European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

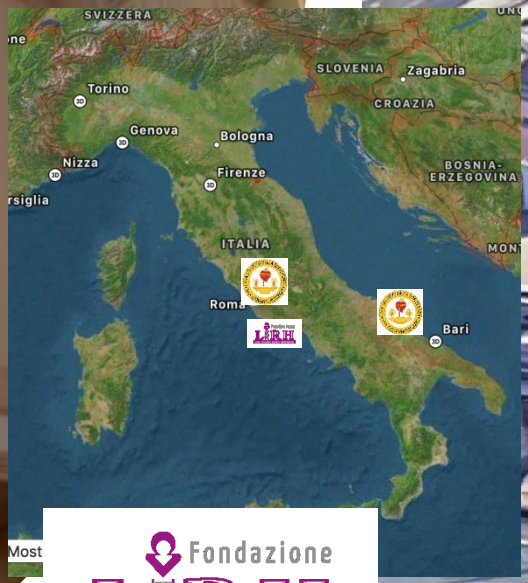
CASA SOLLIEVO DELLA SOFFERENZA • SAN GIOVANNI ROTONDO •

Ferdinando Squitieri

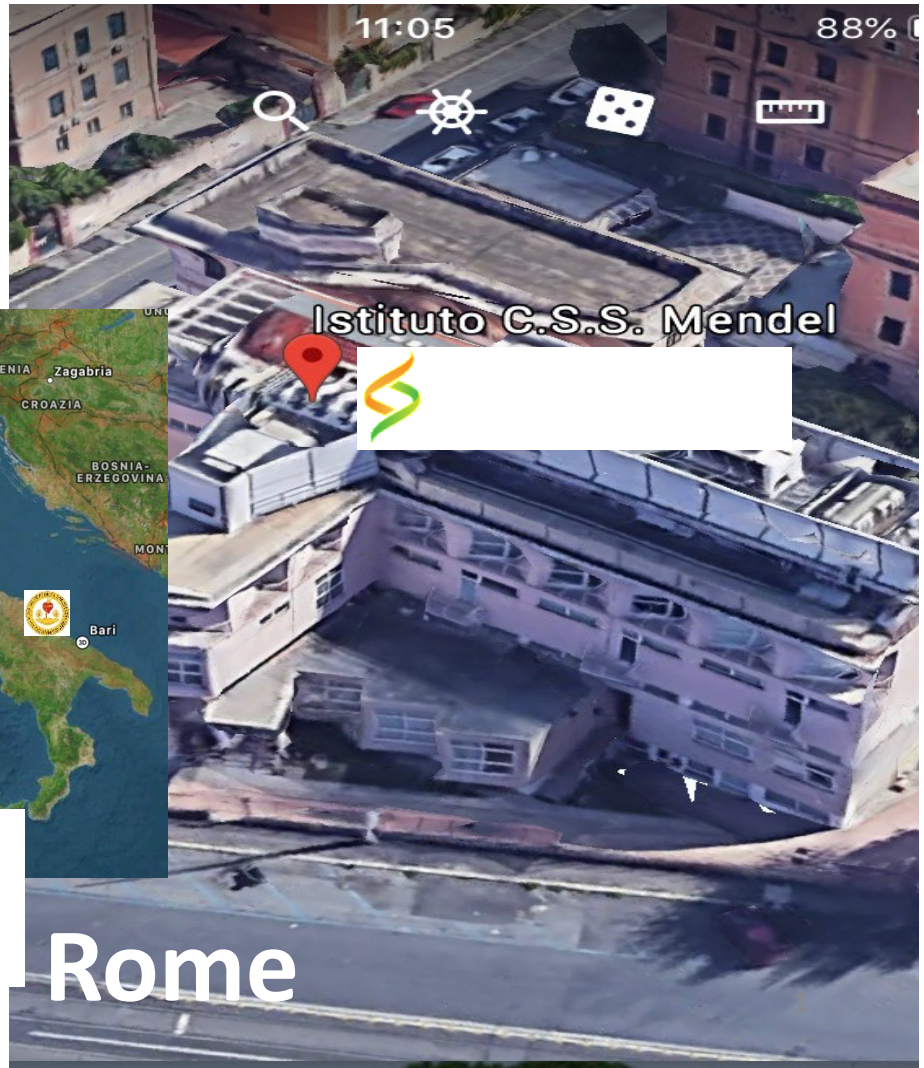
Head of Huntington Centre

Casa Sollievo della Sofferenza Research Hospital

San Giovanni Rotondo



Fondazione LIRH
LEGA ITALIANA RICERCA HUNTINGTON
Enroll-HD



Rome

Webinar outline

Huntington disease (HD)

Quick Overview

- What's HD
- Adulthood HD

Pediatric HD (PHD)

Clinics & Genetics

- Juvenile onset HD
- When HD affects a kid
- Epidemiology
- Clinical features
- Genetics implication

Pediatric HD (PHD)

Future perspectives

- News from research

Learning objectives

Recognize

CLINICS

Understand

GENETICS

Take action

RESEARCH

Q&A 1: Participant's background and previous experience

PARTICIPATNT'S BACKGROUND

a) Adult Neurology?
b) Child Neurology?
c) Psychiatry?
d) Psychology?
e) Biology?
f) Family member?
g) Rehabilitation?
h) Nursery?
i) Clinical & Genetic Counseling

Have you ever met a kid (*i.e. < 18 years old) affected by Huntington disease?**

1) Never
2) Once, as a professional
3) A few times, as a professional
4) Several times, as a professional
5) Yes, as a family member

- Genetic
- Dominant
- Transmission

tingtin gene (HTT) – Chromosome 4p16.3

Normal HTT size

[HD Coll Group, Cell 1993
Kremer et al., NEJM 1994]

xpanded CAG repeat mutation

Mutated HTT gene

From 36 to > 100 repeats

Accumulation

Conformational change

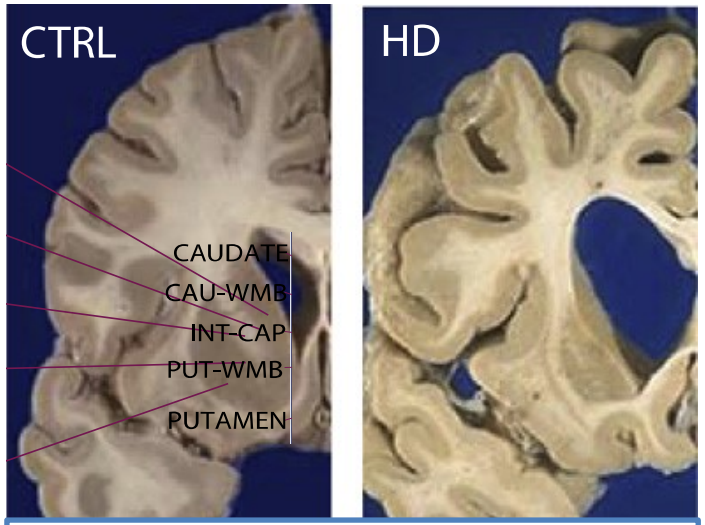
Aberrant Interaction

Many other abnormal effects

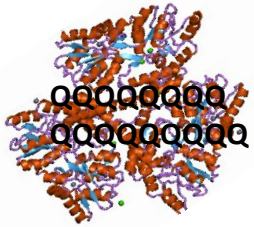
HUNTINGTIN

Protein **MEDIUM SPINY NEURONS**

RTICAL PROJECTION NEURONS



Jean-Paul Vonsattell work since 80'



e have further evidence that other cell opulations are also involved:

- **Astrocytes**
- **Oligodendrocytes**
- **Microglia**
- **Endothelial cells (*BBB*)**
- **Connections**

Cortico-striatal projections

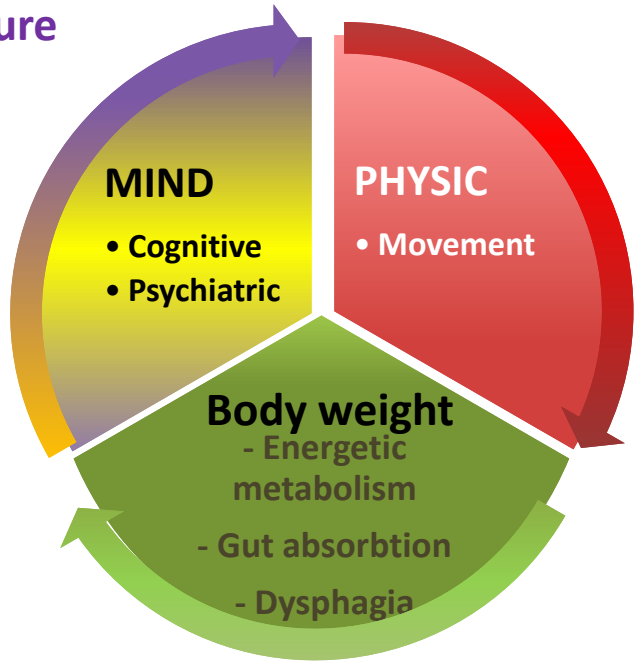
Reviewed in Saudou & Humbert, Neuron 2016

40 – 50 CAG / Usual onset in mid life

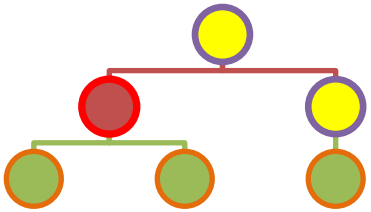
Huntington Disease Paradigm

symptom heterogeneity usually in adulthood

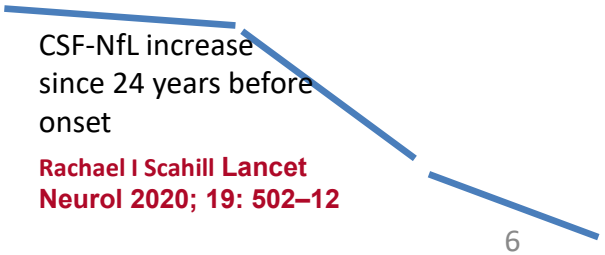
Executive function failure
Memory failure
Dementia
Personality changes
Obsessions
Perseverations
Aggressiveness
Apathy
Depression
Suicide



- **Coordination**
- **Dysarthria**
- **Dysphagia**
- **Gaze impairment**
- **Gait Impairment**
- **Balance**
- **Chorea**
- **Dystonia**
- **Parkinsonism**



Cachexia in the final stage



CSF-NfL increase since 24 years before onset

Rachael I Scahill Lancet Neurol 2020; 19: 502–12

Frequency of HD juveniles

Huntington disease can manifest at any age:

21 years
at the

18 years
on time)

EU and US

pha.net/consor/cgi-
ber 24, 2014].

l., *Mov Disord 2019*

ell dispersed

Shared neurological symptoms by adult and most of JoHD patients'

- Behavioural abnormalities
- Depression and psychosis
- Clumsiness
- Cognitive alteration
- Eye movement abnormalities
- Chorea and tourettisms
- Dysphagia
- Dysarthria
- Memory loss
- Gait disturbances
- Hyperreflexia and Incontinence
- Bradykinesia
- Rigidity
- Dystonia

Weight loss

Additional neurological symptoms manifested by HD kids only

- Autism, severe behavioural changes
- Seizures and myoclonic epilepsy
- Predominant cerebellar features
- Learning problems
- Intellectual developmental delay
- School failure
- Spasticity
- Muscular pain (due to severe dystonia)
- EEG abnormalities

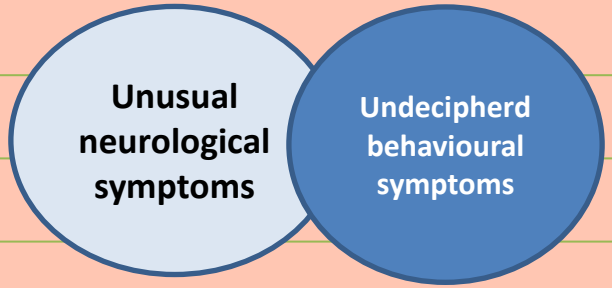
SUBTLE

SOCIALITY

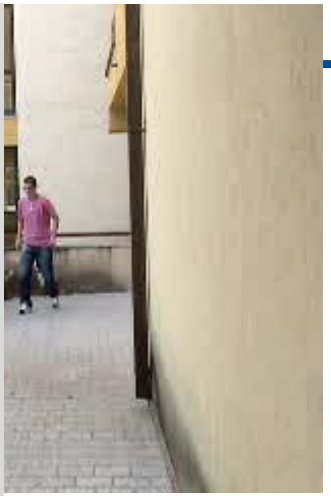
ATYPICAL

STIGMA

Quarrell et al., Managing juvenile HD - Neurodegener Dis Manag 2013



Roger Barker and Ferdinando Squitieri Oxford University Press Book, 2009, Chapter 4: "JHD (and other trinucleotide repeat disorders)"



The dx is hard to confirm by a clinical exam and the genetic test is always a valuable resource, however:

- Large repeat expansions hard to detect (**specialized labs needed**)
- Careful **genealogical analysis** is mandatory
- **Parents unprepared** to accept
- **No genetic test in minors*** with no suggestive signs

Diagnostic criteria for childhood-onset Huntington's disease (< 10 years)

A FAMILY HISTORY OF HUNTINGTON'S DISEASE (USUALLY THE FATHER) AND TWO OR MORE OF:

- **Declining school performance**
- **Seizures**
- Oral motor dysfunction
- Rigidity
- **Gait disturbance**

Nance M, Neurology 1997

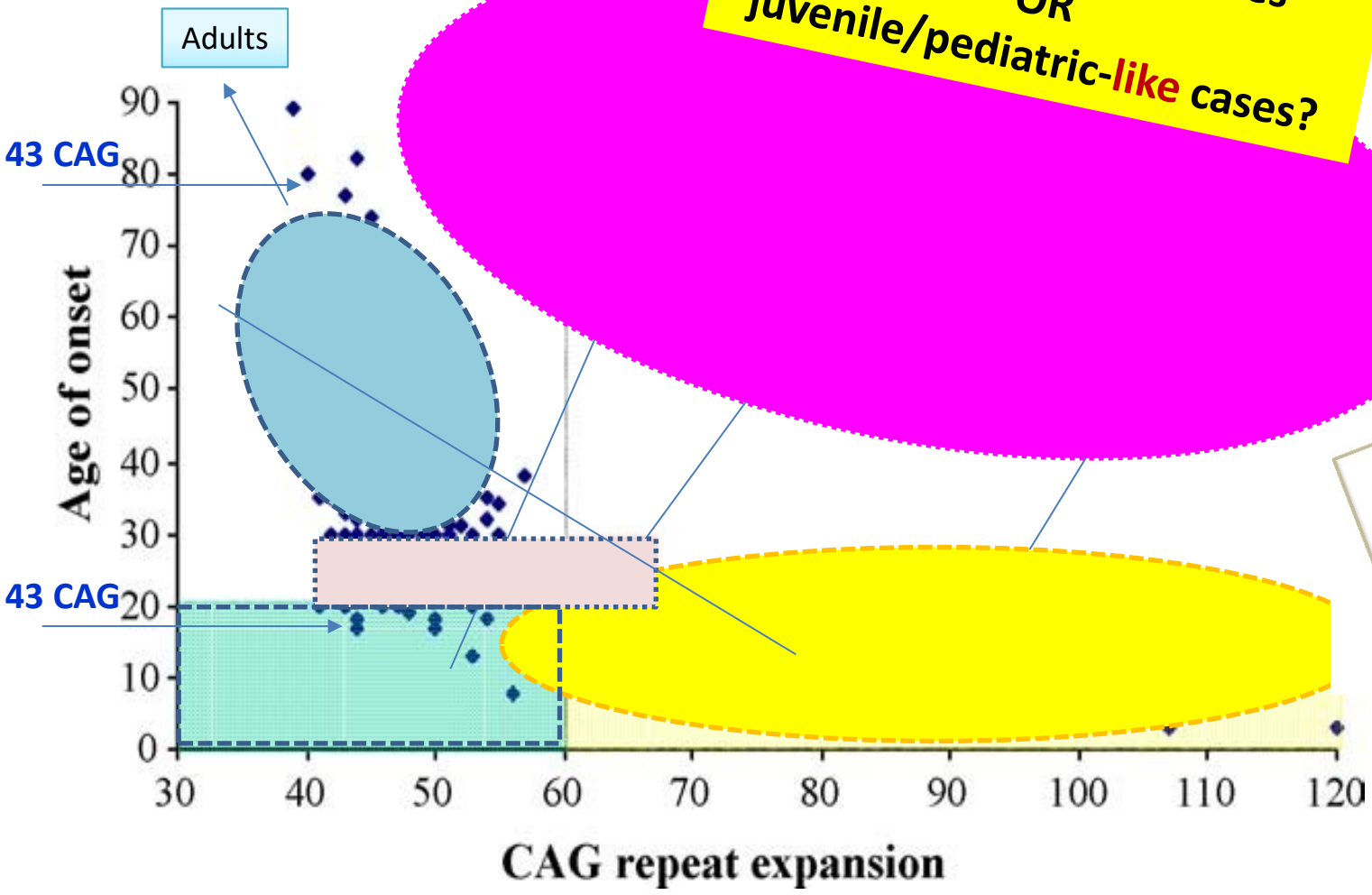
***Koutsis G et al.,** Neurology. (2013); **Anderson J et al.**, Clin Genet. (2015); *Reviewed* in **Migliore, Jankovic, Squitieri**. Front Neurol 2019.

CHALLENGING QUESTION:

Do long mutations always affect kids?

APPARENTLY NOT ALWAYS!

Are all these real juvenile/pediatric cases OR juvenile/pediatric-like cases?



Juveniles as a wide spectrum of colors

Squitieri et al., [modified] 2006

Genetics and Age at Onset Anticipation

RESEARCH ARTICLE

Population-specific genetic modification of Huntington's disease in Venezuela

Michael J. Chao[1,2], Kyung-Hee Kim[1,2], Jun Wan Shin[1,2], Diane Lucente[1,2], Vanessa C. Wheeler[1,2], Hong Li[3], Jared C. Roach[3], Leroy Hood[3], Nancy S. Wexler[4], Laura B. Jardim[5,6], Peter Holmans[7], Lesley Jones[7], Michael Orth[8], Seung Kwak[9], Marcy E. MacDonald[1,2,10], James F. Gusella[1,10,11]*, Jong-Min Lee[1,2,10]*

PLOS Genetics 2017 – Haplotypes may influence earlier age at onset

Molecular analysis of juvenile Huntington disease: the major influence on (CAG) repeat length is the sex of the affected parent

Hum Mol Genet 1993
Aggregation of juvenile cases within HD families - Telenius et al.

IT - Platform

Enroll-HD

Genetics

Environment

Tracing the mutated *HTT* and haplotype of the African ancestor who spread Huntington disease into the Middle East

Ferdinando Squitieri, MD, PhD[1], Tommaso Mazza, PhD[2], Sabrina Maffi, PsyD[1], Alessandro De Luca, PhD[3], Qasem AlSalmi, MD[4], Salma AlHarasi, PhD[4], Jennifer A. Collins, BA[5], Chris Kay, PhD[5], Fiona Baine-Savanhu, PhD[6], Bernard G. Landwhermeyer, MD[7], Umberto Sabatini, MD[8,9] and Michael R. Hayden, MD[5]

Genetics in Medicine 2020 – Haplotypes influencing earlier age at onset are connected with high frequency of juvenile onset cases

Plus a number of gene modifiers and yet unknown environmental causes

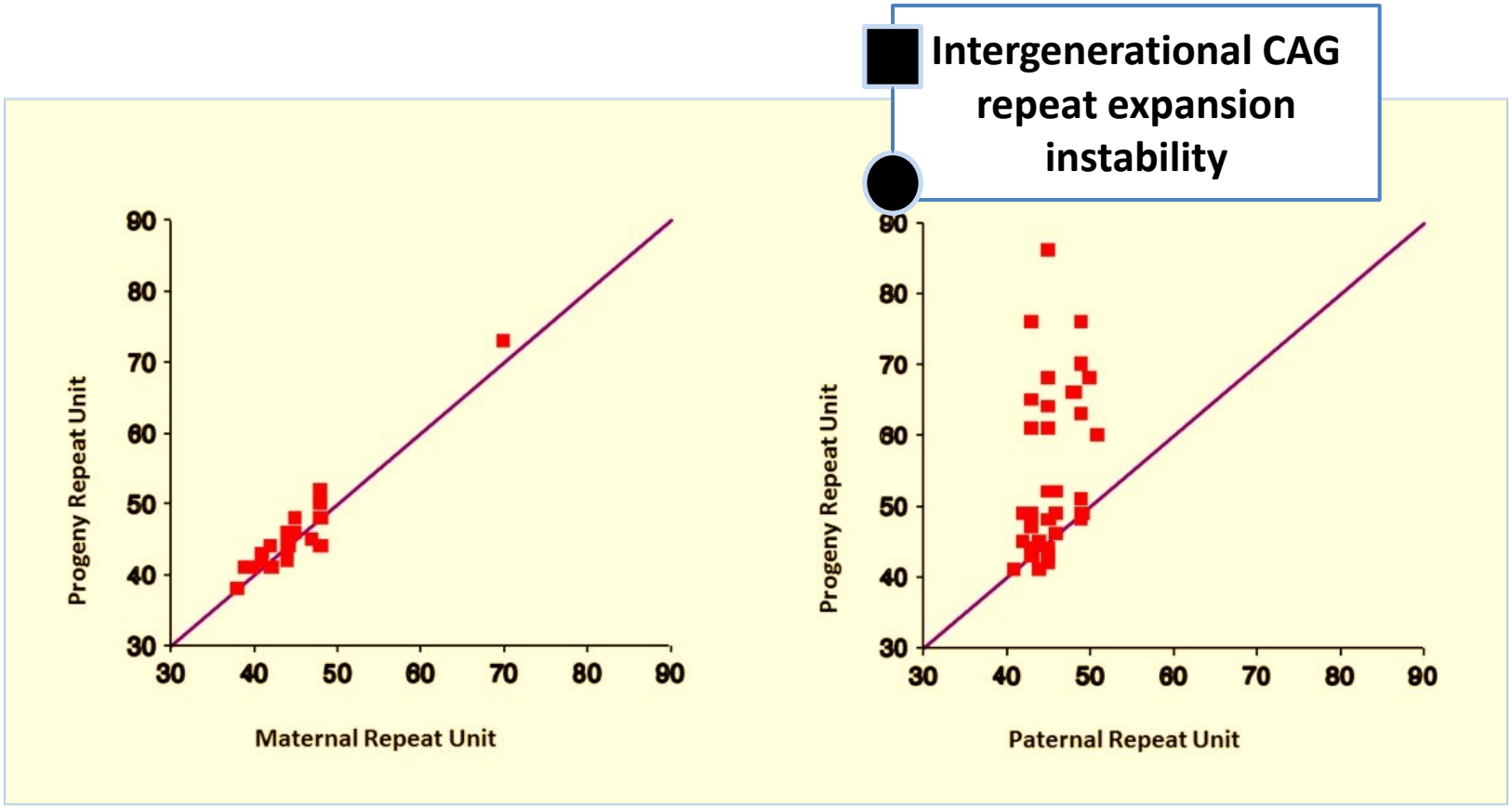
What's the very first and best example of pediatric Huntington disease?

Cell, Vol. 87, 493–506, November 1, 1996, Copyright ©1996 by Cell Press

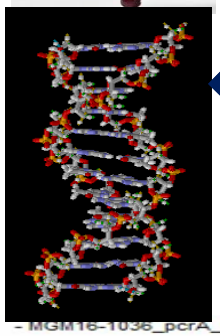
Exon 1 of the *HD* Gene with an Expanded CAG Repeat Is Sufficient to Cause a Progressive Neurological Phenotype in Transgenic Mice

R6/2 transgenic mouse model – Gillian Bates 1996

Long expansions are often a consequence of paternal transmissions

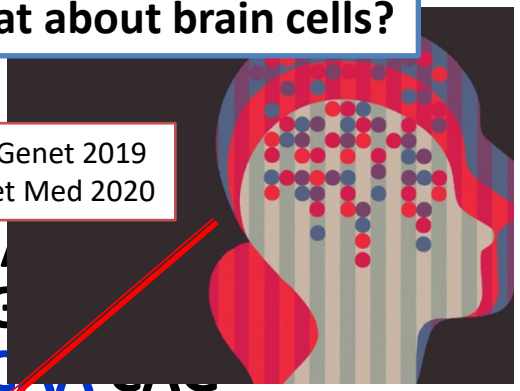


Does the mutation show length variability in cells?



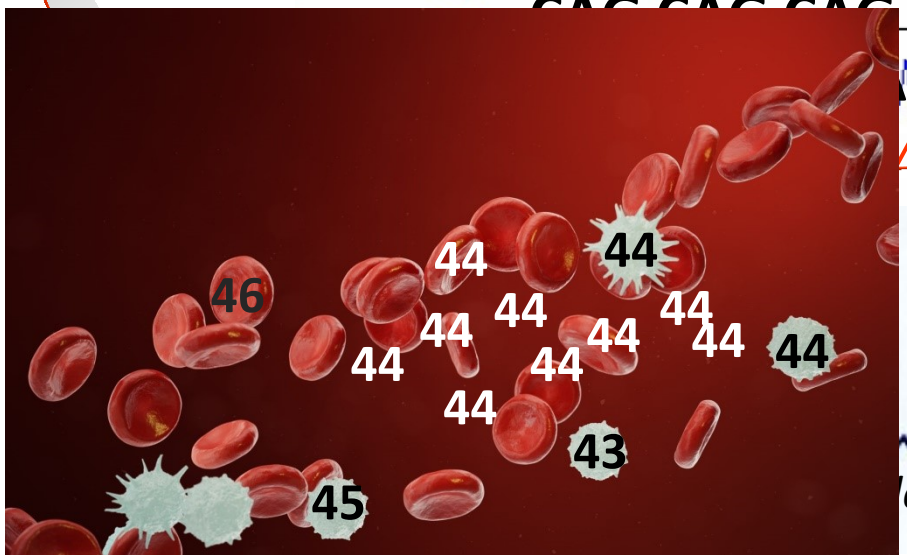
YES! there is variability

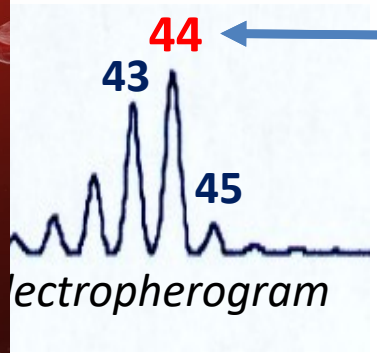
What about brain cells?

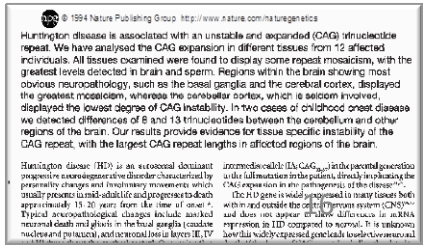


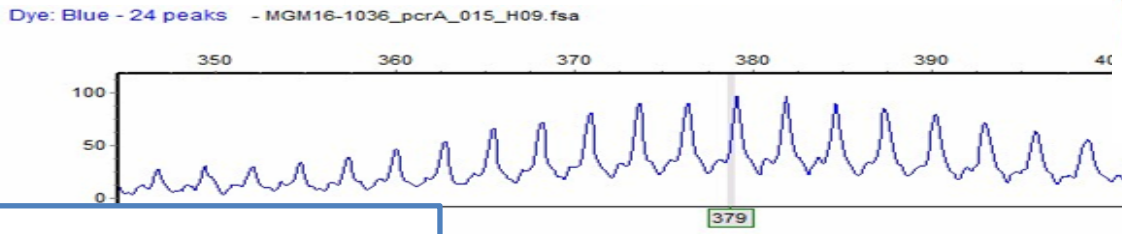
- Wright et al., Am J Hum Genet 2019
- Findlay Black et al., Genet Med 2020

CAG CAG CAG CAG C
CAG CAG CAG CAG CAG
CAG CAG CAG CAG CAG CAA CAG
CAG CAG CAG CAG CAA CAG
G CAG CAA CAG









The number of CAG-repeats may INCREASE in brain regions during life (somatic instability)

The size of somatic expansion in human brain can be staggering

DNA instability in postmitotic neurons

Roman Gonitel*, Hilary Moffitt*, Kirupa Sathasivam*, Ben Woodman*, Peter J. Detloff†, Richard L. M. Faull‡, and Gillian P. Bates*§

*Department of Medical and Molecular Genetics, King's College London School of Medicine, London SE1 9RT, United Kingdom; †Department of Biochemistry and Molecular ... iversity of Alabama at Birmingham, Birmingham, AL 35294; and ‡Department of Anatomy with Radiology, ...ersity of Auckland, Private Bag 92019, Auckland, New Zealand

...husetts Institute of Technology, Cambridge, MA, January 3, 2008 (received for review December 10, 2007)

...y a CAG repeat expansion ...nission and exhibits mosa- ...region-specific CAG repeat

Therefore, CAG repeat mosaicism in neuronal populatio... dentato-rubral pallido-luysian atrophy and HD postmo... brains has been shown, but, crucially, it has not been establi...

Human Molecular Genetics, 2003, Vol. 12, No. 24 *3359–3367*
DOI: 10.1093/hmg/ddg352

...lishing Group http://www.nature.com/naturegenetics

We have generated mice transgenic for a 1.9-kb genomic fragment encompassing the 5′ end of the HD gene[26]. The fragment includes exon 1 containing the CAG repeat flanked by approximately 1 kb of upstream sequences and 262 bp of intron 1. We established 4 transgenic lines (R6/0, R6/1, R6/2 and R6/5) from a chimaeric founder. We analysed the size of the CAG repeat in F1 progeny (Fig 1a). Transgenes R6/1, R6/2 and R6/5 are

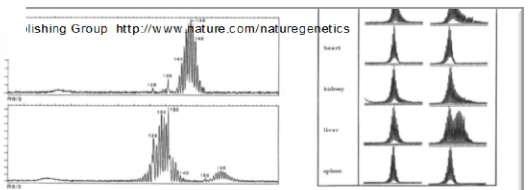


Fig. 1 a, Genescan traces of the CAG repeat in the R6 transgenic lines. Repeat size was estimated in tail DNA taken at approximately 3 weeks of age. The upper panel contains the trace corresponding to the R6 founder

Dramatic tissue-specific mutation length increases are an early molecular event in Huntington disease pathogenesis

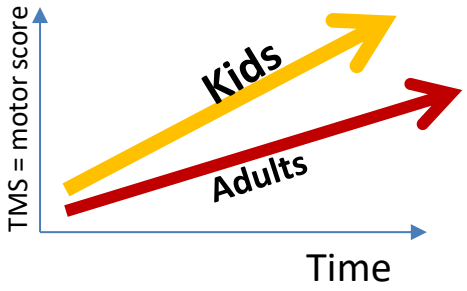
Laura Kennedy[1], Elizabeth Evans[1], Chiung-Mei Chen[1], Lyndsey Craven[1], Peter J. Detloff[2], Margaret Ennis[1] and Peggy F. Shelbourne[1,*]

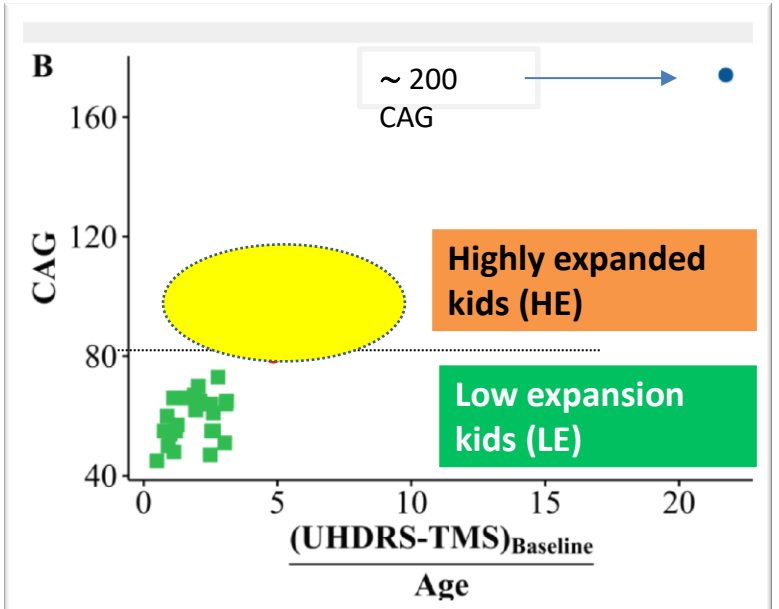
1000 CAG repeats

Fusilli et al., Lancet Neurology Nov;17(11):986-993 ***2018***

When HD kids get a Highly Expanded (HE) mutation, they manifest differently:

- Psychic and motor **developmental delay**
- Early and progressive **gait disturbance**
- Progressive **dystonia with no chorea**
- Increased frequency of **seizures**



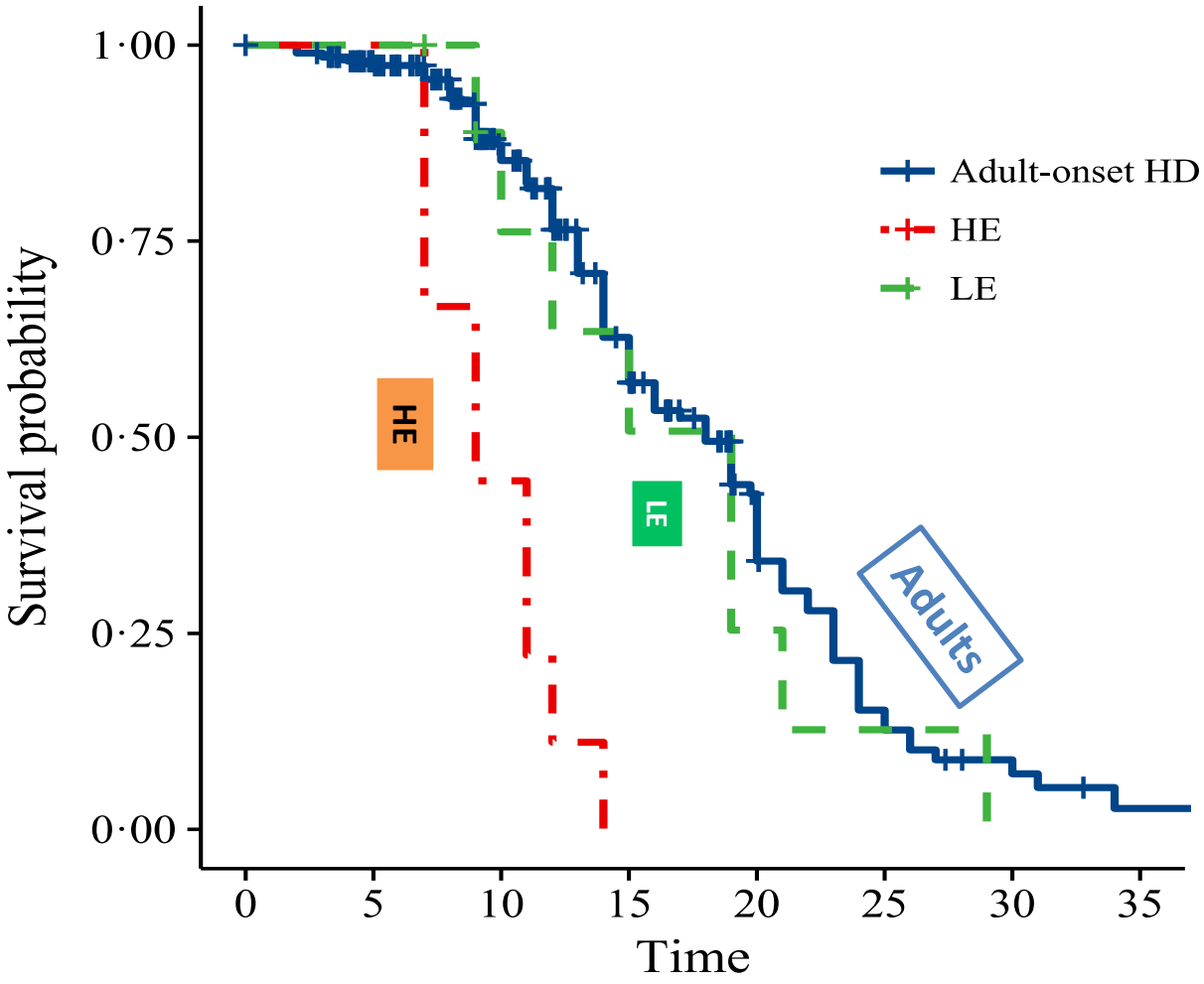


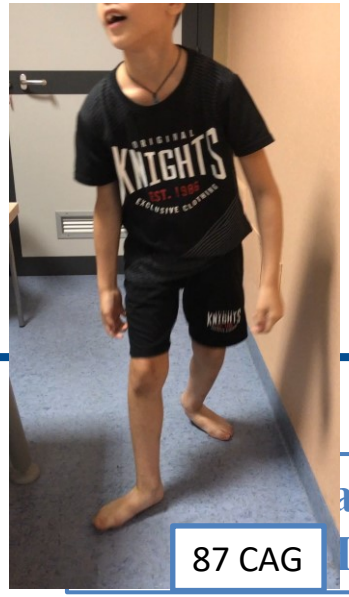
Kids show severe Huntington disease progression severity and reduced lifespan

Fusilli et al., Lancet Neurology Nov;17(11):986-993 ***2018***

B

Chi-Square = 32·74; DF = 2; P < 0·0001





87 CAG

ain manifestations occurring
IE or in JHD-LE subjects overtime

Gait disturb	Chorea	Devel delay	Obsess Behav.	Seizure
HE	LE	HE	LE	HE
90%	35%	90%	73%	80%

80 CAG

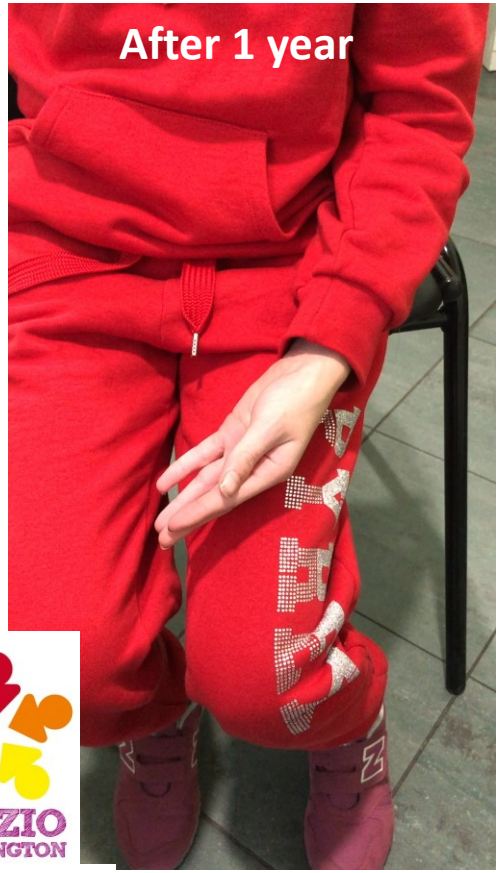
HE = symptomatic Kids with very large mutations above 80 CAG repeats

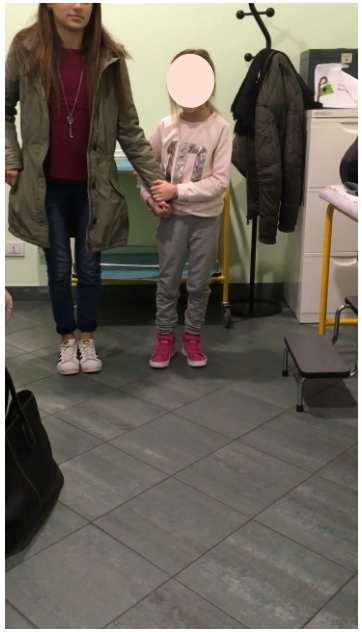
LE = symptomatic Kids with mutations like in adult patients

Fusilli et al., Lancet Neurology Nov;17(11):986-993 ***2018***

Video 3 PHD

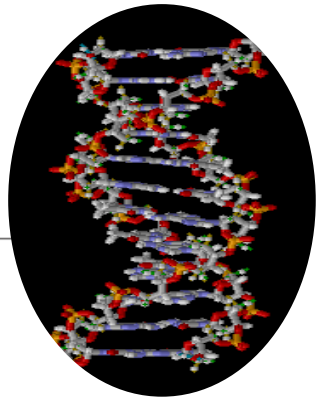
Tracking *Pediatric* Huntington disease Longitudinally





After 1 year

The mutation length affects clinical presentation in kids with "other CAG diseases"

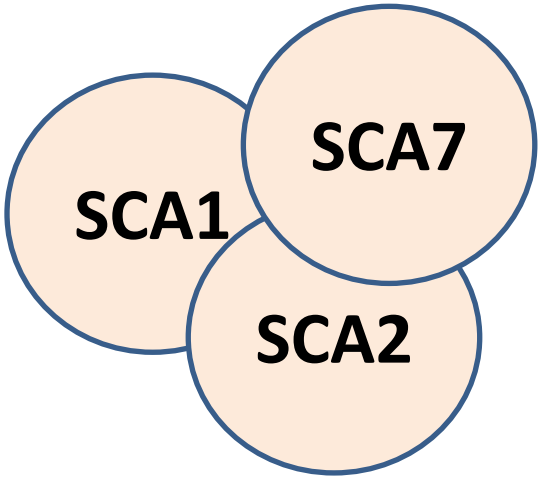


ORIGINAL ARTICLE

Eur J Neurol 2020

Deciphering the natural history of SCA7 in children

M. G. Bah[a], D. Rodriguez[b], C. Cazeneuve[a], F. Mochel[c], D. Devos[d], A. Suppiej[e,f], A. Roubertie[g,h], I. Meunier[g], C. Gitiaux[i], A. Curie[j], F. Klapczynski[k], N. Allani-Essid[l], M. Carneiro[j], R. Van Minkelen[m], A. Kievit[m], J. Fluss[n], B. Leheup[o], L. Ratbi[p], D. Heron[a], D. Gras[q], J. Do Cao[q], S. Pichard[q], I. Strubi-Villaume[r], I. Audo[s,t], G. Lesca[u], P. Charles[a], F. Dubois[v], P. Comet-Didierjean[h], Y. Capri[w], C. Barondiot[x], M. Barathon[y], C. Ewenczyk[a], A. Durr[c] and C. Mignot[a]



Observation is a fundamental starting point

By playing with them, we may perform the same motor exams of adults and collect data

[Example of an ongoing UHDRS-Total Motor Score]

Combination of neurological, behavioural and non neurological symptoms are possible (e.g. weight loss)

SCIENTIFIC REPORTS

OPEN

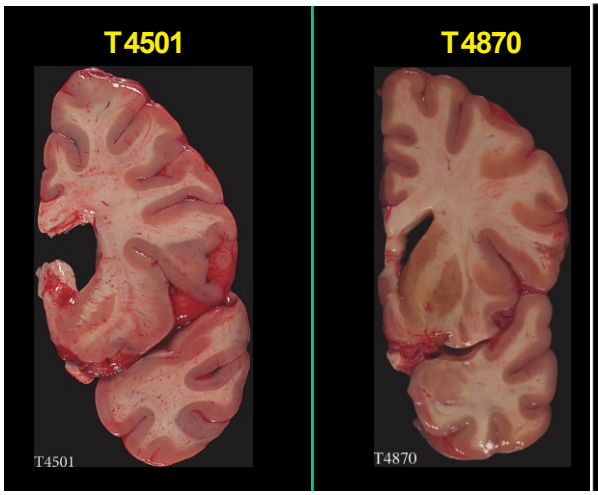
Peripheral Expression of Mutant Huntingtin is a Critical Determinant of Weight Loss and Metabolic Disturbances in Huntington's Disease

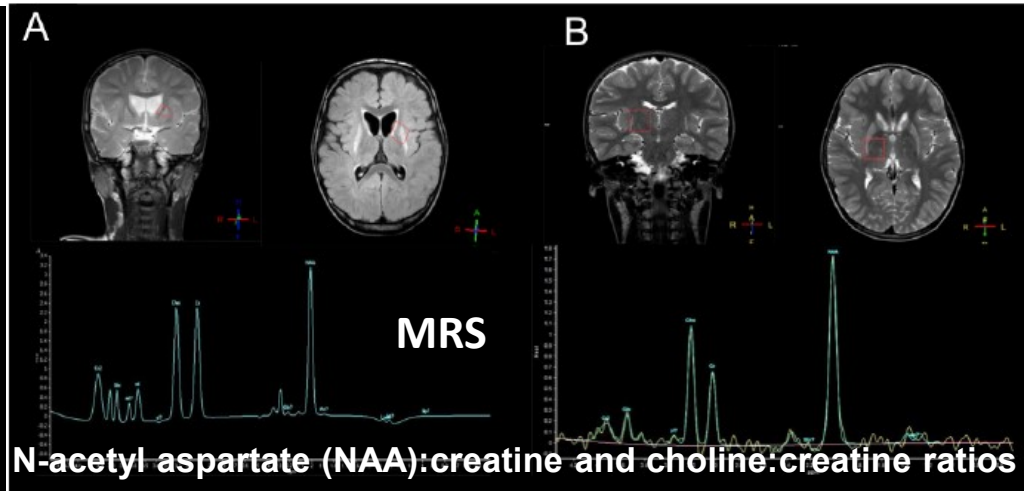
J Huntington dis

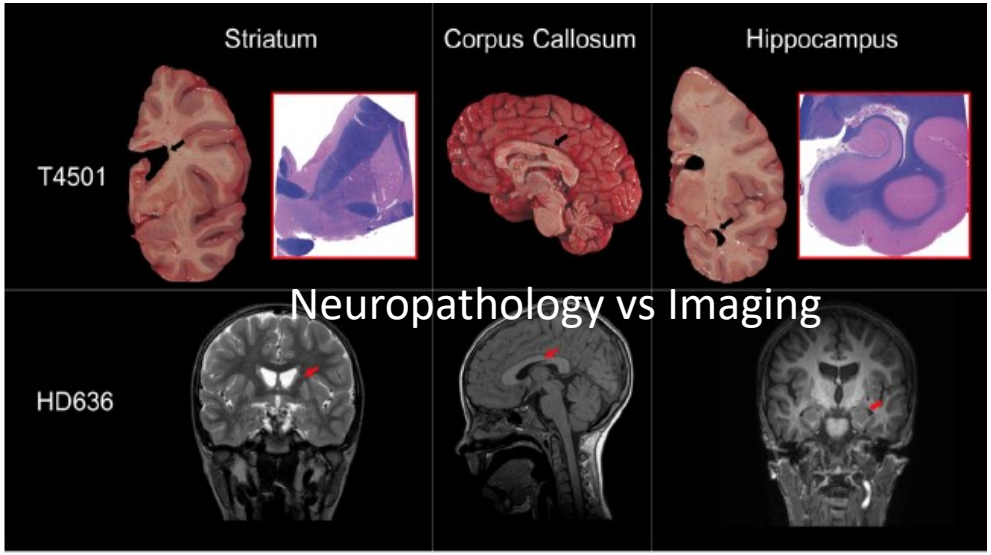
Abnormal Weight and Body Mass Index in Children with Juvenile Huntington's Disease Tereschchenko et al 2015

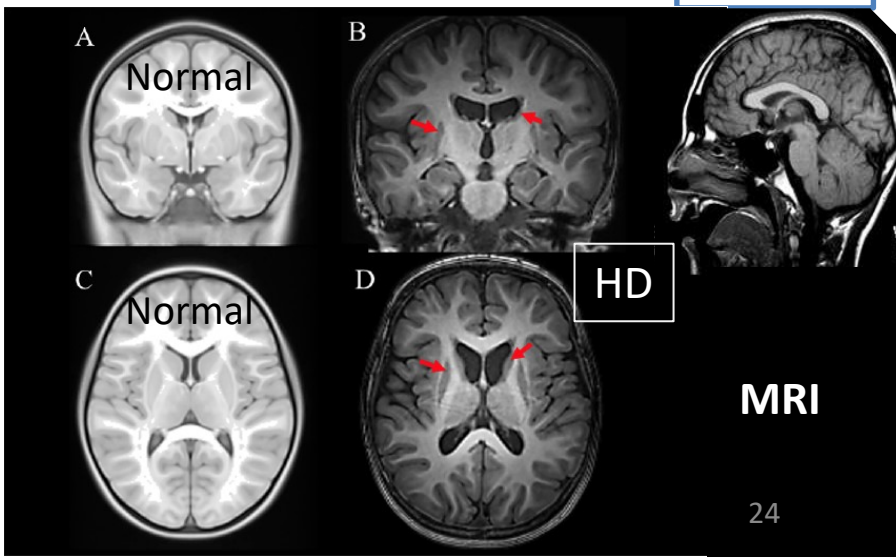
Brain changes in kids

Fusilli et al., Lancet Neurology Nov;17(11):986-993 ***2018***









Brain changes in kids

Lancet Neurology Nov;17(11):986-993 ***2018***

Biological and clinical manifestations of juvenile Huntington's disease: a retrospective analysis

Caterina Fusilli, Simone Migliore, Tommaso Mazza, Federica Consoli, Alessandro De Luca, Gaetano Barbagallo, Andrea Ciammola, Emilia Mabel Gatto, Martin Cesarini, Jose Luis Etcheverry, Virginia Parisi, Musallam Al-Oraimi, Salma Al-Harrasi, Qasem Al-Salmi, Massimo Marano, Jean-Paul Gerard Vonsattel, Umberto Sabatini, Georg Bernhard Landwehrmeyer, Ferdinando Squitieri

Correspondence
Dr Squitieri
f.squitieri@css-mendel.it

ARTICLE OPEN ACCESS

Brain structure in juvenile-onset Huntington disease

Alexander Tereshchenko, BS, Vincent Magnotta, PhD, Eric Epping, MD, PhD, Katherine Mathews, MD, Patricia Espe-Pfeifer, PhD, Erin Martin, DO, Jeffrey Dawson, ScD, Wenzhen Duan, MD, PhD, and Peg Nopoulos, MD

Correspondence
Dr. Nopoulos
peggy-nopoulos@uiowa.edu

Neurology® 2019;92:e1-e9. doi:10.1212/WNL.0000000000007355

Concurrent mechanisms

Neural

Dysfunction

+

Degeneration

Neuro Developmental delay

Nat Neurosci. 2017 May ; 20(5): 648–660. doi:10.1038/nn.4532.

Developmental alterations in Huntington's disease neural cells and pharmacological rescue in cells and mice

The HD iPSC Consortium*

and synaptic pathology in HD model R6/2 mice. These data suggest that mutant huntingtin impairs neurodevelopmental pathways that could disrupt synaptic homeostasis and increase vulnerability to the pathologic consequence of expanded polyglutamine repeats over time.

Evidence from human HD tissues from fetuses

Science

RESEARCH ARTICLES

Cite as: M. Barnat *et al.*, *Science* 10.1126/science.aax3338 (2020).

Huntington's disease alters human neurodevelopment

Monia Barnat[1], Mariacristina Capizzi[1*], Esther Aparicio[1*], Susana Boluda[2], Doris Wennagel[1], Radhia Kacher[1], Rayane Kassem[1], Sophie Lenoir[1], Fabienne Agasse[1], Barbara Y. Braz[1], Jeh-Ping Liu[3], Julien Ighil[4], Aude Tessier[5], Scott O. Zeitlin[3], Charles Duyckaerts[2], Marc Dommergues[4], Alexandra Durr[6†], Sandrine Humbert[1†]

Mislocalization of mutant huntingtin and junctional complex proteins

Defects in neuroprogenitor cell polarity and **differentiation**

Changes in **mitosis** and **cell cycle** progression

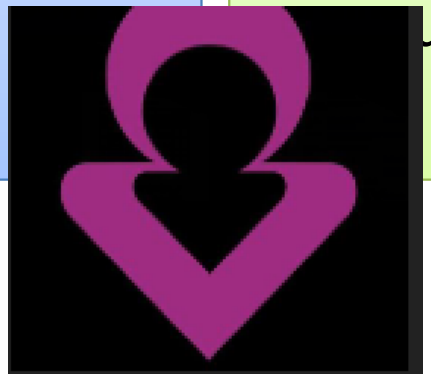
Same phenomena observed in several HD mouse models.

Final remarks: *Having said all this... what we can do if we meet a kid with HD?*

Clinical support: Multidisciplinary management according to the HD phase

Social support: address the family to the HD organizations

unity



Scientific support: To enhance knowledge by improving and supporting observation (biomarkers needed)

Enroll-HD

OUR MAIN AIMS:

To include HD kids in clinical trials*

Look at HD kids as heroes that may help us to shed light on the mystery of HD

…and not as just the neglected and rarest variant of a rare, still uncurable, disorder

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Commentary

Raising Awareness of Therapeutic Misconception and Optimism Around Clinical Trials in Huntington's Disease

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* *EMA - PEDIATRIC INVESTIGATION PLAN (PIP):* ***Revocation of the waiver*** *for all medicines for treatment of Huntington chorea*

Conclusions

HD may affect kids

Clinical presentation in kids is very different from adults

Brain pathology in kids is also different from adults

Stronger research efforts on PHD are needed

Cooperation among researchers, HD families and pharma is crucial

Q&A 2:

If a child with a risk of HD (i.e. with a parent affected by HD) shows the autistic spectrum disorder, what is the clinical exam you would perform in the first place?

a) Neurological exam
b) Cognitive assessment
c) Magnetic Resonance Imaging
d) Genetic test

Q&A 3:

Which one/s, among the following, is/are the main clinical manifestation of PHD?

a) **Declining school performance**
b) **Seizures**
c) **Choreic movements**
d) **Gait impairment**

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Joint webinar series

THANK YOU

Next Webinar: ‘How can we develop and implement evidence based rehabilitation in rare disorders?‘
29. September 2020, 15-16h CET