Which Came First, Validity or Clinical Testing? Assessing the Long QT Genes

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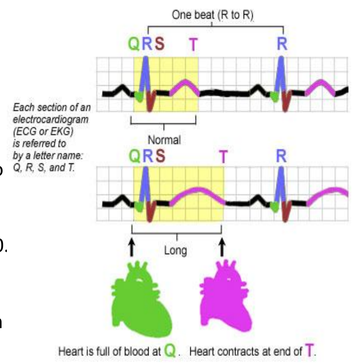
INTRODUCTION

Advances in technology now allow for larger, more expansive gene tests. While beneficial for conditions with significant genetic heterogeneity, more genes may not always be better. There is a need for uniform assessment of the validity of gene-disease pairs. To explore this, we evaluated the relationship between gene validity and available clinical testing for the 13 genes associated with Long QT syndrome (LQTS) using the draft clinical validity classification scheme developed by the Clinical Genome Resource (ClinGen) working group (see poster 390 for a description of this metric). Categories that are considered in determining validity include: year the gene was linked to disease, number of probands and total cases, number of independent clinical reports, segregation data, and functional data. Using this metric, it was possible to determine how the strength of evidence for LQTS genes has changed from the initial disease causality report.

LONG QT SYNDROME

LQTS is an inherited cardiac electrophysiologic disorder that is characterized by prolongation of the QTc interval on an ECG. This electrical disturbance causes the heart muscle to take longer to prepare for each beat. Penetrance is incomplete for all genes, and prevalence in estimated at 1/3,000. Symptoms range from syncope to sudden death. Cardiac events may occur at any age but are most common in the 2nd and 3rd decade.



METHODS

Process of curation

- ClinGen Clinical Validity Classifications
  - Definitive- role of gene has been repeatedly demonstrated in research and clinical diagnostic settings and upheld over time
  - Strong- evidence from at least two independent studies to support causal role for gene in disease, gene demonstrates excess of pathogenic variants in affected compared to control individuals
  - Moderate- evidence to support a causal role includes at least 3 unrelated probands with pathogenic variants and some supporting experimental data
  - Limited- evidence to support causal role includes fewer than three observations of a pathogenic variant, report of causality is recent
- Current validity and validity at 1st test

Interviews

1-on-1 phone interviews with personnel from 9 US laboratories were conducted. Labs were identified via public records and testing databases. The following questions were asked:

- When did you first offer testing for LQTS? What genes were included and why?
- How has your offering changed since its inception? Why?
- Describe factors that you feel may have influenced the decision to add a new gene to the test.
- Going forward, what do you think would impact the decision to add or remove genes from your LQTS test?

RESULTS

	Genes labs currently test	# of labs testing for this set of genes
LQT panels	KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5	4
	KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1	2
	KCNQ1, KCNH2, SCN5A	1
Special focus tests	KCNJ2, CAV3	1
	CACNA1C	1

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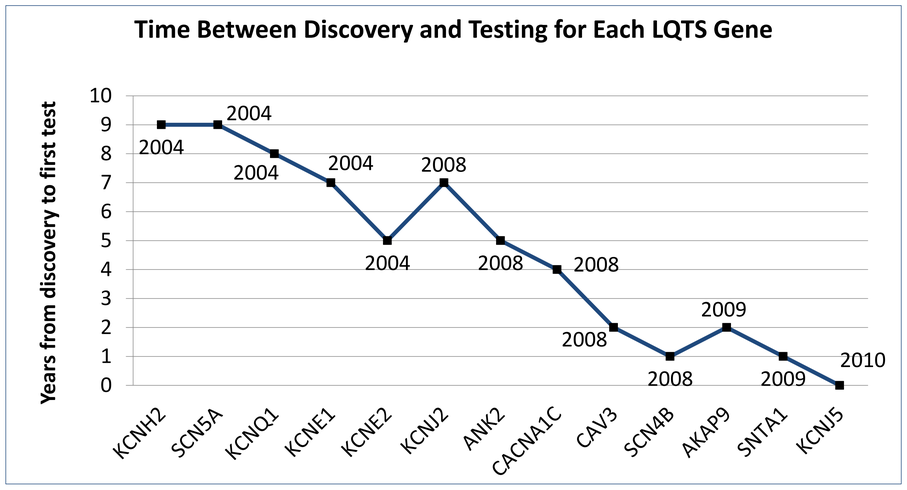


Figure 1. The length of time between when a LQTS gene was first linked to disease in a human and first offering of the gene on a genetic test.

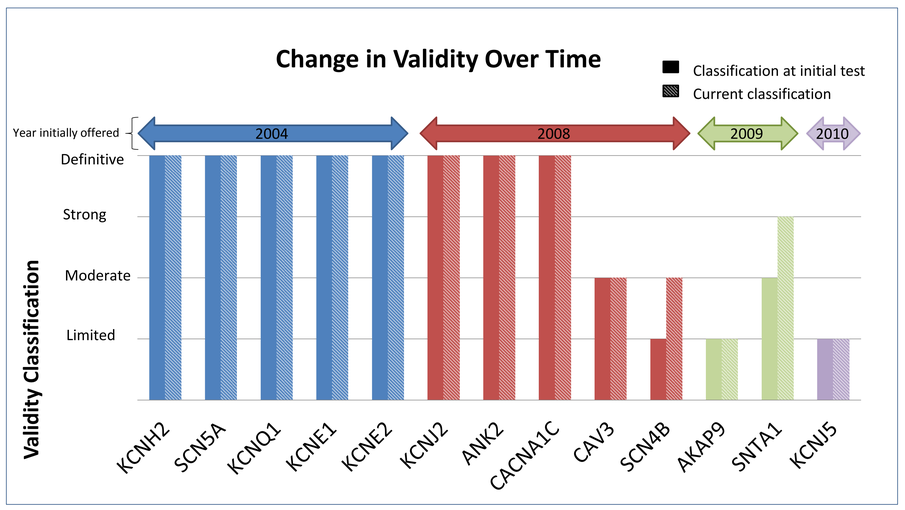
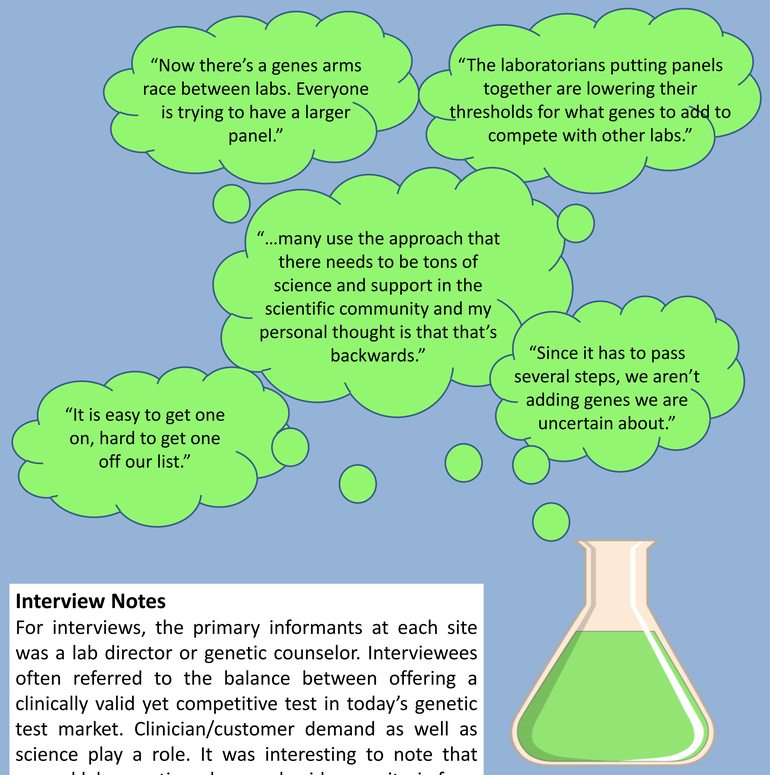


Figure 2. Earlier discovered genes had a higher validity at the time they were first offered on a genetic test than more recently discovered genes.

LQT Genes Symbol	Disease Associated Disease	Year of 1st publication assertion association	Year first test was offered by any lab	Current Validity
KCNQ1	LQTS 1	1996	2004	Definitive
KCNH2	LQTS 2	1995	2004	Definitive
SCN5A	LQTS 3	1995	2004	Definitive
ANK2	LQTS 4	2003	2008	Definitive
KCNE1	LQTS 5	1997	2004	Definitive
KCNE2	LQTS 6	1999	2004	Definitive
KCNJ2	LQTS 7	2001	2008	Definitive
CACNA1C	LQTS 8	2004	2008	Definitive
CAV3	LQTS 9	2006	2008	Moderate
SCN4B	LQTS 10	2007	2008	Moderate
AKAP9	LQTS 11	2007	2009	Limited
SNTA1	LQTS 12	2008	2009	Strong
KCNJ5	LQTS 13	2010	2010	Limited



Interview Notes

For interviews, the primary informants at each site was a lab director or genetic counselor. Interviewees often referred to the balance between offering a clinically valid yet competitive test in today's genetic test market. Clinician/customer demand as well as science play a role. It was interesting to note that several labs mentioned general evidence criteria for a gene to be placed on a panel but no one mentioned specifically what was needed to remove a gene.

DISCUSSION/CONCLUSIONS

- Technology, clinician request, literature searches, patents, and lab size influence genetic tests. The turnaround between discovery and testing for more recent genes has dropped precipitously. This is likely due to both competitive pressure and technology advances.
- Labs that have a narrower phenotypic focus tended not to use NGS panels.
- Historically, labs required more evidence to add a gene to a test due to costs of development. NGS technologies have significantly altered development costs. Once the NGS system is in place, expanding a test can be trivial.
- Two of the more recently discovered genes have already increased their validity classifications since first being placed on a genetic test. This implies that availability of testing may uncover evidence needed to strengthen initial discovery.
- Some labs leave off KCNJ5 but not AKAP9 even though they have the same validity classification. This may be because AKAP9 was discovered first and possibly expected to be more high yielding. It also may reflect the trend to rarely remove genes once they are on a test.
- Recently another AKAP9 variant has been found that could increase the gene's validity, but it has not been published, only reported in ClinVar. This raises the question of how national gene validation efforts can utilize this resource.
- For most labs, it requires more evidence to remove a gene than to add a gene to their clinical test.

FUTURE CONSIDERATIONS

Does validity matter?

- There is a significant psychosocial impact of learning risk for sudden death for the patient and their families. Does validity influence this?
- What role, if any, should validity play in a clinician determining whether or not to order a test and in choosing a lab?
- Time from discovery to test has decreased. Would insurance companies use validity since moving to a gene-by-gene basis for coverage?
- Not sharing clinical variant data through ClinVar or a traditional publication could negatively impact the perceived validity of a gene. Is this additional motivation to share?

REFERENCES

- Alders, Marielle, and Mannens, Marcel. Romano-Ward Syndrome. GeneReviews. *University of Washington, Seattle* (2012).
- See supplemental page for sources used for gene curation.