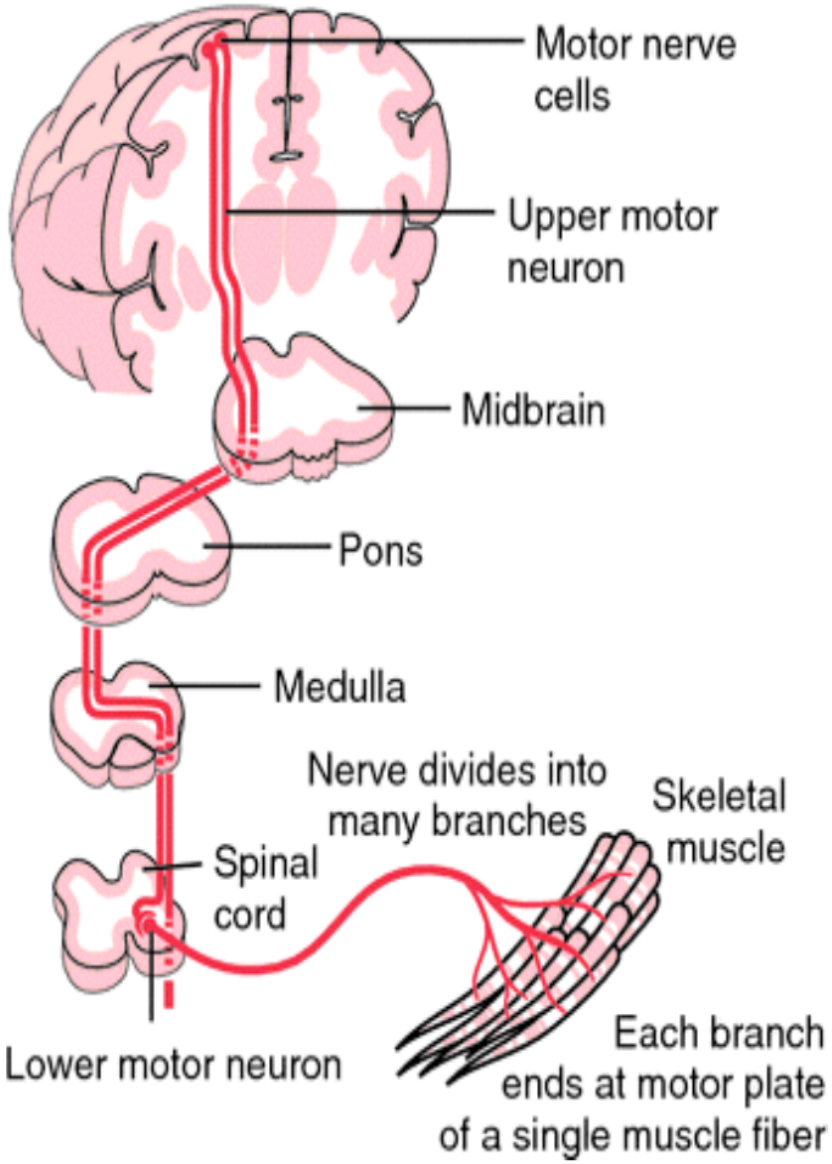
Amyotrophic Lateral Sclerosis

- Neuro-degenerative disorder affecting upper and lower motor neurons
- Etiology poorly understood
- Median survival = 3 years
- No effective treatments

JM Charcot
1825 – 1893

Lou Gehrig
1903 - 1941

Amyotrophic Lateral Sclerosis (ALS)



- Affects adults in mid-to-late life
- progressive muscle weakness
- muscle atrophy
- Selective degeneration of motor neurons in brain-stem and spinal cord
- Sporadic and Familial Forms
- *SOD1* mutations linked to FALS
- *SOD1* mutations only account for ~2% of ALS. What are other causes?

Epidemiology of ALS

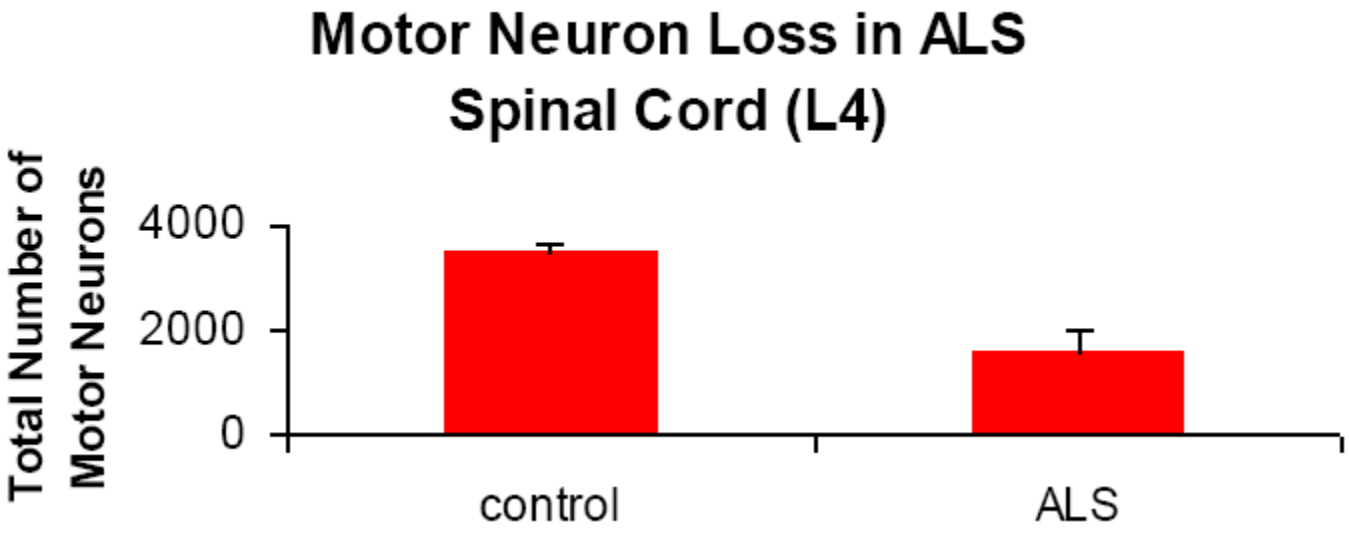
Incidence: 1-2 in 100,000 each year. At the moment in the U.S. there are 25,000 people affected by the disease. Median age of onset is 55 years old. Gender-related incidence: female:male ratio is 4:5.

10% of the cases are inherited, familial cases (FALS), whereas the 90% of the cases are sporadic (SALS)

The life-span of a patient affected by ALS is 3 to 5 years, after the diagnosis.

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


Motor Neuron Loss in ALS
Spinal Cord (L4)
Total Number of Motor Neurons
4000
2000
0
control
ALS

Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis

Daniel R. Rosen*, Teepu Siddique†, David Patterson‡, Denise A. Figlewicz§, Peter Sapp*||, Afif Hentati†, Deirdre Donaldson‡, Jun Goto§, Jeremiah P. O'Regan*||, Han-Xiang Deng†, Zohra Rahmani‡, Aldis Krizus§, Diane McKenna-Yasek*, Annarueber Cayabyab†, Sandra M. Gaston*¶, Ralph Berger‡, Rudolph E. Tanzi¶, John J. Halperin#, Brian Herzfeldt†, Raymond Van den Bergh**, Wu-Yen Hung†, Thomas Bird††, Gang Deng†, Donald W. Mulder‡‡, Celestine Smyth†, Nigel G. Laing§§, Edwin Soriano†, Margaret A. Pericak–Vance||||, Jonathan Haines¶¶, Guy A. Rouleau§, James S. Gusella¶¶, H. Robert Horvitz|| & Robert H. Brown Jr*##

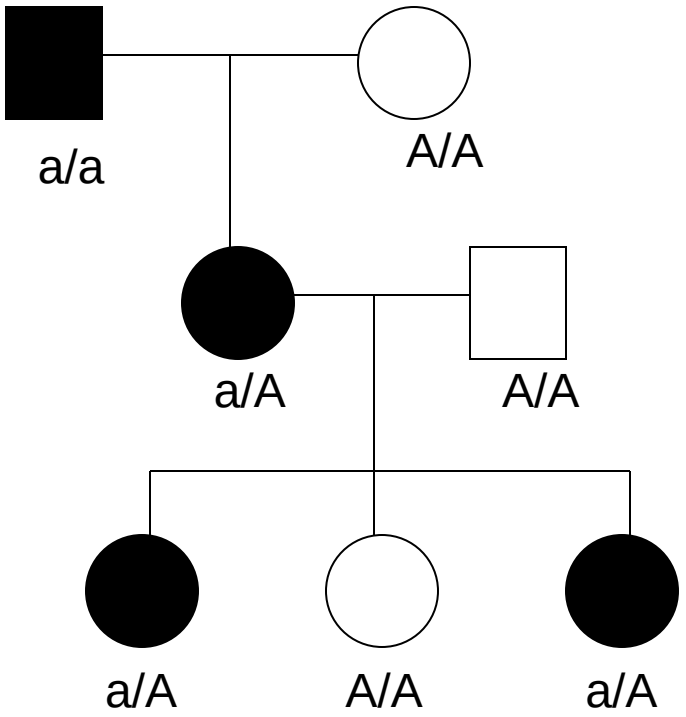
First a CA dinucleotide polymorphic marker linked to ALS found . A cosmid containing this CA is found to contain SOD1 exon

Used linkage to get the first ALS gene ? Positional cloning

D21S223 z 6.8 at $\theta = 0$)

Found mutations in SOD1

LINKAGE you know inheritance ALS dominant



NR NR NR

$1-\theta$ $1-\theta$ $1-\theta$ if linked

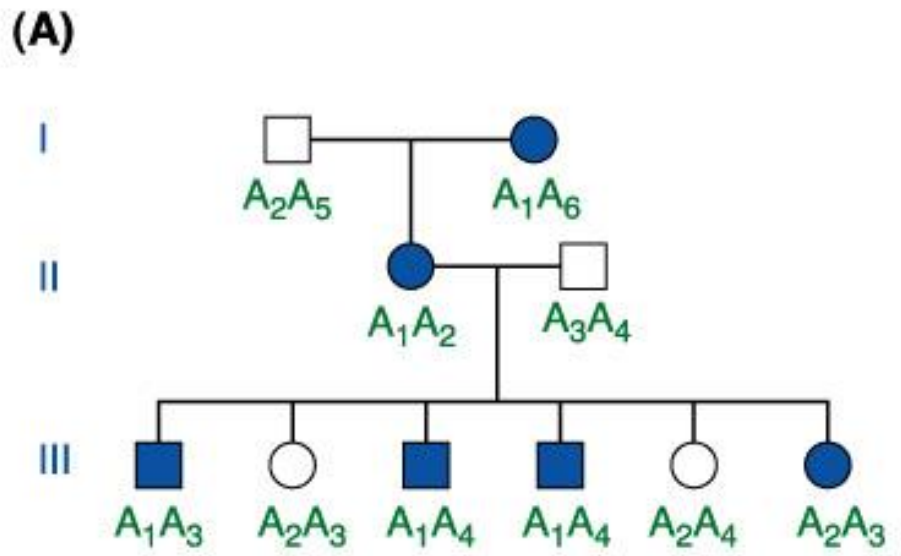
.5 .5 .5 If not linked

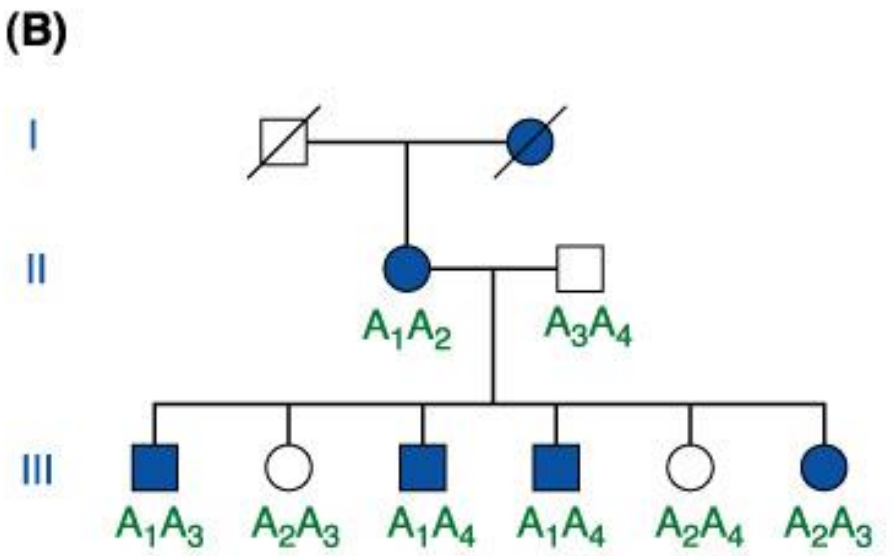
$$\log_{10} \frac{\text{Likehood (or odds) if linked}}{\text{Likehood if segregate independently}} = \text{LOD}$$

$$\log_{10} \left(\frac{(1-\theta)\,(1-\theta)\,(1-\theta)}{.5 \;\; x.5 \; x \; .5} \right)$$

If $\theta = 0$

Then LOD $= \text{Log}_{10} \frac{(1x1x1)}{(.5x.5x.5)} = .903$





θ	0,	0.1,	0 .2	0 .3	0.4	0.5
$Z-$	.57,	.62,	.51,	.3,	0	

II) $1/2((1-\theta)/0.5) + 1/2(q/0.5) = 1, \log_{10} 1 = 0$

III) $(1-\theta)^5\theta/(.5)^6$

θ	0,	0.1,	0 .2	0 .3	0.4	0.5
$Z-$	.28,	.32,	.22,	.076,	0	

Do not know phase of gen III

$1/2((1-\theta)^5\theta/(.5)^6) + 1/2((1-\theta)\theta^5/(.5)^6)$

not recomb recomb

Superoxide Dismutase 1 SOD1

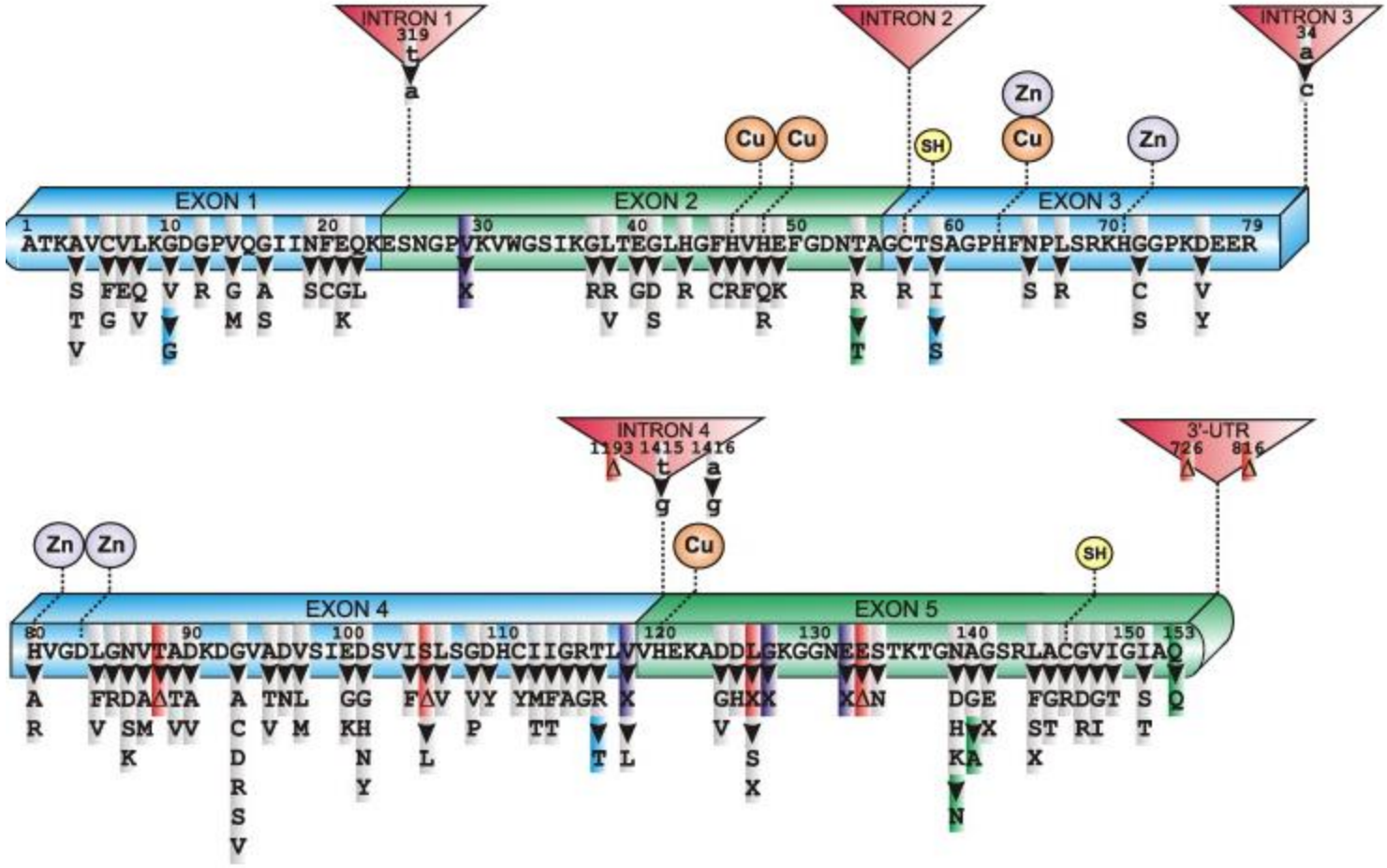
SOD1 is a ubiquitous mostly cytosolic protein

SOD1 is comprised of 153 aa with an approximate molecular weight of 16kDa and is an active homodimer

Each of the two dimers of SOD1 binds a Cu^{++} and a Zn^{++} ion. The reduction of Cu^{++} to Cu^{+} is behind the mechanism of SOD1 in regulating the dismutation of superoxide ion $\mathbf{O_2^{-\cdot}}$ into hydrogen peroxide $\mathbf{H_2O_2}$

$$Cu^{2+} + O^{2-\cdot} \longrightarrow Cu^{+} + O_2$$
$$Cu^{+} + O^{2-\cdot} + 2H^{+} \longrightarrow Cu^{2+} + H_2O_2$$
$$2\ O^{2-\cdot} + 2H^{+} \longrightarrow H_2O_2 + O_2$$

A catalase will subsequently reduce hydrogen peroxide to water.


INTRON 1
319
t
a
INTRON 2
INTRON 3
34
a
c
Zn
Cu
Cu
SH
Cu
Zn
Zn
EXON 1
EXON 2
EXON 3
1 10 20 30 40 50 60 70 79
ATKAVCVLKGDGPVQGIINFEQKESNGPVKVWGSIKGLTEGLHGFHVHEFGDNTAGCTSAGPHFNPLSRKHGGPKDEER
S T V
FEQ G V
V G
R
G M
A S
SCGL K
K
RR V
GD S
R
CRFQK R
R
R T
I S
S
R
C S
V Y
INTRON 4
1193 1415 1416
Δ
t g
a g
3'-UTR
726 816
Δ Δ
Zn
Zn
Cu
SH
EXON 4
EXON 5
80 90 100 110 120 130 140 150 153
HVGDLGNVTADKDGVADVSIEDSVISLSGDHCIIGRTLVVHEKADDLGKGGNEESTKTGNAGSRLACGVIGIAQ
A R
FRDA ΔTA
V SM K VV
A C D R S V
TNL V M
GG KH N Y
F ΔV L
VY P
YMFAGR T
X L
GHKX V S X
X ΔN
DGE H X KA N
FGRDGT ST X RI
S T
Q

Most common mutations in SOD1 related FALS

A4V	This is the **most severe and aggressive** form of SOD1 mutation, **early onset, short survival** (about 1 year) and limited upper neuron involvement. **Most common in the U.S.**	Extremely unstable
D90A	**Benign polymorphism in Scandinavian heterozygous**, but not homozygous patients, who show **low progressive disease and have prolonged survival** (over a decade)	Very unstable
G37R	**Dismutase activity as in wild-type**	Very unstable
G85R	Expression of low copies of the mutated gene in the animal model leads to reproducibility of typical human ALS phenotype: **late onset, extremely fast progression to death.**	Very unstable
G93A	Typical onset and progression of the disease. **First animal model created.** In the mouse, the phenotype is comparable to human ALS.	Very unstable

Peter Andersen (Umeå):

Different SOD mutations give variable phenotype in ALS
Age of onset vary considerable within the same mutation
Disease duration short in som familial ALS and long in others

Table 2 *Main features of the five CuZn-SOD mutations*

	Mutation					
	Ala4Val	Val14Gly	Asp76Tyr	Asp90Ala	Asp90Ala	Gly127ins4TGGG
Zygosity	Hetero	Hetero	Hetero	Homo	Hetero	Hetero
Exon	1	1	3	4	4	5
Patients identified (*n*)	4	1	2	44	2	3
Patients genotyped (*n*)	1	1	1	34	2	2
Uniform phenotype	No	–	No	Yes	Yes	No
Site of onset	B,UE,LE	LE	B,LE	LE	B	UE,LE
Mean age at onset in years (*n*)	58.5 (4)	39 (1)	58 (2)	44,8 (44)	64 (2)	50 (3)
Onset range (years)	50–68	39	49–67	20–94	54–74	41–59
Mean survival time in years (*n*)	0.9 (4)	–	–	14.2 (15)	2.5 (2)	2.8 (3)
Asymptomatic individuals (*n*)	2	0	1	11*	1†	4
CuZn-SOD activity in erythrocyte hemolysate mean ± SD (U/mg Hb)	24.1 ± 1.7 (3)	30.2 (1)	27.4 ± 0.6 (2)	49.1 ± 5.9 (44)	43.6 ± 4.3 (2)	21.2 ± 2.4 (4)
Geographical area	Central Sweden	Central Sweden	Denmark	Finland Sweden	Northern Finland	Denmark

Motor Neuron Degeneration in Mice That Express a Human Cu,Zn Superoxide Dismutase Mutation

Mark E. Gurney,* Haifeng Pu, Arlene Y. Chiu, Mauro C. Dal Canto, Cynthia Y. Polchow, Denise D. Alexander, Jan Caliendo, Afif Hentati, Young W. Kwon, Han-Xiang Deng, Wenje Chen, Ping Zhai, Robert L. Sufit, Teepu Siddique

Science 1993

NEWS\ Mouse Model Found for ALS Mice carrying a mutant gene associated with a hereditary form of ALS develop motor neuron degeneration much like that of the human disease

SOD1 mutation in ALS: gain of toxic function rather than loss of physiologic function

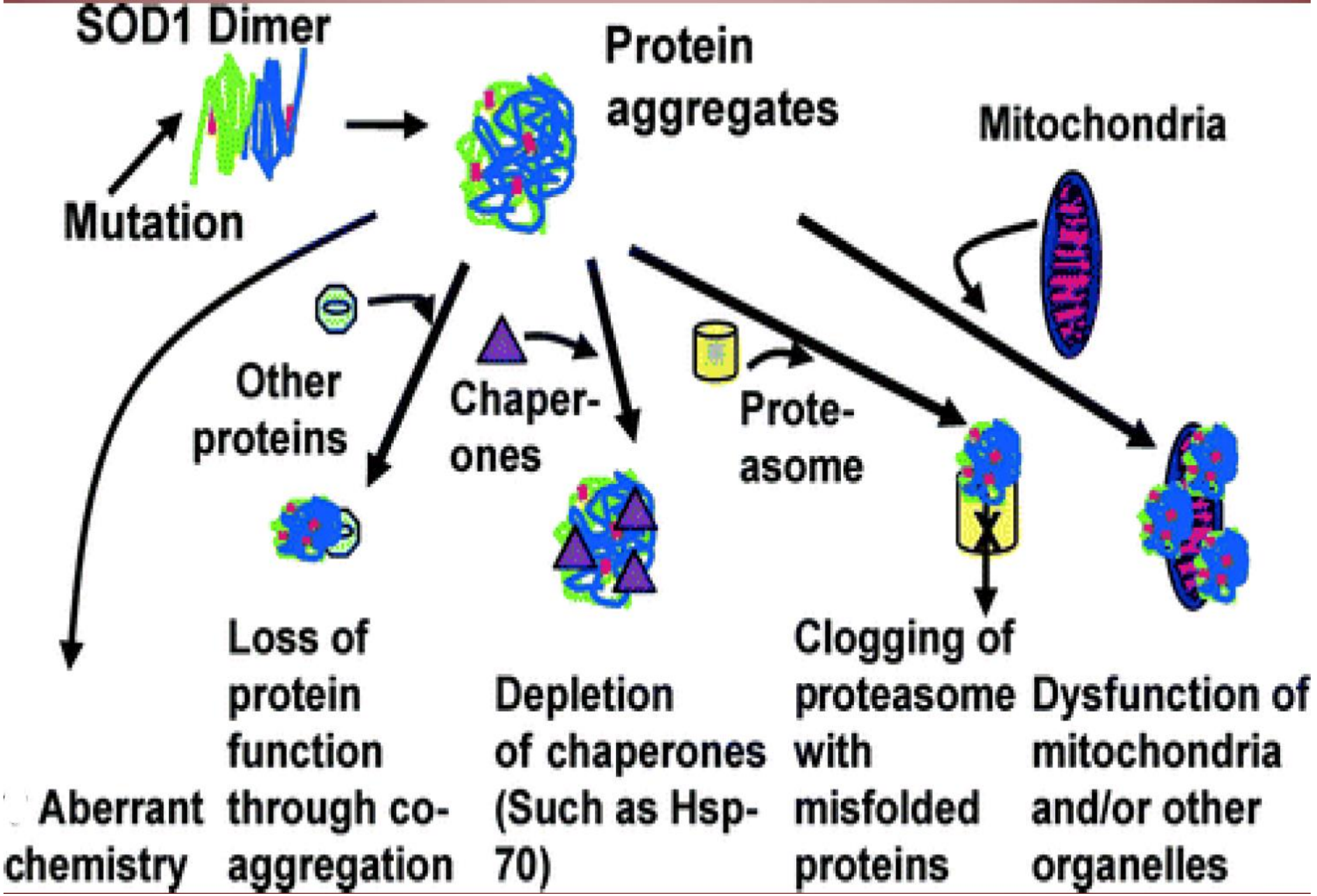
Gain of function not influenced by background i.e. loss of SOD1 or more SOD1 should not change phenotype. Kind of some do not agree.
If Gain of function should be able to mutate the mutant construct to remove
Not Done
At lot of biochemical changes but no strong suppressor which are primary and real?

Possible roles of mutated SOD1 in FALS

Loss of physiological function: impaired dismutase activity

Gain of toxic function:
1) Aberrant redox chemistry, probably due to changes in the conformation of SOD1, that leave the channel (the portion of the molecule accepting superoxide ion, i.e.) able to accept larger molecules. This can lead to **peroxidation, tyrosine nitrosylation and reverse catalysis** (due to improper binding of Zn^{++} to the molecule that leads to formation of superoxide ion rather than dismutase activity). **These activities are not a characteristic of ALL SOD1 mutations, thus remain partially controversial.**

2) Protein instability and SOD1 aggregation. These activities are characteristic of all SOD1 mutants.



Two many mechanisims without sufficient evidence easy to say all mech are right but is it true

But can genetics be used to dissect and determine the important mechanisms

What mechanism is supported by genetics can you suppress the SOD1 mutation? Most studies except knockdown of SOD1 have small impact is a 10% change meaningful?

Opinion this is weak at present 10% survival not good enough!!!!

No genetic proof of most mechanism and far from clear they work additively

What could be done

1) If it is a gain of function can make second mutation that will remove what is gained? This can be screened for relatively easily in lower organisms and then the result further confirmed in mice.
2) High bar for modification of phenotype.
3) Identification of modifiers from human pedigrees

TDP-43 Mutations Linked to ALS

TDP-43 A315T Mutation in Familial Motor Neuron Disease

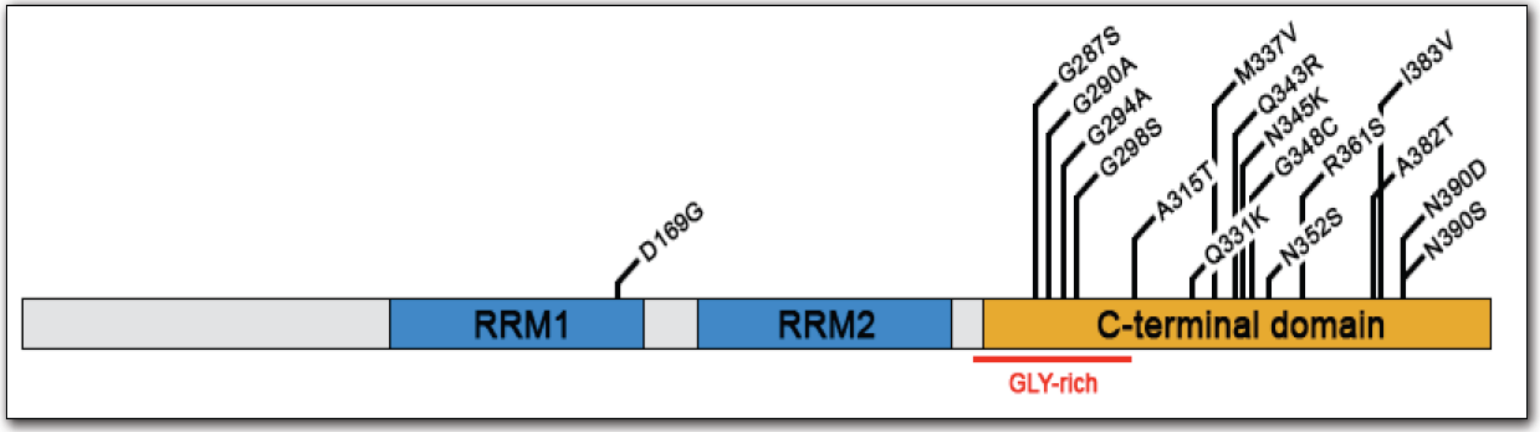
Michael A. Gitcho, PhD,[1,2] Robert H. Baloh, MD, PhD,[2] Sumi Chakraverty, MS,[1,3] Kevin Mayo, BS,[3] Joanne B. Norton, RN,[1,3] Denise Levitch, RN,[1,3] Kimmo J. Hatanpaa, MD, PhD,[4] Charles L. White III, MD,[4] Eileen H. Bigio, MD,[5,6] Richard Caselli, MD,[7] Matt Baker, BSc,[8] Muhammad T. Al-Lozi, MBBS,[2] John C. Morris, MD,[1,2,9] Alan Pestronk, MD,[2] Rosa Rademakers, PhD,[8] Alison M. Goate, DPhil,[1–3,10] and Nigel J. Cairns, PhD, FRCPath[1,2,9]

TDP-43 Mutation in Familial Amyotrophic Lateral Sclerosis

Akio Yokoseki, MD,[1] Atsushi Shiga, Mmed,[1,2] Chun-Feng Tan, MD, PhD,[3] Asako Tagawa, MD,[1] Hiroyuki Kaneko, Mmed,[1,2] Akihide Koyama, Mmed,[1,2] Hiroto Eguchi, MD,[4] Akira Tsujino, MD,[4] Takeshi Ikeuchi, MD, PhD,[2] Akiyoshi Kakita, MD, PhD,[3] Koichi Okamoto, MD, PhD,[5] Masatoyo Nishizawa, MD, PhD,[1] Hitoshi Takahashi, MD, PhD,[3] and Osamu Onodera, MD, PhD[2]

TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis

Edor Kabashi[1,6], Paul N Valdmanis[1,6], Patrick Dion[1], Dan Spiegelman[1], Brendan J McConkey[2], Christine Vande Velde[1], Jean-Pierre Bouchard[3], Lucette Lacomblez[4], Ksenia Pochigaeva[4], Francois Salachas[4], Pierre-Francois Pradat[4], William Camu[5], Vincent Meininger[4], Nicolas Dupre[1,3] & Guy A Rouleau[1]



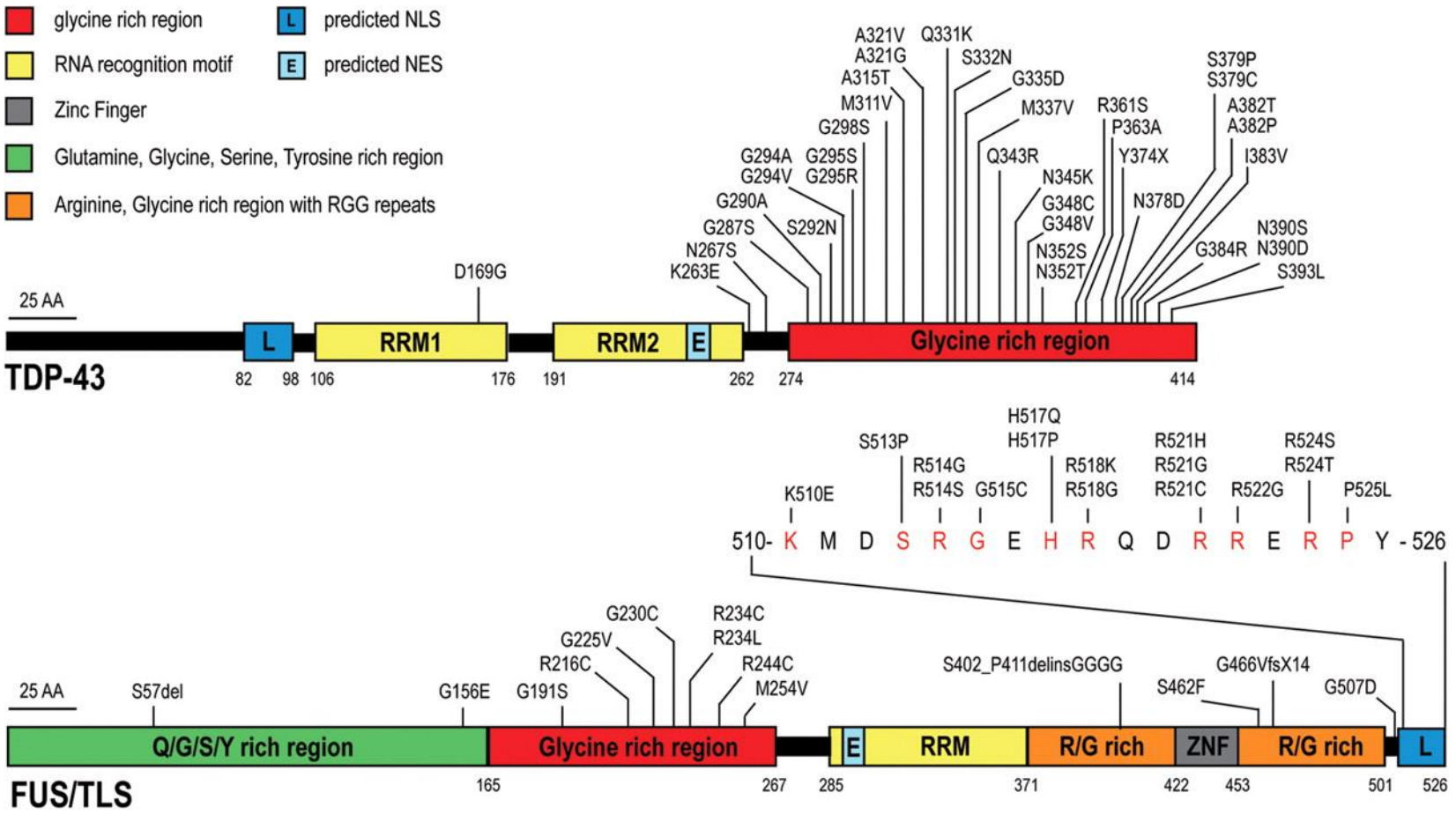
TDP-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis

Jemeen Sreedharan,[1*] Ian P. Blair,[3,4*] Vineeta B. Tripathi,[1*] Xun Hu,[1] Caroline Vance,[1] Boris Rogelj,[1] Steven Ackerley,[1,2] Jennifer C. Durnall,[3] Kelly L. Williams,[3] Emanuele Buratti,[5] Francisco Baralle,[5] Jacqueline de Belleroche,[6] J. Douglas Mitchell,[7] P. Nigel Leigh,[1] Ammar Al-Chalabi,[1] Christopher C. Miller,[1,2] Garth Nicholson,[3,4,8*] Christopher E. Shaw[1*†]

TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis

Vivianna M Van Deerlin, James B Leverenz, Lynn M Bekris, Thomas D Bird, Wuxing Yuan, Lauren B Elman, Dana Clay, Elisabeth McCarty Wood, Alice S Chen-Plotkin, Maria Martinez-Lage, Ellen Steinbart, Leo McCluskey, Murray Grossman, Manuela Neumann, I-Lin Wu, Wei-Shiung Yang, Robert Kalb, Douglas R Galasko, Thomas J Montine, John Q Trojanowski, Virginia M-Y Lee, Gerard D Schellenberg, Chang-En Yu

TDP-43 and FUS/TLS mutations in ALS and FTLD patients.



Lagier-Tourenne C et al. Hum. Mol. Genet. 2010;19:R46-R64

Human Molecular Genetics

Mendelian Genes for ALS

Gene	Protein	Location	Inheritance
ANG	Angiogenin	14q11.2	dominant
ALS2	alsin	2q33.1	recessive
FIG4	SAC1 lipid phosphatase domain containing	6q21	recessive
FUS	Fused in sarcoma	16p11.2	both
OPTN	Optineurin	10p13	both
SETX	Senataxin	9q34.13	dominant
SOD1	Superoxide dismutase 1	21q22.11	both
SPG11	Spastic paraplegia 11	15q21.1	recessive
TARDBP	TDP-43	1p36.22	dominant
UBQLN2	Ubiquilin 2	Xp11.21	x-linked dominant
VAPB	VAMP	20q13.32	dominant
VCP	Valosin-containing protein	9p13.3	dominant
PFN1	profilin 1	17p13.3	dominant
C9ORF72	C9Orf72	9p21	dominant

~70% of FALS causative genes are now known
but only 5-10% of SALS causative genes are known

Candidate and Genome wide association Studies GWAS

Collect controls preferably a large sample matched to disease sample

Collect ALS cases

Determine what Single nucleotide polymorphism
(SNP) alleles are present in control and cases
How many patients have allele A? How many have allele B?
How many controls have allele A? How many have allele B?

Need to determine whether an allele is represented more frequently
in ALS. Use 2 x 2 contingency tables and Fischer exact test on table.

Hoped reason for allele to be associated is linkage disequilibrium
Mutation occurred on a particular allele for a marker and marker lies close
to mutation therefore does not recombine frequently and tracks with mutant.

1) Dependent on time to reach equilibrium founder populations useful
2) New mutation rate needs to be low

ODDS

The "odds" are defined as the probability that an event will occur divided by the probability that the event will not occur.

If we let *p* equal the probability of an event occurring, then the probability of it not occurring is 1-*p* (remember that the highest probability is 1).

The odds would be *p* divided by 1- *p*.

2x 2 Contingency table

	allele1 Present	Absent	row totals
Patients	a	b	a +b
Controls	c	d	c + d
column totals	a+c	b+d	N= a+b+c+d

Null hypothesis no association

Expected frequency for a is (a+b)(a+c)/N

Observed – Expected for each cell

Sum of $(O-E)^2/E$ = Chi square X^2

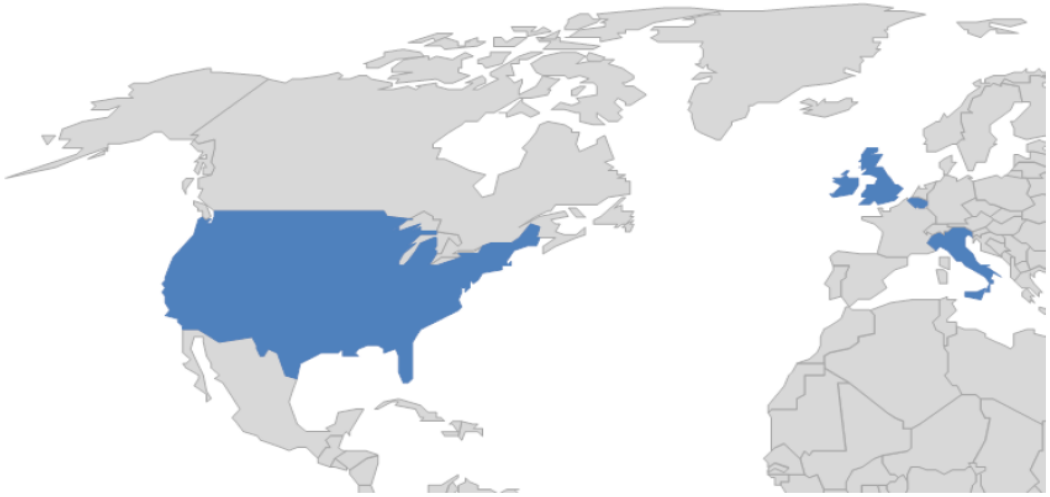
Odds ratio
a/c divided by b/d

Ie the odds of being affected when Having allele / odds of being affected Without allele

Candidate gene approach has been disappointing

- Schizophrenia Gene database:
  - 1,179 publications on 3,608 variants in 516 genes
  - 4 variants showed “strong epidemiological credibility

Allen et al, Nat Genetics 2008



ALS GWAS

Center	Number of cases	Putative loci
NIH, USA	**276 cases and 271 controls**	**-**
TGEN, USA	386 cases and 542 controls	FBBY
Utrecht, The Netherlands	461 cases and 450 controls	ITPR2, DPP6
Ireland/NIH	**221 cases and 210 controls**	**DPP6**
NIH, USA	**2,289 cases and 4,532 controls**	**SUNC1**
Boston, USA	1,821 cases and 2,258 controls	Kifap3 (survival)
Utrecht, The Netherlands	2,532 cases and 5,940 controls	UNC13A, (chr 9)

Susceptibility Loci for ALS

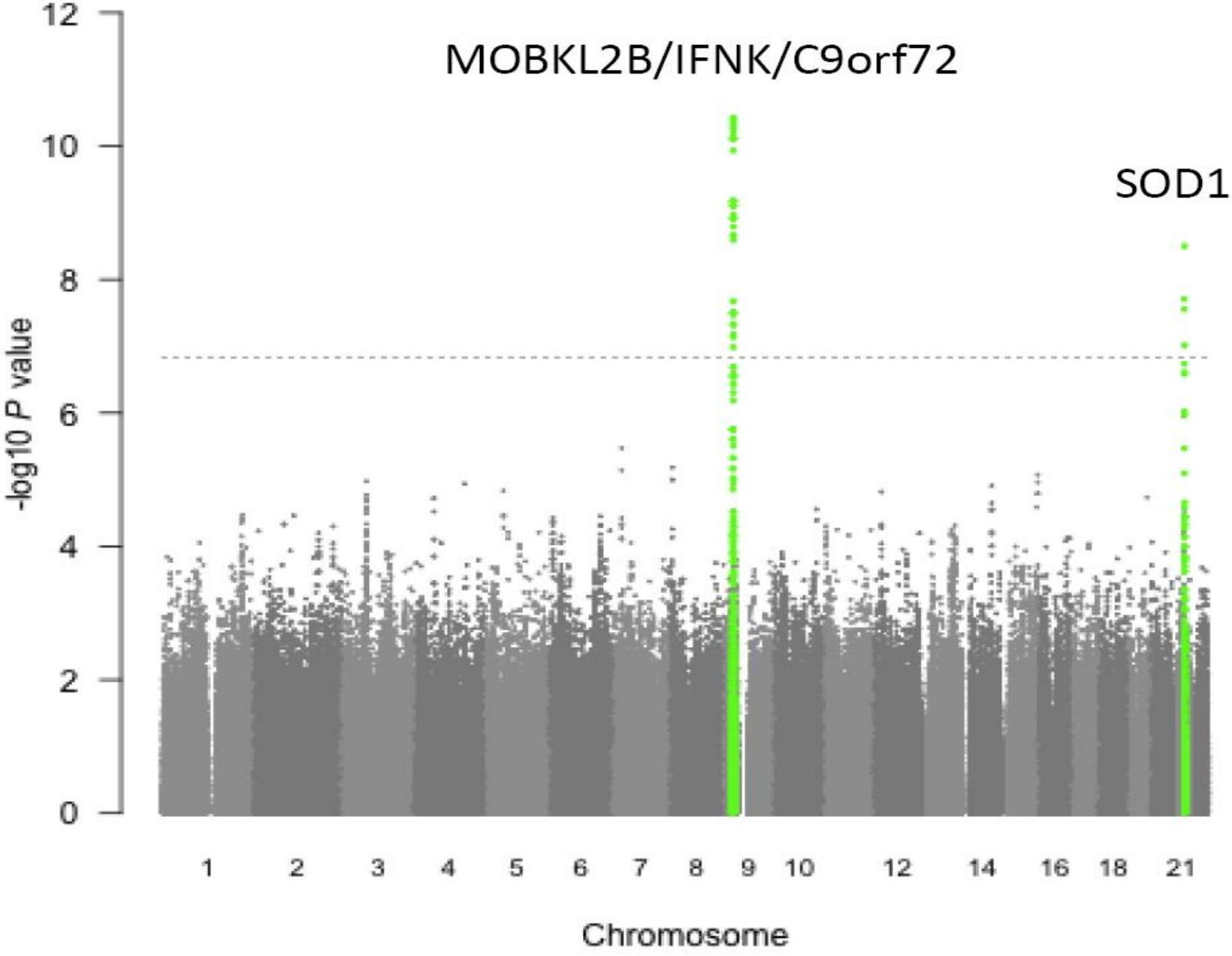
Gene	Protein	Location	Polymorphism	OR (95% CI)
UNC13A	unc-13 homolog A	19p13.11	rs12608932	1.18 (1.13-1.24)
GWA_9p21.2	Unknown	9p21.2	rs2814707	1.25 (1.19-1.32)
ATXN2	ataxin 2	12q24.12	PolyQ	n.a.

What have we learned from GWAS?

- No large effect risk locus in ALS
- None of the loci have replicated thus far
- ALS is more genetically heterogeneous than we realized

Finland is ideal for GWAS

- Incidence: 8.2/100,000
- Founder population
- High prevalence of SOD1 D90A allele
- 414 Finnish ALS cases and 511 controls genotyped on 370K SNP chips


MOBKL2B/IFNK/C9orf72
SOD1
-log10 P value
12
10
8
6
4
2
0
1
2
3
4
5
6
7
8
9
10
12
14
16
18
21
Chromosome

- GWAS of ALS in Finland has identified the first loci in ALS that clearly exceeded bonferroni
- Narrowed the locus to 140kb region containing three genes
- Affected families shared a 42 SNP haplotype
- No variants/CNV/translocations found

Neuron
Article

Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS

Mariely DeJesus-Hernandez,[1,10] Ian R. Mackenzie,[2,10,*] Bradley F. Boeve,[3] Adam L. Boxer,[4] Matt Baker,[1] Nicola J. Rutherford,[1] Alexandra M. Nicholson,[1] NiCole A. Finch,[1] Heather Flynn,[5] Jennifer Adamson,[1] Naomi Kouri,[1] Aleksandra Wojtas,[1] Pheth Sengdy,[6] Ging-Yuek R. Hsiung,[6] Anna Karydas,[4] William W. Seeley,[4] Keith A. Josephs,[3] Giovanni Coppola,[7] Daniel H. Geschwind,[7] Zbigniew K. Wszolek,[8] Howard Feldman,[6,9] David S. Knopman,[3] Ronald C. Petersen,[3] Bruce L. Miller,[4] Dennis W. Dickson,[1] Kevin B. Boylan,[8] Neill R. Graff-Radford,[8] and Rosa Rademakers[1,*]

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DOI 10.1016/j.neuron.2011.09.011

Yes GWAS did indicate region but already new the region from large families linkage analysis of ALS/FTD. Most likely reason detected on GWAS was frequency in Finish sporadic cases.

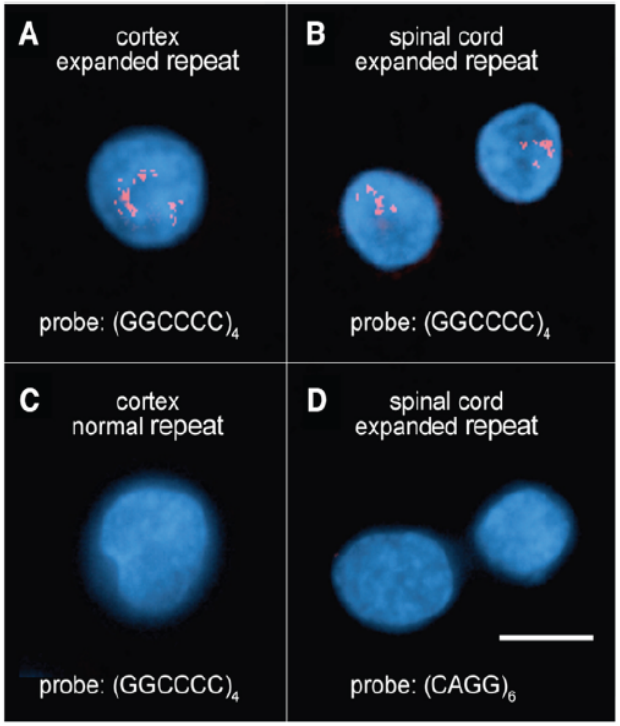
Neuron
Article

A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

Alan E. Renton,[1,38] Elisa Majounie,[2,38] Adrian Waite,[3,38] Javier Simón-Sánchez,[4,5,38] Sara Rollinson,[6,38] J. Raphael Gibbs,[7,8,38] Jennifer C. Schymick,[1,38] Hannu Laaksovirta,[9,38] John C. van Swieten,[4,5,38] Liisa Myllykangas,[10] Hannu Kalimo,[10] Anders Paetau,[10] Yevgeniya Abramzon,[1] Anne M. Remes,[11] Alice Kaganovich,[12] Sonja W. Scholz,[2,13,14] Jamie Duckworth,[7] Jinhui Ding,[7] Daniel W. Harmer,[15] Dena G. Hernandez,[2,8] Janel O. Johnson,[1,8] Kin Mok,[6] Mina Ryten,[6] Danyah Trabzuni,[8] Rita J. Guerreiro,[6] Richard W. Orrell,[16] James Neal,[17] Alex Murray,[18] Justin Pearson,[3] Iris E. Jansen,[4] David Sondervan,[4] Harro Seelaar,[5] Derek Blake,[3] Kate Young,[6] Nicola Halliwell,[6] Janis Bennion Callister,[6] Greg Toulson,[6] Anna Richardson,[19] Alex Gerhard,[19] Julie Snowden,[19] David Mann,[19] David Neary,[19] Michael A. Nalls,[2] Terhi Peuralinna,[9] Lilja Jansson,[9] Veli-Matti Isoviita,[9] Anna-Lotta Kaivorinne,[11] Maarit Hölttä-Vuori,[20] Elina Ikonen,[20] Raimo Sulkava,[21] Michael Benatar,[22] Joanne Wuu,[23] Adriano Chiò,[24] Gabriella Restagno,[25] Giuseppe Borghero,[26] Mario Sabatelli,[27] The ITALSGEN Consortium,[28] David Heckerman,[29] Ekaterina Rogaeva,[30] Lorne Zinman,[31] Jeffrey D. Rothstein,[14] Michael Sendtner,[32] Carsten Drepper,[32] Evan E. Eichler,[33] Can Alkan,[33] Ziedulla Abdullaev,[34] Svetlana D. Pack,[34] Amalia Dutra,[35] Evgenia Pak,[35] John Hardy,[8] Andrew Singleton,[2] Nigel M. Williams,[3,38] Peter Heutink,[4,38] Stuart Pickering-Brown,[6,38] Huw R. Morris,[3,36,37,38] Pentti J. Tienari,[9,38] and Bryan J. Traynor[1,14,38,*]

How do GGGGCC expansions in *C9ORF72* cause FTLD/ALS?

Clues



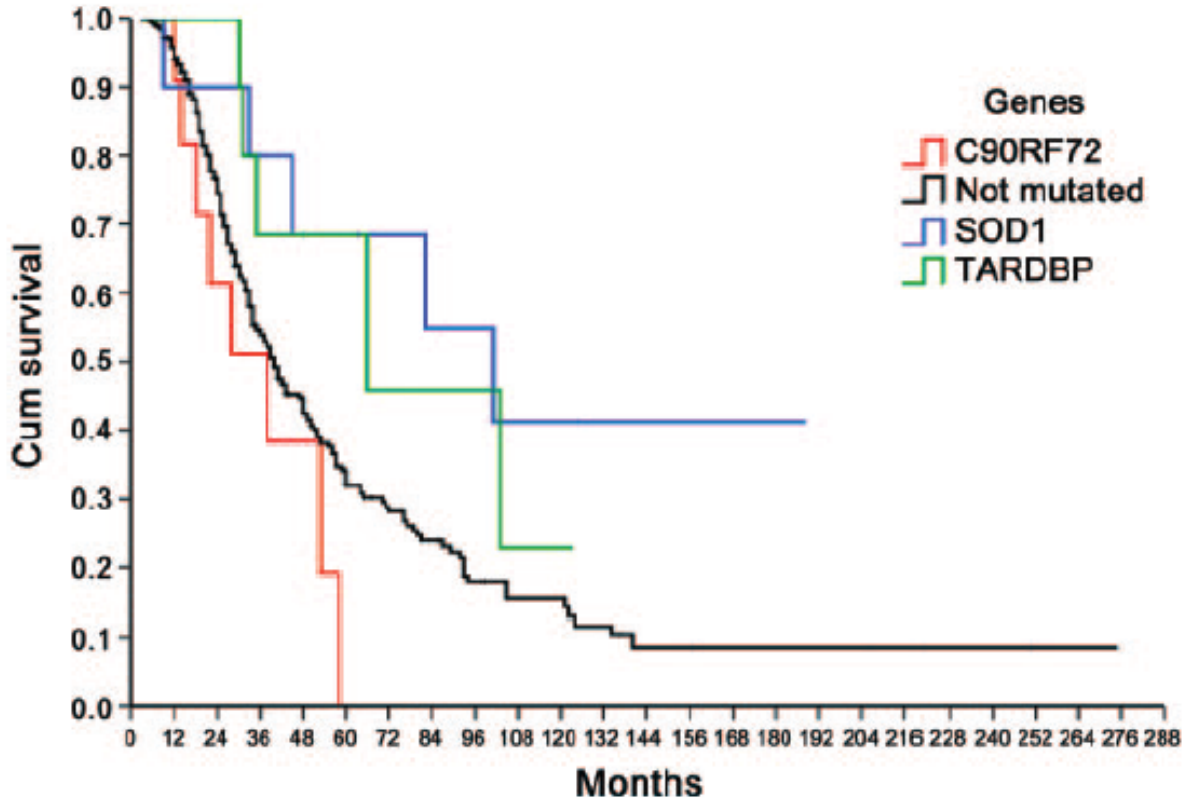
? RNA toxc or RAN translation peptide

C9orf72 hexanucleotide repeat expansion

- Identified in large families with FTD/ALS
- Length of expansion ranges from 30-1600 repeats
  - Majority of controls have 2 repeats up to 23
- Accounts for ~12% of familial FTD and 3% sporadic FTD
- Accounts for ~24% of familial ALS and 4% sporadic ALS
- More severe course on average

Rate of progression in ALS depends on mutation

Figure 3 Survival analysis



Survival curves of patients carrying *SOD1*, *TARDBP*, and *C9ORF72* mutations and of patients without detectable mutations.

Contribution of major amyotrophic lateral sclerosis genes to the etiology of sporadic disease

Table 1 Clinical and demographic findings

	Patients with mutations								Without mutations, total
	SOD1	*TARDBP*	*FUS*	*ANG*	*OPTN*	*ATXN-2*	*C9ORF72*	Total	
No. (%) of patients	10 (2.1)	13 (2.7)	3 (0.6)	6 (1.2)[a]	3 (0.6)	8 (1.7)	12 (2.5)	53 (11)	427 (89)
Age at onset, y (range)	56.3 (36-71)	53.2 (27-75)	37 (11-58)	60 (38-86)	70 (67-76)	57.5 (42-76)	58.8 (38-75)	57.9 (27-86)[b]	60.1 (22-84)
No. (%) of men	2 (20)	7 (53.8)	2 (66.7)	1 (16.6)	1 (33.3)	6 (75)	7 (58.3)	26 (49)	256 (59.9)
Site of onset, n (%)									
Bulbar	0	3 (23.1)	1 (33.3)	1 (16.6)	1 (33.3)	2 (25)	3 (25)	11 (20.7)	124 (29)
Spinal	10 (100)	10 (76.9)	2 (66.7)	5 (83.4)	2 (66.7)	6 (75)	9 (75)	42 (79.3)	299 (70)
Respiratory	0	0	0	0	0	0	0	0	4 (1)
Phenotype, n (%)									
Classic	5	5	1	3	3	7	7 (1)[c]	30 (1)[c]	271 (21)[c]
UMN-D	3	7	1	3	—	—	3	15	107 (1)[c]
Flail	—	1	1	—	—	1	—	3	21
LMN	2	—	—	—	—	—	2	5	28 (1)[c]
Median survival, mo	101	66	24	33	16	54	38	53	40

Abbreviations: LMN = lower motor neuron; UMN-D = upper motor neuron dominant.
[a] Two of the 6 patients are also included in *SOD1* and *C9ORF72* groups.
[b] The patient with juvenile amyotrophic lateral sclerosis was excluded.
[c] In brackets are reported the number of cases with associated FTD.

Other and Future

Chesi et al 2013 Nat Neurosci. 2013 Jul;16(7):851-5.
Mutations in chromatin remolding protein CREST (associates with Fus)

Exome sequenced 47 trios ALS proband and parents

Six trios proband has two or three de novo variations in genes

Does denovo mutation play a role and how??

Genetic interaction does this occur difficult to be sure depends on frequencies

Whole genome or exome sequencing of more famalies to address these issues.
Trios father mother proband

All C9ORF expansions share a founder haplotype ? Penetrance UK screen .15% of controls

Other ALS genes HnRNPA1 and 2B1 and *MATR3*

Prion domain theories (TDP43, Fus) ? Could you have a somatic mutation that the spreads like prions through the nerve?

Mechanism of ALS Do we know ?

1) Some ALS mutations not completely penetrant have the mutation but never get ALS or delays onset markedly. Can factors effecting penetrance be identified? Do they work for different ALS mutations and are they therapeutic targets?

2) Is there a common mechanism for different ALS mutations?

3) Can genetics be used to confirm refute biochemical mechanism importance to the phenotype? I think yes and should be done.

4) Complex models ie two or three genes with additive effects?