MVIMG 7470

Neuromuscular Biology and Disease

The C9ORF72 repeat expansion in ALS

Kathrin Meyer, PhD
Nationwide Children's Hospital
Center for Gene Therapy
Columbus, Ohio, USA

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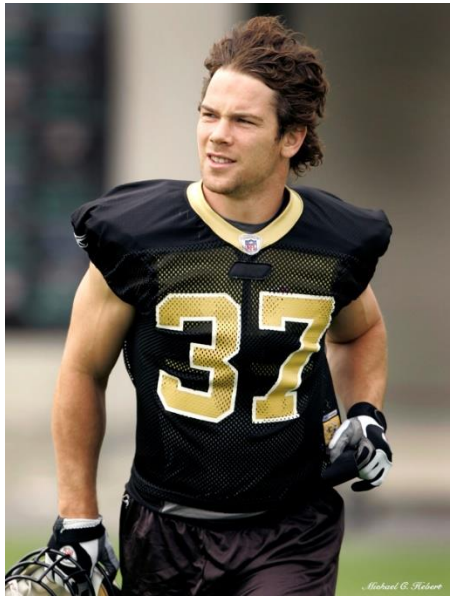
THE OHIO STATE UNIVERSITY Medical Center

The C9ORF72 repeat expansion in ALS

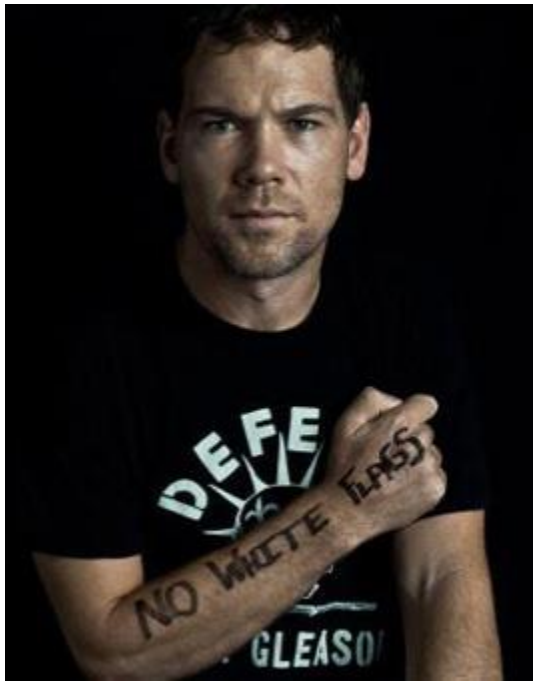


Steve Gleason

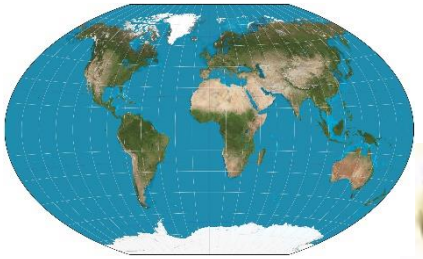
It's complicated…

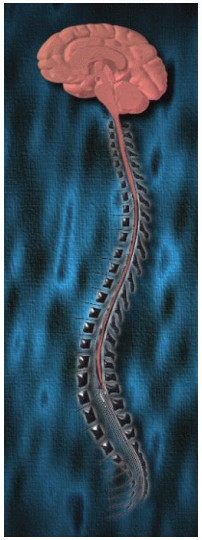
…sometimes frustrating…

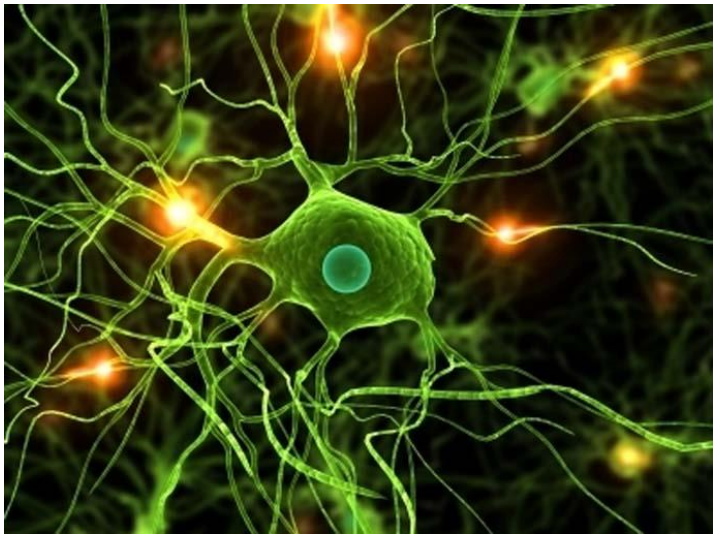
more questions than answers!



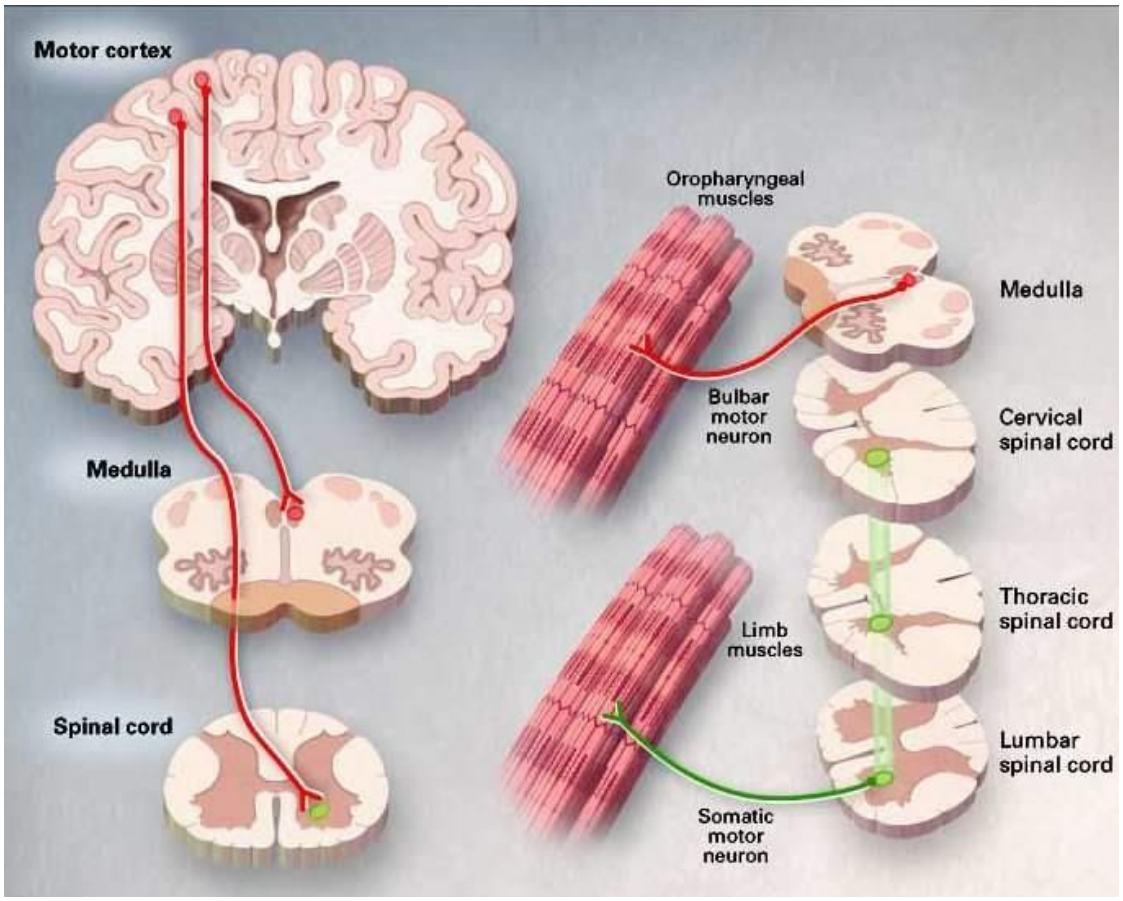
Overview







Amyotrophic Lateral Sclerosis



→ Adult onset neurodegeneration

→ appr. 20’000 individuals in USA

→ Degeneration of upper and lower motor neurons

→ Paralysis and ultimately death

→ ~ 90% sporadic, 10% familial cases

→ Various disease causing genes identified (SOD1, TDP-43, FUS, C9ORF72)

→ Vast majority of cases: cause unknown

Discovery of the Repeat

Recent efforts have revealed new genes involved in ALS

Neuron
Article

Cell PRESS

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,[8] Mina Ryten,[8] Danyah Trabzuni,[8] Rita J. Guerreiro,[8] 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,*]

Neuron
Article

2011: 2 publications linking a repeat expansion in C9ORF72 to ALS and FTD

Cell PRESS

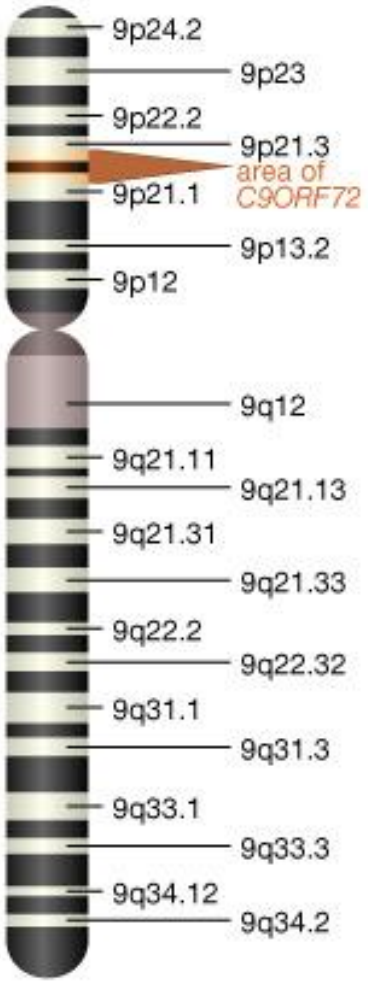
How did they discover the repeat?

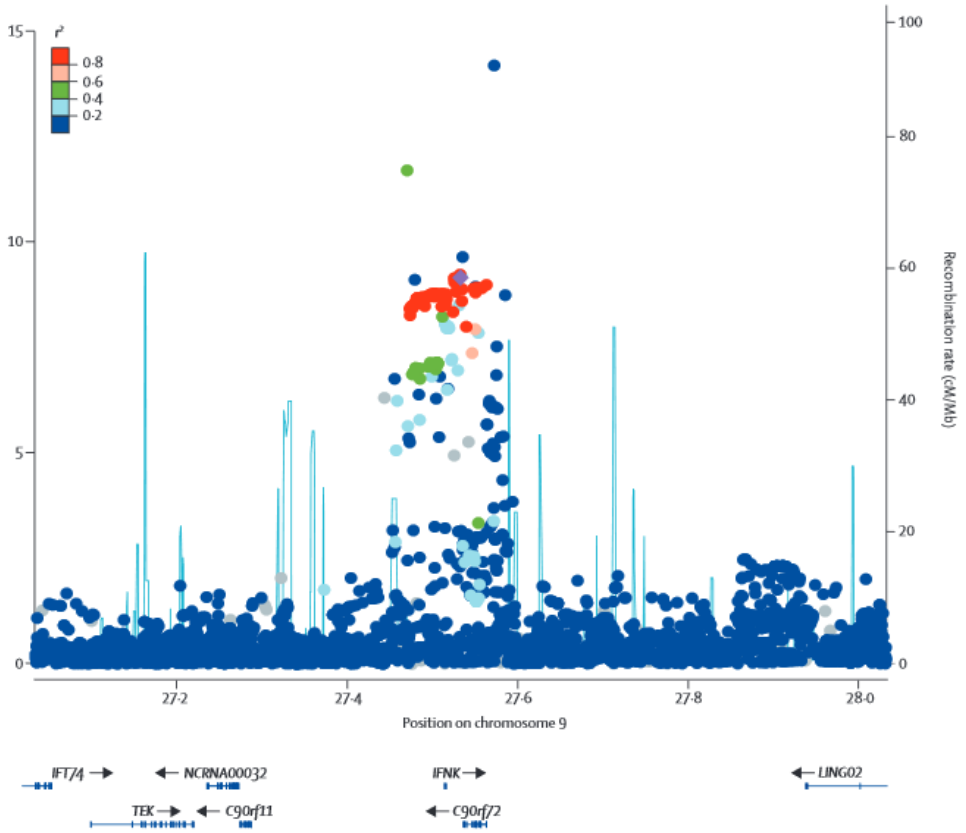
Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS

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,*]
[1]Department of Neuroscience, Mayo Clinic Florida, Jacksonville, FL 32224, USA

Discovery of the Repeat

Association of risk locus in the region of C9ORF72

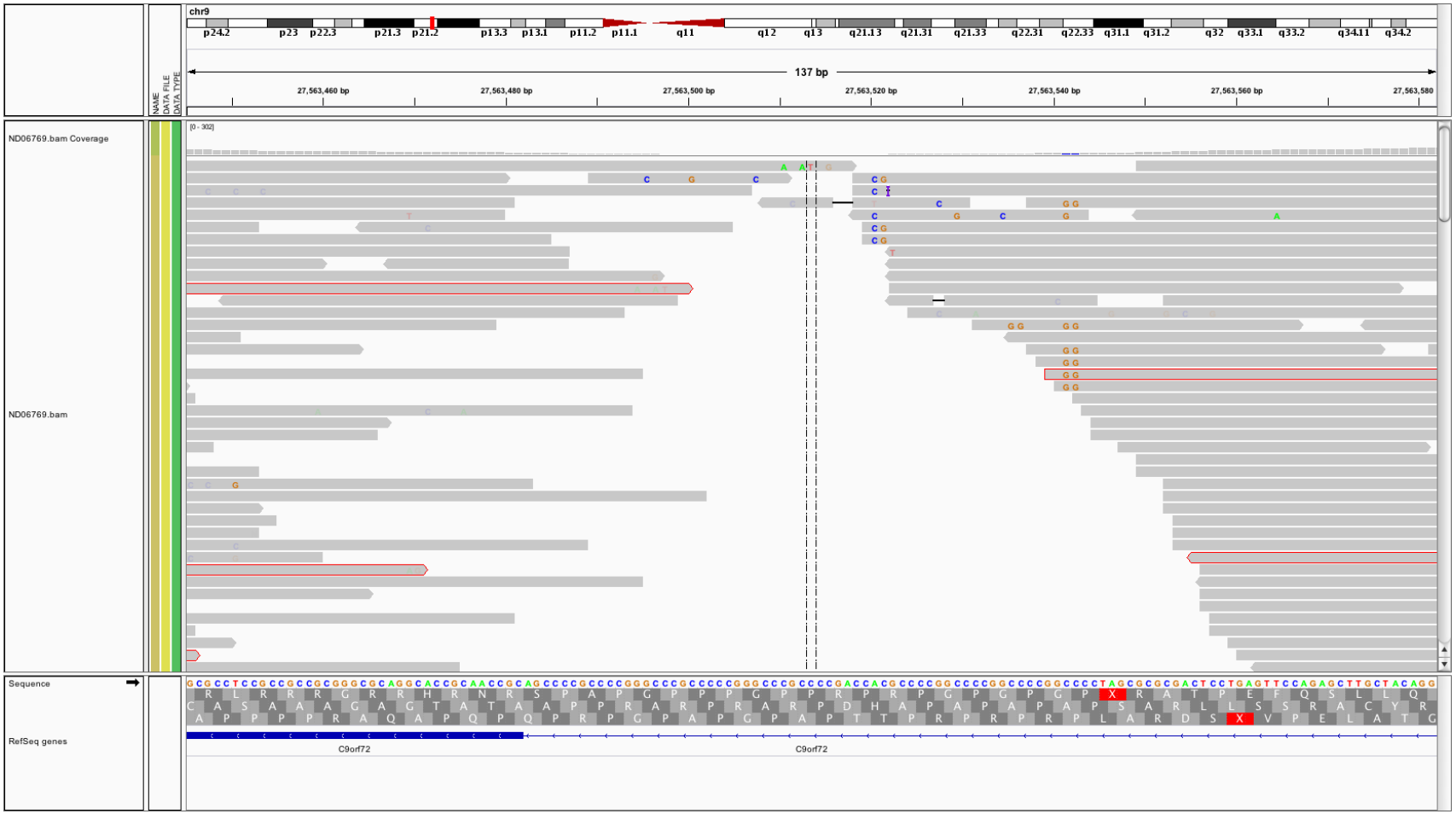




Shatunov et al., Lancet Neurol 2010

Discovery of the Repeat

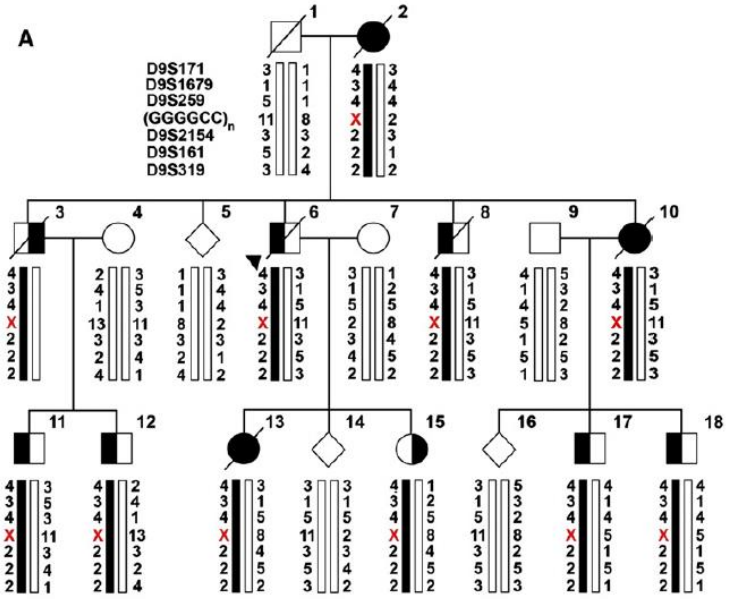
Next generation sequencing methods failed to amplify the repeat containing region...

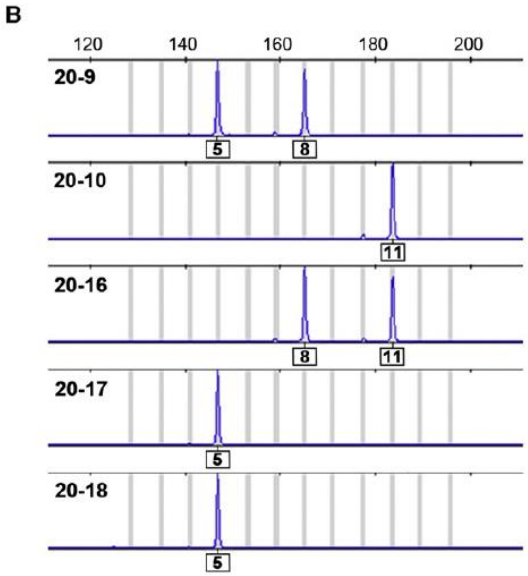


Renton et al, Neuron 2011

Discovery of the Repeat

Affected individuals seemed all homozygous via PCR based detection methods...





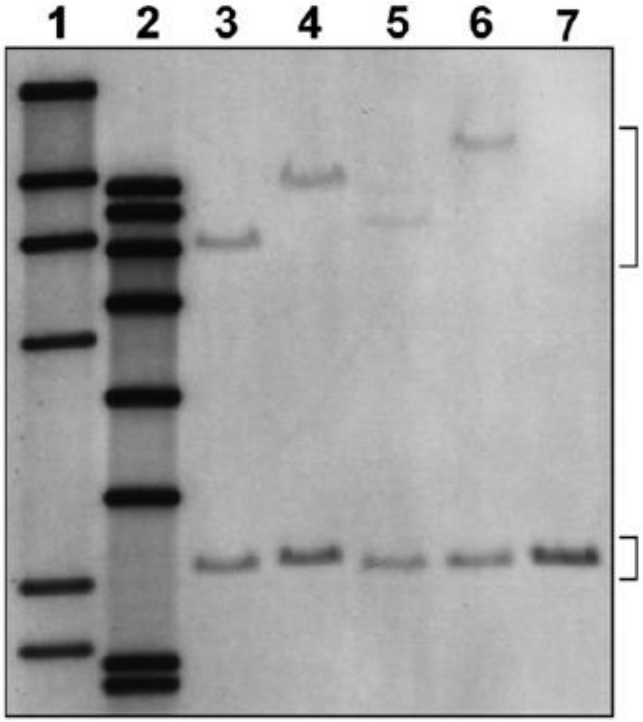
DeJesus-Hernandez, Neuron 2011

Or is amplification inhibited?

Back to the ancient methods...

Discovery of the Repeat

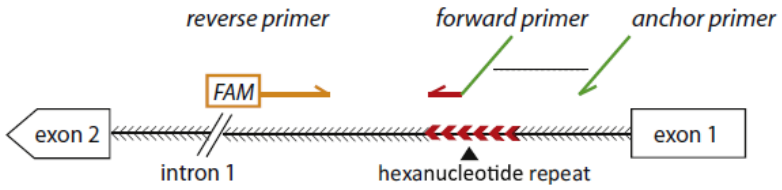
Back to the ancient methods...

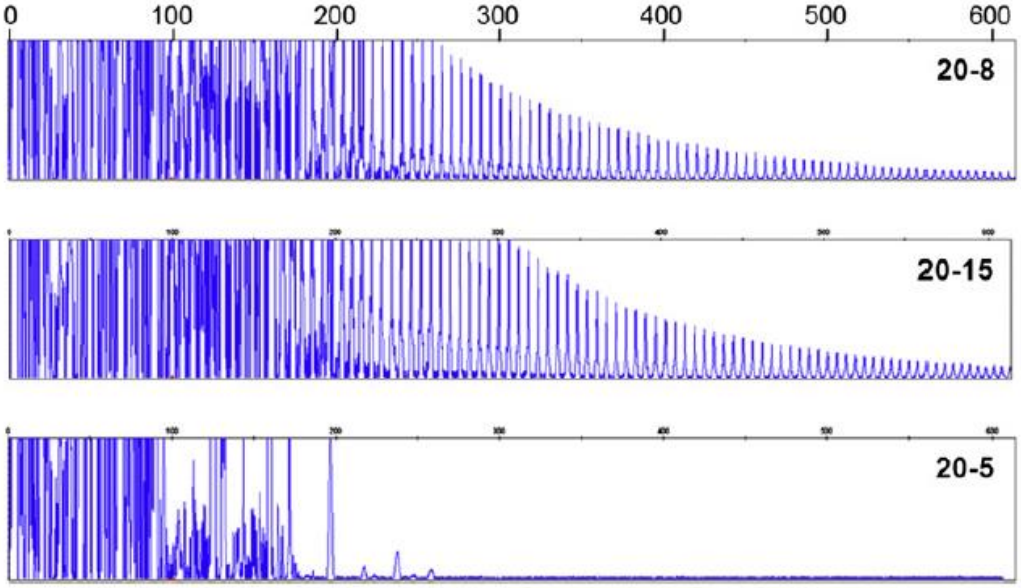


Southern blot revealed repeat expansion

Discovery of the Repeat

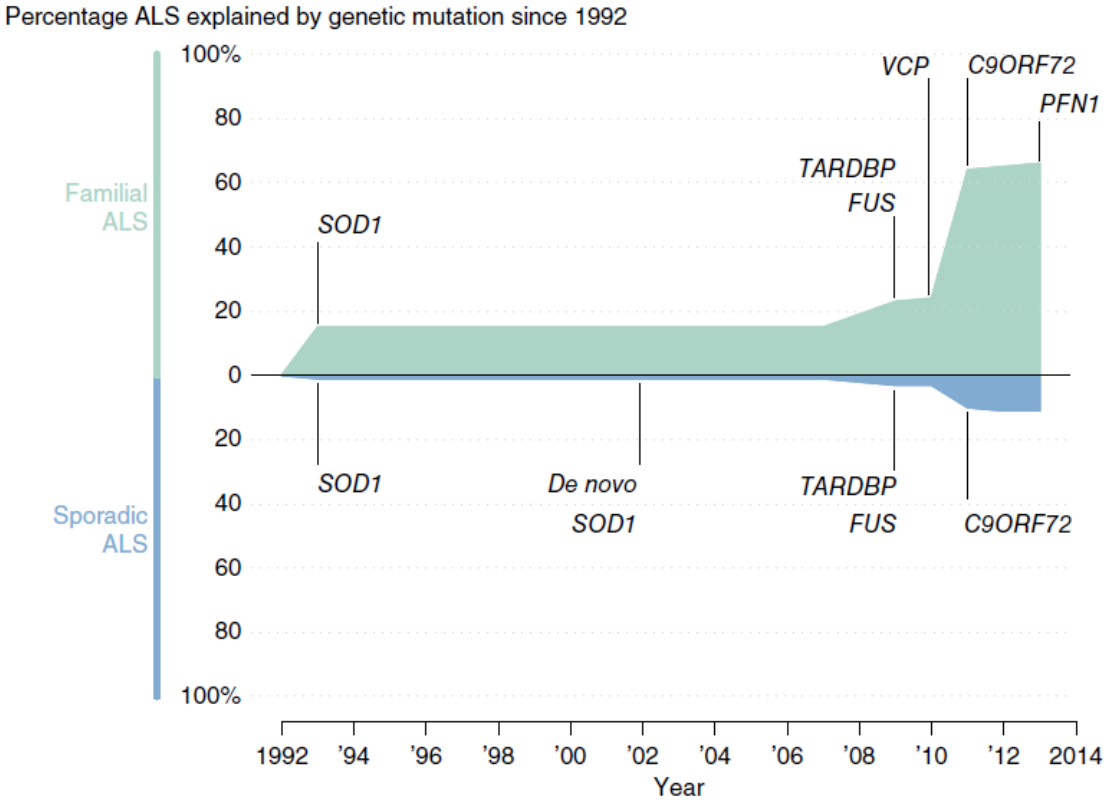
Confirmation with repeat primed PCR methods...





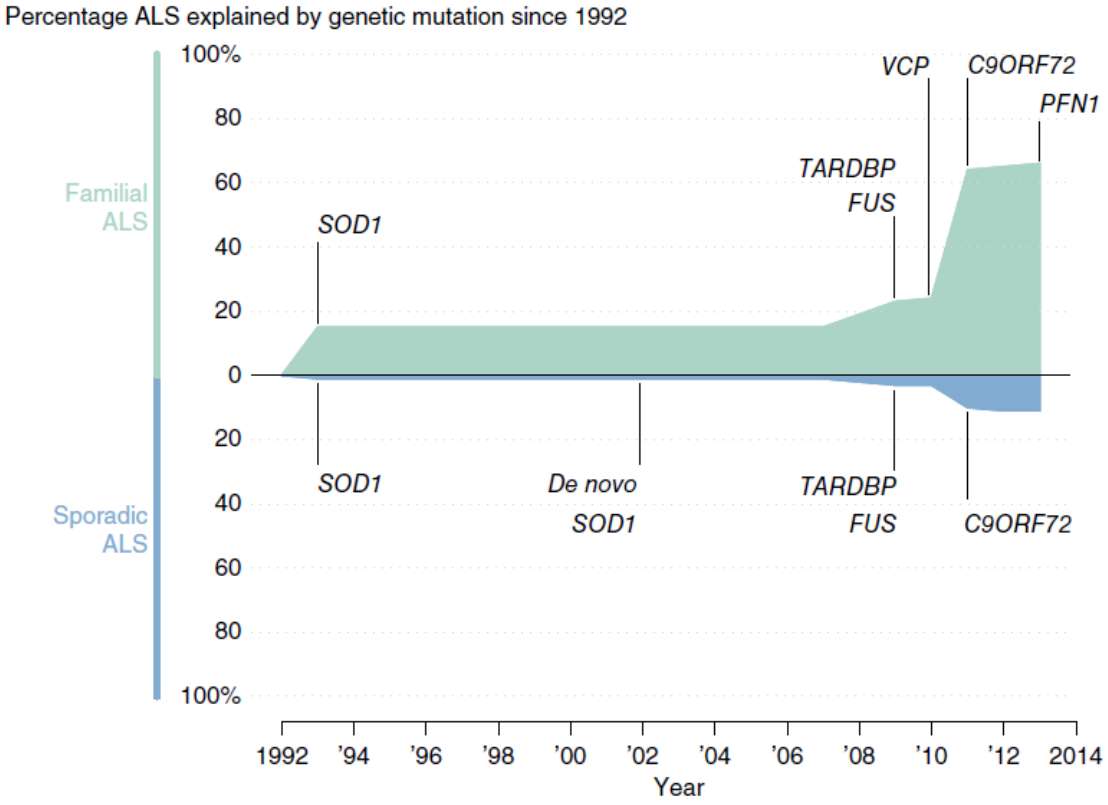
Not able to determine repeat size

Why is C9ORF72 important in ALS?



- **C9ORF72 mutations are the most frequent cause of familial ALS and the most frequent known cause of sporadic ALS**

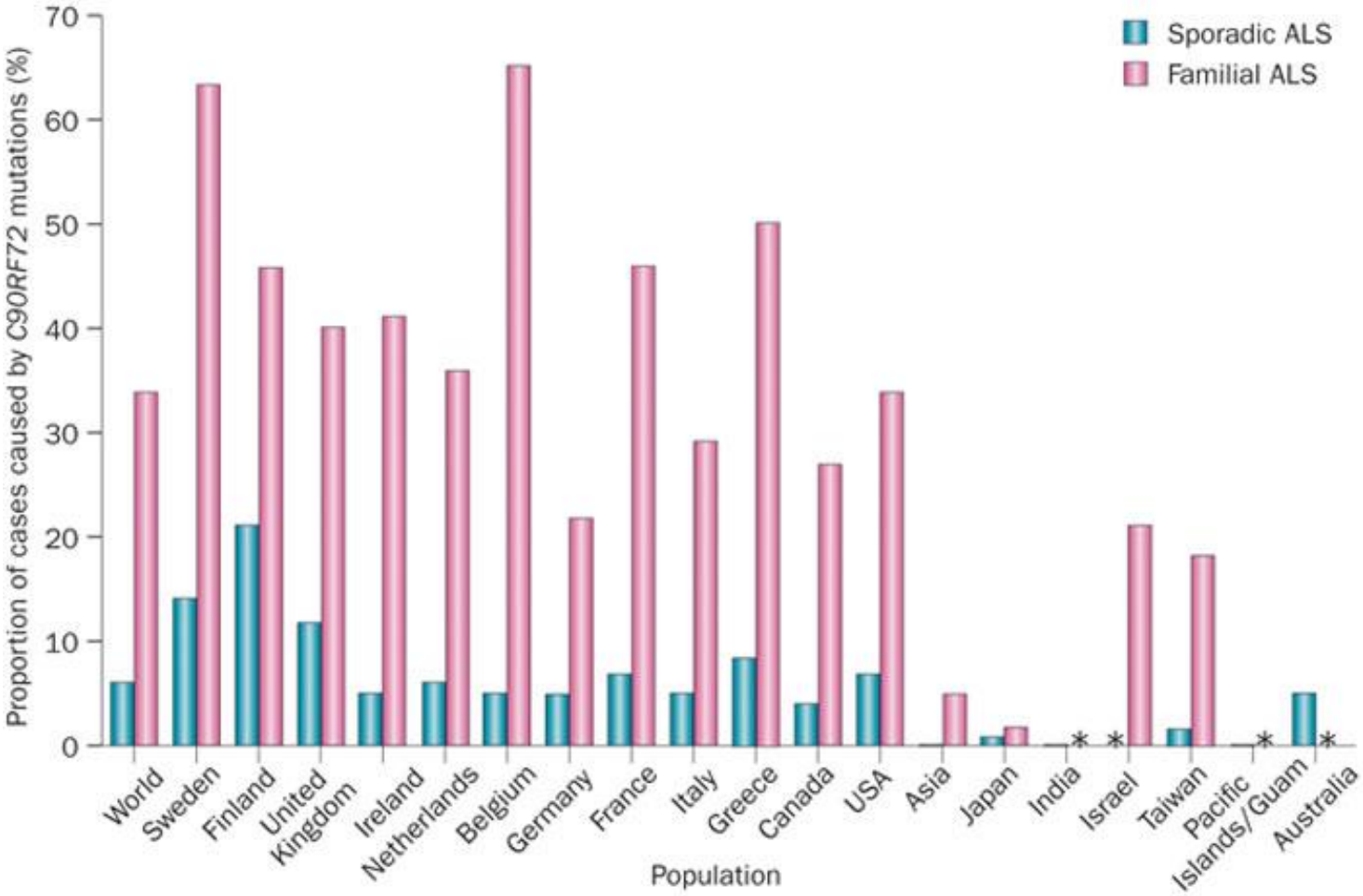
Why is C9ORF72 important in ALS?



Where does it come from?

Origin and distribution of C9ORF72

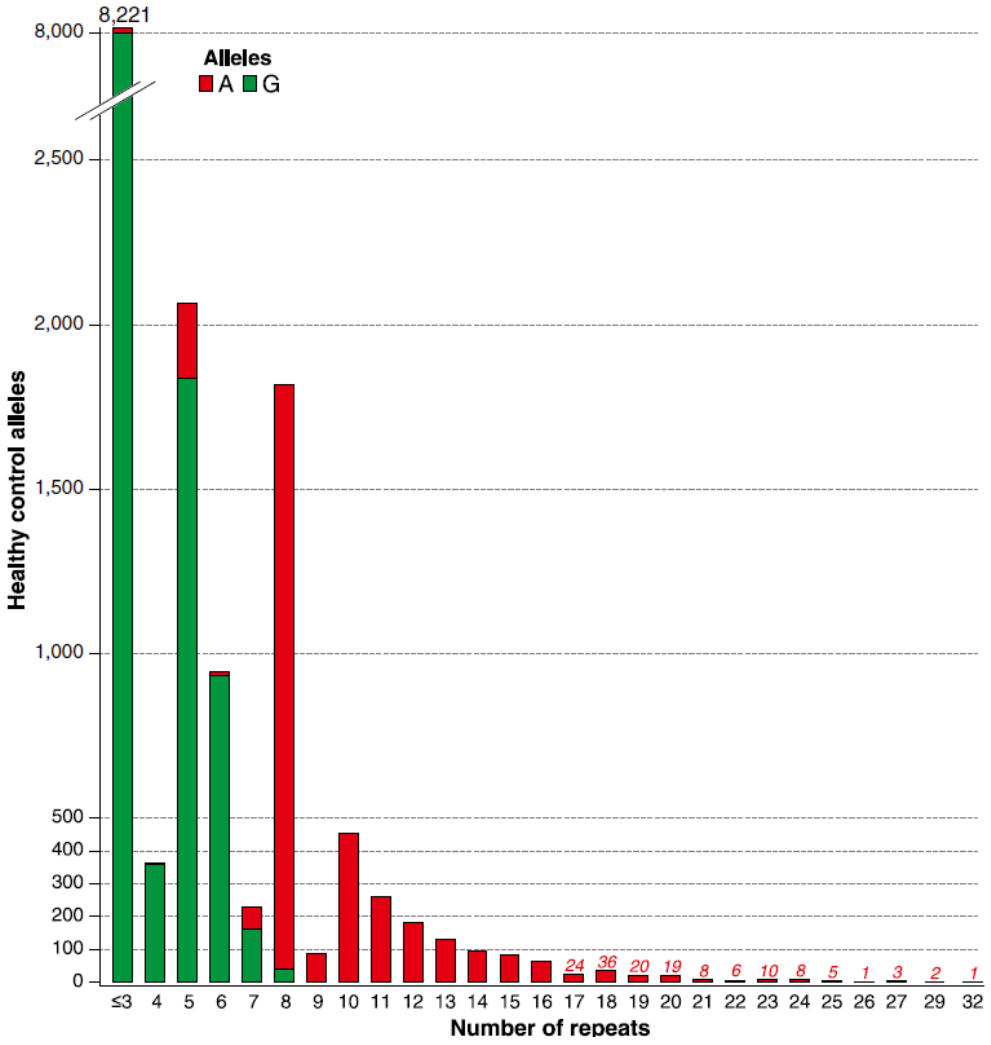
High prevalence of the mutation in northern Europe



Rademaker and van Blitterswijk, Nature Rev Neurology 2012

- **Distribution of this mutation worldwide varies extensively**

Origin and distribution of C9ORF72

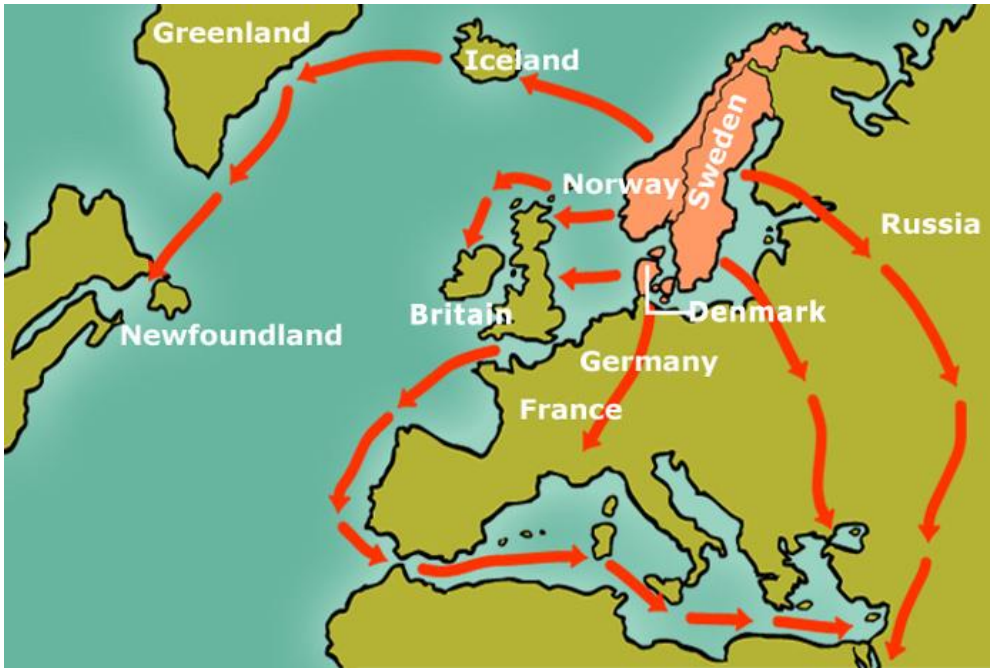


Beck et al, the American J of Human Genetics, 2013

- **Risk allele is common in healthy population in europe**
- **Associated with higher instability and bigger repeat length in healthy individuals**
- **Most, but not all patients with C9ORF72 expansions carry this risk haplotype**
- **Even without repeat expansion, allele still associates with disease**
- **Is the repeat or the instability of the region inherited?**

Origin and distribution of C9ORF72

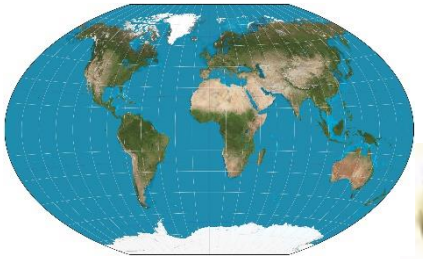
Existence of single founder allele spread by the Vikings?

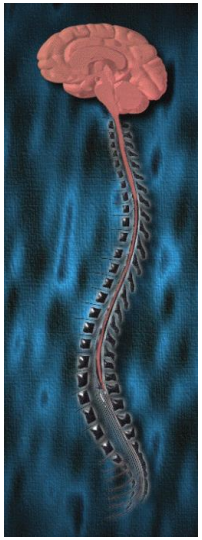


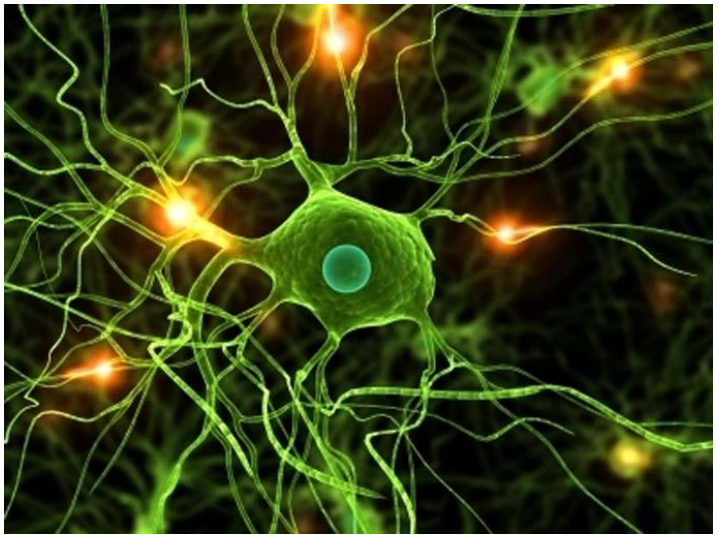
- Theory currently debated – high prevalence in certain other populations difficult to be explained by this migration (S Europe + E Asia)

- Larger study including 82 SNPs indicates that this founder haplotype is likely older – found in European, African and distant Asian populations
  (Smith et al, Eur J Hum Genet 2013)

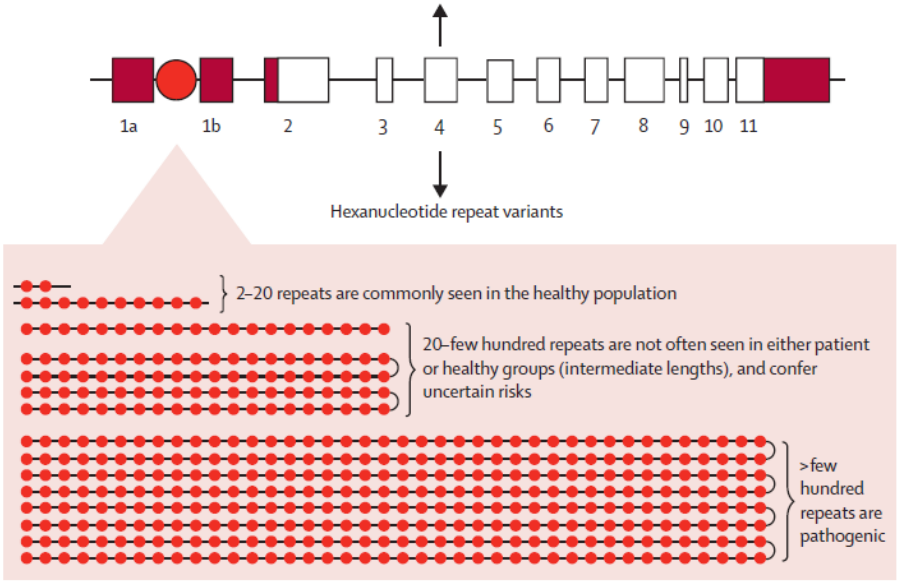
Overview







Pathogenic C9ORF72 repeat size

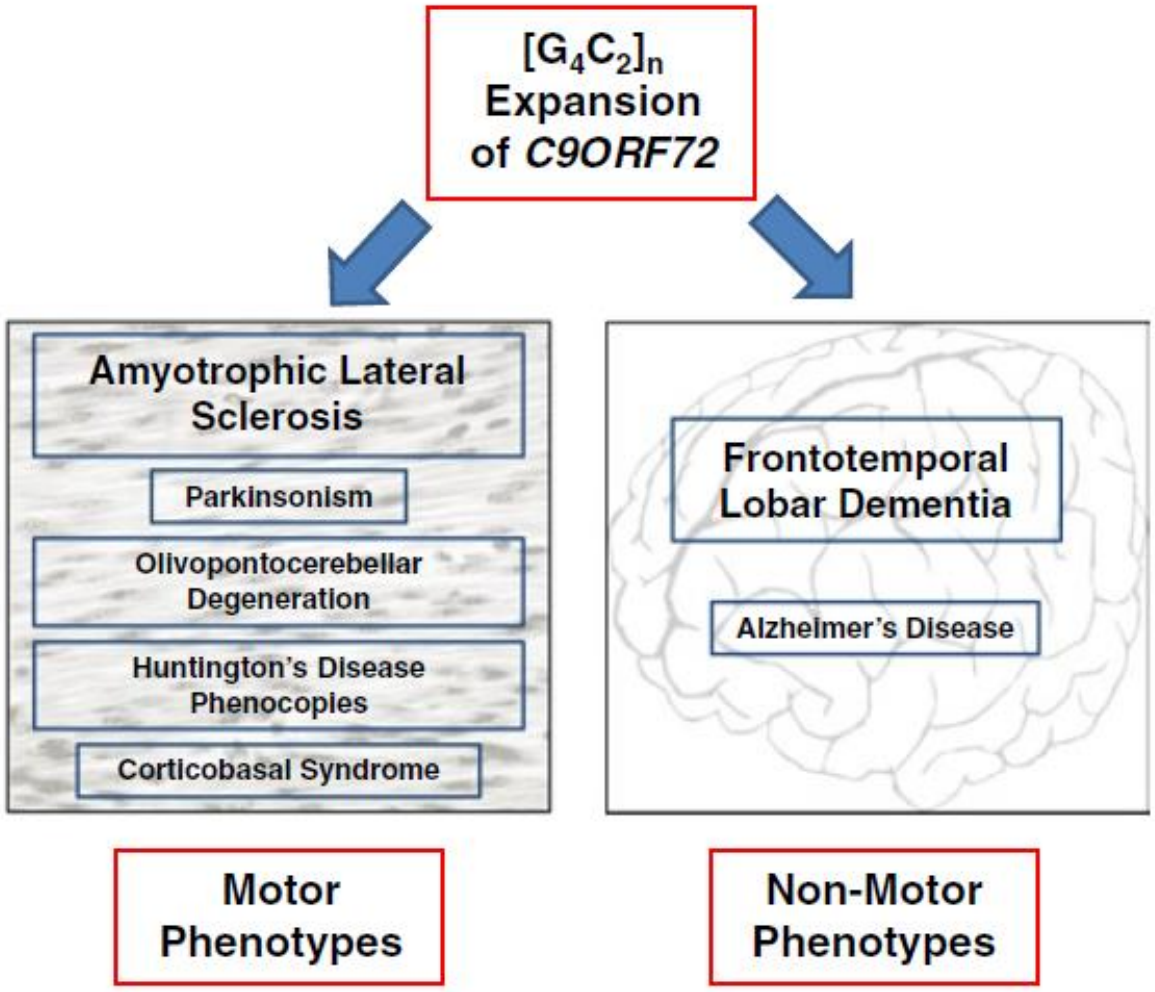


Rohrer et al.,Lancet Neurol 2015

- **Normal repeat size = variable – more than 90% of Europeans 2-10 repeats**
- **Small: Larger than 30 repeats can be found in healthy individuals, although rare**
- **Intermediate: 20 – several hundred can be pathogenic or not**
- **Big: Repeat size in patients usually several hundreds or thousands of repeats**

Disease characteristics of C9ORF72

Clinical spectrum broad, even within families



Cooper-Knock et. al, Acta Neuropathol 2014

Disease characteristics of C9ORF72

Mixed phenotype might be more common than usually thought in general

- **Up to 50% of sporadic ALS cases could show cognitive impairments**

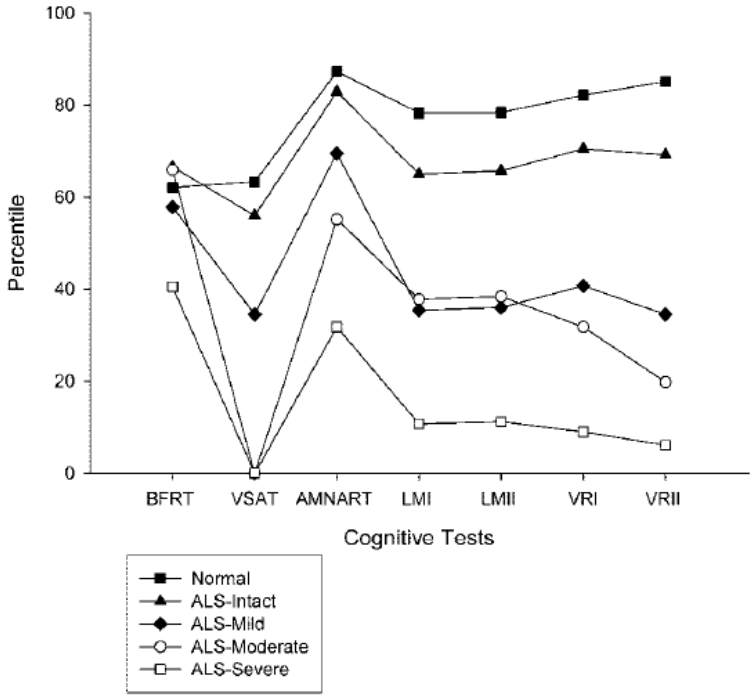
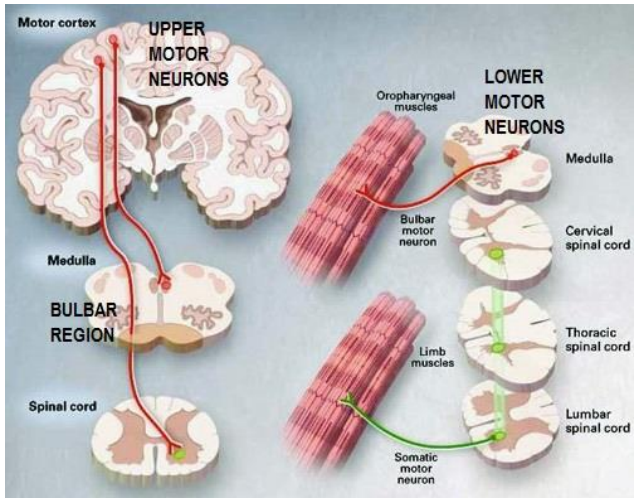


Figure. Comparison of cognitive performance in normal controls vs four amyotrophic lateral sclerosis groups. BFRT = Benton Facial Recognition Test; VSAT = Verbal Series Attention Test; AMNART = American National Reading Test; LMI = Logical Memory subtest from the Wechsler Memory Scale-Revised (immediate recall); LMII = Logical Memory subtest from the Wechsler Memory Scale-Revised (delayed recall); VRI = Visual Reproduction subtest from the Wechsler Memory Scale-Revised (immediate recall); VRII = Visual Reproduction subtest from the Wechsler Memory Scale-Revised (delayed recall).

Ringholz et. al, Neurology 2005

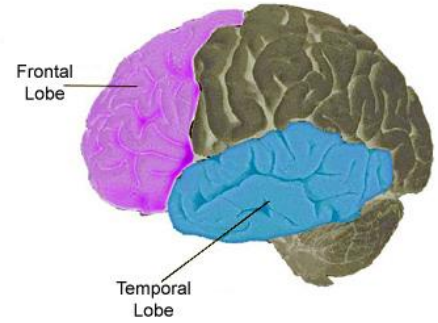
Disease characteristics of C9ORF72

ALS: Amyotrophic Lateral Sclerosis



- Most common adult onset motor neuron disorder
- 1-2/100'000 individuals, onset 50-60 years
- Average survival ~ 3 years

FTD: Frontotemporal Dementia



- Second most common form of pre-senile dementia after Alzheimer's disease
- 10-30/100'000 individuals, onset 45-65 years
- Average survival ~ 7 years

Short disease length = increased life time risk

Diverse clinical phenotype implicates presence of disease modifiers

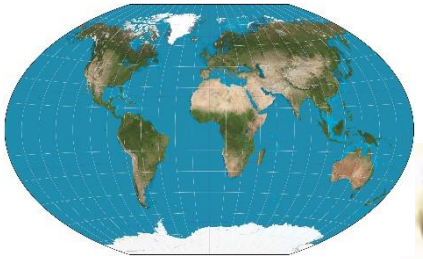
Disease characteristics of C9ORF72

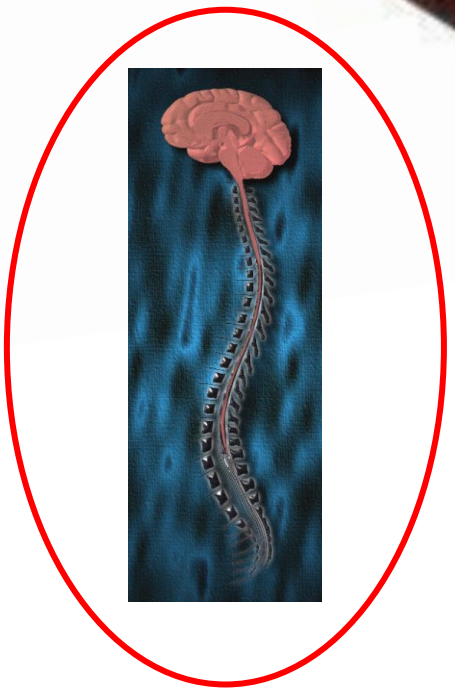
Variation in time and type of onset

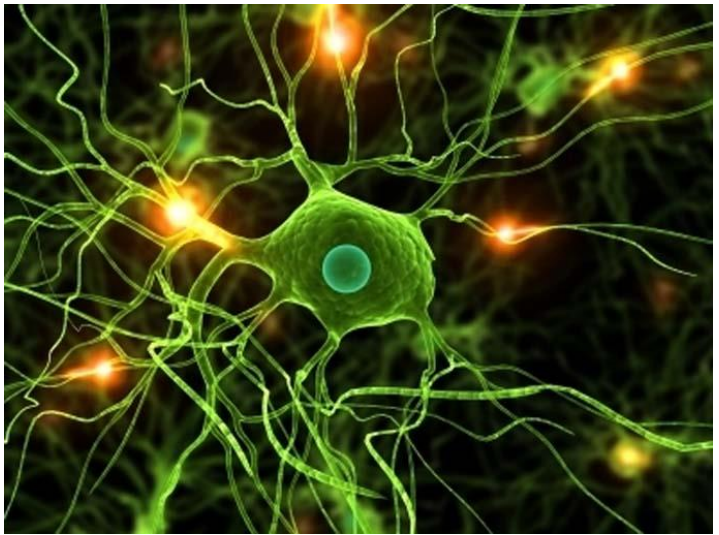
- Penetrance = age dependent, but nearly 100% at the age of 80
- Several studies show overrepresentation of bulbar onset for C9ORF72-ALS
- Incidence of dementia or family history of dementia is higher in C9ORF72-ALS cases
- Potential evidence for younger age of disease onset in ALS caused by C9ORF72 repeat expansions
- Potential evidence for shorter survival of C9ORF72 ALS cases compared to non-C9ORF72 cases
- Gender might be important – males showed earlier onset in 1 study

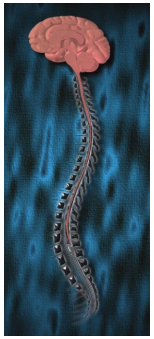
Reviewed in Cooper-Knock et al, Acta Neuropathol 2013

Overview

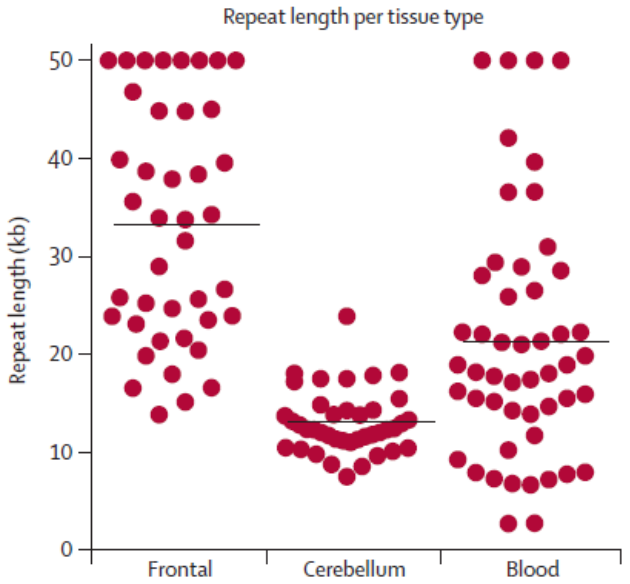


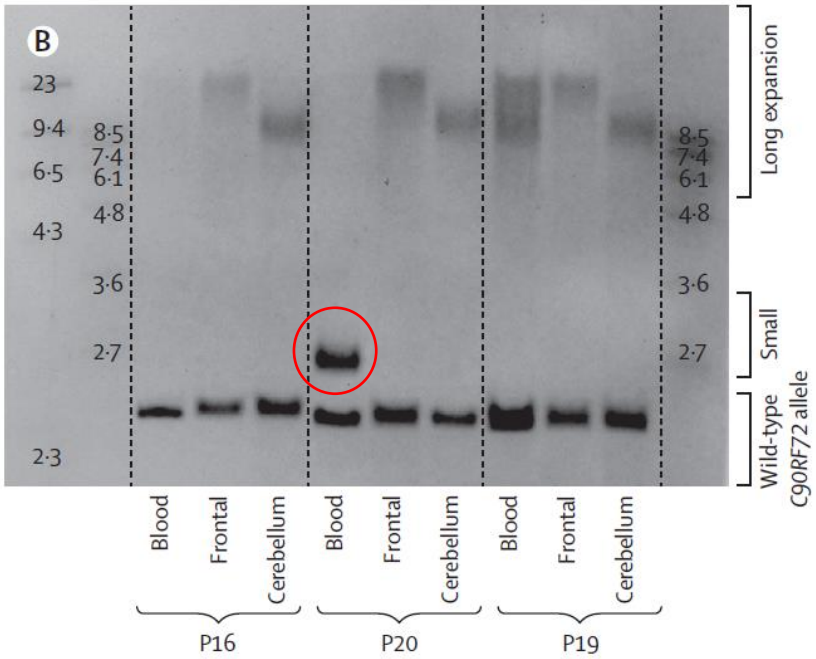






Somatic heterogeneity of C9ORF72 repeat expansions



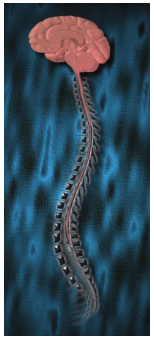


Blitterswijk et al.,Lancet Neurol 2013

→ **Tissue specific variation in repeat size**

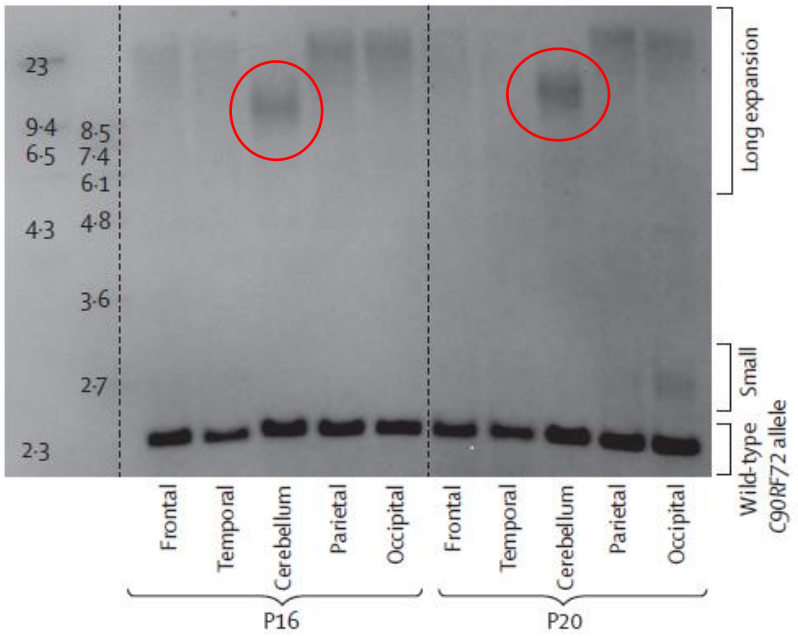
→ **Expansions can increase throughout life span**

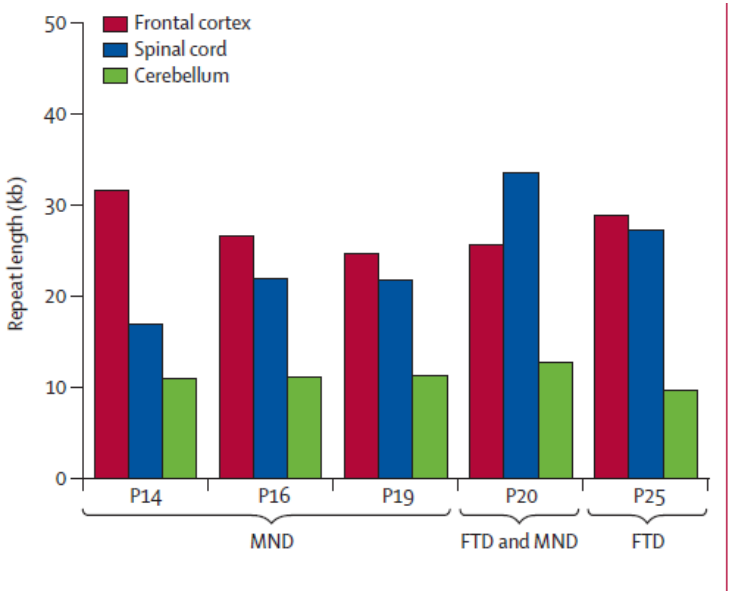
→ **Substantial problem for testing of patients due to CNS sample availability**



Somatic heterogeneity of C9ORF72 repeat expansions

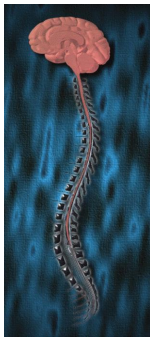
Repeat size in the CNS varies between regions





Blitterswijk et al.,Lancet Neurol 2013

- **Repeats are shorter and less variable in the cerebellum (mean ~ 1'667 vs 5'250 repeats in frontal cortex)**



Origin somatic heterogeneity

- **Similar observations found in mouse models of other repeat expansions**

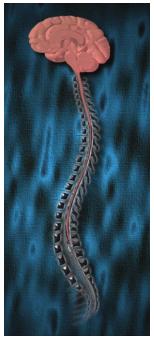
Table 3. Tissue-specificity phenotypes found in the mouse models in Table 2

Mouse model	Repeat length	Brain	Cerebellum	Cerebral cortex	Heart	Kidney	Liver	Skeletal muscle	Spleen	Striatum
DM1 knock in	84	++			–	+++	++	+		
DM300	360	++	–		–	++	+++	+		
Hdh^{Q111}	111		+	+	–	++	+++		–	+++
SCA1	154		–	++	+	++	+	+		+++
SCA7-CTCF-I-mut	94		+	++	–	+++	+++			+++
SCA7-CTCF-I-wt	92		+	++	–	+	+++			++
R6/1	116	+++	–	+	–	++	+++		–	+++
R6/2	144		–	+	–	+	+		–	+++

Blank, not tested; –, no instability detected; + to +++, marginal to extreme instability.
This list was updated from that in [108]. Only tissues with measurements in at least three different mouse models are shown.

Dion, Trends in Genetics, 2014

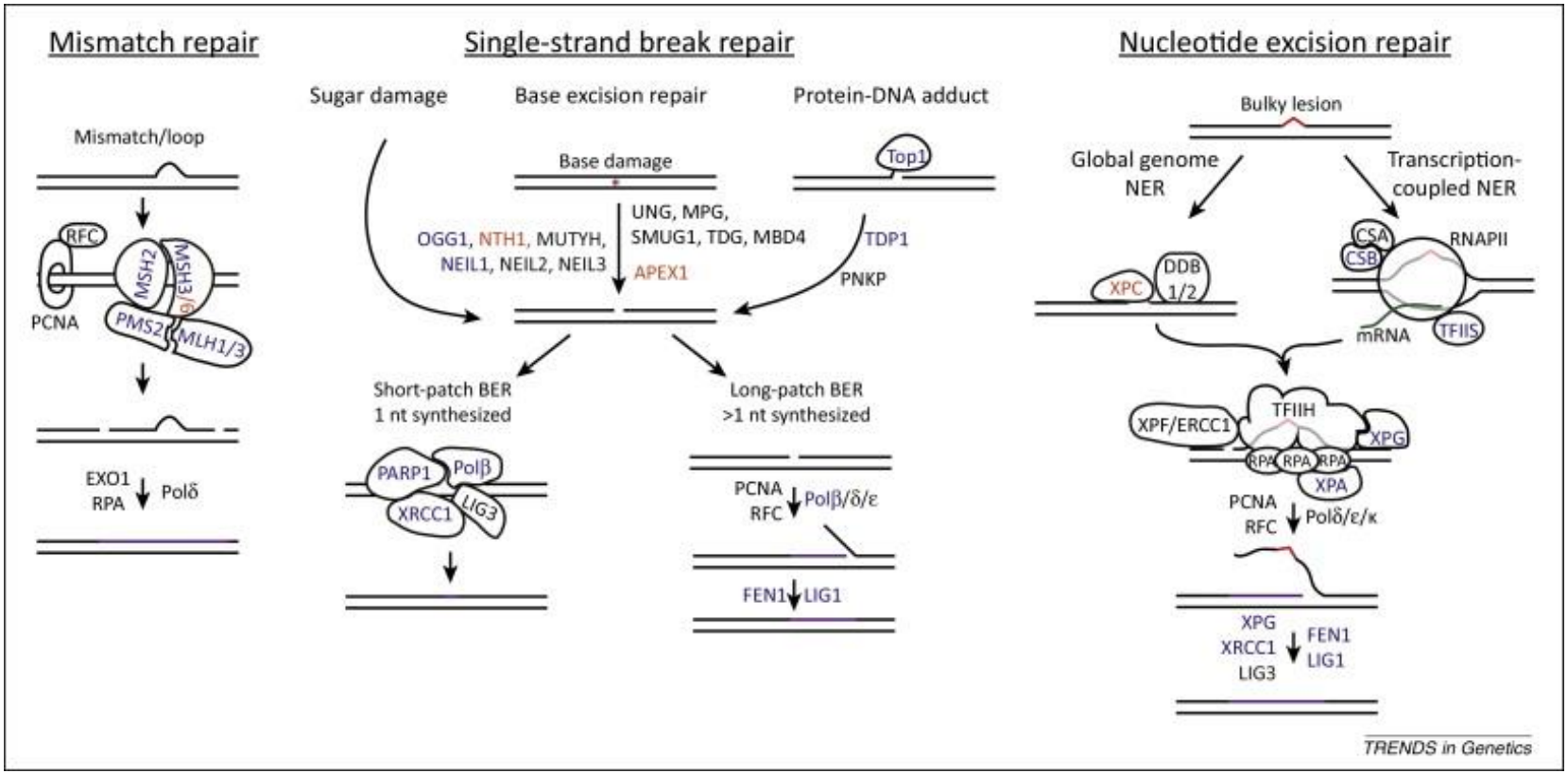
- **Cerebellum seems to have few alterations in repeat length in different mouse models of repeat expansion**



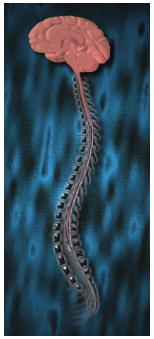
Origin somatic heterogeneity

How to cope with DNA damage

- **Approximately 100’000 lesions in DNA PER cell PER day**
- **3 major repair pathways were shown to participate in repeat instability**



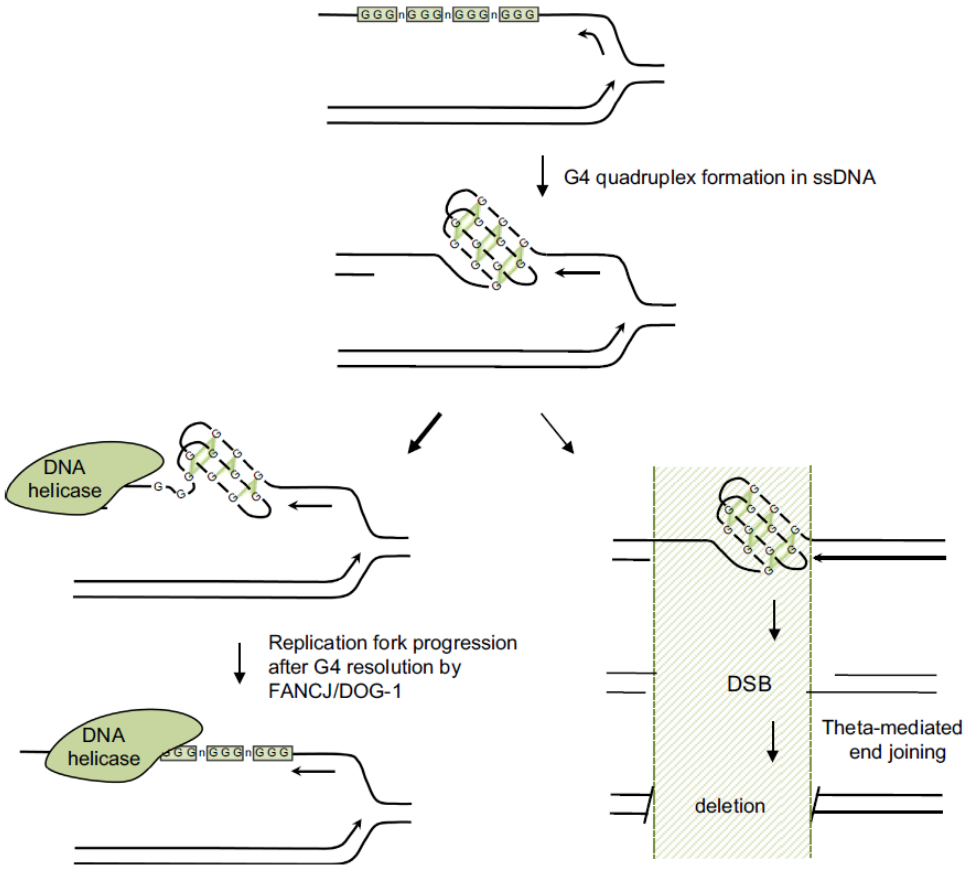
Dion, Trends in Genetics, 2014



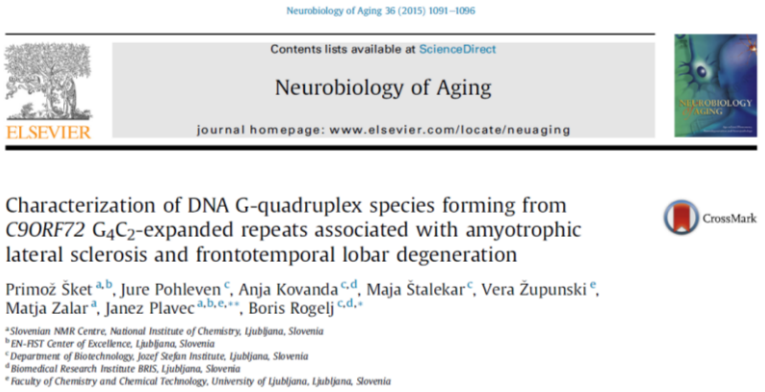
Origin somatic heterogeneity

How to cope with DNA damage

- A 4th one was recently suggested to be involved in repeat instability



- G-quadruplexes were recently observed from C9ORF72 repeat expansion DNA



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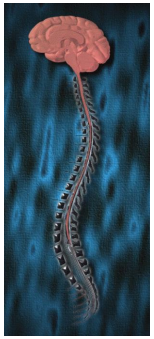
ELSEVIER

Characterization of DNA G-quadruplex species forming from *C9ORF72* G_4C_2-expanded repeats associated with amyotrophic lateral sclerosis and frontotemporal lobar degeneration

Primož Šket [a,b], Jure Pohleven [c], Anja Kovanda [c,d], Maja Štalekar [c], Vera Župunski [e], Matja Zalar [a], Janez Plavec [a,b,e,**], Boris Rogelj [c,d,*]

[a] Slovenian NMR Centre, National Institute of Chemistry, Ljubljana, Slovenia
[b] EN-FIST Center of Excellence, Ljubljana, Slovenia
[c] Department of Biotechnology, Jozef Stefan Institute, Ljubljana, Slovenia
[d] Biomedical Research Institute BRIS, Ljubljana, Slovenia
[e] Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia

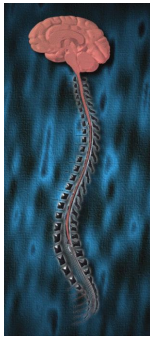
Van Kregten, Experimental Cell Res, 2014



Origin somatic heterogeneity

- Repeat expansions per se have very high mutation rates
- Mutation rates depend on different DNA repair pathways and often lead to tissue specific disease phenotypes
- Different tissues preferably use different repair pathways
- Sensitivity to different types of damage depend on the mitotic state and metabolic rate and age
- Repeat instability could depend on frequency of repair initiation, variation in repair protein expression, replication rate, transcription and chromatin structure
- Recently described DNA structure formation requires special DNA helices for solvation

Reviewed in Van Kregten and Tijsterman, Exp Cell Res 2014

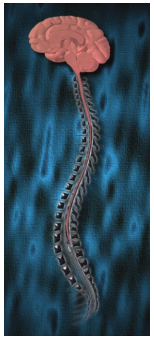


Disease characteristics of C9ORF72

Repeat length and disease

- **Pure ALS:**
  - **no phenotypic aspect significantly correlated with length of expansion**

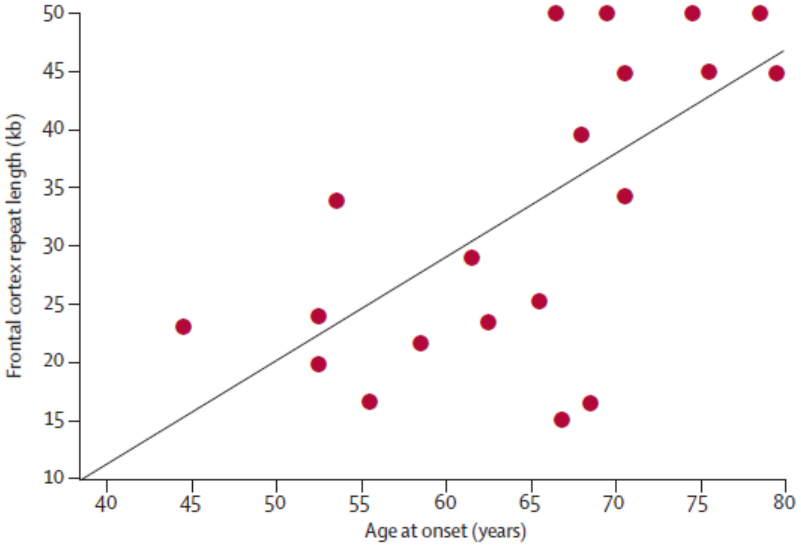
Blitterswijk et al.,Lancet Neurol 2013

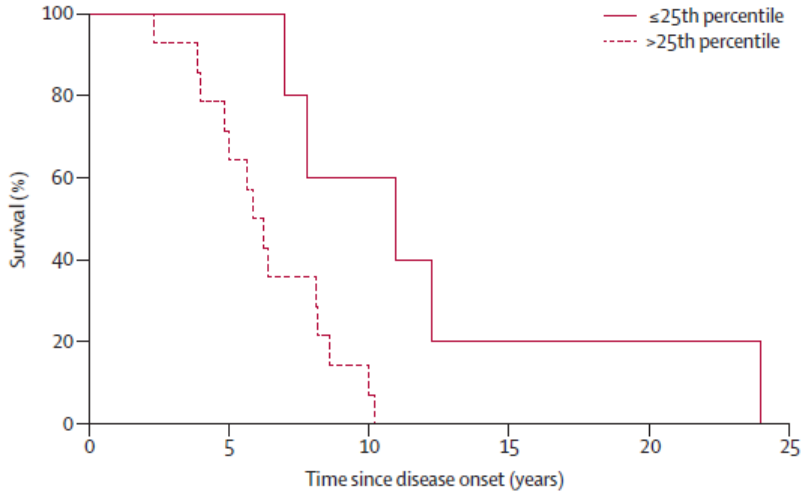


Disease characteristics of C9ORF72

FTLD:

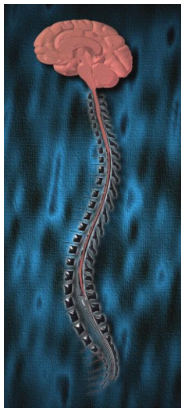
- **Correlation: age of onset and repeat size in frontal cortex**
- **Correlation: reduced survival and repeats < 11.1kb in cerebellum**



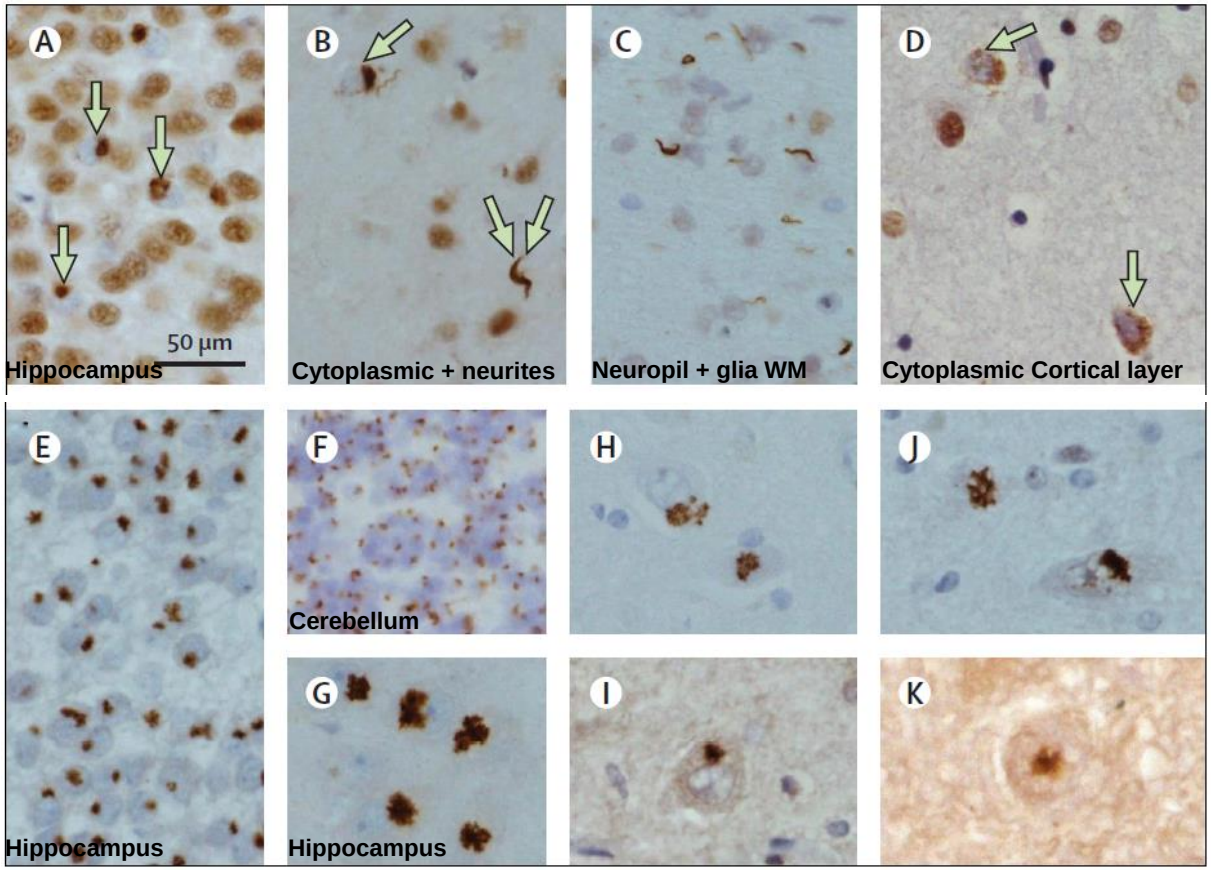


Blitterswijk et. al, Lancet Neurology 2013

These studies might require the analysis of larger numbers of cases due to the noise introduced by additional modifiers (similar to Myotonic Dystrophy DM1 – 100+ patients needed)

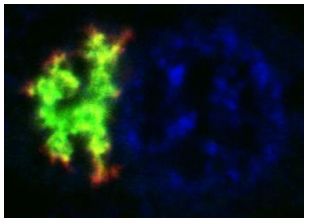


Pathology of C9ORF72 repeat expansions



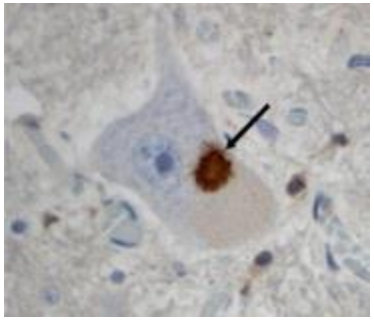
Rohrer et al, Lancet Neurol, 2015

- **TDP43+ inclusions**
- **Star-like p62+/TDP43- inclusions containing polypeptides**



Dipeptide repeat protein inclusions are unique and highly characteristic for C9ORf72 cases

Pathology of C9ORF72 repeat expansions



TDP43+ inclusions correlate with clinical phenotype and pattern of neurodegeneration

- **C9ORF72 FTD patients with no signs of ALS: significantly less degeneration + TDP43 pathology in lower motor neurons compared to patients with mixed phenotype**

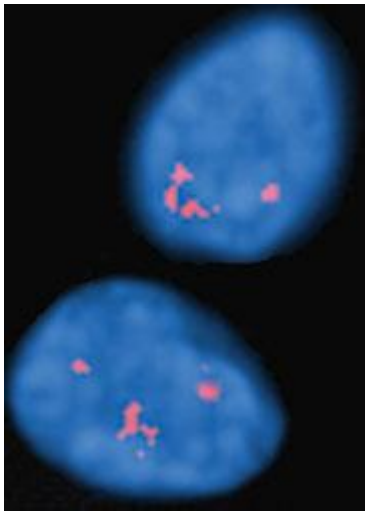
Stewart et al, Acta Neuropathol 2012

- **C9ORF72 ALS patients: predominant degeneration and TDP43+ inclusions in upper, lower and brainstem and spinal cord motor neurons (extra-motor regions are only mildly affected)**

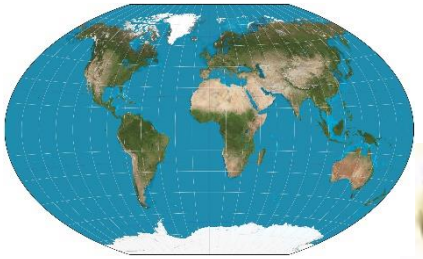
Davidson et al, Acta Neuropathol 2014

Pathology of C9ORF72 repeat expansions

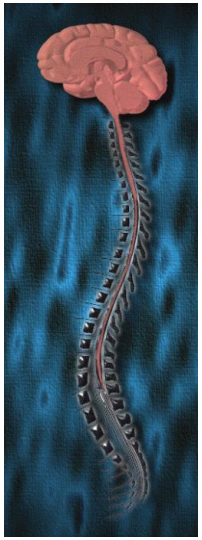
RNA foci

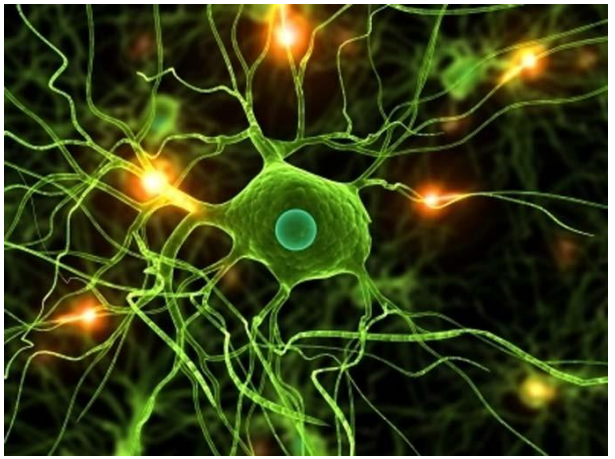


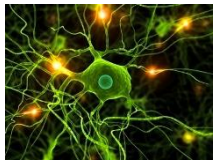
- RNA foci in the nucleus were identified in FTD and ALS patients in the cortex and spinal cord in many studies
- These are common hallmarks of many repeat expansion disorders



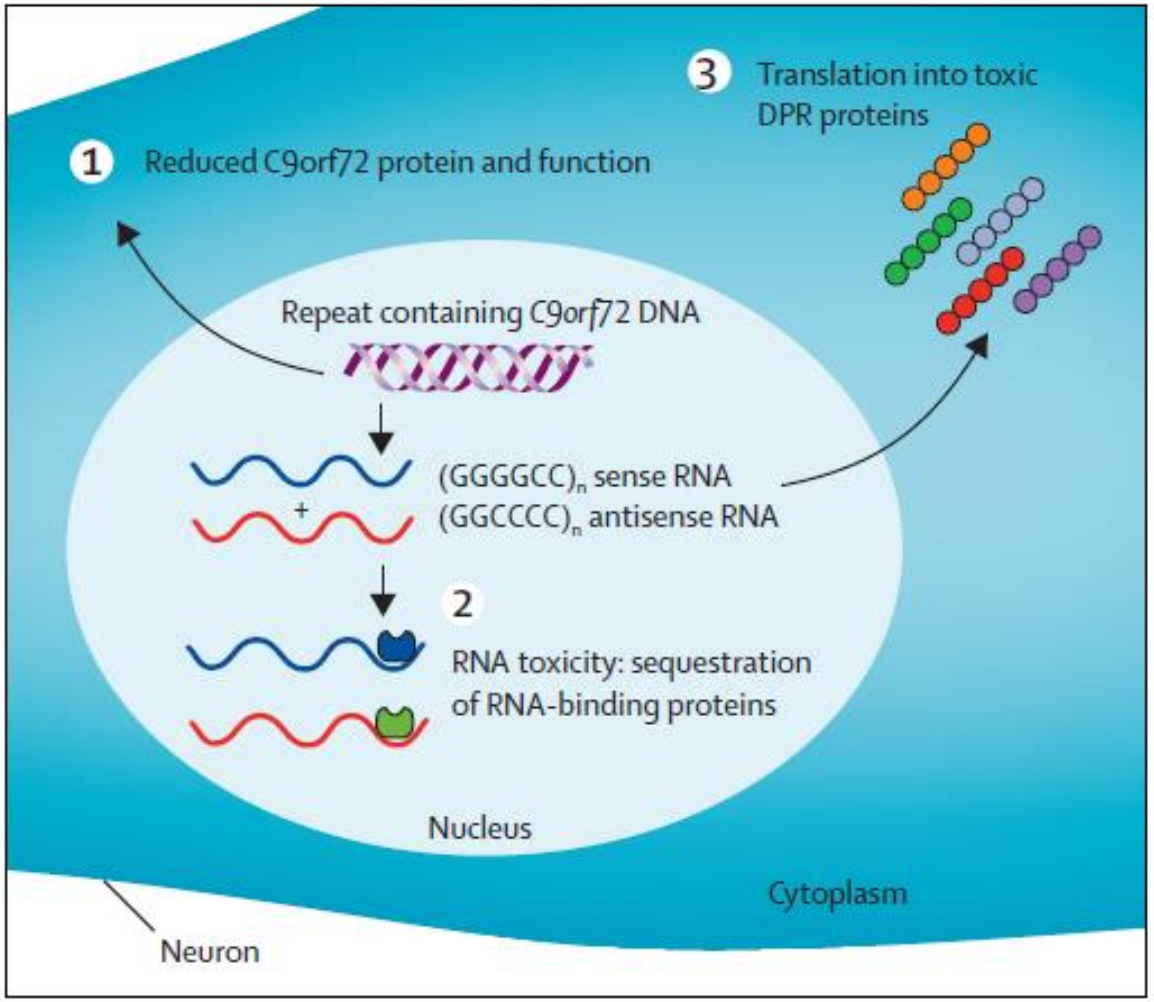
Overview



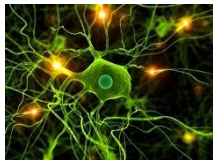




Mechanisms of C9ORF72 mediated neurodegeneration

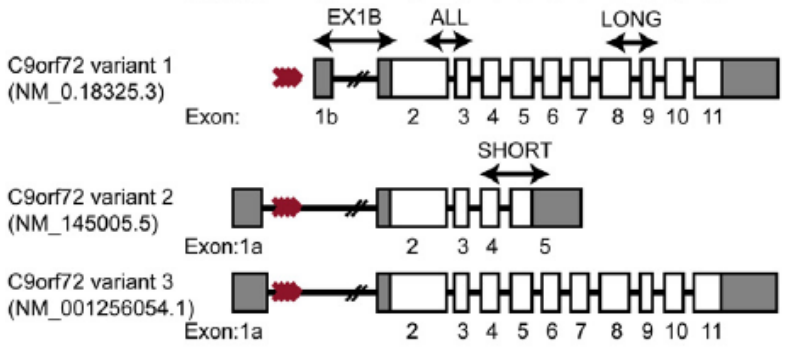


Rohrer, Lancet Neurol 2015

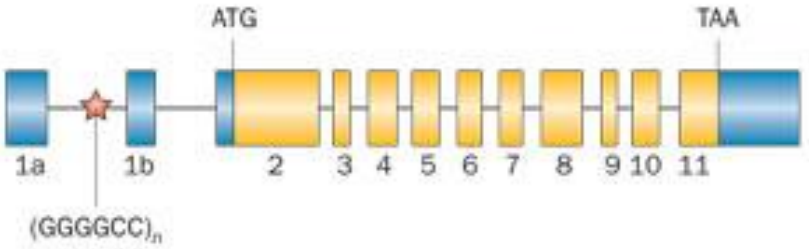


Mechanisms of C9ORF72 mediated neurodegeneration

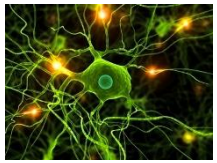
1. Haploinsufficiency



Waite et al, Neurobiology of Ageing, 2014

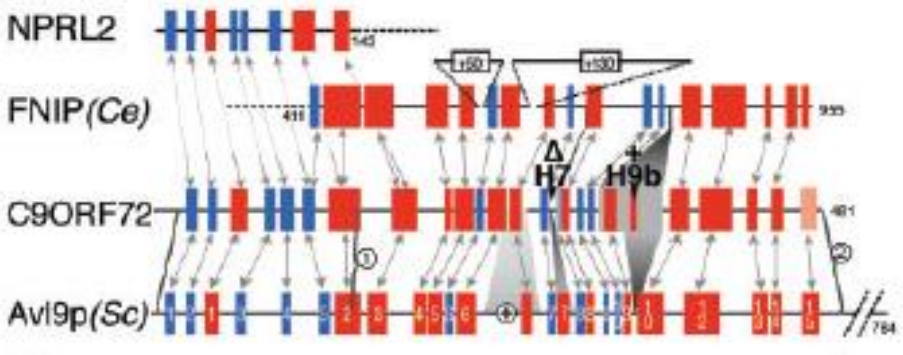


- **3 mRNA variants described**
- **2 potential protein isoforms**
- **Reduction of abundance of all 3 transcripts has been reported**
- **Evidence for v1 being more affected (repeat in promoter)**
- **Model organisms C. elegans and zebrafish show that C9ORF72 loss is pathogenic for motor neurons and causes motor deficits**



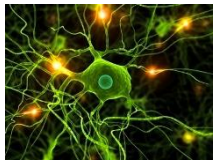
Mechanisms of C9ORF72 mediated neurodegeneration

1. Haploinsufficiency



Levine, Bioinformatics 2013

- **C9ORF72 protein has strong homology with DENN-like proteins**
- **DENN protein family involved in membrane trafficking**
- **Members of this protein family have been linked to neurodegeneration**

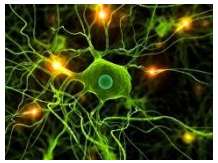


Mechanisms of C9ORF72 mediated neurodegeneration

1. Haploinsufficiency

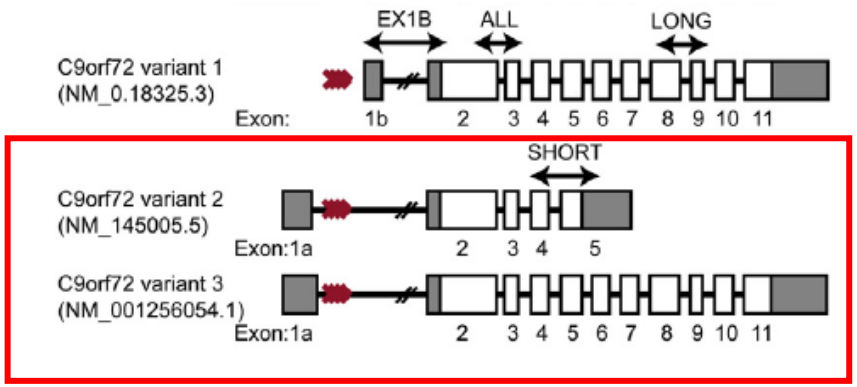
- Yeast homologue of C9ORF72 has been linked to sorting of endosome-localized proteins to cell surface (avoidance of lysosomes)
- Is endo-lysosomal pathway affected by reduced C9ORF72 protein levels?
- Disease modifying gene in FTD TMEM106B is involved in lysosome function and transport in dendrites
- p62+ inclusion pathology could point towards dysfunctional lysosomal degradation
- Mutations in another gene involved in lysosomal degradation of proteins (CHMP2B) causes FTD in a Danish family

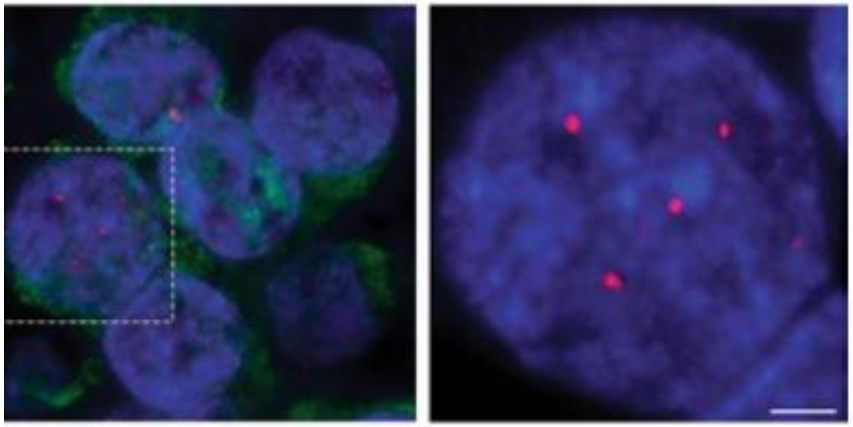
Reviewed in Yokoyama et al, Am J Neurodegener Dis 2014

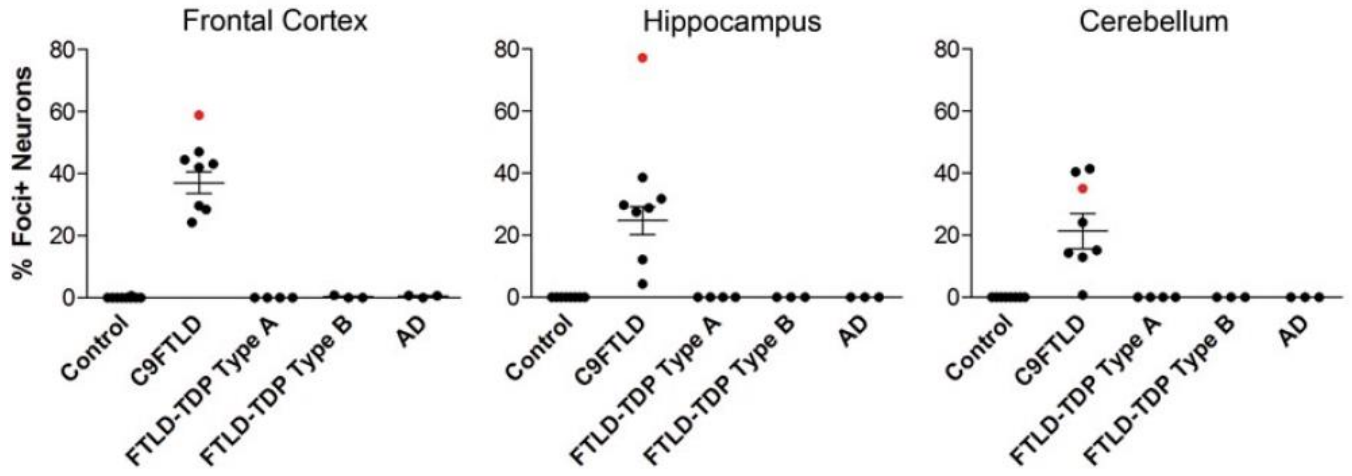


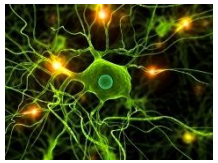
Mechanisms of C9ORF72 mediated neurodegeneration

2. RNA toxicity



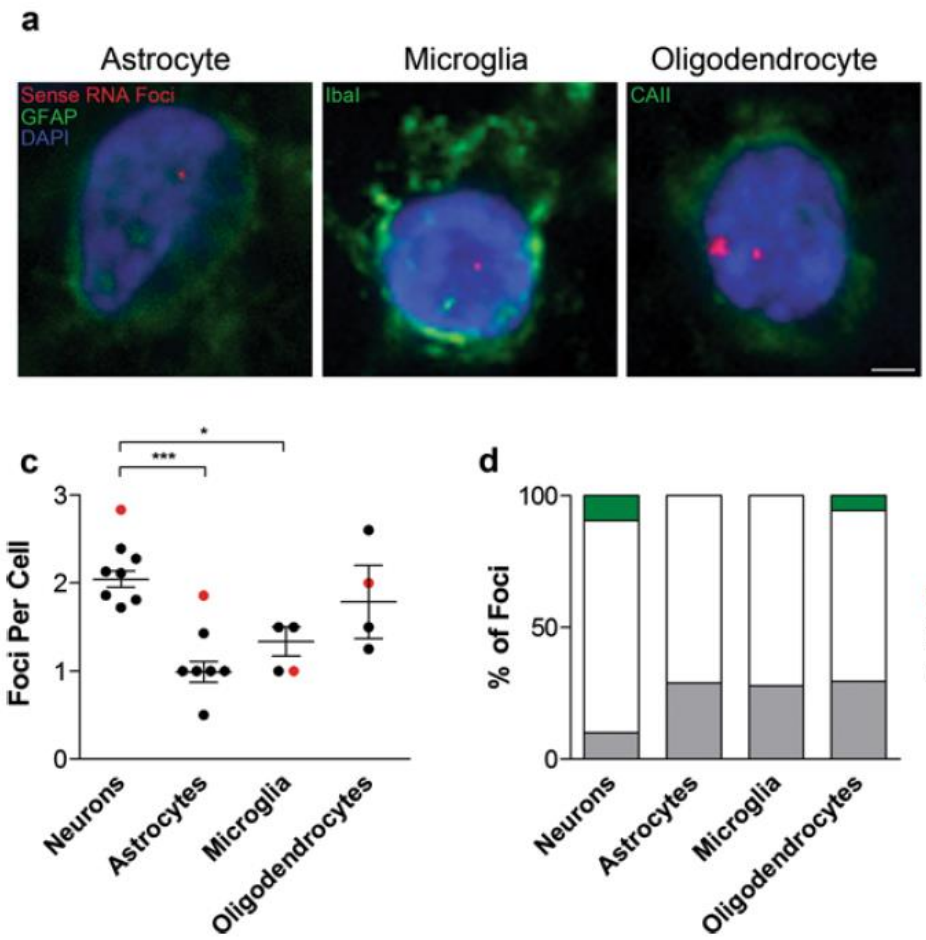






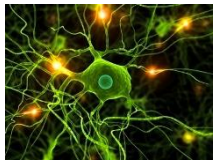
Mechanisms of C9ORF72 mediated neurodegeneration

2. RNA toxicity



- **Inclusions found in several disease affected cell types**

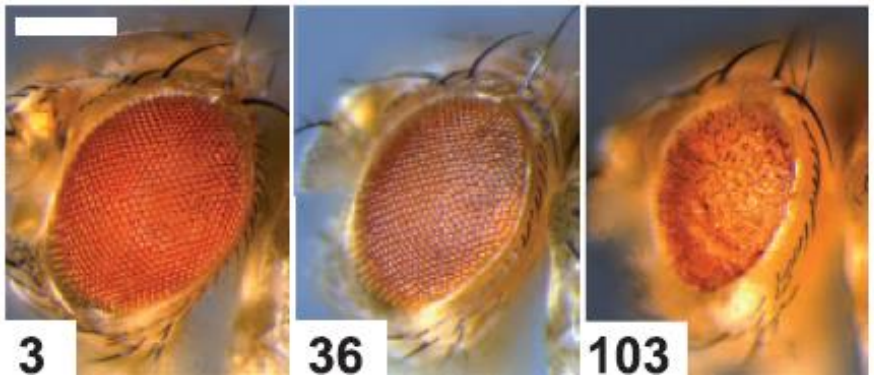
Mizielinska, Acta Neuropathol, 2013 and Largier-Tourenne, PNAS 2013



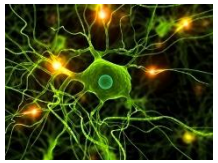
Mechanisms of C9ORF72 mediated neurodegeneration

2. RNA toxicity

- Repeat RNA foci frequently found in affected brain regions in FTD
- Burden correlates with clinical disease phenotype
- Overexpression of repeat itself causes neurodegeneration in several animal models (zebrafish, drosophila)

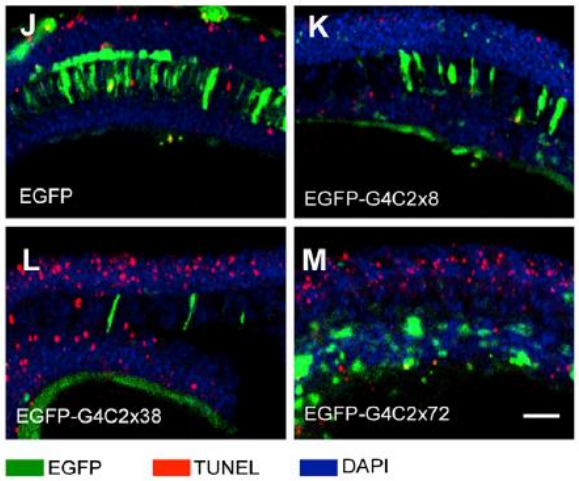


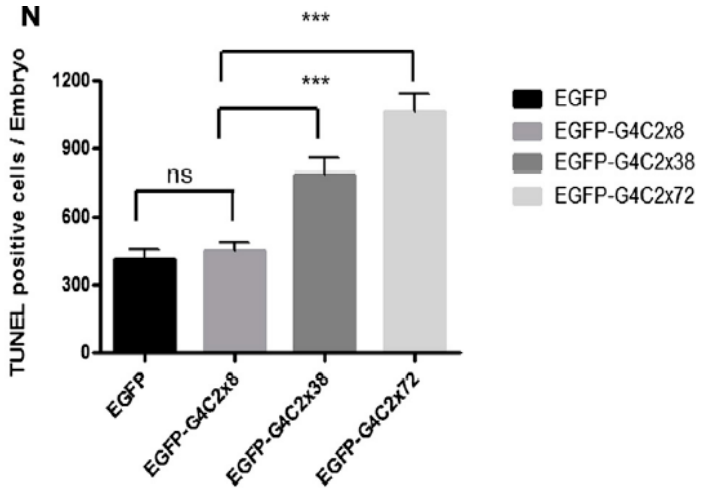
Mizielinska, Science Reports 2014



Mechanisms of C9ORF72 mediated neurodegeneration

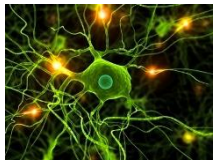
2. RNA toxicity





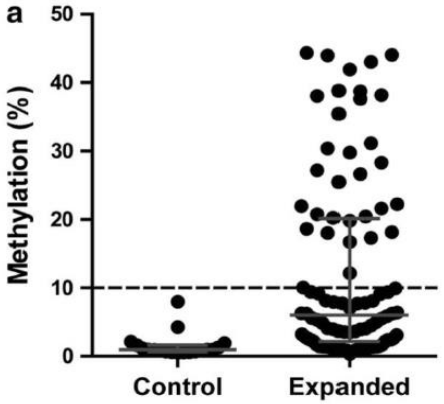
- **Overexpression of 38x or 72x repeats sufficient to cause neurodegeneration in neuronal cell lines and zebrafish** *Le et al, Cell Reports 2013*

- **Likely via sequestration of RNA binding proteins involved in nuclear retention, pre-mRNA splicing or RNA trafficking (hnRNP H)**



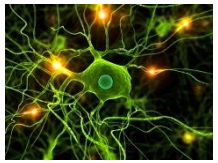
Mechanisms of C9ORF72 mediated neurodegeneration

- DNA hypermethylation which reduces repeat RNA expression is a disease modifier in FTD



- Hypermethylation is associated with later age at death in FTD, longer disease duration
- Hypermethylation is associated with shorter repeat length
- This correlation was not observed for ALS in the same study

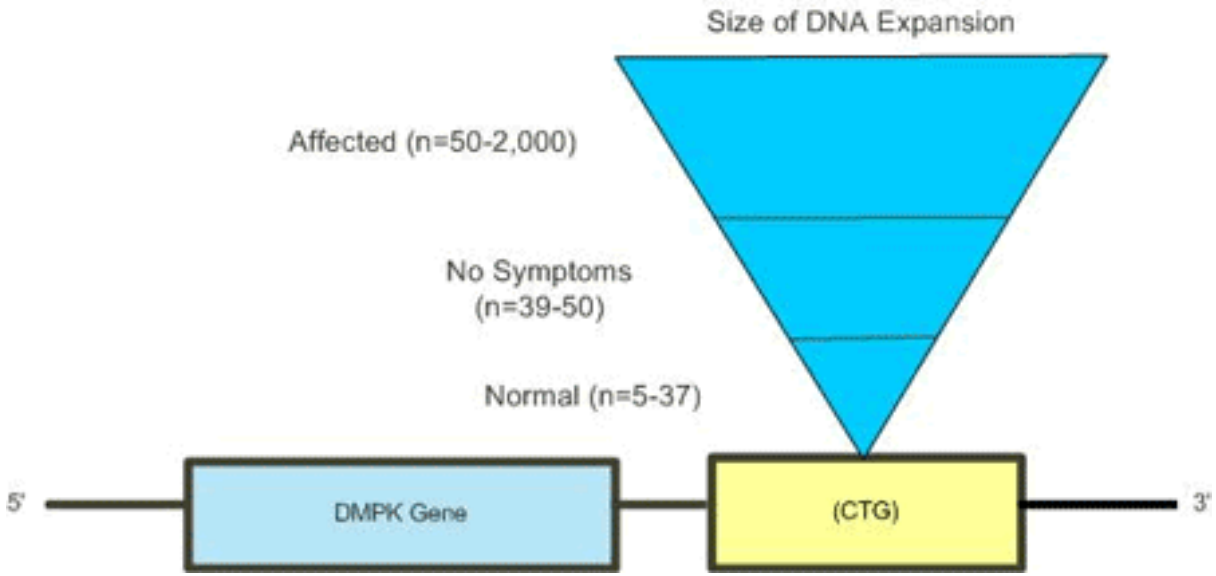
Russ, Acta Neuropathol 2014

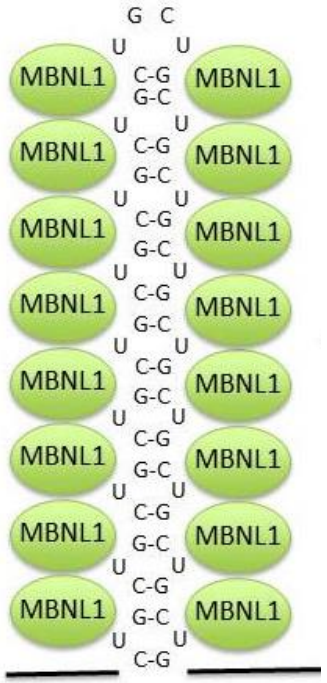


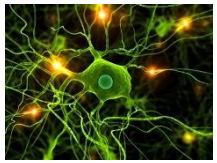
Mechanisms of C9ORF72 mediated neurodegeneration

2. RNA toxicity

- **Repeat RNA was shown to be toxic in other expansion disorders (DM1 and DM2) by sequestration of RNA binding proteins (muscle-blind-like proteins)**







Mechanisms of C9ORF72 mediated neurodegeneration

3. Dipeptide repeat protein translation - RAN

OPEN ACCESS Freely available online

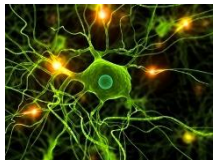
PLoS GENETICS

Review

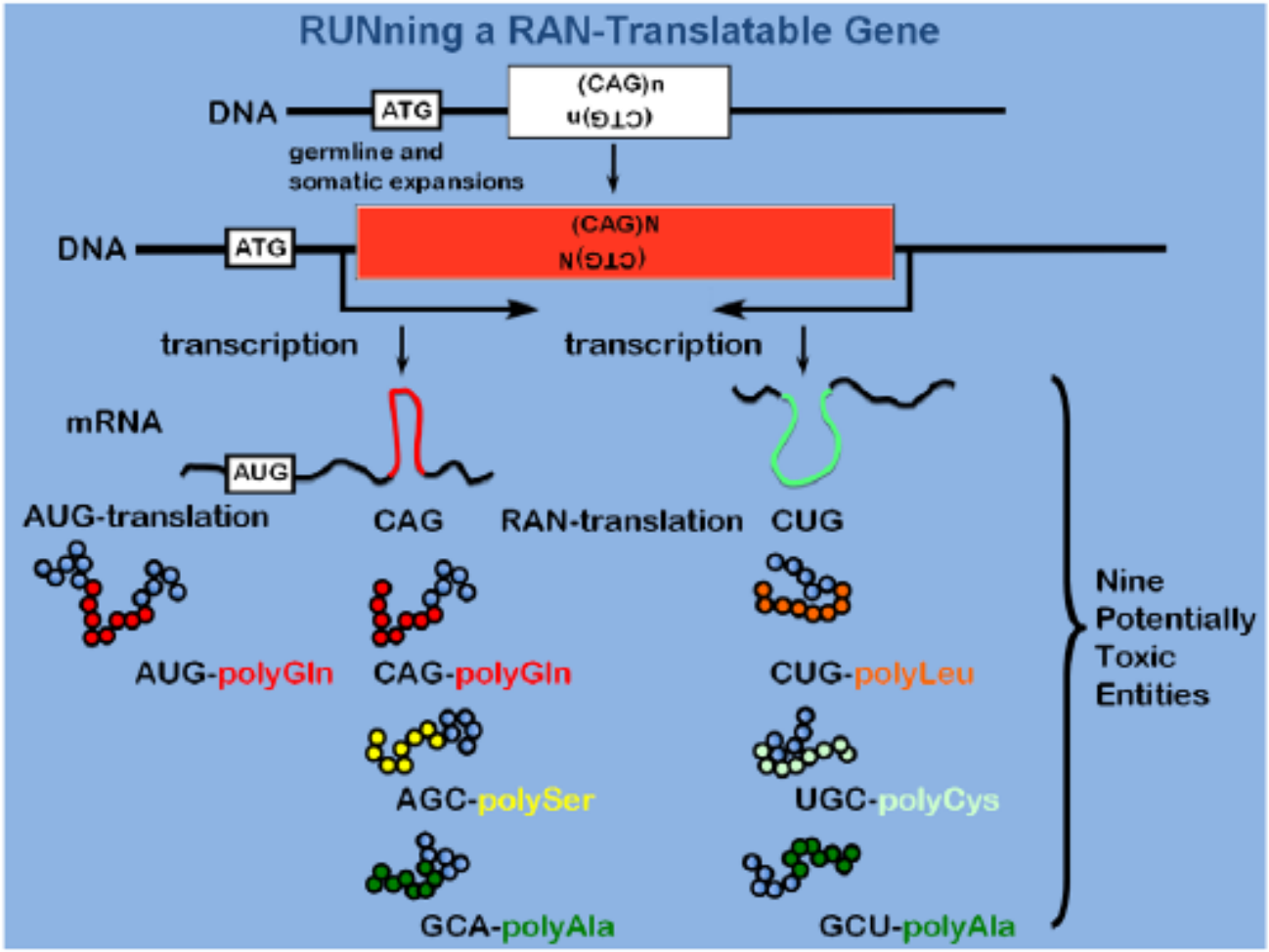
Repeat Associated Non-ATG Translation Initiation: One DNA, Two Transcripts, Seven Reading Frames, Potentially Nine Toxic Entities!

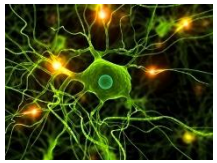
Christopher E. Pearson[1,2]*

1 Program of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada, **2** Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada



Mechanisms of C9ORF72 mediated neurodegeneration





Mechanisms of C9ORF72 mediated neurodegeneration

3. Dipeptide repeat protein translation - RAN

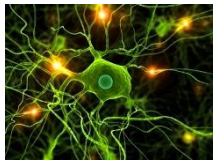
- **Initially discovered in SCA8, found in other repeat expansion disorders**

Table 1. *In vitro* characteristics and *in vivo* detection of RAN translation

Disorder	Repeat	RAN protein (*in vitro*)	Threshold (*in vitro*)	Tissue (*in vivo*)	Refs.
SCA8	CAG	poly**Gln**	>42 repeats	ATG-polyGln, cerebellum and brain stem (14)	(11)
		poly**Ala**	>73 repeats	Cerebellum	(11)
		poly**Ser**	>58 repeats	ND	(11)
DM1	CAG[a]	poly**Gln**	ND	Myoblasts, skeletal muscle, peripheral blood leukocytes	(11)
FXTAS	CGG	poly**Gly**	>30 repeats	Frontal cortex, cerebellum, hippocampus	(24)
		poly**Ala**	>88 repeats	ND	(24)
		poly**Arg**	UD	ND	(24)
ALS/FTD	GGGGCC	poly**GlyPro**	>145 repeats	Cerebellum, hippocampus, iPSC-derived neurons, neocortex, medial and lateral geniculate nuclei, testes	(25–27)
		poly**GlyAla**	>38 repeats	Cerebellum, hippocampus	(26)
		poly**GlyArg**	UD	Cerebellum, hippocampus	(26)

ND, not examined and not determined; UD, examined but undetermined.
[a]Antisense transcript.

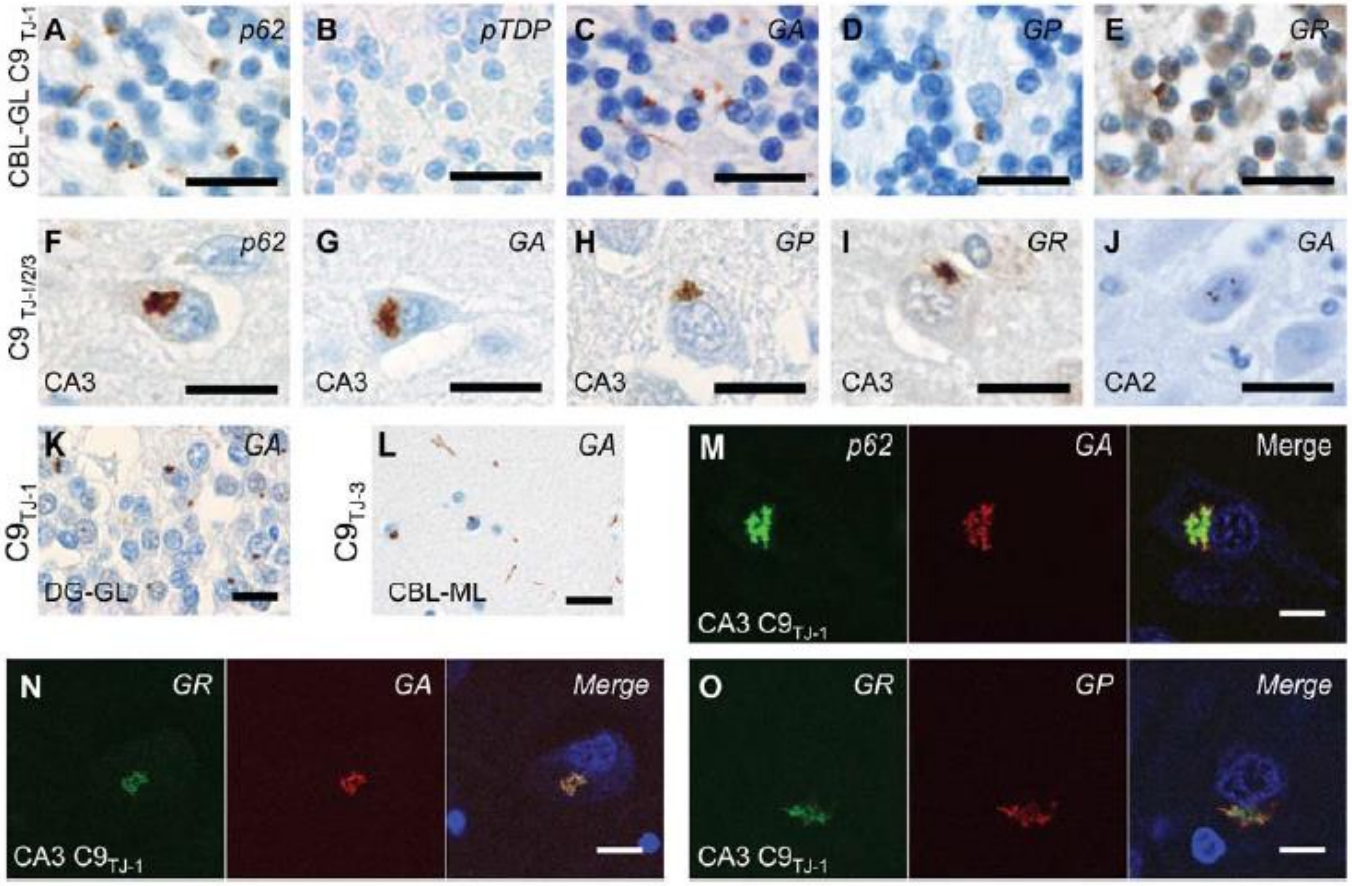
Cleary and Ranum, Hum Mol Genet 2013



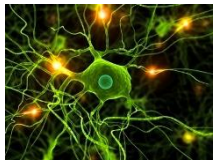
Mechanisms of C9ORF72 mediated neurodegeneration

3. Dipeptide repeat protein translation - RAN

- **Many studies on C9ORF72 found evidence for DRPs in C9ORF72 ALS and FTD**



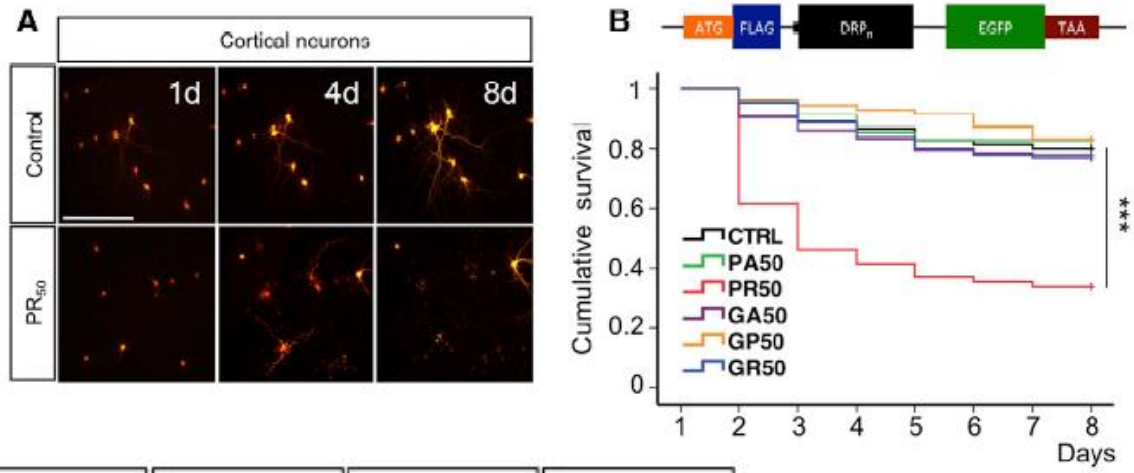
Mori, Science Report 2013

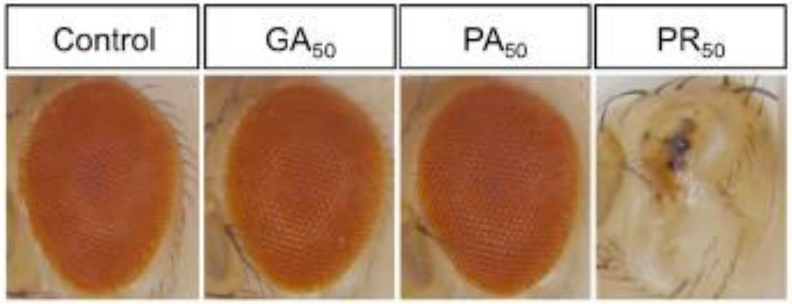


Mechanisms of C9ORF72 mediated neurodegeneration

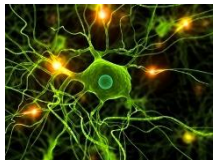
3. Dipeptide repeat protein (DRP) translation - RAN

- **Overexpression of Proline-Arginie DRP is toxic in vitro and in vivo**



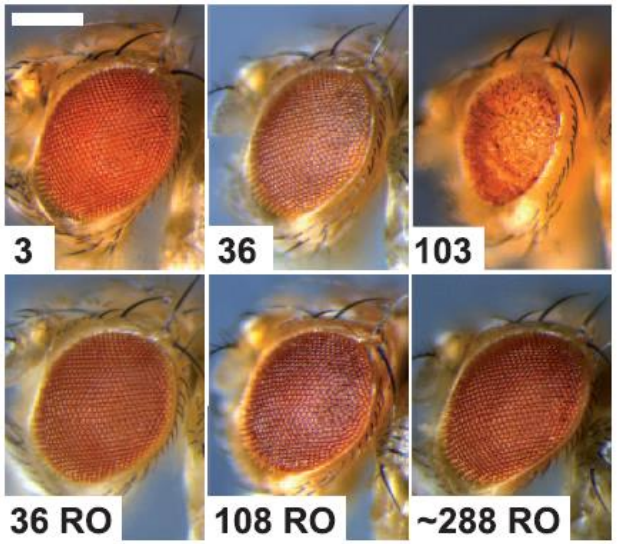


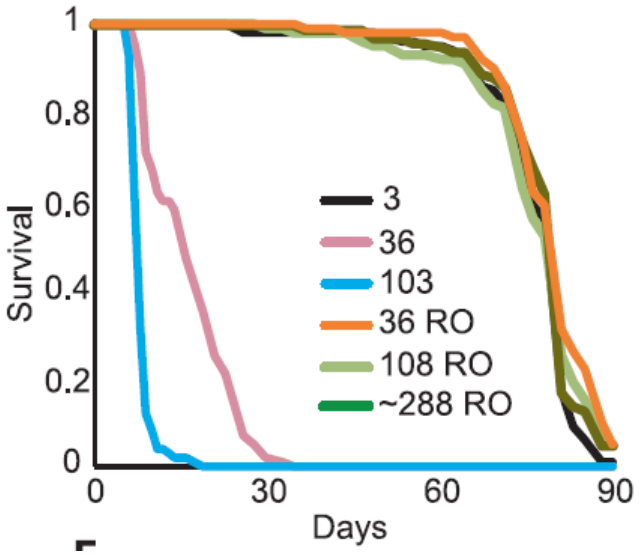
Wen, Neuron 2014



Mechanisms of C9ORF72 mediated neurodegeneration

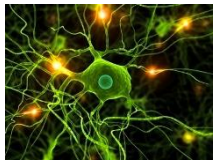
3. Dipeptide repeat protein (DRP) translation - RAN





Mizielinska, Science Reports 2014

- **RNA repeats that are not translated do not cause neurodegeneration**
- **Repeat RNA toxicity and DRP peptide production seem to be linked**



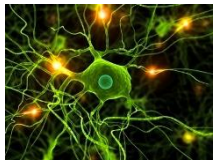
Mechanisms of C9ORF72 mediated neurodegeneration

3. Dipeptide repeat protein translation - RAN

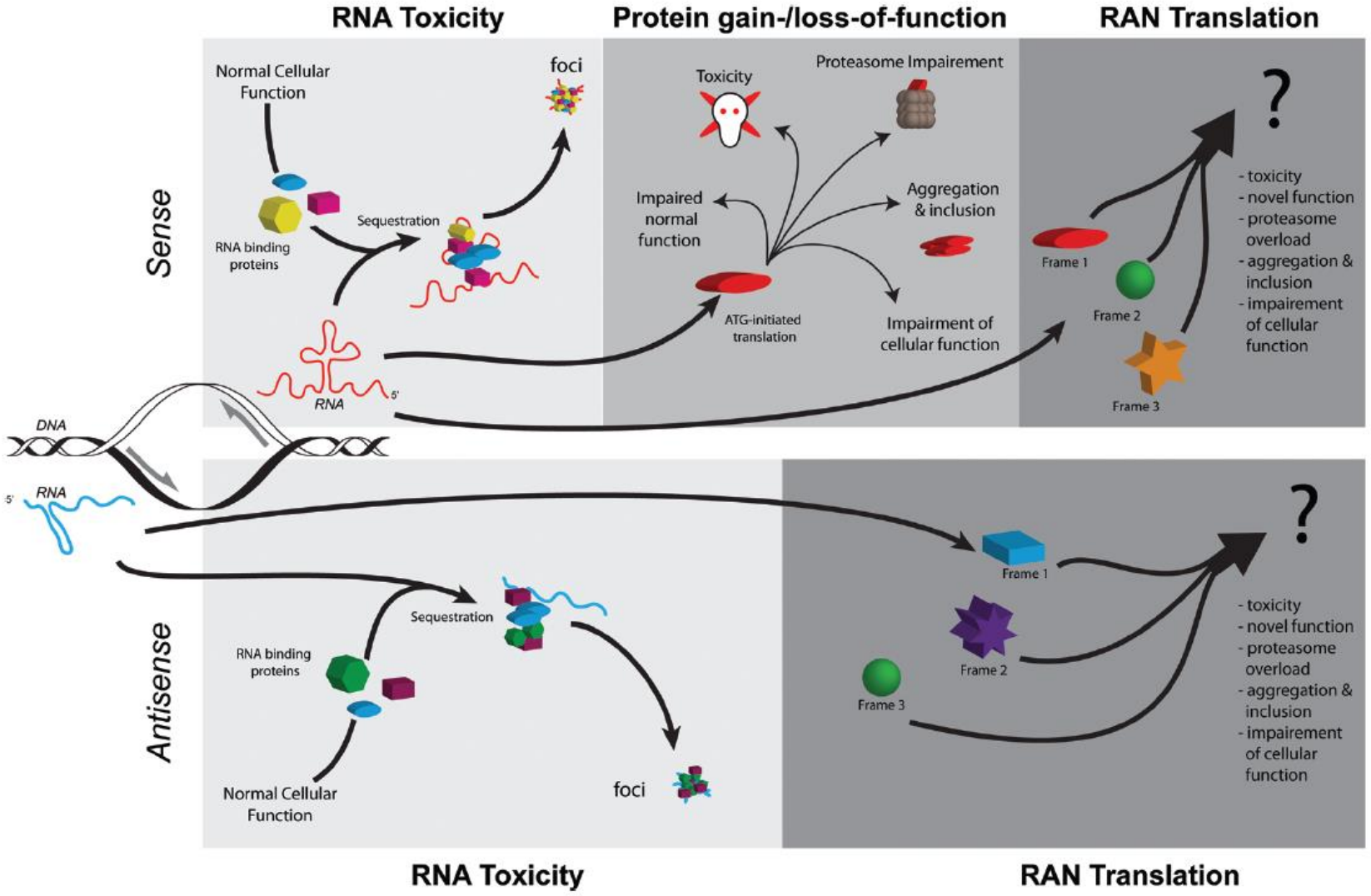
But…dipeptide repeat protein pathology does not always seem to correlate with either phenotype or degeneration pattern

More studies will be needed to decipher the correlation between disease course, clinical manifestation and DRPs

Davidson et al. Acta Neuropathol. Communications 2014, 2:70, Mackenzie, Acta Neuropathol. 2013, Reviewed in Mann, Neurobiology of Aging 2014

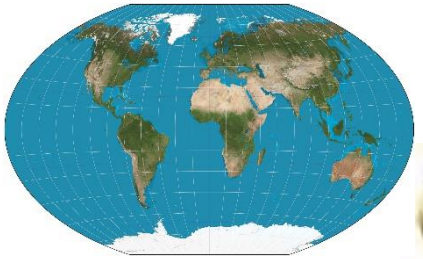


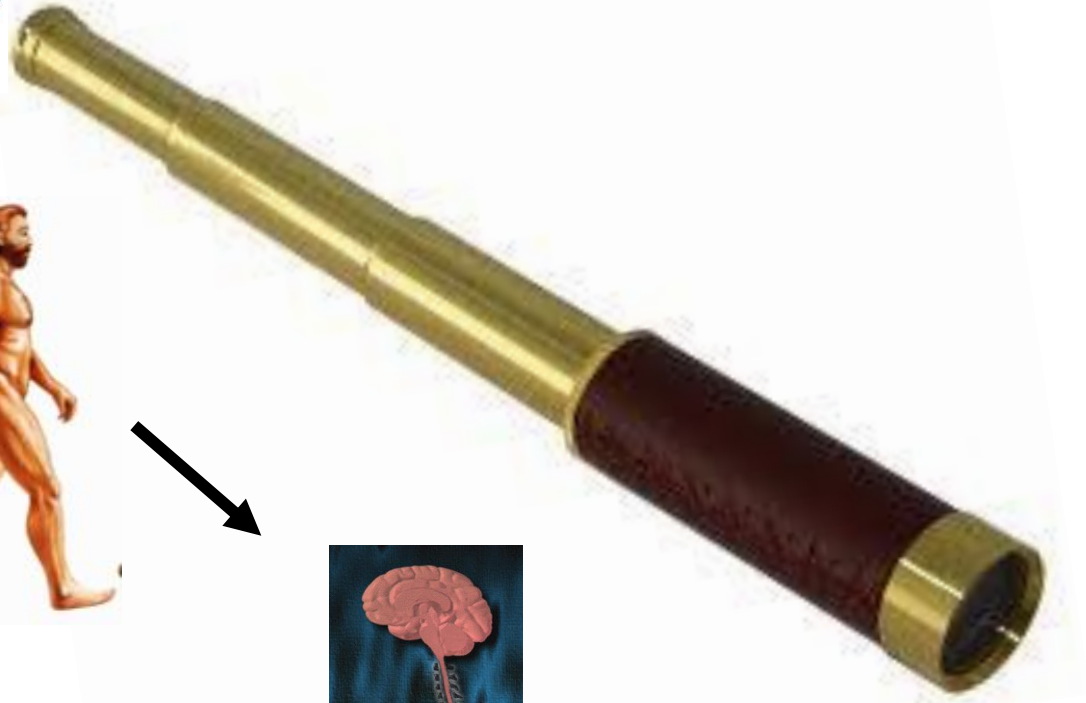
Summary of potential toxic mechanisms

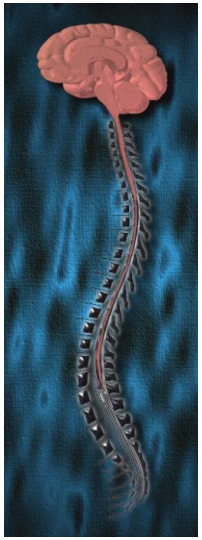


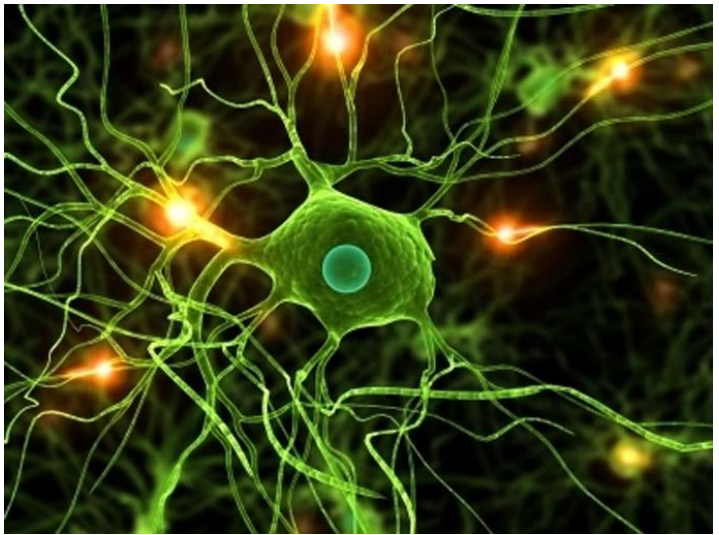
Cleary and Ranum, Hum Mol Genet 2013

Overview









Thank you!

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THE OHIO STATE UNIVERSITY Medical Center

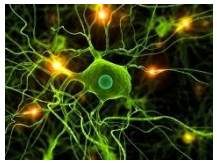
Other repeat expansion disorders causing neurological disorders

Neurological disorders caused by expanded repeats.

Disease	Repeat Unit	Repeat Locus	Repeat Location	Affected Gene	Disease Causing Repeat Length	Mechanisms of Pathogenesis
Myotonic Dystrophy type 1 (DM1)	CTG	19q13	3' UTR	*DMPK*	50–6500	Altered RNA function
Myotonic Dystrophy type 2 (DM2)	CCTG	3q21	Intron	*CNBP*	75–11,000	Altered RNA function
Spinocerebellar ataxia 1 (SCA1)	CAG	6p23	Coding	*ATXN1*	> 44	Polyglutamine gain-of-function
Spinocerebellar ataxia 2 (SCA2)	CAG	12q24	Coding	*ATXN2*	> 32	Polyglutamine gain-of-function
Spinocerebellar ataxia 3 (SCA3)	CAG	14q24-q32	Coding	*ATXN3*	> 52	Polyglutamine gain-of-function
Spinocerebellar ataxia 6 (SCA6)	CAG	19p13	Coding	*CACNA1A*	20–33	Polyglutamine gain-of-function
Spinocerebellar ataxia 7 (SCA7)	CAG	3q21	Coding	*ATXN7*	37–460	Polyglutamine gain-of-function
Spinocerebellar ataxia 8 (SCA8)	CTG/CAG	13q21	3' UTR	*ATXN8*	80–1300	Polyglutamine gain-of-function
Spinocerebellar ataxia 10 (SCA10)	ATTCT	22q13	Intron	*ATXN10*	800–4500	Altered RNA function
Spinocerebellar ataxia 12 (SCA12)	CAG	5q31-q33	5' UTR	*PPP2R2B*	55–78	Unknown
Spinocerebellar ataxia 17 (SCA17)	CAG	6q27	Coding	*TBP*	49–66	Polyglutamine gain-of-function
Spinocerebellar ataxia 31 (SCA 31)	TGGAA	16q21-q22	Intron	*TK2-BEAN*	2.5- to 3.8-kb	RNA gain-of-function
Spinocerebellar ataxia 36 (SCA 36)	GGCCTG	20p13	Intron	*NOP56*	1500–2500	RNA gain-of-function
Fragile X mental retardation 1 (FMR1)	CGG	Xq27	5' UTR	*FMR1*	> 200	Altered RNA function
Fragile X-associated tremor ataxia syndrome (FXTAS)	CGG	Xq27	5' UTR	*FMR1*	55–200	RNA gain-of-function
Fragile X mental retardation 2 (FMR2)	CCG	Xq28	5' UTR	*FMR2*	200–900	Loss of protein function
Huntington's disease (HD)	CAG	4p16	Coding	*HTT*	> 35	Polyglutamine gain-of-function
Huntington's disease-like 2 (HDL2)	CTG	16q24	3' UTR	*JPH3*	> 41	Altered RNA function
Friedreich's Ataxia (FRDA)	GAA	9q13	Intron	*FXN*	66–1700	Loss of protein function
Epilepsy progressive myoclonia (EPM1)	CCCCGCGCGCGCGCG	21q22	Promoter	*CSTB*	30–75	Loss of protein function
Oculopharyngeal muscular dystrophy (OPMD)	GCG	14q11	Coding	*PABPN1*	11–17	Polyalanine gain-of-function
Spinal and bulbar muscular atrophy (SBMA)	CAG	Xq12	Coding	*AR*	> 37	Polyglutamine gain-of-function
X-linked mental retardation	GCG	Xp21	Coding	*ARX*	17–23	Loss of protein function
Dentatorubral-pallidoluysian atrophy (DRPLA)	CAG	12p13	Coding	*ATN1*	48–93	Polyglutamine gain-of-function
ALS and/or FTD	GGGGCC	9p21	Intron	*C9ORF72*	Up to thousands	RNA gain-of-function?

For more information we refer to recent reviews [84,87–89,90*–92*,93–97], articles [85,86**,98–103], and GeneReviews (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review).

Blitterswijk, Curr Opinion Neurol 2012



Other repeat expansion disorders

- **At least 24 other neurological disorders**
- **Non-coding repeat expansions usually display RNA foci (DM2, FXTAS, HDL2, SCA36, SCA31, SCA8, SCA10)**
- **Commonality points towards similar RNA gain-of-function mechanism**
- **Intronic repeats usually long**

Add table Marka van Blitterswijk, Curr Opin Neurol 2012 how do c9orf72 repeat expansions cause als and ftd