CPEB alteration and aberrant transcriptome-polyadenylation unveil a treatable SLC19A3 deficiency in Huntington's disease

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Introduction

Huntington's disease

Autosomal dominant progressive neurodegenerative disorder.

Cause: expansion of (>40) CAG trinucleotide repeat in the huntingtin (*HTT*) gene.

- Other CAG trinucleotide repeat disorders: SBMA, SCAs…

Age of onset (approx 40 years).

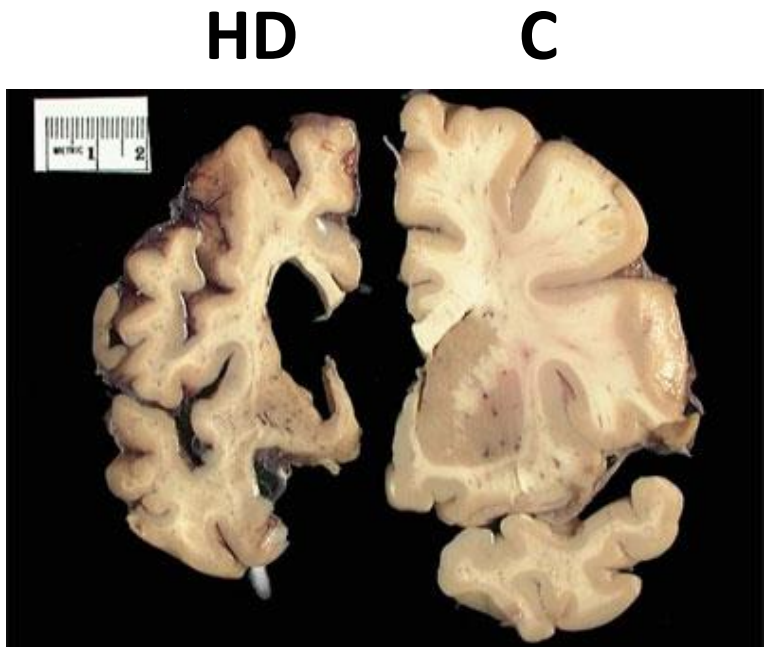
Symptoms

- Motor (chorea, rigidity), psychiatric, dementia.

Neuropathology

- Striatal and cortical atrophy.
- **No** curative **treatment**.

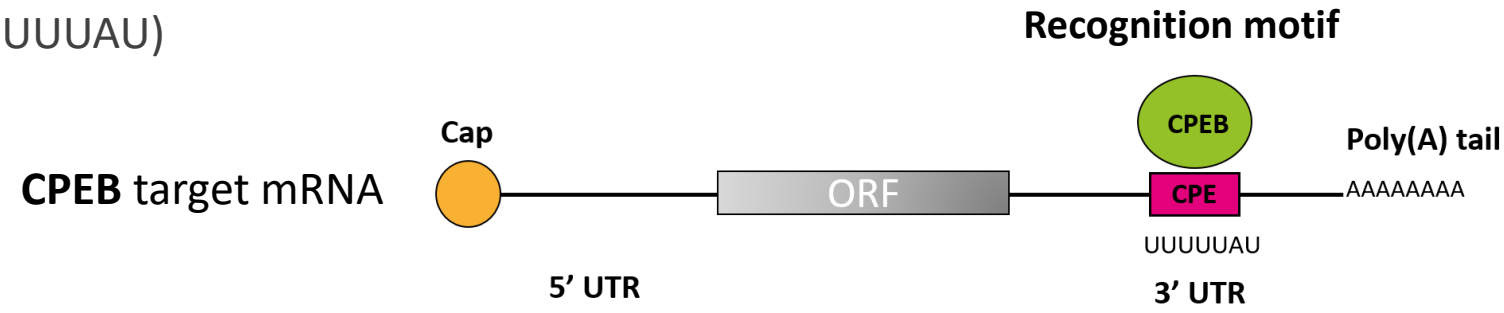
Exact **molecular mechanisms** by which *HTT* mutation leads to neuronal dysfunction and eventual death are not fully elucidated.



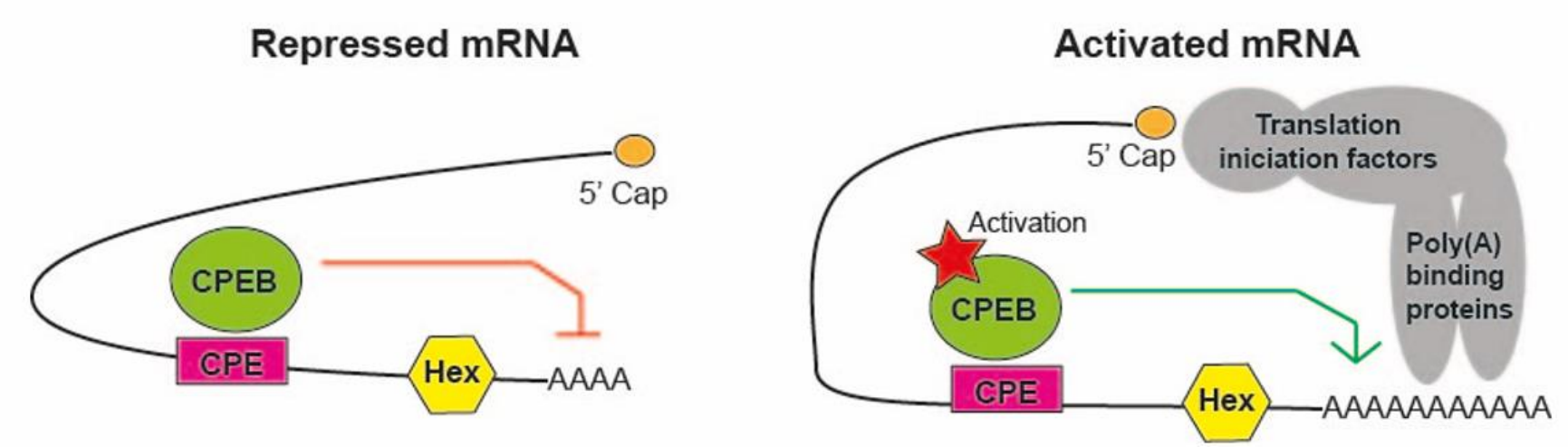
Introduction

CPEBs: Cytoplasmic polyadenylation element binding proteins

- Family of RNA binding proteins.
- Bind the CPE sequence (UUUUUAU)



- Control cytoplasmic poly(A)-tail length:

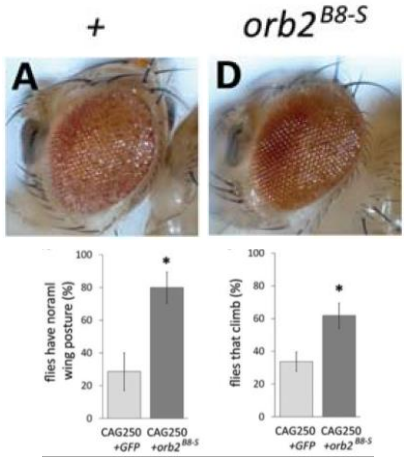


CPEB-mediated regulation provides **temporal & local control of translation** of specific mRNAs.

Introduction

Evidence supporting a role of CPEBs in HD

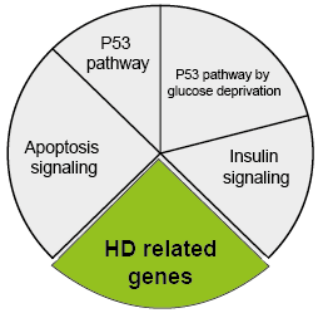
1. Fly model of SCA3
Orb2 modulates CAG/polyQ toxicity



Shieh and Bonini, 2011

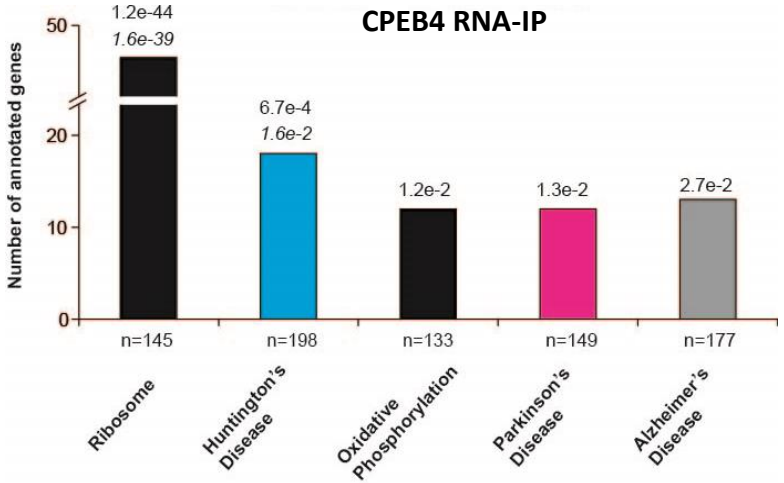
2. HD related genes are CPEB1 targets

Polysome pull-down from CPEB1 KO



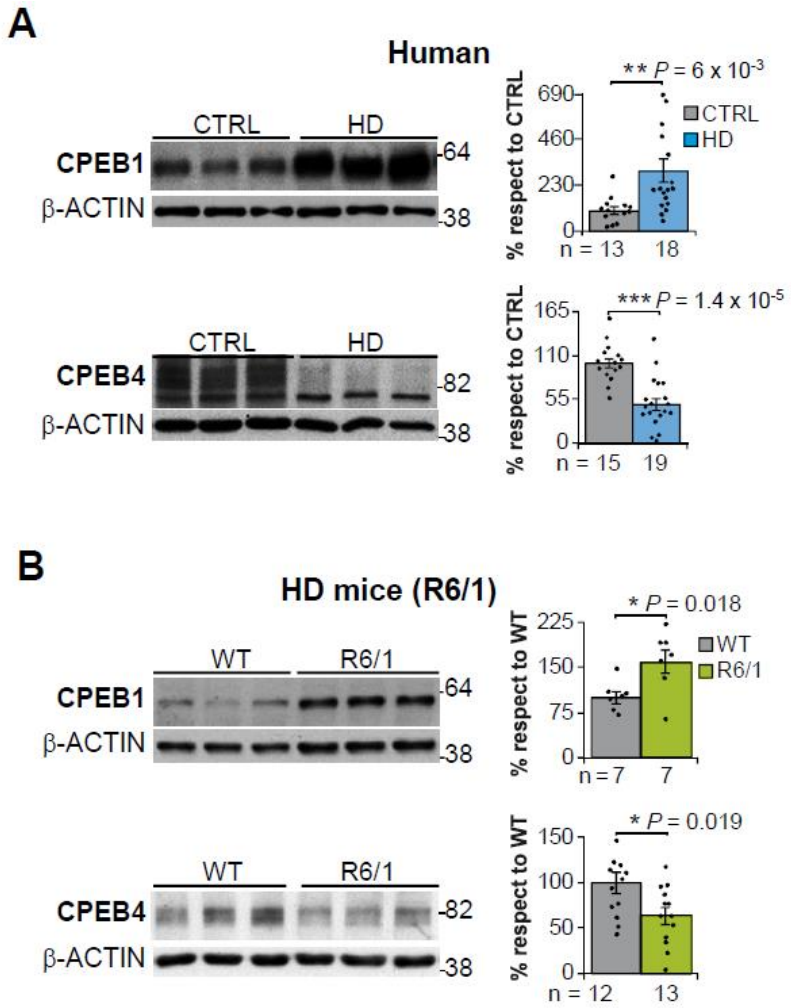
Modified from Alexandrov et al., 2012.

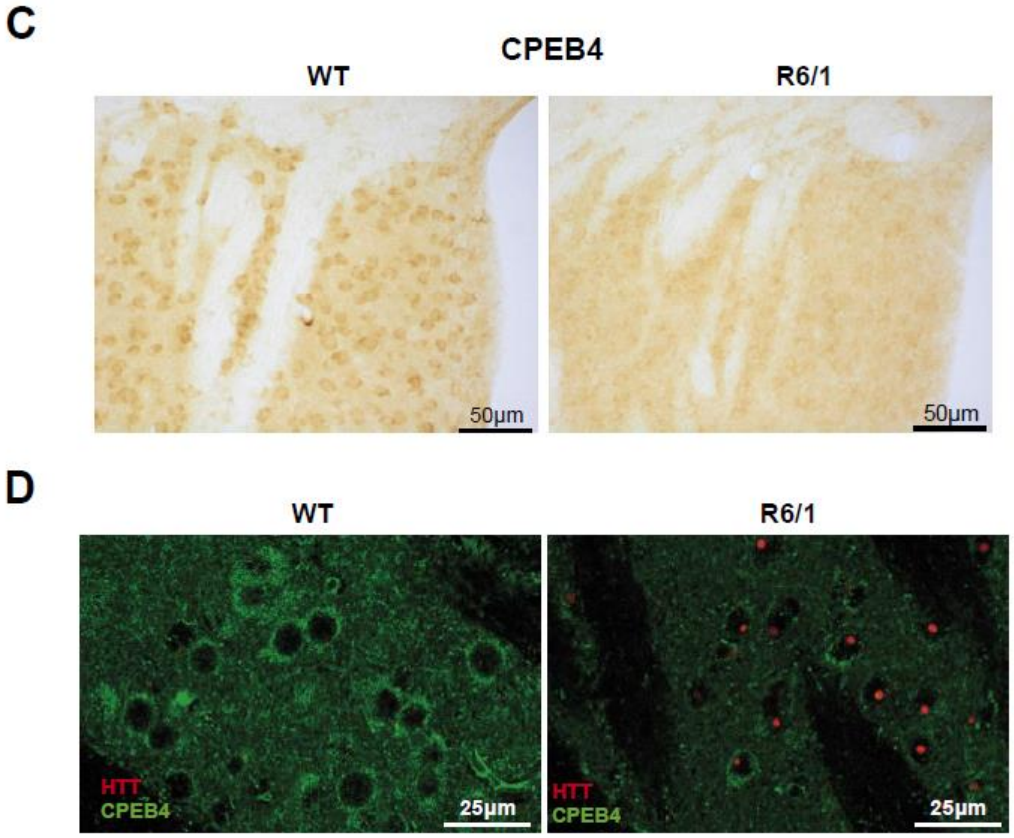
3. HD related genes are CPEB4 targets



Generated from Ortiz-Zapater et al. 2011

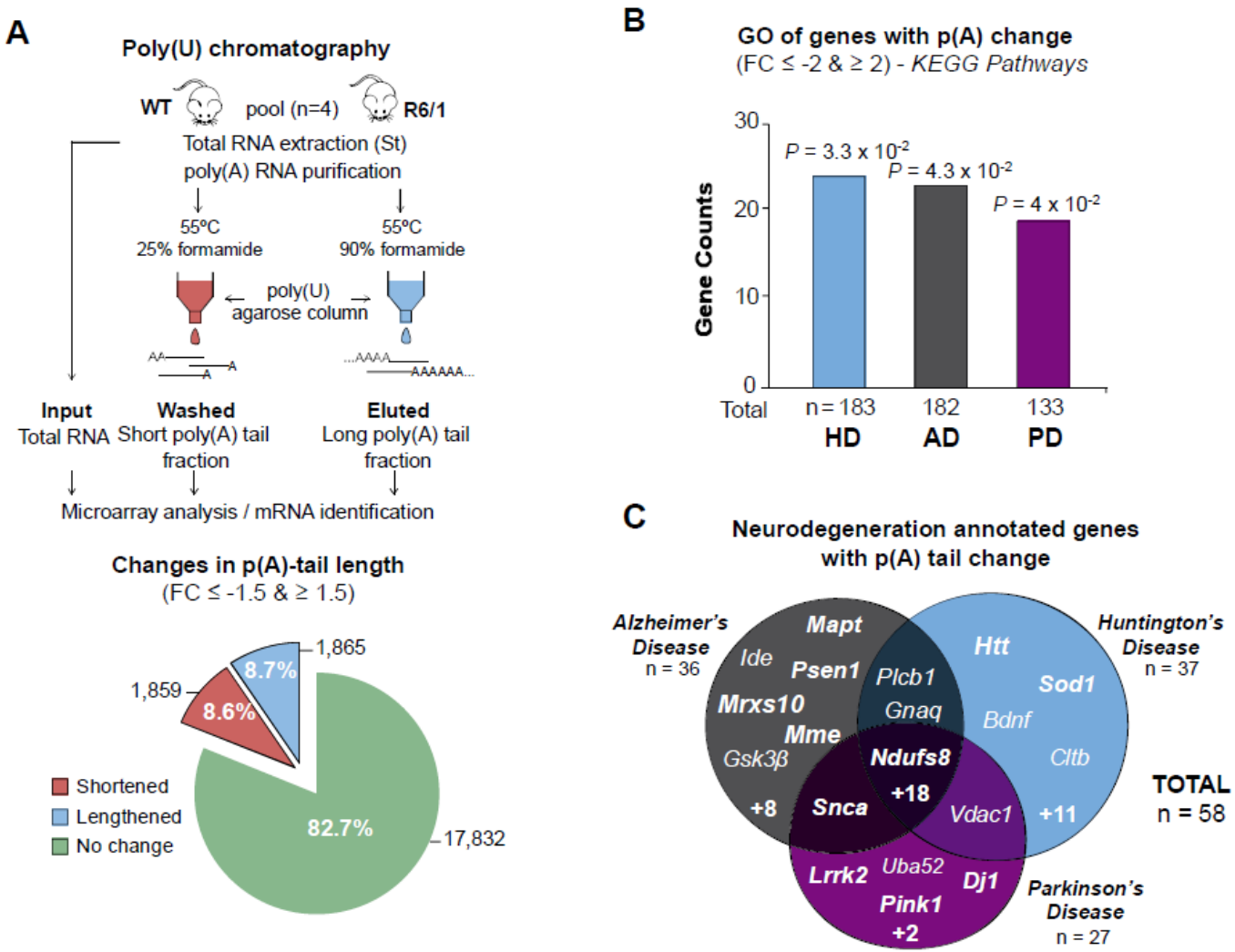
There is a CPEB1/4 imbalance in HD striatum





CPEB1 levels increase and CPEB4 decrease in brain of HD patients and R6/1 mice.

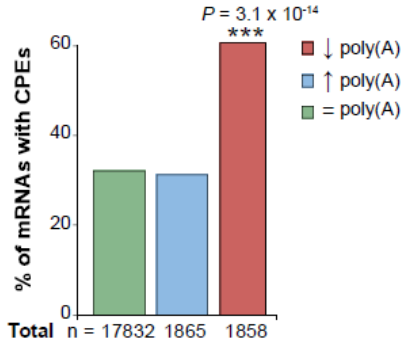
Global poly(A) alteration in HD affects neurodegeneration related genes



New molecular mechanism in the aetiology of HD and possible also in other major neurodegenerative diseases

Top deadenylated transcripts show decreased protein levels

A

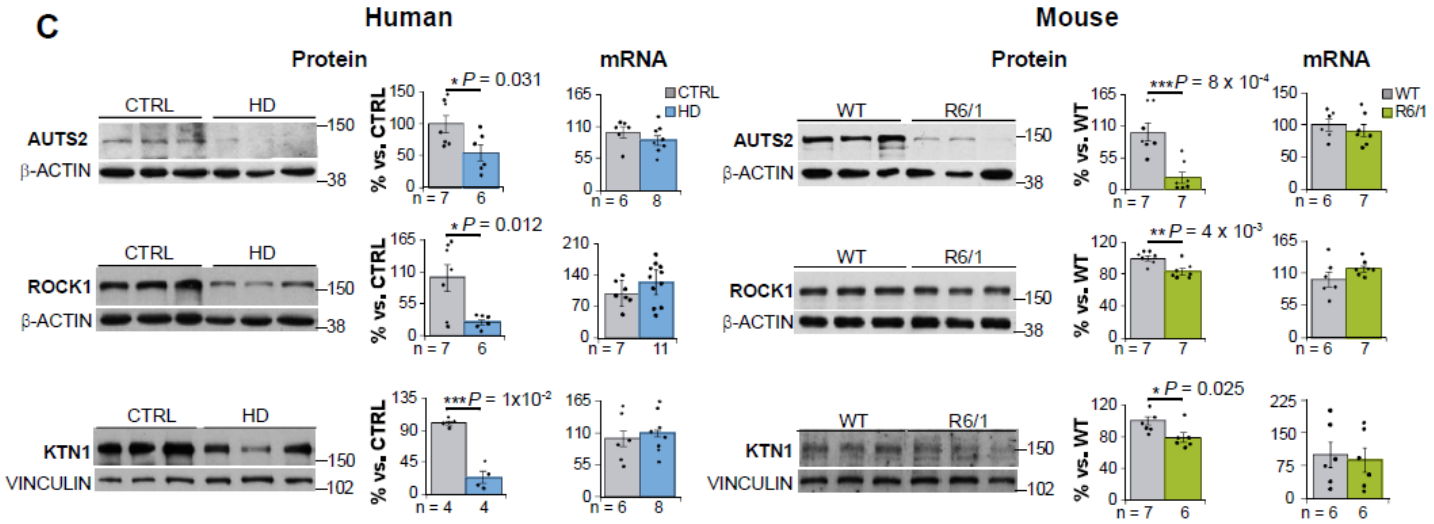


B

Transcripts with shortened p(A)-tail length (FC < -4.0)

FC	Symbol	Gene Name	n. CPEs
-5.4	*Auts2*	Autism susceptibility candidate 2	2
-5.3	*Akap10*	A kinase (PRKA) anchor protein 10	1
-5.0	*Zfp518a*	Zinc finger protein 518A	5
-5.0	*Tcf12*	Transcription factor 12	2
-4.9	*Zw10*	Zw10 kinetochore protein	0
-4.9	*Rock1*	Rho-associated coiled-coil containing protein kinase 1	4
-4.9	*Tmem161b*	Transmembrane protein 161B	3
-4.9	*Spcs1*	Signal peptidase complex subunit 1	2
-4.7	*Lax1*	Lymphocyte transmembrane adaptor 1	1
-4.6	*Memo1*	Mediator of cell motility 1	2
-4.5	*Ktn1*	Kinectin 1	3
-4.3	*Tfrc*	Transferrin receptor	2
-4.2	*Nmd3*	NMD3 homolog (S. cerevisiae)	3
-4.1	*Slc19a3*	Solute carrier family 19, member 3	3

C



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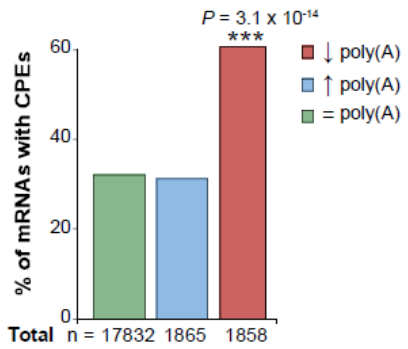

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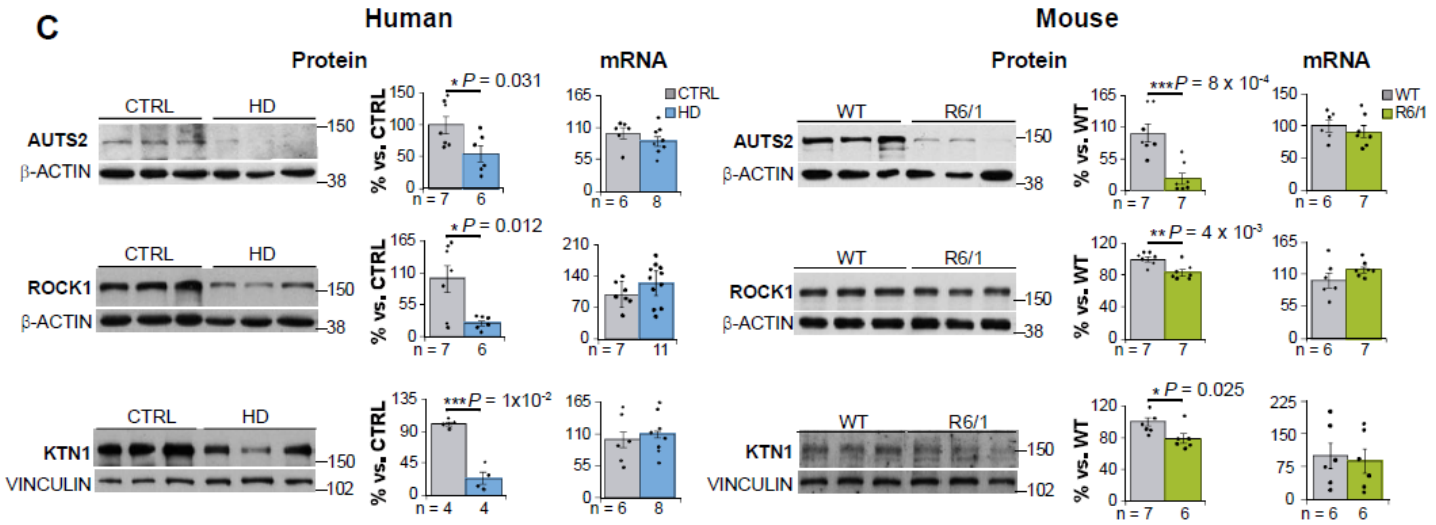
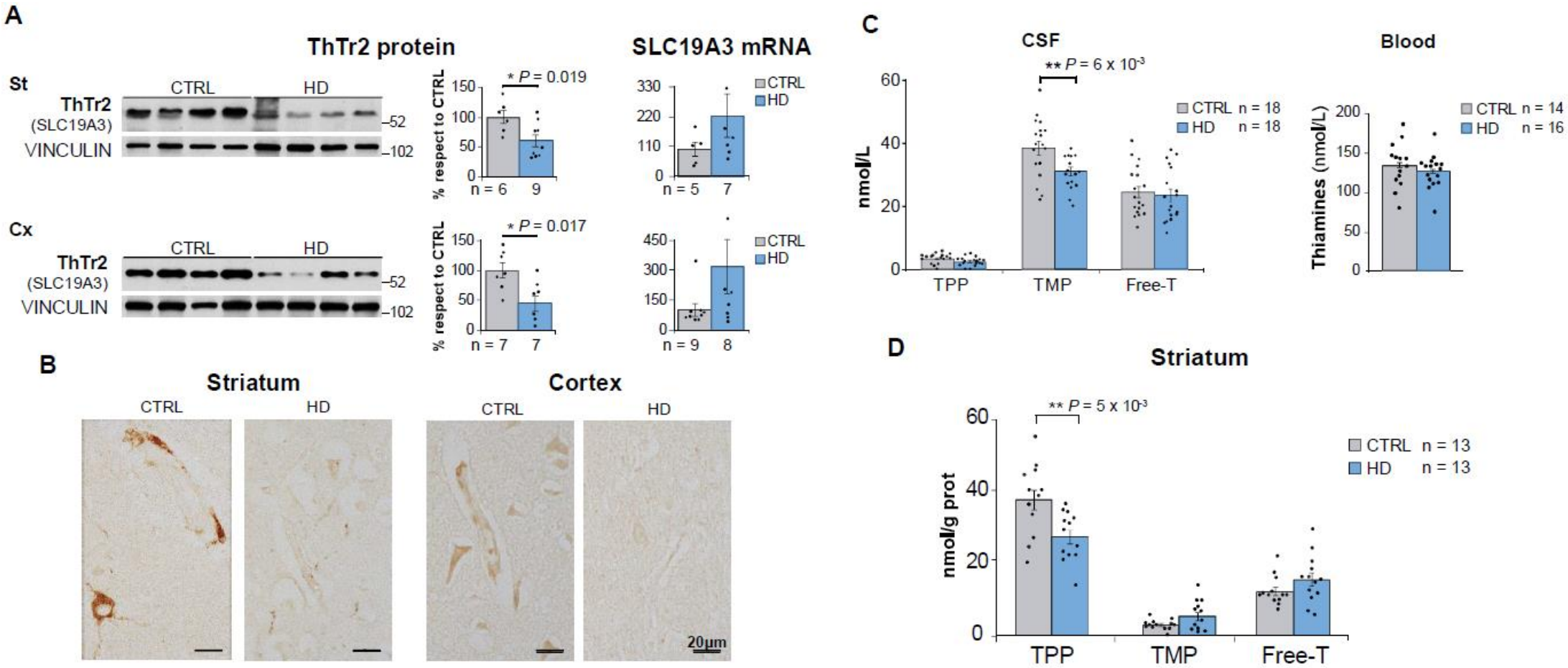
Biotin-thiamine-responsive basal ganglia disease.

C



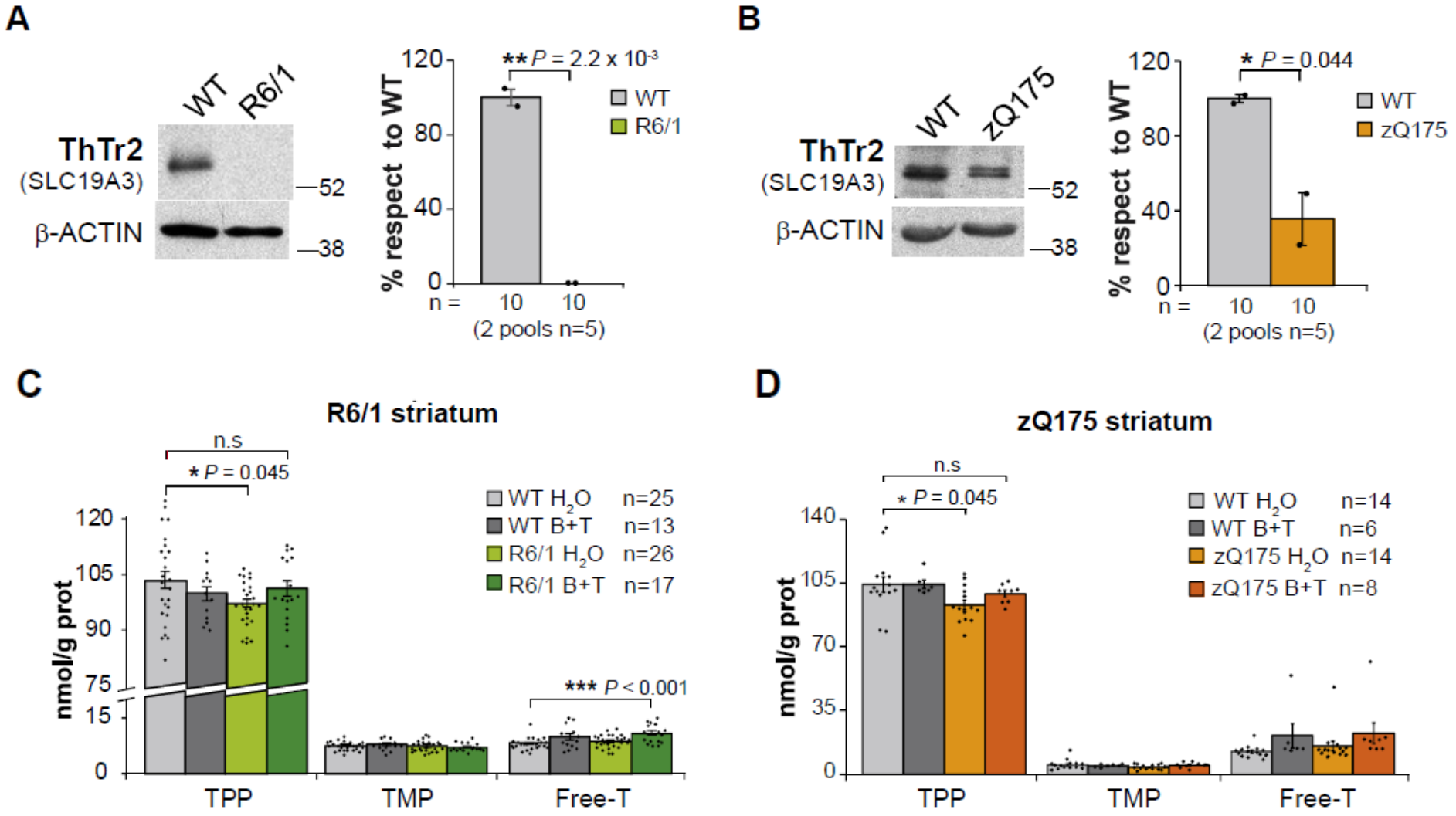
New mechanistic clue about HD as well as a potential novel therapy

Decreased ThTr2 and thiamine in HD



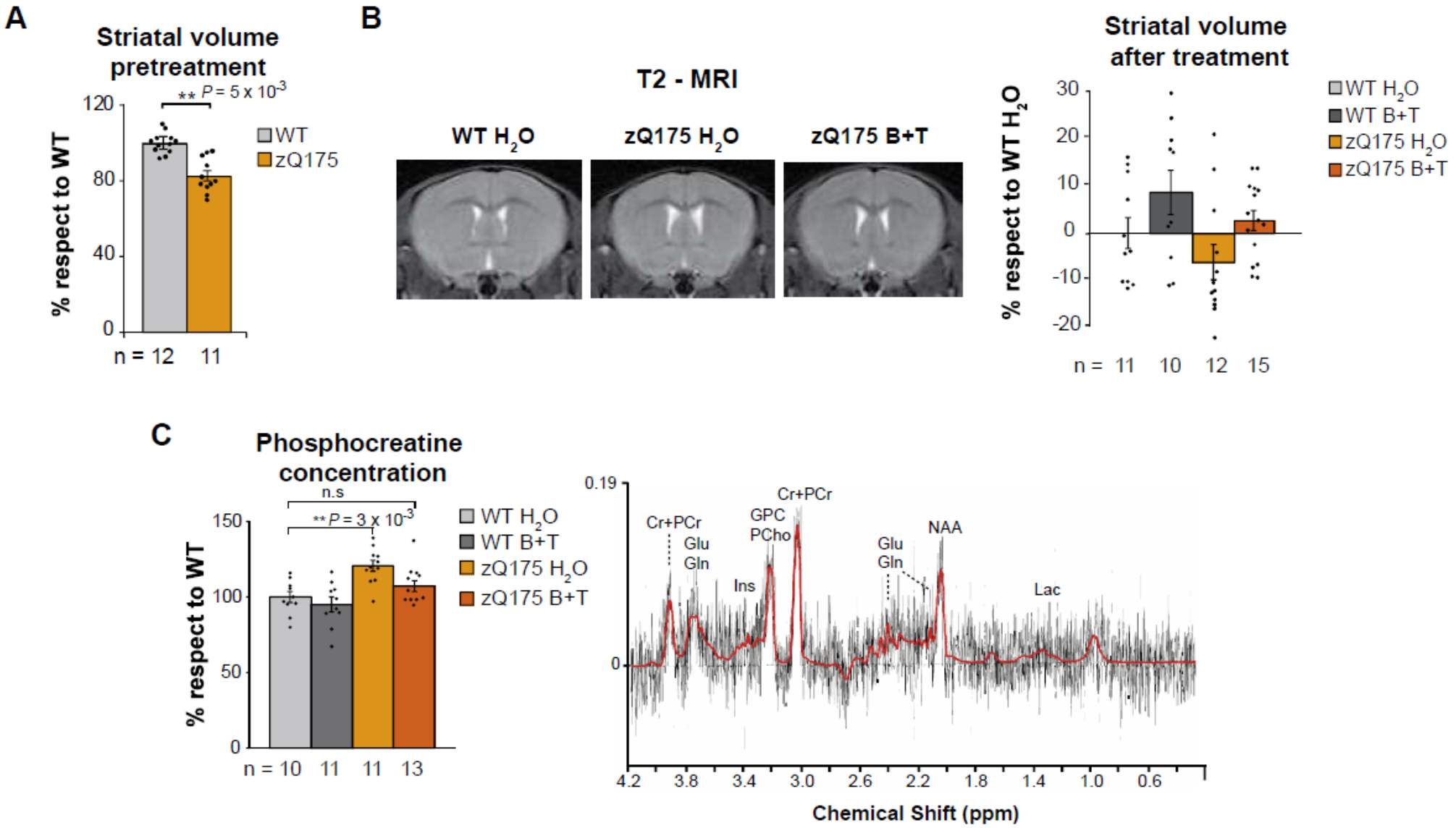
HD is a thiamine deficiency suggesting that a vitamin therapy could alleviate symptoms in patients.

Decreased ThTr2 and thiamine in HD mice.

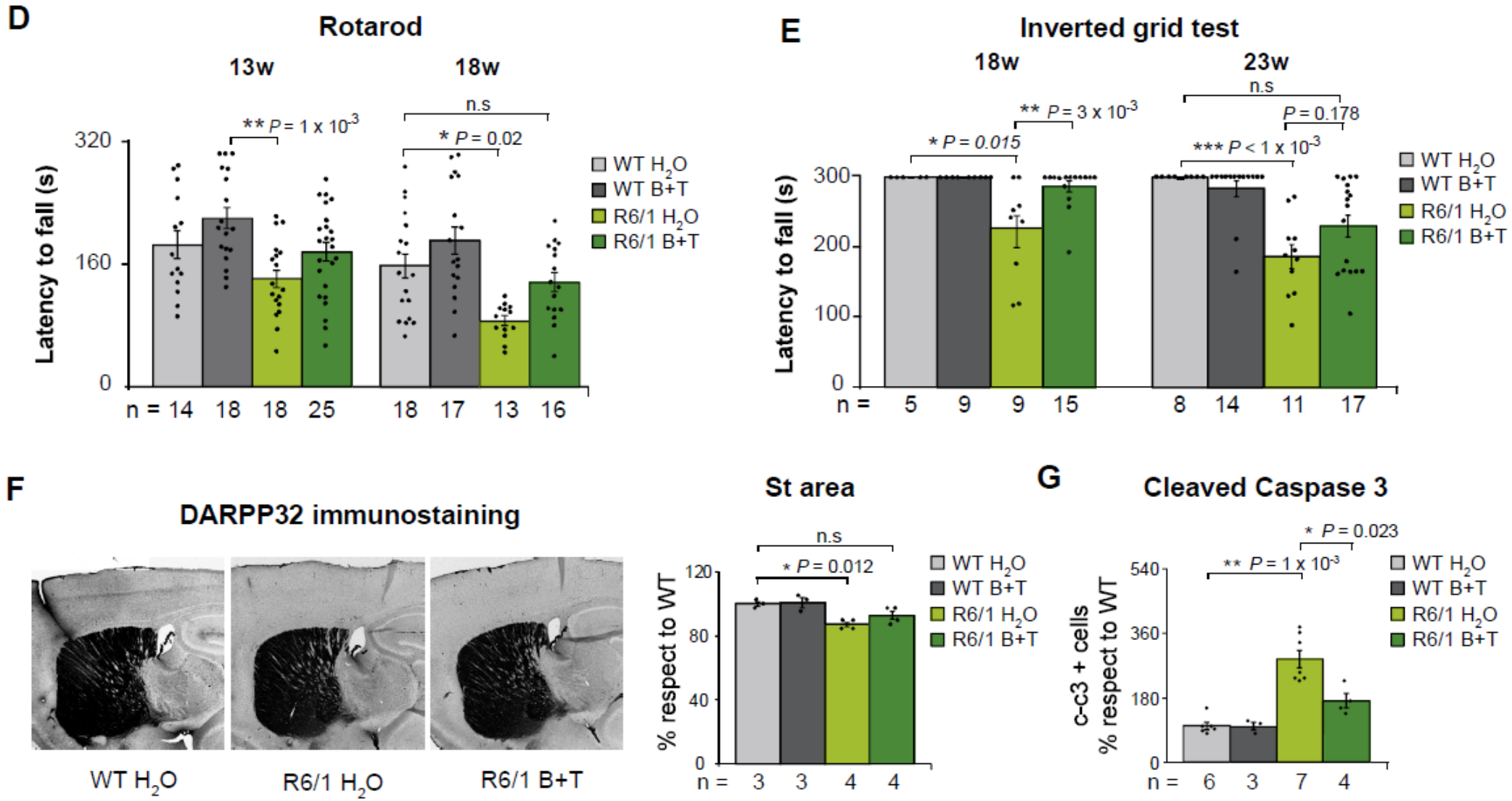


A combined therapy in the drinking water prevented the decreased striatal content of TPP in both models.

Attenuation of HD mice phenotype upon biotin+thiamine (B+T)

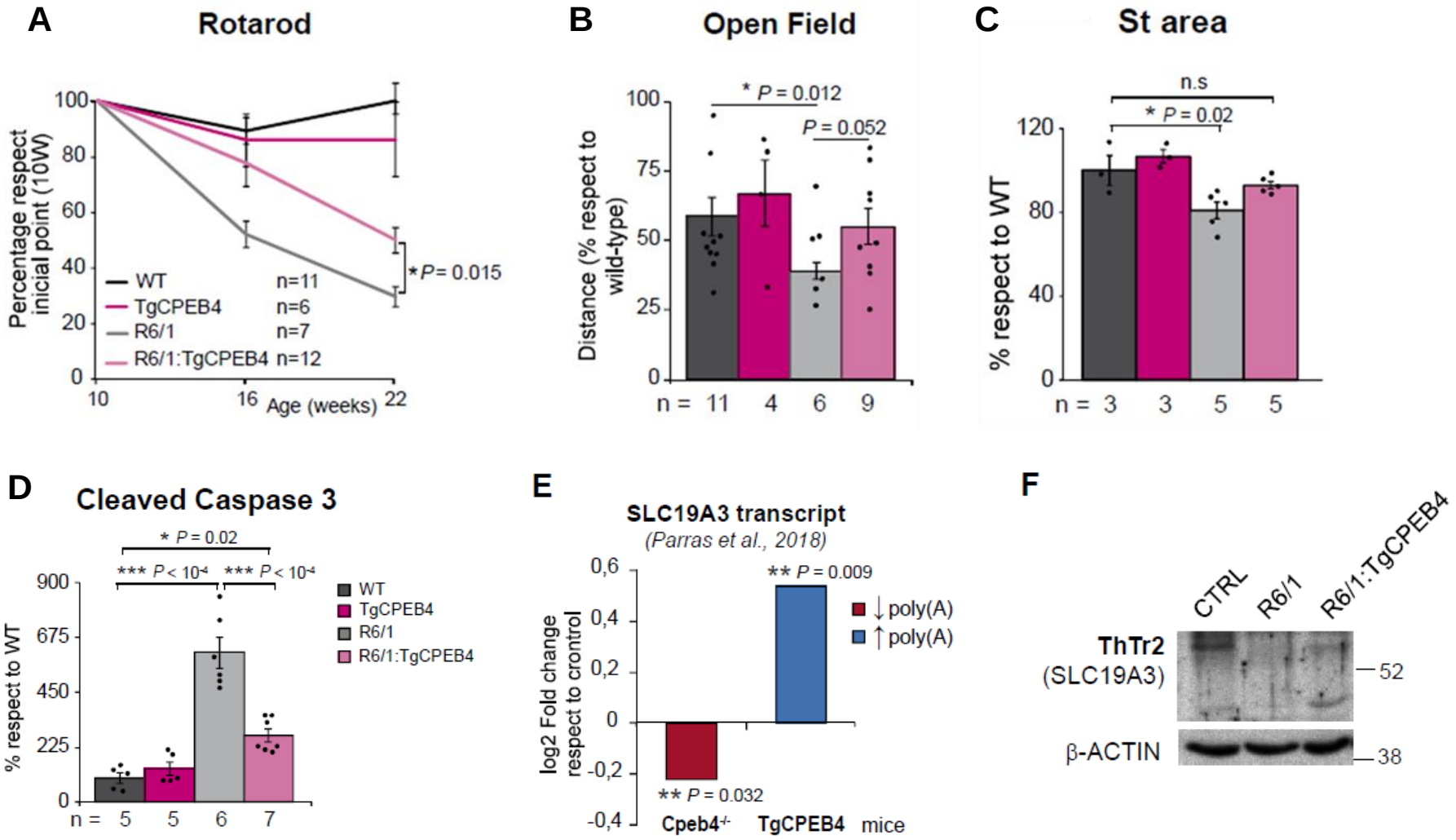


Attenuation of HD mice phenotype upon biotin+thiamine (B+T)



A B+T treatment is able to prevent the brain thiamine deficiency observed in HD mice and to attenuate their phenotypes.

CPEB4 overexpression attenuates R6/1 HD-like phenotypes and decrease ThTr2 levels



CPEB-alteration, particularly the decrease in CPEB4, contributes to HD pathogenesis.

Conclusions

1. There is a **CPEB1/4 imbalance** in HD striatum which leds to **altered polyadenylation** of neurodegeneration linked genes, thus unveiling a **new molecular mechanism**.

2. Top deadenylated genes include striatal atrophy-linked genes and show decreased protein levels.

3. **Huntington's disease** is a BTBGD-like **thiamine deficiency**.

4. **Treatment** with high dosis of biotin and thiamine **improves** radiology, neuropathology and motor phenotype of **HD mice**.

HD patients might benefit from biotin and thiamine supplementation therapy, as BTBGD patients do.

Acknowledgements

CBMSO, Madrid

J.J. Lucas
Alberto Parras
Ivó Hernández
Ainara Elorza
Sara Picó
Ivana Ollà
María Santos-Galindo
Miriam Lucas
Claudia Rodríguez
David Lozano
Enrique Fraga

Instituto de Investigaciones Biomédicas "Alberto Sols", Madrid
Teresa Iglesias, Julia Pose-Utrilla

Centro for Molecular Biology "CBMSO", Madrid
Félix Hernández

Inst. Biomedicina de Sevilla (IBiS)
Pablo Mir, Daniel Macías-García

Hospital Ramón y Cajal, Madrid
José Luis López-Sendón

Centro de Diagnóstico de Enfermedades Moleculares (CEDEM), Madrid
Belén Pérez, Margarita Castro

Institute for Research in Biomedicine (IRB), BCN
Raúl Méndez, Eulàlia Belloc

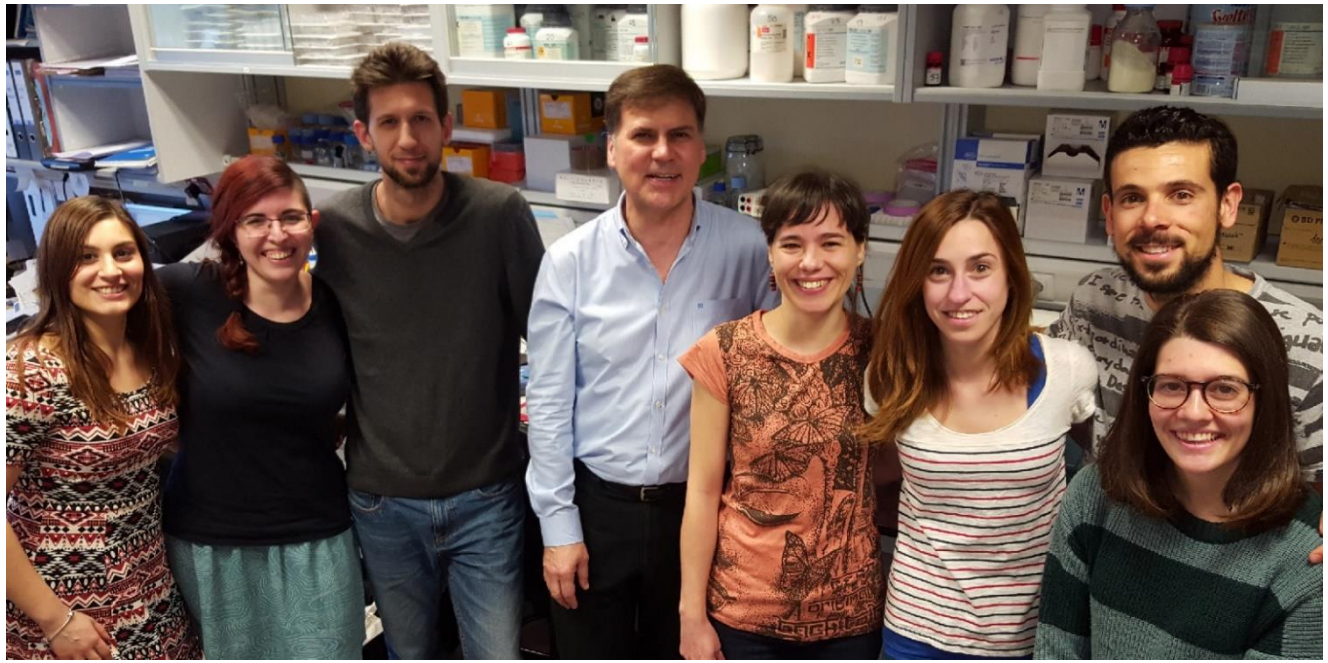
Institut de Recerca Sant Joan de Déu, BCN
Rafael Artuch, Laura Martí Sánchez

Instituto Cajal, Madrid
Juan J. Garrido

Institute of Biomedical Research of Barcelona (IIBB-CSIC), Barcelona
Pilar Navarro

IDIBELL-University Hospital Bellvitge, Barcelona
Isidro Ferrer, Paula García-Esparcia

David Geffen School of Medicine, UCLA, Los Angeles
X. William Yang, Nan Wang



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