

GENETIC CHANNELOPATHIES

Relevant Guidelines

AHA/ACC/HRS 2017 Guideline on ventricular arrhythmias and prevention of sudden cardiac death

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *JACC*. 2017

ESC 2022 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022.

2017 ACC/AHA/HRS Guideline on syncope

2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope. *JACC* 2017

ESC 2018 guidelines on syncope

2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018.

ESC 2020 Guidelines on sports

Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2020.

ESC 2025 guidelines on pregnancy

2018 ESC Guidelines on pregnancy. *Eur Heart J* 2025.

Relevant Scientific Statements and Position Papers

HRS 2019 expert consensus statement on arrhythmogenic cardiomyopathy

2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. 2019.

AHA 2020 Scientific Statement on Drug-induced Arrhythmias

Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. *Circulation*. 2020

AHA 2017 Statement for Electrocardiographic Monitoring

Update to Practice Standards for Electrocardiographic Monitoring in Hospital Settings: A Scientific Statement From the American Heart Association. *Circulation*. 2017;136:e273-e344.

EHRA/HRS/APHRS/LAHRS 2022 Expert Consensus Statement on Genetic Testing

Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases. *Europace* 2022

AHA 2025 Policy Statement on Genetic and Genomic Testing

Genetic and Genomic Testing in Cardiovascular Disease: A Policy Statement From the American Heart Association. *Circulation*. 2025 Dec 16;152(24):e474-e489.

DEFINITIONS OF INHERITED ARRHYTHMIAS

Definitions

Heritable cardiovascular diseases have generally been divided into two broad categories. The first category encompasses Mendelian genetic diseases such as inherited cardiomyopathies (e.g. hypertrophic cardiomyopathy, HCM) and ventricular arrhythmia syndromes (e.g. long QT syndrome, LQTS) that are usually caused by a rare genetic variant (a so-called ‘mutation’) that has a large risk-increasing effect size. In the second category are common complex diseases such as hypertension and coronary artery disease where environmental factors act in conjunction with a large number of common genetic variants, each with a small risk-increasing effect size.¹

Inherited arrhythmias comprise a group of disorders with inherited susceptibility to arrhythmias and conduction disturbances due to mutations in genes mainly encoding the Na⁺, and K⁺ channels, and other arrhythmogenic mechanisms such as those linked to Ca⁺⁺ transport (Figure 1).²⁻⁴ The DNA among humans consists of the same nucleotide sequence, but normal variations in small sections of sequence or single nucleotides do exist among individuals (polymorphisms). Single nucleotide substitutions that occur with a measurable frequency (ie >1% allelic frequency) among a particular ethnic population are single-nucleotide polymorphisms, whereas permanent changes in the nucleotide sequence that occur less frequently are mutations. **Loss of function mutations** of a particular gene produce different phenotypes than gain of function mutations of the same gene: loss-of-function mutations in the gene *KCNQ1* encoding for voltage-gated potassium channels that affect the repolarizing current I_{Ks} causes long QT syndrome, whereas gain-of-function mutations of the same gene cause a phenotype of short QT syndrome or AF. **Gain-of-function mutations** of gene *SCN5A* cause long QT syndrome, whereas loss-of-function mutations cause Brugada syndrome, conduction disorders and a form of dilated cardiomyopathy (Table 1). The majority of heritable cardiomyopathies and channelopathies are associated with disease-susceptibility genes characterized by incomplete penetrance, ie low likelihood that the mutation will cause clinically recognizable disease. Thus, although these disease entities are monogenic, there is variable penetrance, which reflects contribution by modifier genes, thus resulting in diverse phenotypes.⁵ Modifier genes may promote higher risk for symptomatic disease and/or more severe disease expression, or might protect an individual from developing the disease.⁶ Mutation type (missense vs. nonmissense, i.e. nonsense, frameshift, in-frame insertions/deletions and splice-site mutations) and location (transmembrane and pore region, cytoplasmic loop vs. N- or C-terminus^{13–15}) are differently associated with clinical severity. Similarly, dominant-negative mutations appear to be more severe than those causing

haploinsufficiency.⁷ Co-morbidities also modulate disease severity. There has been evidence for a role of hypertension/hypertrophy in modulating arrhythmic risk in *SCN5A* mutation-positive patients.⁸ Usually, inherited arrhythmias are familial, rather than sporadic, and autosomal dominant rather than autosomal recessive.

Genetic testing

Genetic testing has now emerged as a useful clinical tool for the diagnosis and risk stratification of genetic conditions but distinguishing pathologic mutations from innocent genetic variants is not always straightforward. Currently, genetic testing may establish the diagnosis in LQTS, CPVT, BrS and HCM, and may also facilitate risk stratification in LQTS and HCM (Table 1).⁴

New techniques such as chromosomal microarray and **next-generation DNA sequencing (NGS)** have facilitated genetic testing (Table 2).⁹ Single genes are usually analyzed by Sanger sequencing, which has been proven to be a reliable technique to identify variants underlying genetic disease. With increasing numbers of genes identified as underlying a specific cardiac disorder (genetic heterogeneity) and the fact that more than one gene and/ or variant (digenic inheritance or polygenic inheritance) can contribute to the disease phenotype, next-generation sequencing (NGS)-based methods enable the parallel sequencing of several targeted genes at the same time and at relatively low cost.¹⁰⁻¹² A clinical NGS test can be designed to target a panel of selected genes, the exome (all known genes, or approximately 1 to 2% of the genome), or the entire genome. In addition to these targeted NGS panels, sequencing of all protein coding genes (exome) of the human genome (whole exome sequencing [WES]) or even all DNA nucleotides (whole genome sequencing [WGS]) can be performed. **Gene panels** target curated sets of genes associated with specific clinical phenotypes. Clinical **exome sequencing** targets approximately 22,000 protein-coding genes, and thus covers the majority of known genes, including genes that have not yet been associated with human disease. Clinical **genome sequencing** (also called “whole-genome sequencing,” or genome-wide association” even though coverage is not 100%), is untargeted, generating sequence data from a region that is 50 to 100 times as large as that covered by exome sequencing.

NGS gene panel tests cover a set of genes defined by the clinical diagnostic laboratory. Each test type has an associated pattern of false negative results. For instance, a gene panel may not include a mutated gene and an exome may miss deep intronic splice mutation. In addition, some regions of the genome are difficult to sequence with any existing method. Targeted gene panels are faster and cheaper. Recently, a comprehensive sequencing assay for inherited cardiac condition genes was developed and performed better than

conventional exome and genome sequencing.¹³ These are exciting advancements, although questions remain about their clinical applicability and cost-effectiveness.^{9,14-20} A poor concordance among laboratories has been reported, and pathogenic genetic variants may not be associated with an abnormal phenotype.¹⁹ A freely available internet resource, GeneTests, provides a searchable database of clinical genetic testing laboratories, specialty clinics, and other relevant information.¹⁸ In November 2013, the FDA allowed marketing of four diagnostic devices that can be used for high throughput gene sequencing. The American College of Medical Genetics and Genomics (**ACMG**) has published a list of genes with both a clinically significant health association and a potential to modify therapeutic decision,²¹ and has released recommendations for the interpretation of sequence variants.²² The National Institutes of Health has initiated the development of the Clinical Genome Resource (**ClinGen**), a resource comprised of an international consortium of clinicians, geneticists, genetic counselors and researchers that aims to define the clinical relevance of genes and genetic variants in the application of precision medicine for patient care.²³

General indications for genetic testing are presented in Table 3. Genetic counselling is also recommended before **pregnancy** in women with primary arrhythmia syndromes.²⁴

Glossary of Terms

Allele: One of several alternative versions of a particular gene. An allele can refer to a segment of DNA or even a single nucleotide. The normal version of genetic information is often considered the “wildtype” or “normal” allele. The vast majority of the human genome represents a single version of genetic information. Multiple alleles are when one phenotype is controlled by more than 2 alleles but only a combination of 2 determine the phenotype. For example blood group has three alleles A, B and O but people only have a 2 allele phenotype.

Autosomal Dominant: The situation in which the disease can be expressed even when just one chromosome harbors the mutation.

Autosomal Recessive: The situation in which the disease is expressed only when both chromosomes of a pair are abnormal.

Cascade Testing: Procedure whereby all first-degree relatives of a genotype-positive index case are tested in concentric circles of relatedness. If one of the family members is genotype positive, all his/her first-degree relatives should be tested continuing this process following each genotypepositive family member.

Compound heterozygosity: more than one genetic defect in the same gene.

Digenic heterozygosity: more than one genetic defect in a second complementary gene.

Epigenetics: Mitotically and/or meiotically heritable variations of gene function that cannot be explained by changes of DNA sequence.

Exome: Part of the genome formed by exons, 1-2% of the coding portion of the human genome; it encompasses approximately 19000 genes.

Exons: Segments of genes that are spliced together after gene transcription to form messenger RNA, which, in turn, is translated into protein.

Expressivity: The level of expression of the phenotype, and when the manifestations of the phenotype in individuals who have the same genotype are diverse, the phenotype is said to exhibit variable expressivity.

Filtering analysis: The process of excluding DNA variants from further consideration because of various attributes, with the use of bioinformatics and manual curation. For example, most filtering analyses exclude synonymous variants (DNA variants that are predicted not to change the amino acid sequence of a protein).

Genome: A genome is an organism's complete set of DNA, including all of its genes, as well as non-coding and mitochondrial DNA. In humans, a copy of the entire genome—more than 3 billion DNA base pairs—is contained in all cells that have a nucleus.

Genotype: A person's genetic or DNA sequence composition at a particular location in the genome.

Genotypic heterogeneity: Genetic variability among individuals with similar phenotypes.

Genotype–phenotype plasticity: The concept that the link between genotype and phenotype is subject to broad variability with as yet limited predictability.

Germline variant: A DNA sequence variant that was transmitted by means of a gamete (sperm or egg) or that was caused by a mutation in the zygote or at a very early stage of fetal development and is presumed to be present in all of a person's nucleated cells.

Haploinsufficiency: The situation in which an individual who is heterozygous for a certain gene mutation or hemizygous at a particular locus, often due to a deletion of the corresponding allele, is clinically affected because a single copy of the normal gene is incapable of providing sufficient protein production as to assure normal function. This is an example of incomplete or partial dominance.

Heterozygote: An individual who has different alleles at a particular gene locus on homologous chromosomes (carrier of a single copy of the mutation).

Homozygote: An individual who has the same allele at a particular gene locus on homologous chromosomes (carrier of a double copy of the mutation).

Human genome reference sequence: A reference sequence that provides a haploid mosaic of different DNA sequences from multiple donors, which is revised periodically and is not necessarily normal.

Matrilinear inheritance: Women but not men transmit the disease to offspring (male or female), as happens with disease due to mitochondrial DNA mutations.

Modifier: Gene variants or environmental factors that are insufficient to cause observable disease on their own, but which are capable of interacting with the disease gene to alter the phenotype.

Monogenic risk variants: Rare and typically disruptive or protein-truncating variants that confer large risks of disease; typically follow classic mendelian patterns of inheritance.

Mutation: A change of the DNA sequence within the genome. A mutation considered in the context of a genetic disease usually refers to an alteration that causes a Mendelian disease, whereas a genetic polymorphism refers to a common genetic variation observed in the general population.

Mutation – Deletion/Insertion: The removal (deletion) or addition (insertion) of nucleotides to the transcript that can be as small as a single nucleotide insertion/deletion or as large as several hundreds to thousands of nucleotides in length.

Mutation – Disease Causing: A DNA sequence variation that represents an abnormal allele and is not found in the normal healthy population but exists only in the disease population and produces a functionally abnormal product.

Mutation – Frameshift: Insertions or deletions occurring in the exon that alter the “reading frame” of translation at the point of the insertion or deletion and produce a new sequence of amino acids in the finished product. Frameshift mutations often result in a different product length from the normal gene product by creating a new stop codon, which produces either a shorter or longer gene product depending on the location of the new stop codon.

Mutation – Germline: Heritable change in the genetic make-up of a germ cell (sperm or ovum) that when transmitted to an offspring is incorporated into every cell in the body.

Mutation – In-Frame Insertion/Deletion: In-frame insertions and deletions occur when a multiple of three nucleotides is affected and result in a single or multiple amino acids being removed or added without affecting the remainder of the transcript.

Mutation – Missense: A single nucleotide substitution that results in the exchange of a normal amino acid in the protein for a different one.

Mutation – Nonsense: A single nucleotide substitution resulting in a substitution of an amino acid for a stop codon. A nonsense mutation results in a truncated (shortened) gene product at the location of the new stop codon.

Mutation – Somatic: Variants/mutations are said to be somatic if they occur in cells other than gametes. Somatic mutations cannot be transmitted to offspring.

Penetrance: The likelihood that a gene mutation will have any expression at all, by means of any recognizable symptom, sign, or laboratory feature of the disease associated with that variant.

In the situation in which the frequency of phenotypic expression is less than 100%, the genetic defect is said to be associated with reduced or incomplete penetrance.

Phenocopy: An individual who manifests the same phenotype (trait) as other individuals of a particular genotype but does not possess this genotype himself/herself.

Phenotype: A person’s observed clinical expression of disease in terms of a morphological, biochemical, or molecular trait.

Phenotypic heterogeneity: Phenotypic variability among individuals with similar genotypes.

Polygenic risk variants: Commonly occurring variants in the population that typically confer an individually small risk of developing a disease

Polymorphism: Normal variations at distinct loci in the DNA sequence. The vast majority of the human genome represents a single version of genetic information. The DNA from one person is mostly made up of the same exact nucleotide sequence as another person. However, there are many small sections of sequence or even single nucleotides that differ from one individual to another.

Proband or index case or probandus: The first affected family member who seeks medical attention for a genetic disease.

Single Nucleotide Polymorphism (SNP): A single nucleotide substitution that occurs with a measurable frequency (i.e., >0.5% allelic frequency) among a particular ethnic population(s).

SNP – Nonsynonymous: A single nucleotide substitution whereby the altered codon encodes for a different amino acid or terminates further protein assembly (i.e., introduces a premature stop codon).

SNP – Synonymous: A single nucleotide substitution occurring in the coding region (exon), whereby the new codon still specifies the same amino acid.

X-linked inheritance: a recessive mode of inheritance in which a mutation in a gene on the X chromosome causes the phenotype to be expressed in males (who are necessarily hemizygous for the gene mutation) and in females who are homozygous for the gene mutation.

Variant: A difference in a DNA sequence in comparison with the normal reference sequence. A variant may be benign (sometimes referred to as a polymorphism) or pathogenic (sometimes referred to as a mutation).

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