Genetics and Inherited Arrhythmia Syndromes

(The Good, The Bad and The Ugly)

Melanie Care, MSc, CCGC

Genetic Counsellor

Inherited Arrhythmia Clinic, Toronto General Hospital

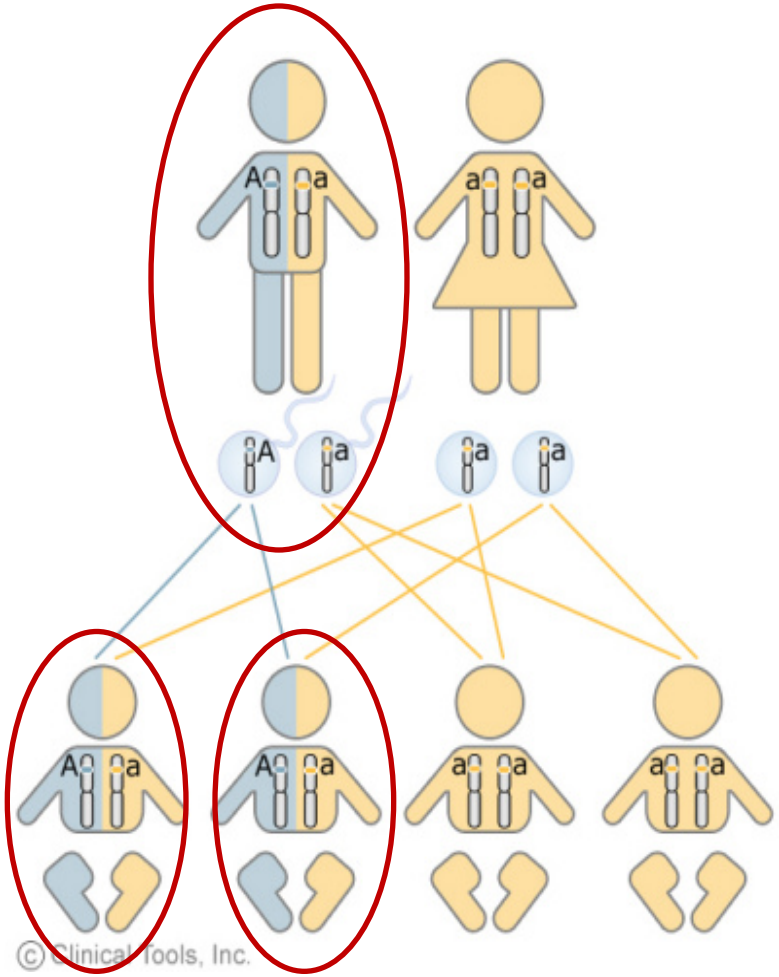
UHN Peter Munk Cardiac Centre

- No COI to disclose

Objectives

- To review basic inheritance in hereditary arrhythmias
- To discuss interpretation of genetic test results
- To demonstrate utility and limitations of genetic testing

Inherited Arrhythmias



A = disease-causing variant
a = normal copy

Autosomal dominant

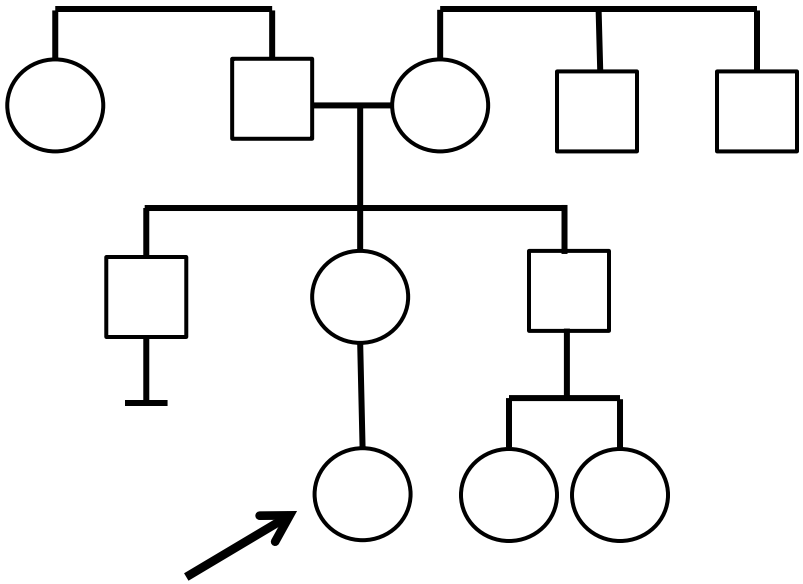
Reduced Penetrance

Variable Expression

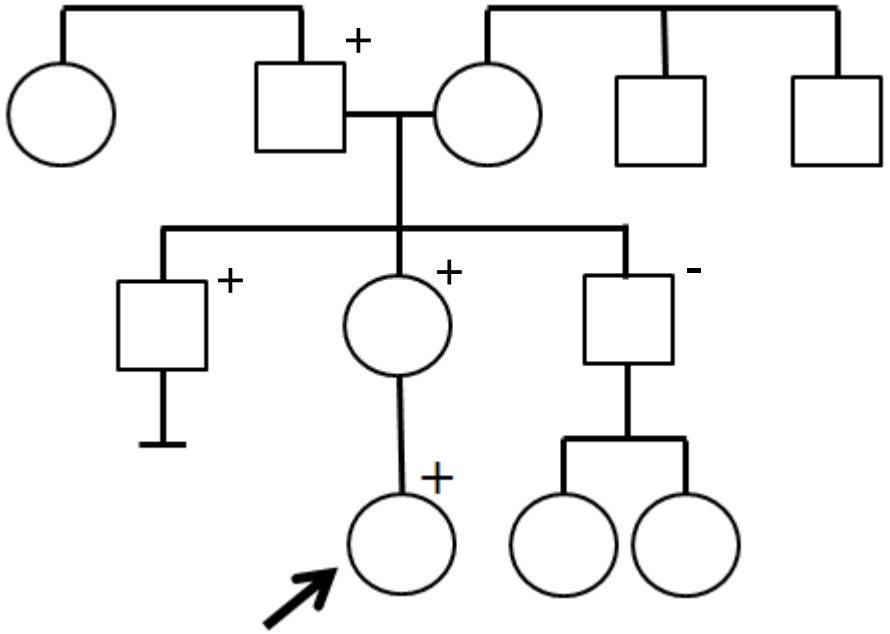
Genetic Testing

- Rapid, high-throughput DNA analysis
- Simultaneous testing of large numbers of gene

The Good….



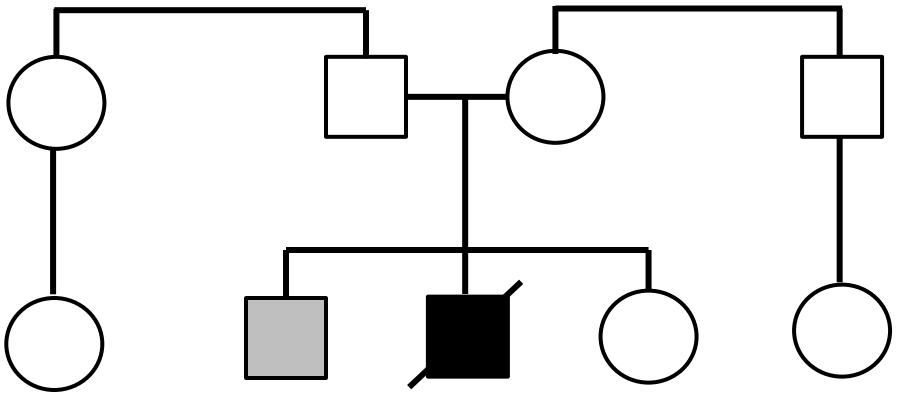
- 21 yo with recurrent syncope
- Resting ECG shows borderline QT
- Exercise test shows abnormal QT dynamics s/o LQTS



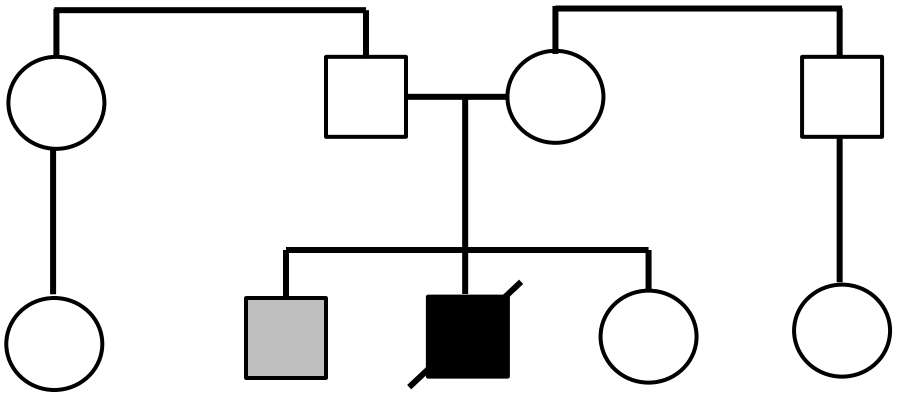
***KCNQ1*, p. Gln356X**
LONG QT SYNDROME

- Confirmation of diagnosis
- Management recommendations
- Accurate family risk assessment
- Cascade screening

The Bad...



- 18 yo sudden death, autopsy consistent with ARVC
- Parents, siblings referred for clinical evaluations
- 20 yo brother has features s/o ARVC



Genetic testing - negative

No mutations/variants detected

OR

Gene variants detected known not to cause disease

- Clinical diagnosis not excluded

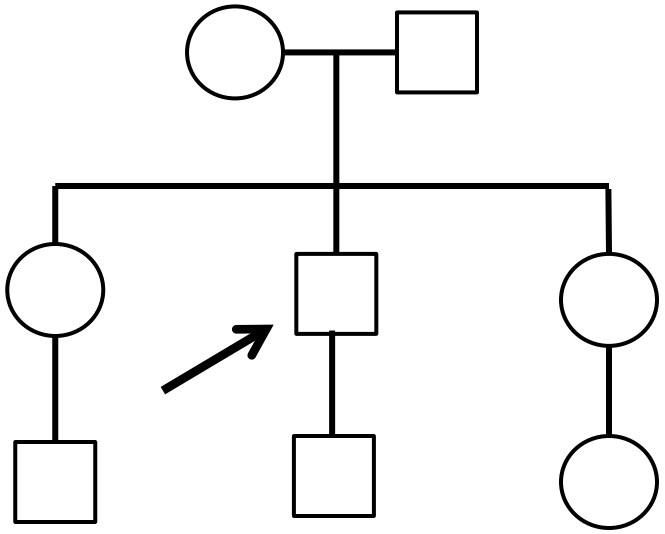
Table 1 Overview of inherited heart disease genes and genetic testing detection rates [2, 3, 5, 16–18]

Inherited heart condition	Associated genes			Genetic testing detection rate
	Autosomal dominant inheritance	Autosomal recessive inheritance	X-linked inheritance	
ARVC	*PKP2*[a], *DSP*[a], *DSG2*[a], *DSC2*, *TMEM43*, *JUP*, *PLN*, *RYR2*	*JUP*[b], *DSP*[b], *DSC2*[b]	NA	25–60%
BrS	*SCN5A*[a], *SCN10A*, *GPD1L*, *CACNA1C*, *PKP2*, *CACNB2*, *SCN1B*, *KCNE3*, *SCN3B*, *HCN4*, *CACNA2D1*, *RANGRF*, *TRPM4*, *SLMAP*, *KCNJ8*, *ABCC9*, *KCND3*, *KCNH2*, *FGF12*, *SEMA3A*	NA	*KCNE5*	25–30%
CPVT	*RYR2*[a], *KCNJ2*, *CALM1*, *CALM2*, *ANK2*	*CASQ2*, *TRDN*	NA	50–60%
DCM	*MYH7*[a], *TTN*[a], *LMNA*[a], *MYBPC3*, *ABCC9*, *ACTC1*, *ACTN2*, *BAG3*, *CAV3*, *CRYAB*, *CSRP3*, *DES*, *EYA4*[b], *FKRP*, *FLNC*, *PKP2*, *PLN*, *RAF1*[b], *RBM20*, *SCN5A*, *TCAP*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*, *TTR*[b], *VCL*, *PSEN1*[b], *PSEN2*[b], *MYH6*, *ANKRD1*, *MYPN*, *PDLIM3*, *LDB3*, *LAMA4*, *KHL2*, *TMPO*, *GATAD1*	*SGCD*[b], *DOLK*[b], *TCAP*[b], *FKTN*[b], *SLC22A5*[b], *MYPN*[b], *GATAD1*	*DMD*[b], *TAZ*, *DES*[b], *EMD*[b], *LAMP2*[b]	10–30%
HCM	*MYBPC3*[a], *MYH7*[a], *TNNT2*, *TNNI3*, *ABCC9*, *ACTC1*, *ACTN2*, *CSRP3*, *MYL2*, *MYL3*, *MYOZ2*, *NEXN*, *TNNC1*, *TPM1*, *TTR*[b], *PRKAG2*, *CAV3*, *JPH2*, *PLN*, *CALR3*, *LDB3*, *TCAP*, *VCL*, *ANKRD1*, *MYPN*, *RAF*[b], *PTPN11*[b]	NA	*GLA*[b], *LAMP2*[b]	35–60%
LQTS	*KCNQ1*[a], *KCNH2*[a], *SCN5A*[a], *ANK2*, *KCNE1*, *KCNE2*, *KCNJ2*[b], *CACNA1C*[b], *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *CALM1*, *CALM2*, *CACNA2D1*	*KCNQ1*[b], *KCNE1*[b], *TRDN*	NA	75–80%
SQTS	*KCNH2*, *KCNQ1*, *KCNJ2*	NA	NA	UK
IVF	*DPP6*, *CALM1*, *RYR2*, *IRX3*	NA	NA	UK
PCCD	*SCN5A*, *TRPM4*, *SCN1B*, *SCN10A*, *KCNK17*, *NKX2.5*[c], *GATA4*[c], *LMNA*[b], *DES*[b]	NA	NA	UK

  - If clinical suspicion is high, negative results must be interpreted with caution
- Hereditary condition not ruled out
- At-risk family members require comprehensive evaluation and f/u

Care et al, Curr Cardiol Rep, 2017

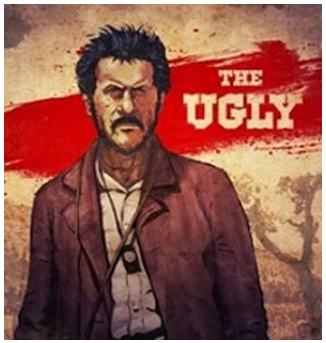
The Ugly…

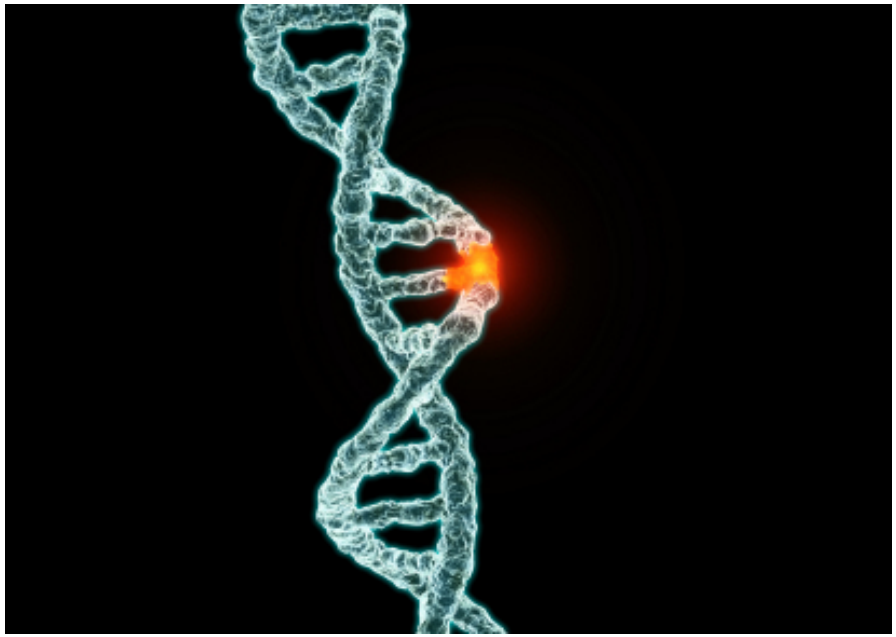


- 49 y.o. man presents at local ER with fever
- ECG shows Brugada pattern
- Additional investigations equivocal

Summary

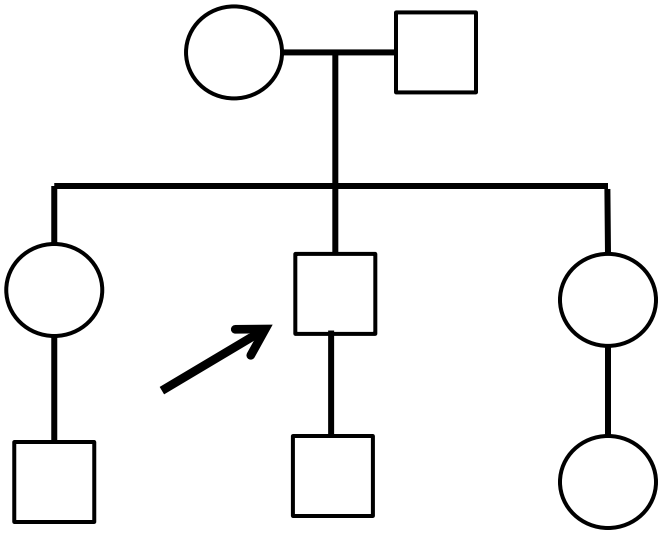
Variant of Uncertain Significance identified in SCN10A.





Not all gene variants cause disease

Variants of Uncertain Significance

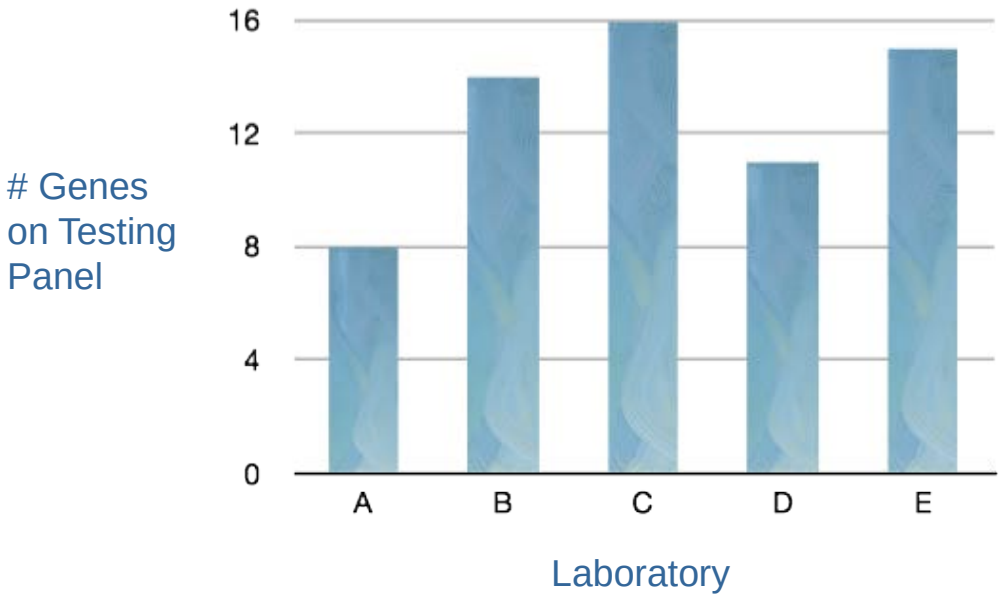


- Diagnosis not confirmed/eliminated
- Genetic cause not confirmed/eliminated
- Genetic testing not useful for unaffected family members

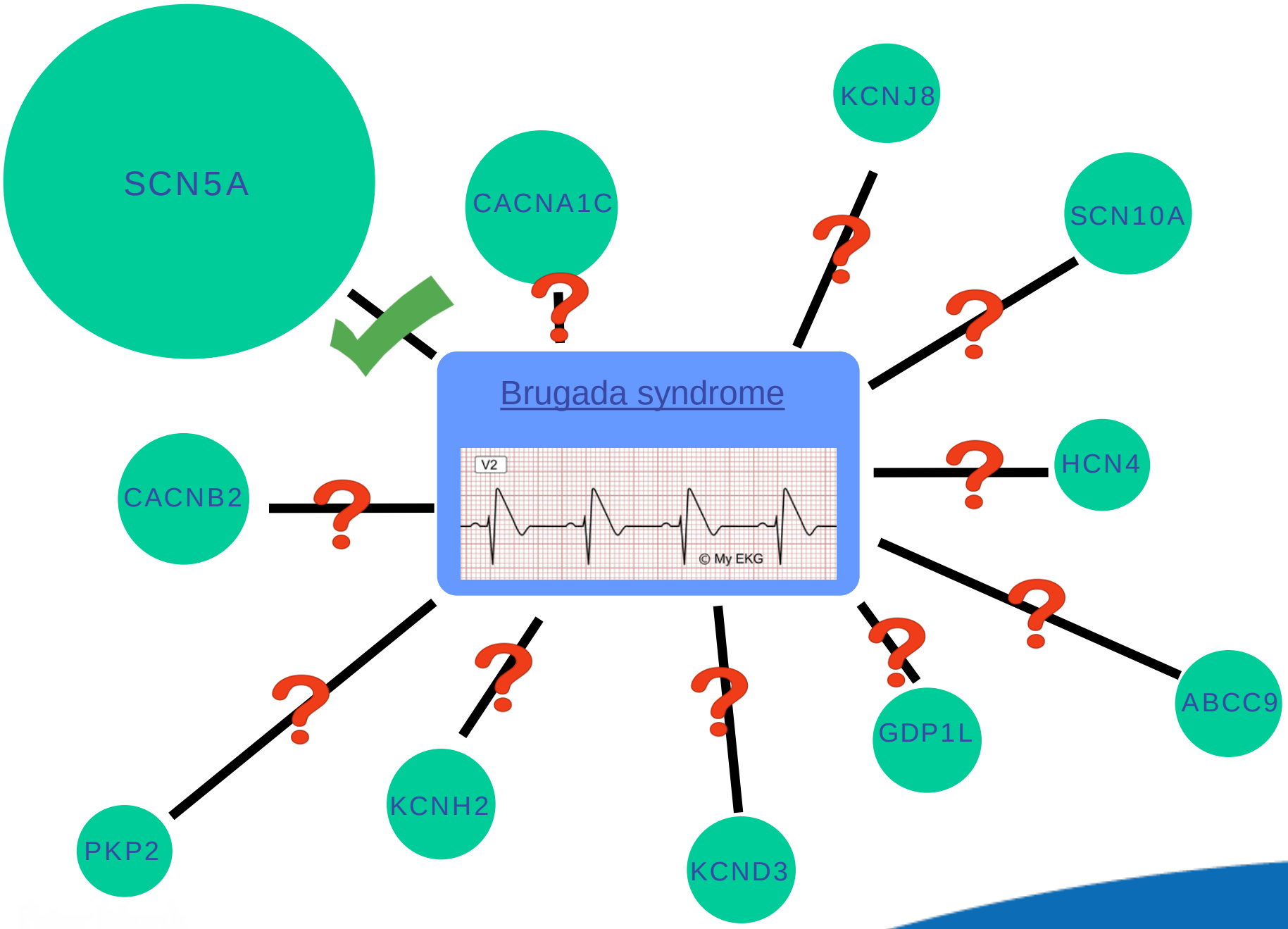
Does this gene cause disease?

- How was the gene discovered?
- Is there good evidence to support gene-disease association

Brugada syndrome - Genetic testing panels



The presence of a gene on a genetic testing panel does not equal association with disease


SCN5A
CACNA1C
KCNJ8
SCN10A
Brugada syndrome
V2
© My EKG
CACNB2
HCN4
PKP2
KCNH2
KCND3
GDP1L
ABCC9

Does this variant cause disease?

Rare gene variants are present in the general population!

The Achilles' Heel of Cardiovascular Genetic Testing: Distinguishing Pathogenic Mutations From Background Genetic Noise

AP Landstrom[1] and **MJ Ackerman**[2]

Clin Pharmacol Ther. 2011 October ; 90(4): 496–499. doi:10.1038/clpt.2011.192.

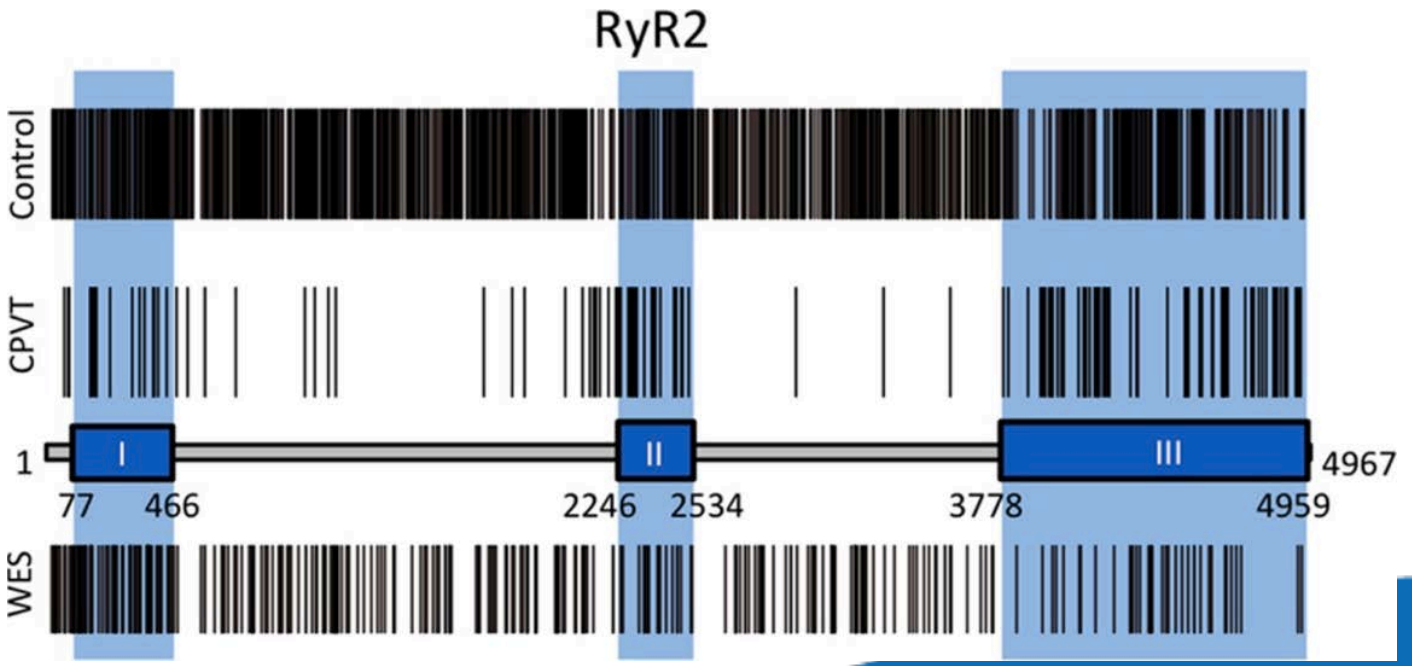
ORIGINAL ARTICLE

Interpreting Incidentally Identified Variants in Genes Associated With Catecholaminergic Polymorphic Ventricular Tachycardia in a Large Cohort of Clinical Whole-Exome Genetic Test Referrals

Andrew P. Landstrom, Andrew L. Dailey-Schwartz, Jill A. Rosenfeld, Yaping Yang, Margaret J. McLean, Christina Y. Miyake, Santiago O. Valdes, Yuxin Fan, Hugh D. Allen, Daniel J. Penny, Jeffrey J. Kim

DOI https://doi.org/10.1161/CIRCEP.116.004742
Circulation: Arrhythmia and Electrophysiology. 2017;10:e004742
Originally published April 12, 2017

RYR2 rare variants identified in 9% of individuals referred for whole exome sequencing (all indications)



ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

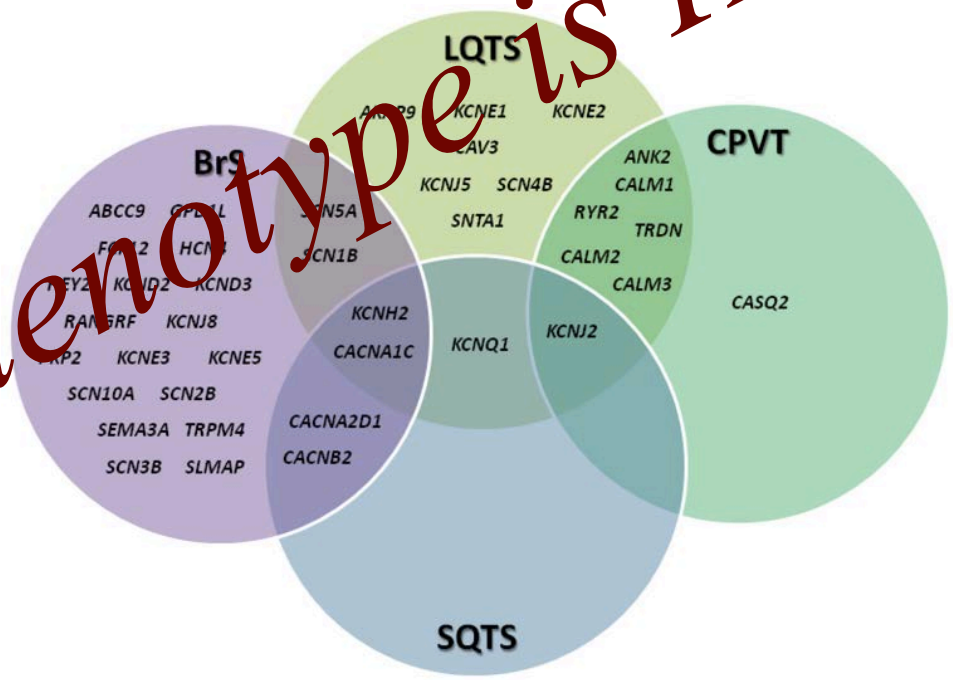
Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

	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*	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	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & 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*			

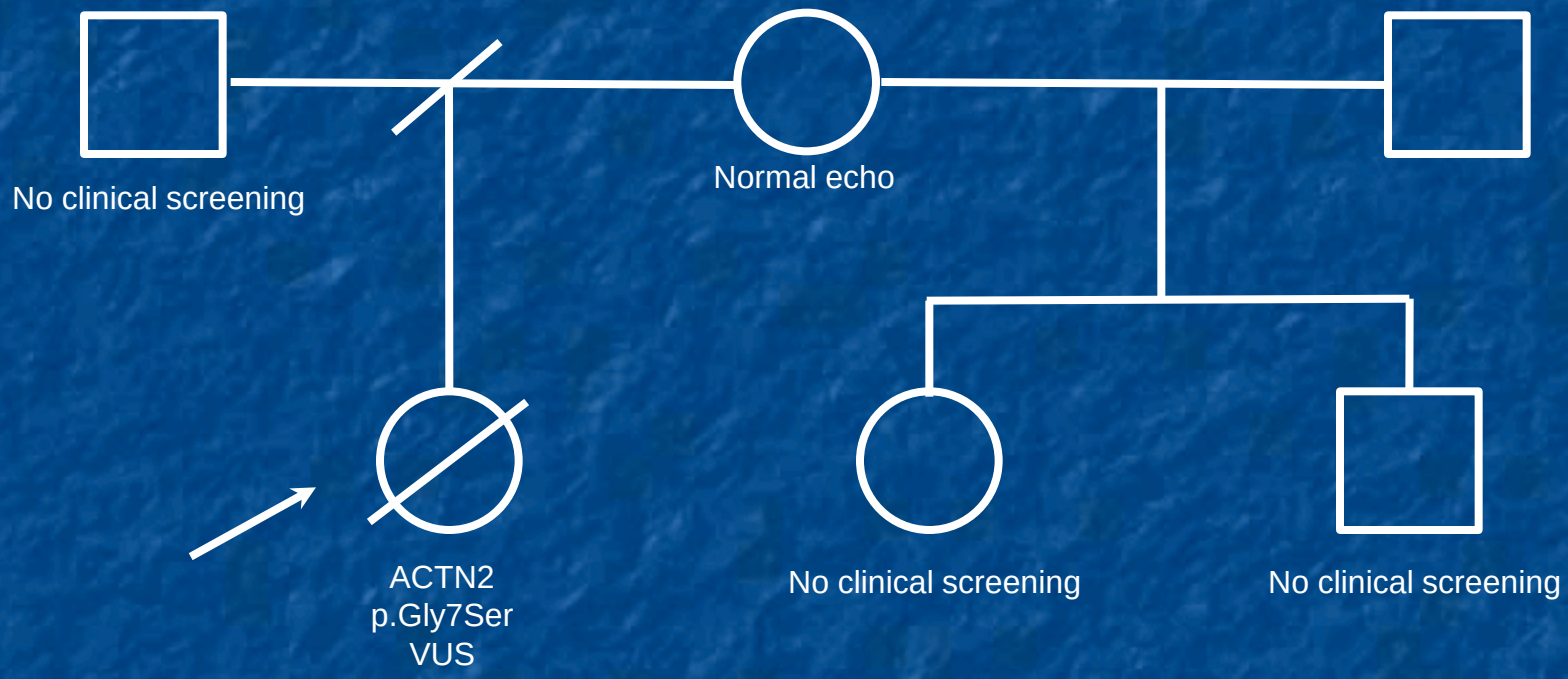
Does this result make sense?

- Genetic results must be interpreted in the context of clinical presentation



Phenotype is King!!

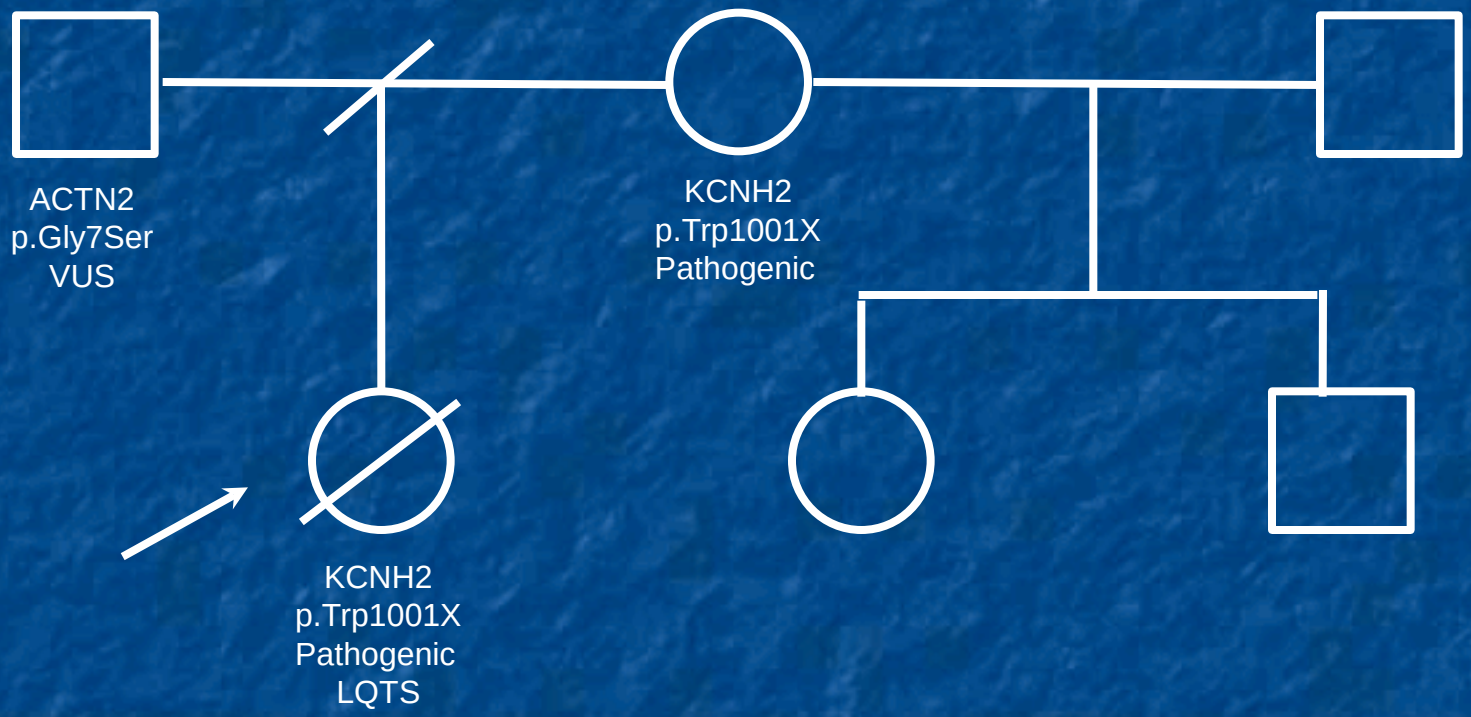
Why It Matters



Medical Advice Given:

- Genetic testing for mother
- IF result positive, genetics on other children and f/u for those who test positive
- IF result negative, other children not at risk and no further f/u or testing required

Why It Matters

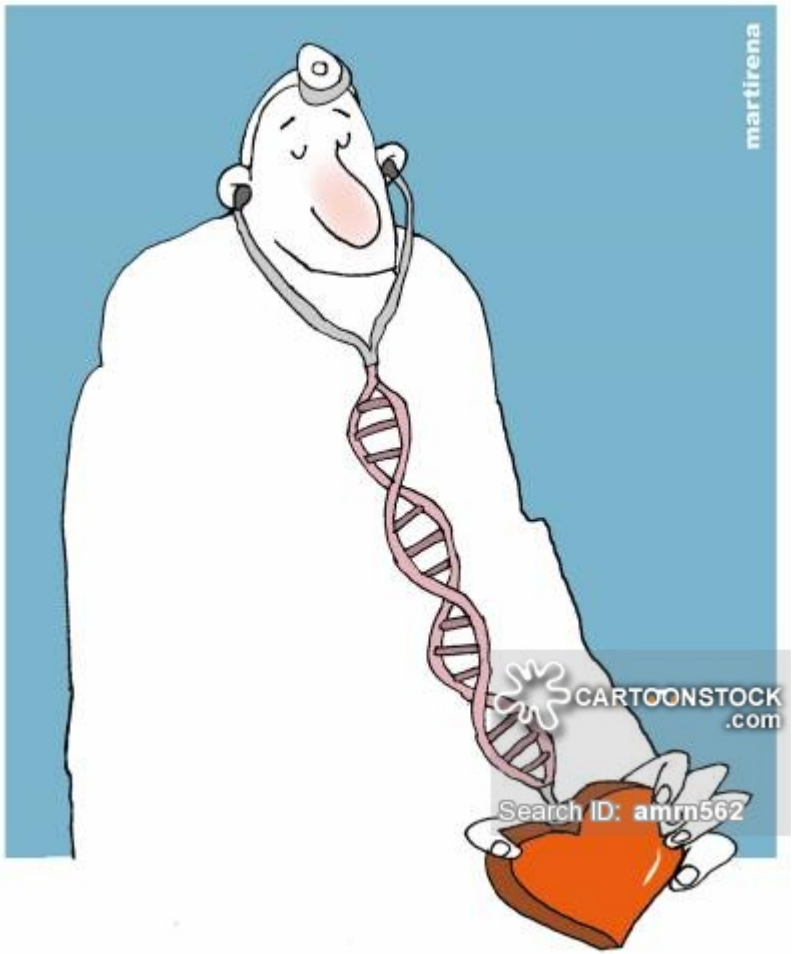


- Mother – negative for ACTN2, positive for KCNH2
- Half-siblings AT RISK, clinical evaluations and genetic testing recommended

Conclusion

- Genetic testing can be a useful and powerful tool in confirming diagnoses, managing risk in affected patients, identifying at-risk family members
- Genetic testing is one piece of the puzzle
- Genetic testing should be undertaken in the context of expert, clinical evaluation and appropriate genetic counselling

Thank you!



melanie.care@uhn.ca

UHN Peter Munk Cardiac Centre