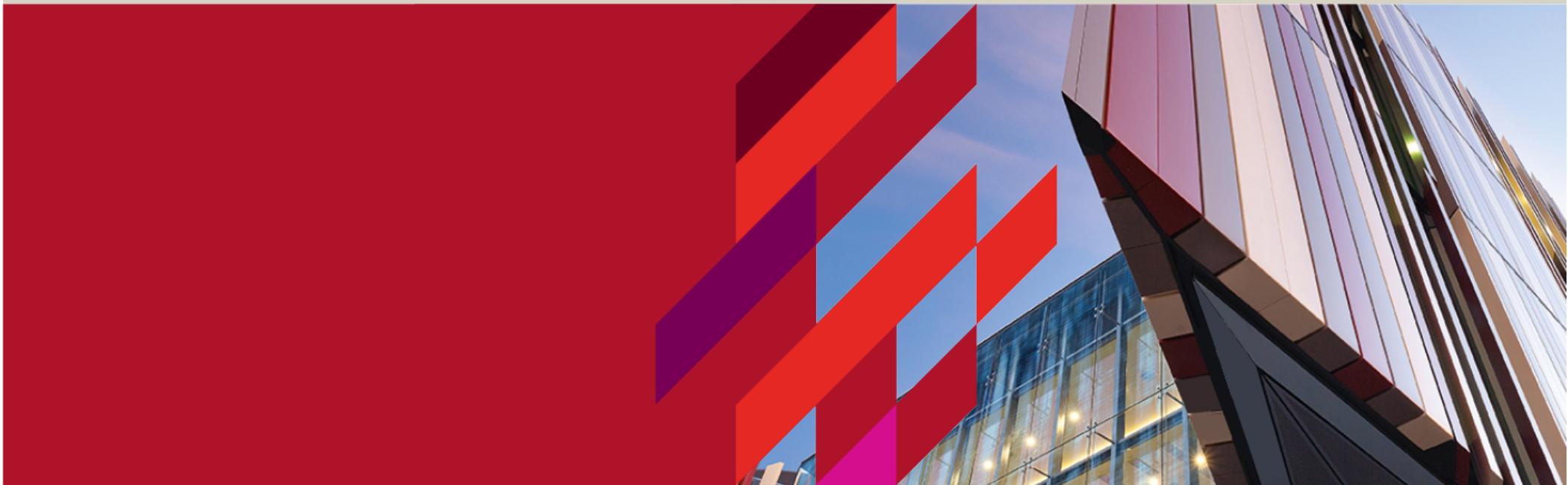




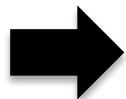
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# Introduction to motor neuron disease (MND) and MND biology/genetics

Ian Blair (Macquarie University Centre for Motor Neuron Disease Research)



# Motor neuron disease (MND)



**Death** 0.5 - 5 years  
(typically 2-3 years)

**Paralysis**

**Dementia**

Affects 1 in 5000  
over 50 years

Clinical presentation

Symptom management



Diagnostic tools

Prognosis



Treatment

# MND, also known as ALS. ALS ice-bucket challenge



[https://www.youtube.com/watch?v=jr9f1pfib\\_8](https://www.youtube.com/watch?v=jr9f1pfib_8)



**Macquarie University  
Centre for Motor Neuron  
Disease Research**



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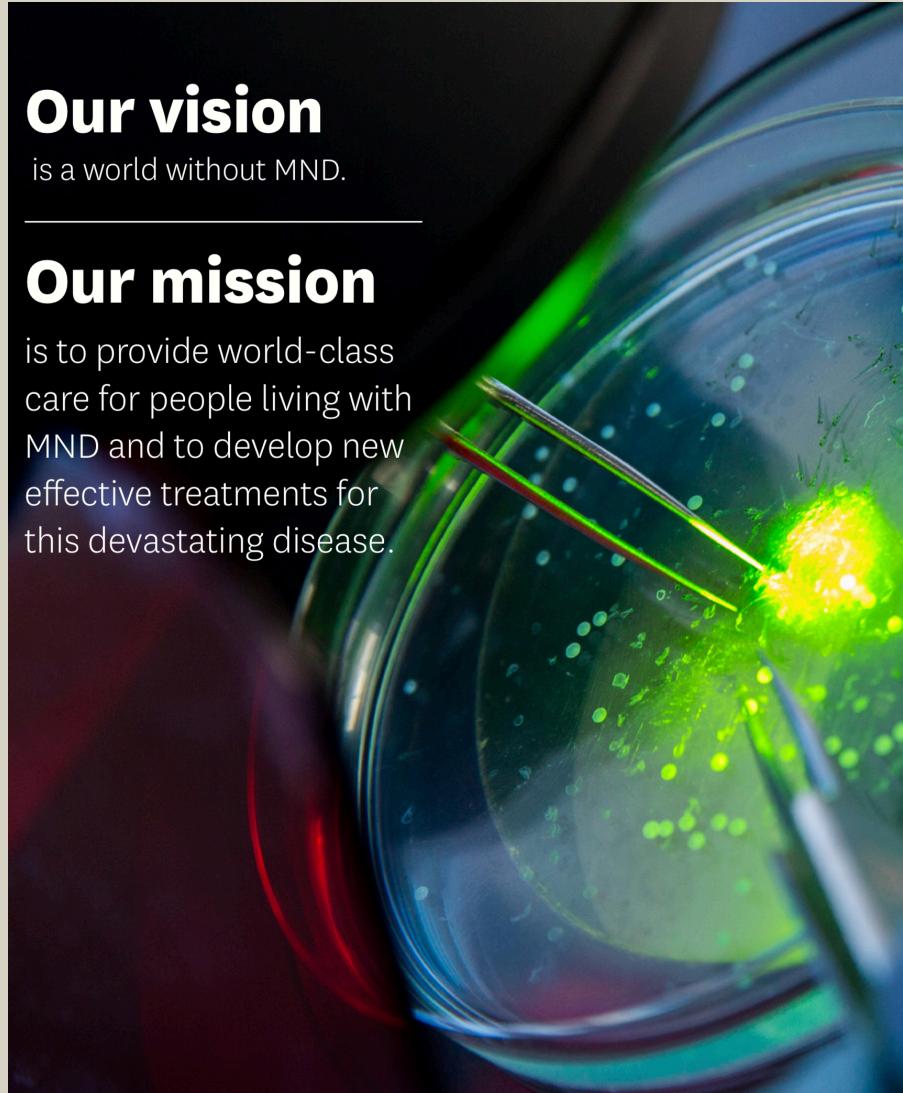
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## Our vision

is a world without MND.

## Our mission

is to provide world-class care for people living with MND and to develop new effective treatments for this devastating disease.



# Centre for Motor Neuron Disease Research

## Our research teams

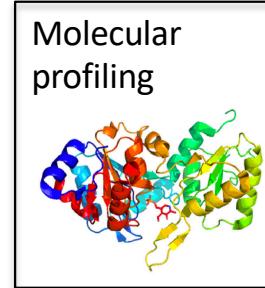
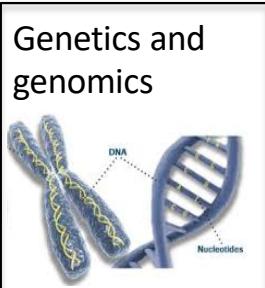
*'Success would look like us being able to slow and stop this disease that's robbing families of fathers, mothers, wives and husbands, sons and daughters ... If we can stop some deaths, that's success.'*

- Professor Dominic Rowe



*Collaboration  
is key*

# Macquarie University Centre for Motor Neuron Disease Research



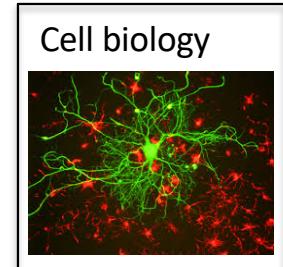
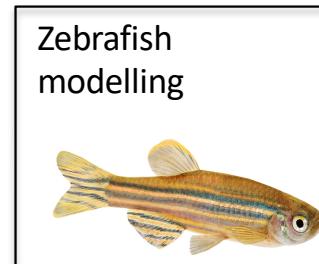
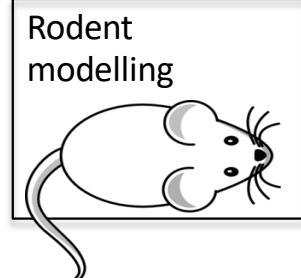
- Clinical genetics
- Clinical trials
- Genetic counselling
- Biobanking



neuroimaging  
post-translational-modification  
preclinical-testing  
stem-cells  
genomics  
sporadic  
clinical-trials  
proteomics  
phosphorylation  
familial  
big-data  
epigenetics

neurodegeneration  
environment  
cell-biology  
drug-discovery  
genetic-counselling  
biochemistry  
neurology  
neuropathology  
development  
transcriptomics  
protein-chemistry  
metabolomics  
genetics  
animal-models

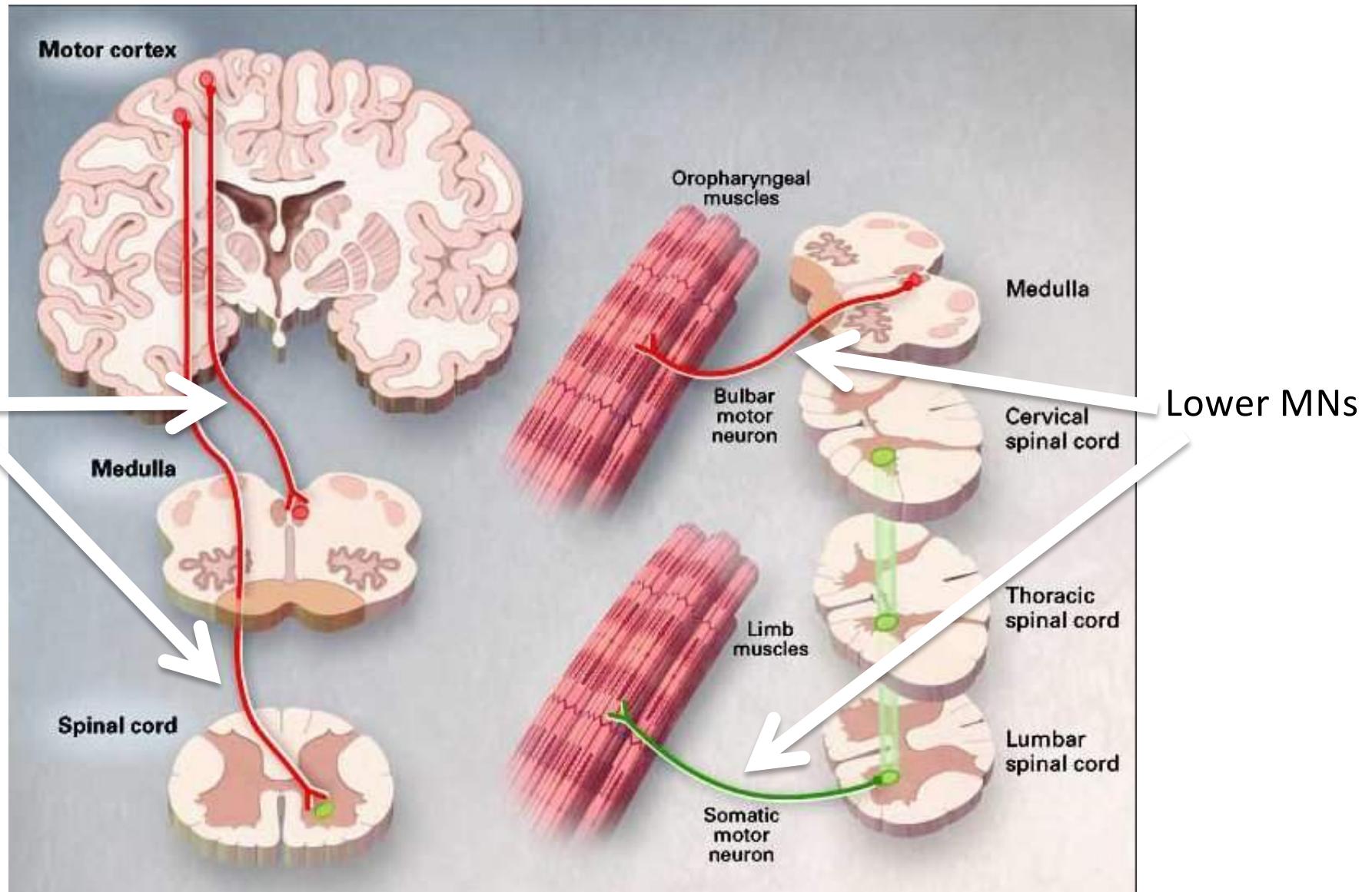
## Systems-Biology



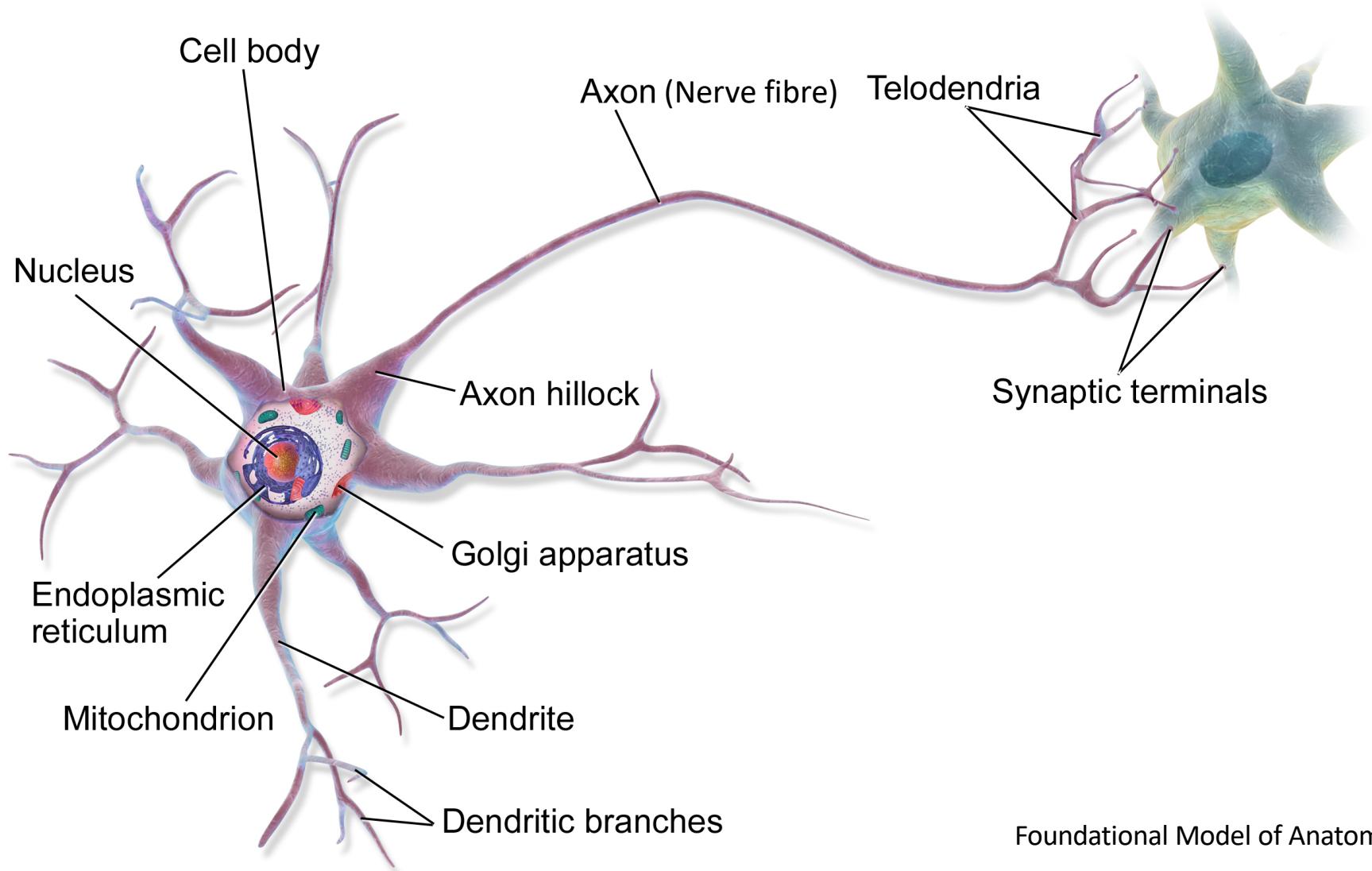
## Motor neurons

Upper MNs

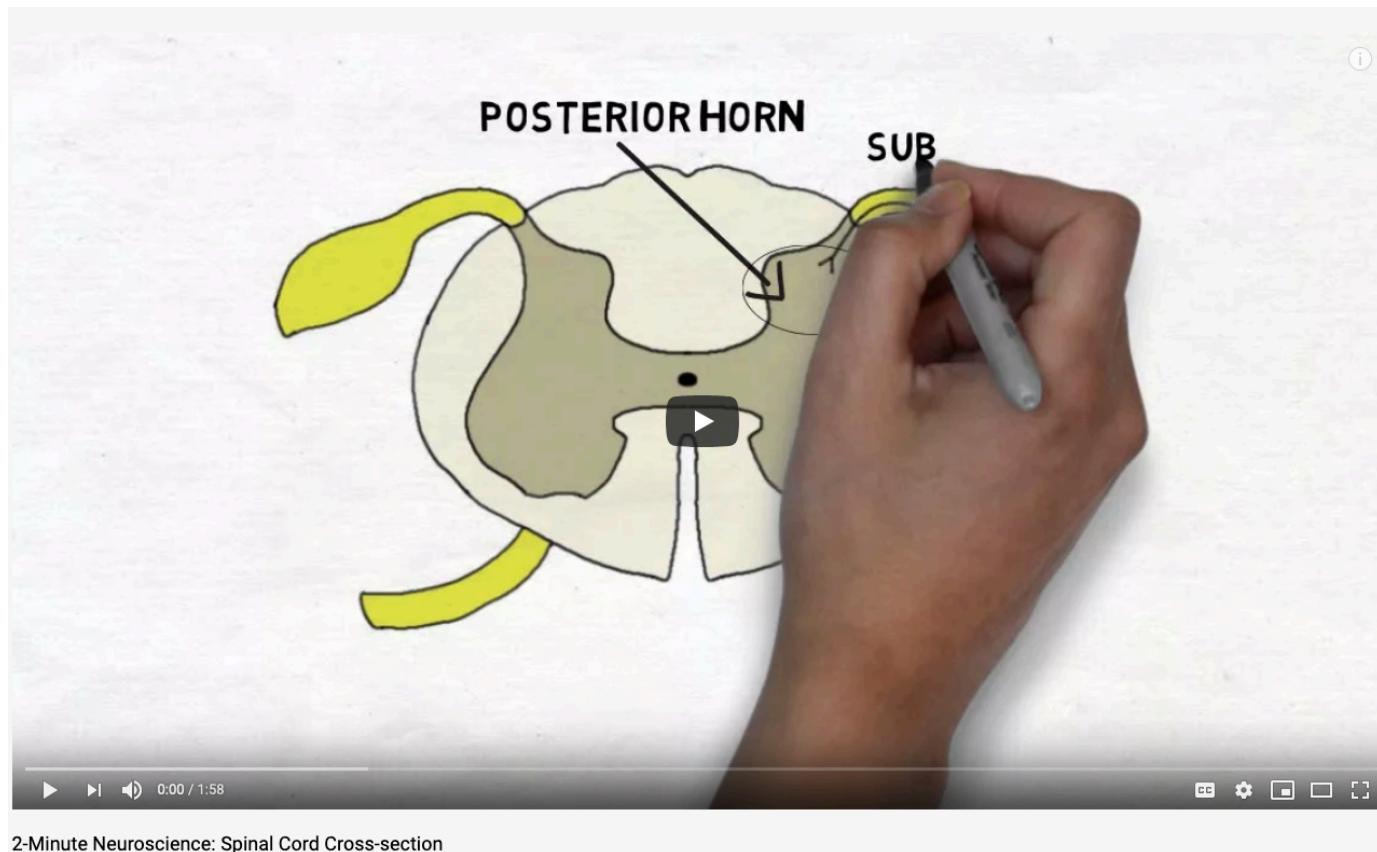
Lower MNs



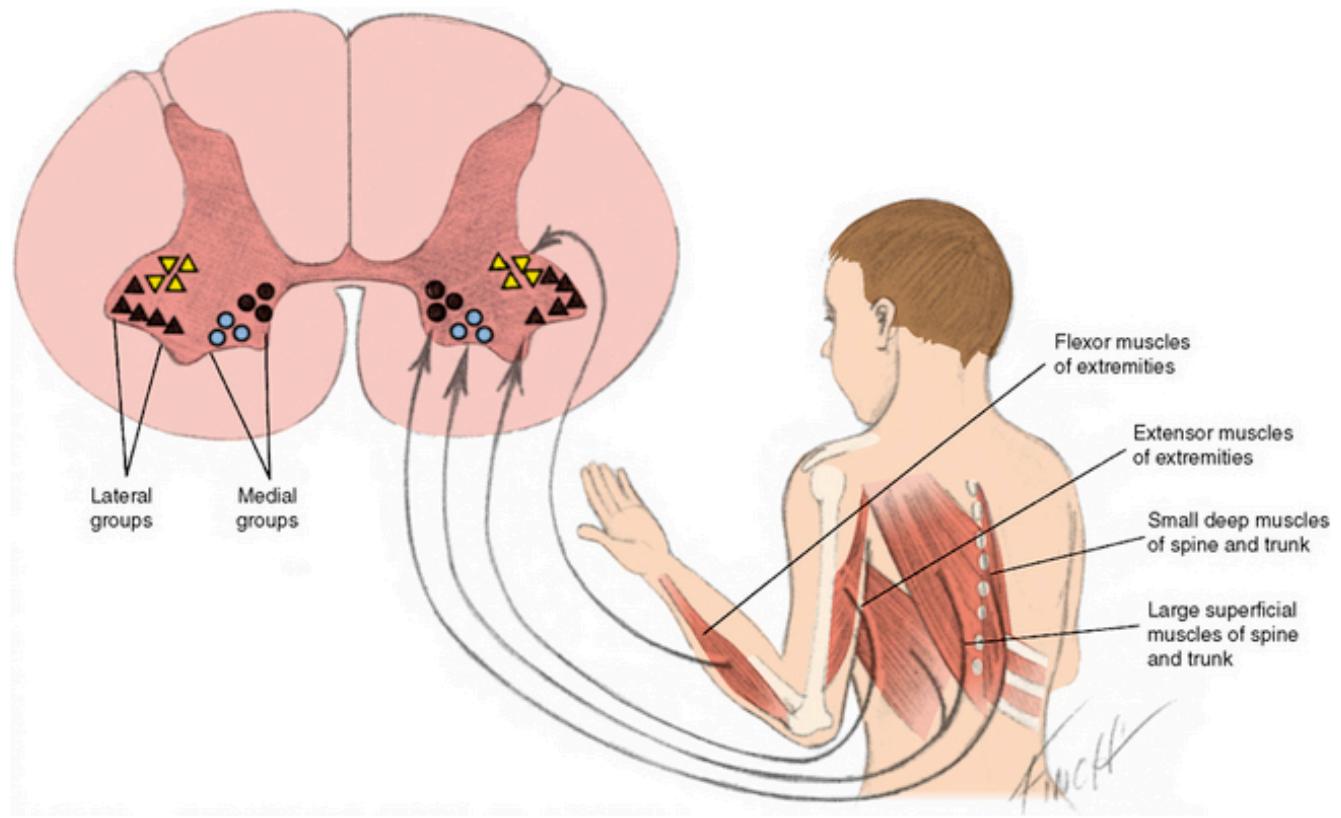
## Basic structure of a motor neuron



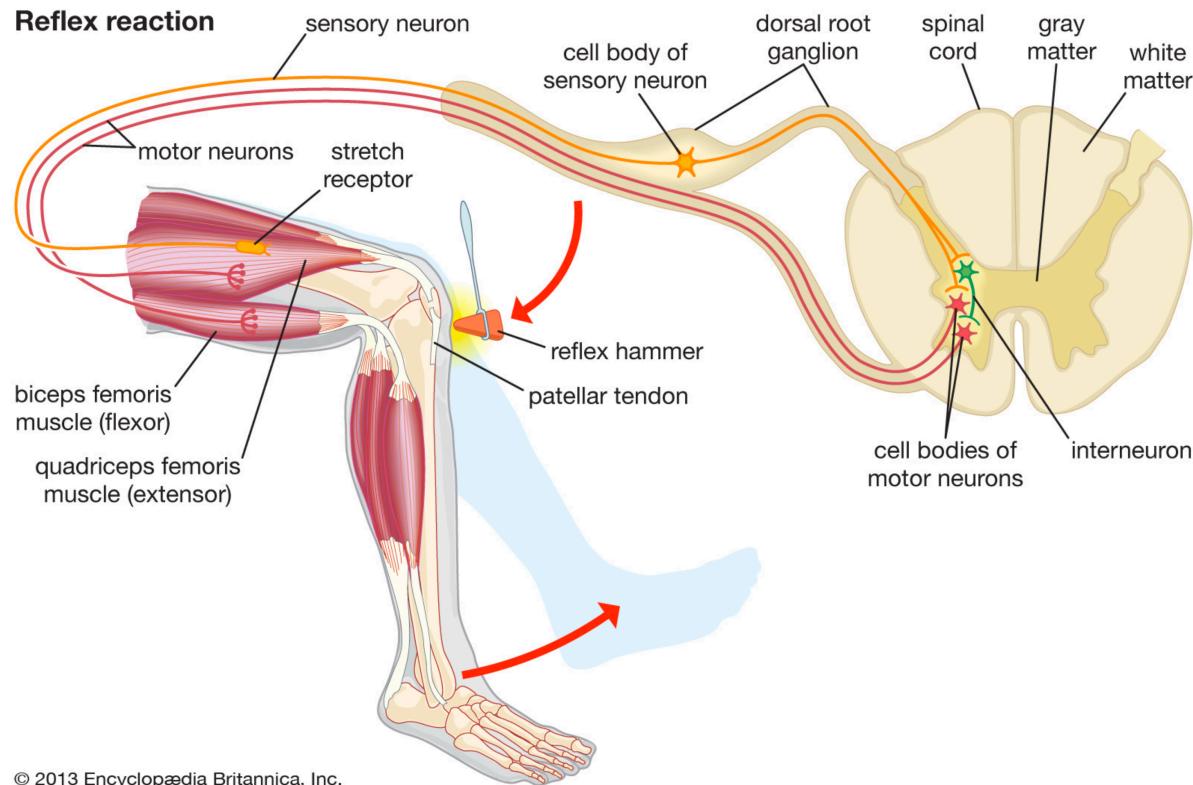
[https://www.youtube.com/watch?v=fbt3H3JxRMA&feature=emb\\_logo](https://www.youtube.com/watch?v=fbt3H3JxRMA&feature=emb_logo)



## Motor neurons



# Motor neurons



**Neurodegenerative diseases** occur when nerve cells in the brain and/or peripheral nervous system lose function over time and ultimately die.

For example

- Motor neuron disease (MND)
- Alzheimer's disease (AD) and other dementias
- Parkinson's disease (PD) and PD-related disorders
- Prion disease
- Huntington's disease (HD)
- Spinocerebellar ataxia (SCA)
- Spinal muscular atrophy (SMA)

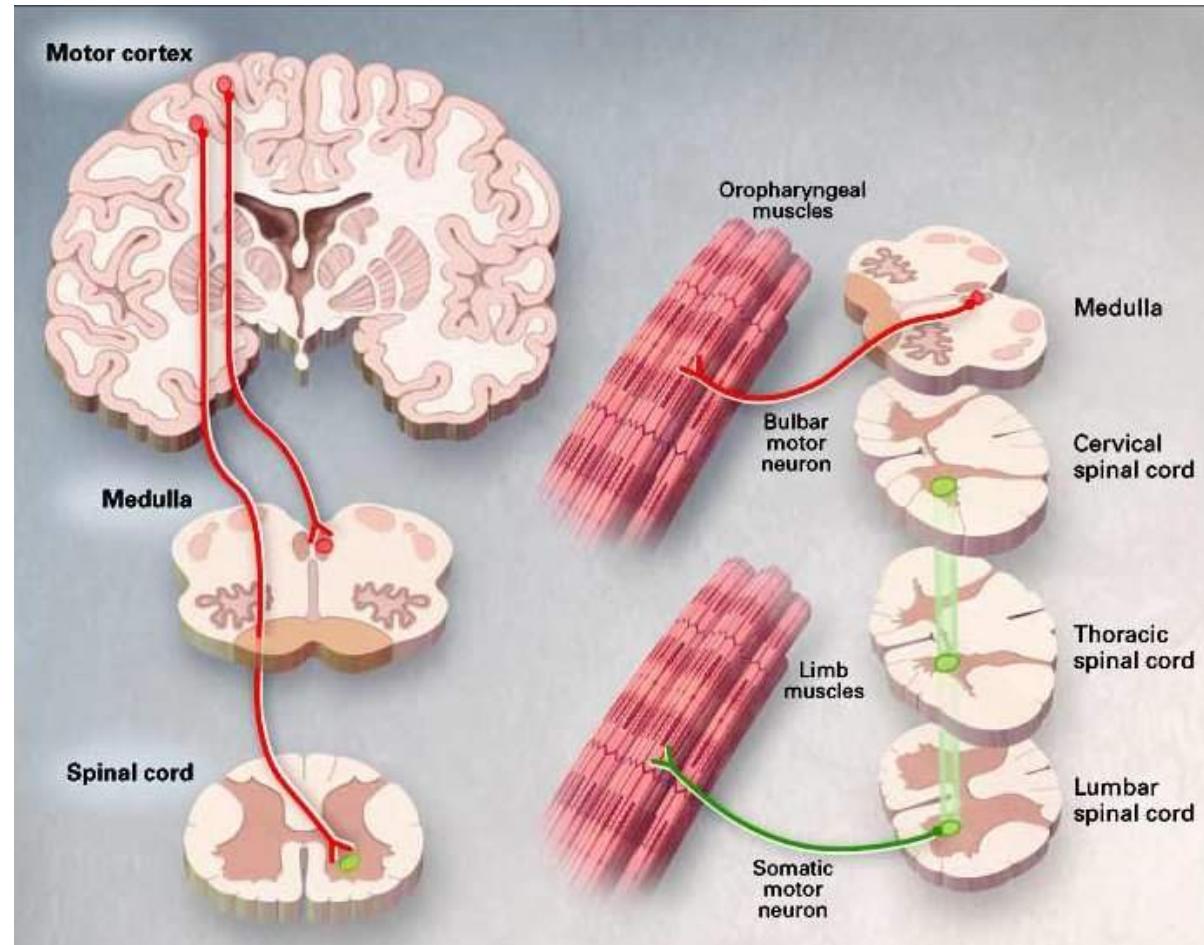
Contrast with a congenital disorder, which is a condition present at birth.

## Motor neuron disease

MND is the most common degenerative disease of the motor neuron system.

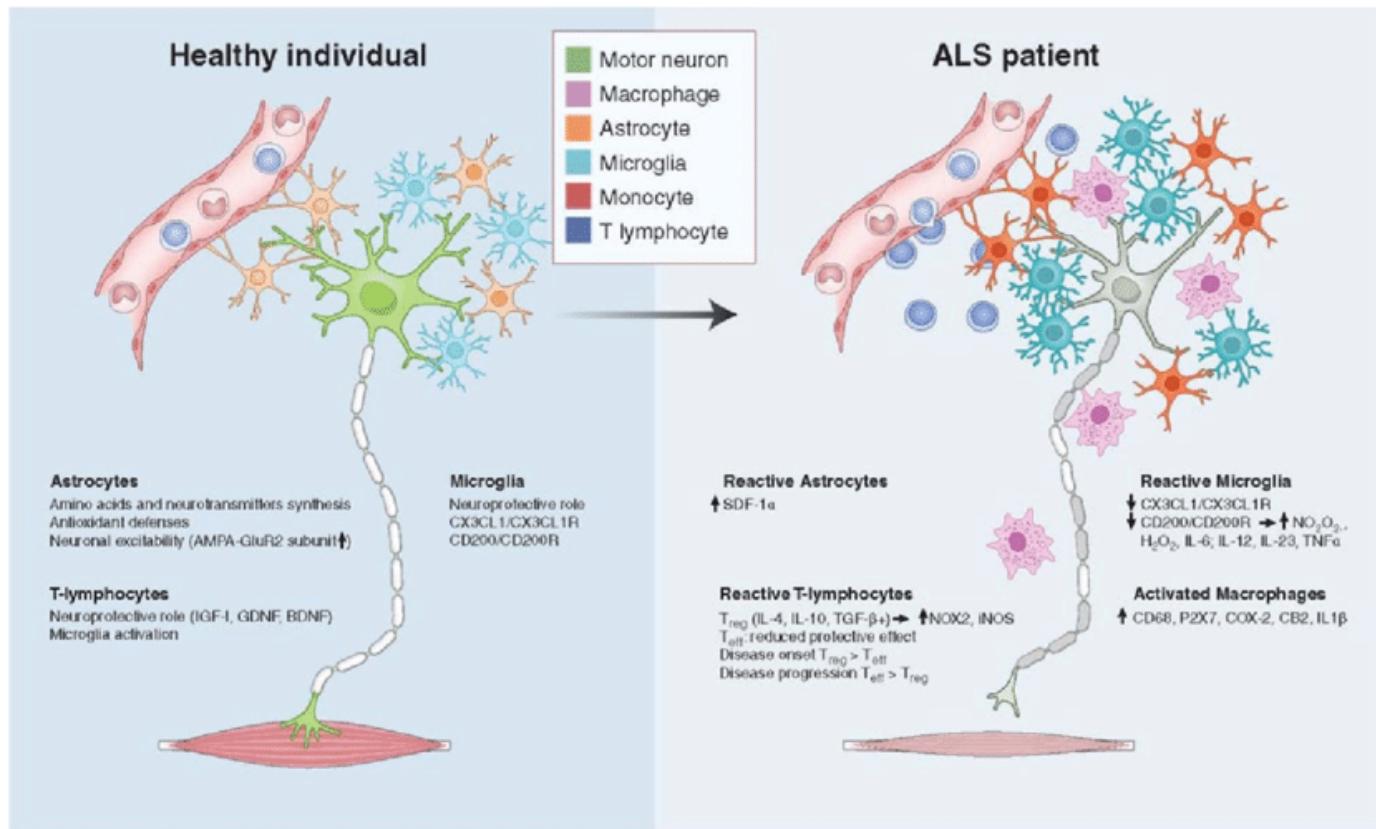
A **neurodegenerative disease** caused by the **progressive** death of both upper motor neurons (located in the motor cortex of the brain) and lower motor neurons (located in the brainstem and spinal cord)

Progressive paralysis (whole body)  
Death is typically from respiratory failure



## Progression of MND involves more than just motor neuron loss

Neuronal health is dependent on a range of other cell types collectively known as glia, which surround motor neurons and provide nutritional and trophic support



Glial activation and neuroinflammation

## Presentation of MND

### Symptoms (at presentation)

- painless weakness in one extremity that extends to the other extremities
- fasciculations (muscle twitch)
- impaired speech or swallowing
- reduced head control
- breathing difficulty
- muscle cramping
- sensory remains normal

### Physical exam

- neck ptosis (neck drop) due to neck extensor weakness
- manual muscle testing elicits muscle cramping

### upper motor neuron (UMN) signs

- spasticity
- hyperreflexia
- spastic dysarthria

### lower motor neuron (LMN) signs

- muscular atrophy
- weakness
- fasciculations
- clumsiness

## Evaluation of MND

### Diagnosis

- dependent on demonstration of both UMN and LMN involvement
- combination of UMN and LMN in the same extremity, in the absence of pain or sensory symptoms, and cranial nerve findings is highly indicative of ALS

### Laboratory diagnosis

- With the exception of familial MND, there are currently no laboratory tests that confirm the diagnosis

### Nerve Conduction Studies and Electromyography (NCS/EMG, measure electrical activity of muscles).

- shows denervation + reinnervation
- slowed motor conduction velocity
- abnormal spontaneous fibrillation & fasciculation potentials
- normal sensory studies

## Treatment of MND

### Currently no cure or effective treatment

- goals of treatment
- provide supportive care
- prevent progression
- maintain independent patient function and comfort

### Current treatments

delay onset of ventilator-dependence and may prolong survival

#### Riluzole

- modest benefits only
- prolongs life by 2-3 months
- Mechanism - blocks sodium channels associated with damaged neurons

#### Edaravone

- modest benefits to a small % of cases only
- Mechanism - antioxidant properties, protects neurons by mopping up free radicals

## Question

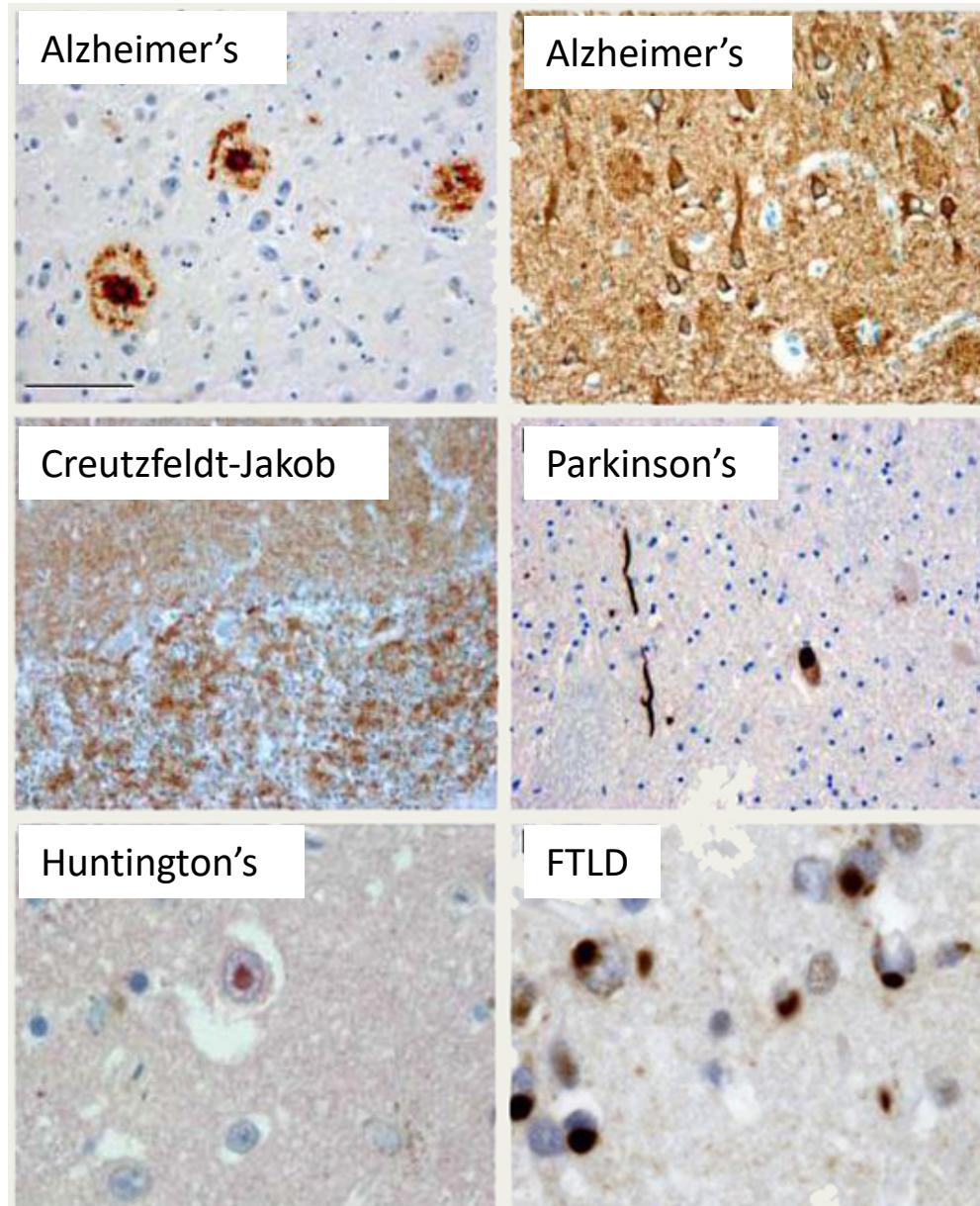
Which of the following investigative studies is **most useful** in the definitive diagnosis of MND?

- A. Genetic testing
- B. MRI brain and spinal cord
- C. Muscle biopsy
- D. Serum protein electrophoresis and immunolectrophoresis
- E. Electrodiagnostic studies

## Question - Answer

## Neuronal inclusions (protein aggregates) in neurodegenerative diseases

### Post mortem studies

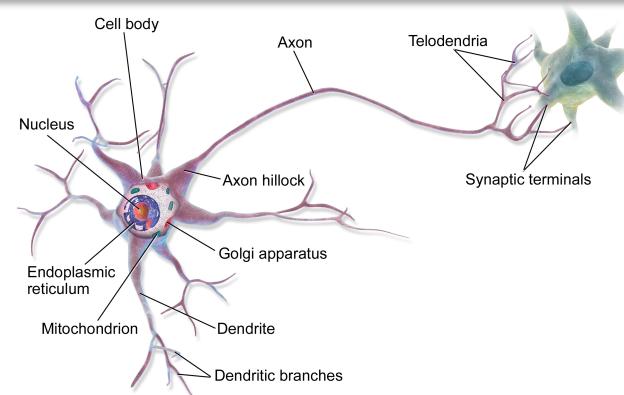
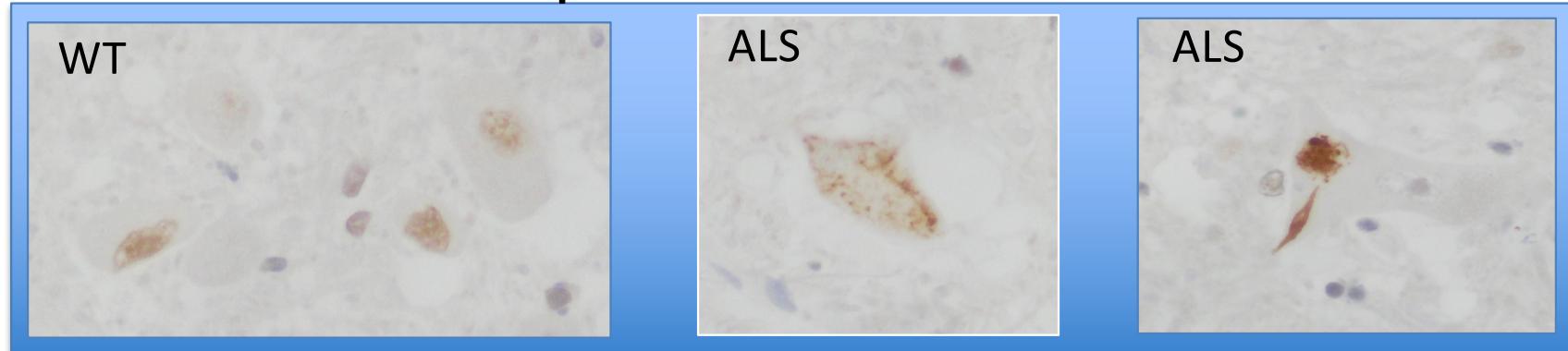


## MND neuronal pathology – post mortem studies

**Ubiquitinated TDP-43 positive inclusions (protein aggregates) in the motor neurons of most MND patients** Neumann et al, *Science* 2006

TDP-43 normally localises to the nucleus, but mislocalises and aggregates in the cytoplasm of MND patient motor neurons

**Spinal motor neurons**



## Causes of MND?

### Environmental risk factors

- Exposure to heavy metals, solvents, agricultural chemicals?
- Smoking (Risk? Protective?)



Many extensive studies (longitudinal, case-control).

To-date, no association of any exogenous environmental risk factor with MND has been demonstrated consistently or convincingly. The environmental risk factors remain unknown

## Causes of MND?

Exercise? Increased risk among elite athletes?



Increased risk of dying from MND in a series of Italian professional football players. (Chiò et al 2005)

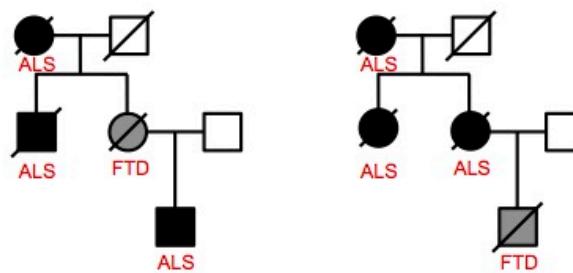
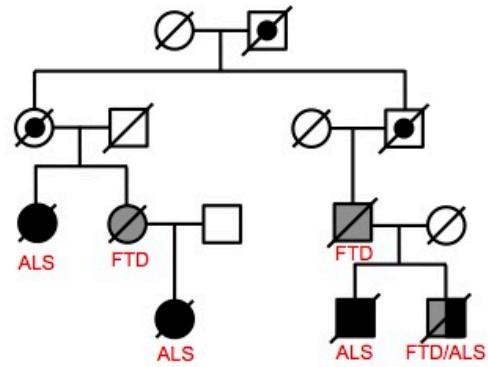


Inconsistent support from studies of other cohorts

## Causes of MND

**Only proven causes of MND are gene mutations (familial)**

### Familial MND

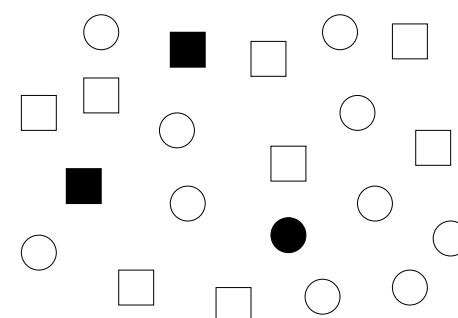


MND & FTD  
genetic overlap

### Sporadic MND

Complex genetic trait

Combination of environment & genetic risk



### Genetics

- Around 10% of patients have a familial form of the disease (familial MND/ALS)
- Remaining cases are classified as sporadic
- But...this is a false dichotomy. **Reduced penetrance** is not uncommon among those with MND gene mutations, i.e. some mutation carriers do not develop the disease and may be misclassified as sporadic

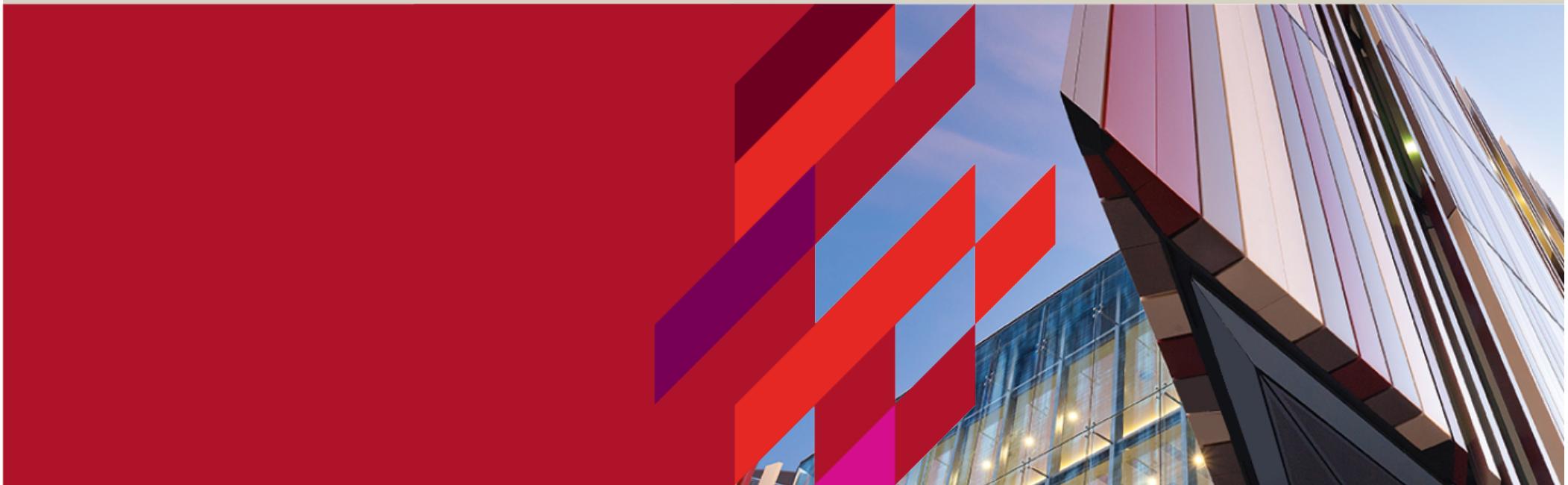
Indeed, reduced penetrance is not uncommon among other neurodegenerative diseases



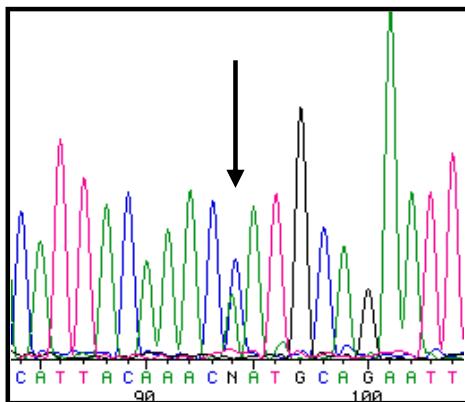
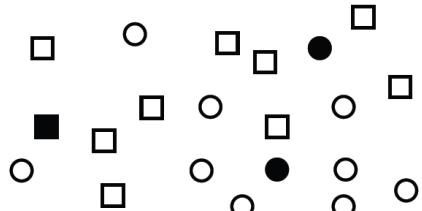
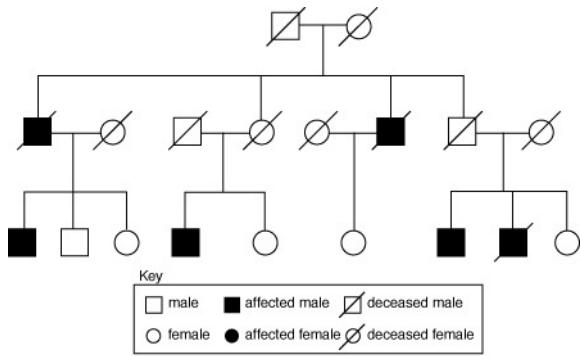
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# Genetic basis of motor neuron disease (MND)

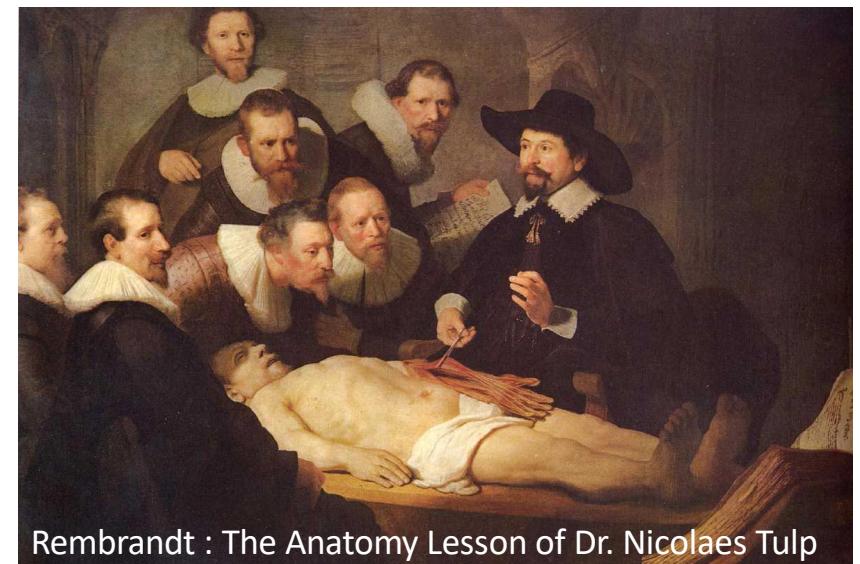
Ian Blair (Macquarie University Centre for Motor Neuron Disease Research)



## The goals of human genetic research



- Disease mechanisms
- Disease models
- Diagnostic tests
- Therapeutic discovery





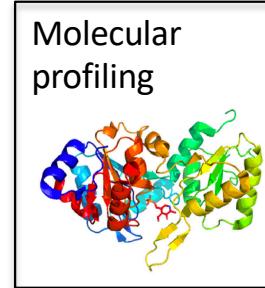
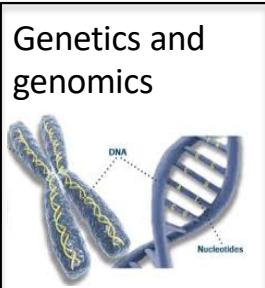
## Why study genes?

- Gene defects cause familial MND
- Genetic and environmental risk factors in sporadic MND
- Diagnosis
- Prognosis
- Identify those who will respond to treatment
- Understand disease mechanisms (biology of disease)
- Allow us to mimic the disease in the laboratory

# MND, also known as ALS. ALS ice-bucket challenge



# Macquarie University Centre for Motor Neuron Disease Research



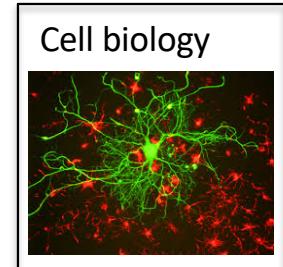
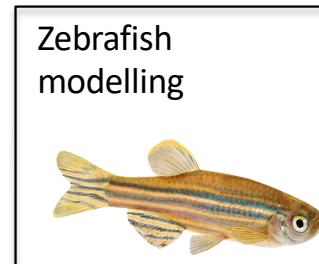
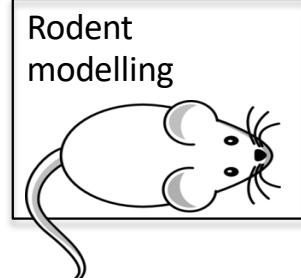
- Clinical genetics
- Clinical trials
- Genetic counselling
- Biobanking



neuroimaging  
post-translational-modification  
preclinical-testing  
stem-cells  
genomics  
sporadic  
clinical-trials  
proteomics  
phosphorylation  
familial  
big-data  
epigenetics

neurodegeneration  
environment  
cell-biology  
drug-discovery  
genetic-counselling  
biochemistry  
neurology  
neuropathology  
development  
transcriptomics  
protein-chemistry  
metabolomics  
genetics  
animal-models

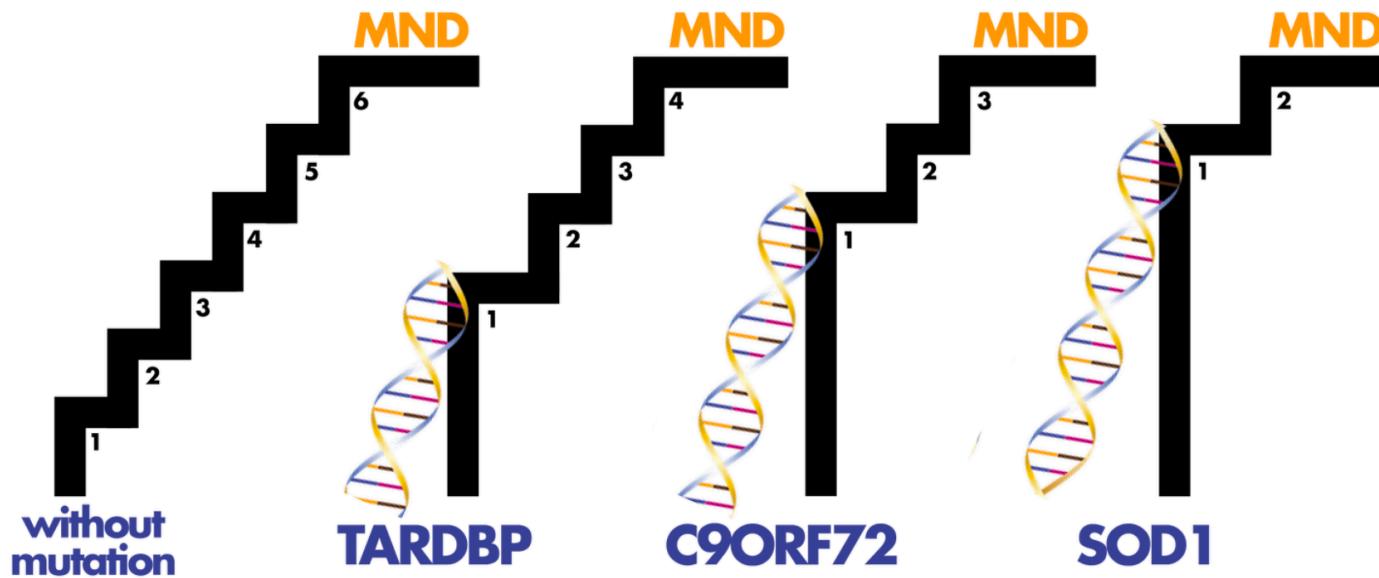
## Systems-Biology



# The search for gene mutations that cause **familial MND**

And

genetic and environmental risk factors  
that underlie **sporadic MND**



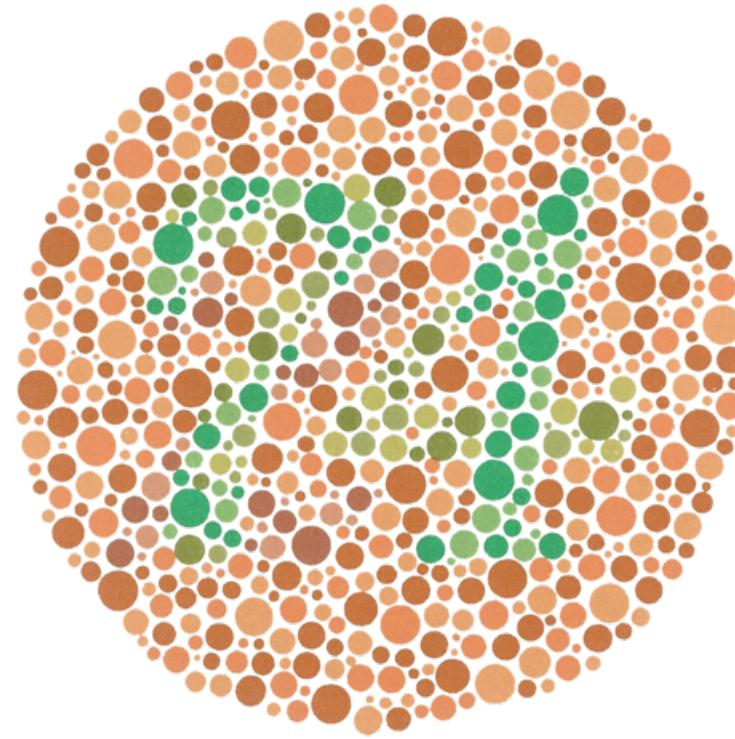
CAUSES AND DISEASE MECHANISMS / MND RESEARCH

## Steps to understanding MND

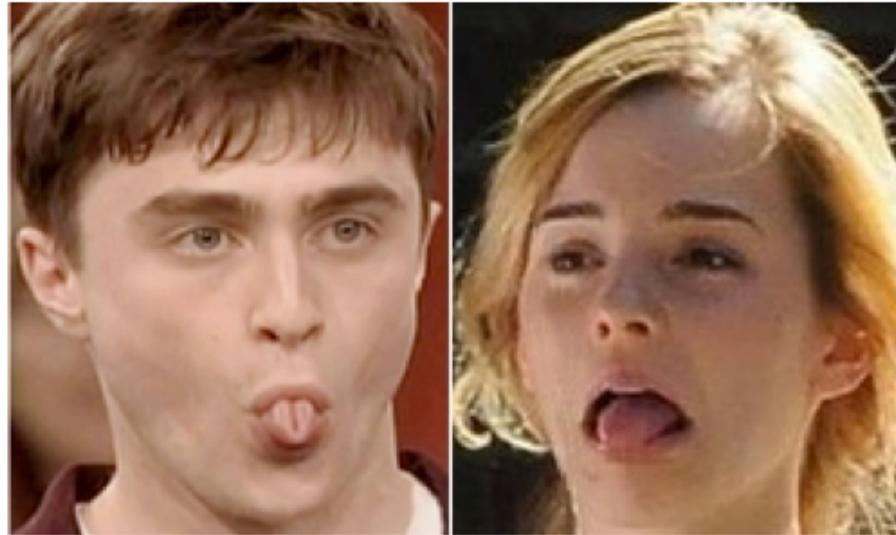
© AUGUST 3, 2018    NICKJAMESCOLE    2 COMMENTS



Al-Chalbi *et al* Lancet Neurol; 13: 1108–13, 2014  
Chio et al Neurology :e1-e8, 2018



**Single gene mutation - strong effect**



Parents	R offspring	NR offspring	Percent R
R x R	928	104	90%
R x NR	468	217	68%
NR x NR	48	92	34%

McDonald, J.H. 2011. Myths of Human Genetics. Sparky House Publishing, Baltimore, Maryland. pp. 64-66

“Risk” - Multiple gene trait that (likely) includes a gene of major effect

# Genetic and environmental risk factors



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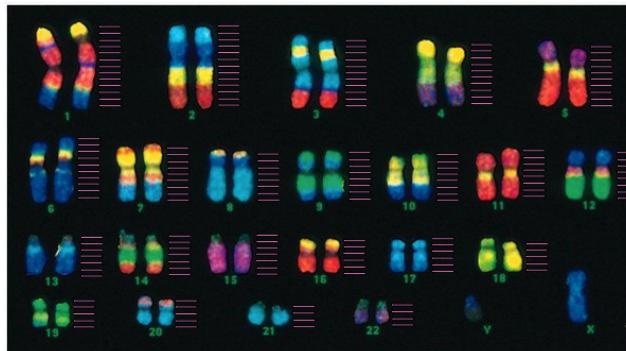
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**Smoke, drink, eat the wrong  
food and live to 100... if  
you've inherited the right  
genes**

Risk:  
Genetic and  
environmental  
(including  
lifestyle)



## Identifying MND genes - Modern genetic strategies



Chromosomes include

- Autosomes and
- Sex chromosomes

**Targeted genotyping** : Genotyping genetic variants in a specific gene(s)

- e.g. Screening for mutations in a known gene  
Single nucleotide polymorphisms (SNP).  
Copy number variants (CNV)

Genome-wide association study (GWAS) or linkage analysis

**Whole exome sequencing**: Just the protein coding sequences

Relatively cheap

**Whole genome sequencing**: Costly but getting cheaper

## Effects of dominant and recessive mutant alleles on phenotype in diploid organisms

DIPLOID GENOTYPE	= Wild type =	= Dominant =	= Dominant =	= Recessive =	= Recessive =
DIPLOID PHENOTYPE	Wild type	Mutant	Mutant	Wild type	Mutant

**Figure 6-2**  
*Molecular Cell Biology*, Eighth Edition  
© 2016 W. H. Freeman and Company

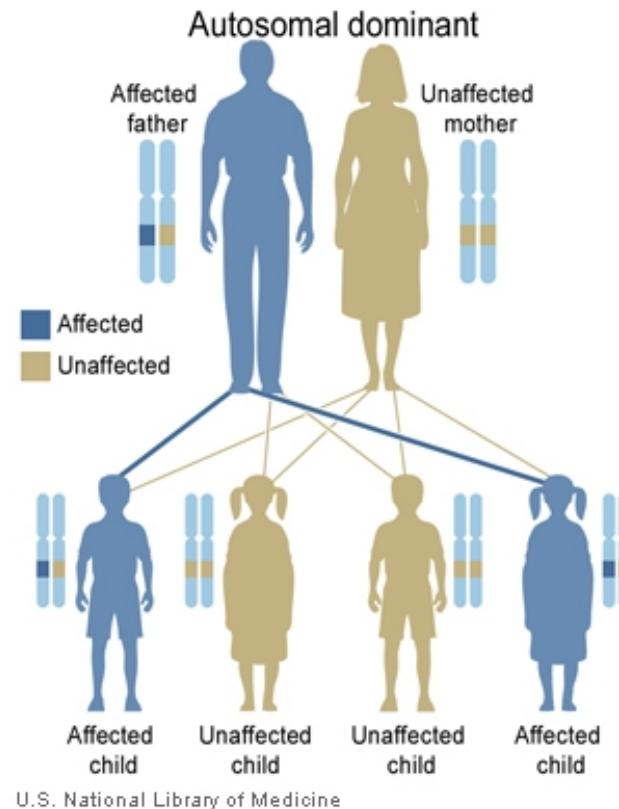
### Dominant mutation:

- Single copy of a dominant mutant allele is sufficient to produce a mutant phenotype.

### Recessive mutation:

- Both copies of a recessive mutant allele must be present to cause a mutant phenotype.

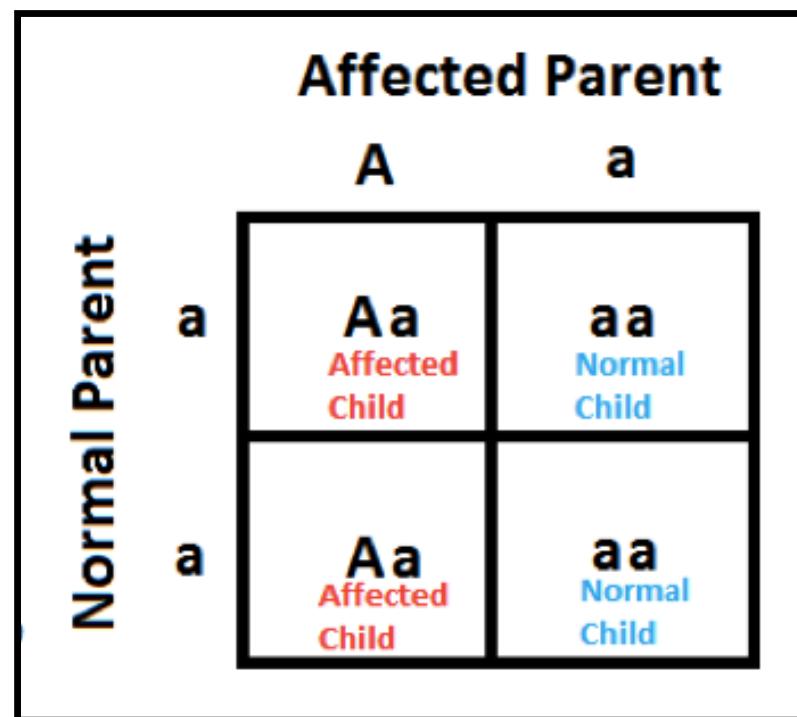
## Autosomal dominant inheritance



Most families with MND show dominant inheritance of the disease

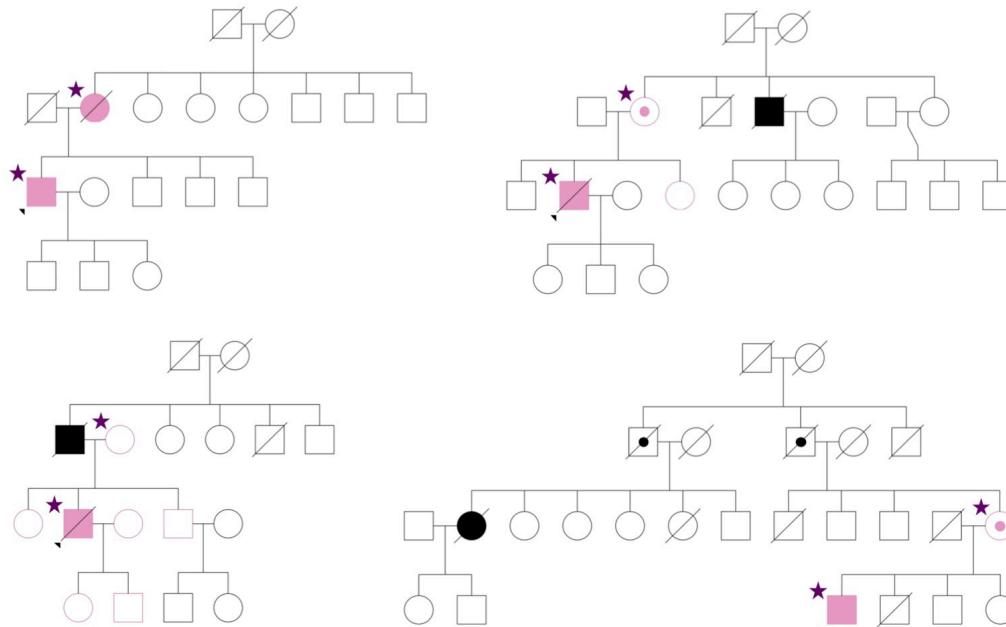
Autosomal dominant inheritance  
(Punnett square – inheritance of parental alleles)

A = mutation  
a = normal allele



## Some MND mutations show reduced penetrance

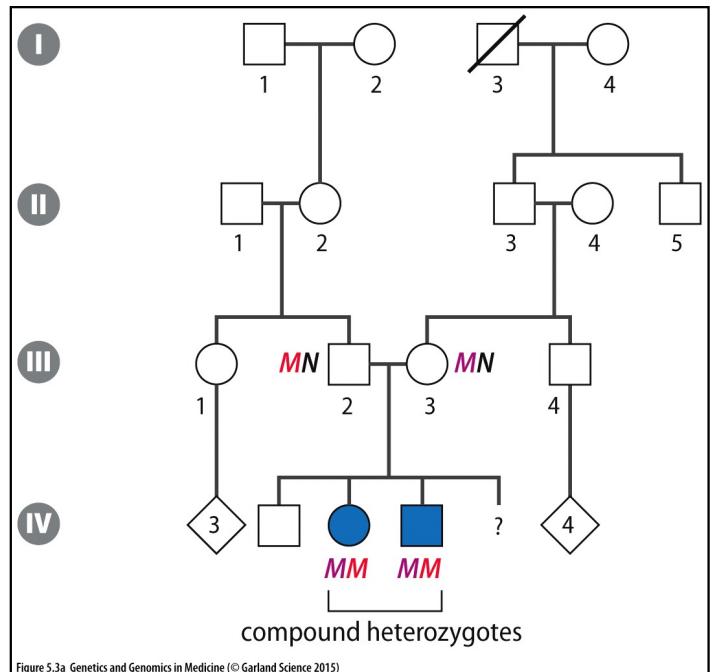
Example of pedigrees with reduced penetrance from the Australian cohort:



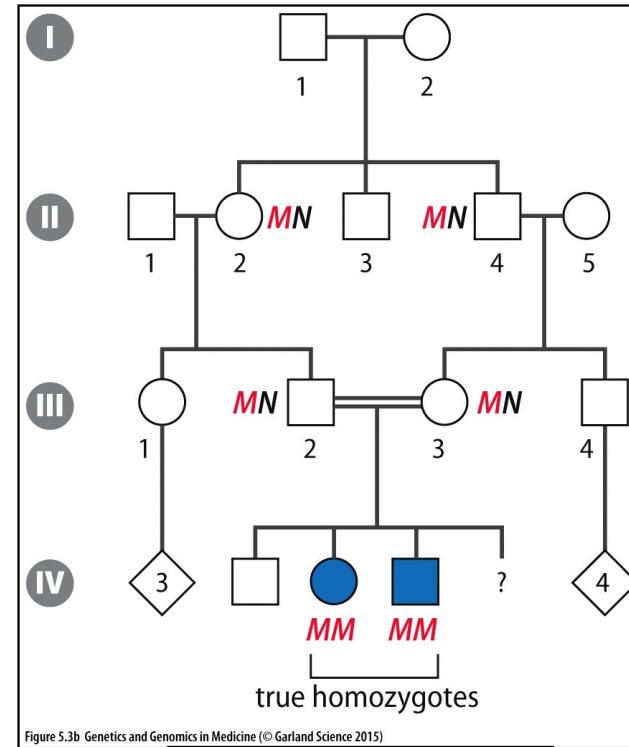
### “Missing heritability”

- An individual’s genetic and epigenetic background is critical
- Complex interaction of genetic and environmental factors can influence disease onset and progression
- Monogenic, Oligogenic and Polygenic

## Autosomal recessive inheritance



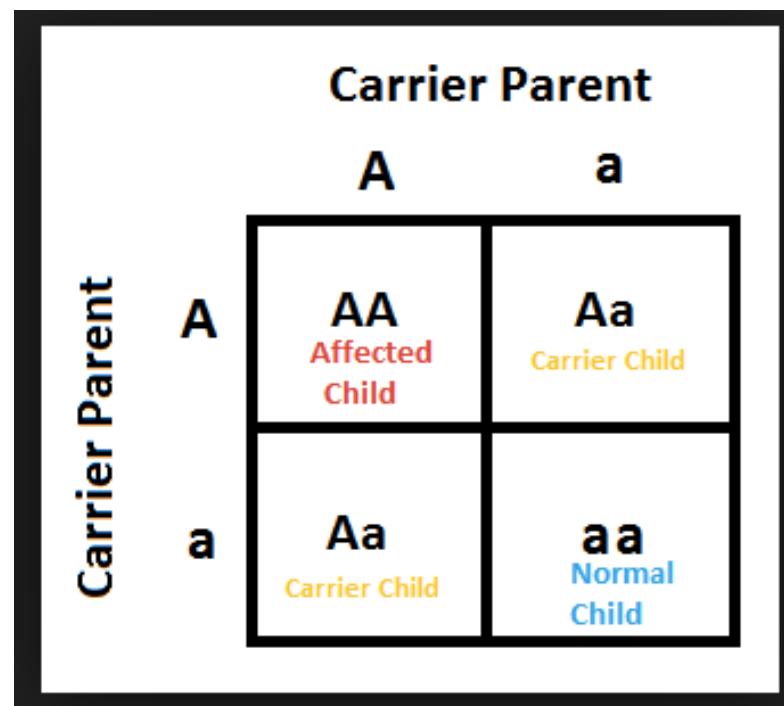
Different mutations in the same gene



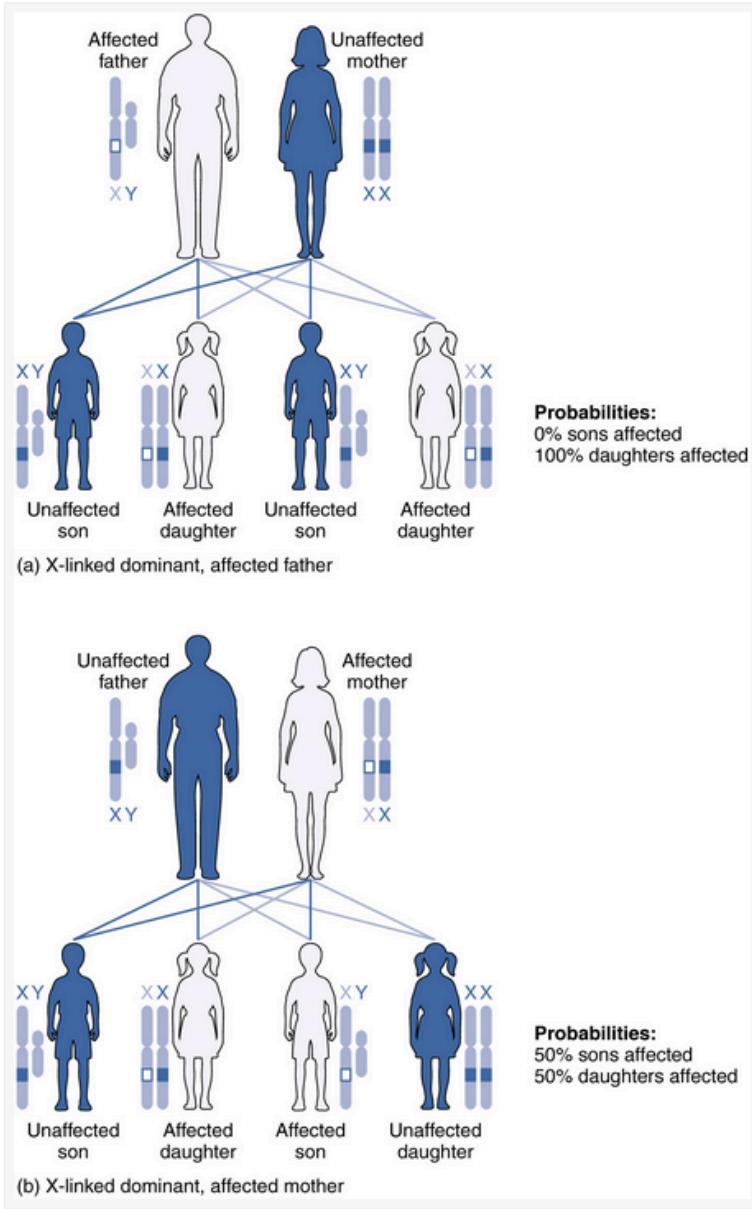
Identical mutation  
(consanguinity)

## Autosomal recessive inheritance (Punnett square – inheritance of parental alleles)

A = mutation  
a = normal allele



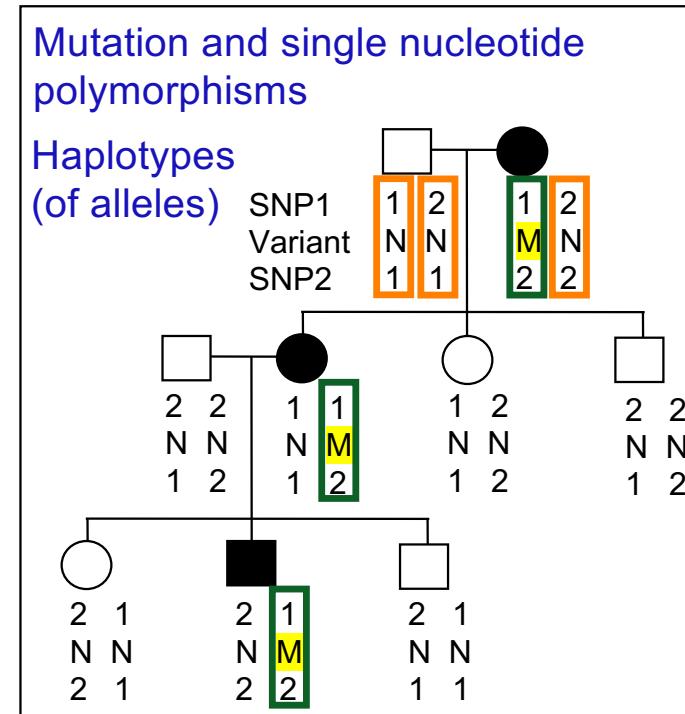
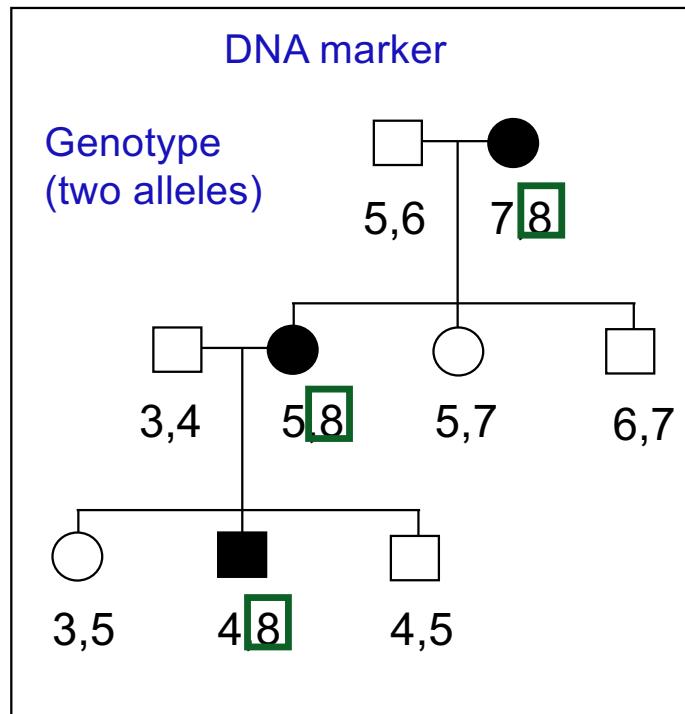
## X-linked dominant inheritance



U.S. National Library of Medicine

## Inheritance of alleles (or haplotypes of alleles) at known genetic loci

### Examples

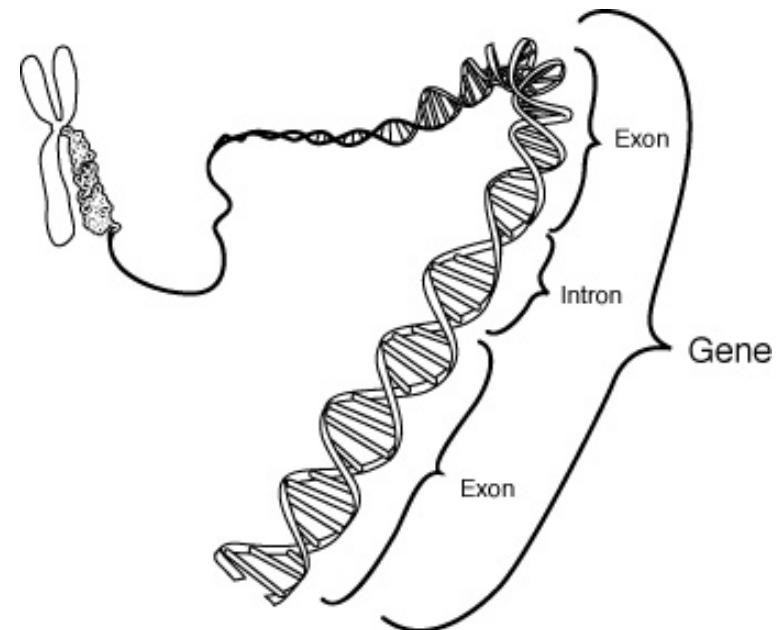


The basis of **genetic linkage analysis**  
Mendelian (autosomal dominant in these examples)

## Next-generation sequencing

Disease gene discovery by ***whole exome sequencing***

- Exome makes up 1.5% of human genome
- Majority of disease causing variants found to date are in the coding regions (i.e. exons).
- Capture the exome
- Massive parallel sequencing  
e.g. (Illumina X-Ten sequencing platforms)



## Next-generation sequencing

Disease gene discovery by *whole genome sequencing*

Year	Cost	Genome sequence time
1990	\$3,000,000,000	10 years
2009	\$48,000	4 weeks
2010	\$20,000	2 weeks
Jan 2011	\$10,000	4 days
July 2011	\$4,000	2 days
2012	\$3,000	1 day
2020	\$1,500	hours

# Power of combining family-based studies (genetic linkage analysis) with next-generation sequencing



## ARTICLE

Received 10 Aug 2015 | Accepted 7 Mar 2016 | Published 15 Apr 2016

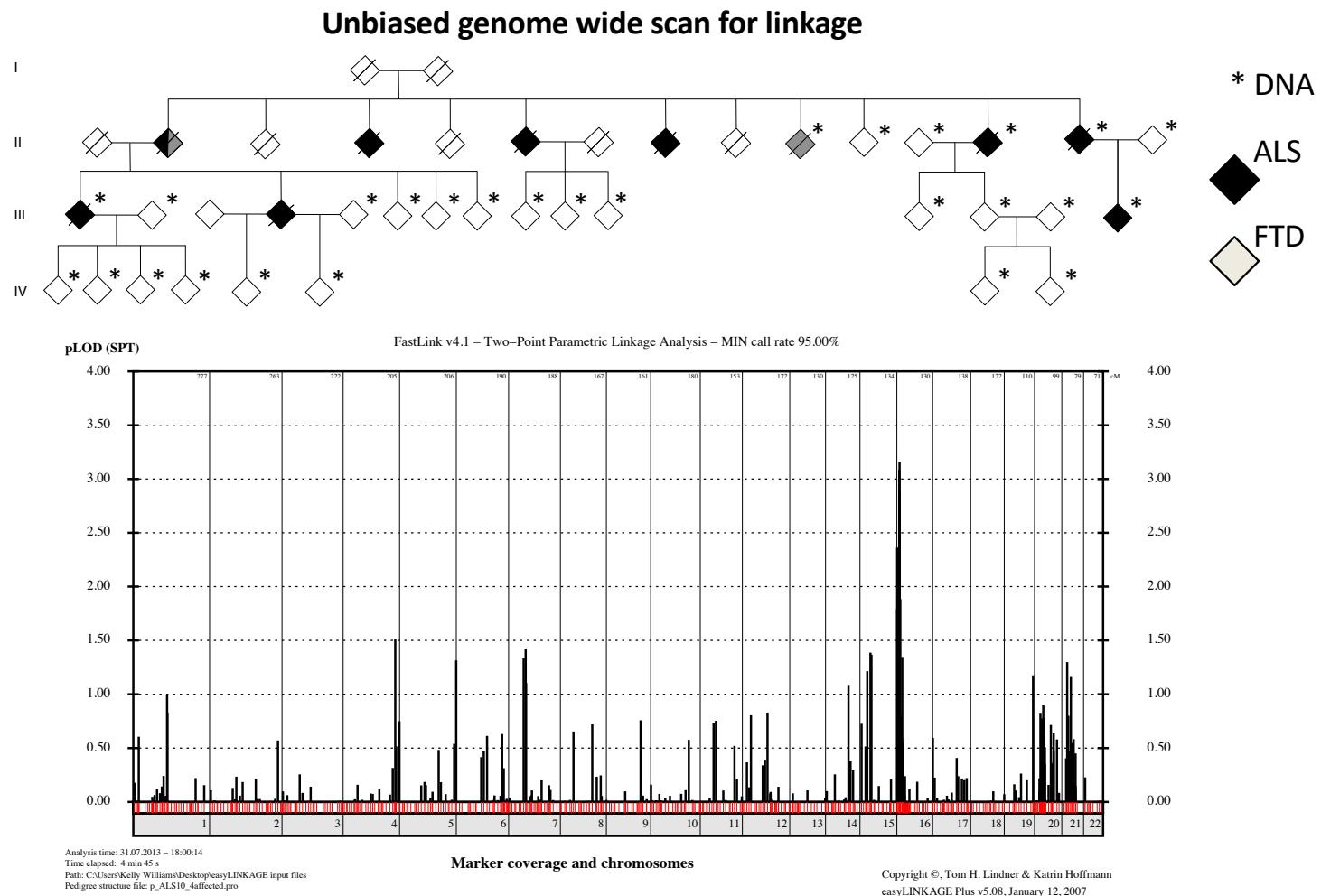
DOI: 10.1038/ncomms11253

OPEN

## CCNF mutations in amyotrophic lateral sclerosis and frontotemporal dementia

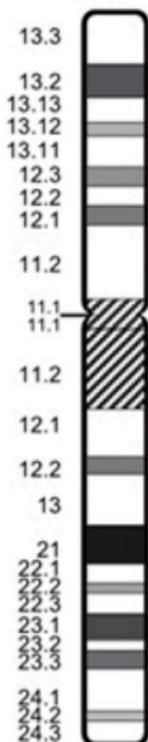
Kelly L. Williams<sup>1,2,3</sup>, Simon Topp<sup>4</sup>, Shu Yang<sup>1,2</sup>, Bradley Smith<sup>4</sup>, Jennifer A. Fifita<sup>1,2</sup>, Sadaf T. Warraich<sup>1</sup>, Katharine Y. Zhang<sup>1</sup>, Natalie Farrell<sup>5</sup>, Caroline Vance<sup>4</sup>, Xun Hu<sup>4</sup>, Alessandra Chesi<sup>6</sup>, Claire S. Leblond<sup>7,8</sup>, Albert Lee<sup>1,9</sup>, Stephanie L. Rayner<sup>1</sup>, Vinod Sundaramoorthy<sup>1,10</sup>, Carol Dobson-Stone<sup>11,12</sup>, Mark P. Molloy<sup>1,9</sup>, Marka van Blitterswijk<sup>13</sup>, Dennis W. Dickson<sup>13</sup>, Ronald C. Petersen<sup>14</sup>, Neill R. Graff-Radford<sup>15</sup>, Bradley F. Boeve<sup>14</sup>, Melissa E. Murray<sup>13</sup>, Cyril Pottier<sup>13</sup>, Emily Don<sup>1</sup>, Claire Winnick<sup>1</sup>, Emily P. McCann<sup>1</sup>, Alison Hogan<sup>1</sup>, Hussein Daoud<sup>7,8</sup>, Annie Levert<sup>7,8</sup>, Patrick A. Dion<sup>7,8</sup>, Jun Mitsui<sup>16</sup>, Hiroyuki Ishiura<sup>16</sup>, Yuji Takahashi<sup>16</sup>, Jun Goto<sup>16</sup>, Jason Kost<sup>17,18</sup>, Cinzia Gellera<sup>19</sup>, Athina Soragia Gkazi<sup>4</sup>, Jack Miller<sup>4</sup>, Joanne Stockton<sup>20</sup>, William S. Brooks<sup>11</sup>, Karyn Boundy<sup>21</sup>, Meraida Polak<sup>22</sup>, José Luis Muñoz-Blanco<sup>23</sup>, Jesús Esteban-Pérez<sup>24,25</sup>, Alberto Rábano<sup>26</sup>, Orla Hardiman<sup>27</sup>, Karen E. Morrison<sup>20,28,29</sup>, Nicola Ticozzi<sup>30,31</sup>, Vincenzo Silani<sup>30,31</sup>, Jacqueline de Belleroche<sup>32</sup>, Jonathan D. Glass<sup>22</sup>, John B.J. Kwok<sup>11,12</sup>, Gilles J. Guillemin<sup>1</sup>, Roger S. Chung<sup>1</sup>, Shoji Tsuji<sup>16,33</sup>, Robert H. Brown Jr<sup>18</sup>, Alberto García-Redondo<sup>24,25</sup>, Rosa Rademakers<sup>13</sup>, John E. Landers<sup>18</sup>, Aaron D. Gitler<sup>6</sup>, Guy A. Rouleau<sup>7,8</sup>, Nicholas J. Cole<sup>1,3</sup>, Justin J. Yerbury<sup>5</sup>, Julie D. Atkin<sup>1,10</sup>, Christopher E. Shaw<sup>4</sup>, Garth A. Nicholson<sup>1,2,3,34</sup> & Ian P. Blair<sup>1,2</sup>

# Power of combining family-based studies (genetic linkage analysis) with next-generation sequencing



## Power of combining family-based studies (genetic linkage analysis) with next-generation sequencing

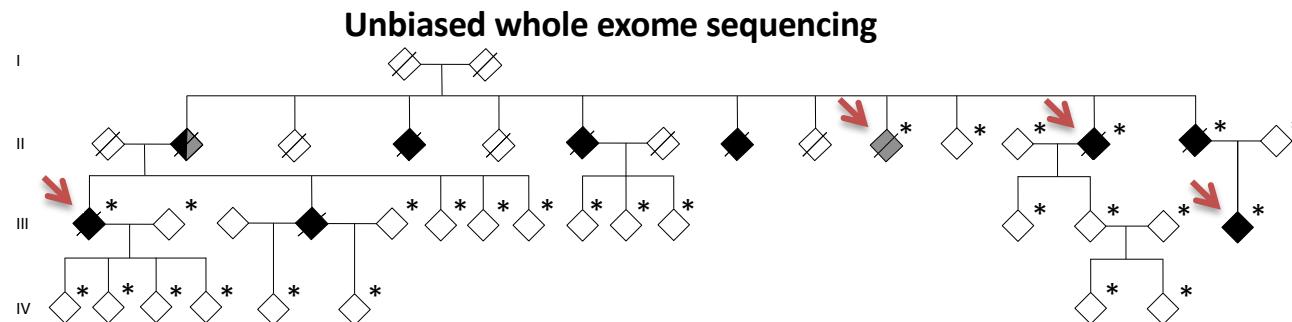
Linkage analysis identifies a disease locus on Chr 16p13.3



Marker	LOD score
Tel	
-D16S521	1.72
-D16S3401	2.55
-D16S3024	1.79
-D16S3082	<b>3.24</b>
-D16S475	2.89
-D16S2622	2.48
-D16S3065	<b>3.19</b>
-D16S3134	2.06
-D16S423	0.79
-D16S3088	0.57
-D16S418	<b>-3.23</b>

Maximum genome-wide LOD score

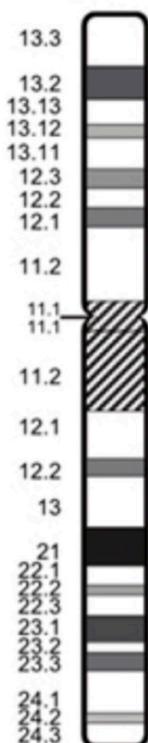
## Power of combining family-based studies with next-generation sequencing



Filter	Variants
<b>Total variants identified</b>	292,989
<b>Present in all affected</b>	35,930
<b>Alters amino acid sequence</b>	5,109
<b>Novel variants</b>	2
<b>Within linkage region 16p13.3</b>	1

## Power of combining family-based studies with next-generation sequencing

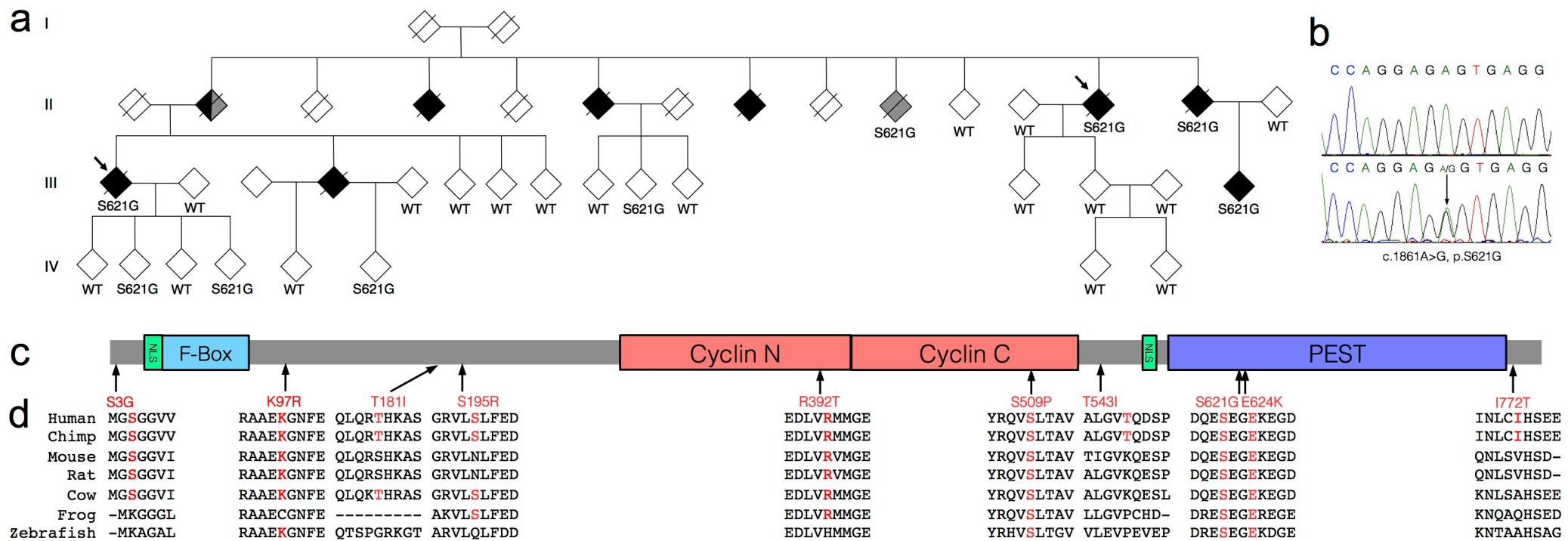
Linkage analysis identifies a disease locus on Chr 16p13.3



Marker	LOD score
Tel	
-D16S521	1.72
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<b>-CCNF</b>	
-D16S3082	<b>3.24</b>
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-D16S3088	0.57
-D16S418	<b>-3.23</b>

Maximum genome-wide LOD score

## Mutations in CCNF cause MND



- Missense substitutions present in patients and absent from unaffected people (public databases)
- Multispecies conservation of the sequence most reliably suggests that a genomic variant is functionally important and thereby more likely to cause disease when mutated

## CCNF mutations in MND/FTD

**Table 1 | ALS and/or FTD mutations in CCNF.**

Amino-acid change	Nucleotide change	Exon	Cohort	Control samples (Sanger and exome)	Public database MAF
<i>Familial</i>					
p.S3G	7A>G	USA	1	1/99 US FTLD-ALS 0/1038 US controls 0/657 AU controls 0/967 AU control exomes	Absent
p.K97R	290A>G	UK	4	1/159 UK FALS 0/897 UK controls 0/967 AU control exomes	Absent
p.S195R	585T>G	Spain	6	1/30 SP FALS 0/967 AU control exomes	Absent
p.S509P	1525T>C	Italy	13	1/99 IT FALS 0/361 CA controls	Absent
p.S621G	1861A>G	Canada	16	1/168 CA SALS 0/967 AU control exomes 0/864 AU Sanger controls	Absent*
p.I772T	2315T>C	UK	17	1/159 UK FALS 0/897 UK controls 0/967 AU control exomes	Absent
<i>Sporadic</i>					
p.T181I	542C>T	Japan	6	1/283 JA SALS 0/514 JA controls 0/967 AU control exomes	Absent*
p.R392T	1175G>C	USA	11	1/99 US FTLD 0/1038 US controls 0/967 AU control exomes	Absent
p.T543I	1628C>T	Japan	15	1/283 JA SALS 0/514 JA controls 0/967 AU control exomes	Absent
p.E624K	1870G>A	USA	16	1/49 US SALS trios 0/801 AU Sanger controls 0/967 AU control exomes	Absent*

Williams *et al.* (2016) *Nature Comms.*

# Frontotemporal dementia (FTD) & MND: shared molecular origins

## Clinical, pathological and **genetic** overlap

Table 1. Currently known causal genes in FTD, ALS and FTD-ALS.

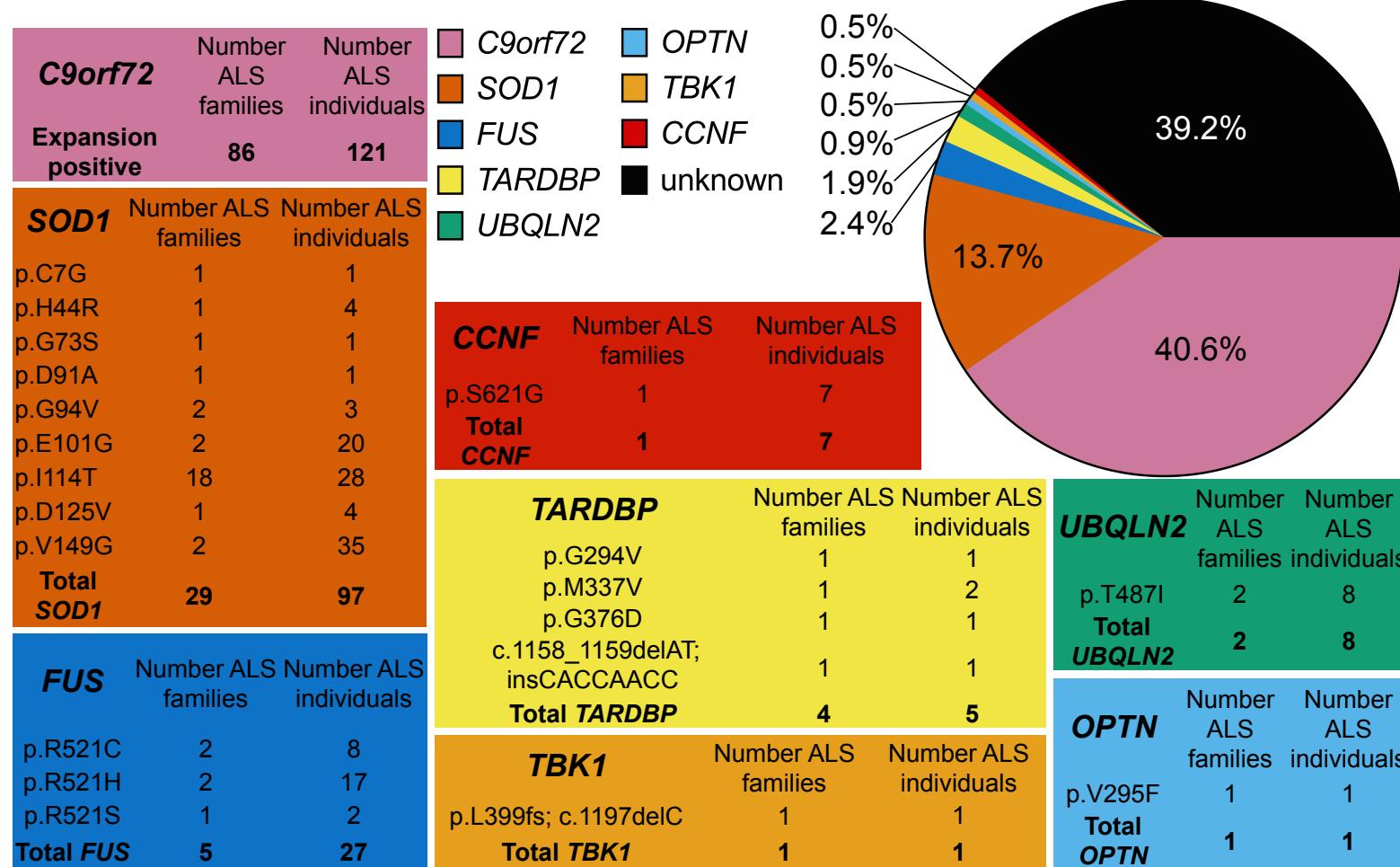
Major causal genes	ALS <sup>1</sup>	FTD <sup>2</sup>	Other clinical associations
<i>SOD1</i>	✓		
<i>OPTN</i>	✓		primary open angle glaucoma
<i>PFN1</i>	✓		
<i>MATR3</i>	✓		
<i>TUBA4A</i>	✓		
<i>TBK1</i>	✓	✓	
<i>C9orf72</i>	✓	✓	
<i>TARDBP</i>	✓	✓	
<i>FUS</i>	✓	✓	
<i>CCNF</i>	✓	✓	
<i>VCP</i>	✓	✓	Paget disease of bone, inclusion body myopathy
<i>UBQLN2</i>	✓	✓	spastic paraparesis, multiple sclerosis
<i>CHCHD10</i>	✓	✓	
<i>SQSTM1</i>	✓	✓	Paget disease of bone
<i>CHMP2B</i>		✓	
<i>PGRN</i>		✓	
<i>MAPT</i>		✓	

Crook et al, *Amyotroph Lateral Scler Frontotemp Degener* 2017

<i>C9orf72</i>	%
Familial FTD	20-30%
Sporadic FTD	5-10%
Familial MND	35-40%
Sporadic MND	5%
AD	Small %

Majounie et al, *Lancet Neurol* 2012

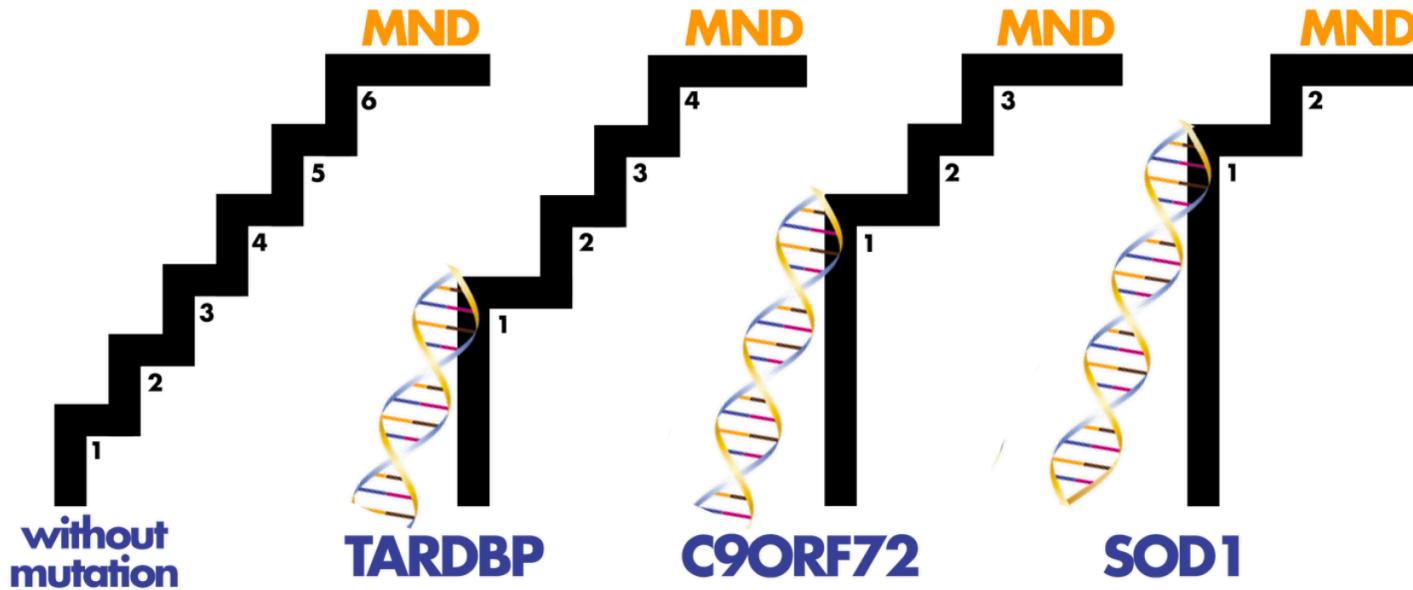
## Distribution of MND mutations among Australian families with a history of MND



McCann et al, Clin Genet 2017

The search for genetic and environmental  
**risk factors (susceptibility)**  
that underlie MND in patients with  
no family history of the disease (sporadic)

## Genetic and environmental risk factors



CAUSES AND DISEASE MECHANISMS / MND RESEARCH

### Steps to understanding MND

⌚ AUGUST 3, 2018

👤 NICKJAMESCOLE

💬 2 COMMENTS

THE OFFICIAL BLOG OF THE



Al-Chalbi *et al* Lancet Neurol; 13: 1108–13, 2014  
Chio et al Neurology :e1-e8, 2018

## Genetic susceptibility to complex disease

**Complex disease:** Most medical problems such as heart disease, diabetes, obesity, Alzheimer's disease, asthma, Parkinson's disease, multiple sclerosis, osteoporosis, and sporadic MND, do not have a single genetic cause—they are likely associated with the effects of **multiple genes** in combination with **lifestyle and environmental factors**. These are called complex or multifactorial disorders.

**Susceptibility (risk) alleles:** an allele, usually inherited, that increases the likelihood of developing a complex disease. The combination of multiple susceptibility alleles and environmental factors may be additive or synergistic, leading to disease.

On their own, they are neither necessary nor sufficient to cause disease

## Identifying risk (susceptibility) alleles that contribute to complex disease

### Association studies

- Case-control studies
  - candidate gene association studies
  - **genome-wide association studies (GWAS)**

### Case-control study

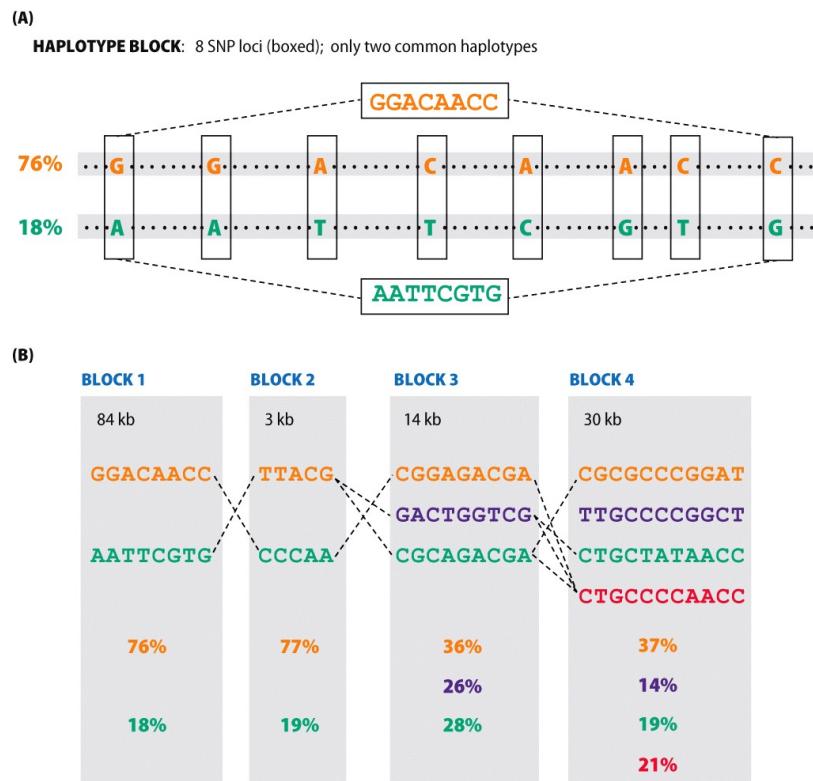
Genotyping of:

- Unrelated cases (patients) with one phenotype (trait/disease)
- Unrelated controls from the same population, matched (with cases) for age, sex and ancestry

## Haplotype blocks in a population

Association studies depend on linkage disequilibrium

- Shared chromosomal segments (haplotypes) among the population due to very distant common ancestors



**Tag SNP:** A representative SNP, in a region with high linkage disequilibrium, that represents a group of SNPs (haplotype).

The other SNP genotypes may be **imputed** from the tag SNP genotype.

It is possible to identify genetic variation and association to phenotypes without genotyping every SNP in a chromosomal region

## Genome wide association study (GWAS)

The “matched” cases and controls are genotyped for a large number of genetic variants (usually SNPs) from across the genome

Statistical analysis (often an odds ratio, the odds of being affected if the SNP is present divided by the odds of being affected if the SNP is absent)

To identify genetic factors that confer significantly increased disease risk (susceptibility/risk factors) or significantly reduced disease risk (protective factors)

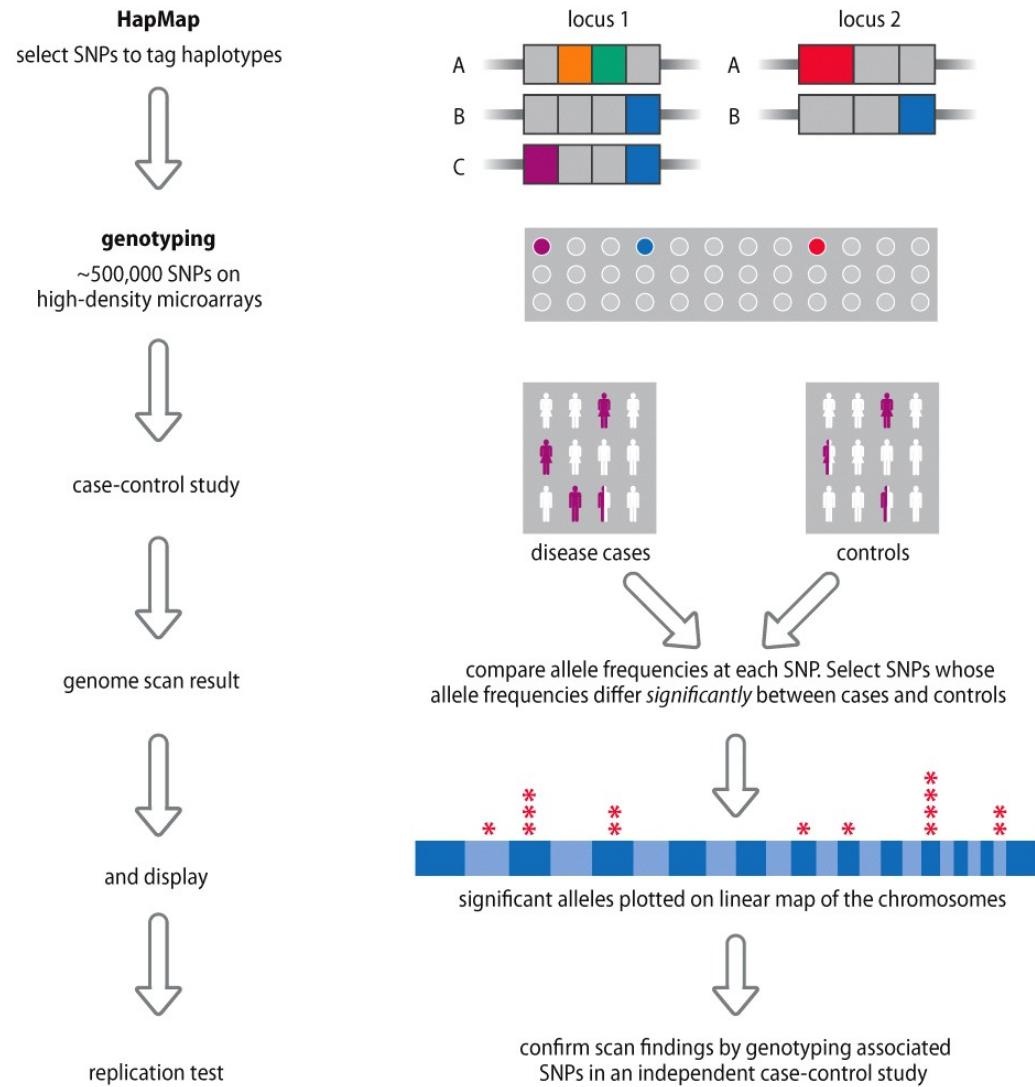


Figure 8.13 Genetics and Genomics in Medicine (© Garland Science 2015)

# A ‘human genome project’ for MND

## MND risk gene discovery by whole genome sequencing

The screenshot shows the Project MinE website with a dark blue header bar. The header includes the logo 'project MinE Make it yours' with a hand icon, and navigation links: Log in, Campaigns, About, Status, News, Participating countries ▾, and a prominent orange 'Donate now' button.

The main content area features a large map of Australia. Overlaid on the map is a circular progress bar indicating '51% raised of goal'. To the left of the map, the text 'Project MinE' and 'Australia' is displayed, along with a small Australian flag icon. Below this, a call to action reads: 'Join the fight and help us discover the genetic basis of ALS. Start or support a local initiative to raise funds. Project MinE, make it yours!'

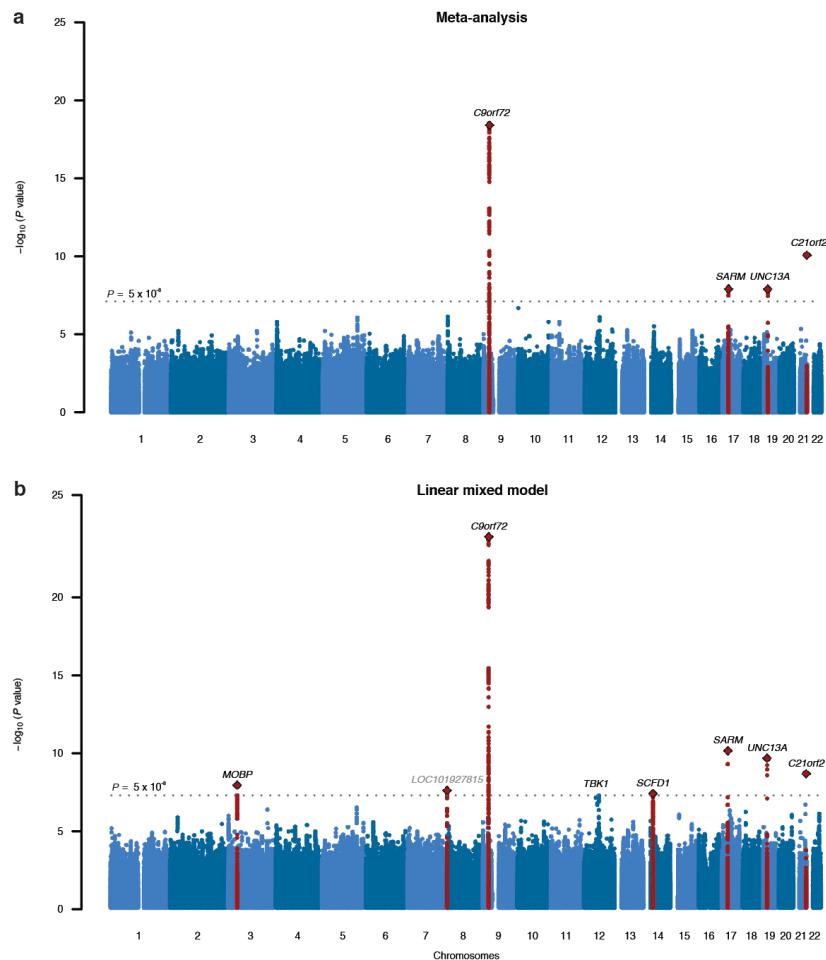
To the right of the map, a dark blue box contains the text 'Collected in Australia' and '503.28 DNA profiles'. Below this box is another orange 'Donate now' button.

## Goals

- Whole genome sequencing of 15,000 “sporadic” MND patients and 7,500 controls
- Identify *common* and *rare* genetic variants with *high*, *intermediate* and *low* risk for MND
- Genome wide association studies (GWAS) (common variants)
- Rare variant burden analysis

# Genetic factors that confer significantly increased disease risk for sporadic MND (from GWAS)

Figure 2



## Manhattan plots

nature genetics

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NATURE GENETICS | LETTER



日本語要約

### Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis

Wouter van Rheenen, Aleksey Shatunov, Annelot M Dekker, Russell L McLaughlin, Frank P Diekstra, Sara L Pulit, Rick A A van der Spek, Urmo Võsa, Simone de Jong, Matthew R Robinson, Jian Yang, Isabella Fogh, Perry TC van Doormaal, Gijs H P Tazelaar, Max Koppers, Anna M Blokhuis, William Sproviero, Ashley R Jones, Kevin P Kenna, Kristel R van Eijk, Oliver Harschnitz, Raymond D Schellevis, William J Brands, Jelena Medic, Androniki Menelaou + et al.

Affiliations | Contributions | Corresponding authors

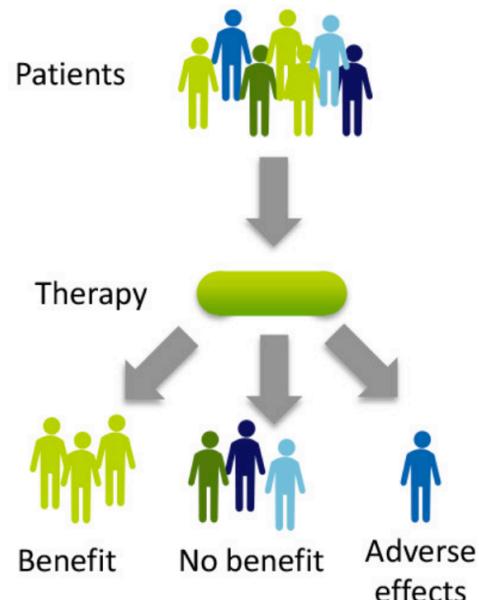
Nature Genetics 48, 1043–1048 (2016) | doi:10.1038/ng.3622

Received 07 January 2016 | Accepted 20 June 2016 | Published online 25 July 2016

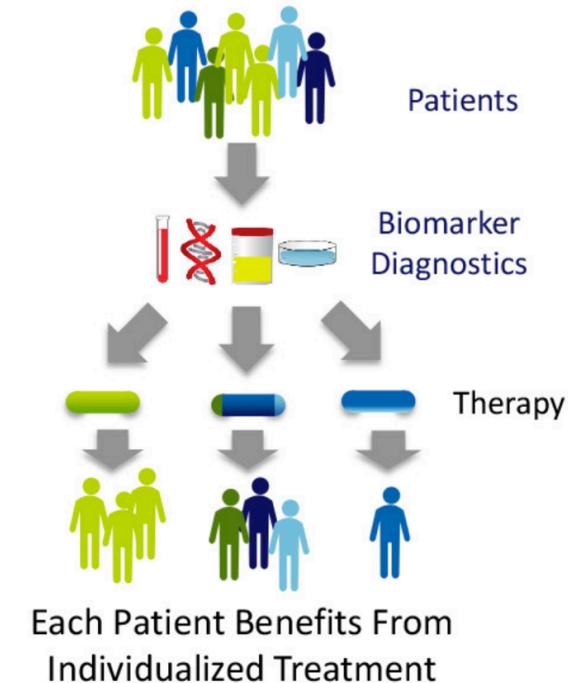
## Personalised medicine. Precision medicine (Whole genome sequencing)



### **Without Personalized Medicine:** Some Benefit, Some Do Not



### **With Personalized Medicine:** Each Patient Receives the Right Medicine For Them



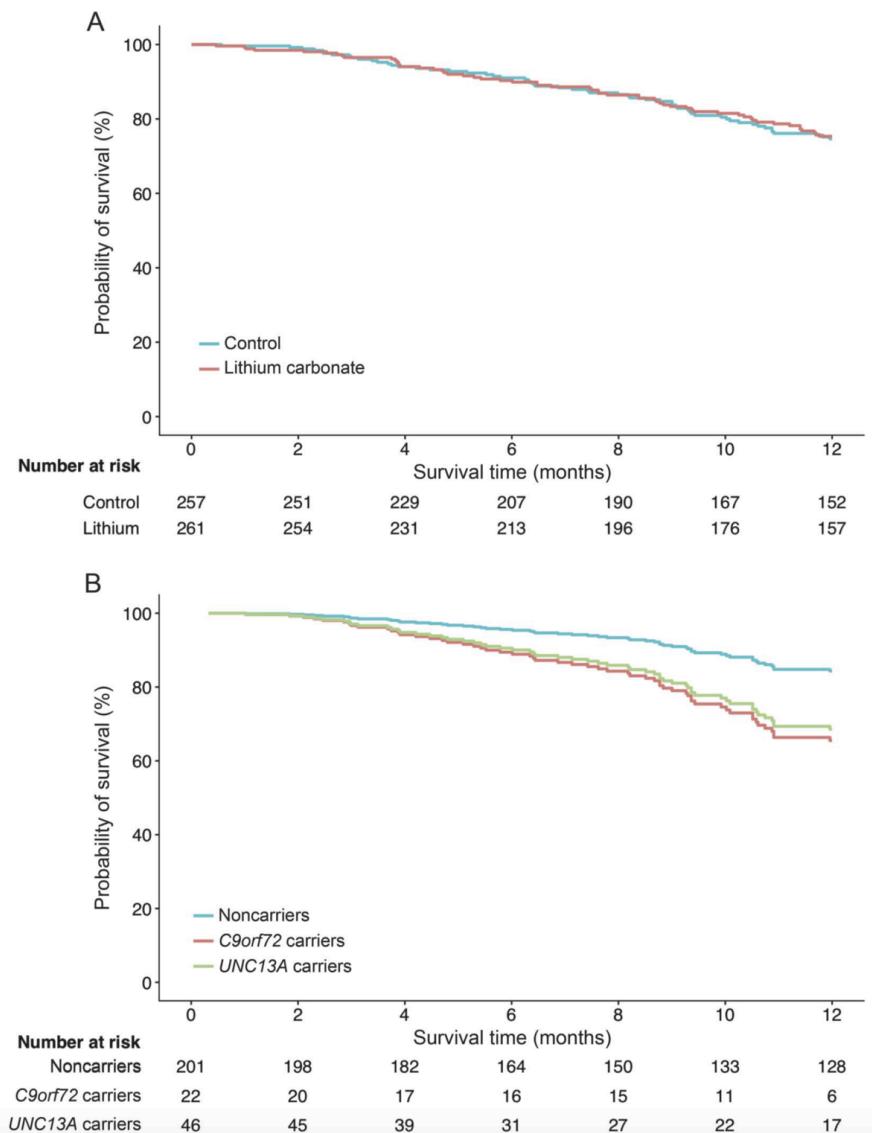
## MND - clinical trials - Lithium

### Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials      van Eijk *et al* **Neurology® 2017;89:1915-1922**

**Table 1** Characteristics and risk of bias of the 5 identified studies by systematic search

Study (year)	Patients, n	Study design	Inclusion criteria				Control group	Lithium dose, mEq/L
			Disease duration, mo	Revised El Escorial category <sup>33</sup>	Predicted vital capacity, %			
Fornai <i>et al.</i> <sup>26</sup> (2008)	44	Randomized, single-blind	≤60	All	—	Riluzole	0.4-0.8	
Aggarwal <i>et al.</i> <sup>24</sup> (2010)	88	Randomized, double-blind	≤36	All	≥60	Placebo	0.4-0.8	
Chio <i>et al.</i> <sup>22</sup> (LITALS, 2010)	171	Randomized, double-blind	≤36	Definite, probable, probable laboratory-supported	≥50	0.2-0.4 mEq/L	0.4-0.8	
Verstraete <i>et al.</i> <sup>34</sup> (LITRA, 2012)	133	Randomized, double-blind	6-36	Definite, probable, probable laboratory-supported	≥70	Placebo	0.4-0.8	
UKMND-LiCALS Study group <sup>35</sup> (2013)	214	Randomized, double-blind	6-36	All	—	Placebo	0.4-0.8	

**Figure 1** Pooled analysis of treatment effect for lithium carbonate and 12-month survival for each genetic subgroup



MND - clinical trials – Lithium

## UNC13A genotype

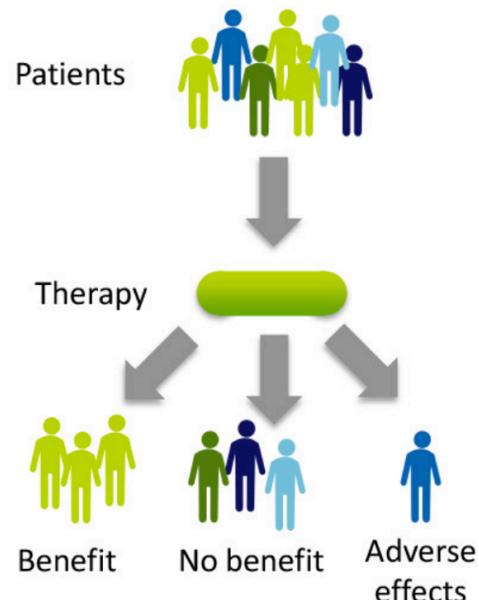
## Genetic risk factor

Appears to determine  
treatment effect

van Eijk *et al*  
Neurology® 2017;89:1915-1922

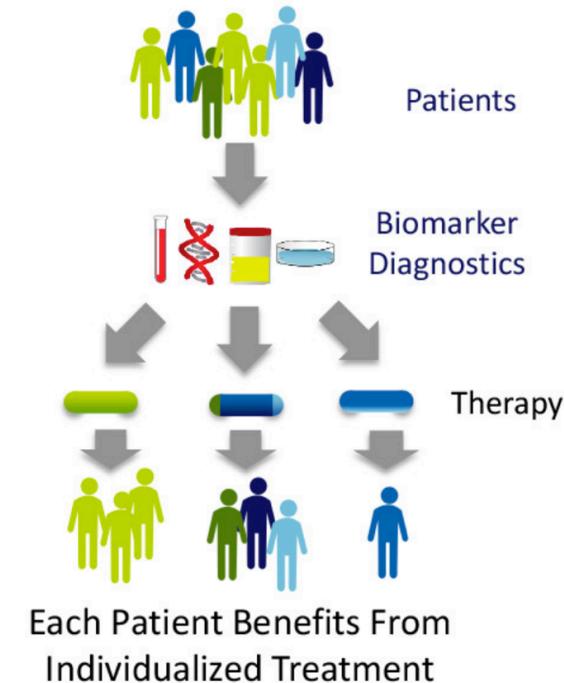
### **Without Personalized Medicine:**

Some Benefit, Some Do Not



### **With Personalized Medicine:**

Each Patient Receives the Right Medicine For Them



# Translation - impact for patients

## Clinical genetics

- Symptomatic testing.
- Early diagnosis aids in clinical management and delay the time to ventilator and death
- Predict progression
- Clinical trials - Predict response to therapies

## Genetic counselling

- Presymptomatic testing. Individual choice. Weigh the benefits and burdens of testing.

## Preimplantation genetic diagnosis (PGD) – IVF

- Prevent transmission to the next generation.
- Can be performed “blind”

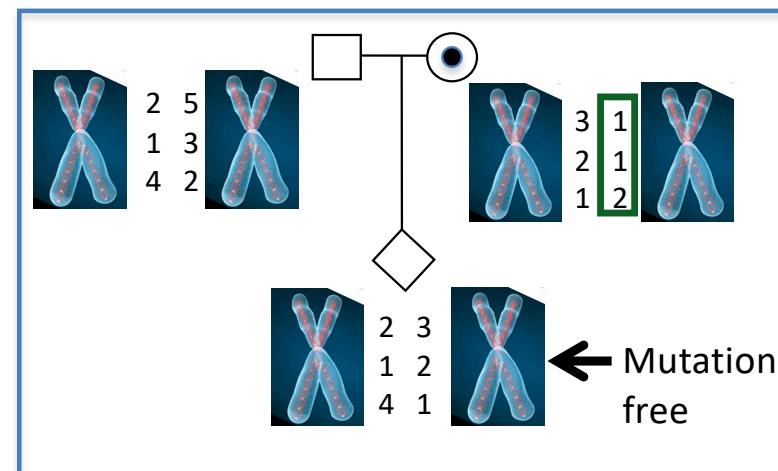
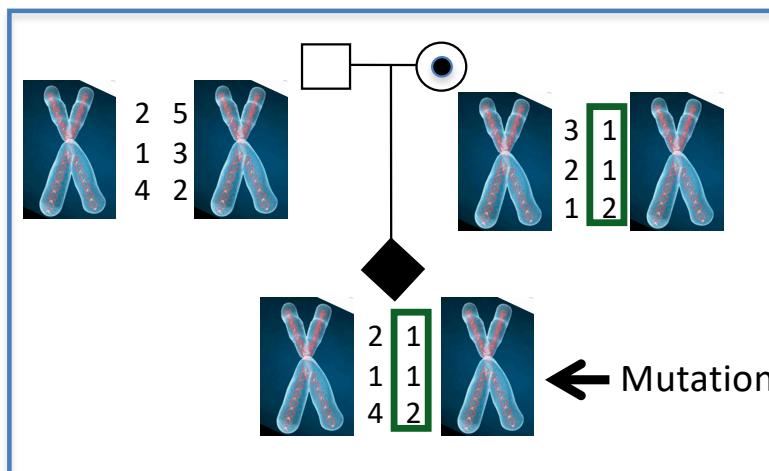
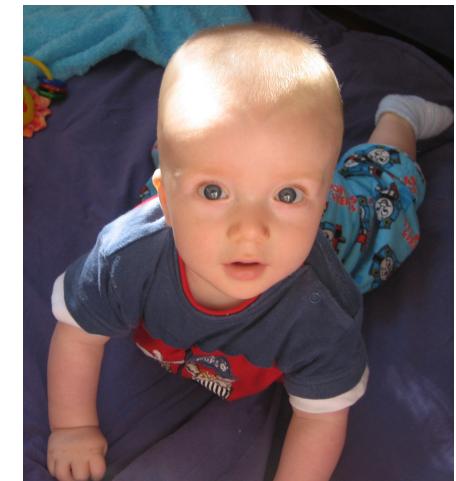


**Genetic testing results in babies born through IVF without a faulty MND gene.**



## Translation to medical diagnosis Pre-implantation genetic diagnosis, PGD (IVF)

**Haplotype analysis** (PCR genotyping to determine alleles and chromosomal phase for adjacent markers flanking a mutation)



# **Macquarie University Centre for Motor Neuron Disease Research**

## **Faculty of Medicine, Health and Human Sciences**

