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Review

Genetics of heart failure ☆

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ABSTRACT

Heart failure (HF) occurs when the cardiac output, no longer compensated by endogenous mechanisms, fails to meet the metabolic demands of the body. In most populations, the prevalence of heart failure continues to rise, constituting a major public health burden, especially in developed countries. There is some evidence that the risk of HF in the general population depends on genetic predisposition, necessarily characterised by a very complex architecture. In a small, but probably underestimated proportion, HF is caused by Mendelian inherited forms of myocardial disease. The genetic background of these genetic conditions is a matter of intensive research that is already shedding light onto the genetics of common sporadic forms of HF. In this review, we briefly review the insights provided by candidate gene and genome-wide association approaches in common HF and then describe the main genetic causes of inherited heart muscle disease. Finally we present the current challenges and future research needs for both forms of HF. This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

1. Introduction

Heart failure (HF) occurs when the cardiac output, no longer compensated by endogenous mechanisms, fails to meet the metabolic demands of the body. Clinically, it is defined [1–3] as a syndrome characterised by symptoms of breathlessness, fatigue, signs of fluid retention and a cardiac structural abnormality. Its prevalence is growing in developed and emerging countries as a result of population aging, the successful management of coronary artery disease and an increasing prevalence of diabetes and hypertension. At 40 years of age, the lifetime risk of developing HF for men and women is 20%, with a prevalence of 2–4% individuals in Europe and the USA. The prognosis remains poor, with a reported 50% survival four years after diagnosis [1,4–6].

Whilst most cases of HF are caused by coronary artery disease, hypertension, diabetes and valvular heart disease [1], epidemiological studies suggest that, even in these acquired disorders, the risk of HF depends to some extent on genetic predisposition. In the Framingham cohort [7], the relative risk of developing HF is 1.69 if one parent is affected and 1.92 if both parents have HF. These acquired forms of HF are themselves characterised by a very complex genetic architecture (Fig. 1) that includes the predisposition for the individual conditions themselves, genetic variation that modulates the maladaptive pathophysiological response to pathophysiological stressors, and genetic modifiers of the response to therapy. Not surprisingly, studies of individual genetic contributors to sporadic heart failure are typified by poorly reproducible or only modest effect size.

In a small but important proportion of cases, HF is caused by Mendelian genetic disorders. The various clinical phenotypes are classified according to ventricular morphology and function into hypertrophic, dilated, restrictive, arrhythmogenic and unclassified cardiomyopathies [8]. They are mostly inherited as autosomal dominant traits, characterised by locus and allelic heterogeneity and highly variable intra- and interfamilial expressivity with incomplete/age-related clinical penetrance [8,9]. The highly variable expressivity and penetrance may be explained by modifier genes, epigenetic effects, post-transcriptional and post-translational modifications, and environmental effects [10,11]. The complexity and clinical heterogeneity of genetic heart muscle disease has challenged the understanding of the genotype–phenotype relationships but is a matter of intensive research that is shedding light on all forms of heart failure.

2. Genetics of acquired forms of heart failure

2.1. Neurohormonal activation — candidate gene studies

The maladaptive activation of adrenergic pathways and the renin–angiotensin–aldosterone system that perpetuate injury independently of the initial aetiology is well described. Similarly, the clinical benefits of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors are established [1,2,12]. Numerous candidate gene studies examining different molecular components of the neurohumoral system and their impact on response to therapy have been published. In most cases, data supporting an influence of particular polymorphisms on the course of the disease are inconsistent or lack sufficient power. Nevertheless,

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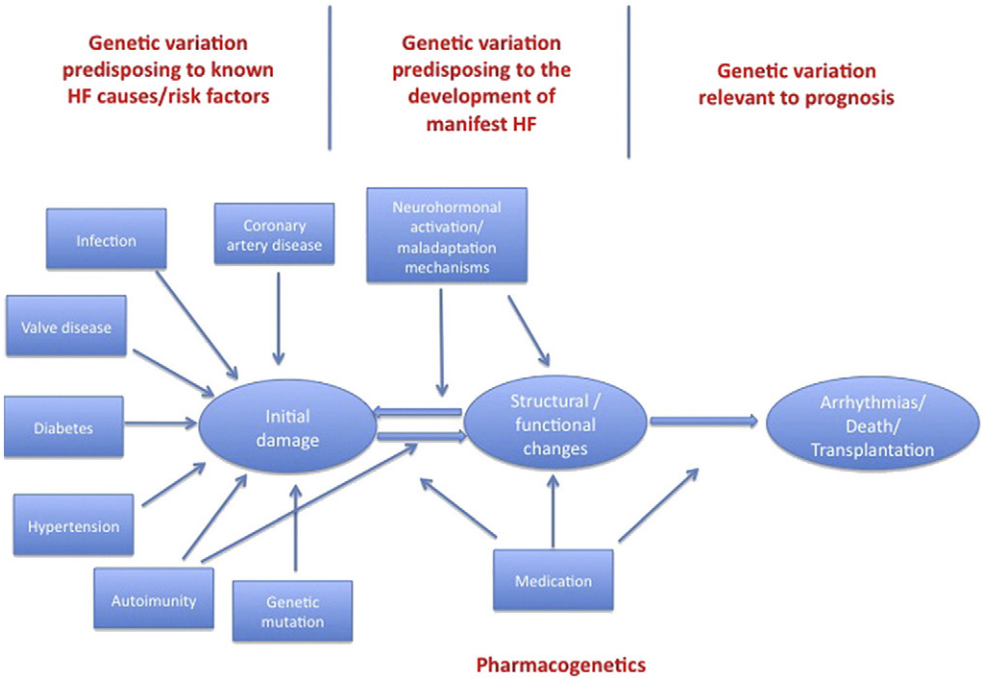

Fig. 1. The complex genetic architecture of common/acquired heart failure.

candidate gene approaches and genome-wide association studies do support a role for common polymorphisms on disease progression.

2.1.1. Adrenergic pathway polymorphisms

2.1.1.1. β -1 adrenergic receptor. The predominant beta-adrenergic receptor in the heart is the β-1 receptor (ADRB1) [13]. ß-1 receptors mediate the chronotropic, inotropic and lusitropic effects of catecholamines and various candidate gene studies have analysed the possible effects of common beta-1 adrenoreceptor polymorphisms as modifiers of heart failure risk and prognosis [13]. The more consistent and reproducible associations involve the Arg389Gly polymorphism (rs1801253, MAF = 0,304) [14], occurring in a highly conserved position. Mechanistic studies [15–21] have demonstrated that the Arg389 allele is characterised by increased adenylyl cyclase signalling, enhanced inotropy and an increased susceptibility to beta-blockers. In contrast, the Gly389 allele is characterised by decreased inotropy and reduced sensitivity to beta-blockers.

Clinical studies have suggested a beneficial effect of Arg389 homozygosity on exercise capacity and peak oxygen consumption [22,23] as well as an enhanced therapeutic response to metoprolol [24,25] and carvedilol [26] in the presence of the allele, either in heterozygosity or homozygosity. A recent study investigating the combination of the Arg389Gly polymorphism in the ADRB1 gene and the Gln27Glu polymorphism (rs1042714, MAF = 0,234) in the adrenergic β(2)-receptor gene (ADRB2) found that the combination was associated with a two-fold increase in mortality relative to all other genotype combinations in HF patients treated with carvedilol. There was no difference in survival in metoprolol-treated HF patients between genotype groups [27]. If confirmed in larger studies, this suggests a role of beta-adrenergic genotyping in choosing therapeutic options in HF.

2.1.1.2. G protein-coupled receptor kinases. Myocardial β-adrenergic receptor down-regulation and desensitisation is mediated by G protein-coupled receptor kinases (GRKs). The hypothesis that gain-of-function genetic variation could be responsible for desensitisation and protection against the hyperactive adrenergic system in HF and loss-of-function for an increase in the risk for HF development and a worse prognosis has been studied in candidate gene approaches. The best studied single nucleotide polymorphism (SNP) is Gln41Leu in GRK5 (rs17098707; MAF = 0.087; 0.20 in individuals of African ancestry) [14]. Mechanistic studies show that Leu41 allele increases desensitisation [28,29] mimicking a beta-blockade effect. Two studies showed improved transplant-free survival in individuals homozygous or heterozygous for this allele [30,31].

2.1.2. Renin–angiotensin–aldosterone system

2.1.2.1. Angiotensin converting enzyme insertion–deletion polymorphism. The observation that angiotensin converting enzyme (ACE) levels are characterised by familial clustering, led to the identification of a common 287 bp insertion–deletion polymorphism located in intron 16 of the ACE gene [32] that is responsible for approximately half of the variation in ACE plasma levels. Homozygous carriers of two deletion alleles (DD) have higher ACE levels and homozygous carriers of two insertion alleles (II) have lower levels; heterozygotes (ID) have intermediate enzyme levels [33]. Given its location in a non-coding region, this polymorphism is probably not directly responsible for the variation in ACE plasma levels, but is considered to be in close linkage disequilibrium with the genetic variation that is responsible for serum ACE levels at the molecular level.

The most reproducible finding regarding this polymorphism is the association between DD genotype and the progression of ischaemic or nonischaemic heart failure, with decreased transplant-free survival [34–38]. Some studies have also shown that patients with the DD genotype have the greatest benefit from ACE inhibitor and beta-blocker therapy [37,38] as well as a relationship between the DD genotype and left ventricular hypertrophy (LVH) [39–47]. Nevertheless, these case–control studies are characterised by small and heterogeneous samples. A recent meta-analysis challenged the significance of the associations between this ACE polymorphism and risk of HF [48], but another meta-analysis confirmed the association between the DD genotype and LVH [49].

A very recent paper by Kolder et al. [50] further explored the role of renin–angiotensin–aldosterone system (RAAS) polymorphisms in the phenotypic expression of hypertrophic cardiomyopathy (HCM).

Five candidate RAAS polymorphisms (ACE, rs4646994; AGTR1, rs5186; CMA, rs1800875; AGT, rs699; and CYP11B2, rs1799998) were analysed in subjects carrying truncating mutations in the MYBPC3 gene and no major effects on the HCM phenotype were observed.

2.2. Other genetic susceptibility loci — genome-wide association studies

Genome-wide association studies (GWAS) allow a high-throughput and unbiased approach to the identification of risk loci for common diseases, because they do not assume an initial hypothesis for the location of genetic variants that impact on a complex trait. Using microarray platforms consisting of millions of SNPs distributed along the genome, this method typically identifies common variants with small individual effects [51,52].

In the HF arena, two recently published GWAS [53,54] using >2.4 million SNPs in >20,000 subjects, associated two SNPs with the development of heart failure: one involving the USP3 gene (ubiquitin-specific protease) in individuals of European ancestry, and the other the LRIG3 gene (leucine-rich, immunoglobulin like domain) in individuals of African ancestry. A third SNP located in the CMTM7 gene (CKLF-like MARVEL transmembrane domain containing 7) was associated with HF mortality. For all three SNPs the odds ratios were around 1.5.

In a subgenome approach, using 50,000 SNPs in 2000 genes potentially associated with cardiovascular disorders, another recent study revealed an association between HF and the SNP rs1739843, located in an intronic region of the HSPB7 gene, that encodes a heat shock protein [55]. This finding was reproduced in a multicentre European study [56]. Given the absence of apparently functional SNPs upon resequencing of the HSPB7 gene (all variants were synonymous or intronic) and due to the fact that this gene is in high linkage disequilibrium with CLCNKA (renal ClC-Ka chloride channel), also located at 1p36, Cappola et al. [57] resequenced the latter gene and found a significant association with HF for a missense variant, Arg83Gly, with an odds ratio of 1.27 per allele copy. This means that the risk is increased by 54% in homozygotes. Importantly, one quarter of Caucasians are homozygotes.

Finally, a European consortium study on dilated cardiomyopathy (DCM) [58] identified three DCM-associated SNPs. Two of these, rs10927875 and rs2234962, were replicated in independent samples (1165 DCM patients and 1302 controls), with p-values of 0.002 and 0.009, respectively. rs10927875 maps to a region on chromosome 1p36.13 which encompasses several genes, including HSPB7. The second identified locus involves rs2234962, a non-synonymous SNP (c.T757C, p. C151R) located within the coding sequence of BAG3 (BCL2-associated athanogene 3) on chromosome 10q26. The authors also identified rare variants in this gene, which segregated in families with familial dilated cardiomyopathy. This is in keeping with another recent study by Norton et al. [59] which used GWAS of copy number variation and whole-exome sequencing, and identified rare variants in BAG3 as a cause for familial dilated cardiomyopathy. This is one of the rare examples of the same genetic locus showing an association between rare variants with large effect and rare familial monogenetic disease and common variants with small effects with sporadic common disease.

2.3. Genetic susceptibility loci for cardiovascular risk factors and atherosclerotic heart disease

Several recent GWAS investigated genetic susceptibility for atherosclerotic disease and risk factors that are in turn important causes of acquired heart failure. These studies were reviewed in two very recent publications [60,61]. A large number of loci are associated with an increased risk of coronary artery disease [62,63] or myocardial infarction [64]. Other recently described loci confer increased susceptibility to established cardiovascular risk factors, such as high blood pressure [65], dyslipidaemia [66] and diabetes [67,68].

2.4. Genetic susceptibility for myocarditis

A recent publication explored the role of DNA variation in toll-like receptor 3 (TLR3) as a possible risk factor for myocarditis [69]. The authors sequenced this gene in patients diagnosed with enteroviral myocarditis and identified a rare variant (c.1660C3T, p.P554S) in one patient with Coxsackievirus B3 myocarditis as well as an increased frequency of a common polymorphism (rs3775291, c.1235C>T, p.I412F) compared with controls. Expression of either variant resulted in significantly reduced TLR3-mediated signalling in *in vitro* studies, suggesting a role for rare and common variation in innate immune response genes as a mechanism for increased susceptibility to myocarditis.

3. Genetics of inherited heart failure

3.1. Dilated cardiomyopathy

Familial dilated cardiomyopathy (FDCM) is defined as idiopathic dilated cardiomyopathy (DCM) occurring in two or more related family members or in the presence of sudden death of a relative younger than 35 years of age [8,70]. Epidemiological studies using family history and clinical, electrocardiographic and echocardiographic screening of first degree relatives have established the prevalence of FDCM as 20–50% in idiopathic DCM cases [71–74]. This proportion varies depending on the extent of family screening in different studies. A diversity of inheritance patterns is recognised [75] with more than 80 reported genes including those encoding sarcomere proteins, cytoskeleton and nuclear envelope proteins and, more recently, membrane ion-channels and desmosomes [76–78] (Table 1).

An identifiable genetic cause is present in around 25–30% of FDCM cases [77]. Until very recently, LMNA was considered the most prevalent causal gene in FDCM, responsible for 4–8% of cases, but a new study has found potentially disease-causing titin (TTN) truncating mutations in 25% of patients with FDCM and 18 % of patients with sporadic DCM [79]. Nevertheless, detection of LMNA variants are important as they are an exception to almost all other genetic findings in patients with cardiomyopathy which do not, for the moment, usually imply any change in management. The presence of non-missense lamin variants was recently confirmed as a risk factor for malignant ventricular arrythmias in a multicentre study [80] and other studies have shown that the presence of a lamin mutation is associated with a poor prognosis [81,82] even in patients with mild dilation. Increased arrhythmogenicity is also reported to be a feature of SCN5A (sodium channel, voltage-gated, type V, alpha subunit) [83] and DCM associated with desmosomal gene variants [78] but there is as yet no consensus on the treatment of patients with such variants.

The genetic spectrum and heterogeneity of inherited DCM continues to expand. In a very recent paper, genome-wide mapping and exome sequencing in a unique family, where DCM segregated as an autosomal recessive trait, were used to identify GATAD1 (GATA zinc finger domain-containing protein 1) as a disease-causing gene for autosomal recessive DCM [84]. It is likely that further mutations will continue to emerge with the application of high throughput sequencing technology.

3.2. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy (LVH) in the absence of abnormal loading conditions sufficient to explain the observed degree of hypertrophy. It has a population prevalence of approximately 1 in every 500 adults and presents with cardiovascular symptoms at any age [85,86]. Ventricular hypertrophy frequently develops during periods of rapid somatic growth, but can appear *de novo* at any time from infancy to old age. Presentation

Table 1
Genes associated with dilated cardiomyopathy. Adapted with permission from [76].

Gene	Protein	OMIM	% of familial DCM cases
LMNA	Lamin A/C	150330	6%
MYH7	β-myosin heavy chain	160760	4.2%
MYPN	Myopalladin	608517	3.5%
TNNT2	Cardiac troponin T	191045	2.9%
SCN5A	Sodium channel	600163	2.6%
MYBPC3	Myosin-binding protein C	600958	2%
RBM20	RNA binding protein 20	613171	1.9%
TMPO	Thymopoietin	188380	1.1%
LAMA4	Laminin a-4	600133	1.1%
VCL	Metavinculin	193065	1%
LDB3	Cypher/ZASP	605906	1%
TCAP	Titin-cap or telethonin	604488	1%
PSEN1/2	Presenilin 1 / 2	104311/600759	1%
ACTN2	α-actinin-2	102573	0.9%
CRYAB	Alpha B crystalin	123590	0.7%
TPM1	α-tropomyosin	191010	0.6%
ABCC9	SUR2A	601439	0.6%
ACTC1	Cardiac actin	102540	0.5%
PDLIM3	PDZ LIM domain protein 3	605889	0.5%
ILK	Integrin-linked kinase	602366	0.5%
TNNC1	Cardiac troponin C	191040	0.4%
TNNI3	Cardiac troponin I	191044	0.4%
PLN	Phospholamban	172405	0.4%
DES	desmin	125660	0.3%
SGCD	δ-sarcoglycan	601411	0.3%
CSRP3	Muscle LIM protein	600824	0.3%
MYH6	α-myosin heavy chain	160710	Unknown
TTN	Titin	188840	Unknown
EYA4	Eyes-absent 4	603550	Unknown
ANKRD1	Ankyrin repeat domain-containing protein 1	609599	Unknown
DMD	Dystrophin	300377	Unknown
GATAD1	GATA zinc finger domain containing 1	614518	Unknown
BAG3	BCL2-associated athanogene 3	603883	Unknown
TAZ/G4.5	Tafazzin	300394	Unknown

in infancy is associated with symptoms of heart failure and failure to thrive. In older children and adults the most common symptoms are dyspnoea, syncope and chest pain. HCM is generally considered to be the commonest cause of sudden cardiac death in individuals below 35 years of age with a peak incidence in adolescence and young adulthood, often in minimally symptomatic individuals [87–89]. In the long-term, many patients develop progressive symptoms caused by gradual deterioration in left ventricular function. This so-called "end-stage" is characterised by severe impairment of contractile performance and is associated with an annual mortality rate of 11% per year from sudden ventricular arrhythmia, stroke and progressive diastolic and systolic left ventricular failure [89].

HCM is often inherited as an autosomal dominant trait. Mutations in cardiac sarcomere genes are found in approximately 60% of patients with familial HCM and approximately 40% of patients with unexplained LVH without a family history [90]. Since the identification of the first cardiac disease-causing mutation in 1990, more than 900 mutations have been reported [91–96]. The majority affect cardiac ß-myosin heavy chain (MYH7) and cardiac myosin binding protein C (MYBPC3). Mutations in cardiac troponin T (TNNT2), troponin I (TNNI3), alpha-tropomyosin (TPM1), myosin light chains (MYL2, MYL3) and cardiac actin (ACTC1) are also reported. Mutations in other sarcomere or related genes, including alpha-myosin heavy chain (MYH6), titin (TTN), Z-disc protein genes such as muscle LIM protein (CSRP3) or calcium-handling genes (*e.g.* phospholamban), individually account for less than 1% of cases. A further 5% of adult and adolescent patients with apparently unexplained left ventricular hypertrophy have metabolic or storage disorders (*e.g.* Anderson–Fabry disease and respiratory chain disorders), neuromuscular disorders, chromosome abnormalities and genetic syndromes such as cardiofacial cutaneous disorders. Table 2 shows the genes that have been associated with hypertrophic cardiomyopathy. When all these disorders are excluded, approximately 30–40% of familial cases remain genetically unexplained [96].

3.3. Left ventricular non-compaction

Left ventricular non-compaction (LVNC) of the myocardium is considered an unclassified cardiomyopathy in the European Society of Cardiology (ESC) classification scheme for heart muscle disease [8]. It is characterised by prominent trabeculations and deep intertrabecular recesses in association with a thin compacted epicardial muscle layer [97,98]. In some patients, LVNC is associated with left ventricular dilatation and systolic dysfunction. LVNC occurs in association with many congenital cardiac disorders, but it is still not clear whether isolated LVNC is a separate cardiomyopathy or a morphological trait shared by phenotypically distinct cardiomyopathies. The prevalence of LVNC, estimated from retrospective imaging studies, ranges from 4.5 to 26 per 10,000 adult patients [8]. Many patients are completely asymptomatic, but some present with congestive heart failure, thromboembolism, arrhythmias and sudden cardiac death.

Familial disease is estimated to occur in 18% to 50% of adults with isolated LVNC, mostly with an autosomal dominant pattern of inheritance [99]. An exception is Barth syndrome, caused by Tafazzin gene (G4.5 / TAZ) mutations that result in protein truncation, an X-linked disorder that causes severe cardiolipin deficiency in the mitochondrial membrane and that is clinically characterised by neutropenia and LVNC [100].

In adult patients with LVNC, numerous mutations in genes encoding sarcomere proteins have been reported. In 2008, using a panel of 6 sarcomere protein genes – MYH7, ACTC1, TNNT2, TNNI3, MYL2 and MYL3 – Klaassen et al. [101] reported that LVNC was associated with mutations in sarcomere genes (MYH7, TNNT2 and ACTC1) in 17% of 63 adult patients with LVNC. In a more recent study by Hoedemakers et al. [102], variants in 11 genes were reported in 41% of 56 patients with LVNC: 6 sarcomere protein, 2 calcium-handling genes and other genes such as lamin A/C (LMNA), ZASP (LDB3), and Tafazzin (TAZ) were implicated. The cardiological screening of relatives and the molecular analysis of probands and relatives combined suggested that 67% of LVNC is familial. HCM and DCM were identified in 11 (34%) families.

Table 2
Genes associated with hypertrophic cardiomyopathy. Adapted from [132].

Gene	Protein	OMIM	% of genotype-positive cases
MYH7	Myosin heavy chain, cardiac muscle beta isoform	160760 192600	40%
MYBPC3	Myosin-binding protein C, cardiac-type	600958	40%
TNNT2	Troponin T, cardiac muscle	115195	5%
TNNI3	Troponin I, cardiac muscle	191044	5%
TPM1	Tropomyosin 1 alpha chain	115196 191010	2%
MYL2	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform	160781 608758	Unknown
MYL3	Myosin light polypeptide 3	160790 608751	1%
ACTC1	Actin, alpha cardiac muscle 1	102540	Unknown
CSRP3	Cysteine and glycine-rich protein 3, muscle LIM protein	600824	Unknown
TTN	Titin	188840	Unknown
ACTN2	Alpha-actinin-2	102573	Unknown
MYH6	Myosin heavy chain, cardiac muscle alpha isoform	160710	Unknown
TCAP	Telothonin	604488	Unknown
TNNC1	Troponin C, slow skeletal and cardiac muscles	191040	Unknown

Table 3
Genes associated with left ventricular non-compaction.

Gene	Protein	OMIM	% of cases
MYH7	Myosin heavy chain, cardiac muscle beta isoform	160760 192600	Unknown
MYBPC3	Myosin-binding protein C, cardiac-type	600958	Unknown
TNNT2	Troponin T, cardiac muscle	115195	Unknown
TNNI3	Troponin I, cardiac muscle	191044	Unknown
TPM1	Tropomyosin 1 alpha chain	115196 191010	Unknown
ACTC1	Actin, alpha cardiac muscle 1	102540	Unknown
LDB3	Cypher/ZASP	605906	Unknown
LMNA	Lamin A/C	150330	Unknown
TAZ/G4.5	Tafazzin	300394	Unknown
DTNA	Dystrobrevin, alpha	601239	Unknown
CASQ2	Calsequestrin	114251	Unknown

Table 4
Genes associated with arrhythmogenic ventricular cardiomyopathy. Adapted from [133].

Gene	Protein	OMIM	% of cases
RYR2	Ryanodine receptor 2	180902	Rare
DSP	Desmoplakin	125647	6%–16%
TMEM43	Transmembrane protein 43	612048	Unknown
PKP2	Plakophilin 2	602861	11%–43%
DSG2	Desmoglein 2	125671	12%-40%
DSC2	Desmocollin 2	125645	Rare
TGFB3	Transforming growth beta 3	190230	Rare
JUP	Junction plakoglobin	173325	Rare
DES	Desmin	125660	Unknown
TTN	Titin	188840	Unknown
LMNA	Lamin A/C	150330	Unknown

Finally, a recent paper extended these findings to an analysis of disease penetrance and genotype–phenotype correlations in families [103]. Eighteen mutations were identified in 29% of the probands. Fifteen distinct heterozygous mutations were found in 5 sarcomere protein genes: MYH7, MYBPC3, TPM1, ACTC1, and TNNT2. Mutations occurred most frequently in MYH7 and MYBPC3 (13% and 8%, respectively). Familial disease was present in 16 probands (25%), 8 of whom were mutation-positive and 8 mutation-negative for sarcomere genes. Despite the negative findings concerning the phenotypic comparison between mutation-positive and mutation-negative probands, this study confirmed sarcomere gene mutations as an important cause of LVNC, present in nearly one third of the probands.

Table 3 summarises the main genes that have been associated with left ventricular non-compaction.

3.4. Arrhythmogenic cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (increasingly designated arrhythmogenic cardiomyopathy (AVC) due to the recognition of biventricular and left-dominant forms) has an estimated prevalence of 1 in 1000 and is a major cause of sudden cardiac death in the young [104]. It often presents with ventricular ectopy and ventricular tachyarrhythmias, in the presence of a structurally normal heart or only very mild changes in size and function of one or both ventricles. Advanced disease is characterised by wall motion abnormalities, aneurysms and severe dilatation of the right ventricle and left ventricular dysfunction. The histopathological hallmark of the disease is fibrofatty replacement of the myocardium.

As in other cardiomyopathies, there is high allelic heterogeneity, extremely variable expressivity and incomplete penetrance. In most patients the disease is inherited as an autosomal dominant trait caused by mutations in five genes encoding desmosomal proteins [105]: plakophilin-2 (PKP2), desmoplakin (DSP), plakoglobin (JUP), desmoglein-2 (DSG2) and desmocollin-2 (DSC2) (Table 4). Non-desmosomal genes implicated in the disease include the transforming growth factor beta 3 (TGFB3), the cardiac ryanodine receptor 2 (RYR2) and the transmembrane protein 43 (TMEM43). Around 40% of patients with AVC carry disease-causing or likely disease-causing mutations in the previously mentioned genes.

An autosomal recessive pattern of inheritance is observed in a rare syndromic presentation [106], Naxos syndrome, characterised by a triad of arrhythmogenic right ventricular cardiomyopathy, woolly hair, and diffuse keratoderma over the pressure areas of the palms and soles. Plakoglobin (JUP) is the causal gene and was the first AVC-associated gene described. A similar phenotype is described in patients with homozygous mutations in desmoplakin [107].

An ARVC-like phenotype has also been described as part the heterogeneous spectrum of manifestations in patients with desmin (DES)-related myopathy [108]. More recently, titin (TTN) mutations were suggested to be an additional cause of ARVC [109]. A mutation in the spring region demonstrated complete cosegregation in a large family and reduced structural stability in functional studies. Finally in a recent study, four ARVC probands without desmosomal mutations were shown to carry lamin A/C variants, suggesting that rare variation in this gene can be an additional cause of ARVC-like phenotypes [110]. Importantly, these lamin associated cases were characterised by conduction disease, a rare feature in patients with desmosomal variants.

3.5. Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is defined phenotypically by normal (or reduced) sized ventricles with bi-atrial enlargement and

Table 5
Indications for genetic testing, according to the most recent guidelines. Adapted from [119] and [120], with permission. HCM: hypertrophic cardiomyopathy, DCM: dilated cardiomyopathy, RCM: restrictive cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, LVNC: left ventricular non-compaction. Levels of evidence as per the original text [120].

Diagnosis (proband)	Predictive testing	Prognosis
Indicated: rare or particular cardiomyopathy, especially in the presence of atypical phenotypic features, in the setting of expert teams after detailed clinical and family assessment. *Level of evidence:* • HCM: A • DCM: B • ARVC: A • LVNC: C • RCM: C • Associated with extracardiac manifestations: A *Not indicated:* borderline or doubtful cardiomyopathy, except selected cases in the setting of expert teams after detailed clinical and family assessment	• asymptomatic relatives of a patient with a cardiomyopathy, when the disease-causing mutation has been previously characterized in the family (proband) • whether 'familial' or 'sporadic' in HCM and ARVC, but questionable in sporadic DCM and sporadic RCM (except in the presence of atypical associated phenotype or red-flags) • predictive diagnosis in children can be considered at the age at which cardiac examination is useful (10–12 years of age for most cardiomyopathies).	*Not indicated*: genetic testing cannot be systematically recommended for prognostic stratification. *Indicated*: should be considered in selected patients or for selected types of cardiomyopathies, in the setting of expert teams after detailed clinical and family assessment.

functionally by diastolic dysfunction with restrictive pathophysiology. The main clinical manifestations are heart failure due to the diastolic dysfunction, atrial arrhythmias and thromboembolism. As with all cardiomyopathies, RCM can be a familial disease or an acquired condition, often as part of a systemic disorder [10]. In familial disease, the majority of described disease-causing mutations are located in the sarcomere protein genes TNNI3, TNNT2, ACTC1 and MYL3 [111,112]. Additionally, RCM can also be a manifestation of desmin-related cardiomyopathy, caused my mutations in the desmin gene (DES), which should be suspected in the presence of skeletal muscle symptoms and conduction system disease [113].

4. Challenges and future research needs

4.1. Searching for the missing heritability in heart failure

The search for genetic loci that predispose to the development of heart failure and that influence response to therapy and disease progression has been dominated by two major study designs. The first, candidate gene studies, have focused mainly on genes likely to be important in the pathophysiology of the heart failure syndrome and molecular targets for commonly used drugs. The second approach, genome-wide association studies, looks for associations between common variants and HF risk and prognosis at a population level using array platforms containing million of SNPs [114]. Whilst the influence of genetic background in heart failure is generally accepted, a limitation of the data accrued so far has been their poor reproducibility and the relatively small risk (usually <1.5-fold), associated with individual variants. However, given the aetiological complexity of heart failure, this is not particularly surprising (Fig. 1). [52,115–117]. A new approach to the investigation of genetic determinants of heart failure may come from the use of new high-throughput sequencing technologies [118] that allow whole exome or genome sequencing of large populations. Re-sequencing studies can directly identify millions of rare mutations and may, therefore, be able to identify variants that are not tagged by panels of common SNPs in patients with common HF [52]. High throughput sequencing is already being applied to patients with Mendelian forms of heart muscle disease as advances in massive parallel sequencing technology permit sequencing of substantially larger genomic regions at the same or lower cost compared to capillary Sanger sequencing [118]. High-throughput sequencing (HTS) platforms facilitate the interrogation of many genes simultaneously making HTS the ideal tool in the setting of inherited cardiomyopathy. The technique can also be applied to study the effect of putative modifier genes and the effect of rare variants in large cohorts of patients with apparently acquired forms of HF.

However, in the clinical context, the introduction of HTS approaches also creates new challenges, particularly for whole-exome or genome strategies. One of the greatest is that the majority of novel rare variants identified using HTS are missense mutations that may or may not be pathological. Proof of pathogenicity is classically supported by co-segregation analysis, functional studies and the absence of the variant in normal controls. Nevertheless, application of all these methods is challenging in a clinical setting because of the massive amounts of sequencing information generated by HTS. There seems little doubt that the translation of HTS into clinical practice will require the development of new tools for discriminating disease-causing from benign variation. These might include more sophisticated *in silico* prediction models and the generation of large well-annotated disease-specific databases that incorporate detailed clinical phenotyping.

4.2. Inherited heart failure: clinical application of genetic testing

In inherited heart muscle disease, clinical guidelines [119,120] recommend routine molecular genetic testing of the most clearly affected member of the family. Given the high level of biological discrimination afforded by genetic testing, the finding of a potentially causal DNA sequence variant theoretically supports the diagnosis but the most important goal of genetic testing is to guide therapy and counselling strategies for families [119,120]. Table 5 summarises the current indications for genetic testing, according to recent guidelines [119,120]. However, the use of genetic testing in everyday clinical practice is challenging, for a number of reasons including the cost and complexity of conventional sequencing technologies and the relatively low yield of genetic testing which only results in the identification of a causal variant in around 50% of familial HCM or ARVC cases and even less in familial DCM (20–30%).

A third factor that still hampers the use of genetics for clinical decision-making is the poor understanding of genotype–phenotype relationships. Many of the initial clinical associations established for individual mutations are not reproducible [121–127]. An exception

Table 6
Genetic overlap between different inherited cardiomyopathy phenotypes.

	DCM	HCM	ARVC	RCM	LVNC
Sarcomere					
ACTC1	X	X		X	X
MYH7	X	x		X	X
MYH6	x	X			
MYBPC3	X	X			X
TNNT2	X	X		X	X
TNNI3	X	X		X	
TNNC1	X	X			
TPM1	X	X			X
MYL2		X			
MYL3		X		x	
TTN	X	X	x		
Z-disc					
TCAP	X	X			
CSRP3	X	X			
ACTN2	X	x			
MYPN	X				
ANKRD1	X				
MYOZ2		X			
Cytoskeleton and plasma membrane					
DES	X		x	x	
LDB3	X	X			X
PDLIM3	X				
VCL	X				
CRYAB	X			x	
ILK	X				
LAMA4	X				
SGCD	X				
DMD	X				
DTNA					X
Desmosomes					
DSP	X		X		
DSG2			X		
DSC2			X		
PKP2	X		X		
JUP			x		
Nuclear envelope					
LMNA	X		x		x
TMEM43			x		
TMPO	X				
Transcription /post-transcription regulation					
RBM20	X				
EYA4	X				
GATAD1	X				
Ion-channel/calcium handling					
SCN5A	X				
ABCC9	X				
RYR2			x		
PLN	X	X			
CASQ2					x
JPH2		x			
Others					
TAZ/G4.5	X				x
TGFB3			X		
BAG3	x				
PSEN1/2	X				

may be the poor prognosis for compound or double heterozygotes [96,128,129], especially in individuals with HCM and AVC (approximately 5 to 10% of patients). Patients carrying multiple variants tend to present earlier and with more severe disease. A further recently suggested genotype–phenotype association in HCM came from studies that showed increased numbers of cardiovascular events and a more frequent evolution to dilated phenotype in the presence of any sarcomere gene mutation compared to genotype-negative patients [130,131]. However, this was not reproduced for LVNC, in another recent paper exploring the same hypothesis [103].

Finally, it is increasingly recognised that the genetic background of different inherited cardiomyopathies overlap substantially. This further challenges current attempts to model genotype–phenotype relationships. Widely different phenotypes (dilation, non-compaction, and hypertrophy) can result from mutations in the same gene or even from the same mutation. This genetic overlap is illustrated by Table 6. How variation in one single gene can lead to different cardiomyopathy phenotypes is not known but current hypotheses being investigated include transcription regulation, post-translational modifications, modifier variants in other genes, environmental influences and the differential effects of specific region/domain of the protein affected by the mutation [10,11].

5. Conclusions. Translating new genetic insights into clinically relevant data

As inherited cardiomyopathies constitute “naturally-occurring” HF disease models, improved understanding of their genetic background and genotype–phenotype relationships may ultimately increase knowledge of HF disease pathways and pathophysiology, and lead to development of new therapies. For acquired and inherited forms of HF alike, a better definition of the underlying common and rare genetic variation will eventually promote to an era of personalised guidance, counselling and therapeutic options. For these goals to be accomplished though, further exploration of the molecular pathways (transcriptome and proteome) that lead from rare and common genetic variation to a final cellular and organ-level phenotype (phenome) is required. At the same time, an improved knowledge of the complex mechanisms of gene expression regulation (*e.g.* miRNAs effects, DNA methylation, and histone modification) is crucial.

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Competing Interests

The authors have no conflicts of interest to declare.

References

[1] K. Dickstein, A. Cohen-Solal, G. Filippatos, J.J. McMurray, P. Ponikowski, P.A. Poole-Wilson, A. Stromberg, D.J. van Veldhuisen, D. Atar, A.W. Hoes, A. Keren, A. Mebazaa, M. Nieminen, S.G. Priori, K. Swedberg, E.S.C. Guidelines for the diagnosis and treatment of acute and chronic heart failure, the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM), Eur. Heart J. 29 (2008) (2008) 2388–2442.

[2] S.A. Hunt, W.T. Abraham, M.H. Chin, A.M. Feldman, G.S. Francis, T.G. Ganiats, M. Jessup, M.A. Konstam, D.M. Mancini, K. Michl, J.A. Oates, P.S. Rahko, M.A. Silver, L.W. Stevenson, C.W. Yancy, 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation, Circulation 119 (2009) e391–e479.

[3] J.J. McMurray, S. Adamopoulos, S.D. Anker, A. Auricchio, M. Bohm, K. Dickstein, V. Falk, G. Filippatos, C. Fonseca, M.A. Sanchez, T. Jaarsma, L. Kober, G.Y. Lip, A.P. Maggioni, A. Parkhomenko, B.M. Pieske, B.A. Popescu, P.K. Ronnevik, F.H. Rutten, J. Schwitter, P. Seferovic, J. Stepinska, P.T. Trindade, A.A. Voors, F. Zannad, A. Zeiher, J.J. Bax, H. Baumgartner, C. Ceconi, V. Dean, C. Deaton, R. Fagard, C. Funck-Brentano, D. Hasdai, A. Hoes, P. Kirchhof, J. Knuuti, P. Kolh, T. McDonagh, C. Moulin, Z. Reiner, U. Sechtem, P.A. Sirnes, M. Tendera, A. Torbicki, A. Vahanian, S. Windecker, L.A. Bonet, P. Avraamides, H.A. Ben Lamin, M. Brignole, A. Coca, P. Cowburn, H. Dargie, P. Elliott, F.A. Flachskampf, G.F. Guida, S. Hardman, B. Iung, B. Merkely, C. Mueller, J.N. Nanas, O.W. Nielsen, S. Orn, J.T. Parissis, P. Ponikowski, ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Eur. Heart J. 33 (14) (2012) 1787–1847.

[4] M.R. Cowie, K.F. Fox, D.A. Wood, C. Metcalfe, S.G. Thompson, A.J. Coats, P.A. Poole-Wilson, G.C. Sutton, Hospitalization of patients with heart failure: a population-based study, Eur. Heart J. 23 (2002) 877–885.

[5] D. Lloyd-Jones, R.J. Adams, T.M. Brown, M. Carnethon, S. Dai, G. De Simone, T.B. Ferguson, E. Ford, K. Furie, C. Gillespie, A. Go, K. Greenlund, N. Haase, S. Hailpern, P.M. Ho, V. Howard, B. Kissela, S. Kittner, D. Lackland, L. Lisabeth, A. Marelli, M.M. McDermott, J. Meigs, D. Mozaffarian, M. Mussolino, G. Nichol, V.L. Roger, W. Rosamond, R. Sacco, P. Sorlie, R. Stafford, T. Thom, S. Wasserthiel-Smoller, N.D. Wong, J. Wylie-Rosett, Executive summary: heart disease and stroke statistics–2010 update: a report from the American Heart Association, Circulation 121 (2010) 948–954.

[6] L.R. Loehr, W.D. Rosamond, P.P. Chang, A.R. Folsom, L.E. Chambless, Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study), Am. J. Cardiol. 101 (2008) 1016–1022.

[7] D.S. Lee, M.J. Pencina, E.J. Benjamin, T.J. Wang, D. Levy, C.J. O'Donnell, B.H. Nam, M.G. Larson, R.B. D'Agostino, R.S. Vasan, Association of parental heart failure with risk of heart failure in offspring, N. Engl. J. Med. 355 (2006) 138–147.

[8] P. Elliott, B. Andersson, E. Arbustini, Z. Bilinska, F. Cecchi, P. Charron, O. Dubourg, U. Kuhl, B. Maisch, W.J. McKenna, L. Monserrat, S. Pankuweit, C. Rapezzi, P. Seferovic, L. Tavazzi, A. Keren, Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases, Eur. Heart J. 29 (2008) 270–276.

[9] D. Jacoby, W.J. McKenna, Genetics of inherited cardiomyopathy, Eur. Heart J. 33 (2012) 296–304.

[10] H. Watkins, H. Ashrafian, C. Redwood, Inherited cardiomyopathies, N. Engl. J. Med. 364 (2011) 1643–1656.

[11] S. Sen-Chowdhry, P. Syrris, A. Pantazis, G. Quarta, W.J. McKenna, J.C. Chambers, Mutational heterogeneity, modifier genes, and environmental influences contribute to phenotypic diversity of arrhythmogenic cardiomyopathy, Circ. Cardiovasc. Genet. 3 (2010) 323–330.

[12] M. Packer, The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure, J. Am. Coll. Cardiol. 20 (1992) 248–254.

[13] G.W. Dorn II, Adrenergic signaling polymorphisms and their impact on cardiovascular disease, Physiol. Rev. 90 (2010) 1013–1062.

[14] A map of human genome variation from population-scale sequencing, Nature 467 (2010) 1061–1073.

[15] D.A. Mason, J.D. Moore, S.A. Green, S.B. Liggett, A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor, J. Biol. Chem. 274 (1999) 12670–12674.

[16] S.S. Joseph, J.A. Lynham, A.A. Grace, W.H. Colledge, A.J. Kaumann, Markedly reduced effects of (−)-isoprenaline but not of (−)-CGP12177 and unchanged affinity of beta-blockers at Gly389-beta1-adrenoceptors compared to Arg389-beta1-adrenoceptors, Br. J. Pharmacol. 142 (2004) 51–56.

[17] D.A. Rathz, K.N. Gregory, Y. Fang, K.M. Brown, S.B. Liggett, Hierarchy of polymorphic variation and desensitization permutations relative to beta 1- and beta 2-adrenergic receptor signaling, J. Biol. Chem. 278 (2003) 10784–10789.

[18] J. Mialet Perez, D.A. Rathz, N.N. Petrashevskaya, H.S. Hahn, L.E. Wagoner, A. Schwartz, G.W. Dorn, S.B. Liggett, Beta 1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure, Nat. Med. 9 (2003) 1300–1305.

[19] S.B. Liggett, N.M. Tepe, J.N. Lorenz, A.M. Canning, T.D. Jantz, S. Mitarai, A. Yatani, G.W. Dorn II, Early and delayed consequences of beta(2)-adrenergic receptor overexpression in mouse hearts: critical role for expression level, Circulation 101 (2000) 1707–1714.

[20] H. Bruck, K. Leineweber, T. Temme, M. Weber, G. Heusch, T. Philipp, O.E. Brodde, The Arg389Gly beta1-adrenoceptor polymorphism and catecholamine effects on plasma-renin activity, J. Am. Coll. Cardiol. 46 (2005) 2111–2115.

[21] F. Rochais, J.P. Vilardaga, V.O. Nikolaev, M. Bunemann, M.J. Lohse, S. Engelhardt, Real-time optical recording of beta1-adrenergic receptor activation reveals supersensitivity of the Arg389 variant to carvedilol, J. Clin. Invest. 117 (2007) 229–235.

[22] L.E. Wagoner, L.L. Craft, P. Zengel, N. McGuire, D.A. Rathz, G.W. Dorn II, S.B. Liggett, Polymorphisms of the beta1-adrenergic receptor predict exercise capacity in heart failure, Am. Heart J. 144 (2002) 840–846.

[23] A.J. Sandilands, J. Parameshwar, S. Large, M.J. Brown, K.M. O'Shaughnessy, Confirmation of a role for the 389R>G beta-1 adrenoceptor polymorphism on exercise capacity in heart failure, Heart 91 (2005) 1613–1614.

[24] S.G. Terra, K.K. Hamilton, D.F. Pauly, C.R. Lee, J.H. Patterson, K.F. Adams, R.S. Schofield, B.S. Belgado, J.A. Hill, J.M. Aranda, H.N. Yarandi, J.A. Johnson, Beta1-adrenergic receptor polymorphisms and left ventricular remodeling

changes in response to beta-blocker therapy, Pharmacogenet. Genomics 15 (2005) 227–234.
[25] S.G. Terra, D.F. Pauly, C.R. Lee, J.H. Patterson, K.F. Adams, R.S. Schofield, B.S. Belgado, K.K. Hamilton, J.M. Aranda, J.A. Hill, H.N. Yarandi, J.R. Walker, M.S. Phillips, C.A. Gelfand, J.A. Johnson, beta-Adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure, Clin. Pharmacol. Ther. 77 (2005) 127–137.
[26] L. Chen, D. Meyers, G. Javorsky, D. Burstow, P. Lolekha, M. Lucas, A.B. Semmler, S.M. Savarimuthu, K.M. Fong, I.A. Yang, J. Atherton, A.J. Galbraith, W.A. Parsonage, P. Molenaar, Arg389Gly-beta1-adrenergic receptors determine improvement in left ventricular systolic function in nonischemic cardiomyopathy patients with heart failure after chronic treatment with carvedilol, Pharmacogenet. Genomics 17 (2007) 941–949.
[27] M. Petersen, J.T. Andersen, B.R. Hjelvang, K. Broedbaek, S. Afzal, M. Nyegaard, A.D. Borglum, S. Stender, L. Kober, C. Torp-Pedersen, H.E. Poulsen, Association of beta-adrenergic receptor polymorphisms and mortality in carvedilol-treated chronic heart-failure patients, Br. J. Clin. Pharmacol. 71 (2011) 556–565.
[28] S.B. Liggett, S. Cresci, R.J. Kelly, F.M. Syed, S.J. Matkovich, H.S. Hahn, A. Diwan, J.S. Martini, L. Sparks, R.R. Parekh, J.A. Spertus, W.J. Koch, S.L. Kardia, G.W. Dorn II, A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure, Nat. Med. 14 (2008) 510–517.
[29] W.C. Wang, K.A. Mihlbachler, E.R. Bleecker, S.T. Weiss, S.B. Liggett, A polymorphism of G-protein coupled receptor kinase5 alters agonist-promoted desensitization of beta2-adrenergic receptors, Pharmacogenet. Genomics 18 (2008) 729–732.
[30] G.W. Dorn II, Genetics of common forms of heart failure, Curr. Opin. Cardiol. 26 (2011) 204–208.
[31] S. Cresci, R.J. Kelly, T.P. Cappola, A. Diwan, D. Dries, S.L. Kardia, G.W. Dorn II, Clinical and genetic modifiers of long-term survival in heart failure, J. Am. Coll. Cardiol. 54 (2009) 432–444.
[32] B. Rigat, C. Hubert, F. Alhenc-Gelas, F. Cambien, P. Corvol, F. Soubrier, An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels, J. Clin. Invest. 86 (1990) 1343–1346.
[33] A.H. Danser, M.A. Schalekamp, W.A. Bax, A.M. van den Brink, P.R. Saxena, G.A. Riegger, H. Schunkert, Angiotensin-converting enzyme in the human heart. Effect of the deletion/insertion polymorphism, Circulation 92 (1995) 1387–1388.
[34] B. Andersson, C. Sylven, The DD genotype of the angiotensin-converting enzyme gene is associated with increased mortality in idiopathic heart failure, J. Am. Coll. Cardiol. 28 (1996) 162–167.
[35] B.R. Palmer, A.P. Pilbrow, T.G. Yandle, C.M. Frampton, A.M. Richards, M.G. Nicholls, V.A. Cameron, Angiotensin-converting enzyme gene polymorphism interacts with left ventricular ejection fraction and brain natriuretic peptide levels to predict mortality after myocardial infarction, J. Am. Coll. Cardiol. 41 (2003) 729–736.
[36] W. Huang, C. Xie, H. Zhou, T. Yang, M. Sun, Association of the angiotensin-converting enzyme gene polymorphism with chronic heart failure in Chinese Han patients, Eur. J. Heart Fail. 6 (2004) 23–27.
[37] D.M. McNamara, R. Holubkov, K. Janosko, A. Palmer, J.J. Wang, G.A. MacGowan, S. Murali, W.D. Rosenblum, B. London, A.M. Feldman, Pharmacogenetic interactions between beta-blocker therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure, Circulation 103 (2001) 1644–1648.
[38] D.M. McNamara, R. Holubkov, L. Postava, K. Janosko, G.A. MacGowan, M. Mathier, S. Murali, A.M. Feldman, B. London, Pharmacogenetic interactions between angiotensin-converting enzyme inhibitor therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure, J. Am. Coll. Cardiol. 44 (2004) 2019–2026.
[39] A.J. Marian, Q.T. Yu, R. Workman, G. Greve, R. Roberts, Angiotensin-converting enzyme polymorphism in hypertrophic cardiomyopathy and sudden cardiac death, Lancet 342 (1993) 1085–1086.
[40] F. Tesson, C. Dufour, J.C. Moolman, L. Carrier, S. al-Mahdawi, L. Chojnowska, O. Dubourg, E. Soubrier, P. Brink, M. Komajda, P. Guicheney, K. Schwartz, J. Feingold, The influence of the angiotensin I converting enzyme genotype in familial hypertrophic cardiomyopathy varies with the disease gene mutation, J. Mol. Cell. Cardiol. 29 (1997) 831–838.
[41] M. Lechin, M.A. Quinones, A. Omran, R. Hill, Q.T. Yu, H. Rakowski, D. Wigle, C.C. Liew, M. Sole, R. Roberts, A.J. Marian, Angiotensin-I converting enzyme genotypes and left ventricular hypertrophy in patients with hypertrophic cardiomyopathy, Circulation 92 (1995) 1808–1812.
[42] N. Iwai, N. Ohmichi, Y. Nakamura, M. Kinoshita, DD genotype of the angiotensin-converting enzyme gene is a risk factor for left ventricular hypertrophy, Circulation 90 (1994) 2622–2628.
[43] H. Schunkert, H.W. Hense, S.R. Holmer, M. Stender, S. Perz, U. Keil, B.H. Lorell, G.A. Riegger, Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy, N. Engl. J. Med. 330 (1994) 1634–1638.
[44] S.G. Myerson, H.E. Montgomery, M. Whittingham, M. Jubb, M.J. World, S.E. Humphries, D.J. Pennell, Left ventricular hypertrophy with exercise and ACE gene insertion/deletion polymorphism: a randomized controlled trial with losartan, Circulation 103 (2001) 226–230.
[45] P.B. Clarkson, N. Prasad, C. MacLeod, B. Burchell, T.M. MacDonald, Influence of the angiotensin converting enzyme I/D gene polymorphisms on left ventricular diastolic filling in patients with essential hypertension, J. Hypertens. 15 (1997) 995–1000.
[46] E. Osono, S. Kurihara, N. Hayama, Y. Sakurai, K. Ohwada, N. Onoda, M. Takeuchi, T. Tomizawa, Y. Komaba, K. Hashimoto, S. Matsunobu, H. Yoneshima, Y. Iino, Insertion/deletion polymorphism in intron 16 of the ACE gene and left ventricular hypertrophy in patients with end-stage renal disease, Am. J. Kidney Dis. 32 (1998) 725–730.
[47] J.E. Jalil, A.M. Piddo, S. Cordova, G. Chamorro, S. Braun, R. Jalil, J. Vega, P.L. Jadue, S. Lavandero, P. Lastra, Prevalence of the angiotensin I converting enzyme insertion/deletion polymorphism, plasma angiotensin converting enzyme activity, and left ventricular mass in a normotensive Chilean population, Am. J. Hypertens. 12 (1999) 697–704.
[48] Y. Bai, L. Wang, S. Hu, Y. Wei, Association of angiotensin-converting enzyme I/D polymorphism with heart failure: a meta-analysis, Mol. Cell. Biochem. 361 (2012) 297–304.
[49] X. Li, Y. Li, N. Jia, S. Guo, S. Chu, W. Niu, Angiotensin-converting enzyme gene deletion allele increases the risk of left ventricular hypertrophy: evidence from a meta-analysis, Mol. Biol. Rep. 39 (12) (2012) 10063–10075.
[50] I.C. Kolder, M. Michels, I. Christiaans, F.J. Ten Cate, D. Majoor-Krakauer, A.H. Danser, R.H. Lekanne Deprez, M.W. Tanck, A.A. Wilde, C.R. Bezzina, D. Dooijes, The role of renin–angiotensin–aldosterone system polymorphisms in phenotypic expression of MYBPC3-related hypertrophic cardiomyopathy, Eur. J. Hum. Genet. 20 (10) (2012) 1071–1077.
[51] Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls, Nature 447 (2007) 661–678.
[52] T.A. Manolio, F.S. Collins, N.J. Cox, D.B. Goldstein, L.A. Hindorff, D.J. Hunter, M.I. McCarthy, E.M. Ramos, L.R. Cardon, A. Chakravarti, J.H. Cho, A.E. Guttmacher, A. Kong, L. Kruglyak, E. Mardis, C.N. Rotimi, M. Slatkin, D. Valle, A.S. Whittemore, M. Boehnke, A.G. Clark, E.E. Eichler, G. Gibson, J.L. Haines, T.F. Mackay, S.A. McCarroll, P.M. Visscher, Finding the missing heritability of complex diseases, Nature 461 (2009) 747–753.
[53] N.L. Smith, J.F. Felix, A.C. Morrison, S. Demissie, N.L. Glazer, L.R. Loehr, L.A. Cupples, A. Dehghan, T. Lumley, W.D. Rosamond, W. Lieb, F. Rivadeneira, J.C. Bis, A.R. Folsom, E. Benjamin, Y.S. Aulchenko, T. Haritunians, D. Couper, J. Murabito, Y.A. Wang, B.H. Stricker, J.S. Gottdiener, P.P. Chang, T.J. Wang, K.M. Rice, A. Hofman, S.R. Heckbert, E.R. Fox, C.J. O'Donnell, A.G. Uitterlinden, J.I. Rotter, J.T. Willerson, D. Levy, C.M. van Duijn, B.M. Psaty, J.C. Witteman, E. Boerwinkle, R.S. Vasan, Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium, Circ. Cardiovasc. Genet. 3 (2010) 256–266.
[54] A.C. Morrison, J.F. Felix, L.A. Cupples, N.L. Glazer, L.R. Loehr, A. Dehghan, S. Demissie, J.C. Bis, W.D. Rosamond, Y.S. Aulchenko, Y.A. Wang, T. Haritunians, A.R. Folsom, F. Rivadeneira, E.J. Benjamin, T. Lumley, D. Couper, B.H. Stricker, C.J. O'Donnell, K.M. Rice, P.P. Chang, A. Hofman, D. Levy, J.I. Rotter, E.R. Fox, A.G. Uitterlinden, T.J. Wang, B.M. Psaty, J.T. Willerson, C.M. van Duijn, E. Boerwinkle, J.C. Witteman, R.S. Vasan, N.L. Smith, Genomic variation associated with mortality among adults of European and African ancestry with heart failure: the cohorts for heart and aging research in genomic epidemiology consortium, Circ. Cardiovasc. Genet. 3 (2010) 248–255.
[55] T.P. Cappola, M. Li, J. He, B. Ky, J. Gilmore, L. Qu, B. Keating, M. Reilly, C.E. Kim, J. Glessner, E. Frackelton, H. Hakonarson, F. Syed, A. Hindes, S.J. Matkovich, S. Cresci, G.W. Dorn II, Common variants in HSPB7 and FRMD4B associated with advanced heart failure, Circ. Cardiovasc. Genet. 3 (2010) 147–154.
[56] K. Stark, U.B. Esslinger, W. Reinhard, G. Petrov, T. Winkler, M. Komajda, R. Isnard, P. Charron, E. Villard, F. Cambien, L. Tiret, M.C. Aumont, O. Dubourg, J.N. Trochu, L. Fauchier, P. Degroote, A. Richter, B. Maisch, T. Wichter, C. Zollbrecht, M. Grassl, H. Schunkert, P. Linsel-Nitschke, J. Erdmann, J. Baumert, T. Illig, N. Klopp, H.E. Wichmann, C. Meisinger, W. Koenig, P. Lichtner, T. Meitinger, A. Schillert, I.R. Konig, R. Hetzer, I.M. Heid, V. Regitz-Zagrosek, C. Hengstenberg, Genetic association study identifies HSPB7 as a risk gene for idiopathic dilated cardiomyopathy, PLoS Genet. 6 (2010) e1001167.
[57] T.P. Cappola, S.J. Matkovich, W. Wang, D. van Booven, M. Li, X. Wang, L. Qu, N.K. Sweitzer, J.C. Fang, M.P. Reilly, H. Hakonarson, J.M. Nerbonne, G.W. Dorn II, Loss-of-function DNA sequence variant in the CLCNKA chloride channel implicates the cardio-renal axis in interindividual heart failure risk variation, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 2456–2461.
[58] E. Villard, C. Perret, F. Gary, C. Proust, G. Dilanian, C. Hengstenberg, V. Ruppert, E. Arbustini, T. Wichter, M. Germain, O. Dubourg, L. Tavazzi, M.C. Aumont, P. DeGroote, L. Fauchier, J.N. Trochu, P. Gibelin, J.F. Aupetit, K. Stark, J. Erdmann, R. Hetzer, A.M. Roberts, P.J. Barton, V. Regitz-Zagrosek, U. Aslam, L. Duboscq-Bidot, M. Meyborg, B. Maisch, H. Madeira, A. Waldenstrom, E. Galve, J.G. Cleland, R. Dorent, G. Roizes, T. Zeller, S. Blankenberg, A.H. Goodall, S. Cook, D.A. Tregouet, L. Tiret, R. Isnard, M. Komajda, P. Charron, F. Cambien, A genome-wide association study identifies two loci associated with heart failure due to dilated cardiomyopathy, Eur. Heart J. 32 (2011) 1065–1076.
[59] N. Norton, D. Li, M.J. Rieder, J.D. Siegfried, E. Rampersaud, S. Zuchner, S. Mangos, J. Gonzalez-Quintana, L. Wang, S. McGee, J. Reiser, E. Martin, D.A. Nickerson, R.E. Hershberger, Genome-wide studies of copy number variation and exome sequencing identify rare variants in BAG3 as a cause of dilated cardiomyopathy, Am. J. Hum. Genet. 88 (2011) 273–282.
[60] C.J. O'Donnell, E.G. Nabel, Genomics of cardiovascular disease, N. Engl. J. Med. 365 (2011) 2098–2109.
[61] S. Kathiresan, D. Srivastava, Genetics of human cardiovascular disease, Cell 148 (2012) 1242–1257.
[62] H. Schunkert, I.R. Konig, S. Kathiresan, M.P. Reilly, T.L. Assimes, H. Holm, M. Preuss, A.F. Stewart, M. Barbalic, C. Gieger, D. Absher, Z. Aherrahrou, H. Allayee, D. Altshuler, S.S. Anand, K. Andersen, J.L. Anderson, D. Ardissino, S.G. Ball, A.J. Balmforth, T.A. Barnes, D.M. Becker, L.C. Becker, K. Berger, J.C. Bis, S.M. Boekholdt, E. Boerwinkle, P.S. Braund, M.J. Brown, M.S. Burnett, I. Buysschaert,

J.F. Carlquist, L. Chen, S. Cichon, V. Codd, R.W. Davies, G. Dedoussis, A. Dehghan, S. Demissie, J.M. Devaney, P. Diemert, R. Do, A. Doering, S. Eifert, N.E. Mokhtari, S.G. Ellis, R. Elosua, J.C. Engert, S.E. Epstein, U. de Faire, M. Fischer, A.R. Folsom, J. Freyer, B. Gigante, D. Girelli, S. Gretarsdottir, V. Gudnason, J.R. Gulcher, E. Halperin, N. Hammond, S.L. Hazen, A. Hofman, B.D. Horne, T. Illig, C. Iribarren, G.T. Jones, J.W. Jukema, M.A. Kaiser, L.M. Kaplan, J.J. Kastelein, K.T. Khaw, J.W. Knowles, G. Kolovou, A. Kong, R. Laaksonen, D. Lambrechts, K. Leander, G. Lettre, M. Li, W. Lieb, C. Loley, A.J. Lotery, P.M. Mannucci, S. Maouche, N. Martinelli, P.P. McKeown, C. Meisinger, T. Meitinger, O. Melander, P.A. Merlini, V. Mooser, T. Morgan, T.W. Muhleisen, J.B. Muhlestein, T. Munzel, K. Musunuru, J. Nahrstaedt, C.P. Nelson, M.M. Nothen, O. Olivieri, R.S. Patel, C.C. Patterson, A. Peters, F. Peyvandi, L. Qu, A.A. Quyyumi, D.J. Rader, L.S. Rallidis, C. Rice, F.R. Rosendaal, D. Rubin, V. Salomaa, M.L. Sampietro, M.S. Sandhu, E. Schadt, A. Schafer, A. Schillert, S. Schreiber, J. Schrezenmeir, S.M. Schwartz, D.S. Siscovick, M. Sivananthan, S. Sivapalaratnam, A. Smith, T.B. Smith, J.D. Snoep, N. Soranzo, J.A. Spertus, K. Stark, K. Stirrups, M. Stoll, W.H. Tang, S. Tennstedt, G. Thorgeirsson, G. Thorleifsson, M. Tomaszewski, A.G. Uitterlinden, A.M. van Rij, B.F. Voight, N.J. Wareham, G.A. Wells, H.E. Wichmann, P.S. Wild, C. Willenborg, J.C. Witteman, B.J. Wright, S. Ye, T. Zeller, A. Ziegler, F. Cambien, A.H. Goodall, L.A. Cupples, T. Quertermous, W. Marz, C. Hengstenberg, S. Blankenberg, W.H. Ouwehand, A.S. Hall, P. Deloukas, J.R. Thompson, K. Stefansson, R. Roberts, U. Thorsteinsdottir, C.J. O'Donnell, R. McPherson, J. Erdmann, N.J. Samani, Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease, Nat. Genet. 43 (2011) 333–338.

[63] A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease, Nat. Genet. 43 (2011) 339–344.

[64] S. Kathiresan, B.F. Voight, S. Purcell, K. Musunuru, D. Ardissino, P.M. Mannucci, S. Anand, J.C. Engert, N.J. Samani, H. Schunkert, J. Erdmann, M.P. Reilly, D.J. Rader, T. Morgan, J.A. Spertus, M. Stoll, D. Girelli, P.P. McKeown, C.C. Patterson, D.S. Siscovick, C.J. O'Donnell, R. Elosua, L. Peltonen, V. Salomaa, S.M. Schwartz, O. Melander, D. Altshuler, P.A. Merlini, C. Berzuini, L. Bernardinelli, F. Peyvandi, M. Tubaro, P. Celli, M. Ferrario, R. Fetiveau, N. Marziliano, G. Casari, M. Galli, F. Ribichini, M. Rossi, F. Bernardi, P. Zonzin, A. Piazza, J. Yee, Y. Friedlander, J. Marrugat, G. Lucas, I. Subirana, J. Sala, R. Ramos, J.B. Meigs, G. Williams, D.M. Nathan, C.A. MacRae, A.S. Havulinna, G. Berglund, J.N. Hirschhorn, R. Asselta, S. Duga, M. Spreafico, M.J. Daly, J. Nemesh, J.M. Korn, S.A. McCarroll, A. Surti, C. Guiducci, L. Gianniny, D. Mirel, M. Parkin, N. Burtt, S.B. Gabriel, J.R. Thompson, P.S. Braund, B.J. Wright, A.J. Balmforth, S.G. Ball, A.S. Hall, P. Linsel-Nitschke, W. Lieb, A. Ziegler, I. Konig, C. Hengstenberg, M. Fischer, K. Stark, A. Grosshennig, M. Preuss, H.E. Wichmann, S. Schreiber, W. Ouwehand, P. Deloukas, M. Scholz, F. Cambien, M. Li, Z. Chen, R. Wilensky, W. Matthai, A. Qasim, H.H. Hakonarson, J. Devaney, M.S. Burnett, A.D. Pichard, K.M. Kent, L. Satler, J.M. Lindsay, R. Waksman, C.W. Knouff, D.M. Waterworth, M.C. Walker, V. Mooser, S.E. Epstein, T. Scheffold, K. Berger, A. Huge, N. Martinelli, O. Olivieri, R. Corrocher, P. McKeown, E. Erdmann, I.R. Konig, H. Holm, G. Thorleifsson, U. Thorsteinsdottir, K. Stefansson, R. Do, C. Xie, D. Siscovick, Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants, Nat. Genet. 41 (2009) 334–341.

[65] G.B. Ehret, P.B. Munroe, K.M. Rice, M. Bochud, A.D. Johnson, D.I. Chasman, A.V. Smith, M.D. Tobin, G.C. Verwoert, S.J. Hwang, V. Pihur, P. Vollenweider, P.F. O'Reilly, N. Amin, J.L. Bragg-Gresham, A. Teumer, N.L. Glazer, L. Launer, J.H. Zhao, Y. Aulchenko, S. Heath, S. Sober, A. Parsa, J. Luan, P. Arora, A. Dehghan, F. Zhang, G. Lucas, A.A. Hicks, A.U. Jackson, J.F. Peden, T. Tanaka, S.H. Wild, I. Rudan, W. Igl, Y. Milaneschi, A.N. Parker, C. Fava, J.C. Chambers, E.R. Fox, M. Kumari, M.J. Go, P. van der Harst, W.H. Kao, M. Sjogren, D.G. Vinay, M. Alexander, Y. Tabara, S. Shaw-Hawkins, P.H. Whincup, Y. Liu, G. Shi, J. Kuusisto, B. Tayo, M. Seielstad, X. Sim, K.D. Nguyen, T. Lehtimaki, G. Matullo, Y. Wu, T.R. Gaunt, N.C. Onland-Moret, M.N. Cooper, C.G. Platou, E. Org, R. Hardy, S. Dahgam, J. Palmen, V. Vitart, P.S. Braund, T. Kuznetsova, C.S. Uiterwaal, A. Adeyemo, W. Palmas, H. Campbell, B. Ludwig, M. Tomaszewski, I. Tzoulaki, N.D. Palmer, T. Aspelund, M. Garcia, Y.P. Chang, J.R. O'Connell, N.I. Steinle, D.E. Grobbee, D.E. Arking, S.L. Kardia, A.C. Morrison, D. Hernandez, S. Najjar, W.L. McArdle, D. Hadley, M.J. Brown, J.M. Connell, A.D. Hingorani, I.N. Day, D.A. Lawlor, J.P. Beilby, R.W. Lawrence, R. Clarke, J.C. Hopewell, H. Ongen, A.W. Dreisbach, Y. Li, J.H. Young, J.C. Bis, M. Kahonen, J. Viikari, L.S. Adair, N.R. Lee, M.H. Chen, M. Olden, C. Pattaro, J.A. Bolton, A. Kottgen, S. Bergmann, V. Mooser, N. Chaturvedi, T.M. Frayling, M. Islam, T.H. Jafar, J. Erdmann, S.R. Kulkarni, S.R. Bornstein, J. Grassler, L. Groop, B.F. Voight, J. Kettunen, P. Howard, A. Taylor, S. Guarrera, F. Ricceri, V. Emilsson, A. Plump, I. Barroso, K.T. Khaw, A.B. Weder, S.C. Hunt, Y.V. Sun, R.N. Bergman, F.S. Collins, L.L. Bonnycastle, L.J. Scott, H.M. Stringham, L. Peltonen, M. Perola, E. Vartiainen, S.M. Brand, J.A. Staessen, T.J. Wang, P.R. Burton, M.S. Artigas, Y. Dong, H. Snieder, X. Wang, H. Zhu, K.K. Lohman, M.E. Rudock, S.R. Heckbert, N.L. Smith, K.L. Wiggins, A. Doumatey, D. Shriner, G. Veldre, M. Viigimaa, S. Kinra, D. Prabhakaran, V. Tripathy, C.D. Langefeld, A. Rosengren, D.S. Thelle, A.M. Corsi, A. Singleton, T. Forrester, G. Hilton, C.A. McKenzie, T. Salako, N. Iwai, Y. Kita, T. Ogihara, T. Ohkubo, T. Okamura, H. Ueshima, S. Umemura, S. Eyheramendy, T. Meitinger, H.E. Wichmann, Y.S. Cho, H.L. Kim, J.Y. Lee, J. Scott, J.S. Sehmi, W. Zhang, B. Hedblad, P. Nilsson, G.D. Smith, A. Wong, N. Narisu, A. Stancakova, L.J. Raffel, J. Yao, S. Kathiresan, C.J. O'Donnell, S.M. Schwartz, M.A. Ikram, W.T. Longstreth Jr., T.H. Mosley, S. Seshadri, N.R. Shrine, L.V. Wain, M.A. Morken, A.J. Swift, J. Laitinen, I. Prokopenko, P. Zitting, J.A. Cooper, S.E. Humphries, J. Danesh, A. Rasheed, A. Goel, A. Hamsten, H. Watkins, S.J. Bakker, W.H. van Gilst, C.S. Janipalli, K.R. Mani, C.S. Yajnik, A. Hofman, F.U. Mattace-Raso, B.A. Oostra, A. Demirkan, A. Isaacs, F. Rivadeneira, E.G. Lakatta, M. Orru, A. Scuteri, M. Ala-Korpela, A.J. Kangas, L.P. Lyytikainen, P. Soininen, T. Tukiainen, P. Wurtz, R.T. Ong, M. Dorr, H.K. Kroemer, U. Volker, H. Volzke, P. Galan, S. Hercberg, M. Lathrop, D. Zelenika, P. Deloukas, M. Mangino, T.D. Spector, G. Zhai, J.F. Meschia, M.A. Nalls, P. Sharma, J. Terzic, M.V. Kumar, M. Denniff, E. Zukowska-Szczechowska, L.E. Wagenknecht, F.G. Fowkes, F.J. Charchar, P.E. Schwarz, C. Hayward, X. Guo, C. Rotimi, M.L. Bots, E. Brand, N.J. Samani, O. Polasek, P.J. Talmud, F. Nyberg, D. Kuh, M. Laan, K. Hveem, L.J. Palmer, Y.T. van der Schouw, J.P. Casas, K.L. Mohlke, P. Vineis, O. Raitakari, S.K. Ganesh, T.Y. Wong, E.S. Tai, R.S. Cooper, M. Laakso, D.C. Rao, T.B. Harris, R.W. Morris, A.F. Dominiczak, M. Kivimaki, M.G. Marmot, T. Miki, D. Saleheen, G.R. Chandak, J. Coresh, G. Navis, V. Salomaa, B.G. Han, X. Zhu, J.S. Kooner, O. Melander, P.M. Ridker, S. Bandinelli, U.B. Gyllensten, A.F. Wright, J.F. Wilson, L. Ferrucci, M. Farrall, J. Tuomilehto, P.P. Pramstaller, R. Elosua, N. Soranzo, E.J. Sijbrands, D. Altshuler, R.J. Loos, A.R. Shuldiner, C. Gieger, P. Meneton, A.G. Uitterlinden, N.J. Wareham, V. Gudnason, J.I. Rotter, R. Rettig, M. Uda, D.P. Strachan, J.C. Witteman, A.L. Hartikainen, J.S. Beckmann, E. Boerwinkle, R.S. Vasan, M. Boehnke, M.G. Larson, M.R. Jarvelin, B.M. Psaty, G.R. Abecasis, A. Chakravarti, P. Elliott, C.M. van Duijn, C. Newton-Cheh, D. Levy, M.J. Caulfield, T. Johnson, Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk, Nature 478 (2011) 103–109.

[66] T.M. Teslovich, K. Musunuru, A.V. Smith, A.C. Edmondson, I.M. Stylianou, M. Koseki, J.P. Pirruccello, S. Ripatti, D.I. Chasman, C.J. Willer, C.T. Johansen, S.W. Fouchier, A. Isaacs, G.M. Peloso, M. Barbalic, S.L. Ricketts, J.C. Bis, Y.S. Aulchenko, G. Thorleifsson, M.F. Feitosa, J. Chambers, M. Orho-Melander, O. Melander, T. Johnson, X. Li, X. Guo, M. Li, Y. Shin Cho, M. Jin Go, Y. Jin Kim, J.Y. Lee, T. Park, K. Kim, X. Sim, R. Twee-Hee Ong, D.C. Croteau-Chonka, L.A. Lange, J.D. Smith, K. Song, J. Hua Zhao, X. Yuan, J. Luan, C. Lamina, A. Ziegler, W. Zhang, R.Y. Zee, A.F. Wright, J.C. Witteman, J.F. Wilson, G. Willemsen, H.E. Wichmann, J.B. Whitfield, D.M. Waterworth, N.J. Wareham, G. Waeber, P. Vollenweider, B.F. Voight, V. Vitart, A.G. Uitterlinden, M. Uda, J. Tuomilehto, J.R. Thompson, T. Tanaka, I. Surakka, H.M. Stringham, T.D. Spector, N. Soranzo, J.H. Smit, J. Sinisalo, K. Silander, E.J. Sijbrands, A. Scuteri, J. Scott, D. Schlessinger, S. Sanna, V. Salomaa, J. Saharinen, C. Sabatti, A. Ruokonen, I. Rudan, L.M. Rose, R. Roberts, M. Rieder, B.M. Psaty, P.P. Pramstaller, I. Pichler, M. Perola, B.W. Penninx, N.L. Pedersen, C. Pattaro, A.N. Parker, G. Pare, B.A. Oostra, C.J. O'Donnell, M.S. Nieminen, D.A. Nickerson, G.W. Montgomery, T. Meitinger, R. McPherson, M.I. McCarthy, W. McArdle, D. Masson, N.G. Martin, F. Marroni, M. Mangino, P.K. Magnusson, G. Lucas, R. Luben, R.J. Loos, M.L. Lokki, G. Lettre, C. Langenberg, L.J. Launer, E.G. Lakatta, R. Laaksonen, K.O. Kyvik, F. Kronenberg, I.R. Konig, K.T. Khaw, J. Kaprio, L.M. Kaplan, A. Johansson, M.R. Jarvelin, A.C. Janssens, E. Ingelsson, W. Igl, G. Kees Hovingh, J.J. Hottenga, A. Hofman, A.A. Hicks, C. Hengstenberg, I.M. Heid, C. Hayward, A.S. Havulinna, N.D. Hastie, T.B. Harris, T. Haritunians, A.S. Hall, U. Gyllensten, C. Guiducci, L.C. Groop, E. Gonzalez, C. Gieger, N.B. Freimer, L. Ferrucci, J. Erdmann, P. Elliott, K.G. Ejebe, A. Doring, A.F. Dominiczak, S. Demissie, P. Deloukas, E.J. de Geus, U. de Faire, G. Crawford, F.S. Collins, Y.D. Chen, M.J. Caulfield, H. Campbell, N.P. Burtt, L.L. Bonnycastle, D.I. Boomsma, S.M. Boekholdt, R.N. Bergman, I. Barroso, S. Bandinelli, C.M. Ballantyne, T.L. Assimes, T. Quertermous, D. Altshuler, M. Seielstad, T.Y. Wong, E.S. Tai, A.B. Feranil, C.W. Kuzawa, L.S. Adair, H.A. Taylor Jr., I.B. Borecki, S.B. Gabriel, J.G. Wilson, H. Holm, U. Thorsteinsdottir, V. Gudnason, R.M. Krauss, K.L. Mohlke, J.M. Ordovas, P.B. Munroe, J.S. Kooner, A.R. Tall, R.A. Hegele, J.J. Kastelein, E.E. Schadt, J.I. Rotter, E. Boerwinkle, D.P. Strachan, V. Mooser, K. Stefansson, M.P. Reilly, N.J. Samani, H. Schunkert, L.A. Cupples, M.S. Sandhu, P.M. Ridker, D.J. Rader, C.M. van Duijn, L. Peltonen, G.R. Abecasis, M. Boehnke, S. Kathiresan, Biological, clinical and population relevance of 95 loci for blood lipids, Nature 466 (2010) 707–713.

[67] B.F. Voight, L.J. Scott, V. Steinthorsdottir, A.P. Morris, C. Dina, R.P. Welch, E. Zeggini, C. Huth, Y.S. Aulchenko, G. Thorleifsson, L.J. McCulloch, T. Ferreira, H. Grallert, N. Amin, G. Wu, C.J. Willer, S. Raychaudhuri, S.A. McCarroll, C. Langenberg, O.M. Hofmann, J. Dupuis, L. Qi, A.V. Segre, M. van Hoek, P. Navarro, K. Ardlie, B. Balkau, R. Benediktsson, A.J. Bennett, R. Blagieva, E. Boerwinkle, L.L. Bonnycastle, K. Bengtsson Bostrom, B. Bravenboer, S. Bumpstead, N.P. Burtt, G. Charpentier, P.S. Chines, M. Cornelis, D.J. Couper, G. Crawford, A.S. Doney, K.S. Elliott, A.L. Elliott, M.R. Erdos, C.S. Fox, C.S. Franklin, M. Ganser, C. Gieger, N. Grarup, T. Green, S. Griffin, C.J. Groves, C. Guiducci, S. Hadjadj, N. Hassanali, C. Herder, B. Isomaa, A.U. Jackson, P.R. Johnson, T. Jorgensen, W.H. Kao, N. Klopp, A. Kong, P. Kraft, J. Kuusisto, T. Lauritzen, M. Li, A. Lieverse, C.M. Lindgren, V. Lyssenko, M. Marre, T. Meitinger, K. Midthjell, M.A. Morken, N. Narisu, P. Nilsson, K.R. Owen, F. Payne, J.R. Perry, A.K. Petersen, C. Platou, C. Proenca, I. Prokopenko, W. Rathmann, N.W. Rayner, N.R. Robertson, G. Rocheleau, M. Roden, M.J. Sampson, R. Saxena, B.M. Shields, P. Shrader, G. Sigurdsson, T. Sparso, K. Strassburger, H.M. Stringham, Q. Sun, A.J. Swift, B. Thorand, J. Tichet, T. Tuomi, R.M. van Dam, T.W. van Haeften, T. van Herpt, J.V. van Vliet-Ostaptchouk, G.B. Walters, M.N. Weedon, C. Wijmenga, J. Witteman, R.N. Bergman, S. Cauchi, F.S. Collins, A.L. Gloyn, U. Gyllensten, T. Hansen, W.A. Hide, G.A. Hitman, A. Hofman, D.J. Hunter, K. Hveem, M. Laakso, K.L. Mohlke, A.D. Morris, C.N. Palmer, P.P. Pramstaller, I. Rudan, E. Sijbrands, L.D. Stein, J. Tuomilehto, A. Uitterlinden, M. Walker, N.J. Wareham, R.M. Watanabe, G.R. Abecasis, B.O. Boehm, H. Campbell, M.J. Daly, A.T. Hattersley, F.B. Hu, J.B. Meigs, J.S. Pankow, O. Pedersen, H.E. Wichmann, I. Barroso, J.C. Florez, T.M. Frayling, L. Groop, R. Sladek, U. Thorsteinsdottir, J.F. Wilson, T. Illig, P. Froguel, C.M. van Duijn, K. Stefansson, D. Altshuler, M. Boehnke, M.I. McCarthy, Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis, Nat. Genet. 42 (2010) 579–589.

[68] J. Dupuis, C. Langenberg, I. Prokopenko, R. Saxena, N. Soranzo, A.U. Jackson, E. Wheeler, N.L. Glazer, N. Bouatia-Naji, A.L. Gloyn, C.M. Lindgren, R. Magi, A.P.

Morris, J. Randall, T. Johnson, P. Elliott, D. Rybin, G. Thorleifsson, V. Steinthorsdottir, P. Henneman, H. Grallert, A. Dehghan, J.J. Hottenga, C.S. Franklin, P. Navarro, K. Song, A. Goel, J.R. Perry, J.M. Egan, T. Lajunen, N. Grarup, T. Sparso, A. Doney, B.F. Voight, H.M. Stringham, M. Li, S. Kanoni, P. Shrader, C. Cavalcanti-Proenca, M. Kumari, L. Qi, N.J. Timpson, C. Gieger, C. Zabena, G. Rocheleau, E. Ingelsson, P. An, J. O'Connell, J. Luan, A. Elliott, S.A. McCarroll, F. Payne, R.M. Roccasecca, F. Pattou, P. Sethupathy, K. Ardlie, Y. Ariyurek, B. Balkau, P. Barter, J.P. Beilby, Y. Ben-Shlomo, R. Benediktsson, A.J. Bennett, S. Bergmann, M. Bochud, E. Boerwinkle, A. Bonnefond, L.L. Bonnycastle, K. Borch-Johnsen, Y. Bottcher, E. Brunner, S.J. Bumpstead, G. Charpentier, Y.D. Chen, P. Chines, R. Clarke, L.J. Coin, M.N. Cooper, M. Cornelis, G. Crawford, L. Crisponi, I.N. Day, E.J. de Geus, J. Delplanque, C. Dina, M.R. Erdos, A.C. Fedson, A. Fischer-Rosinsky, N.G. Forouhi, C.S. Fox, R. Frants, M.G. Franzosi, P. Galan, M.O. Goodarzi, J. Graessler, C.J. Groves, S. Grundy, R. Gwilliam, U. Gyllensten, S. Hadjadj, G. Hallmans, N. Hammond, X. Han, A.L. Hartikainen, N. Hassanali, C. Hayward, S.C. Heath, S. Hercberg, C. Herder, A.A. Hicks, D.R. Hillman, A.D. Hingorani, A. Hofman, J. Hui, J. Hung, B. Isomaa, P.R. Johnson, T. Jorgensen, A. Jula, M. Kaakinen, J. Kaprio, Y.A. Kesaniemi, M. Kivimaki, B. Knight, S. Koskinen, P. Kovacs, K.O. Kyvik, G.M. Lathrop, D.A. Lawlor, O. Le Bacquer, C. Lecoeur, Y. Li, V. Lyssenko, R. Mahley, M. Mangino, A.K. Manning, M.T. Martinez-Larrad, J.B. McAteer, L.J. McCulloch, R. McPherson, C. Meisinger, D. Melzer, D. Meyre, B.D. Mitchell, M.A. Morken, S. Mukherjee, S. Naitza, N. Narisu, M.J. Neville, B.A. Oostra, M. Orru, R. Pakyz, C.N. Palmer, G. Paolisso, C. Pattaro, D. Pearson, J.F. Peden, N.L. Pedersen, M. Perola, A.F. Pfeiffer, I. Pichler, O. Polasek, D. Posthuma, S.C. Potter, A. Pouta, M.A. Province, B.M. Psaty, W. Rathmann, N.W. Rayner, K. Rice, S. Ripatti, F. Rivadeneira, M. Roden, O. Rolandsson, A. Sandbaek, M. Sandhu, S. Sanna, A.A. Sayer, P. Scheet, L.J. Scott, U. Seedorf, S.J. Sharp, B. Shields, G. Sigurethsson, E.J. Sijbrands, A. Silveira, L. Simpson, A. Singleton, N.L. Smith, U. Sovio, A. Swift, H. Syddall, A.C. Syvanen, T. Tanaka, B. Thorand, J. Tichet, A. Tonjes, T. Tuomi, A.G. Uitterlinden, K.W. van Dijk, M. van Hoek, D. Varma, S. Visvikis-Siest, V. Vitart, N. Vogelzangs, G. Waeber, P.J. Wagner, A. Walley, G.B. Walters, K.L. Ward, H. Watkins, M.N. Weedon, S.H. Wild, G. Willemsen, J.C. Witteman, J.W. Yarnell, E. Zeggini, D. Zelenika, B. Zethelius, G. Zhai, J.H. Zhao, M.C. Zillikens, I.B. Borecki, R.J. Loos, P. Meneton, P.K. Magnusson, D.M. Nathan, G.H. Williams, A.T. Hattersley, K. Silander, V. Salomaa, G.D. Smith, S.R. Bornstein, P. Schwarz, J. Spranger, F. Karpe, A.R. Shuldiner, C. Cooper, G.V. Dedoussis, M. Serrano-Rios, A.D. Morris, L. Lind, L.J. Palmer, F.B. Hu, P.W. Franks, S. Ebrahim, M. Marmot, W.H. Kao, J.S. Pankow, M.J. Sampson, J. Kuusisto, M. Laakso, T. Hansen, O. Pedersen, P.P. Pramstaller, H.E. Wichmann, T. Illig, I. Rudan, A.F. Wright, M. Stumvoll, H. Campbell, J.F. Wilson, R.N. Bergman, T.A. Buchanan, F.S. Collins, K.L. Mohlke, J. Tuomilehto, T.T. Valle, D. Altshuler, J.I. Rotter, D.S. Siscovick, B.W. Penninx, D.I. Boomsma, P. Deloukas, T.D. Spector, T.M. Frayling, L. Ferrucci, A. Kong, U. Thorsteinsdottir, K. Stefansson, C.M. van Duijn, Y.S. Aulchenko, A. Cao, A. Scuteri, D. Schlessinger, M. Uda, A. Ruokonen, M.R. Jarvelin, D.M. Waterworth, P. Vollenweider, L. Peltonen, V. Mooser, G.R. Abecasis, N.J. Wareham, R. Sladek, P. Froguel, R.M. Watanabe, J.B. Meigs, L. Groop, M. Boehnke, M.I. McCarthy, J.C. Florez, I. Barroso, New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk, Nat. Genet. 42 (2010) 105–116.

[69] C. Gorbea, K.A. Makar, M. Pauschinger, G. Pratt, J.L. Bersola, J. Varela, R.M. David, L. Banks, C.H. Huang, H. Li, H.P. Schultheiss, J.A. Towbin, J.G. Vallejo, N.E. Bowles, A role for Toll-like receptor 3 variants in host susceptibility to enteroviral myocarditis and dilated cardiomyopathy, J. Biol. Chem. 285 (2010) 23208–23223.

[70] E.L. Burkett, R.E. Hershberger, Clinical and genetic issues in familial dilated cardiomyopathy, J. Am. Coll. Cardiol. 45 (2005) 969–981.

[71] V.V. Michels, P.P. Moll, F.A. Miller, A.J. Tajik, J.S. Chu, D.J. Driscoll, J.C. Burnett, R.J. Rodeheffer, J.H. Chesebro, H.D. Tazelaar, The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy, N. Engl. J. Med. 326 (1992) 77–82.

[72] M.K. Baig, J.H. Goldman, A.L. Caforio, A.S. Coonar, P.J. Keeling, W.J. McKenna, Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease, J. Am. Coll. Cardiol. 31 (1998) 195–201.

[73] A. Gavazzi, A. Repetto, L. Scelsi, C. Inserra, M.L. Laudisa, C. Campana, C. Specchia, B. Dal Bello, M. Diegoli, L. Tavazzi, E. Arbustini, Evidence-based diagnosis of familial non-X-linked dilated cardiomyopathy. Prevalence, inheritance and characteristics, Eur. Heart J. 22 (2001) 73–81.

[74] E. Grunig, J.A. Tasman, H. Kucherer, W. Franz, W. Kubler, H.A. Katus, Frequency and phenotypes of familial dilated cardiomyopathy, J. Am. Coll. Cardiol. 31 (1998) 186–194.

[75] L. Mestroni, C. Rocco, D. Gregori, G. Sinagra, A. Di Lenarda, S. Miocic, M. Vatta, B. Pinamonti, F. Muntoni, A.L. Caforio, W.J. McKenna, A. Falaschi, M. Giacca, Camerini, Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. Heart Muscle Disease Study Group, J. Am. Coll. Cardiol. 34 (1999) 181–190.

[76] R.E. Hershberger, A. Morales, J.D. Siegfried, Clinical and genetic issues in dilated cardiomyopathy: a review for genetics professionals, Genet. Med. 12 (2010) 655–667.

[77] R.E. Hershberger, J.D. Siegfried, Update 2011: clinical and genetic issues in familial dilated cardiomyopathy, J. Am. Coll. Cardiol. 57 (2011) 1641–1649.

[78] P. Elliott, C. O'Mahony, P. Syrris, A. Evans, C. Rivera Sorensen, M.N. Sheppard, G. Carr-White, A. Pantazis, W.J. McKenna, Prevalence of desmosomal protein gene mutations in patients with dilated cardiomyopathy, Circ. Cardiovasc. Genet. 3 (2010) 314–322.

[79] D.S. Herman, L. Lam, M.R. Taylor, L. Wang, P. Teekakirikul, D. Christodoulou, L. Conner, S.R. DePalma, B. McDonough, E. Sparks, D.L. Teodorescu, A.L. Cirino, N.R. Banner, D.J. Pennell, S. Graw, M. Merlo, A. Di Lenarda, G. Sinagra, J.M. Bos, M.J. Ackerman, R.N. Mitchell, C.E. Murry, N.K. Lakdawala, C.Y. Ho, P.J. Barton, S.A. Cook, L. Mestroni, J.G. Seidman, C.E. Seidman, Truncations of titin causing dilated cardiomyopathy, N. Engl. J. Med. 366 (2012) 619–628.

[80] I.A. van Rijsingen, E. Arbustini, P.M. Elliott, J. Mogensen, J.F. Hermans-van Ast, A.J. van der Kooi, J.P. van Tintelen, M.P. van den Berg, A. Pilotto, M. Pasotti, S. Jenkins, C. Rowland, U. Aslam, A.A. Wilde, A. Perrot, S. Pankuweit, A.H. Zwinderman, P. Charron, Y.M. Pinto, Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study, J. Am. Coll. Cardiol. 59 (2012) 493–500.

[81] J.H. van Berlo, W.G. de Voogt, A.J. van der Kooi, J.P. van Tintelen, G. Bonne, R.B. Yaou, D. Duboc, T. Rossenbacker, H. Heidbuchel, M. de Visser, H.J. Crijns, Y.M. Pinto, Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? J. Mol. Med. (Berl) 83 (2005) 79–83.

[82] C. Meune, J.H. Van Berlo, F. Anselme, G. Bonne, Y.M. Pinto, D. Duboc, Primary prevention of sudden death in patients with lamin A/C gene mutations, N. Engl. J. Med. 354 (2006) 209–210.

[83] W.P. McNair, L. Ku, M.R. Taylor, P.R. Fain, D. Dao, E. Wolfel, L. Mestroni, SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia, Circulation 110 (2004) 2163–2167.

[84] J.L. Theis, K.M. Sharpe, M.E. Matsumoto, H.S. Chai, A.A. Nair, J.D. Theis, M. de Andrade, E.D. Wieben, V.V. Michels, T.M. Olson, Homozygosity mapping and exome sequencing reveal GATAD1 mutation in autosomal recessive dilated cardiomyopathy, Circ. Cardiovasc. Genet. 4 (2011) 585–594.

[85] P. Elliott, W.J. McKenna, Hypertrophic cardiomyopathy, Lancet 363 (2004) 1881–1891.

[86] B.J. Maron, W.J. McKenna, G.K. Danielson, L.J. Kappenberger, H.J. Kuhn, C.E. Seidman, P.M. Shah, W.H. Spencer III, P. Spirito, F.J. Ten Cate, E.D. Wigle, American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines, J. Am. Coll. Cardiol. 42 (2003) 1687–1713.

[87] P.M. Elliott, J. Poloniecki, S. Dickie, S. Sharma, L. Monserrat, A. Varnava, N.G. Mahon, W.J. McKenna, Sudden death in hypertrophic cardiomyopathy: identification of high risk patients, J. Am. Coll. Cardiol. 36 (2000) 2212–2218.

[88] P.M. Elliott, J.R. Gimeno Blanes, N.G. Mahon, J.D. Poloniecki, W.J. McKenna, Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy, Lancet 357 (2001) 420–424.

[89] P.M. Elliott, J.R. Gimeno, R. Thaman, J. Shah, D. Ward, S. Dickie, M.T. Tome Esteban, W.J. McKenna, Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy, Heart 92 (2006) 785–791.

[90] H. Morita, H.L. Rehm, A. Menesses, B. McDonough, A.E. Roberts, R. Kucherlapati, J.A. Towbin, J.G. Seidman, C.E. Seidman, Shared genetic causes of cardiac hypertrophy in children and adults, N. Engl. J. Med. 358 (2008) 1899–1908.

[91] A.A. Geisterfer-Lowrance, S. Kass, G. Tanigawa, H.P. Vosberg, W. McKenna, C.E. Seidman, J.G. Seidman, A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation, Cell 62 (1990) 999–1006.

[92] H. Watkins, D. Conner, L. Thierfelder, J.A. Jarcho, C. MacRae, W.J. McKenna, B.J. Maron, J.G. Seidman, C.E. Seidman, Mutations in the cardiac myosin binding protein-C gene on chromosome 11 cause familial hypertrophic cardiomyopathy, Nat. Genet. 11 (1995) 434–437.

[93] L. Thierfelder, H. Watkins, C. MacRae, R. Lamas, W. McKenna, H.P. Vosberg, J.G. Seidman, C.E. Seidman, Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere, Cell 77 (1994) 701–712.

[94] K. Poetter, H. Jiang, S. Hassanzadeh, S.R. Master, A. Chang, M.C. Dalakas, I. Rayment, J.R. Sellers, L. Fananapazir, N.D. Epstein, Mutations in either the essential or regulatory light chains of myosin are associated with a rare myopathy in human heart and skeletal muscle, Nat. Genet. 13 (1996) 63–69.

[95] A. Kimura, H. Harada, J.E. Park, H. Nishi, M. Satoh, M. Takahashi, S. Hiroi, T. Sasaoka, N. Ohbuchi, T. Nakamura, T. Koyanagi, T.H. Hwang, J.A. Choo, K.S. Chung, A. Hasegawa, R. Nagai, O. Okazaki, H. Nakamura, M. Matsuzaki, T. Sakamoto, H. Toshima, Y. Koga, T. Imaizumi, T. Sasazuki, Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy, Nat. Genet. 16 (1997) 379–382.

[96] A. Keren, P. Syrris, W.J. McKenna, Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression, Nat. Clin. Pract. Cardiovasc. Med. 5 (2008) 158–168.

[97] T.K. Chin, J.K. Perloff, R.G. Williams, K. Jue, R. Mohrmann, Isolated noncompaction of left ventricular myocardium. A study of eight cases, Circulation 82 (1990) 507–513.

[98] R. Jenni, E. Oechslin, J. Schneider, C. Attenhofer Jost, P.A. Kaufmann, Echocardiographic and pathoanatomical characteristics of isolated left ventricular noncompaction: a step towards classification as a distinct cardiomyopathy, Heart 86 (2001) 666–671.

[99] S. Sasse-Klaassen, B. Gerull, E. Oechslin, R. Jenni, L. Thierfelder, Isolated noncompaction of the left ventricular myocardium in the adult is an autosomal dominant disorder in the majority of patients, Am. J. Med. Genet. A 119A (2003) 162–167.

[100] F. Ichida, Left ventricular noncompaction, Circ. J. 73 (2009) 19–26.

[101] S. Klaassen, S. Probst, E. Oechslin, B. Gerull, G. Krings, P. Schuler, M. Greutmann, D. Hurlimann, M. Yegitbasi, L. Pons, M. Gramlich, J.D. Drenckhahn, A. Heuser, F. Berger, R. Jenni, L. Thierfelder, Mutations in sarcomere protein genes in left ventricular noncompaction, Circulation 117 (2008) 2893–2901.

[102] Y.M. Hoedemaekers, K. Caliskan, M. Michels, I. Frohn-Mulder, J.J. van der Smagt, J.E. Phefferkorn, M.W. Wessels, F.J. ten Cate, E.J. Sijbrands, D. Dooijes, D.F. Majoor-Krakauer, The importance of genetic counseling. DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy, Circ. Cardiovasc. Genet. 3 (2010) 232–239.
[103] S. Probst, E. Oechslin, P. Schuler, M. Greutmann, P. Boye, W. Knirsch, F. Berger, L. Thierfelder, R. Jenni, S. Klaassen, Sarcomere gene mutations in isolated left ventricular noncompaction cardiomyopathy do not predict clinical phenotype, Circ. Cardiovasc. Genet. 4 (2011) 367–374.
[104] S. Sen-Chowdhry, R.D. Morgan, J.C. Chambers, W.J. McKenna, Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment, Annu. Rev. Med. 61 (2010) 233–253.
[105] A. Azaouagh, S. Churzidse, T. Konorza, R. Erbel, Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update, Clin. Res. Cardiol. 100 (2011) 383–394.
[106] G. McKoy, N. Protonotarios, A. Crosby, A. Tsatsopoulou, A. Anastasakis, A. Coonar, M. Norman, C. Baboonian, S. Jeffery, W.J. McKenna, Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease), Lancet 355 (2000) 2119–2124.
[107] N. Protonotarios, A. Tsatsopoulou, Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy, Cardiovasc. Pathol. 13 (2004) 185–194.
[108] E. Otten, A. Asimaki, A. Maass, I.M. van Langen, A. van der Wal, N. de Jonge, M.P. van den Berg, J.E. Saffitz, A.A. Wilde, J.D. Jongbloed, J.P. van Tintelen, Desmin mutations as a cause of right ventricular heart failure affect the intercalated disks, Heart Rhythm 7 (2010) 1058–1064.
[109] M. Taylor, S. Graw, G. Sinagra, C. Barnes, D. Slavov, F. Brun, B. Pinamonti, E.E. Salcedo, W. Sauer, S. Pyxaras, B. Anderson, B. Simon, J. Bogomolovas, S. Labeit, H. Granzier, L. Mestroni, Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes, Circulation 124 (2011) 876–885.
[110] G. Quarta, P. Syrris, M. Ashworth, S. Jenkins, K. Zuborne Alapi, J. Morgan, A. Muir, A. Pantazis, W.J. McKenna, P.M. Elliott, Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy, Eur. Heart J. 33 (2012) 1128–1136.
[111] J.P. Kaski, P. Syrris, M. Burch, M.T. Tome-Esteban, M. Fenton, M. Christiansen, P.S. Andersen, N. Sebire, M. Ashworth, J.E. Deanfield, W.J. McKenna, P.M. Elliott, Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes, Heart 94 (2008) 1478–1484.
[112] J. Mogensen, T. Kubo, M. Duque, W. Uribe, A. Shaw, R. Murphy, J.R. Gimeno, P. Elliott, W.J. McKenna, Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations, J. Clin. Invest. 111 (2003) 209–216.
[113] K. van Spaendonck-Zwarts, L. van Hessem, J.D. Jongbloed, H.E. de Walle, Y. Capetanaki, A.J. van der Kooi, I.M. van Langen, M.P. van den Berg, J.P. van Tintelen, Desmin-related myopathy: a review and meta-analysis, Clin. Genet. 80 (4) (2010) 354–366.
[114] L.A. Hindorff, P. Sethupathy, H.A. Junkins, E.M. Ramos, J.P. Mehta, F.S. Collins, T.A. Manolio, Potential etiologic and functional implications of genome-wide association loci for human diseases and traits, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 9362–9367.
[115] F.E. Dewey, S. Pan, M.T. Wheeler, S.R. Quake, E.A. Ashley, DNA sequencing: clinical applications of new DNA sequencing technologies, Circulation 125 (2012) 931–944.
[116] K. Wang, S.P. Dickson, C.A. Stolle, I.D. Krantz, D.B. Goldstein, H. Hakonarson, Interpretation of association signals and identification of causal variants from genome-wide association studies, Am. J. Hum. Genet. 86 (2010) 730–742.
[117] G.V. Kryukov, L.A. Pennacchio, S.R. Sunyaev, Most rare missense alleles are deleterious in humans: implications for complex disease and association studies, Am. J. Hum. Genet. 80 (2007) 727–739.
[118] M.L. Metzker, Sequencing technologies — the next generation, Nat. Rev. Genet. 11 (2010) 31–46.
[119] R.E. Hershberger, J. Lindenfeld, L. Mestroni, C.E. Seidman, M.R. Taylor, J.A. Towbin, Genetic evaluation of cardiomyopathy—a Heart Failure Society of America practice guideline, J. Card. Fail. 15 (2009) 83–97.
[120] P. Charron, M. Arad, E. Arbustini, C. Basso, Z. Bilinska, P. Elliott, T. Helio, A. Keren, W.J. McKenna, L. Monserrat, S. Pankuweit, A. Perrot, C. Rapezzi, A. Ristic, H. Seggewiss, I. van Langen, L. Tavazzi, Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, Eur. Heart J. 31 (2010) 2715–2726.
[121] H. Watkins, A. Rosenzweig, D.S. Hwang, T. Levi, W. McKenna, C.E. Seidman, J.G. Seidman, Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy, N. Engl. J. Med. 326 (1992) 1108–1114.
[122] H. Watkins, W.J. McKenna, L. Thierfelder, H.J. Suk, R. Anan, A. O'Donoghue, P. Spirito, A. Matsumori, C.S. Moravec, J.G. Seidman, C. Seidman, Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy, N. Engl. J. Med. 332 (1995) 1058–1064.
[123] H. Watkins, Genotype:phenotype correlations in hypertrophic cardiomyopathy, Eur. Heart J. 19 (1998) 10–12.
[124] R. Anan, H. Shono, A. Kisanuki, S. Arima, S. Nakao, H. Tanaka, Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis, Circulation 98 (1998) 391–397.
[125] M.J. Ackerman, S.L. VanDriest, S.R. Ommen, M.L. Will, R.A. Nishimura, A.J. Tajik, B.J. Gersh, Prevalence and age-dependence of malignant mutations in the beta-myosin heavy chain and troponin T genes in hypertrophic cardiomyopathy: a comprehensive outpatient perspective, J. Am. Coll. Cardiol. 39 (2002) 2042–2048.
[126] F. Pasquale, P. Syrris, J.P. Kaski, J. Mogensen, W.J. McKenna, P. Elliott, Long-term outcomes in hypertrophic cardiomyopathy caused by mutations in the cardiac troponin T gene, Circ. Cardiovasc. Genet. 5 (2012) 10–17.
[127] S.P. Page, S. Kounas, P. Syrris, M. Christiansen, R. Frank-Hansen, P.S. Anderson, P.M. Elliott, W.J. McKenna, Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome, Circ. Cardiovasc. Genet. 5 (2) (2012) 156–166.
[128] F. Girolami, C.Y. Ho, C. Semsarian, M. Baldi, M.L. Will, K. Baldini, F. Torricelli, L. Yeates, F. Cecchi, M.J. Ackerman, I. Olivotto, Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations, J. Am. Coll. Cardiol. 55 (2010) 1444–1453.
[129] B. Bauce, A. Nava, G. Beffagna, C. Basso, A. Lorenzon, G. Smaniotto, M. De Bortoli, I. Rigato, E. Mazzotti, A. Steriotis, M.P. Marra, J.A. Towbin, G. Thiene, G.A. Danieli, A. Rampazzo, Multiple mutations in desmosomal proteins encoding genes in arrhythmogenic right ventricular cardiomyopathy/dysplasia, Heart Rhythm 7 (2010) 22–29.
[130] I. Olivotto, F. Girolami, R. Sciagra, M.J. Ackerman, B. Sotgia, J.M. Bos, S. Nistri, A. Sgalambro, C. Grifoni, F. Torricelli, P.G. Camici, F. Cecchi, Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations, J. Am. Coll. Cardiol. 58 (2011) 839–848.
[131] I. Olivotto, F. Girolami, M.J. Ackerman, S. Nistri, J.M. Bos, E. Zachara, S.R. Ommen, J.L. Theis, R.A. Vaubel, F. Re, C. Armentano, C. Poggesi, F. Torricelli, F. Cecchi, Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy, Mayo Clin. Proc. 83 (2008) 630–638.
[132] A.L. Cirino, C. Ho, Familial hypertrophic cardiomyopathy overview. 2008 Aug 5 [Updated 2011 May 17] in: R.A. Pagon, T.D. Bird, C.R. Dolan, K. Stephens, M.P. Adam (Eds.), GeneReviews™ [Internet], University of Washington, Seattle (WA), 1993. (Available from: http://www.ncbi.nlm.nih.gov/books/NBK1768/).
[133] E. McNally, H. MacLeod, L. Dellefave, Arrhythmogenic right ventricular dysplasia/cardiomyopathy, autosomal dominant. 2005 Apr 18 [Updated 2009 Oct 13] in: R.A. Pagon, T.D. Bird, C.R. Dolan, K. Stephens, M.P. Adam (Eds.), GeneReviews™ [Internet], University of Washington, Seattle (WA), 1993. (Available from: http://www.ncbi.nlm.nih.gov/books/NBK1131/).