

NHLBI / ORD Workshop

Recognition and Treatment of Rare Inherited Arrhythmias

Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) and Office of Rare Diseases (ORD) convened a Workshop on September 14-15, 2006, in Bethesda, Maryland to advise NHLBI and ORD on new research directions needed for improved identification and treatment of: (1) rare inherited sodium channelopathies; (2) rare inherited arrhythmias due to potassium channel mutations; (3) rare inherited arrhythmias due to other arrhythmogenic mechanisms; and (4) to provide recommendations to facilitate research to improve future diagnosis and management of rare inherited arrhythmias.

Discussion:

Current understanding and major gaps in current knowledge were discussed in three broad areas: (1) Inherited Channelopathies; (2) Other Inherited Arrhythmias; and (3) Implications for the Future Diagnosis and Management of Inherited Arrhythmias. The working group agreed that:

Rare genetic diseases provide unique insights into the disease mechanisms of prevalent arrhythmias and sudden cardiac death, and guide identification of therapeutic opportunities that potentially target causal disease mechanisms. From screening of larger patient cohorts with genetic arrhythmias, it has become clear that environmental and genetic modifiers play important roles for disease expression and severity. Further, the study of distinct ion channel diseases requires evaluation of arrhythmia mechanisms in specific genetic disease models that approximate the human electrophysiology and allow for prediction analysis. The *in vivo* disease models may vary from engineered mouse models to larger animal models like transgenic rabbits or larger animals in order to establish data close to and most relevant for abnormalities corresponding to the human electrophysiology. In general, it is desirable to develop novel and relevant arrhythmia models and biomolecular systems that reflect the complex proteomic environment of the human disease phenotype. A multi-level translational approach investigates arrhythmias from identification of a genetic variant and verification of a disease-causing mutation through molecular and biophysical structure-function relationships and cellular mechanisms, to the organ and *in vivo* abnormalities. Investigation of genetic modifier mechanisms may further refine arrhythmia mechanisms, and integrated analysis by modeling approaches will contribute to understand the various levels of arrhythmogenic mechanisms.

Opportunities to develop novel therapeutic approaches depend greatly on comprehensive studies that characterize ion channel function and expression, regulation of these by complex intracellular signaling complexes, alterations and crosstalk of intracellular calcium signals, and therapeutic interventions aimed at specific molecular defects. Development of therapeutic approaches and diagnostic approaches may include identification of novel surrogate clinical markers. To create momentum and continuum of complex arrhythmia disease studies, it will be equally important to establish training mechanisms that integrate young investigators and provide opportunities to build scientific careers in the field.

Recommendations:

- Establish advanced biological and computational models that reflect the biomolecular environment of the human heart to study the functional effects of arrhythmogenic mutations. Biological models, including human stem cell-derived cardiomyocytes and genetically altered model organisms, should enhance the study of normal and mutant ion channel biosynthesis, assembly, macromolecular complexes, post-translational regulation, trafficking, targeting (functional proteomics), and human arrhythmia mechanisms.
- Elucidate the molecular and physiologic basis of arrhythmogenic triggers and substrates using integrative animal, cellular, and computational models.

- Identify new human arrhythmia-susceptibility genes and modifiers and their pathogenic mechanism. Design and utilize more efficient (higher throughput) molecular, cellular (electrophysiological) and integrative approaches to advance our understanding of genotype-phenotype relationships.
- Develop, test, and implement new therapeutic approaches for inherited arrhythmias based upon genetic and molecular/cellular mechanisms.
- Establish methods (including bioinformatics) for evaluating, integrating, and sharing structure-function-genotype-phenotype relationships at the gene, protein, signaling complex, cell, organ, and *in vivo* levels in order to predict the significance of specific genetic variants for arrhythmogenesis and to target research efforts and therapy towards patient and family needs.

Publication Plans:

The working group executive summary is published on the NHLBI public web site.

In addition, a formal report of the detailed workshop proceedings and recommendations will be published in a peer-reviewed scientific journal.

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