MND: back to basics

Tim Williams
Consultant Neurologist & MND Care Centre Director, RVI

Motor Neurone Disease

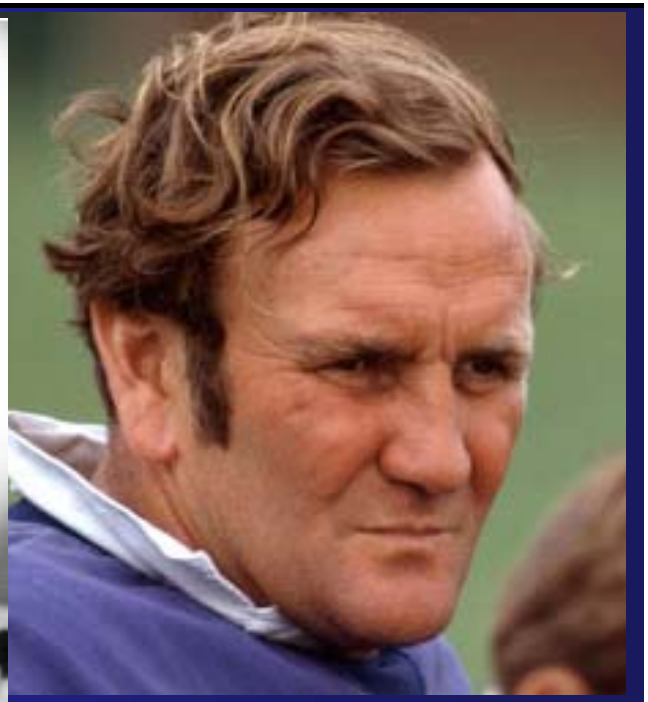
Amyotrophic Lateral Sclerosis (ALS) first described by Charcot in 1860's.

Term "motor neuron(e) disease" first used by British neurologist Lord Brain in 1930's

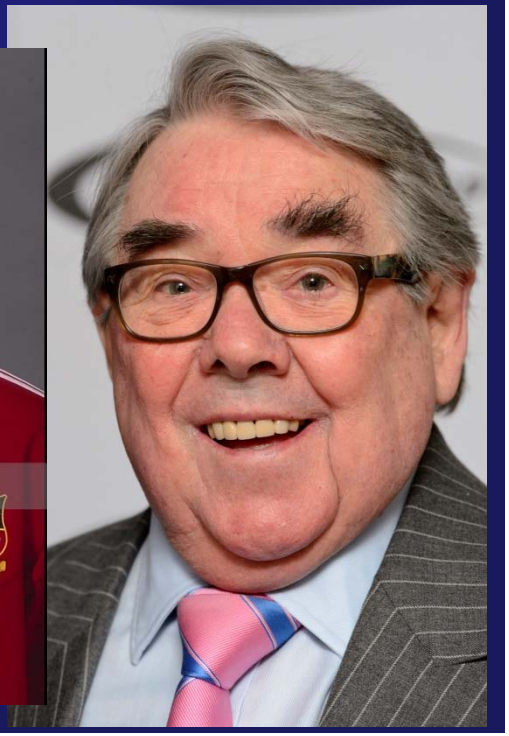
?First description by Charles Bell in 1824

Motor Neurone Disease

Also known as:
- ALS
- anterior horn cell disease
- Lou Gehrig's disease
- maladie de Charcot
- creeping paralysis

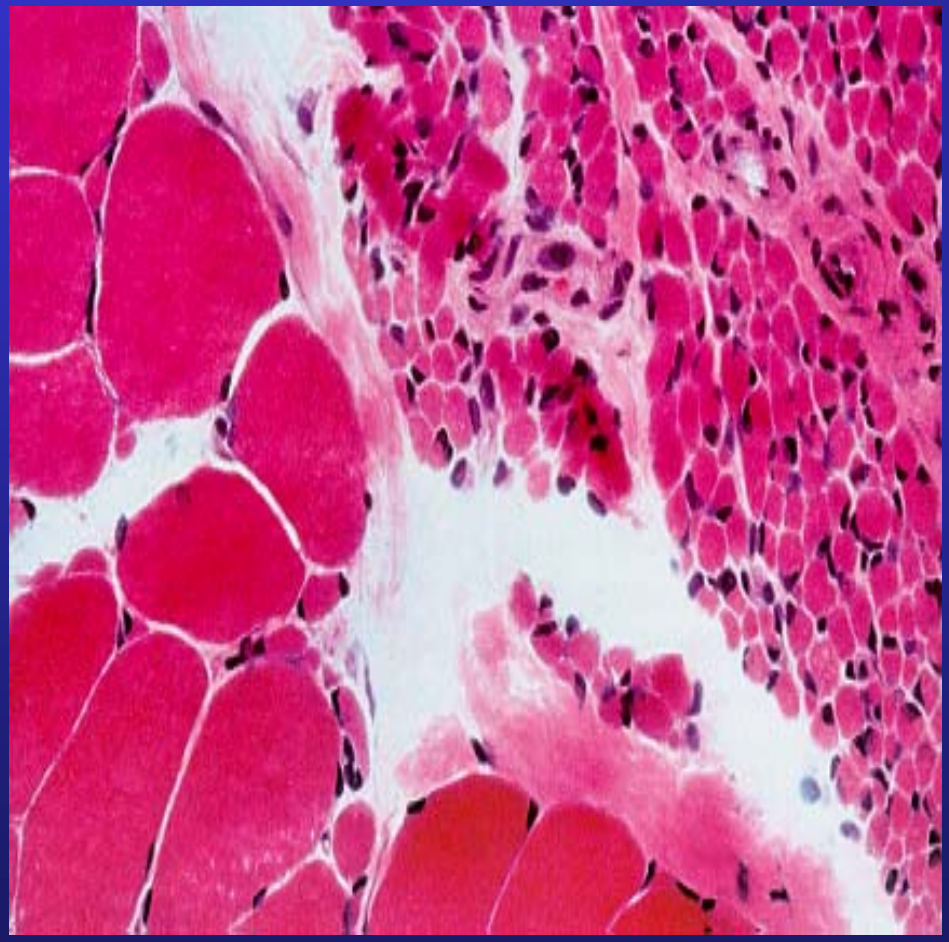



adidas
SCOTTISH
PROVIDENT



Motor Neurone Disease

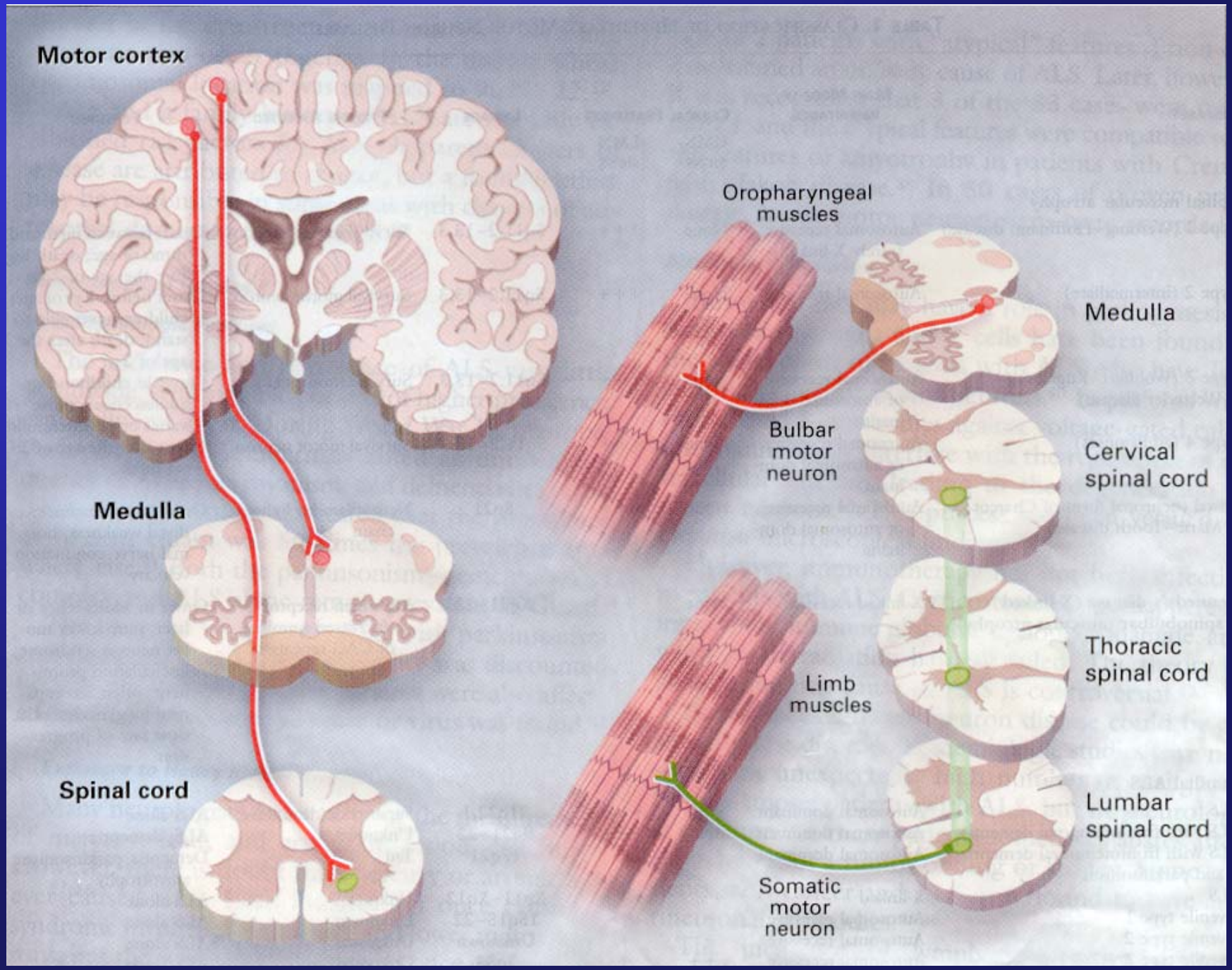
Amyotrophy – muscle wasting

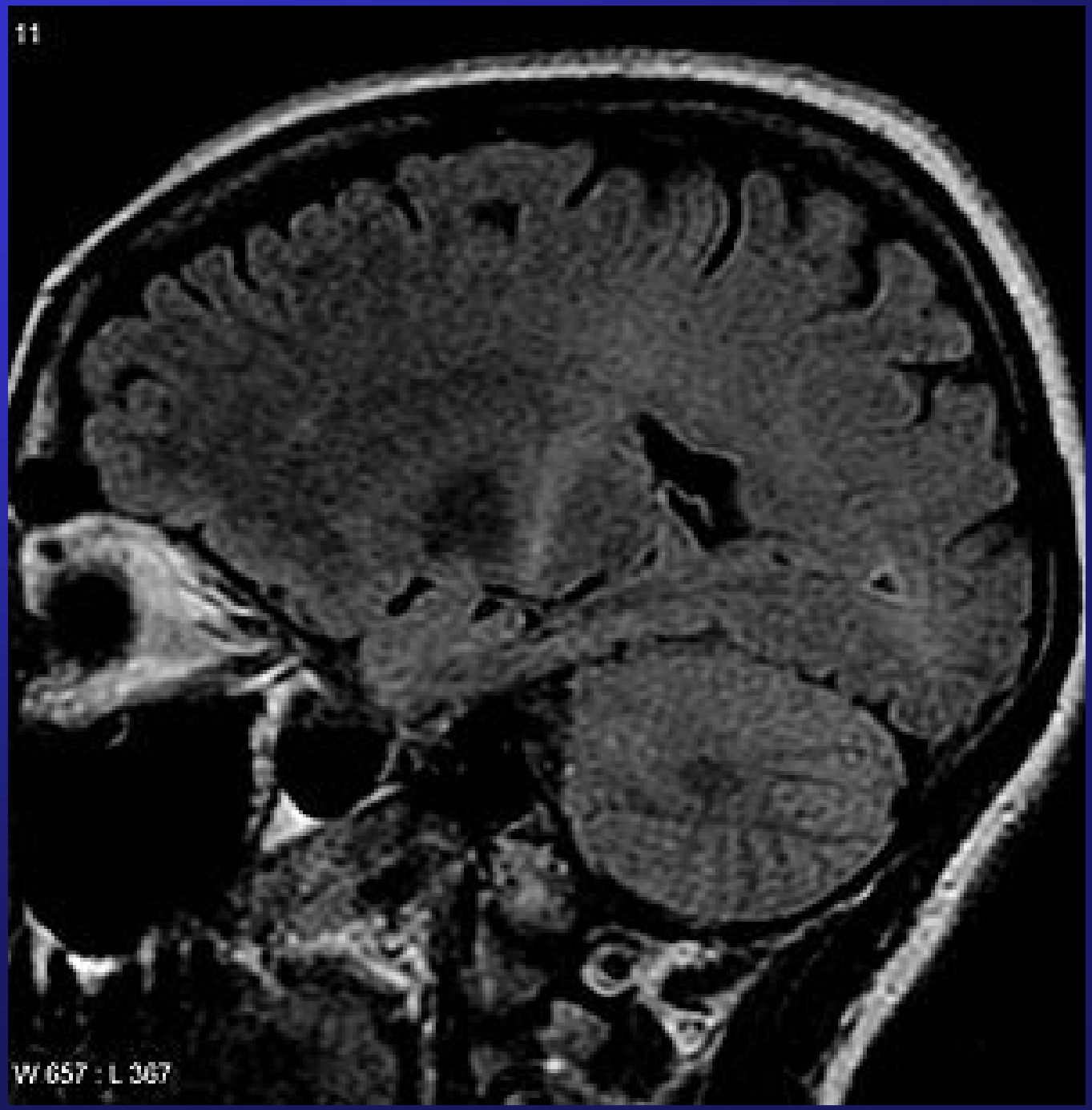


Motor Neurone Disease

Amyotrophy – muscle wasting

Lateral Sclerosis – gliotic sclerosis of the “lateral” corticospinal tracts. Lateral columns firm to palpation


Motor cortex
Medulla
Spinal cord
Oropharyngeal muscles
Bulbar motor neuron
Medulla
Cervical spinal cord
Limb muscles
Thoracic spinal cord
Lumbar spinal cord
Somatic motor neuron


11
W 657 : L 307

What is MND?

Neurodegenerative condition:

neuro: affecting the nervous system (brain, spinal cord and nerves)

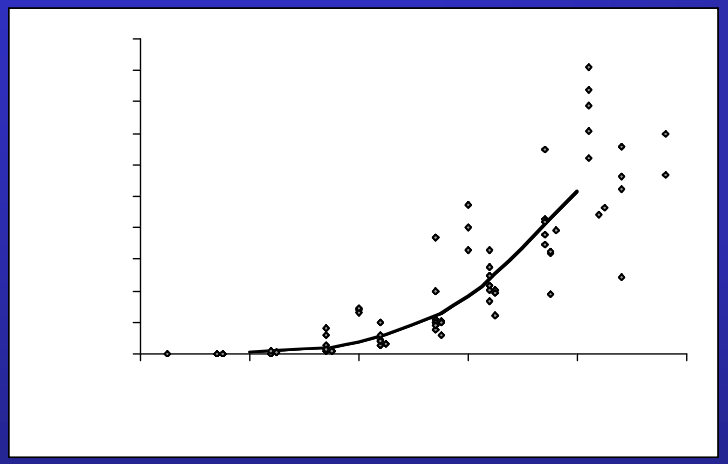
degenerative: premature loss of cellular function & ultimately neuronal death

Neurodegenerative conditions

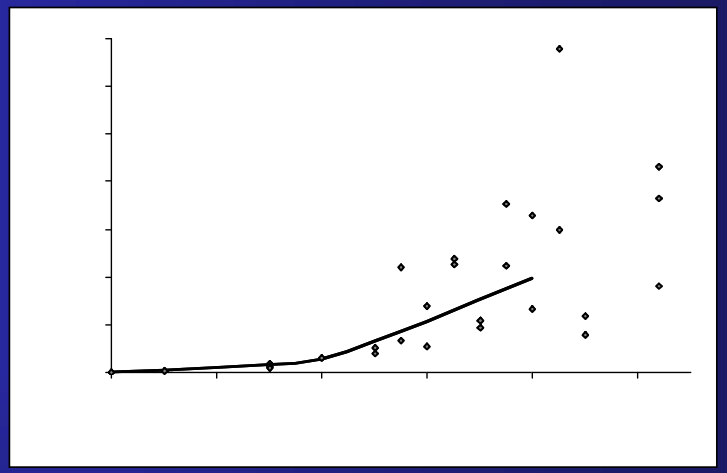
Characterised by:

- selective, irreversible loss of a specific group(s) of neurones
- onset in late/middle life (55-79, 17->90)
- commonest cause of death from neurodegenerative disease in working age!

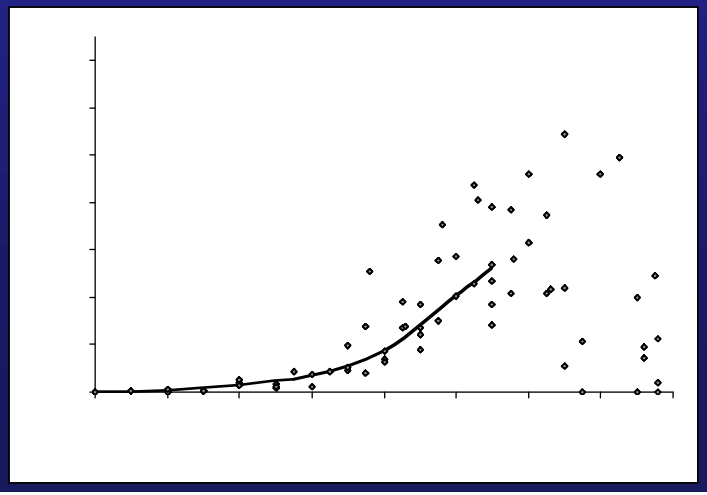
Age-related neurodegenerative disease



Alzheimer's Disease



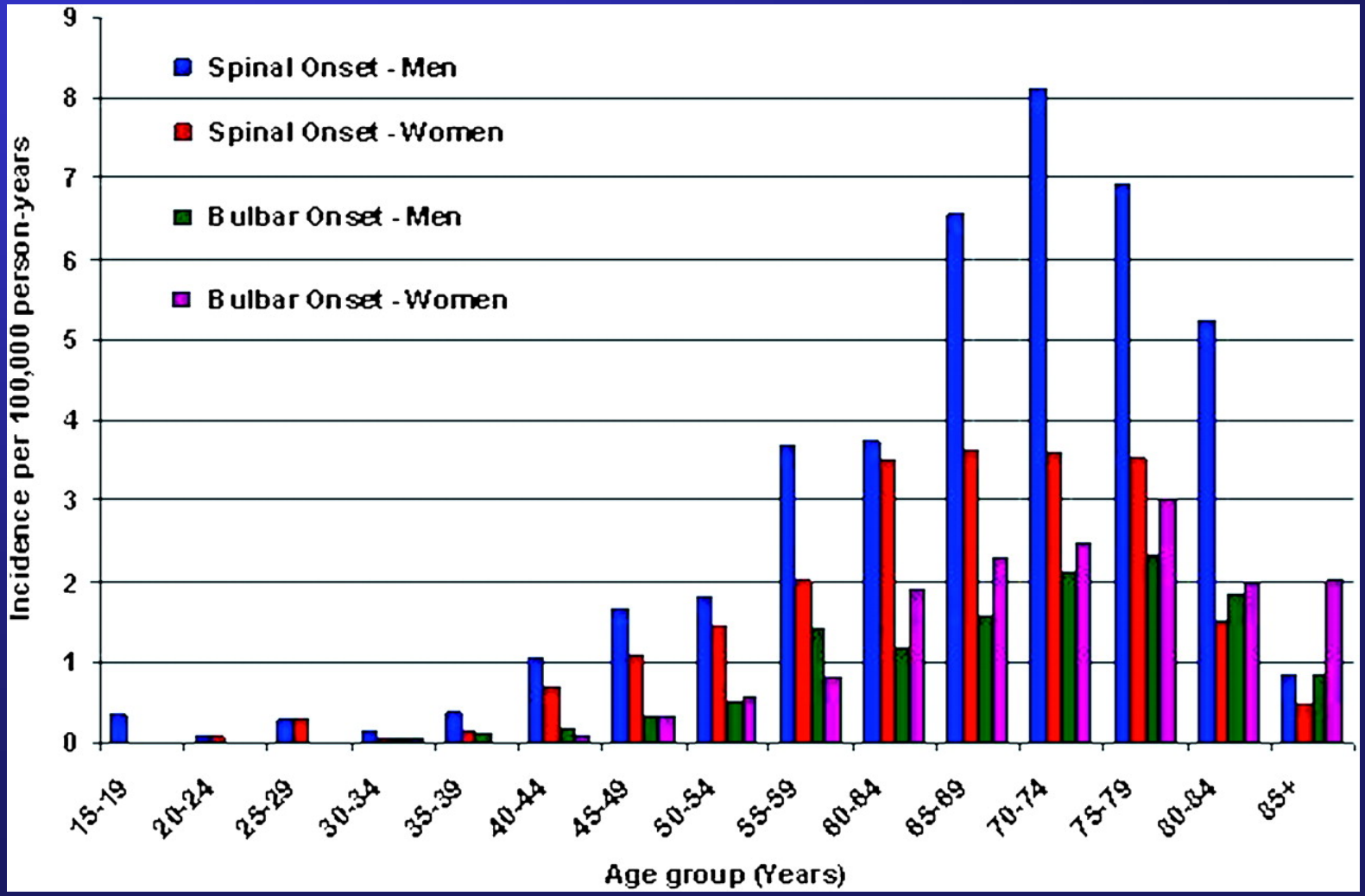
Parkinson's Disease



MND

Hirtz *et al*, NEUROLOGY 2007

Age and gender specific incidence of amyotrophic lateral sclerosis



Logroscino *et al*, JNNP 2010

Neurodegenerative conditions

Characterised by:

- selective, irreversible loss of a specific group(s) of neurones
- onset in late/middle life (55-79, 17->90)
- relentless progression
- absence of clear understanding of aetiology
- no disease modifying treatments
- protein aggregation

Protein aggregates

Alzheimer's disease – tau and amyloid

"tauopathy"

Parkinson's disease – synuclein

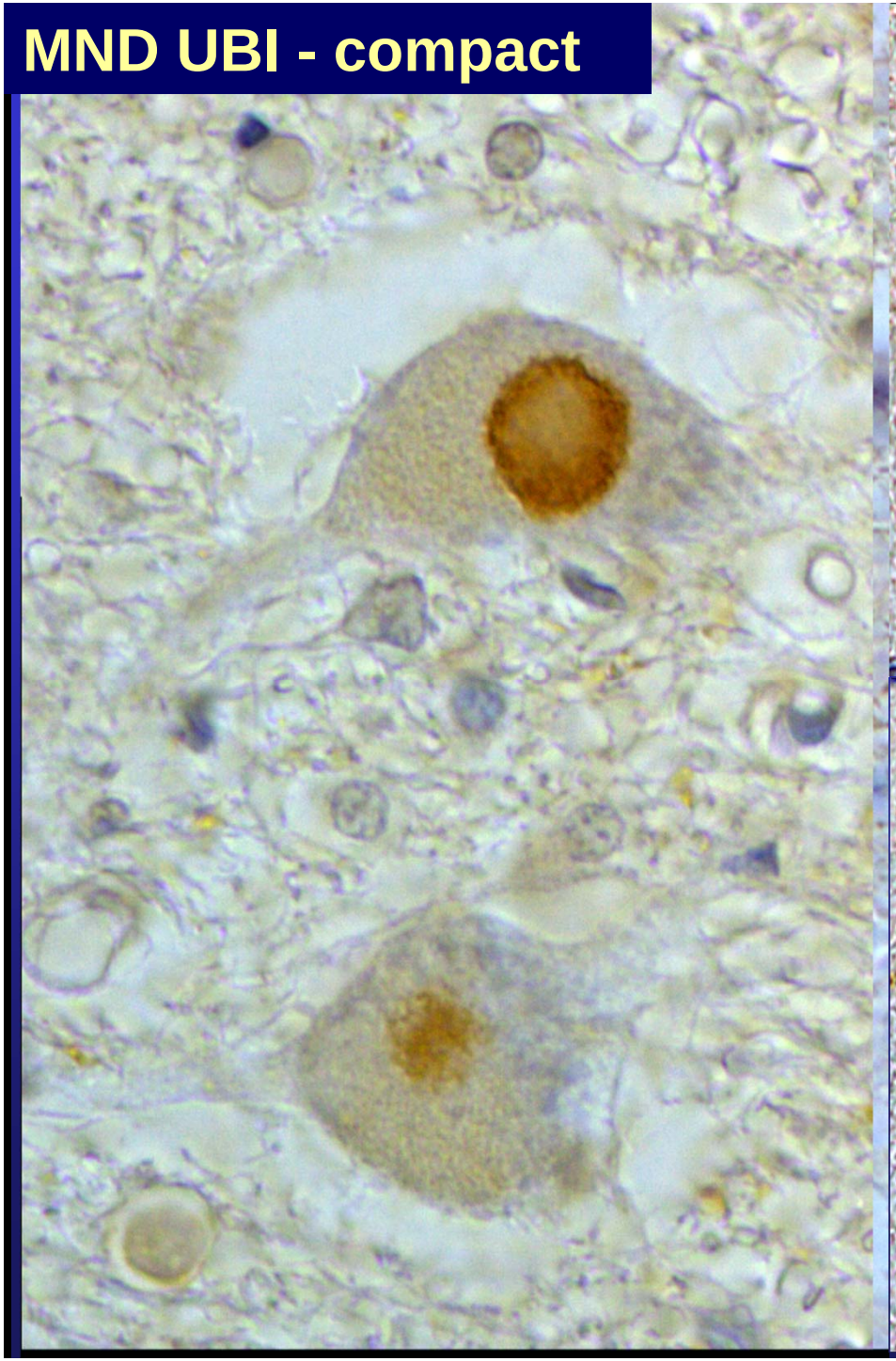
"synucleinopathy"

Huntington's disease – huntingtin

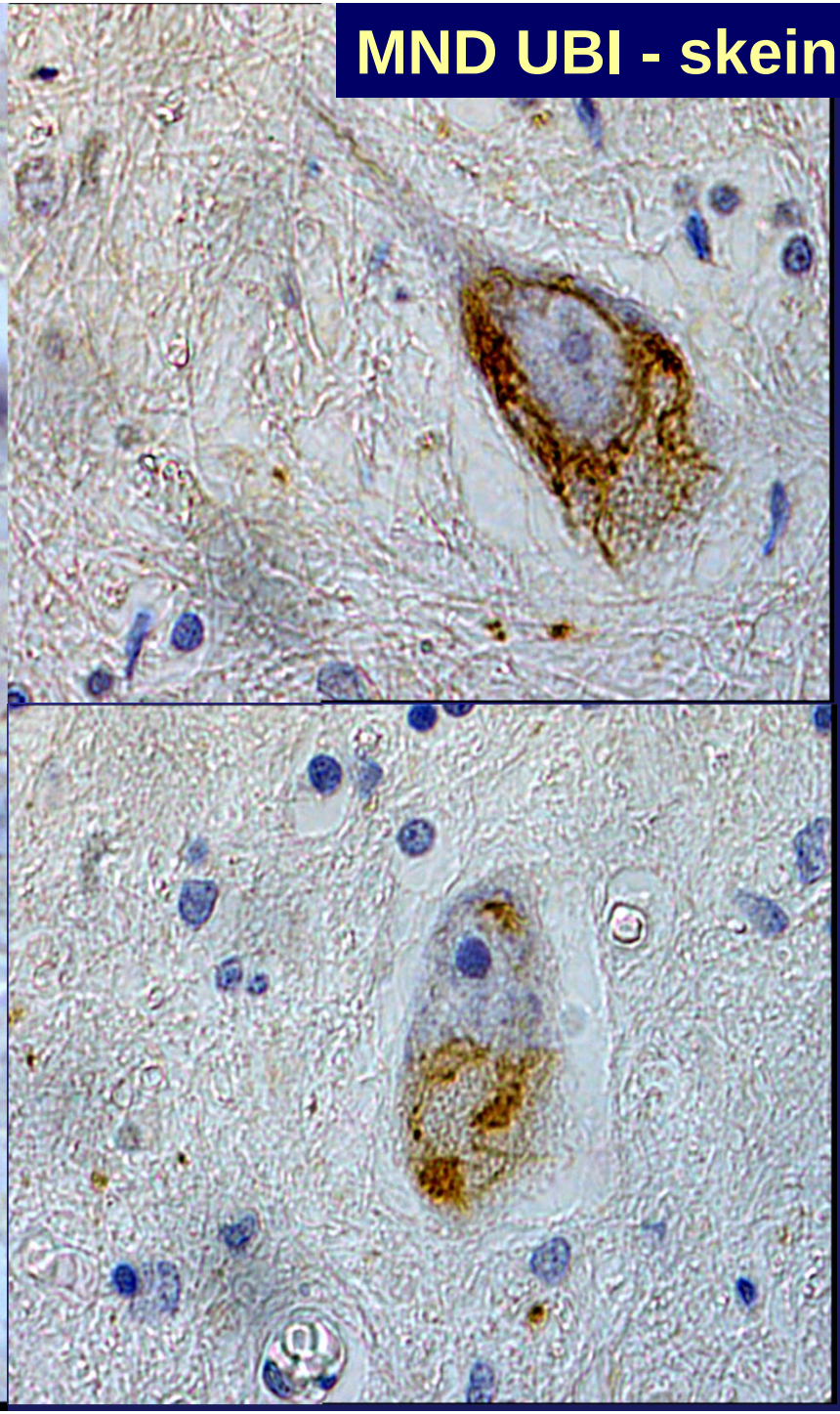
MND – TDP43

"TDP43opathy"

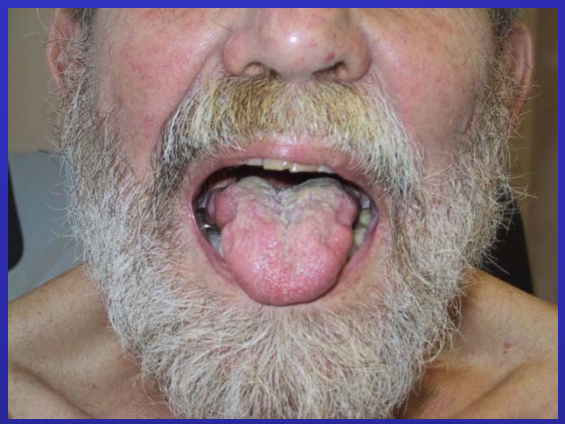
MND UBI - compact

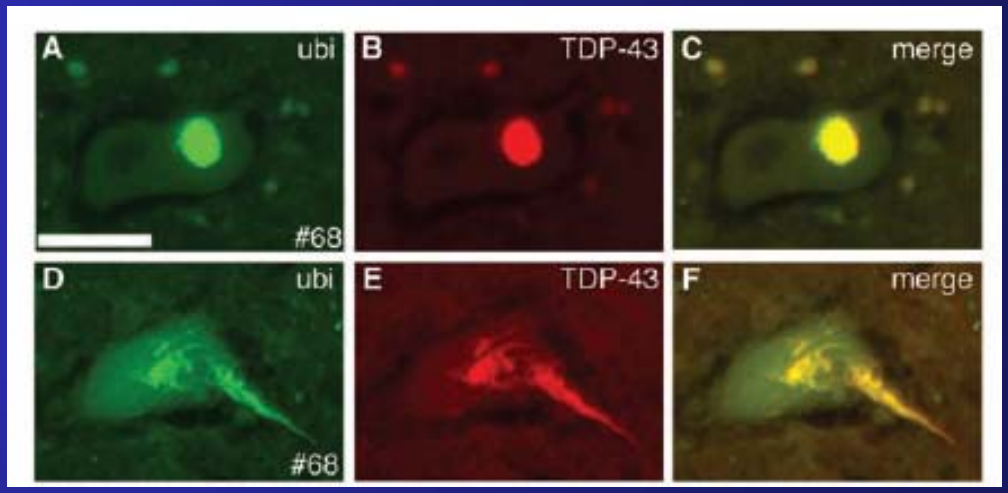


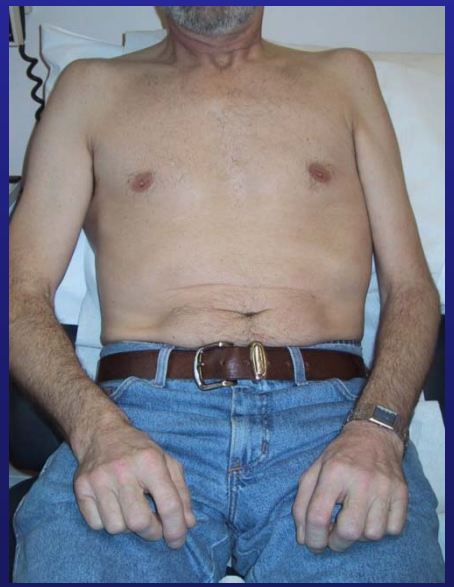
MND UBI - skein

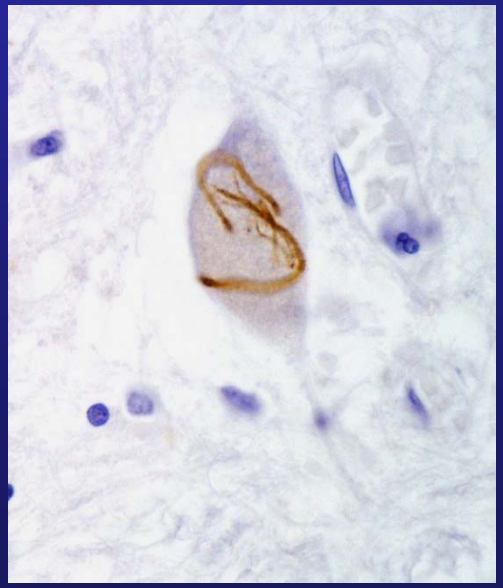


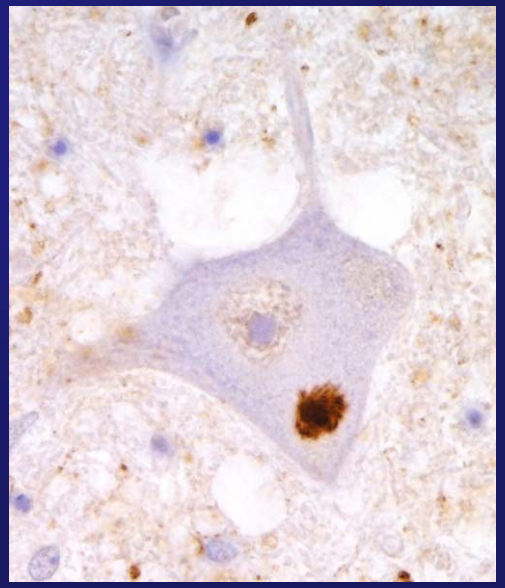
TDP-43 inclusions in MND







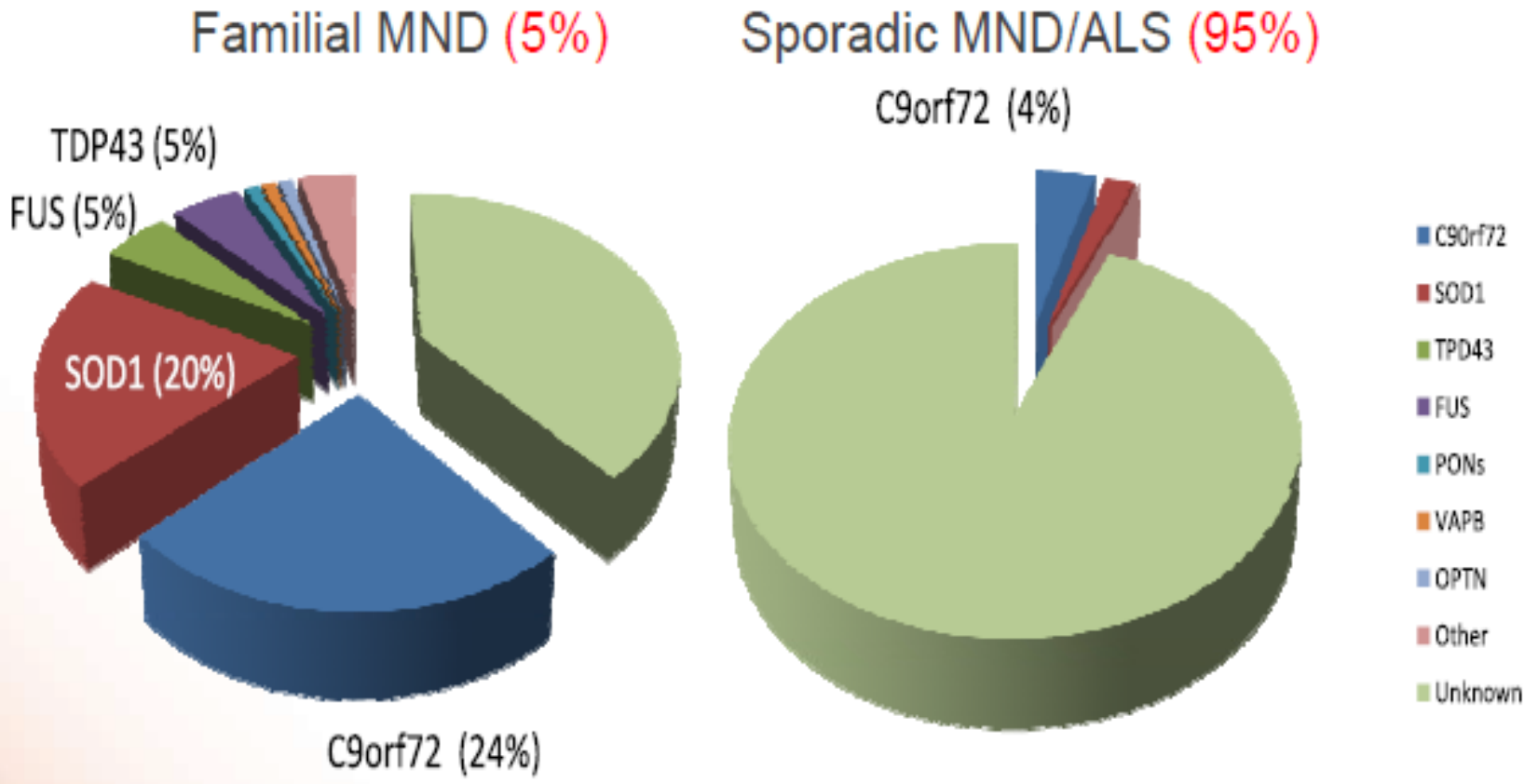




Aetiology

- Unknown!!!
- ~90% of MND is sporadic
- ~10% genetically determined, predominantly in autosomal dominant fashion.
- ~8-10% of sporadic MND cases are genetic

Proportion of MND patients with known gene defects

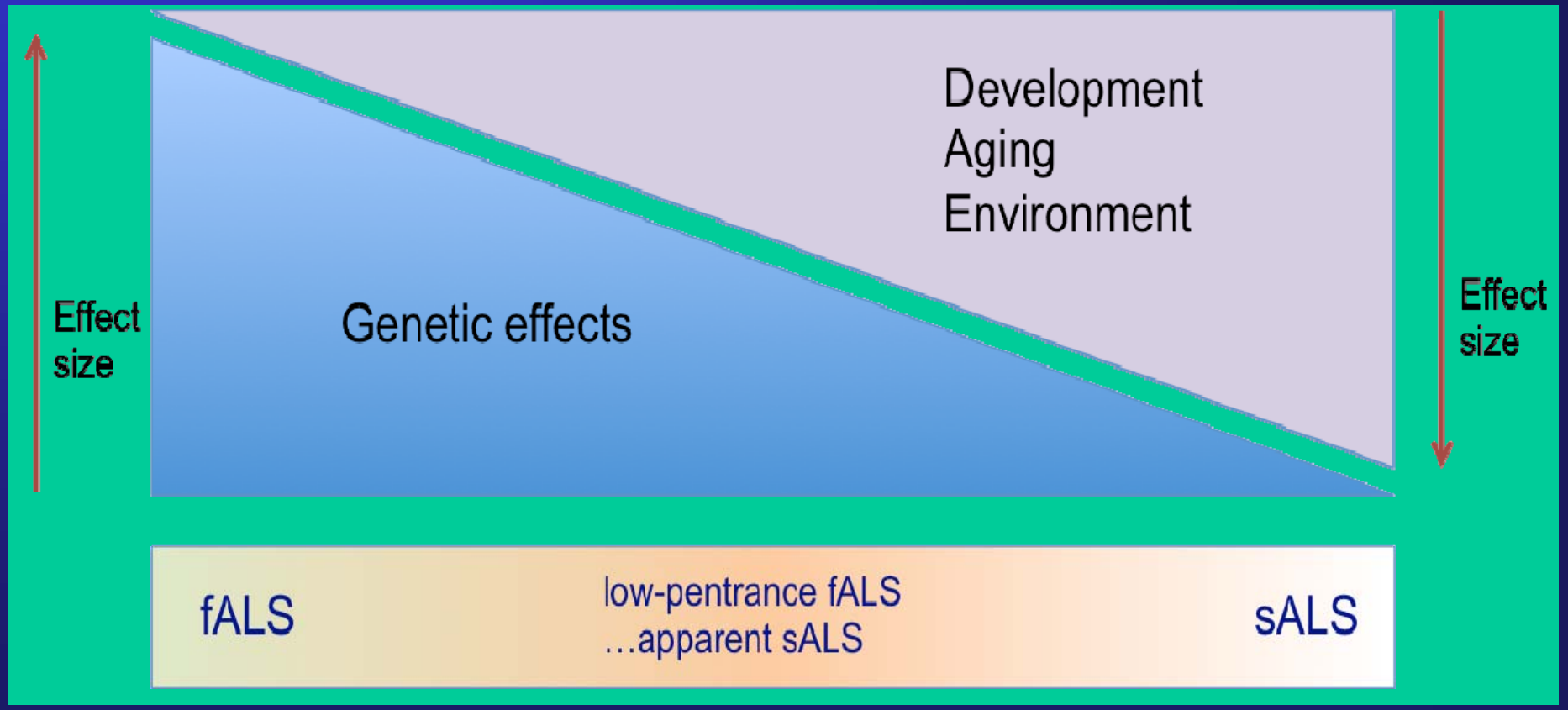


The genes for 55% of familial and 10% of sporadic MND/ALS are known and can be offered for diagnostic and predictive testing in patients

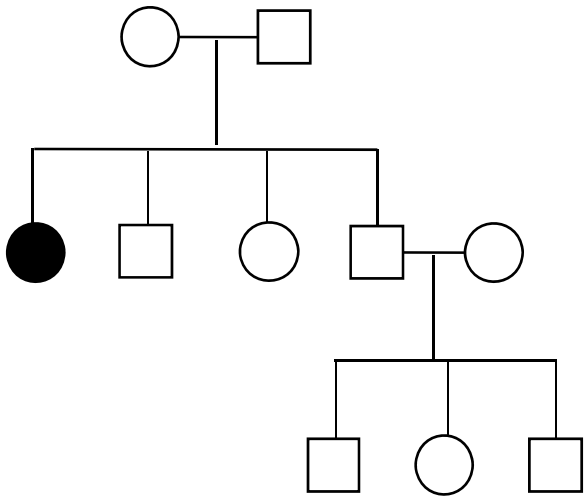
Aetiology

- Unknown!!
- ~90% of MND is sporadic
- ~10% genetically determined, predominantly in autosomal dominant fashion.
- ~8-10% of sporadic MND cases are genetic
- Even sporadic MND has a significant genetic “contribution” – 60%

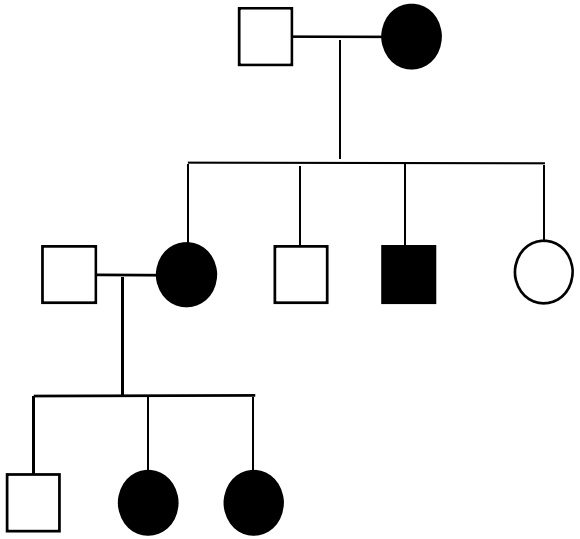
The genetic risk of MND



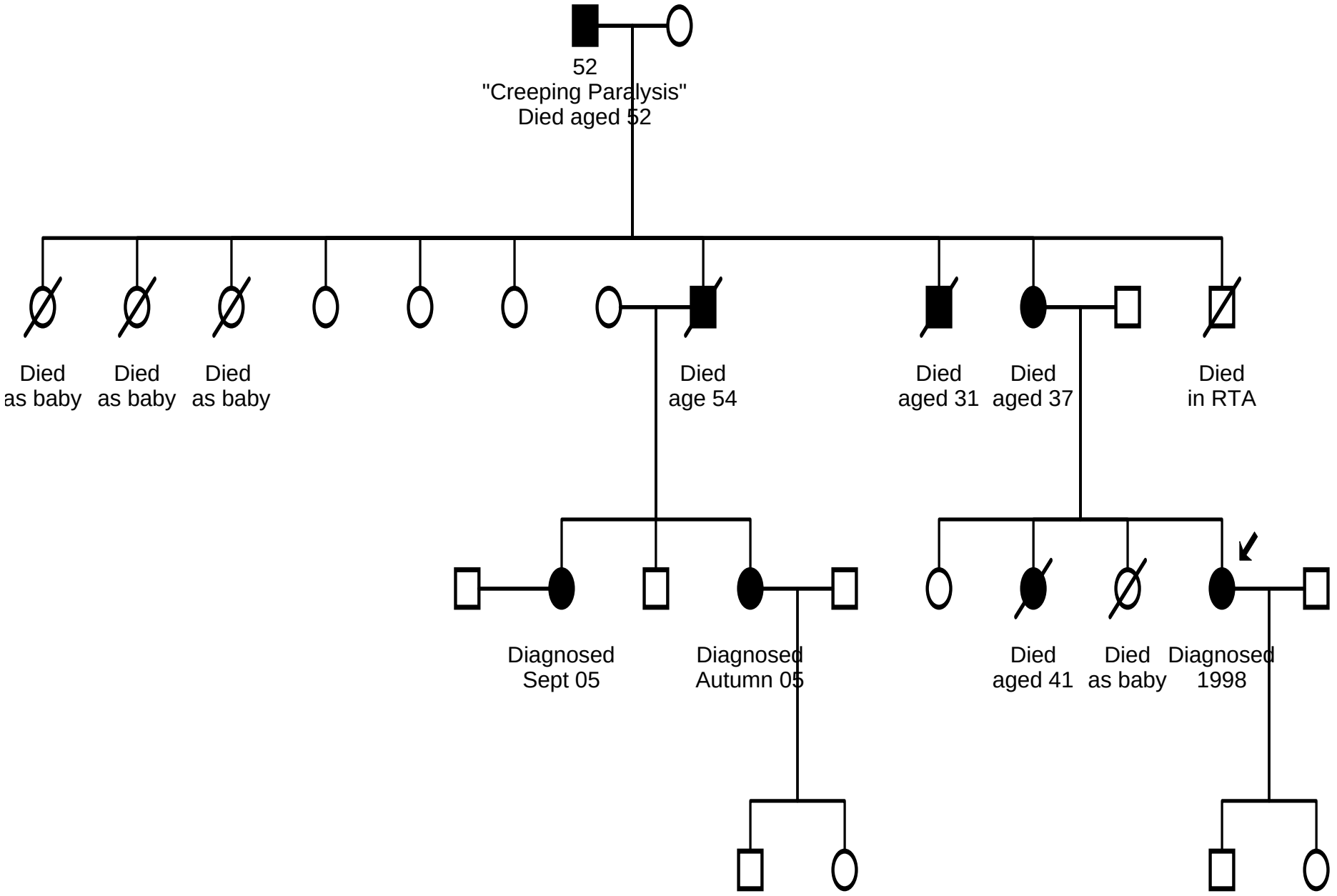
MND: Occasionally a genetic disease



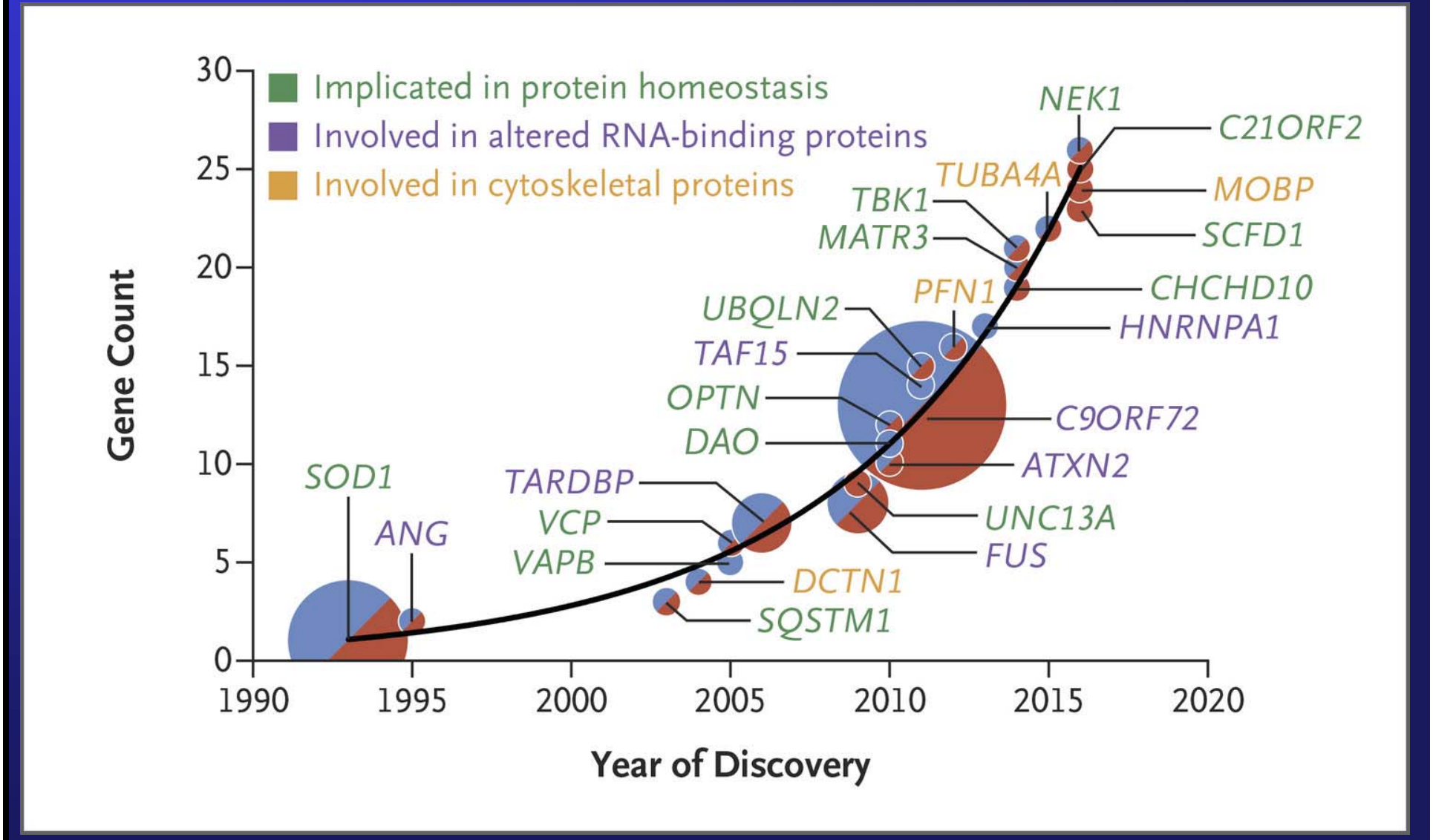
Usual



Rare


52
"Creeping Paralysis"
Died aged 52
Died as baby
Died as baby
Died as baby
Died age 54
Died aged 31
Died aged 37
Died in RTA
Diagnosed Sept 05
Diagnosed Autumn 05
Died aged 41
Died as baby
Diagnosed 1998

MND gene discovery since 1993

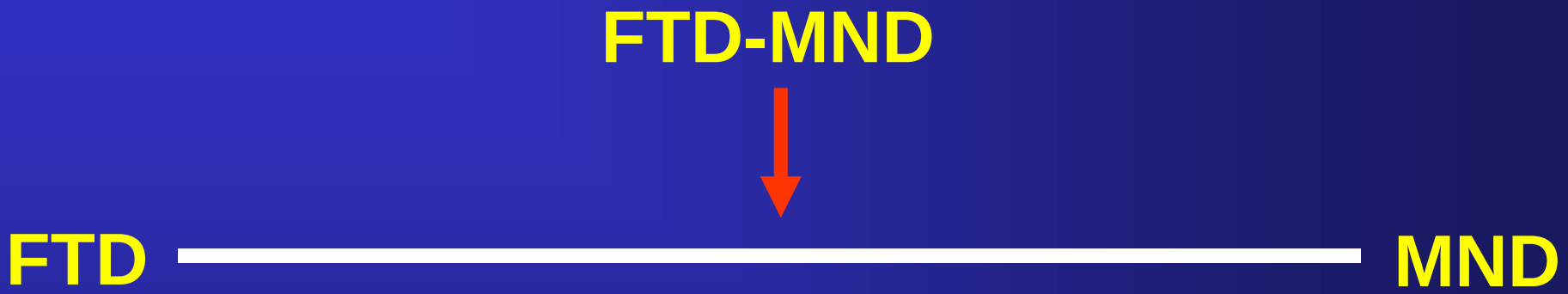


Brown RH, Al-Chalabi A. N Engl J Med 2017;377:162-172.

Genes causing “typical” MND

				Frequency in FALS
ALS1	21q22.1	SOD1	Dominant	20%
ALS6	16q12	TLS/FUS	Dominant	7%
ALS10	1p36.2	TDP43	Dominant	4%
ALS	9p	C9ORF72	Dominant	?40%

C9ORF72 disease phenotype



C9ORF72

- Incomplete penetrance 0-80%
- Tends to be behavioural variant of FTD
- 8% of “sporadic cases
- Rethink family Hx

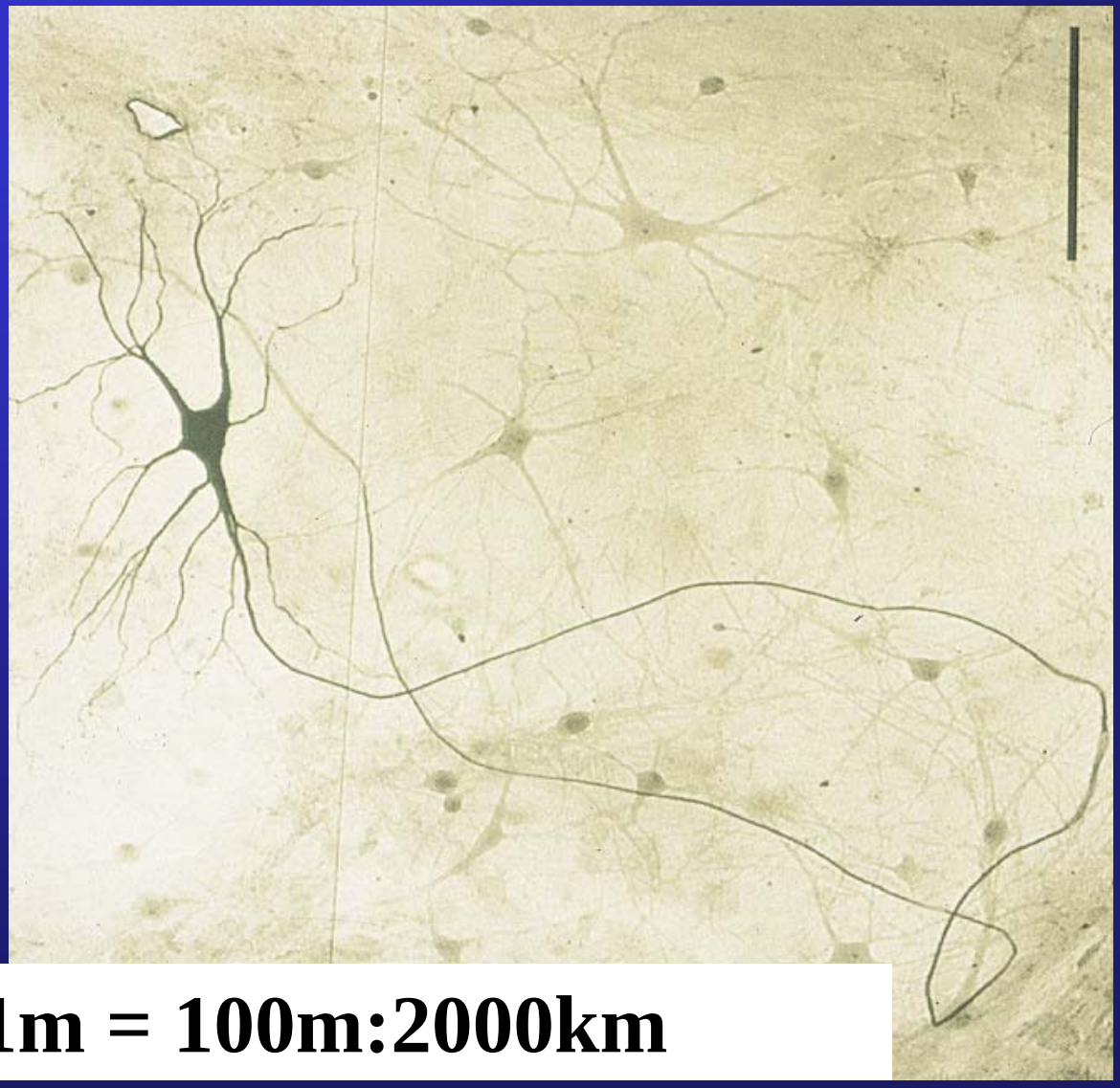
Aetiology

Possible mechanisms of neuronal injury:

1. Protein production and disposal
2. RNA binding, transport, transcription, and translation into protein
3. Neurofilaments making cytoskeletal proteins

AND

selective vulnerability of motor neurones.



50µm:1m = 100m:2000km

How common?

3rd commonest neurodegenerative condition.

Prevalence:

Parkinson's: 1 per 200 (1 in 15)

Dementia: 1 per 70 (1 in 8)

MND: 4-6 per 100,000 (1 in 500 or 0.2% lifetime risk)
10 fold increase if parent affected (still just 2%)

Not common!

MND is rare

Incidence: 2-4/100,000 a year (consistent worldwide.

M:F = 3:2

Modal age of onset 5^{th} - 6^{th} decade (av. 63)

No association with trauma, surgery, electric shock, immunization, prev. polio, infection.

What does that mean?

- On average, a GP sees 1 or 2 “new” cases in a working lifetime.
- 4,500 patients with MND in UK at any one time.
- 3-4 deaths per day in UK

What do we see?

Northern region population = 2.2-2.5 million.

Our Catchment Area

What do we see?

Northern region population = 2.2-2.5 million.

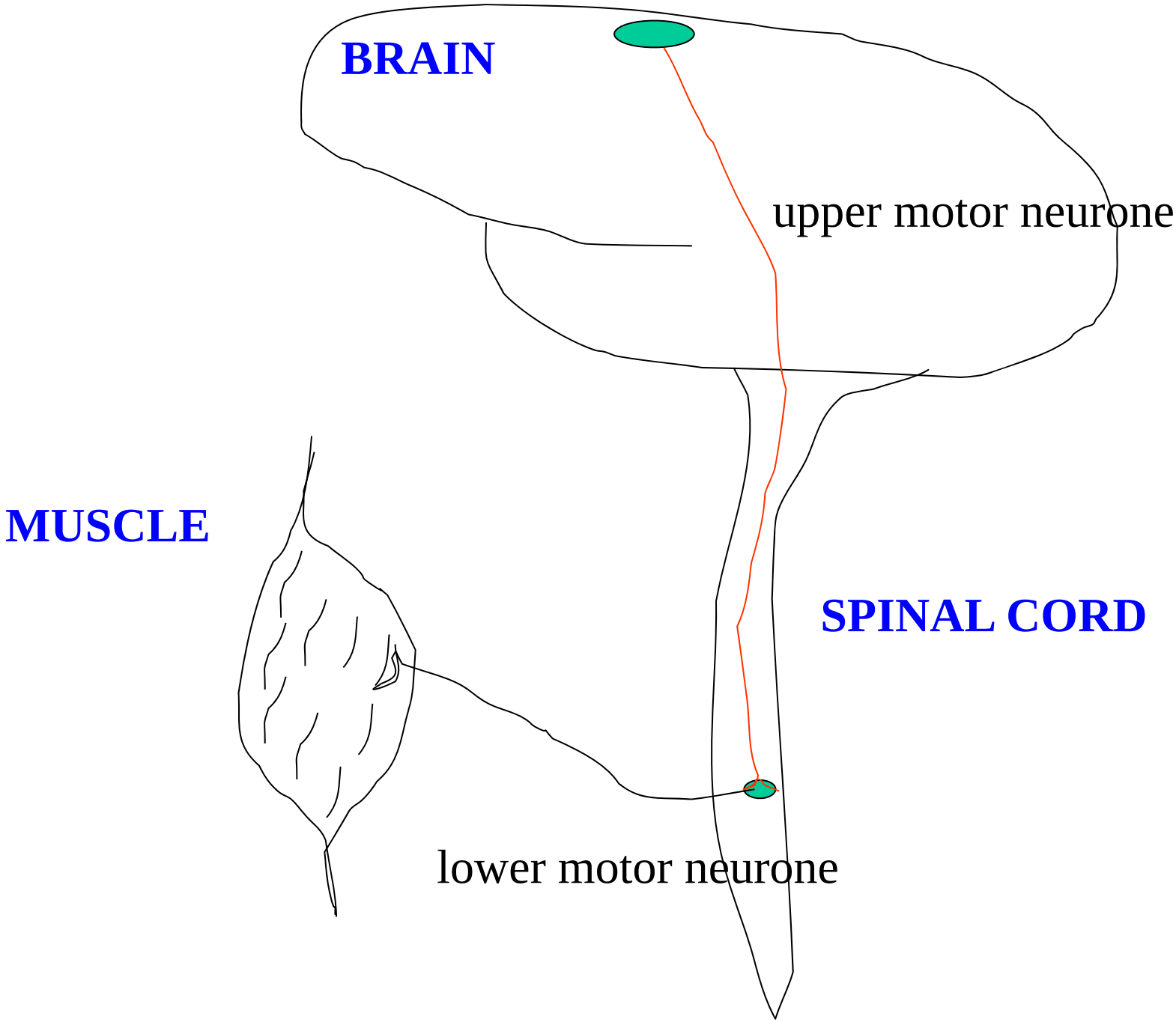
RVI MND care centre,

~75+ new cases referred to the MND centre each year.

~160+ cases under review at any one time.

What does it look like?

- Progressive deterioration in muscle function
- Evidence of upper and lower motor nerve loss


BRAIN
upper motor neurone
MUSCLE
SPINAL CORD
lower motor neurone

What does it look like?

- Progressive deterioration in muscle function
- Evidence of upper and lower motor nerve loss

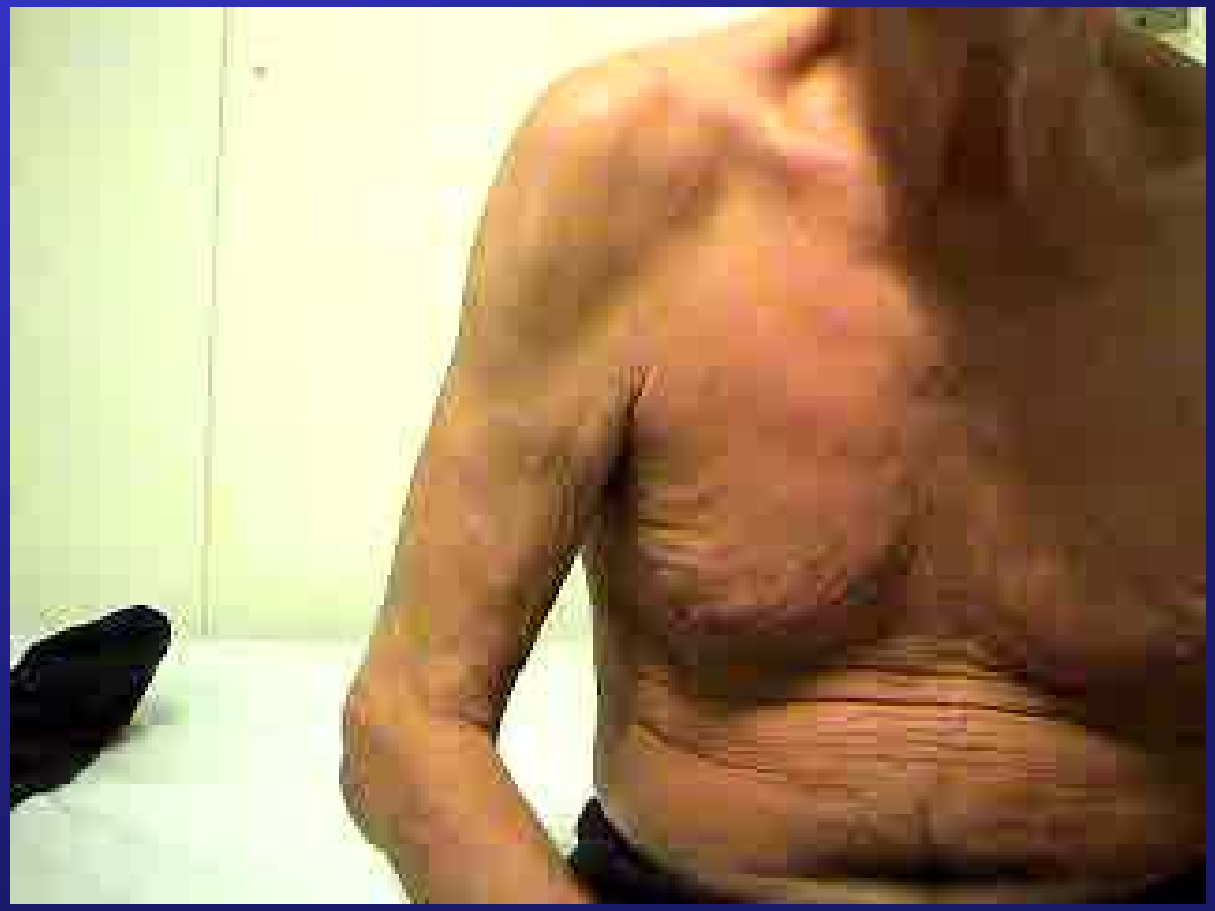
Lower motor neurones (LMN): **excitatory**

- all about strength and bulk
- loss causes weakness and wasting

Upper motor neurones (UMN): **inhibitory**

- all about controlling motor nerve activity
- loss causes spasticity and hyper-reflexia

Fasciculation



What else?

Typical sparing of: - intellect*

- sensation
- bowel & bladder
- eye movement.

*Intellect: - 10-15% with FTD (behavioural)

- further 35% with subtle cognitive changes: emotional blunting, irrational decision making etc

Patterns

- 80% spinal or limb onset
- 20% bulbar onset

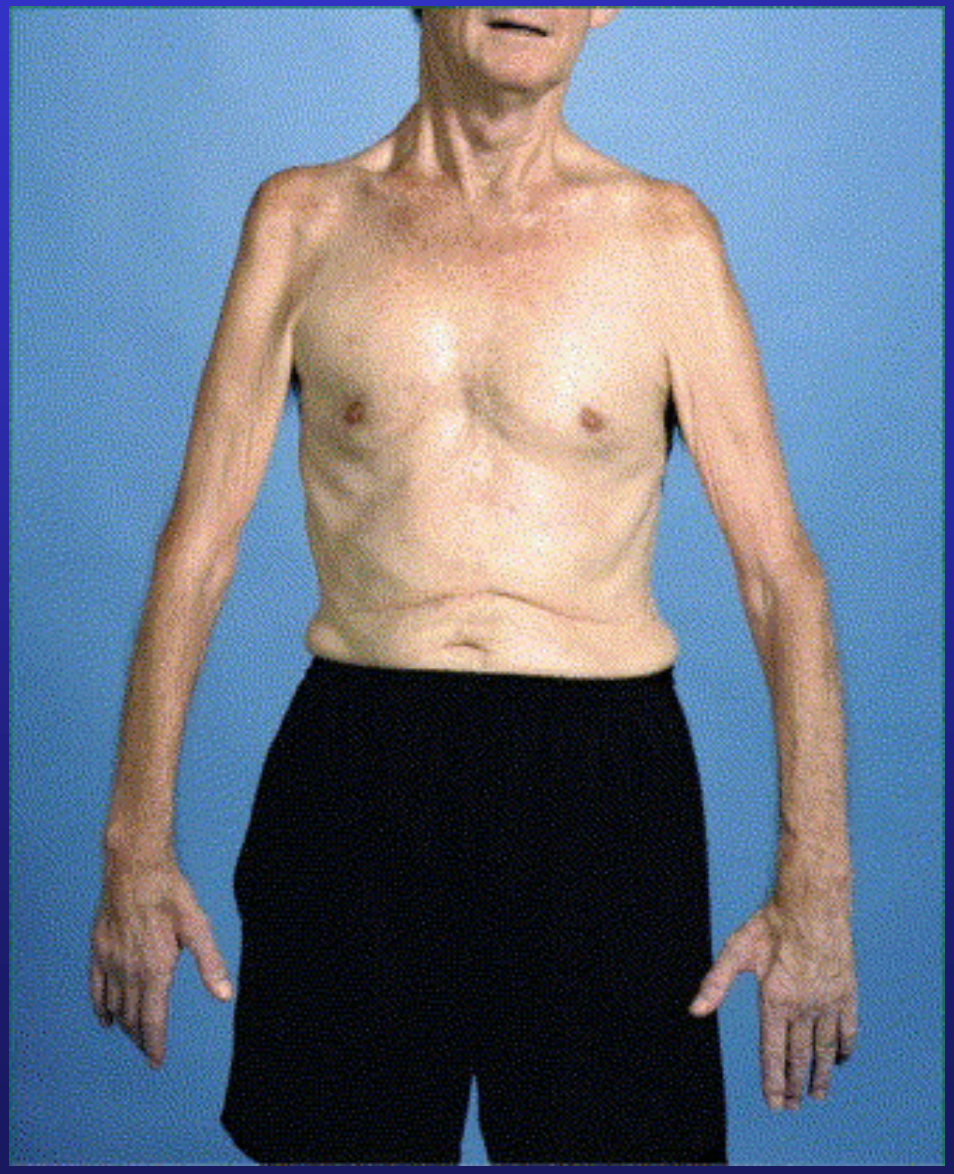
Patterns

- 80% spinal or limb onset

Any muscle any where

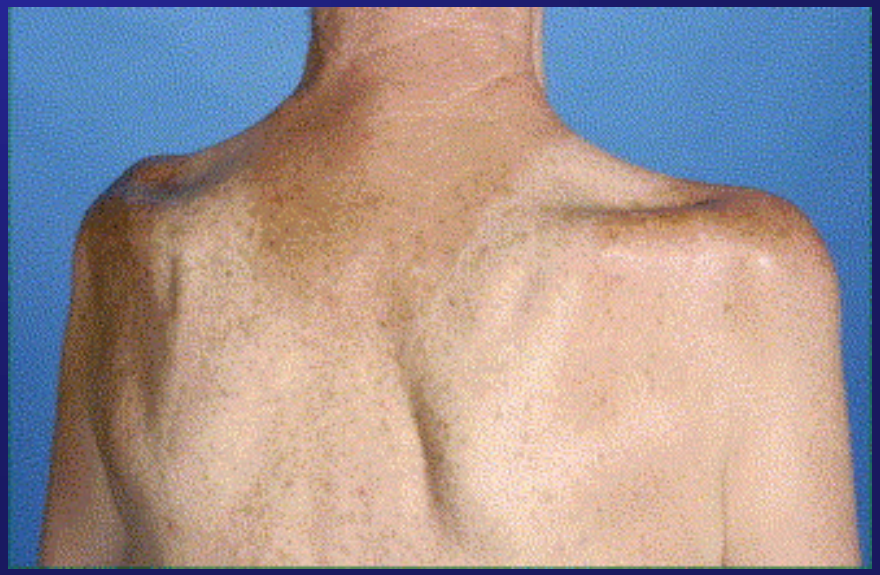
1. ALS – overall 75% of cases (typical MND)
2. Pure LMN syndromes: “flail” arms or legs
3. Pure UMN syndromes: very slow
4. Respiratory failure

The flail-arm variant



Av. survival 5yrs

M:F ratio 6:1 (1.7:1)



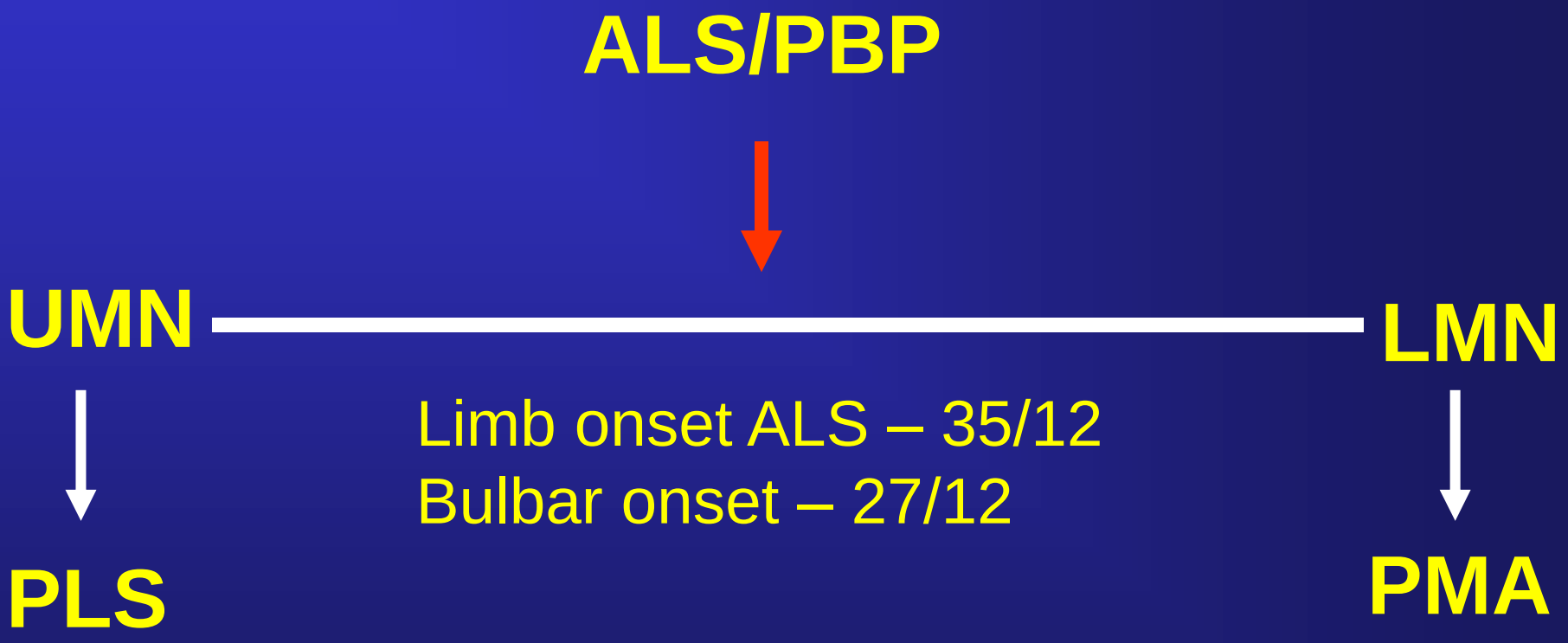
Patterns

- 20% bulbar onset

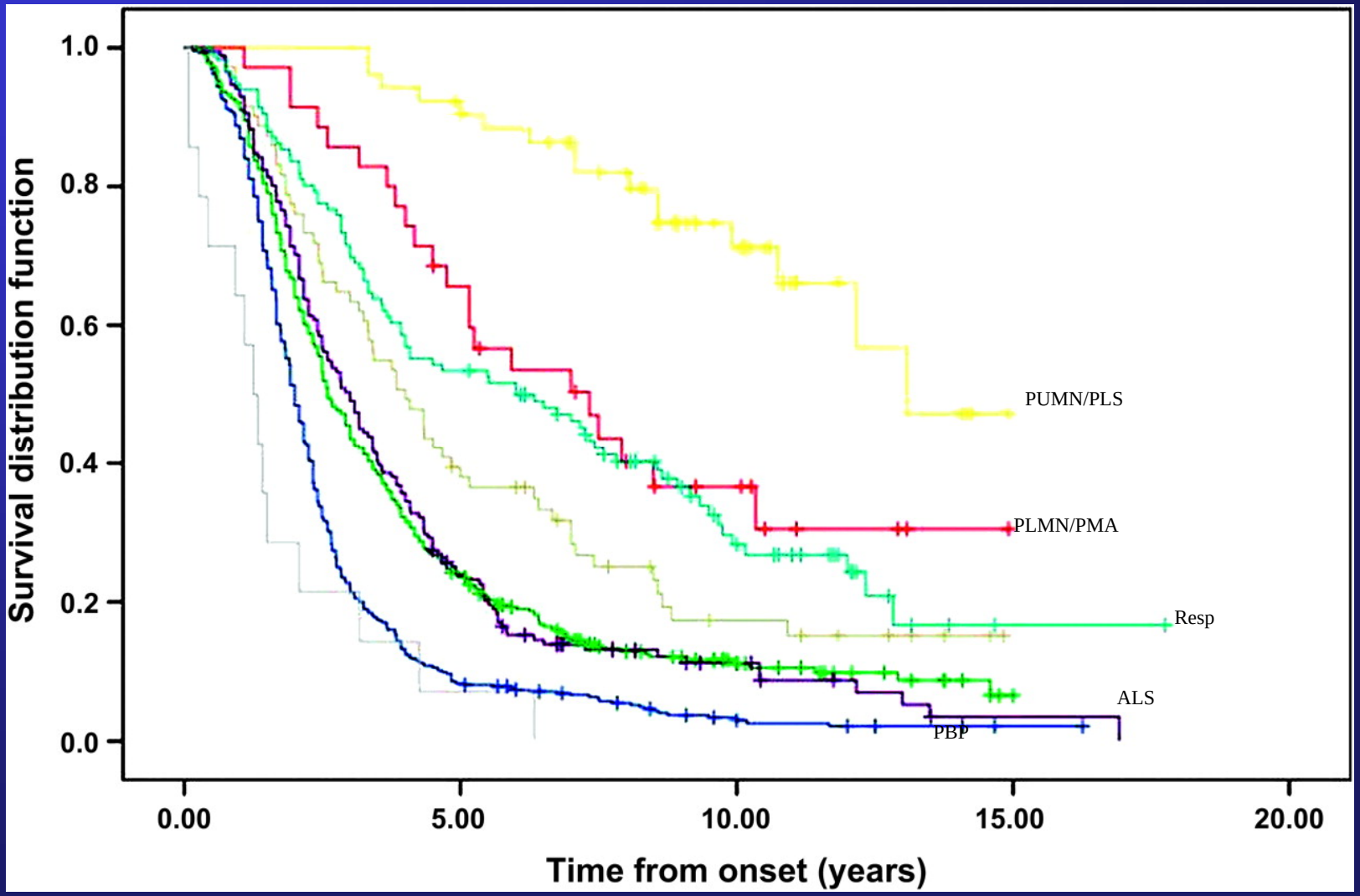
1. Bulbar onset MND – patients do badly
2. Pure progressive bulbar palsy: F>M, typically in late 70's or 80's

   Often more prolonged survival with focal "isolated" disease.

MND: a phenotypic disorder



MND Phenotype

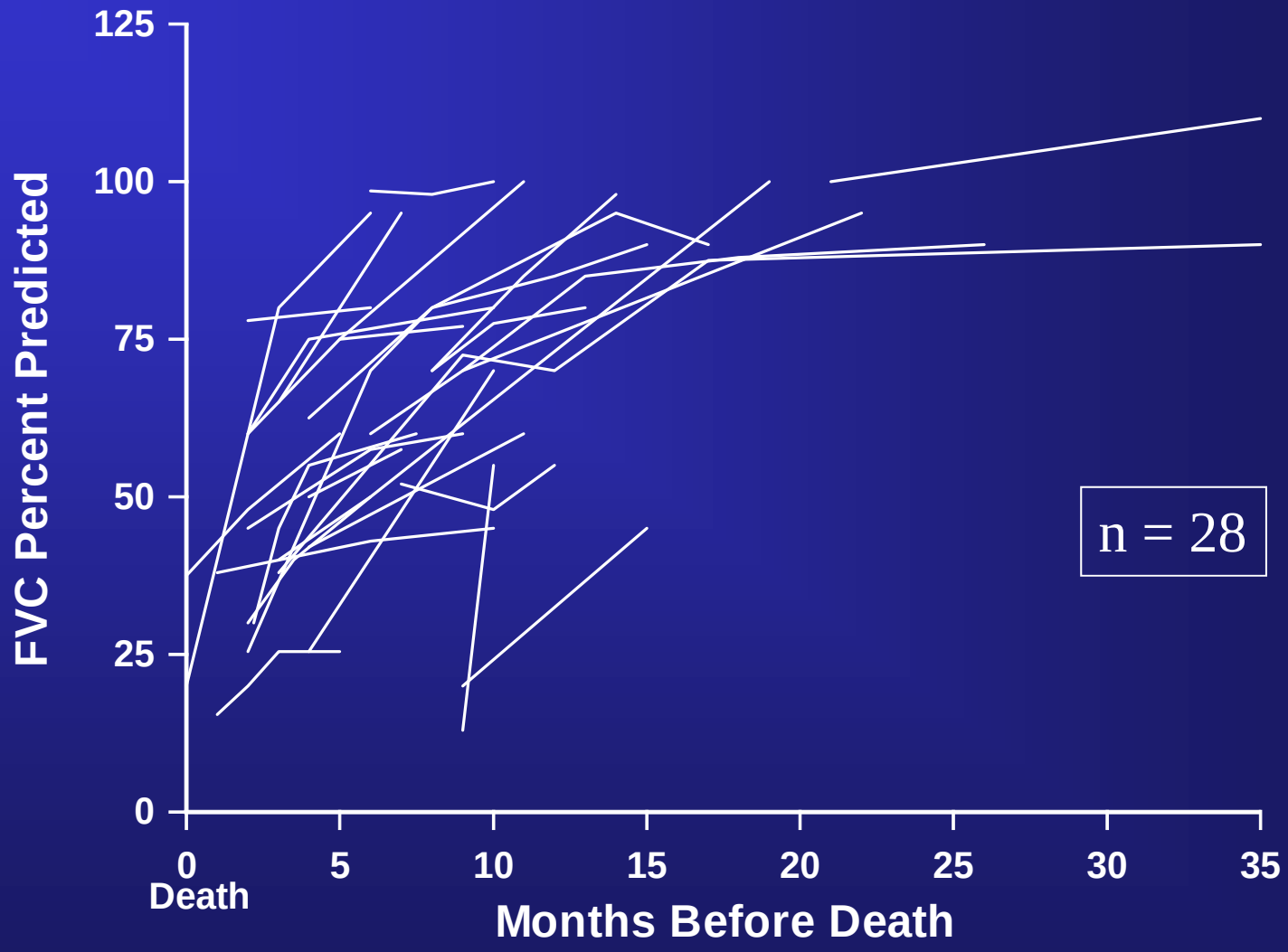


Chiò *et al*. JNNP 2011

What predicts prognosis?

1. Respiratory function

FVC and Survival

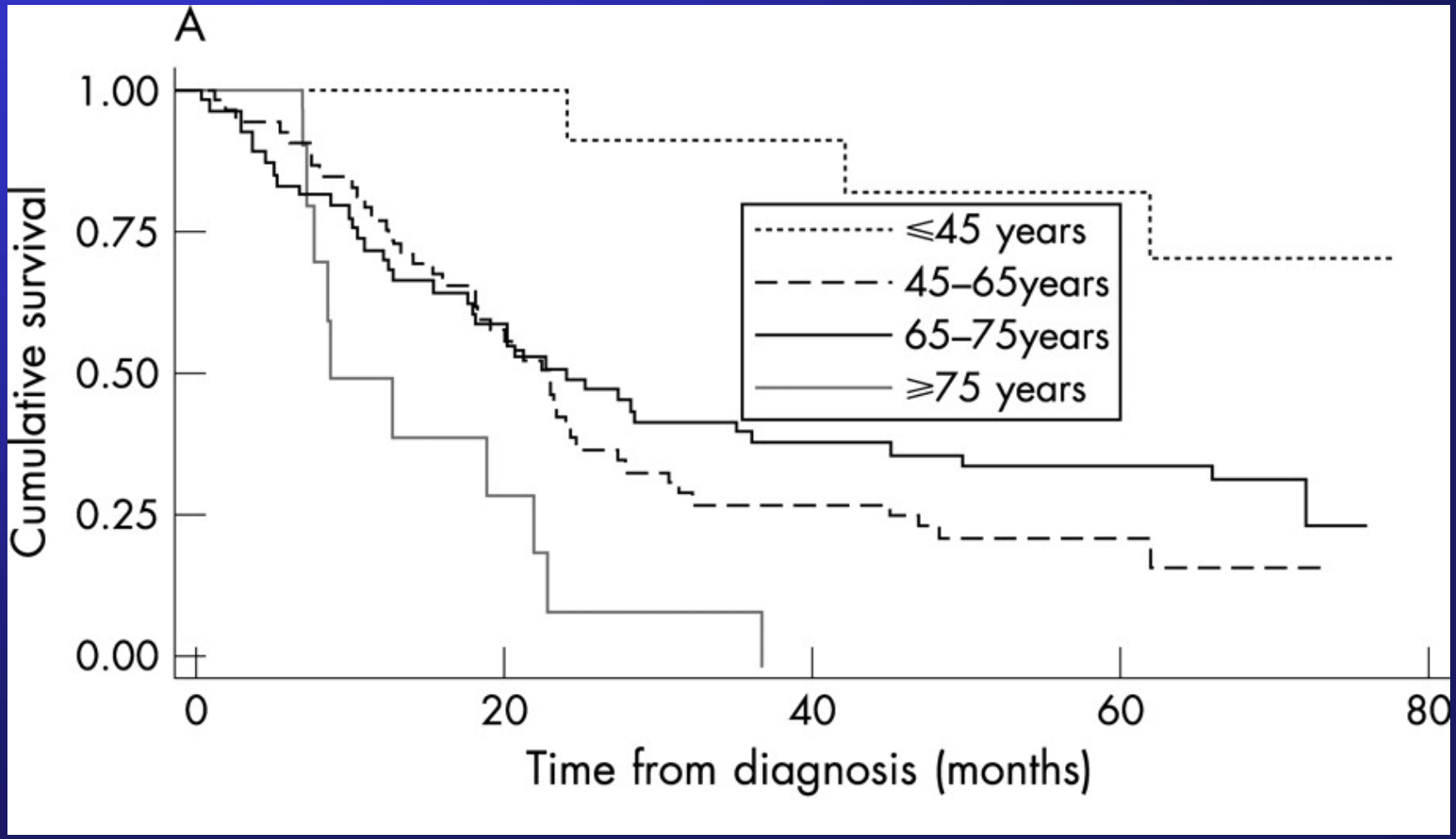


Fallat, Arch Neurol, 1979

What predicts prognosis?

1. Respiratory function
2. Age

Age

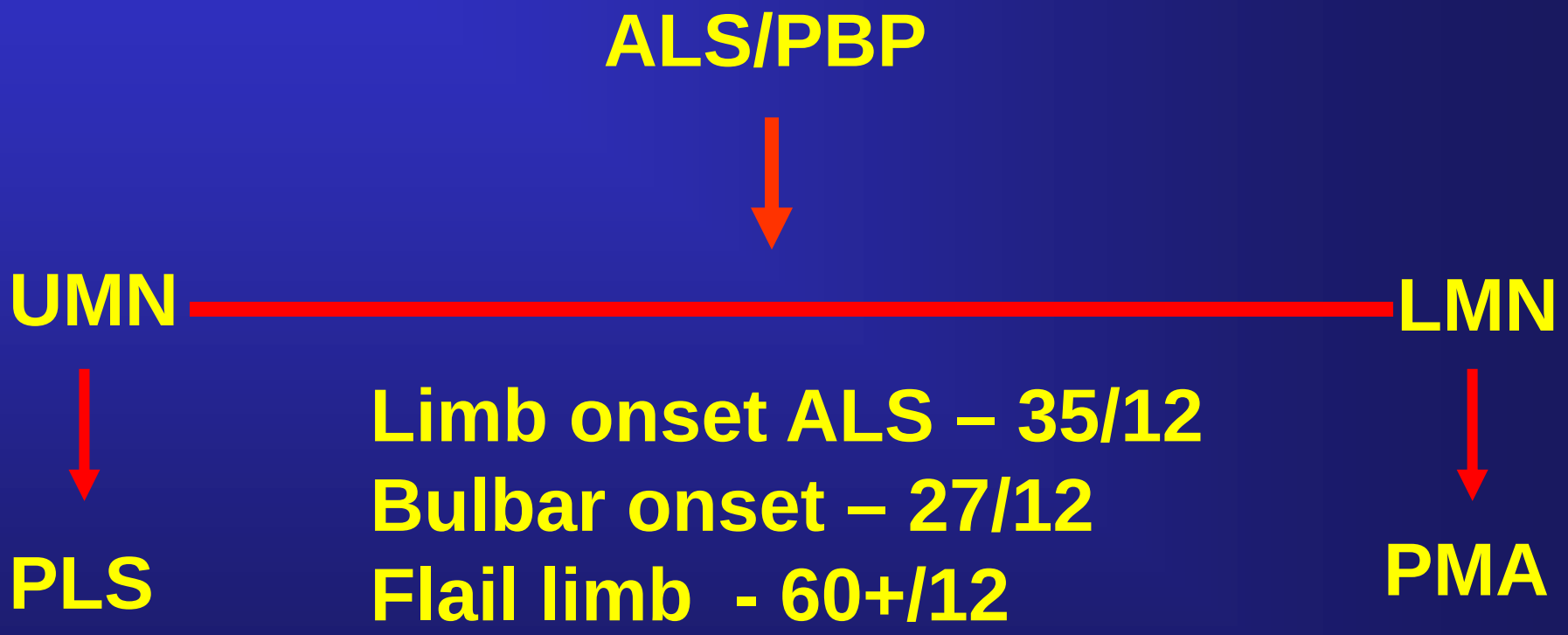


Zoccolella S et al. J Neurol Neurosurg Psychiatry 2008;79:33-37

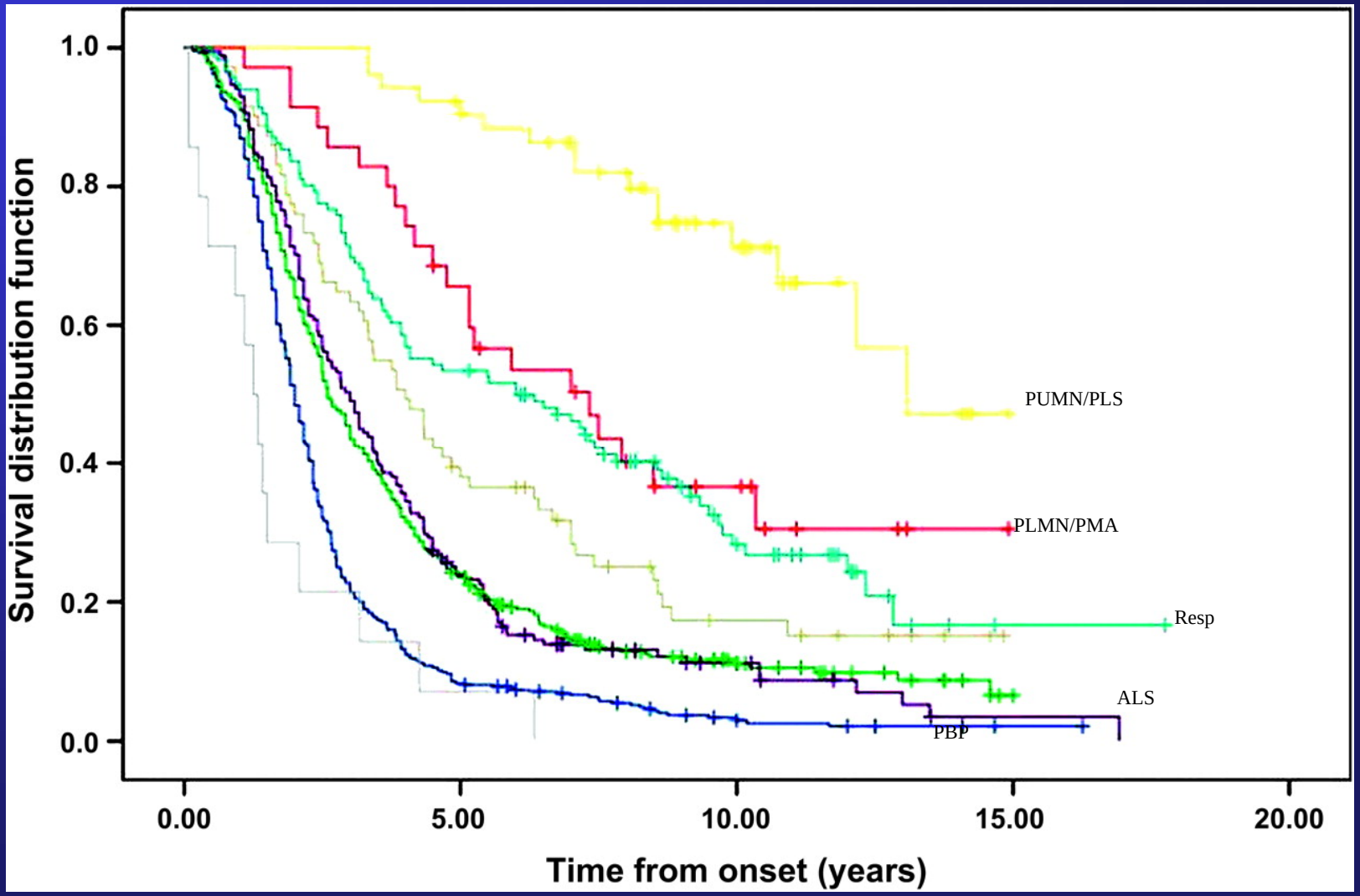
What predicts prognosis?

1. Respiratory function
2. Age
3. Disease phenotype – PBP,

Disease phenotype dictates prognosis



MND Phenotype



Chiò *et al*. JNNP 2011

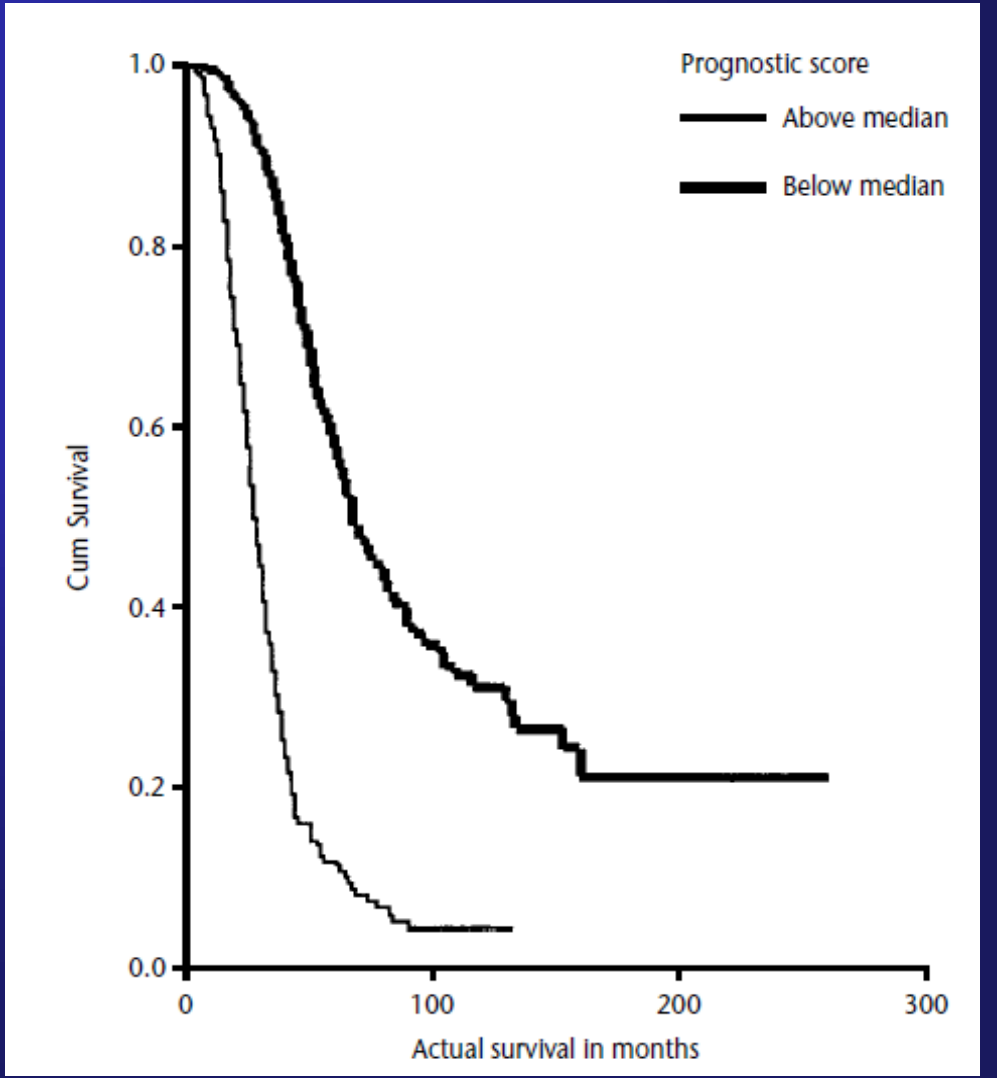
What predicts prognosis?

1. Respiratory function
2. Age
3. Disease phenotype – PBP,
4. Delay to diagnosis – worse if short

Time to Diagnosis

Thick black >6 months

Thin black <6 months

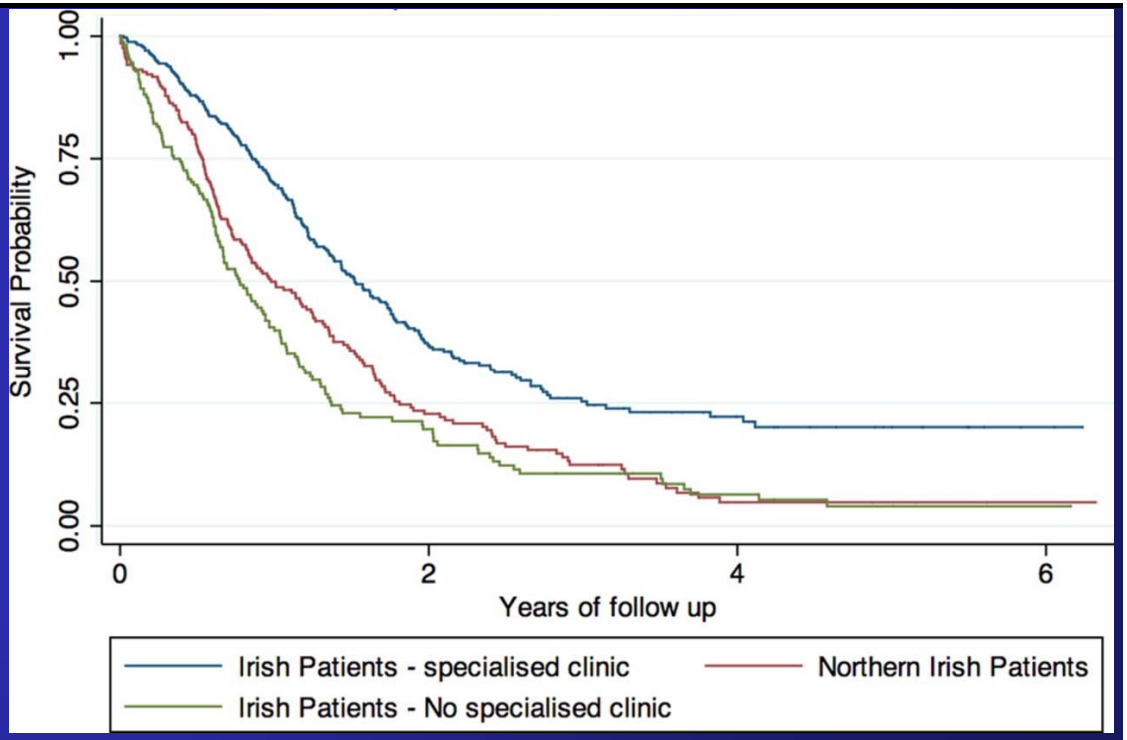


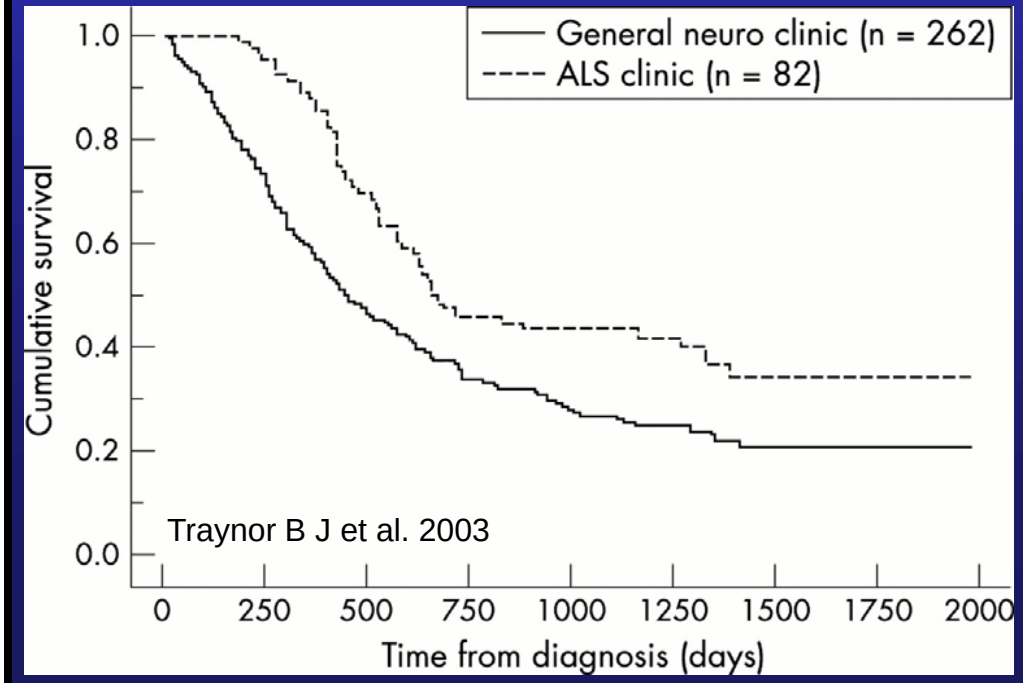
Turner *et al* 2002, ALS & FTD

What predicts prognosis?

1. Respiratory function
2. Age
3. Disease phenotype – PBP,
4. Delay to diagnosis – worse if short
5. Multidisciplinary MND Clinic

MND MDT clinic





Prognosis

- Average survival:
  30-36 months from symptom onset.
  18-24 months from diagnosis, av. diagnostic delay 12 months).
- 50% dead at 30 months
- 10-20% live ≥ 5yrs
- 5-10% live ≥ 10yrs
- V. occasional patients live 20 yrs (or more)