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Webinar

‘Brain Development in Huntington’s Disease’

by Peggy Nopoulos

Carver College of Medicine, University of Iowa, USA

8. March 2022

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Learning objectives

- By the end of this webinar you will be able to:
  - Understand genetic and clinical features of Huntington‘s Disease
  - Describe the effects of the mutant gene on brain development
  - Distinguish clinical features of Adult Onset Huntington‘s (AOHD) and Juvenile Onset Huntington‘s (JOHD)
  - Appreciate the diagnostic challenge for JOHD

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- Huntington's Disease (HD) Basics
- Genetics
  - DNA basics and the HD gene
  - CAG repeat length and age of onset
  - Anticipation
- Pathophysiology
  - Growth and development of the striatum
- Juvenile Onset Huntington's Disease (JOHD)
  - Clinical Features
  - The Diagnostic Challenge

Question #1

- What is your professional background?
  - Neurologist
  - Neuropediatrician
  - Psychiatrist
  - Psychologist
  - Nurse
  - Physiotherapist
  - Geneticist
  - Patient or Family representative
  - Trainee / student

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Huntington‘s Disease Basics

- Fatal, neurodegenerative brain disease
- Prevalence roughly 7 per 100,000
- **SINGLE GENE**, autosomal dominant
  - Each child of a parent with HD has a 50% chance of inheritance
- Triad of Symptoms
  - Motor – hyperkinesis early, hypokinesis later
  - Cognitive – progression to dementia in all patients
  - Psychiatric – mood instability / agitation / aggression

Huntington‘s Disease Basics

- Mean duration of illness = 15 years
- Currently, diagnosis of ‘disease onset’ is defined by ‘significant motor symptoms’
  - However, cognitive and psychiatric symptoms often precede motor symptoms (sometimes by many years)

Huntington‘s Disease Basics

- Romancing a single gene disorder
  - One gene = promise for ‘cure’ with gene therapy
  - Hope and reality
    - In March of 2021, the first gene therapy trial for HD *failed*
    - There continues to be a tremendous amount of research being done

Question #2

- The course of motor symptoms in HD is?
  a. Hypokinesis then hyperkinesis
  b. Hyperkinesis then hypokinesis
  c. Chorea, then tics

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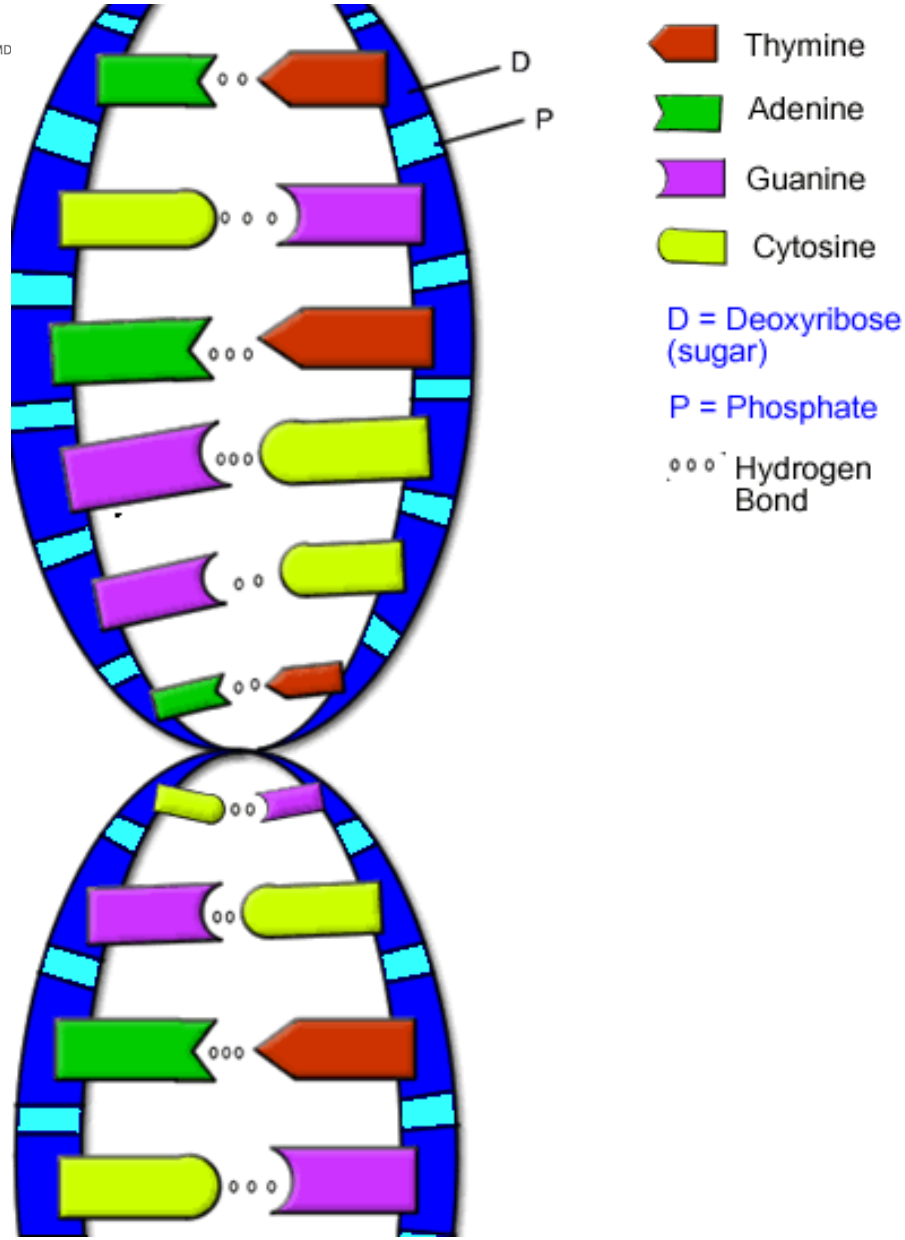
Anatomy of DNA

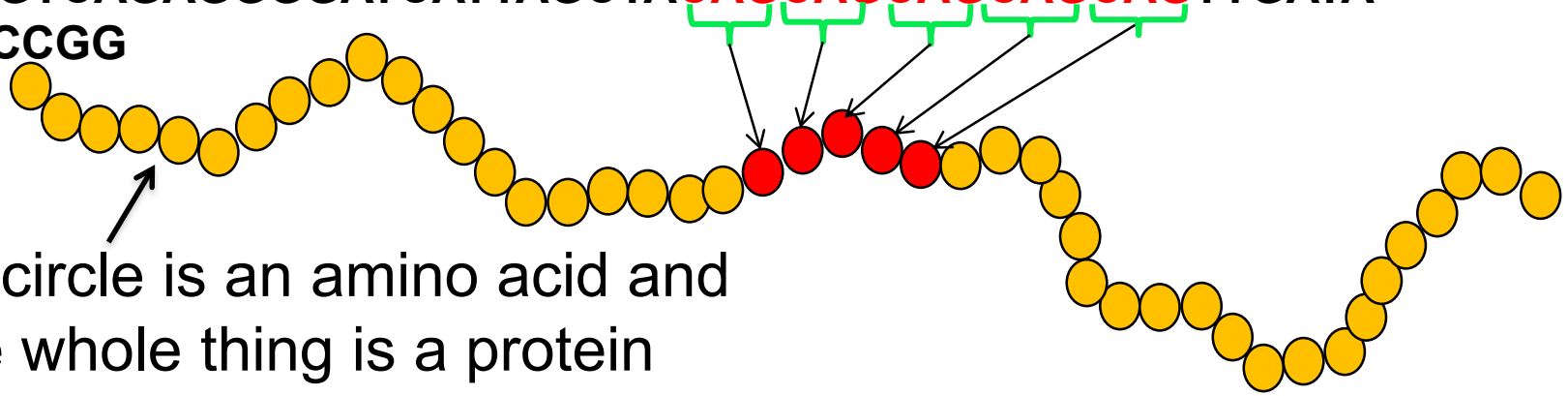
- **DNA is the code for genes**
  - **Code is made up of 4 nucleotides**
    - **Thymine**
    - **Adenine**
    - **Guanine**
    - **Cytosine**
- **Example of a code for a gene:**

  TTACGCCTAACTC



Gene to Protein

- Three nucleotides make up an amino acid; CAG = Glutamine
- Strings of amino acids make up a protein
- The Huntington Gene is called Huntingtin (*HTT*)
  - Has a section where 3 nucleotides are repeated = trinucleotide repeat or 'triplet' repeat.
  - Every human has these repeats (average repeat around 18)
  - GGTCAGAGGGGATCATTAGCTACAGCAGCAGCAGCAGTTGATATCCGG



Each circle is an amino acid and the whole thing is a protein

Huntingtin *(HTT)*

- When the CAG repeat is 40 or greater, the gene is called mutant *HTT* or *mHTT*
  - *At 40 repeats, mHTT is fully penetrant for disease*
  - *Average age of onset of HD = 40 years of age*

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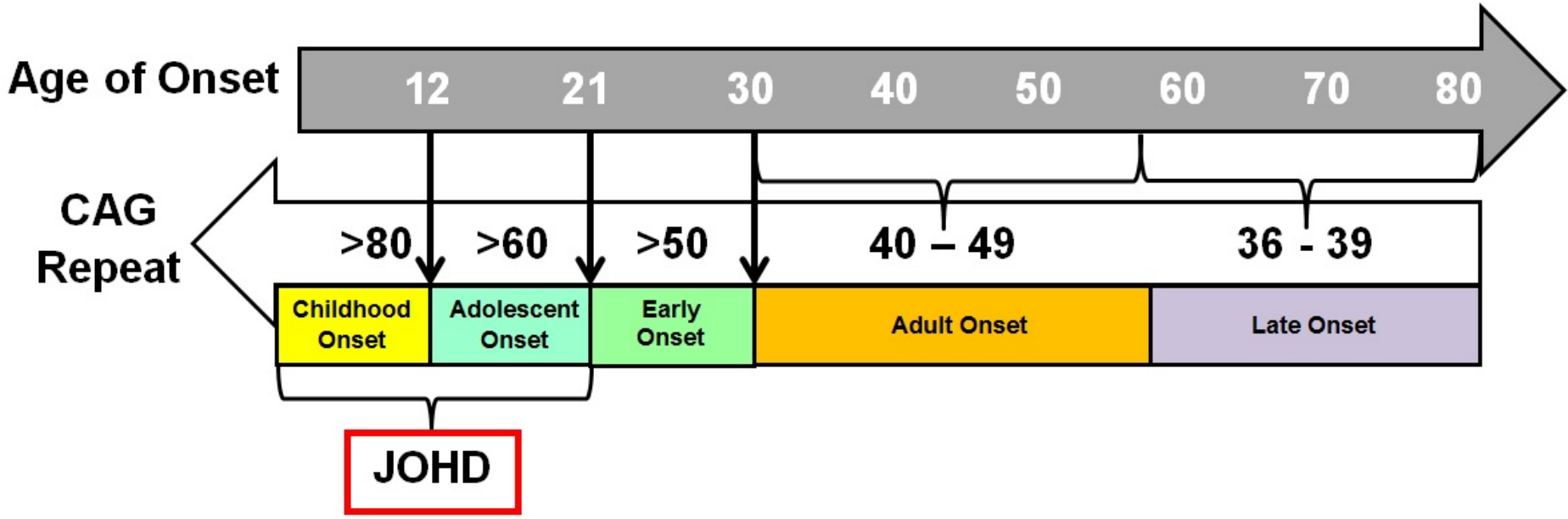
CAG Repeat and Age of Onset



- The longer the repeat, the earlier the onset
- Onset prior to age 21 = Juvenile Onset HD (JOHD)

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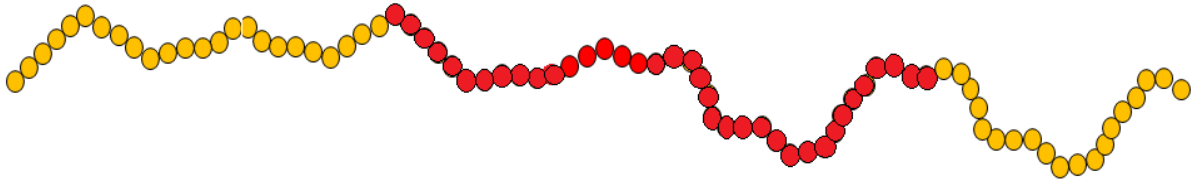
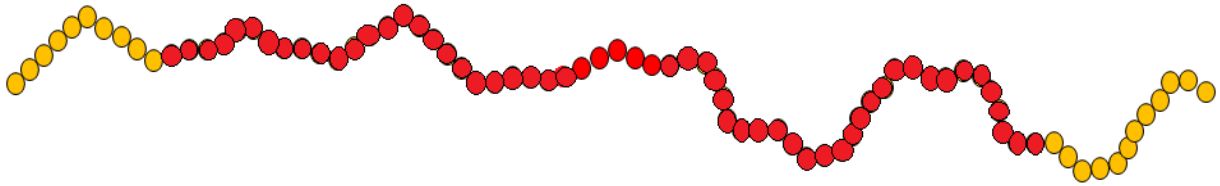
Genetic Anticipation

- When HTT is passed on from parent to child, there is a change it will expand



Example:
Parent CAG = 43



Example:
Child CAG = 65

- This is far more likely to happen when the parent is MALE
  - Most JOHD cases (up to 90%) have a father with HD
  - Converse – vast majority of father with HD will NOT have a child with JOHD; this is still a rare occurance
  - However, the longer the repeat, the more unstable the gene

Question #3

- What is the relationship between CAG repeat and age of onset?
  a. The shorter the repeat, the earlier the onset
  b. The longer the repeat, the longer the disease course
  c. The longer the repeat, the earlier the age of onset
  d. Repeat length is not related to age of onset

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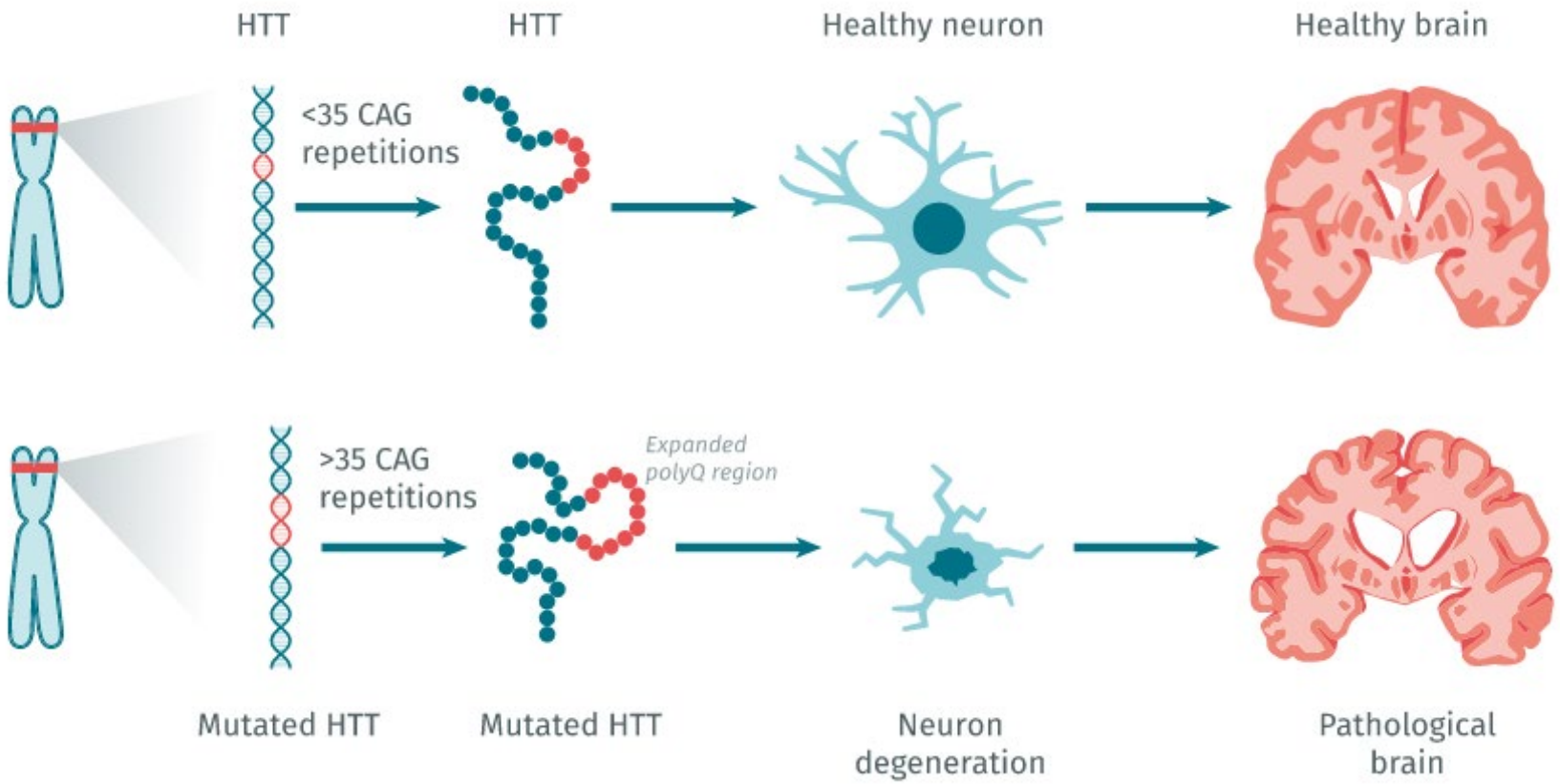
Pathophysiology of HD – simple version



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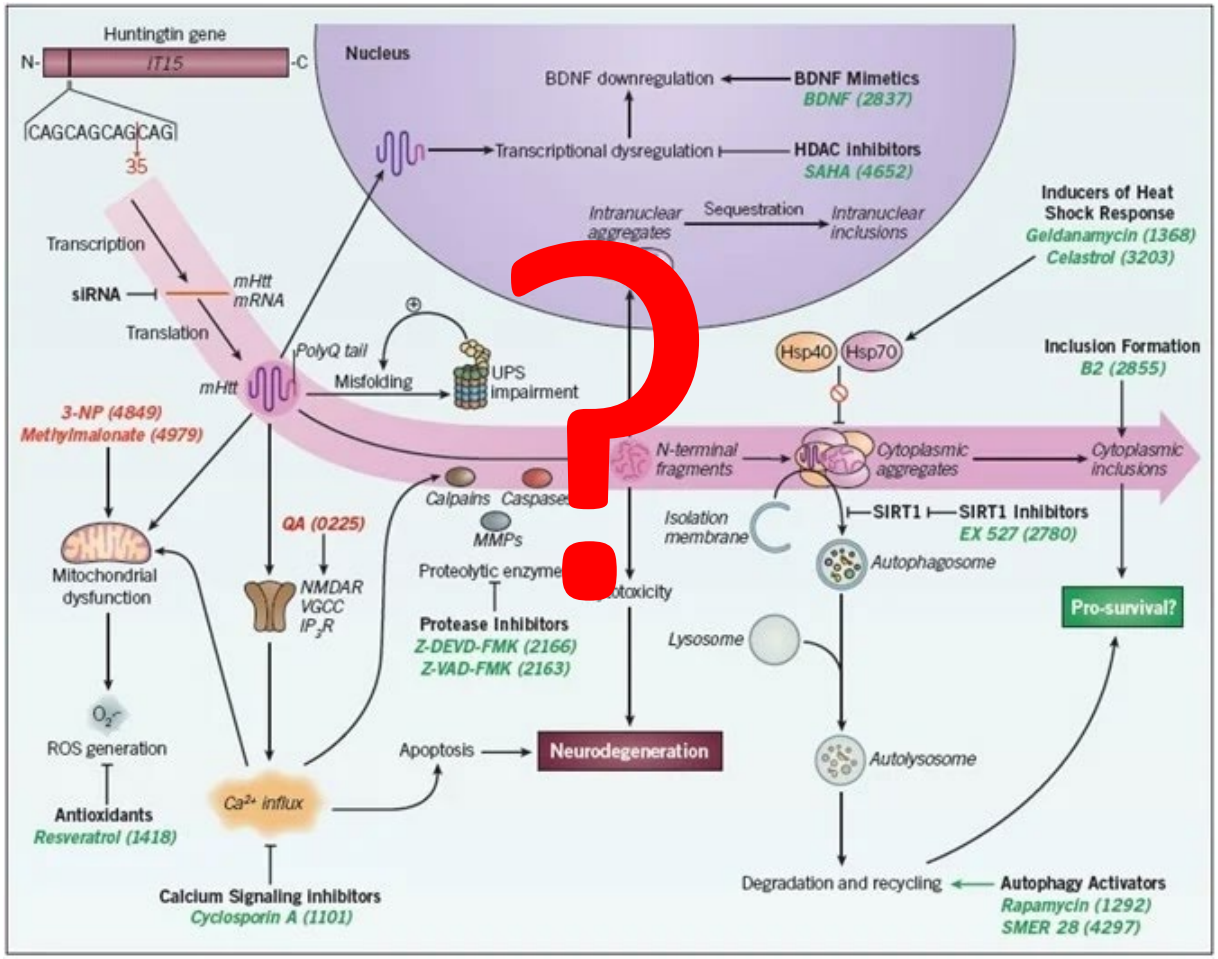
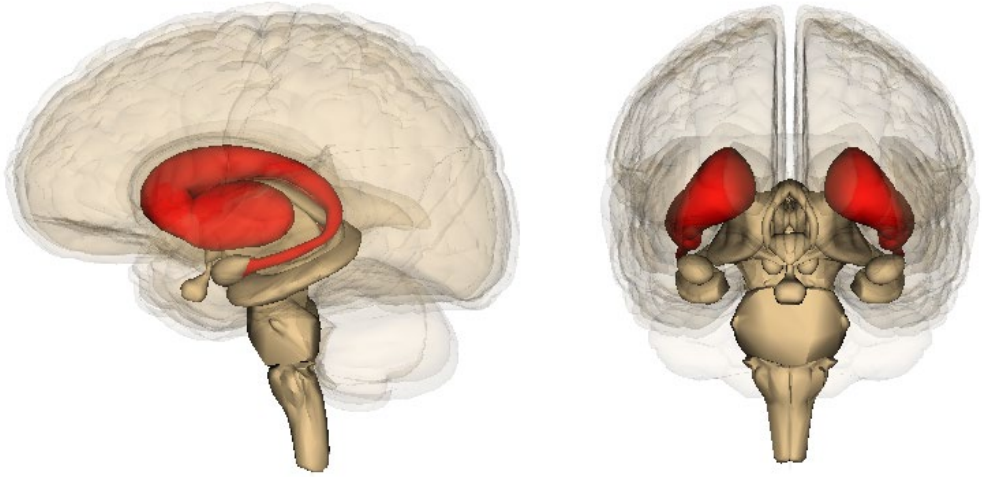
Pathophysiology of HD – Complex version



- We do NOT know how *mHTT* causes degeneration

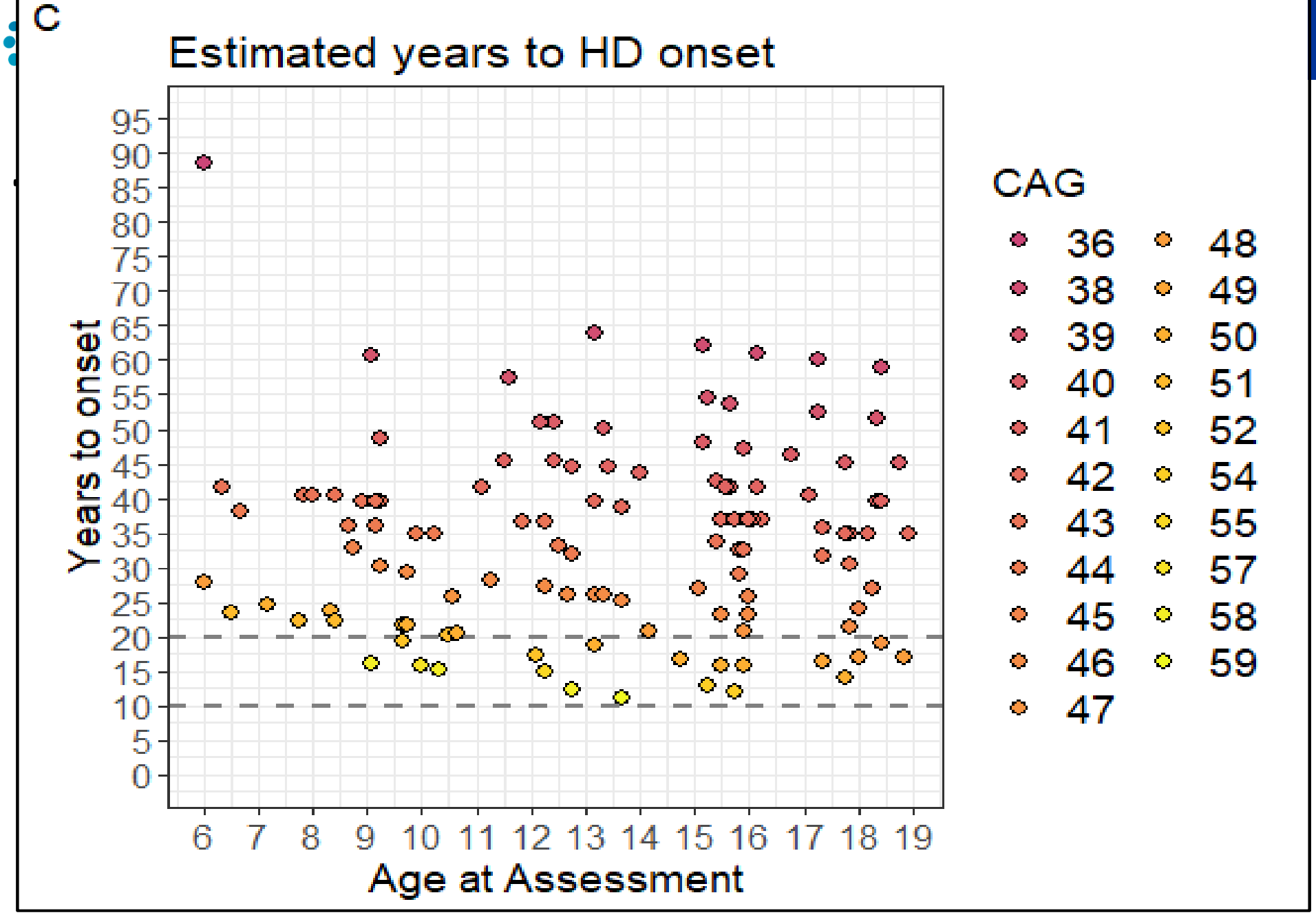
Pathophysiology of HD – What DO we know?

Caudate + Putamen = STRIATUM



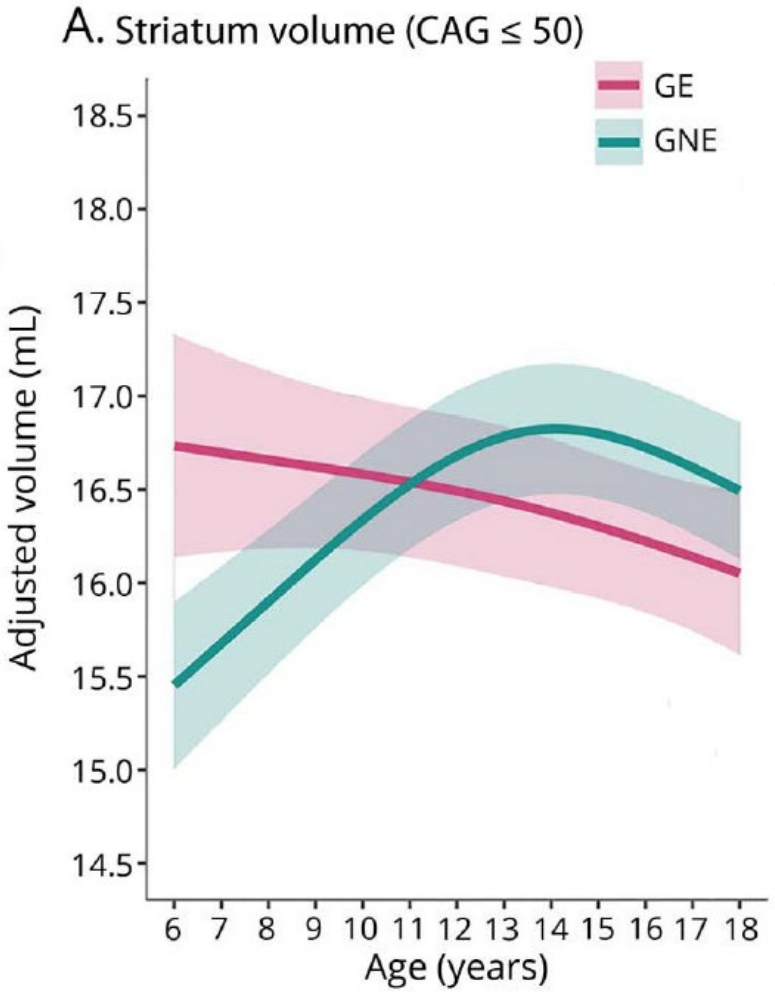
- #1: We know that the striatum is the region of the brain that is specifically affected by HD

- #2 we know that HTT (wild-type, normal gene) is vital for brain development
- What are the effects of *mHTT* on brain development?



- GE subjects are estimated to be on average > 40 years from onset

Growth and Development of the Striatum



- Green line: GNE, normal striatal development
  - Growth then peak and puberty with decline (programmed synaptic elimination or pruning)
- Red line: GE children begin with STRIATAL HYPERTROPHY
  - Likely due to earlier development in infancy
  - Steady decline in volume
  - Markedly different developmental trajectory
    - ✓ *Van der plas et al, Neurology 2019*

Growth and Development of the Striatum

- This developmental trajectory for the GE children is BENEFICIAL early in life
  - Compared to **GNE**, **GE** children have superior cognitive function, motor function, and are protected from depression / anxiety *early in life*
    - ✓ Schultz et al., Annals of Neurology 2021
    - ✓ Reasoner et al., Brain and Behavior 2022
- Hypothesis: *HTT* drives the development of a superior striatal circuit early in life - however this circuit is not meant to last and degenerates later in life

Question #4

- GE children's striatal growth shows
  a. Early smaller than normal volumes and slow increase later on
  b. Early larger than normal volume with slow decline in volume
  c. Normal volumes until after puberty and then slow decline

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Juvenile Onset HD (JOHD)

- Clinical features
  - Ultra-rare – only about 5-10% of all HD
- In many ways, similar to Adult Onset HD **(AOHD)**
  - Motor, Cognitive, Behavioral symptoms
  - Definition of disease onset is significant motor symptoms
  - Cognitive and behavioral can occur many years before onset of motor symptoms

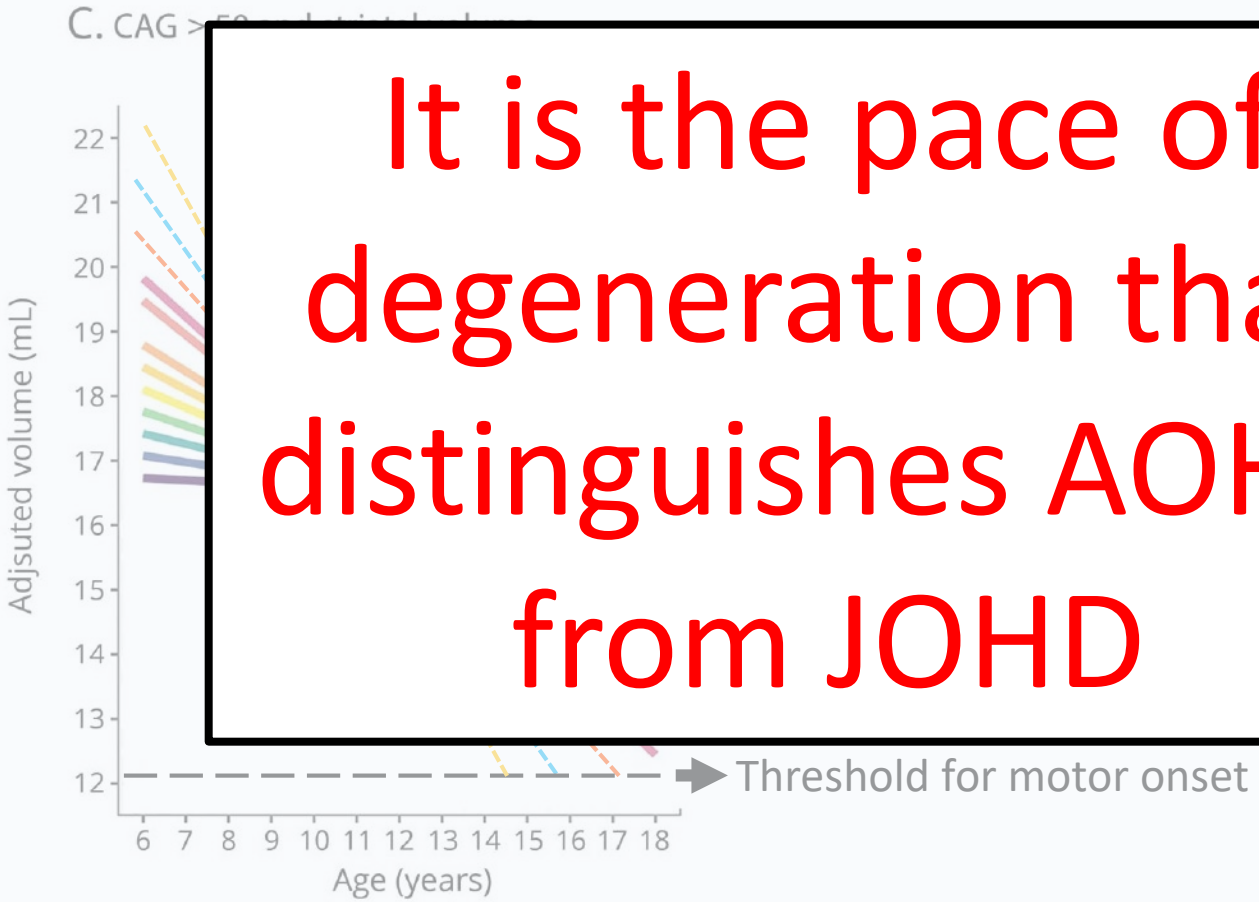
Juvenile Onset HD (JOHD)

- Important difference between JOHD and AOHD
  - AO
  - JO
    - ✓
    - ✓ Rigidity
    - ✓ Dysarthria
    - ✓ Masked face

g, stooped

WHY THE DIFFERENCE?

Growth and Development of the Striatum



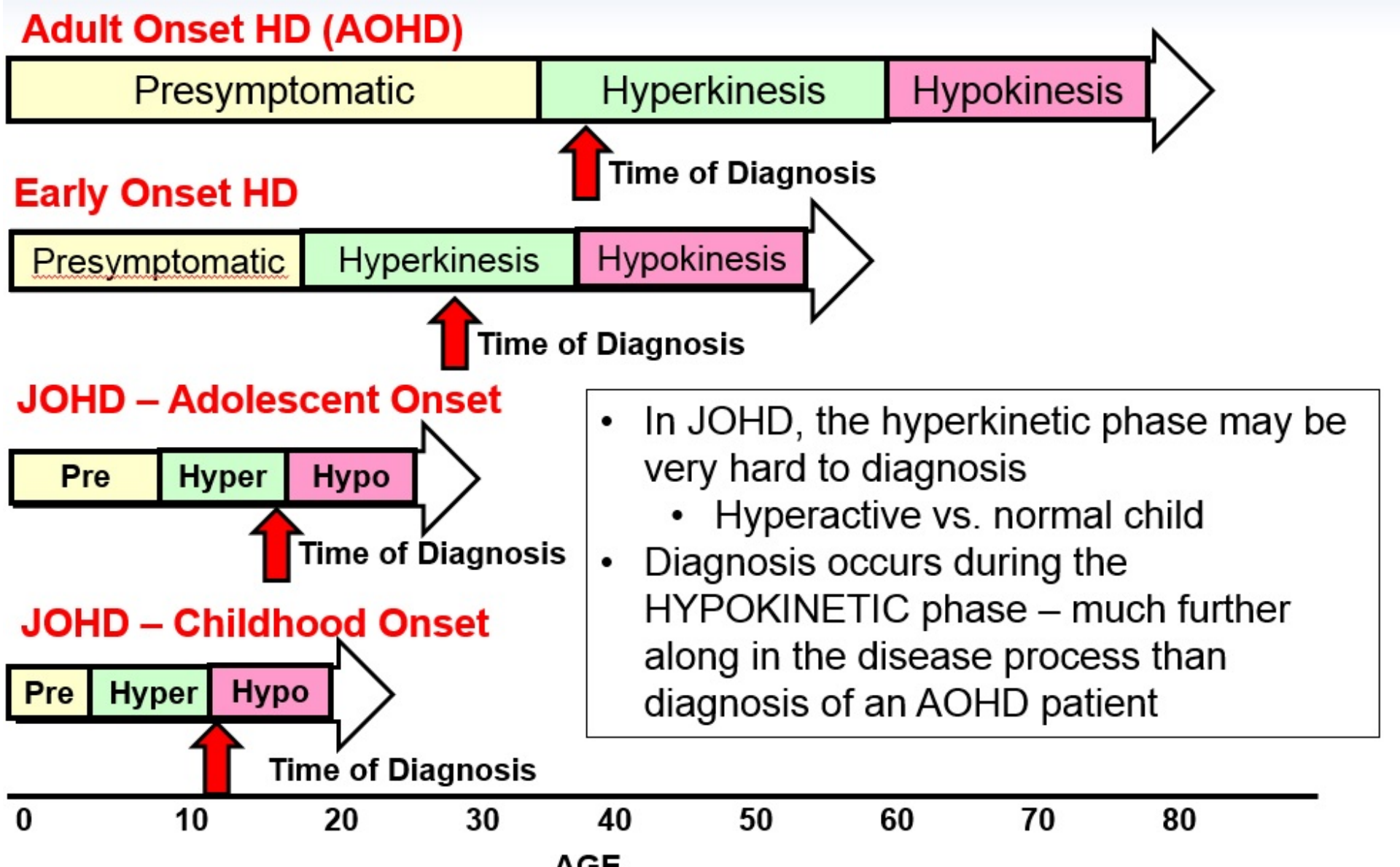
It is the pace of degeneration that distinguishes AOHD from JOHD

is CAG repeat

s start out with
the most rapid

at striatal
old predicts

threshold of
earlie



- In JOHD, the hyperkinetic phase may be very hard to diagnosis
  - Hyperactive vs. normal child
- Diagnosis occurs during the HYPOKINETIC phase – much further along in the disease process than diagnosis of an AOHD patient

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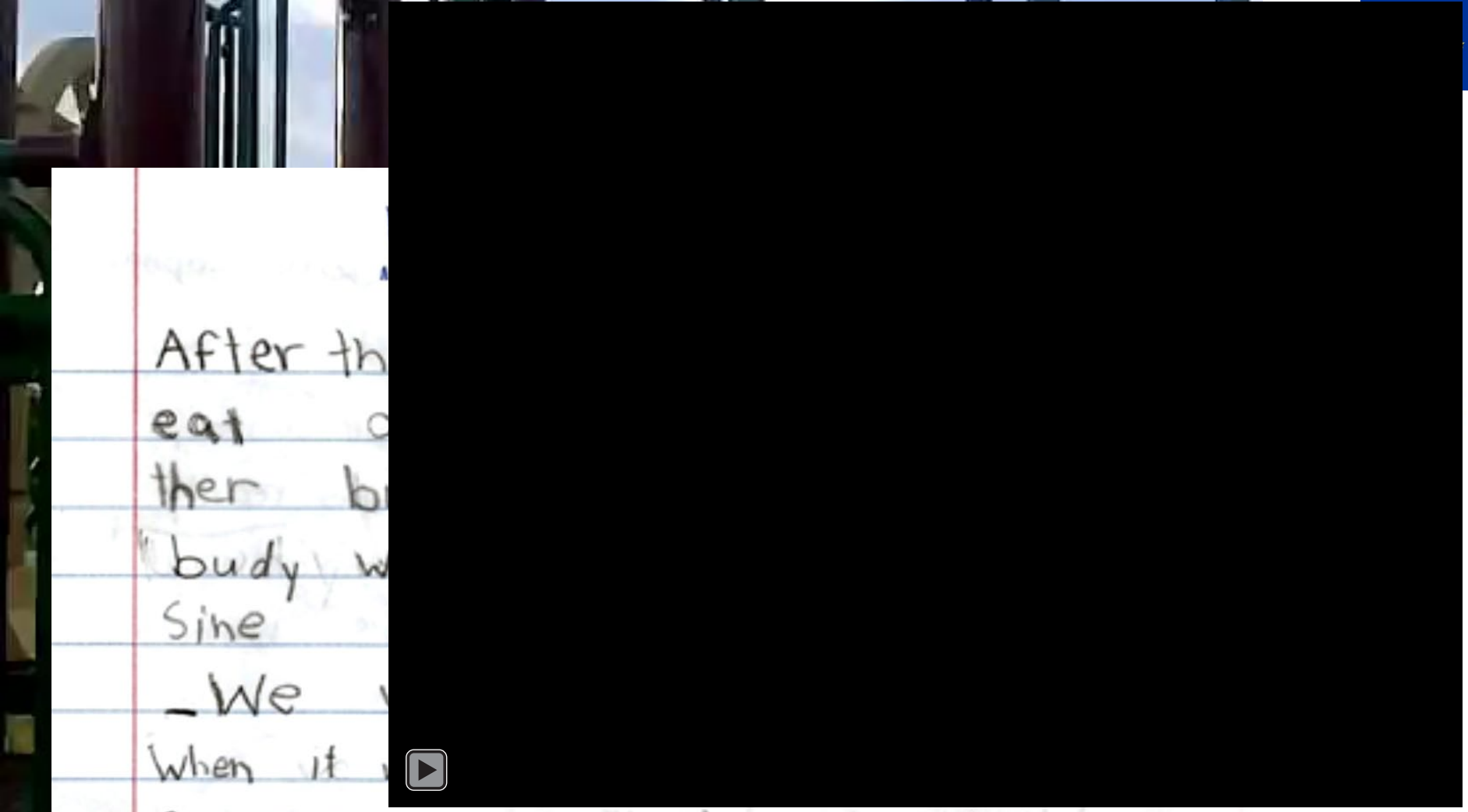
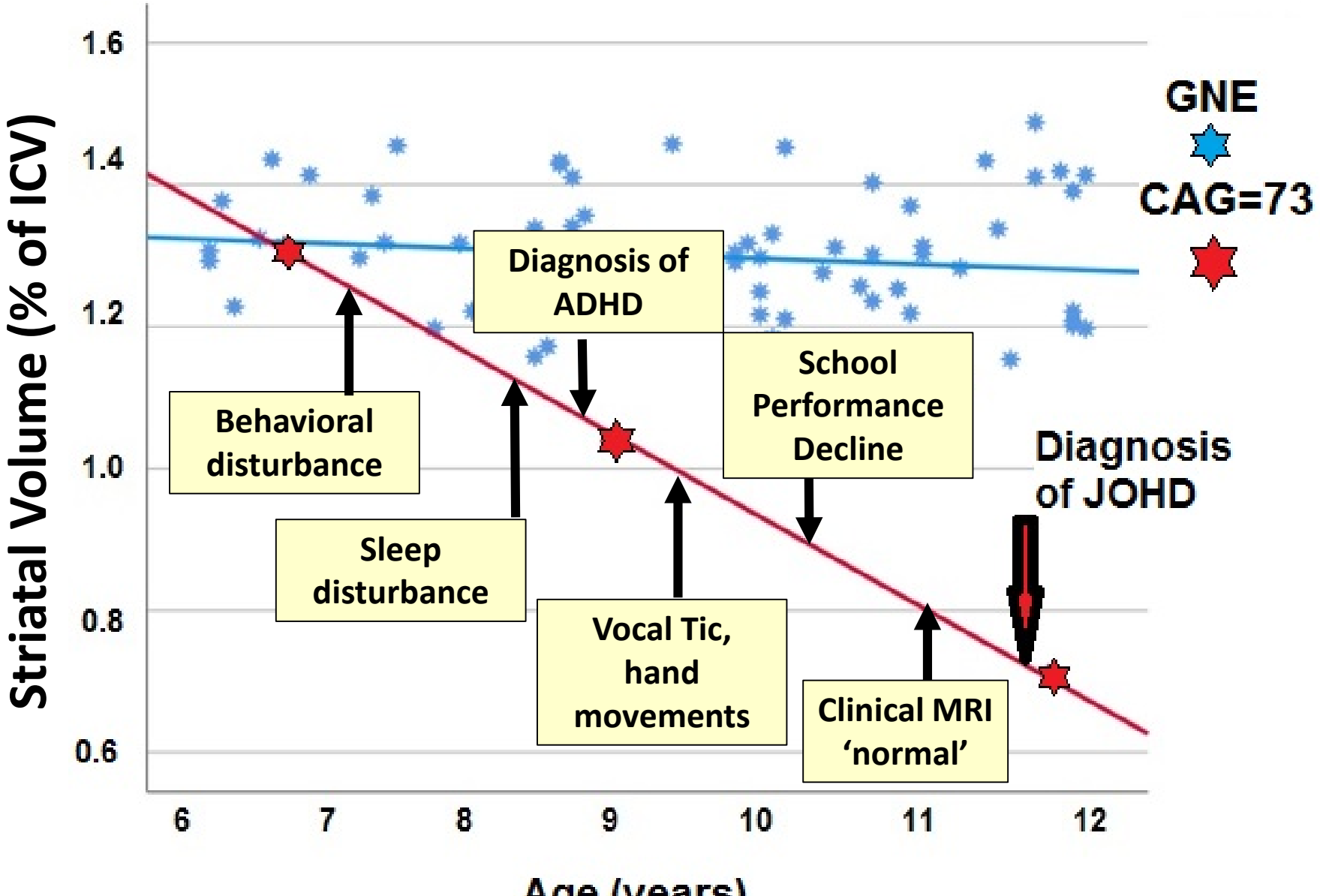
Juvenile Onset HD (JOHD)

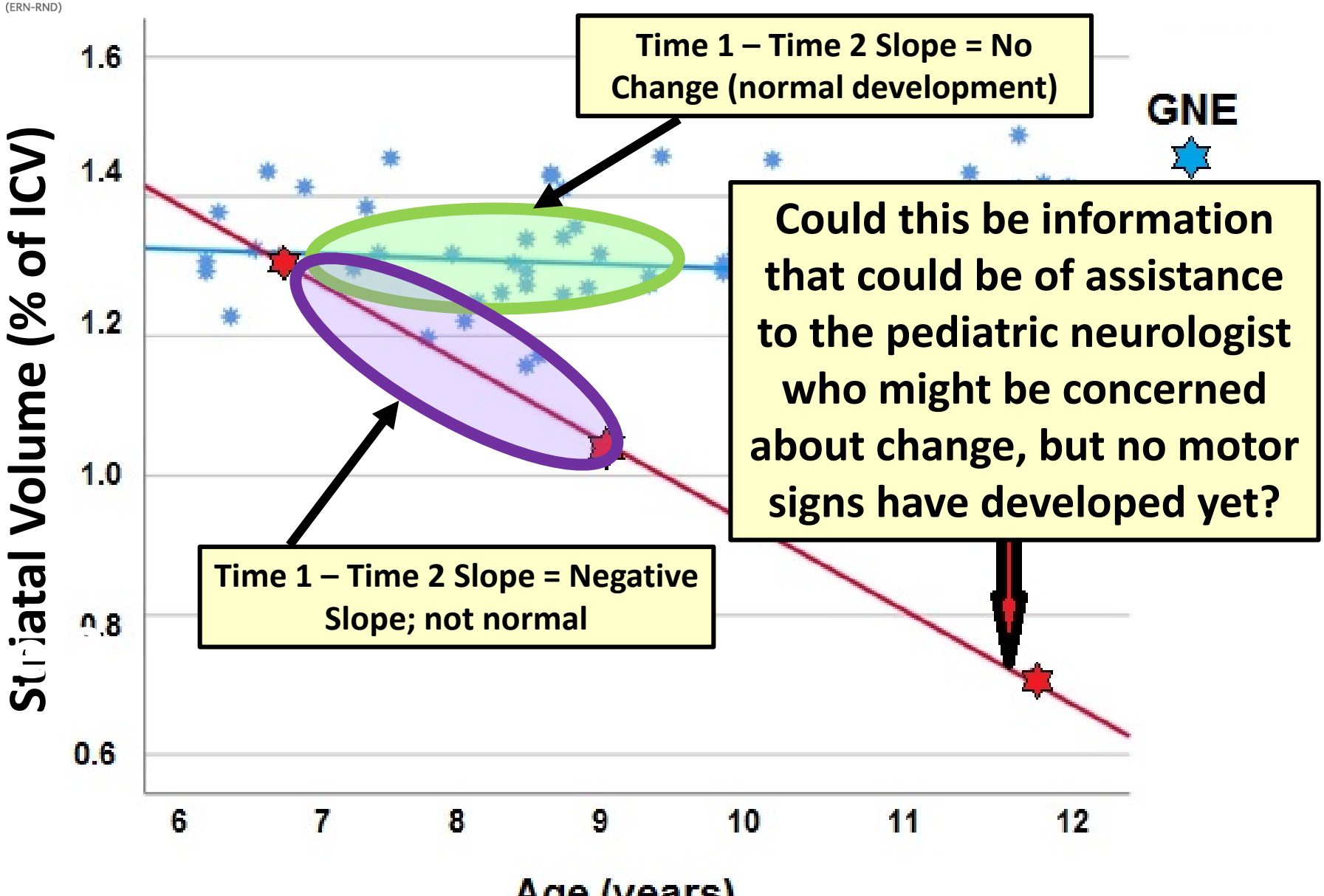
- The Diagnostic challenge
  - Not uncommon for kids to have symptoms many years before clinical diagnosis
  - Why?
    - ✓ Motor onset is ‘significant motor’ symptoms
    - ✓ Behavioral and cognitive changes often years before motor onset
    - ✓ Behavioral changes are not specific to JOHD
    - ✓ Hyperkinesis may look like a ‘fidgety child’ or get diagnosis of ADHD



6 7 8 9 10 11 12

Age (years)


Striatal Volume (% of ICV)
1.6
1.4
1.2
1.0
0.8
0.6
6
7
8
9
10
11
12
Age (years)
GNE
CAG=73
Behavioral disturbance
Diagnosis of ADHD
School Performance Decline
Diagnosis of JOHD
Sleep disturbance
Vocal Tic, hand movements
Clinical MRI 'normal'


Time 1 – Time 2 Slope = No Change (normal development)
GNE
Could this be information that could be of assistance to the pediatric neurologist who might be concerned about change, but no motor signs have developed yet?
Time 1 – Time 2 Slope = Negative Slope; not normal
Striatal Volume (% of ICV)
1.6
1.4
1.2
1.0
0.8
0.6
6
7
8
9
10
11
12
Age (years)

Question #5

- In the diagnosis of JOHD
  a. Easier to make this diagnosis compared to AOHD
  b. Clinical MRI scans may be normal even after significant volume loss over time
  c. Cognitive and behavioral symptoms ALWAYS occur AFTER onset of motor symptoms

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THANK YOU FOR LISTENING

Questions?

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NEXT Webinar

‘Measuring disease severity in chronic progressive myelopathy’

by Marc Engelen,

Amsterdam University medical Center, the Netherlands

15. March 2022

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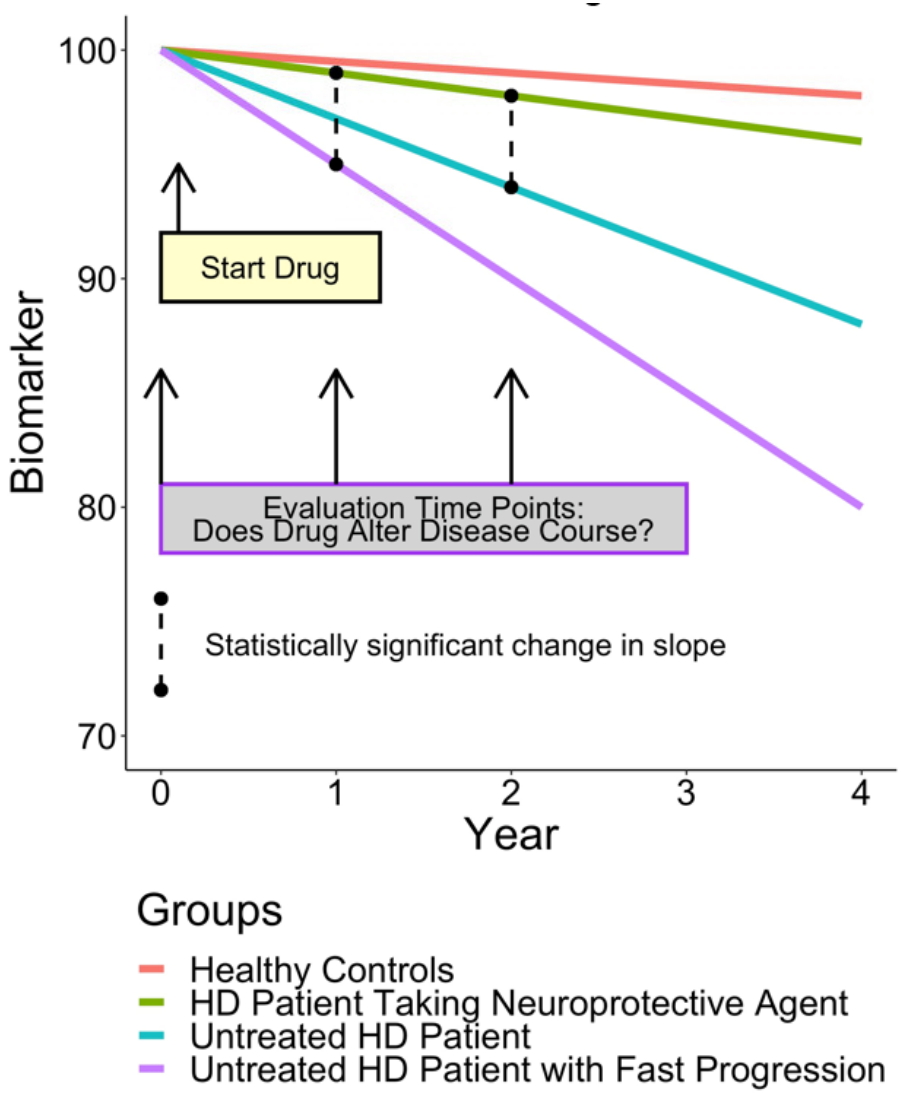
  - Superior group for drug trials?

Model for Neuroprotective Clinical Trial



- In clinical trials, need a biomarker that can show LACK of progression if a medication proves to be neuroprotective
- In a slowly progressive disease, this may take up to 2 years to see difference between groups
- With a faster moving disease, you may be able to see effect of drug in only one year

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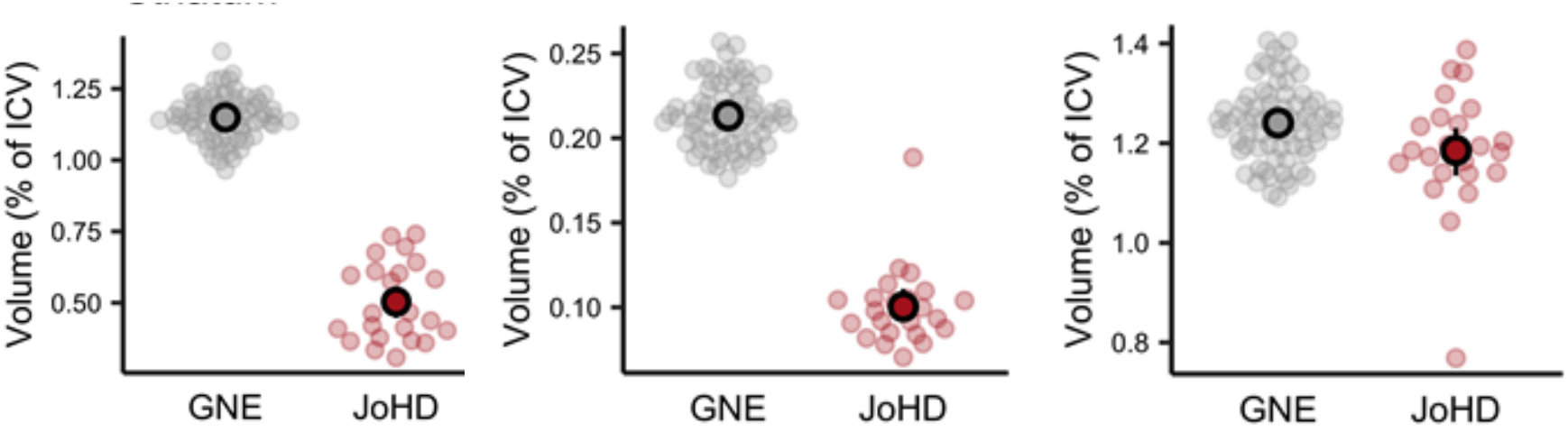
JOHD Study

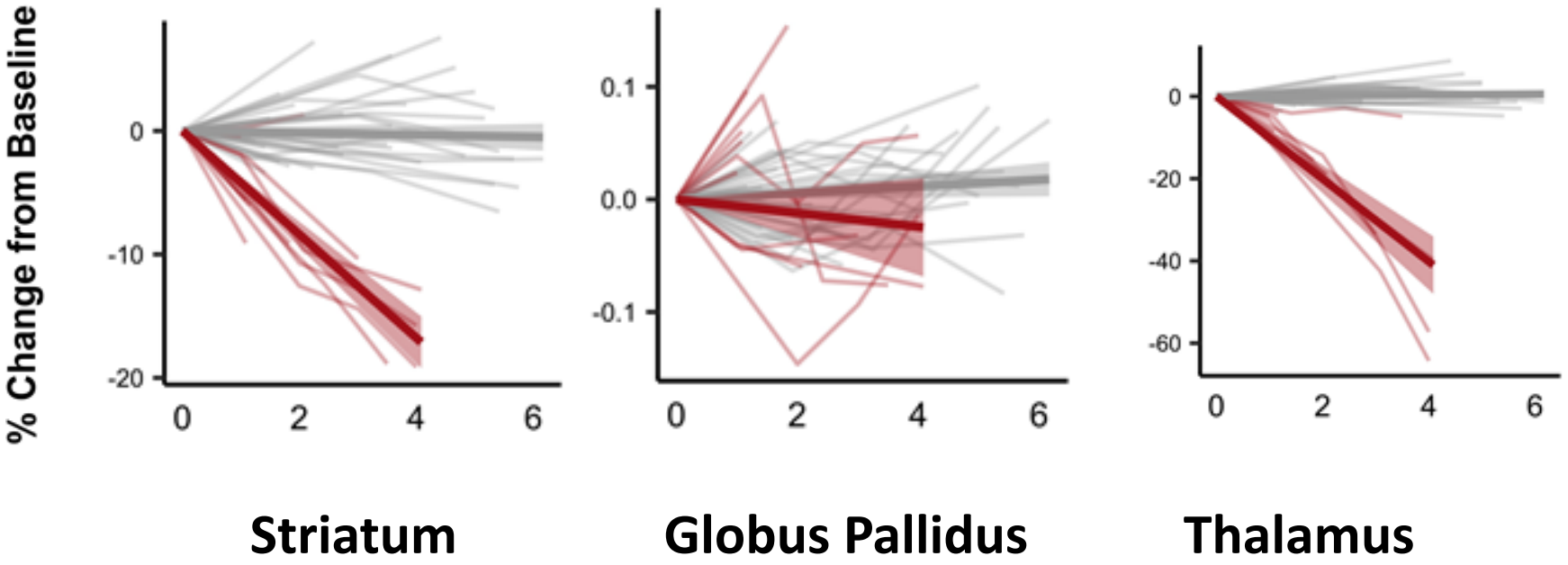
	JOHD	GNE	P-value
N (Visits)	26 (61)	78 (150)	
Age (yrs), mean ± S.D. [range]	16·03 ± 6·14 [5·08 – 25·3]	14·43 ± 3·19 [6·08 – 22·4]	0·090
% Female, n (%)	14 (53·8)	45 (57·70)	0·909
CAG, mean ± S.D. [range]	72·31 ± 14·52 [54 – 102]	20·58 ± 4·31 [15 – 34]	<0·001
Disease Duration, mean ± S.D. [range]	3·51 ± 3·02 [0 – 11]	N/A	N/A

- At baseline, Striatum and Globus Pallidus are already VERY small in volume; Thalamus is normal in volume



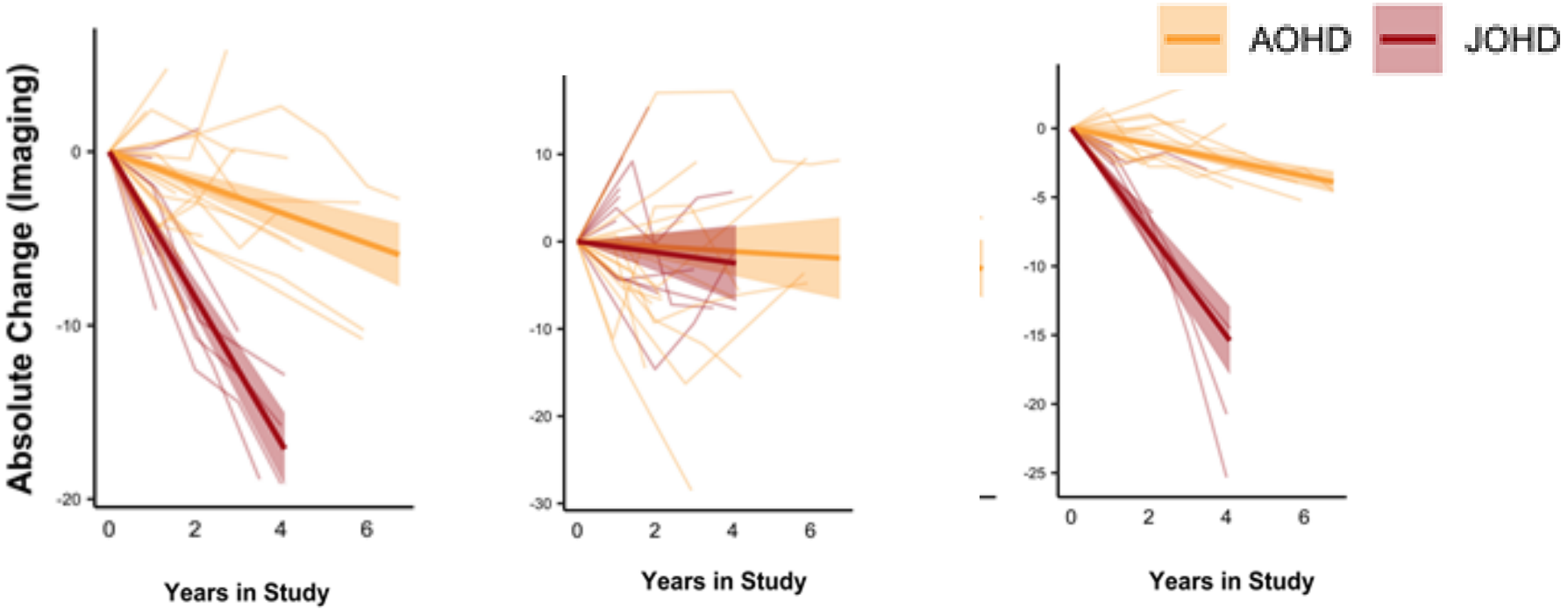
Striatum **Globus Pallidus** **Thalamus**

- Despite starting very low, the Striatum has measurable and dramatic change over time; so does the thalamus



Striatum **Globus Pallidus** **Thalamus**

- Compared to AOHD, JOHD has much faster rate of decline
- This may make them SUPERIOR candidates for clinical trials
- Currently JOHD are not eligible for ANY clinical trial



Striatum **Globus Pallidus** **Thalamus**