How a successful gene hunt is saving lives, changing practices and influencing polices
Settlement along the coast (outports)

20,000-30,000 founders

Large families

50% of outports < 2000

Little emigration or immigration

Segregation by religion

Founder effects

High coefficient of kinship
Arrhythmogenic Right Ventricular Cardiomyopathy

- Clinically difficult to diagnose
- First presentation SCD
- Lethal tachyarrhythmias: VT/VF
Proteins in the myocardial cell
• Large autosomal dominant family
• Ascertained in 1970’s
• 1200 people over 10 generations

RIGHT VENTRICULAR CARDIOMYOPATHY AND Sudden Death in Young People

To the Editor: The interesting article by Thiene et al. [Jan. 21 issue] prompts us to mention our study of a large Newfoundland family. Over a period of several years, five patients have been identified with a diagnosis of arrhythmogenic right ventricular dysplasia (ARVD). Two of these patients were the subject of an earlier report describing their treatment by surgery, during which total destruction of the right ventricular free wall was undertaken in an effort to reduce the risk of ventricular tachycardia to the left ventricle. Testing of relatives has revealed that all five can be found in an extended pedigree of seven generations that has a common female ancestor who married twice. In this pedigree of 130 people, there have been at least 19 cases of sudden death, with the majority occurring in men between the ages of 20 and 40 years and most occurring in association with physical exertion. Assuming that all 24 of these patients had ARVD and including three additional cases that have recently been diagnosed yields a total of 27 cases in the pedigree.

The condition appears to be inherited as an autosomal dominant pattern, since male-to-male transmission has been noted twice among patients who have received a diagnosis of the disorder and in 11 siblings in whom sudden death at a young age was recorded. Expression of the gene in female members is clearly less severe and delayed or may not be apparent. We have been unable to detect carriers among those who are asymptomatic and at risk (about 60 people at present) by means of a screening evaluation that includes a clinical examination, chest radiography, echocardiography, and electrocardiography. So far, prospective Holter monitoring has been tested in only a few subjects, and its usefulness is unknown.

Our study also showed that there was no link between HLA and the gene for ARVD; a possible hint is the focus for the third complement component (C3) was suggested, but she will need further study. This work underscores the importance of developing ways to detect carriers of the gene, preferably by the newer methods of DNA analysis, so that genetic counseling and prophylactic regimens can be implemented.
The circle of care and knowledge transfer

Clinical genetics and cardiology: patient follow up and care

Molecular genetic research

Epidemiology /Ethics research
Ascertained families with similar clinical outcomes

Extended histories obtained with all dates of birth and death, and causes of death

Collected all available medical records on all born at \textit{a priori} 50\% risk

Extracted the retrospective cardiac data from the records (ECG, Echo, Holter monitor, treatment regimes, hospitalisation and symptomology) and placed in large SPSS dataset

Obtained DNA samples following informed consent for gene hunt
Single mutation, single gene

Common Ancestor

Subpedigree of AR10

transmembrane protein: TMEM43

Single missense mutation (S358L)
Newfoundland’s sudden-death riddle resolved

Scientists find gene that stops hearts without warning

BY CAROLYN ABRAHAM
MEDICAL REPORTER

For at least nine generations, a curse of sudden death has stalked Newfoundland families. Men and women have dropped dead in the prime of their lives—eating supper on the sofa, clearing the stove, teaching a math class.

For 22 years, researchers have hunted the culprit behind the scourge that can stop hearts without warning. But that search is over. In a discovery that is already saving lives and soothing minds, researchers at Memorial University in St. John’s have identified the precise genetic glitch responsible for centuries of heartbreak in the province.

"This has caused massive young deaths across the generations... the stories have been recorded in the family Bibles," said Kathy Holdorf, co-author of the report published yesterday in the American Journal of Human Genetics. Newfoundlanders aren’t the only ones who suffer from Type s Arrhythmogenic Right Ventricular Cardiomyopathy, or ARVC. But the cluster of affected families, many of whom descend from the region’s first few settlers, brought attention to the disorder after their plight was described in the New England Journal of Medicine in 1985. Still, ARVC is not well understood and estimates of its prevalence in the general population range from one in 1,000 people to one in 5,000. "It’s hard to diagnose... you have to have a family history of people dropping dead," said co-author and molecular geneticist Terry-Jynn Young. "Some people believe it’s vastly underdiagnosed.

Faculty of Medicine
“Building a Healthy Tomorrow”™
A SEX INFLUENCED AUTOSOMAL DOMINANT DISEASE
Cumulative incidence of symptoms and outcomes in affected males

Cumulative incidence of symptoms and outcomes in affected females

Significant difference between males and females to:

- Presyncope ($p \leq 0.0007$)
- Chest Pain ($p \leq 0.04$)
- Heart Failure ($p \leq 0.002$)
- Hospitalisation ($p \leq 0.0001$)
- Death ($p \leq 0.0001$)
Penetrance defined as the time at which a subject was determined to have an ARVC related clinical event.

- Completely penetrant in males by 63 years and in females by 76 years.
- Median age to penetrance for males 32 yrs (95% CI 28-35), females 44 yrs (95% CI 39-48)
DOES THE ICD WORK?
Males with ARVD5 (n=66)

- ICD cohort (n=30) followed for median 2.6yrs (3 wks - 12.8 yrs)
- Control cohort (n=36) followed for median 9.5yrs (0.5- 31 yrs).
- ICD therapy of 7.3yrs (2-10 yrs).
- Control cohort (n=36), n=35 deaths, n=1 heart transplant
- 5-year mortality following ICD therapy: 0 vs 28% in controls (p=0.009)
Females with ARVD5 (n=40)

- ICD cohort (n=18) followed for median 0.7 yrs (2 wks to 3.9 yrs)

- Control cohort (n=22) followed for median 28.8 yrs (1.9 to 37.8 yrs)

- No deaths in the ICD cohort.

- Control cohort, 10/22 (45%) had died.

- No statistically significant difference between the groups for mortality
First appropriate firing (=death) in males

- 16 subjects (53%) had a first appropriate firing (VT/VF)

- Median follow-up time to first firing was 2.5yrs (95% CI 0.6-4.3yrs, range 2 wks - 5.3yrs.

- 5-year cumulative frequency for first appropriate ICD firing was 88%, significantly greater than the 28% 5-year mortality rate for the control group (p=0.0001)

- Death is ‘steeper’ in ICD subjects
  - Disease process more advanced
  - Control cohort survive sustained VT
  - ICD is pro-arrhythmic

- Re ran analysis for VT > 240 bpm: no difference between 5 year mortality of 28% and first firing.
Established a weekly clinic to assess families with inherited cardiomyopathies. (n=2100 subjects from 590 families)

- Clinical screening
- Genetic testing and genetic counseling,
- Research investigations
- Appropriate treatment AND/OR follow-up through cardiac clinic
- Genetic Epidemiology and phenotype research
Influencing Polices

- REB consent includes receiving results at blood draw
- Establishment of the Provincial Ethics Board
Sudden Cardiac Death Study

**Collaborators**
- Dr. Kathy Hodgkinson
- Dr. Sean Connors (MD, electrophysiologist)
- Dr. Patrick Parfrey
- Dr. Anne Williams (MD, cardiologist)
- Dr. William McKenna (London, UK)
- Dr. Luwig Thierfelder (Berlin, Germany)
- Dr. Andrew Krahn (London, Ontario)
- Fiona Curtis
- Barbara Peddle
- Dr. Bridget Fernandez
- Dr. Barry Gallagher
- Dr. Lynn Morris Larkin
- Dr. Simon Avis
- Dr. Daryl Pullman
- Dr. Proton Rahman

**Funders**
- Genome Canada (AMGGI project)
- Canadian Institutes of Health Research
- NL-Center for Applied Health Research
- Memorial University Opportunities Fund
- General Health Foundation
- Janeway Research Foundation
- St. Jude Medical Foundation
- Atlantic Canada Opportunities Agency
- Canadian Foundation for Innovation
Enormous gratitude to the Newfoundland families who come with us on this journey.