# Bio5663
# **Neurobiology of Disease**

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# Course Objectives

- Logistics
- Expectations

# Schedule/Website

https://hopecenter.wustl.edu/

https://hopecenter.wustl.edu/?page_id=11922

# Lessons from previous years

# Comments on genetic studies

Neuron
Article

## A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

**Hypothesis:** ALS-FTD is a genetic disease and a heritable element can be identified
at chromosome 9p21

# Exome Sequencing Reveals *DNAJB6* Mutations in Dominantly-Inherited Myopathy

**Hypothesis:** Some muscle diseases have a genetic etiology, we hypothesize that exome sequencing will identify a genetic cause.

# Patient phenotyping

- Clinical Neurology is a science in itself

# Two papers of same family

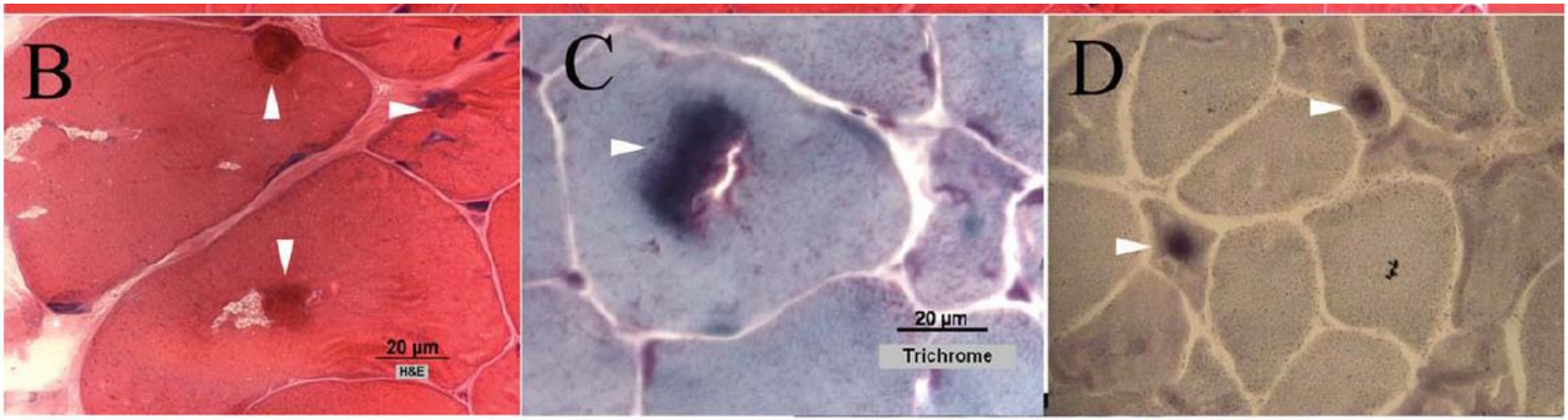
**Linkage of Familial Dilated Cardiomyopathy with Conduction Defect and Muscular Dystrophy to Chromosome 6q23**

*Am. J. Hum. Genet. 61:909–917, 1997*

**Etiology of Limb Girdle Muscular Dystrophy 1D/1E Determined by Laser Capture Microdissection Proteomics**

ANN NEUROL 2012;71:141–145

# Laser microdissection




D

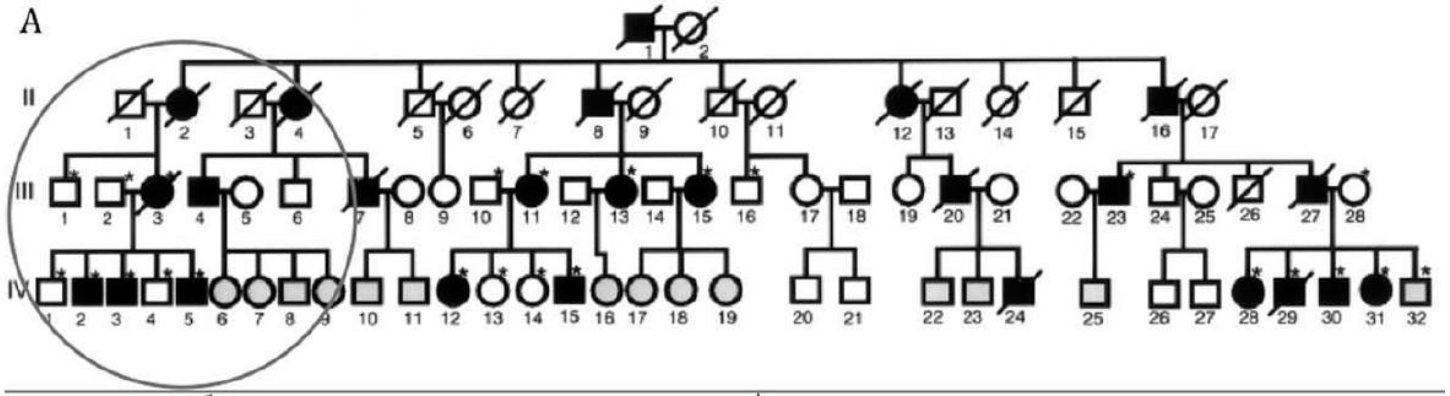
| Unaffected myofibers | Cytoplasmic inclusion myofibers |
|---|---|
| ACTA1 Alpha actin | ACTA1 Alpha actin |
| MYH2 Myosin heavy chain 2 | MYH2 Myosin heavy chain 2 |
| MYH8 Myosin heavy chain 8 | DES Desmin |
| MYH7 Myosin heavy chain 7 | MYH8 Myosin heavy chain 8 |
| ACTB Beta actin | MYH7 Myosin heavy chain 7 |

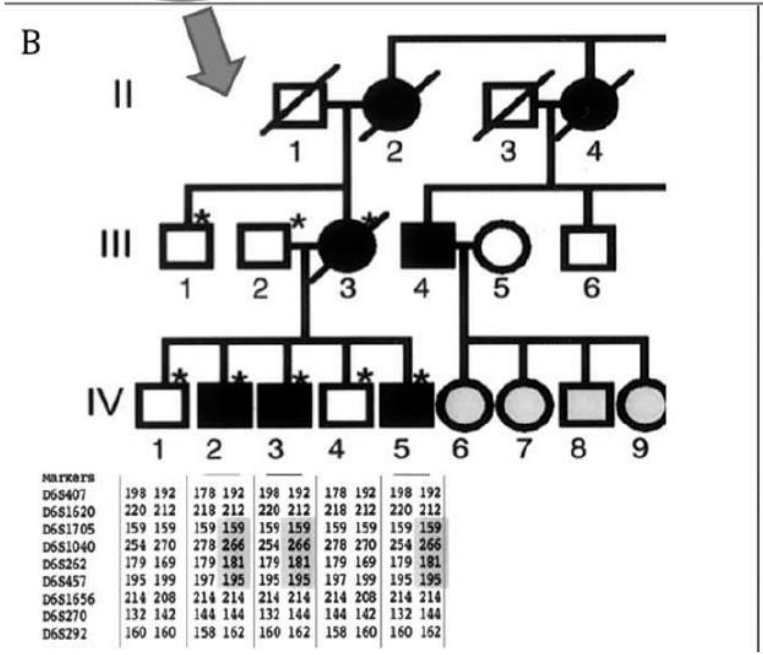
E

| Desmin sequences identified |
|---|
| FASEASGYQDNIAR |
| TSGGAGGLGSLR |
| ADVDAATLAR |
| VAELYEEELR |
| DNLLDDLQR |

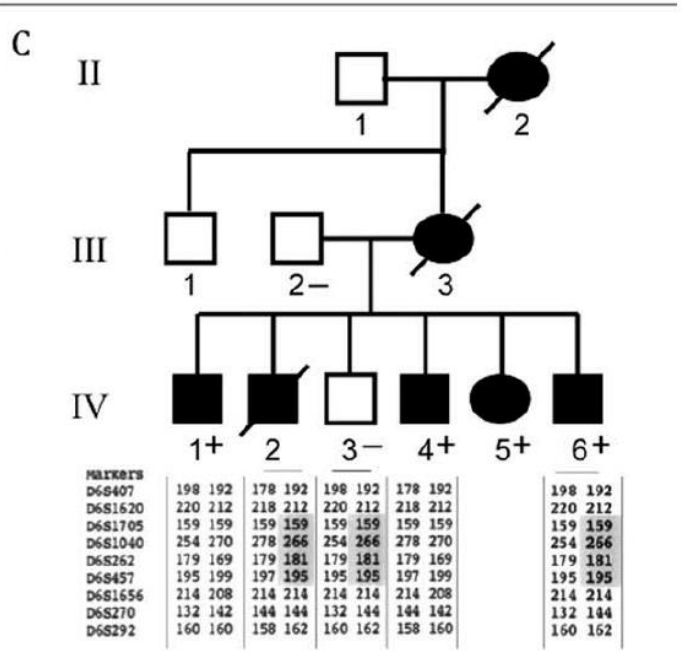
Sequencing identifies known desmin mutations in this family

# Desmin is on chromosome 2q35 not 6q23



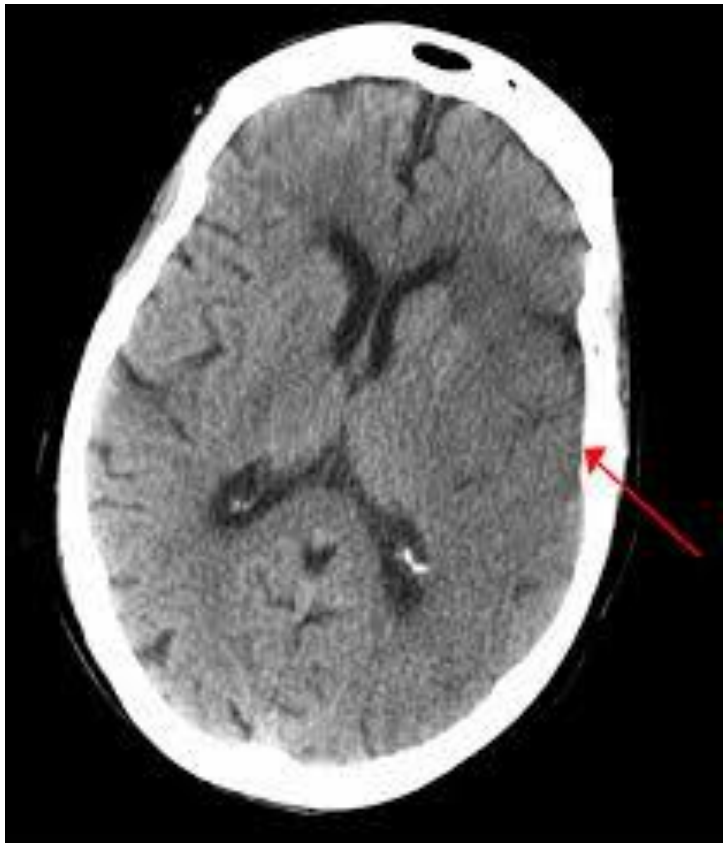

| Markers | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D6S407 | 198 | 192 | 178 | 192 | 198 | 192 | 178 | 192 | 198 | 192 | | | | | | | | |
| D6S1620 | 220 | 212 | 218 | 212 | 220 | 212 | 218 | 212 | 220 | 212 | | | | | | | | |
| D6S1705 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | | | | | | | | |
| D6S1040 | 254 | 270 | 278 | 266 | 254 | 266 | 278 | 270 | 254 | 266 | | | | | | | | |
| D6S262 | 179 | 169 | 179 | 181 | 179 | 181 | 179 | 169 | 179 | 181 | | | | | | | | |
| D6S457 | 195 | 199 | 197 | 195 | 195 | 195 | 197 | 199 | 195 | 195 | | | | | | | | |
| D6S1656 | 214 | 208 | 214 | 214 | 214 | 214 | 214 | 208 | 214 | 214 | | | | | | | | |
| D6S270 | 132 | 142 | 144 | 144 | 132 | 144 | 144 | 142 | 132 | 144 | | | | | | | | |
| D6S292 | 160 | 160 | 158 | 162 | 160 | 162 | 158 | 160 | 160 | 162 | | | | | | | | |



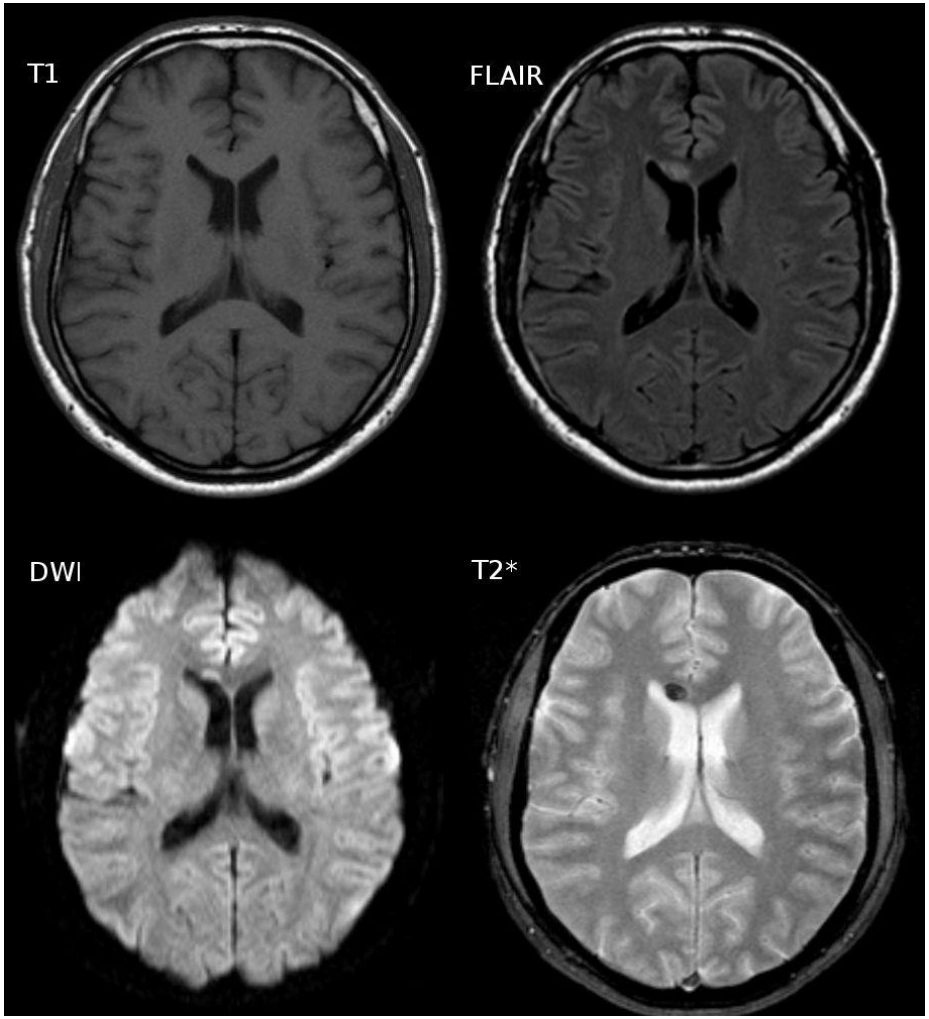

| Markers | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D6S407 | 198 | 192 | 178 | 192 | 198 | 192 | 178 | 192 | | | | | | | 198 | 192 | | |
| D6S1620 | 220 | 212 | 218 | 212 | 220 | 212 | 218 | 212 | | | | | | | 220 | 212 | | |
| D6S1705 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | | | | | | | 159 | 159 | | |
| D6S1040 | 254 | 270 | 278 | 266 | 254 | 266 | 278 | 270 | | | | | | | 254 | 266 | | |
| D6S262 | 179 | 169 | 179 | 181 | 179 | 181 | 179 | 169 | | | | | | | 179 | 181 | | |
| D6S457 | 195 | 199 | 197 | 195 | 195 | 195 | 197 | 199 | | | | | | | 195 | 195 | | |
| D6S1656 | 214 | 208 | 214 | 214 | 214 | 214 | 214 | 208 | | | | | | | 214 | 214 | | |
| D6S270 | 132 | 142 | 144 | 144 | 132 | 144 | 144 | 142 | | | | | | | 132 | 144 | | |
| D6S292 | 160 | 160 | 158 | 162 | 160 | 162 | 158 | 160 | | | | | | | 160 | 162 | | |

# Imaging techniques in neurologic disease

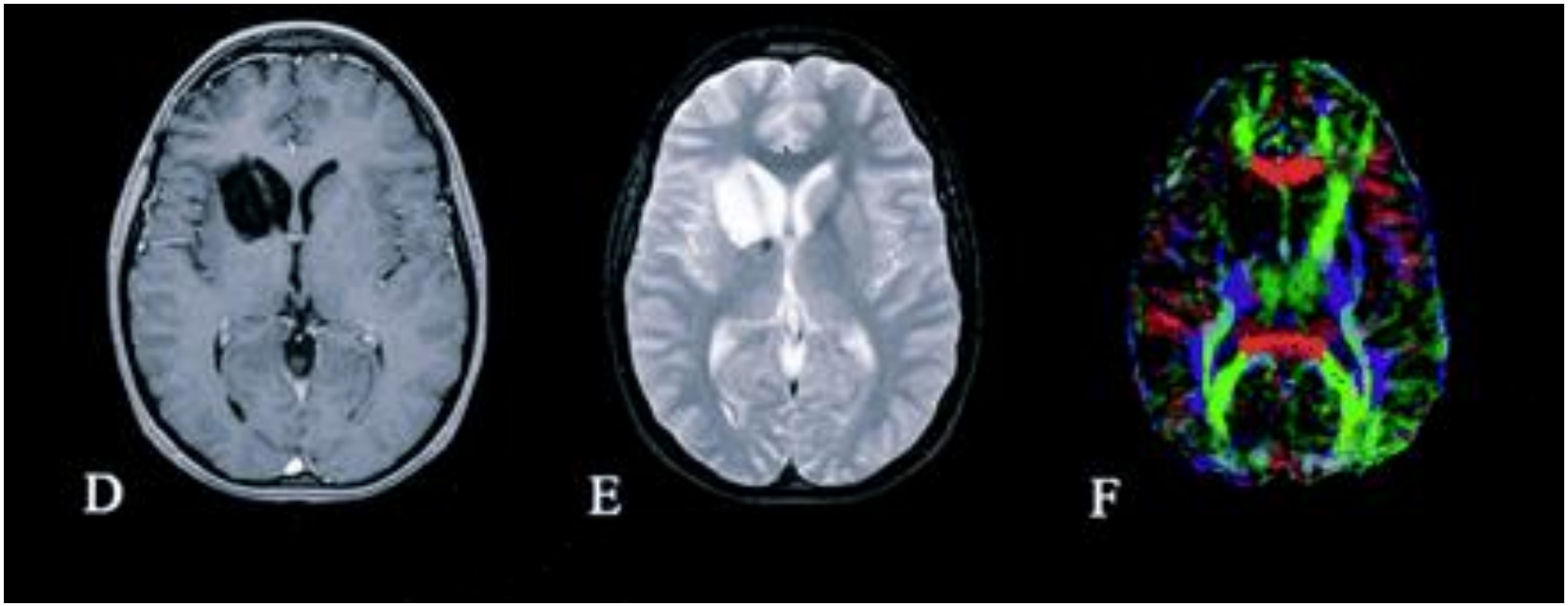
- CT scan



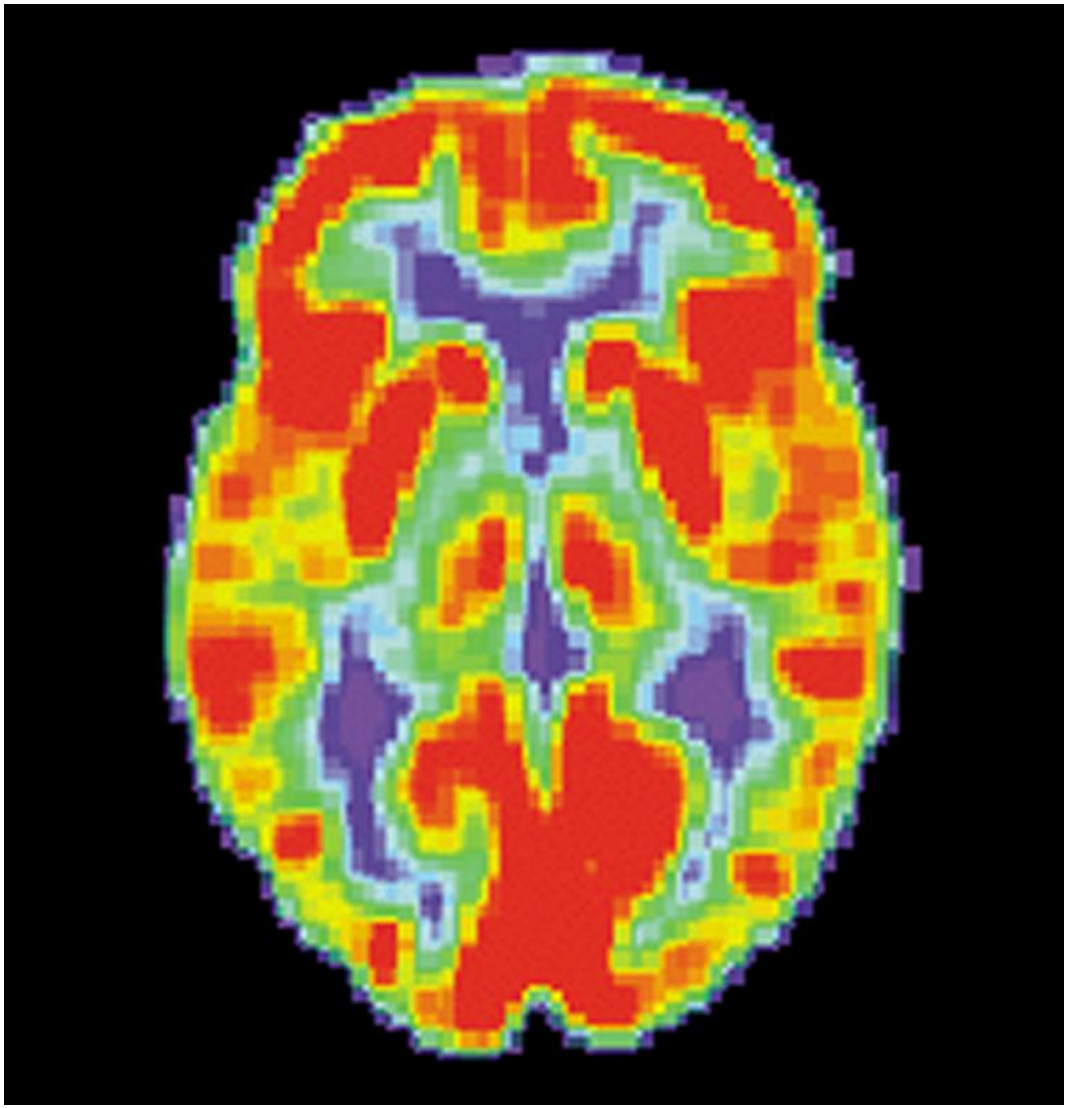
- MRI



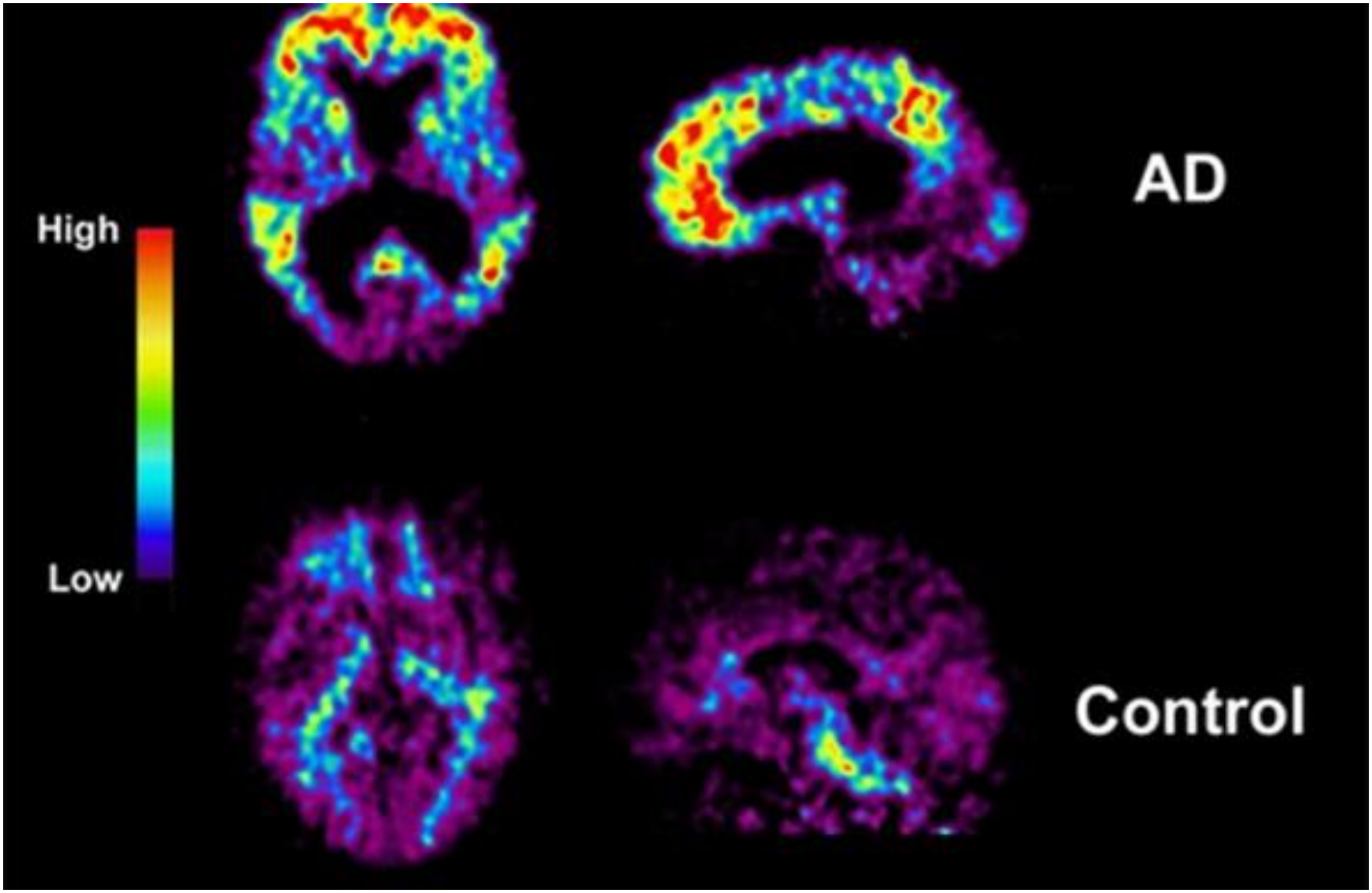
# MRI based Diffusion Tensor imaging



# PET/SPECT imaging

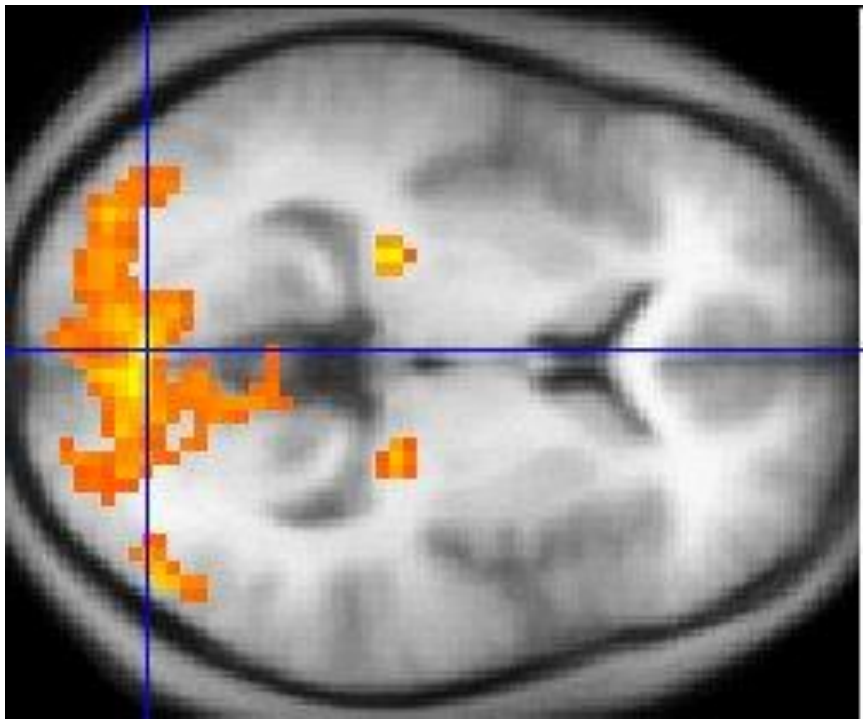


# PET base PIB imaging

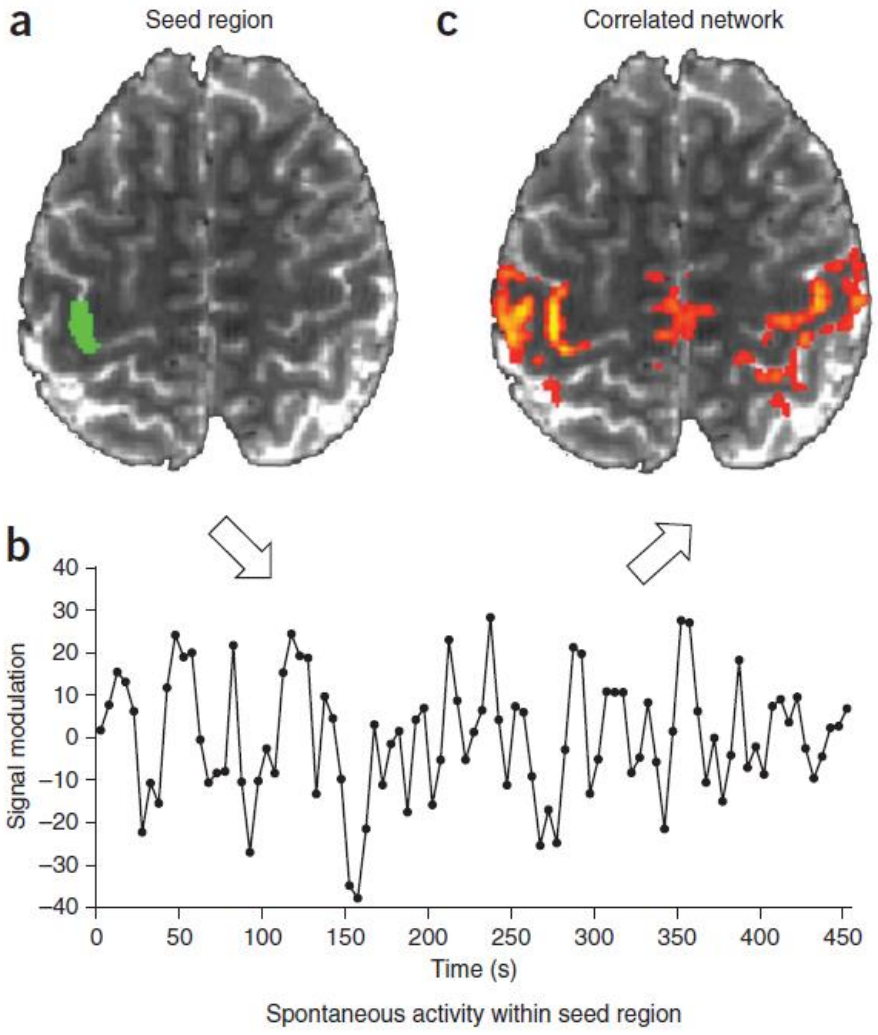


# Functional MRI

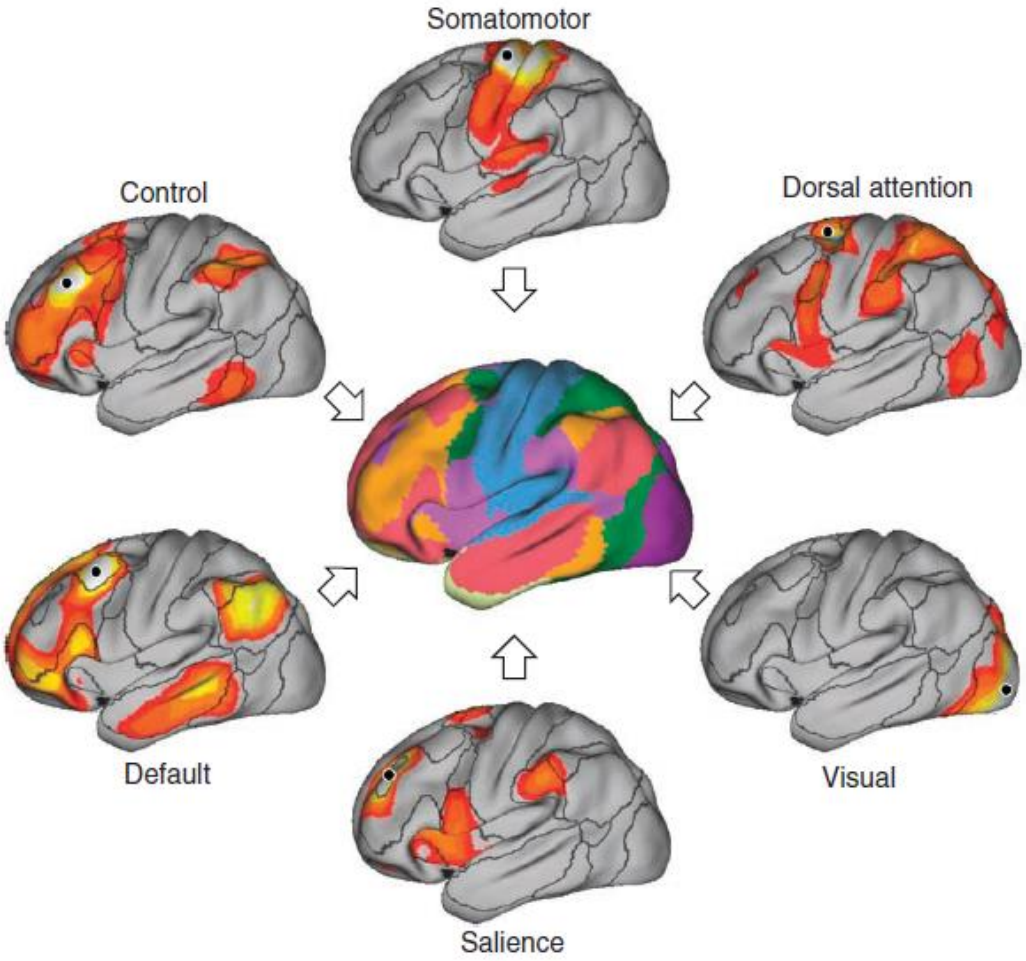
- BOLD contrast (blood-oxygen-level dependent)



# Functional connectivity



# Functional connectivity



# Translational Neuroscience

- Definitions

The New York Times

LETTERS

# Before We Look for Cures (1 Letter)

Published: February 28, 2011



To the Editor:

"Studying Aging, and Fearing Budget Cuts" (Feb. 22) points out that research on aging is seriously underfinanced, but overlooks the reasons.

A major factor is the overemphasis on so-called translational research, which seeks to translate laboratory findings into clinical applications, at the expense of basic research. The push for translational studies by the National Institutes of Health, Congress and our universities is shortsighted and damaging.

We do not even know the normal function of proteins that cause neurodegenerative diseases like Alzheimer's. Moreover, several recent clinical trials to test drugs for dementia are not based on solid scientific evidence. Before we can find rational treatments for these diseases, more resources must be directed to basic studies.

Moses V. Chao

New York

*The writer is a professor in the molecular neurobiology program at New York University School of Medicine.*

# Therapy development

# Where do drug companies get leads?

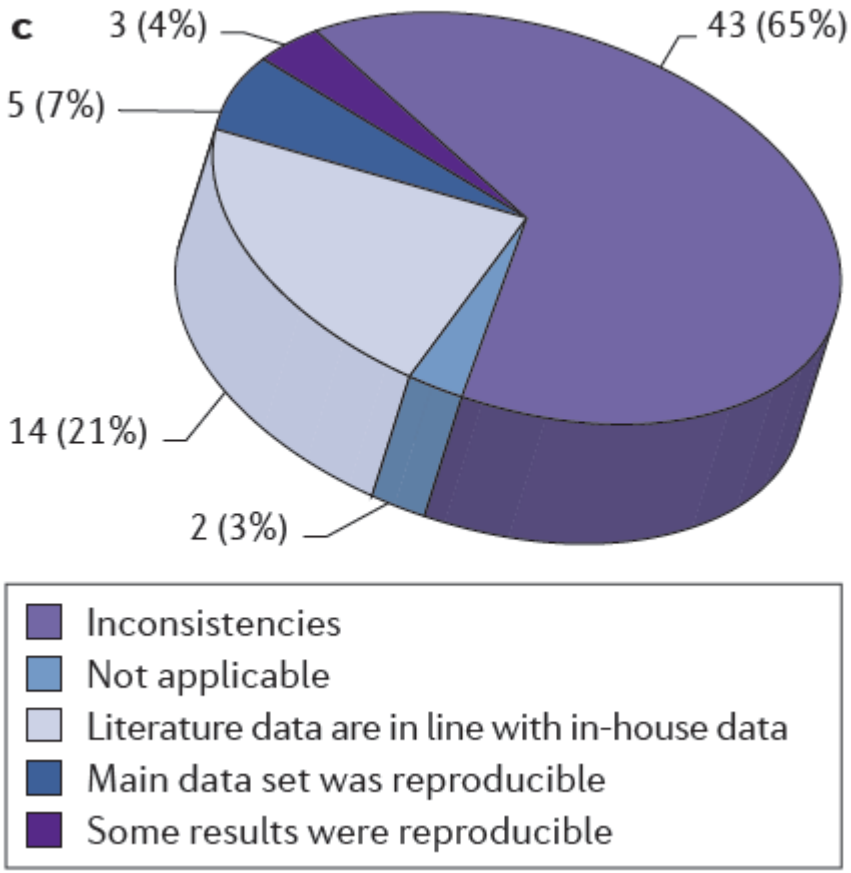
# Believe it or not: how much can we rely on published data on potential drug targets?

NATURE REVIEWS | DRUG DISCOVERY

*Florian Prinz, Thomas Schlange and Khusru Asadullah*

- Bayer HealthCare
- Internal study with 23 labs and 67 projects
- 70% Oncology
- Outcomes of drug target discoveries

**c**




**d**

| | Model reproduced 1:1 | Model adapted to internal needs (cell line, assays) | Literature data transferred to another indication | Not applicable |
|---|---|---|---|---|
| In-house data in line with published results | 1 (7%) | 12 (86%) | 0 | 1 (7%) |
| Inconsistencies that led to project termination | 11 (26%) | 26 (60%) | 2 (5%) | 4 (9%) |

# Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

29 MARCH 2012 | VOL 483 | NATURE | 531

Researchers at Amgen could only reproduce 6/53 published studies (11%)

# Academic labs can reproduce the studies

**REPRODUCIBILITY OF RESEARCH FINDINGS**

Preclinical research generates many secondary publications, even when results cannot be reproduced.

| Journal impact factor | Number of articles | Mean number of citations of non-reproduced articles* | Mean number of citations of reproduced articles |
|---|---|---|---|
| >20 | 21 | 248 (range 3–800) | 231 (range 82–519) |
| 5–19 | 32 | 169 (range 6–1,909) | 13 (range 3–24) |

Results from ten-year retrospective analysis of experiments performed prospectively. The term 'non-reproduced' was assigned on the basis of findings not being sufficiently robust to drive a drug-development programme.
*Source of citations: Google Scholar, May 2011.

# Why discrepancies?

- Unrelated to journal quality
- Unrelated to previous claims regarding the target
- Unrelated to number of independent groups that had validated

- Other thoughts?