FUNCTION OF mGlu5 RECEPTOSOME IN AUTISM SPECTRUM DISORDERS

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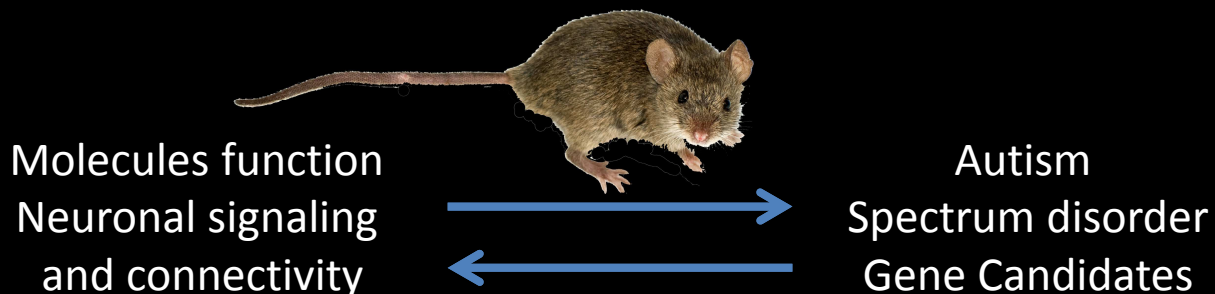


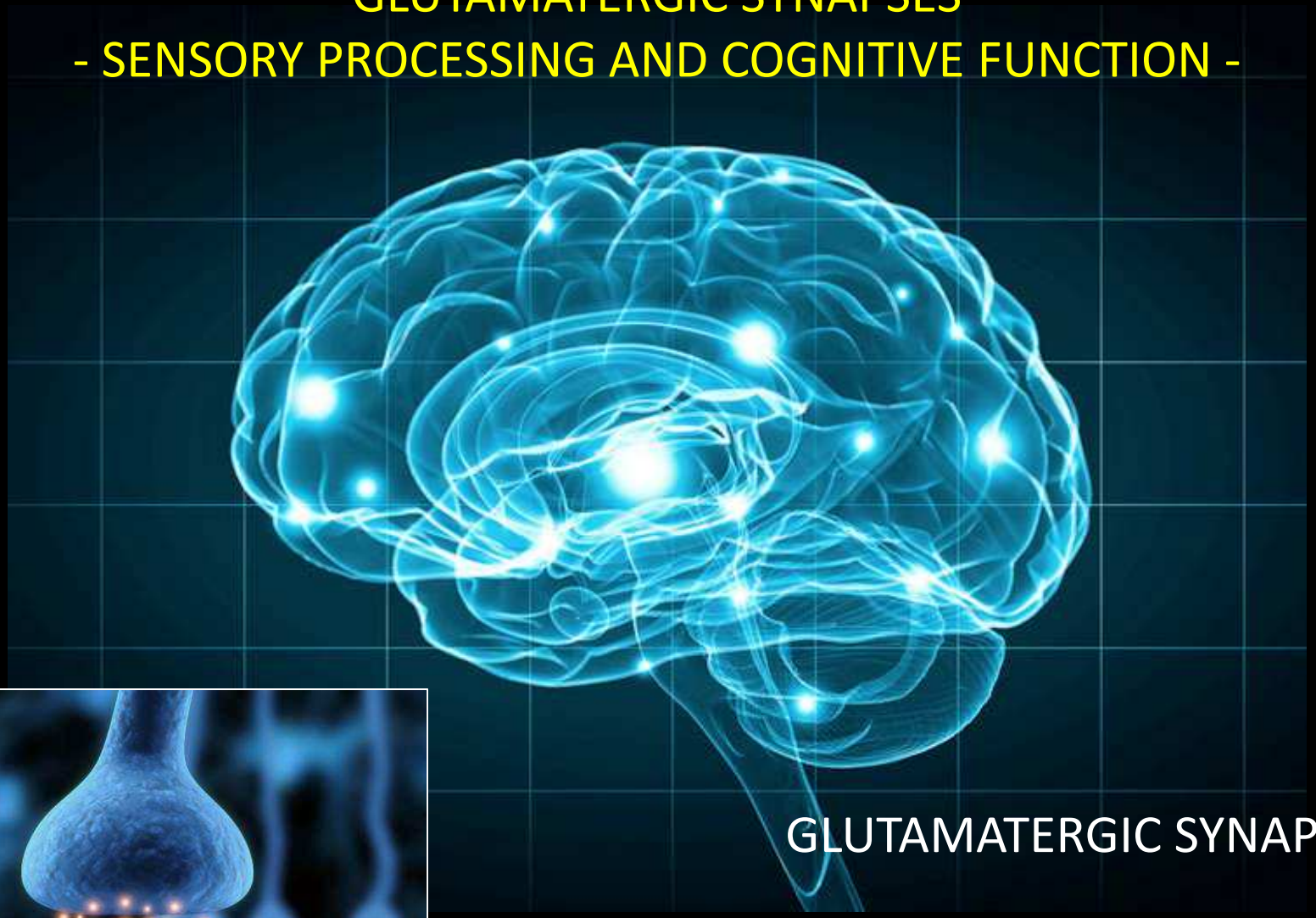
What can we learn from mouse models of ASD ?

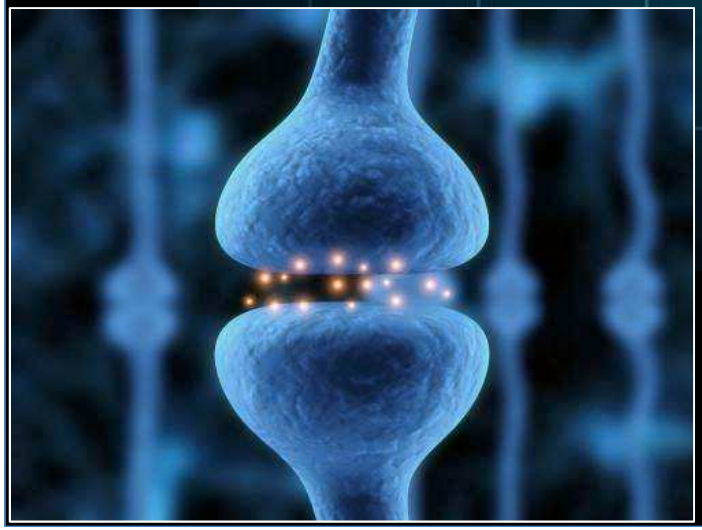
INSTITUT DE GÉNOMIQUE FONCTIONNELLE

Cohorte ELENA

ELENA Workshop
Déterminants des évolutions dans l'autisme

GLUTAMATERGIC SYNAPSES
- SENSORY PROCESSING AND COGNITIVE FUNCTION -





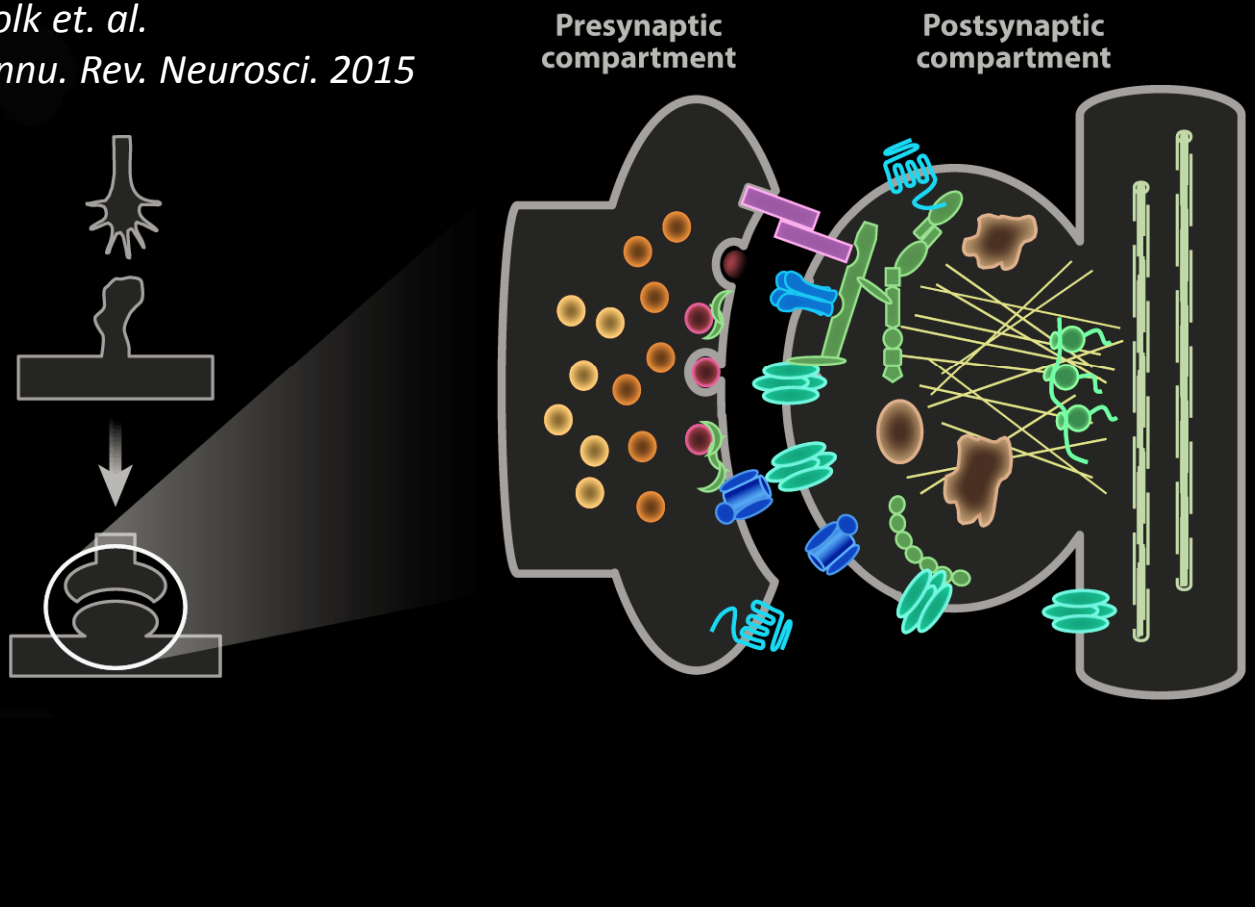
GLUTAMATERGIC SYNAPSES

INTELLECTUAL DISABILITY (FXS)

SCREEN FOR GENE CANDIDATES

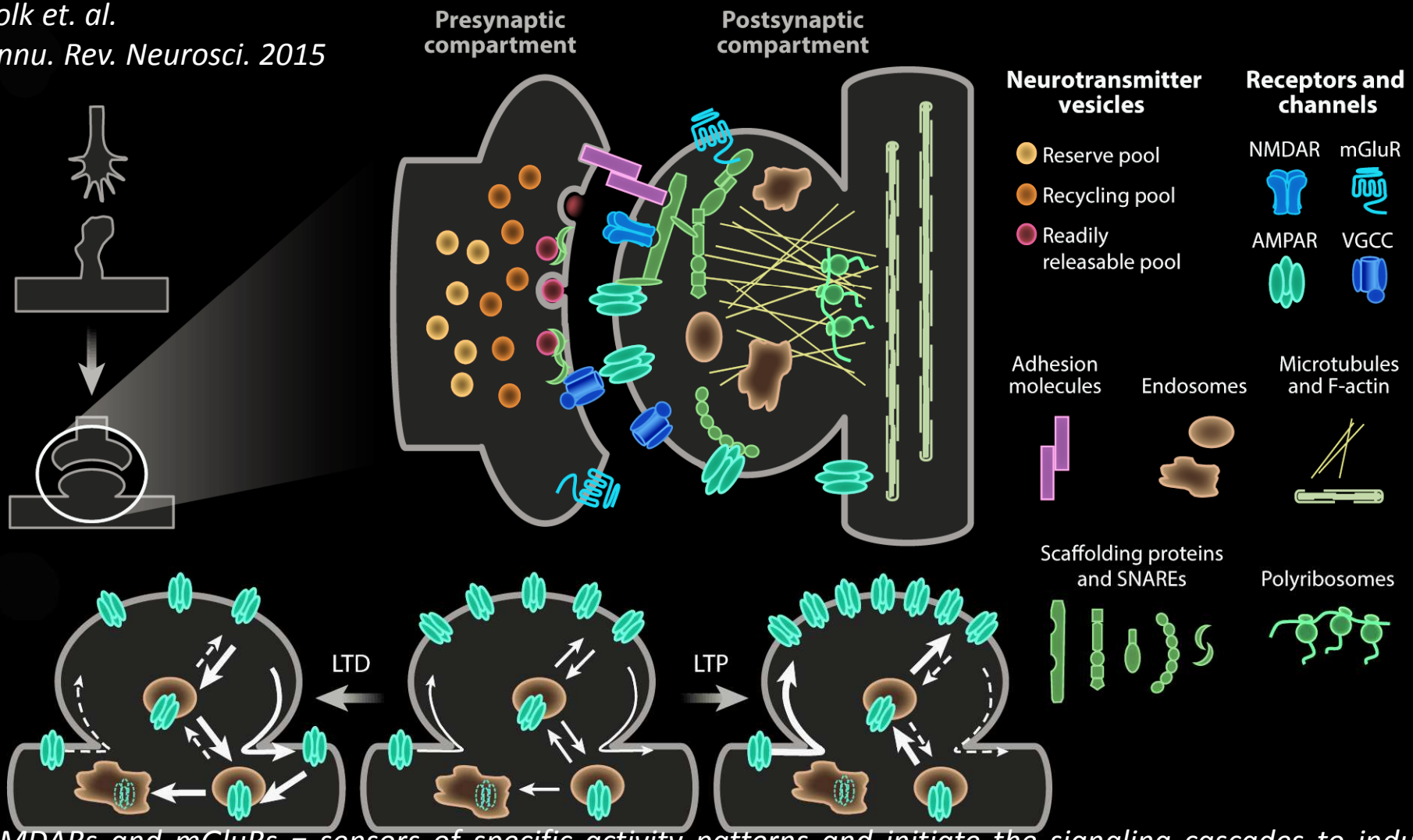
MOLECULES AND SIGNALING CASCADES TRIGER FUNCTIONAL SYNAPSES

Adapted from
Volk et. al.
Annu. Rev. Neurosci. 2015



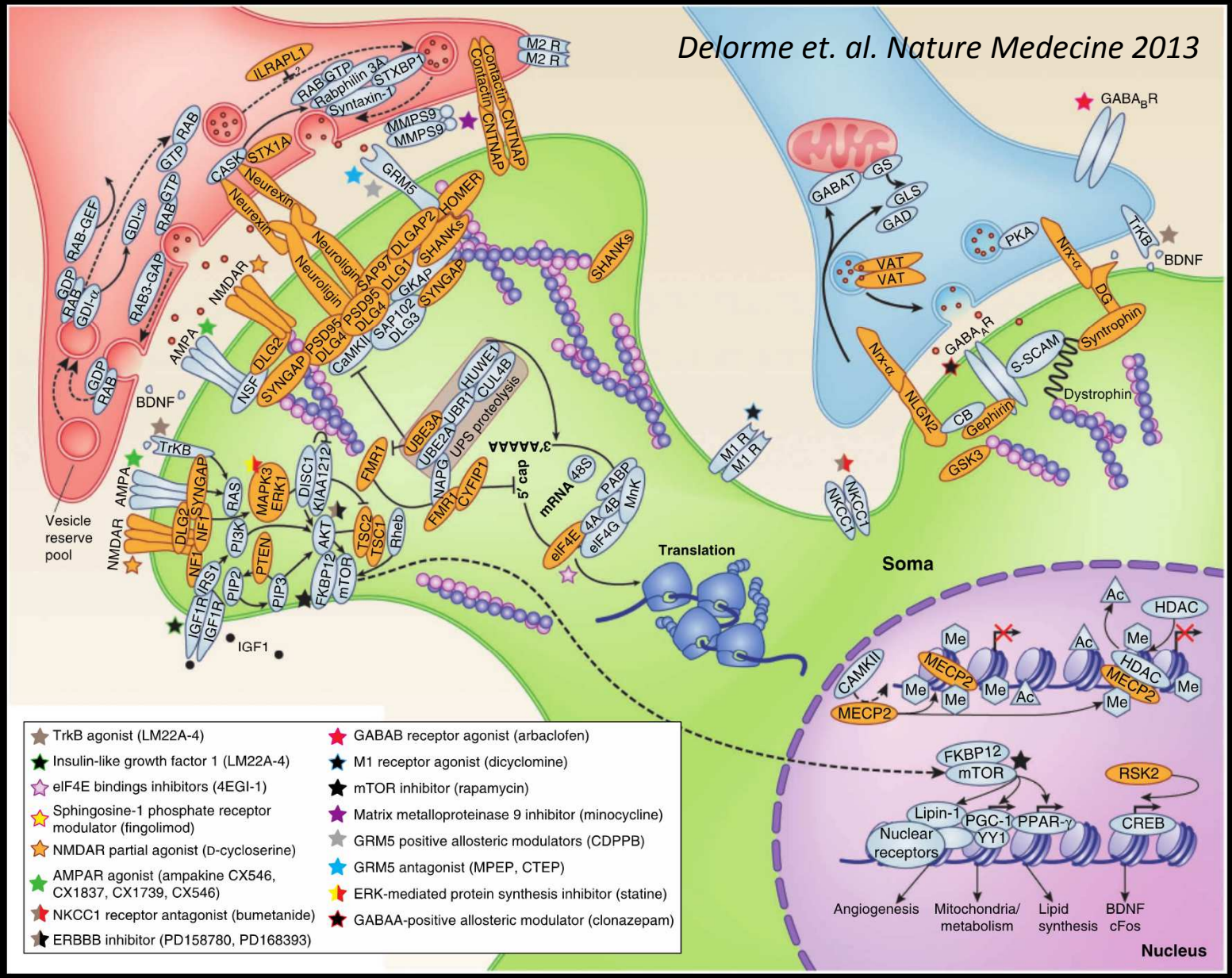
SYNAPTIC PLASTICITY CELLULAR SUBSTRATE FOR ADAPTIVE COGNITIVE PROCESSES

Adapted from
Volk et. al.
Annu. Rev. Neurosci. 2015



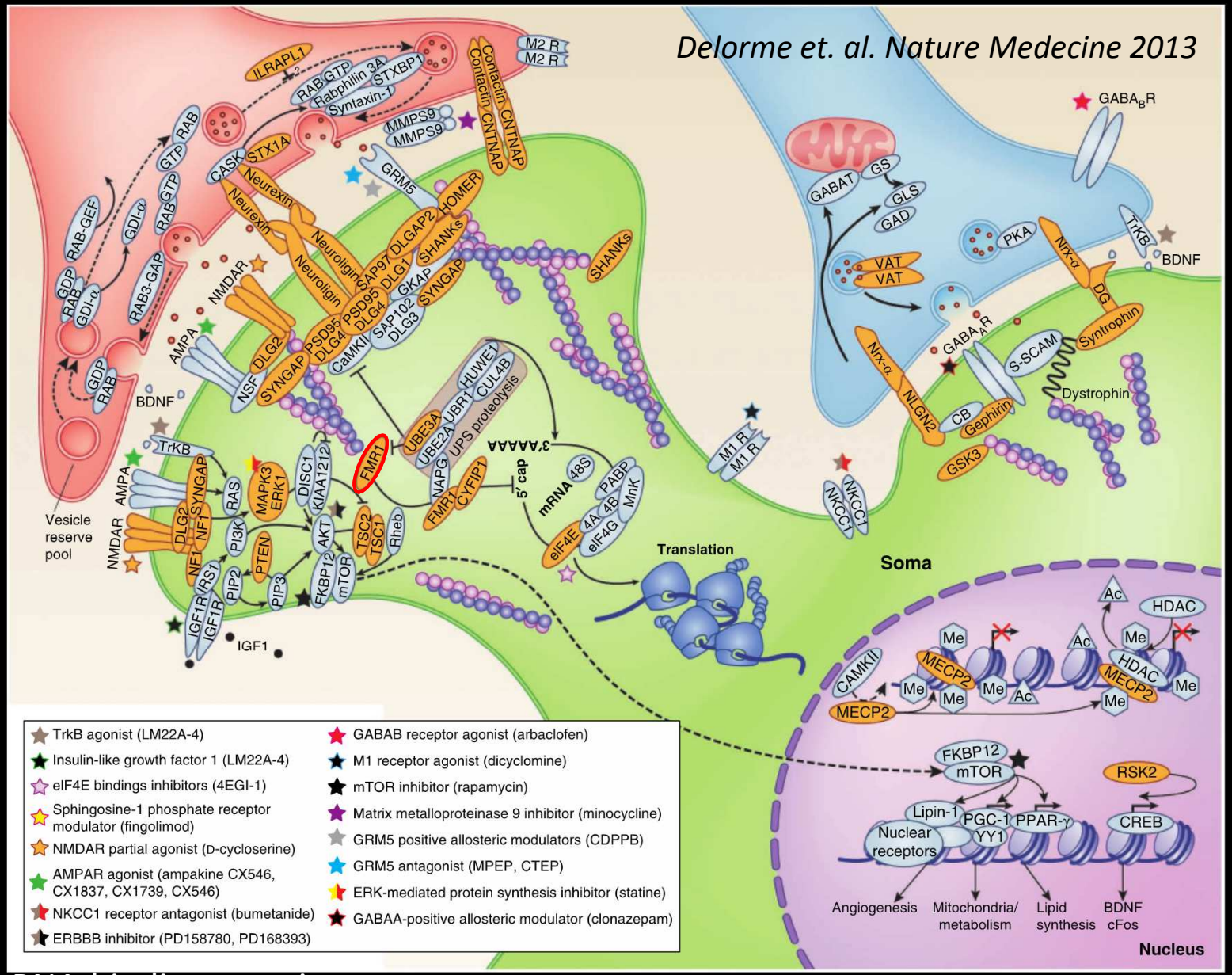
NMDARs and mGluRs = sensors of specific activity patterns and initiate the signaling cascades to induce plasticity ⟶ activity-dependent refinement of synapses and circuits in the developing CNS and for adaptive cognitive processes such as learning and memory

SYNAPTIC PROTEINS INVOLVED IN ASD



MUTATIONS prevent correct associations-dissociation between proteins from the complex, or prevent correct PROTEIN EXPRESSION which is mendatory for LONG TERM PLASTICITY and asociated memory.

SYNAPTIC PROTEINS INVOLVED IN ASD



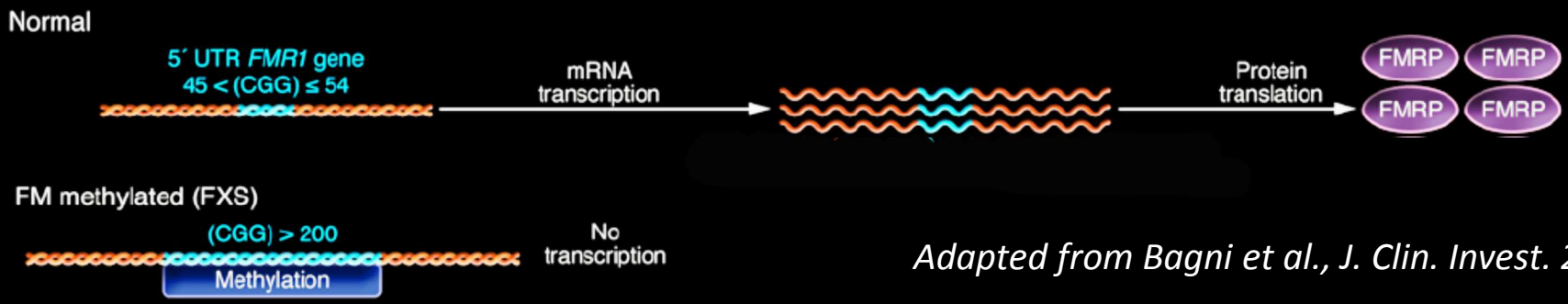
RNA-binding proteins

FMRP loss causes the most common heritable ASD: fragile X syndrome (FXS)

LOSS OF FUNCTION OF THE FRAGILE X MENTAL RETARDATION GENE (FMR1) CAUSES FRAGILE X SYNDROME (FXS)

Fragile X gene and protein:

- Expansion of trinucleotide repeat sequence (CGG) in the 5' UTR
- silencing of Fmr1 gene that encodes the fragile X mental retardation protein (FMRP): mRNA binding protein
- Function as a regulator of translation



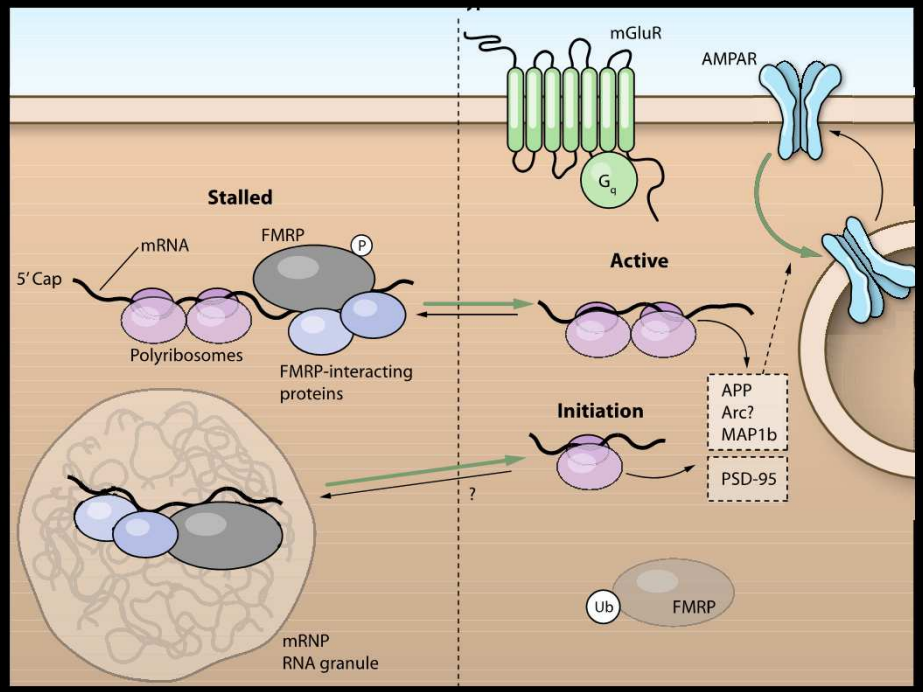
Adapted from Bagni et al., J. Clin. Invest. 2012

PATIENTS:

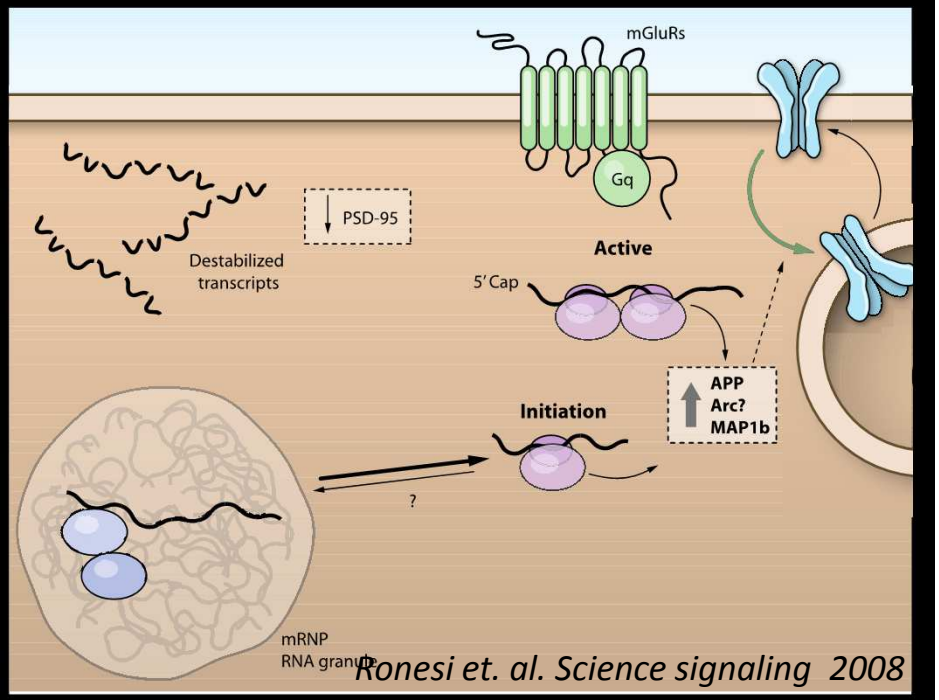
- from mild learning disability to profound mental retardation
  short-term memory deficits
  hyperactivity, anxiety, seizures and autism

EXCESSIVE mRNA TRANSLATION DOWNSTREAM OF mGlu5 RECEPTOR IS A CORE PATHOPHYSIOLOGY OF FXS

Wild Type Mice



Fmr1 KO Mice

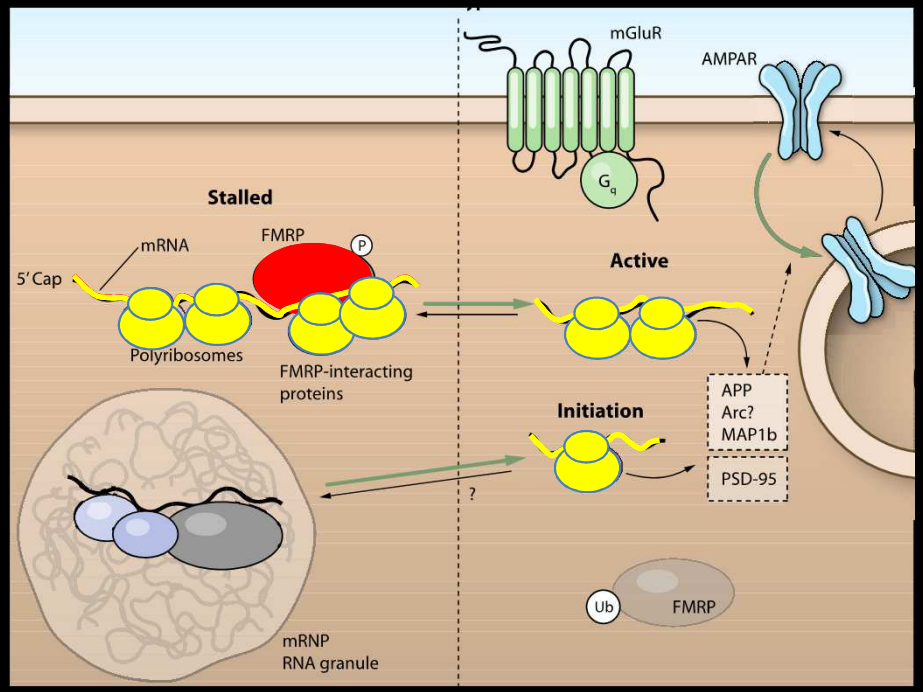


Ronesi et. al. Science signaling 2008

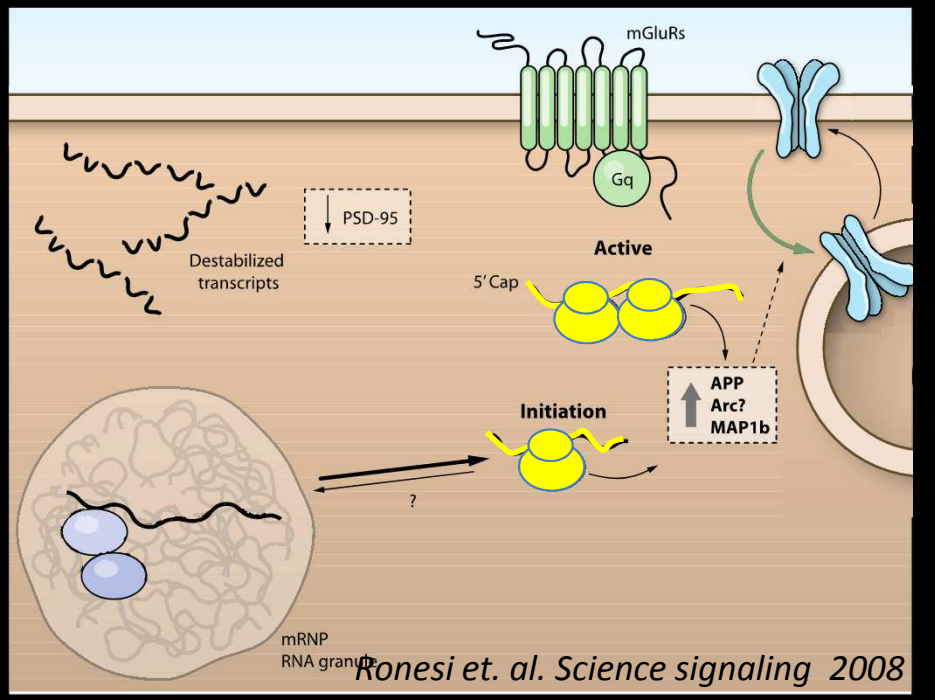
Which mistranslated mRNAs contribute to neurological deficits in FXS ?

EXCESSIVE mRNA TRANSLATION DOWNSTREAM OF mGlu5 RECEPTOR IS A CORE PATHOPHYSIOLOGY OF FXS

Wild Type Mice



Fmr1 KO Mice



Ronesi et. al. Science signaling 2008

Which mistranslated mRNAs contribute to neurological deficits in FXS ?

SUMMARY : COMPARISON OF TRANSLATOME PROFILES BETWEEN *Fmr1* KO AND WT MICE IN A GENETICALLY-IDENTIFIED CELL POPULATION

HOW ?

RiboTag approach

Wfs1-CreERT2:RiboTag mouse line = CA1 pyramidal neurons of the hippocampus

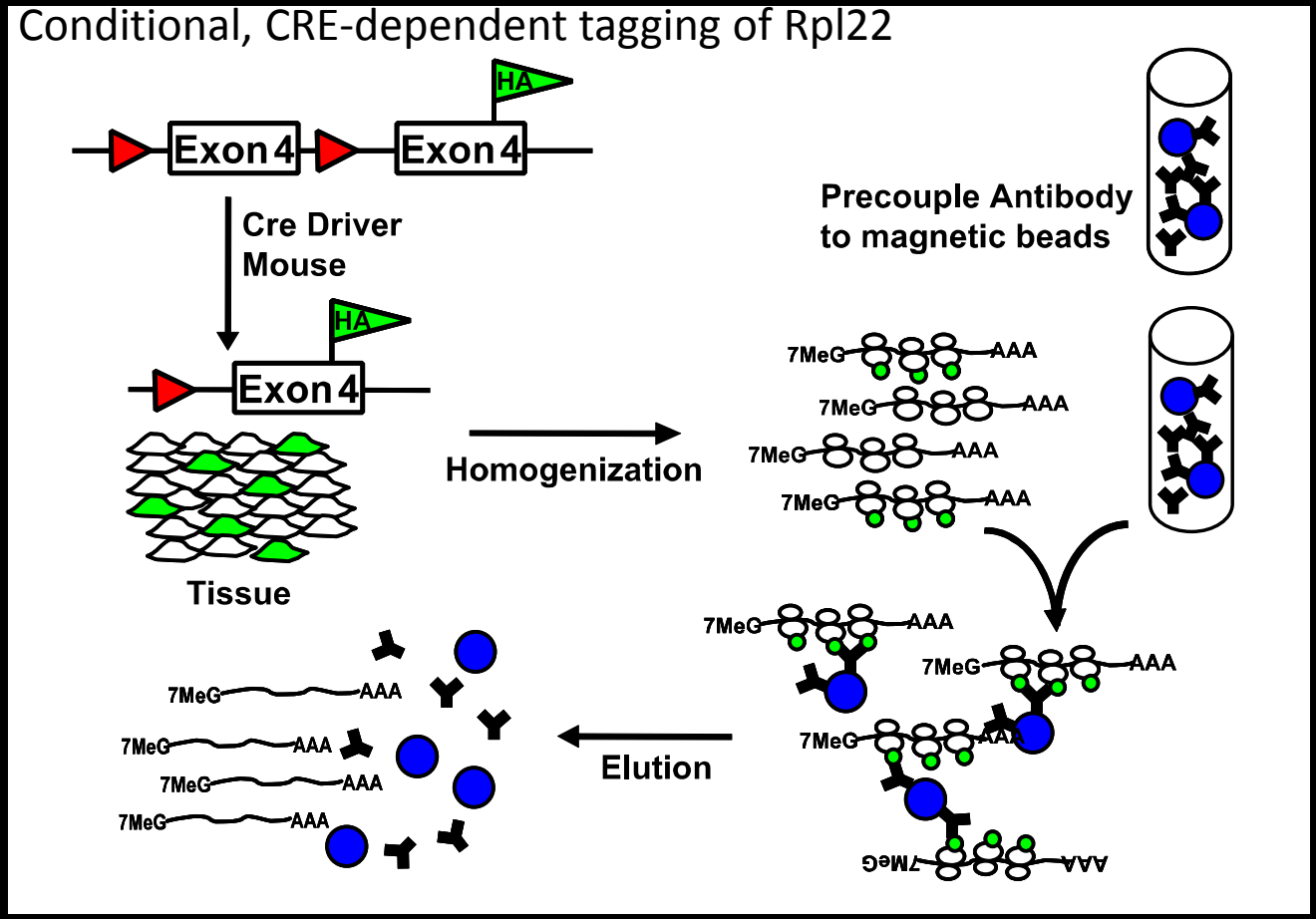
TAKE HOME MESSAGES:

78 genes are differentially regulated in control mice versus *Fmr1*$^{-/y}$ mice
NCBI Gene Expression Omnibus GEO; http://www-ncbi-nlm-nih-gov.insb.bib.cnrs.fr/geo/ GSE94559.

Functional genomics : neuronal connectivity-related functions

KLK8 re-expression in *Fmr1*$^{-/y}$ mice cultured hippocampal neurons restores dendritic spine maturation

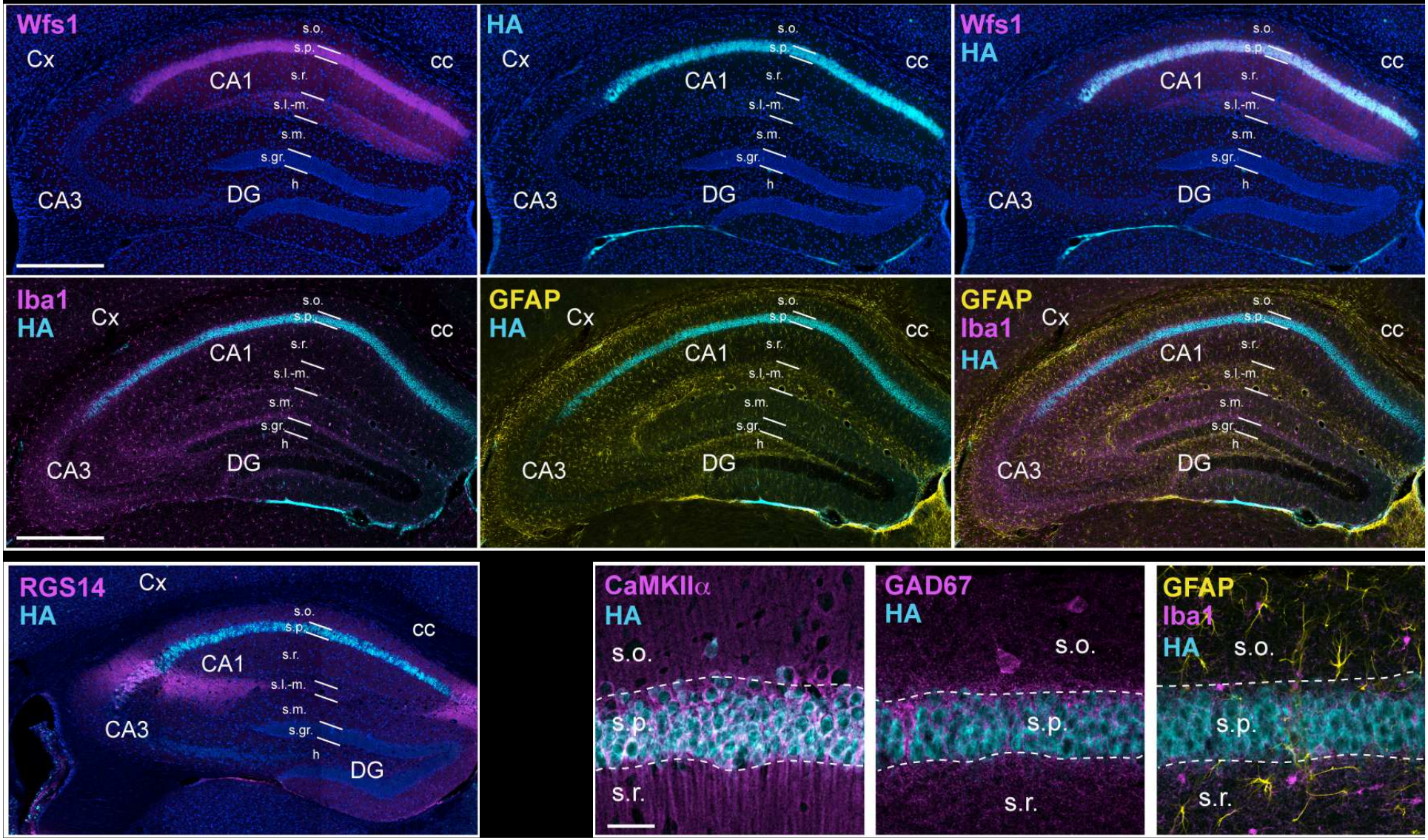
CELL-TYPE-SPECIFIC ISOLATION OF RIBOSOME-ASSOCIATED mRNA FROM COMPLEX TISSUES



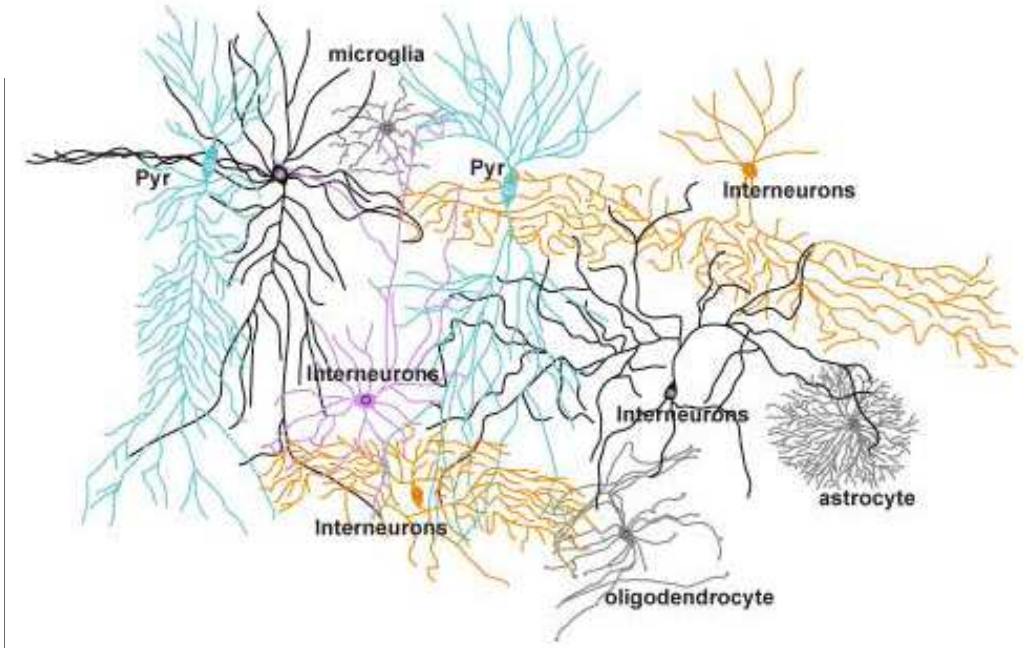
Adapted from Sanz et. al. PNAS(2009)

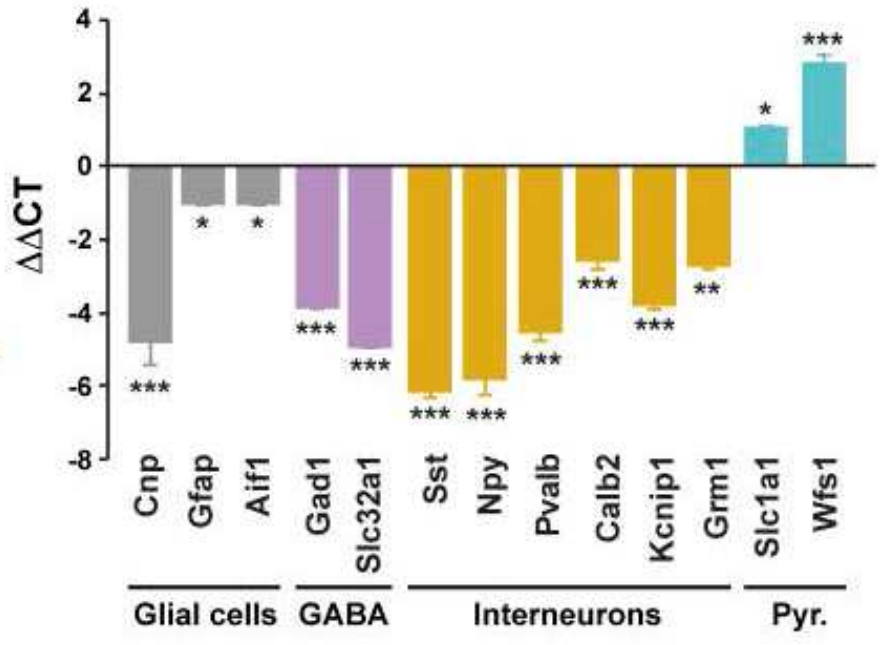
HA-Rpl22 (RiboTag) EXPRESSION IS RESTRICTED TO CA1 PYRAMIDAL CELLS IN THE *Wfs1-CreERT2:RiboTag* MICE

Wfs1-CreERT2:RiboTag = CRE dependent expression of the RiboTag is driven by the Wfs promotor



Wfs1 AND THE GLUTAMATERGIC MARKER *Slc1a1* ARE ENRICHED AFTER HA-IMMUNOPRECIPITATION





Validates the Wfs1-CreERT2:RiboTag mouse line to perform mRNA profiling in CA1 pyramidal cells of the hippocampus

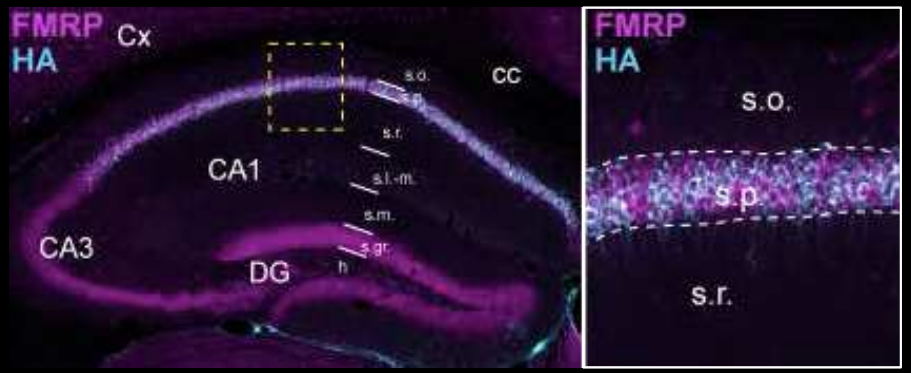
TRANSLATOME PROFILES COMPARISON BETWEEN WT AND Fmr1 KO IN CA1 PYRAMIDAL NEURONS OF THE HIPPOCAMPUS

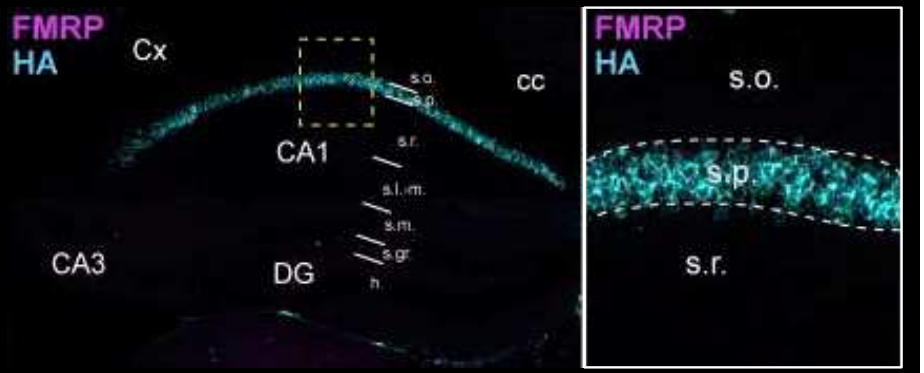
Wfs1-CreERT2:RiboTag$^{HA/+}$
Fmr1$^{+/y}$

♂

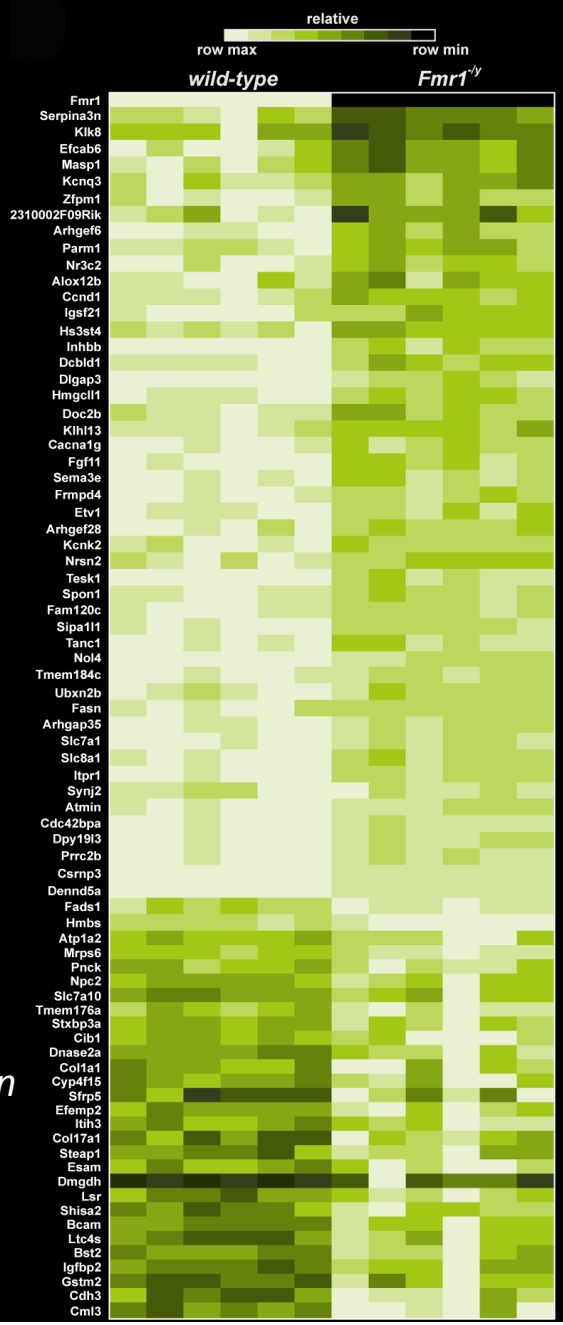
Wfs1-CreERT2:RiboTag $^{HA/+}$
Fmr1$^{-/y}$

♂



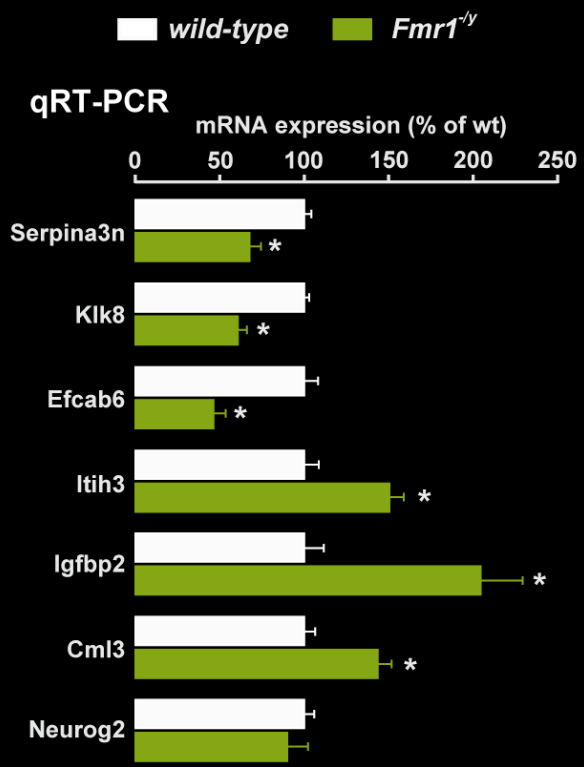


HIGH-THROUGHPUT RNA SEQUENCING (RNAseq)

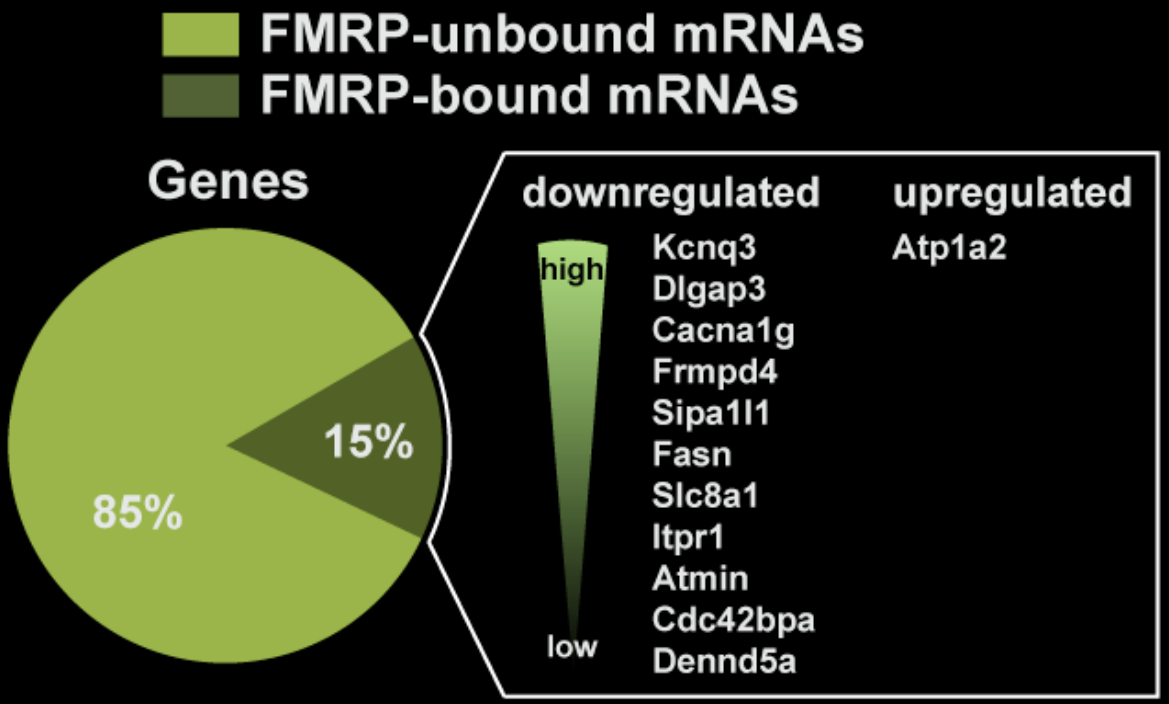


78 genes UP and Down regulation

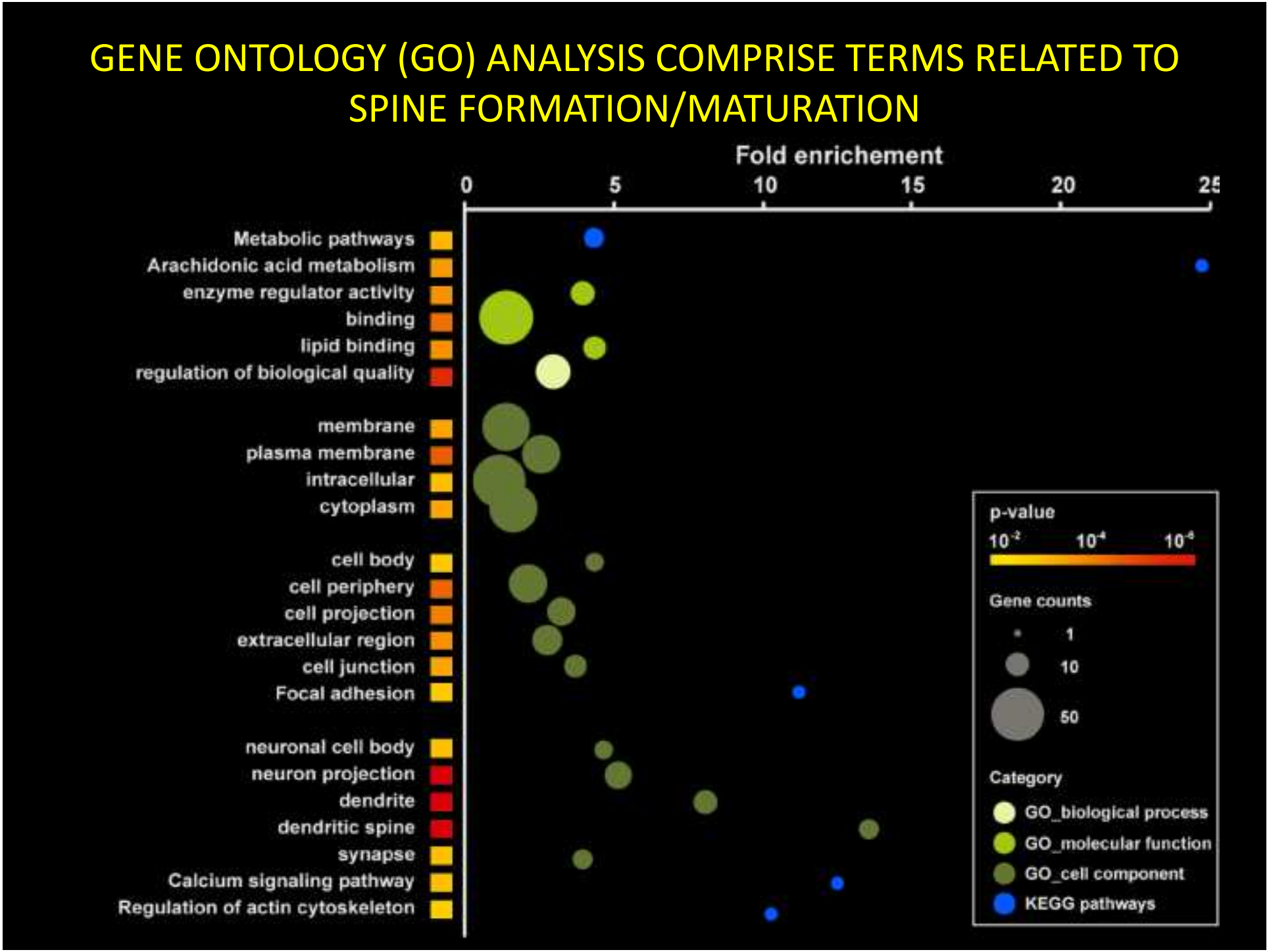
All RNAseq data from this study have been submitted to the NCBI Gene Expression Omnibus GEO; http://www-ncbi-nlm-nih-gov.insb.bib.cnrs.fr/geo/ under accession number GSE94559.



CROSS-ANALYSIS OF RNAseq DATA WITH FMRP-BOUND mRNAs



GENE ONTOLOGY (GO) ANALYSIS COMPRISE TERMS RELATED TO SPINE FORMATION/MATURATION



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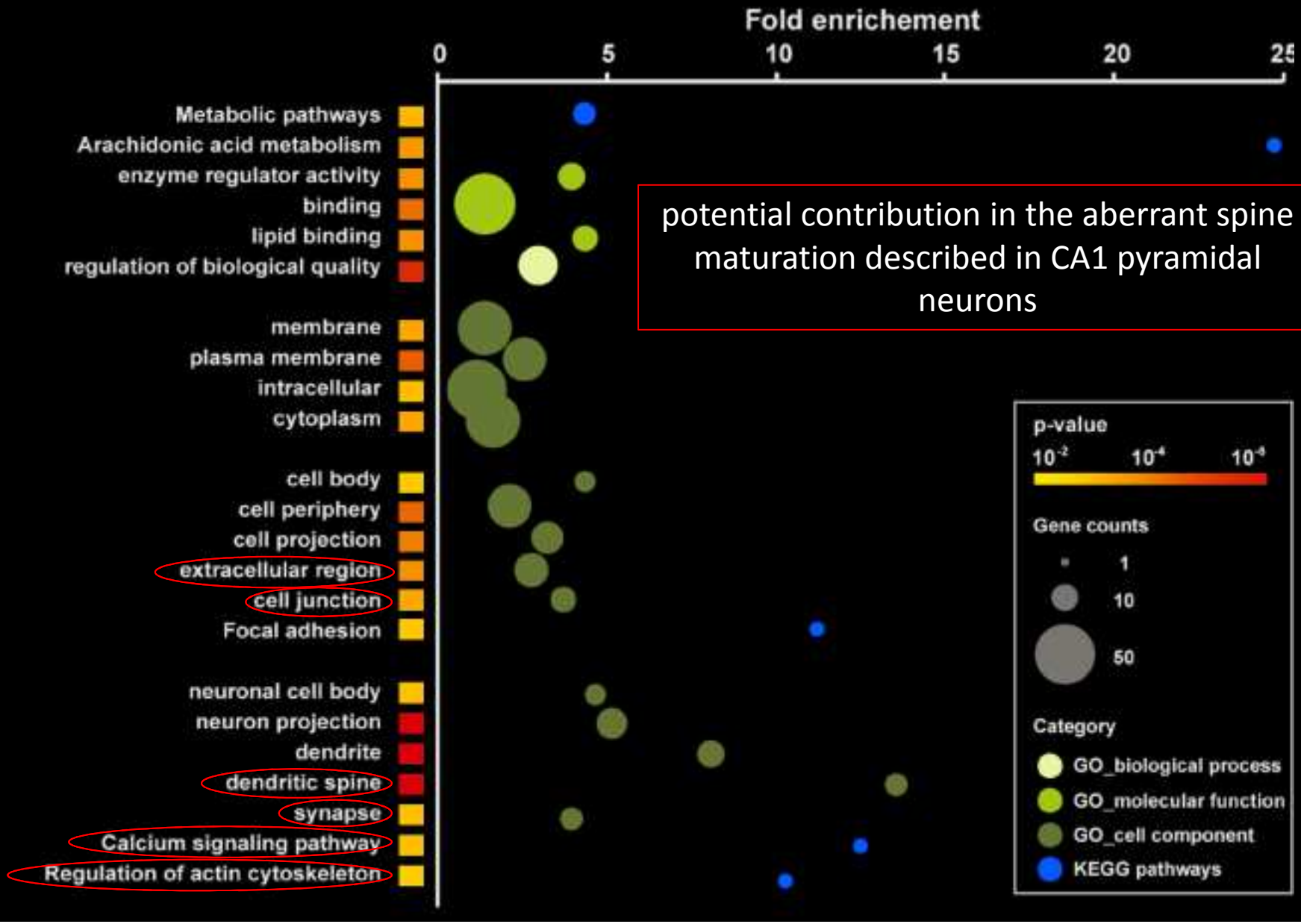
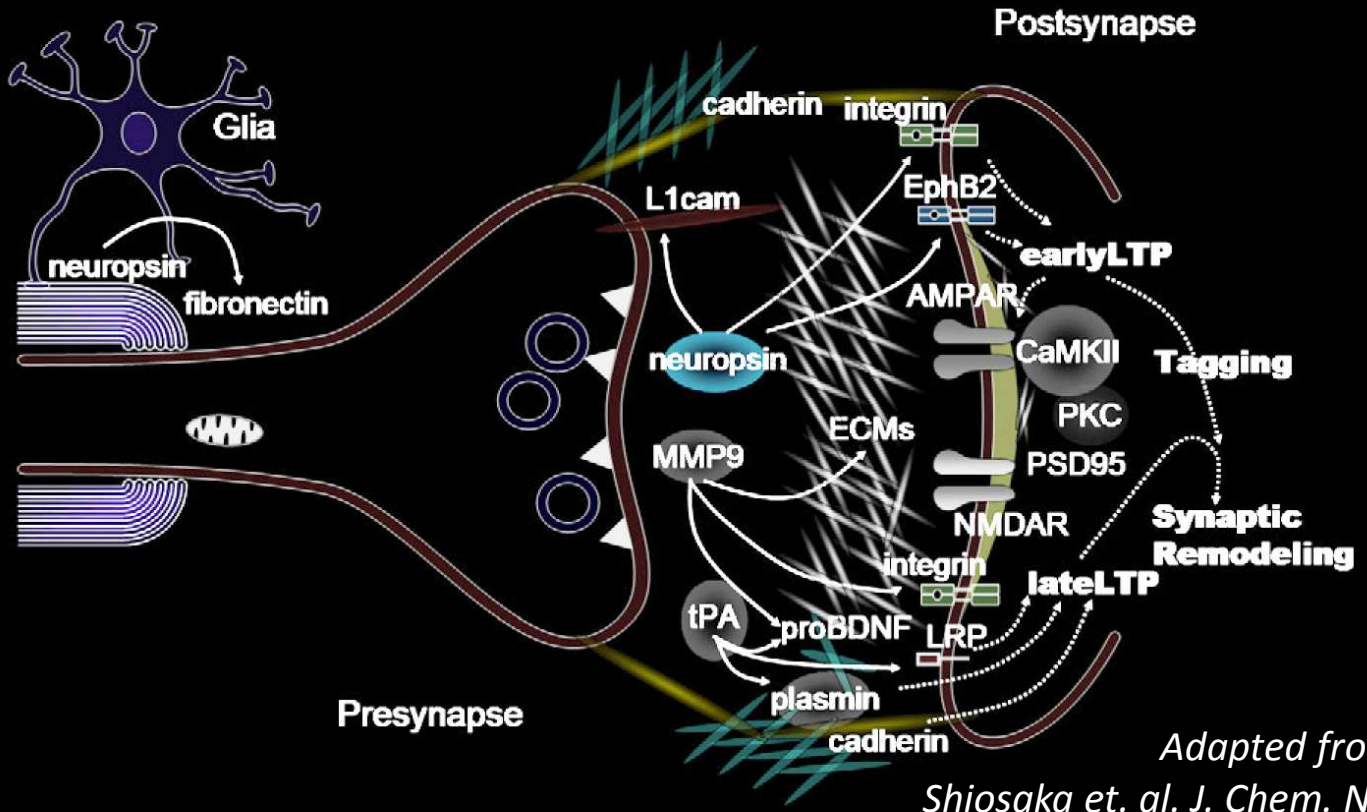


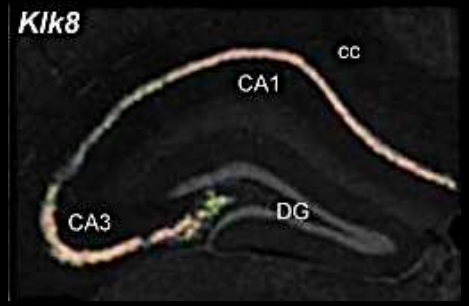
potential contribution in the aberrant spine maturation described in CA1 pyramidal neurons

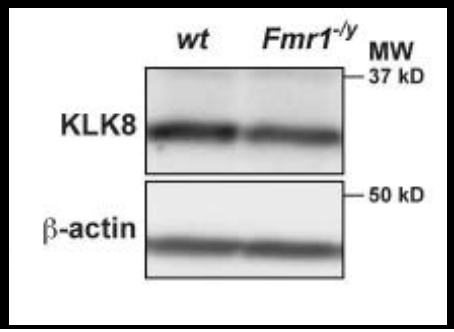
KLK8/NEUROPSIN, PROTEASE FROM THE EXTRACELLULAR MATRIX, ACTS AS REGULATORY MOLECULE IN THE EARLY PHASE OF LTP

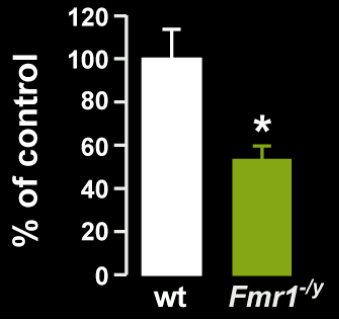


Adapted from
Shiosaka et. al. J. Chem. Neuroanat. 2011

Allen Brain Atlas

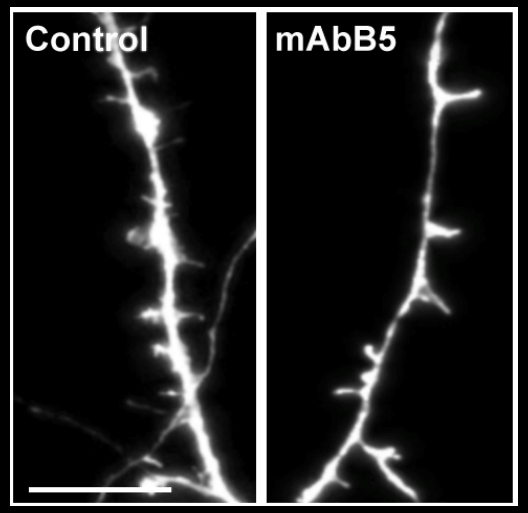


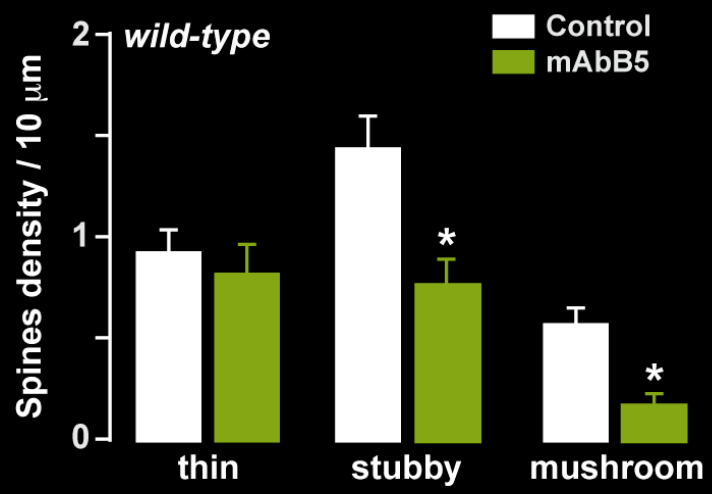




KLK8 ACTIVITY CONTRIBUTES TO DENDRITIC SPINE MATURATION AND ABERRANT SYNAPTOGENESIS IN *Fmr1* KO MICE RELIES ON ALTERED EXPRESSION OF KLK8

Wild-type

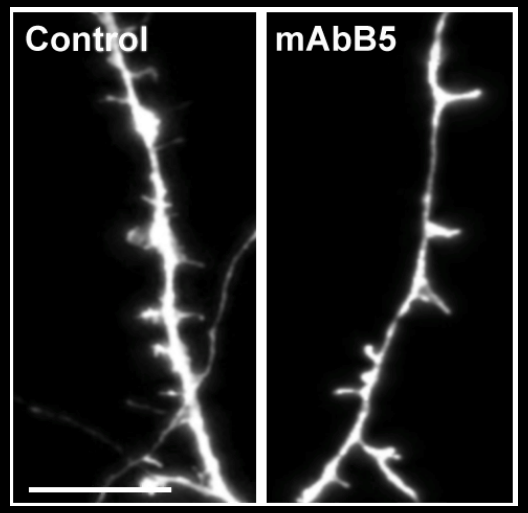


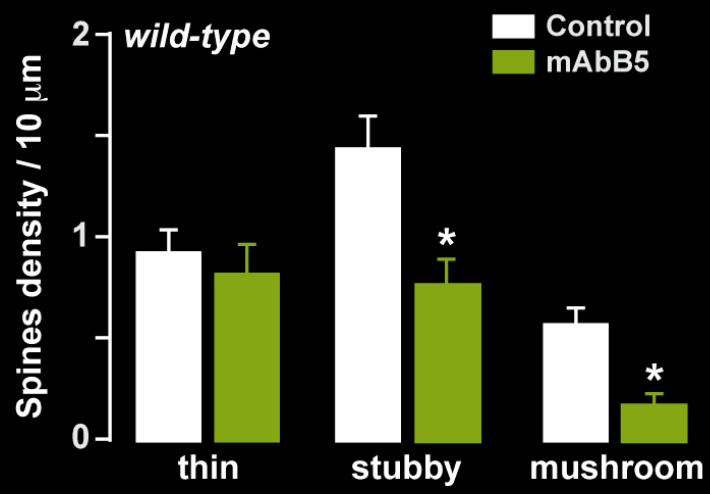


The density and the morphology of dendritic spines are affected by KLK8 activity in WT mice

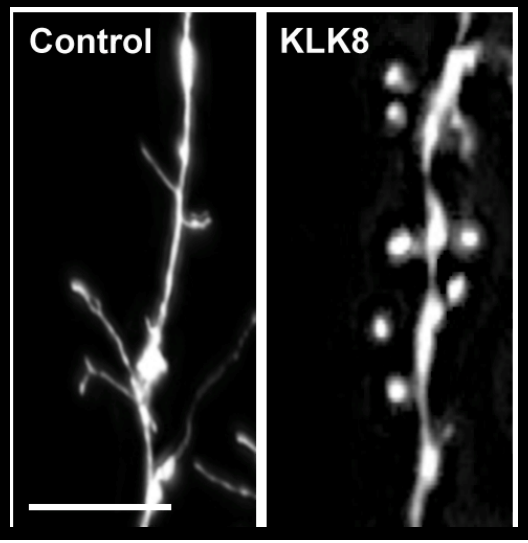
KLK8 ACTIVITY CONTRIBUTES TO DENDRITIC SPINE MATURATION AND ABERRANT SYNAPTOGENESIS IN *Fmr1* KO MICE RELIES ON ALTERED EXPRESSION OF KLK8

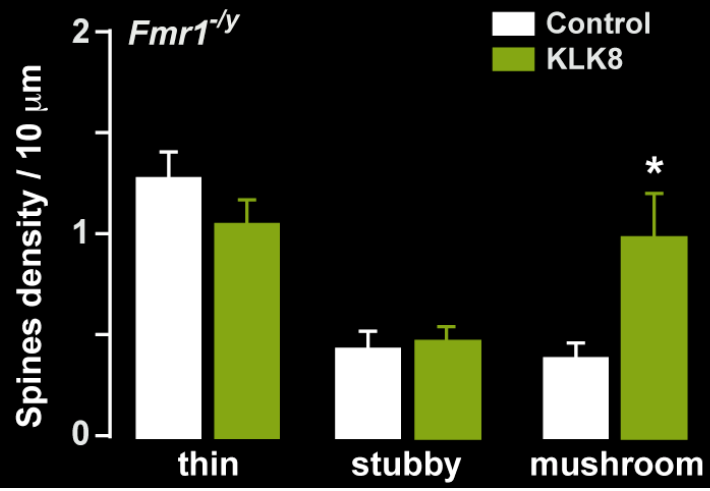
Wild-type





Fmr1$^{-/y}$





CONCLUSIONS

Both FMRP-bound and unbound mRNAs differentially translated

Bidirectional alteration of translation

Restricted to a subset of genes, involved in connectivity-related functions

Those genes candidates together support hippocampus-dependent cognitive processes ?

reduced levels of KLK8 in hippocampal CA1 pyramidal neurons contribute to the abnormal spine morphology observed in *Fmr1*$^{-/y}$ mice by preventing the maturation of mushroom-shaped spines

CELL TYPE-SPECIFIC mRNA DYSREGULATION IN HIPPOCAMPAL CA1 PYRAMIDAL NEURONS OF THE FRAGILE X SYNDROME MOUSE MODEL

PATHOPHYSIOLOGY OF SYNAPTIC TRANSMISION

NEURAL CIRCUITS AND SIGNAL TRANSDUCTION

Julie Perroy

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Nathalie Bouquier

Emma Puighermanal

Jihane Vitre

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