The Genetic Causes of Heart Failure
A focus on sudden death: from the molecular mechanisms to clinical approach.

Andrés Ricardo Pérez Riera
Edgardo Schapachnik
Sergio Dubner

INTRODUCTION

In heart failure (HF), the heart cannot pump enough blood through the body. It can´t fill with enough blood or pump with enough force, or both. HF develops over time as the pumping action of the heart get weaker and it can affect the right, the left or both sides of the heart.

Nearly 5 million of americans are living with HF, and 550,000 new cases are diagnosed each year. Data from the Framingham Heart Study indicate that the incidence of congestive HF increases with age and is higher in men. The single most common etiology is coronary heart disease, but in a third of cases the etiology cannot be determined on the basis of non-invasive investigation alone. To be relevant to clinical practice, future clinical trials in HF should not exclude the elderly.

HF is the final common pathway of most primary cardiovascular diseases, including coronary atherosclerosis, hypertension, cardiomyopathies, myocarditis, diabetes, valvular and congenital heart malformations.

Molecular genetic causes of myocardial diseases have highlighted the importance of single-gene defects in the pathogenesis of HF. Monogenic disorders account for only a small subset of overall HF cases; insights into the responses triggered by gene mutations are likely to also be relevant to more common etiologies of HF.

A selective review of the literature is presented on the disease mechanism of both the Mendelian and multifactorial genetic cardiovascular conditions. The main genetic causes of HF include cardiomyopathies, hemoglobinopathies, Mendelian disorders of the extracellular matrix, and neuromuscular disorders.

Dilated cardiomyopathy, hypertrophic cardiomyopathy, and cardiac rhythm disturbances are important features of certain neuromuscular disorders in children, adolescents, and young adults. The optimal management of these cardiac features remains contentious, but increasingly these patients are referred for routine cardiological assessment in the absence of symptoms.

The genetic research, education, and teaching will lead to a new understanding of genes and pathways, resulting in powerful new therapeutic approaches to cardiovascular disease. The challenge is to translate genetic discoveries into clinical practice that ultimately leads to preventing cardiovascular disease and reducing mortality.

Treatable asymptomatic dilated cardiomyopathy was identified in 4.6% of asymptomatic relatives. In addition, left ventricular enlargement and depressed fractional shortening were common in asymptomatic relatives of patients with dilated cardiomyopathy and were associated with a statistically significant medium-term risk for disease progression. Evaluation of relatives of patients with dilated cardiomyopathy is recommended.

Cardiac hypertrophy is a maladaptive process of the heart in response to intrinsic and extrinsic stimuli. Although hypertrophy can normalize wall tension, it is a risk factor for QT-prolongation and sudden cardiac death. The recognition of hypertrophy as a major risk factor for QT-prolongation and cardiac sudden death is considered an important advance in cardiac medicine.

Researchers in the cardiovascular field have started using large-scale transcriptional analysis to better understand and classify human genetic cardiovascular disease and the mains genetic causes of HF. In this manuscript we provide an overview of the literature about genetics causes of hear failure.

There are multiple pathways that lead to changes in heart structure and function. Defects in myocyte force generation, force transmission, and calcium homeostasis have emerged as particularly critical signals driving cardiomyopathies. Delineation of the cell and molecular events triggered by cardiomyopathy gene mutations provide new fundamental knowledge about myocyte biology and organ physiology that accounts for cardiac remodeling and defines mechanistic pathways that lead to HF and sudden cardiac death.

The principals genetics causes of HF are familial cardiomyopathies, genetic diseases with potential of to unchain HF as hemoglobinopathies, mendelian disorders of the extracellular matrix, and neuromuscular disorders[1].

The table 1 summarize the mains genetic causes of HF.

Table1. MAINS GENETIC CAUSES OF HEART FAILURE

I) FAMILIAL CARDIOMYOPATHIES

(I.1) – Familial Dilated (Congestive) Cardiomyopathy (FDCM);

(I.2) – Familiar hypertrophic cardiomyopathy (FHCM);

(I.3) – Familial restrictive cardiomyopathies (FRCMs);

(I.4) – Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D);

(I.5) Unclassified: It includes a few cases that do not fit readily into any group:

(I.5.a) Familial Non-compaction of left ventricle myocardium;

(I.5.b) Mitochondrial disease;

(I.5.c) Carnitine deficience;

II) GENETIC DISEASES WITH POTENTIAL OF TO UNCHAIN HF

(II.1) HEMOGLOBINOPATHIES:

(II.1.a) Sickle cell disease.

(II.2.b) Beta Thalassemia.

(II.2) MENDELIAN DISORDERS OF THE EXTRACELLULAR MATRIX: Marfand Syndrome: Dilation by aortic insufficience (normal or thinned walls with enlarged chamber volumes).

(II.3) NEUROMUSCULAR DISORDERS:

(II.3.a) Duchenne muscular dystrophy (DMD);

(II.3.b) Becker muscular dystrophy (BMD);

(II.3.c) Myotonic dystrophy;

(II.3.d) Myotonic dystrophy 2;

(II.3.e) Friedreich's ataxia;

(II.3. f) Emery-Dreifuss muscular dystrophy.

I) FAMILIAL CARDIOMYOPATHIES

Cardiomyopathies are common causes of HF and sudden cardiac death (SCD). They are primary disorders of cardiac muscle associated with abnormalities of cardiac wall thickness, chamber size, contraction, relaxation, conduction, and rhythm. They are a major cause of morbidity and mortality at all ages and, like acquired forms of cardiovascular disease, often result in HF[2]. Molecular genetic studies of humans and analyses of model organisms have made remarkable progress in defining the pathogenesis of cardiomyopathies. According to the WHO classification, "specific" cardiomyopathies are differentiated from "idiopathic" cardiomyopathies. Thus, this classification is primarily based on pathophysiological characteristics. According to the 1995 World Health Organization definition of cardiomyopathies as "diseases of the myocardium associated with cardiac dysfunction," they should include not only forms with hemodynamic dysfunction, but also rhythm disturbances. Arrhythmias are a sign of cardiac dysfunction and may reflect an underlying myocardial electrical disease with or without structural abnormalities as features[3]. The diagnostic spectrum in cardiomyopathies comprises the entire spectrum of non-invasive and invasive cardiological examination techniques. The exact verification of certain cardiomyopathies necessitates additionally investigations. Immunohistological and molecular biological investigations of endomyocardial biopsies may confirm inflammatory cardiomyopathy, which is often induced by viruses. Several studies have shown that specific immunomodulatory treatment options can halt the progressive course of the disease.

(I.1) – FAMILIAL DILATED CARDIOMYOPATHY (FDCM)

Dilated Cardiomyopathy (DCM) is a cytoskeleton (cytoskeletalopathy) or "force transmission" disease[4] characterized by ventricular dilation and dysfunction is a leading cause of mortality and morbidity.

Dilatation and impaired contraction of the left or both ventricles is observed.

DCM is characterized by the following characteristics[5]:

1) Markedly increased left ventricular volume: End-diastolic and end-systolic;
2) Increased of left ventricular mass;
3) Decreased mass/volume ratio;
4) Decreased systolic function and ejection fraction;
5) Decreased myocardial shortening;
6) Increased wall stress;
7) Decreased chamber stiffness;
8) Increased myocardial stiffness.

Incidence: DCM is the most frequent form of primary myocardial diseases and the third most common cause of HF.

Prevalence: Its prevalence in the United States amounts to 36 cases per 100,000 inhabitants;

Gender: men being almost 3-fold more involved than women.

Etiology: The etiology of DCM is very heterogenous.
Approximately 50% of the cases are due to idiopathic DCM whereas the other half comprises a broad spectrum of various etiologies[6].

DCM can be caused by chronic, excessive consumption of alcohol along with dietary deficiencies. It occasionally occurs as a complication of pregnancy and childbirth. Other suggested causes are: various infections, mostly viral, which lead to an inflammation of the heart muscle (myocarditis); toxins; and/or immune. Sometimes drugs used to treat a different medical condition can damage the heart and produce DCM. However, in most cases, the disease is idiopathic -- that is, a specific cause for the damage is never identified.

In a subset of DCM patients, classical inheritance patterns occur (familial DCM), which have led to the identification of specific genomic loci and gene defects causing monogenic DCM subtypes. In the majority of DCM patients, however, there is no evidence for a monogenic etiology of the disorder (sporadic DCM), and in the absence of other recognizable etiological factors, these cases were classified as "idiopathic". [7]

Approximately in 25% to 35% of cases the entity is heredity familial/genetic and named Familial DCM (FDCM)[8]. In approximately 25% of patients a first degree also show evidence of DCM.
The most common mode of inheritance is the autosomal dominant type, however FDCM is a genetically and phenotypically very heterogeneous disease. Thereby there are descriptions of recessive forms[9] associated with mutation on mitochondrial DNA[10] and with X – linked inheritance.
Clarke et al demonstrated linkage to two regions of the X chromosome, Xp22.13 to Xp11.4 and Xq13.1 to Xq22.1, with a maximum logarithm of odds score of 3.25 in the latter region. Affected male family members have a striking pattern of weakness. From birth there is marked ptosis, facial weakness, poor sucking, hypotonia, respiratory weakness, and relatively preserved limb strength. Most affected male individuals die of respiratory failure within the first months of life. A mild dilated

cardiomyopathy developed in infancy in the sole surviving affected male member of this family. Some carrier female individuals manifest milder signs[11].

The diagnosis of dystrophin defect-related dilated cardiomyopathy is important for patients and families, especially for carrier detection. These patients present X-linked inheritance, dominant cardiac involvement and raised levels of serum creatine phosphokinase. Defects of the glycoprotein complex associated to dystrophin are rare skeletal muscle diseases with possible cardiac involvement. [12]

Several gene mutations have been identified in FDCM. The incriminated mechanisms in the pathogeny of dilated cardiomyopathy include mutations on proteins of the sarcomere, the cytosqueletton, the nuclear membrane or involved in calcium signaling[2].

The genes causing FDCM code for proteins that anchor the sarcomere to the cell membrane and extracellular matrix. Multiple genes encoding proteins that are involved in force generation, force transmission, energy production and several signalling pathways. The pathophysiology of HF is complex and not yet fully understood[13].

Hence, mutations have been identified on 14 genes, and 9 loci have been associated to FDCM. Diversity of clinical presentations and variability in penetrance lead to under-recognition of this disease entity as an inherited disorder.

First-degree relatives should be screened for early stages. Candidate gene screening and linkage analyses in large families were successful in identifying 25 disease genes. Mutations in the beta-myosin heavy chain and in cardiac troponin T are common causes of pure FDCM.

FDCM associated with conduction disease is mainly due to mutations in lamin A/C and X-linked DCM is often caused by mutations in dystrophin. All other disease genes are rare causes of FDCM. Genetic screening in all known disease genes is not possible, but more efficient screening methods are awaited in the near future. Until then, clinical examination of family members and, in case of familial DCM, genetic counseling are recommended in the work-up of patients with idiopathic DCM[14].

Appreciating when DCM is inherited might spare unnecessary diagnostic efforts and, instead, help give appropriate attention to the timely detection of subclinically affected family members. Establishing preventive therapy in asymptomatic family members showing early signs of cardiac dysfunction might prevent death and slow down progression to end-stage HF. [15]

Approach to management of DCM include:

1) **Genetic screening** leads to the identification of symptomatic and asymptomatic mutant carriers. The latter at a young age should be regarded as "presymptomatic" because of the age-dependent disease manifestation. New guidelines are required for the management of these individuals.[16] Treatable asymptomatic dilated cardiomyopathy was identified in 4.6% of asymptomatic relatives. In addition, left ventricular enlargement and depressed fractional shortening were common in asymptomatic relatives of patients with DCM and were associated with a statistically significant medium-term risk for disease progression. Evaluation of relatives of patients with DCM is recommended[17];
2) **Initial pharmacological approach:** the combination of several different drugs present challenges for their optimal prescription, requiring a thorough knowledge of potential side effects and complex interactions. Pharmacological treatment is essential and should include an angiotensin converting enzyme inhibitor and beta blocker where possible. Angiotensin converting enzyme inhibitor offered 15% decrease in hospitalization for moderate HF and, depending on the severity of the disease, produced a 16% to 31% reduction in mortality. The armamentarium include: digoxin, diuretics(furosemide), beta-blockers (carvedilol)**,** aldosterone antagonists, angitensin-converting enzyme inhibitors, angiotensin II receptor blockers, and antiarrhythmic if necessary;
3) **Anticoagulation:** EF<0.30, positive history of thrombo-embolic episode or mural thrombi. There is a lack of evidence for any antithrombotic agent that is effective in patients with HF therefore, randomised clinical trials need to be designed to test the hypothesis that patients with chronic HF would have benefit from anticoagulant therapy.
4) **New drugs:** Although that the results must be confirmed in larger studies that also examine the effects on morbidity and mortality, studies suggest a role for thalidomide in the management of CHF in addition to traditional cardiovascular medications.[18]
5) **Primary prevention of SCD:** shows increasing superiority of the implantable defibrillator compared with pharmacological approaches (i.e. amiodarone).[19]

6) **Heart transplantation:** DCM is an uncommon cause of HF but has widespread importance because it is the cause of 45% of heart transplantations[20.]

(I.2) FAMILIAL HYPERTROPHIC CARDIOMYOPATHY (FHCM)

Certain patterns can be distinguished in the mutated genes, e.g. in general the genes causing HCMs code for proteins involved in the contractile apparatus, the sarcomere. So it is a sarcomeric disease or sarcomyopathy.

Hypertrophic Cardiomyopathy (HCM) is a relatively common primary cardiac disorder (with an incidence of 1 in 500 and prevalence of 0.2%) defined as the presence of disproportionate hypertrophied left ventricle (LV) in the absence of any other diagnosed etiology. HCM is the most common cause of SCD in young people (especially in athletes) which often occurs without precedent symptoms.

As HCM is a common cause of SCD among athletes, differentiating this condition from the non-pathological "athlete's heart" presents an important challenge. Generally the entity has a benign prognosis.

The annual SCD mortality rate is 1% and, in selected populations, it ranges between 3 and 6%. In recent years it has been suggested that genetic defects could be the major markers of prognosis. Thus, some mutations would carry a good prognosis whereas others, so-called “malignant” mutations, would be associated with premature SCD.

FHCM is a common inherited cardiac disease and a major cause of SCD. In patients younger than 35 years of age SCD is primarily due to genetic causes. FHCM accounting for 30% to 40% is associated with structural heart disease.

It is diagnosed most commonly using clinical data (anamnesis and physical examination) electrocardiogram and transthoracic echocardiography. HCM was the first cardiac disorder in which a genetic basis was identified and as such, has acted as a paradigm for the study of an inherited cardiac disorder.
It is an autosomal dominant disorder predominantly caused by mutations in genes encoding for sarcomeric proteins (sarcomyopathy).

To date, over 300 independent mutations in 9 sarcomeric protein genes have been linked to FHCM, thus the clinical variability is matched by significant genetic heterogeneity. The final clinical phenotype in patients with FHCM is a result of modifier genes, environmental influences and genotype. Screening studies had suggested that individual gene mutations could be linked to specific prognoses. Given that the sarcomeric genes linked to FHCM encode proteins with known functions, a vast array of biochemical, biophysical and physiologic experimental approaches have been applied to elucidate the molecular mechanisms that underlie the pathogenesis of this complex entity[21].

The representative gene mutations from each of the major structural components of the cardiac sarcomere:

1) The thick filament (beta MyHC): The myosin binding protein C (MYBPC3) gene, ß-cardiac myosin heavy chain (*MYH7)*;
2) The thin filament actin (cTnT and Tm) and associated proteins (MyBP-C): regulatory myosin light chain (*MYL2*), -tropomyosin (*TPM1*), cardiac actin (*ACTC*)[22],
3) HCM-associated titin/connectin mutation (TTN): titin/connectin mutation (Arg740Leu) was found to increase the binding to actinin. Other mutations in the N2-B region of titin/connectin found in HCM and dilated cardiomyopathy. Since the N2-B region expresses only in the heart, it was speculated that functional alterations due to the mutations cause cardiomyopathies. Matsumoto et al. investigated the functional changes caused by the N2-B region mutations by using yeast-two-hybrid assays. It was revealed that a HCM-associated mutation (Ser3799Tyr) increased the binding to FHL2 protein, whereas a dilated cardiomyopathy-associated mutation (Gln4053ter) decreased the binding. In addition, another TTN mutation (Arg25618Gln) at the is2 region was found in familial DCM. Because FHL2 protein is known to tether metabolic enzymes to N2-B and is2 regions of titin/connectin, these observations suggest that altered recruitment of metabolic enzymes to the sarcomere may play a role in the pathogenesis of cardiomyopathies.[23]

The results of these studies will lead to a better understanding of FHCM and eventually identify targets for therapeutic intervention. Studies in both cell culture and animal models of HCM are now beginning to shed light on the signalling pathways involved in HCM, and the role of both environmental and genetic modifying factors. Understanding these mechanisms will ultimately improve our knowledge of the basic biology of heart muscle function, and will therefore provide new avenues for treating cardiovascular disease in man. [24]

Only 50-60% of HCM probands have mutations in known genes suggesting the presence of additional disease genes. FHCM can result from mutations in 11 genes that encode 9 sarcomere proteins. Aproximatly 60% to 90% of cases of HCM are FHCM. Clinical genetic testing for HCM is becoming available, with significant implications for the clinician. [25]

Noonan and LEOPARD syndromes are characterized by multiple dysmorphia and cardiac defects with HCM present in approximately 20% of cases. Mutations in the PTPN11 gene are not a cause of HCM in the absence of Noonan/LEOPARD syndromes. [26]

LEOPARD syndrome is an autosomal dominant syndrome characterized by multiple lentigines and cafe-au-lait spots, electrocardiographic-conduction abnormalities, ocular hypertelorism/obstructive cardiomyopathy, pulmonary stenosis, abnormalities of the genitalia in males, retardation of growth, and deafness. LEOPARD syndrome shares many features with Noonan syndrome, in which lentigines and deafness are usually not present. [27]

The prognosis varies according to the localization, the degree of hypertrophy and, in some cases, on the underlying genetic mutation. SCD is a significant risk of the disease in young people. A systematic stratification of patients at a higher risk of SCD is desperately needed.

The basis medication therapy of symptomatic patients uses calcium antagonists or beta-blockers. In high-degree HF the typical therapy is applied mainly in combination with beta-blockers and, if indicated, also with antiarrhythmics.

The implantation of an Implantable cardioverter-defibrillator (ICD) is the most effective preventive measure against SCD in high risk. The planned MADIT-CRT trial is designed to determine if CRT-D will reduce the risk of mortality and HF events by approximately 25% in subjects with ischemic (NYHA class I-II) and non-ischemic (NYHA class II) cardiomyopathy, left ventricular dysfunction (EF<or=0.30), and prolonged intraventricular conduction (QRS duration>or=130 ms). [28]

When a high degree of outflow obstruction is present, in patients with drug-refractory symptoms Percutaneous Transluminal Septal Myocardial Ablation (PTSMA) or myectomy is indicated. PTSMA is a catheter-based approach that involves instilling alcohol into the septal branches of the left anterior descending artery to induce a “controlled” septal myocardial infarct. The result is a decrease in thickness of the hypertrophied interventricular septum and a reduction of the left ventricular outflow tract gradient.

Heart transplantion is performed only in very few patients with terminal HF.

Even though HCM is one of the best-documented genetically based heart diseases, only a few prospective studies and registries have been established, which have produced guidelines and recommendations for diagnostics and therapy. The ACC/ESC Expert Consensus Document is very helpful in this respect. Therefore, there is still a great need for systematic prospective analyses in large patient populations. [29]

(I.3) – FAMILIAL RESTRICTIVE CARDIOMYOPATHY (FRCM)

Restrictive cardiomyopathy (RCM) is an uncommon heart muscle disorder characterized by impairment of ventricular filling during diastole with reduced volume and preserved systolic function (Normal or near normal LV size and function and atrial enlargement). Its principal abnormality is diastolic dysfunction. (Restrictive filling pattern). It is least-common type in the United States and most other industrial nations. The muscles of the ventricles become excessively rigid, and the filling of the ventricles with blood between heartbeats is impaired. This form of cardiomyopathy may be idiopathic or associated with other systemic disease, which occurs elsewhere in the body but is most often idiopathic.

Restrictive cardiomyopathy does not appear to be inherited, but some of the diseases that lead to the condition are genetically transmitted.

The table 1 below shows the mains causes of familial/genetic restrictive cardiomyopathies

I) Familial/genetic restrictive cardiomyopathies (FRCMs)

- (I.3a) Familial Noninfiltrative restrictive myocardiopaty
- (I.3b) Familial pseudo-Idiopathic
- (I.3c) Familial Scleroderma.

II) Familiar Infiltrative Restrictive cardiomyopathies (FRCMs):

- (II.a) Familial amyloidosis restrictive cardiomyopathy
- (II.b) Gaucher disease type I
- (II.c) Hurler syndrome.

III) Storage disease:

- (III.1) Hereditary hemochromatosis

(III.2) Fabry disease or Sphyngolipid

(III.3)Glycogen storage disorder II and III. (Pompe disease)

IV) Endomyocardial fibrosis-2.

I) Familial/genetic restrictive cardiomyopathies (FRCMs)

(I.3a) Familial Noninfiltrative restrictive myocardiopaty and;

(I.3b) Familial pseudo-Idiopathic

The idiopathic variety of RCM is sometimes familial (Familial pseudo- Idiopathic). In the idiopathic forms, thromboembolic complications are common. Atrial fibrillation and atrioventricular block are also often observed. Non-syndromic idiopathic cardiomyopathies have increasingly been characterized as autosomal dominant conditions caused by single gene mutations. Zang et al identified a family with a mutation on chromosome 10 and autosomal dominant trait associated with restrictive cardiomyopathy.[30]

To determine if idiopathic RCM is part of the clinical expression of TNNI3 mutations, genetic investigations of the gene were performed by Mongensen et al in an additional nine unrelated RCM patients with restrictive filling patterns, bi-atrial dilatation, normal systolic function, and normal wall thickness. Cardiac troponin I (TNNI3) mutations were identified in six of these nine RCM patients. Two of the mutations identified in young individuals were de novo mutations. All mutations appeared in conserved and functionally important domains of the gene.[31]

Cardiac troponin I, one of the sarcomeric thin filament protein, has a role in cardiac function, and its deficiency-related diastolic dysfunction, and the mutation of this protein-mediated restrictive cardiomyopathy.[32]

Troponin consists of three subunits with distinct structure and function: troponin T, troponin I, and troponin C, and their accurate and complex intermolecular interaction in response to the rapid rise and fall of Ca^{2+} in cardiomyocytes plays a key role in maintaining the normal cardiac pump function. More than 60 mutations in human cardiac troponin subunits have been identified in dilated, hypertrophic, and restrictive forms of cardiomyopathy. [33]

(I.3.c) Familial Scleroderma

Scleroderma is an uncommon autoimmune connective tissue disease that results in systemic fibrosis. Recent family, twin, and genetic association studies suggest a genetic basis for the susceptibility to systemic scleroderma. Accumulating data emphasize the role of genetic factors in systemic sclerosis. As in other complex human diseases, multiple genes likely contribute to disease susceptibility and the clinical manifestations of systemic sclerosis. [34]

Only a few reports on single nucleotide polymorphism analysis of candidate genes and transcriptional profiling have been published. To day, single nucleotide polymorphism association studies in systemic scleroderma use small sample sizes and have low reproducibility. To detect associations with candidate genes that confer a modest relative risk for disease in the general population, studies are needed with much larger sample sizes that also account for the effects of population stratification. Candidate genes or pathways identified through microarrays can be explored as potential biomarkers, used for molecular phenotyping of systemic scleroderma, or targeted for future genetic association studies.[35]

The use of genomics has revealed novel targets and genetic associations that may contribute to the cause, the onset, and the subsequent pathologic changes that constitute systemic scleroderma. The identification of potential candidates for gene therapy or disease-specific targets amenable to pharmacologic intervention will benefit patients with the entity who are currently being treated for their symptoms and not the disease process itself.

II) Familiar Infiltrative Restrictive cardiomyopathies (FRCMs):

(II.a) Familial amyloidosis restrictive cardiomyopathy

(II.b) Gaucher disease type I

(II.c) Hurler syndrome.

(II.a) Familial amyloid restrictive cardiomyopathy

Cardiac amyloidosis is caused by amyloid deposits derived from different human plasma proteins. It can lead to cardiac conduction disturbances, RCM, and low output HF. The heart seems to be more frequently affected in immunoglobulin (primary) than in reactive (secondary) amyloidosis. Amyloid is common in the elderly. Isolated atrial amyloid, for which a major subunit is the atrial natriuretic peptide, seems to be three times more frequent than senile cardiac amyloid, which is derived from normal prealbumin (transthyretin).

Senile cardiac amyloidosis is a sporadic disease of late onset associated with restrictive cardiomyopathy. It has been shown that amyloid deposits contained a transthyretin variant with an isoleucine for valine substitution at position 122. Studies show genetic transmission of the isoleucine-122 transthyretin variant associated with this form of cardiac amyloidosis. [36]

Cardiac amyloidosis is a prominent clinical feature of hereditary amyloidosis, namely of the autosomal dominant transthyretin (TTR) type. All are heterozygotes for a single nucleotide change in the gene for TTR that resulted in amino acid substitutions in the mature protein. A TTR genetic variant was reported in a German family where the index patient presented at the age of 63 with anginal pain and arrhythmia.. Amyloid of the TTR type was identified by immunohistochemistry in the endomyocardial biopsy specimen. Hybrid isoelectric focusing established heterozygosity by showing normal TTR protein and an electrically neutral TTR variant differing from all known TTR variants so far. Electrophoretic analysis of the plasma from his first degree relatives (son, daughter, brother, and mother) identified the asymptomatic 22 year old son as an apparently heterozygous carrier of the mutant TTR protein. Comparative tryptic peptide mapping and sequencing showed that isoleucine at position 68 of the amino acid sequence was replaced by leucine.[37]

To identify carriers and non-carriers of the mutant transthyretin methionine 111 linked familial amyloid disease, to detect early signs of the restrictive cardiomyopathy and other clinical manifestations characteristic of this inheritable disease. Out of 125 living family members 99 were available for clinical, echocardiographic and genetic examination. Twenty-five family members were heterozygous carriers of the mutant transthyretin methionine 111 genotype, while 74 were non-carriers. Among the 25 carriers, none had overt clinical signs of heart disease. Eight carriers, all above the age of 35, showed echocardiographic abnormalities suggestive of developing or manifest restrictive cardiomyopathy. Three had biopsy-verified transthyretin-related amyloid cardiomyopathy. None of the 15 carriers in the younger age group exhibited aberrant echocardiographic patterns. Nine carriers had carpal tunnel syndrome as opposed to none of the non-carriers. For early detection of familial amyloid cardiomyopathy, echocardiography is the investigation of choice. The first sign is diastolic dysfunction detected as an abnormal relaxation pattern. The appearance of echocardiographic aberrations solely in the older age group suggests that the cardiomyopathy is a late onset disease. Carpal tunnel syndrome appears to be the earliest presenting clinical symptom. A curative treatment seems to be an early liver transplantation.[38]

Holmgrem et al. related two new amyloidogenic transthyretin (TTR) variants detected in the Swedish population (familial amyloidosis). One variant was previously unknown, while the other

has been described in a French family. In Swedish patients, both variants have caused late-onset cardiac amyloidosis characterised by HF. In both cases, the diagnosis was determined by the detection of amyloid deposits in skin and/or rectal biopsies and identification of TTR mutations by genetic analysis. The index case of the previously unknown mutation (ATTR His88Arg) was a 66-year-old Swedish man, who sought medical attention for increasing dyspnea. Echocardiographic examination disclosed a restrictive cardiomyopathy, and subsequent examinations disclosed TTR amyloidosis. The patient is alive with moderate symptoms one year after the onset of disease. The index case for the new Swedish mutation (ATTR Gly53Glu) is a woman who sought medical attention at the age of 57 because of increasing dyspnea. Echocardiographic examination disclosed a HCM with diastolic impairment. The diagnosis of systemic amyloidosis was made by fat aspiration biopsy and histopathology. The patient developed severe intractable HF, with pulmonary effusion and ascites. She died four years after the onset of her disease of intractable heart and kidney failure. Post mortem examination of biopsy specimens and blood revealed TTR amyloid deposits and the ATTR Gly53Glu mutation was detected. [39]

(II.c) Gaucher disease type I

Gaucher disease is transmitted as an autossomal recessive disorder. Although more than 50 different mutations have been already identified, just 4 specific mutations are responsible for 50% of cases. In addition, this disease is very heterogeneous. Patients with the same mutations can have different symptomatology or even a different type of disease. As an autossomal disorder, males and females have the same chances for it. Gaucher disease, the recessively inherited deficiency of the enzyme glucocerebrosidase and the most common sphingolipidosis, has both non-neurological and neuronopathic forms and a continuum of diverse clinical manifestations. Studies of genotype-phenotype correlations reveal significant genotypic heterogeneity among clinically similar patients, and vastly different phenotypes among patients with the same mutations.

The prevalence of type I Gaucher Disease in general population is 1/60.000 to 1/120.000 births. In the Ashkenazi Jewish population (jews of eastern european ancestry) the prevalence rise to 1/500 births with a rate for heterozygous about 1 in 10 jews. Type II Gaucher Disease has a prevalence lower than 1/100.000 births and type III lower than 1/50.000 births. Both seem to be pan-ethnic, although descriptions of a subtype of type III disease are being made in Nerbottniam, Sweden.

Type I - It is the most frenquent type found, mainly in Jews. It is also called Non-neuropathic or Adult form. The onset is most likely during adulthood, although it could be found in childhood. Painless splenomegaly is the most frequent early sign of disease and it is almost always present in

all patients. Secondary pancytopenia and trombocytopenia are frequent. Anemia, easy bruising and bleeding can occur. Hepatomegaly often occurs beside splenomegaly and loss of hepatic function is not rare. Spleen volume increases up to 20 times the normal and liver volume up to 9 times the normal. Bone crises including pain, lesions, osteopenia, osteonecrosis, avascular necrosis, and pathological fractures are the most debilitating symptoms, however they are often unrecognized manifestations of Gaucher Disease. Primary Central Nervous System disease is absent. Cardiac involvement is not common.

(II.d) Hurler syndrome.

Hurler Syndrome is a form of mucopolysaccharidosis caused by a deficiency of the enzyme alpha-L-iduronidase. There is a group of genetic disorders called mucopolysaccharidoses (MPS) in which critical body enzymes (chemicals) are missing or not enough. In MPS I, alpha-L-iduronidase is deficient. This enzyme breaks down long chains of sugar molecules so the body can dispose of them. Without the enzyme, the big molecules build up and progressively damage parts of the body. Severe form, also known as Hurler syndrome or MPS I H (MPS I, alpha-l-hiduronidase deficiency disease) - Children affected with the severe form may have mental retardation, short stature, stiff joints, speech and hearing impairment, heart disease, pain and a shortened life span. Mucopolysaccharide (Hurler's disease) disorders is easy to diagnose because of obvious extracardiac manifestations. The cardiac involvement is characterize by the paucity of clinical manifestations in sharp contrast with the highly informative echocardiographic results. Valvular dystrophy, usually of the left side of the heart, is the most common anomaly. Whereas some valvular lesions had no consequences, others led to stenosis or incompetence. Asymmetrical hypertrophy of the septum was refered. [40]

Type II A MPS eventually have echocardiographic evidence of impaired left ventricular function, suggesting the presence of myocardial damage. [41]

There is as yet no cure for MPS I, so treatment has focused on relieving symptoms. On April 30, 2003, a treatment for MPS I received U.S. Food and Drug Administration (FDA) approval for marketing. Aldurazyme (laronidase) replaces the deficient enzyme in MPS I. Aldurazyme is given by intravenous infusion once per week for life to people with MPS I. Based on the results of clinical studies, treatment with Aldurazyme will offer a great improvement in the lives of individuals affected by MPS I.

The only cure available for MPS I is bone marrow transplant (putting normal cells in the body that will manufacture the missing enzyme). However, many children with Hurler syndrome have heart disease and are not able to go through the chemotherapy required for the transplant.

III) Storage disease:

(III.1) Hereditary hemochromatosis

Hemochromatosis, the most common form of iron overload disease, is an inherited disorder that causes the body to absorb and store too much iron. The extra iron builds up in organs and damages them. Without treatment, the disease can cause these organs to fail. The most common symptoms are lethargy and arthralgia, and the major complications of end-stage disease are cirrhosis, diabetes, and cardiac and endocrine manifestations. However, with the development of cascade screening for family members of affected probands as well as screening for common diseases at health checks, hemochromatosis is being detected at increasingly early stages, often when there are only biochemical abnormalities.

Genetic or hereditary hemochromatosis is mainly associated with a defect in a gene called *HFE*, which helps regulate the amount of iron absorbed from food. There are two known important mutations in *HFE*, named C282Y and H63D. C282Y is the most important. When C282Y is inherited from both parents, iron is overabsorbed from the diet and hemochromatosis can result. H63D usually causes little increase in iron absorption, but a person with H63D from one parent and C282Y from the other may rarely develop hemochromatosis. Hereditary hemochromatosis is the most common genetic disease among individuals of European descent. Two mutations (845G-->A, C282Y and 187C-->G, H63D) in the hemochromatosis gene are associated with the entity. About 85-90% of patients of northern European descent with Hereditary hemochromatosis are C282Y homozygous. The prevalence of Hereditary hemochromatosis in the Brazilian population, which has a very high level of racial admixture, is unknown. [42]

The genetic defect of hemochromatosis is present at birth, but symptoms rarely appear before adulthood. A person who inherits the defective gene from both parents may develop hemochromatosis. A person who inherits the defective gene from only one parent is a carrier for the disease but usually does not develop it. However, carriers might have a slight increase in iron absorption.

Further study of *HFE* will reveal how the body normally metabolizes iron. It is necessary to learn how iron injures cells and whether it contributes to organ damage in other diseases. Scientists are also working to find out why only some patients with HFE mutations get the disease. Treatment is by regular phlebotomy which, if instituted before the development of cirrhosis, results in normal life expectancy. [43]

Juvenile hemochromatosis and neonatal hemochromatosis are two forms of the disease that are not caused by an *HFE* defect. Their cause is unknown. The juvenile form leads to severe iron overload and liver and heart disease in adolescents and young adults between the ages of 15 and 30, and the neonatal form causes the same problems in newborn infants.

(III.2) Fabry disease or Sphingolipid

Fabry disease is an X-linked recessive disease where the defect is on storage of sphingolipid. Females can be mildly affected. The underlying deficiency is caused by deficient activity of lysosomal hydrolase alpha-galactosidase enzyme resulting in the accumulation of alpha-galactosyl- lactosyl-ceramide in various tissues, including kidney, liver,heart, blood vessels and nerve ganglion cells.

Cardiac manifestation: Cardiac involvement is frequent and, in individuals with some residual enzyme activity, may be the sole manifestation of the disease. Hemizygous men are generally more seriously affected than heterozygous women.

1) Acute myocardial ischemia: angina or myocardial infarction;
2) Generalized vasculopathy[44];
3) Mitral regurgitation by deposition in valvular fibroblast;
4) Miocardiopaty with increased of left ventricular wall thickness (lipid accumulation): The dominant cardiac manifestations include myocardial hypertrophy of the LV, which, in some patients, mimics hypertrophic cardiomypathy;
5) Congestive HF;
6) Sustained ventricular tachycardia[45];
7) Characteristic great variation of morphological cardiac changes and its functional consequences in Fabry cardiomyopathy[46];

Definitive diagnosis by endomyocardial biopsy.

(III.3) Glycogen storage disorder Type II

Others denominations: Acid maltase deficiency, Pompe disease, infantile, acid maltase deficiency and type 2 glycogen storage disease.

A glycogen storage disease (GSD) is the result of an enzyme defect: The enzyme acid alpha-glucosidase (GAA),. These enzymes normally catalyze reactions that ultimately convert glycogen compounds to monosaccharides, of which glucose is the predominant component. Enzyme deficiency results in glycogen accumulation in tissues. In many cases, the defect has systemic consequences; however, in some cases, the defect is limited to specific tissues. Most patients experience muscle symptoms, such as weakness and cramps, although certain GSDs manifest as specific syndromes, such as hypoglycemic seizures or cardiomegaly.

Children have a 1 in 4 chance of inheriting the disease when both parents carry the abnormal gene. It is estimated to occur in about 1 in 40,000 births.

Pompe disease has three forms defined by age of onset and progression of symptoms:

Infantile, or early onset, is noticed shortly after birth. Symptoms include severe lack of muscle tone, weakness, and enlarged liver and heart. Mental function is not affected. Development appears normal for the first weeks or months but slowly declines as the disease progresses. Swallowing may become difficult and the tongue may protrude and become enlarged. Most children die from respiratory or cardiac complications before 2 years of age. Infantile Pompe disease (IPD) is a fatal, autosomal recessive muscle-wasting disorder. Patients develop a generalized myopathy, diaphragmatic weakness, and cardiomyopathy leading to death usually within the first year of life.

Juvenile onset symptoms appear in early to late childhood and include progressive weakness of respiratory muscles in the trunk, diaphragm, and lower limbs, as well as exercise intolerance. Intelligence is normal. Most patients do not live beyond the second or third decade of life.

Adult onset symptoms also involve generalized muscle weakness and wasting of respiratory muscles in the trunk, lower limbs, and diaphragm. Many patients report respiratory distress, headache at night or upon waking, diminished deep tendon reflexes, and proximal muscle

weakness, such as difficulty in climbing stairs. Intellect is not affected. A small number of adult patients live without major symptoms or limitations

Congestive HF or cardiomegaly is an important finding and suggests the diagnosis. This may be accompanied by a systolic murmur. The thorax X-ray show a greatly increased heart with augmented cardiothoracic index. ECG showed high voltages and signs of biventricular enlargement. Cardiac ultrasonography confirm the presence of a big heart with an enormous swollen LV and frequent severe mitral insufficiency.

The safety and efficacy of transgenically derived recombinant human precursor acid alpha-glucosidase (rhGAA) in a 10-month follow-up study in two children with IPD who previously completed a 48-week course of enzyme replacement therapy (ERT) with the same medication at the same dose in a phase II clinical trial. Under this therapy cardiac status and muscle strength had improved, leading to survival beyond the age of one year. These results, together with data from two other phase II clinical trials encouraged further evaluation of the long-term safety and efficacy of enzyme replacement therapy in patients with infantile-onset Pompe disease. During the 10-month follow-up period, ERT was well-tolerated and neither patient experienced a single infusion-associated reaction. The initial improvements in cardiac size and function, as measured by left ventricular mass index and the fractional shortening, were maintained in both patients, and a continued improvement of motor function, as measured by the Alberta infant motor scale, was observed. [47]

III) Endomyocardial fibrosis-2.

It is a type of restrictive cardiomyopathy or obliterative cardiomyopathy occurring in equatorial Africa and less often in other tropical and subtropical regions of the world. It is characterized by severe endocardial disposition of fibrous tissue in the apical and subvalvular regions of either or both ventricles. Endomyocardial fibrosis is a rare case of restrictive cardiomyopathy. Endomyocardial fibrosis (EMF) is a fascinating disease entity of unknown etiology. It is prevalent in the tropical zone. Its essential features are the formation of fibrous tissue on the endocardium and to a lesser extent in the myocardium of the inflow tract and apex of one or both ventricles. It results in endocardial rigidity, atrioventricular valve incompetence secondary to papillary muscle involvement, and progressive reduction of the cavity of the involved ventricle leading to restriction in filling and atrial enlargement. Pericardial effusion is frequently present. The clinical features of tropical and temperate zone endomyocardial fibrosis are the same, allowing for certain regional,

environmental and genetic mutations Locus Xq28; OMIM NO: 302060 and gene symbol: TAZ. The seasonal incidence in rainy humid areas probably reflects the large and repeated parasitic infestations in tropical entity, while the absence of tissue eosinophilia in organs other than the heart in tropical disease may reflect racial and environmental differences between tropical and western geographical areas that have still to be elucidated. That EMF occurs in Europeans who have lived in the tropics is undoubted, but the absence of right ventricular involvement in Europeans in the tropics, but not in temperate climes, is unexplained; perhaps it is a chance finding. It is also apparent that the extreme degrees of right ventricular EMF that are commonly seen in the tropics, with almost complete obliteration of the ventricular cavity are not usually seen in eosinophilic EMF in temperate areas. Involvement of both ventricles and of both atrioventricular valves is, however, common both in the tropics and in temperate climate EMF.

Chest X-ray demonstrates pulmonary venous hypertension and a variable degree of cardiac enlargement. In left-sided involvement the left atrium is enlarged while in the right-sided form the right atrium is enlarged. The presence of a small ventricle with obliteration of the apex and large atrium shown on two-dimensional echocardiography is highly suggestive of EMF. A characteristic feature is intracardiac calcification usually near the cardiac apex. Echocardiography reveals obliteration of the apex of either or both ventricles, strongly echogenic endocardial or subendocardial regions, and atrioventricular valvular regurgitation. Ventriculography shows obliteration of the apical region of one or both ventricles and filling defects caused by the frequently associated ventricular thrombi. MRI has also depicted the obliteration of the apical region(s), thickening of the wall in the inlet regions of the ventricles and alteration of signal intensity of the subendocardial deposition compared with normal myocardium.

General treatment of RCM is based on diuretics, prevention of atrial fibrillation (amiodarone) and oral anticoagulants. Digoxin, which fixes to amyloid fibrils, may be arrhythmogenic in amyloidosis. Cardiac pacing may be used in cases of atrioventricular block and brady-arrhythmias. Cardiac transplantation is available in advanced forms after exclusion of amyloidosis[48].

(I.4) – ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/DYSPLASIA (ARVC/D)
ARVC/D is a cell junction disease of desmosomal (desmosomalopathy) cardiomypathy that predominantly affects the right side of the heart and causes ventricular arrhythmias. It is a rare type of cardiomyopathy in which the muscle tissue in the lower-right chamber of the heart (right ventricle: RV) dies in a programmed way or non-necrotic cell death (apoptosis). Evidences indicate that apoptotic myocardial cell death occurs in ARVC/D and may contribute to the loss of

myocardial cells in this disorder[49]. It is characterized by the progressive replacement of myocardial cells by fat and fibrous tissue. The dead muscle tissue is replaced by fatty or fibro-fatty infiltration. To day the entity is considered a disease of cell adhesion because mutations in desmosomal genes, desmoplakin and plakoglobin, have been implicated in the pathogenesis of ARVC/D. [50,51]

In some cases, symptoms appear in childhood and can quickly worsen. In most cases, however, symptoms do not appear until patients are in theirs 30s or 40s. The entity is characterized by a marked variability of clinical presentation within one family. By that time, ARVC/D may have progressed to congestive HF in the advanced form of the disease with low cardiac output syndrome or third-degree atrioventricular block.[52] The same disease process may also involve the LV.

Moreover, inflammation can be superimposed on ARVC/D, resulting in a wide spectrum of clinical presentation which can mimick idiopathic dilated cardiomyopathy.[53]

ARVC/D is an important cause of ventricular arrhythmias in children and young adults. It is seen predominantly in males, but French authors from 200 consecutives autopsies observed that both sexes are equally affected, and 35% of cases have a familial distribution. It is usually inherited in an autosomal dominant pattern, with variable expression. The penetrance (disease absence in some individuals with disease gene) is 20-35% in general, but significantly higher in Italy. Several gene loci have been implicated in ARVC/D. These loci were found by studying families where more than tree people were diagnosed, and more than one generation was affected. However, about 50% of families that express ARVC/D that undergo genetic screening do not show linkage with any of the known chromosomal loci. It is unclear whether the pathogenesis varies with the different loci involved. A standard genetic screening test is not available.

In approximately 65% of the cases this entity is sporadic, and in the remaining 35%, is genetically determined. Familial dominant autosomal (autosomal dominant inheritance is typical) or rarely recessive in the regional form from the Greek island of Naxos, which affects the long arm of chromosome 17 (17q21) associated to non-epidermolytic palmoplantar keratoderma with woolly hair[54]. Positive family background may be found in very variable percentages.

To this moment, ten varieties have been identified, nine dominant and only two recessive forms. Both affect the gene encoding plakoglobin. The identification of causative mutations in cell adhesion proteins has shed new light on its pathogenesis.[55]

I) ARVC1 or ARVD1

Autosomal Dominant pattern of inheritance. The affected locus was mapped to the long arm of chromosome 14. 14q23-q24. (Chromosome: structures that carry genes within the nucleus of a cell.) (Loci D14S42) The OMIM number is 107979 and the symbols of the gene are ARVC1 or ARVD1 or arrhythmogenic right ventricular cardiomyopathy Type 1 [56-58]

An intronless gene was detected within the ARVD1 critical region, of 4839 bp and mapped to 14q24.3. It is primarily expressed in the heart tissue. This gene encodes a 796-amino-acid, proline-rich protein showing polyglutamine and polyalanine tracts with variable length at the N-terminus and a C3HC4 RING finger domain at the C-terminus. CREB and AP-2 binding sites are present in the promoter region. The 5' flanking region contains neither a TATA box nor a CAAT box, but it is high in GC content and includes several Sp1 binding sites. The search for protein similarity exposed a significant match between the C-terminus and a human hypothetical protein, whose gene is located on the long arm of chromosome 19. The predicted protein shows PEST sequences, suggesting its rapid degradation[59].

The novel intronless gene, provisionally named C14orf14, and probably encoding a nuclear protein, was excluded from being the ARVD1 gene. Direct sequencing of DNA from individuals belonging to established ARVD1 families did not detect causative mutations in exonic sequences of four genes (POMT2, TGFbeta3, KIAAA1036 and KIAA0759) expressed in the heart, and which defects could possibly induce plasma membrane instability or apoptosis, key features of ARVC/D pathogenesis.[60]

Beffagna et al identified a nucleotide substitution (c.-36G>A) 5' untranslated regions(UTR) of TGFbeta3 gene, as the disease gene involved in ARVD1. The identification of a novel ARVC gene will increase the power of the genetic screening for early diagnosis of asymptomatic carriers among relatives of ARVC/D patients. [61]

II) ARVC/D Type 2. (ARVC2 or ARVD2) Arrhythmogenic Right Ventricular Cardiomyopathy Type 2: Autosomal Dominant pattern of inheritance.

The affected locus was mapped to the long arm of chromosome 1. Cytogenetics is 1q42-q43 and the OMIN number is 600996, while the symbols of the gene are ARVC2 and ARVD2. This variant

is characterized by presenting as a minor or "concealed phase", showing PVT induced by strain. Since both loci, ARVD1 and ARVD2, were mapped near the alpha-actin gene, it is possible to involve it with these myofibrillar proteins in the pathogenesis of ARVC/D.[62]

Recently, a RYR2 mutation has been identified in four independent families. The RyR2 protein in myocardial cells activated by ion calcium Ca^{2+} induces cation release from the sarcoplasmic reticulum to cytosol. The RyR2 protein is the equivalent to the ryanodine receptor protein of the skeletal muscle, known as RyR1. The skeletal muscle ryanodine receptor has a role in malignant hyperthermia and in susceptibility in the so-called central core disease (CCD)[63-64]

Clinically it causes PVT induced by strain or emotional stress in a similar way to familial catecholaminergic PVT without structural heart disease.[65]

This dominant autosomal entity affects the intracellular Ca^{2+} regulation signalers, and is characterized by bursts of bidirectional VT and PVT or idiopathic ventricular fibrillation (IVF) due to strain or stress (adrenergic stimulation) that causes RyR2 phosphorilation by protein kinase A (PKA). PKA phosphorilation of RyR2 activates the channel, originating delayed after depolarizations that may trigger fatal ventricular arrhythmias. This entity is observed in children and young adults without evidence of structural heart disease and mapped to chromosome 11q42-q43, where three missense mutations were detected (P2328S, Q4201R, V4653F) located in the sarcoplasmic reticulum of the ryanodine receptor type 2 or RyR2. Clinically it is heterogeneous and responds to beta-blockers; however, in a 30% of the cases ICD is necessary. Those without genotypic alteration are predominantly female and present a more delayed onset. Those with demonstrable alteration are predominantly male and present earlier clinical manifestations[66]

In brief, the cardiac ryanodine receptor (RyR2) is the greatest Ca^{2+} releaser of the sarcoplasmic reticulum in cardiomyocytes and it involves at least two forms responsible for SCD: (1) Catecholaminergic polymorphic ventricular tachycardia (CPVT) or familial polymorphic VT (FPVT); and (2) and ARVC/D or ARVD type 2, arrhythmogenic right ventricular dysplasia type 2 (ARVD2) [67]

More rarely, mutations in calsequestrin 2, binding protein of the sarcoplasmic reticulum with inhibition function of the ryanodine receptor in its Ca^{2+} ion release function, it may also cause CPVT with 2 new amino-acid polymorphisms having been identified (T66A and V76M). [68]

III) - ARVC/D Type 3: Autosomal Dominant pattern of inheritance, affects the long arm of chromosome 14. Cytogenetics is 14q12-q22; ARVC3 or ARVD3 being the symbols for the gene,

with multipoint linkage analysis. A maximal cumulative lod score of 4.7 was obtained in the region between loci D14S252 and D14S257.[69,70]

IV) - ARVC/D Type 4: in these families the disease appears to be transmitted by three DNA polymorphic markers of the locus affected, which was mapped to chromosome 2 with alterations in the long arm (2q32.1-q32.3) within the chromosomal region that includes the D2S152, D2S103 and D2S389. The symbol of the gene is ARVC4 or ARVD4. Autosomal Dominant pattern of inheritance.[71] It is clinically characterized by LV involvement.

V) - ARVC/D Type 5: the affected locus was mapped to chromosome 3. The locus is 3p21.3.3p23 and 3p25 deoxyribonucleic acid (DNA) haplotype at locus ARVD5 but different from BrS. Autosomal Dominant pattern of Inheritance. Cytogenetics is 3p23. A peak 2-point lod score of 6.91, which was obtained with marker D3S3613 at a recombination fraction of 0.0. Haplotype analysis identified a shared region of 9.3 cM between markers D3S3610 and D3S3659. The gene symbols are ARVC5 or ARVD5.[72] On the other hand, in the BrS the cardiac sodium channel isoform encodes hH1 and has been mapped to the short arm of chromosome 3 p21-24 loci.[73]

Furthermore, the risk of SCD is probably variable among different types of ARVC/D. In Newfoundland, Canada, ARVD5 was reported to cause SCD in 44% of affected males, while females had a more benign course with no SCD. It is coincident with BrS[74] .
The unknown mutation at the ARVD5 locus causing ARVC/D results in high mortality. Risk stratification using genetic haplotyping and ICD therapy produced improved survival for males. In the high risk group, 50% of males were dead by 39 years and females by 71 years: relative risk of death was 5.1 (95% confidence interval 3 to 8.5) for males. The five-year mortality rate after ICD in males was zero compared with 28% in control subjects (p = 0.009). Within five years, the ICD fired for VT in 70% and for VT >240 beats/min in 30%, with no difference in discharge rate when analyzed by ICD indication.[75]

VI)- ARVC/D Type 6: The locus affected was mapped in the short arm of chromosome 10 (10p13-14), the symbols of the gene being ARVC6 or ARVD6. Autosomal Dominant pattern of Inheritance.[76] This region coincides with that of the Protein Tyrosine Phosphatase-Like (PTPLA), which possesses a role in myogenesis and cardiogenesis, regulating cardiac development and other cellular events;

VII) - ARVC/D Type 7: Autosomal Dominant pattern of Inheritance, mapped to the long arm of chromosome 10 (10q22). The gene symbol is ARVC7 or ARVD7. The entity may affect the cardiac muscle and striated muscle, while in the latter, axial myopathy is verified in patients mildly affected, and distal in those affected moderately. The electromyogram showed signs of myopathy in 10 patients from 22 cases studied. Muscle biopsy specimens showed myopathic changes, rimmed vacuoles, and accumulation of desmin, dystrophin, and other proteins. EM revealed granulofilamentous changes and disorganization of myofibrils. A maximum 2-point LOD score of 2.76 was shown by linkage analysis of candidate chromosomal regions, for marker locus D10S1752 on chromosome 10q. A multipoint peak LOD score of 3.06 between markers D10S605 and D10S215 suggests linkage to chromosome 10q22.3. This region may hold a genetic defect for myofibrillar myopathy with ARVC/D[77]

Cardiac involvement seems less frequent. Three ARVC/D patients were reported as presenting non-sustainded ventricular tachycardia (NS-VT), atrial flutter, and dilatation of the ventricles mainly affecting the RV. Two of them had a pacemaker implanted due to atrioventricular block and sick sinus syndrome. Neuroblastoma apoptosis-related RNA-binding protein (NAPOR, HGMW-approved symbol CUGBP2) is a newly discovered gene prominently induced during apoptosis, suggesting that it plays a role during apoptosis. The authors have found that it is encoded by a gene located on chromosome 10p13-p14 between Genethon markers D10S547 and D10S223. A gene responsible for ARVC/D has recently been localized in this region. The genomic organization of the human NAPOR gene was determined to examine its possible role in the pathogenesis of ARVD, including its exon-intron boundaries and the putative promoter sequence. These offer a probable mechanism for its alternative mRNA splicing. It has also been demonstrated that three isoforms of the NAPOR transcript were differently expressed, with NAPOR-3 being nearly neuron specific, while the other two forms were ubiquitously expressed. NAPOR expression is differentially regulated during development. The members of the ARVD family were screened for mutations, and two DNA sequence variants were identified in the protein-coding exons of NAPOR, neither of which was responsible for ARVD. The function of NAPOR has yet to be found. Nevertheless, the current characterization of the NAPOR gene will prove to be valuable for further clinical and functional study[78].

VIII) - ARVC/D Type 8: Autosomal Dominant pattern of Inheritance. and causes arrhythmogenic right ventricular dysplasia. It was mapped in the short arm of chromosome 6 (6p24). The symbol of the gene is ARVC8 or ARVD8. It does not present skin, hair or nail alterations[79].

The S299R mutation in desmoplakin and in exon 7 of desmoplakin (DSP) modifies the putative site of phosphorilation in the N-terminal domain binding with plakoglobin (gamma-catenin). It is interesting that a DSP mutation not sensed was described in literature with a recessive inheritance pattern, and causing cardiomyopathy with biventricular dilatation associated to palmoplantar keratoderma and woolly hair. These mutations in DSP may produce different phenotypes with different inheritance transmission modes.

In 32 of 120 unrelated individuals with ARVC/D, Gerull et al identified heterozygous mutations in PKP2, which encodes plakophilin-2, an essential armadillo-repeat protein of the cardiac desmosome. In two kindreds with ARVC/D, disease was incompletely penetrant in most carriers of PKP2 mutations[80].

IX) Norman et al. have described a new dominant mutation in desmoplakin that causes left-sided ARVC, with arrhythmias of LV origin, lateral T-wave inversion, and late gadolinium enhancement in the LV on magnetic resonance images. Truncation of the carboxy terminus of desmoplakin and consequent disruption of intermediate filament binding may account for the predominant LV phenotype. [81]

The proband presented with SCD and fibrofatty replacement of the LV myocardium. The family was evaluated. Diagnosis was based on modified diagnostic criteria for ARVC/D. Seven had inferior and/or lateral T-wave inversion on ECG, LV dilatation, and ventricular arrhythmia, predominantly PVCs of LV origin. Three had S-VT; 7 had LPs on SAECG.

Cardiovascular MRI in 4 patients revealed wall-motion abnormalities of the RV and patchy, late gadolinium enhancement in the LV, suggestive of fibrosis. Linkage confirmed cosegregation to the desmoplakin intragenic marker D6S2975. A heterozygous, single adenine insertion (2034insA) in the desmoplakin gene was identified in affected individuals only. A frameshift introducing a premature stop codon with truncation of the rod and carboxy terminus of desmoplakin was confirmed by Western blot analysis.

X) - Naxos disease

It is an Autosomal recessive variant of ARVC/D, described initially on the Greek island of Naxos. There, the penetrance is >90% (disease absence in some individuals with disease gene), It

involves the gene that codes for plakoglobin. The entity is caused by a deletion in plakoglobin. (a protein that is involved in cellular adhesion), on the long arm of chromosome 17p.(17q21)[82,83]

Remodeling of gap junctions occurs early in Naxos disease, presumably because of abnormal linkage between mechanical junctions and the cytoskeleton. Gap junction remodeling may produce a coupling defect which, combined with the subsequent development of pathologic changes in myocardium, could contribute to a highly arrhythmogenic substrate and enhance the risk of SCD in Naxos disease.Connexin43 expression at intercellular junctions was reduced significantly in both right and left ventricles in all patients with Naxos disease. Electron microscopy revealed smaller and fewer gap junctions interconnecting ventricular myocytes. Mutant plakoglobin was expressed but failed to localize normally at intercellular junctions. Localization of N-cadherin, alpha- and beta-catenins, plakophilin-2, desmoplakin-1, and desmocollin-2 at intercalated disks appeared normal. [84]

Naxos disease is described as a triad of ARVC/D, non-epidermolytic palmoplantar keratosis, and wooly hair. The signs of Naxos disease are more severe than with autosomal dominant ARVC/D.

XI) - Recessive Autosomal familial form:

With wooly hair, pemphigous-like skin disorder, and mutation in chromosome 6 in the desmoplakin gene [85].

The authors identified a homozygous missense mutation in exon 24 of the desmoplakin gene, which causes Gly2375Arg substitution in the C-terminal of the protein, where the binding site with the intermediate filaments is. Eight out of 12 members of the family, without skin or hair diseases, were heterozygous for this mutation. The remaining 4 and 90 normal controls of the same ethnicity were homozygous for the normal allele.

The table 2 submarize all ARVC/D Types.

Table 2 **ARVC/D Types**

Type	Chromosomal Locus	Genetic Mutation
ARVC/D1	14q23-q24	
ARVC/D2	1q42-q43	Mutation in the ryanodine receptor, type 2 (RYR2)
ARVC/D3	14q12-q22	
ARVC/D4	2q32.1-q32.3	
ARVC/D5	3p23	
ARVC/D6	10p14-p12	
ARVC/D7	10q22.3	
ARVD8	6p24	Mutation in desmoplakin
ARVD9		Mutation in desmoplakin Left-sided ARVC, with arrhythmias of LV origin, lateral T-wave inversion, and late gadolinium enhancement in the LV on MRI. Truncation of the carboxy terminus of desmoplakin and consequent disruption of intermediate filament binding may account for the predominant LV phenotype.
Naxos Disease Recessive autosomal familial form	17q2117p.	Mutation in plakoglobin; woolly hair and keratoderma
Recessive autosomal familial form	6	Desmoplakin gene

ARVC/D types 1 through 8 are inherited as an autosomal dominant condition, while in Naxos disease and desmoplakin are the recessives.

Genetic abnormalities have been located on chromosome 1, 2, 3, 6, 10, 14 and 17 suggesting a multi-genic form of the disease.

The incidence of ARVC/D is about 1/10,000 in the general population in the United States. It accounts for up to 17% of all SCD in the young. In Italy, the incidence is 40/10,000, making it the most common cause of SCD in the young in Italy.

The table3 summarize the main genetic entities and its predominant HF modalities

Table 3. GENETIC ENTITIES AND PREDOMINANT HF MODALITIES

ENTITY	VENTRICULAR REMODELING TYPE
Familial dilated (Congestive) cardiomyopathy (FDCM)	Characterized by a progressive course of ventricular dilatation and systolic dysfunction. The genes causing FDCM code for proteins that anchor the sarcomere to the cell membrane and extracellular matrix.
Familiar hypertrophic cardiomyopathy (FHCM). Sarcomeric disease (sarcomyopathy):	Systolic function is normal. Diastolic relaxation is impaired. In general the genes causing FHCM code for proteins involved in the contractile apparatus, the sarcomere.
RESTRICTIVE CARDIOMYOPATHIES (RCMs): I) Noninfiltrative: Idiopathic, scleroderma; II) Infiltrative: Amyloid, Sarcoid, Gaucher disease type I and	Impairment of ventricular filling during diastole with preserved systolic function (Normal or near normal LV size and function). Fabry disease It is an X-linked recessive genetic disorder

Hurler syndrome. III) Storage disease: Hereditary hemochromatosis. Fabry disease or Sphingolipid, Glycogen storage disorder II and III. (Pompe disease) IV) Endomyocardial: Endomycocardial fibrosis-2 (Locus Xq28 OMIM NO: 302060, GENE SYMBOL: TAZ), Hypereosinophilic syndrome, carcinoid, radiation, anthracylic toxicity.	of glycosphingolipid metabolism, due to deficiency of the lysosomal enzyme alpha-galactosidase A.[86]
Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D):	Predominantly affects the right side of the heart and causes ventricular arrhythmias. It usually occurs in the diaphragmatic, apical, and infundibular regions: Right Ventricular Outflow Tract (RVOT) and right ventricular inflow tract (RVIT). (Known as the triangle of dysplasia).
	Myocardial abnormalities are characterized mainly by left ventricular wall thickening without significant cavity dilatation, the most frequent abnormal structural pattern being concentric LV hypertrophy. Systolic function is preserved in a large majority of affected individuals. Mild to moderate impairment of diastolic filling is a relatively common finding, representing probably the most important cause of shortness of breath on effort.
Glicogen storage disease II(Pompe disease):	Irreversivel congestive HF during the first year

Mutations(Ser548Pro) in the gene encoding the gamma 2 subunit of AMP-activated protein kinase (PRKAG2)	Cause familial hypertrophic cardiomyopathy, and a severe conduction system abnormalities, with glycogen accumulation in the heart of affected patients.[87]
Non-compaction of LV myocardium or Isolated non-compaction of the ventricular myocardium (INVM), LV hypertrabeculation or spongy myocardium, belongs to the "unclassified" cardiomyopathies according to the World Health Organization. Locus Xq28; OMIM NO: 302060, Gene symbol: TAZ	Cardiomyopathy is due to an arrest of intrauterine compaction of the myocardial fibers in the absence of any other structural heart disease. The main characteristic is a prominent trabeculation of the LV with deep intertrabecular recesses communicating with the ventricular cavity. A correct diagnosis of noncompaction has important implications due to the possible association with other cardiac abnormalities and/or muscle disorders, progressive LV dysfunction, risk of thromboembolism, and life-threatening arrhythmias. Echocardiography of first relatives is recommended. Since echocardiography is the diagnostic technique of choice, missed diagnoses may be due to nonoptimal imaging of the lateral and apical myocardium, and/or insufficient disease awareness by echocardiographers.[88]
Mitochondrial disease, mitochondrial cytopathies or oxidative-phosphorylation diseases: Pathogenic mitochondrial DNA (mtDNA) mutations are found in at least one in 8000 individuals.	Represent a heterogeneous group of disorders associated with a wide array of clinical manifestations. Mitochondrial disease, result from the structural, biochemical, or genetic derangement of mitochondria. Because mitochondrial

Unlike nuclear chromosomal rearrangements, incidence of mtDNA deletion disorders does not increase with maternal age, and unaffected mothers are unlikely to have more than one affected child. Affected women were previously thought to have a negligible chance of having clinically affected offspring, but the actual risk is, on average, about one in 24 births.[89]

Disorders of mitochondrial metabolism affect complex I, II, III, IV and V, in addition to multiple respiratory chain defects.

Main Phenotypes:

1) Kearns-Sayre syndrome: ptosis, limited movement of both eyes and atypical retinal pigmentary change (salt-pepper like appearance). Occasionally, it is combined with other neurologic, cardiac and endocrinologic symptoms such as ataxia, dementia, diabetes, and hyperaldosteronism.
2) MELAS syndrome: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.
3) MERRF: myoclonic encephalopathy with ragged-red fibers
4) Myopathy
5) Chronic progressive external

dysfunction can affect the most highly energy-dependent organs, cardiac involvement is frequent in these diseases. The entities can be progressive resulting CHF and end-stage heart disease.

The contribution that mitochondria make to cardiac function extends well beyond their critical bioenergetic role as a supplier of ATP. The organelle plays an integral part in the regulatory and signaling events that occur in response to physiological stresses, including but not limited to myocardial ischemia and reperfusion, hypoxia, oxidative stress, and hormonal and cytokine stimuli.[90]

Mitochondrial disease may cause either hypertrophic or dilated cardiomyopathy. The cardiomyopathy is predominantly hypertrophic flowed by dilated. Conduction and rhythm abnormalities are present in 40% of cases. Mitochondrial dysfunction frequently affects the heart and may cause both hypertrophic and dilated cardiomyopathy. The cardiomyopathy is usually a part of a multisystem involvement and may rarely be isolated. The course may be stable for many years, but rapid deterioration may occur. Understanding the biochemical and genetic features of these diseases will enable us to understand the clinical heterogeneity of these disorders.[91]

ophthalmoplegia 6) Progressive ophthalmoplegia plus ataxia 7) Encephalopathies.	
Carnitine deficience: Measurement of carnitine in the plasma and urine is a more sensitive test for the diagnosis of the diagnosis of primary carnitine deficiency.	Several studies have shown that levocarnitine reduces myocardial injury after ischemia and reperfusion by counteracting the toxic effect of high levels of free fatty acids, which occur in ischemia, and by improving carbohydrate metabolism. To increase the rate of fatty acid transport into mitochondria, levocarnitine reduces the intramitochondrial ratio of acetyl-CoA to free CoA, thus stimulating the activity of pyruvate dehydrogenase and increasing the oxidation of pyruvate. Idiopathic DCM and coeliac disease are two pathological conditions which may lead, by different mechanisms, to malabsorption of various micronutrients, including carnitine, active in cardiac metabolism. Patients presenting IDCM associated with coeliac disease show a greater decrease in serum total carnitine levels than patients presenting the isolated form of IDCM. A gluten-free diet, in these patients, leads to a progressive increase in serum levels of this substance. [92] The results of phase-2 studies in chronic HF patients showed that long-term oral treatment with propionyl-L-carnitine improves maximum exercise duration and

	maximum oxygen consumption over placebo and indicated a specific propionyl-L-carnitine effect on peripheral muscle metabolism. A multicenter trial on 537 patients showed that propionyl-L-carnitine improves exercise capacity in patients with HF, but preserved cardiac function.[93]
Sickle cell disease or sickle cell anaemia (SCA): Mutation in the codon for the sixth amino acid of beta globin chain from glutamic acid to valine.	Hyperdynamic hear failure. The increase preload and decreased afterloada is characteristic. Left ventricular diastolic dysfunction is not a frequent finding in patients with SCA without congestive HF and tissue Doppler imaging is a more reliable and easy method to evaluate diastolic function.[94]
Thalassemia β thalassemia major or Cooley's anemia	HF by chronic anemia, iron overload of the heart, Impairment systolic and diastolic function. SCD by arrhythmias;[95]
Marfan Syndrome	Diastolic overloading by aortic insuficience and/or mitral regurgitation.
Muscular dystrophy Duchenne like DMD: X-linked recesive disorder; with abnormality in dystrophin gene; Locus: 17q12-q21.33; OMIM NO: 600119, Gene symbol: SGCA. Incidence: 1; 3500 male birth.	Cardiomyopathy develops in most patients by the age of 18 years and can cause HF, leading to 10-40% of deaths. Cardiac involvement is segmentar with póstero-basal and lateral LV involvement. Presence of sinus tachycardia may suggest early cardiac involvement. Cardiomyopathy of DMD is characterized by lack of symptoms and few physical signs. In DMD may not only comprise rhythm abnormalities, valve abnormalities, and dilative cardiomyopathy, but

	exceptionally left ventricular hypertrabeculation. Around 30% patients had cardiomegaly. In about 10% cases of DMD, death is due to cardiac dysfunction.[96] Gene deletion is associated with higher CT ratio. Specific dystrophin gene mutations appear to be predictive of cardiac involvement, while other mutations may protect against or inhibit development of DCM. DNA analysis in 47 cases (68%) revealed a significant association between DCM and exon 12 and 14 to 17 mutations, possible protection against DCM by exon 51 to 52 mutations, and a trend toward significant association between onset of DCM and exon 31 to 42 mutations[97]. European group recommended in 2003 an ECG and echocardiogram at diagnosis, then every 2 years until the age of 10, and annually thereafter. If progressive abnormalities occurred they recommended treatment with angiotensin-converting enzymes inhibitors and, if needed, beta-blockers. Not all cardiologists agree with these guidelines.
Becker muscular dystrophy (BMD): X-linked recesive disorder with abnormality in dystrophin gene. Considered a milder allelic variant of Duchenne.	Later in onset but the severity of cardiac involvement is not related to age. Severe familial dilated cardiomyopathy is possible. Frequent dromotropic arrhtymias and SCD tendency.
Myotonic dystrophy: Locus: 19q13.2-q13.3; OMIM NO160900; Gene symbol: DMPK Type 1 myotonic dystrophy or DM1 (Steinert's disease)	Myotonia, and involvement of the brain, eyes, smooth muscle, cardiac conduction apparatus, and endocrine system. Morbidity is high, with a substantial

	mortality relating to cardiorespiratory dysfunction.[98] There are conduction disturbances, arrhythmias, and ventricular dysfunction. Clinical congestive HF was found in 1.8% of cases. Left ventricular hypertrophy in 19.8%, left ventricular dilatation in 18.6%, left ventricular systolic dysfunction was associated with increasing age and observed in 14.0%. P-R >200 ms was predictive of regional wall motion abnormalities. QRS >120 ms correlated with regional wall motion abnormalities and left atrial dilatation.[99]
Myotonic dystrophy 2, proximal myotonic myopathy (PROMM), proximal myotonic dystrophy (PDM), or DM2: Locus: 3q; OMIM NO: 602668, Gene symbol: DM2. It is caused by a CCTG repeat expansion in intron 1 of the zinc finger protein 9 (ZNF9) gene.	90% have electrical myotonia, 82% weakness, 61% cataracts, 23% diabetes, and 19% cardiac involvement[100]. Older patients show mildly increased LV volumes, increase of end-systolic volume index (≈60%) and 35% increase of end-diastolic volume index and an increase of LV mass (26%).[101]
Friedreich's ataxia: Locus: 9q13; OMIM NO: 229300; Gene symbol: FRDA; Transmission: Autosomal recessive mode. It is caused by deficiency of mitochondrial protein frataxin, which is responsible for the degenerative impairment of the spinocerebellar and corticospinal tracts and posterior columns of the spinal cord and for the heart damage.	Heart involvement is a condition marked by inevitable progressive deterioration, with premature death. HCM is frequent. Myocardial involvement usually follows symptoms of nervous system degeneration later in the course, but seems not to be secondary. These cardiac disturbances are the main cause of death in Friedreich's ataxia patients. All patients with GAA expansion have

	electrocardiographic abnormalities, and only 25% of the cases without GAA expansion have some abnormality on this exam. Pharmacotherapy: coenzyme Q10 and carnitine. High-dose beta-blocker[102]. Causal treatment is still impossible.
Emery-Dreifuss muscular dystrophy (EDMD): Locus: on chromosome 1q.21.2; OMIM NO:150330, Gene symbol: LMNA. Lamin A/C gene; Transmission: Autosomal dominant mode.	Common form of muscular dystrophy frequently leading to dilated cardiomyopathy. Clinical outcome and prognosis is frequently determined by the involvement of the cardiac conduction system causing symptomatic bradyarrhythmias, as well as tachyarrhythmias and, if untreated, frequent SCD.[103]

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