

## R E V I E W

# Genetics and pharmacogenetics in the diagnosis and therapy of cardiovascular diseases

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**Summary.** Cardiovascular diseases are the main cause of death worldwide. The ability to accurately define individual susceptibility to these disorders is therefore of strategic importance. Linkage analysis and genome-wide association studies have been useful for the identification of genes related to cardiovascular diseases. The identification of variants predisposing to cardiovascular diseases contributes to the risk profile and the possibility of tailored preventive or therapeutic strategies. Molecular genetics and pharmacogenetics are playing an increasingly important role in the correct clinical management of patients. For instance, genetic testing can identify variants that influence how patients metabolize medications, making it possible to prescribe personalized, safer and more efficient treatments, reducing medical costs and improving clinical outcomes. In the near future we can expect a great increment in information and genetic testing, which should be acknowledged as a true branch of diagnostics in cardiology, like hemodynamics and electrophysiology. In this review we summarize the genetics and pharmacogenetics of the main cardiovascular diseases, showing the role played by genetic information in the identification of cardiovascular risk factors and in the diagnosis and therapy of these conditions. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** molecular genetics, cardiovascular diseases, risk factors, NGS, pharmacogenetics

## Introduction

Cardiovascular diseases (CVDs) are the principal cause of death worldwide. They include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases and venous thromboembolism (1). CVDs are complex genetically heterogeneous conditions resulting from many gene-gene and gene-environment interactions (2). Molecular genetics and pharmacogenetics play a key role in the diagnosis, prevention and treatment of CVDs. Genetic testing is normally used to identify underlying genetic etiology in patients with suspected cardiovascular disease and to determine who in the

family has inherited the causal variant and is therefore at risk of developing CVD. Genetic testing should be carried out in well phenotyped individuals, ideally coupled with comprehensive family evaluation to aid in interpretation and application of the results (3). Molecular genetics technologies applied to cardiovascular studies have enabled chromosome mapping and identification of many genes involved in primary etiology, as well as significant risk factors for the development of CVDs, including environmental risk factors. Cardiovascular diseases and related risk factors may be monogenic or polygenic (4). Since many genetic variations have an association with CVDs, routine genetic testing of patients with these conditions is important.

Pharmacogenetics is the study of interpatient genetic variations associated with different responses to drugs, including toxicity. Pharmacogenetic testing reveals variations in drug metabolism genes. These genes encode metabolic enzymes that can be defined as either “poor metabolizers” or “rapid metabolizers” in relation to the efficiency of their activity. Identifying how a patient metabolizes a medication enables personalized and safer treatments, leading to improved clinical outcomes and reduced medical costs. Pharmacogenetic testing can be performed prior to prescription to guide drug selection and dosage (5,6) or after unsuccessful treatment. For instance, platelet aggregation inhibitors (PAI), oral anticoagulants (OA), anti-hypertensive and cholesterol-lowering drugs are abundantly prescribed for cardiovascular disease, but individual responses may vary significantly, since genetic variability is partly responsible for such differences in efficacy (7). Pharmacogenetics and pharmacogenomics can be expected to optimize therapy and reduce toxicity through individualized genetically guided therapy (8).

This brief review summarizes the principal cardiovascular diseases and the role molecular genetics and pharmacogenetics can have in the identification of cardiovascular risk factors, and in the diagnosis and therapy of cardiovascular diseases.

### Monogenic forms

In monogenic CVDs, a single gene determines the onset of symptoms, although genotype-phenotype correlation can be complex due to genetic phenomena (pleiotropy and variable penetrance and expressivity) and environmental factors (4).

#### *Cardiac conduction defects*

- Long QT syndrome (LQTS) is a genetic heart disease characterized by prolongation of the QT interval that can lead to arrhythmia, palpitations, syncope or sudden death. It typically manifests in patients under 40 years of age, and sometimes in early infancy (9). LQTS follows two distinct patterns of inheritance: autosomal dominant (Romano-Ward syndrome) with an estimated

prevalence between 1:2000 and 1:5000 (10,11) and autosomal recessive (Jervell and Lange-Nielsen syndrome) with an estimated prevalence between 1:1,000,000 and 1:4,000,000 in the general population (11), although depending strongly on the study population (12).

- Short QT syndrome (SQTS) is a channelopathy characterized by an abnormally short QT interval and increased risk of atrial and ventricular arrhythmias and sudden death. Clinical presentation is heterogeneous, since some patients may be asymptomatic and others may have episodes of syncope or fall victim to sudden cardiac death. It may occur at any age from early infancy to old age. The prevalence is estimated at 1:1000 to 5:1000. SQTS is sporadic or has autosomal dominant inheritance (13,14).
- Brugada syndrome (BrS) is a genetic heart disorder involving ion channel dysfunction associated with progressive age-related conduction abnormalities, more prevalent among males. It is estimated to be responsible for up to 20% of all sudden deaths in individuals with an apparently normal heart. BrS usually manifests with syncope or sudden cardiac death at a young age, in the absence of structural heart anomalies, and typically has autosomal dominant inheritance. Prevalence is estimated at 5:10,000 worldwide (15).
- Familial atrial fibrillation (FAF) is a heterogeneous genetic heart disorder characterized by erratic activation of the atria and irregular ventricular response. The heterogeneous clinical presentations of FAF include palpitations, dyspnea, chest pain, dizziness and syncope. FAF increases the risk of stroke and sudden death. The prevalence of FAF is approximately 1% in the general population. FAF is genetically heterogeneous with autosomal dominant or recessive inheritance (16).
- Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited heart disorder characterized by electrical instability during acute activation of the adrenergic nervous system, in a structurally normal heart. The ECG is normal but arrhythmia may occur during physi-

cal activity or emotional stress, causing syncope or even cardiac arrest unless the disease is recognized and treated. Prevalence is estimated at 1:10,000. CPVT has autosomal dominant and autosomal recessive inheritance (17).

- Wolff-Parkinson-White syndrome (WPW) is a heart disease characterized by arrhythmia due to one or more abnormal electrical pathways in the heart, known as accessory pathways, that allow electrical signals to bypass the atrioventricular node or may transmit electrical impulses abnormally in the reverse direction. WPW may present with palpitations, dyspnea, dizziness or even syncope. In rare cases it can lead to cardiac arrest and sudden death. WPW affects 1 to 3 in 1000 persons worldwide. It may be sporadic or familial. The familial form typically has autosomal dominant inheritance (18).

Table 1 summarizes the different genes associated with cardiac conduction defects

#### Cardiomyopathies

- Hypertrophic cardiomyopathy (HCM) is a common myocardial disease characterized by hypertrophy of the left ventricle with histological

features of cell hypertrophy, myofibril disarray and interstitial fibrosis. This condition can remain asymptomatic throughout life or manifest with variable symptoms. It is the most common cause of sudden cardiac death in young people. HCM affects an estimated 1 in 500 persons worldwide (45). It is most often caused by variations in genes essentially encoding sarcomeric, ion channel and metabolic regulatory proteins. Around 70% of all cases are found to be familial with dominant inheritance (46-48).

- Dilated cardiomyopathy (DCM) is characterized by dilation leading to systolic and diastolic dysfunction of the left and/or right ventricles, causing heart failure or arrhythmia. It is essentially an adult-onset disease, but has shown a highly variable age of onset. The prevalence of DCM has been estimated at 36.5 per 100,000. It has autosomal dominant inheritance in 85% of cases (49).
- Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic disease characterized by the death of ventricular myocytes and their replacement with fibrous and fatty tissue. It predisposes to ventricular tachycardia and sudden death in young individuals and athletes. The

**Table 1.** Genes associated with cardiac conduction defects

| Cardiac conduction defects                            | Mutant genes   | Reference  |
|---|--|------------|
| Long QT syndrome                                      | <i>KCNQ1, SCN5A, AKAP9, ANK2, CACNA1C, CALM1, CALM2, CAV3, KCNE1, KCNE2, KCNJ2, KCNJ5, SCN4B, SNTA1, KCNH2</i>   | (19)       |
| Short QT syndrome                                     | <i>KCNH2, KCNQ1, KCNJ2, CACNA1, CACNB2, CACNA2D1</i>   | (14,20,21) |
| Brugada syndrome                                      | <i>SCN5A, CACNA1C, CACNB2, GPD1L, KCND3, KCNE3, HCN4, SCN1B, SCN3B</i>   | (22)       |
| Familial atrial fibrillation                          | <i>KCNQ1, KCNE2, NPPA, KCNA5, KCNJ2, SCN5A, GJA5, ABCC9, SCN1B, SCN2B, SCN3B, SCN4B, MYL4, GATA4, GATA5, GATA6, PITX2, TBX5, NKX2-5, KCND3, KCNE1, KCNH2, LMNA, PRKAG2, RYR2, ZFHX3, SHOX2, PRRX1, KCNN3, NUP155</i> | (23-40)    |
| Catecholaminergic polymorphic ventricular tachycardia | <i>RYR2, CALM1, ANK2, KCNJ2, CASQ2, TRDN</i>   | (41-43)    |
| Wolff-Parkinson-White syndrome                        | PRKAG2   | (44)       |

symptoms (palpitations, shortness of breath, swelling of the legs and syncope) are not frequent in the early stages, but there is risk of sudden death during intense exercise. The estimated prevalence of ARVC is estimated at 1:1000. Most familial cases of ARVC have autosomal dominant inheritance, whereas autosomal recessive inheritance is rare (50).

- Left ventricular non-compaction (LVNC) is a rare condition characterized by prominent left ventricular trabeculae, a thin compacted layer and deep intertrabecular recesses continuous with the left ventricular cavity but separate from the epicardial coronary arteries. It is frequently diagnosed in children, being due to an arrest in cardiac development during embryogenesis (51). LVNC is estimated to affect 8 to 12 per million individuals per year. This genetically heterogeneous disorder has sporadic and familial forms (52). LVNC can have autosomal dominant, autosomal recessive, X-linked and mitochondrial inheritance (53,54).
- Restrictive cardiomyopathies (RCM) are the least common cardiomyopathies and are characterized by impaired diastolic function with

restrictive filling and reduced diastolic volume of one or both ventricles, preserved systolic function, and invariably normal or mildly increased wall thickness. The prevalence of RCM is unknown. RCM can be idiopathic, familial (autosomal dominant, autosomal recessive or X-linked), or secondary to systemic disorders (55).

Table 2 summarizes the different genes associated with hereditary cardiomyopathies.

#### *Familial hyperlipidemia*

Dyslipidemias are a heterogeneous group of disorders characterized by abnormal levels of circulating lipids and lipoproteins. A minority of forms of dyslipidemia are monogenic. These forms are familial diseases with a well-defined hereditary component.

- Familial hypercholesterolemia (FH) is the most frequent condition and is characterized by severely elevated LDL-C and by xanthomas (patches of yellowish cholesterol buildup) that occur around the eyelids and in the tendons of the elbows, hands, knees and feet. FH has a prevalence of 1:200-250. An estimated 70-95% of cases are caused by a pathogenic variant in the

**Table 2.** Genes associated with hereditary cardiomyopathies

| Cardiomyopathies                                | Mutant genes  | Reference      |
|---|---|----------------|
| Familial hypertrophic cardiomyopathy            | <i>MYH7, TNNT2, TPM1, MYBPC3, PRKAG2, TNNI3, MYL3, TTN, MYL2, ACTC1, CSRP3, TNNC1, MYH6, VCL, MYOZ2, PLN, NEXN, ACTN2, CAV3, JPH2, LDB3, MYPN, CALR3, FLNC, MYLK2, TCAP</i>   | (46,47)        |
| Dilated cardiomyopathy                          | <i>LMNA, MYH7, MYH6, SCN5A, ACTN2, DSG2, LDB3, TNNT2, RBM20, TTN, BAG3, DES, DSP, CRYAB, EYA4, LAMA4, MYPN, SGCD, CSRP3, ABCC9, PLN, ACTC1, TCAP, MYBPC3, NEXN, PRDM16, PSEN1, PSEN2, TPM1, VCL, RAF1, NKX2-5, ANKRD1, TMPO, ILK, TNNC1, TNNI3, GATAD1, FKTN, SDHA, DSP, DMD, TAZ</i> | (56-62)        |
| Arrhythmogenic right ventricular cardiomyopathy | <i>TGFB3, RYR2, TMEM43, DSP, PKP2, DSG2, JUP, CTNNA3, TTN, DES, LMNA, PLN, DSC2</i>   | (63-68)        |
| Left ventricular non-compaction                 | <i>MYBPC3, TPM1, PRDM16, MIB1, TNNT2, MYH7, ACTC1, LDB3, SOX6, LMNA, SCN5A, HCN4, DTNA, TAZ, PLEKHM2, PKP2</i>  | (53,54, 69-77) |
| Restrictive cardiomyopathy                      | <i>TNNT2, TNNI3, ACTC1, MYH7, MYBPC3, MYPN, TPM1, MYL1, MYL2, FLNC</i>  | (78-81)        |

genes *APOB*, *LDLR* and *PCSK9* inherited in an autosomal dominant manner (82).

- Primary hypertriglyceridemia arises from genetic defects in the metabolism or synthesis of triglycerides. It usually presents in adulthood, except for lipoprotein lipase deficiency that presents in childhood. Disorders in this category include familial chylomicronemia, severe hypertriglyceridemia, infantile hypertriglyceridemia and hyperlipoproteinemia type 3. The incidence of primary hypertriglyceridemia is approximately 2 per 10,000 persons. Common genetic variants found in *LPL*, *APOC2* and *LMF1* are associated with triglyceride levels in patients with primary hypertriglyceridemia. Except for rare severe mutations in *APOE*, monogenic hypertriglyceridemia is autosomal recessive (83).
- Familial HDL deficiency is a rare genetic condition that causes low levels of “good” cholesterol (HDL) in the blood, associated with cardiovascular risk. The prevalence of familial HDL deficiency is unknown. Familial HDL deficiency is inherited by autosomal dominant transmission of variations in the *ABCA1* and *APOA1* genes (84).

#### *Arterial hypertension*

Hypertension is a long-term condition in which arterial blood pressure is persistently elevated. High blood pressure usually does not cause symptoms. About 30% of cases of arterial hypertension are caused by a variation in a single gene. Three mechanisms are recognized to explain the pathophysiology of monogenic hypertension:

- increased sodium reabsorption leading to plasma volume expansion;
- excessive aldosterone synthesis;
- deficiencies of enzymes regulating adrenal steroid hormone synthesis and deactivation (85).

Arterial hypertension is an important risk factor for cardiovascular events including stroke, coronary artery disease, heart failure and atrial fibrillation. The monogenic forms are characterized by early-onset hypertension. Known genetic factors explain only 3% of blood pressure variability (85,86,87).

#### *Coronary artery disease*

Coronary artery disease (CAD) is the major cause of death and disability among all cardiovascular diseases. It comprises a wide variety of clinical entities that include asymptomatic subclinical atherosclerosis and its clinical complications, such as angina pectoris, myocardial infarction and sudden cardiac death. The long-recognized familial clustering of CAD suggests that genetic factors play important roles: the heritability of CAD and myocardial infarction are estimated at 50-60%. Based on their apparent patterns of inheritance, genetic diseases are classified in two broad categories: monogenic and polygenic. In monogenic forms, familial variation in one gene is responsible for all or most of the disease incidence. Monogenic coronary artery diseases (MCAD) include genes and mutations that are considered to be causal of CAD. Most are involved in lipid metabolism, while others are involved in inflammation, cell proliferation and vascular remodeling. The age of onset of clinical symptoms is variable, however MCAD is associated with early onset of symptoms with respect to multifactorial atherosclerosis (88,89).

#### **Oligogenic/polygenic forms**

Oligogenic/polygenic forms of CVDs are genetic disorders caused by the combined action of more than one gene.

#### *Hyperlipidemia*

In developed countries, most dyslipidemias are hyperlipidemias, i.e. an elevation of lipids in the blood. The etiology of dyslipidemias is primarily polygenic, being determined by interaction of many susceptibility genes with environmental factors. Polygenic dyslipidemias combine underlying genetic predispositions with disease states such as diabetes, thyroid disease or drug-related changes in lipid metabolism. High levels of cholesterol in the blood are one of the most widespread cardiovascular risk factors in the human population (90,91).



### *Arterial hypertension*

Arterial hypertension is a significant public health problem and is principally considered a multifactorial disorder. Controlling blood pressure is a complex process and besides environmental factors, many genes presumably collaborate to influence it. About 22% of the world population has hypertension. Long-term high blood pressure is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral vascular disease, vision loss, chronic kidney disease and dementia (92).

### *Coronary artery disease*

A group of gene variants are responsible for the intricate patterns of inheritance of polygenic coronary artery diseases. Their interplay with each other often has little effect, whereas their interplay with a number of environmental factors may determine outcome. These genetic factors are independent of traditional risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, obesity, plasma homocysteine, low physical activity and smoking, but may contribute directly or through traditional risk factors to the development and manifestation of coronary artery disease (93).

### *Thrombophilia*

Thrombophilia (also known as hypercoagulable state) is a coagulation disorder that predispose to clot formation (thrombus). Normal blood hemostasis is guaranteed by a balance between prothrombotic and antithrombotic processes, mediated by cell components, soluble plasma proteins and endothelium-derived factors. Genetic alterations that impair the production, activity, bioavailability and metabolism of specific factors can modify physiological balance in favor of thrombosis and predispose to thromboembolic events. Thrombophilia is caused by inherited or acquired conditions. Primary disorders or genetic causes of thrombophilia include factor V Leiden mutation, deficiency of antithrombin III, protein C and S deficiency, histidine-rich glycoprotein deficiency and prothrombin-related thrombophilia, while secondary

disorders include heparin-induced thrombocytopenia, antiphospholipid antibody syndrome, neoplasia, oral contraceptive use, obesity, smoking and surgery (94).

### **Genetic testing for monogenic and polygenic cardiovascular diseases**

The characterization of genes associated with CVDs improves prevention, treatment and quality of care. Linkage studies and genome-wide linkage analysis are useful for identifying genes related to CVDs and pinpointing new causative genes may indicate targets for molecular diagnosis and therapeutic intervention (95). The distinction between monogenic and polygenic forms is important for cardiovascular risk assessment, counseling and treatment of patients.

Monogenic conditions are generally associated with higher cardiovascular risk. Early implementation of pharmacological treatment is therefore necessary to control risk (96). Genetic testing for monogenic forms has a fundamental role in identifying the molecular causes of cardiovascular diseases and in aiding prevention and treatment, also being crucial for early detection of potentially lethal cardiovascular events. The possibility of giving physicians a tool for predicting individual sensitivity or resistance to a specific pharmacological treatment (97) makes it possible to prescribe the best drug and the best dosage for each patient. This strategy is part of the complex perspective of personalized medicine (98,99).

Polygenic forms associated with most risk factors are of clinical interest due to their high frequency in the general population. Genetics is useful to define the susceptibility of single patients, although the contribution of each genetic variant to overall risk of onset is low. At present, the most important application of genetic testing for polygenic forms of CVDs is related to the possibility of predicting the effect of a specific therapy, mainly in the initial phases of treatment (99). Next generation sequencing (NGS), a rapid and cost-effective method for identifying mutations in genes associated with multigenic disorders, has revolutionized genetic testing in CVDs. Because CVDs are genetically heterogeneous, genetic testing can be performed with NGS and multigene panels targeted

at a specific phenotype, or including a broader array of genes associated with different diseases that may share overlapping features. Meta-analysis studies to identify predisposing genetic variants, enrolling thousands of CVDs patients, have led to the identification of certain gene variants having a modest contribution when taken individually but which are involved in the pathogenesis of CVDs in synergy with other variants and with environmental risk factors. Compared to the study of single genes, this approach makes it possible to more precisely predict the risk of developing CVDs (95,100).

Genetic testing should be offered to index patients who fulfill diagnostic criteria for CVDs; a comprehensive clinical evaluation should precede genetic testing, which should be performed in certified laboratories and combined with genetic counseling by trained healthcare professionals. Pre-test and post-test genetic counseling are important steps in the genetic testing process. Pre-test counseling provides the information necessary for proper informed consent, including description of the genetic test, its yield, benefits and limitations, and implications for family members, as well as the possibility of reclassifying the disease.

The results of genetic testing can be complex. Although a result may be classified as positive, negative or inconclusive, its clinical significance depends on the patient's personal and family history (95). The goals of family assessments of phenotype and genotype are to identify individuals with hitherto unrecognized disease and currently healthy family members at risk of developing disease, in the latter case through longitudinal follow-up. Phenotypic evaluation starts with first-degree relatives of affected individuals and is repeated periodically because penetrance for some conditions may be delayed and diagnostic features may not manifest until adulthood. If a pathogenic variant has been identified in the family, predictive genetic testing can be done to determine which relatives have inherited the variant. Relatives confirmed to carry the family variant should undergo serial phenotypic evaluation and be informed of the risk of transmission to offspring. A definitive diagnosis and familial disease increase the probability of positive genetic test results, but the absence of a family history of disease does not preclude genetic testing. Genetic forms of cardiovas-

cular disease may occur without affected relatives, due to recessive inheritance, *de novo* mutations or reduced penetrance (101). Clinicians and patients should have accurate and realistic expectations about the yield of genetic testing and its role in management. The ethical, legal and social concerns of genetic testing must also be considered. Various guidelines on appropriate use of genetic testing have been published (102).

### Pharmacogenetics and cardiovascular diseases

Pharmacogenetics is the search for genetic variations that affect responses to drug therapy and toxicity. Drug response is determined by physiological mechanisms (age, sex, nutritional status), pathological mechanisms (renal and liver function, comorbidities), environmental factors and above all individual genetic profile. Pharmacogenetic testing reveals variations in drug metabolism genes encoding metabolic enzymes that may be more or less efficient and which are defined as rapid or poor metabolizers, respectively (Table 3). Identifying how a patient metabolizes a medication enables personalized treatment, which besides being safer for the patient, decreases medical costs and improves clinical outcomes. The test can be performed prior to prescription, in order to guide medical selection and dosing, or can be performed after initial treatment that has proved inefficient (100,101).

Pharmacogenetics has many possible applications in the drug therapy of CVDs. Many studies have found associations between genetic variations and responses to cardiovascular drugs. Some of these relationships have been demonstrated in large patient populations, such as patients with ischemic heart disease receiving statins (102). Once the genetic variations that best determine the response to a particular drug are known and tests to rapidly identify these variations are available, individual patients may be screened for genetic variations before drug therapy is begun and the information used to choose agents with the greatest potential for efficacy and the least toxicity (102).

Pharmacogenomics, on the other hand, is a new field arising from the development of NGS technologies. It deals with the correlation between genetic profile and response to a drug for the purpose of devel-

**Table 3.** Genes associated with response to cardiovascular drugs

| Gene (OMIM ID)   | Metabolic role   | Drug  | Main therapeutic effect   | Reference |
|--|--|---|---|-----------|
| <i>PTGS1</i> (176805);   | PTGS1: prostaglandin biosynthesis - <i>ITGB3</i> : fibrinogen receptor   | Aspirin   | Platelet aggregation inhibitor  | (103,104) |
| <i>ITGB3</i> (173470)<br><i>CYP2C19</i> (124020);<br><i>P2RY12</i> (600515);<br><i>ITGB3</i> | CYP2C19: drug metabolism;<br>P2RY12: regulation of platelet shape and aggregation  | Clopidogrel                                     | Platelet aggregation inhibitor  | (105-107) |
| <i>CYP2C9</i> (601130)   | Drug metabolism  | Nonsteroidal anti-inflammatory drugs            | Platelet aggregation inhibitor  | (108)     |
| <i>CYP2C9</i> ; <i>VKORC1</i> (608547)   | VKORC1: vitamin K pathway  | Cumarin, warfarin, phenprocoumon, acenocoumarol | Anticoagulant   | (109)     |
| <i>CES1</i> (114835)   | Hydrolysis of compounds containing amides or esters  | Dabigatran                                      | Anticoagulant   | (110)     |
| <i>SLCO1B1</i> (604843)  | Eicosanoids, thyroid hormones, steroid transporters  | Statin  | Reduction of blood cholesterol (HMG-CoA reductase inhibitor)                        | (110)     |
| <i>LPL</i> (609708)  | Triglyceride hydrolysis, lipoprotein uptake  | Lovastatin                                      | Reduction of blood cholesterol (HMG-CoA reductase inhibitor)                        | (111)     |
| <i>HMGCR</i> (142910)  | Cholesterol biosynthesis   | Pravastatin                                     | Reduction of blood cholesterol (HMG-CoA reductase inhibitor)                        | (111)     |
| <i>CYP7A1</i> (118455);<br><i>ABCB1</i> (171050);<br><i>CETP</i> (118470)                    | CYP7A1: cholesterol catabolism<br>- <i>ABCB1</i> : drug-transport pump<br>- <i>CETP</i> : uptake of cholesterol by hepatocytes | Atorvastatin                                    | Reduction of blood cholesterol (HMG-CoA reductase inhibitor)                        | (112-114) |
| <i>LDLR</i> (606945);<br><i>SREBF1</i> (184756)  | LDLR: low density lipoprotein receptor - <i>SREBF1</i> : sterol biosynthesis.  | Fluvastatin                                     | Reduction of blood cholesterol (HMG-CoA reductase inhibitor)                        | (115,116) |
| <i>LDLR</i> (606945)   | Low density lipoprotein receptor   | Lomitapide                                      | Reduction of blood cholesterol (microsomal triglyceride transfer protein inhibitor) | (115)     |
| <i>ABCB1</i>   | Drug-transport pump  | Digoxin   | Inhibition of the Na <sup>+</sup> /K <sup>+</sup> ATPase in the myocardium          | (117)     |
| <i>ADRB1</i> (109630)  | Adrenergic receptor beta-1   | Atenolol, metoprolol, carvedilol                | Adrenoceptor beta inhibitor   | (118,119) |
| <i>ACE</i> (106180)  | Blood pressure control   | Enalapril, perindopril, imidapril, capropril    | Angiotensin-converting-enzyme inhibitor   | (120)     |
| <i>CYP2C9</i>  | Drug metabolism  | Losartan  | Angiotensin II receptor type 1 antagonist   | (120)     |



oping new drugs. Many government research groups have taken an active role in promoting pharmacogenomic research and clinical implementation. One noteworthy example is the NIH-funded Pharmacogenomics Research Network (PGRN), which focuses on understanding genetic determinants of response to various medications, including medications used to treat cardiac arrhythmias. Drug gene panels are commercially available or may be custom built for this type of approach (103).

#### *Genes involved in drug response*

Most variations in the genes in Table 3 are single nucleotide polymorphisms (SNPs). Genetic screening of the coding sequence of *PTGS1* in 92 healthy individuals revealed five variants that conferred decreased metabolic basal activity to *PTGS1 in vitro* (121). Heterozygous variants in the genes *CYP2C9* (OMIM disease 122700), *VKORC1* (OMIM disease 122700) and *CYP2A6* (OMIM disease 122700) cause variable drug responses transmitted by autosomal dominant inheritance. Homozygous and/or compound heterozygous mutations in the genes *CYP2C19* (OMIM disease 609535) and *ADRB1* cause variable drug responses transmitted by autosomal recessive inheritance.

#### **Times and costs of genetic testing**

The rapid expansion of genetic testing has reduced costs and increased utilization. The costs for genetic testing include genetic counseling, biotechnologists' labor time, laboratory supplies, equipment, and data interpretation and reporting. The standard protocol for molecular diagnosis of CVDs includes DNA extraction from biological samples (peripheral blood or saliva) and analysis of genetic regions of interest through automatic sequencing or polymerase chain reaction amplification with specific primers followed by enzyme digestion of the amplification. The time required to perform the analysis varies with the number of genes screened, the length of the sequence and the number of mutations analyzed. Thus costs vary, although in recent years, genetic tests have be-

come faster and cheaper, thanks to new developments. NGS is a rapid cost-effective tool for identifying mutations in genes associated with CVDs. It enables the optimization of times and costs in specialized genetic laboratories (92,104).

#### **Conclusions**

Genetic testing in cardiology has become an important tool for studying and understanding the etiology, pathogenesis and development of CVDs and is beginning to change clinical practice. Advances in DNA sequencing methodology have made gene-based diagnosis increasingly feasible in routine clinical practice, while maintaining clinical accuracy. There is much evidence that molecular genetics and pharmacogenetics are playing an increasingly important role in the correct clinical management of heart patients. Knowledge of these methods should not be limited to a closed group of researchers, but should be disseminated to clinical cardiologists in contact with patients who can actually benefit from genetic diagnostics. In the near future we can expect a great increment in information and tests regarding genetic diagnosis, which will be acknowledged as a true branch of cardiology, on a par with hemodynamics and electrophysiology. Third millennium cardiologists should therefore become familiar with the diagnostic and therapeutic opportunities offered by genetic testing and be prepared for the great leap forward it will bring. The genetic test is particularly important in conditions that can lead to sudden death (e.g. long QT syndrome, Brugada syndrome, arrhythmogenic cardiomyopathies). Next generation sequencing makes it possible to analyze all the causative genes in a single experiment and can become the basis for prescribing preventive devices, such as the pacemaker.

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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