UPDATE ON SCA RESEARCH

George Wilmot, MD, PhD

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PRESENTER DISCLOSURES

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- Biohaven Pharmaceuticals
- Forward Pharma
- Santhera Pharmacueticals

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SCA UPDATE

- What is SCA?
  - **S**pino**C**erebellar **A**taxia
    - Autosomal Dominant ataxia -correct
    - Any ataxia –incorrect, though used
- Three areas of Advancement
  - Diagnostic
  - Pre-clinical
  - Clinical

DIAGNOSTIC ADVANCES IN SCA

- New ataxias
  - SCA 41 (gene TRCP3)
  - SCA 42 (gene CACNA1G)
  - Italian Spinone dog ataxia (gene ITPR1)

DIAGNOSTIC ADVANCES IN SCA

- New ataxias
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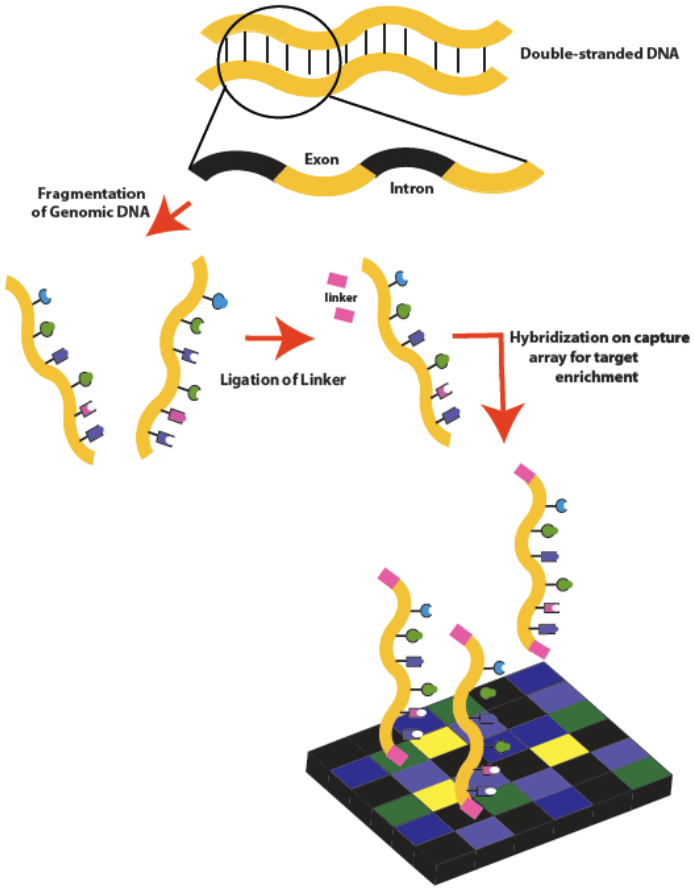
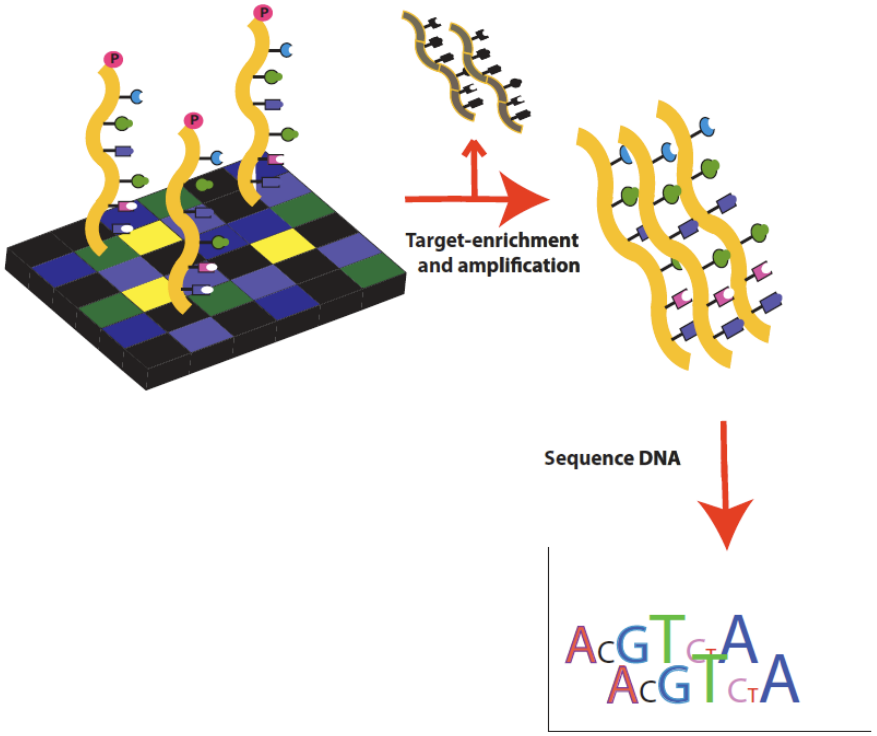
- Increased availability of Whole Exome Testing

WHOLE EXOME TESTING

- Exome
  - Concept
  - Total of all coding portions ("exons") of all genes
    - 30,000 genes
    - Coding portions are about 1% of the genome
    - 180,000 exons
    - 30 million base pairs

WHOLE EXOME TESTING

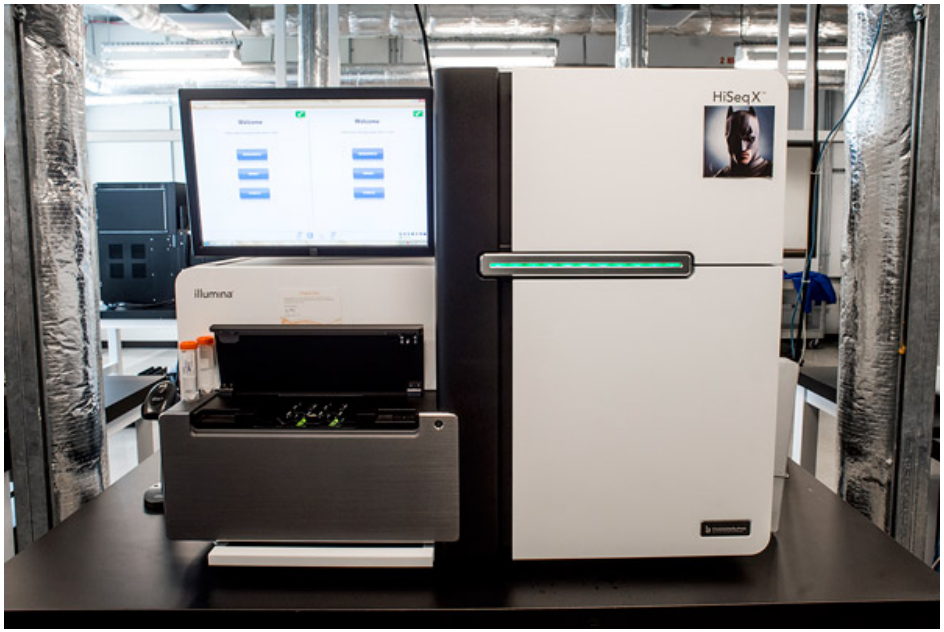




WHOLE EXOME TESTING

- "This example provides proof of concept of the use of whole-exome sequencing as a clinical tool in evaluation of patients with undiagnosed genetic illnesses. These findings further underscore the ability to parse large quantities of sequence data to produce clinically useful information that combines clues from the clinical condition in conjunction with the genetic data to arrive at a correct diagnosis. **We can envision a future in which such information will become part of the routine clinical evaluation of patients with suspected genetic diseases in whom the diagnosis is uncertain."**
  - Choi *et al.* 2009

WHOLE EXOME TESTING



Many exomes per run (1-3 days)

Some machines up to 1.5 Tb per run

Whole Genome (not Exome!!!) now < $1000 in costs to the lab.

PRECLINICAL ADVANCES

- Improved understanding of disease mechanisms
- Development of potential therapeutics
  - Anti-sense Oligonucleotides (ASO's), siRNA
  - Gene Therapy (delivery systems)
  - Stem cells
  - Small molecules (more traditional)

SCA1 mice

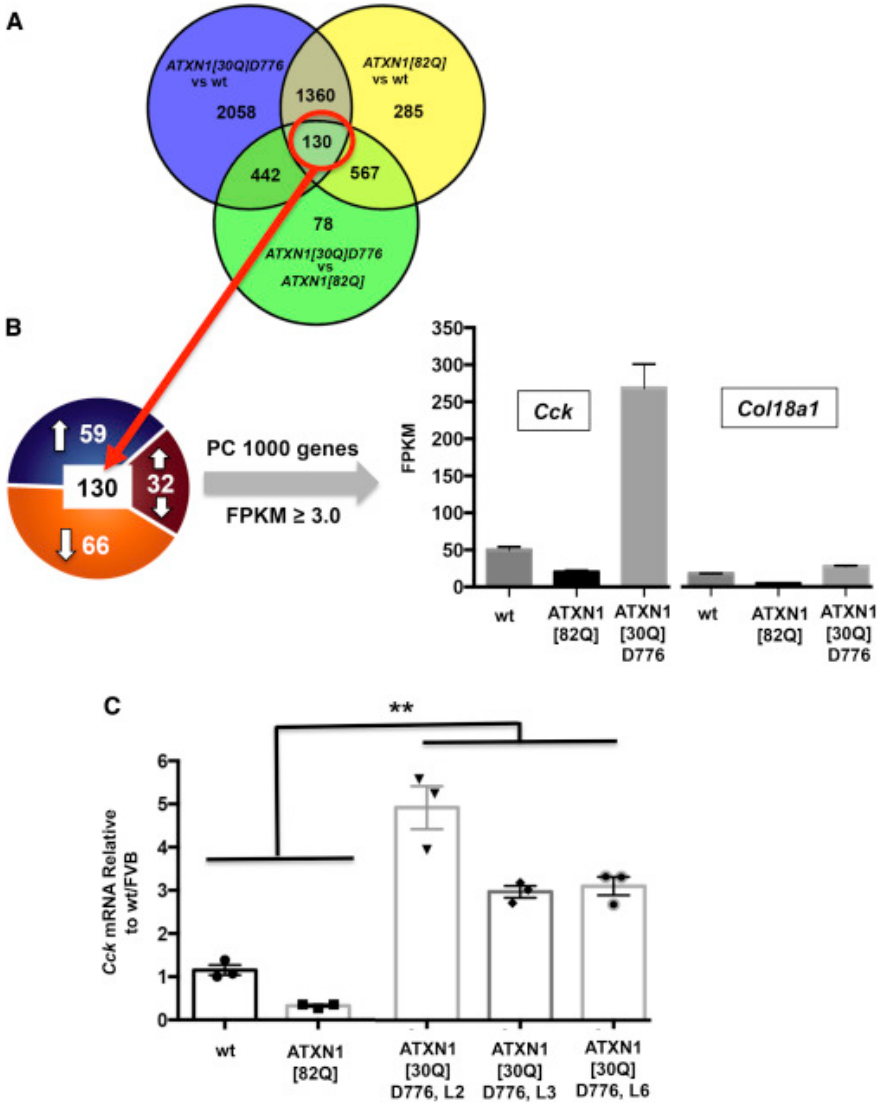
-Transcriptome analysis in engineered SCA1 mice

-find co-regulated genes

-CCK elevated in a non-progressive mouse

-without CCK, mice progress

-maybe CCK is neuroprotective Ingram et al. 2016



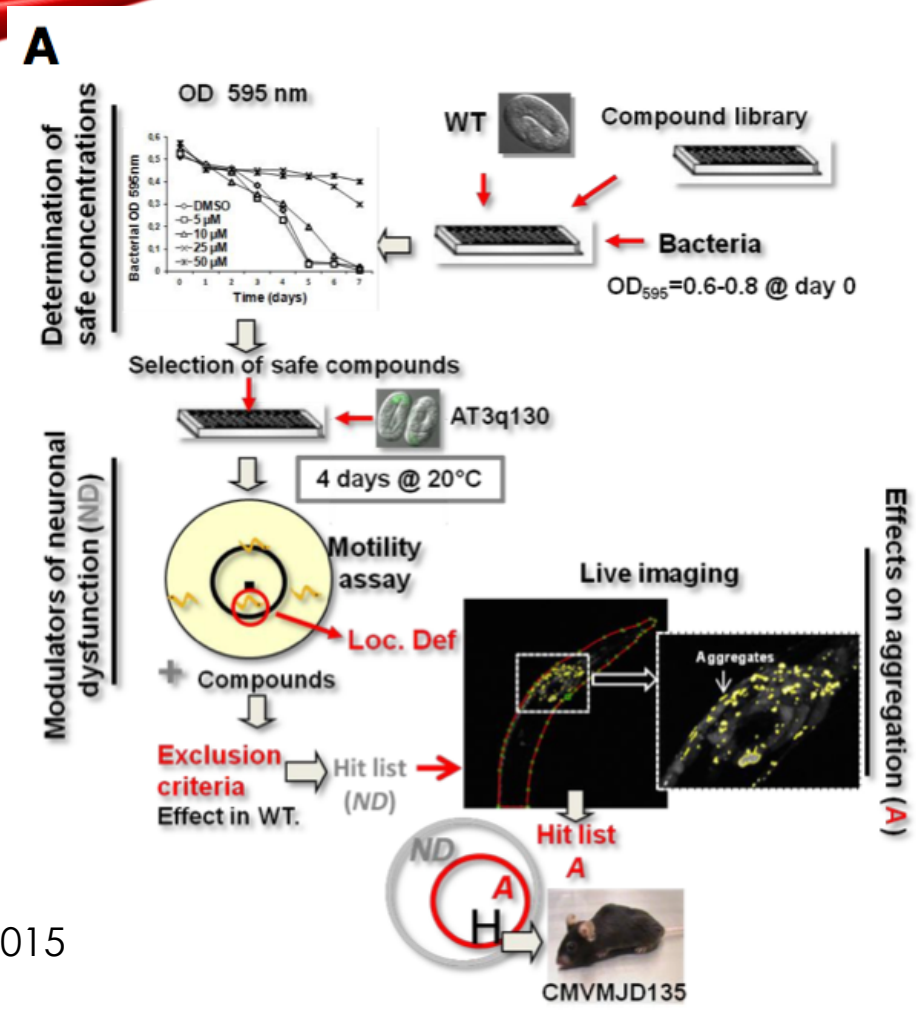
PRECLINICAL ADVANCES

- Drug Screens
  - models are important
    - Now 9 SCA3 mouse models

  - Lower level models < ---------- > Higher level models
    Worms < ---------- > Mice
    Efficiency < ---------- > Accuracy

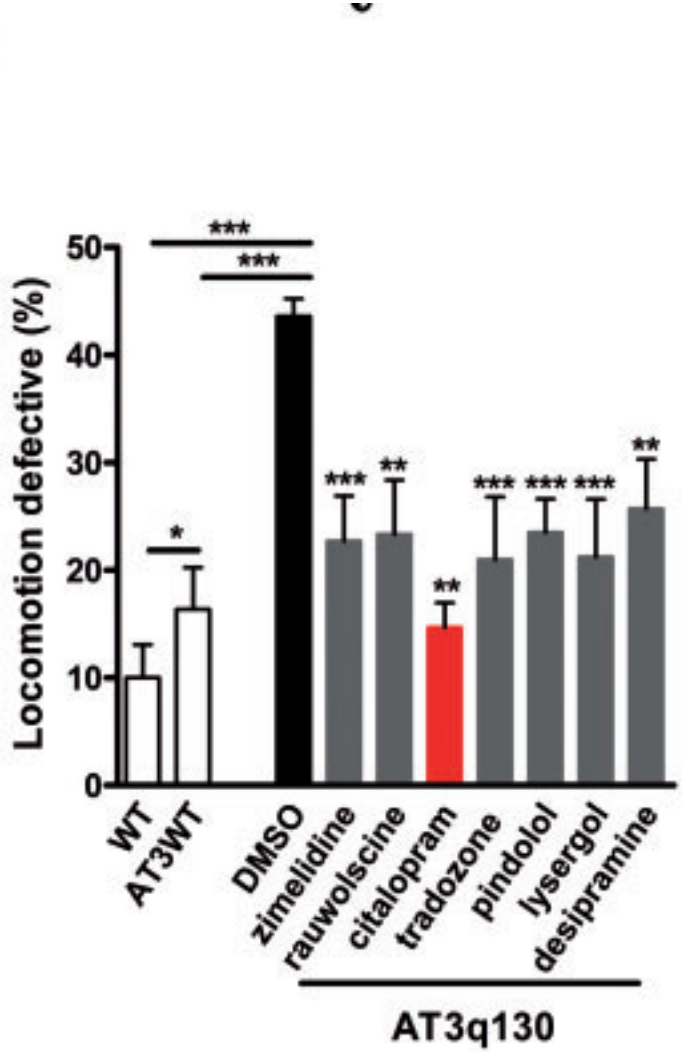
Screen for SCA3

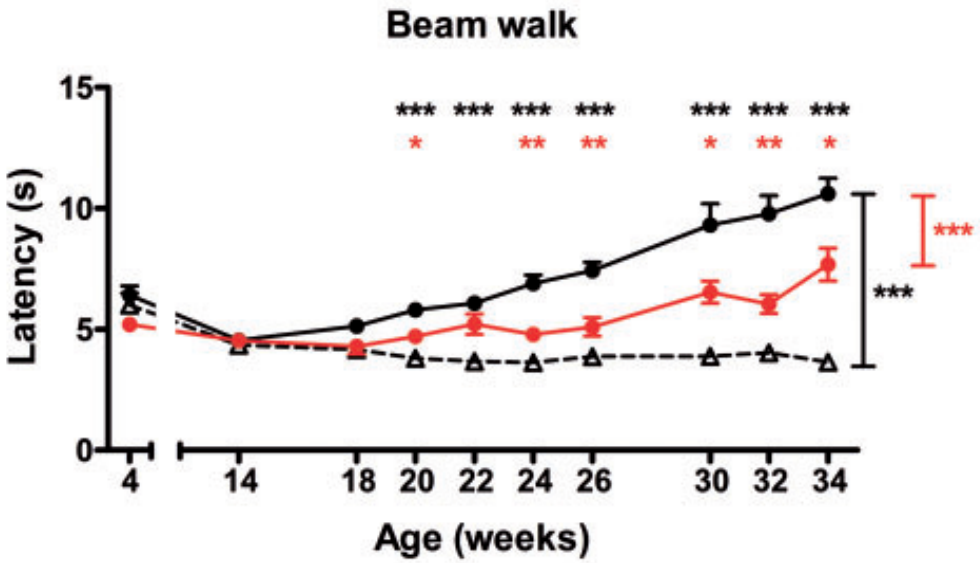
-worms and mice

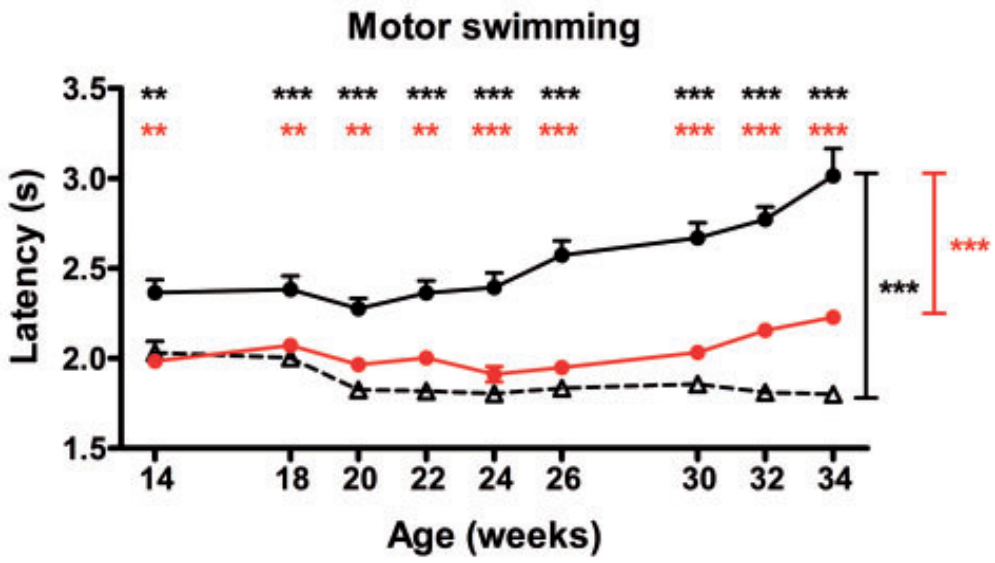


Teixeira-Castro *et al*. 2015

Citalopram improved locomotion and reduced aggregates in worms







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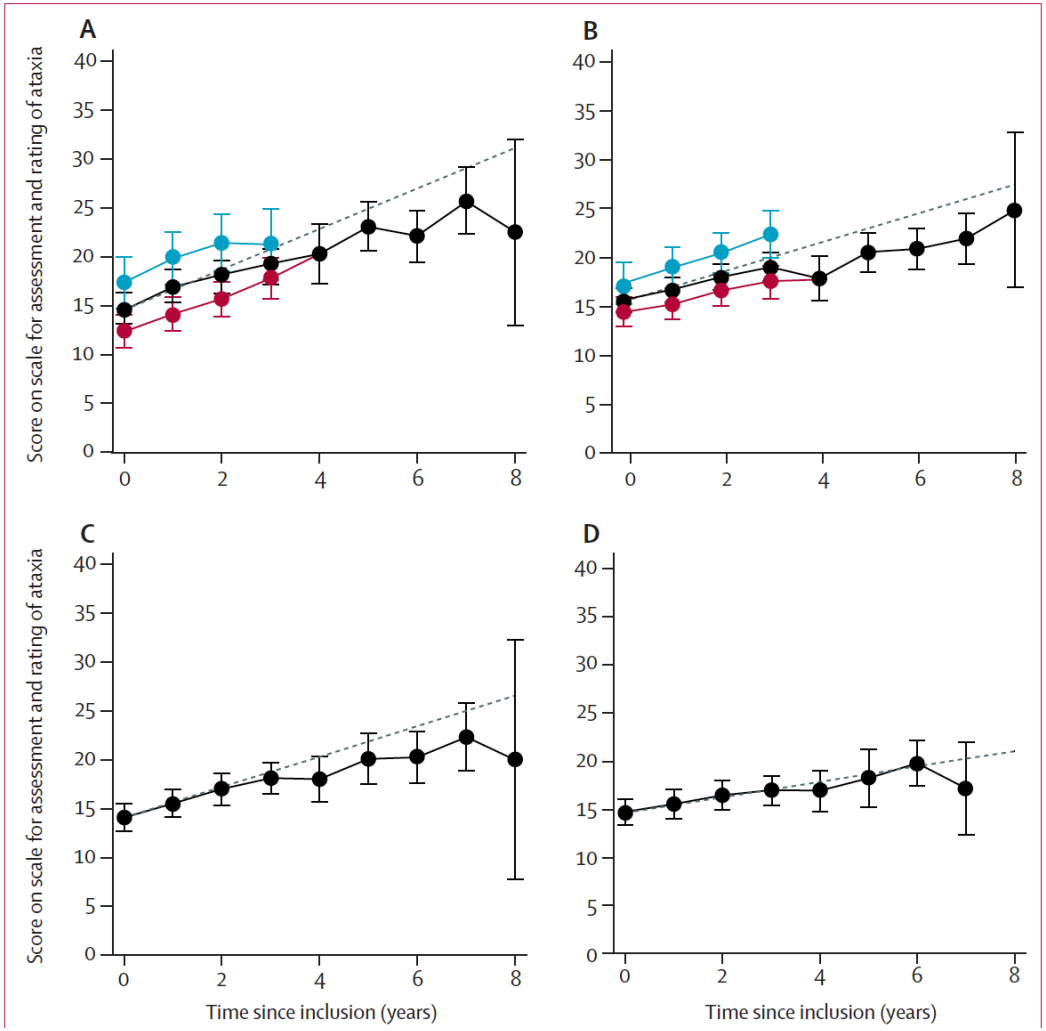
…and had some benefit in mice

CLINICAL ADVANCES

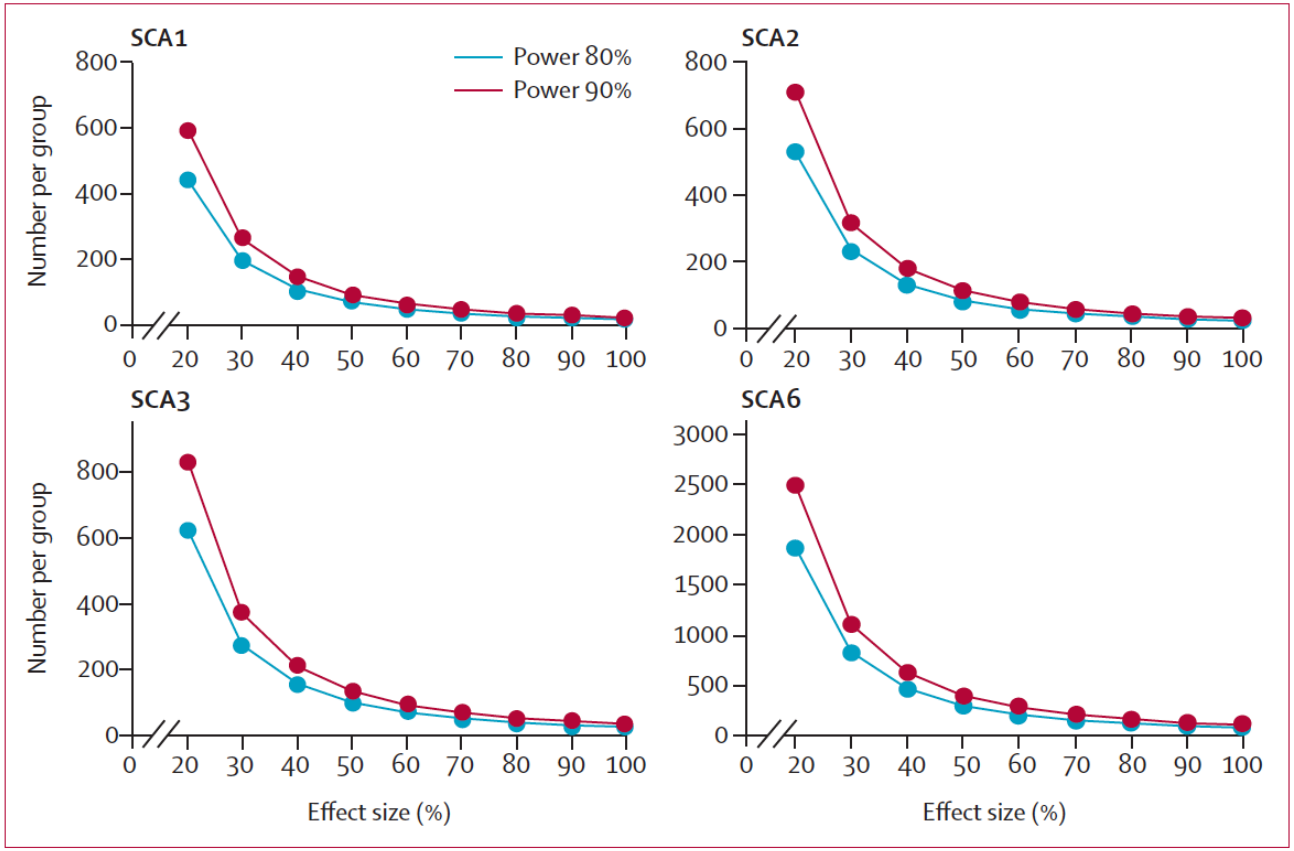
- Longitudinal Studies

Multi-year follow-up of SCA 1,2,3 and 6



Jacobi *et al.* 2015

How many patients are needed for a 1 year clinical study?



CLINICAL ADVANCES

- Should we use something other than an ataxia scale?
  - -imaging and other biomarker studies

- Do we have therapeutic candidates?
  - Exercise
  - Existing medicines that are used for other conditions (riluzole, varenicline, citalopram)
  - Disease-specific therapies based on disease mechanisms

CLINICAL ADVANCES

- Longitudinal Studies
- **Possible treatments**

CLINICAL ADVANCES

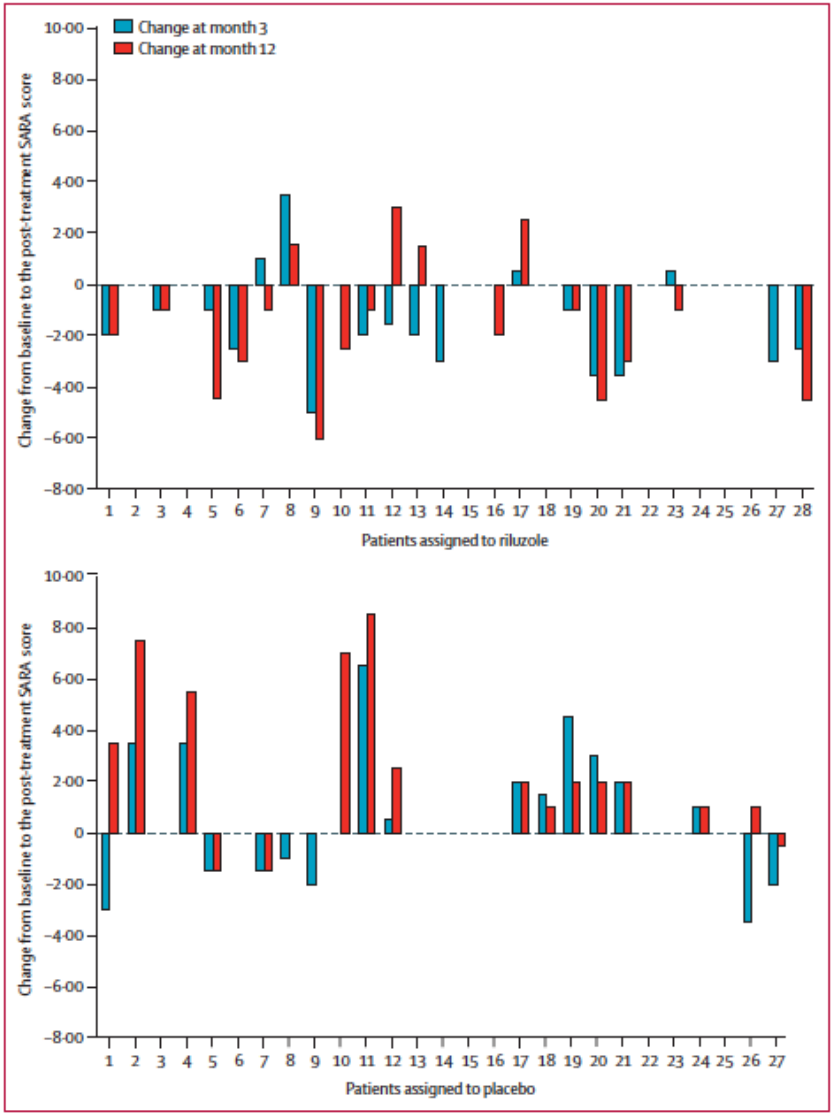
- Riluzole
  - Used for ALS
  - Expensive
  - Liver toxicity
  - Multiple mechanisms, some of which may be relevant to ataxia

Italian Study 2015

30 patients each
placebo and riluzole
SARA at 3 and 12 months.

Results:
-Indications of benefit
-heterogeneity of subjects a problem
-low numbers of subjects a problem

Romano *et al.* 2015



- So the question you will no doubt have is …

- **How should I be treated, right now, not in the future, but now?**

- My best answer: Work it out with your own doctor. But please continue to recognize the imperative nature for rigorous research. If everyone is taking unproven treatments, it may become more difficult to enroll subjects in the upcoming trials.

FUTURE DIRECTIONS

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- **Find new ataxias**
- **Refine therapeutic screens of existing compounds and development of new agents (ASOs etc.)**
- **Find biomarkers and better clinical outcome measures**
- **Cautiously proceed with clinical studies**
  - **Riluzole derivatives**
  - **Citalopram**
  - **Stem cells**
  - **Others**

- **PLEASE do the CoRDS Registry!**

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THANKS!!!

- Funding - FARA, NIH, NAF
- Colleagues
- Most of all, my patients