In 2004, a medical examiner contacted Michael J. Ackerman MD PhD, pediatric cardiologist and director of the Windland Smith Rice Sudden Death Genomics Laboratory at Mayo Clinic in Rochester, Minnesota. The medical examiner had performed post-mortem studies on two children from an Amish family who had died suddenly while playing, their deaths occurring only several months apart. The autopsies were negative, and Dr. Ackerman was asked if genetic testing might shed light on the causes of death. Dr. Ackerman has pioneered the concept of the molecular autopsy; that is, using genetic testing to understand the cause of death and better predict risk for surviving family members. He suspected that the ryanodine receptor (RYR2) gene might be culpable, as mutations of this gene are frequently responsible for exercise-associated ventricular arrhythmias. However, initial testing was unrevealing.

In subsequent years, two additional children from this family died, again while engaging in physical activity. An additional seemingly unrelated family was identified who had lost children under similar circumstances. Using new technology, Dr. Ackerman’s team has recently been able to identify the underlying genetic cause for these deaths.

The incidence of death in otherwise young, seemingly healthy individuals is 1.3 per 100,000 persons, and nearly half of these deaths remain unexplained after conventional autopsy. Families with multiple unexplained sudden deaths in young individuals are exceedingly rare. Post-mortem testing for inheritable cardiac channelopathy- and cardiomyopathy-associated genes sometimes identify the cause of death. In addition to providing closure for surviving family members, that information is critical to identifying additional at-risk family members.

Dr. Ackerman and his colleagues performed testing on autopsy samples from the deceased children from the first family and blood samples from living first degree relatives. Of note, the index child had been evaluated after an episode of exercise-associated syncope, and had a normal resting ECG and a normal exercise stress test without ectopy. The child died several years later during physical activity. A sibling experienced sudden cardiac arrest while playing and survived, but died a month later during another activity-related sudden cardiac arrest. Two other children died of sudden cardiac death, one of with documented ventricular fibrillation.

Subsequently, a second Amish family reached out to Dr. Ackerman. This family consisted of more than 250 individuals, of whom 15 had experienced either exercise-related death or survived sudden cardiac arrest. As in the first family, no evidence of cardiomyopathy or channelopathy was observed in those affected individuals. One of those survivors in the second family had an ICD implanted after sudden cardiac arrest survival; this individual had three documented episodes of R-on-T ventricular ectopy that triggered torsades de pointes ventricular fibrillation, successfully treated by the device.

Dr. Ackerman and his team utilized copy number variation (CNV) analysis, which revealed a homozygous tandem duplication in the cardiac RYR2 promoter location in all affected individuals (Figure). CNV alterations result in an abnormal number of gene copies, such as duplications, deletions, translocations, and inversions. The RYR2 gene is responsible for the functional integrity of the cardiac sarcoplasmic