Inherited Arrhythmias – Where do we Stand?

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Abstract

This review discusses inherited arrhythmias and conduction disturbances due to genetic disorders. Known channel mutations that are responsible for these conditions are presented, the indications and value of genetic testing are discussed, and a glossary of terms related to the discipline of genetic cardiology has been compiled.

Keywords

Inherited arrhythmias; conduction disturbances ; genetic channelopathies; mutations

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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 (Table 1).¹ The majority of heritable cardiomyopathies and channelopathies are associated with disease-susceptibility genes characterised by incomplete penetrance, ie low likelihood that the mutation will cause clinically recognisable disease. Thus, although these disease entities are monogenic, there is variable penetrance, which reflects contribution by modifier genes, thus resulting in diverse phenotypes.² Usually they are familial, rather than sporadic, and autosomal dominant rather than autosomal recessive.

Genetic testing has now emerged as a useful clinical tool for the diagnosis and risk stratification of genetic conditions but distinguishing pathological mutations from innocent genetic variants is not always straightforward. Currently, genetic testing may put the diagnosis in long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS) and hypertrophic obstructive cardiomyopathy (HOCM), and may also facilitate risk stratification in LQTS and HOCM.³ According to the 2010 consensus statement of HRS/EHRA, genetic testing is recommended in cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of a genetic test is high (likelihood of positive result >40 % and signal/noise ratio <10) (Table 2).⁴

The conventional approach of genetic linkage analysis has been replaced with the newer approach of genome-wide association studies (GWAS), and high-throughput, next-generation DNA sequencing (NGS).⁵ The application of high-throughput techniques for whole genome and exome sequencing are exciting future advancements of this technology,^{6–8} although questions remain about its clinical applicability and cost-effectiveness.⁹ In November 2013,

the FDA approved marketing of four diagnostic devices that can be used for high-throughput gene sequencing.

The DNA of 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 >0.5 % allelic frequency) among a particular ethnic population are called single-nucleotide polymorphisms, whereas those that occur less frequently are termed mutations.

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 'wild-type' or 'normal' allele. The vast majority of the human genome represents a single version of genetic information. One phenotype may be controlled by multiple alleles, but only a combination of two will determine the phenotype. For example, the blood group gene has three alleles – A, B and O – but people only have a two-allele phenotype.

Autosomal Dominant: The situation in which the disease can be expressed even when just one chromosome harbours 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 for each genotype-positive family member.

Table 1: Known channel mutations in genetic channelopathies. New mutations are continuously discovered. Most conditions are inherited in an autosomal dominant pattern, although both recessive (JLN1, JLN2, CPVT2) and X-linked patterns (BRS) have been described

Chromosomal Locus	Gene	Protein	Current	Function	Syndrome	Phenotype
11p15.5	<i>KCNQ1</i>	K _v 7.1	I _{KS}	Loss of function Loss of function Gain of function Gain of function	LQTS1 JLNS SQTS AF	Long QT Long QT, deafness Short QT Atrial fibrillation
7q35-q36	<i>KCNH2</i>	HERG	I _{Kr}	Loss of function Gain of function Gain of function	LQTS2 SQTS AF	Long QT Short QT Atrial fibrillation
3p21	<i>SCN5A</i>	Na _v 1.5	I _{Na}	Gain of function Loss of function Loss of function Loss of function Loss of function Loss of function Gain of function	LQT3 BrS1 AF PCCD SSS DCM MEPPC	Long QT Brugada syndrome Atrial fibrillation Conduction defects Sick sinus syndrome Dilated cardiomyopathy Ventricular premature conduction
4q25-q27	<i>ANKB</i>	Ankyrin B	I _{Na-Kr}	Loss of function	LQTS	Long QT Atrial fibrillation CPVT
21q22.1 2	<i>KCNE1</i>	MinK	I _{KS}	Loss of function Loss of function Loss of function	LQTS JLNS AF	Long QT Long QT, deafness Atrial fibrillation
21q22.1	<i>KCNE2</i>	MiRP1	I _{Kr}	Loss of function Gain of function	LQTS AF	Long QT Atrial fibrillation
17q24.3	<i>KCNJ2</i>	Kir2.1	I _{K1}	Loss of function Gain of function Gain of function	LQTS SQTS AF	Long QT, AV block, potassium-sensitive periodic paralysis, hypoplastic mandible (Andersen-Tawil syndrome) Short QT Atrial fibrillation
12p13.3	<i>CACNA1C</i>	Cav1.2	I _{Ca}	Gain of function Loss of function Loss of function	LQTS BrS SQTS	Long QT, syndactyly, septal defects (Timothy syndrome) Brugada syndrome Short QT
3p24	<i>CAV3</i>	Caveolin-3	I _{Na}	Gain of function	LQTS	Long QT
11q23.3	<i>SCN4B</i>	Navβ4	I _{Na}	Gain of function	LQTS	Long QT
7q21-q22	<i>AKAP9</i>	A-kinase anchorin (yotiao)	I _{KS}	Reduced due to loss of cAMP sensitivity	LQTS	Long QT
20q11.2	<i>SNTA1</i>	α-1 syntrophin	I _{Na}	Increased due to S-nitrosylation of SCN5A	LQTS	Long QT
11q24.3	<i>KCNJ5</i>	Kir3.4 subunit	I _{KAch}	Loss of function	LQTS	Long QT
14q32.11	<i>CALM1</i>	Calmodulin 1	Ca kinetics	Defective Ca binding	LQTS IVF	Long QT Idiopathic ventricular fibrillation
14q32.11	<i>CALM2</i>	Calmodulin 2	Ca kinetics	Defective Ca binding	LQTS	Long QT
10p12.33	<i>CACNB2b</i>	Cavβ2β	I _{Ca}	Loss of function Loss of function	SQTS BrS	Short QT Brugada syndrome
7q21-q22	<i>CACNA2D1</i>	Ca _v α2δ-1	I _{Ca}	Loss of function Loss of function	SQTS BrS	Short QT Brugada syndrome
13p22.3	<i>GPD1L</i>	glycerol-3-phosphate dehydrogenase 1-like	I _{Na}	Reduced	BrS	Brugada syndrome
19q13	<i>SCN1B</i>	Na _v β1	I _{Na}	Loss of function Conduction disease Atrial fibrillation	BrS	Brugada syndrome
11q13.4	<i>KCNE3</i>	beta subunit	I _{to} , I _{KS}	Gain of function	BrS	Brugada syndrome
11q23.3	<i>SCN3B</i>	beta subunit	I _{Na}	Loss of function	BrS	Brugada syndrome
15q24.1	<i>HCN4</i>	HCN4	I _f	Loss of function	BrS	Brugada syndrome
1p13.3	<i>KCNDB3</i>	K _v 4.3	I _{to}	Gain of function	BrS	Brugada syndrome

(Continued)

Table 1: Known Channel Mutations in Genetic Channelopathies (Continued)

Chromosomal Locus	Gene	Protein	Current	Function	Syndrome	Phenotype
12p11.23	<i>KCNJ8</i>	α subunit	I_{KATP}	Gain of function	BrS, ERS	Brugada syndrome
17p13.1	<i>MOG1</i>	MOG1 (RAN guanine nucleotide release factor 1)	I_{Na}	Impaired trafficking of channel	BrS	Brugada syndrome
3p21.2-p14.3	<i>SLMAP</i>	SLMAP	I_{Na}	Impaired trafficking of channel	BrS	Brugada syndrome
Xq22.3	<i>KCNE5</i>	β subunit	I_{to}	Loss of function	BrS	Brugada syndrome
3q29	<i>DLG1</i>	synapse-associated 97	Junction	Reduced functions	BrS	Brugada syndrome
12p11	<i>PKP-2</i>	plaphilin-2	I_{Na}	Loss of function	BrS ARVC	Brugada syndrome Arrhythmogenic cardiomyopathy
1q42-43	<i>RyR2</i>	Cardiac ryanodine	Ca kinetics	Diastolic Ca	CPVT1	Catecholaminergic tachycardia receptor release bradycardia, AF, AV block, dilated cardiomyopathy
1p13-21	<i>CASQ2</i>	Cardiac calsequestrin	Ca kinetics	Diastolic Ca	CPVT2	Catecholaminergic tachycardia release
17q23	<i>KCNJ2</i>	Kir2.1	I_{K1}	Loss of function	CPVT3	Catecholaminergic tachycardia
14q32.11	<i>CALM1</i>	Calmodulin 1	Ca kinetics	Binding to RyR2	CPVT	Catecholaminergic tachycardia
6q22.31	<i>TRDN</i>	Triadin	Ca kinetics	Binding to RyR2	CPVT	Catecholaminergic tachycardia

I_{Ks} =rectifier K current, slow component. I_{Kr} =rectifier K current, rapid component. I_{Na} =inward Na current. I_{Na-K} =Na⁺/K⁺ ATPase current (Na/K pump). I_{Na-Ca} =Na-Ca exchanger current. I_{K1} =inward rectifier K channel. I_{Ca} =Ca current. SSS: sick sinus syndrome, ERS: early repolarisation syndrome, MOG1: Multicopy suppressor of Gsp1 (Nav β 1 partner), CPVT: catecholaminergic polymorphic VT, MEPPC: multifocal ectopic Purkinje-related premature contractions.

Table 2: Yield and Signal-to-Noise Associated with Disease-Specific Genetic Testing (HRS/EHRA Statement 2011)

Disease	Yield of Genetic Test*	% of Control with a rare VUS [#]	Signal-to-Noise (S:N) Ratio ⁺
LQTS	75 % (80%)	4%	19:1
CPTV	60 % (70%)	3 %	20:1
BrS	20 % (30%)	2 % (just SCN5A)	10:1
CCD	Unknown	Unknown	Unknown
SQTS	Unknown	3 %	Unknown
AF	Unknown	Unknown	Unknown
HCM	60 % (70 %)	~5 % (unpublished data)	12:1
ACM/ARVC	60 %	16 %	4:1
DMC	30 %	Unknown	Unknown
DMC + CCD	Unknown	4 % (for SCN5A and LMNA)	Unknown
LVNC	17 %–41 %	Unknown	Unknown
RCM	Unknown	Unknown	Unknown

* Yield of Genetic Test is a published/unpublished estimate, derived from unrelated cases with unequivocal disease phenotype. First number is the yield associated with the targeted major gene scan. The number in parentheses is the total yield when including all known disease-associated genes that have been included in commercial disease gene panels. When only a single percentage is provided, this represents the estimate from a comprehensive disease gene panel. These yield values represent estimates for whites with the particular disease phenotype. Evidence is lacking to establish point estimates for minority populations.

[#] % of controls with a rare variant of uncertain significance (VUS) represents a frequency of rare amino acid substitutions found in whites in the major disease-associated genes that, had it been found in a case, would have been reported as a 'possible disease-associated mutation'. This number does not include the frequency of rare genetic variants present in the minor disease-associated genes. Thus it represents a lower point estimate for the potential false positive rate.

⁺ The signal-to-noise (S:N) ratio is derived by dividing the yield by the background rate of VUS in controls. This provides a sense of the positive predictive value of a positive genetic test result. HRS/EHRA 2011 expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies, Heart Rhythm 2011;8:1308-39, by permission of Oxford University Press.

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: The subset of the human genome that encodes proteins (1–2 % of the total genome); it encompasses approximately 19,000 genes.

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

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.

Genome-wide association studies: Examination of many common genetic variants in individuals with and without a disease trait, to identify a possible higher frequency (ie association) of single-nucleotide polymorphisms in people with the trait.

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 for 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).

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.

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 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 amino acid.

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. 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.

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 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 proband: 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.

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