein, are reported to cause a rare form of familial cardiomyopathy [11]. Further scrutiny of the locus containing rs1738943 shows that it resides in a block of high LD that spans *HSPB7* and a nearby gene, *CLCNKA*, which encodes a voltagesensitive chloride channel expressed mainly in the kidney [13]. Variation in *CLCNKA* has been associated with alterations in renal sodium re-absorption and salt-sensitive hypertension [13, 14]. The SNP rs6787362 is located in a 3'intronic region of the *FRMD4B* gene. FRMD4B (FERM- domain containing protein 4B) is known to physically interact with CYTH3, a downstream effector of PI-3 kinase signaling [15]. PI3K is a mediator of many different signaling pathway and PI3K/AKT pathway is extensively reported in cardiovascular system.

Despite rs1739843 were observed to be genome-wide associated with HF, no evidence showed how this variant changes the biological function of protein HSPB7 and causes the incidence of HF. So it is worth noting to explore the causal SNP for the common variants in *HSPB7*. In a follow-up study [16], SNPs in 4 biologically relevant genes associated with the incidence of sporadic heart failure(α 1-adrenergic receptor (*ADRA1A*), β 2-adrenergic receptor (*ADRB2*), phospholamban (*PLN*) and *HSP7* gene) were analyzed in two large Caucasian populations by pooled sample sequencing strategy, coupled with novel computational algorithms and second-generation DNA sequencing platforms. While no SNPs leading to HF risk were found in *ADRA1A*, *ADRB2* and *PLN*, twelve of the *HSPB7* SNPs were associated with systolic heart failure and independently validated

in a second heart failure population. However, none of them changed the amino acid sequence. Since the 12 SNPs were in linkage disequilibrium within a haplotype block that extends beyond *HSPB7*, the causative genetic variant was supposed to be in another gene or in the intergenic region.

It is worth mentioning that rs1739843 in *HSPB7* gene were also reported to have a significant association with non-familial idiopathic dilated cardiomyopathy(IDC) risk in a case-control study of 664 dilated cardiomyopathy(DCM) cases and 1874 population-based healthy controls from Germany using a 50K human cardiovascular disease bead chip covering more than 2000 genes preselected for cardiovascular relevance [17]. This study together with the results from Cappola *et al.* [9] and Matkovich *et al.* [16], implicating the importance of rs1739843 and other related polymorphisms in the *HSPB7* locus for DCM and HF.

2. Common Variants Associated with DCM (Table 2)

DCM is a severe cardiovascular disorder with an estimated prevalence of 37 in 100000 people. It is the most frequent cause leading to heart failure and cardiac transplantation in young adults and accounts for up to 30~40 percent of all heart failure cases as found in large randomized trials [18]. About one-third of all patients have a suspected familial disease indicating a genetic basis of DCM [19, 20]. And it has been mentioned above that a certain SNP(rs1739843) is associated with both HF and DCM incidence. Hence, Genome-wide association studies about DCM can not only facilitate the search for novel susceptibility genetic mechanisms of DCM but also offer a new insight into the HF genetic risk.

The first genome-wide association study to identify common variants contributing to sporatic DCM [21] was carried out in a case-control cohort with 1179 DCM patients from three European studies (CARDIGENE, EUROGENE-EHF, and PHRC-DCM) and 1108 controls from the respective populations, replicated in independent samples. Individual genotyping of 517382 single nucleotide polymorphisms (SNPs) by human 610-quad bead chip arrays unravelled two SNPs rs10927875 and rs2234962 involved in sporadic DCM. The SNP rs10927875 are located in a region at chromosome 1p36.13 which encompasses several genes including *HSPB7* while rs 2234962 maps to the *BAG3* gene on chromosome 10q26. *HSPB7* hasbeen extensively discussed in our review and here, rs10927875 is a novel identified SNP near *HSPB7*, whether it has a genome wide association with HF is uncovered. BAG3 is a member of a conserved family of cytoprotective co-chaperone proteins containing a conserved domain able to interact with HSC70/HSP70 and sHSPs proteins [22]. BAG3 is involved in numerous activities including macroautophagic protein degradation in aging cells [23]. A mutation in BAG3(P209L) causes severe childhood muscular dystrophy with cardiomyopathy [24]. To date, no study of mutual association between BAG3 and HSPB7 has been recorded; however, exploring the association of these two proteins in the heart may lead to a novel pathophysiological pathway underlying HF and DCM which are characterized by cardiomyocyte dysfunction.

A genome-wide association study published last year [25] revealed a novel SNP(rs9262636) maps to *HCG22*gene with the major histocompatibility complex (MHC) region 6p21.3. This result came from a three-staged case-control study with more than 4100 individuals of European descent with DCM and 7600 controls. Despite the knowledge that region 6p21 harbours several candidate genes responsible for inflammatory disease [26-29], the molecular pathways by which genetic variants in MHC heavy chains may affect DCM and its progression remains elusive.

In addition, a genome wide association study about peripartum cardiomyopathy (PPCM) was performed in women with verified PPCM diagnosis from 3 independent groups. The results showed that rs258415 at chromosome 12p11.22. near *PTHLH* genes [30].

3. Common Variants Associated with HF Mortality (Table 3)

The CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortium firstly investigated 2526 incident HF cases of European ancestry from ARIC, CHS, FHS and RS and 466 incident HF cases of African ancestry from ARIC and CHS for an association between genome-wide variation and all-cause mortality [31]. A total of 1645 deaths from all causes occurred at a weighted average of 3.6 years were of European ancestry. A total of 281 deaths occurred among the 466 individuals with incident HF of African ancestry at a weighted average of 3.4 years. One SNP(rs12638540) was significantly associated with all-cause mortality in individuals of European ancestry with HF and no SNP was found to be significantly associated with mortality in individuals with HF of African ancestry. The SNP rs12638540 maps to chromosome 3p22 in an intron of CKLF-like MARVEL transmembrane domain containing 7(*CMTM7)* gene. *CMTM7* is one of several chemokine-like factor genes clustered in the same region on chromosome 3p22. CMTM7 is highly expressed in leukocytes and is also expressed in the heart, but its function is unknown. Former

Table 2. Common variants associated with dilated cardiomyopathy.

Common Variants	Locus	Genes	Races	References
rs10927875	1p36.13	*HSPB7*	European	[Villard *et al.*; 2011]
rs2234962	10q26	*BAG3*	European	
rs9262636	6p21.3	*HCG22*	European	[Meder *et al.*; 2013]
rs258415	12p11.22	*PTHLH*	European	[Horne *et al.*; 2011]

Table 3. Common variants associated with heart failure mortality.

Common Variants	Locus	Genes	Races	References
rs12638540	3p22	*CMTM7*	European	[Morrison *et al.*; 2010]
rs2207418	20p12		European	[Parsa *et al.*; 2010]
rs12567209	1q23.3	*NOS1AP*	Chinese	[LIU *et al*.; 2014]

studies indicated that chemokine receptor gene expression is upregulated among HF patients compared with controls [32], suggesting that chemokines may play a role in survival of heart failure patients.

In the following year, a three-stage approach was undertaken using genome-wide, case-control, and case-only association studies to identify genetic variants associated with HF mortality [33]. In the first step, 21 genome-wide significant candidate SNPs were derived in 851 Old Order Amish individuals with cardiac hypertrophy. The follow-up genotyping and association analysis were performed in the normal and heart failure cohorts. The heart failure cohort established by the NHLBI-sponsored Specialized Center of Clinically Oriented Research (SCCOR) and consisted of unrelated prospectively enrolled white patients from the University of Cincinnati College of Medicine (n= 1302) and the University of Maryland School of Medicine (n= 308). The control group consisted of 463 asymptomatic Caucasians with normal electrocardiograms and echocardiograms. One of the 21 SNPs (rs2207418) was associated with HF risk and mortality. Rs2207418 is located on chromosome 20p12 and is within a repeat element that belongs to MIR family of short interspersed nuclear elements (SINE), and is over 500 kb away from the nearest known genes. There are five annotated genes, however, within about 2Mb of this SNP: *C20orf94*, *BTBD3*, *SNAP25*, *MKK5* and *JAG1*. A further analysis of this region showed that it is highly conserved. And this degree of conservation suggests that this region may serve as an enhancer or repressor element for one of the five mentioned genes, or other genes that are more remote.

This year, a prospective study of patients with chronic heart failure(CHF) caused by idiopathic dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (ICM) from 2005 to 2009 referred from 10 hospitals in mainland China was conducted to analyze the genetic associations with HF mortality. A total of 1428 patients with CHF and 480 control subjects were genotyped for 6 SNPs of NOS1AP, revealing that The A allele of s12567209 in NOS1AP may serve as an independent predictor of all-cause death and SCD in patients with CHF in the Chinese Han population [34]. NOS1AP is located at chromosome 1q23.3 and encodes neuronal nitric oxide (NO) synthase 1 (nNOS) adaptor protein, regulating nNOS activity through interaction with the nNOS PDZ domain [35]. Several common variations in NOS1AP had been formerly reported to be associated with cardiac repolarization and risk of SCD in several independent populations [36, 37]. In addition, rs12567209 were associated with prolonged QTc interval in the Chinese Han population, rather than in just the CHF group, suggesting that rs12567209 can cause HF mortality by other mechanisms than prolonged QTc interval.

IMPLICATIONS FOR THE CLINIC

Genome-wide association studies have provided new insights in exploring the genetic factors for the development and progression of HF. More and more common variants for the candidate genes of HF incidence have been identified associated with HF risk and mortality. These common variants have shown great potential in predicting the incidence and outcome of heart failure; however, there is still a long way to go to translate these findings into clinical therapy.

More than one GWAS unraveled that the common variants within the region encompassing *HSPB7* are genome-wide associated with the risk of HF and DCM [9, 16, 21]; however, no data to date revealed the causal variants for these *HSBP7* SNPs, either for other SNPs mentioned in this review. Figuring out the causal variants can offer us a profound and overall understanding of the fundamental mechanism underlying the complex pathological process of HF. Hence, more studies need to be performed to identify the predisposing factor for various SNPs already validated in genome-wide association studies.

In several studies it is observed that common variants for HF risk and outcome in different population are different from each other, indicating that the genetic background varies among populations of different ancestries. It is also observed that there is no overlap between the genetic variants for HF incidence and HF mortality. These findings implicate that clinical treatment should be personalized for HF patients with different genetic backgrounds and during different pathological stages.

In conclusion, several common variants have been identified within different gene regions and these variants are genome-wide associated with heart failure and its predisposing disease such as dilated cardiomyopathy. These common variants are promising to offer a new way to the clinical therapy for heart failure in the future.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the grants from National Natural Science Foundation of China (81370332 and 81170201 to XL Li), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD 20102013 to XL Li). Dr XL Li is an Associate Fellow at the Collaborative Innovation Center For Cardiovascular Disease Translational Medicine while Dr XQ Kong is a Fellow at the

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Received on: November 02, 2014 **Revised on: December 08, 2014** **Accepted on: January 06, 2015**