Understanding the biology of huntingtin for clinical applications

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Grenoble excellence in neurodegeneration

Outline

- **Introduction:**

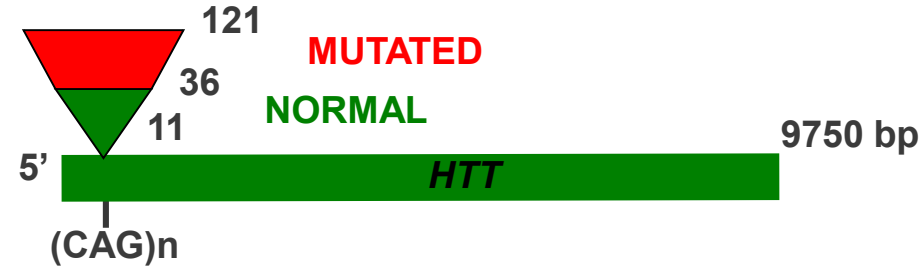
Huntington's disease & Huntingtin protein

- **Huntingtin regulates key cellular functions**

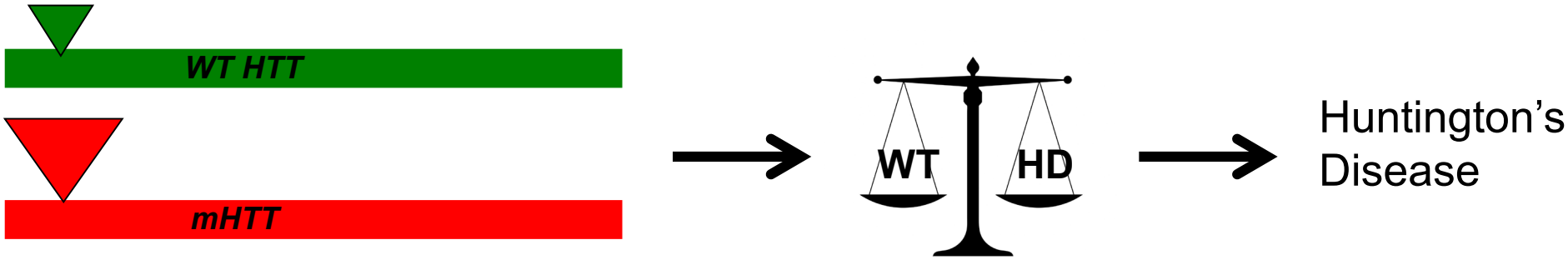
Huntingtin axonal transport and ciliogenesis

- **Concluding remarks**

How does mHTT cause toxicity?

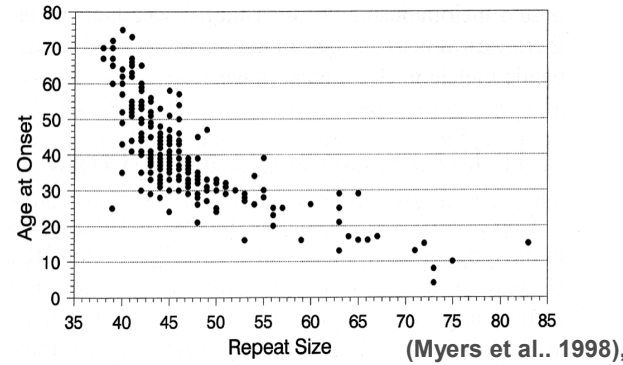


- **Gain of toxic functions**
  - Disease is dominant



  - HTT knock-out is embryonic lethal

Duyao et al. Science 1995; Nasir et al. Cell 1995; Zeitlin et al. Nat Genet 1995



(Myers et al.. 1998),

How does mHTT cause toxicity?

- **Loss of normal functions**

  - Knock-out in mice at post-natal stage leads to neurodegeneration

    Dragatsis et al. Nat Genet 2000

  - Mice heterozygotes for WT HTT show cognitive defects and neurodegeneration

    Nasir et al. Cell 1995; O'Kusky et al. Brain Res 1999

  - The levels of WT and mutant HTT regulate disease progression

    Becanovic et al. Nature Neurosci, 2015

  - HTT has central cellular functions

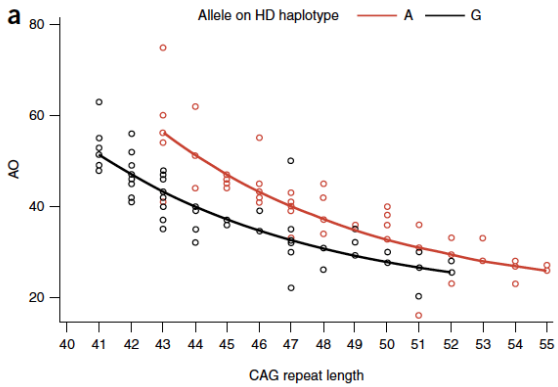
    Saudou & Humbert Neuron 2016

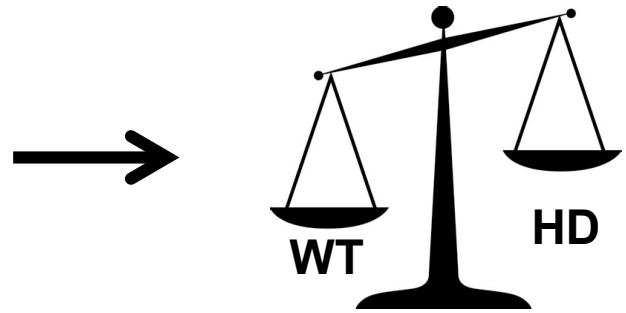
nature neuroscience

A SNP in the *HTT* promoter alters NF-κB binding and is a bidirectional genetic modifier of Huntington disease

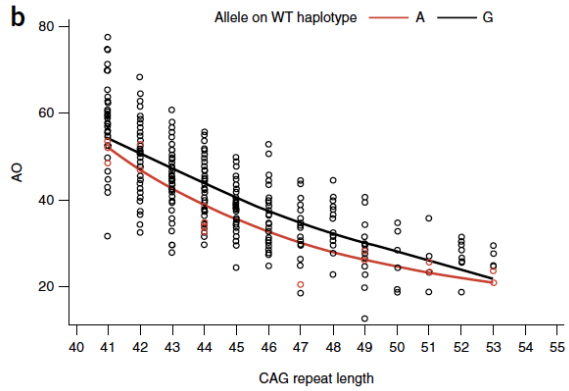
Kristina Bečanović[1,2], Anne Nørremølle[3], Scott J Neal[1], Chris Kay[1], Jennifer A Collins[1], David Arenillas[1],
Tobias I
Elodie P
of the Eu
Michael

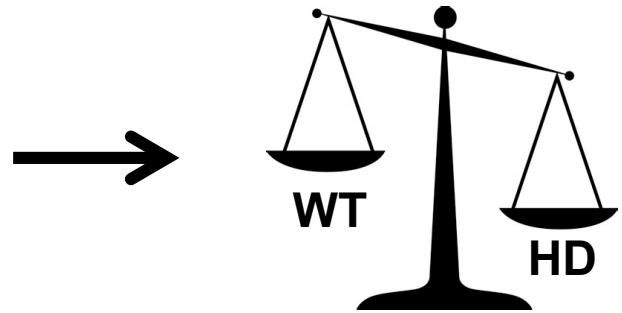
transcriptional activity. A non-coding SNP, rs13102260:G > A, in this binding site impaired NF-κB binding and reduced *HTT* transcriptional activity and HTT protein expression. The presence of the rs13102260 minor (A) variant on the HD disease allele was associated with delayed age of onset in familial cases, whereas the presence of the rs13102260 (A) variant on the wild-type *HTT* allele was associated with earlier age of onset in HD patients in an extreme case–based cohort. Our findings suggest a previously unknown mechanism linking allele-specific effects of rs13102260 on *HTT* expression to HD age of onset





Disease starts later

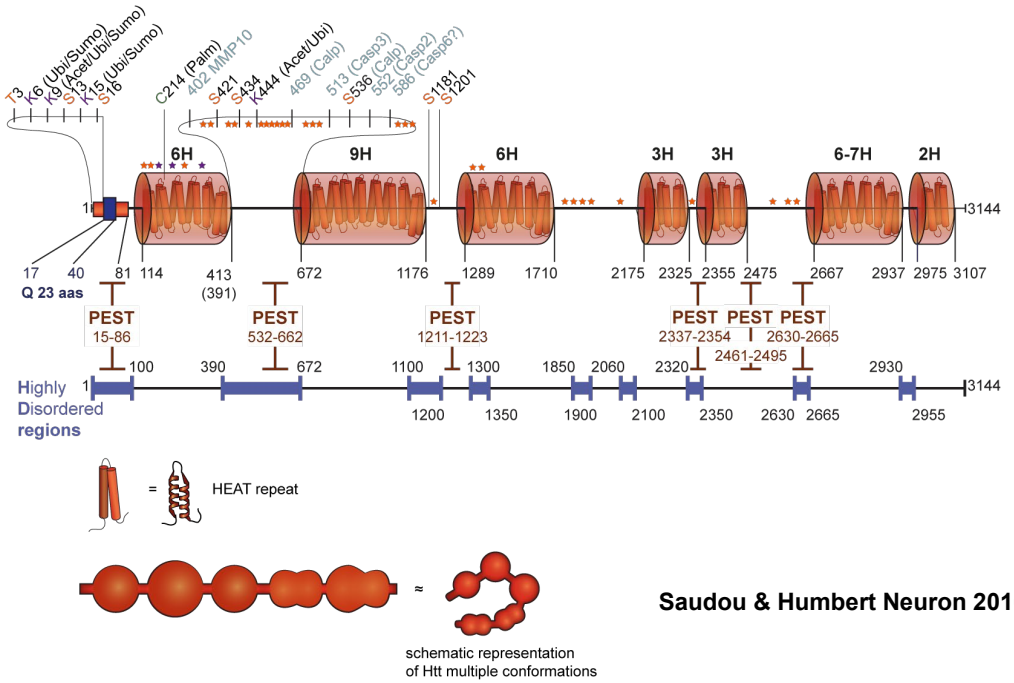




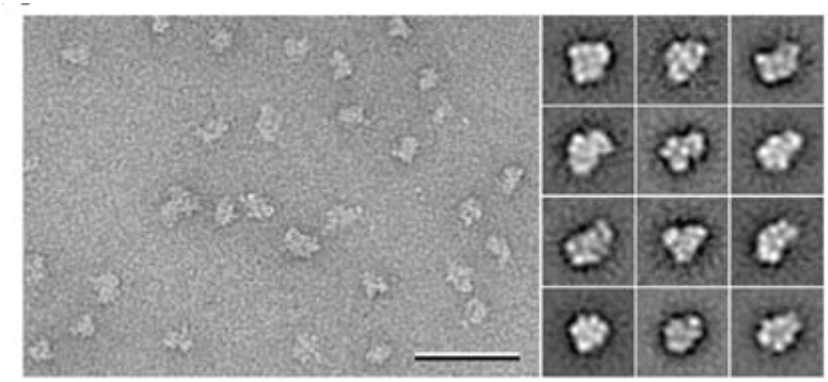
Disease starts earlier

Becanovic, Nat Neurosci 2015

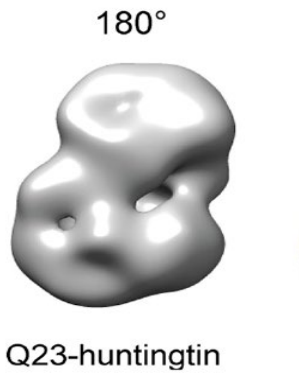
The huntingtin protein



Saudou & Humbert Neuron 2016



Seong et al HMG 2010



Vijayvargia et al elife 2016

Interactors/ protein complex A

Interactors/ protein complex B

Interactors/ protein complex …

Fonction 1

Fonction 2

Fonction 3

Fonction 4

Fonction 5

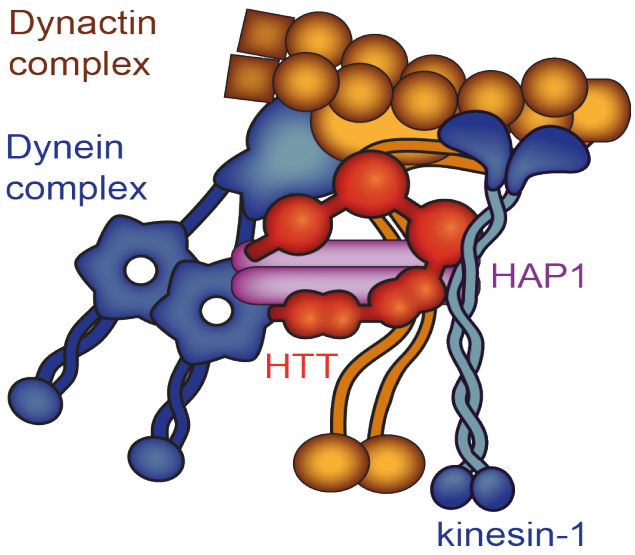
Fonction 6

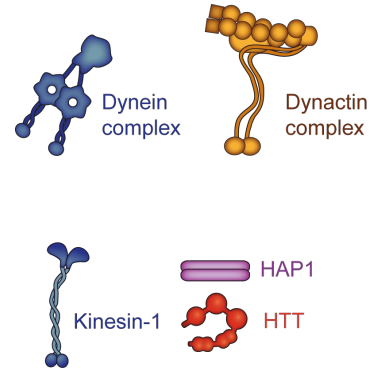
Fonction 7

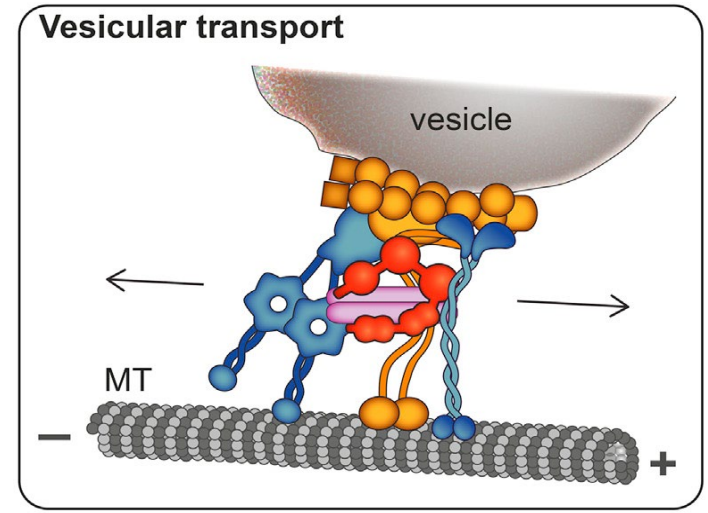
Fonction …

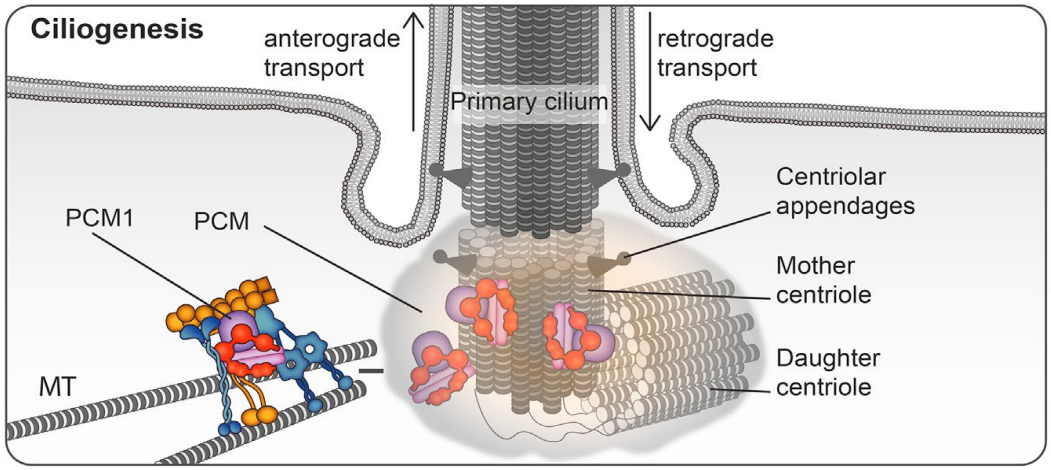
Huntingtin and the dynein/dynactin complex

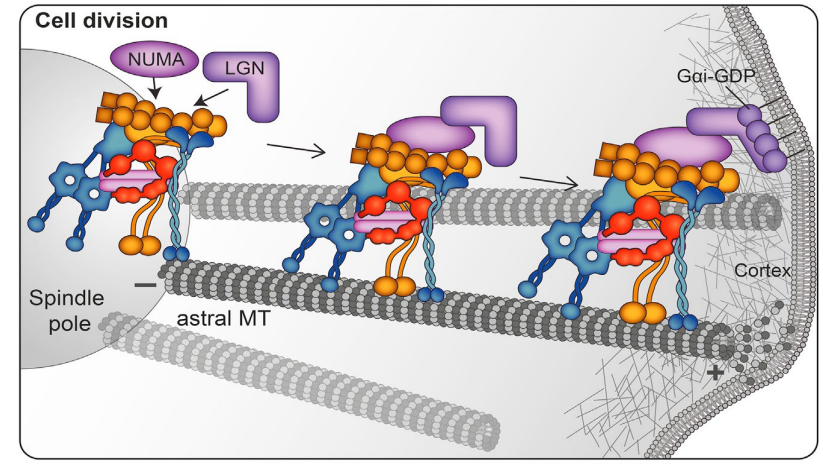
HTT regulates MT-based transport, cell division and ciliogenesis





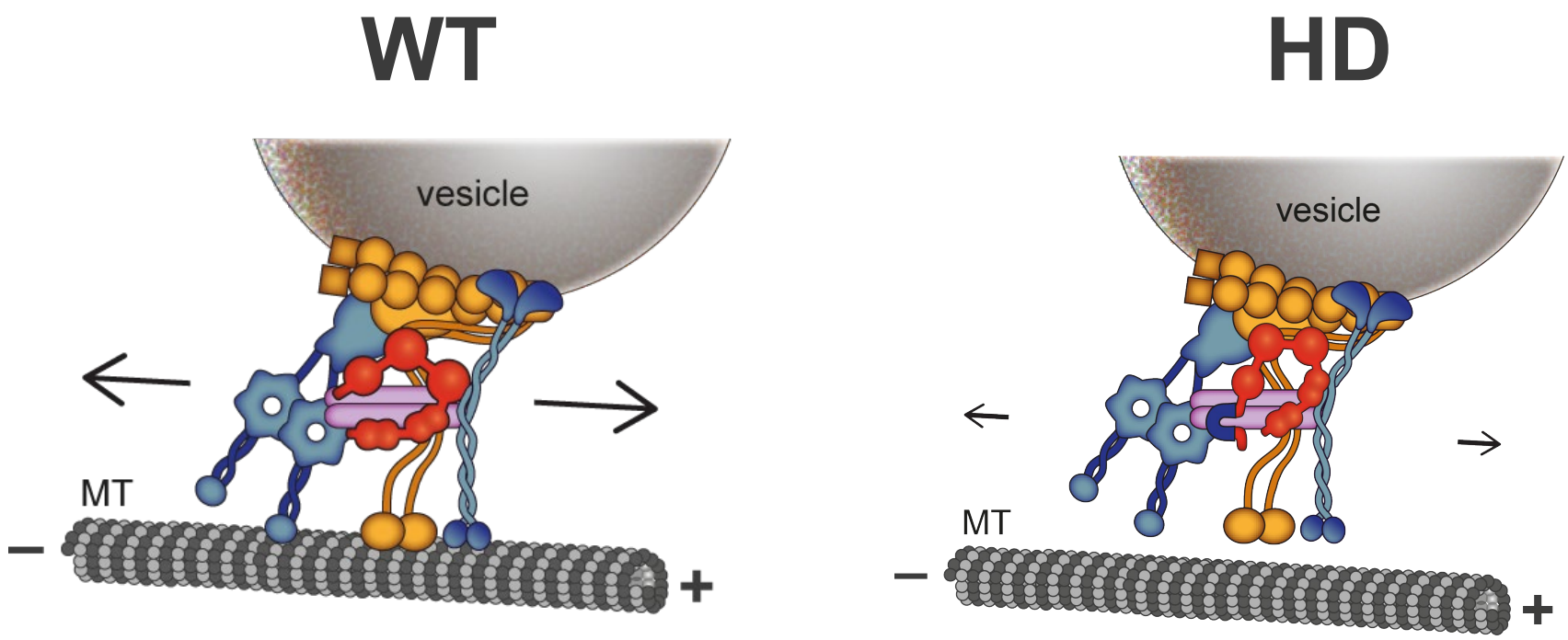




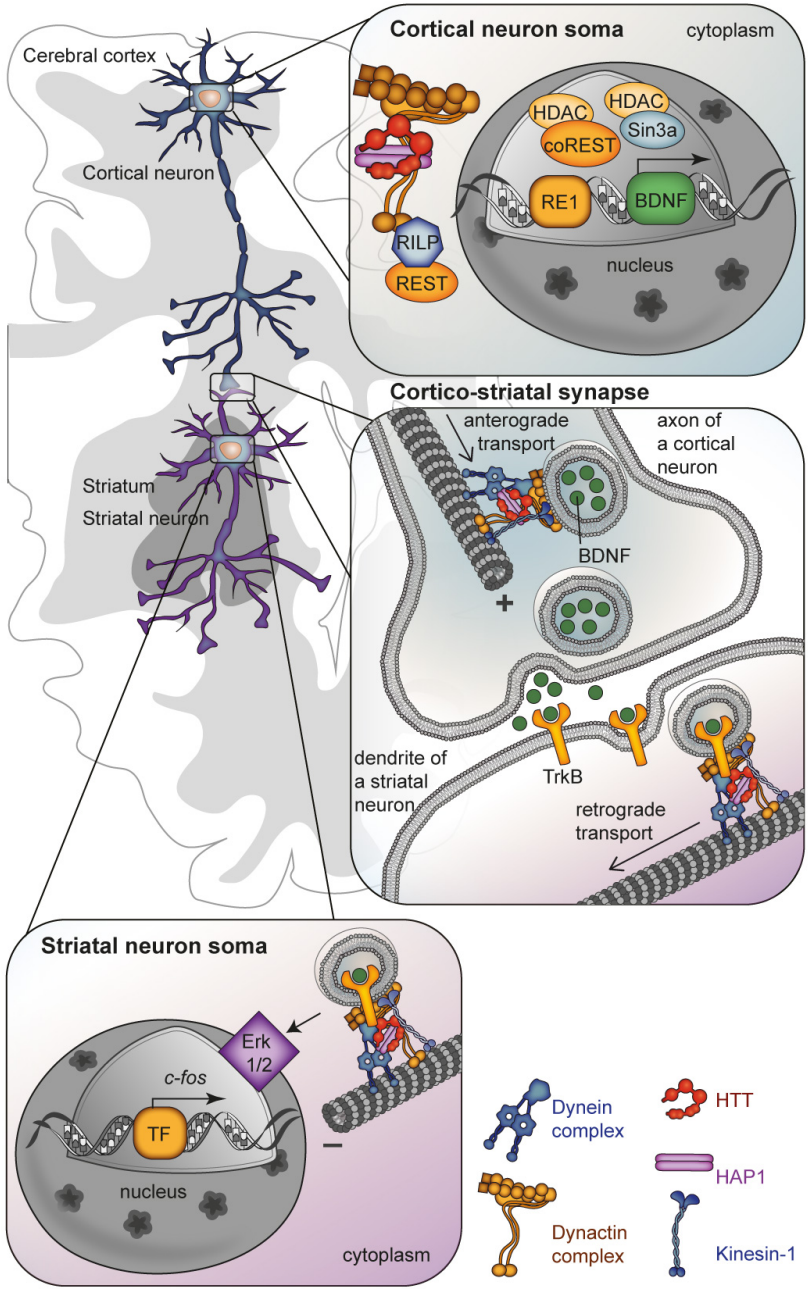


Godin et al Neuron 2010; Keryer et al JCI 2011; Elias et al Stem Cell Rep 2014; Haremaki et al Dev Biol 2015; Gauthier et al Cell 2004; McGuire et al JBC 2006; Caviston et al PNAS 2007; Dompierre et al J Neurosci 2007; Colin et al EMBO J 2008; Zala et al HMG 2008

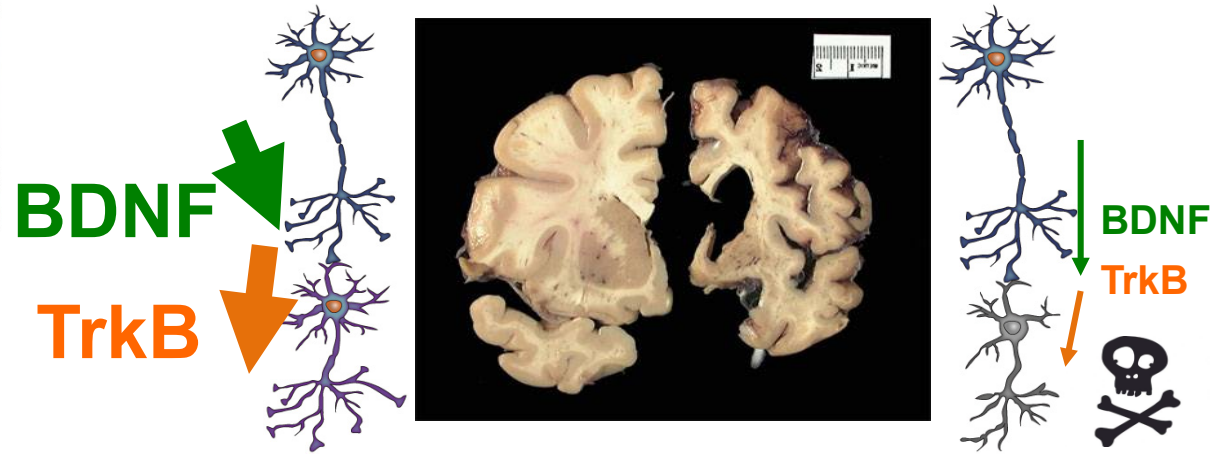
Vesicular transport along microtubules is facilitated by huntingtin and is altered in disease



Gauthier, Cell 2004; McGuire JBC 2006;Caviston, PNAS 2007; Dompierre J Neurosci 2007; Colin, EMBO J 2008; Zala HMG 2008; Pineda Mol Brain 2009; Pardo Mol Brain 2010

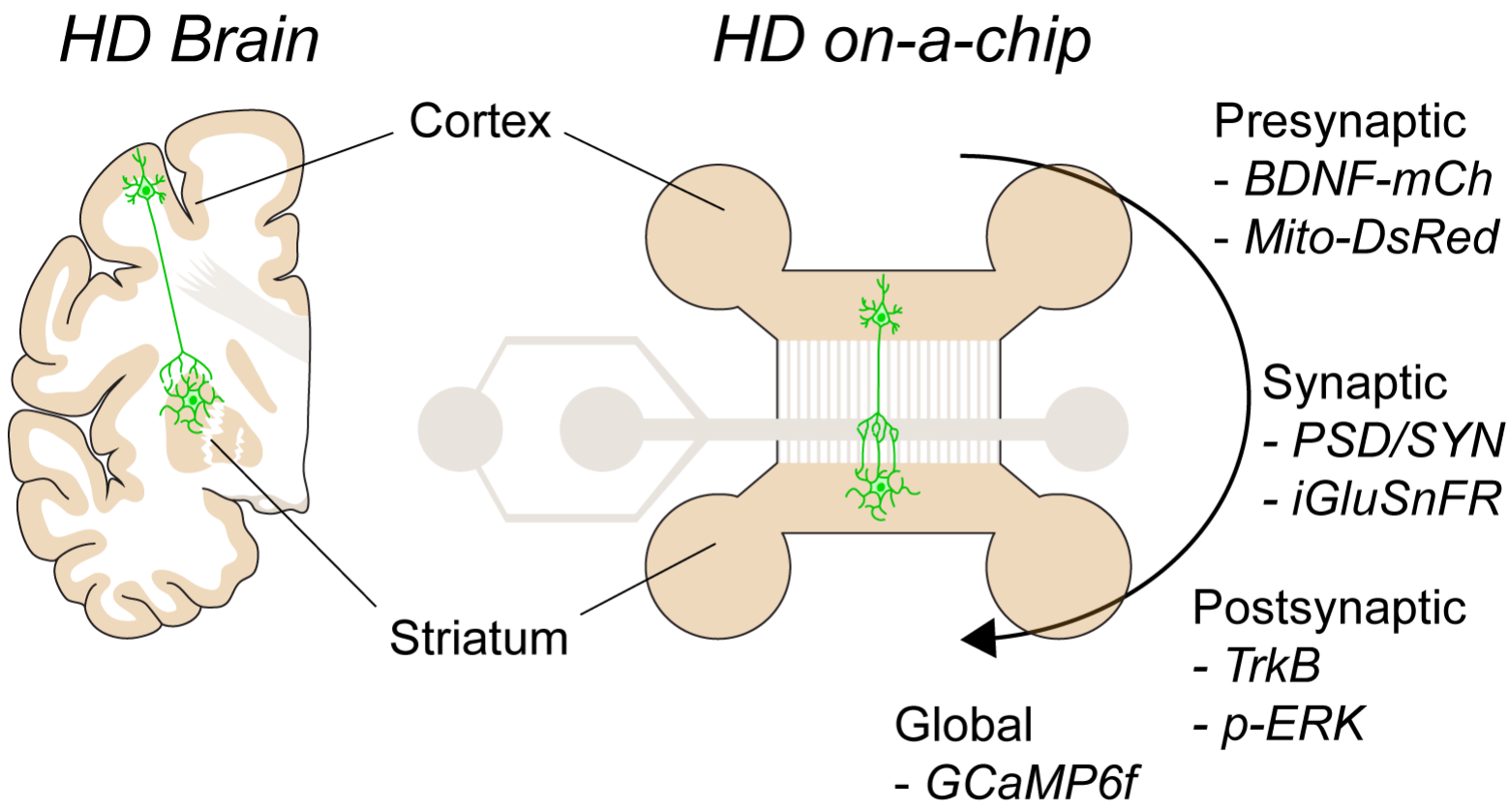


The corticostriatal projections are particularly sensitive in HD



Reviewed in Saudou & Humbert Neuron 2016; see also Liot J Neurosci 2013; Plotkin, Neuron 2014, Brito, JCI, 2014, Zhao, PNAS, 2016,

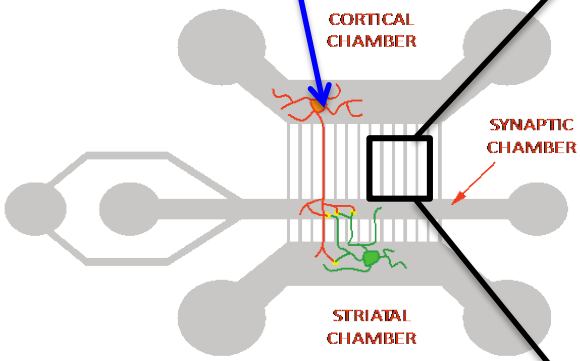
Global alteration of the corticostriatal circuit in HD

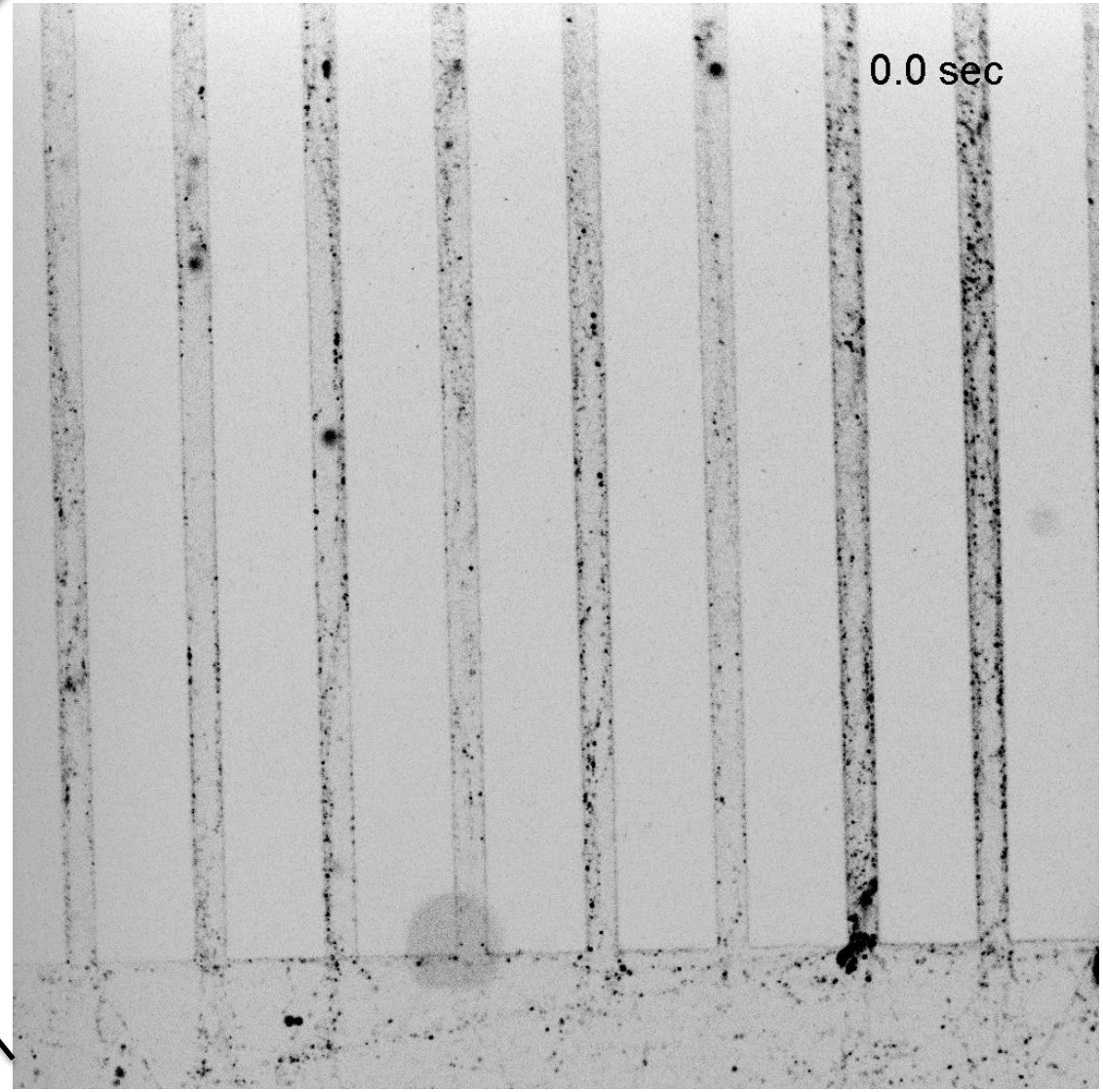


Virlogeux et al., Cell Reports 2018

Microfluidic chambers for the analysis of axonal transport

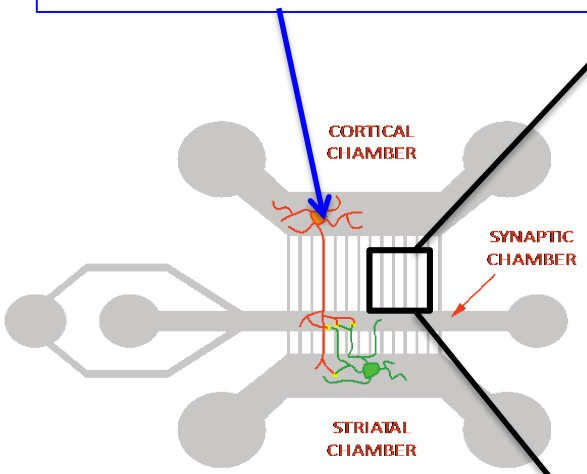
Cortical neurons from rat embryos transduced with Lentivirus encoding Brain derived Neurotrophic factor (BDNF-mCherry)

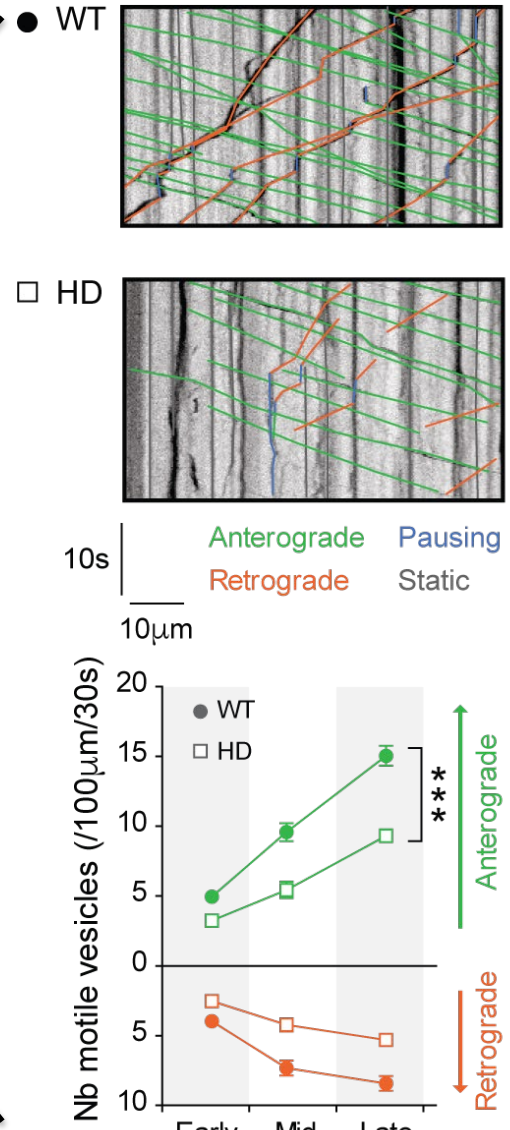


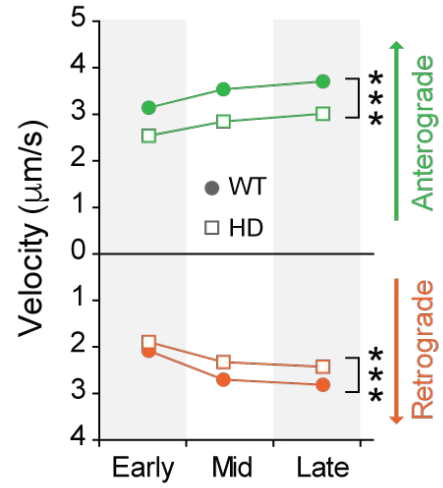


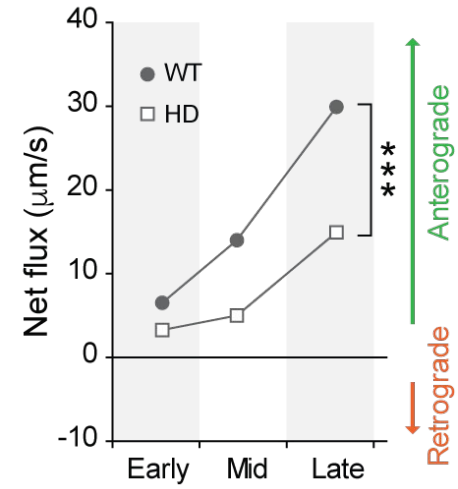
Early alteration of BDNF trafficking in HD network

Cortical neurons from WT or HD mouse embryos transduced with Lentivirus encoding Brain derived Neurotrophic factor (BDNF-mCherry)



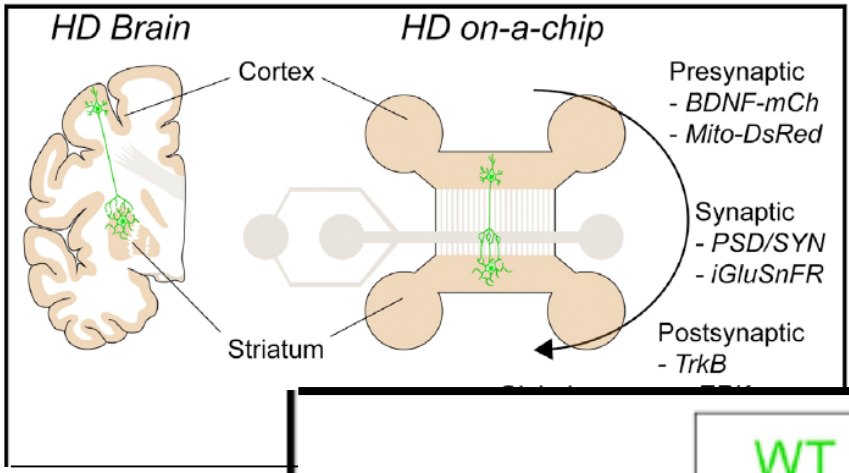




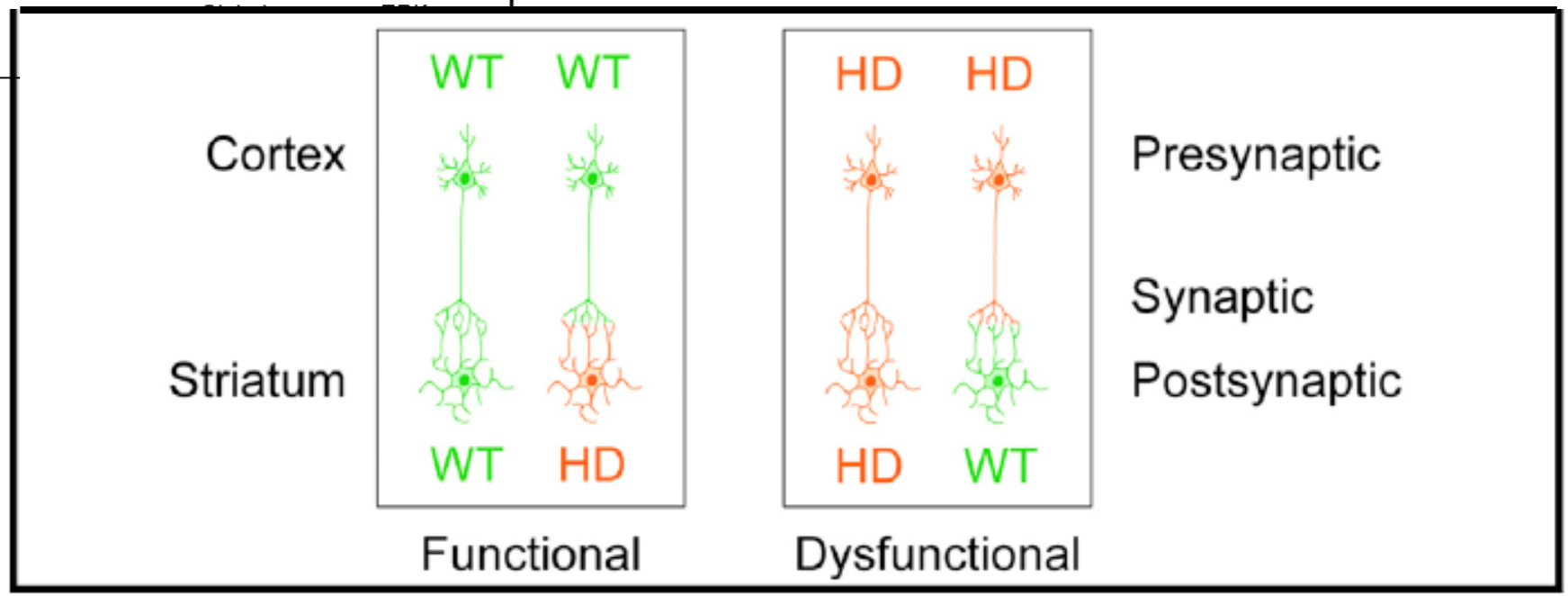


Virlogeux et al. Cell Reports 2018

Manipulating the genetic status of the cortex and striatum

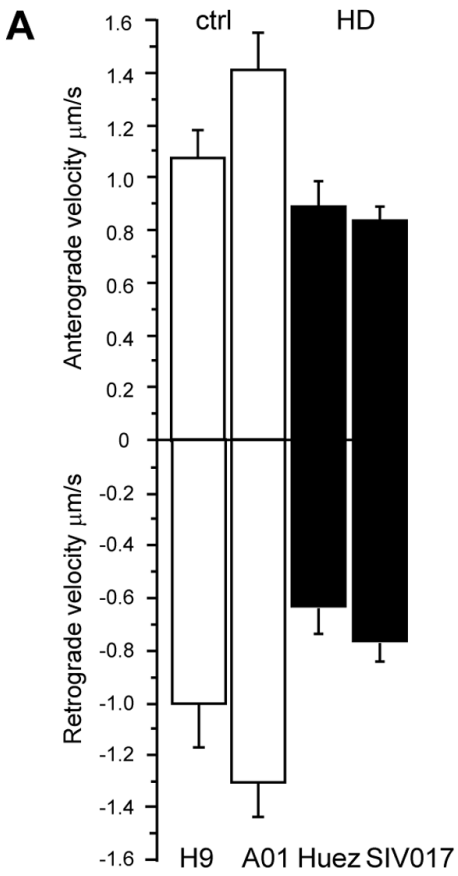


Presynaptic compartment determines the integrity of the network



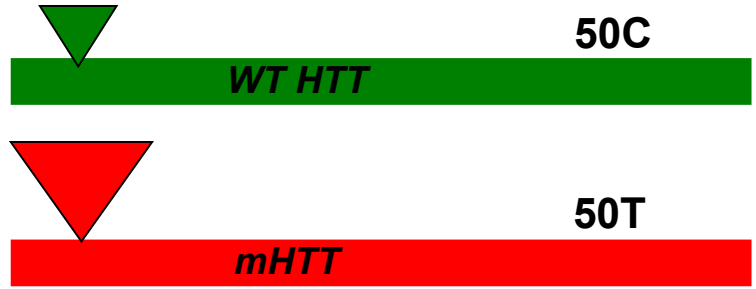
Virlogeux et al., Cell Reports 2018

Silencing mHTT but not WT HTT restores axonal transport in Neural Stem Cells from Human Embryos



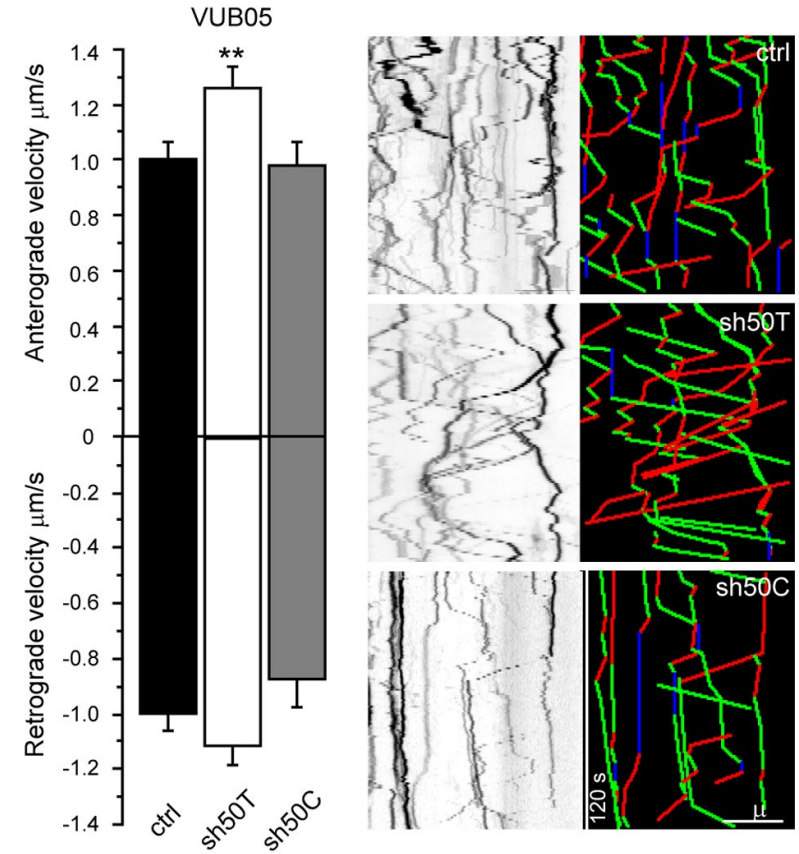
Exon 50 contains a C/T SNP

VUB05 line is heterozygous do 50C/T

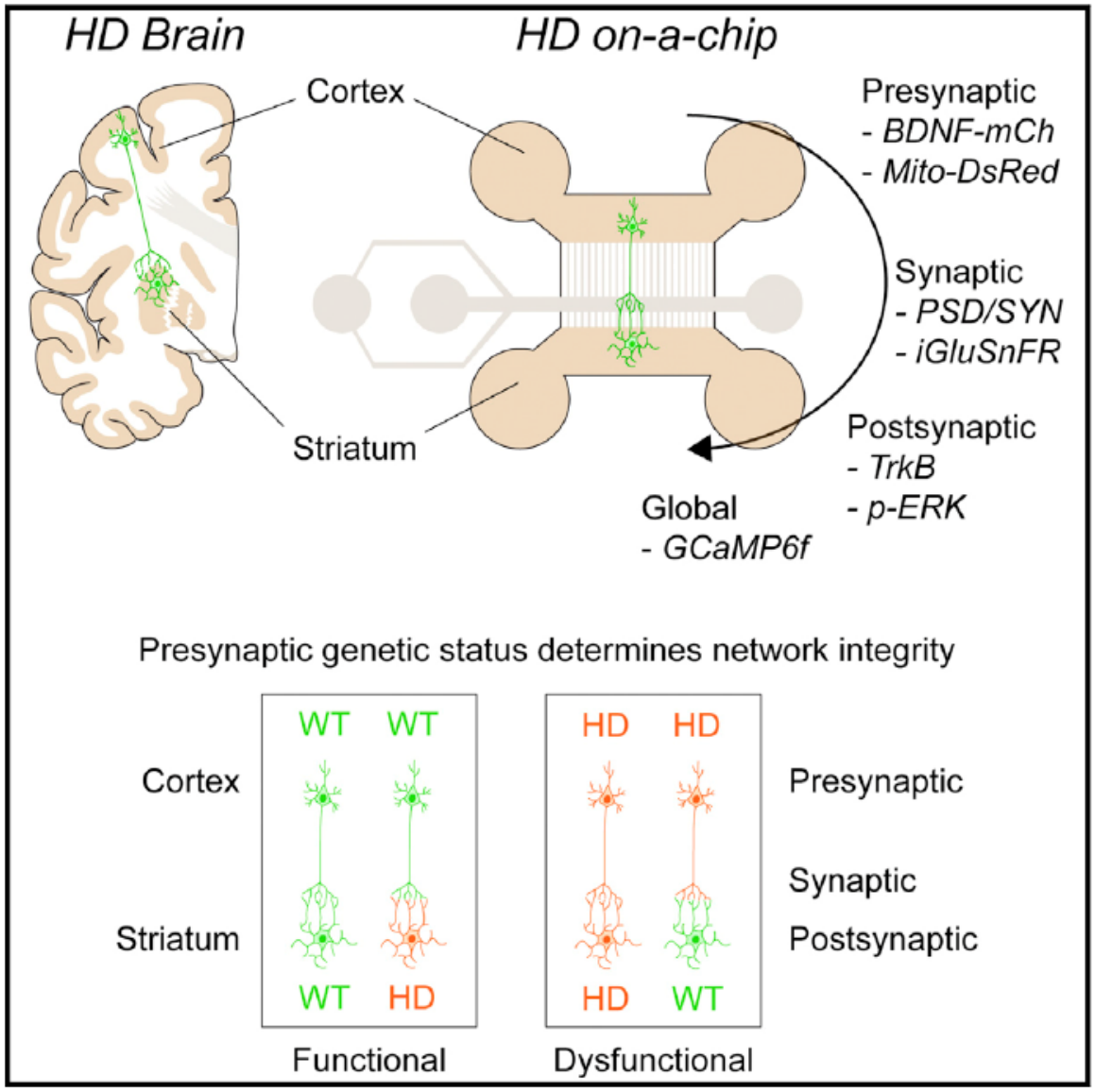


→ sh50T silences mutant allele

→ sh50C sllences WT allele



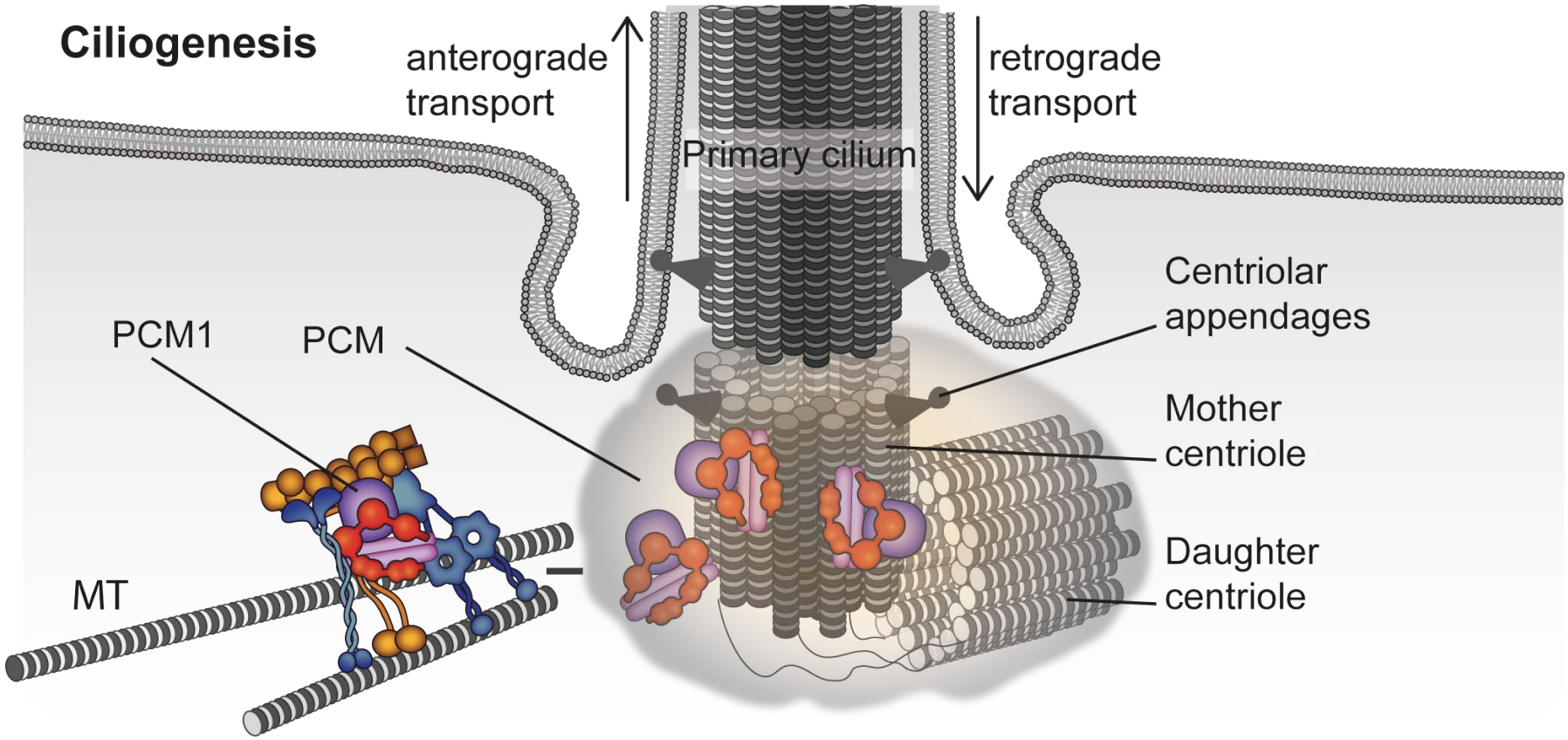
Drouet el al. Plos One 2014



Conclusion 1

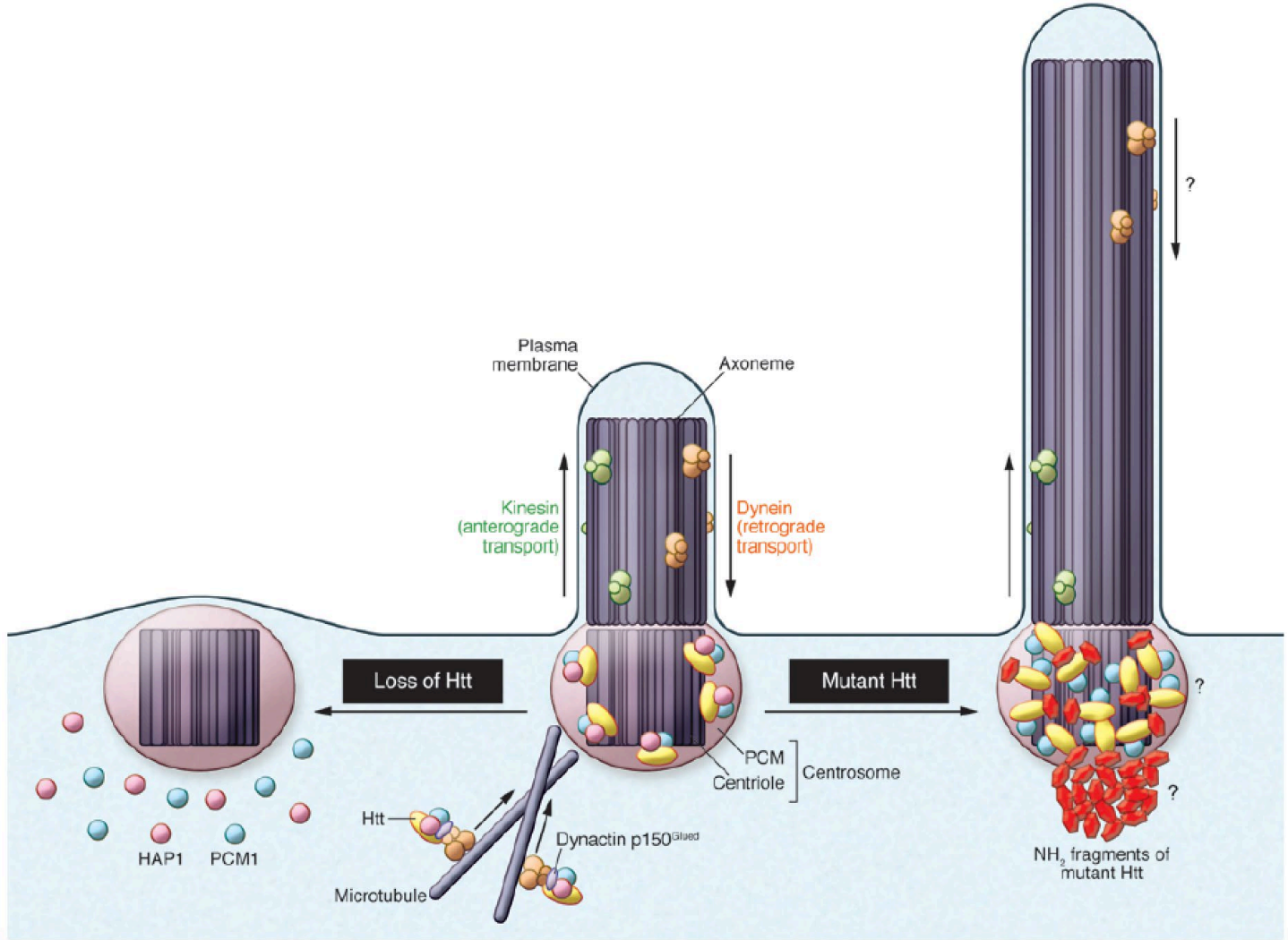
- Defects in axonal transport of vesicles are key early components of HD pathogenesis
- Modifying WT and mutant HTT levels regulate BDNF transport efficiency
- Huntingtin function in axonal transport is important to maintain corticostriatal ciruitry
- Cortex has also to be considered for therapies

Huntingtin and ciliogenesis



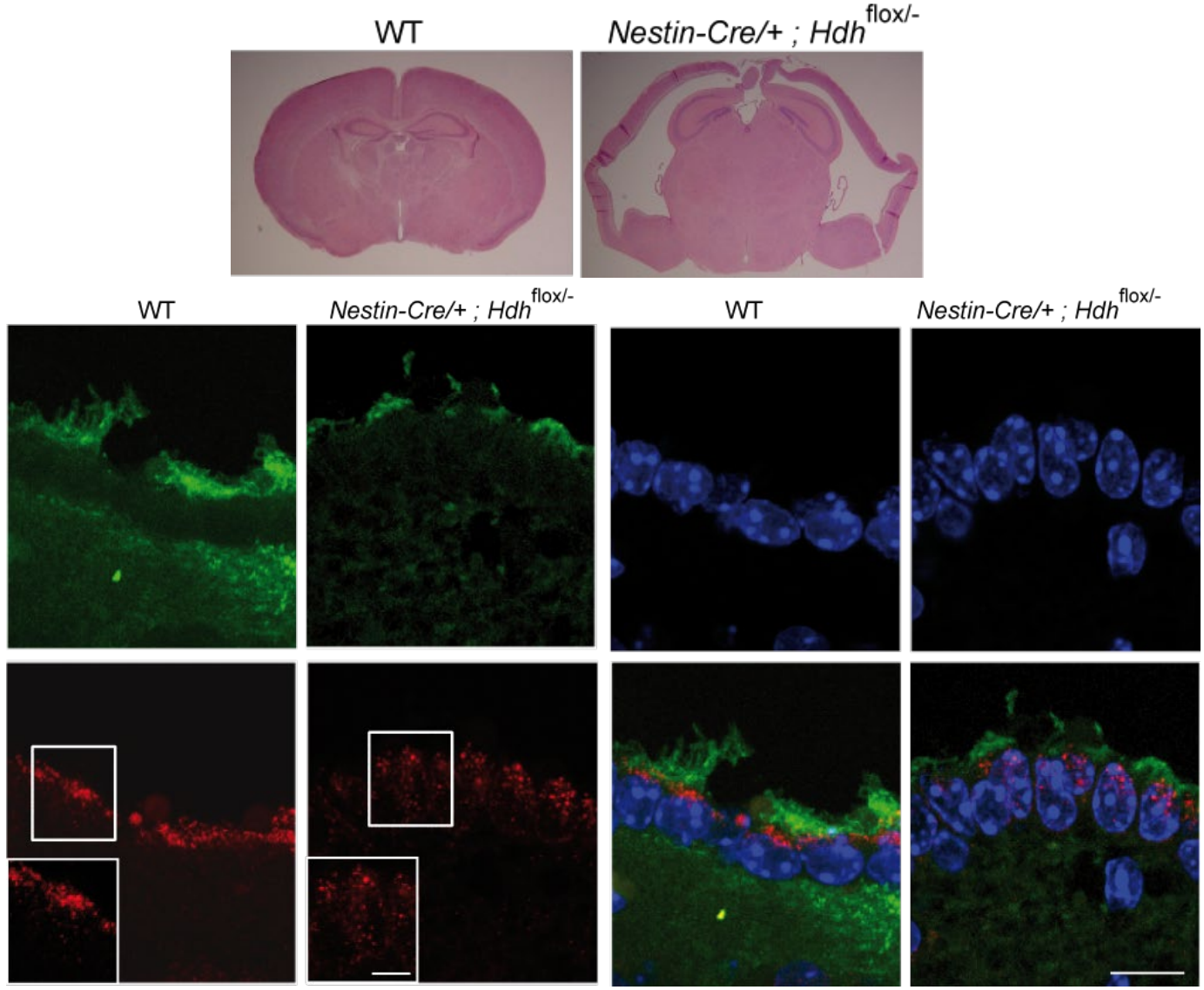
Keryer et al, J Clin Invest 2011, Saudou & Humbert, Neuron 2016

HTT, polyQ HTT and ciliogenesis



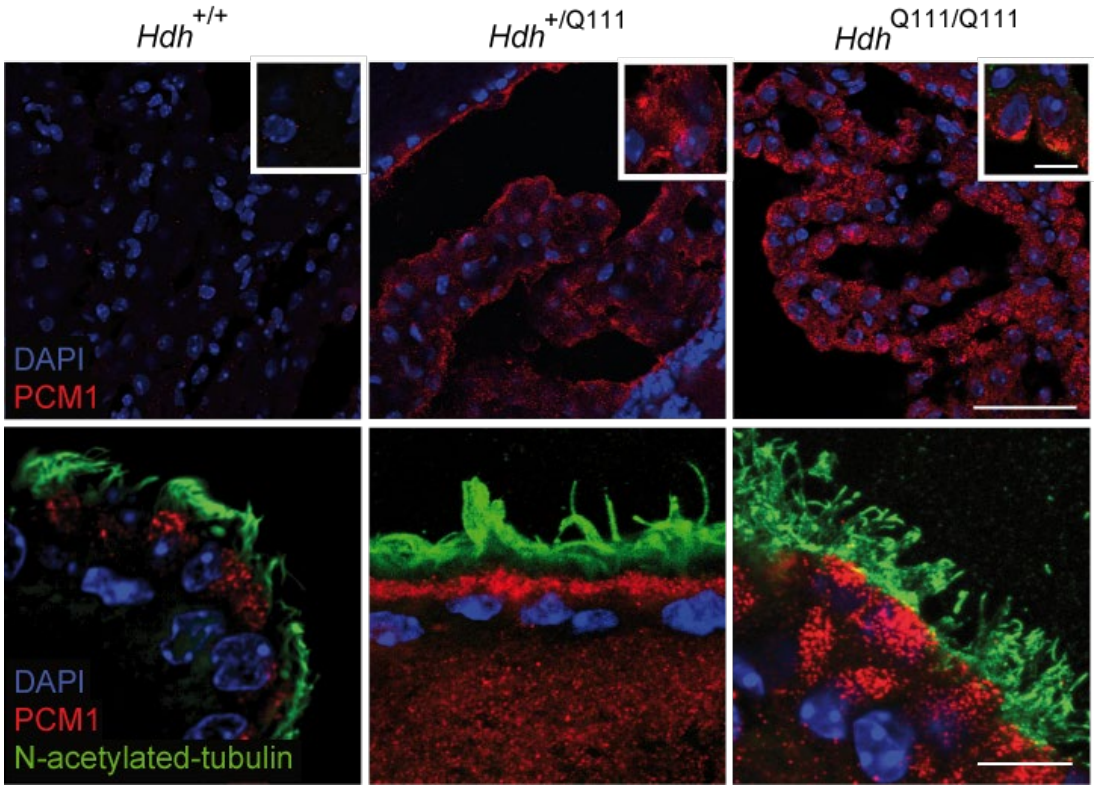
Keryer et al, J Clin Invest 2011, Liu & Zeitlin, JCI, 2011

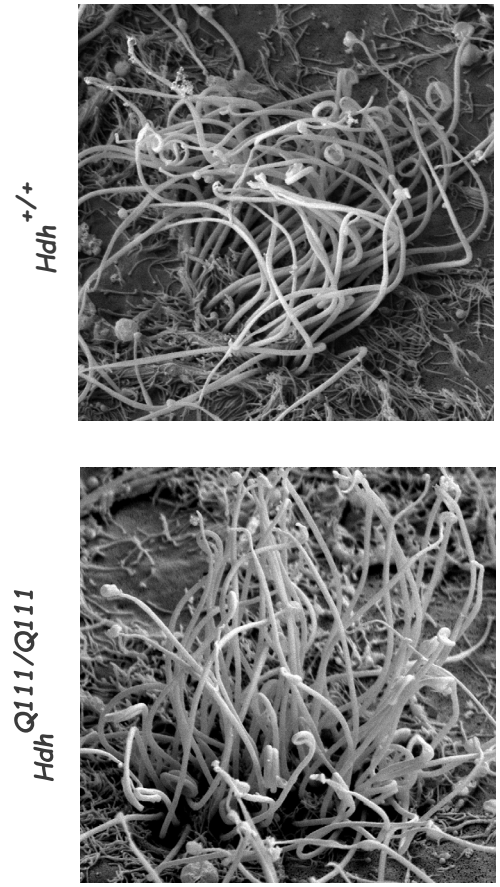
Nestin-Cre;*Hdh*$^{flox/-}$ mice show hydrocephaly, reduced cilia layer and altered PCM1 distribution

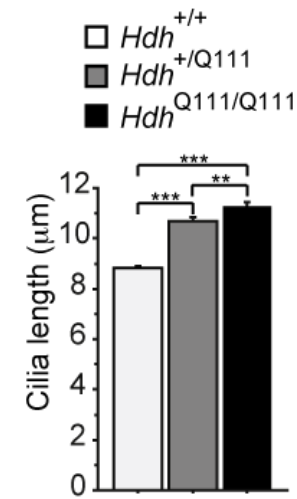


Keryer et al, J Clin Invest 2011

HD mice show PCM1 aggregation and increased ciliogenesis

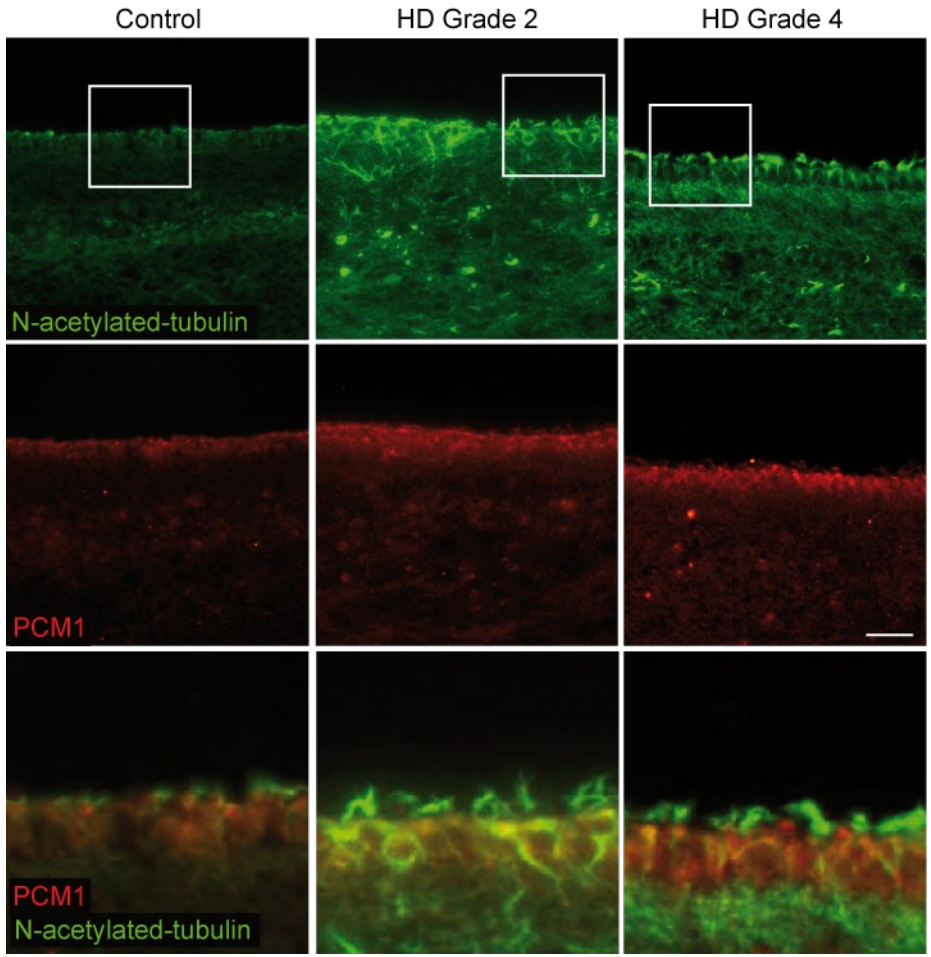


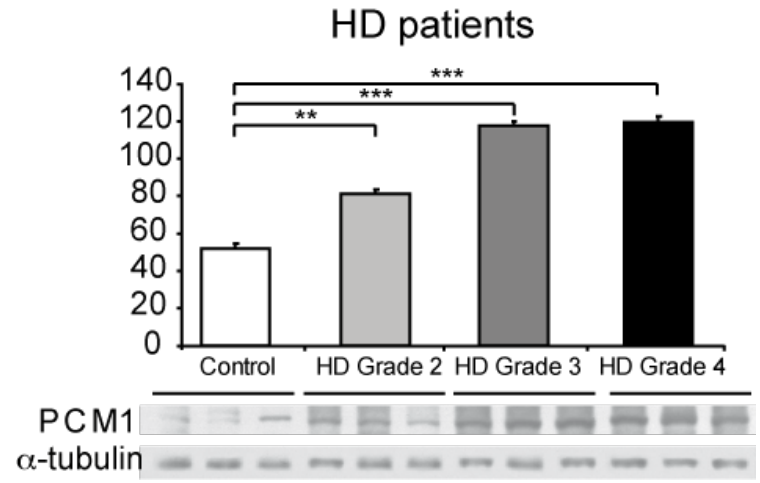




Keryer et al, J Clin Invest 2011

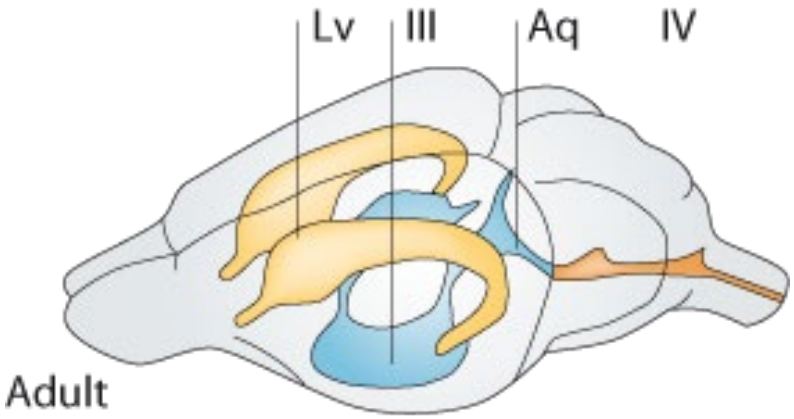
PCM1 accumulates and cilia increase in the ependymal cell layer of HD patients

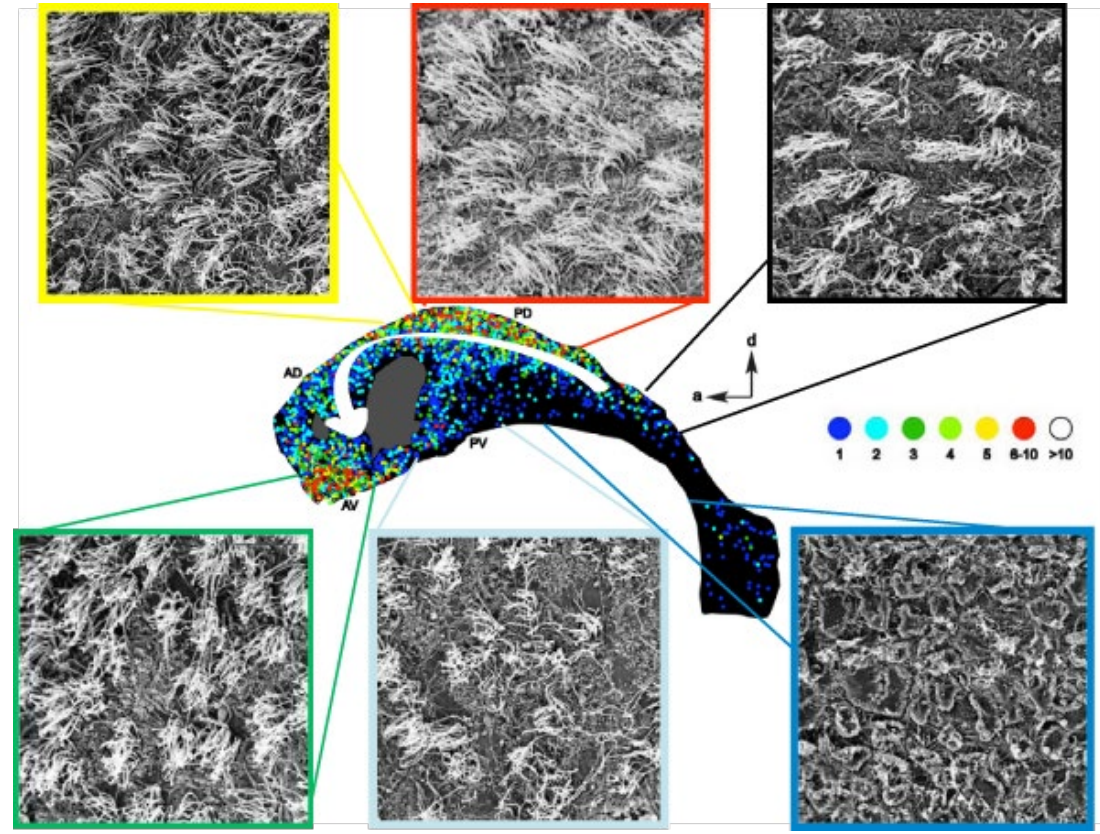




Keryer et al, J Clin Invest 2011

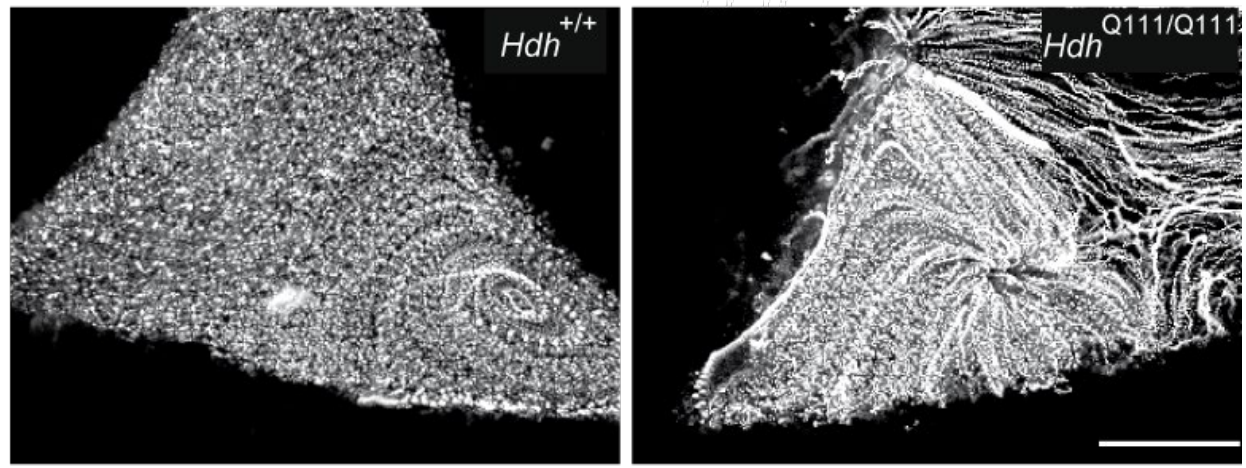
Cilia tufts and cerebrospinal fluid flow in mice

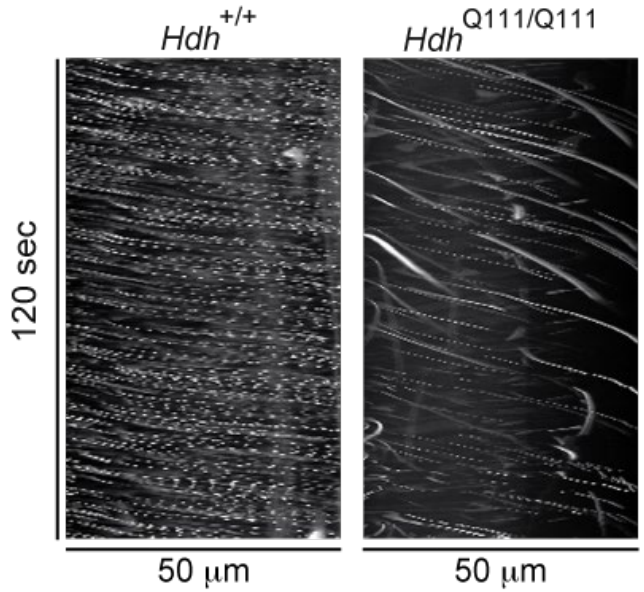


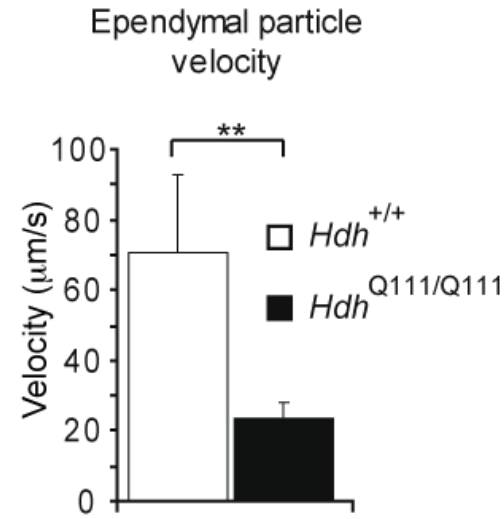


From Fliegauf et al., 2009; Mirzadeh et al., 2010 & N. Spassky

CSF flow is altered in $Hdh^{Q111/Q111}$ mice







Keryer et al, J Clin Invest 2011

Conclusion 2

- Huntingtin function in ciliogenesis is important for CSF circulation and for brain homeostasis

- Huntingtin function in in ciliogenesis is altered in HD

Concluding remarks

- **One protein**

→ Many interactors

→ Many cellular functions

→ Many essential physiological functions

- **All described HTT functions are altered in HD**

→ Understanding HD pathogenesis

→ Identifying new therapeutic targets

→ Restoring or preserving wild type HTT function

- **Is mutant HTT acting as a dominant negative on wild type HTT?**

Grenoble Institut Neurosciences

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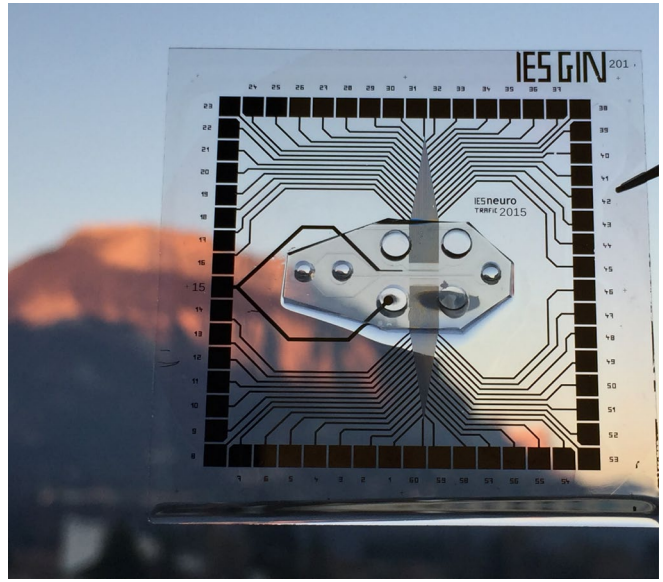

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Reagents and discussions:

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& The Humbert's laboratory

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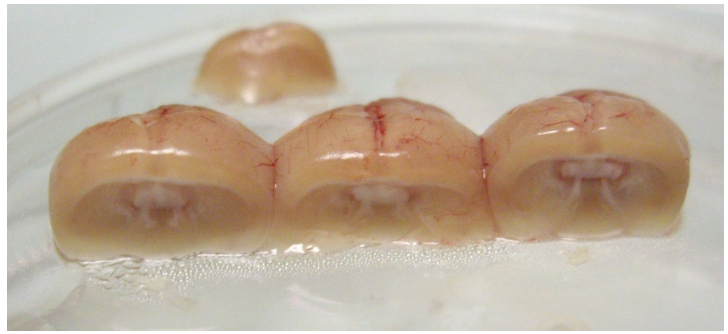
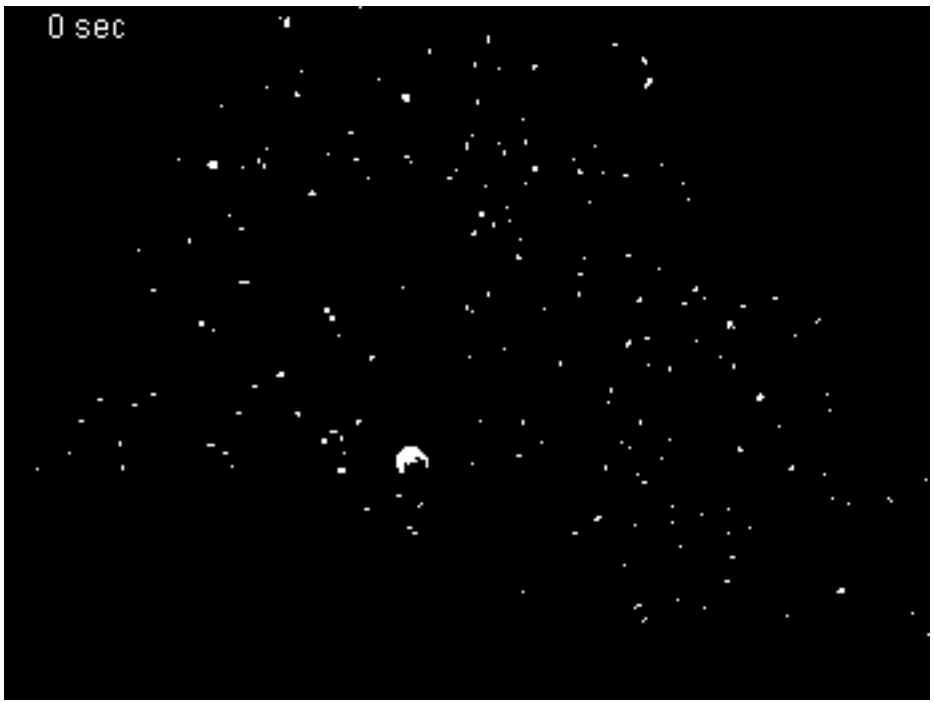
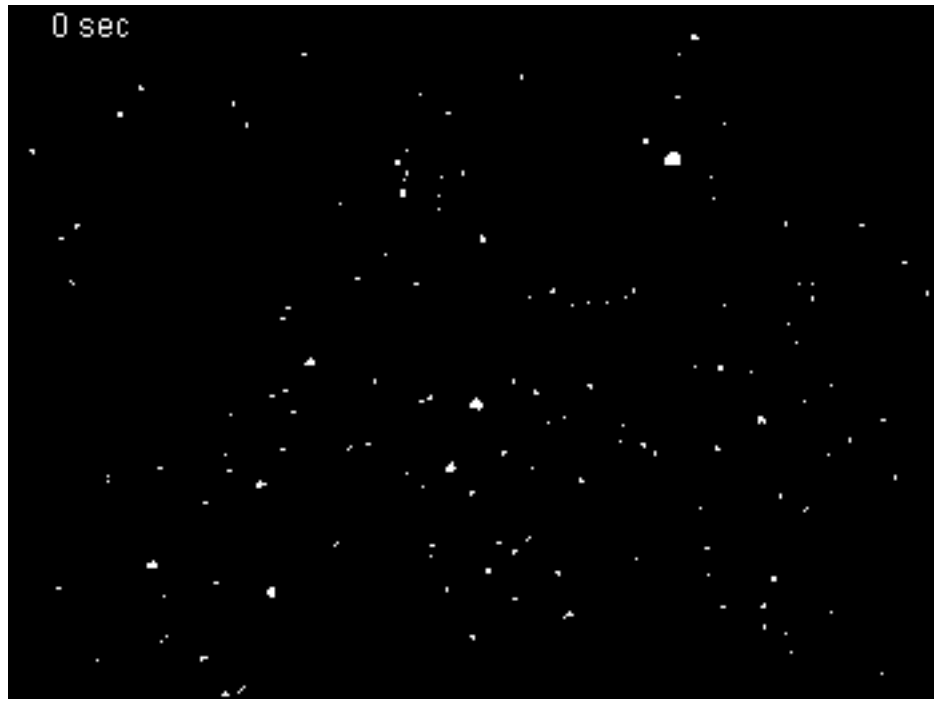
CSF flow is altered in Hdh$^{Q111/Q111}$ mice





Hdh$^{+/+}$ mice



Hdh$^{Q111/Q111}$ mice

Keryer, Pineda et al, J Clin Invest In Press