Genetics and Huntington Disease
Michelle Fox, MS, LCGC
Genetic Counselor
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Presenter Disclosures

Michelle Fox, MS, LCGC

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

Michelle is an independent genetics consultant working for Invitae, a genetic information and testing laboratory which does not provide Huntington Disease testing.
HD Topics

• HD overview
• Historical Aspects
• Genetics Review
• Manifestations of HD
• Genetic Testing
• Important Issues
Huntington’s Disease: Overview

• Autosomal dominant
• Adult-onset (late 30’s-40’s)
  – As early as age 1 or as late as age 90
  – 6% present before the age of 20 (Juvenile HD)
• Prevalence 7-10 per 100,000
  – Likely underestimated
• 15-20 year duration
• Triad of clinical findings: Motor, Cognitive and Psychiatric
Over fifty years ago, in riding with my father on his professional rounds, I saw my first cases of ‘that disorder’, which was the way in which the natives always referred to the dreaded disease. We suddenly came upon two women, mother and daughter, both tall, thin, almost cadaverous, both bowing, twisting, grimacing...my medical education had its inception. From this point on my interest in the disease has never wholly ceased."

- Adult-onset
- Progression
- Tendency to insanity and suicide
- Inheritance pattern.
- ‘Hereditary Chorea’
US-Venezuela Collaborative HD Project

- 1972: Centennial celebration of Huntington’s paper
  - Description of HD families around Lake Maracaibo in Venezuela
- 1979: First American expedition to Maracaibo led by Dr. Nancy Wexler
- 1981: First of annual trips to the region
- 1983: Discovery of HD gene marker on chromosome 4
Where is our genetic information stored?

- Cell
- Nucleus
- Chromosomes
Fig. 1 Pedigree of an American Huntington’s disease family.

Fig. 2 Pedigree of the Venezuelan Huntington’s disease family. This pedigree represents
A polymorphic DNA marker genetically linked to Huntington’s disease

James F. Gusella*, Nancy S. Wexler†‖, P. Michael Conneally‡, Susan L. Naylor§,
Mary Anne Anderson*, Rudolph E. Tanzi*, Paul C. Watkins*, Kathleen Ottina*,
Margaret R. Wallace‡, Alan Y. Sakaguchi§, Anne B. Young‖, Ira Shoulson‖,
Ernesto Bonilla‖ & Joseph B. Martin*

* Neurology Department and Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA
† Hereditary Disease Foundation, 9701 Wilshire Blvd, Beverley Hills, California 90212, USA
‡ Department of Medical Genetics, Indiana University Medical Center, Indianapolis, Indiana 46223, USA
§ Department of Human Genetics, Roswell Park Memorial Institute, Buffalo, New York 14263, USA
‖ Venezuela Collaborative Huntington’s Disease Project*
Ancient history of HD

Some descriptions may date back to an unknown time before the discovery of Huntington's Disease (HD). The HD gene, responsible for the disease, is located on the short arm of chromosome 4 (4p). This location is presumed but not definitively identified.
The frustrating search for the gene

- The gene’s approximate location was found in 1983
- Linkage testing could give a likelihood of being affected, but not a certainty.
- The actual gene was not found until 1993
- Required world-wide collaboration of scientists and families
A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group.

The Huntington's disease (HD) gene has been mapped in 4p16.3 but has eluded identification. We have used haplotype analysis of linkage disequilibrium to spotlight a small segment of 4p16.3 as the likely location of the defect. A new gene, IT15, isolated using cloned trapped exons from the target area contains a polymorphic trinucleotide repeat that is expanded and unstable on HD chromosomes. A (CAG)n repeat longer than the normal range was observed on HD chromosomes from all 75 disease families examined, comprising a variety of ethnic backgrounds and 4p16.3 haplotypes. The (CAG)n repeat appears to be located within the coding sequence of a predicted approximately 348 kd protein that is widely expressed but unrelated to any known gene. Thus, the HD mutation involves an unstable DNA segment, similar to those described in fragile X syndrome, spinobulbar muscular atrophy, and myotonic dystrophy, acting in the context of a novel 4p16.3 gene to produce a dominant phenotype.

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Discovering the HD Gene

• 1993: Identification of the gene, **IT-15** Interesting transcript-15 on short arm of chromosome 4 encoding **huntingtin**
  – Expanded CAG repeat in exon 1 as causative mutation
    • Normal: <27
    • Intermediate: 27-35
    • Reduced penetrance: 36-39
    • Pathogenic: ≥40
  – Higher CAG repeat length correlates with earlier age of onset of disease
    • But CAG repeat length accounts for only 50-60% of onset age variability.
  – Belongs to family of expanded CAG repeat disorders
Direct Gene Testing

• Previous testing by linkage/probability
• CAG measurement-direct test
• Highly accurate
• Small percentage of individuals in the gray zone
Key points on **autosomal dominant** inheritance:

**Autosomal**- Both males and females can be affected with HD. Both males and females can pass HD to their children.

**Dominant**- If a person has Huntington disease, there is a 50% risk for each of their children.

If a person does not inherit HD from their parent, they cannot pass it to their children.

Each child of a person with HD has an **independent** 50% risk. (i.e. their risk is not changed by whether or not their brothers’ or sisters’ test results).
Official repeat ranges for HD

- **9-26 repeats** = Normal
  - No risk for HD and no known risk to children.

- **27-35 repeats** = Intermediate
  - No risk for HD, but a small risk to children

- **36-39 repeats** = Reduced penetrance
  - May develop HD and a 50% risk to children

- **40+ repeats** = Full penetrance
  - Will develop HD and a 50% risk to children

15 and 20 CAG repeats

17 and 63 CAG repeats
Genetic Testing for HD

• Diagnostic
• Predictive
• Preconception
• Prenatal
Discovery of HD gene answers many of the “mysteries” of HD

- Anticipation- The observation that the age of onset becomes consistently younger in some families
- Prior to the discovery of CAG repeats, many scientists discounted this observation and attributed it to “hyper-awareness” of families and physicians.
Anticipation is due to expansion of CAG repeats

- CAG repeat numbers can expand when passed to offspring.
- Expansion occurs more often with male transmission.
- Expansion occurs more with larger repeat numbers.
CAG repeats explain anticipation

Diagnosis-65
17,40
Diagnosis-40
17,44
Diagnosis-25
17,50
Juvenile HD
17,68
HD Without Family History

- Parent with intermediate allele/no symptoms HD
- Offspring with symptoms/expansion of CAG repeats
HD without a family history

A molecular explanation:

• Expansion of an intermediate repeat number

16, 35
17, 18
42, 18
Huntington Disease Pathology

Striatal huntingtin inclusions
14 yo with 82 CAG repeats

Photos courtesy of Jean-Paul Vonsattel
HD Symptoms

**MOTOR**
- Chorea
- Dystonia
- Eye movement abnl
- Gait, balance problems
- Rigidity, bradykinesia
- Dysarthria
- Dysphagia

**COGNITIVE**
- Executive Dysfunction
- Concentration
- Attention
- Multi-tasking
- Visuospatial Dysfunction
- Memory Problems

**PSYCHIATRIC**
- Depression
- Anxiety
- Obsessions, Compulsions
- Hallucinations, Delusions
- Apathy
- Impulsivity
  - Suicidality
HD Symptoms

**MOTOR**
- Chorea
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**COGNITIVE**
- Executive Dysfunction
- Concentration
- Attention
- Multi-tasking
- Visuospatial Dysfunction
- Memory Problems

**FUNCTION**
- Employment
- Family Obligations
- Social Activities
- ADLs

**PSYCHIATRIC**
- Depression
- Anxiety
- Obsessions, Compulsions
- Hallucinations, Delusions
- Apathy
- Impulsivity
- Suicidality
HD Progression

Symptoms

Motor
Cognitive
Behavioral
Functional

Prodrome

Manifest

Time

Enroll-HD
Huntington's Disease Society of America
HD Treatment

• There is currently no cure for Huntington disease
• Treatments are geared toward symptom management
• HD treatments are **NOT** easily standardized
• Depending on the constellation of symptoms, certain medications may be preferred
• **Treatment must be individualized**
• Data are lacking to support best treatments
  – Most symptomatic HD treatments in use have not been studies in well-designed, randomized, placebo-controlled trials
HD Treatment

• Motor Symptoms

• Behavior Symptoms

• Cognitive Symptoms

• Psychiatric Symptoms
Juvenile-onset HD

- Dystonia and parkinsonism predominate
- Seizures
- Typically paternal inheritance due to anticipation; expansion of CAG repeat
  - > 60 CAG repeats
- Faster progression (duration 5-15 years)
Delay Onset and Progression

Delay onset or slow progression

Prodrome

Manifest

Delay onset or slow progression

Time

Symptoms
Genetic Counseling

- Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial explanations of hereditary disease.
- Informed decision making
- Shared decision making
Genetic Counseling

- Obtain family history/establish rapport
- Information about HD
- Genetics of HD
- CAG triplet repeats/ranges/age of onset
- Explanation of juvenile onset HD
- Discuss motivations for testing
- Experience with HD: living with HD vs new dx in family
- Timing of testing
Genetic Counseling

- History of depression, suicidality, therapy
- Support system, family, community
- Coping strategies
- Concerns about current at risk status
- Issues of privacy, confidentiality
- Insurance concerns
- Predictive HD testing as model for genetic testing
Testing Perspective

We are all at risk for something

Predictive HD testing
model/multidisciplinary approach

Predictive genetic testing available for many disorders
Last 20 years

- Advances in genetic testing technology
- Genetics affecting all areas of medical care/availability of predictive genetic tests
- Internet/blogs/chat rooms
- Sharing experiences
- Rise of consumer demands
- Interest in genetics/genomics
- Reproductive testing options
- Decreasing paternalism/Shared decision making
Issues to Consider

- Is knowing better than not knowing?
- What would I do differently if I know my gene status?
- No testing of minors
- Privacy
- Health Insurance, Long Term Care, Life Insurance
- Financial considerations
Genetic Information Nondiscrimination Act of 2008
http://www.genome.gov/10002328
Genetic Testing: Motivations

• 18-25 year old
  – Waiting for years to be tested
  – Education/career pathways
• 25-40 year old
  – Reproductive options
  – Financial planning
• Over 40 years
  – Want to know HD status for children
  – Financial planning
Issues to Consider

• Bringing a support person
• Sharing the decision to be tested
• What will I do differently if I find out I am “positive” for the HD gene?
• What will I do differently if I find out I am “negative”?
• Returning for results
Reproductive Options

- Not knowing gene status/not monitoring pregnancy
- Preimplantation Genetic Diagnosis
- Prenatal diagnosis-CVS/Amniocentesis
- Sperm/Egg Donor
- Adoption
Preimplantation Genetic Diagnosis: PGD

PGD Process

Egg + Sperm → Embryo 8 cells → Biopsy → PGD → Embryo transfer
Future of Prenatal Testing

• NIPT Non invasive prenatal screening/testing
• Blood test during first trimester of pregnancy
• Measure CAG repeats
• Confirm with diagnostic test
Importance of Huntington Disease

- Huntington Disease informs on many levels
  - Clinical
    - Hyperkinetic movement disorder: chorea, dystonia, gait and postural instability
    - Treatment of hyperkinetic movements
  - Research
    - Common pathophysiological mechanisms with many other neurodegenerative diseases (including the most common: Alzheimer disease, Parkinson disease)
    - Treatments aimed at neuroprotection can be applied to these other diseases
  - Diagnosis
    - Gene test identifies premanifest and symptomatic patients
    - Serves as model for genetic counseling for all other autosomal dominant neurogenetic diseases
  - Treatment
    - Stage is set for gene therapy and stem cell studies.
Take Home Message

• YOU ARE NOT ALONE
• HDSA Centers of Excellence and HDSA Genetic Testing Centers can help
• National Society of Genetic Counselors NSGC.org
• Collaborative Research

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