UPDATE ON SCA RESEARCH

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▪ George Wilmot, MD, PhD
▪ The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:
  ▪ Biohaven Pharmaceuticals
  ▪ Forward Pharma
  ▪ Santhera Pharmaceuticals

National Ataxia Foundation
• What is SCA?
  • SpinoCerebellar Ataxia
    • 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
  • SCA 41 (gene TRCP3)
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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
...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?
• 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
• 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
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• Continue to advance our understanding of known ataxias
• Find new ataxias
• Refine therapeutic screens of existing compounds and development of new agents (ASOs etc.)
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• Find biomarkers and better clinical outcome measures
FUTURE DIRECTIONS

• Continue to advance our understanding of known ataxias
• 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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National Ataxia Foundation
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• Colleagues
• Most of all, my patients