Ataxia
Molecular and cellular mechanisms

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Disclosures

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National Institutes of Health/National Ataxia Foundation

References


In ataxia, cerebellum typically is front and center...

...but damage throughout neuro-axis can cause ataxia (e.g., pons, spinocerebellar tracts, DRG).

Accordingly, causes of ataxia are diverse. And many are genetic.
Cerebellum: Common site of neuronal vulnerability in human genetic disease

Purkinje cell is a pacemaker neuron

Adapted from Paulson et al Nat Rev Neurosci (2017)
Genetics of ataxia has been a key driver of ataxia research. Most common ataxias are associated with repeat expansions.
Filling out the genetic causes of ataxia

candidate gene vs. exome vs. genome analysis

Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome

over 1,000 entries for ataxia in OMIM…
Many causes of recessive ataxias

- all recessive disorders with ataxia (occasional, frequent or predominant)
- recessive disorders with ataxia as a predominant or frequent feature

Year of publication (with an ataxia syndrome)

Total number of genes

Neuron 2019 101560-583
DOI: (10.1016/j.neuron.2019.01.049)
Many causes of dominant ataxias, also known as Spinocerebellar ataxias (SCAs) up to at least SCA49 and still counting…

<table>
<thead>
<tr>
<th>widespread CNS</th>
<th>pure cerebellar</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA17</td>
<td>SCA7</td>
</tr>
<tr>
<td>SCAs 1,2,3</td>
<td>SCA6</td>
</tr>
</tbody>
</table>
Growth in range of ataxias has shed light on shared mechanisms

- bioenergetics
- impaired protein homeostasis
- channelopathies
- DNA repair
- repeat expansions

Routes to common therapies?
Varied manifestations in hereditary ataxias largely reflect repeat expansions

adapted from Ashizawa, Oz and Paulson. Nat Rev Neurol (2018)
Repeat expansions cause diverse phenotypes: example of SCA3

- Normal repeats
- Intermediate repeats
- Disease-causing repeats

12 40 50 60 70 80

RLS

Type I
- Dystonia

Type II
- Ataxia

Type III
- Weakness

Parkinsonism (Type IV)
Varied manifestations in hereditary ataxias largely reflect repeat expansions

adapted from Ashizawa, Oz and Paulson. Nat Rev Neurol (2018)
Basis of Friedreich ataxia: reduced frataxin

(GAA)$_n$ (GAA)<30

(GAA)100-1500

Exon 1 Exon 2 Exon 3 Exon 4 Exon 5

L106X G130V I154F

Frataxin

Tubulin

Age at Onset (yr)

No. of GAA Repeats in the Smaller Allele
Shared mechanisms

- bioenergetics
  - Friedreich ataxia
- impaired protein homeostasis
- polyQ diseases
- channelopathies
- DNA repair
- repeat expansions
Shared mechanisms

- bioenergetics
- impaired protein homeostasis
- polyQ diseases
- channelopathies
- repeat expansions
- DNA repair
DNA repair defects in ataxias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>gene/function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia telangiectasia</td>
<td><em>ATM</em> central kinase that signals response to DSB</td>
</tr>
<tr>
<td>AT-like disease (ATLD)</td>
<td><em>MRE11</em> part of MRN complex that senses DSB</td>
</tr>
<tr>
<td>Nijmegen Breakage syndrome</td>
<td><em>NBS1</em> part of MRN complex that senses DSB</td>
</tr>
<tr>
<td>AOA1</td>
<td><em>APTX</em> DNA ligase proofreader (deadenylase) primarily acting at SSB</td>
</tr>
<tr>
<td>AOA2</td>
<td><em>SETX</em> RNA/DNA helicase involved in transcription, transcription-coupled DNA repair</td>
</tr>
<tr>
<td>AOA4</td>
<td><em>PNKP</em> dual kinase and phosphatase implicated in multiple DNA repair pathways</td>
</tr>
<tr>
<td>SCAN1</td>
<td><em>TDP1</em> removes DNA/topoisomerase adducts</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>many genes genome/transcription-coupled NER*</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td><em>CKN1,ERCC6</em> transcription-coupled NER*</td>
</tr>
</tbody>
</table>

Why do DNA repair defects particularly damage Purkinje cells, and sensory and motor neurons?

*nucleotide excision repair
Figure 5

Neuron 2019 101560-583DOI: (10.1016/j.neuron.2019.01.049)
Shared mechanisms

- channelopathies
- bioenergetics
- impaired protein homeostasis
- polyQ diseases
- DNA repair
- repeat expansions
Cerebellum: Common site of neuronal vulnerability in human genetic disease

Purkinje cell is a pacemaker neuron
## Ataxia from ion-channel mutations

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<thead>
<tr>
<th>Disorder</th>
<th>Ion channel mutation (gene/protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA6</td>
<td>CACNA1A/Cav2.1</td>
</tr>
<tr>
<td>SCA13</td>
<td>KCNC3/Kv3.3</td>
</tr>
<tr>
<td>SCA15/16 and SCA29</td>
<td>ITPR1/IP3 receptor</td>
</tr>
<tr>
<td>SCA19/22</td>
<td>KCND3/Kv4.3</td>
</tr>
<tr>
<td>SCA41</td>
<td>TRPC3/Trpc3</td>
</tr>
<tr>
<td>SCA42</td>
<td>CACNA1G/Cav3.1</td>
</tr>
<tr>
<td>Episodic ataxia 1</td>
<td>KCNA1/Kv1.1</td>
</tr>
<tr>
<td>Episodic ataxia 2</td>
<td>CACNA1A/Cav2.1</td>
</tr>
<tr>
<td>Episodic ataxia 5</td>
<td>CACNB4/ Ca channel beta subunit</td>
</tr>
<tr>
<td>Ataxia myoclonic epilepsy</td>
<td>KCNA2/Kv1.2</td>
</tr>
<tr>
<td>SMEI</td>
<td>SCN1A/Nav1.1</td>
</tr>
</tbody>
</table>

Mostly dominantly inherited…
Growing evidence for channel dysfunction in SCAs

Klockgether, Marrioti and Paulson.
Nat Rev Dis Prim. (2019)
Channel function also perturbed in ataxias not caused by channel mutations (e.g. SCA3)

Purkinje cell is a pacemaker neuron

SCA3 neuron

Depolarization block in Purkinje cells of SCA3 mice

K channel activator improves motor function

SCA1: Motor deficits linked to Calcium-activated K (BK) channels (e.g. SCA1)

Similar results in SCA2 and SCA7 (Stoyas et al, Neuron, 2020)
Neurodegenerative ataxias: principle of parsimony may not apply

Protein/cell-of-origin viewpoint

Circuit disorder viewpoint

Srinivasan, S. (in press)
Shared mechanisms

- impaired protein homeostasis
- polyQ diseases
- repeat expansions
- DNA repair
- channelopathies
- bioenergetics

polyQ diseases

Shared mechanisms
SCA3 and other polyQ diseases are due to expanded CAG repeats that encode glutamine (“Q”) in the disease proteins

**Normal:**
DNA: ..nnCAGCAGCAGnn..
protein: ..XQQQXX..

**Disease:**
..nnCAGCAGCAGCAGCAGCAGCAGCAG..nn
protein: ..XXQQQQQQQQQQQQQQQQQQQQQQQXX..
Other SCAs:
  SCA1
  SCA2
  SCA6
  SCA7
  SCA17

PolyQ diseases differ greatly

SCA3

PolyQ diseases

SBMA

Huntington disease
Spinobulbar muscular atrophy
SCA3 and other SCAs
Shared neuropathological feature of all polyQ diseases is protein aggregation.

Examples shown here for SCA3, but examples exist for all polyQ ataxias.
Protein context specifies pathogenesis in each polyQ disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Protein Name</th>
<th>Protein Size, PolyQ Position and Disease Repeat Range</th>
<th>Protein Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBMA</td>
<td>Androgen Receptor</td>
<td><img src="image" alt="Androgen Receptor" /></td>
<td>Testosterone-activated steroid receptor</td>
</tr>
<tr>
<td>HD</td>
<td>Huntington</td>
<td><img src="image" alt="Huntington" /></td>
<td>Possible scaffolding protein linked to diverse cellular pathways</td>
</tr>
<tr>
<td>DRPLA</td>
<td>Atrophin-1</td>
<td><img src="image" alt="Atrophin-1" /></td>
<td>Possible transcriptional co-repressor</td>
</tr>
<tr>
<td>SCA1</td>
<td>Ataxin-1</td>
<td><img src="image" alt="Ataxin-1" /></td>
<td>Transcriptional co-repressor involved in transcription regulation, cell specification, synaptic activity</td>
</tr>
<tr>
<td>SCA2</td>
<td>Ataxin-2</td>
<td><img src="image" alt="Ataxin-2" /></td>
<td>Component of RNA processing and translational regulation pathways</td>
</tr>
<tr>
<td>SCA3</td>
<td>Ataxin-3</td>
<td><img src="image" alt="Ataxin-3" /></td>
<td>Deubiquitinating enzyme involved in protein quality control</td>
</tr>
<tr>
<td>SCA6</td>
<td>P/Q type Calcium Channel Subunit α1A</td>
<td><img src="image" alt="P/Q type Calcium Channel Subunit α1A" /></td>
<td>Voltage-sensitive calcium channel subunit / α1ACT</td>
</tr>
<tr>
<td>SCA7</td>
<td>Ataxin-7</td>
<td><img src="image" alt="Ataxin-7" /></td>
<td>Component of histone acetyl-transferase complex (TFTC/STAGA) and transcriptional regulation pathways</td>
</tr>
<tr>
<td>SCA17</td>
<td>TATA-box Binding Protein</td>
<td><img src="image" alt="TATA-box Binding Protein" /></td>
<td>Component of core transcriptional complex TFIID</td>
</tr>
</tbody>
</table>

Williams and Paulson, TINS (2008)
Dizzying array of potential mechanisms

Nucleotide-based gene silencing targets proximal steps in pathogenic cascade (e.g. SCA3)

SCA3 disease protein

neuronal dysfunction and cell death

[Diagram showing DNA, RNA, protein, oligomers, fibrils, inclusions, and their relationship to neuronal dysfunction and cell death]
Preclinical success in polyQ SCAs

Miller VM et al. Allele-specific silencing of dominant disease genes. PNAS. 2003 PMID:12782788 (SCA3)
Anti-sense oligonucleotide (ASO)-based silencing as therapy

SCA3 disease gene ATXN3

Antisense oligonucleotide (ASO)

5-8-5 MOE ASO “Gapmer” Design

Mixed backbone [AGTmC]

MOE Unmodified Bases MOE

ATXN3 suppression in SCA3 fibroblasts

Prolonged action of anti-ATXN3 ASO in SCA3 mice

SCA3 mice express full human ATXN3 disease gene

ASO corrects incoordination in SCA3 mice

Biogen Phase 1 clinical trial of BIIB132 (anti-ATXN3) ASO is now under way

Speed bumps in the road to therapy

- Do we know enough about disease progression?
- Can we reduce the noise in clinical assessment?
- Are there sensitive biomarkers that can facilitate trial design and power?
- For approaches like ASOs or RNAi, can we measure “target engagement”?
- Do we know which cells we need to target?
- Will knocking down the wild type allele a problem?
Ataxias are complex mechanistically… remember these shared, common mechanisms!

Routes to therapy will come from better understanding of mechanisms.
Funding: NIH (NINDS, NIA), National Ataxia Foundation, ALS Association, Taubman Medical Research Institute

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Biswa Ramani, MD PhD
Edgar Rodriguez, PhD
Li Zeng, MD PhD
Haiyong Luo, MD
Brett Winborn PhD
Ginny Harris, MD PhD

Protein Folding Disease Initiative

Michigan Neuroscience Institute

Funding: NIH (NINDS, NIA), National Ataxia Foundation, ALS Association, Taubman Medical Research Institute

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Regional Brain and Spinal Cord Volume Loss in SCA3
Faber et al (2021) Movement Disorders, 36: 2273-2281
Mutations in the *STUB1* gene cause neurodegeneration

**SCAR16**
- Recessive disease
- LOF mutations, most destabilize CHIP

**SCA48**
- Dominant disease
- LOF of either chaperone binding or E3 ligase activity
- TPR mutants have a GOF that modulates RNA production/processing

**SCA17-DI**
- Caused by a mutation in STUB1 and an intermediate polyglutamine expansion in TBP

De Michele, Neurol. Sci., 2020