Family Planning and Huntington’s Disease

Lisa Kinsley, MS, CGC
Senior Genetic Counselor
Northwestern University
Feinberg School of Medicine
Department of Neurology
The information provided by speakers in workshops, forums, sharing/networking sessions and any other educational presentation made as part of the 2017 HDSA Convention program is for informational use only.

HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.
Presenter Disclosures

Lisa Kinsley, MS, CGC

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

No relationships to disclose or list
Genetic Counseling

What is it?
Who am I?
What do I do?
Who are Genetic Counselors?

- Health professionals with specialized graduate degrees and experience working in the areas of medical genetics and counseling
- Work as members of a health care team
- Provide information and support to families who have members with birth defects or genetic disorders and to families who may be at risk for a variety of inherited conditions
- Act as resources for other health care professionals and for general public
- Many engage in research activities related to field of medical genetics and/or genetic counseling
Genetic Counseling is…

- the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease

- this process integrates:
  - **interpretation** of family and medical histories to assess the chance of disease occurrence or recurrence
  - **education** about inheritance, testing, management, prevention, resources, and research
  - **counseling** to promote informed choices and adaptation to the risk or condition
Genetic Counseling Training

- Master’s degree in Genetic Counseling
- 2-3 year program
- Training in medical genetics and psychosocial counseling
  - guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families
  - interpret test results
Genetic Counseling Session

- Session components
  - Obtain family history
  - Give information about HD
  - Explain genetics of HD
  - Discuss motivations for testing
  - Explore person’s experience with HD
  - Discuss timing of testing
  - Testing process logistics
    - Insurance coverage? Blood vs. saliva?
  - Review protections for employment, insurance discrimination
  - Results disclosure
Genetics Refresher

genes
chromosomes
proteins
The basics

- cell
- nucleus
- chromosomes
Male chromosomes
Female chromosomes
Chromosome structure
Different genes, different cells

bone cell

pancreas cell

brain cell
DNA
DNA to proteins

- Cell
- Nucleus
- Chromosomes
- Gene
- Protein
Mutated DNA leads to altered proteins

cell
nucleus
chromosomes

gene
protein

Huntington’s Disease Society of America
Inheritance

autosomal dominant
50% risk
Gene location

1 2 3 4 5 6 7 8
9 10 11 12 13 14 15 16
17 18 19 20 21 22 X Y

HTT
Mutation inheritance

- Mutation in the egg DNA
- Mutation in the sperm DNA
- Fertilized egg
- Reproductive
- Bone
- Pancreas
- Brain

Mutation inheritance involves the transmission of a mutation from the DNA of the egg or sperm to the fertilized egg, which then affects different organs and tissues such as reproductive, bone, pancreas, and brain.
DNA expansions

...CATGTGCTACAGCAGCAGCAGCAGCGGTAGCTAGTG...

...CATGTGCACCAGCAGCAGCAGCAGCAGCAGCAGCAGCGGTAGCTAGTG...
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 HD, there is a 50% risk to each child

• 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
  – Their risk is not changed by their siblings’ status
Autosomal dominant inheritance

unaffected

affected
Example pedigree
HD Overview

- Onset can range from 1 year to 90 years of age
- ~6% present before the age of 20 years (juvenile HD)
- Prevalence is 7-10 per 100,000
  - Likely an underestimate
- 15-20 year duration
HD Anticipation

- CAG repeat numbers can expand when passed to offspring
- Expansion occurs more often with male transmission
- Expansion occurs more with larger repeat sizes
Genetic Testing

gene identification
diagnostic vs presymptomatic results
History of HTT

Timeline | Benchmarks in Huntington disease research

- George Huntington's paper is published.
- Mendel's work is rediscovered.
- Restriction fragment-length polymorphisms (RFLPs) are first described.
- The HD gene is mapped to the short arm of chromosome 4 (REF. 15).
- The HD gene is isolated and a CAG repeat mutation is identified.
- The first mouse model for HD is described.
- Transcriptional dysregulation is first proposed.
- The first phase-III clinical trials for HD are published.


- Hoffman describes juvenile Huntington disease (HD).
- Punnett cites HD as autosomal dominant.
- The Venezuela project is initiated.
- Clone contigs of the candidate region are established.
- Exon trapping is developed.
- The Working Group on HD of the WFN/IHA publishes guidelines on counselling for predictive testing.
- Aggregates are described in mouse and patient brains.
- An inducible mouse model of HD is described.
- The first high-throughput screen is published.

WFN/IHA, World Federation of Neurology and the International Huntington Association.
Diagnostic testing process

- Test is done on a blood sample
- Must be ordered by a physician
- Genetic counseling is involved in the process
- Laboratory extracts DNA from white blood cells
- Test ‘counts’ the number of repeats in each gene copy
- Final result report gives two numbers
Diagnostic vs presymptomatic testing

- Diagnostic testing is for individuals who have symptoms
  - fairly straightforward
  - can have psychosocial implications
- Presymptomatic testing is for individuals who are at risk of developing symptoms
  - need family information for this to be an option
  - very likely to have psychosocial implications
  - Huntington’s disease testing protocol
    » meet with genetic counselor and neurologist
    » pre-test counseling, exam, results disclosure, post-test followup
- Cannot prevent or predict for many adult onset conditions
  - Onset of symptoms, age of onset, or disease progression
DNA expansions

...CATGTGCTACAGCAGCAGCAGCAGCAGTAGCTAGTG...

...CATGTGCAACCAGCAGCAGCAGCAGCAGCAGCAGCAGCGGTAGCTAGTG...
## Expansion sizes

<table>
<thead>
<tr>
<th>Type</th>
<th>CAG repeats</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal alleles</td>
<td>26 or fewer</td>
<td>unaffected</td>
</tr>
<tr>
<td>Intermediate alleles</td>
<td>26-35</td>
<td>not at risk of developing symptoms of HD, but because of instability, may be at risk of having a child with an allele in the HD-causing range.</td>
</tr>
<tr>
<td>Gray zone alleles</td>
<td>27-35</td>
<td>at risk for HD but may not develop symptoms. In rare cases, elderly asymptomatic individuals with CAG repeats in this range have been identified.</td>
</tr>
<tr>
<td>Reduced-penetrance alleles</td>
<td>36-39</td>
<td></td>
</tr>
<tr>
<td>HD-causing alleles</td>
<td></td>
<td>Huntington Disease</td>
</tr>
<tr>
<td>Affected alleles</td>
<td>40 or more</td>
<td></td>
</tr>
</tbody>
</table>

**Size of expansion is inversely correlated with age of onset but do not provide an exact age.**
Reproductive Options

- testing a pregnancy
- adoption
- donor egg or sperm
- IVF with PGD
Prenatal testing
Testing a pregnancy

Chorionic villus sampling
10 – 12 weeks

Amniocentesis
15 – 20 weeks
Testing a Pregnancy

**Pros**
- Greatly reduces risk of passing on disease
- "Natural pregnancy"
- Biological relationship with offspring

**Cons**
- May have ethical considerations with decision to terminate pregnancy
- Costs will vary
- Procedure carries small risk of miscarriage
- Could reveal untested parent’s status
Adoption
<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminates risk of passing on disease</td>
<td>Expensive process</td>
</tr>
<tr>
<td>Helping a child, family, or woman in need</td>
<td>– ～$20,000</td>
</tr>
</tbody>
</table>

- Long process
- No biological relationship
- Possible long-term sequelae of adoption
Donor egg or sperm
Donor gametes

Pros
• Eliminates risk of passing on disease

Cons
• May involve several processes
  – *In-vitro* fertilization (IVF)
  – Artificial insemination
  – Egg donor/surrogacy
• Costs vary
  – $8,500 for donor eggs
  – $500 for donor sperm
• No biological relationship
Preimplantation genetic diagnosis

- aka PGD
- Method of screening embryos for a known genetic condition
- Must be performed in conjunction with IVF
  - Literally means ‘fertilization in glass’
  - Historically referred to as ‘test tube babies’
IVF with PGD
### IVF with PGD

**Pros**
- Significantly reduces risk of passing on disease
- Non-disclosure testing available
- Reduced guilt
- No increased risk of birth defects
- Biological relationship
- Acceptable option for at-risk couples that would not consider terminating an affected pregnancy

**Cons**
- ‘Experimental’
  - Maximum accuracy is 98%
  - DNA contamination
  - Testing process can fail
- Emotional and ethical considerations
  - Discarding embryos that could lead healthy, productive lives
- ‘Take-home Baby’ rate
- Can’t predict future
- Risk of prenatal testing, multiple births
- May involve several processes
- Expensive process
IVF with PGD - financial

- IVF cycles
  - $16,000 - $18,000
    - Drugs are $3,000 - $5,000
    - Donor eggs ~$8,500
    - Donor sperm $500
- PGD testing per cycle
  - Additional $2,500 - $6,000
- More than one cycle is usually necessary
- Can be an economic barrier
- 15 of 50 states have laws requiring coverage
  - Eight states mandate coverage of IVF
“PGD for adult-onset conditions is ethically justified when the condition is serious and no safe, effective interventions are available. It is ethically allowed for conditions of lesser severity or penetrance. The Committee strongly recommends that an experienced genetic counselor play a major role in counseling patients considering such procedures.”
Family Stories

Genetic counseling issues
Things to consider
Prenatal Testing

- 25 year old pregnant woman seeking genetic counseling because her partner is at risk for HD.
- She wants prenatal diagnosis.
- Partner is 27 years old and has not been tested. He does not want to know his HD status.

Issues
- Couple’s disagreement
- Family pressures from both sides
- Who is the patient?
Adoption

- Couple at risk for HD – husband has tested positive
- Still want to start a family
- Considering adoption

- Issues
  - Facing future with HD
  - No guarantee of any child having two healthy parents
  - Will adoption agency ask about health?
Asymptomatic Parent

- 28-year-old wants to know her gene status for family planning purposes
- Her 45-year-old mother does not want to know her genetic status

Issues
- Testing daughter could reveal mom’s status
- Disagreement
- Right to information
- Keeping health information from family members
- How to proceed?
Things to consider

- Must have a confirmed familial mutation!
- PGD can have implications for family members’ risks
- Can undergo IVF with PGD without learning one’s own status
- None are risk free, but reproductive options do exist for HD families

- Complex issues involved
- Seek help from qualified professionals
- Identify your support system
Take Home Messages

- HD is an autosomal dominantly inherited condition
- Family planning options exist for individuals who want to reduce the risk of passing the condition on to their children
  - Each method has pros and cons
- Affected and at-risk individuals can benefit from genetic counseling
- Genetic counseling can answer questions and address options for testing, family planning, and research participation
Any questions?