Genomic Medicine: Opportunities for OSU/NCH Collaboration

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No conflicts, nothing to disclose

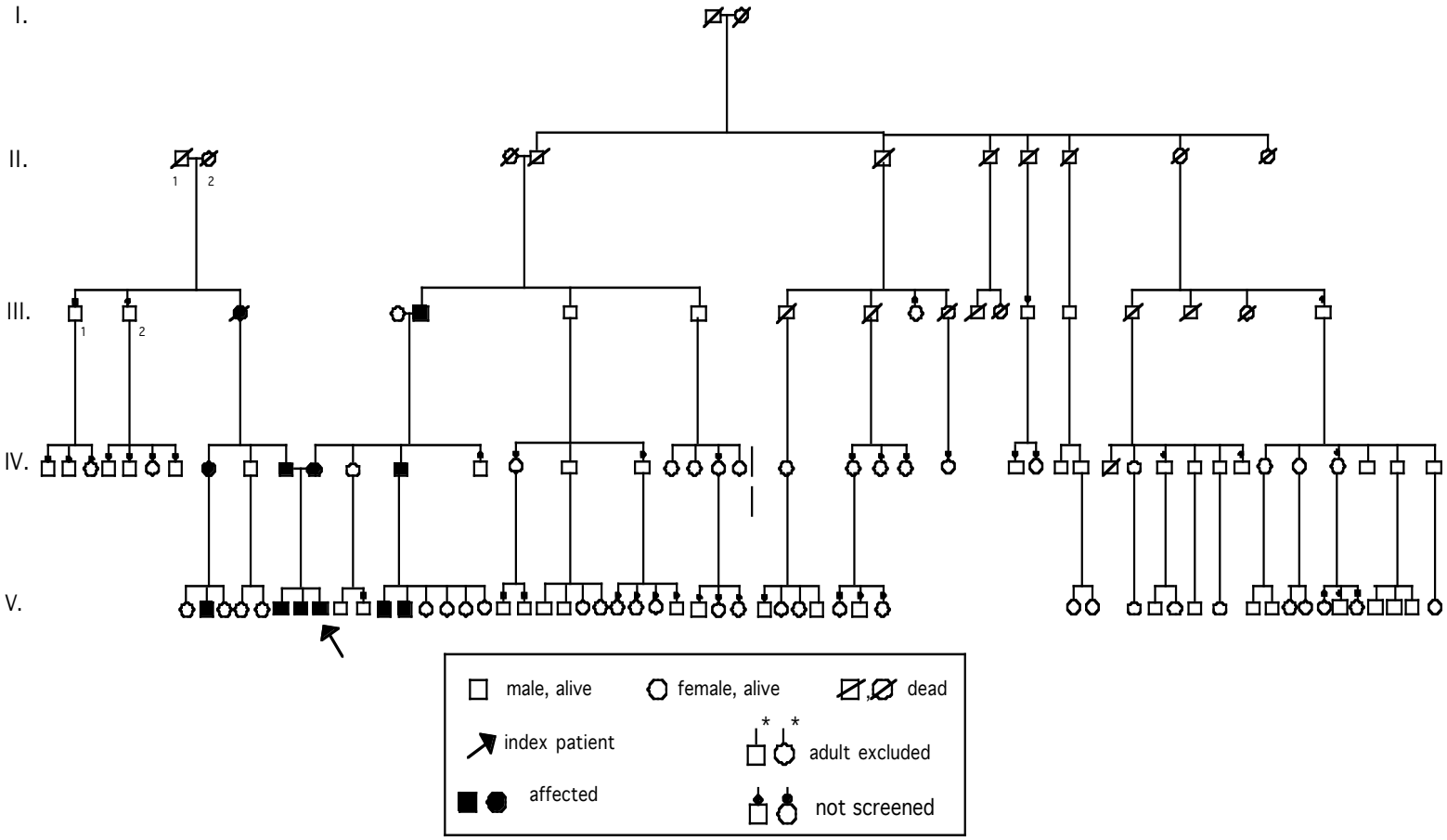
Familial Dilated Cardiomyopathy (FDC) Research Program

OHSU 1992-2007 / U Miami 2007–12 / Ohio State U 2012 - present

Aims

To identify and characterize genetic causes of dilated cardiomyopathy

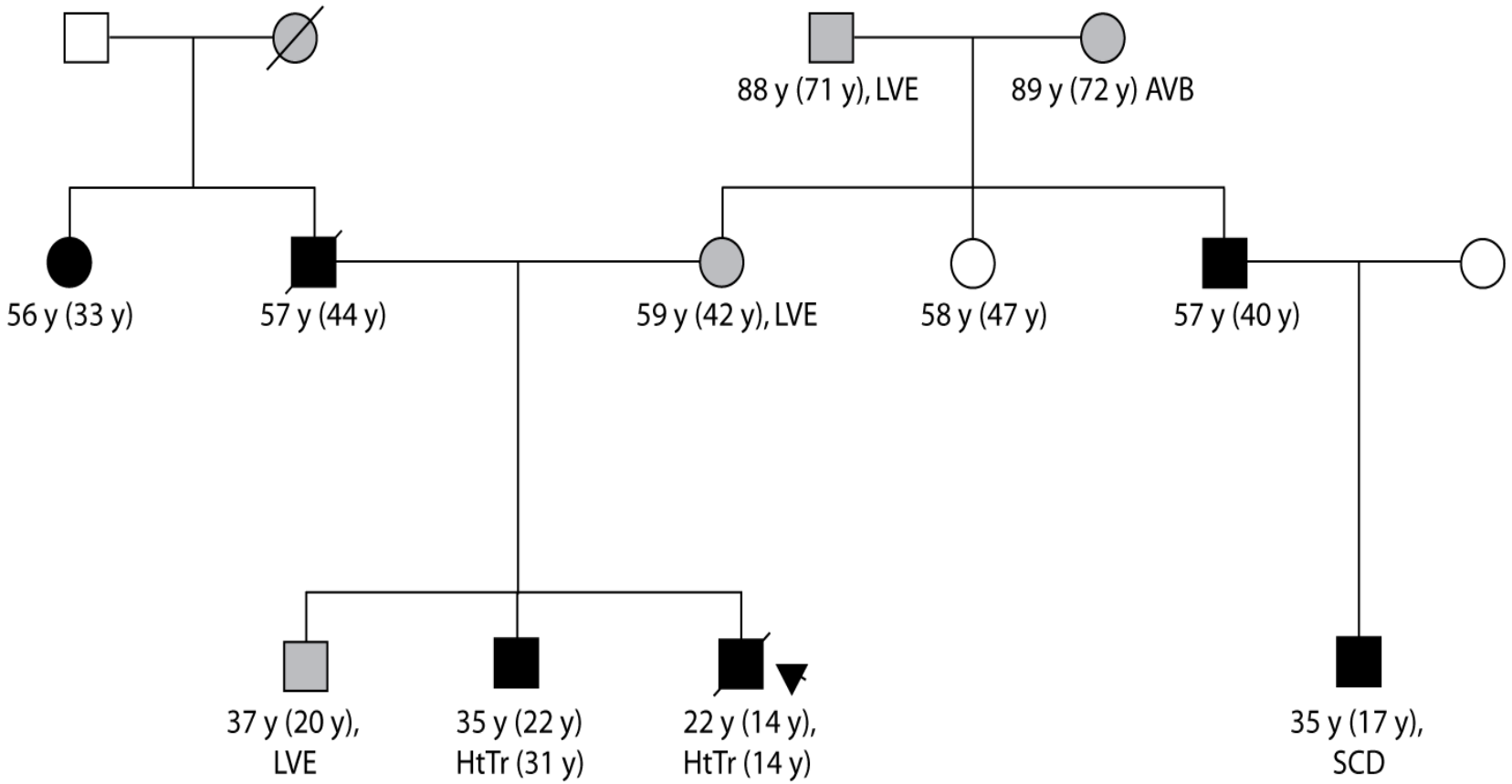
To translate new genetic knowledge into the practice of cardiovascular medicine



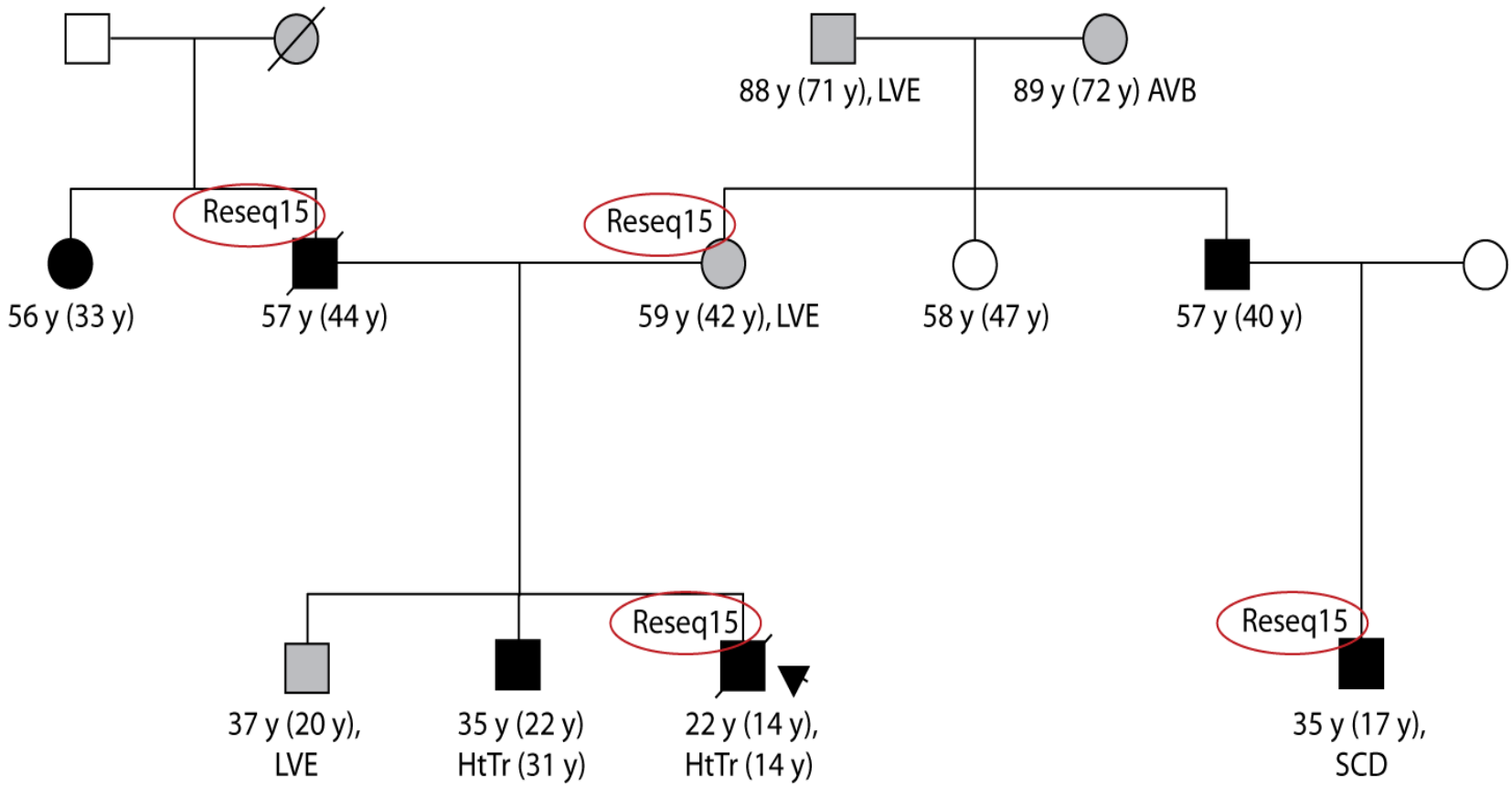
Crispell, et al, JACC, 1999; 34:837-47

Unexpected Complexity

- Presented as simplex disease, but really familial
- Bilineal inheritance in this family, how common?
- Genetic model?
  - conventional - autosomal dominant, incomplete penetrance, variable expressivity, variable age of onset (even with a single disease allele)
  - multiple alleles? - rare variants (mutations) contributing to a multigenic model (compound heterozygosity, epistasis)
  - other complex oligogenic models, rare and common variants?
  - something else – environmental impact?


88 y (71 y), LVE
89 y (72 y) AVB
56 y (33 y)
57 y (44 y)
59 y (42 y), LVE
58 y (47 y)
57 y (40 y)
37 y (20 y), LVE
35 y (22 y) HtTr (31 y)
22 y (14 y), HtTr (14 y)
35 y (17 y), SCD

Resequencing studies 2004, 2005, 2008, 2009:



Kushner, et al, J Card Failure 2006;12:422-29; Li et al, Am J Hum Genetics 2006;1030-39; Parks et al, Am Heart J 2008;156:161-69; Hershberger, et al, Clin Trans Sci 2008;1:21-26; Hershberger, et al, 2010 Circ Genetics 2010;3:155-16

What does this pedigree tell us?

It's all about analysis!

- Yes, we need to collect and phenotype families
- Yes, we need to sequence (exome, genome, etc)
- All which is necessary but is NOT sufficient
- It's all about the analysis

It's like a triathlon:

- You can swim
- You can bike
- You may be great at both
- But it always comes down to the run!

Genetics/Genomics Terminology

Genetics – classically, the study of genes and their role in inheritance, how traits are passed from one generation to the next

- Single gene, Mendelian diseases

Genomics – more recently, the study of all genes, the interaction of genes with the environment

- Complex (non-Mendelian) diseases

From the NHGRI http://www.genome.gov/19016904

Genomic Medicine Terminology

Genetic Medicine (Medical Genetics) - the specialty of medicine that involves the diagnosis and management of hereditary disorders.

Genomic Medicine - An emerging practice of medicine that uses genomic data to better predict, diagnose or treat disease.

Personalized Medicine - ? (all of medicine is personal)

Precision Medicine - coupling established clinical–pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements

Mirnezami et al NEJM 2012;366:489-91

Genomic Medicine

Genomic Medicine – what it means to me

‘genomic’ – we don’t just stop at ‘genetics’, ‘Mendelian’, or usual understandings – it’s a commitment to understand it all!

‘medicine’ – we do it for people, for those individuals and families in front of us, in our clinics and in our hospitals.

Genomic Medicine

So Genomic Medicine for the OSU Division of Human Genetics:

Understanding heritable disease, but expanding the view

Beyond traditional Mendelian

Beyond traditional methods (single gene sequencing or small gene panels)

Even though these approaches remain the staple of our practice

Mirnezami et al NEJM 2012;366:489-91

The necessary components to move ahead

My view is framed by my training and work as a clinician/scientist:

- We need a 'Division of Human Genetics' – expert (and usually specialized) clinicians within phenotypes who know and thoroughly understand genetic disease
  - We need to vigorously define what we know, what we don't know, and prioritize the most relevant questions
- We need sequence – as much as we can get
- We need total overlap of clinical and research venues
  - Complete integration of clinicians and sequence
  - Phenotype and genotype
- We need a huge database for all phenotype and genomic data
- We need analysis:
  - These are people – not machines: smart and well trained, in
  - Statistical genetics, genetic epidemiology, informatics
  - To fully collaborate with and evolve clinicians into scientists
  - And to move PhD's to understand the clinical realities

The necessary components to move ahead

Do we have these necessary components?

- YES!
- Yes, we have a 'Division of Human Genetics'
- Yes, we have specialized clinicians who thoroughly understand genetic disease.
- Yes, we do vigorously define what we know, and what we don't.
- Yes, we are able to prioritize the most relevant questions.
- Yes, we do obtain sequence – and we (at OSU) are working to expand the sequence we get routinely for clinical testing
- Yes, we are now developing a total overlap of clinical and research venues:
  - Genomic medicine working group
  - Implementing a huge database for all phenotype and genomic data (BC Platforms)
- Yes, we have some analysis, we need to recruit a lot more:
  - Statistical genetics, genetic epidemiology
  - Cardiovascular, cancer, neuroscience

OSU/NCH genetics/genomics

We need to leverage each other as much as possible

- Recruiting
- Specialized expertise
  - Especially analysis, e.g. analysis ‘pipelines’
  - Clinical or research
  - Biobanks
  - Consent, ELSI (Ethical, Legal and Social Issues)
  - Counseling
- Seminar series (e.g. Human Genomics ‘Big Data’ Collaborative Forum)
- Research collaborations
  - Specific studies/PI’s, questions, methods
  - Larger consortia, RFA’s

OSU/NCH genetics/genomics

Other (final) thoughts

- We do need to ‘get acquainted’
- We do need recurrent (annual?) research review, reporting to one another
- Consider a joint annual 1 day clinical symposium
- Consider strategic joint investments
  - Especially analysis
  - Areas of expertise (cardiovascular, cancer, neuroscience, others)
  - Seminar series
  - Educational, training, CME opportunities

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Thank you!