Genetics and Inherited Arrhythmia Syndromes
(The Good, The Bad and The Ugly)

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• 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

Autosomal dominant
Reduced Penetrance
Variable Expression

A = disease-causing variant
a = normal copy
Genetic Testing

- Rapid, high-throughput DNA analysis
- Simultaneous testing of large numbers of genes
• 21 yo with recurrent syncope
• Resting ECG shows borderline QT
• Exercise test shows abnormal QT dynamics s/o LQTS
• Confirmation of diagnosis
• Management recommendations
• Accurate family risk assessment
• Cascade screening

**KCNQ1, p. Gln356X**

**LONG QT SYNDROME**
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

  – 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
49 y.o. man presents at local ER with fever
ECG shows Brugada pattern
Additional investigations equivocal
**Not all gene variants cause disease**

Summary

Variant of Uncertain Significance identified in SCN10A.
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**
Brugada syndrome

SCN5A
CACNA1C
KCNJ8
SCN10A
HCN4
ABCC9
CACNB2
PKP2
KCNH2
KCND3
KCNJ8
KCND3
GDP1L

V2
© My EKG
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 Landstrom¹ and MJ Ackerman²

RYR2 rare variants identified in 9% of individuals referred for whole exome sequencing (all indications)
## 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, PhD¹, Nazneen Aziz, PhD²,¹⁶, Sherri Bale, PhD³, David Bick, MD⁴, Soma Das, PhD⁵, Julie Gastier-Foster, PhD⁶,⁷,⁸, Wayne W. Grody, MD, PhD⁹,¹⁰,¹¹, Madhuri Hegde, PhD¹², Elaine Lyon, PhD¹³, Elaine Spector, PhD¹⁴, Karl Voelkerding, MD¹³ and Heidi L. Rehm, PhD¹⁵; on behalf of the ACMG Laboratory Quality Assurance Committee

### Table: Criteria for Determining Benign vs. Pathogenic Variants

<table>
<thead>
<tr>
<th>Population Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAF is too high for disorder</td>
<td>In general, no effect on gene product</td>
<td>Absent in population databases</td>
<td>Prevalence in affecteds statistically increased over controls</td>
<td></td>
</tr>
<tr>
<td>Other factors consistent with disease penetrance</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Computational And Predictive Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple lines of computational evidence suggest no impact on gene product</td>
<td>Multiple lines of computational evidence support a deleterious effect on gene product</td>
<td>Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PMS</td>
<td>Same amino acid change as an established pathogenic variant</td>
<td>Predicted null variant in a gene where LOF is a known mechanism of disease</td>
</tr>
<tr>
<td>Mis-sense in gene where only-translating cause disease BP</td>
<td>Mis-sense in gene with low rate of benign mis-sense variants and path. mis-sense common</td>
<td>Mutation hot spot or well-studied functional domain in the absence of benign variation</td>
<td>Well-established functional studies show a deleterious effect</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Functional Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-established, functional studies show no deleterious effect</td>
<td>Mis-sense in gene with low rate of benign mis-sense variants and path. mis-sense common</td>
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<table>
<thead>
<tr>
<th>Segregation Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-segregation with disease BP</td>
<td>Co-segregation with disease in multiple affected family members</td>
<td>Increased segregation data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>De novo Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo (without paternity &amp; maternity confirmed)</td>
<td>De novo (paternity &amp; maternity confirmed)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Allele Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed in trans with dominant variant BP</td>
<td>For recessive disorders, detected in trans with a pathogenic variant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed in cis with a pathogenic variant BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Database</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reputable source w/out shared data = benign BP</td>
<td>Reputable source = pathogenic BP</td>
<td></td>
<td></td>
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<td>Found in case of an alternate cause BP</td>
<td>Patient's phenotype or PP highly specific for gene BP</td>
<td></td>
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</table>
• Genetic results must be interpreted in the context of clinical presentation

Does this result make sense?

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!

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