Huntington's Disease Society of America

HDSA Annual Convention June 2015

Diagnosing Juvenile Huntington's Disease (JHD)

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Huntington's Disease Society of America

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Presenter Disclosures

Peg Nopoulos

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose
or list

Juvenile Huntington's Disease

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Juvenile Huntington's Disease

- Genetics
- CAG repeat length and age of onset
- Prevalence
- Clinical features
- The diagnostic challenge

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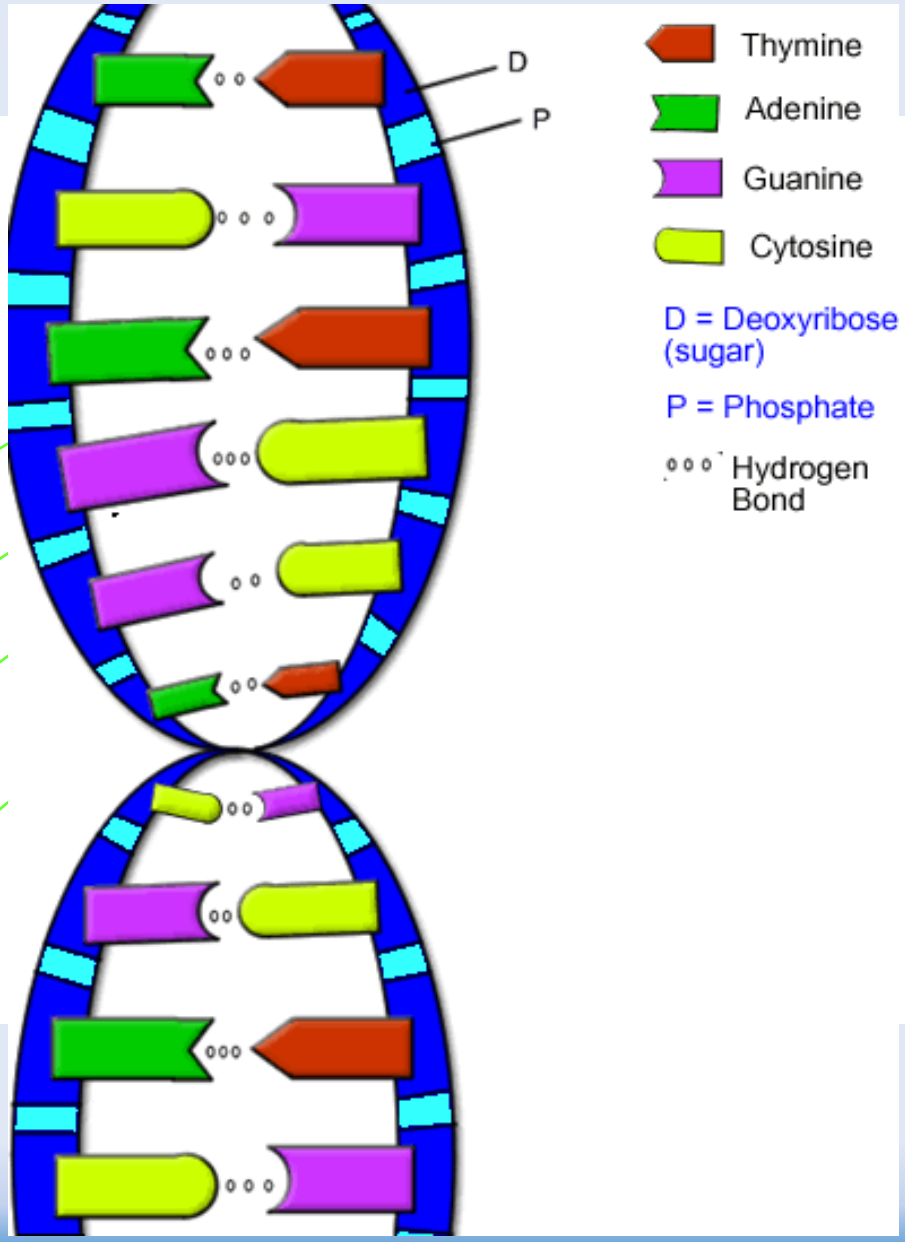
Anatomy of DNA

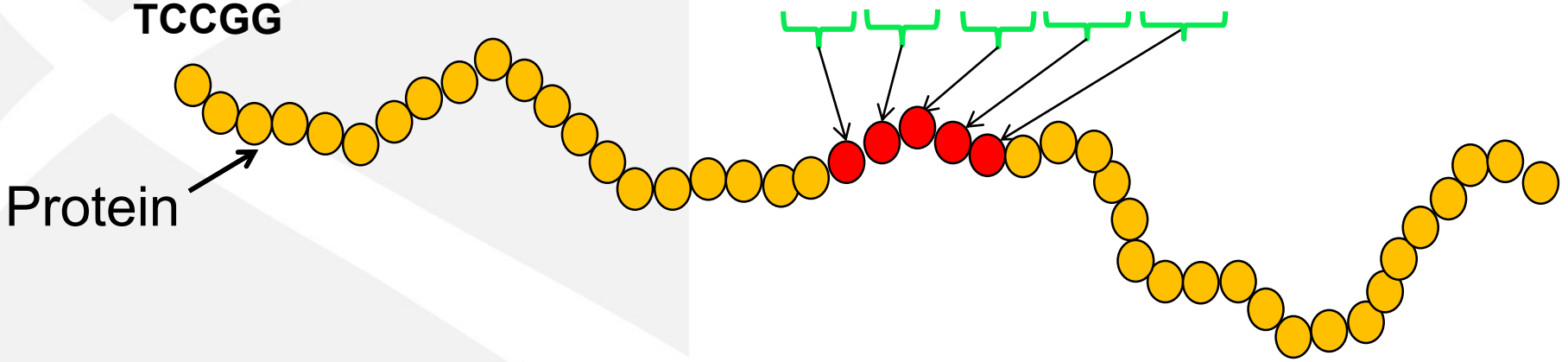
- DNA is the 'code' for genes
  - Genes code for a protein. Proteins work in the cell and eventually direct the formation of a trait (eye color)
- The code for genes is made up of 4 'nucleotides'
  - T A G C
- This is the 'dna alphabet'
- Example of a code for a gene:
  - TTAGCGTAGCC



The Huntington Gene

- **Is named Huntingtin (*HTT*)**
  - **Has a section where 3 nucleotides are repeated = trinucleotide repeat or 'triplet' repeat.**
  - **Every human has these repeats**
  - **Three nucleotides make up an amino acid**
  - **Strings of amino acids make up a protein**

GGTCAGAGGGGATCATTAGCTACAGCAGCAGCAGCAGTTGATA TCCGG



The Huntington Gene

- When the repeat is 40 or greater, then the gene is called mutant *HTT* or *mHTT*
  - When CAG is greater or equal to 40, then Huntington's Disease (HD) will develop
  - Onset and diagnosis of HD is average age of 40 years of age
- **When the diagnosis of HD is made at age 21 or before = Juvenile Huntington's Disease or JHD**

Juvenile Huntington's Disease

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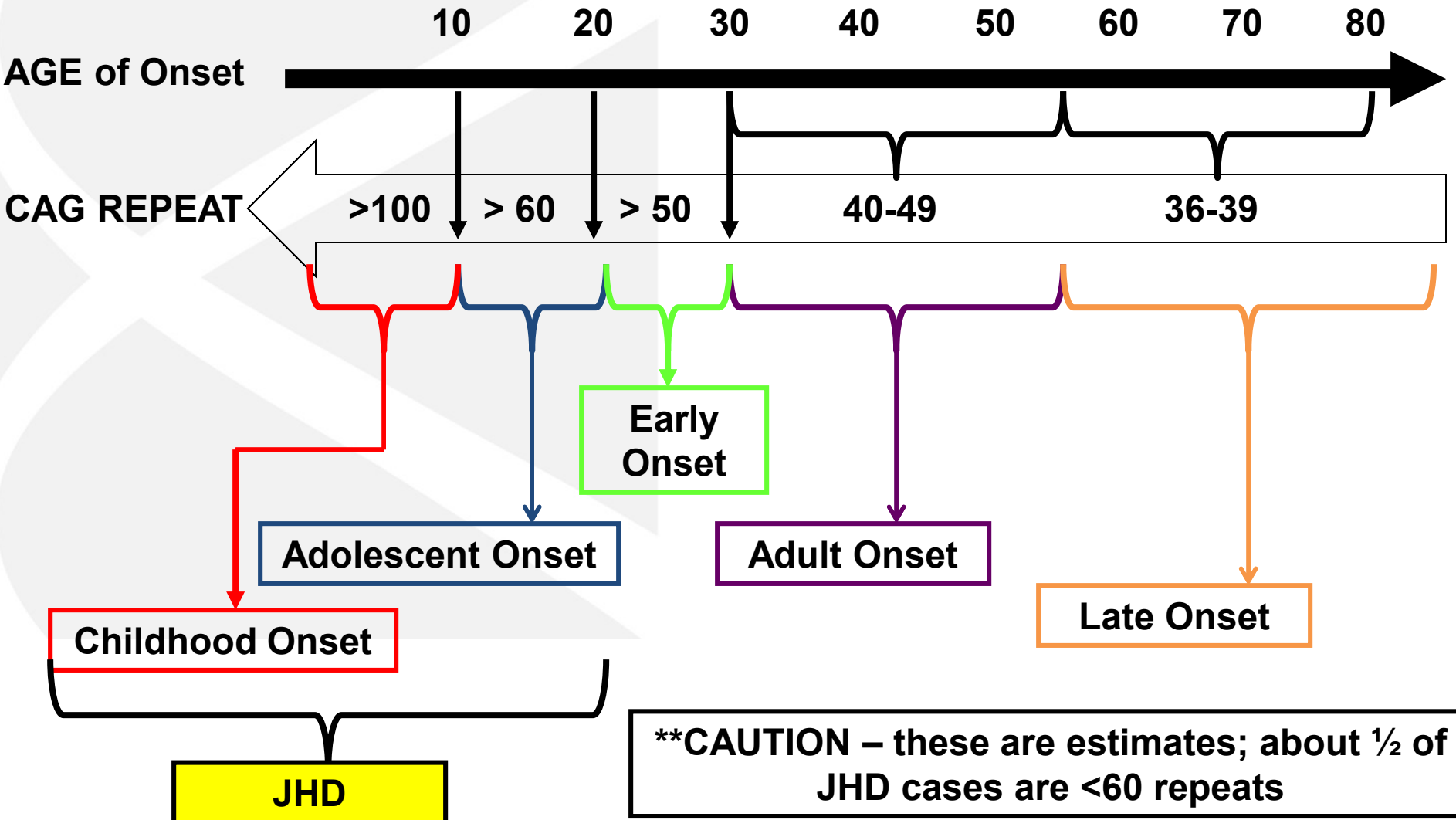
Juvenile Huntington's Disease

- Onset is defined as
  - The presence of unmistakable (not subtle) neurologic (motor) signs

The number of CAG repeats is related to the age of onset



Juvenile Huntington's Disease

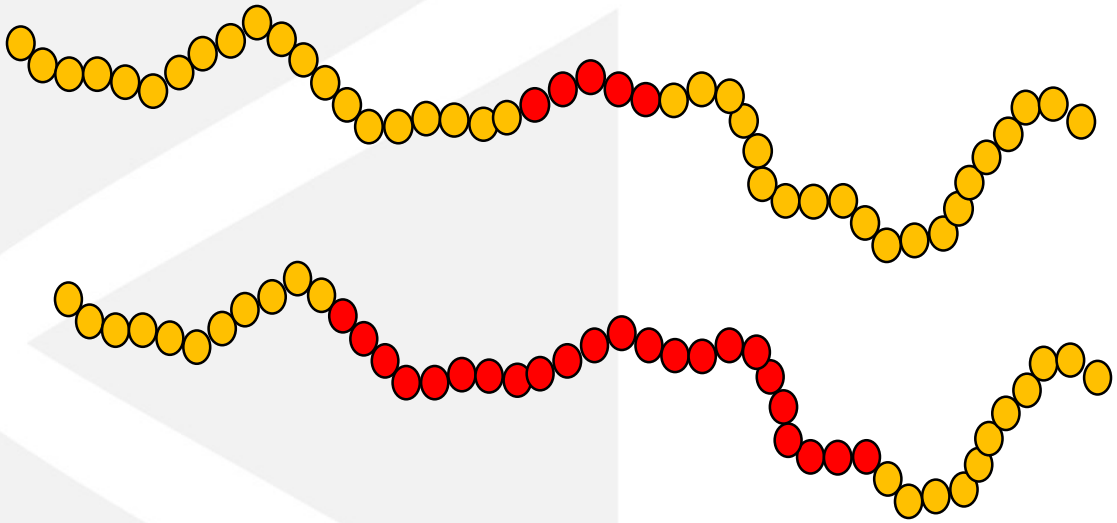
- Genetics
- CAG repeat length and age of onset
- Prevalence – How Common is it?
- Clinical features
- The diagnostic challenge

Juvenile Huntington's Disease

- Rare
  - Best estimate is around 5% of all HD cases
  - Even more rare for childhood onset

Genetic Anticipation

child, there is a chance it will expand



Example:
Parent
CAG = 43

Example:
Child
CAG = 65

- **This expansion is more likely to happen when the parent is MALE**
  - **Most JHD cases (up to 90%) have a father with HD**
  - **Converse – vast majority of fathers with HD will NOT have a child with JHD**

Juvenile Huntington's Disease

- Genetics
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Clinical Features

- Like all forms of HD, symptoms cluster in 3 main categories
  - Motor symptoms
  - Cognitive symptoms
  - Behavioral symptoms
- A common accompanying feature is seizures or epilepsy

Motor Symptoms

- Bradykinesia – slowing of movements
- Rigidity – stiff muscles
- Dystonia – muscles contract in abnormal position
- Ataxia – slow, shuffling, stooped walk
- Dysarthria – slurred speech
- Tremor
- Masked face – lack of movement in face
- Chorea – dance-like movements

Motor Symptoms

- These symptoms are often referred to as ‘Parkinsonian’ as they are similar to features of Parkinson’s disease.
- Chorea is much less common than is seen in adult onset HD
  - often comes later in the disease

Cognitive Symptoms

- Cognitive Skills = Thinking skills
  - Everything from general intelligence (IQ) to specific functions such as memory, attention, language and visuospatial skills
- For children with childhood onset (before the age of 10), this may be a failure of thinking skills development
- For JHD it is often seen as declining school or academic performance
- Like Adult onset, these thinking skills deficits will progress over time

Behavioral / Psychiatric Symptoms

- **Externalizing Behaviors** – behavior that other people can see
  - Hyperactivity
  - Inattention
  - Opposition (not wanting to follow rules, talking back)
  - Aggression
- **Internalizing Behaviors** – what people feel inside
  - Sad or depressed
  - Anxious
  - Obsessions

Behavioral /Psychiatric Symptoms

- Externalizing – the most common
  - Attention Deficit Hyperactivity Disorder (ADHD) may be diagnosed
  - Aggression may come on quickly, with unclear triggers
- Psychosis: hallucinations and delusions
    - More common in onset in teens and 20's

Presenting Symptoms

- In a large study of 53 cases *(Siesling et al.)*
  - 70% presented with Behavior symptoms
  - 48% with motor symptoms
  - 27% with cognitive symptoms
  - During the course, the number of cases that experienced behavioral disturbances:
    - ✓Males: 93%
    - ✓Females: 81%

Other Accompanying Features

- Seizures
  - Up to 30-40% of cases
    - Generalized or tonic-clonic - ‘’grand mal”
      - ✓Lose consciousness; entire brain involved
    - Partial complex
      - ✓Impaired consciousness; parts of the brain involved
    - myoclonic epilepsy
      - ✓Muscle jerks, no impairment of consciousness
  - Tend to be more common in the earliest onset cases and can be a presenting symptom

Duration of Disease

- Somewhat controversial
- Duration of disease in JHD does NOT seem to be much different than duration of disease in adult onset
  - ✓Average 15 years from diagnosis to death
- Thus even though CAG repeat can predict age of onset, it does NOT seem to predict duration of disease

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The Diagnostic Challenge

- Average length of time from first symptom to diagnosis – NINE YEARS *(Ribai et al)*
- Most common presenting symptom is behavior
  - *BUT DIGNOSIS IS NEVER MADE BASED ON BEHAVIOR*

The Diagnostic Challenge

- What is the risk of getting a genetic test based on a non-specific symptom?
  - Behavioral problems are common
  - That symptom may not be related to HD
- Example, child with ADHD but no motor symptoms
  - Genetic test: CAG=43
  - So onset of symptoms likely to be in adulthood – this is NOT JHD
  - However, now this child has the knowledge that they have the expanded gene
    - ✓This may be psychologically difficult for many reasons

Research Programs at the University of Iowa Iowa City, Iowa USA

Funded by the National Institutes of Health and CHDI

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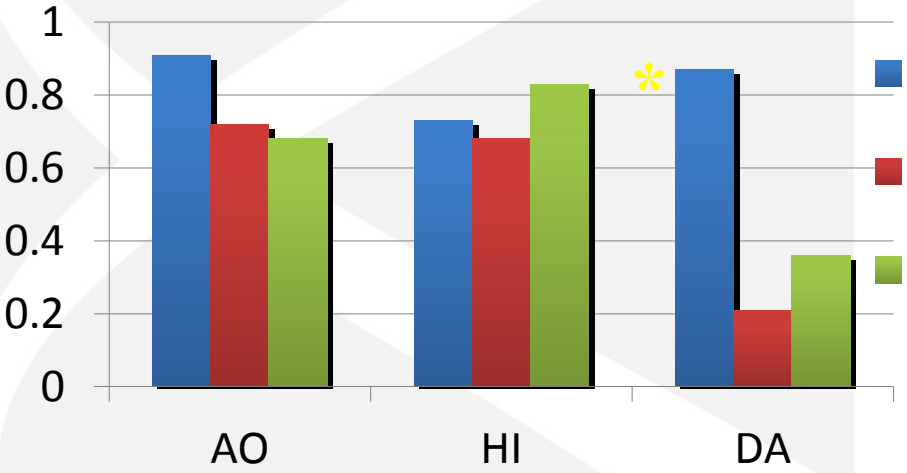
Kids-HD Program

- Study of brain structure (using Magnetic Resonance Imaging or MRI) and brain function (thinking or cognitive tests, motor tests, ratings of behavior)
- Subjects are children ages 6-18 years who
  - Have a parent with HD (at-risk)
    - ✓NO symptoms – preHD children (no JHD)
  - Have no family history of HD (controls)
- *For Research purposes only*, DNA from blood or saliva is used to measure CAG repeats in HTT; 3 groups:
  - Children at risk who are gene non-expanded (GNE)
  - Children at risk who are gene expanded (GE)
  - Healthy controls

Behavior is a non-specific symptom

- Data from Kids-HD study
- Parent ratings of behavior
  - **AO** = aggression / opposition
  - **HI** = Hyperactivity / inattention
  - **DA** = Depression / anxiety

The higher the score, the worse the behavior



GNE = at risk, Gene Non-Expanded

GE = at risk, Gene Expanded SHORT CAG 40-49

GE = at risk, Gene Expanded LONG CAG 50-73

- Behavior does NOT distinguish groups
  - Exception being more depression in the gene non-expanded group

The Diagnostic Challenge

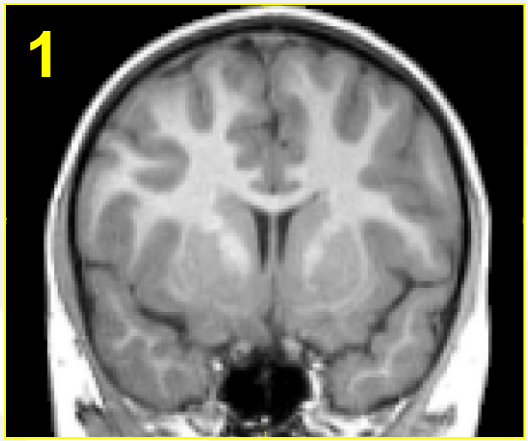
- Can we do anything to make the diagnosis earlier?
- *Can we provide doctors with tools that will allow them to make the decision to get the gene test sooner?*

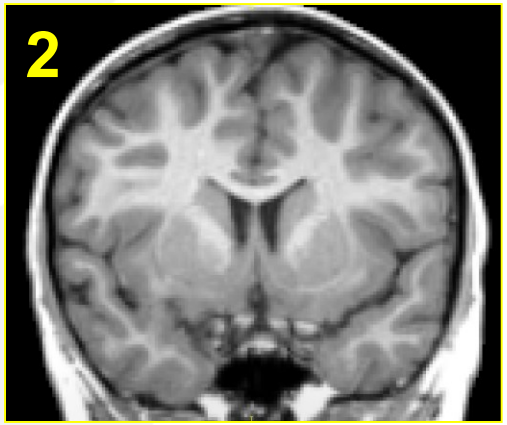
Kids-JHD Program

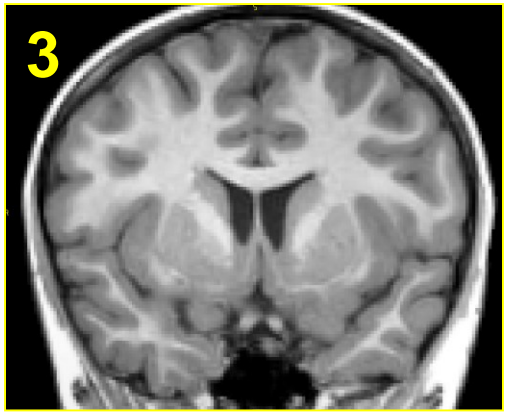
- Study of brain structure (using Magnetic Resonance Imaging or MRI) and brain function (thinking or cognitive tests, motor tests, ratings of behavior)
- Subjects are children ages 6-18 years who
  - Have been diagnosed with JHD

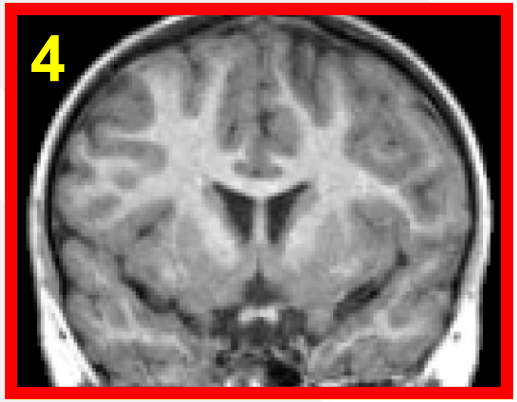
Can MRI imaging help the diagnosis of JHD?

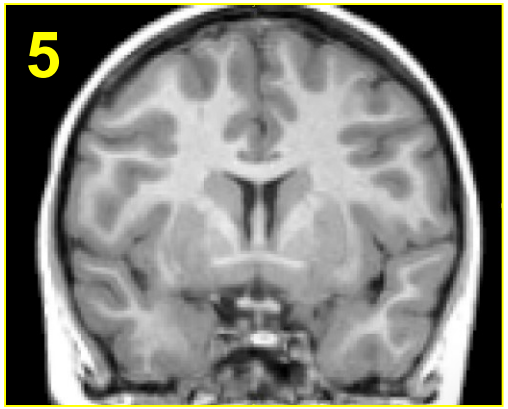
- Here are 5 Seven year old females
- Which one has JHD, age onset 6, CAG 101?









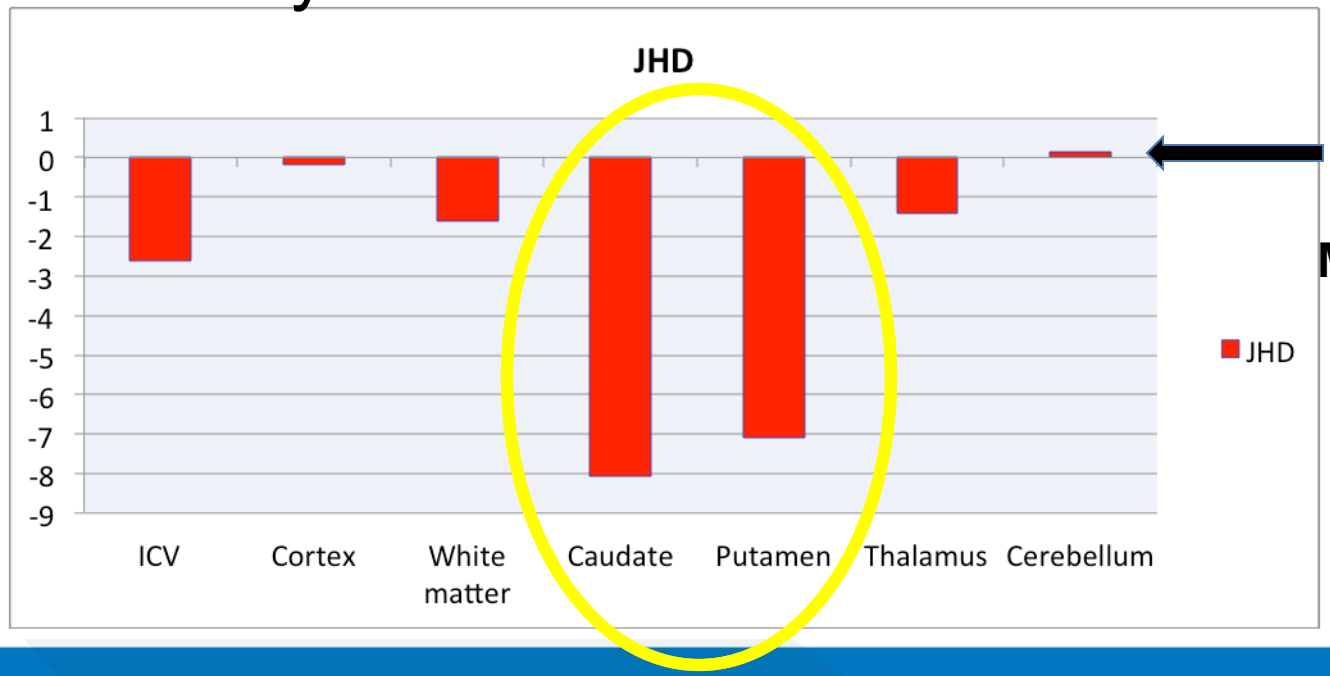


A 'clinical' scan, read by a radiologist – qualitative assessment: does this brain 'look' different?

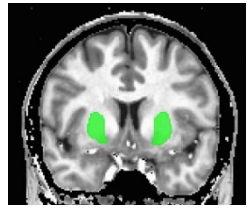
No – this will not help diagnosis

QUANTITATIVE MRI

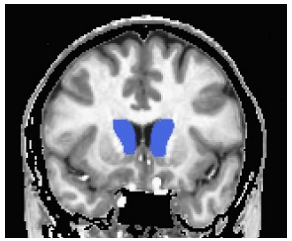
- Currently done for research
- Computer program calculates volumes
- JHD case compared to 7 age matched females, healthy controls



Healthy Control Mean = 0



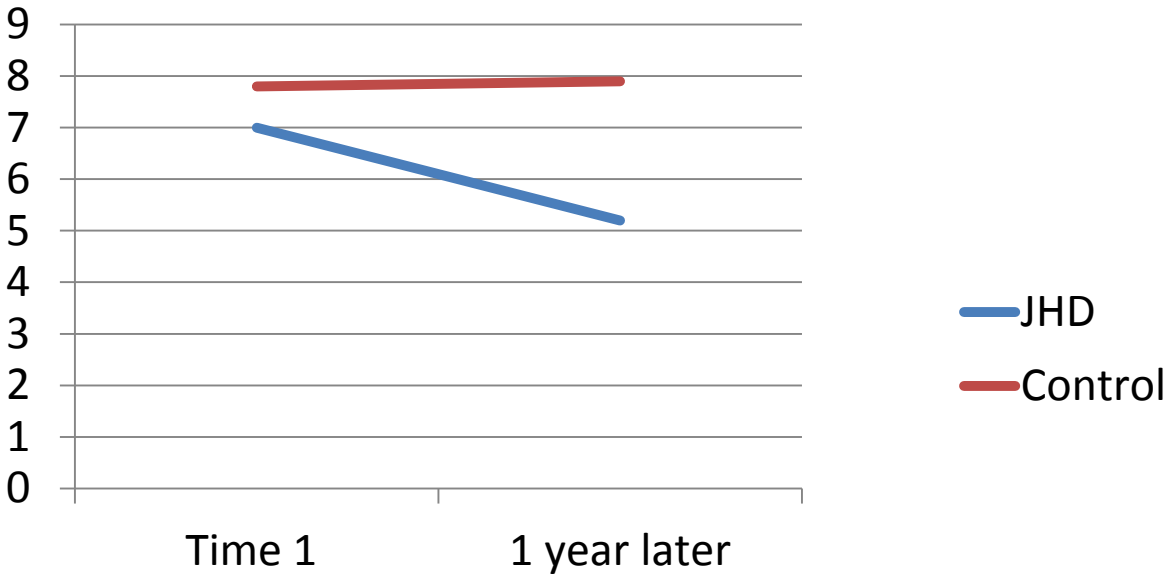
Putamen

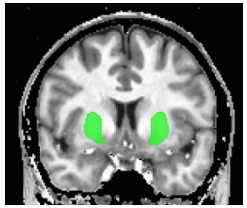


Caudate

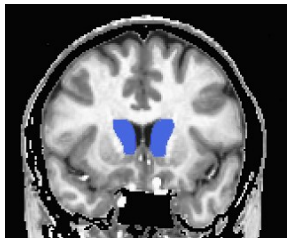
QUANTITATIVE MRI

- Also could look at CHANGE OVER TIME
- In a span of one year, is the volume of the caudate/putamen shrinking compared to a healthy control?
- If so, this could also provide evidence to the doctor even though motor symptoms haven't started yet





Putamen



Caudate

The Diagnostic Challenge

- Maybe **QUANTITATIVE MRI** can be used to provide the doctor with better information so they will feel more comfortable in ordering a gene test even when motor symptoms are not present or significant

Acknowledgements – Nopoulos Lab

Front Row: Jane Brumbaugh, Amanda Benavides, Christina Saenz, Thomasin McCoy, Jessica Lee, Amy Conrad, Jessica Forbes.

Back Row: Carrie Heald, Andrea Aerts, Peg Nopoulos, Sonia Slevinski, Michael McHugh, Nick Baker, Sasha Tereschencko, Ian DeVolder

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Questions & Discussion

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