MEMORIAL UNIVERSITY

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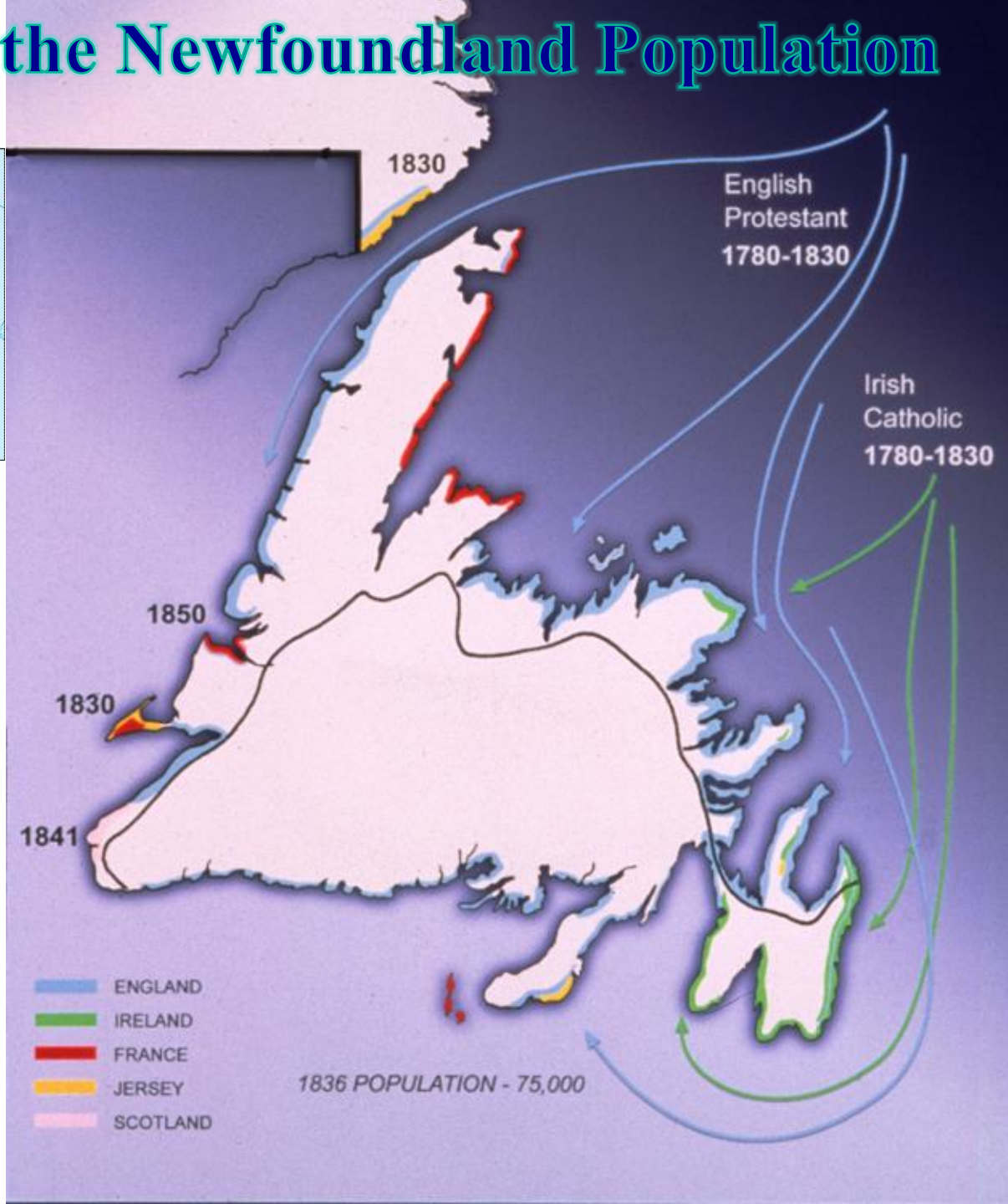
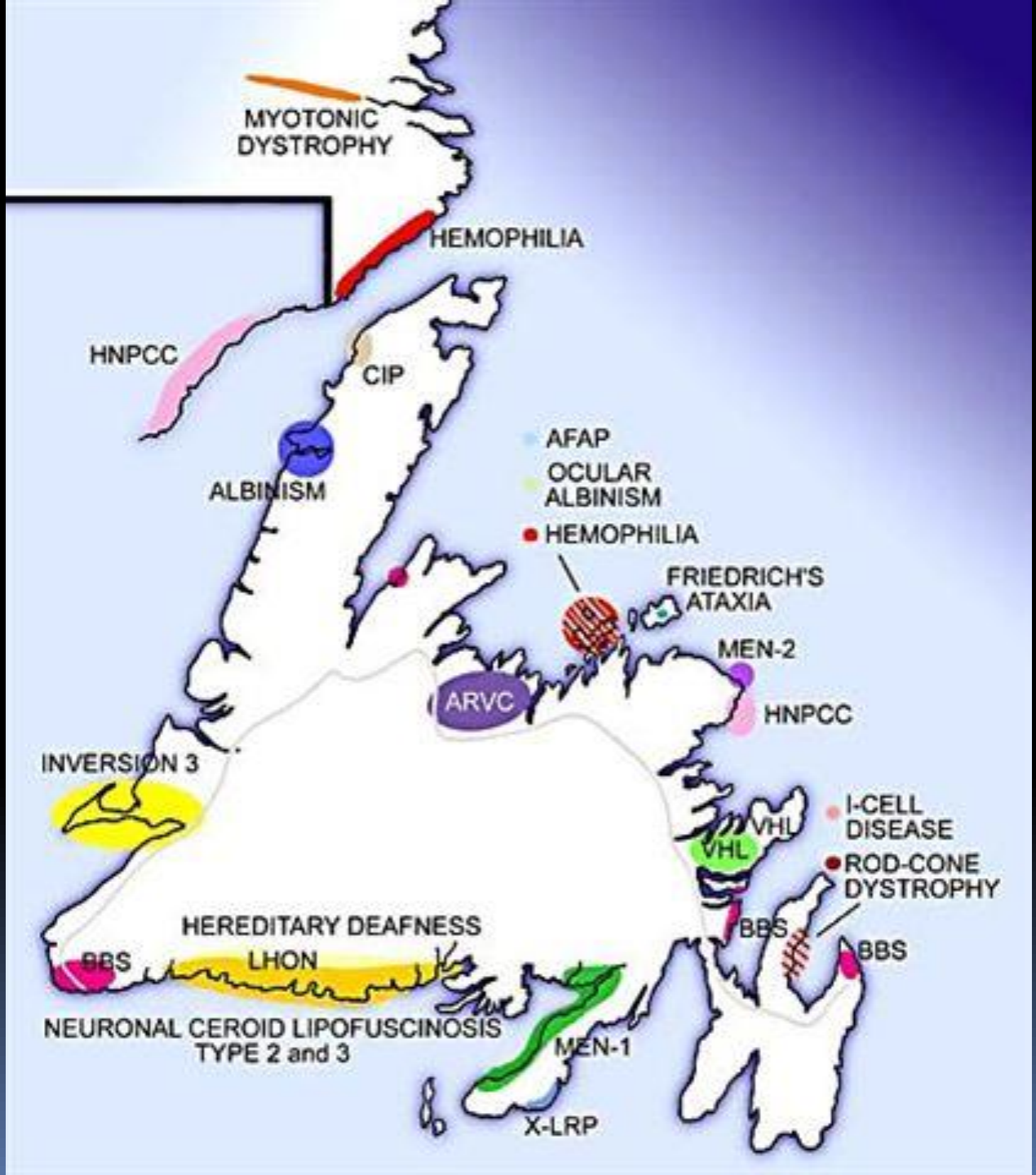
April 17 2013

How a successful gene hunt is saving lives, changing practices and influencing polices

Characteristics of the Newfoundland Population

- 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**




MYOTONIC DYSTROPHY
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HNPCC
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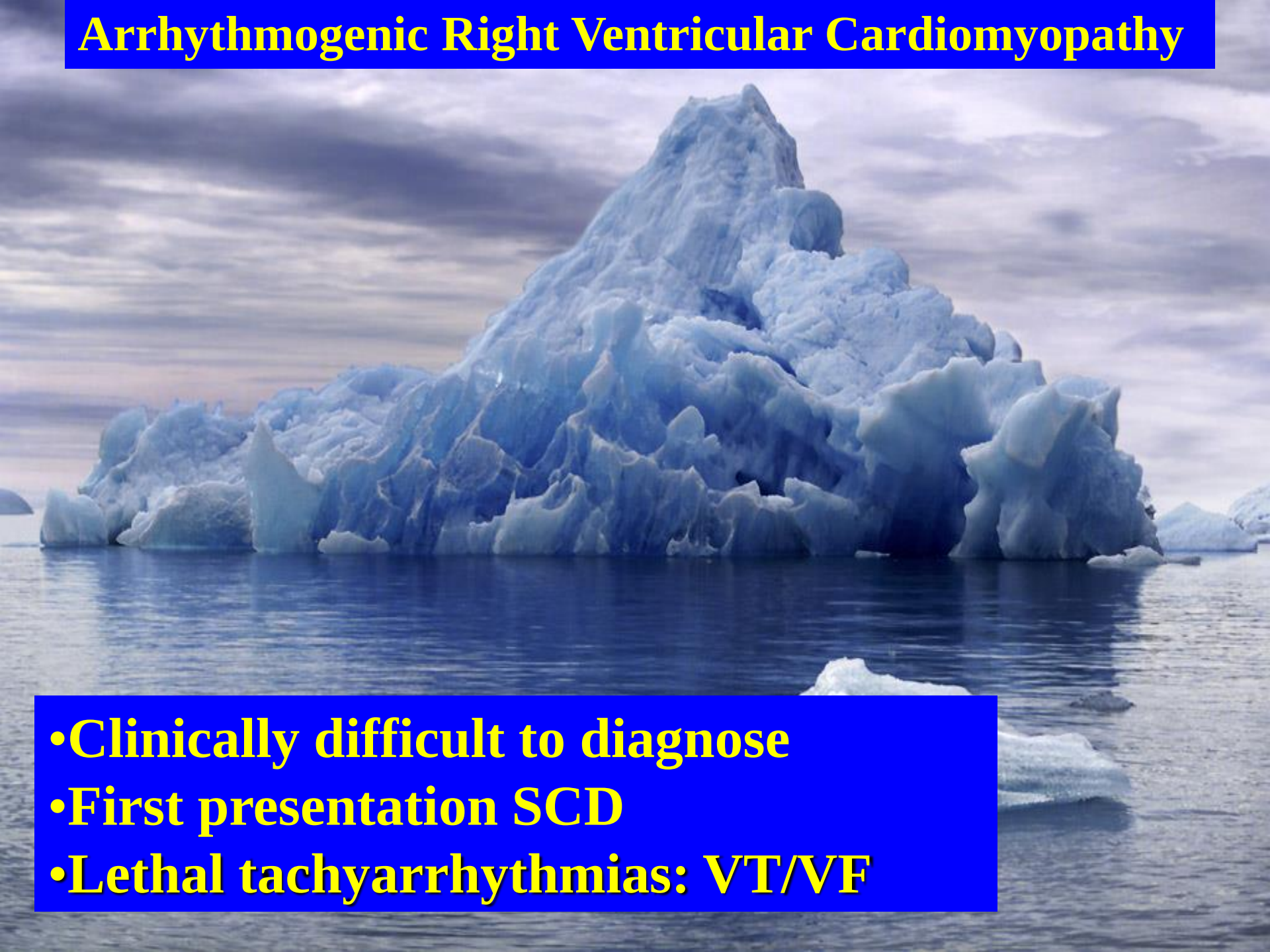
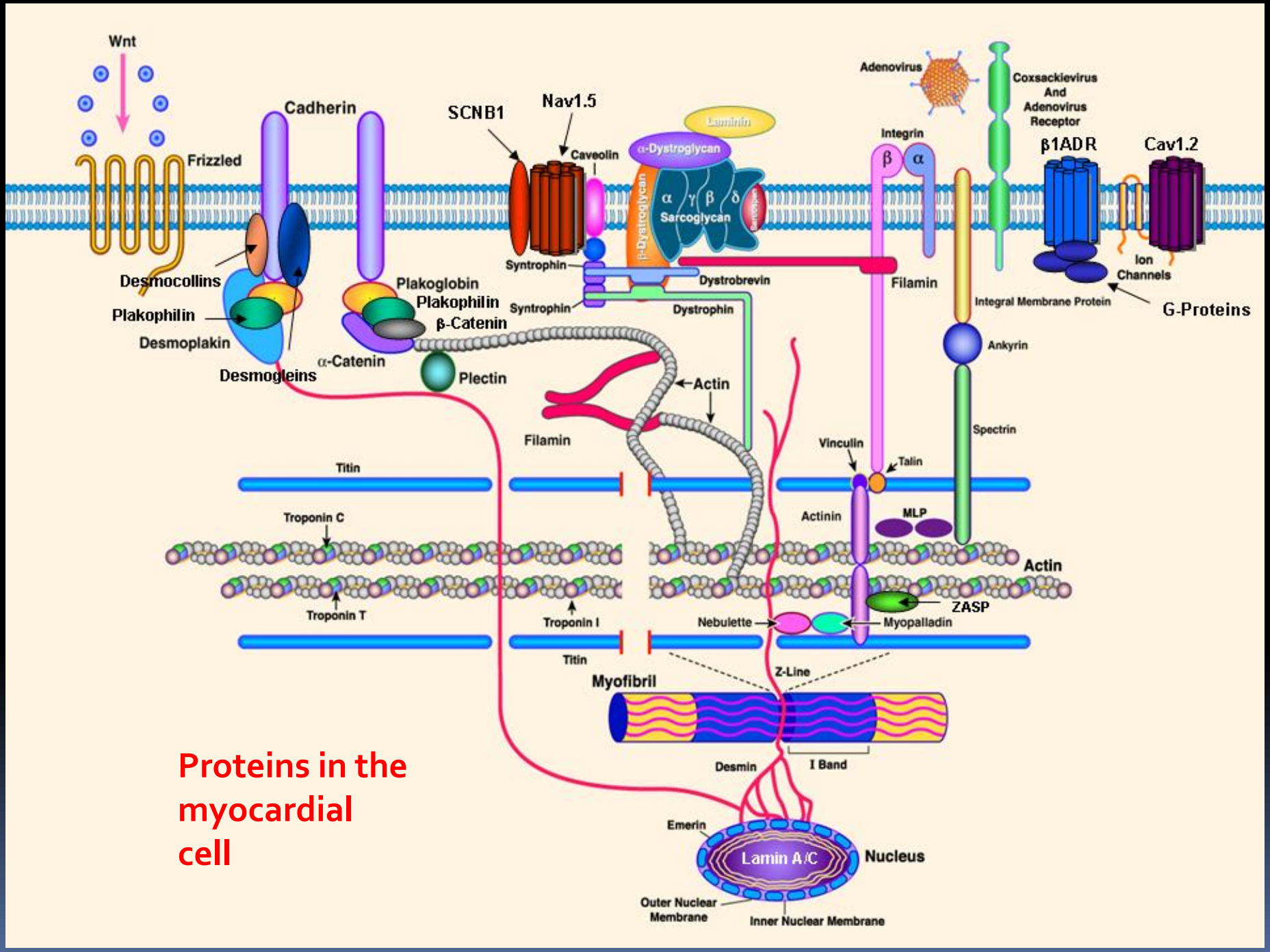
ALBINISM
AFAP
OCULAR ALBINISM
HEMOPHILIA
FRIEDRICH'S ATAXIA
MEN-2
ARVC
HNPCC
INVERSION 3
I-CELL DISEASE
VHL
VHL
ROD-CONE DYSTROPHY
BBS
BBS
HEREDITARY DEAFNESS
LHON
BBS
NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 and 3
MEN-1
X-LRP

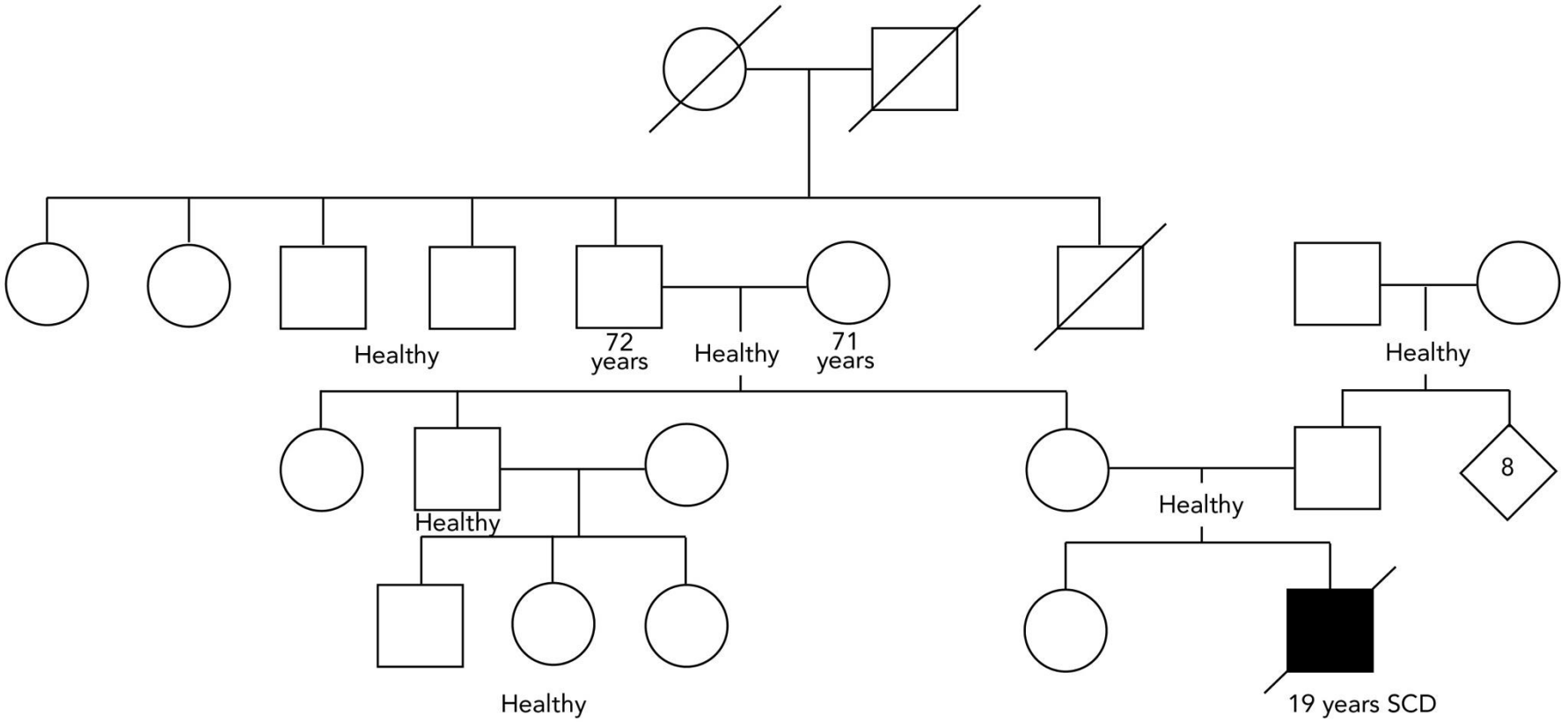
Arrhythmogenic Right Ventricular Cardiomyopathy



- Clinically difficult to diagnose
- First presentation SCD
- Lethal tachyarrhythmias: VT/VF



Proteins in the myocardial cell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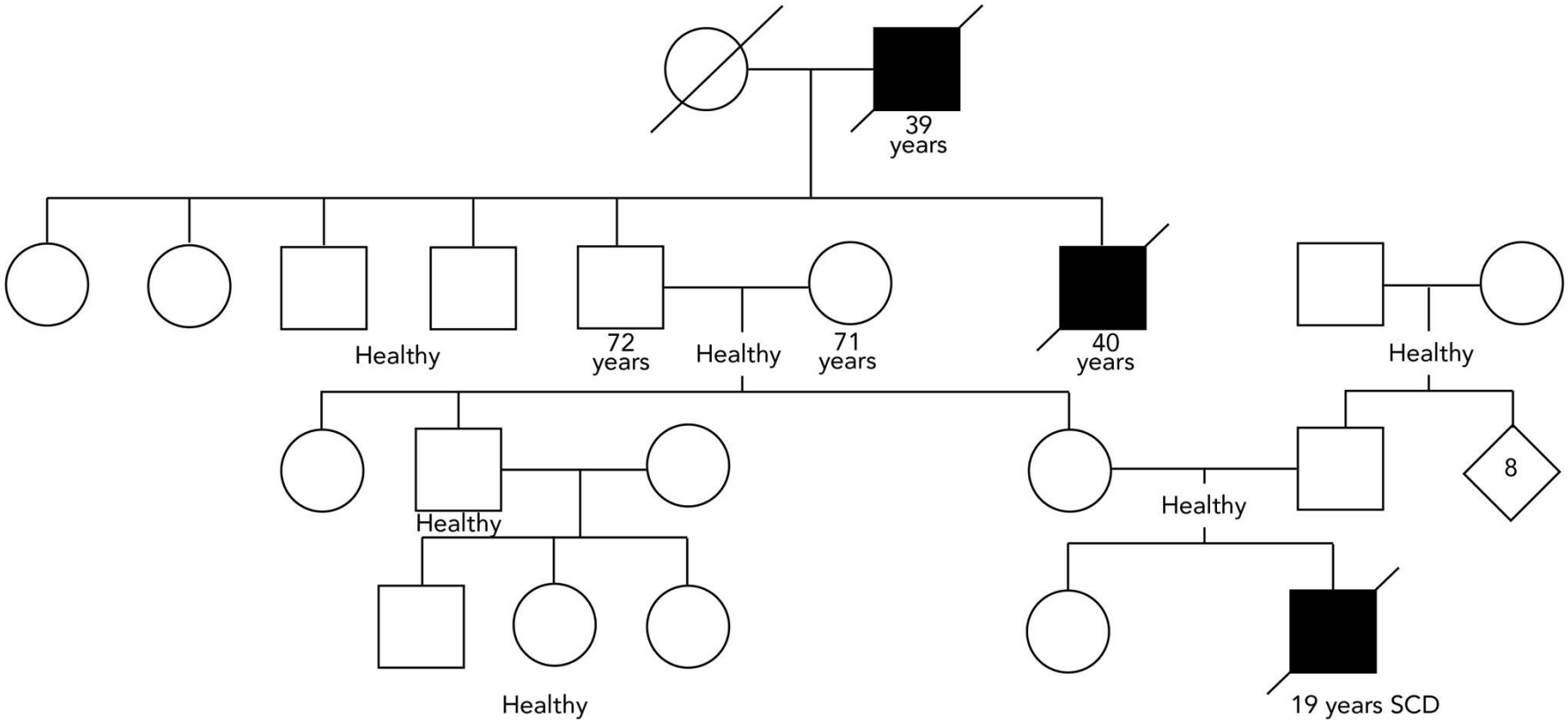
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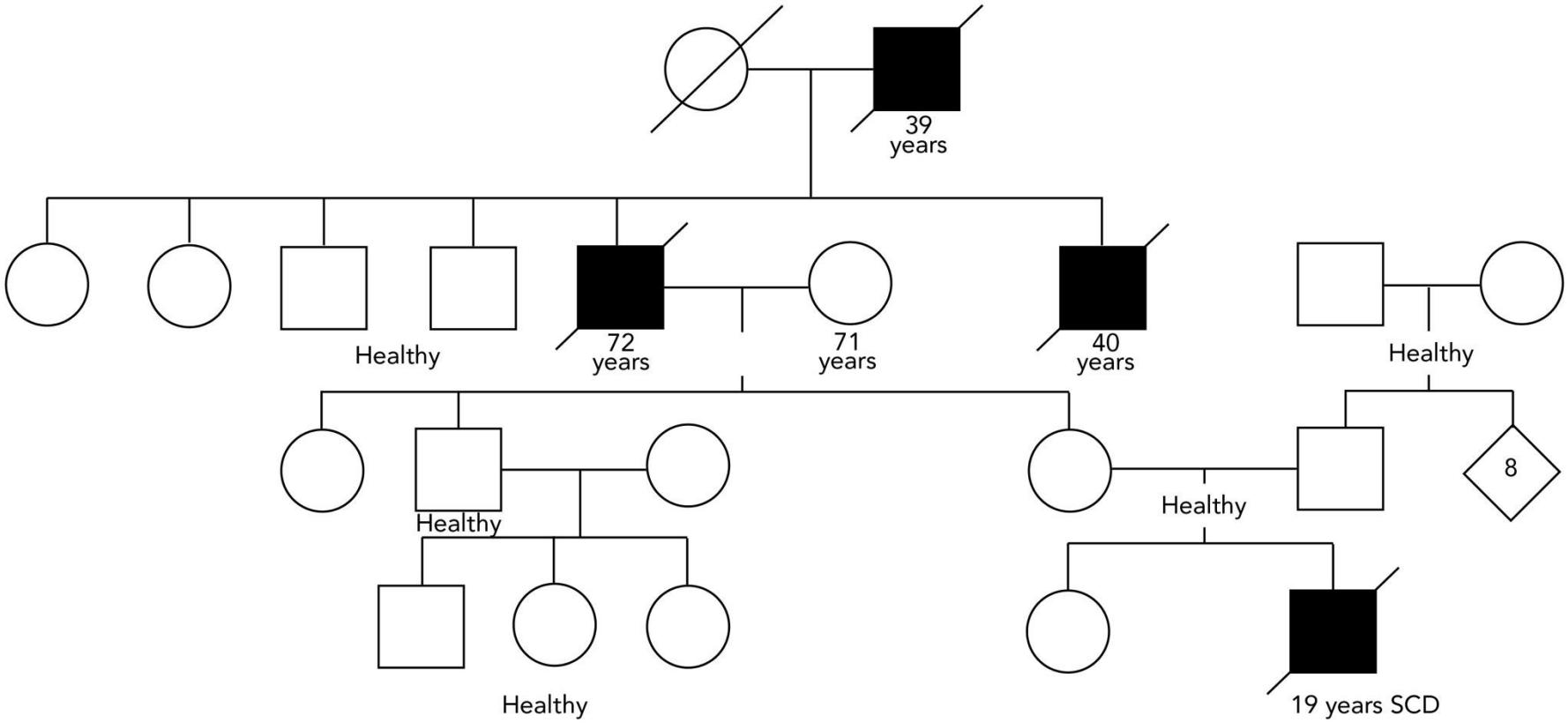
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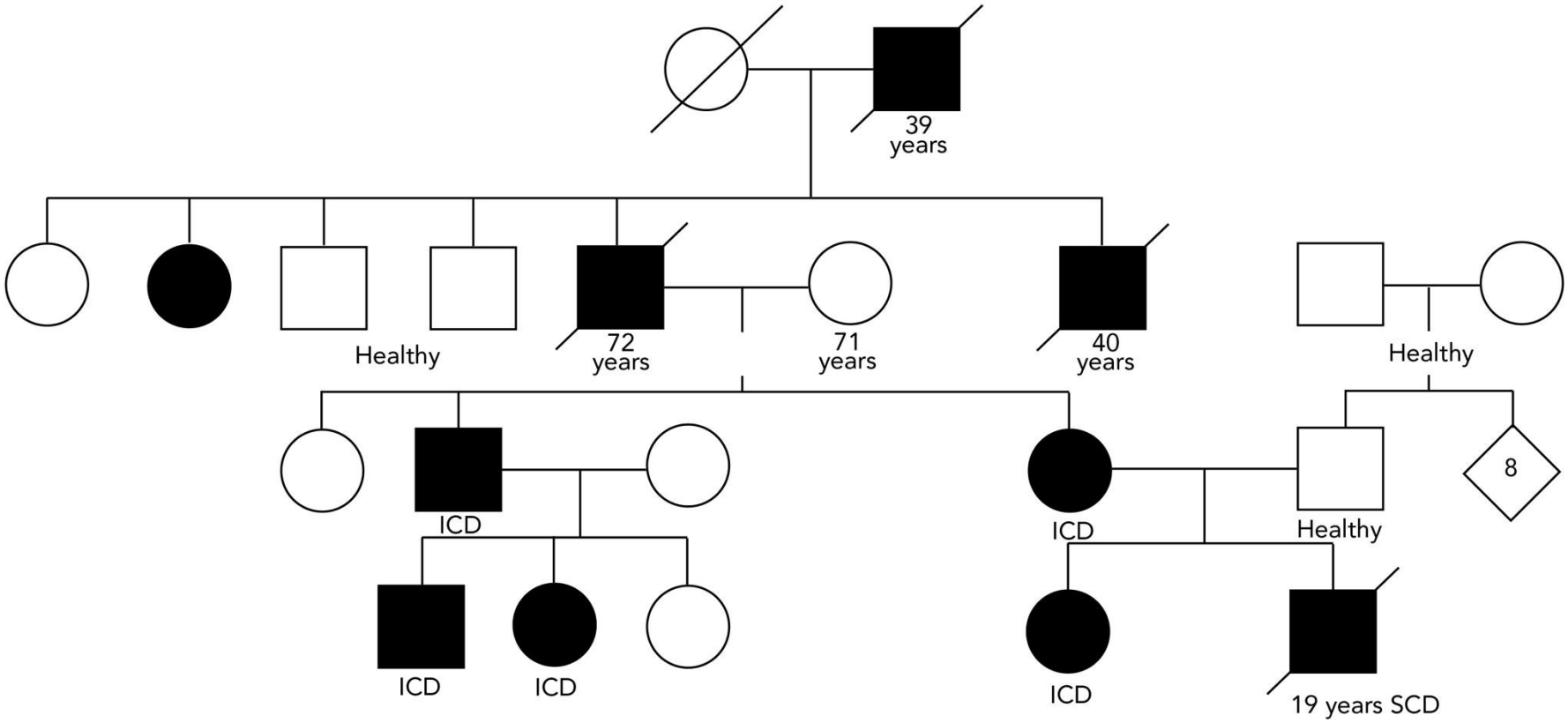
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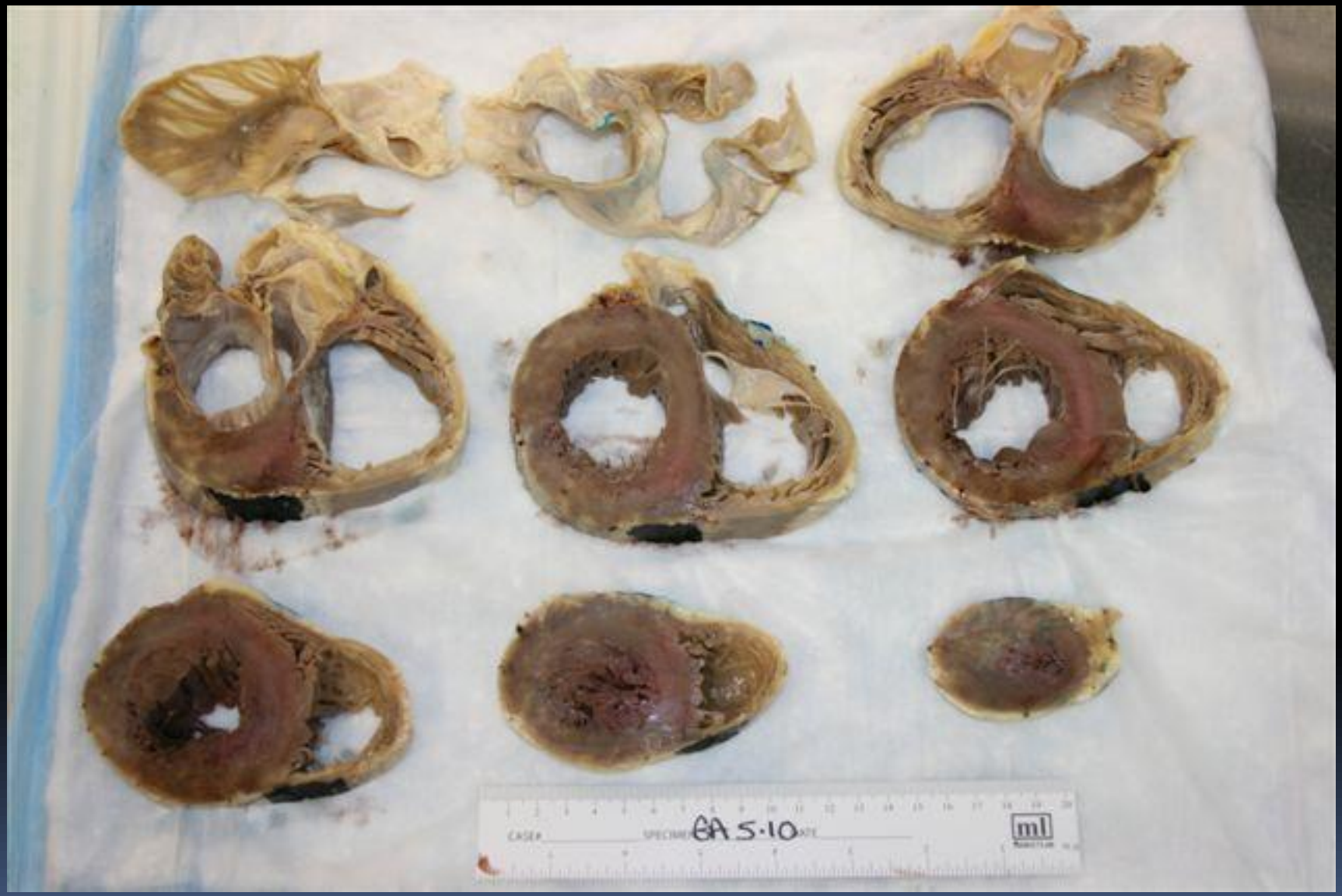
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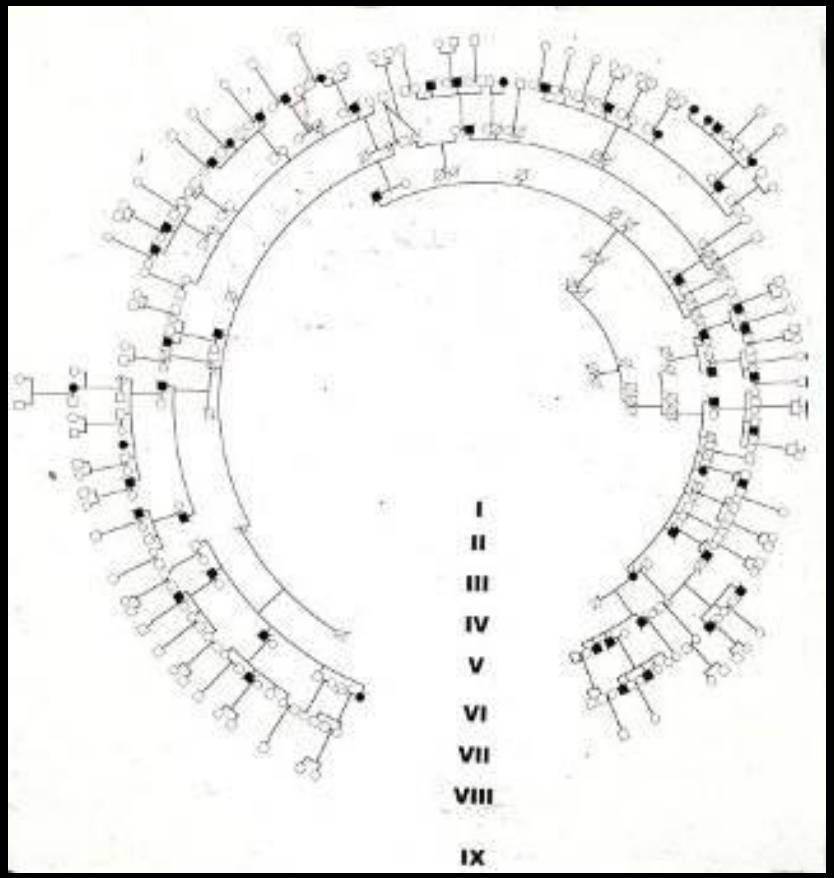

RIGHT VENTRICULAR CARDIOMYOPATHY AND SUDDEN DEATH IN YOUNG PEOPLE

To the Editor: The interesting article by Thiene et al. (Jan. 21 issue)[1] prompts us to mention our study of a large Newfoundland family. Over a period of several years, five patients here received a diagnosis of arrhythmogenic right ventricular dysplasia (ARVD). Two of these patients were the subject of an earlier report[2] describing their treatment by surgery, during which total disconnection of the right ventricular free wall was undertaken to reduce the risk of the spread of ventricular tachycardia to the left ventricle. Tracing of pedigrees has revealed that all five can be fitted into one 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 in 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 others in whom sudden death at a young age was recorded. Expression of the gene in female members is clearly milder and delayed or may not be apparent. We have been unable to detect carriers among those who are asymptomatic and at risk (about 46 people at present) by means of a screening evaluation that includes a clinical examination, chest radiography, electrocardiography, and echocardiography. So far, prospective Holter monitoring has been tried 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 link with the locus for the third complement component (C3) was suggested, but this will need further study. This work underlines 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.

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Hong Kong — PATRICK T.H. KO, M.D., 33 Queens Road Central
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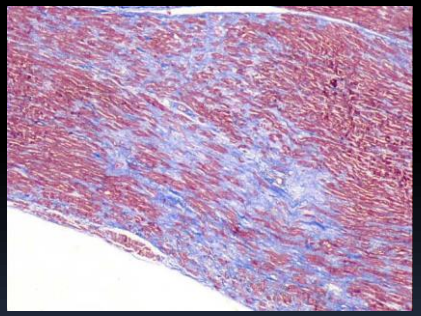
1. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988; 318:129-33.
2. Guiraudon GM, Klein GJ, Gulamhusein SS, et al. Total disconnection of the right ventricular free wall: surgical treatment of right ventricular tachycardia associated with right ventricular dysplasia. Circulation 1983; 67:463-70.



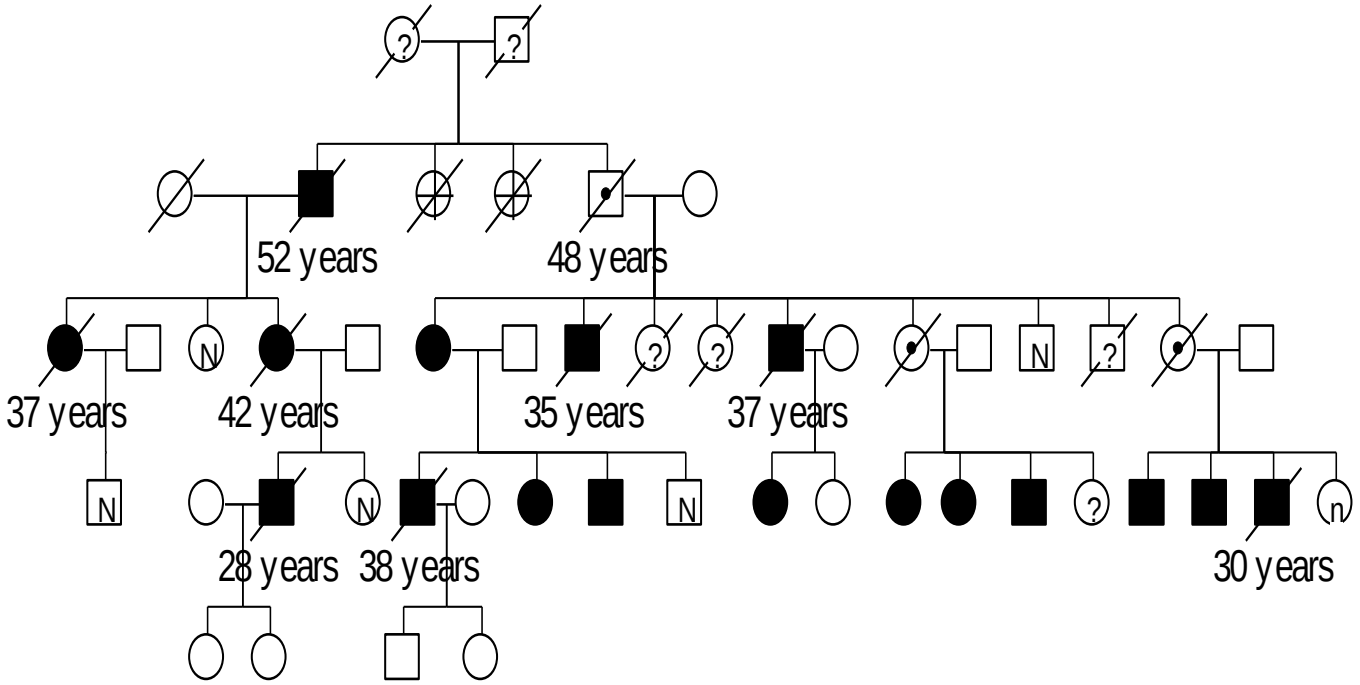
- Large autosomal dominant family
- Ascertained in 1970's
- 1200 people over 10 generations

The circle of care and knowledge transfer

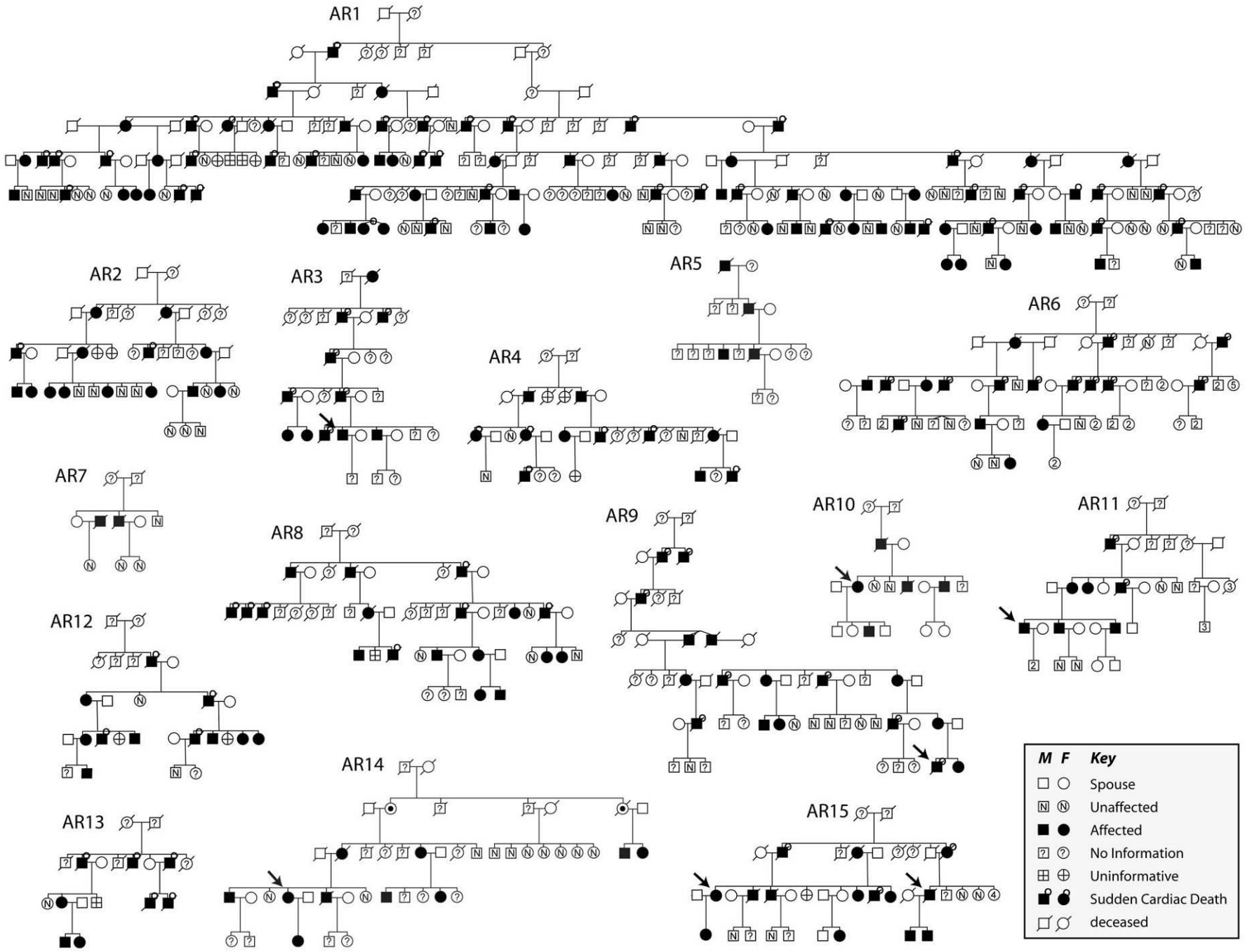
Clinical genetics and cardiology: patient follow up and care

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 *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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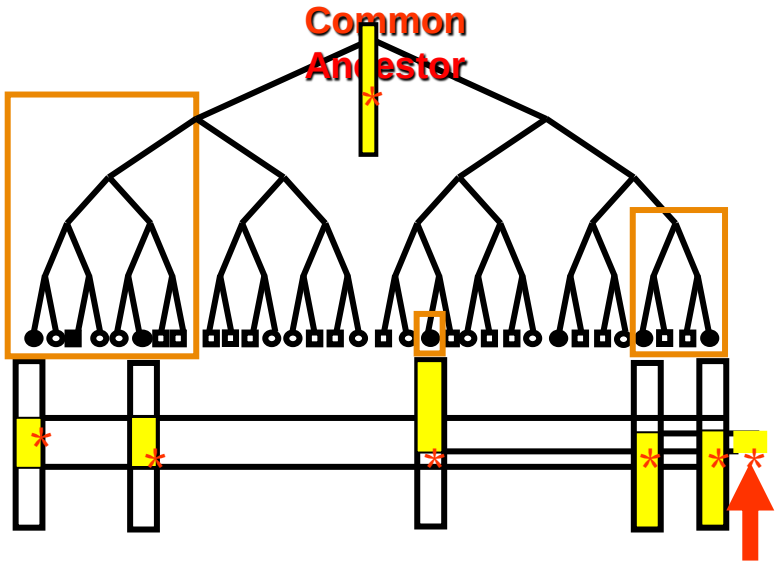
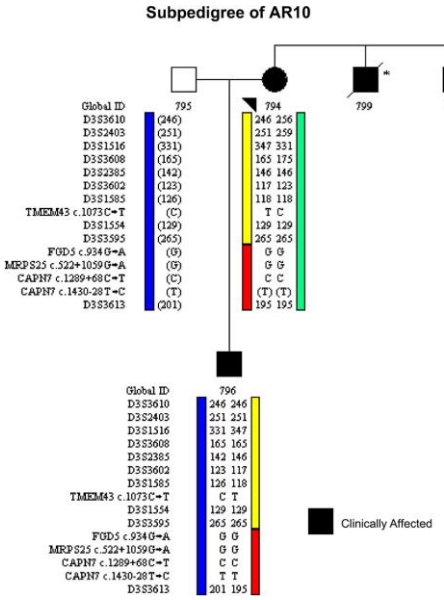
AR2
AR3
AR4
AR5
AR6
AR7
AR8
AR9
AR10
AR11
AR12
AR13
AR14
AR15
M F Key
Spouse
Unaffected
Affected
No Information
Uninformative
Sudden Cardiac Death
deceased

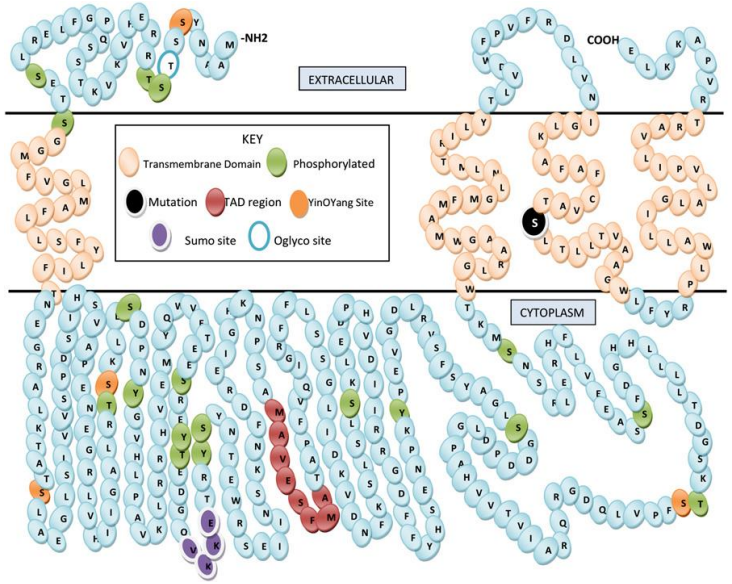


Single mutation, single gene

transmembrane protein: TMEM43

Single missense mutation (S358L)





ATLANTIC EDITION » FRIDAY, FEBRUARY 29, 2008 HALIFAX, MAINLY SUNNY, HIGH -8 LOW -11

THE GLOBE AND MAIL
CANADA'S NATIONAL NEWSPAPER

GENETICS » ISOLATING A GLITCH RESPONSIBLE FOR CENTURIES OF HEARTBREAK

Shown in St. John's yesterday, Rosalie Carter lost her grandfather, mother and brothers to ARVC. The 56-year-old says discovering the culprit is 'the best news anyone can ever hope for.' PAUL DALY FOR THE GLOBE AND MAIL

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, cleaning the stove, teaching a math class.

For 12 years, researchers have hunted the culprit behind the scourge that can stop hearts without warning. But that search is over.

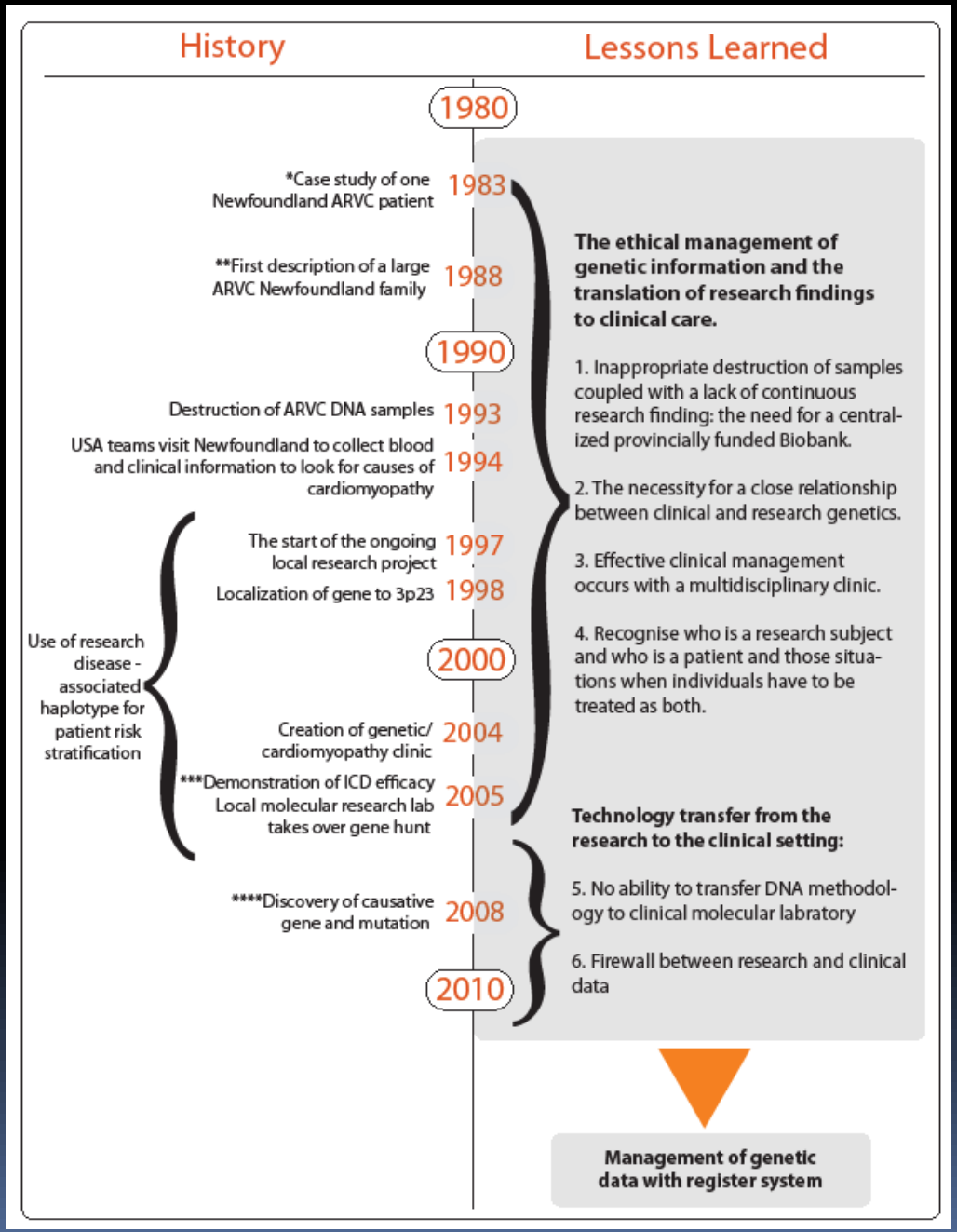
In a discovery that is already saving lives and soothing minds, researchers at Memorial University in St. John's have identified the precise genetic glitch responsible for centuries of heartbreak in the province.

"This has caused massive young deaths across the generations ... the stories have been recorded in the family Bibles," said Kathy Hodgkinson, co-author of the report published yesterday in the American Journal of Human Genetics.

Newfoundlanders aren't the only ones who suffer from Type 5 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 the 1980s. 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.

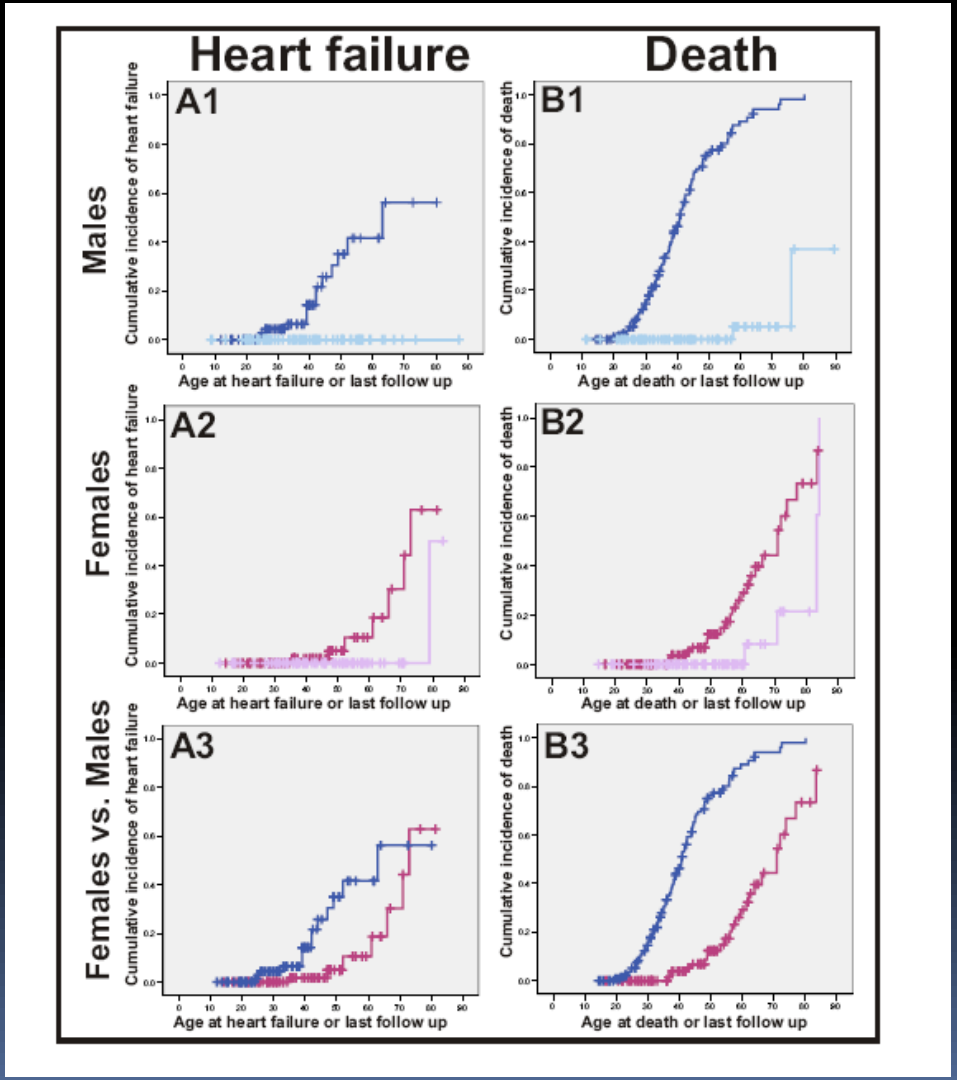
"It's hard to diagnose ... you have to have a family history of people dropping dead," said co-author and molecular geneticist Terry-Lynn Young. "Some people believe it's vastly underdiagnosed."

» SEE 'SUDDEN DEATH' PAGE 8

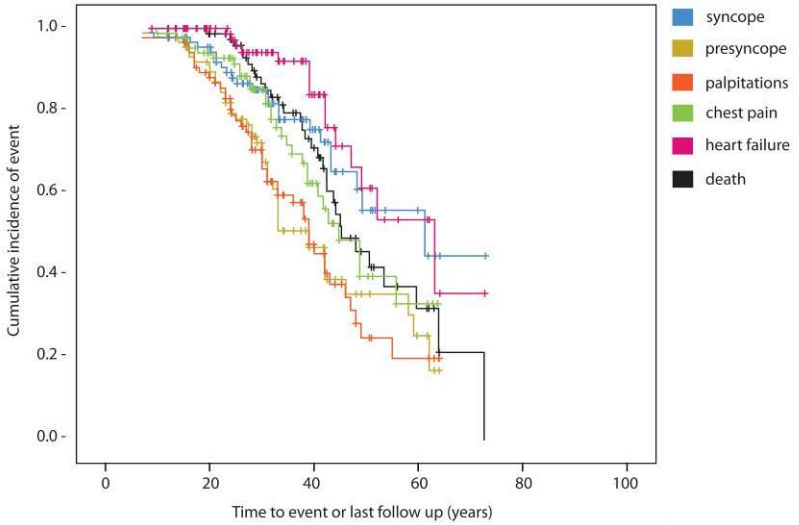


Hodgkinson et al Translation of research discoveries to clinical care in arrhythmogenic right ventricular cardiomyopathy in Newfoundland & Labrador: lessons for health policy in genetic disease Genet Med. **2009** Dec;11(12):859-65

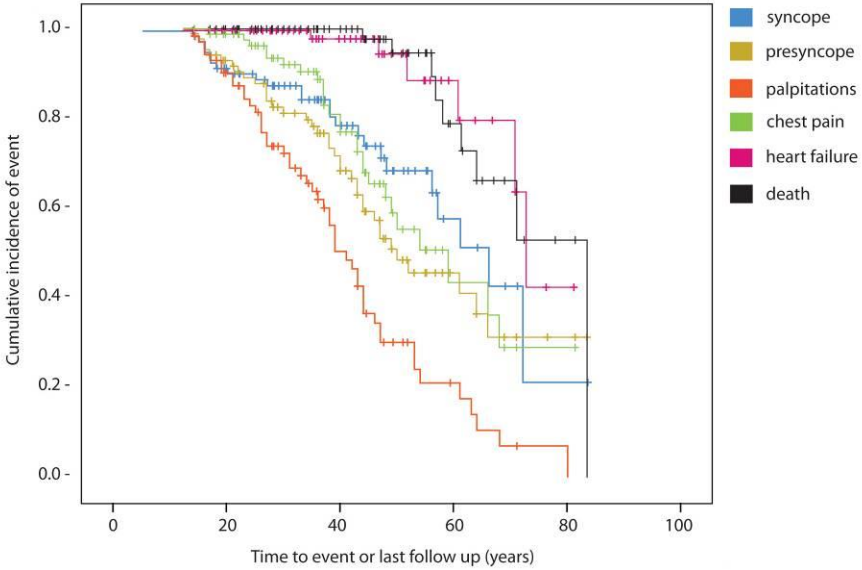
A SEX INFLUENCED AUTOSOMAL DOMINANT DISEASE



Cumulative incidence of symptoms and outcomes in affected males



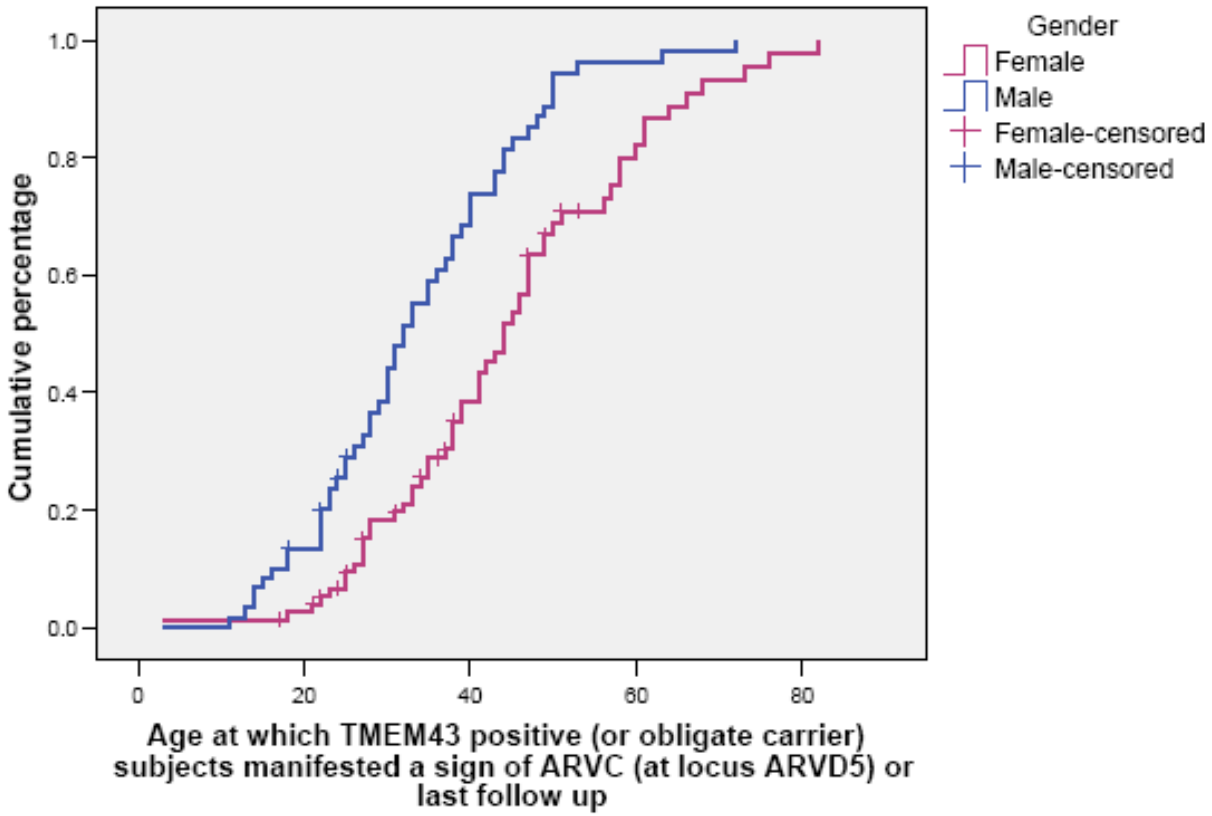
Cumulative incidence of symptoms and outcomes in affected females



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	**($p \leq 0.0001$)**

A



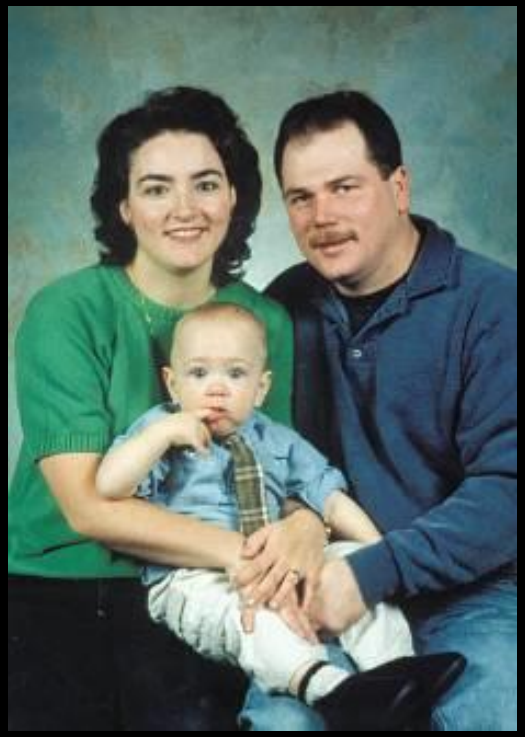
B

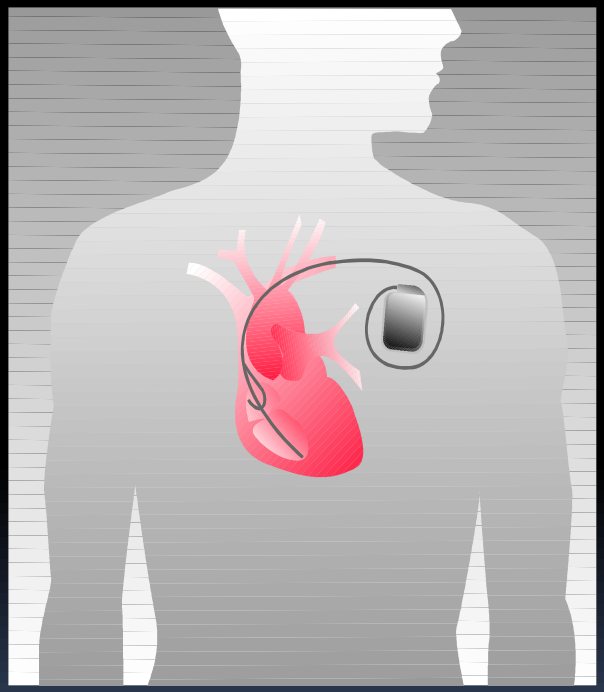
Percentage of subject's penetrant by each age

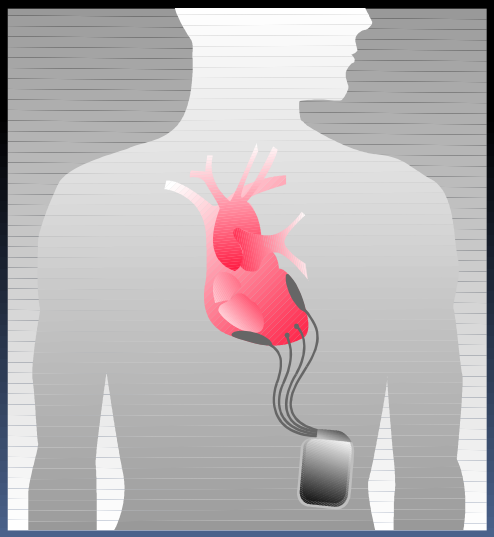
Age (years)	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Males	13	39	68	89	96	100	100
Females	3	18	38	67	80	97	100

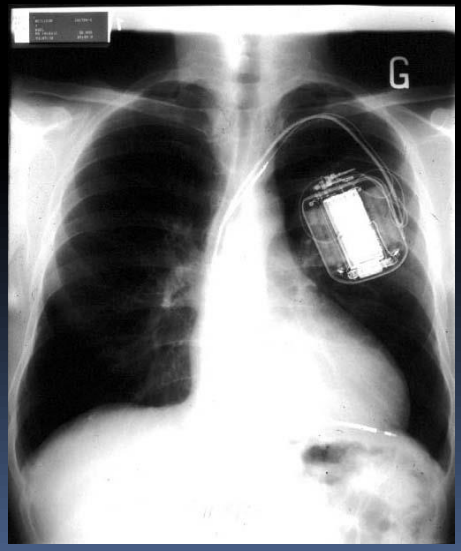
- Penetrance defined as the time at which a subject was determined to have an ARVC related clinical event
- Completely penetrant in males by 63 years and in females by 76 years
- Median age to penetrance for males 32 yrs (95% CI 28-35), females 44 yrs (95% CI 39-48)

DOES THE ICD WORK?



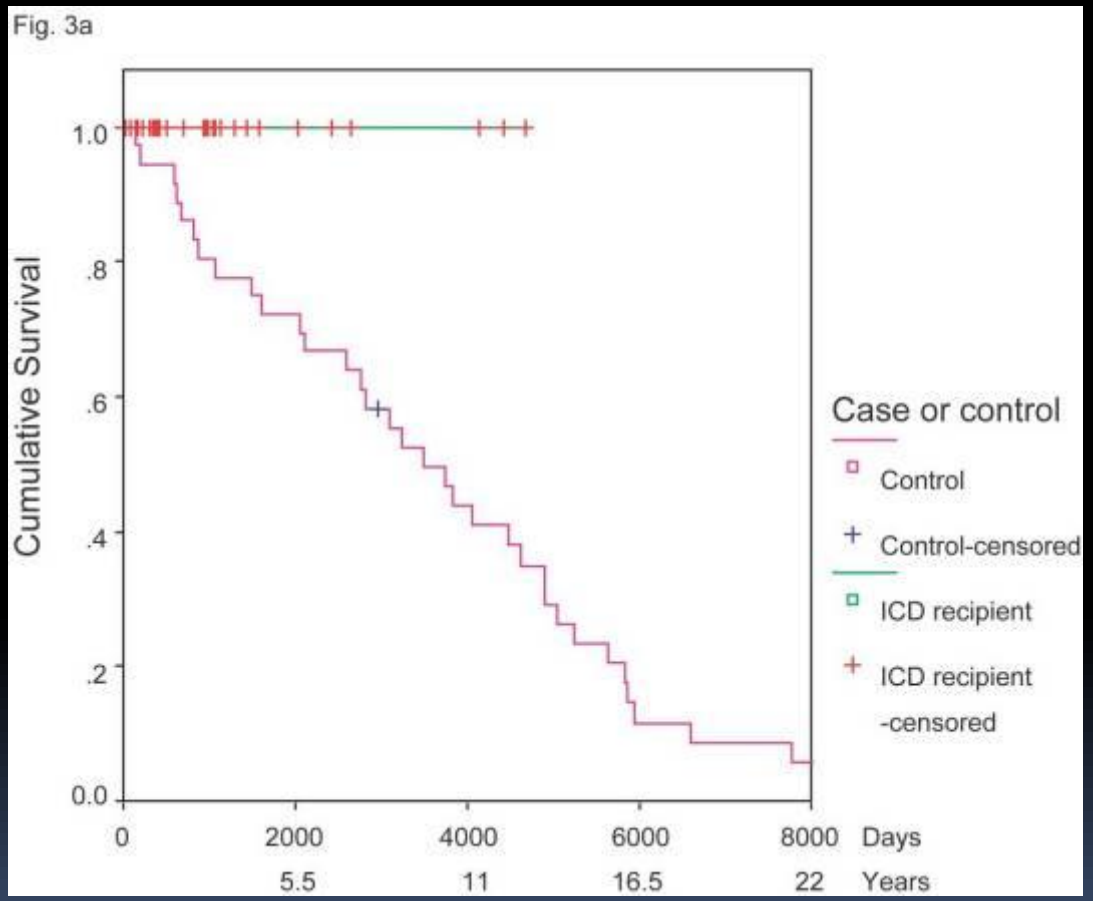






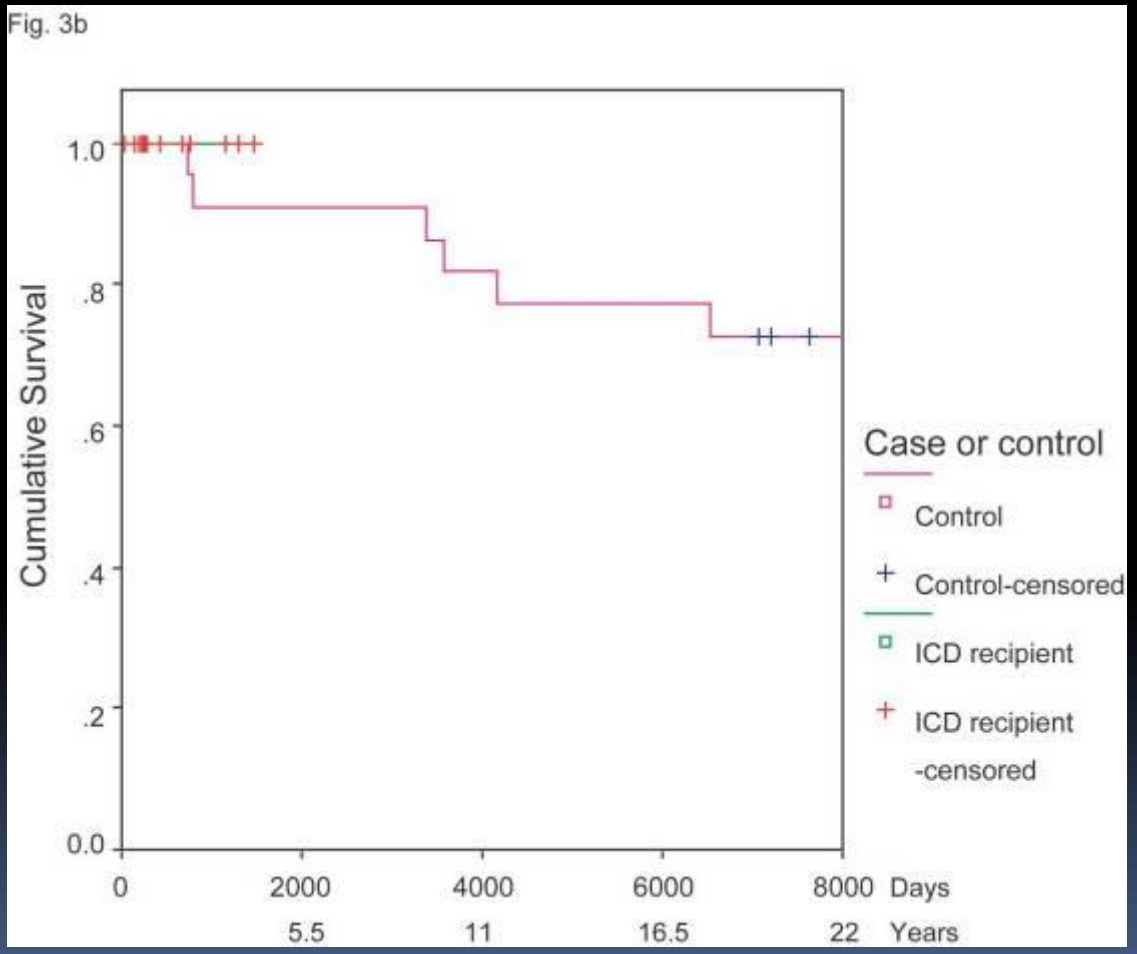
Males with ARVD5 (n=66)

- 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)



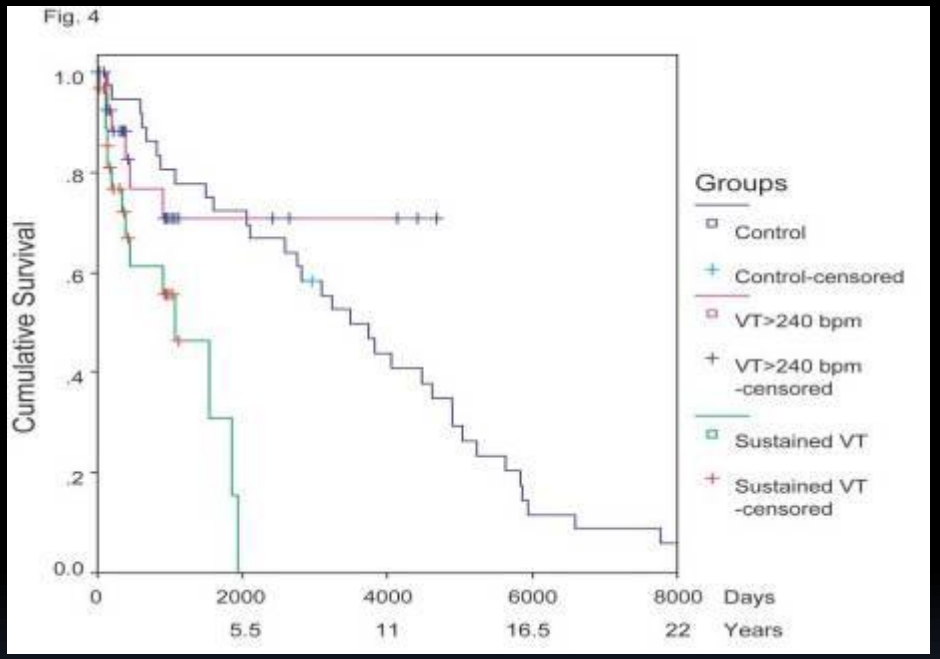
Females with ARVD5 (n=40)

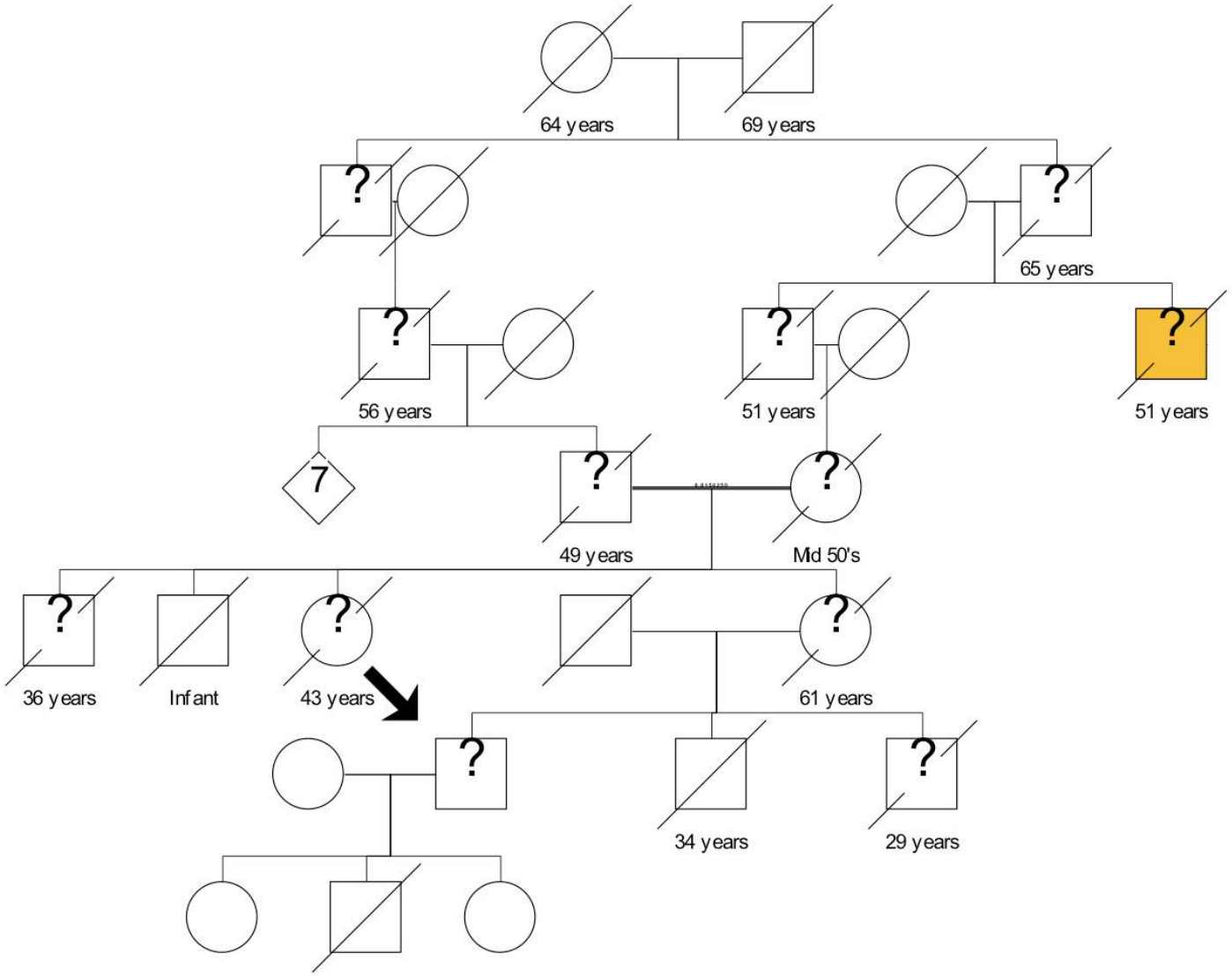
- ICD cohort (n=18) followed for median 0.7yrs (2 wks to 3.9 yrs)
- Control cohort (n=22) followed for median 28.8 yrs (1.9 to 37.8 yrs)
- No deaths in the ICD cohort.
- Control cohort, 10/22 (45%) had died.
- No statistically significant difference between the groups for mortality



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.

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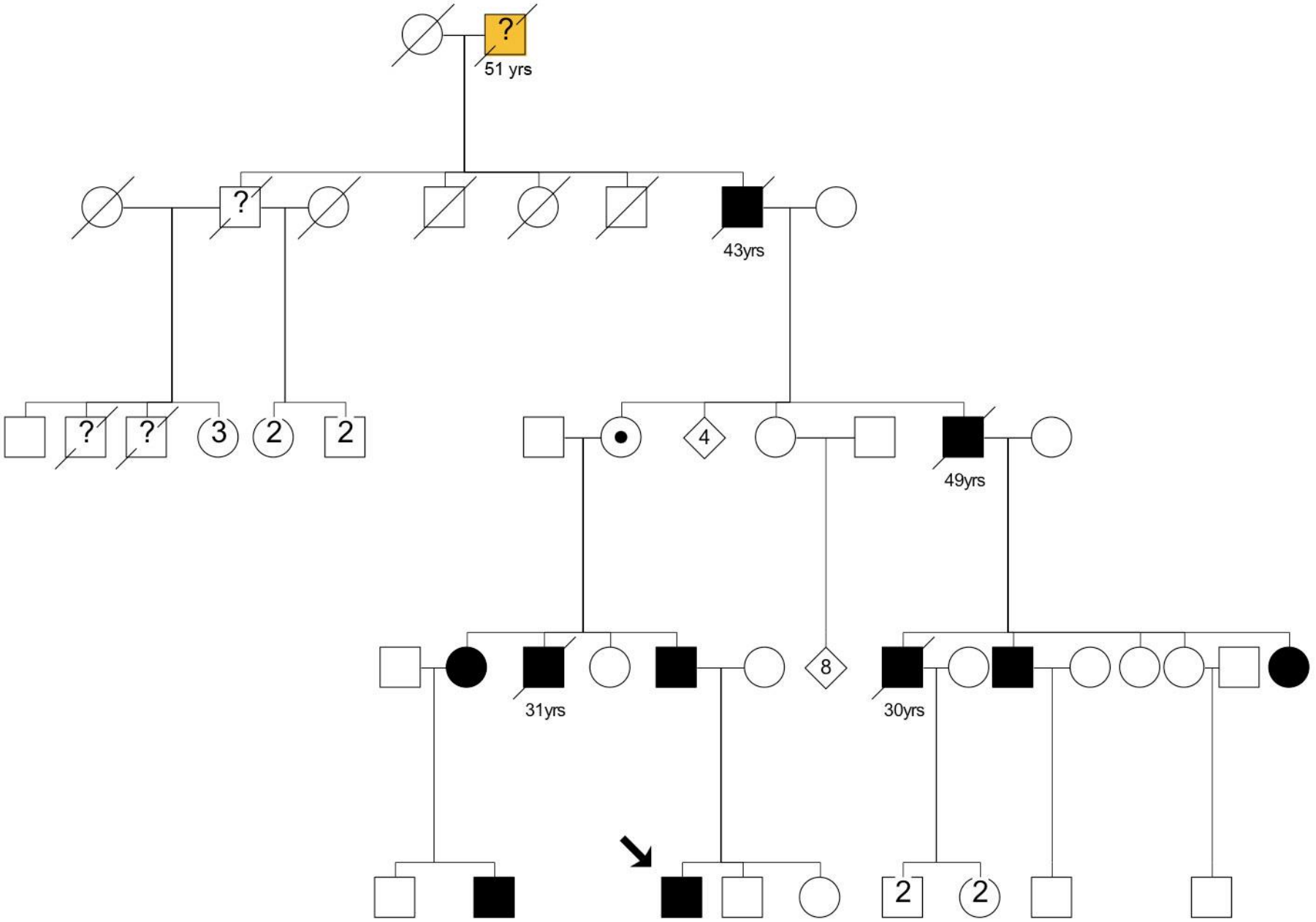
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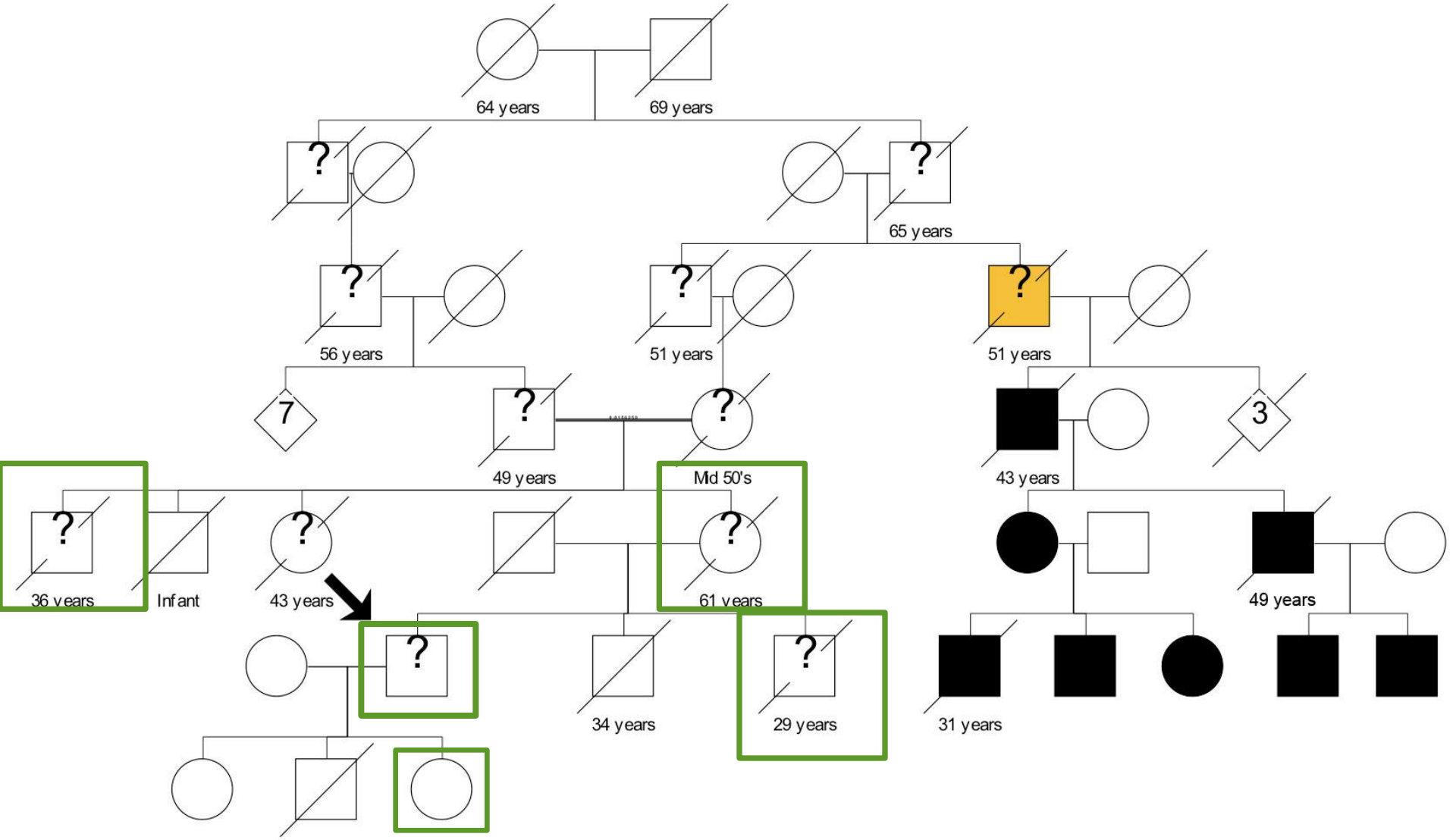
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Infant
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34 years
29 years
31 years

Changing Clinical Practices

- 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. Judes Medical Foundation
Atlantic Canada Opportunities Agency
Canadian Foundation for Innovation

Enormous gratitude to the Newfoundland families who come with us on this journey