A Tangled Web
Is Heart Failure Alzheimer’s of the Heart?

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FINANCIAL DISCLOSURE:
No relevant financial relationship exists
Brain and Heart Amyloid

Plaques

Neurofibrillary Tangles

AL or Transthyretin-related
iDCM plaques- & tangles-like
Common and specific genetic variants

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>UCSC Genome Sequence Database (36.1)</th>
<th>SNP ID If available</th>
<th>Minor Allele frequency</th>
<th>Genotype frequency (variant/20 DCM patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSEN1</td>
<td>-92delC</td>
<td>chr14:72672839</td>
<td></td>
<td>0.02</td>
<td>CC 19/20 (95%) GA 1/20 (5%)</td>
</tr>
<tr>
<td>PSEN1</td>
<td>-21G&gt;A</td>
<td>chr14: 72673257</td>
<td></td>
<td>0.02</td>
<td>GG 19/20 (95%) GA 1/20 (5%)</td>
</tr>
<tr>
<td>PSEN1</td>
<td>A953G/ E318G</td>
<td>chr14:72742931</td>
<td>rs17125721</td>
<td>0.025</td>
<td>AA 19/20 (95%) AG 1/20 (5%)</td>
</tr>
<tr>
<td>PSEN2</td>
<td>G185A/R62H</td>
<td>chr1: 225138072</td>
<td></td>
<td>0.05</td>
<td>GG 18/20 (90%) GA 2/20 (10%)</td>
</tr>
</tbody>
</table>

7 variants in PSEN 1
20 variants in PSEN 2
PS2KO mouse model

**Graphs:**
- **HW/BW** and **HW/TL**
- **LWW/LWD**
- **QRS Interval (s)**

**Bar Charts:**
- **LVEDD**
- **FS**

* Symbols indicate statistical significance.
**ER Ca\(^{2+}\) reuptake**

SERCA2b and PS1/PS2 are co-localized and interact (Kim N; JBC)

Cells lacking both presenilins exhibit a phenotype similar to SERCA knockdown and endogenous presenilins interact with SERCA ([Green et al., 2008](#)).

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**Figure:**

- **Western Blot:**
  - Serca-2b (97 kD)
  - Actin (45 kD)

- **Graph:**
  - Fluorescence change over time
  - PSDKO vs Control

- **Diagram:**
  - L-type Ca\(^{2+}\) channels
  - SERCA
  - Presenilin
  - RyR
  - Ca\(^{2+}\) influx/extrusion pathways

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**References:**

- Green et al., 2008
Presenilin have been shown to interact with the ryanodine receptor, via its N terminus, and to increase the open channel probability and mean current (Rybalchenko et al., 2008),
SR Ca\textsuperscript{2+} Content

WT

PS2KO

400 nmol/L

5 s

Ca Requirements for Contractile Activation

Donald M. Bers Circulation Research. 2000;87:275-281

Twitch [Ca\textsuperscript{2+}]/[Caffeine Δ [Ca\textsuperscript{2+}]]

leak/load (arbitrary)

tetracaine-sensitive Ca\textsuperscript{2+} leak (μmol/l cytosol)

SR Ca\textsuperscript{2+} (μmol/l cytosol)

[Image: Graphs and data for SR Ca\textsuperscript{2+} Content]
What forms iDCM aggregates?
Never Ever give Up
Cofilin in the pathogenesis of AD

Hyper-phosphorylation of Cofilin 1 causes actin bundle accumulation within cell bodies and the formation of dystrophic neuritis.

Hypo-phosphorylation of Cofilin 1 in neurons causes formation of cofilin-actin rod precipitates.
Cofilin in human iDCM

Expression

Activity

![Graph showing cofillin/GAPDH ratio and p-cofilin/GAPDH ratio for soluble and insoluble samples in donors and iDCM.](image)
Cofilin & myocardial aging

Subramanian et al JACC 2015
Cofilin-2 KO mouse model

- **Cofilin/tot ERK Ratio**
  - WT littermates
  - CSC2
  - MW (kDa): Cofilin-2 20, Total ERK 37

- **Ejection Fraction**
  - WT littermates: 7, 3, 11
  - CSC2: 7, 3, 11

- **Fractional Shortening**
  - WT littermates: 7, 3, 11
  - CSC2: 7, 3, 11

- **LVEDd, LVEDs**
  - WT littermate: 7, 3, 11
  - αMHC-Cre: 7, 3, 11
  - CSC2: 7, 3, 11

- **Note:**
  - Don’t play with him, he is Wild Type.

- **Figure Details**
  - Statistical significance marked with * and #.
Cofilin phosphorylation induced stress fiber formation

Wild type cofilin

Constitutively active cofilin

Phosphomimetic cofilin

DAPI
α-Sarcomeric Actin
RFP
Phalloidin

Wild type cofilin

Constitutively active cofilin

Phosphomimetic cofilin

DAPI
α-Sarcomeric Actin
RFP
Phalloidin
Adenoviral Expression of Phosphomimetic Cofilin

Cardiac function

FS

Non injected WT CFLPhospho Constit. active

Dilated

Normal

Thick
Aging a promiscuous disease

Presenilin

Cofilin

PAO Toxicity
A Tangled Web

Aggregate independent

Genetic

Acquired

Aggregate dependent

Ca^{2+}

Cell death/dysfunction

Protein folding, misfolding, and disease
Thank you