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Editorial

The era of clinical application of gene diagnosis in cardiovascular diseases is coming

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Abstract

Gene diagnosis refers to the use of genetic testing in the diagnosis of inheritable conditions, which has gradually been applied in clinical practice with the completion of the gene sequencing efforts of the Human Genome Project and the advancement of gene detection technology. In the specialty field of cardiology, monogenic cardiovascular diseases are defined as monogenic inherited diseases with cardiovascular damage as the only phenotype, or accompanied by cardiovascular damage. Although the incidence of such diseases is relatively low, in the country of China with its vast population of 1.33 billion, the sheer volume of patients with monogenic cardiovascular diseases is alarming. With early onset, severe symptoms, and poor prognosis, delays in diagnosis and treatment of monogenic cardiovascular diseases often have serious consequences. Gene testing is perfectly suited for early diagnosis of monogenic cardiovascular diseases, especially for "pre-symptomatic" diagnosis. In this article, we generally review the characteristics of common monogenic cardiovascular diseases, summarize the progress of the standardized application of gene testing technology in clinical practice, describe the applicable population and condition of genetic testing for different monogenic cardiovascular diseases, analyze the practicality of genetic diagnosis of these inheritable conditions, and provide guidance on identifying suitable candidates for gene diagnosis. In conclusion, gene diagnosis provides new insights into the way physicians diagnose diseases, and is well-positioned to guide clinical decision making and treatment, especially in cardiology.

Keywords: Cardiovascular diseases; Precision medicine; Gene testing; Early diagnosis; Cardiovascular diagnostic techniques

In monogenic inheritance, individual traits are controlled by a pair of alleles and are transmitted according to Mendel's laws of inheritance. Monogenic cardiovascular diseases refer to monogenic inherited diseases with cardiovascular damage as the only phenotype, or accompanied by cardiovascular damage. There are more than 100 kinds of monogenic cardiovascular disease.[1]

Clinically, the most common monogenic cardiovascular diseases include cardiomyopathy (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, metabolic cardiomyopathy), cardiac ion channel diseases (long QT

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syndrome, short QT syndrome, Brugada syndrome, catecholamine-sensitive polymorphic ventricular tachycardia, inherited sick sinus syndrome, progressive cardiac conduction diseases), monogenic inherited hypertension (Liddle syndrome, Gordon syndrome, apparent mineralocorticoid excess, systemic glucocorticoid resistance, congenital adrenal hyperplasia, familial hyperaldosteronism, pheochromocytoma), inherited aortic diseases (Marfan syndrome and other syndromes with similar phenotypes, familial thoracic aortic aneurysm and dissection, Ehlers-Danlos syndrome), pulmonary hypertension, inherited thrombophilia, familial hypercholesterolemia, and more than 20 other diseases (Table 1). Although the incidence of most monogenic cardiovascular diseases is not high, with a huge population of 1.33 billion, China has nearly 7 million people with familial hyperlipidemia, nearly 700,000 people with monogenic hypertension, and about 1 million people with hypertrophic cardiomyopathy.[2] It is estimated that at least 10 million people may have at least one of the more than 100 monogenic cardiovascular diseases.[1] In addition, monogenic cardiovascular diseases generally have early onset, severe symptoms, and poor prognosis. They are the main cause of sudden cardiac death and heart transplantation in adolescents, and have high mortality and disability rates.[3] Therefore, the impact on patients and the health burden imposed by monogenic cardiovascular diseases should not be underestimated.

Previously, monogenic cardiovascular diseases could only be diagnosed by traditional clinical testing methods, such as blood testing for biochemical markers, electrocardiogram monitoring, imaging, or pathological testing. There is no doubt that these clinical methods play an irreplaceable role in the diagnosis and treatment of diseases, but they are all "post-symptomatic" testing methods. In other words, only after the patient demonstrates the corresponding clinical phenotype will they reveal positive results on such tests, leading in delayed diagnosis and treatment of the disease. This is especially tragic for patients whose first clinical manifestation is sudden death, which can occur with hypertrophic cardiomyopathy, cardiac ion channel diseases, etc. With the completion of the gene sequencing efforts of the Human Genome Project and the advancement of gene detection technology, the medical model of precision medicine has gradually been applied to clinical practice. The above monogenic cardiovascular diseases have been cloned into specific pathogenic genes (Table 1). Most instances of hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, genetic sick sinus syndrome, Liddle syndrome, Gordon syndrome, Marfan syndrome, Ehlers-Danlos syndrome, inherited or idiopathic pulmonary hypertension, inherited thrombophilia, and familial hypercholesterolemia can be screened for pathogenic mutations through gene sequencing. Therefore, gene diagnosis is now the earliest method for identifying monogenic cardiovascular diseases. The genetic information of these diseases is innate, and genetic diagnosis has the huge advantage of "pre-symptomatic" diagnosis. Therefore, an increasing number of clinicians are finding value in these tests in clinical settings, and are gradually recommending these tests by related disease guidelines or consensuses (Table 2). Additionally, to make the application of gene testing technology more rational and convenient in clinical practice, the Chinese Society of Cardiology (CSC) and the China International Exchange and Promotive Association for Medical and Health Care (CPAM) have compiled the first guideline for the genetic diagnosis of monogenic cardiovascular diseases.[1]

The applicable population for genetic testing for monogenic cardiovascular diseases and guidelines for testing are as follows: 1. Patients diagnosed with monogenic cardiovascular disease with clinical evidence. 2. Patients suspected for monogenic cardiovascular disease with clinical evidence. 3. Patients found to have pathogenic gene mutation. It is important that the same gene mutation be detected by Sanger sequencing in the lineal relatives within the family of the patient. If the pathogenic gene mutation is not linked to the disease in the family, next-generation sequencing is recommended, such as targeted gene sequencing and full exome sequencing, to re-screen the gene of the unlinked patients and detect the existence of other pathogenic gene mutations. 4. When the proband is found to carry genetic variants of unknown significance. The pathogenicity of the mutation should be clarified by family screening. 5. When the proband is not found to carry a mutation in the pathogenic gene, genetic testing is not recommended for members of the family (whether or not they are sick).[1]

The following are the recommended clinical applications of gene detection for monogenic cardiovascular diseases: 1. If a patient is found to have a mutation in the pathogenic gene combined with corresponding clinical phenotype, testing can help make a definite diagnosis and differential diagnosis. 2. Genetic pathogenicity cannot be completely excluded if no pathogenic gene mutation was detected in the proband. 3. The genetic screening of the family where evidence of pathogenic

Table 1
Pathogenic gene spectrum of clinically common monogenic cardiovascular diseases.[1]

Monogenic cardiovascular diseases	Prevalence rate	Evidence-based pathogenic genes	Mutation ratio
Cardiomyopathy			
Hypertrophic cardiomyopathy	80/100,000	*MYH7, MYBPC3, TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC1, PLN, FLNC, GLA, LAMP2, PRKAG2, TTR, GAA*	60%−70%
Arrhythmogenic right ventricular cardiomyopathy	20−50/100,000	*PKP2, DSP, DSG2, DSC2, JUP, TMEM43*	60%
Familial dilated cardiomyopathy	19−36.5/100,000	*MYH7, MYBPC3, TNNT2, DSP, TTN, LMNA, MYH6, MYPN, RBM20, SCN5A, ANKRD1, RAF1, DES, DMD*	40%
Metabolic cardiomyopathy			−
Glycogen storage diseases	25/100,000	*GYS1, GAA, LAMP2, AGL, GBE1, PHKA1, PHKA2, PHKB, PHKG2, PRKAG2*	−
Fatty acid oxidative metabolic diseases	−	*SLC22A5, CPT1A, SLC25A20, CPT2, VLCAD, HADHA, ACADM, ETFA, ETFB, ETFDH*	−
Mucopolysaccharide storage diseases	−	*IDUA, IDS, SGSH, NAGLU, HGSNAT, GNS, GALNS, ARSB, GUSB*	−
Lysosomal storage diseases	−	*GBA, GLA, GLB1, HEXB, GNPTAB, GNPTAB, GNPTG*	−
Mitochondrial diseases	−	*SURF1, mtDNAb, mtDNAb, mtDNAb, mtDNAb, TAZ, AGK*	−
Organic acid and peroxide metabolic diseases	−	*FAH, AGXT, GRHPR, HOGA1, PCCA, PCCB, MLYCD, PHYH*	−
Cardiac ion channel diseases			
Long QT syndrome	50/100,000	*KCNQ1, KCNH2, SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, CALM1, CALM2*	>75%
Short QT syndrome	−	*KCNH2*	20%
Brugada syndrome	50/100,000	*SCN5A*	10%−15%
Catecholaminergic polymorphic Ventricular tachycardia	10/100,000	*RYR2, CASQ2*	60%−70%
Genetic sick sinus syndrome	−	*SCN5A, HCN4, MYH6, GNB2*	100%
Progressive cardiac conduction diseases	−	*SCN5A, SCN1B, TRPM4, LMNA, NKX2-5, DES*	50%
Monogenic inherited hypertension			
Liddle syndrome	−	*SCNN1B, SCNN1G*	≈100%
Gordon syndrome	−	*WNK4, WNK1, KLHL3, CUL3*	89%
Apparent mineralocorticoid excess	−	*HSD11B2*	−
Systemic glucocorticoid resistance	−	*NR3C1*	−
Congenital adrenal hyperplasia	−	*CYP11B1, CYP17A1*	−
Familial hyperaldosteronism	−	*CYP11B2/CYP11B1, CLCN2, KCNJ5, CACNA1H*	−
Pheochromocytoma/paraganglioma	−	*VHL, RET, NF1, SDHB, SDHC, SDHD, MAX, TMEM127, EPAS1, SDHA, FH, SDHAF2*	40%−55%
Inherited aortic diseases			
Marfan syndrome	6.5−20.0/100,000	*FBN1, TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, SKI*	70%−93%
Thoracic aortic aneurysm and dissection	−	*ACTA2, FBN1, MYH11, MYLK, SMAD3, TGFBR1, TGFBR2, PRKG1, LOX, COL3A1, TGFB2, TGFB3*	20%−25%
Ehlers-Danlos syndrome	−	*COL3A1*	90%
Pulmonary arterial hypertension	1.5−2.0/100,000	*BMPR2, BMPR1B, CAV1, KCNK3, SMAD9, ACVRL1, ENG, EIF2AK4*	>90%
Inherited thrombophilia	400/100,000	*PROS1, SERPINC1, FVL* mutation in *F5 gene, PT20210A* mutation in *F2 gene*	70%−80%
Familial hypercholesterolemia	410−500/100,000	*LDLR, APOB, PCSK9, LDLRAP1*	92%−95%

−, Unknown.

Table 2
Monogenic cardiovascular diseases that have been suggested by relevant guidelines, consensus, or recommendations for genetic testing.

Monogenic cardiovascular diseases	Guideline/Consensus
Hypertrophic cardiomyopathy	1. Genetic evaluation of cardiomyopathy-a Heart Failure Society of America practice guideline[4] 2. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy[5] 3. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy[6] 4. 2017 Guidelines for the diagnosis and treatment for Chinese adult patients with hypertrophic cardiomyopathy[7] 5. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[8]
Arrhythmogenic right ventricular cardiomyopathy	1. Genetic evaluation of cardiomyopathy-a Heart Failure Society of America practice guideline[4] 2. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[8]
Familial dilated cardiomyopathy	1. Genetic evaluation of cardiomyopathy-a Heart Failure Society of America practice guideline[4]
Cardiac ion channel diseases	1. Chinese expert consensus on diagnosis and treatment of inherited primary arrhythmia syndrome 2015[9] 2. China expert consensus statement on genetic testing for cardiac channelopathies and cardiomyopathies[10] 3. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies[11] 4. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 10: the cardiac channelopathies: a scientific statement from AHA/ACC[12] 5. International recommendations for electrocardiographic interpretation in athletes[13] 6. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[8]
Monogenic inherited hypertension	1. 2018 ESC/ESH Guidelines for the management of arterial hypertension[14] 2. Consensus Statement on next generation-sequencing-based diagnostic testing of hereditary pheochromocytomas and paraganglioma[15] 3. Expert consensus on diagnosis and treatment of pheochromocytoma and paraganglioma[16]
Inherited aortic diseases	1. Editor's Choice - Management of descending thoracic aorta diseases: clinical practice guidelines of ESVS[17]
Pulmonary hypertension	1. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension[18] 2. Guidelines on the diagnosis and treatment of pulmonary hypertension in China 2018[19] 3. Guidelines on the diagnosis and treatment of pulmonary hypertension: summary of recommendations[20]
Familial hypercholesterolemia	1. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of EAS[21] 2. 2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk[22]

ACC: the American College of Cardiology; ACCF: the American College of Cardiology Foundation; AHA: the American Heart Association; EAS: European Atherosclerosis Society; EHRA: the European Heart Rhythm Association; ERS: the European Respiratory Society; ESC: the European Society of Cardiology; ESH: the European Society of Hypertension; ESVS: the European Society for Vascular Surgery; HRS: the Heart Rhythm Society.

Table 3
Genotypic value of monogenic cardiovascular diseases.[1]

Monogenic cardiovascular diseases	Genotype-phenotype relationship
Hypertrophic cardiomyopathy	Carrying ≥2 sarcomere disease-causing mutations increases the risk of cardiovascular death in patients.
Arrhythmogenic right ventricular cardiomyopathy	Patients with a gene mutation have worse prognosis than those without gene mutations; patients with ≥2 gene mutations are prone to develop ventricular tachycardia/ventricular fibrillation and a high proportion of left ventricular dysfunction, heart failure, and heart transplantation. Adult males and females over 30 years old with the *TMEM43* gene *P. S358L* mutation implanted with an ICD as a primary prevention can have increased survival rates.
Familial dilated cardiomyopathy	Patients with specific pathogenic genes have poor prognosis, and genetic testing is helpful for risk stratification. Patients with *LMNA* or *DES* gene mutations and cardiac conduction abnormalities (1−3 atrioventricular block) and/or a family history of sudden death are at higher risk of SCD. The *DMD* gene mutation may be associated with muscular dystrophy.
Metabolic cardiomyopathy	Due to extracardiac involvement, attention should be paid to the detection of related genes in patients with unexplained myocardial lesions with multi-system involvement, and infants or adolescents with onset of myocardial lesions.
Long QT syndrome	Patients with ≥2 disease-causing gene mutations or patients with congenital deafness with Jervell-Lange-Nielsen syndrome are at high risk of SCD, and preventive ICD implantation should be actively considered. LQTS1 patients should avoid strenuous exercise, especially swimming; LQTS2 patients should avoid sudden loud sounds (such as alarms, telephones, etc.). Patients with LQTS1 who have not been treated with beta blockers and have suffered cardiac arrest should first consider beta blocker oral therapy or left sympathetic neurotomy, rather than ICD implantation, unless the patient develops early onset.
Short QT syndrome	Quinidine shall be considered in patients diagnosed with SQTS1 by genetic testing. Sotalol should be used in patients with SQTS other than SQTS1.
Catecholaminergic polymorphic ventricular tachycardia	Patients with the *RYR2* gene mutation have earlier onset and worse prognosis. Flecainide can effectively reduce the occurrence of ventricular arrhythmia in *RYR2* gene mutation carriers.
Progressive cardiac conduction disease	Implantation of ICD may be useful in patients with pathogenic *LMNA* gene mutations and other clinical risk factors, such as paroxysmal ventricular tachycardia, male gender, and non-missense mutations, and especially patients with left ventricular ejection fraction <45%.
Familial hyperaldosteronism	Patients with FHA I fusion of *CYP11B2/CYP11B1* are recommended to be treated with physiological doses of glucocorticoid.
Marfan syndrome	Personalized treatment can be prescribed based on genotypes and phenotypes, such as surgery in advance (e.g., when the maximum internal diameter of the thoracic aorta reaches 4.0−5.0 cm) to prevent dissection and rupture. For LDS patients with *TGFBR1* and *TGFBR2* pathogenic gene mutations, surgery can be considered with a maximum internal diameter of 4.2 cm in the thoracic aorta. Patients with LDS have a higher risk of developing aneurysms in locations other than aorta, and should be observed and monitored closely.
Thoracic aortic aneurysm and dissection	Personalized treatment can be prescribed based on genotypes and phenotypes, such as surgery in advance (e.g., when the maximum internal diameter of the thoracic aorta reaches 4.0−5.0 cm) to prevent dissection and rupture. For carriers of mutations in the pathogenic genes of *TGFBR1* and *TGFBR2*, surgery can be considered with a maximum internal diameter of 4.2 cm in the thoracic aorta. For patients with *ACTA2* gene mutations, surgery can be considered with a maximum internal diameter of 4.5 cm in the thoracic aorta. Patients with *ACTA2* gene mutation have a higher risk of early stroke and coronary artery disease, and should be observed and monitored closely.

(*continued on next page*)

Table 3 (*continued*)

Monogenic cardiovascular diseases	Genotype-phenotype relationship
Ehlers-Danlos syndrome	Carriers of *COL3A1* gene mutations are recommended to undergo surgery in advance (e.g., when the maximum internal diameter of the thoracic aorta reaches 4.0−5.0 cm) to avoid aortic rupture. Female patients have a higher risk of uterine rupture during pregnancy, and should be observed and monitored closely.
Pulmonary hypertension	Patients with *BMPR2* mutations have worse clinical phenotypes and a worse prognosis.

ICD: implantable cardioverter-defibrillator; SCD: sudden cardiac death; LQTS: long QT syndrome; SQTS: short QT syndrome; FHA: Familial hyperaldosteronism; LDS: Loeys-Dietz syndrome.

gene mutations is first found will help to find new patients and carriers of pathogenic gene mutations. In uninfected gene mutation carriers, clinical follow-up and appropriate intervention should be carried out. The risk of the disease can be practically eliminated in the members without pathogenic gene mutation, and targeted clinical follow-up and intervention are not recommended. 4. Patients who carry a specific pathogenic gene mutation can, if they wish and if it is ethical, have offspring that do not carry the pathogenic gene mutation through selective reproduction.[1]

The availability of genetic testing for definitive diagnosis and differential diagnosis of monogenic cardiovascular diseases is known, but evidence for risk stratification of these diseases is inconsistent because there have been many contradictions in the reporting of the genotype-phenotype relationships in monogenic cardiovascular diseases. This is the main bottleneck restricting adoption of gene diagnosis. The reasons for genotype-phenotype heterogeneity of monogenic cardiovascular diseases are mainly related to the following aspects: 1. The genome alone is not sufficient to explain the disease. It also needs to be interpreted with respect to genetic modification (epigenome), gene transcription (transcriptome), protein expression (proteome), and protein function metabolism (metabolome). 2. Drawbacks in some of the previous studies, especially in the identification of the pathogenicity of mutations. For hypertrophic cardiomyopathy patients, 6.5% of mutations previously known as “pathogenic” are actually false positives after the redefinition of some of the data within the Exome Aggregation Consortium (ExAC) database.[23] 3. Other influencing factors such as biomarkers, single nucleotide polymorphisms, gender, environmental factors, and combined diseases affect the manifestation of disease. However, the mutant genotypes of some monogenic cardiovascular diseases have value in phenotypic prediction or risk stratification, which have been recommended by guidelines (Table 3). These materials have important reference value in clinical practice. With improvements in the quality and quantity of genetic and clinical data, the study of genotype-phenotype relationships will become increasingly accurate, and the major obstacles to the adoption of genetic diagnosis will be eliminated.

In summary, genetic testing for monogenic cardiovascular diseases can be maturely applied in clinical practice. Currently, it is mainly used for the definitive diagnosis and differential diagnosis of diseases. There is also value for risk stratification for some genotypes, which can be effectively used to guide clinical treatment.

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Conflicts of interest

None.

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