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Genetics and clinics: current applications, limitations, and future developments

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Summary

Genetic cardiovascular (CV) diseases encompass major groups of Mendelian (>90%) and non-Mendelian, (matrilinear) familial (*F*) disorders including cardiomyopathies (CMP), aneurysmal diseases, ventricular and supraventricular arrhythmogenic disorders, and pulmonary hypertension (PH). In *F-cardiomyopathies* (F-CMP), a pathologic mutation provides specific vs. phenotype-based descriptive diagnosis, early, pre-clinical diagnosis in families. Subsets of dilated cardiomyopathies (DCM) (e.g. cardiolaminopathies) include genotype in indications for primary prevention of sudden cardiac death (SCD). Pathologic mutations are one of the major diagnostic criteria for arrhythmogenic CMP. For *F-aneurysms*, syndromic and non-syndromic, genetics plays a diagnostic role. Syndromes are recognized on phenotypes, while non-syndromic aneurysms are diagnosed on imaging and genetic testing. Risk of events varies, according to the genetic cause. In *F-Arrhythmogenic disorders*, genetics offers diagnostic, therapeutic, and prognostic benefits, in particular Long QT Syndrome (LQTS), Short QT Syndrome (SQTS), Brugada Syndrome (BS), and Catecholaminergic Polymorfic Ventricular Tachycardia (CPVT); medications may vary according to genotypes. F-atrial arrhythmias, typically atrial fibrillation (AF), are still poorly investigated. F-pulmonary hypertension may have genetic basis (Groups I and V, last classification). Early diagnosis is mandatory given the new available drugs that influence the natural history of the disease. In the future, clinical family screening, genetic counselling, and testing should become systematic; treatments are going to be driven by genetic cause.

Genetic cardiovascular diseases

The majority of genetic CV diseases are single gene disorders characterized by either syndromic presentation or exclusive involvement of the heart (i.e. CMP) or vessels (i.e. heritable aortopathies). Their overall burden is difficult to establish: some diseases are common [i.e. hypertrophic cardiomyopathy (HCM)], while others are extremely rare [restrictive cardiomyopathy (RCM), arterial tortuosity syndrome (ATS), etc.). Most of them demonstrate clinical and genetic heterogeneity. The inheritance is autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL) either dominant (rare) or recessive (more common).[1] Most of these diseases are transmitted in AD mode (up to 80% of cases): CMPs,[2] aneurysmal diseases, both syndromic [e.g. Marfan syndrome (MFS)] and non-syndromic,[3] primary pulmonary hypertension (PPH);[4] AF.[5] Autosomal recessive CV diseases are less common, but include rare CMPs such as atrial dilated cardiomyopathy (ADCM) caused by homozygous mutations in *NPPA* gene;[6] sick sinus syndrome (SSS) caused by mutations in *SCN5A* gene;[7,8] ATS,[9] lysosomal storage diseases involving heart and vessels:[10] parental consanguinity or geographically isolated populations should be explored. X-linked diseases, frequently demonstrate recessive inheritance (XLR): heterozygous females are phenotypically healthy or manifest minor/mild phenotypes. Examples include XLR defects of Dystrophin or Emerin[11,12] or Danon Disease and Anderson Fabry disease, which cannot be simply defined as XLR because females may manifest a later onset and milder phenotype than males.

Work-up in genetic cardiovascular diseases: common principles

The fundament of clinical genetics in CV diseases is the deep phenotyping in probands and relatives. The clinical evaluation is preceded by genetic counselling with pedigree generation. Genetic visit of the proband aims at exploring the phenotypic traits related with the suspected disease/syndrome. For systemic/multi-organ diseases/syndromes, multidisciplinary evaluation may add important clues and specifications on each observed trait. Imaging and biomarkers systematically support the phenotype characterization. Clinical family screening [clinical visit, electrocardiogram (ECG), and two dimension Trans Toracic Echocardiography (2D-TTE)] is performed irrespective of genetic testing: it provides immediate diagnoses in relatives [e.g. bicuspid aortic valve (BAV), aneurysmal aortopathy, early CMP, congenital heart disease (CHD), PH]. Once the clinical diagnosis is formulated in the proband, genetic testing may analyse either a single disease gene (e.g. AD MFS or XL Danon Disease) or multi-gene panels in genetically heterogeneous diseases [e.g. HCM or familial-thoracic aortic aneurysm/thoracic aortic aneurysm and dissection (F-TAA/TAAD)]. When a potential disease-causing mutation is identified in the proband, cascade genetic testing is offered to relatives. The parallel achievement of phenotype and genetic data gives the essential data for segregation studies in families. This implies that mutations that are sufficient, by themselves, to cause the observed phenotype, should be present in all affected family members and absent in non-affected ones. The age-related penetrance of the disease has to be considered in segregation studies. For this reason, long-term monitoring of relatives can be uniquely useful.

Major genetic cardiovascular diseases

Familial cardiomyopathies

The clinical diagnosis of CMP in probands does not need, by itself, genetic testing. The phenotype-based diagnosis of HCM, DCM, RCM, or arrhythmogenic cardiomyopathy (ACM) (or genetic mimics vs. acquired phenocopies) is feasible on the basis of clinical data and imaging. The recent introduction of the non-dilated hypokinetic cardiomyopathy (NDHC) by the ESC[13] and of the HCM $<$ 15 mm in relatives of probands, expands the possibility of diagnosing DCM and HCM in patients that would not fulfil past WHO criteria. Familial CMP is diagnosed when two or more members of the same family are affected: the family screening defines the familial vs. non-familial (sporadic) disease (*Figure 1*). Genetic CMP can be diagnosed in unique affected family member when the disease-causing mutation is identified (*de novo* mutation, small families, and adoption). The clinical management and diagnoses of CMP such as dilated cardiolaminopathies[14] or ACM (in Task Force-2010 criteria, a pathologic mutation in disease gene is a major diagnostic criterion) are influenced by the genetic cause. The novel diagnoses of NDHC[13] and HCM $<$ 15 mm[16] are supported by the identification of the genetic causes, especially in relatives of affected probands. The feasibility of genetic testing deserves a few considerations: with NGS techniques, the time for testing is shorter but costs remain high (needs for confirmation with a different method, complex bioinformatics analysis, and high number of genes to be tested). Therefore, although costs and time are abated with respect to the past, resources needed to run these programs are still consistent. The sustainability therefore is an open issue, given the little institutional investments done in the setting of clinical and molecular genetics in the public care.

Familial arrhythmogenic diseases

Inherited atrial diseases

Inherited atrial diseases include rare ADCM, autosomal recessive, or dominant SSS, and a certain proportion of lone AF. Atrial dilated cardiomyopathy is a rare AR disease characterized by 'clinical onset in adulthood, bi-atrial dilatation up to giant size, early supraventricular arrhythmias with progressive loss of atrial electric activity to atrial standstill, thrombo-embolic complications, stable, normal left ventricular function, and New York Heart Association functional class during the long-term course of the disease, and severely decreased levels of atrial natriuretic peptide'.[6] Sick sinus syndrome is clinically characterized by *sinus bradycardia, sinus arrest, chronotropic incompetence, and susceptibility to atrial arrhythmias*.[17] Sick sinus syndrome can be sporadic, such as the common SSS observed in old patients,[18] or familial, typically manifesting in young patients. Familial SSS is either AD or AR.[19,20] The genetic diagnosis (*SCN5A* gene in SSS1 and *HCN4 in* SSS2)[8,19,20] contributes to identify at-risk family members, to schedule monitoring for prevention of arrhythmias, and to support decisions for ablation of atrial arrhythmias or pacemaker (PM) implantation. Atrial fibrillation can be sporadic or familial;[21] about 30% of patients have a positive family history and individuals with at least one parent with AF have a 85% relative risk of developing AF.[22] Numerous disease genes have been identified to date.[23] The role of clinical genetics is to exclude other diseases that can explain the arrhythmia. In fact, some of the disease genes may also cause other heritable atrial disease.[6] Genes such as *SCN5A* that cause LQTS, SQTS, or BS may also cause AF, and long-term follow-up of mutation carriers is necessary to exclude other arrhythmogenic phenotypes or explore why the same mutations may manifest different arrhythmogenic phenotypes.

Inherited channelopathies and life-threatening ventricular arrhythmias

Cardio-channelopathies encompass a large genetically heterogeneous group of electrical abnormalities that can be associated with unexpected sudden death.[1] The major groups of channelopathies associated with risk of sudden death include diseases that affect the QT interval, BS, and CPVT. Long QT Syndrome encompasses genetically heterogeneous diseases, AD in the majority of cases, and sharing prolonged QT interval on resting 12-lead surface ECG in the absence of structural heart disease. Inheritance is AR in the rare Jervell and Lange-Nielsen syndrome. Patients with LQTS may be asymptomatic during their entire life or manifest syncope, aborted cardiac arrest or SCD. The latter can be the first

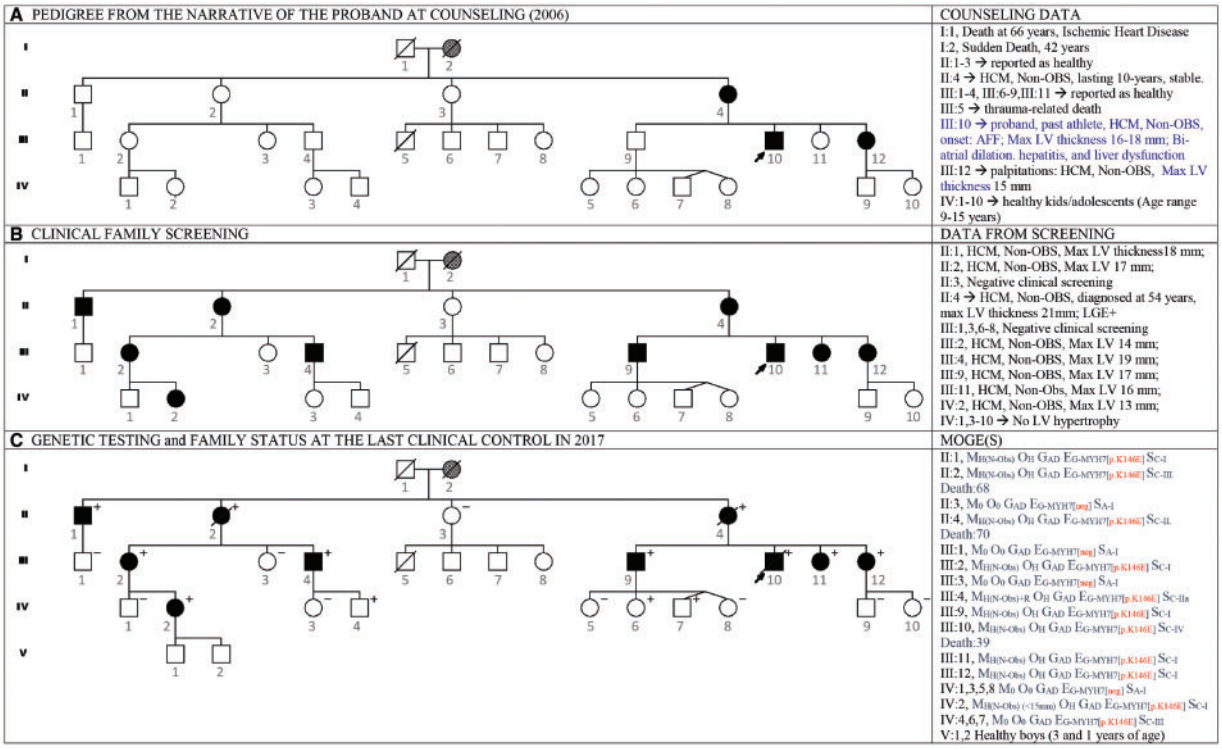

Figure 1 The figure shows the pedigree of a family with autosomal dominant hypertrophic cardiomyopathy, the diagnostic impact of clinical family screening, and the phenotype–genotype description. The proband, III: 10, was diagnosed with hypertrophic cardiomyopathy at the age of 30 years, when he developed heart failure with atrial fibrillo-flutter (AFF). His medical history was characterized by recurrence of the atrial arrhythmias, ablations, and further recurrence of atrial fibrillo-flutter. He further suffered pneumonia with sepsis, pleuritis, and pericardial effusion, liver failure and progressed to end-stage heart failure. (*A*) The panel shows the first pedigree of the family, before performing clinical family screening and genetic testing. According to the narrative of the proband and to the health status of his relatives the only affected family members were II: 4, and III: 12. His grand-mother was probably affected (I: 2). (*B*) The panel shows the pedigree after completion of family screening: seven additional members were affected and asymptomatic, all unaware of their disease status. (*C*) The panel shows the pedigree after the completion of genetic testing: there are three healthy carriers in the third generation. Individual IV: 2 decided to have pregnancy and was supported and monitored during both pregnancy and delivery; her children are healthy and have not been tested yet. In the right column, phenotype and cause of the cardiomyopathies are precisely described using MOGE(S) nosology.[14] In the right column, the summary of clinical data shows that genetically negative family members are not affected, supporting the segregation of the genotype with the phenotype up to the third generation. Future clinical monitoring of the family will demonstrate whether the healthy carriers of the fourth generation will develop the disease, further confirming the segregation of the phenotype with the genotype in the family. This is especially important in this family because the mutation identified in *MYH7* is not reported.

manifestation of the disease. In 90% of cases, mutations are identified in *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) genes.[24] The remaining 10% of mutations occurs in genes encoding other ion channels or proteins interacting with ion channels. The diagnosis of LQTS is based on consensus criteria[25] and supported by a score system that sums points assigned to ECG findings (baseline and after exercise stress), evidence of torsade de pointes, history of syncope, congenital deafness, family history, and members with LQTS, unexplained SCD below age 30 among immediate family members.[26] Genotype is not included in the score. Short QT Syndrome is an inherited arrhythmogenic disease associated with increased risk of AF, ventricular tachycardia (VT)/ventricular fibrillation (VF), and SCD.[27] Current estimates indicate a prevalence of 0.02% to 0.1% in the adult population and 0.05% in children/adolescents.[28] The diagnosis is done when QT interval is $\leq$330 ms in the absence of tachycardia or bradycardia. Gain-of-function mutations in three genes encoding potassium channels, *KCNQ1, KCNH2,* and *KCNJ2*, have been associated with the SQTS.[25] Brugada Syndrome is a genetically heterogeneous, AD arrhythmogenic disease characterized by *ST elevation with negative T wave in the right precordial leads in the absence of structural cardiac abnormalities.*[29] The disease burden ranges from 5 to 20 individuals in 10 000. Although mean age of patients manifesting life-threatening arrhythmias is around 40, arrhythmic events can occur at any age; arrhythmias typically occur while sleeping or at rest or after heavy meals or during episodes of fever.[29] Pathogenic mutations are identified in about 30% of patients, with *SCN5A* gene accounting for the majority of cases and other genes accounting for about 5% of genotyped cases.[30] Overlap phenotypes (long QT, short QT, coved-type ST-segment elevation in the right precordial leads) are possible in affected members of the same families (e.g. *SCN5A*). A recent 'oligogenetic inheritance' hypothesis postulates that mutations in more than one disease gene is needed to induce a clinical phenotype.[31] Ajmaline provocation test supports clinical

Table 1 Marfan syndrome—diagnostic criteria (*J Med Genet* 2010;47:476–85)

(A) Diagnosis of Marfan syndrome		
In the absence of family history	Aortic root dilatation Z score $\geq$ 2 AND ectopia lentis	
	Aortic root dilatation Z score $\geq$ 2 AND FBN1	
	Aortic root dilatation Z score $\geq$ 2 AND systemic score $\geq$ 7[a]	
	Ectopia lentis AND FBN1 with known aortic root dilatation	
In the presence of family history	Aortic root dilatation Z score $\geq$ 2 AND ectopia lentis	
	Aortic root dilatation Z score $\geq$ 2 AND FBN1	
	Aortic root dilatation Z score $\geq$ 2 AND systemic score $\geq$ 7[a]	
	Ectopia lentis AND FBN1 with known aortic root dilatation	
(B) Systemic score		Value
Skeletal		
Reduced upper segment/lower segment and increased arm span/height		1
Wrist AND thumb sign		3
Wrist OR thumb sign		1
Pectus carinatum deformity		2
Pectus excavatum or chest asymmetry		1
Hindfoot deformity		2
Plain flat foot		1
Spontaneous pneumothorax		2
Dural ectasia		2
Protrusio acetabuli		2
Scoliosis or thoracolumbar kyphosis		1
Reduced elbow extension		1
Facies		
Three of five facial features		1
Dolichocephaly		
Downward slanting palpebral fissures		
Enophthalmos		
Retrognathia		
Malar hypoplasia		
Skin		
Skin striae		1
Eye		
Severe myopia (>3 diopters)		1
Heart		
Mitral valve prolapse		1

[a]A score of $\geq$ 7 is considered a positive systemic score.

diagnosis especially in patients with equivocal baseline ECG pattern as unique evidence of possible disease;[25] other conditions potentially manifesting a Brugada-like ECG patterns (ischaemic heart disease, hyperkalaemia, hypercalcaemia, ACM, myocarditis, mechanical compression of the right ventricle outflow tract, or pulmonary embolism) should be excluded. In symptomatic patients, risk stratification includes history of VT/VF, syncope, and spontaneous coved-type ST-segment elevation. In asymptomatic patients risk stratification includes male gender and fragmented QRS, which is a marker of conduction abnormality and a predictor of prognosis.[32] Catecholaminergic Polymorfic Ventricular Tachycardia is a rare disease (1:10 000) that typically presents with syncope or cardiac arrest triggered by exercise or emotion in children/adolescents.[33] Mortality is high in unrecognized and untreated patients. The baseline ECG is normal, but exercise induces the polymorphic ventricular arrhythmias; a few patients may demonstrate bidirectional VT.[34] The disease is genetically heterogeneous: CPVT1 (60–70%) is AD and caused by mutations in the gene *RYR2* gene. CPVT2 is AR and is associated with mutations in the cardiac *Calsequestrin gene* (*CASQ2*) both involved in myocyte calcium homeostasis.[35] Less common genes include *KCNJ2* (CPVT3), *Calmodulin* (*CALM1*), and *Triadin* (*TRDN*).[36] Risk factors for arrhythmias are young age, male gender, history of cardiac arrest, arrhythmias while taking beta-blockers, and mutation in the c-terminus of the *RYR2* gene.[33,36]

Familial aneurysmal diseases: thoracic aorta (F-TAA)

Heritable aneurysmal diseases include more than 40 genetically different disorders.[37] Thoracic aorta is most commonly affected. Thoracic aortic aneurysm may occur in syndromes or be the unique (or main) manifestation of the disease. Syndromic diseases such as MFS (*Table 1*), vascular Ehlers-Danlos syndrome (EDS-IV), and Loeys-Dietz syndromes (LDS) are characterized by phenotypic traits that usually allow clinical diagnosis.[3] Recent identification of novel disease genes for LDS and overlapping phenotypes

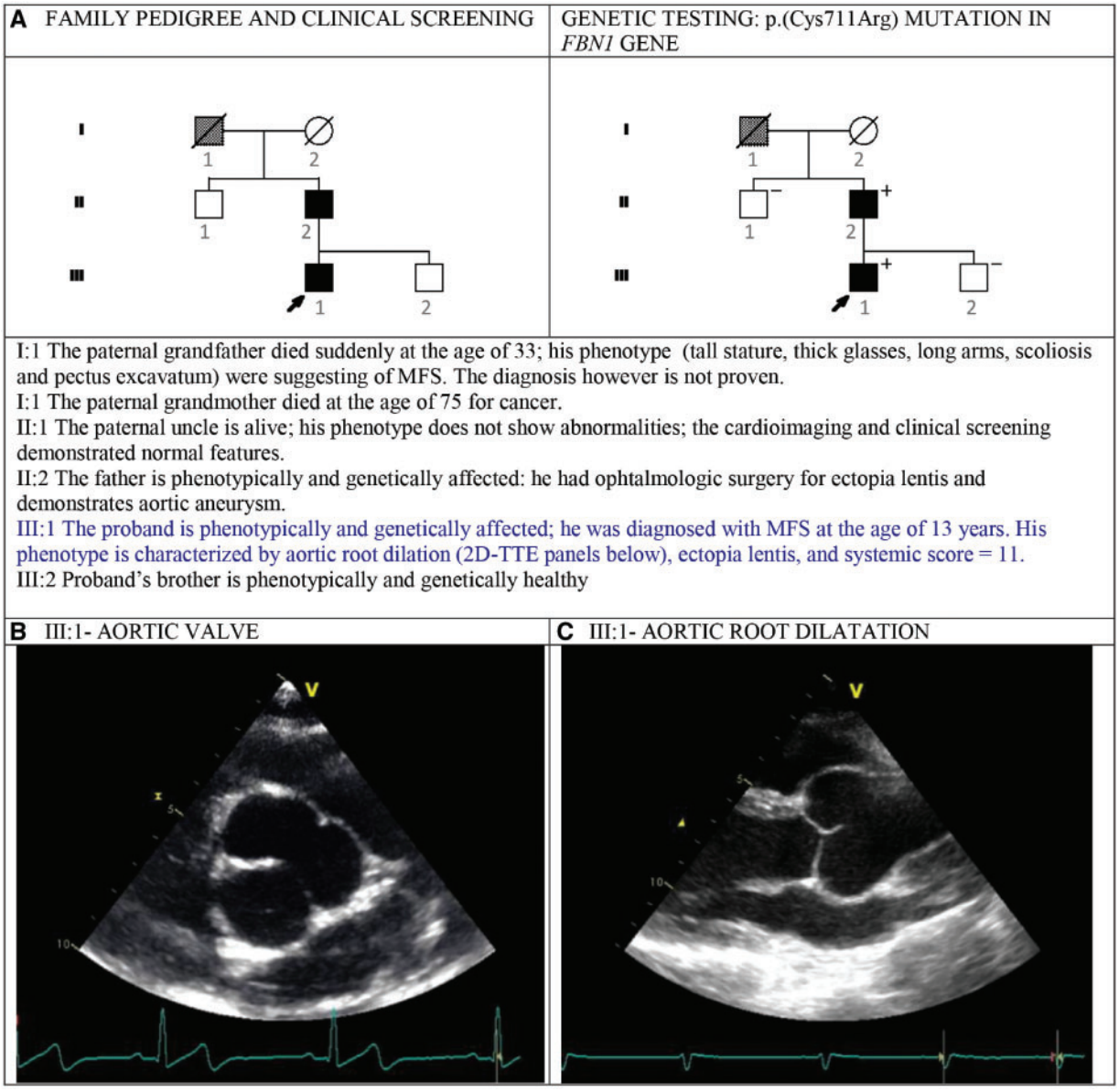

Figure 2 The figure shows the pedigree of this small family with autosomal dominant Marfan syndrome (*A*) and the 2D-TTE view (*B*, *C*) of the aortic root of family member III: 1 demonstrating aortic root aneurysm.

assigns to genetic testing a diagnostic role.[37] When TAA/TAAD occurs as isolated trait genetic testing plays an essential diagnostic role (*Figure 2*). Non-syndromic F-TAA/TAAD are diagnosed on imaging data. They can be grouped according to the molecular pathway/structure in which disease genes are involved[3,38] and include defects in the structural and functional proteins of vascular smooth muscle cells, extracellular matrix (ECM), or transforming growth factor (TGF-β) signalling pathway.[38] The former include *ACTA2* (smooth muscle alpha-actin), *MYH11* (myosin heavy chain 11), *MYLK* (myosin light chain kinase), and *PRKG1* (cyclic guanosine monophosphate-dependent protein kinase). Extracellular matrix genes include *Fibrillin 1* and *2*, *COL3A1*, *MFAP5* that encodes the ECM component MAGP-2 and *MAT2A* that encodes methionine adenosyltransferase II alpha (MAT IIa). Transforming growth factor-β pathway includes *TGFBR1* (LDS type 1), *TGFBR2* (LDS type 2), *SMAD3* (LDS type 3), *TGFB2* (LDS type 4), and *TGFB3* (LDS type 5). Bicuspid aortic valve is common in the general population (1–2%); in 25% of cases, it is associated with dilation of the ascending aorta.[39] Bicuspid aortic valve-associated aortopathy should be distinguished from that recurring in CHD (such as hypoplastic left heart syndrome, coarctation of aorta, and septal defects) and in syndromes (Andersen-Tawil, DiGeorge, Noonan, LEOPARD, and Turner).[39,40] Non-syndromic F-BAV has been associated with mutations in *NOTCH1*[39] and in *GATA5*[40] and in isolated FTAAD-*TGFBR1*, FTAAD-*TGFBR2*, FTAAD-*SMAD3*, FTAAD-*TGFB2*, and FTAAD-*ACTA2*.[3] The major clinical risk in genetic TAA, syndromic and non-syndromic, is dissection and

Table 2 Genetic pulmonary hypertension

PH WHO GROUP	TYPE	Inheritance	MIM # phenotype	Gene	MIM *Gene locus	Protein
Primary pulmonary hypertension (PPH)						
1	PPH1	AD		*BMPR2*[a]	600799	Bone Morphogenetic protein receptor 2
1	PPH2	AD		*SMAD9*	603295	Mothers against decapentaplegic drosophila, homologue of, 9
1	PPH3	AD		*CAV1*	601047[b]	Caveolin1
1	PPH4	AD		*KCNK3*	603220	Potassium channel, subfamily K, member 3
1	Dexfenfluramine-associated PH	AD		*CYP1B1*	601771	Cytochrome P450; subfamily 1; polypeptide 1
Pulmonary veno-occlusive disease (PVOD)						
1	PVOD1	AD		*BMPR2*	600799	Bone Morphogenetic protein receptor 2
1	PVOD2	AR		*EIF2AK4*	609280	Eukaryotic translation initiation factor-2, alpha kinase 4
Hereditary haemorrhagic telangiectasia (HHT)						
1	HHT1 (Rendu-Osler-Weber)	AD		*ENG*	131195	Endoglein (CD105)
1	HHT2	AD		*ACVRL1*	601284	Activin A receptor, type II-like 1
Lymphangioleiomyomatosis (LAM)						
5	Tuberous sclerosis-1; LAM	AD		*TSC1*	605284	Amartin
5	Tuberous sclerosis-2 and LAM somatic mutations	AD		*TSC2*	191092	Tuberin
Lysosomal storage diseases						
5	Glycogen Storage disease type 1	AR		*G6PC (1a)*	232200	Glucose-6-phosphatase
				SLC37A4 (1b)	232220	Glucose-6-phosphate translocase
5	Glycogen Storage disease types 3a and b	AR		*AGL*	610860	Glycogen debrancher enzyme
5	Gaucher Disease type 1 (with or without splenectomy)	AR		*GBA*	606463	Acid beta-glucosidase

[a]Including fenfluramine-/dexfenfluramine associated PH.
[b]Disorders allelic at the same locus: 'Lipodystrophy, congenital, generalized type 3' and 'Partial lipodystrophy, congenital cataracts and neurodegeneration syndrome'.

rupture of the aorta; non-aortic arteries can be involved in EDS-IV, ATS, and LDS. The identification of the disease-causing mutation in each proband provides the tool for early, preclinical diagnosis, tailored monitoring, and preventive surgery. Surgical indications are guided by the imaging characteristics of the aneurysm (size in particular), rate of progression, family history of rupture, coexistence of risk factors (hypertension), or electively planned (e.g. in fertile women who plan pregnancy). Although guidelines provide general indications, each patient should be cared for on individual basis.

Familial pulmonary hypertension

Pulmonary arterial hypertension is a rare (1–2 per 100 000 and 1 per 1 000 000 people), life-threatening disease. Pulmonary hypertension is defined as an *increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization*.[41] Current clinical classification is based on the principles of similarities in pathobiology, clinical features, and therapeutic options.[4] More than 40 different diseases are divided into five groups.[4] Groups 1 and 5 include forms of pulmonary hypertension of genetic origin (Table 2). For these latter, a clinically oriented approach is feasible for familial AD PPH in which mutations of *bone morphogenetic protein receptor 2* (*BMPR2*) recur in up to 80% of patients and families. Less common disease genes, such as *SMAD9*, play a role in the same BMP pathway as downstream modulators of the BMP signalling pathway and cause a phenotypically similar, AD disease. Other disease genes such as *ALK-1* and *Endoglin* (*ENG*) account for a minority of familial PPH. Defects in other rare disease genes such as *CAVEOLIN 3* (*CAV3*) or genes coding ion channels such as *KCNH3*, result in a similar phenotype, but via different mechanisms. Pulmonary veno-occlusive hypertension is allelic at the PPH1 locus (*BMPR2*), while the recessive form is caused by mutations

in *EIF2AK4*.[42] Finally, Group 5 PH includes a variety of acquired and heritable diseases such as the AD lymphangioleiomyomatosis[43] and lysosomal storage diseases such as glycogen storage disease types 1 and 3[44,45] and Gaucher disease type 1.[46,47] Clinical genetics with counselling and pedigree construction, search for known risk factors and annotation of novel potential risk factors, family investigation, and genetic testing are currently being translated in the clinical setting. Clinical attention to PH is encouraged by the availability of new medical treatments (endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase stimulators, and prostanoids) that continue to be trialled in patients with idiopathic, heritable, drug-induced, and connective tissue disease-associated pulmonary hypertension.

Current applications, limits, and future developments

Current applications

Genetic diagnosis is now part of the diagnostic work-up of familial CV diseases; it provides preclinical, early, and prenatal diagnosis and supports treatment decisions. Its translation is still limited for atrial arrhythmias and pulmonary hypertension, while it is substantially implementing in cardiomyopathies, ventricular arrhythmias and aneurysmal aortopathies. *Limits* include the small resources for genetics and cardiology, both genetic testing and clinical family screening, the still incomplete list of disease-causing genes and the complex interpretation of NGS data. A major limit for genetic arrhythmogenic diseases is the possible non-informative ECG at baseline in family screening and therefore segregation studies. The *future*, in general, is the expansion of clinical screening of relatives, the better segregation studies in families for both CMP and arrhythmogenic diseases and individual risk stratification for preventable catastrophic aortic dissection in families as well as the identification of pulmonary hypertension for early treatments with new medications.

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