Huntington's Disease Society of America

Presymptomatic Testing for Huntington's Disease

Lisa Kinsley, MS, CGC
Senior Genetic Counselor
Northwestern University
Feinberg School of Medicine
Department of Neurology

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Presenter Disclosures

Lisa M 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
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Symptomatic or Diagnostic Genetic Testing

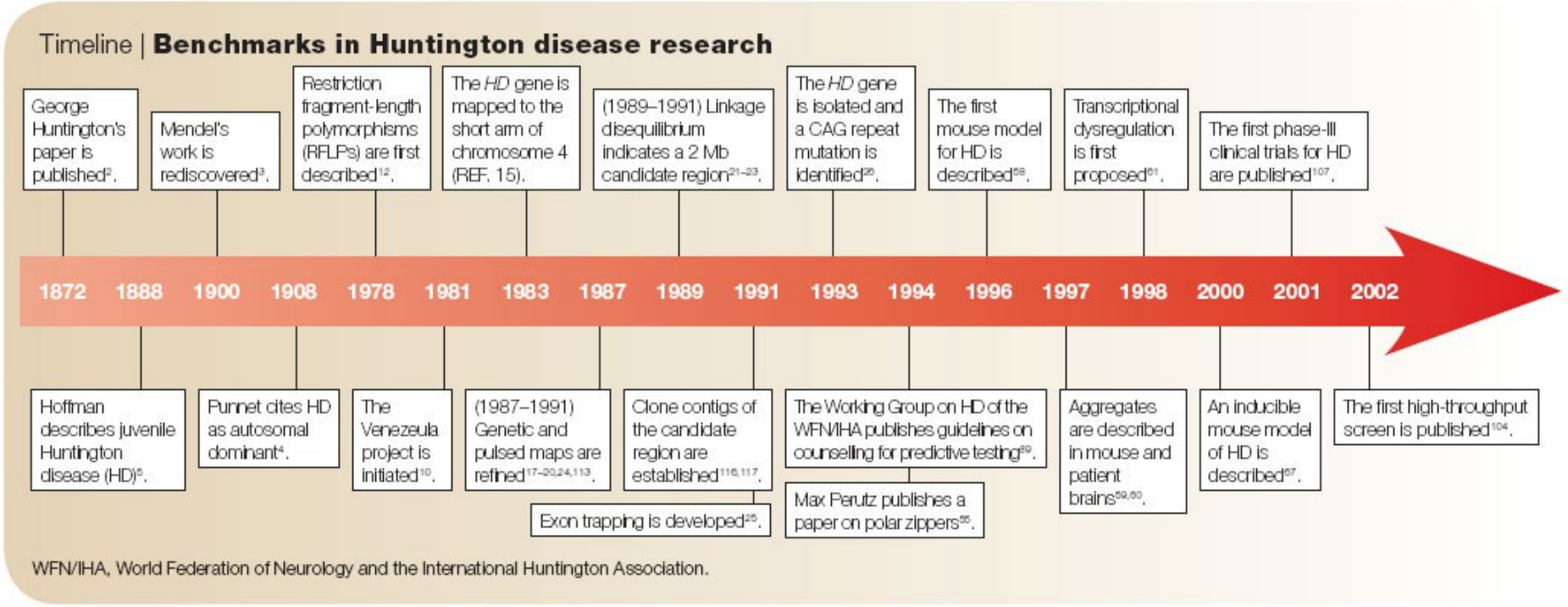
- Genetic testing on someone who has symptoms of the disease in question
  - To clarify the genetic diagnosis
    - Disease subtypes
    - Predictive information about onset/course
  - To provide genetic information for other family members
  - For HD - to confirm clinical diagnosis
  - For possible changes to medical management (less common for neurological/dementia conditions)

Presymptomatic Genetic Testing

- If genetic testing has been done in a family for the disease and a mutation has been identified:
  - For at-risk individuals (no symptoms)
  - Genetic test should be available and adequately interpreted (or if not, full disclosure as to why not)
  - Patient wants information (empowerment)
  - Patient has reasonable likelihood of carrying the altered susceptibility gene
  - Curable vs. incurable genetic disease
  - Personal decision

Presymptomatic testing

- For a known mutation...
- Cannot prevent or predict for many adult onset conditions:
  - Onset of symptoms, age of onset, or disease progression
- Lots of factors to consider:
  - Psychological manifestations
  - Incomplete penetrance (ex: ALS)
  - No preventative treatment
  - Results could influence medical management


Timeline | Benchmarks in Huntington disease research
George Huntington's paper is published[2].
Mendel's work is rediscovered[3].
Restriction fragment-length polymorphisms (RFLPs) are first described[12].
The HD gene is mapped to the short arm of chromosome 4 (REF. 15).
(1989–1991) Linkage disequilibrium indicates a 2 Mb candidate region[21–23].
The HD gene is isolated and a CAG repeat mutation is identified[26].
The first mouse model for HD is described[58].
Transcriptional dysregulation is first proposed[61].
The first phase-III clinical trials for HD are published[107].
1872
1888
1900
1908
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1981
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2002
Hoffman describes juvenile Huntington disease (HD)[5].
Punnet cites HD as autosomal dominant[4].
The Venezeula project is initiated[10].
(1987–1991) Genetic and pulsed maps are refined[17–20,24,113].
Clone contigs of the candidate region are established[116,117].
Exon trapping is developed[25].
The Working Group on HD of the WFN/IHA publishes guidelines on counselling for predictive testing[89].
Max Perutz publishes a paper on polar zippers[55].
Aggregates are described in mouse and patient brains[59,60].
An inducible mouse model of HD is described[67].
The first high-throughput screen is published[104].
WFN/IHA, World Federation of Neurology and the International Huntington Association.

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

HD Predictive Testing Protocol (1994)

- ≥ 18 years old
- Pretest counseling
  - Information about HD, current level of risk, options for testing, limitations/accuracy of test, outcomes
  - Ensure testing is desired for the patient and not to benefit other family members
  - Address impact of all results: +/-/uninformative: on future medical status, family members, career/financial planning, family planning
  - Advised to institute waiting period

HD Presymptomatic Testing Protocol (1994)

- Neurologic examination
- Psychological/psychiatric screening
  - Provide those at risk with frequently needed services and identify people at risk for suicide
- Results disclosure
  - Must be done in person
- Post test follow-up
  - Monitor effects of result and provide support

A Multi-Step Process

Provide post-test counseling and follow-up
Disclose results
Select and offer test
Provide informed consent
Provide pretest counseling
Identify at-risk patients

Presymptomatic Testing Discussion

- What is your understanding of the condition?
- What do you think your risk of inheriting it is?
- What do you think your risk is for developing symptoms in the future?
- How is your <relative> handling the idea that he carries the gene mutation?
  - Has it changed the way he lives his life at all?
  - Do you feel that you treat him differently since you learned he has the condition?
  - Do other people know?
- What will you do with the information if you are found to have the mutation?
- If you are negative, how would it change your view? Survivor guilt for not inheriting the mutation, change the way you figured your life would turn out?

Presymptomatic Testing Discussion

- How do you see a positive result changing your life?
  - Would it affect whether you would be in a relationship with someone, get married, have children, save money, travel, job/career path taken?
  - If any would be affected, what if symptoms never get appear?
  - Would you look back on your life and have regrets for not doing these things figuring you would get symptoms?
  - If no children - donor egg? PGD?
  - If not saving money not expecting to live to old age, and then you do, then what?
- Timing of testing
  - Stressful time in life? (middle of divorce or break-up of relationship) at work, school, or good time in life such as right before or after marriage, or around the holidays?

Presymptomatic Testing Discussion

- Disclosure of results
  - Who will you tell about the results?
  - Will you tell them the same day you are given the results?
  - What will you do the day you get the results? Will you go back to work or take the day off?
- Relationships
  - Is your spouse supportive of your decision to be tested?
  - Is someone pushing you to have testing?
  - Have you discussed decisions affecting you as a couple that you might make differently depending on your test results?
  - Have you been fearful of your spouse leaving you when you show symptoms of the condition?

Presymptomatic Testing Discussion

- Children
  - Do you children know about the condition?
  - Will you tell them the results?
- Extended family
  - How do you perceive the results of the testing will impact your interactions with your siblings?
  - If you do not have the mutation, you may experience survivor guilt. How do you think you will cope with these feelings?
  - Who do you plan on telling the results to in your family?
- Friends
  - Are there people in your life that you feel you can talk to about your decision to be tested?

Reasons to Decline Presymptomatic Testing

- Psychiatric consequences from positive result
  - "I want to get tested but only if it's negative."
- Employment or insurance discrimination
  - GINA
- Interpersonal relationships/family dynamics
- People at 25% risk

Early predictive testing studies

- Schoenfeld et al. 1984 and Stern & Eldridge 1975 surveyed those at risk for HD and 73% and 77%, respectively said they would use a safe and reliable predictive test if one were available.
- In 1987 (after announcement of linkage analysis), five surveys were performed which suggested the number of at-risk individuals intending to take test was still high, 59-79%.
- Quaid et al (1989). n=349 at 50% risk. Only 65 (18%) contacted them for testing. 33 completed educational component: 21 requested testing; 12 did not request testing
- Lower than expected uptake of test of 5-24% for studies in the 1990s-early 2000

Behaviors of those undergoing predictive testing

- Those who have had prior exposure to severe HD and at 50% risk (compared to 25%) have longer waiting period to testing, but once were tested, were more likely to receive the results.
- Those who didn't complete testing: younger, less experience with severe disease, at <25% risk, knew about risk for shorter time period

Anna

Brendan

Bridget

QUESTIONS?

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