Screening of Genetic Life-threatening Arrhythmia: Who to Screen and How to Screen

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Disclosure: None

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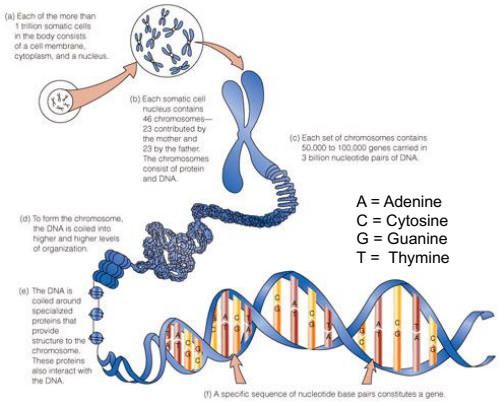
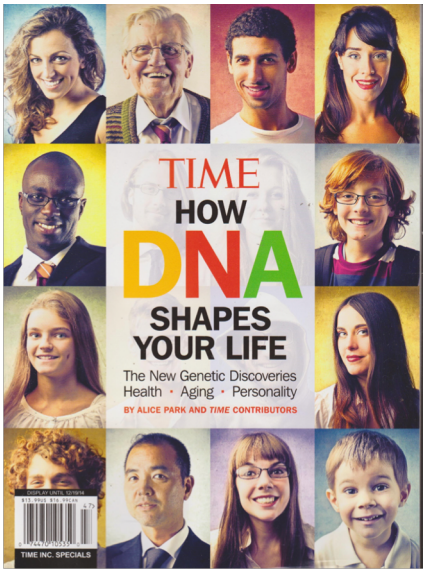
Chromosomes, DNA, genes, and nucleotides

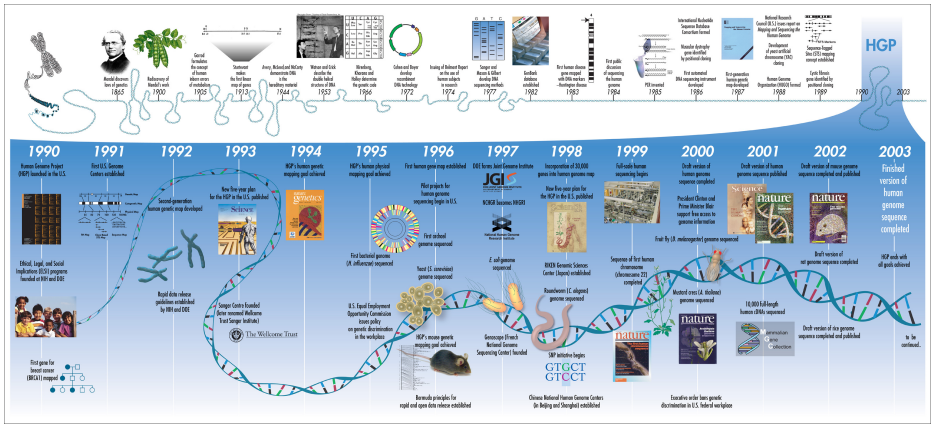


A = Adenine
C = Cytosine
G = Guanine
T = Thymine



- 99% of human genome is the same in all humans
- Common single nucleotide changes (i.e., Allele Frequency > 1%) → **single nucleotide polymorphism (SNPs)**
- Rarer genetic changes (<1% frequency), can be single nucleotide changes or bigger changes in the DNA sequence

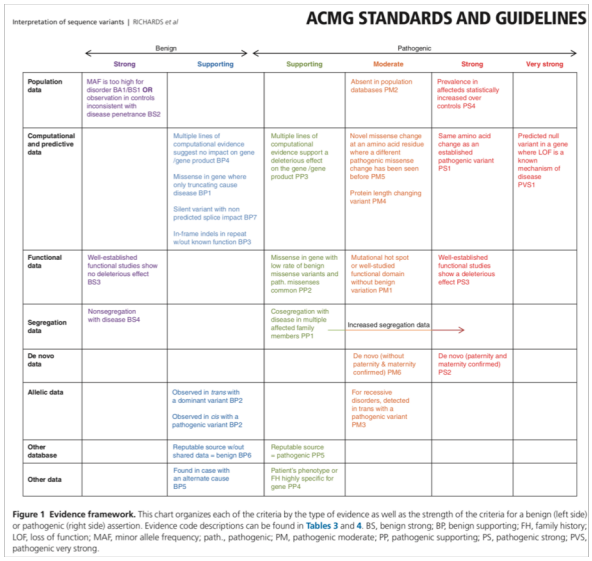
Human Genome Project
1990-2003: 1 Genome = US$ 3 Billion



2018: 1 Genome << US$ 1,000

American College of Medical Genetics (ACMG): Standard and guidelines for the interpretation of sequence variants 2015

- Five-tier terminology system to call 'variants'
  - **Pathogenic (P)**
  - **Likely Pathogenic (LP)**
  - Uncertain Significance (VUS)
  - Likely Benign (LB)
  - Benign (B)



Interpretation of sequence variants | RICHARDS *et al*

ACMG STANDARDS AND GUIDELINES

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Figure 1 Evidence framework. This chart organizes each of the criteria by the type of evidence as well as the strength of the criteria for a benign (left side) or pathogenic (right side) assertion. Evidence code descriptions can be found in **Tables 3** and **4**. BS, benign strong; BP, benign supporting; FH, family history; LOF, loss of function; MAF, minor allele frequency; path., pathogenic; PM, pathogenic moderate; PP, pathogenic supporting; PS, pathogenic strong; PVS, pathogenic very strong.

Hereditary Arrhythmias

- Long QT syndrome
- Brugada syndrome
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
- Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)
- Short QT syndrome

Genetic Considerations (1)

- Provide opportunity to confirm a suspected clinical diagnosis
- Sometimes provide prognostic information for the proband
- Offer cascade screening of potentially affected family members when a disease-causing mutation is identified in the proband
  - Lifestyle changes
  - Therapy
  - Ongoing monitoring

Genetic Considerations (2)

- Yield of genetic testing varies by disease
- Verification of pathogenicity of mutation is an evolving field
- Genotyping can have therapeutic implications for some phenotypes (LQTS and Fabry's disease)
- Role is less certain in other diseases (e.g., Brugada syndrome)
  - Environmental factors influence disease progression
- Absence of mutation does not exclude the presence of disease

Genetic Considerations (3)

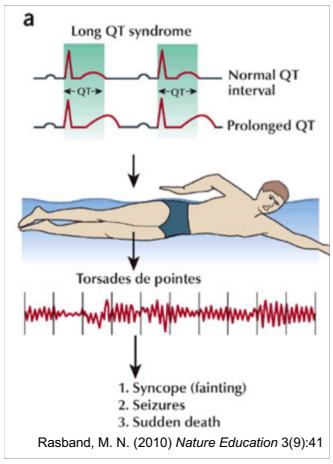
- Decision to proceed with genetic testing
  - Discussion regarding clinical use of genetic information
  - Important psychological, financial, employment implications of positive genotyping
  - Family dynamics, geographic proximity and access to health care
  - **Genetic counseling generally occurs before proceeding with genetic testing (physician + genetic counselors)**

Genetic Considerations in Arrhythmia

- In patients and family members in whom genetic testing for risk stratification for SCD is recommended, genetic counseling is beneficial. *Class I*
- In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended. *Class I*

Long QT syndrome

- **QT Prolongation and T-wave abnormalities on ECG**
- Associated with tachyarrhythmias, typically VT torsade de pointes (TdP); degenerates to VF and SCD
- Causing **syncope during exercise, emotional stress, less frequently during sleep, without warning.**
- Cardiac events may occur from infancy to middle age, most common from preteen through the 20s
- Prevalence 1:3,000 to 1:5,000
- Diagnosed by **prolonged QTc without specific known conditions** and/or **by genetic testing** that identifies variant(s) in one of 15 genes



Rasband, M. N. (2010) *Nature Education* 3(9):41

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Genetic Mutations and Clinical Characteristics Associated with Long QT Syndrome

LQTS	Gene	Protein	% of LQTS	Clinical Syndrome	Clinical Presentation
LQT1	*KCNQ1*	Kv7.1	45%	RWS; JLNS	Prolonged QT, syncope with physical activity (with congenital sensorineural hearing loss for JLNS)
LQT2	*KCNH2*	Kv11.1	45%	RWS	Prolonged QT, syncope with sudden emotion or noise
LQT3	*SCN5A*	Nav1.5	7%	RWS; Brugada syndrome	Prolonged QT, syncope at rest, characteristic ECG pattern (Brugada)
LQT4	*ANK2*	Ankyrin-B	Unknown	Prolonged QT	Prolonged QT, atrial arrhythmias
LQT5	*KCNE1*	minK	<1%	RWS; JLNS	Prolonged QT (with congenital sensorineural hearing loss for JLNS)
LQT6	*KCNE2*	miRP1	<1%	RWS	Prolonged QT
LQT7	*KCNJ2*	Kir2.1	<1%	Andersen-Tawil syndrome	Periodic paralysis, high-frequency bidirectional ventricular tachycardia, prolonged QT
LQT8	*CACNA1C*	Cav1.2	<1%	Timothy syndrome	Prolonged QT with syndactyly and facial and neurodevelopmental changes
LQT9	*CAV3*	CAV3	Unknown	Cavelinopathy	Prolonged QT
LQT10	*SCN4B*	Navbeta4	<1%	RWS	Prolonged QT
LQT11	*AKAP9*	Yotiao	Unknown		Prolonged QT
LQT12	*SNTA1*	Alpha1 syntrophin	Unknown		Prolonged QT
LQT13	*KCNJ5*	Kir3.4	Unknown	RWS	Prolonged QT
LQT14	*CALM1*		<1%	RWS	Prolonged QT
LQT15	*CALM2*		<1%	RWS	Prolonged QT

>90 % of genetically confirmed LQTS

Loss of function

Loss of function

Gain of function

Swimming

Alarm clock

At rest

ECG = electrocardiogram; JLNS = Jervell and Lange-Nielsen syndrome; RWS = Romano-Ward syndrome.

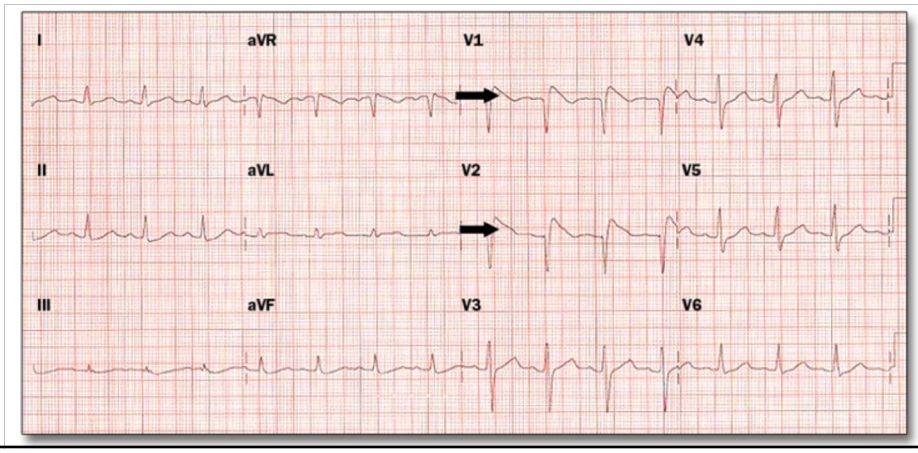
Modified from Vincent GM. Romano-Ward Syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens K, eds. GeneReviews. Seattle: University of Washington, Seattle; 1993, and Goldenberg I, Zareba W, Moss AJ. Long QT Syndrome. Curr Probl Cardiol 2008;33:629-94.

LQTS: *Genetic screening*

- Genetic testing offers **diagnostic, prognostic, and therapeutic information**
- Positive test facilitates establishing **risk for family members**
- Yield of genetic testing in phenotype-positive: **50-86%**
  - Higher range in marked QT prolongation or positive family history
  - Negative test does NOT exclude the diagnosis of LQTS
- Help confirm the diagnosis and supplement prognostic information in asymptomatic patients with unexplained QTc > 480

Brugada syndrome

- Characterized by right ventricular (RV) conduction abnormalities and **coved-type ST segment elevation in the right precordial leads (V1-V2)** on ECG (2nd, 3rd, 4th ICS)
- Can cause VF and SCD at an early age
- Relatively rare, 3 in 10,000 people, 8-10 fold more in men than women



Brugada syndrome: *genetic mutations*

- Autosomal dominant pattern with variable penetrance and expressivity
  - Ranging from asymptomatic individuals to SCD during the first year of life
- Most mutations occur in genes within or related to the sodium channel (*SCN5A*)
  - SCN5A causes 20-25% of Brugada Syndrome
- Several genes encoding auxiliary proteins of sodium channel linked to Brugada Syndrome
  - *SCN5A*
  - *SCN1B*
  - *SCN3B*
  - *GPDL1*
  - *CACNA1C*
  - *CACNB2B*

Brugada syndrome: *genetic consideration*

- In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing **may be useful** to
  - Help risk-stratify and confirm the diagnosis in the proband
  - Facilitate cascade screening of relatives, allowing for lifestyle modification and potential treatment. *Class IIb*
- Diagnostic yield is low, up to 70% of patients not having an identifiable mutation on genetic testing

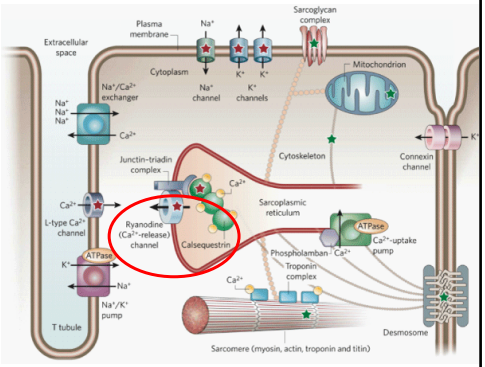
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

- Characterized by exertion-related polymorphic or bidirectional VT associated with syncope or sudden cardiac arrest (3-13%)
- Swimming often precipitates an arrhythmia
- Generally have a **structurally normal heart** with high risk for SCD

CPVT: *Genetic mutations*

Two types:

- **Autosomal dominant** caused by mutation in cardiac ryanodine receptor 2/calcium release channel gene (*RYR2*) 60%
  - Regulates calcium from sarcoplastic reticulum (SR)
- **Autosomal recessive** form caused by mutations in cardiac calsequestrin (*CASQ2*) <5%
  - Calcium storage protein within lumen of SR
- Rare causes: triadin, *KCNJ2*, Calmodulin



CPVT: *Genetic screening*

- In patients with CPVT and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable. *Class IIa*
  - *Therapy for CPVT not guided by genotype status*
  - *Facilitate screening of first-degree relatives*
- 15% of proposed pathogenic mutations in CPVT found in general population
  - *Raising questions for monogenic cause of CPVT*

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

- **Characterized by a cardiomyopathy affecting RV predominantly**
  - Syncope
  - Palpitations
  - Sudden cardiac death
  - Abnormal ECG
  - Abnormal right ventricle seen through cardiac imaging
- **Fibrofatty replacement of cardiomyocytes**
- Increase risk of SCD due to ventricular arrhythmias at a young age
- 2010 Task Force criteria for clinical diagnosis of ARVD/C
  - Two major criteria
  - One major and two minor criteria
  - Four minor criteria
- Six categories encompassing the clinical criteria
  - Global/regional RV dysfunction/structural alterations
  - Tissue characterization of wall (endomyocardial biopsy)
  - ECG repolarization abnormalities (inverted T waves)
  - Depolarization/conduction abnormalities (epsilon wave in V1-V3)
  - Arrhythmias (VT or NSVT)
  - Family history

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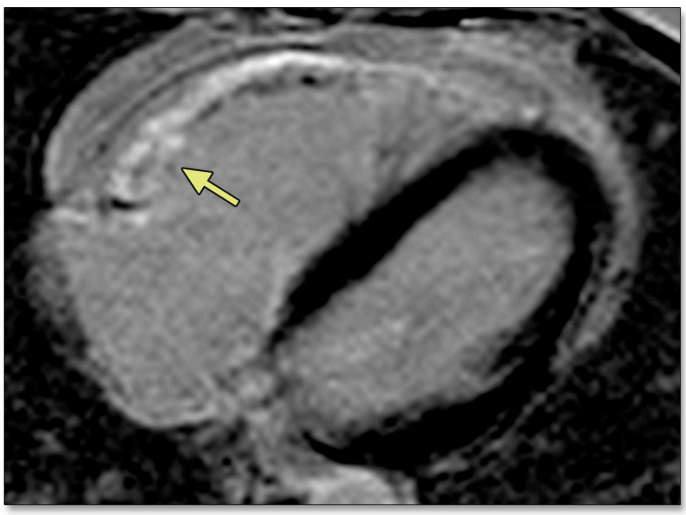
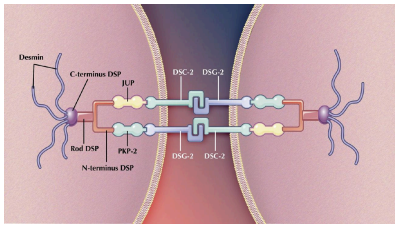


PSIR Image showing a delayed gad enhancement at the area under the TV, suggestive of fibrosis.
Anneline S.J.M. te Riele et al. JIMG 2015;8:597-611

ARVC: *Genetic mutations*

- **Autosomal dominant pattern**
  - Low penetrance
  - High variability
- Mutations in genes encoding cardiac desmosome
  - Important for **mechanical cell to cell adhesion**
- 15 genes have been described in ARVD/C
  - Plakophilin 2 (*PKP2*) 43%
  - Desmocollin-2 (*DSC2*)
  - Desmoplakin (*DSP*)
  - Desmoglein-2 (*DSG2*)
  - Plakoglobin (*JUP*)
  - *TGFB3*
  - *TMEM43*
- Given low yields and unclear implication, role of genetic testing is not well established
  - Negative result does not rule out the disease



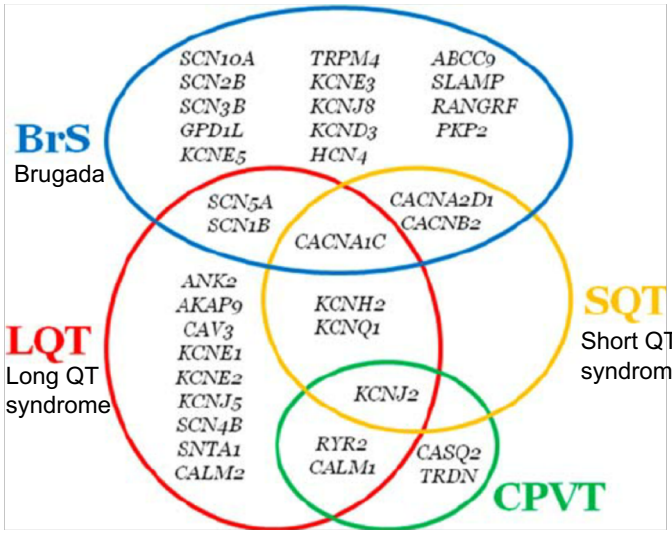
Srijita Sen-Chowdhry et al. JACC 2007;50:1813-1821

ARVC: *Genetic consideration*

- In patients with clinically diagnosed or suspected ARVC, genetic counseling and genetic testing can be useful for diagnosis and for gene-specific targeted family screening (*Class IIa*)
- For the proband with a clinical diagnosis of ARVC, identification of pathogenic mutations provides **limited prognostic information relative to the risk of VT/VF or development of HF**
- Presence of positive mutations among probands was not associated with a difference in mortality or cardiac transplantation
- The identification of a pathogenic mutation facilitates targeted genetic screening for that mutation in first- degree relatives

Overlapping genes associated with cardiac channelopathies

Changing landscape



Thank you!