Reproductive Options and Huntington Disease
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Presenter Disclosures

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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.
Overview

• HD Basics
• Reproductive Options
• Issues to consider
• Family stories
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
Where is our genetic information stored?

Cell

Nucleus

Chromosomes
Ancient history of HD

• Some descriptions may date back
Some descriptions may date back to the ancient history of HD.

Presumed location of the HD gene.
Autosomal dominant

- Affected father
- Unaffected mother

- Affected child
- Unaffected child
- Unaffected child
- Affected child

U.S. National Library of Medicine
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).
The Huntington 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
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

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.
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)
15 and 20 CAG repeats

17 and 63 CAG repeats
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
Pre-Conception Genetic Counseling

- Explore thoughts, feelings, values
- Partner disagreement
- When to start family
- Taking care of affected family member and children
- Experience with HD
- Weigh pros and cons of reproductive options
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
Reproductive Options

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

- NIPT/Non invasive prenatal screening/testing
- Blood test during first trimester of pregnancy
- Cell free fetal DNA
- Determine CAG repeats
- Confirm with diagnostic test
Family Stories

Genetic Counseling Issues
Prenatal HD Testing

• 25 year old pregnant woman seeks genetic counseling because partner is at risk for HD. Wants prenatal diagnosis.

• Partner is 27 years old and has not been tested; does not want to know HD status.

• Issues: Couple disagrees, family pressures, who is the patient?
Prenatal HD Testing

- 17 year old, unplanned pregnancy wants HD testing and prenatal diagnosis for HD
- Moratorium for testing minors
- Issues: who makes the decisions?
Not knowing

- 35 year old woman with long history of infertility in early pregnancy
- Tested positive for HD gene at the age of 30
- Does not want to take small chance to miscarry with invasive diagnostic procedure
- Issues: cure/effective treatment in the future
Adoption

• Couple at risk for HD (husband has tested positive)
• Facing the future with HD
Unplanned Pregnancy

• 22 year old, gene positive, determined to end legacy of HD in her family
• Decides on CVS and facing 50/50 risk to fetus
• What to do?
Asymptomatic parent

- 28 year old wants to know gene status for family planning purposes
- 45 year old mother does not want to know gene status
- What to do?
• 30 year old at risk for HD, wants PGD but not to know her own HD status
• IVF costs, ?pregnancy rate
• IVF Center to implant only embryos without HD CAG expansion
Reproductive Decision Making

- Complex issues
- Preconception genetic counseling
- Preconception psychological counseling
- Seeking help from qualified professionals
- Identifying support system
Take Home Message

• You are not alone
• HDSA Centers of Excellence
• HDSA Predictive Testing Centers
• National Society of Genetic Counselors