Amyotrophic Lateral Sclerosis
Clinical and Genetic Features

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“Final Common Pathway”

“…to move things is all that mankind can do, for such the sole executant in muscle, whether in whispering a syllable or felling a forest.”

- Charles Sherrington, 1924
Nerve-cells stained by Nissl's method, with toluidin blue.
Magnified 750 diameters. (Schäfer.)

A. From anterior horn of spinal cord, monkey.
B and C. From facial nucleus, dog.

C. Shows Nissl degeneration, consequent on section of the facial nerve 15 days previously. a. a. axons.
Cell Body = 50uM Diameter; Axon Length = 1M
Motor Neuron Disease Clinical Forms

- Progressive muscular atrophy
- Primary lateral sclerosis
- Progressive bulbar palsy
- Amyotrophic lateral sclerosis
Charcot’s Disease

- 1869 - Suggested grouping together diseases that affect the lateral horn of the spinal cord
- Degeneration of corticospinal tracts and extensive loss of lower motor neurons
Figure 2–3. Age-specific incidence of sporadic ALS for males and females is seen to increase until the eighth decade, with a dramatic decline after a peak between 55 and 75 years of age. Sex-related incidence is higher in males, although this is less pronounced over 65 years of age. General population data based on United States census (US Department of Commerce, 1982). (Reprinted from J Neurol Sci 118 (1), Norris, F, Shepherd, R, Denys, E, et al: Onset, natural history and outcome in idiopathic adult motor neuron disease, pp 51, 1993, with kind permission of Elsevier Science - NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.)
Epidemiology of Amyotrophic Lateral Sclerosis

- Incidence of ALS in Europe = 2.2 per 100,000
  - Men = 3 per 100,000; Women = 2.4 per 100,000

- Overall lifetime risk
  - Men = 1:350; Women = 1:400

- Peak age at onset
  - Sporadic = 58 – 63 yrs; Familial = 47 – 52

- Rates of ALS in Cuba are 60% lower than in US or Europe
Survival

- Median survival 2-4 yrs
- Shortest survival ~ 1 yr
- Up to 25% survival beyond 10 years
- > 30 fold difference between fast/slow
- Causes of death
  - respiratory failure
  - aspiration/malnutrition

Figure 9-1: A composite figure of survival curves that have been reported in various studies. The shortest survival curve was derived from a study done in Rochester, Minnesota (Jorgensen, et al.). In most studies, 50% survival ranges from 2 to 4 years after the onset of illness. Approximately 10% or so of patients survive beyond 10 years.
Segmental Onset

• Limb: 78%
  – Asymmetric 60%
• Bulbar: 22%
• Respiratory: 1%
• Axial: ?
Begins Focally - Spreads Segmentally

- Leg onset

Figure 9-1. In patients with leg onset ALS, symptoms appear in the opposite leg, ipsilateral and contralateral arms, and bulbar muscles. The opposite leg is affected in the shortest interval, whereas the bulbar muscles take the longest interval. (From Brooks, BR, et al: Design of clinical therapeutic trials in amyotrophic lateral sclerosis. In Ransford, LP (ed): Amyotrophic Lateral Sclerosis and Other Motor Neuron Disease. Adv Neurol 56:526, 1991, with permission.)
Begins Focally - Spreads Segmentally

- Arm onset

*Figure 3-3. In patients with arm-onset ALS, symptom accrual occurs first in the opposite arm, then in the ipsilateral and contralateral legs, and last in the bulbar muscles. (From Brooks, B.R. et al: Design of clinical therapeutic trials in amyotrophic lateral sclerosis. In Ropper, A.H. (ed): Amyotrophic Lateral Sclerosis and Other Motor Neuron Disease. Adv Neurol 56:927, 1991, with permission.)*
Symptoms

• Bulbar
  – dysarthria, dysphagia, voice change
  – chewing difficulty, tongue weakness
  – sialorrhea, pseudobulbar affect

• Limb
  – weakness, stiffness, slowness, clumsiness
  – cramping, muscle twitching
Symptoms

• Axial
  – Head drop, truncal instability, increased lordosis, protuberant abdomen

• Diaphragm/intercostal
  – Dyspnea, orthopnea, sleep disordered breathing, excessive daytime sleepiness, AM headaches, confusion
Signs

• Upper motor neuron
  – weakness, slowness
  – increased reflexes
  – pathologic reflexes
  – loss of cutaneous reflexes
  – spastic tone
  – pseudobulbar affect

• Lower motor neuron
  – atrophy
  – fasciculations
  – reduced reflexes
  – reduced tone
Clinical Features of ALS
Pathophysiology of ALS

A

B

Surviving motor unit
Collateral sprouts from surviving motor axon reinnervating denervated muscle fibres
Degenerated motor unit

C
Diagnostic Criteria

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(B) the absence of
   (1) electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and
   (2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs
Axon length is 20,000 x soma diameter
Diagnostic Criteria

Diagnostic categories:
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**Clinically definite ALS** is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions.
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**Clinically probable ALS** is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

**Clinically possible ALS** is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded.
Differential Diagnosis

ALS mimics

- Multifocal motor neuropathy => EDX, ganglioside GM1 antibodies
- X-linked spinobulbar muscular atrophy => CAG repeats in AR gene
- Poliomyelitis => History, EDX
- Hexosaminidase A deficiency => white cell enzyme testing
- Spinal muscular atrophy => SMN deletion
- Heavy metal poisoning => urine and blood screens
- Cramp-fasciculation syndrome => EDX
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Error Rate:
- False Positive = 8%
- False Negative = up to 44%
Management

Goal: Optimize health care delivery, prolong survival and enhance quality of life
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Referral to multidisciplinary ALS clinic: Prolongs survival and increased utilization of therapies in multiple studies.

Neurology, 2009: 73:1218-1226 and 1227-1233
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**Riluzole should be offered:** Four separate clinical trials have confirmed prolonged survival 2-3 months. Large retrospective studies indicate that benefit may be more substantial (~ 6 to 21 months)

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Non-invasive ventilatory (NIV) support should be considered: Prospective studies indicate a survival benefit of 5 – 11 months (excluding bulbar predominant patients)
Nutritional Management

Diagnosis: ALS

Monitor body weight
Dysphagia assessment instrument

Monitor Respiratory status (FVC, MIP, etc.)

Clinic visits every 3 months

Early dysphagia detected

Nutritional education including PEG

Symptom progression or continuing weight loss

Discuss PEG to stabilize weight and possibly prolong survival

FVC >50%
Low risk for PEG

PEG accepted

Anesthesia evaluation
Experienced gastroenterologist
Respiratory support during PEG if needed

Oral intake as tolerated
Enteral nutrition via PEG as needed

FVC 30-50%
Moderate risk

PEG declined

Oral intake as tolerated
Palliative IV hydration
Palliative NG feeding

FVC <30%
High risk
Respiratory Management

Text in bold = evidence-based
Text in italics = consensus-based

- Diagnosis ALS
- Symptom evaluation* and PFTs
  Initiate NIV orientation, Pneumovax and flu vaccine
- Orthopnea or SNP < 40cm or MIP < -60cm or Abnl nocturnal oximetry or FVC < 50%
  - Consider NIV
  - NIV tolerated?
    - No
      - Further education regarding documented benefits. Evaluate reasons for noncompliance.
    - Yes
      - Ongoing evaluations and adjustment of pressures
      - Reintroduce NIV
      - Unable to maintain pO₂ > 90%, pCO₂ < 50mmHg or unable to manage secretions
      - Hospice referral for palliative care
      - Invasive ventilation
Diaphragmatic Pacing

Approved by FDA for humanitarian use in ALS
Management

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**Sialorrhea should be treated aggressively:** An important cause of aspiration pneumonia and embarrassing, prevalence of 50%. Anticholinergic medication tried first. Botulinum toxin type B injections into parotid and submandibular glands has been effective in clinical trials

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**Pseudobulbar affect should be treated:** Occurs in 20 - 50% and should not be confused with a mood disorder. Dextromethorphan and quinidine combination is effective (Nuedexta)
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Screening for cognitive impairment should be considered: Estimates of cognitive impairment range from 10 – 75%. Dementia in 15 – 41%. Insufficient data to support treatment of cognitive impairment.

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Axon length is 20,000 x soma diameter

Diameter of earth = approx. 12,756.2 km

Earth’s Axon Length

12,756.2 km X 20,000
= 255,124,000 km
= 1.705 Astronomical Unit
= 14.18 light-minutes
Evidence for Genetic Contribution to ALS

- Familial ALS by family history: 5 – 20%

- Mutations in Mendelian genes account for:
  - 75% of inherited forms
  - 14% of those with no obvious family history

- Twin studies indicate heritability of apparently sporadic ALS is ~ 0.61

- There is clustering of neurodegenerative diseases in relatives of PALS
## Gene Variants in ALS genes (Feb, 2015)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Reported inheritance model</th>
<th>Reported FALS explained</th>
<th>Reported SALS explained</th>
<th>Best model with case enrichment in present study (p-value)</th>
<th>Cases with variant in best model</th>
<th>Controls with variant in best model</th>
<th>Potential ALS cases explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBK1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Dom not benign (D = 1.13x10^-9; R = 5.78x10^-7; C = 3.63x10^-5)</td>
<td>D = 23 (0.86%); R = 23 (1.745%); C = 46 (0.907%)</td>
<td>D = 12 (0.187%); R = 5 (0.211%); C = 17 (0.194%)</td>
<td>0.904%</td>
</tr>
<tr>
<td>NEK1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Dom LoF (D = 1.08x10^-5; R = 0.001; C = 3.29x10^-4)</td>
<td>D = 25 (0.870%); R = 10 (0.755%); C = 35 (0.835%)</td>
<td>D = 6 (0.094%); R = 2 (0.084%); C = 8 (0.091%)</td>
<td>0.744%</td>
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<tr>
<td>SQD1</td>
<td>AR/AD</td>
<td>12%</td>
<td>1.50%</td>
<td>Dom coding (7.23x10^-5)</td>
<td>25 (0.870%)</td>
<td>5 (0.078%)</td>
<td>0.792%</td>
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<tr>
<td>TARDBP</td>
<td>AD</td>
<td>4%</td>
<td>1%</td>
<td>Dom coding (2.97x10^-5)</td>
<td>15 (0.661%)</td>
<td>6 (0.094%)</td>
<td>0.567%</td>
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<tr>
<td>OPTN</td>
<td>AR/AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom not benign (D = 0.023; R = 0.002; C = 0.002)</td>
<td>D = 18 (0.626%); R = 8 (0.667%); C = 26 (0.620%)</td>
<td>D = 16 (0.25%); R = 4 (0.169%); C = 20 (0.228%)</td>
<td>0.392%</td>
</tr>
<tr>
<td>SPG11</td>
<td>AR</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom LoF (D = 0.015; R = 0.183; C = 0.017)</td>
<td>D = 21 (0.731%); R = 5 (0.379%); C = 26 (0.620%)</td>
<td>D = 20 (0.312%); R = 7 (0.295%); C = 27 (0.308%)</td>
<td>0.313%</td>
</tr>
<tr>
<td>VCP</td>
<td>AD</td>
<td>1%</td>
<td>1%</td>
<td>Dom coding (0.072)</td>
<td>8 (0.778%)</td>
<td>4 (0.062%)</td>
<td>0.216%</td>
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<tr>
<td>HNRNPA1</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom coding (0.103)</td>
<td>6 (0.090%)</td>
<td>5 (0.078%)</td>
<td>0.131%</td>
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<td>ATXN2</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Rec coding (0.206)</td>
<td>4 (0.139%)</td>
<td>2 (0.031%)</td>
<td>0.108%</td>
</tr>
<tr>
<td>ANG</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom LoF (0.217)</td>
<td>2 (0.070%)</td>
<td>1 (0.016%)</td>
<td>0.054%</td>
</tr>
<tr>
<td>CHCHD10</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom coding (0.225)</td>
<td>2 (0.070%)</td>
<td>0 (0%)</td>
<td>0.070%</td>
</tr>
<tr>
<td>SIGMAR1</td>
<td>AR/AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom LoF (0.226)</td>
<td>1 (0.035%)</td>
<td>0 (0%)</td>
<td>0.035%</td>
</tr>
<tr>
<td>FIG4</td>
<td>AR/AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom LoF (0.233)</td>
<td>9 (0.313%)</td>
<td>12 (0.187%)</td>
<td>0.126%</td>
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<td>SS18L1</td>
<td>AD</td>
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<td>&lt;1%</td>
<td>Dom LoF (0.341)</td>
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<td>0 (0%)</td>
<td>0.035%</td>
</tr>
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<td>GRN</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom not benign (0.357)</td>
<td>14 (0.467%)</td>
<td>24 (0.375%)</td>
<td>0.112%</td>
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<td>SETX</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Rec not benign (0.380)</td>
<td>3 (0.104%)</td>
<td>4 (0.062%)</td>
<td>0.042%</td>
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<td>HNRNPA2B1</td>
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<td>&lt;1%</td>
<td>Dom not benign (0.423)</td>
<td>3 (0.104%)</td>
<td>4 (0.062%)</td>
<td>0.042%</td>
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<td>SQSTM1</td>
<td>AD</td>
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<td>1%</td>
<td>Dom LoF (0.546)</td>
<td>1 (0.035%)</td>
<td>2 (0.031%)</td>
<td>0.004%</td>
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<td>TAF15</td>
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<td>&lt;1%</td>
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<td>1 (0.016%)</td>
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<td>FUS</td>
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<td>3 (0.047%)</td>
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<td>ALS2</td>
<td>AR</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Rec coding (0.659)</td>
<td>2 (0.070%)</td>
<td>4 (0.062%)</td>
<td>0.007%</td>
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<td>VAPB</td>
<td>AD</td>
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<td>&lt;1%</td>
<td>Dom not benign (0.688)</td>
<td>3 (0.104%)</td>
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<td>0.026%</td>
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<tr>
<td>NEFH</td>
<td>AD</td>
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<td>&lt;1%</td>
<td>Dom coding (0.777)</td>
<td>22 (0.765%)</td>
<td>37 (0.578%)</td>
<td>0.188%</td>
</tr>
<tr>
<td>C9orf72*</td>
<td>AD</td>
<td>40%</td>
<td>7%</td>
<td>Dom not benign (1.000)</td>
<td>4 (0.139%)</td>
<td>7 (0.109%)</td>
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<tr>
<td>CHMP2B</td>
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<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Rec coding (1.000)</td>
<td>1 (0.035%)</td>
<td>1 (0.016%)</td>
<td>0.019%</td>
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<tr>
<td>MATR3</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom coding (1.000)</td>
<td>15 (0.661%)</td>
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<td>0.115%</td>
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<tr>
<td>PN1I</td>
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<td>&lt;1%</td>
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<td>9 (0.113%)</td>
<td>15 (0.234%)</td>
<td>0.079%</td>
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<tr>
<td>PRPH</td>
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<td>&lt;1%</td>
<td>Dom LoF (1.000)</td>
<td>1 (0.035%)</td>
<td>2 (0.031%)</td>
<td>0.004%</td>
</tr>
<tr>
<td>SPAST</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom coding (1.000)</td>
<td>6 (0.205%)</td>
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<td>0.021%</td>
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<tr>
<td>TUBA4A†</td>
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<td>7 (0.109%)</td>
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<tr>
<td>ELF3†</td>
<td>Allelic</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Rec coding (1.000)</td>
<td>0 (0%)</td>
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<td>0%</td>
</tr>
<tr>
<td>DAO†</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Rec coding (1.000)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0%</td>
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<tr>
<td>DCTN1†</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom coding (0.668)</td>
<td>32 (1.133%)</td>
<td>76 (1.187%)</td>
<td>0%</td>
</tr>
<tr>
<td>EWSR1†</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom coding (0.375)</td>
<td>10 (0.348%)</td>
<td>28 (0.437%)</td>
<td>0%</td>
</tr>
<tr>
<td>GLE1†</td>
<td>AD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Rec LoF (1.000)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0%</td>
</tr>
<tr>
<td>UBLN2†</td>
<td>XD</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Dom LoF (1.000)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Cirulli et al. Science 2015;Feb 19. aaa3650
Ubiquitin-positive inclusions

Dense anti-ubiquitin positive deposit

“Skein-like” filamentous arrays

Scale bars = 5 µm

Neuroscience Letters, 1988: 93:197-203
TDP-43 inclusions in FTD and ALS

FTLD Ubiquitinated inclusions

ALS Ubiquitinated inclusions

Manuela Neumann et al. Science 2006;314:130-133
Mutations in TDP-43 result in FTD and ALS

RNA Recognition Motif
- 210 proteins known to have these domains

29 RNA binding proteins contain prion-like domains!

Prion-like domain:
- enriched in polar residues and glycine
- Confer “prionogenicity”

King et al. Brain Res. 2012;1462:61
Why prion-like domains in RNA-binding proteins?

Ramaswami et al. Cell 2013;154
Link between RNA metabolism and Pathological Inclusions

A  Genetics of ALS and FTD

- Genes: SOD1, FUS, TDP-43, UBQLN2, C9ORF72, VCP, CHMP2B, TAU, PGRN

- Genetic spectrum: ALS, FTD-ALS, FTD

Ling et al. Neuron 2013;79:416
Link between RNA metabolism and Pathological Inclusions

A  Genetics of ALS and FTD

% of known mutations leading to ALS or FTD

ALS  FTD-ALS  FTD

SOD1  TDP-43  UBQLN2  C9ORF72  VCP  CHMP2B  TAU  PGRN

B  Pathological inclusions in ALS and FTD

ALS

TDP-43 (97%)

SOD1 (2%)  FUS (<1%)

FTD

TAU (45%)

TDP-43 (45%)

FUS (9%)  UPS (1%)
C9orf72 hexanucleotide repeat expansion

- Identified in large families with FTD/ALS
- Length of expansion ranges from 700-1600 repeats
  - Majority of controls have 2 repeats
- Accounts for ~12% of familial FTD and 3% sporadic FTD
- Accounts for ~24% of familial ALS and 4% sporadic ALS
Another Link between FTD and ALS

(A) Haploinsufficiency of C9ORF72 gene

(B) Repeat RNA-mediated toxicity

(C) Dipeptide protein toxicity

Ling et al. Neuron 2013;79:416
Putative downstream consequences of aberrant RNP formation

Cirulli et al. Science 2015;Feb 19. aaa3650
“Final Common Pathway?”

Protein degradation pathways
RNA metabolism pathways
Autophagy Pathways
Neuroinflammation Pathways
Prion-like progression

What is the molecular basis of motor neuron vulnerability?
The Future

ALS Patient

Induced-pluripotent Stem Cells + Genotype

Delivery of Customized DNA or RNA-based therapy

Personalized Motor Neuron Model System
“Let us keep looking, in spite of everything. Let us keep searching. It is indeed the best method of finding, and perhaps thanks to our efforts, the verdict we will give such a patient tomorrow will not be the same we must give this man today.”

Charcot (1889)