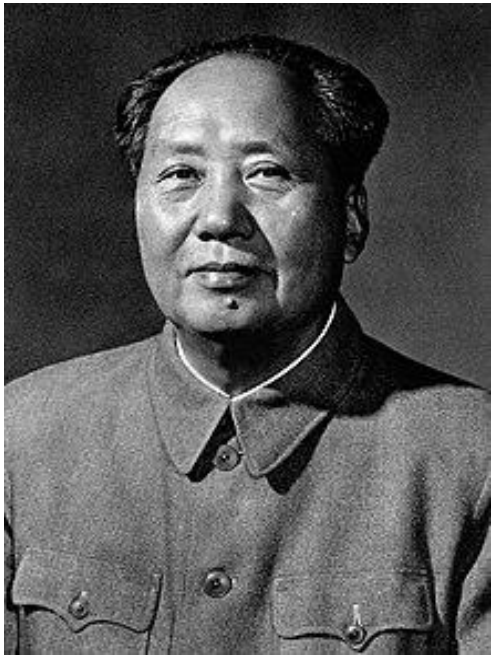
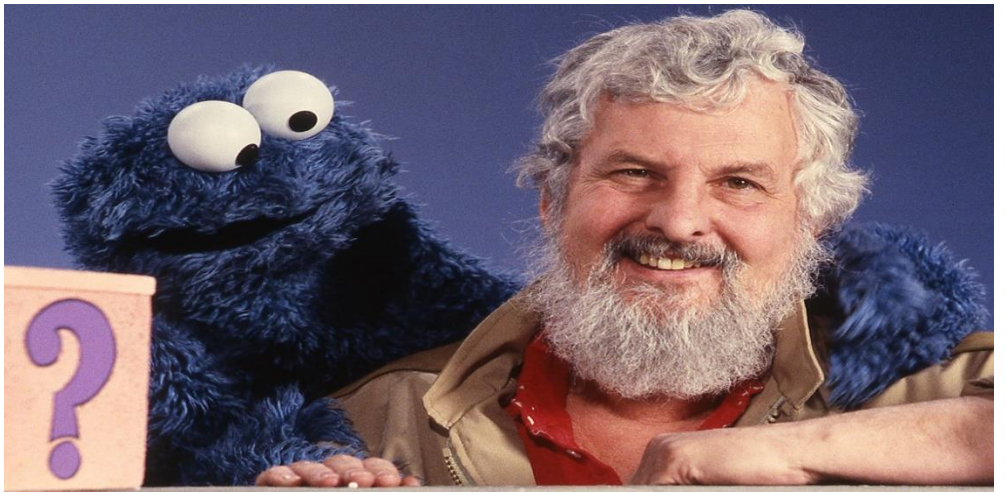
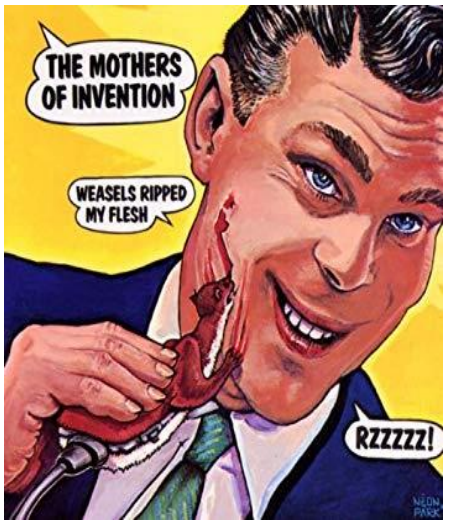
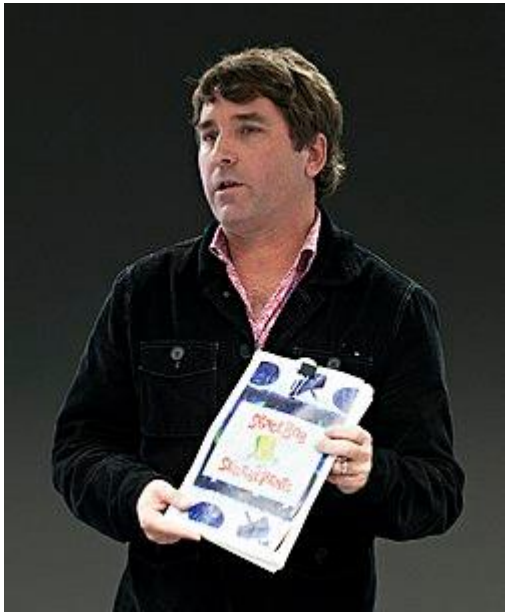
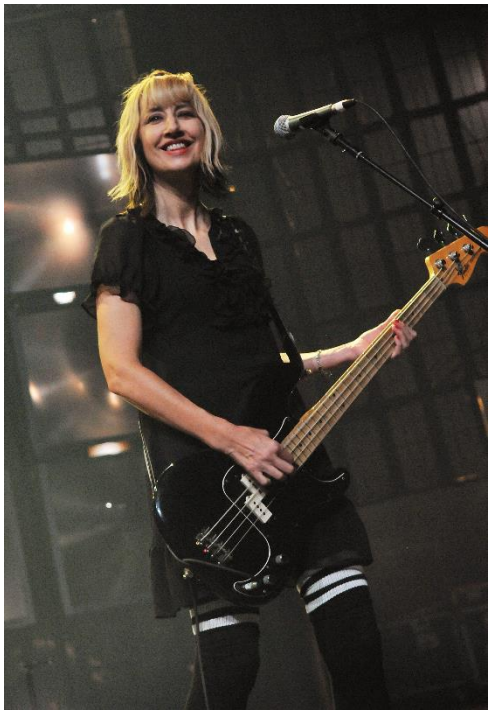
Overview of Motor Neuron Disease









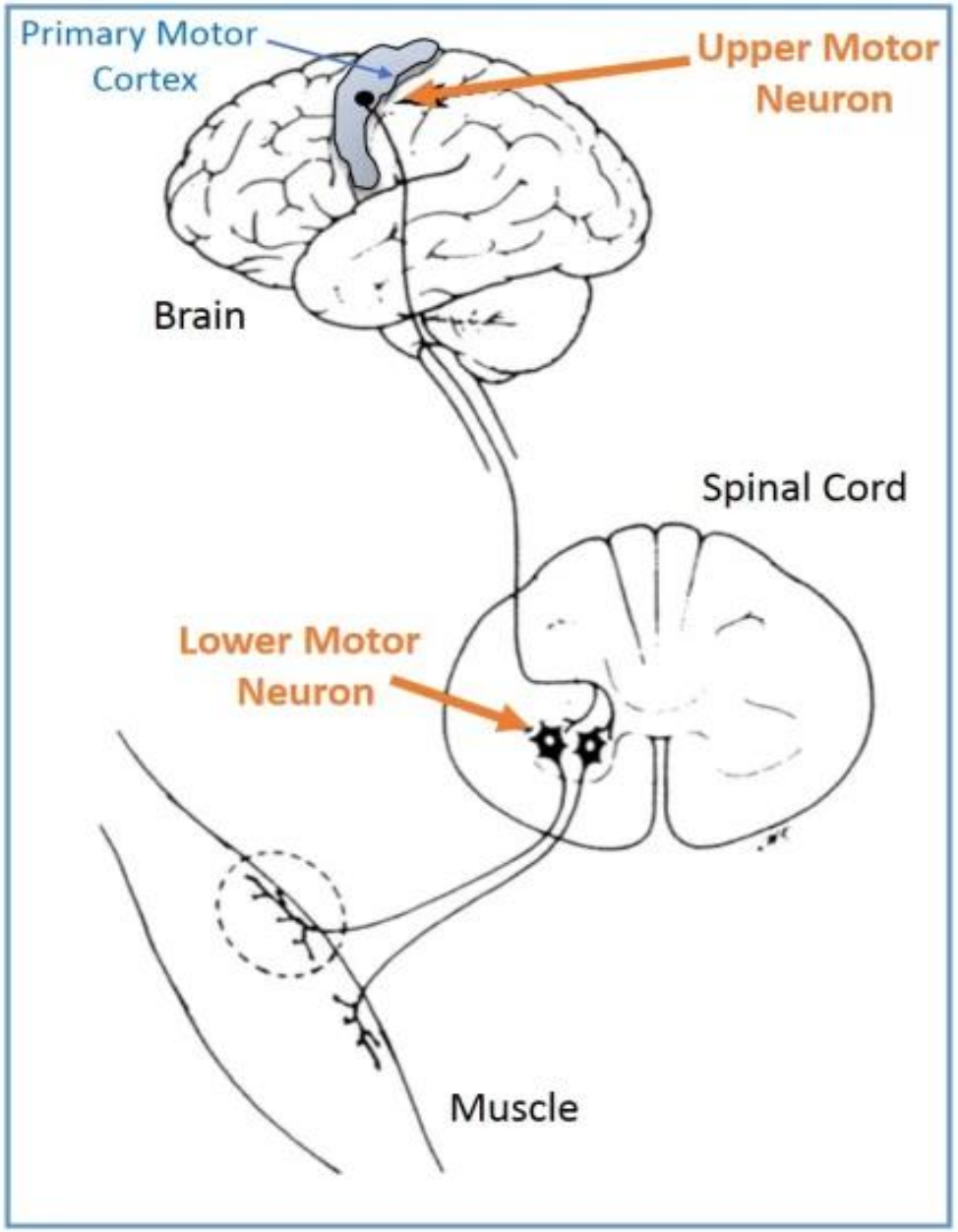


Alan Stanley
Neurologist – Hawke's Bay DHB

Overview

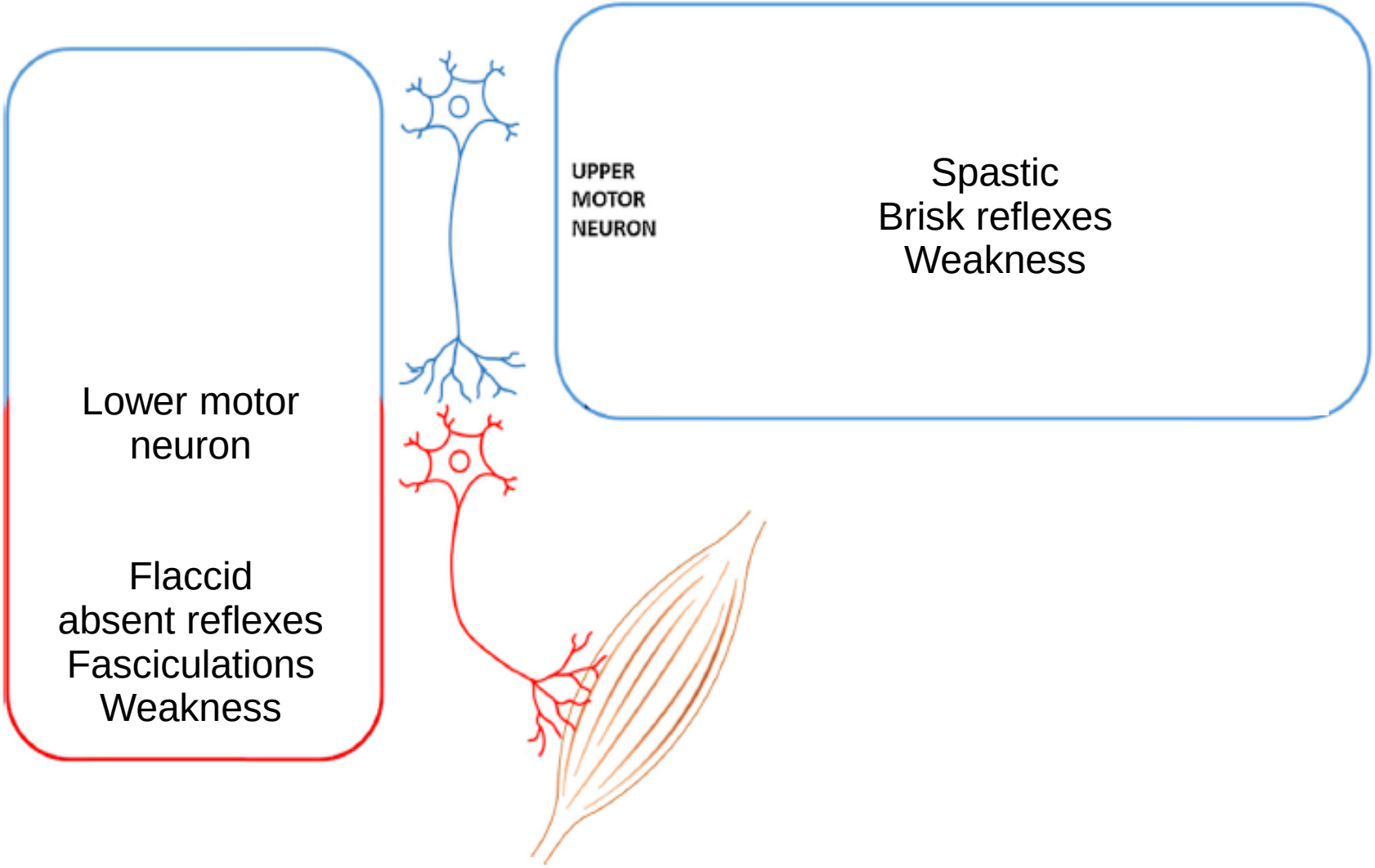
- Terminology
- History
- Clinical features
- Types and diagnosis
- Some cases
- Pathophysiolgy
- Causes
- Treatment

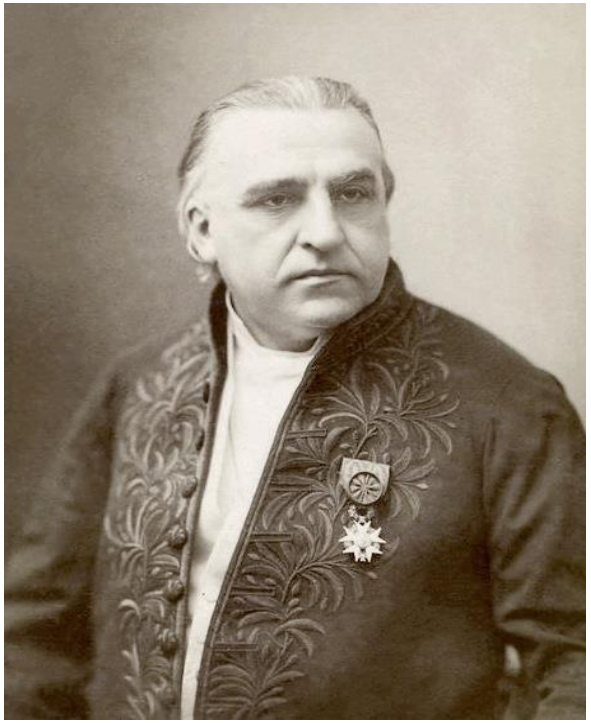
Brief neuroanatomy/ neuroscience



https://alsadotorg.wordpress.com/2017/02/17/upper-motor-neurons-contribute-to-als-in-human-brain-tissue/

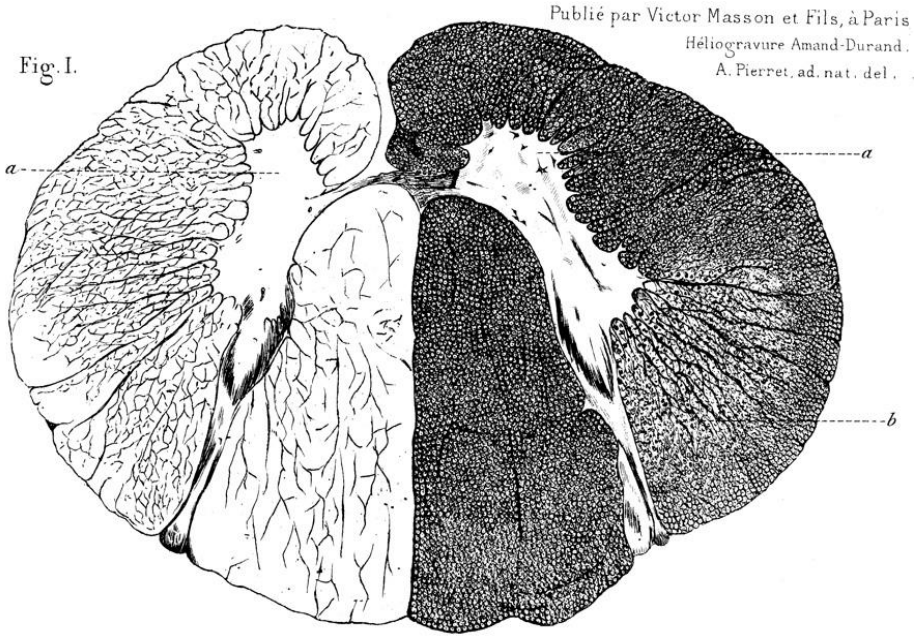
Brief neuroscience/ neuroanatomy





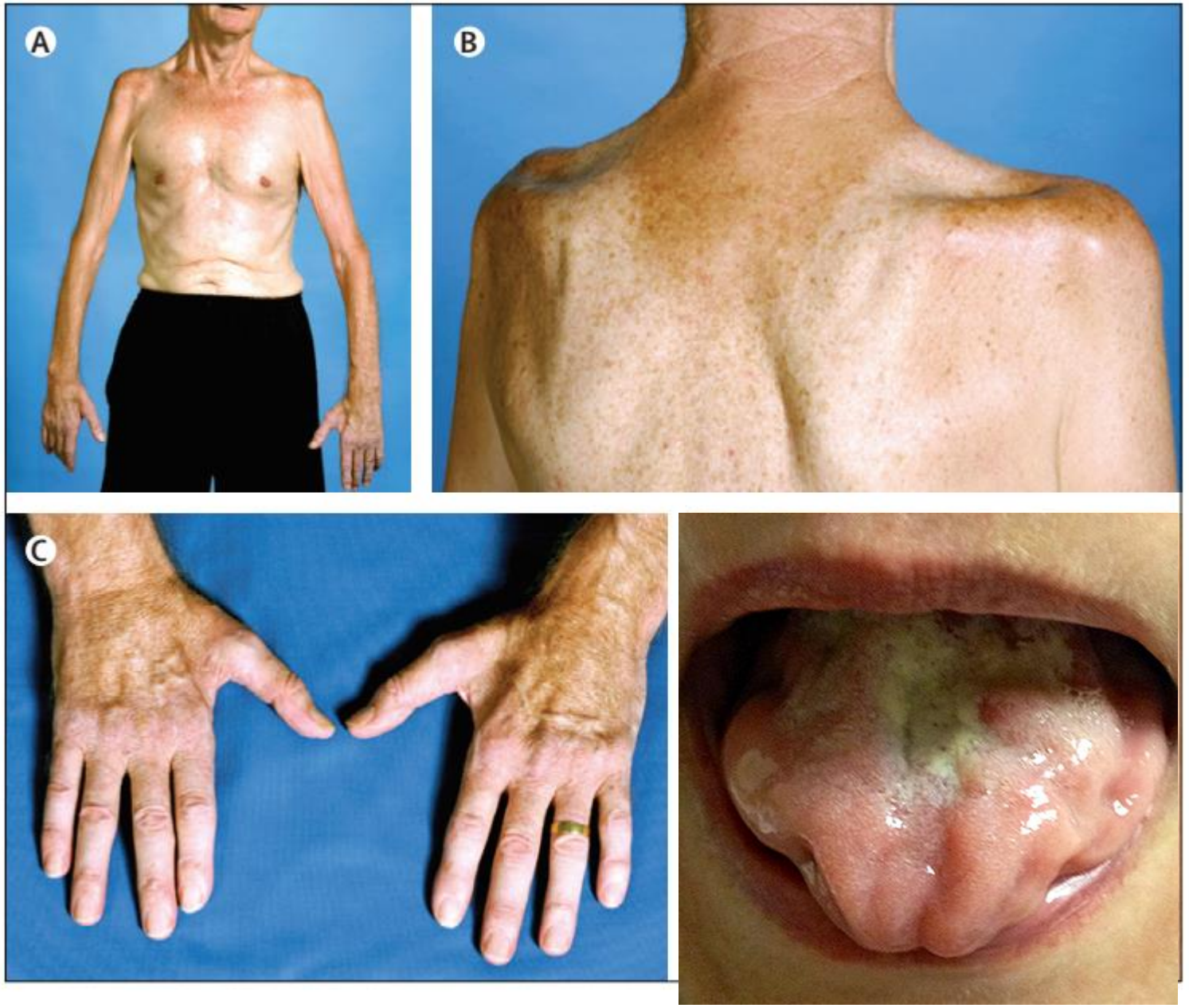
A History

- 1800‘s – Several practitioners described the syndrome
  - Focused on clinical manifestations of disease
- 1869 – Charcot (First to name it)
  - Provided the first detailed description with pathology
    - Muscle wasting and weakness
  - Recognised the involvement of anterior horn cells (motor neurons) and consequent lateral sclerosis
  - This is led to differing terminologies:
    - UK: Motor neuron disease
    - USA: Amyotrophic lateral sclerosis
- 1939 – Lou Gehrig diagnosed (died 1941)



What is it clinically?

- Painless progressive wasting and weakness
  - No sensory involvement
- “Mixed” neurological signs
  - Upper and lower motor neuron involvement
- Weakness affects any skeletal muscle
  - spares cardiac and smooth muscle



Lancet 2011; 377: 942–55

https://neuromuscular.wustl.edu/synmot.html#Hereditaryals

Fasciculations

- Not specific to motor neuron disease
- A feature of lower motor neuron involvement
- Occur in a range of diseases and in the normal population

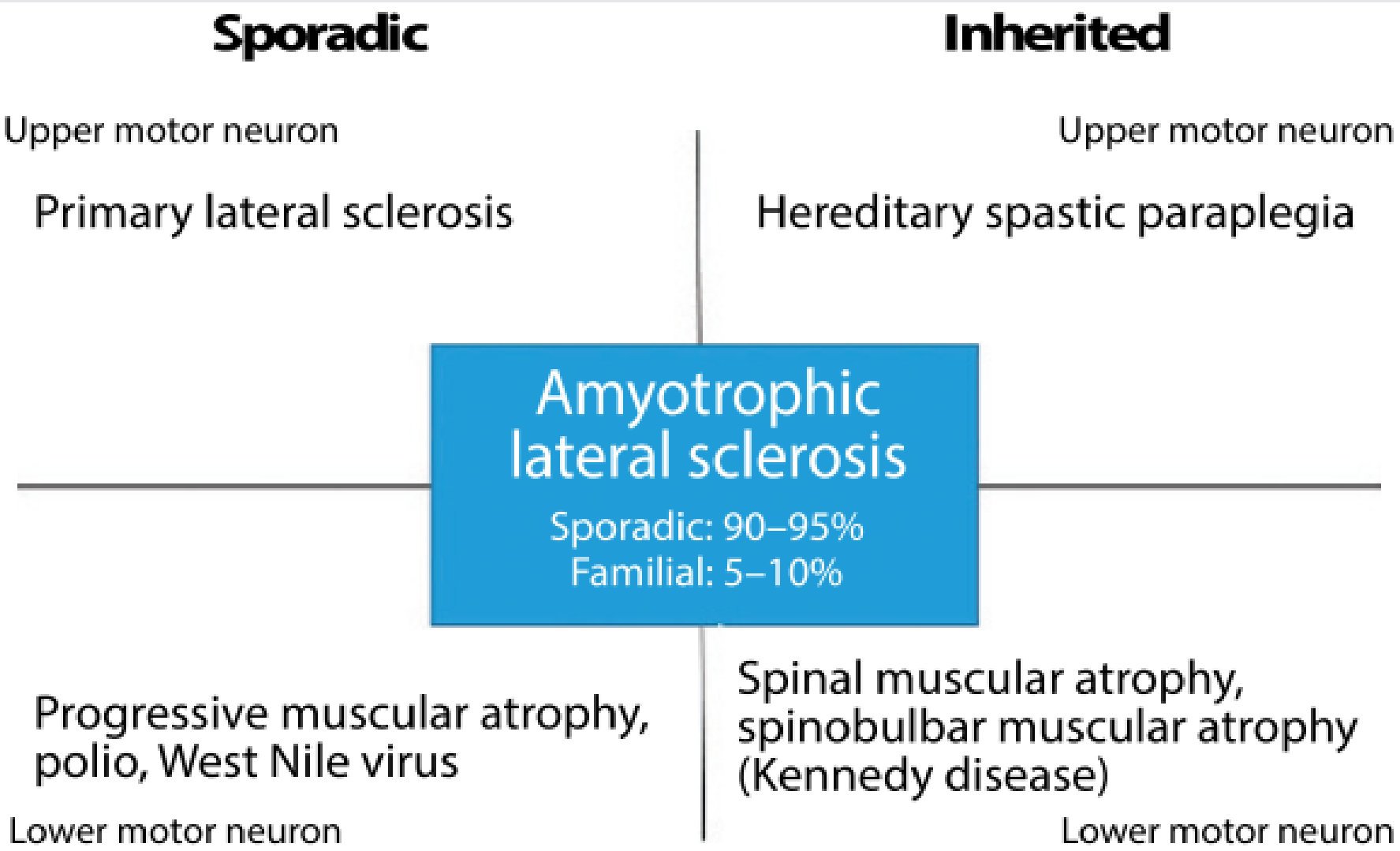
https://youtu.be/u421daHAgpY

Types of MND

- Amyotrophic lateral sclerosis (Spinal/ Bulbar)
- Primary lateral sclerosis
- Primary muscular atrophy
- Progressive bulbar palsy
- ALS/ Frontotemporal dementia

- Pattern variants:
  - Bulbar onset
  - Flail arm/ Flail leg variant
  - Hemiplegic/ pseudoneuralgic/ respiratory/ ALS+...

Spectrum of motor neuron diseases



Continuum (Minneap Minn) 2017;23(5):1332–1359.

How is it diagnosed?

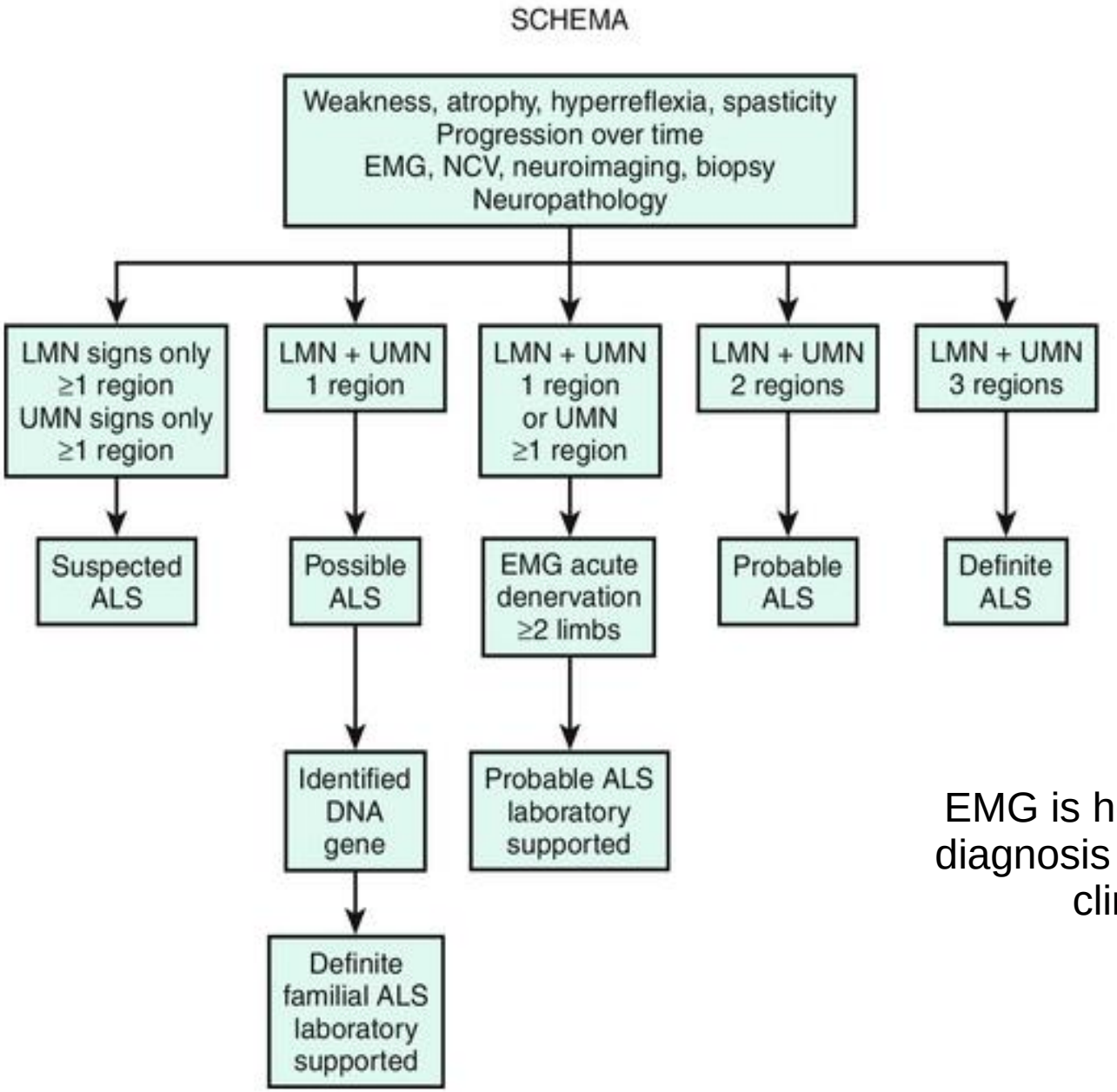
- Clinical suspicion
  - UMN signs can only be detected clinically
- EMG:
  - To exclude other diseases (eg CIDP and variants)
  - To demonstrate LMN signs not clinically apparent
- Appropriate other tests

- Overall it remains a clinical diagnosis

Awaji Criteria

- Older criteria (el Escorial/ Arlie house)
  - 21% of patients die without meeting criteria
- Awaji criteria proposed 2008 (Sens 81%/ Spec 98%)
- Allow clinical and EMG features to be combined

Clinical certainty	Clinical + Electro-physiological findings
Definite	UMN + LMN findings in 3 body regions
Probable	UMN + LMN in 2 body regions, UMN findings rostral to LMN
Possible	UMN +LMN in 1 region; UMN in 2 regions; LMN findings rostral to UMN



EMG is helpful but the diagnosis can be made clinically

Differential diagnosis of amyotrophic lateral sclerosis

Disease	Distinguishing features
Multifocal motor neuropathy	Multifocal nerve conduction block, very high GM1 ganglioside antibody titers
Cervical spondylosis or extramedullary tumor with compressive radiculopathy and myelopathy	Sensory symptoms and signs, Lhermitte's symptom, LMN signs at level(s) of compression and UMN signs in legs, sphincter dysfunction, MRI of spine shows significant cord compression with intrinsic spinal cord signal abnormality
Benign fasciculations	No weakness or atrophy, no electromyographic abnormality of motor unit morphology
Inclusion body myositis	Disproportionate finger flexor weakness, no UMN signs, slow progression, diagnosis requires muscle biopsy, electromyography usually with myopathic features
Primary lateral sclerosis	A clinical variant of ALS: Spastic paraparesis, often with pseudobulbar palsy, prominent spasticity and hyperreflexia, no LMN signs
Progressive bulbar palsy	A clinical variant of ALS: Bulbar involvement predominates, pronounced dysarthria and dysphagia, limb musculature mostly spared
Progressive muscular atrophy	A clinical variant of ALS: Muscle weakness and atrophy with no UMN signs
Myasthenia gravis	Diplopia, ptosis, ocular dysmotility, weakness improved by acetylcholinesterase inhibitors, no UMN or LMN features
Monomelic (benign focal) amyotrophy	Onset usually in youth, slow and self limited course, no UMN features
Hereditary spinal muscular atrophy	Symmetric, slow course, no UMN signs, usually diagnostic changes detected in the survival motor neuron 1 gene (SMN1)
Hereditary spastic paraplegia	Slowly progressive lower extremity spastic UMN weakness, minimal or no LMN symptoms and/or signs, sphincter dysfunction, sensory symptoms and signs, HSP gene positive if available
Post-polio progressive muscular atrophy	Slow course, no UMN signs
Spinobulbar muscular atrophy (Kennedy disease)	X-linked recessive disorder, slow progression, expansion of a CAG trinucleotide repeat (>40 CAGs) in the androgen receptor gene
Late-onset Tay-Sachs disease (GM2 gangliosidosis)	Late adolescent and early adult onset, progressive atrophic paralysis, hexosaminidase A deficiency
Motor neuron syndromes with lymphoproliferative disorders	Lymphoma (Hodgkin or non-Hodgkin), multiple myeloma, chronic lymphocytic leukemia, Waldenström macroglobulinemia; some have paraproteinemia
Motor neuron syndromes in lung, breast, and other cancers	May improve on treatment of the tumor, may be paraneoplastic or coincidental
Radiation brainstem injury/radiation myelopathy	History of radiation therapy for cancer, location of injury within the radiation ports, delay of months to a few years from treatment, LMN symptoms and signs at the level of the injury, possible UMN symptoms and signs below the level of the injury, possible sensory symptoms and signs below the level of the injury (eg, Lhermitte sign), self limited: does not progress to a diffuse LMN/UMN disorder
Thyrotoxic myopathy with fasciculations	Overt or covert hyperthyroidism
Intraspinal tumors and other lesions	Imaging studies show syringomyelia, syringobulbia, or intraspinal tumors

ALS: amyotrophic lateral sclerosis; LMN: lower motor neuron; UMN: upper motor neuron.

Modified from: Layzer RB. Chapter 415. Hereditary and acquired intrinsic motor neuron diseases. In: Bennett and Plum (Eds), Cecil Textbook of Medicine, W.B. Saunders, Philadelphia 1999.

The differential diagnosis is important

Where does it start?

- From the earliest descriptions it was assumed to have a spinal onset
  - Spinal pathology was most prominent
  - Muscle/ NMJ toxicity was theorised

- But some features didn't fit eg split hand

Split hand - a small detour into neurological localisation

FDI and APB
Wasted

FDI – Ulnar; C8/T1
APB – Median C8/T1

ADM spared

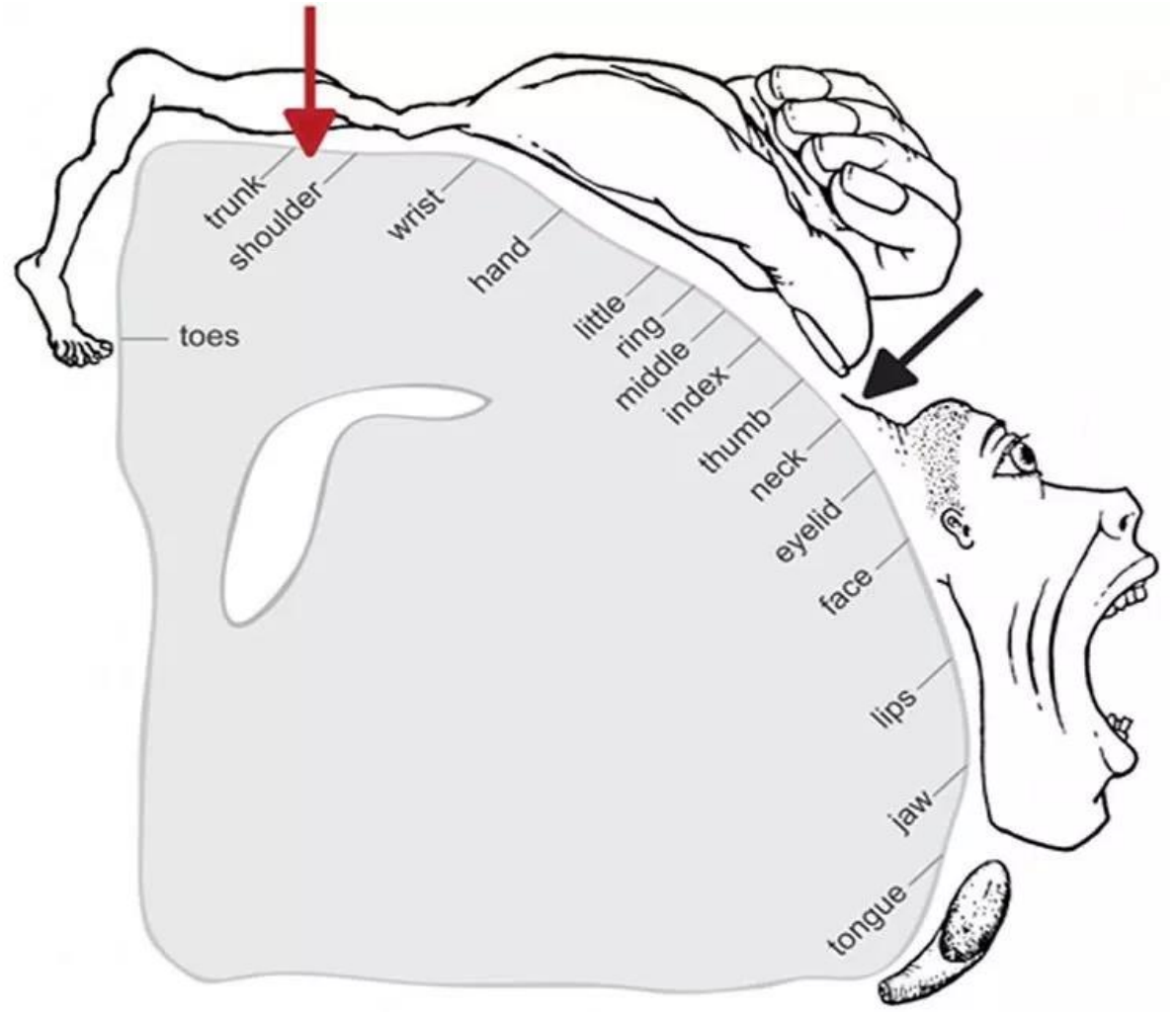
ADM – Ulnar; C8/T1

Same nerve roots
Different nerves

So why is there differential Involvement?

Case Reports 2014;2014:bcr2014207647.

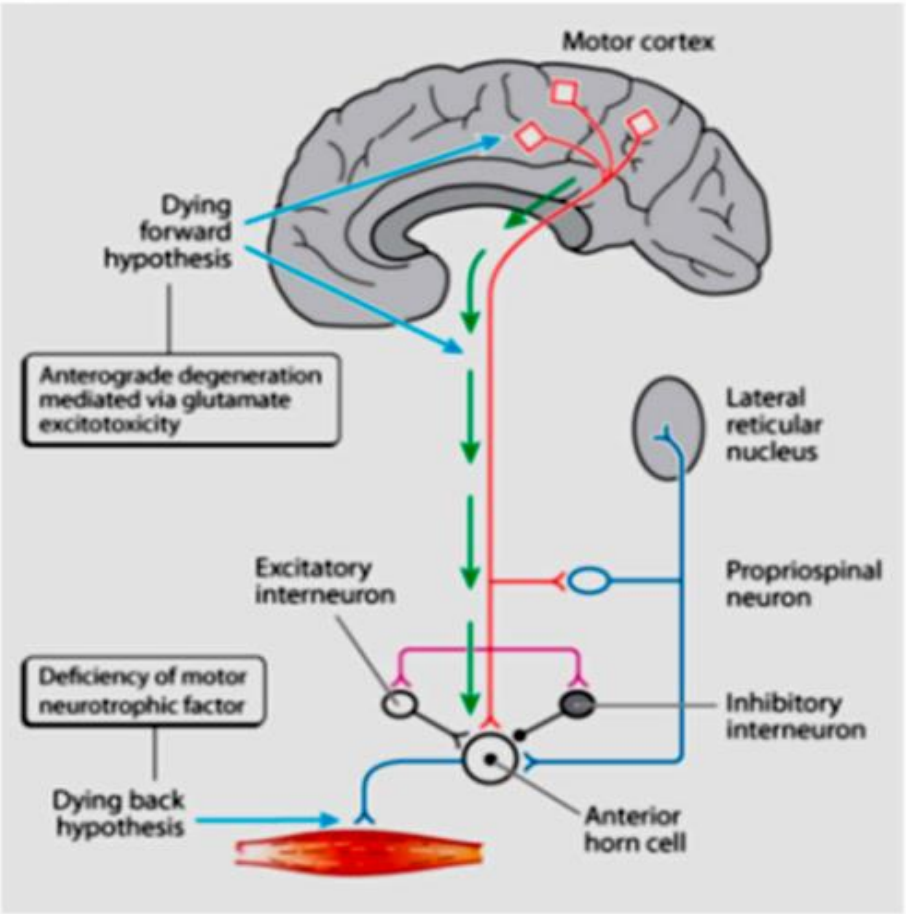
Cortical representation – Cortical onset?

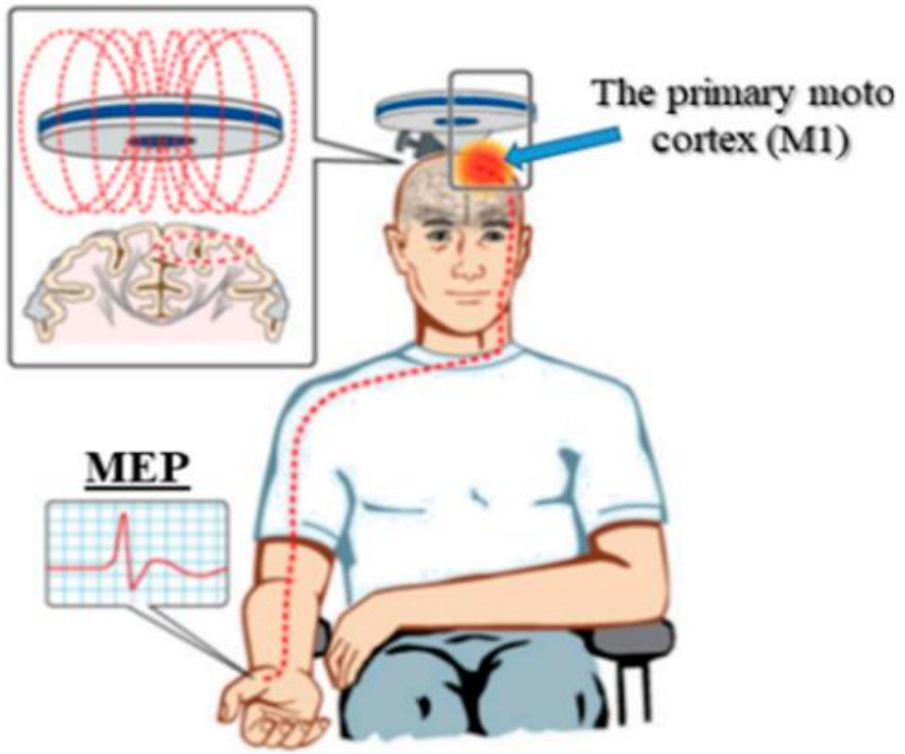


Motor homunculus

And with more modern pathology changes are found in the motor cortex and elsewhere in the brain

Cortical hyperexcitabilty seems to be a very early feature





… and its a biomarker/ test for upper motor neuron dysfunction
… and it offers a new target for therapy
… and it explains the association with frontotemporal dementia

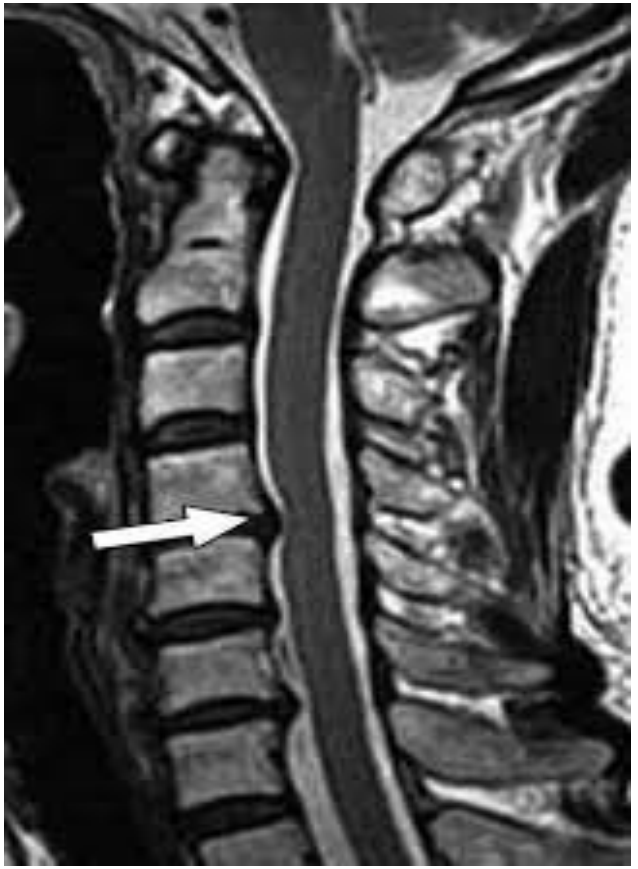
Case studies – case 1

- 69yo woman presents with weakness of her right shoulder. On examination she has increased tone and brisk reflexes in her legs with asymmetrical weakness of both shoulders (R>L)

- What next?

Case 1

- MRI – mild stenosis of the cervical spine with some degenerative bony changes



Case 1

- MRI – mild stenosis of the cervical spine with some degenerative bony changes
- EMG: Chronic neurogenic units in all limbs with scattered fasciculations and fibrillations
- Meets criteria for probable ALS (definite if bulbar features)

Case 2

- 47 yo man presents with twitches in his muscles
  - He's noticed them in multiple muscles
- Examination normal reflexes and strength, no wasting. Occasional fasciculations seen in the calves.
- Diagnosis?

Case 3

- 75 year old man with progressive speech difficulty. On examination stiff, atrophic tongue with slow movement. Noted to be very emotional – crying easily. Questionably brisk reflexes.
- Speech therapy detects impaired swallowing.
- Wife reports odd behaviour – disinhibited and making odd, inappropriate comments
- MRI Brain – age appropriate atrophy

Case 3

- Probable progressive bulbar palsy (+ frontotemporal dementia)
- But by criteria only possible (1 segment involved)
- EMG may show lower motor neuron signs in other regions

Case 4

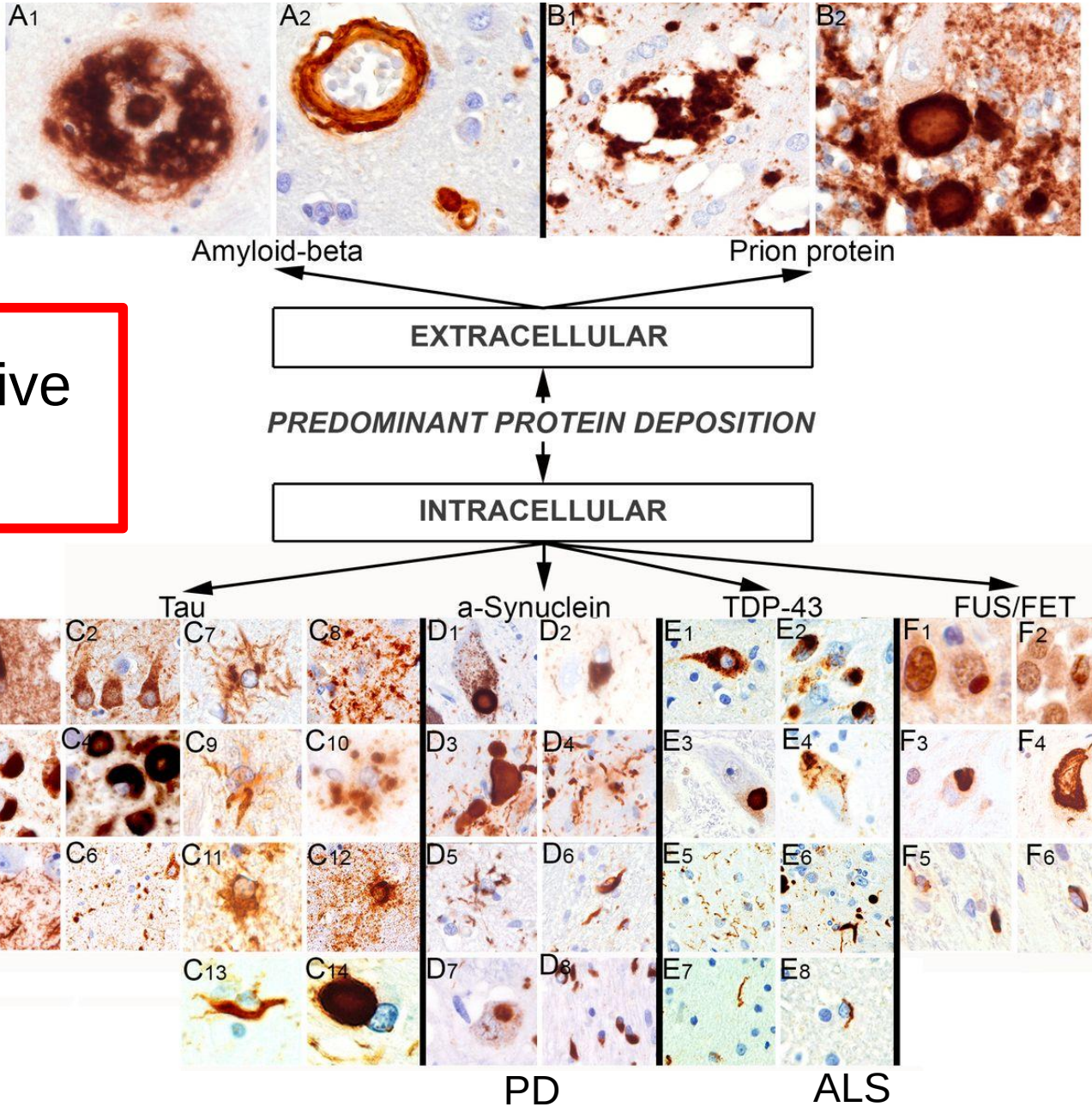
- 81 yo man presents to the emergency unit after a fall. Noted to be breathless and dysarthric. He has been deteriorating over approximately 6 months with progressive weakness. Also known to have a large orbital groove menigioma.
- On examination very stiff atrophic tongue with fasiculations, brisk jaw jerk. Fasciculations also seen in the arms and chest with slightly brisk upper limb reflexes. Type 2 respiratory failure.
- Should he be ventilated?

Case 4

- CT brain largely unchanged
- Diagnosed clinically as probable motor neuron disease
- He and his wife were very accepting and had a strong preference for a death at home
- Very tricky!

What is it Pathologically?

Alzheimer's



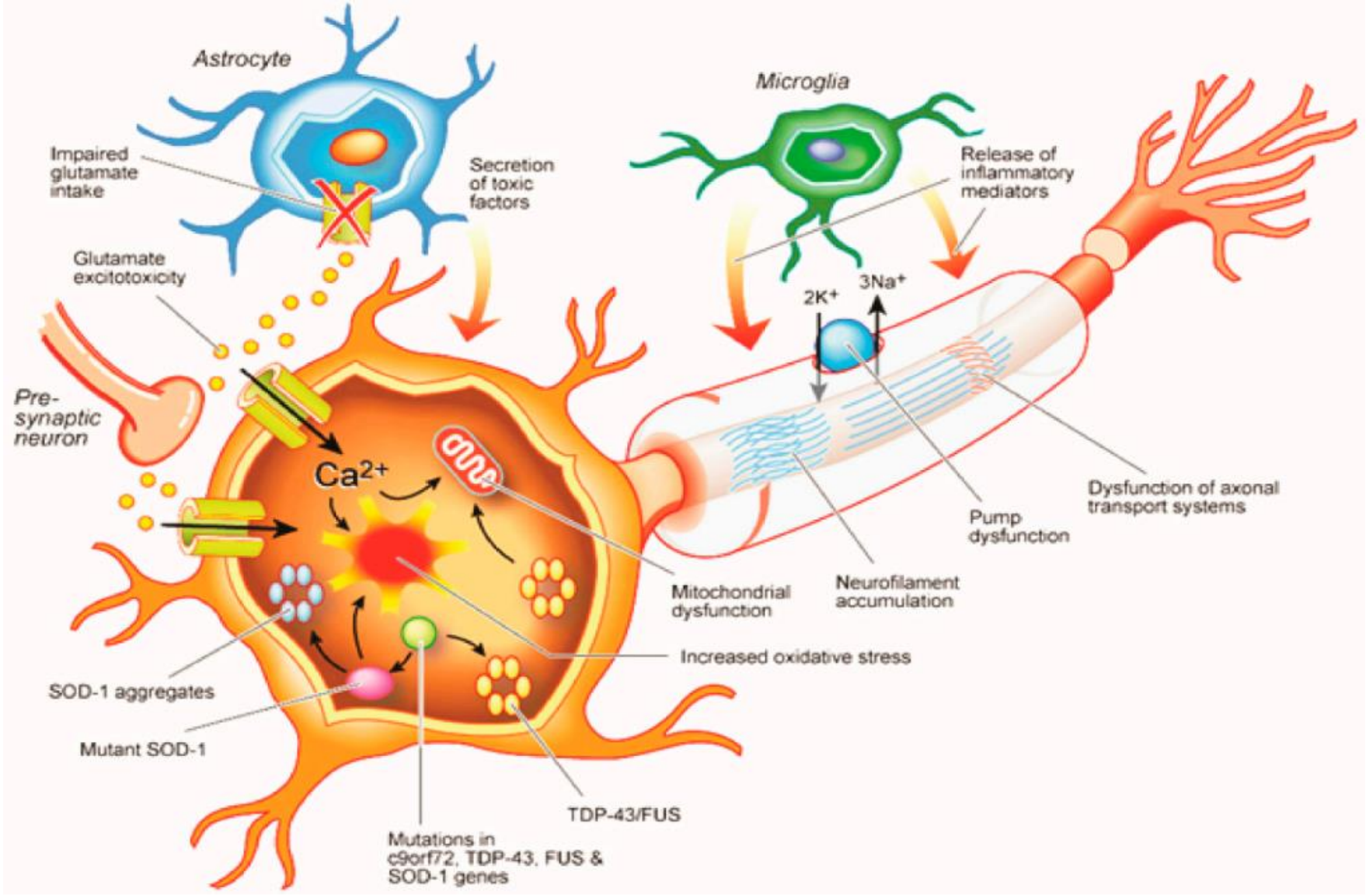
CJD

Neurodegenerative proteinopathy

What is it Pathologically?

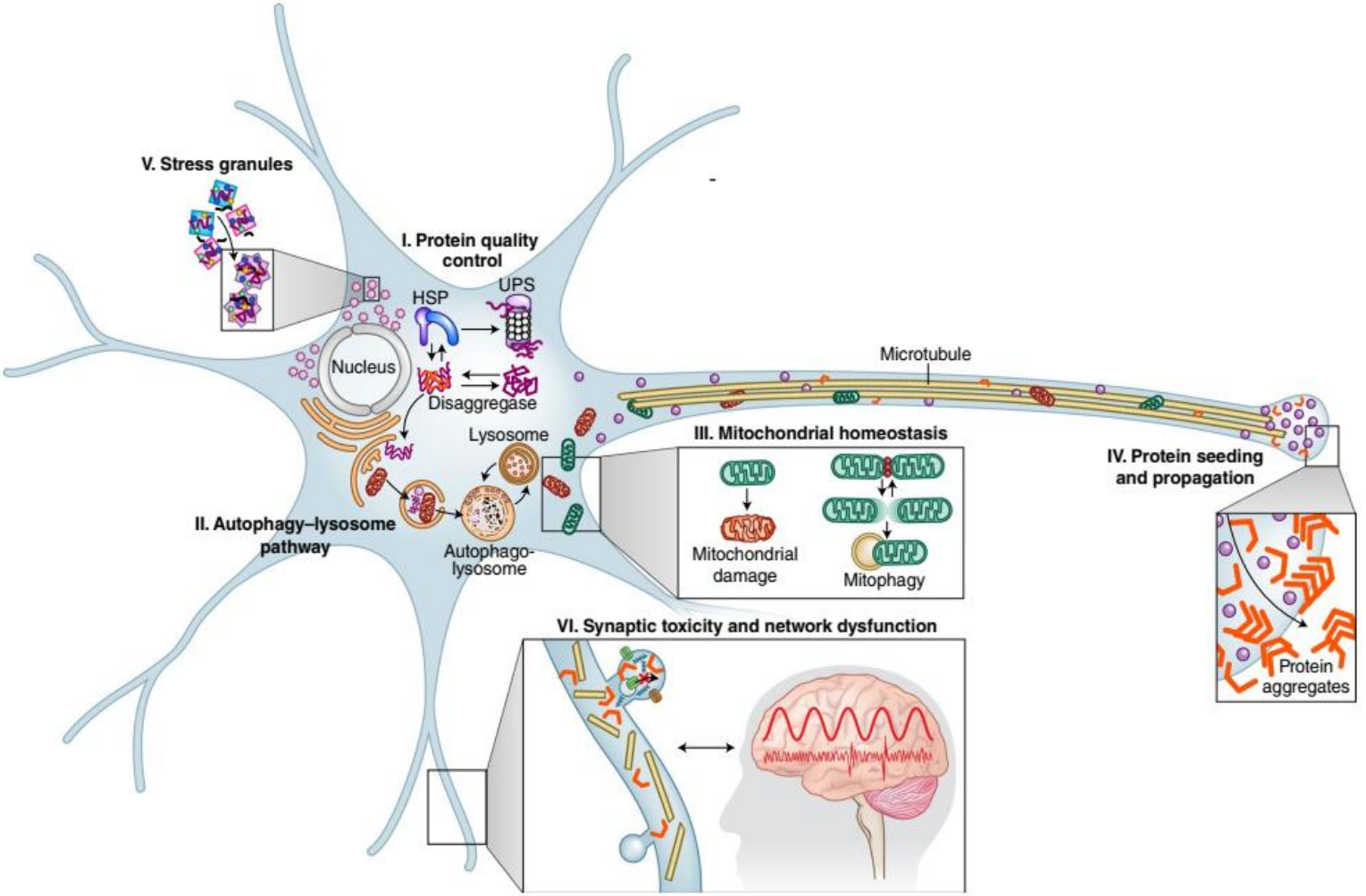
- Essential a failure of cellular housekeeping leading to death of motor neurons
- Dysfunction has been described in multiple cellular systems
  - Motor neurons
  - Astrocytes
  - Glial cells
  - Inflammation?

Pathophysiology



Int. J. Mol. Sci. **2019**, *20*, 2818; doi:10.3390/ijms20112818

Its interesting that those processes looks a lot like other neurodegenerative diseases



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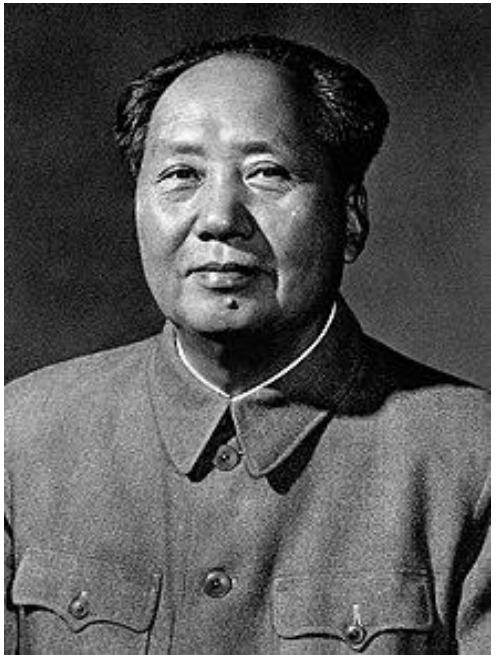
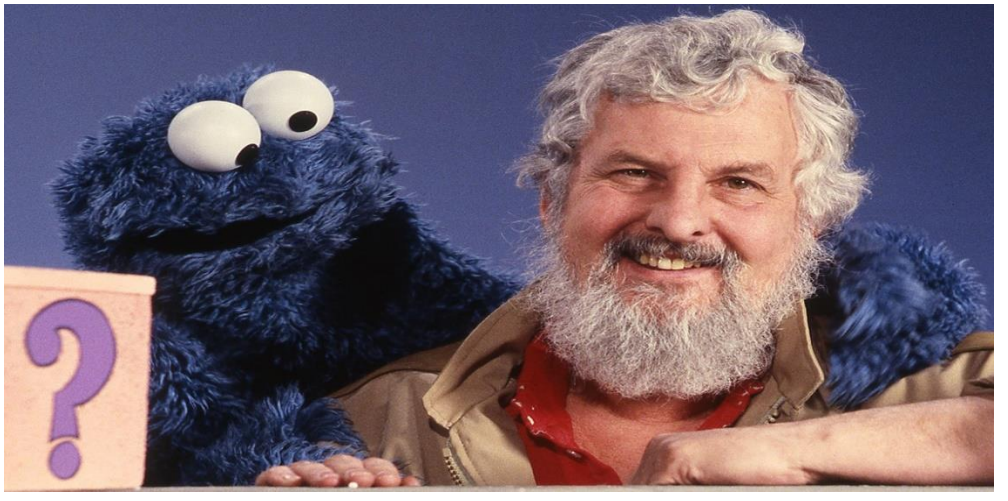
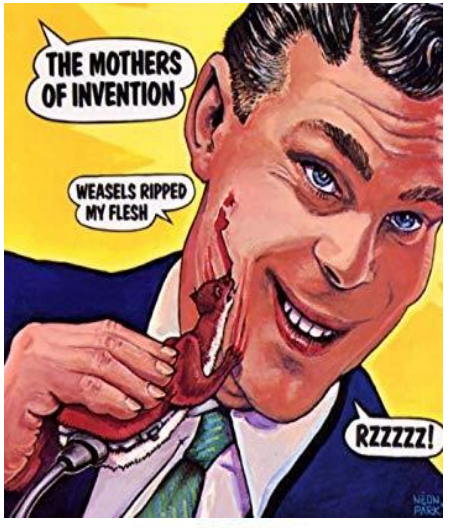
The **BIG** question

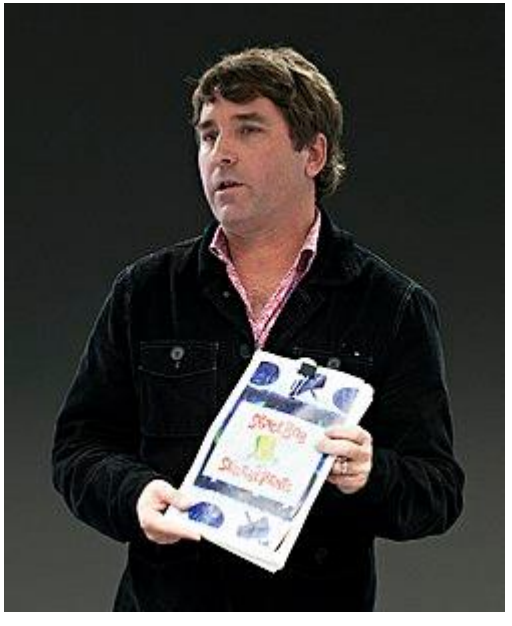
What causes it?

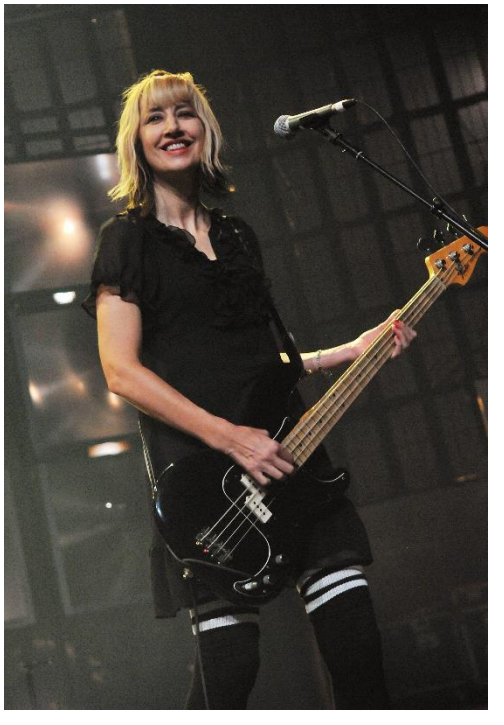
Any environmental links?











What causes it?

- Multiple environmental associations but very inconsistent reports and small studies
  - Older age, male gender
  - Smoking, pesticides, heavy metals?
- Increasingly recognised genetic component
  - Similar to cancer
- Known genes account for ~20% of risk
- Twin studies suggest heritability of ~60%
  - Likely to be a multistep/ polygenic risk
  - At least 6 mutation steps required

Very brief basic genetics...

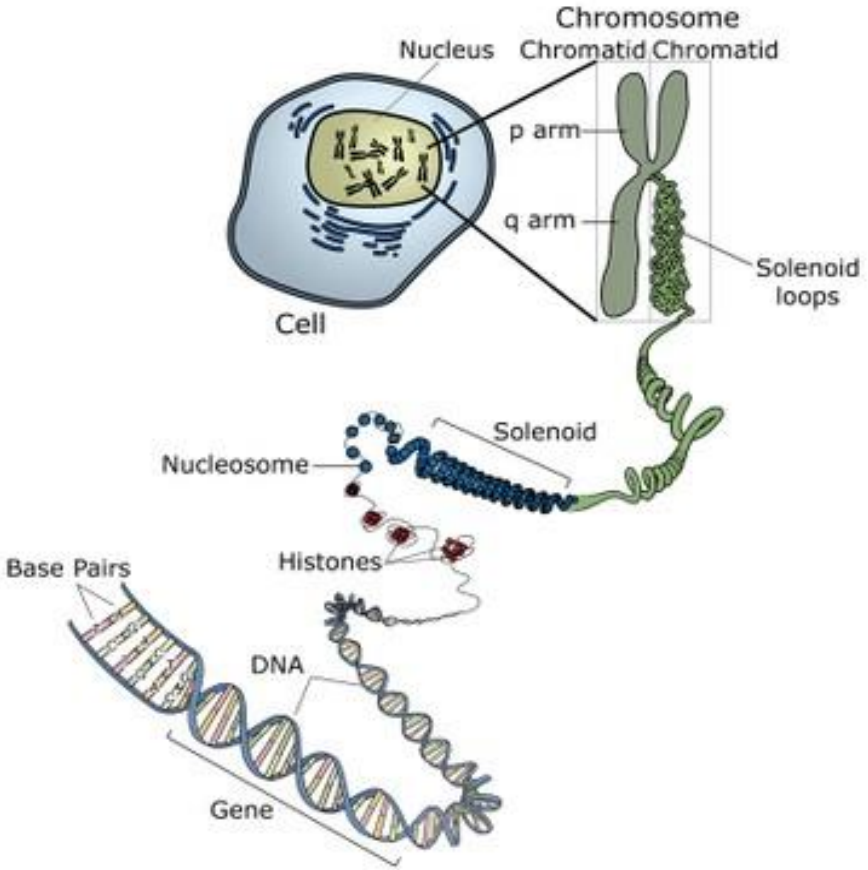
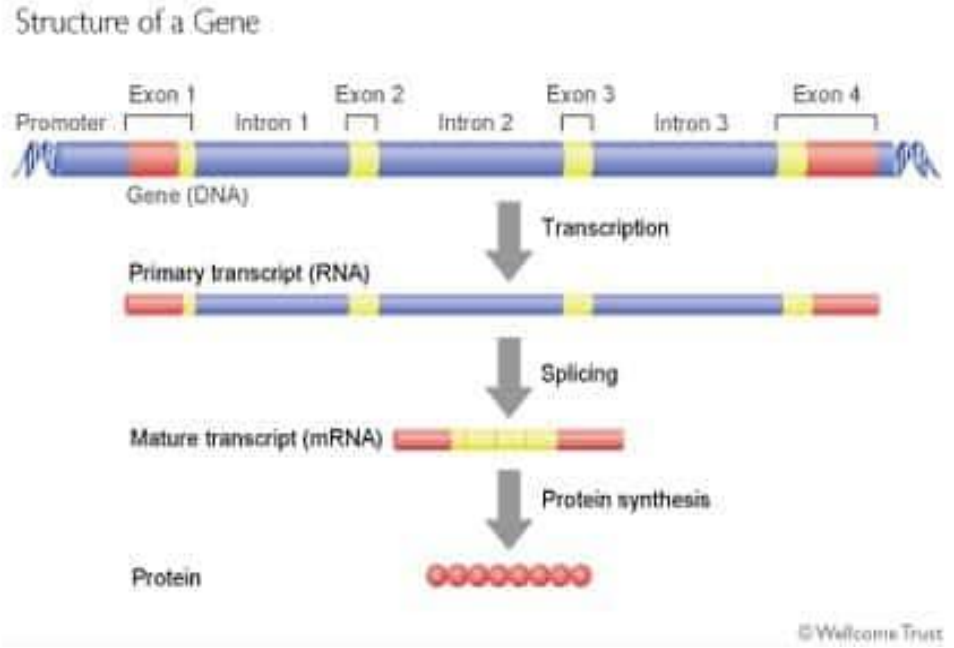


Image adapted from: National Human Genome Research Institute.



https://www2.le.ac.uk/projects/vgec/highereducation/topics/dna-genes-chromosomes

https://schoolworkhelper.net/dna-mrna-introns-and-exons/

Types of Mutations

Normal gene

AS THE MAN SAW THE DOG HIT THE CAN END ITIS

Point mutation

AS THE MAN SAW THE DOT HIT THE CAN END ITIS

Deletion

AS THE MAN SAW THE HIT THE CAN END ITIS

Insertion

AS THE MAN SAW THE FAT DOG HIT THE CAN END ITIS

Frame Shift

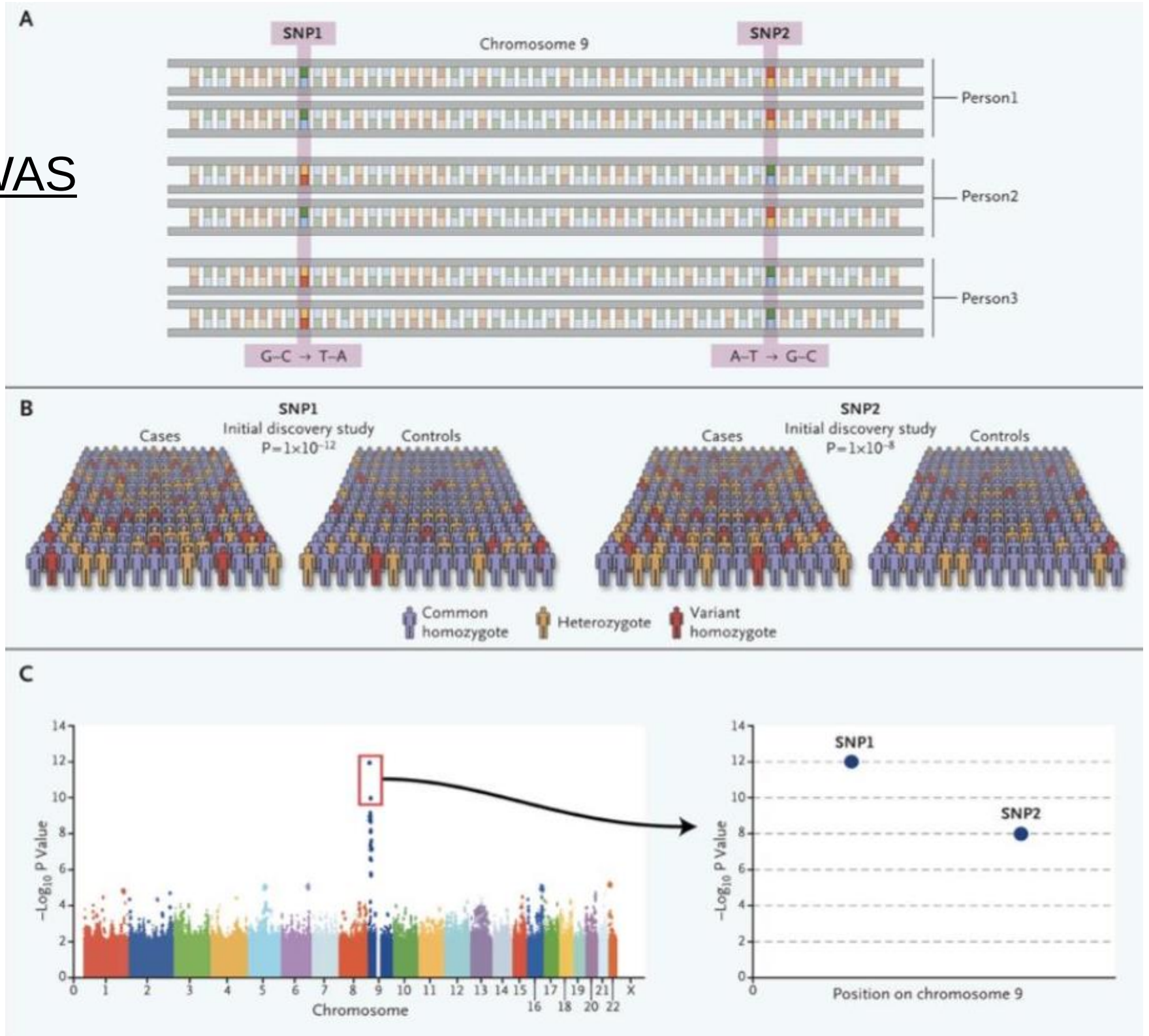
AS THE MAN SAW THE OGH ITT HEC ANE ND ITI S

Different techniques are suited to finding different types of mutations

Some are easier to find than others

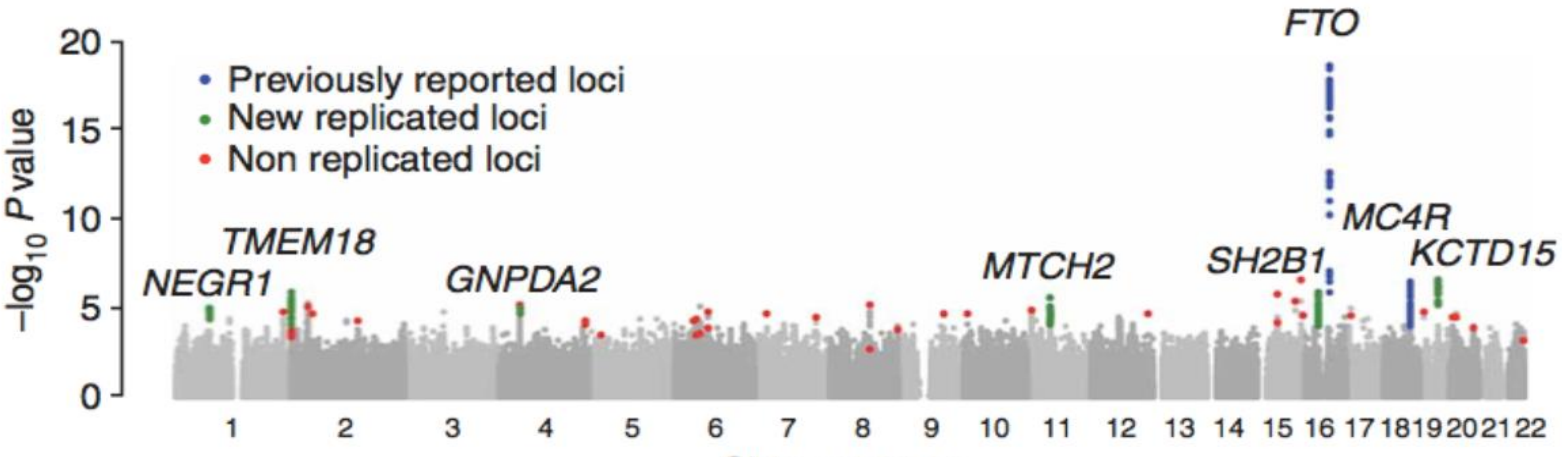
- Genes leading to defective proteins are often very heritable (eg Huntingtons, familial ALS)
- That makes it easier to find the cases and easier to find the gene
  - eg SOD-1 mutations
- Smaller contributions are more difficult to find

GWAS

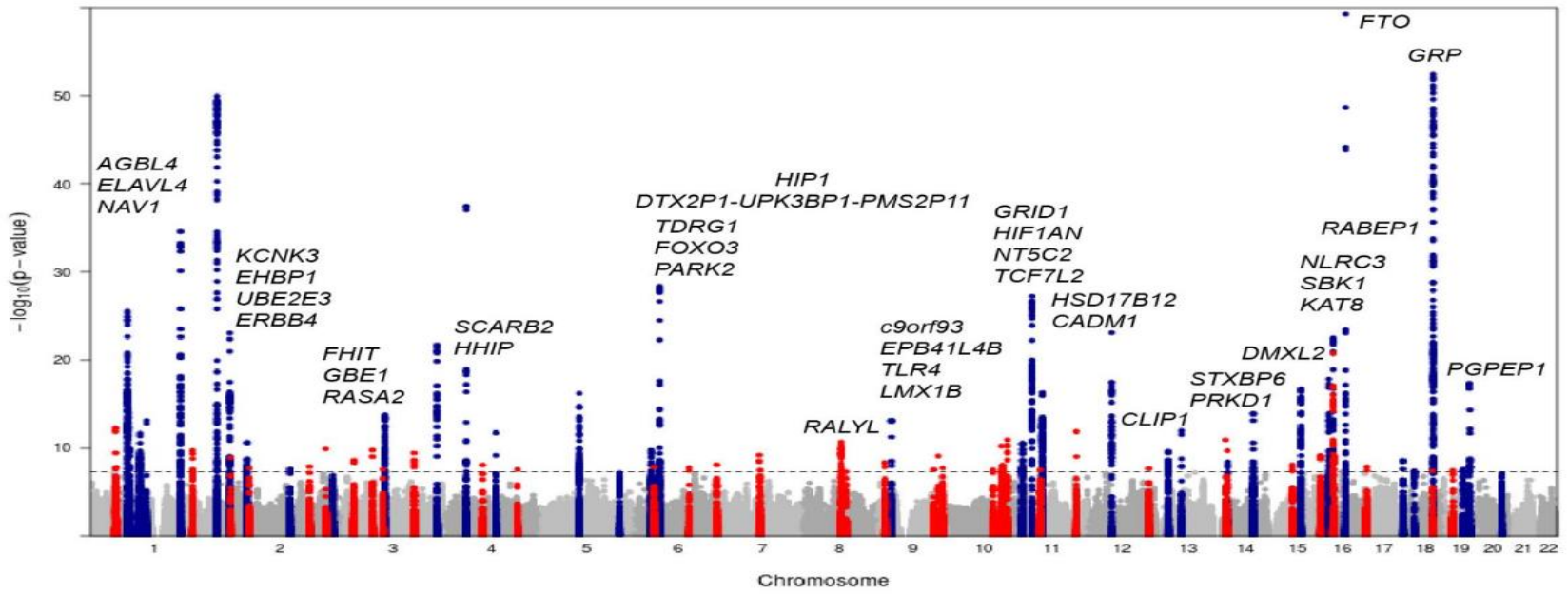

A
SNP1
Chromosome 9
SNP2
Person1
Person2
Person3
G–C → T–A
A–T → G–C
B
SNP1
Initial discovery study
P=1×10⁻¹²
Cases
Controls
SNP2
Initial discovery study
P=1×10⁻⁸
Cases
Controls
Common homozygote
Heterozygote
Variant homozygote
C
−Log10 P Value
Chromosome
SNP1
SNP2
Position on chromosome 9

You need LOTS of cases

• Body mass index (2000 in 91,000 individuals)



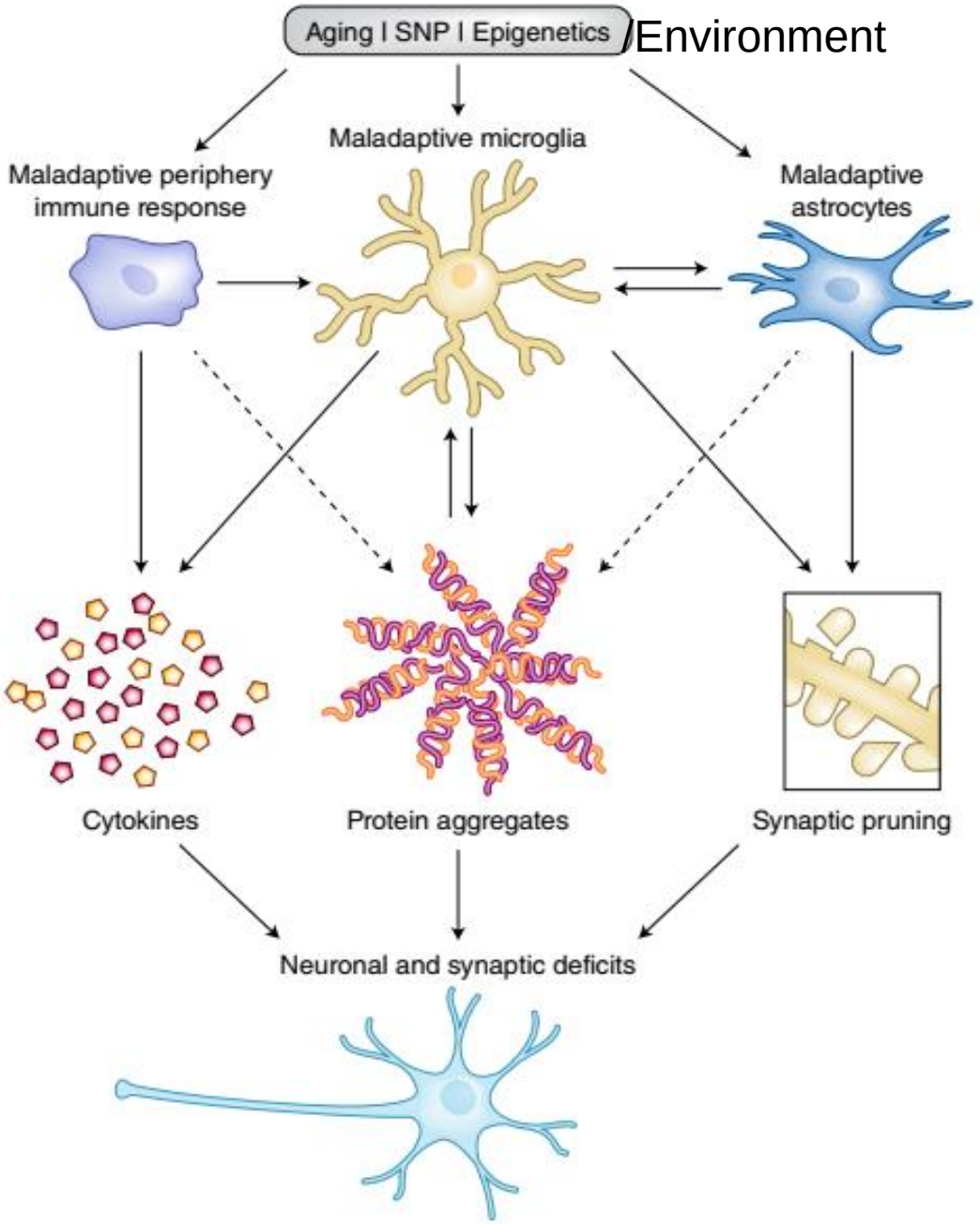
• Body mass index (2015 in 339,000 individuals)



Most techniques focus on the exome

- Other DNA has been regarded as junk but probably isn't
- Whole genome sequencing is becoming cheaper and will probably help
- But its hard to analyse 6.4 Billion base pairs for variation

The process probably goes something like this for all neurodegenerative diseases



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Therapy

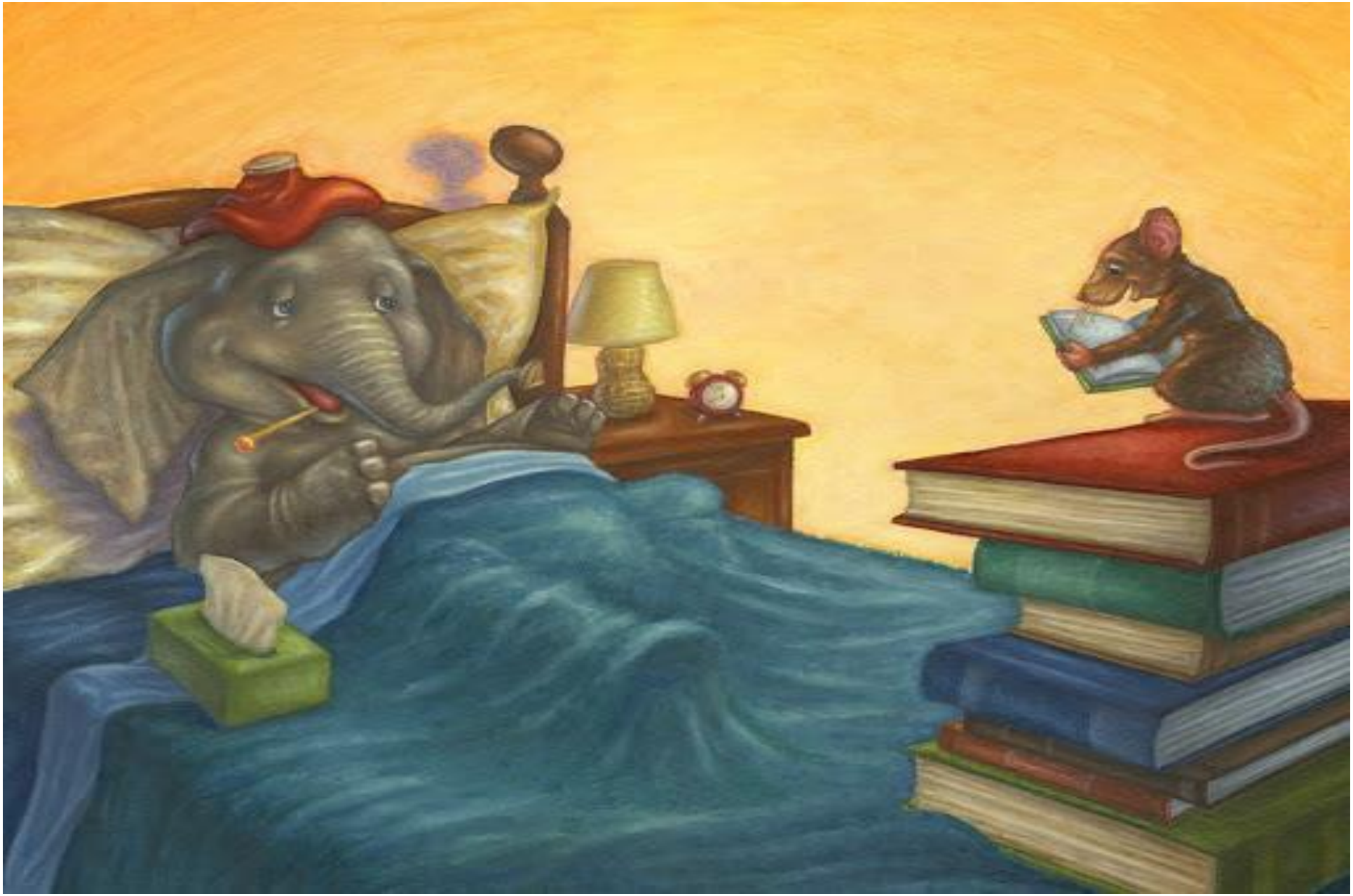


TABLE 2. Symptoms of amyotrophic lateral sclerosis and suggested treatment

Symptom	Suggested medication	Nonpharmacologic interventions
Fatigue	Modafinil 100-300 mg/d	Adequate sleep
Spasticity	Baclofen, Tizanidine, Dantrolene, Benzodiazepines, Levetiracetam, Cannabinoids[a]	Physical therapy, stretching, ROM exercise; Hydrotherapy, Cryotherapy, Heat, Ultrasound
Pain (muscle cramps)	NSAIDs, Non-opioid analgesics, Muscle relaxants, Levetiracetam, Gabapentin, Botulinum toxin, Tricyclic antidepressants	Physical therapy
Immobility		Physical therapy, Occupational therapy, Pressure-relieving mattress, Foam wedges to facilitate proper positioning, Daily ROM exercise, Orthotics, Walkers, wheelchairs, Quad cane, Hand-held shower, bath bench, grab bars, raised toilet seat, commode, ADL aids (occupational therapy consultation); Removal of throw rugs, Exercise strategies: ROM, stretching, resistance, aerobic
Constipation		Fiber supplement, Fluid increase, Stool softeners, Lactulose/polyethylene glycol (osmotic agents), Mild laxatives
Excessive salivation (can cause choking and aspiration pneumonia)	Amitriptyline 10 mg tid, Atropine drops 0.5%-1% SL qid, Glycopyrrolate 1 mg tid, Transdermal scopolamine 1.5 mg every third day	Botulinum toxin injection into salivary glands, Salivary gland radiation
Sleep disruption	Benzodiazepines, Zolpidem tartrate 10 mg qhs Antidepressant: mirtazapine 15 mg qhs	Electrical hospital bed to enhance positioning, NIPPV
Pseudobulbar affect (uncontrollable laughter, crying, emotional outbursts)	SSRI antidepressants, Tricyclic antidepressants, Dextromethorphan 20 mg/quinidine sulfate, 10 mg (Nuedexta)	
Respiratory insufficiency (due to respiratory muscle weakness, lack of full inspiration; most patients asymptomatic until FVC <50% of predicted value)		NIPPV
Dysphagia		Puréed food, Fluid thickeners, Enteral feeding
Communication difficulty (dysarthria)		Speech therapy, Computerized communication boards
Infection		Flu vaccine annually, Pneumovax (pneumococcal polysaccharide vaccine)

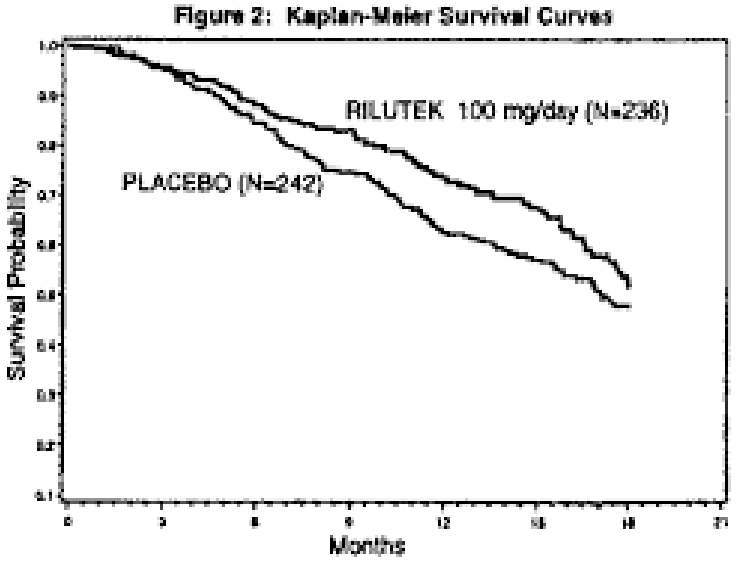
ADL, activities of daily living; **FVC**, forced vital capacity; **NIPPV**, noninvasive positive pressure ventilation; **NSAIDs**, nonsteroidal anti-inflammatory drugs; **qhs**, each bedtime; **qid**, 4 times daily; **ROM**, range of motion; **SL**, sublingually; **SSRI**, selective serotonin reuptake inhibitor; **tid**, 3 times daily.

[a] See Amtmann et al.[37]

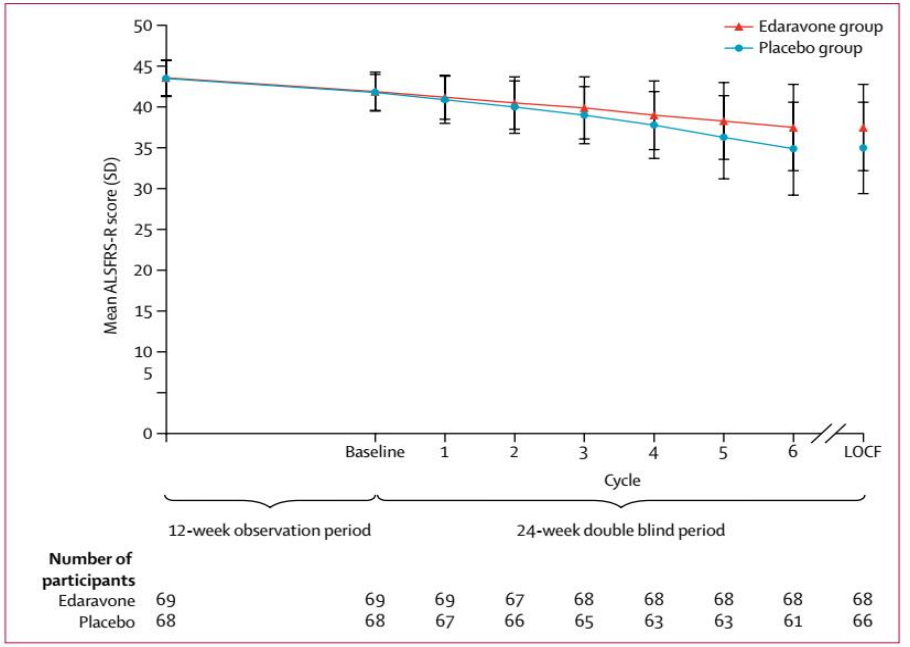
Adapted from Hobson EV and McDermott CJ[26] and from Hardiman O et al.[38]

Disease modifying therapy

- Riluzole (1995)
  - Mortality benefit (~2/12)
  - Inhibits NMDA receptors
  - ↑Glutamate uptake



- Endavarone (2017)
  - Slows disability progression
  - Very select group
  - Free radical scavenger



Lancet Neurol 2017

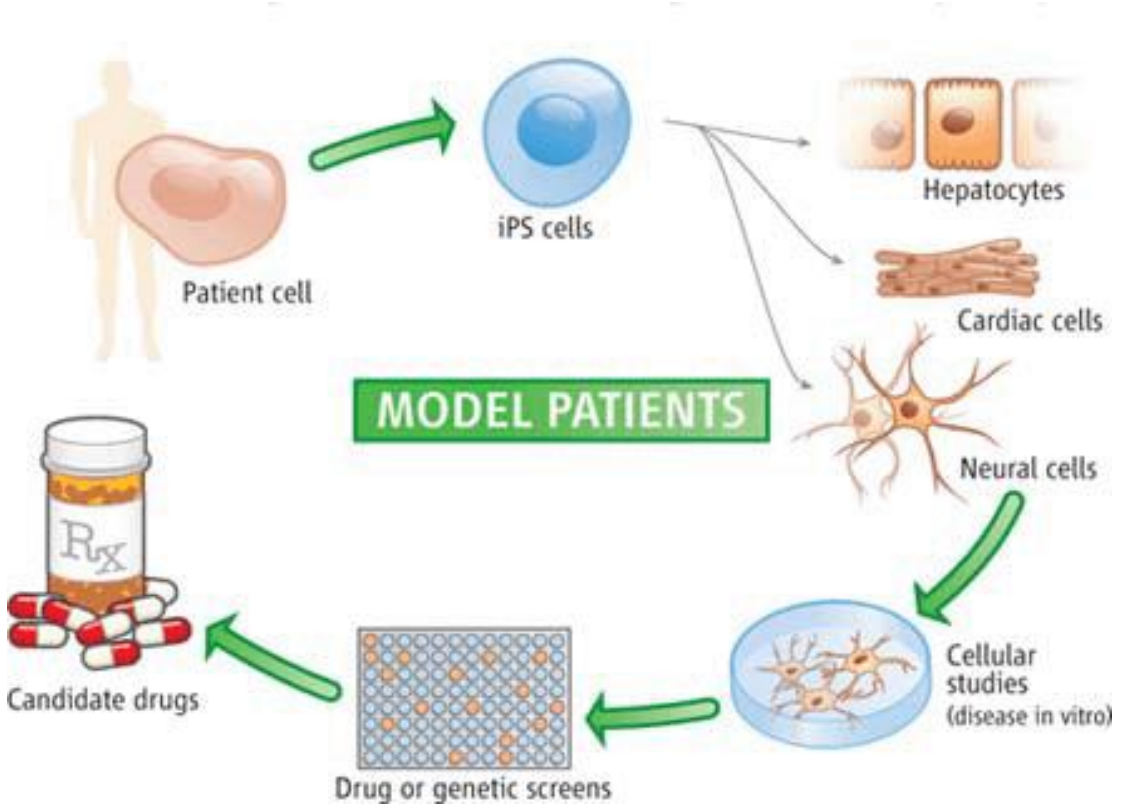
What does the future hold?

Better understanding of pathophysiology is helping to target more promising drugs

- Excitotoxicity: Perampanel, memantine...
- Oxidative stress: Endavarone, Co-Q10, Vitamin E...
- Mitochondrial dysfunction: Rasagaline
- Autophagy and protein quality control: Arimoclomol, Guanabenz, L-serine...
- Neuroinflammation: Ravalizumab, Zilucoplan...
- Apoptosis: Tauroursodeoxycholic acid, GDC—134...

Stem cells (but not the way you think)

- Stem cell therapies have been disappointing
- Induced pluripotent stems cells offer new ways of testing treatments



This has already started to accelerate drug discovery

Candidates include:

- Ropinerol
- Retigabine
- Bosutinib

https://science.sciencemag.org/content/330/6008/1172.full

Stem cells (but not the way you think)

Table 1 Comparison of the Three Therapeutic Candidates for ALS Developed by iPSC Drug Discovery

	Known drug target	Potential mechanism	Targeted ALS subtype
ROPI	Dopamine receptor agonist	Suppressing oxidative stress Inhibiting TDP-43 and FUS aggregation Improving mitochondrial function Suppressing neurite retraction and cell death (sporadic, *TDP-43*, *FUS* mutation)	Most of sporadic *TDP-43* mutation *FUS* mutation NOT *SOD1* mutation
Retigabine	Kv7 or KCNQ voltage-gated potassium channel activator	Inhibiting motor neuronal excitability Decreasing activation of endoplasmic reticulum (ER) stress pathway Suppressing cell death (*SOD1* mutation)	*SOD1* mutation *C9orf72* mutation *FUS* mutation
Bosutinib	Src/c-Abl inhibitor	Inducing autophagy Inhibiting misfolded SOD1 aggregation Suppressing cell death (*SOD1*, *TDP-43*, *C9orf72* mutation, a part of sporadic)	*SOD1* mutation *TDP-43* mutation *C9orf72* mutation A part of sporadic

https://www.cell.com/trends/pharmacological-sciences/fulltext/S0165-6147(19)30274-3

BMJ Open. 2019 Dec 2;9(12):e033131. doi: 10.1136/bmjopen-2019-033131.

Induced pluripotent stem cell-based Drug Repurposing for Amyotrophic lateral sclerosis Medicine (iDReAM) study: protocol for a phase I dose escalation study of bosutinib for amyotrophic lateral sclerosis patients.

Imamura K[1], Izumi Y[2], Banno H[1], Uozumi R[3], Morita S[3], Egawa N[4], Ayaki T[4], Nagai M[5], Nishiyama K[5], Watanabe Y[6], Hanajima R[6], Oki R[2], Fujita K[2], Takahashi N[7], Ikeda T[8], Shimizu A[8], Morinaga A[9], Hirohashi T[9], Fujii Y[9], Takahashi R[4], Inoue H[10].

Author information

Regen Ther. 2019 Dec 1; 11: 143–166.
Published online 2019 Jul 26. doi: 10.1016/j.reth.2019.07.002

PMCID: PMC6661418
PMID: 31384636

Ropinirole hydrochloride remedy for amyotrophic lateral sclerosis – Protocol for a randomized, double-blind, placebo-controlled, single-center, and open-label continuation phase I/IIa clinical trial (ROPALS trial)

Satoru Morimoto,[a,b] Shinichi Takahashi,[b] Komei Fukushima,[a] Hideyuki Saya,[c] Norihiro Suzuki,[b,d] Masashi Aoki,[e] Hideyuki Okano,[a,*] and Jin Nakahara[b]

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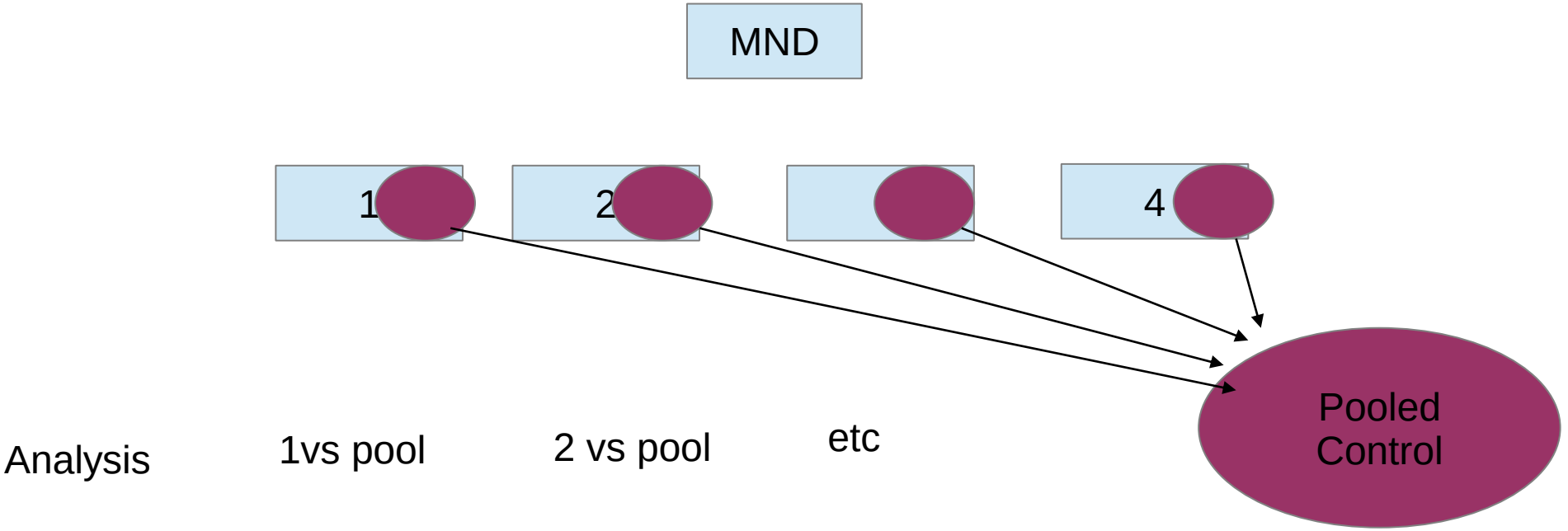
Conclusion

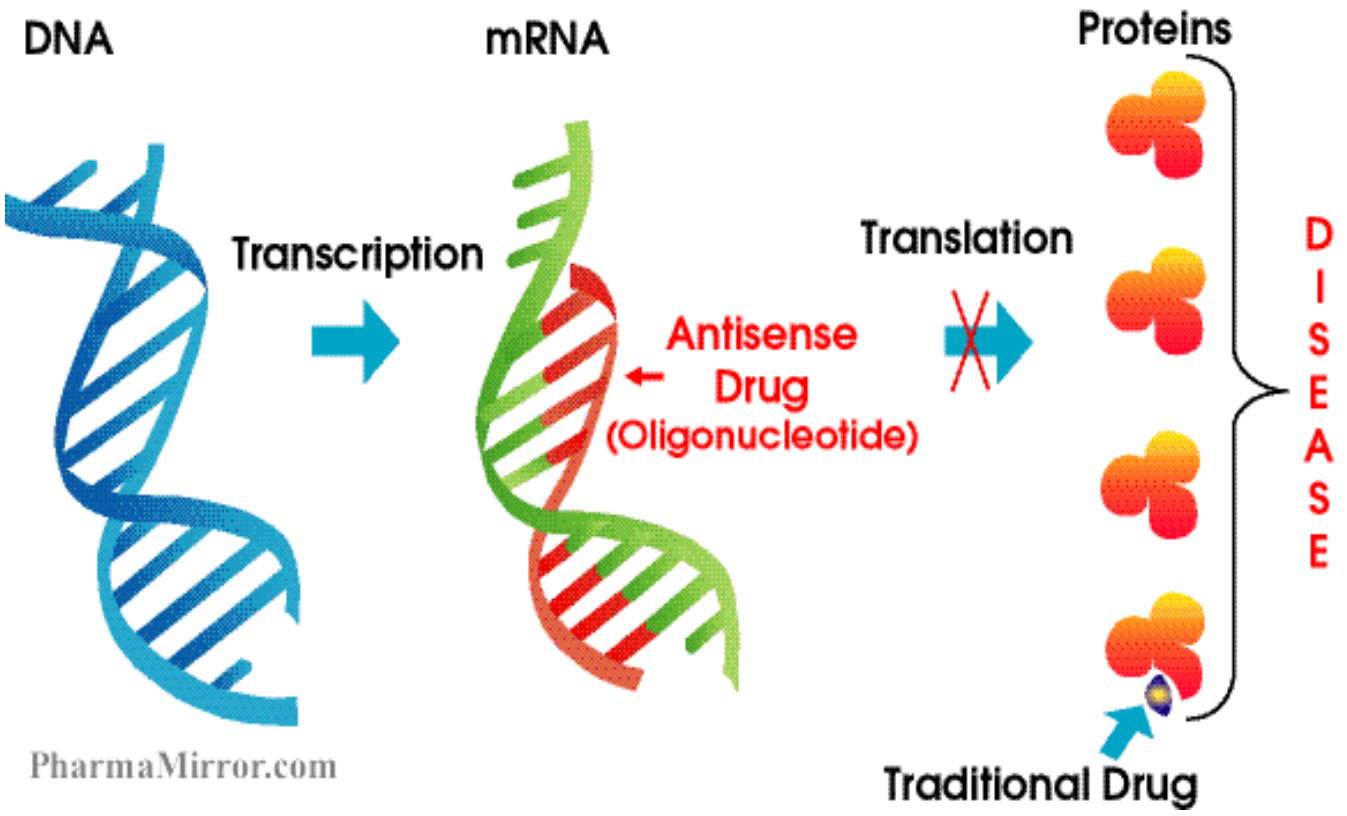
Patient recruitment began in December 2018 and the last patient is expected to complete the trial protocol in November 2020.

Better trial design

- Platform trials
  - Allows multiple medications to be tested
  - Shared infrastructure and protocol
  - Shared control groups

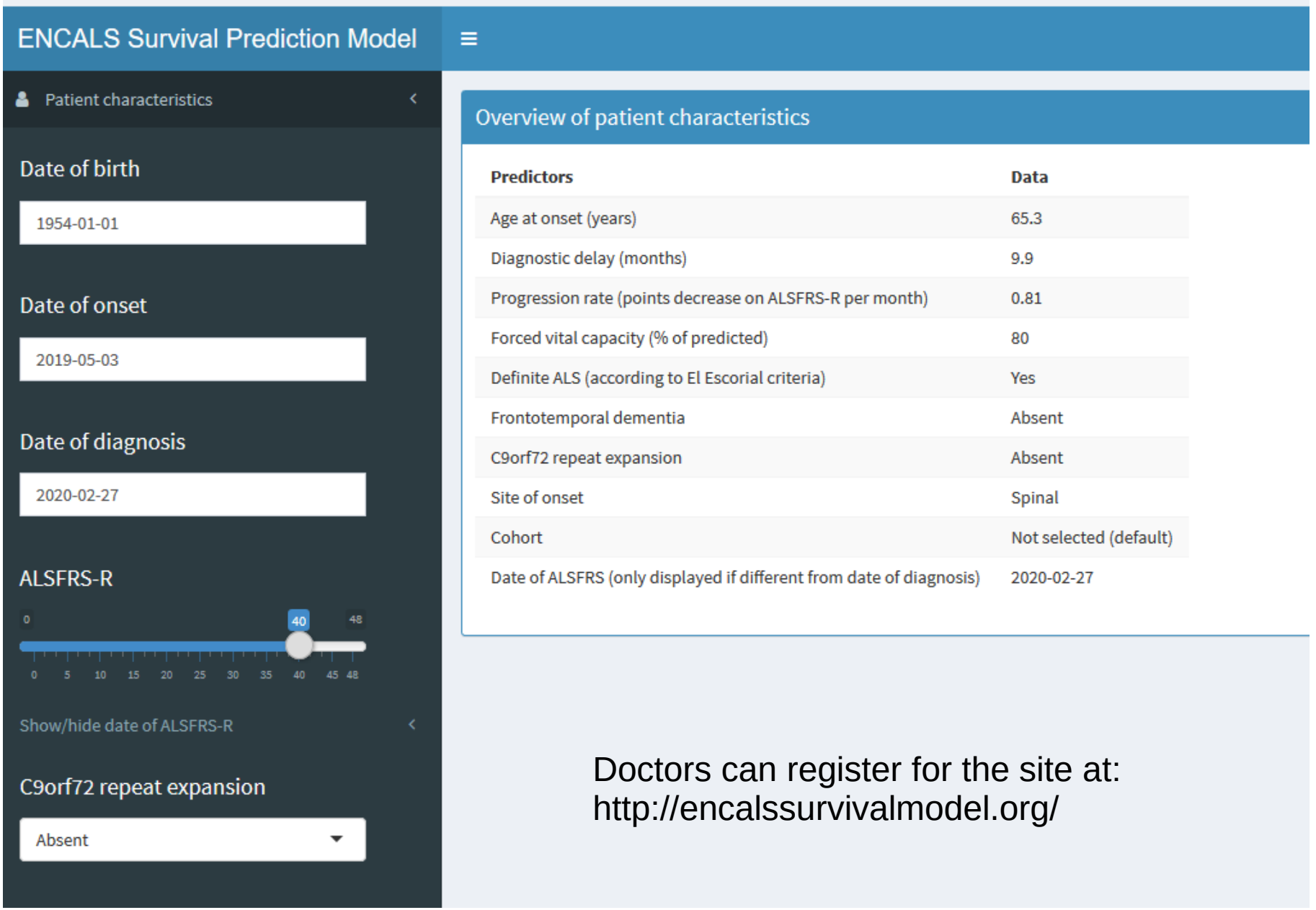


Genetic therapy is a reality



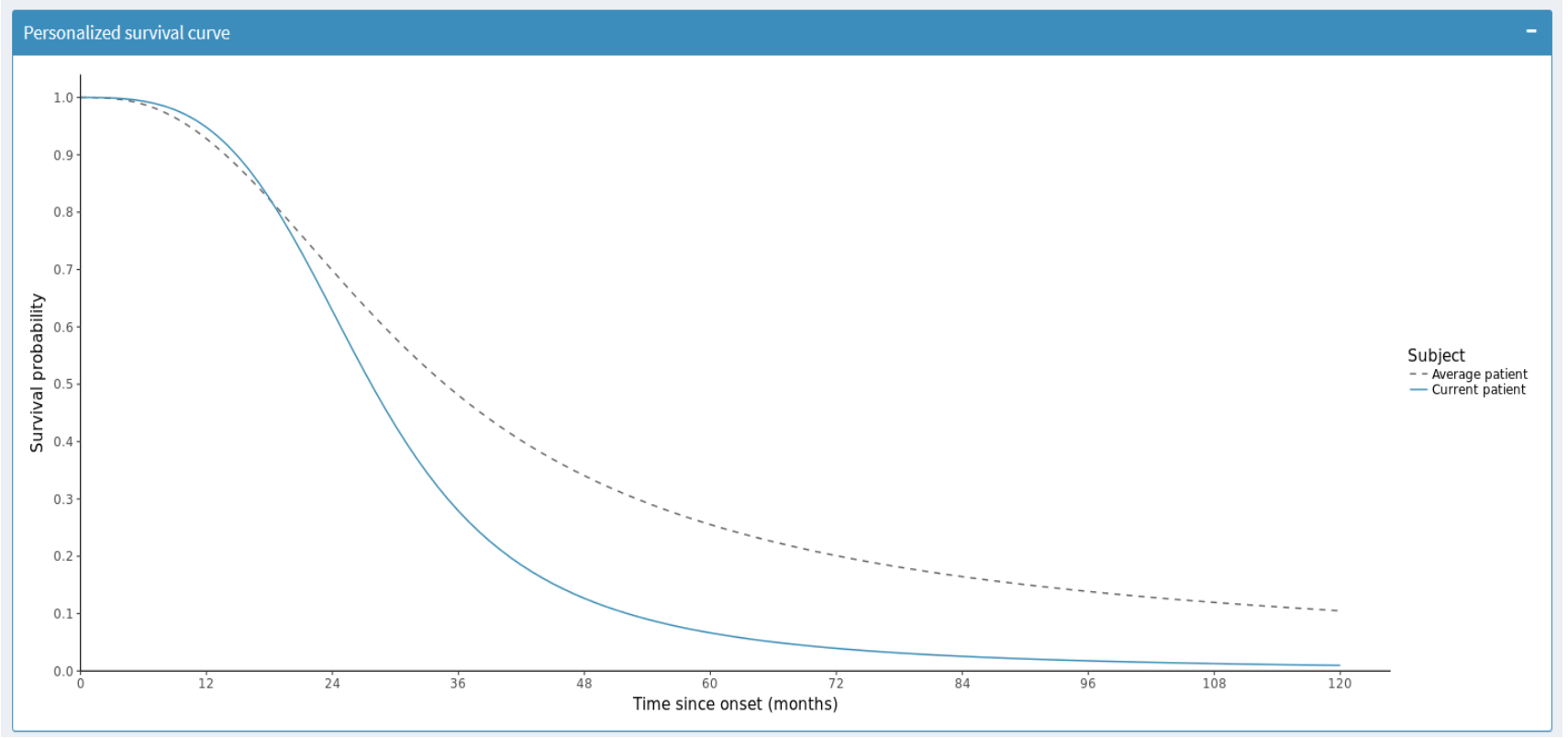
Registered for spinomuscular atrophy - In trials for SOD-1 ALS and Huntington's

Refining prognosis



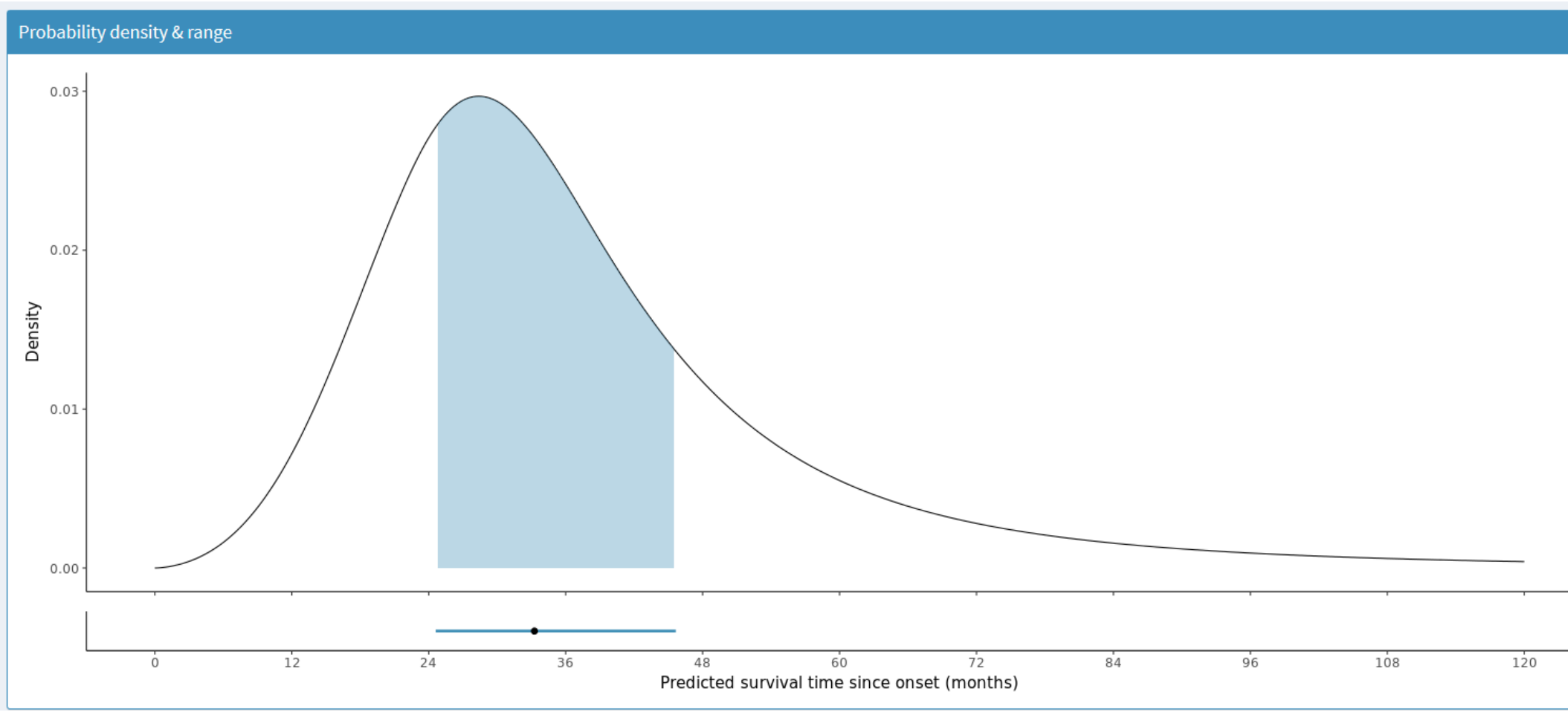
Doctors can register for the site at:
http://encalssurvivalmodel.org/

Personalised survival curve



- AUC 0.75
- ~80% accurate

Survival probability



Take home points

- Wasting and weakness are the main features
- The cause is still unclear but better understood:
  - Genetics/ Age/ epigenetics/environment
- It begins in the cortex and is a neurodegenerative proteinopathy
- Better treatment is not too far away (Hopefully!)
- Until then there is lots of care to offer

Thank you