# FUS in C9orf72

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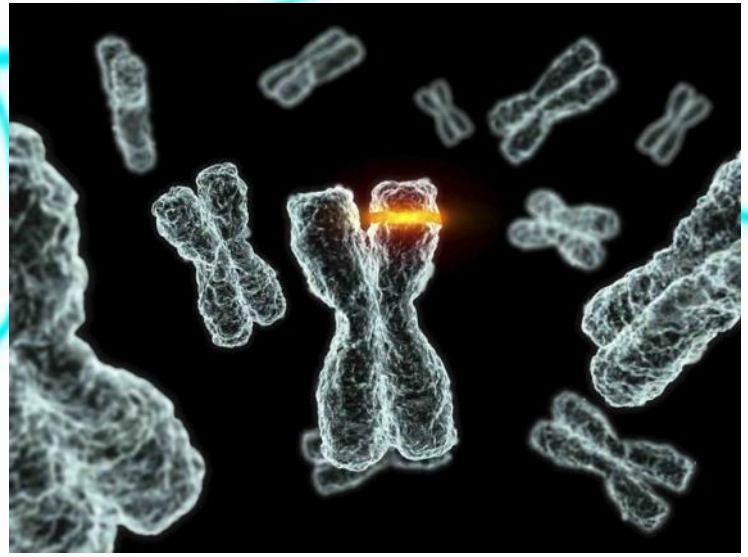
# Mutacije FUS pri ALS



been implicated in tumorigenesis (*6*, *16*, *17*) and RNA metabolism. *FUS/TLS* knockout mice show perinatal mortality (*18*) or male sterility and radiation sensitivity (*19*). FUS/TLS–deficient neurons show decreased spine arborization with abnormal morphology. In hippocampal neuronal slice cultures, the protein is found in RNA granules that are transported to dendritic spines for local RNA translation in response to metabotropic glutamate receptor (mGluR5) stimulation (*20*).

We detected 13 FUS/TLS mutations in patients with FALS but none in patients with SALS. We estimate that FUS/TLS mutations are detected in about 5% of FALS; this is comparable to the frequency of *TDP43* gene mutations in ALS but less than that for *SOD1* (mutated in ~20% of FALS cases). The FUS/TLS mutations described here led to cytoplasmic retention and apparent aggregation of FUS/TLS. This is reminiscent of several models of the pathogenesis of FALS that are mediated by the aggregation of mutant superoxide dismutase (*21*) and the mislocalization in ALS of both mutant and WT TDP43 (*4*, *22*). FUS/TLS has also been reported to be a major nuclear aggregate–interacting protein in a model of Huntington's disease (*23*). Genes implicated in other motor neuron diseases also involve aspects of DNA and RNA metabolism [table S5 in (*24*)]; understanding the convergent pathophysiologies of these genetic variants will provide insights into new targets for therapies for the motor neuron diseases.

### References and Notes


1. L. M. Nelson, *Clin. Neurosci.* **3**, 327 (1995).
2. D. R. Rosen, *Nature* **364**, 362 (1993).
3. E. Kabashi *et al.*, *Nat. Genet.* **40**, 572 (2008).


# Mutations in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6

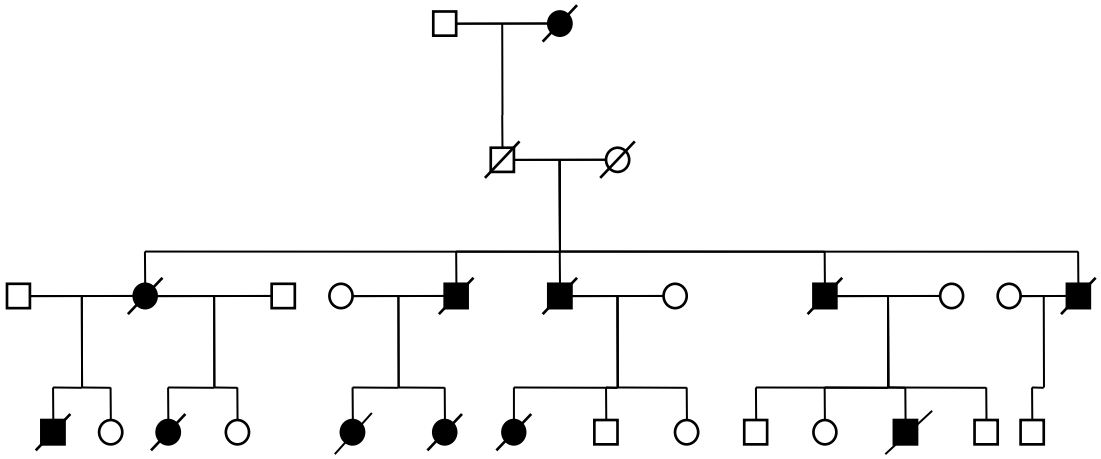

Caroline Vance,[1*] Boris Rogelj,[1*] Tibor Hortobágyi,[1*] Kurt J. De Vos,[2*] Agnes Lumi Nishimura,[1] Jemeen Sreedharan,[1] Xun Hu,[1] Bradley Smith,[1] Deborah Ruddy,[1] Paul Wright,[1] Jeban Ganesalingam,[1] Kelly L. Williams,[3] Vineeta Tripathi,[1] Safa Al-Saraj,[1] Ammar Al-Chalabi,[1] P. Nigel Leigh,[1] Ian P. Blair,[3,5] Garth Nicholson,[3,4,5] Jackie de Belleroche,[6] Jean-Marc Gallo,[1] Christopher C. Miller,[1,2] Christopher E. Shaw[1]†

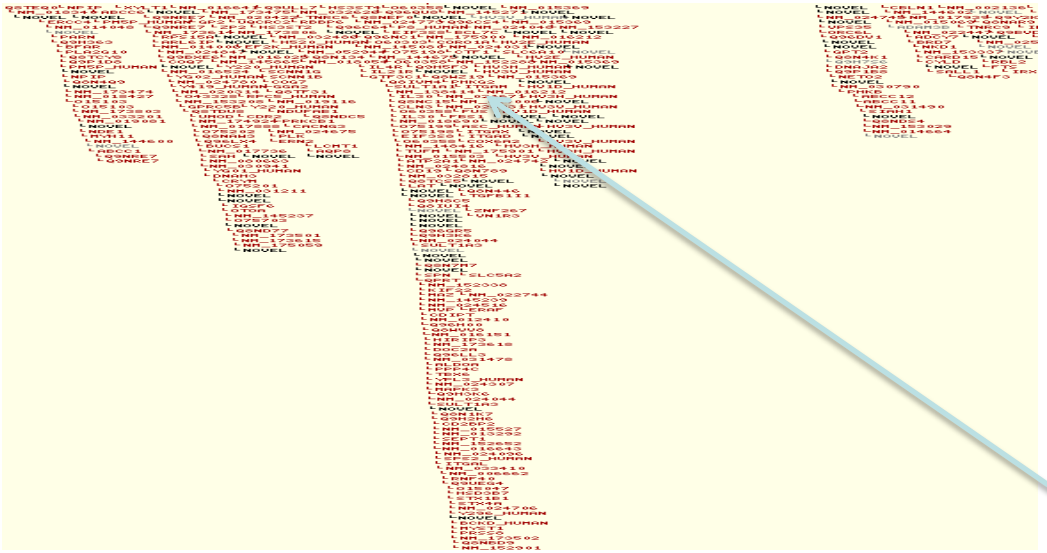


Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that is familial in 10% of cases. We have identified a missense mutation in the gene encoding fused in sarcoma (FUS) in a British kindred, linked to ALS6. In a survey of 197 familial ALS index cases, we identified two further missense mutations in eight families. Postmortem analysis of three cases with FUS mutations showed FUS-immunoreactive cytoplasmic inclusions and predominantly lower motor neuron degeneration. Cellular expression studies revealed aberrant localization of mutant FUS protein. FUS is involved in the regulation of transcription and RNA splicing and transport, and it has functional homology to another ALS gene, *TARDBP*, which suggests that a common mechanism may underlie motor neuron degeneration.


Amyotrophic lateral sclerosis (ALS) causes progressive muscular weakness due to the degeneration of motor neurons in the brain and spinal cord. The average age at onset is 60 years, and annual incidence is 1 to 2 per 100,000. Death due to respiratory failure occurs on average 3 years after symptom onset (*1*). Autosomal dominant familial ALS (FALS) is clinically and pathologically indistinguishable from sporadic disease (SALS) and accounts for ~10% of cases (*2*). Three genes have been confidently linked to classical FALS: *SOD1*, encoding CuZn superoxide dismutase (SOD1) (*ALS1* OMIM 105400) (*3*); *ANG*, encoding angiogenin (*4*–*6*); and *TARDP*, encoding TAR DNA binding protein TDP-43 (*ALS10* OMIM 612069) (*7*). SOD1 mutations are detected in 20% of FALS and 5% of SALS cases (*3*, *8*). Mice transgenic for mutant human SOD1 develop selective motor neuron degeneration due to a toxic gain of function (*9*) that is not cell autonomous

# Družina iz Essex-a ima mutacijo na kromosomu 16





Starost pri nastopu ~38 let.

Povprečen čas preživetja 13 mesecev.

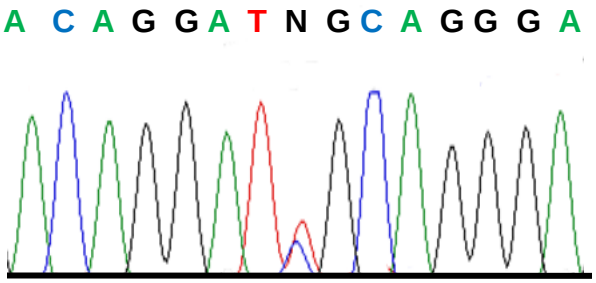
Začne se s šibkostjo rok.

Z uporabo 400 genskih markerjev je določeno, da je mutirani gen na enem delu kromosoma 16 – vendar kateri od >400 genov?

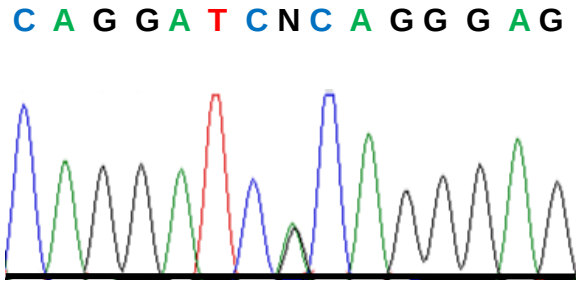
Po dolgotrajni raziskavi smo ugotovili mutacije v genu Fused in Sarcoma (FUS)

Ruddy, *AJHG* 2003
Vance/Rogelj, *Science* 2009

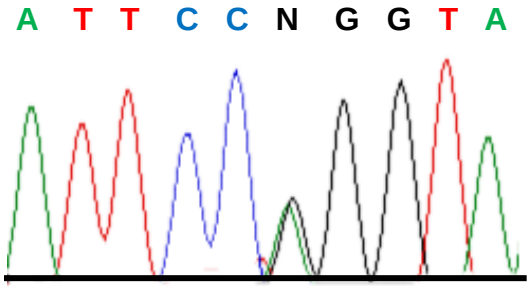
# Tri mutacije FUS-a pri 8 ALS družinah



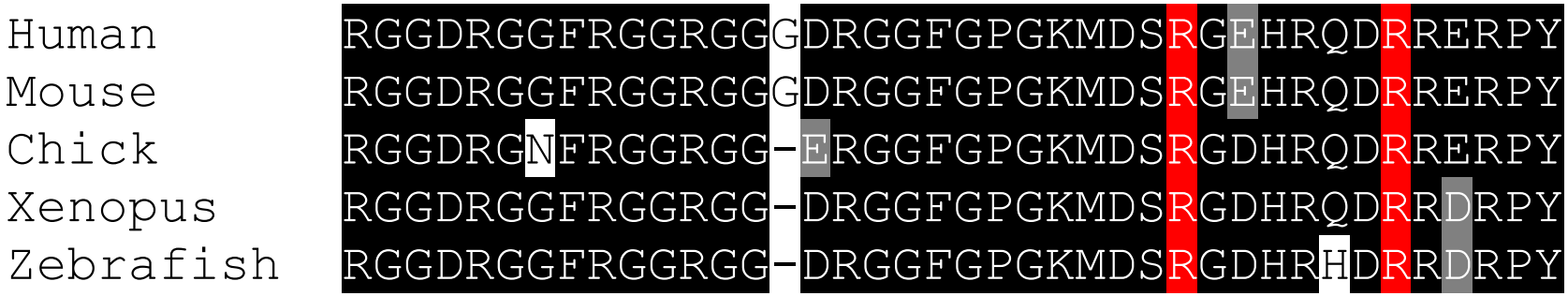

1561 C>T R521C




1562 G>A R521H

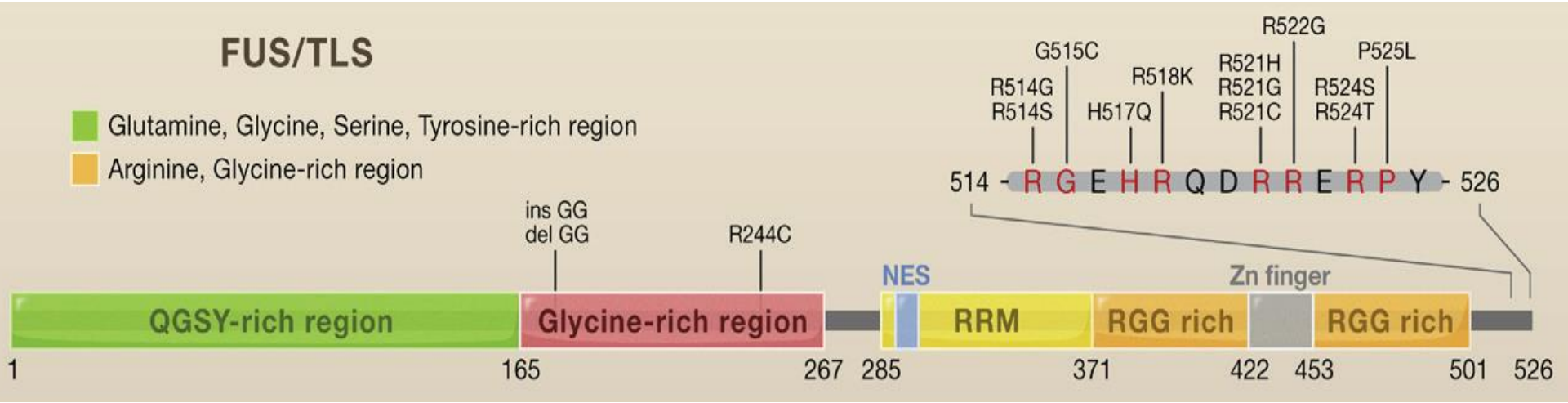



1540 A>G R514G




Vance/Rogelj, *Science* 2009

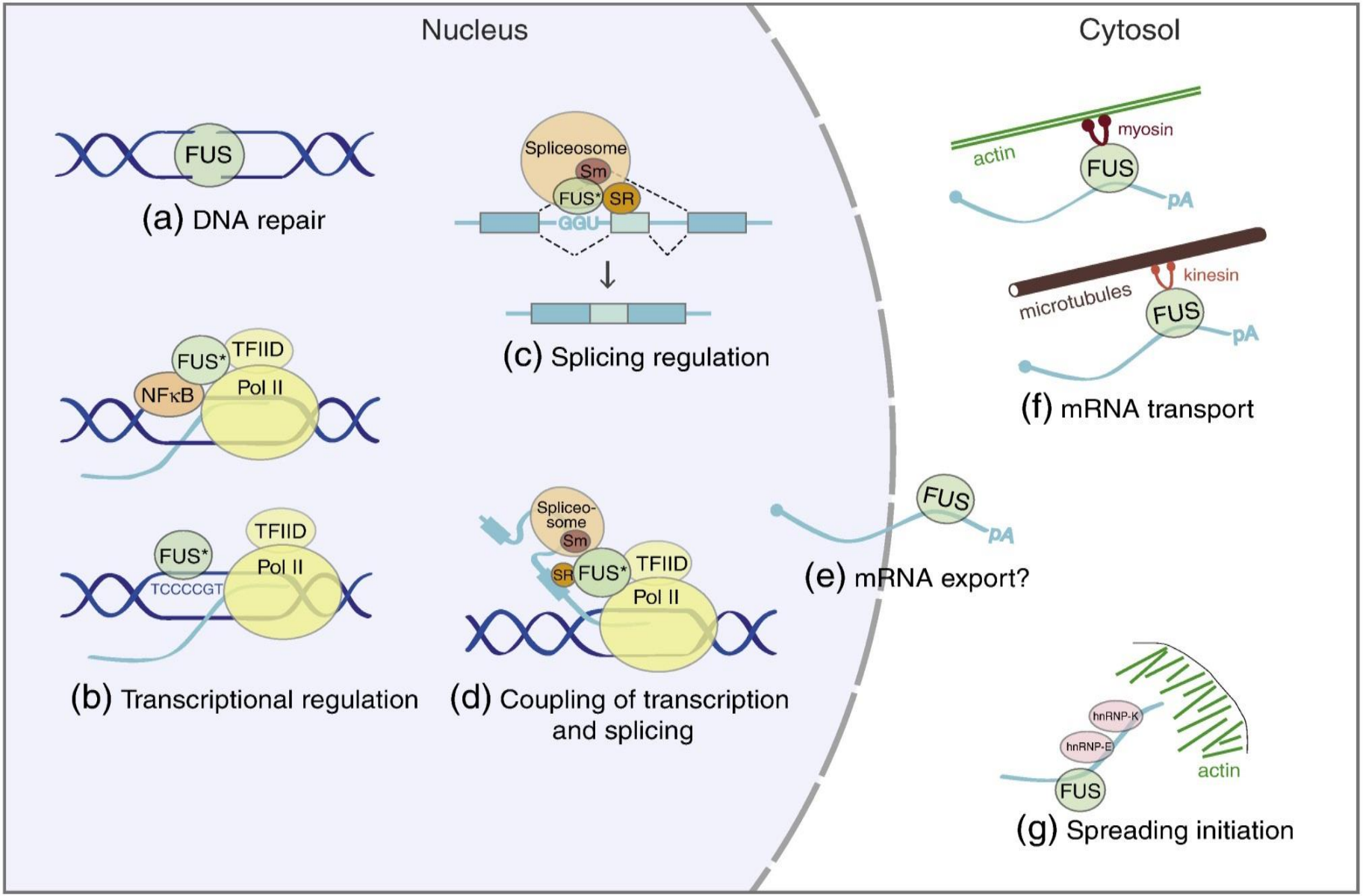
# FUS mutacije pri dedni ALS




**Lagiere-Tourenne, *Cell* 2009**

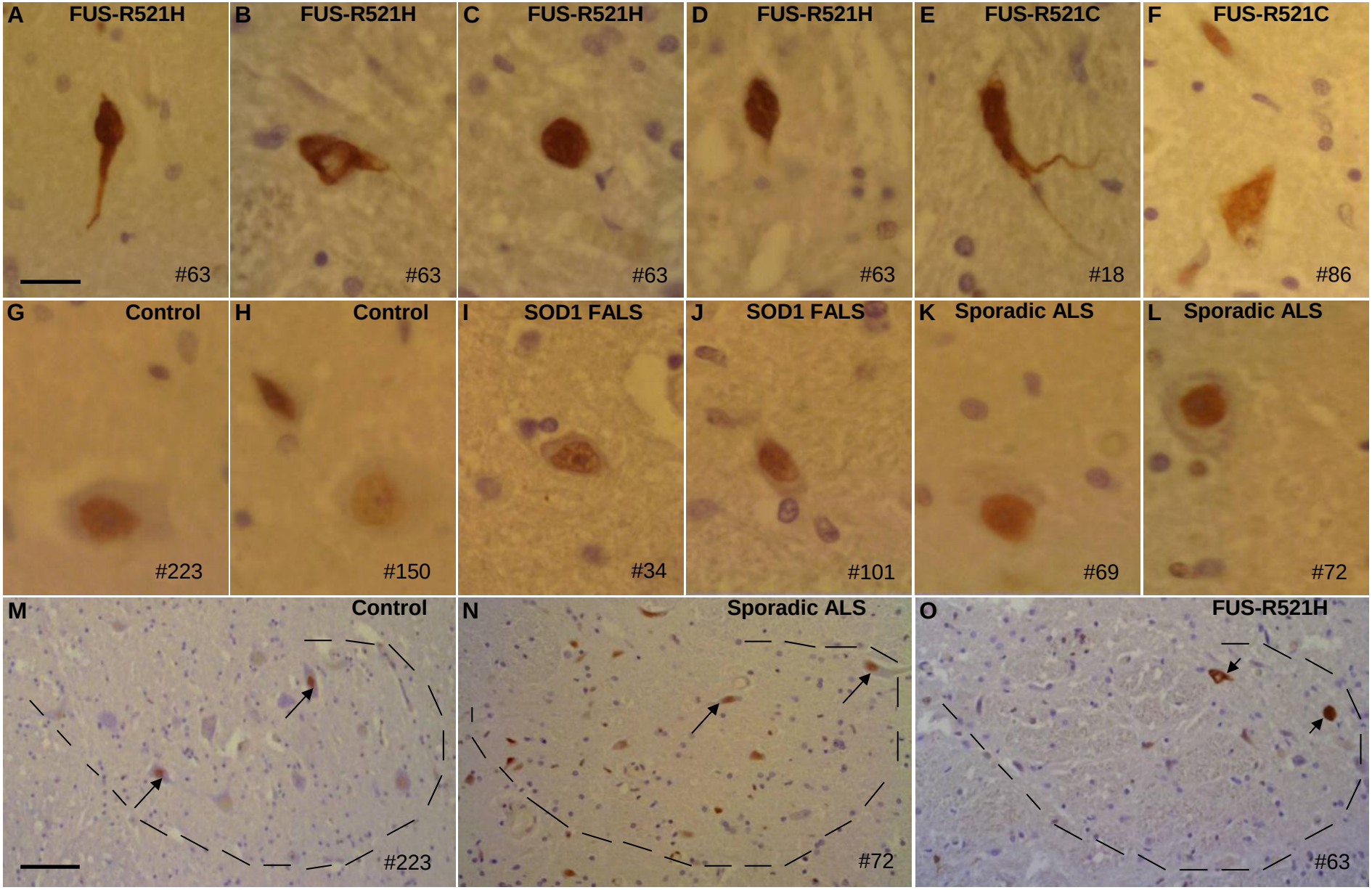
- >40 mutacij.
- 2/3 mutacij je na C-terminalu proteina.
- 1/3 mutacij je v G-bogati regiji.

# Funkcije FUS



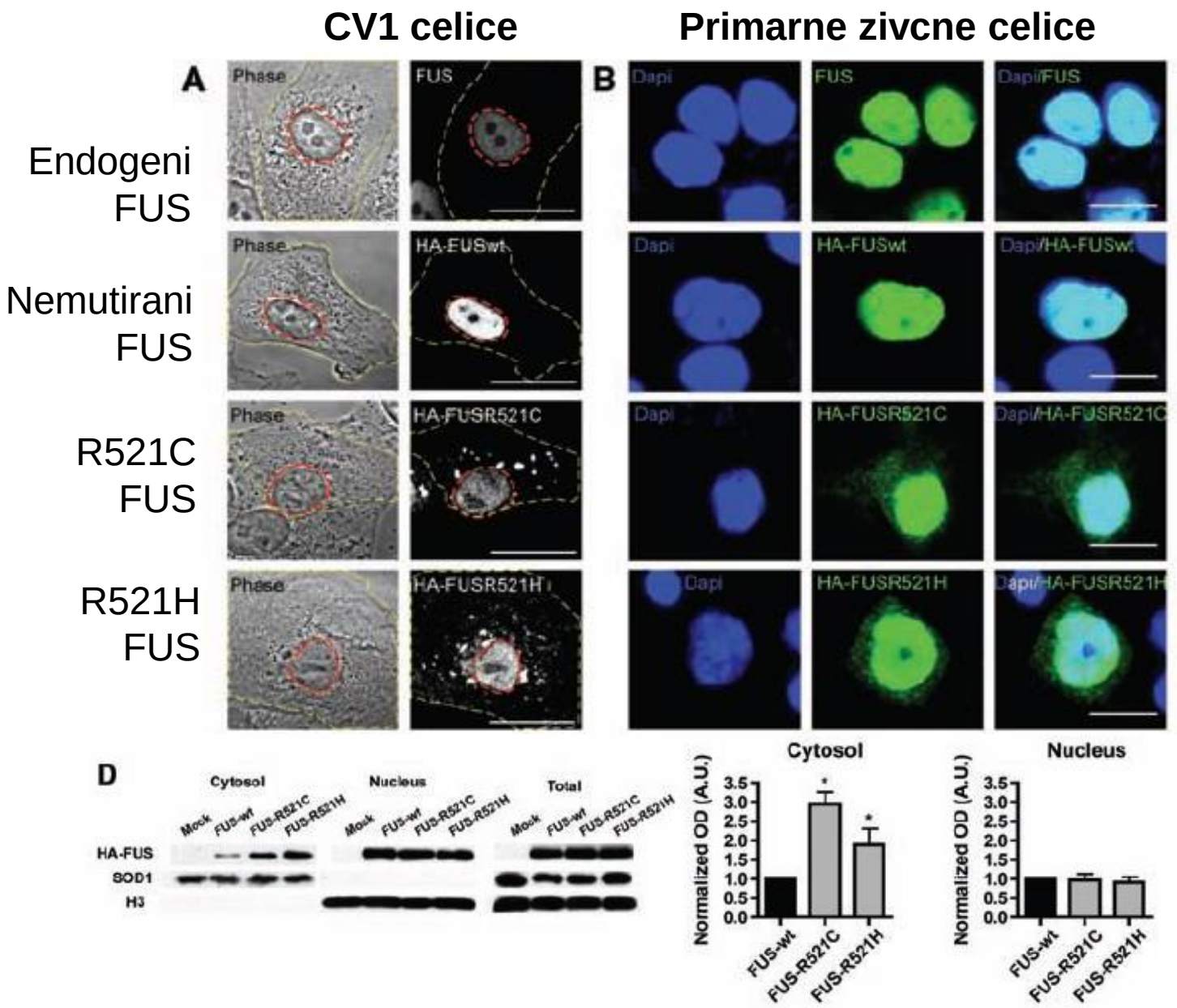

Doorman et al., Mol Cel Neurosci 2013

# FUS agregati pri ALS pacientih z mutacijo




Vance/Rogelj, *Science* 2009

# Mutacije v FUS vplivajo na lokalizacijo v celici




Vance/Rogelj, *Science* 2009

*Human Molecular Genetics*, 2013 **1–13**
doi:10.1093/hmg/ddt117

# ALS mutant FUS disrupts nuclear localization and sequesters wild-type FUS within cytoplasmic stress granules

**Caroline Vance[1], Emma L. Scotter[1], Agnes L. Nishimura[1], Claire Troakes[1], Jacqueline C. Mitchell[1], Claudia Kathe[1], Hazel Urwin[1], Catherine Manser[2], Christopher C. Miller[1,2], Tibor Hortobágyi[1], Mike Dragunow[3], Boris Rogelj[1,4,†] and Christopher E. Shaw[1,*,†]**

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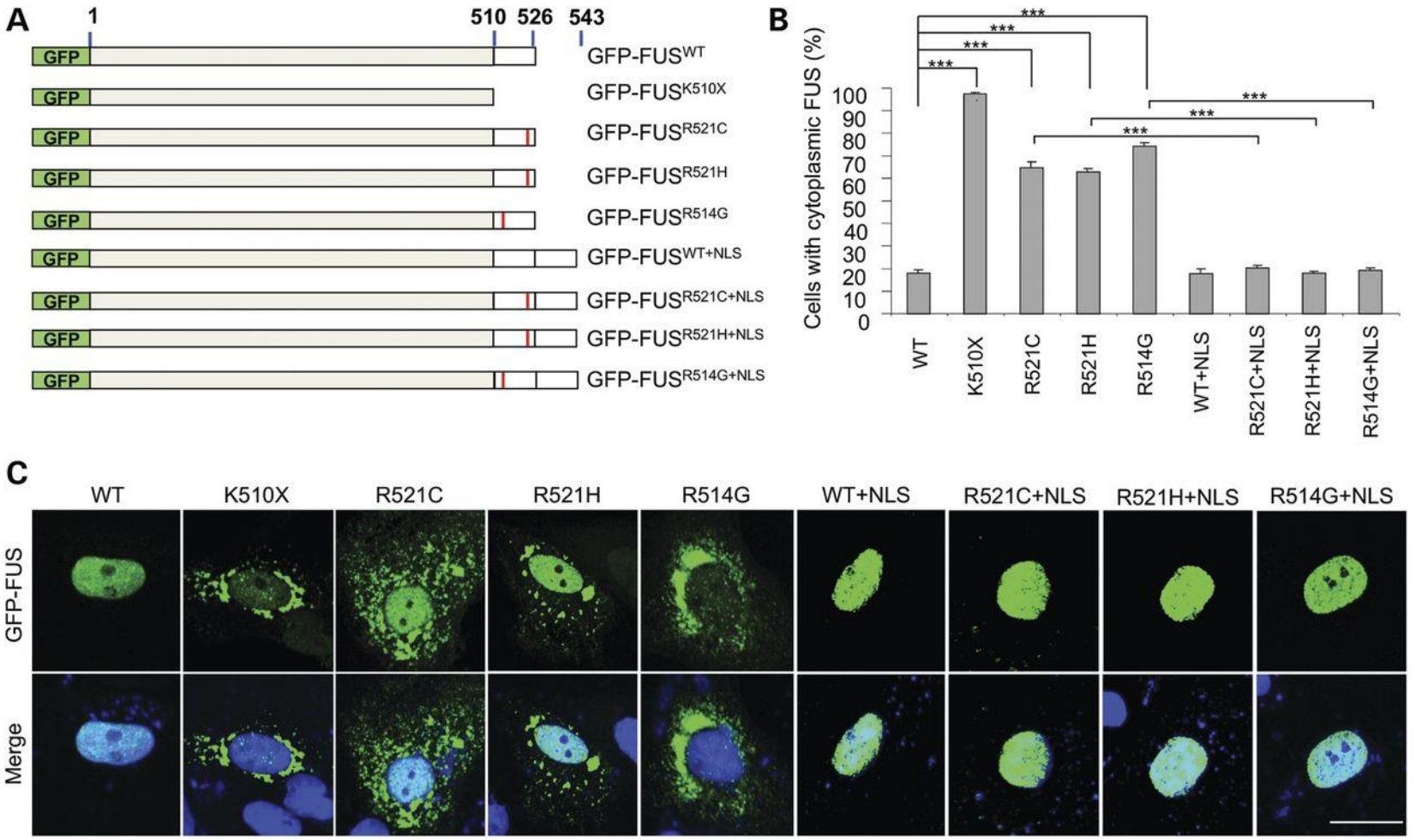
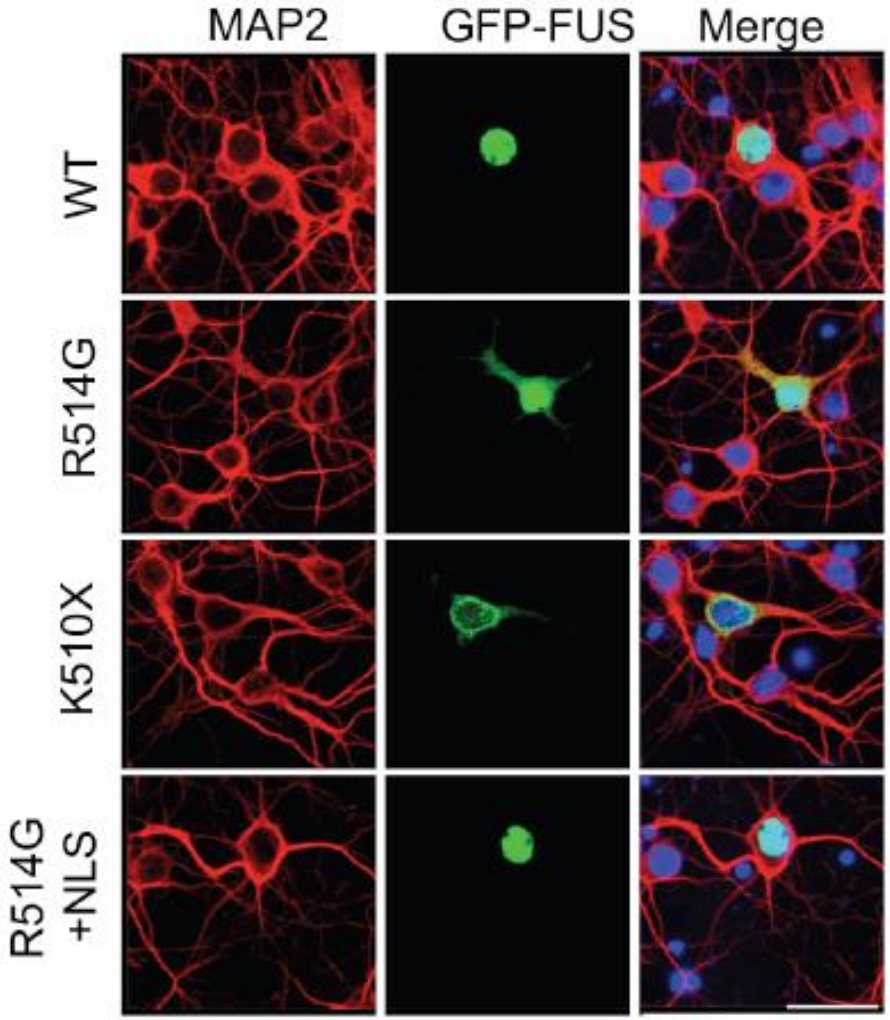
**Mutations in the gene encoding *Fused in Sarcoma* (*FUS*) cause amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disorder. FUS is a predominantly nuclear DNA- and RNA-binding protein that is involved in RNA processing. Large FUS-immunoreactive inclusions fill the perikaryon of surviving motor neurons of ALS patients carrying mutations at post-mortem. This sequestration of FUS is predicted to disrupt RNA processing and initiate neurodegeneration. Here, we demonstrate that C-terminal ALS mutations disrupt the nuclear localizing signal (NLS) of FUS resulting in cytoplasmic accumulation in transfected cells and patient fibroblasts. FUS mislocalization is rescued by the addition of the wild-type FUS NLS to mutant proteins. We also show that oxidative stress recruits mutant FUS to cytoplasmic stress granules where it is able to bind and sequester wild-type FUS. While FUS interacts with itself directly by protein–protein interaction, the recruitment of FUS to stress granules and interaction with PABP are RNA dependent. These findings support a two-hit hypothesis, whereby cytoplasmic mislocalization of FUS protein, followed by cellular stress, contributes to the formation of cytoplasmic aggregates that may sequester FUS, disrupt RNA processing and initiate motor neuron degeneration.**

# C-konec FUSa vsebuje NLS



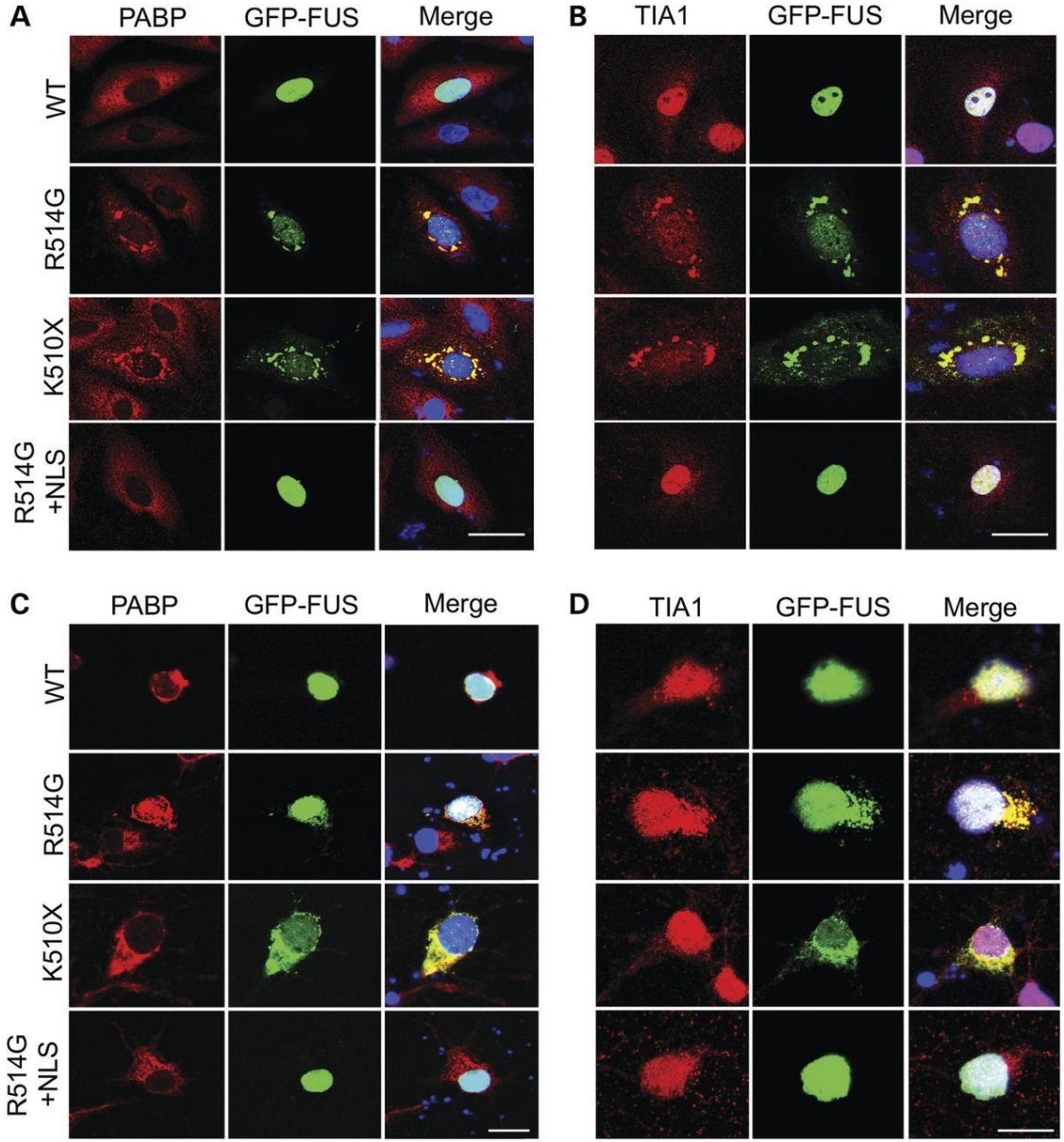

Vance C et al. Hum. Mol. Genet. 2013

# Mutirani FUS se napačno izraža tudi v nevronih




Vance C et al. Hum. Mol. Genet. 2013

# Mutirani FUS kolokalizira s stresnimi granulami




Vance C et al. Hum. Mol. Genet. 2013

# Mutirani FUS ne kolokalizira z markerij za P telesca, jedrnimi granulami in RNA transportnimi zrnci

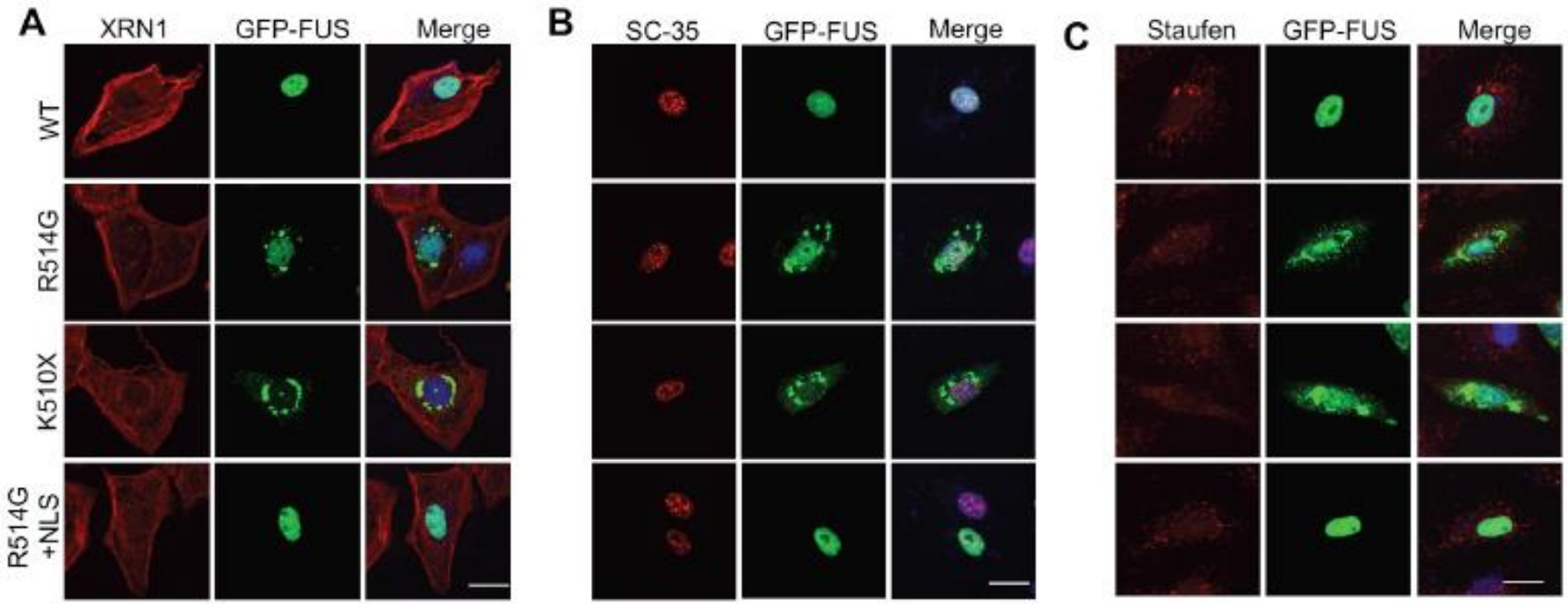
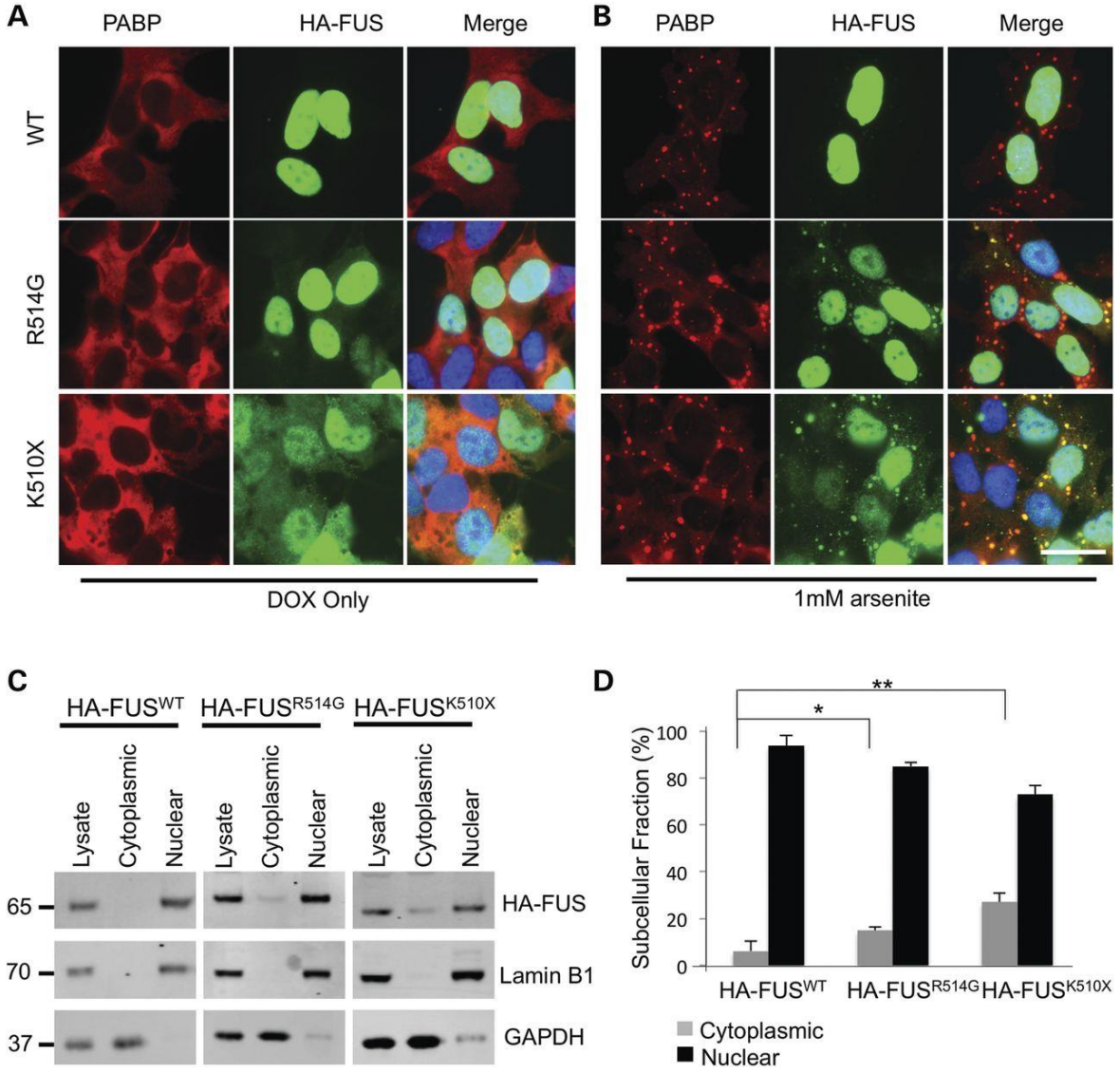



**Figure S1: GFP-FUS does not co-localise with markers for p-bodies ,nuclear speckles or RNA transport granules.**

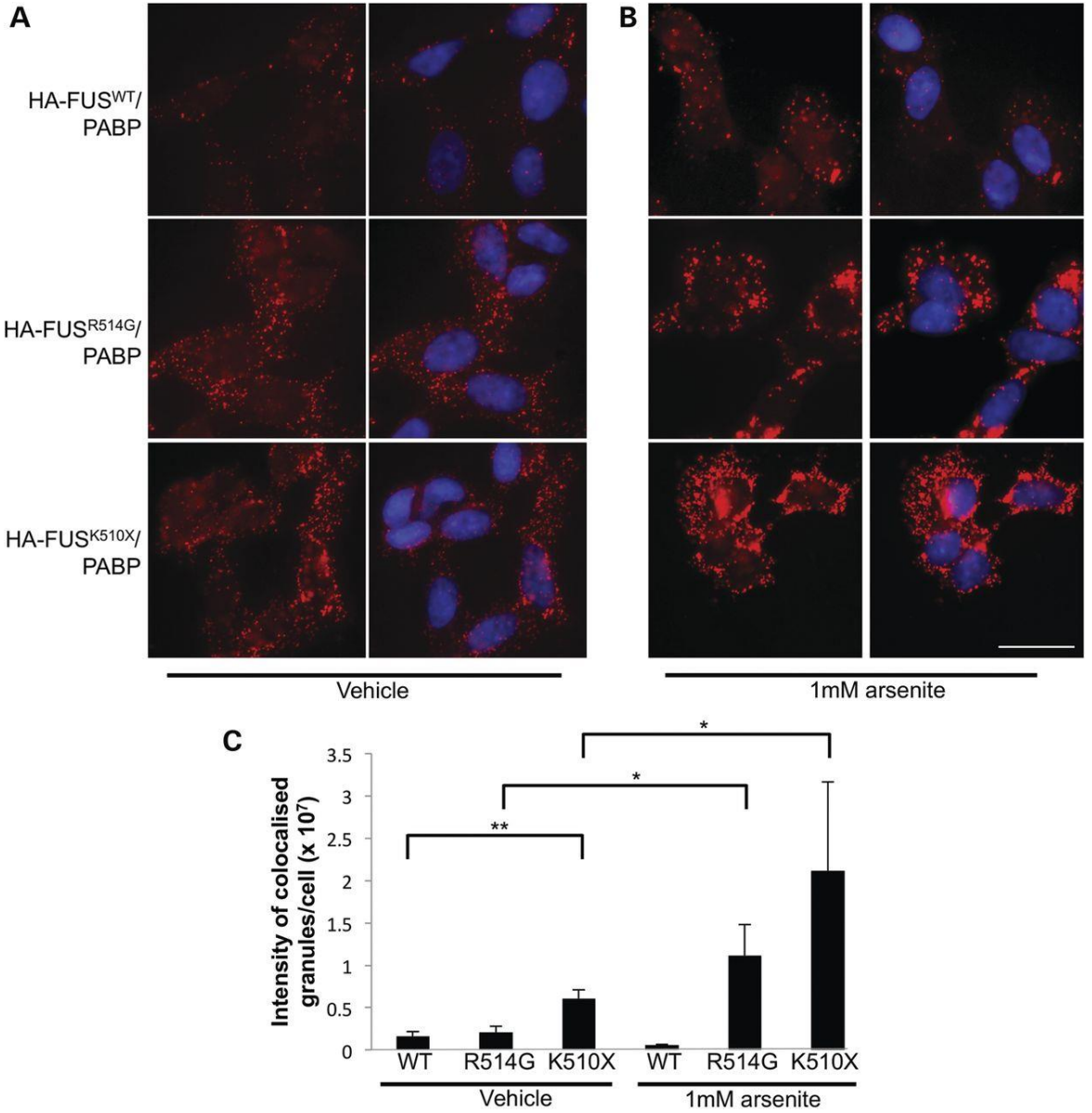
Vance C et al. Hum. Mol. Genet. 2013

# Stabilno transfecirani mutirani FUS potrebuje oksidativni stres za tvorbo SG



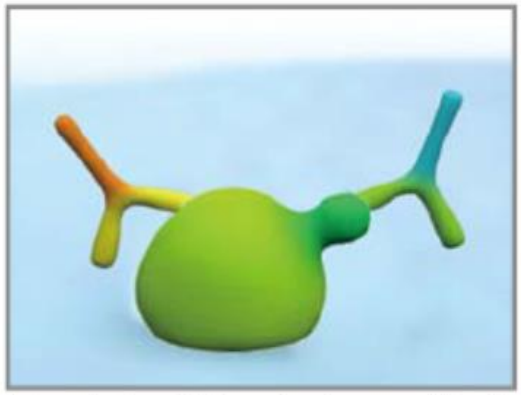

Vance C et al. Hum. Mol. Genet. 2013

# FUS in PABP se nahajata v bližini drug drugega

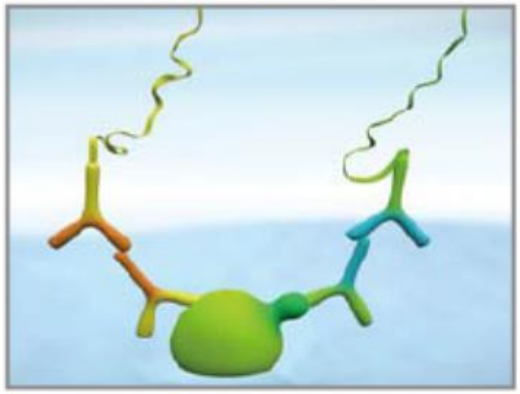



Vance C et al. Hum. Mol. Genet. 2013

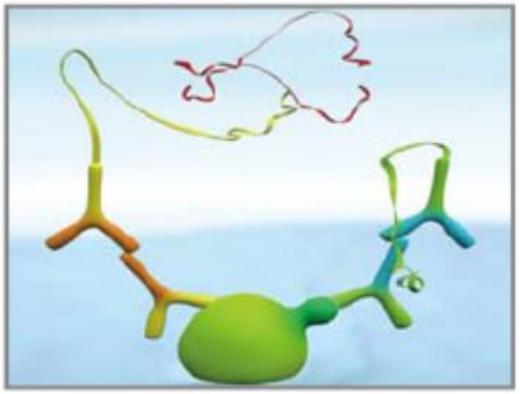
# Ligacijski test bližine (PLA -proximity ligation assay)



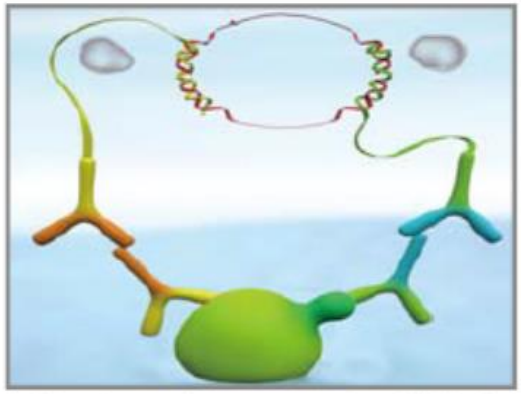
1. Incubate with target primary antibodies from two different species



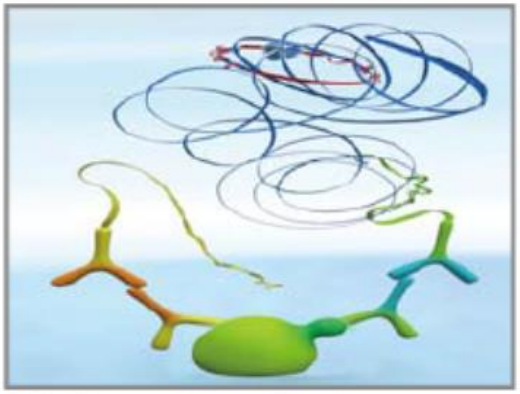
2. Add PLA probes PLUS and MINUS



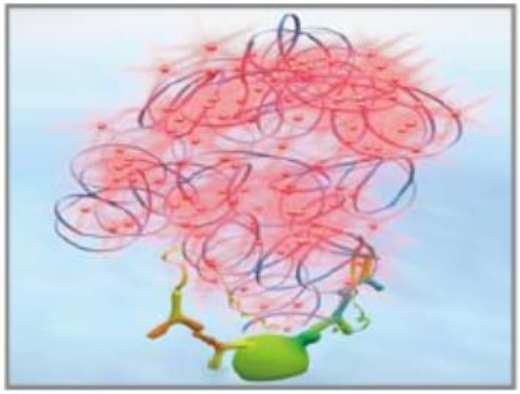
3. Hybridize connector oligos



4. Ligation to form a complete DNA circle

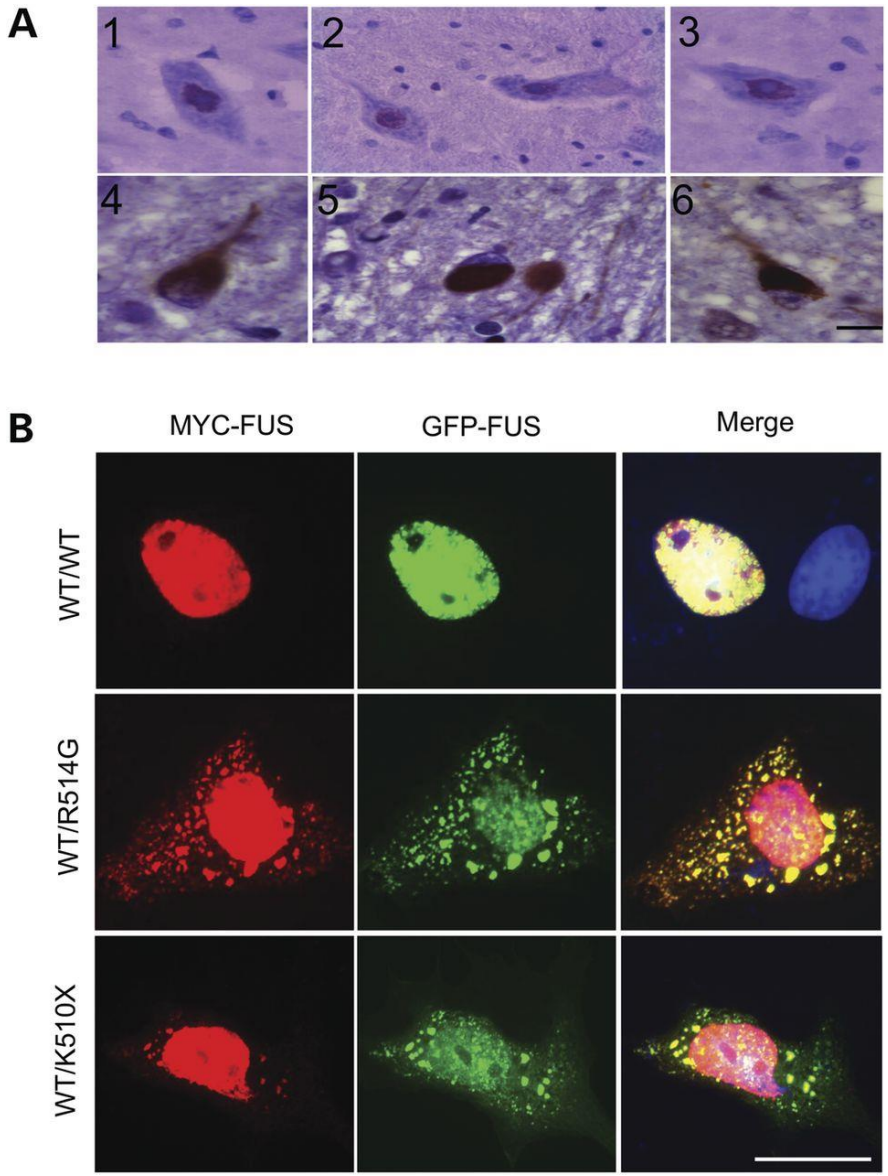


5. Rolling circle amplification



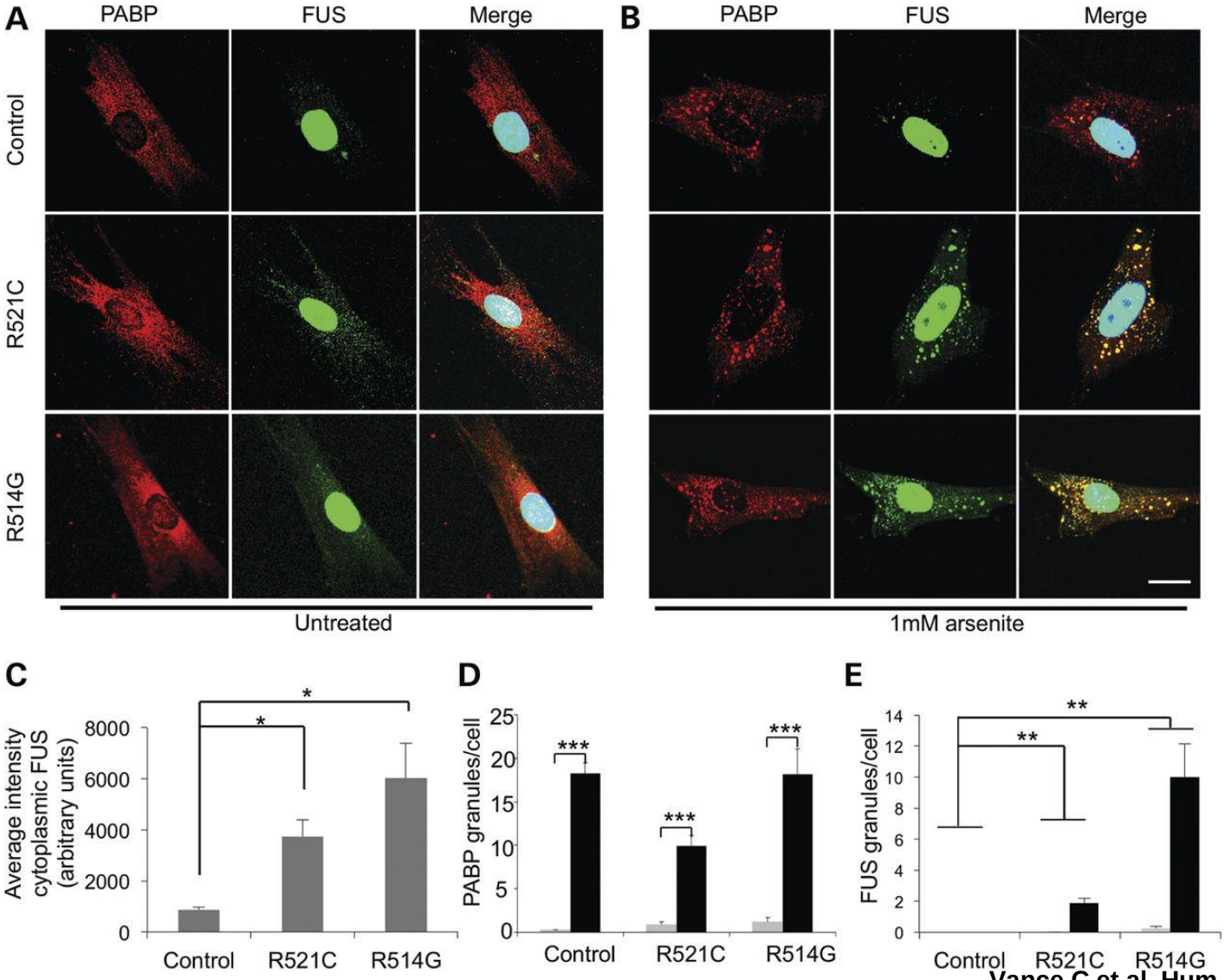
6. Add fluorescent probes to reveal phosphorylation

# Mutirani FUS privleče tudi nemutirani FUS v SG




Vance C et al. Hum. Mol. Genet. 2013

# V fibroblastih pacientov s FUS mutacijami je FUS v SG




Vance C et al. Hum. Mol. Genet. 2013

Acta Neuropathol
DOI 10.1007/s00401-012-1043-z

ORIGINAL PAPER

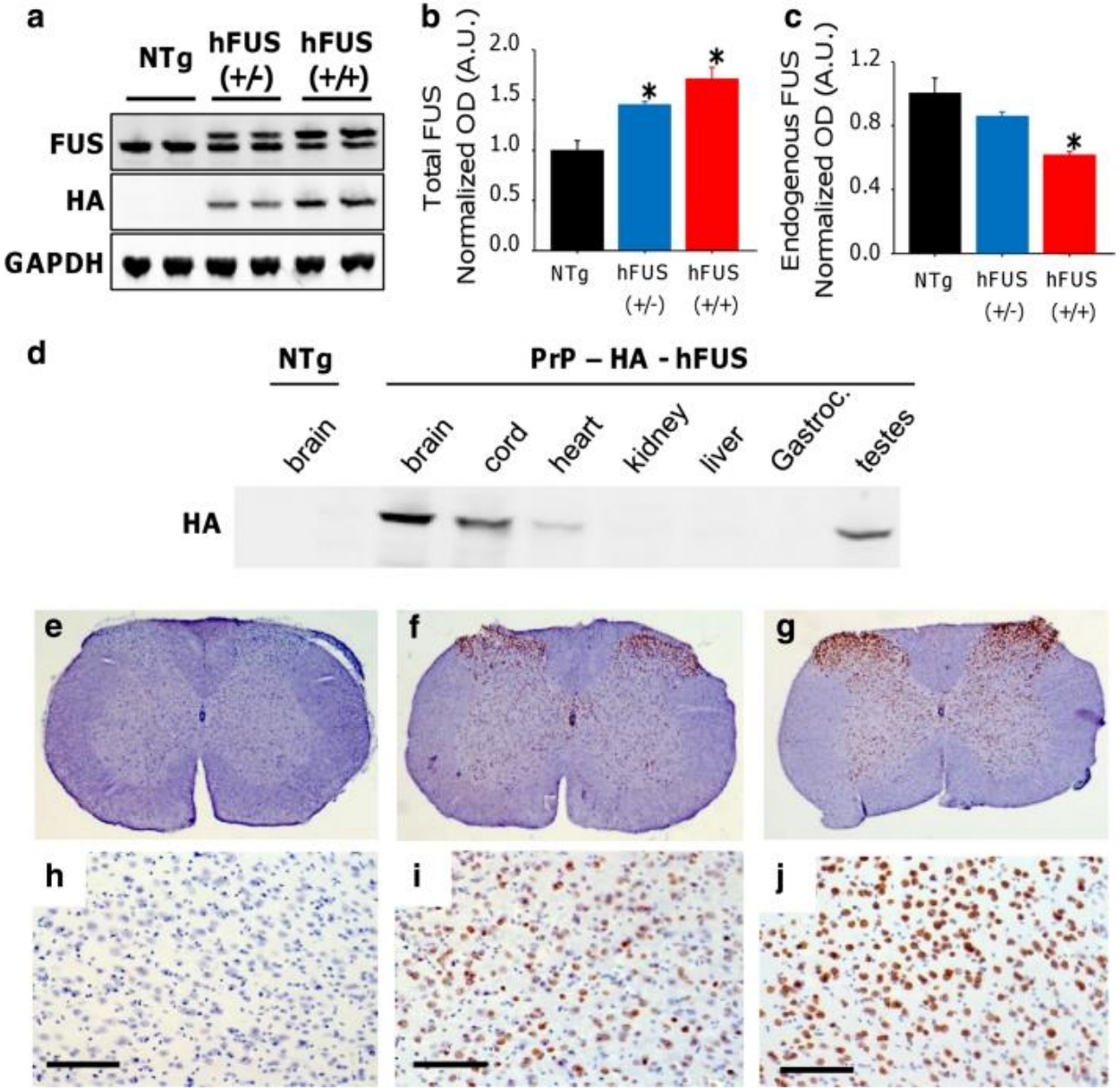
# Overexpression of human wild-type FUS causes progressive motor neuron degeneration in an age- and dose-dependent fashion

**Jacqueline C. Mitchell · Philip McGoldrick · Caroline Vance · Tibor Hortobagyi · Jemeen Sreedharan · Boris Rogelj · Elizabeth L. Tudor · Bradley N. Smith · Christian Klasen · Christopher C. J. Miller · Jonathan D. Cooper · Linda Greensmith · Christopher E. Shaw**

Received: 13 June 2012 / Revised: 30 August 2012 / Accepted: 30 August 2012

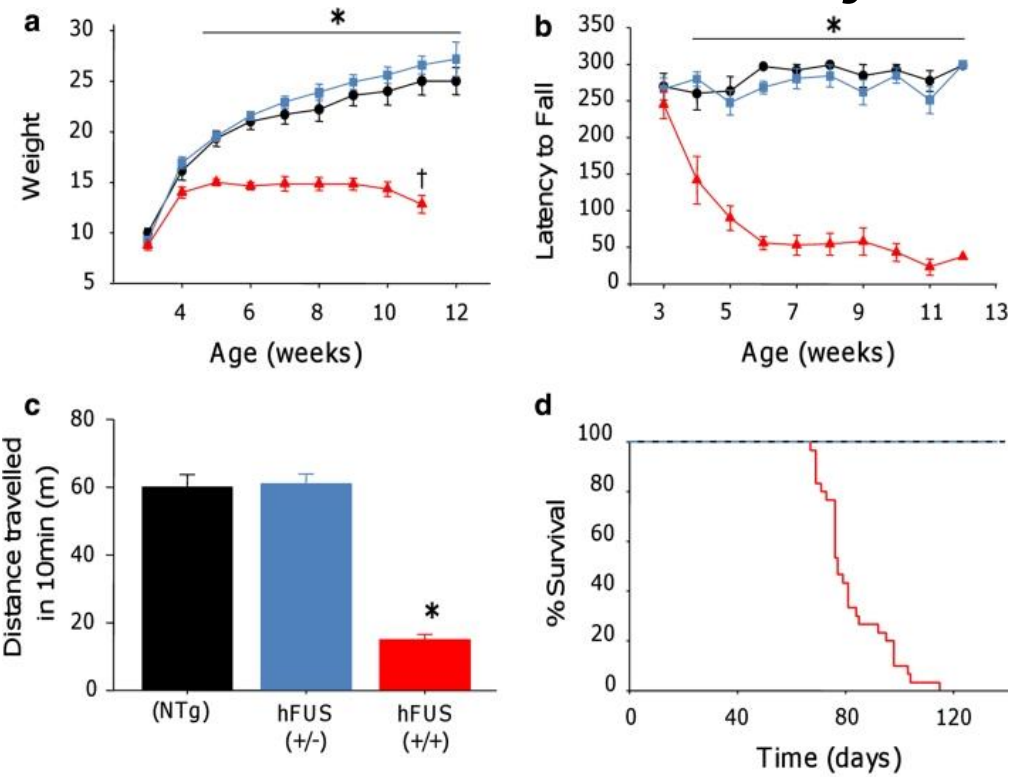

**Abstract** Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are relentlessly progressive neurodegenerative disorders with overlapping clinical, genetic and pathological features. Cytoplasmic inclusions of fused in sarcoma (FUS) are the hallmark of several forms of FTLD and ALS patients with mutations in the *FUS* gene. FUS is a multifunctional, predominantly nuclear, DNA and RNA binding protein. Here, we report that transgenic mice overexpressing wild-type human FUS develop an aggressive phenotype with an early onset tremor followed by progressive hind limb paralysis and death by 12 weeks in homozygous animals. Large motor neurons were lost from the spinal cord accompanied by neurophysiological evidence of denervation and focal muscle atrophy. Surviving motor neurons in the spinal cord had greatly increased cytoplasmic expression of FUS, with globular and skein-like FUS-positive and ubiquitin-negative inclusions associated with astroglial and microglial reactivity. Cytoplasmic FUS inclusions were also detected in the brain of transgenic mice without apparent neuronal loss and little astroglial or microglial activation. Hemizygous FUS overexpressing mice showed no evidence of a motor phenotype or pathology. These findings recapitulate several pathological features seen in human ALS and FTLD patients, and suggest that overexpression of wild-type FUS in vulnerable neurons may be one of the root causes of disease. Furthermore, these mice will provide a

# Transgeni FUS zmanjša izražanje endogenega




Mitchell et al., Acta Neuropath 2013

# Transgene miške imajo lokomotorne težave in krajše življenje

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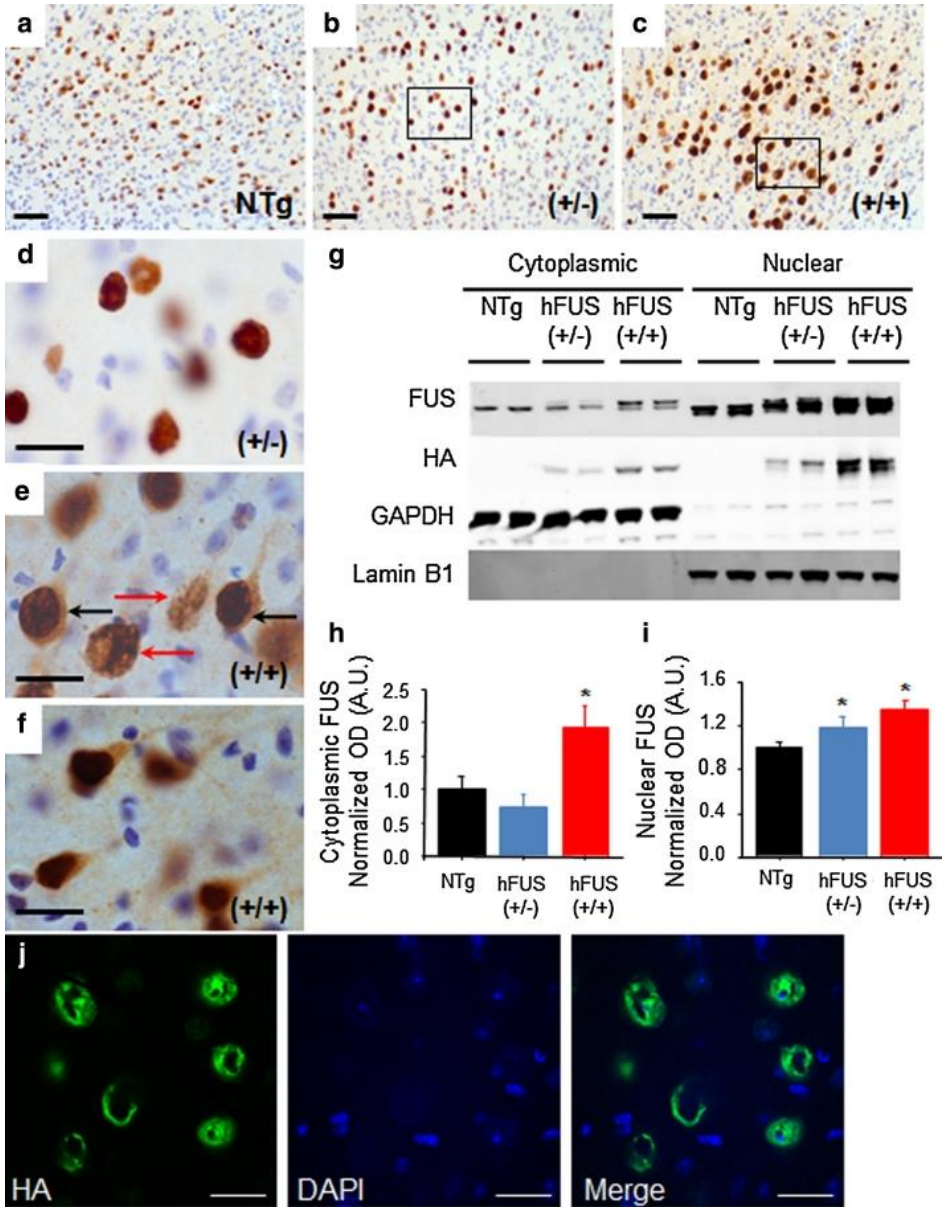
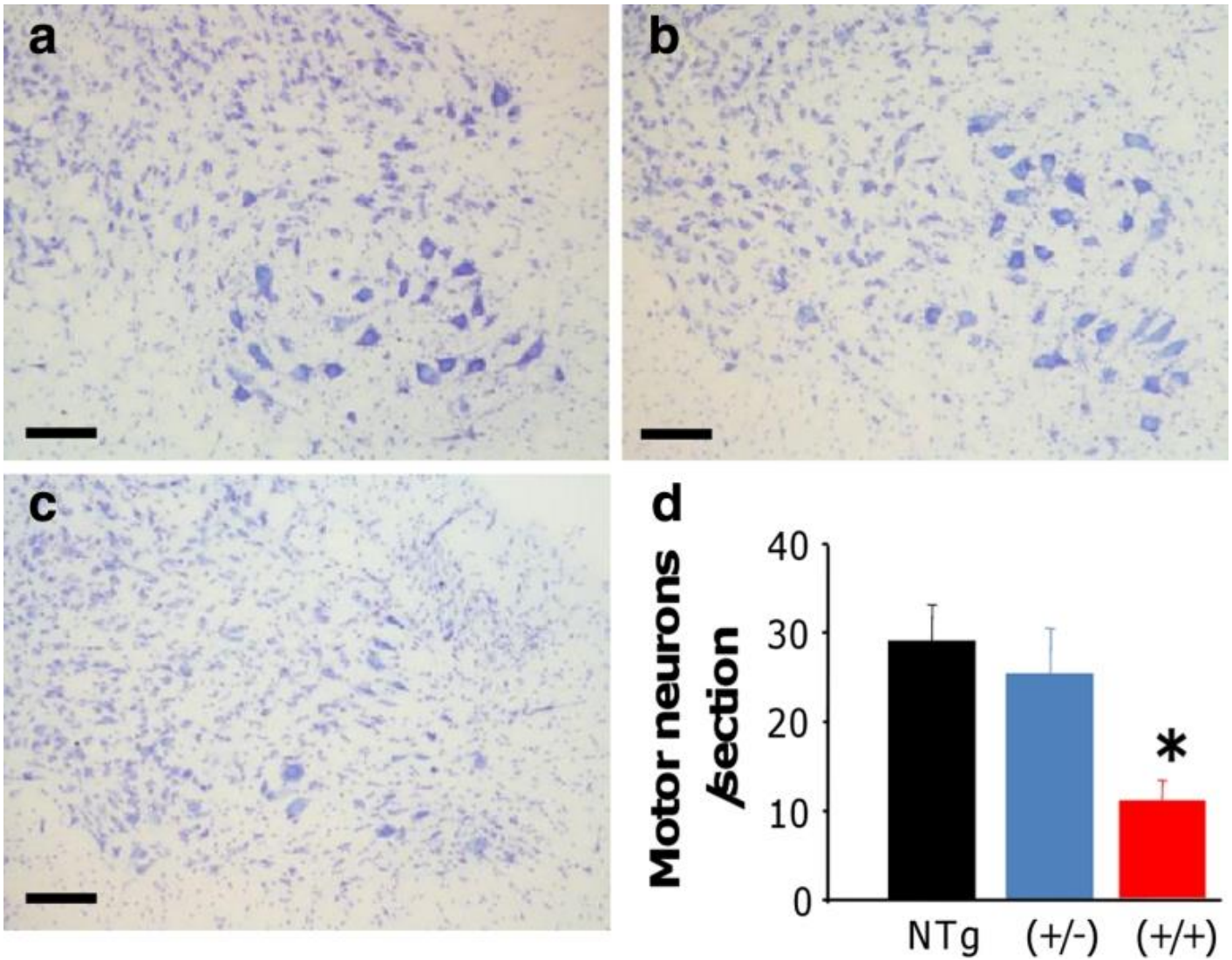
# Povečana lokalizacija FUS v citoplazmi pri homozigotih




Mitchell et al., Acta Neuropath 2013

# Homozigoti izgubijo motorične nevrone




Mitchell et al., Acta Neuropath 2013

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# Widespread binding of FUS along nascent RNA regulates alternative splicing in the brain

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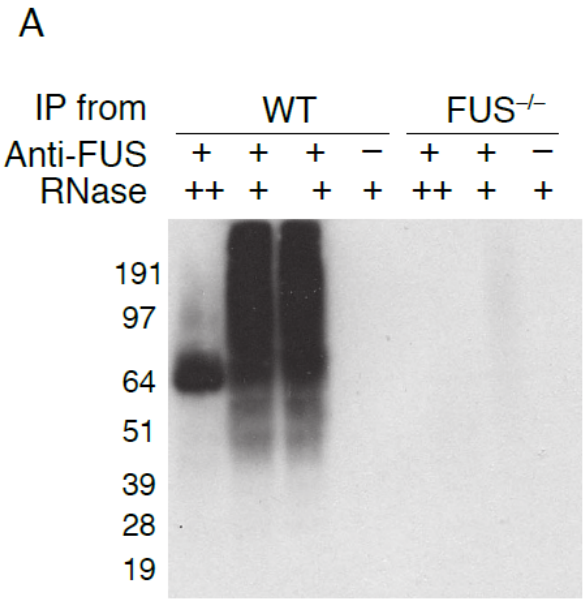
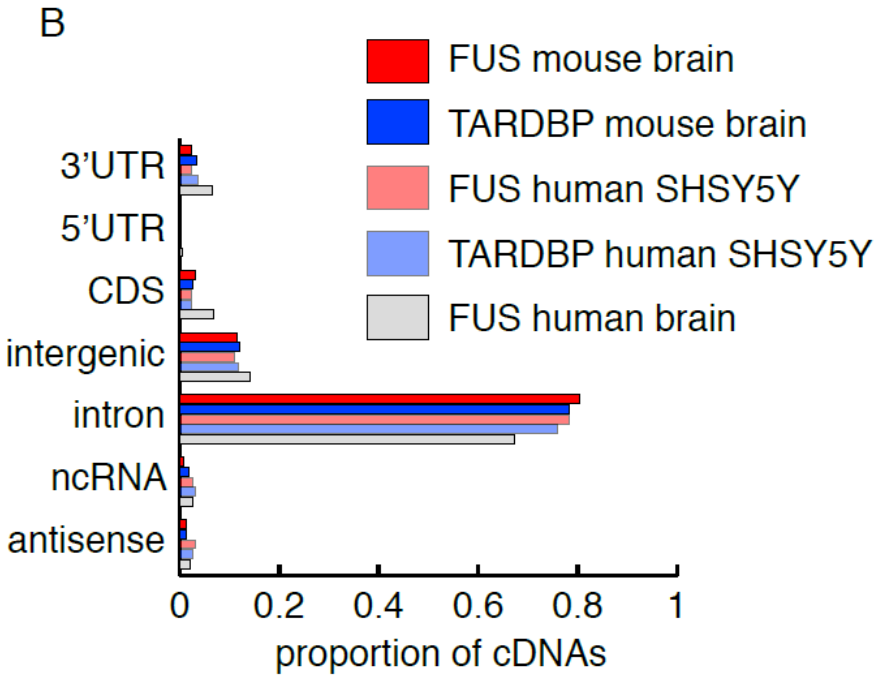
[1]Centre for Neurodegeneration Research, King's College London, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK, [2]MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 0QH, UK, [3]Stem Cell and Developmental Biology Group, Genome Institute of Singapore, 60 Biopolis Street, S(138672), Singapore, [4]Faculty of Computer and Information Science, University of Ljubljana, Tržaška 25, SI-1000, Ljubljana, Slovenia, [5]Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami, Hiroshima 734-8553, Japan, [6]Now at: Department of Biotechnology, Jožef Stefan Institute, Jamova 39, SI-1000, Ljubljana, Slovenia, [7]Now at: The Buck Institute for Research on Aging, 8001 Redwood Blvd., Novato, CA 94945, USA.

Fused in sarcoma (FUS) and TAR DNA-binding protein 43 (TDP-43) are RNA-binding proteins pathogenetically linked to amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), but it is not known if they regulate the same transcripts. We addressed this question using crosslinking and immunoprecipitation (iCLIP) in mouse brain, which showed that FUS binds along the whole length of the nascent RNA with limited sequence specificity to GGU and related motifs. A saw-tooth binding pattern in long genes demonstrated that FUS remains bound to pre-mRNAs until splicing is completed. Analysis of $FUS^{-/-}$ brain demonstrated a role for FUS in alternative splicing, with increased crosslinking of FUS in introns around the repressed exons. We did not observe a significant overlap in the RNA binding sites or the exons regulated by FUS and TDP-43. Nevertheless, we found that both proteins

# FUS iCLIP

- možgani E18 mišk
- FUS -/- miške kot kontrola
(Hicks et al. Nat Genetics 2000)
- 1,06 X $10^6$ posameznih zaporedij
- 14.840 genov




**Rogelj/Easton, *Scientific Reports* 2012**

# Specifičnost RNA vezave FUS

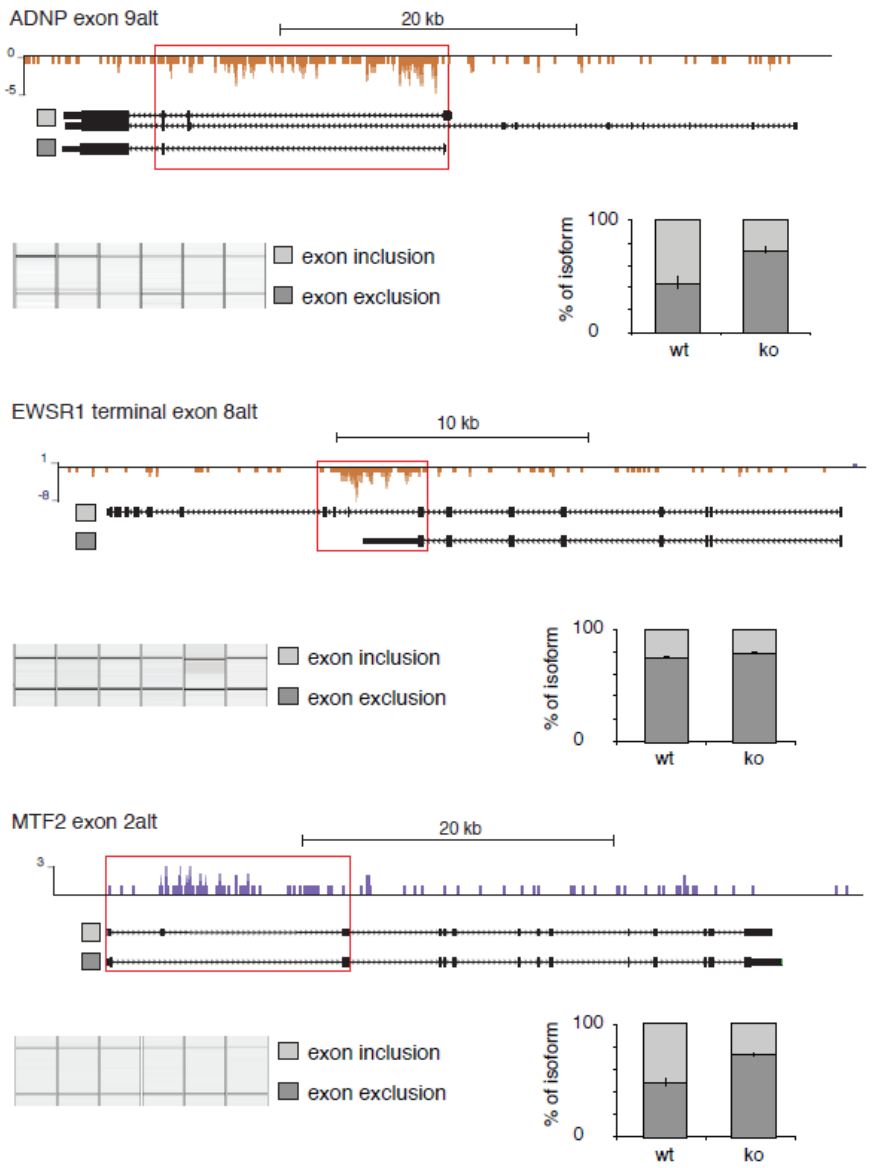
- FUS nima specifične RNA, na katero se veže (kot je UG pri TDP-43).

- Ali se FUS veže nespecifično na RNA?

- FUS ima tri domene, ki lahko vežejo RNA (RRM, Zn-finger, RGG motivi). Vsaka domena ima lahko specifično vezavo na RNA, vendar pri CLIPu celega proteina tega ne moremo razločiti.

- Obstaja preferenca za enoverižno RNA, ki je pred GC bogatim regijam.

# FUS uravnava izrezovanje in spajanje RNA




**Rogelj/Easton, *Scientific Reports* 2012**

# FUS uravnava gene aksonogeneze in adhezije

| GO term | P-value | reference exons | FUS regulated exons | |
|---|---|---|---|---|
| axonogenesis | 0.0126 | 312 | 13 | Ablim1_E23, Adnp_E16, Apc_E5, Cdh2_E16, Enah_E15, Enah_E5, Mapt_E15, Mapt_E8, Nrcam_E33, Ntng1_E11, Ntng1_E9, Picalm_E19, Slitrk4_E2 |
| cell-substrate adhesion | 0.0239 | 175 | 9 | Agt_E2, Cd36_E4, Col8a1_E5, Lims1_E16, Npnt_E3, Sorbs1_E27, Spp1_E2, Spp1_E8, Tsc1_E2 |
| positive regulation of Rho GTPase activity | 0.0328 | 28 | 4 | Rap1gds1_E3, Rap1gds1_E7, Rasgrf1_E2, Tsc1_E2 |

**Rogelj/Easton, *Scientific Reports* 2012**

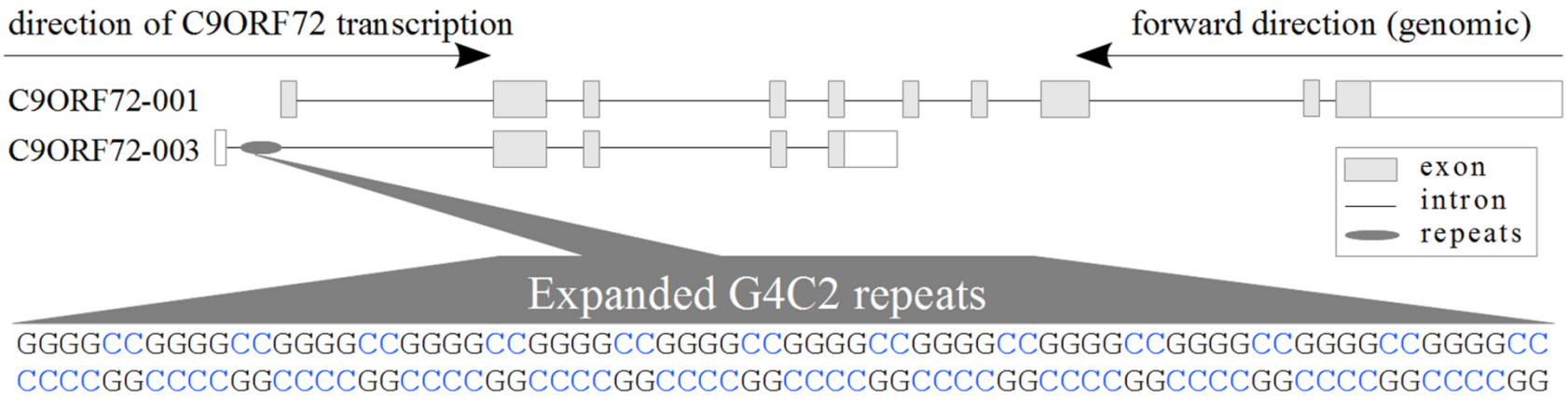
GGGGCC

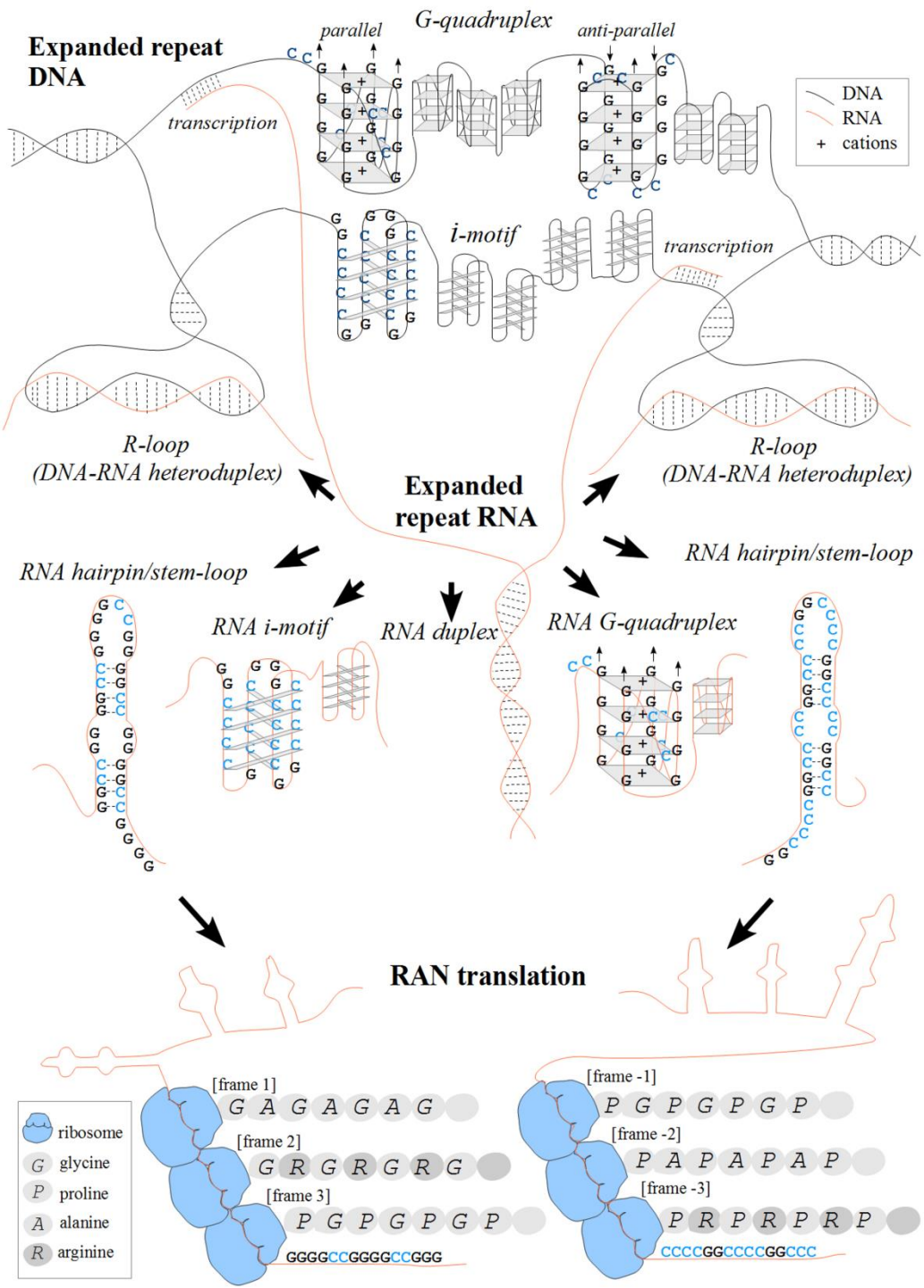
# C9orf72

# C9orf72 (bralno zaporedje 72 na kromosomu 9)

- Nova mutacija, povezana s proteinopatijami TDP-43.
- V genu se nahaja ponavljujoče zaporedje šestih nukleotidov GGGGCC.
- Normalno povprečno število ponovitev = 2 (0-22), pri bolezni >1000.
- Mutacija je nastala pred približno 6300 let v evropski populaciji.
- Čez 80 % dedne ALS v severni Evropi, 20 % na jugu.
- Vloga proteina C9orf72 še ni znana.
- Možno je, da prihaja do toksičnosti RNA prepisa GGGGCC zaporedja.
- RNA toksičnost drugih ponovitev je že znan vzrok za bolezni kot je miotonična distrofija.

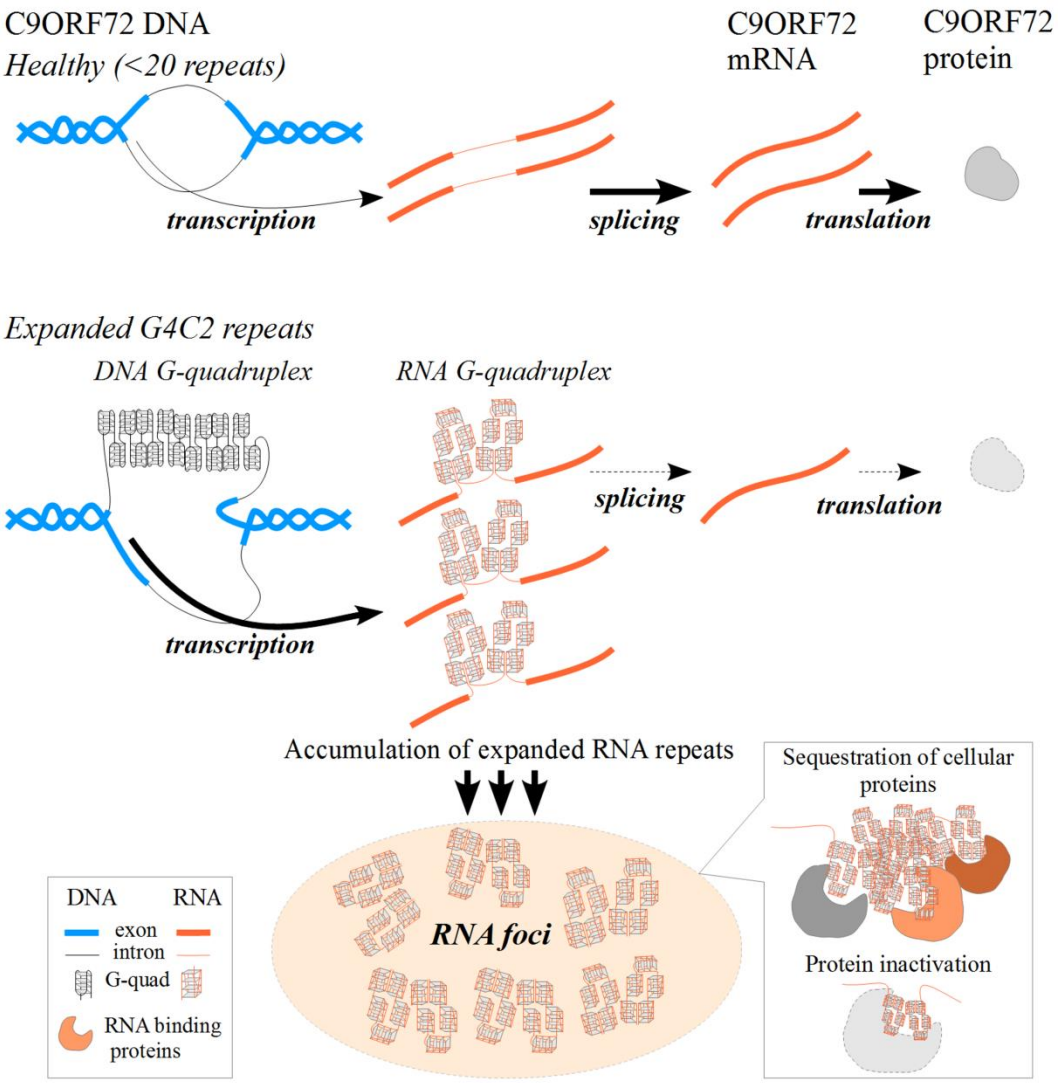
# Genomska lokacija HREM






# Sekundarne strukture HREM

# Vplivi HREM na transkripcijo in translacijo



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Cell Reports
Report

# Hexanucleotide Repeats in ALS/FTD Form Length-Dependent RNA Foci, Sequester RNA Binding Proteins, and Are Neurotoxic

Youn-Bok Lee,[1] Han-Jou Chen,[1] João N. Peres,[2] Jorge Gomez-Deza,[1] Jan Attig,[5,6] Maja Štalekar,[3] Claire Troakes,[1] Agnes L. Nishimura,[1] Emma L. Scotter,[1] Caroline Vance,[1] Yoshitsugu Adachi,[4] Valentina Sardone,[1,7] Jack W. Miller,[1] Bradley N. Smith,[1] Jean-Marc Gallo,[1] Jernej Ule,[6] Frank Hirth,[4] Boris Rogelj,[3] Corinne Houart,[2] and Christopher E. Shaw[1,*]

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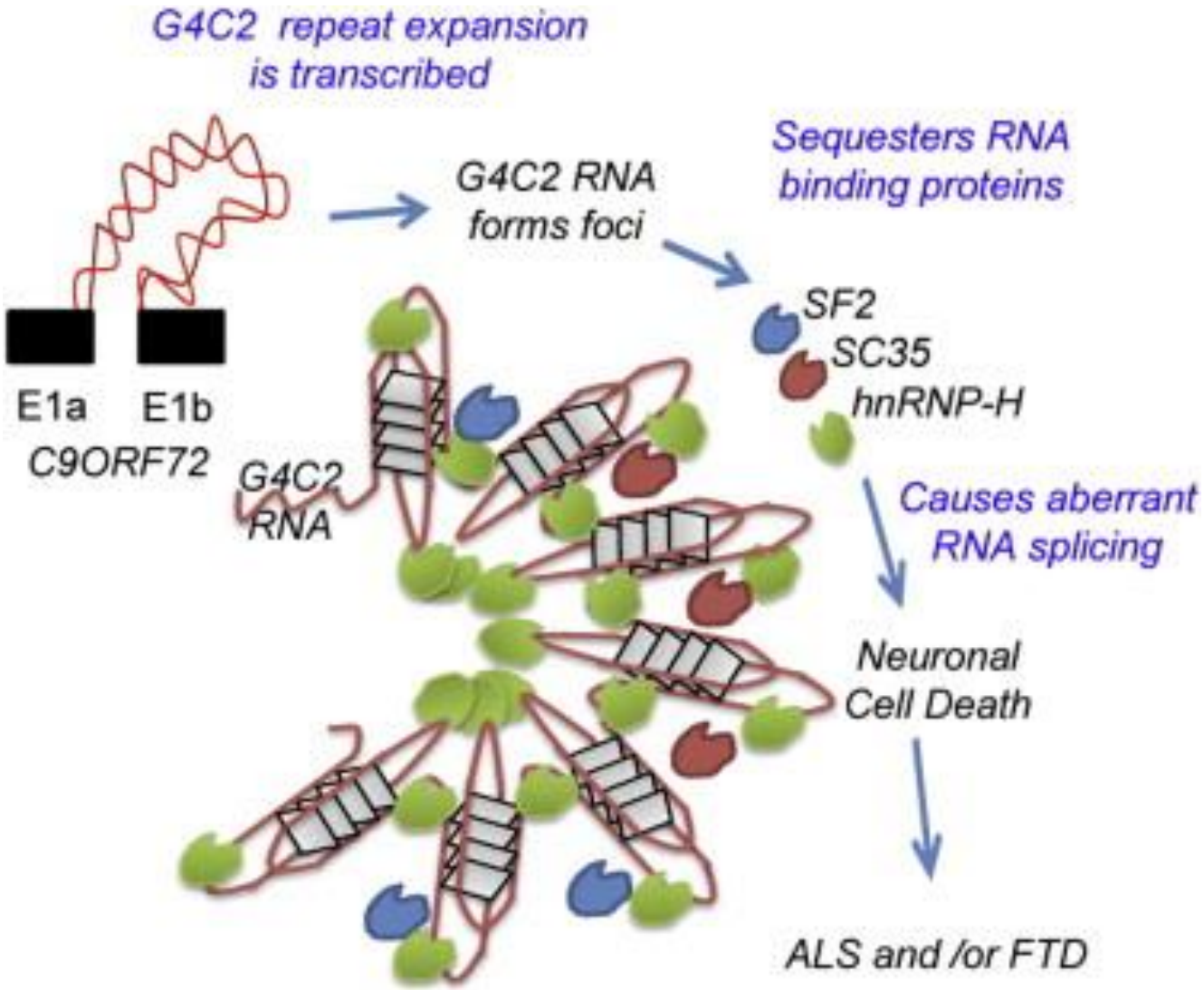
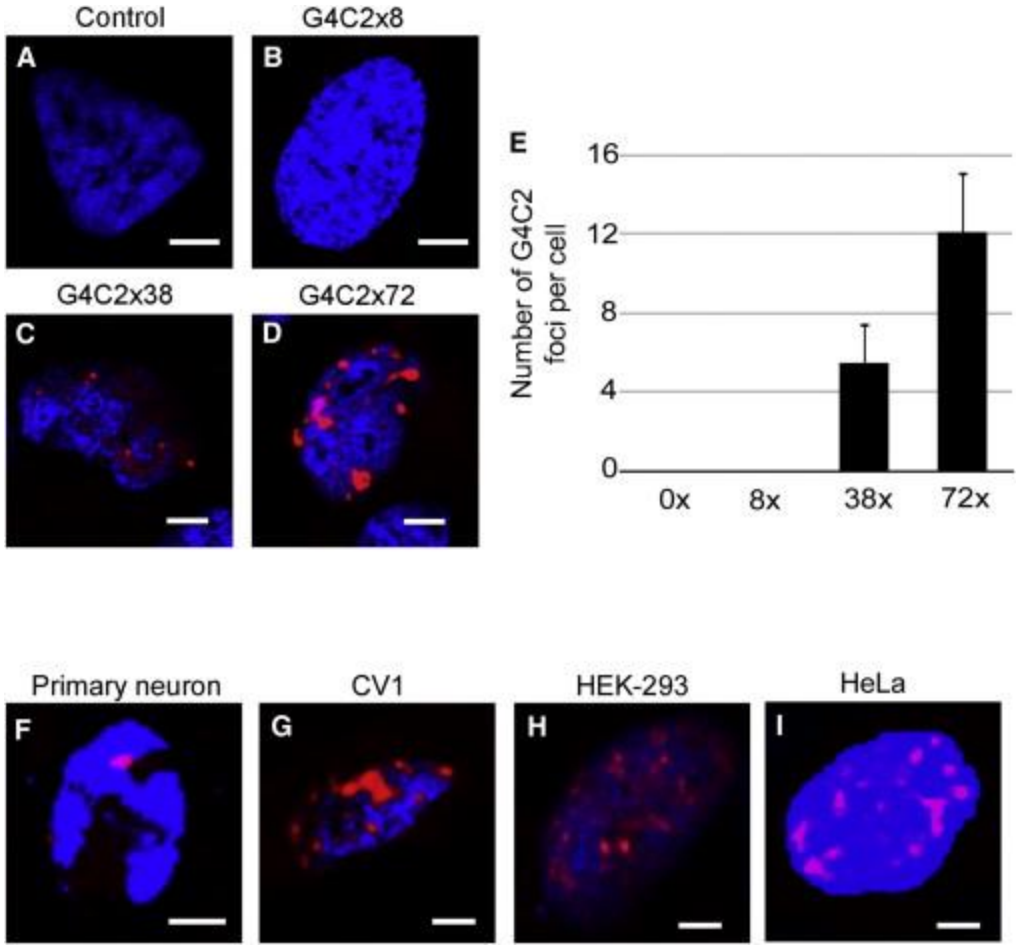
*Correspondence: christopher.shaw@kcl.ac.uk
http://dx.doi.org/10.1016/j.celrep.2013.10.049

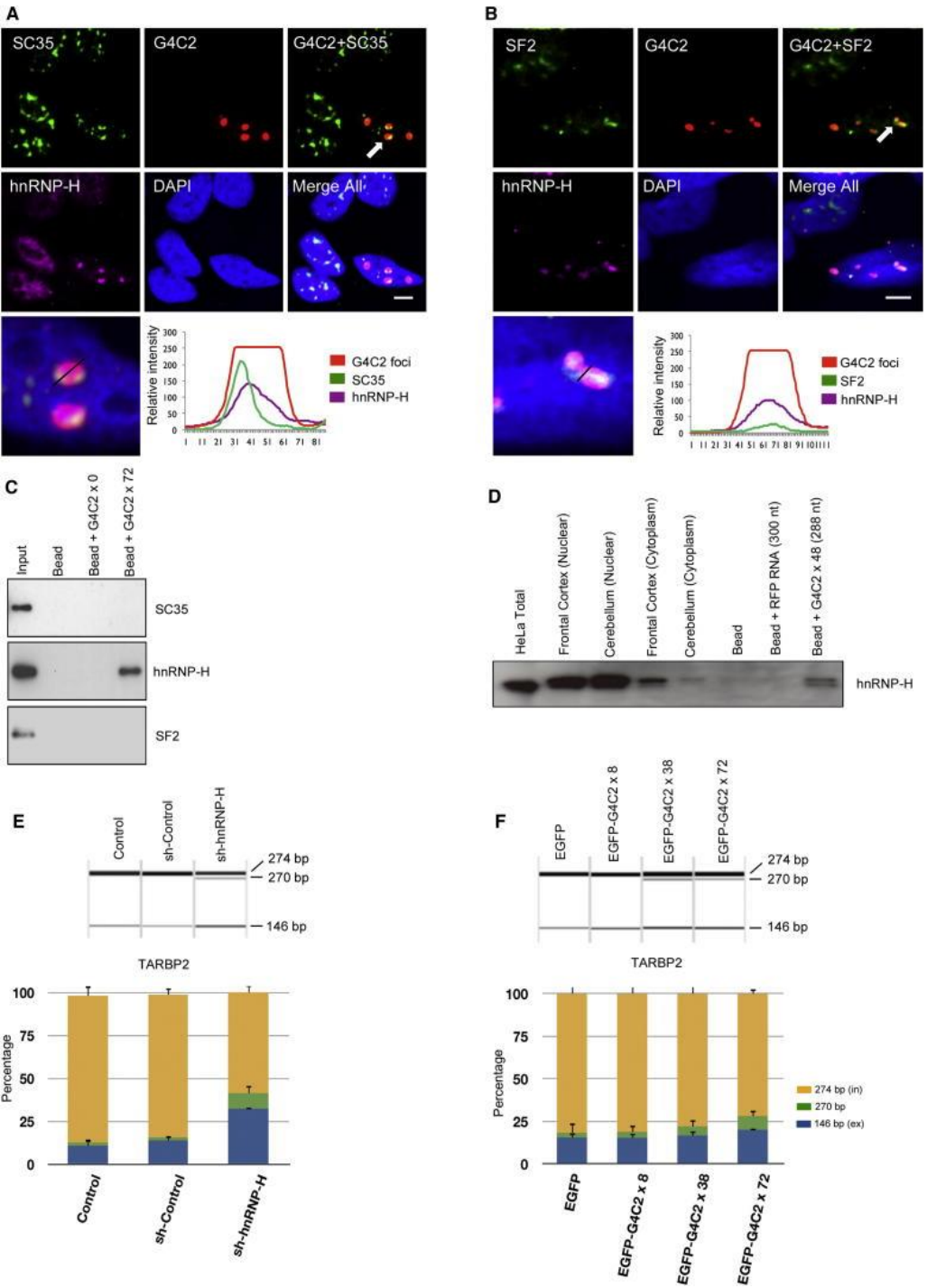
# Sekvestracija proteinov



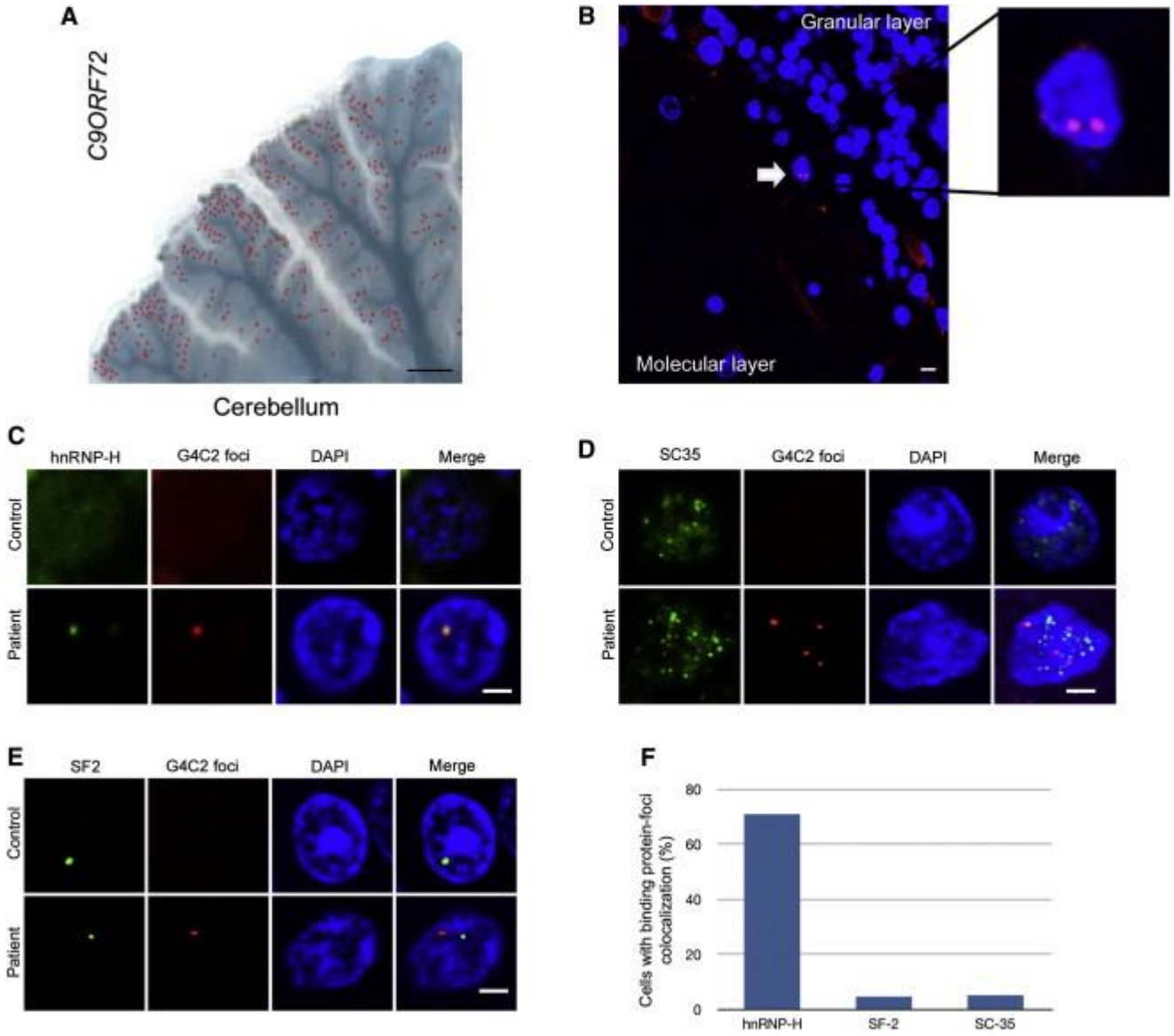
# HREM RNA tvori RNA skupke v jedru



# Kolokalizacija s SC35, SF2 in hnRNPH



# Kolokalizacija v možganih



# The *C9orf72* GGGGCC Repeat Is Translated into Aggregating Dipeptide-Repeat Proteins in FTLD/ALS

Kohji Mori,[1]* Shih-Ming Weng,[2]* Thomas Arzberger,[3] Stephanie May,[2] Kristin Rentzsch,[2] Elisabeth Kremmer,[4] Bettina Schmid,[2,5] Hans A. Kretzschmar,[3] Marc Cruts,[6,7] Christine Van Broeckhoven,[6,7] Christian Haass,[1,2,5] Dieter Edbauer[1,2,5]†

Expansion of a GGGGCC hexanucleotide repeat upstream of the *C9orf72* coding region is the most common cause of familial frontotemporal lobar degeneration and amyotrophic lateral sclerosis (FTLD/ALS), but the pathomechanisms involved are unknown. As in other FTLD/ALS variants, characteristic intracellular inclusions of misfolded proteins define *C9orf72* pathology, but the core proteins of the majority of inclusions are still unknown. Here, we found that most of these characteristic inclusions contain poly-(Gly-Ala) and, to a lesser extent, poly-(Gly-Pro) and poly-(Gly-Arg) dipeptide-repeat proteins presumably generated by non-ATG–initiated translation from the expanded GGGGCC repeat in three reading frames. These findings directly link the FTLD/ALS-associated genetic mutation to the predominant pathology in patients with *C9orf72* hexanucleotide expansion.

Frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) are the extreme ends of a spectrum of overlapping neurodegenerative disorders variably associated with dementia, personality changes, language abnormalities, and progressive muscle weakness (*1*–*3*). The majority of patients show intracellular inclusions that are strongly positive for phosphorylated TDP-43 (classified as FTLD-TDP, FTLD/ALS-TDP, or ALS-TDP). Recently, expansion of a GGGGCC hexanucleotide repeat in the gene *C9orf72* has been identified as the most common pathogenic mutation in families with autosomal dominant FTLD, FTLD/ALS, and ALS (*4*–*6*). The expansion is located upstream of the *C9orf72* coding region, either in the first intron or the promoter region, depending on the transcript isoform (fig. S1A). Although the extreme GC content precludes sequencing in patients, the number of GGGGCC repeat units is believed to be at least several hundred, compared with fewer than 25 in healthy controls (*7*).

Patients with a *C9orf72* repeat expansion mutation have clinical symptoms similar to other FTLD/ALS-TDP patients but show several unique

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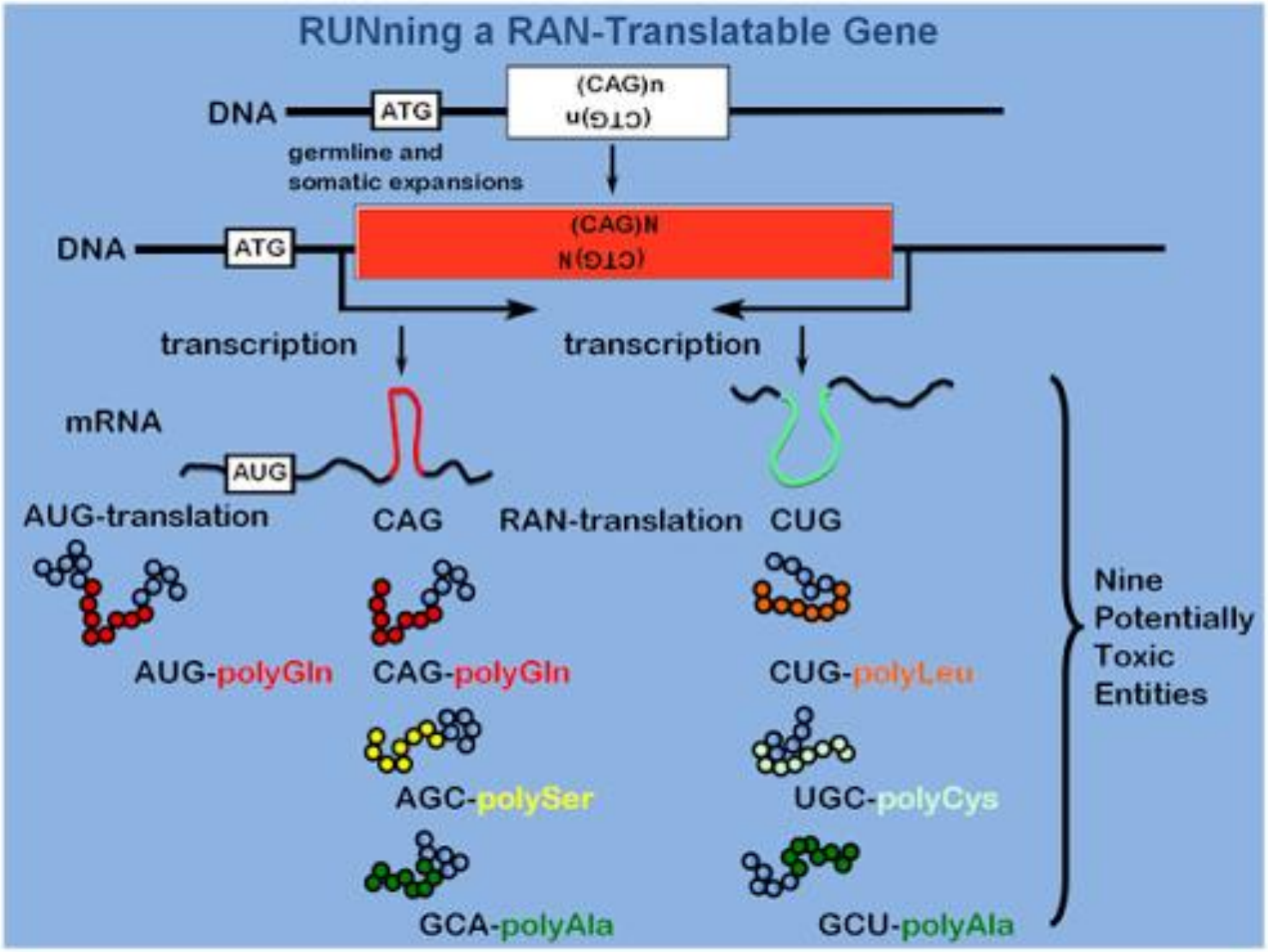
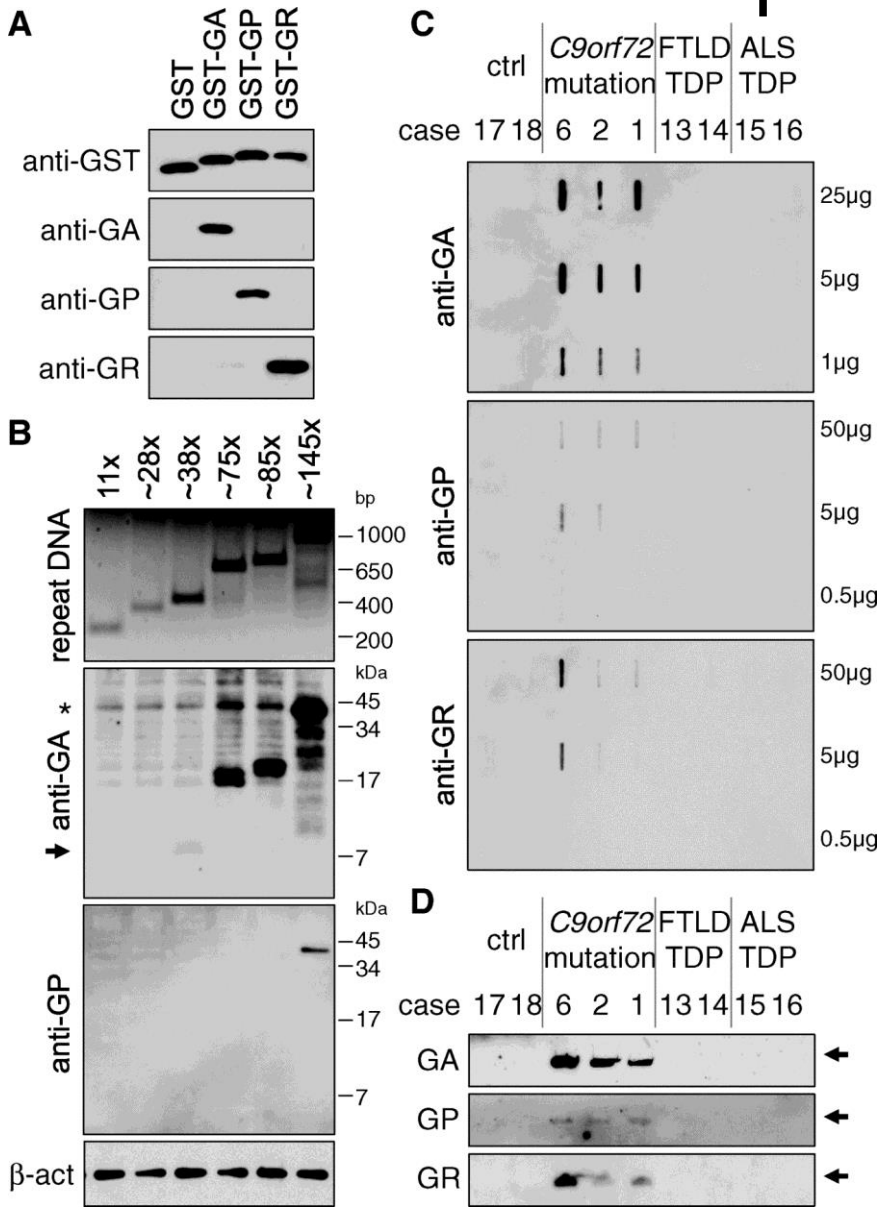
*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: dieter.edbauer@dzne.de

# Translacija, povezana s ponovitvami

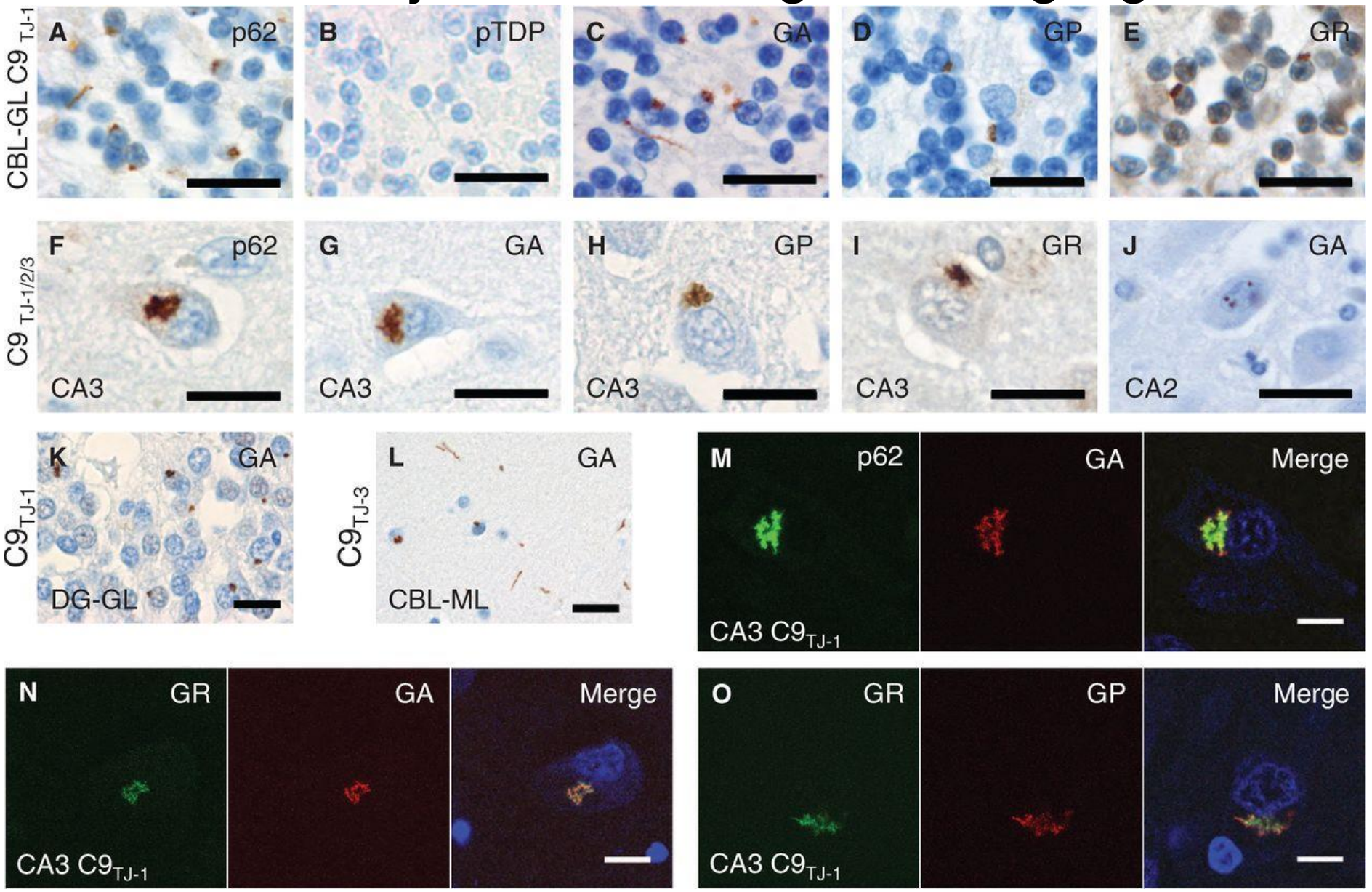


# GGGGCC ponovitev se prevede v dipeptidno ponovitev

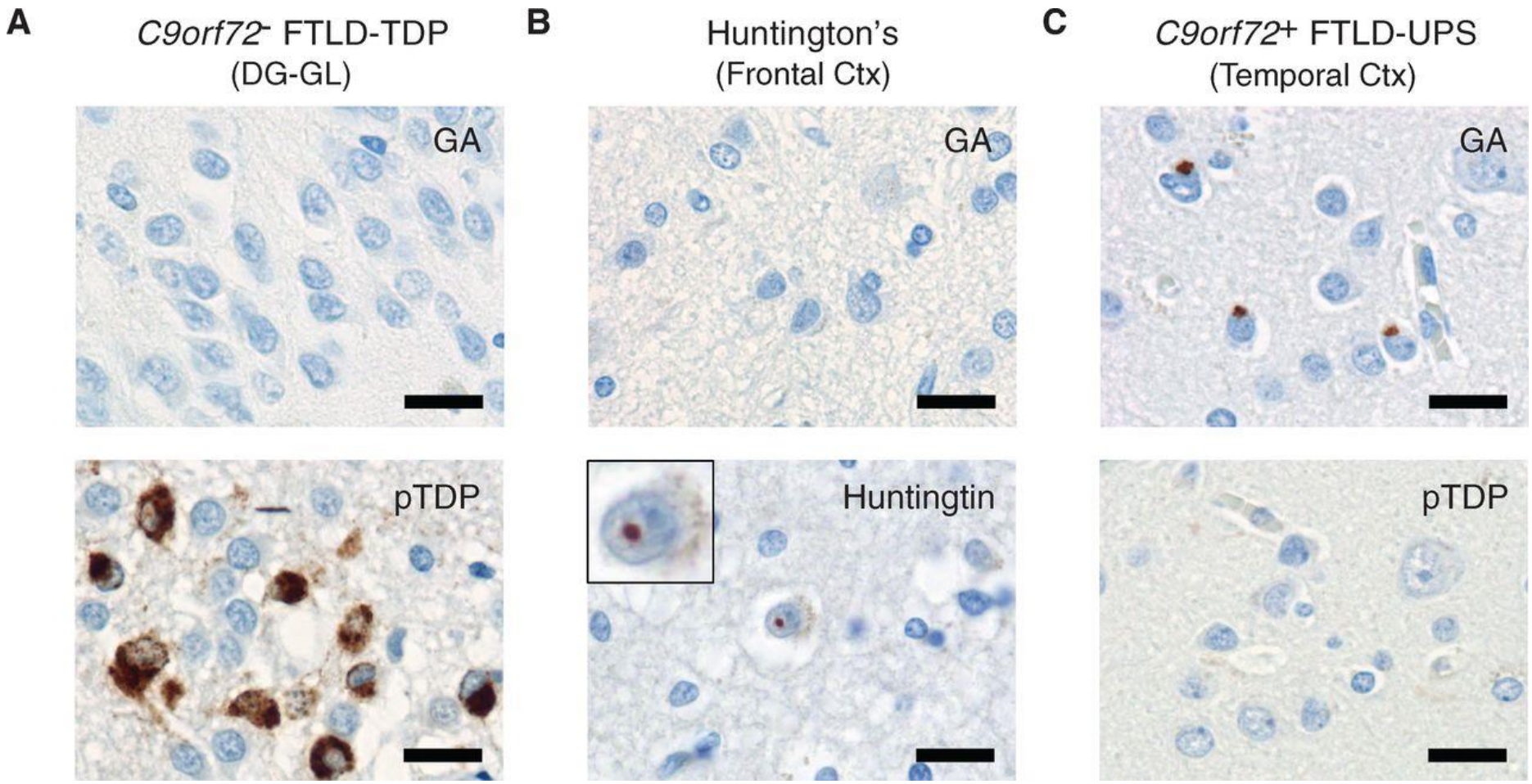



- $(GGGGCC)_n$ se prevede v $(GA)_n$, $(GP)_n$ ali $(GR)_n$.
- (B) Protitelesa proti dipeptidnim ponovitvam (DPR) prepoznajo le te.
- (C) DPR so tudi v lizatih možganov pacientov s C9orf72 mutacijo.

# DPR tvorijo TDP-43 negativne agregate

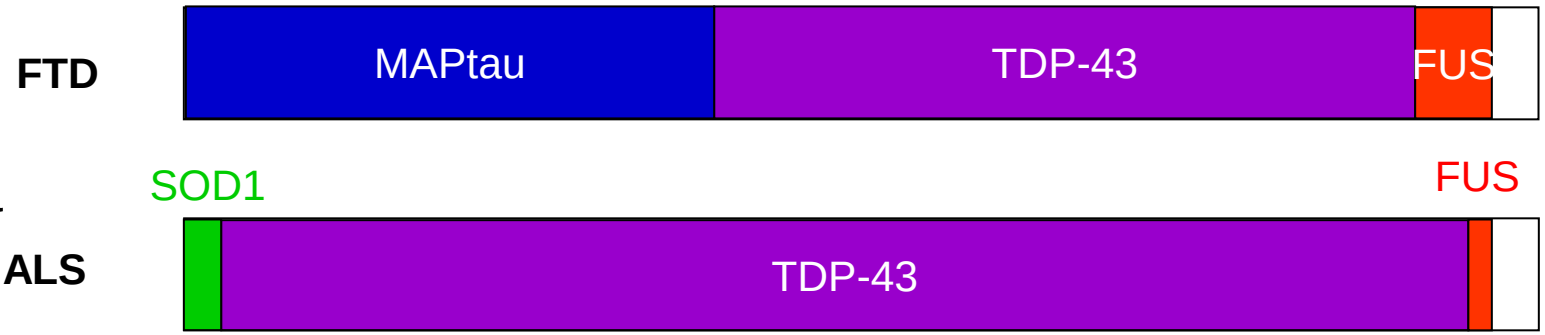


# …samo v možganih pacientov s C9orf72 mutacijo

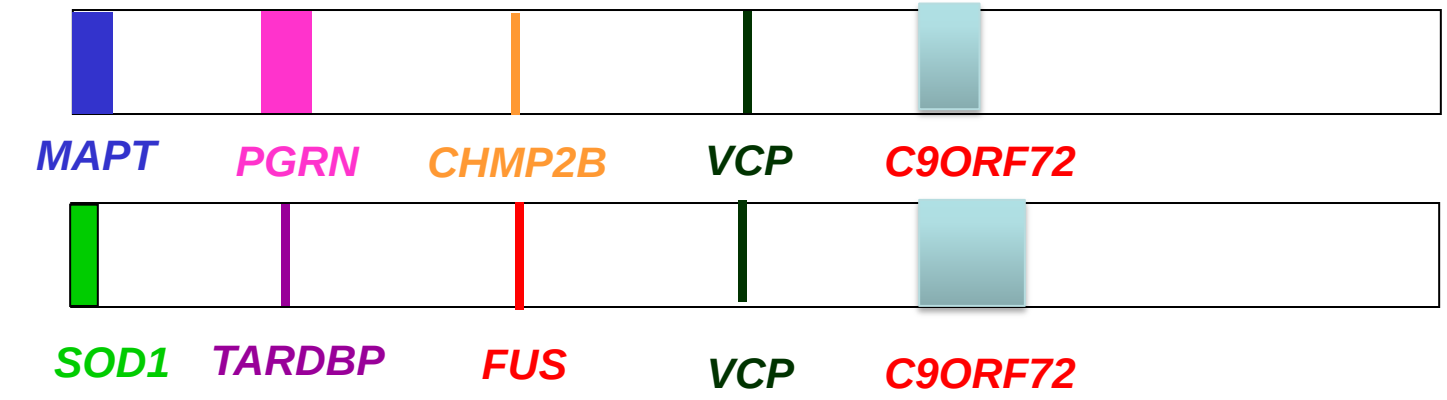


# Patologija in genetika FTD in ALS

Patologija




Genetika



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Vera Župunski (FKKT), Tomaž Bratkovič (FFA)

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|---|---|
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