[I-S06-01] Genetic and Mechanistic Final Common Pathways of Cardiomyopathies

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BACKGROUND: Cardiomyopathies are heterogeneous primary heart muscle disorders that primarily present with predominantly systolic dysfunction or diastolic dysfunction with or without arrhythmias. These cardiomyopathies include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), LV noncompaction (LVNC), and arrhythmogenic cardiomyopathy (AVC). The genetic and mechanistic causes of the phenotype has been the focus of intense study over the past 25 years. Here, an approach successfully used for gene and mechanistic identification will be discussed and the findings revealed.

FINDINGS: We used the concept that a "final common pathway" in which a consistent group of interacting proteins that, when disturbed, leads to a consistent phenotype. The primary defect can occur via a disease-causing mutation that directly disrupts the function of a primary key protein in the pathway directly or in a gene encoding a binding partner protein that, due to its mutant protein, has abnormal or no binding to its key partners leading to disturbance of the pathway. This approach has successfully identified mutant genes and, using animal and cellular models, mechanisms for all of the cardiomyopathies and arrhythmia disorders, many syndromes, connective tissue disorders and congenital heart diseases. Here, the genetic and mechanistic basis of cardiomyopathies and overlapping cardiomyopathy/arrhythmia disorders will be described.

CONCLUSIONS: The "final common pathway" hypothesis provides insight into the causes of the cardiomyopathic phenotype and could provide insight into severity, progression, and therapeutic options.