Huntington's Disease Society of America

Genetics and Huntington disease

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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

Matthew Bower, MS

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

No relationships to disclose

Huntington's Disease Society of America

Roadmap:

- Ancient history (aka before 1993)
  - Mapping the HD gene
- Modern history
  - The era of predictive testing
- Life in a molecular lab
- Molecular explanations for HD mysteries

HD history--Making genetics interesting!

$$\mathrm{Var}\,[LR(G)] = \mathrm{Var}\,(\alpha_{CC} + \beta + \gamma X^T + \delta) \tag{B6}$$

$$= \mathrm{Var}\,(\alpha_{CC}) + \sum_{i=1}^{n} \mathrm{Var}\,(\beta_i) + \sum_{i=1}^{p_1} X_i^2\,\mathrm{Var}\,(\gamma_i)$$

$$+ \sum_{i=1}^{p_2} \mathrm{Var}\,(\delta_i) + 2\sum_{i=1}^{n} \mathrm{Cov}\,(\alpha_{CC},\beta_i) + 2\sum_{i=1}^{p_1} X_i\,\mathrm{Cov}\,(\alpha_{CC},\gamma_i) + 2\sum_{i=1}^{p_2} \mathrm{Cov}\,(\alpha_{CC},\delta_i)$$

$$+2\sum_{i=1}^{n}\sum_{i=1}^{p_1} X_i\,\mathrm{Cov}\,(\beta_i,\gamma_i) + 2\sum_{i=1}^{n}\sum_{i=1}^{p_2} \mathrm{Cov}\,(\beta_i,\delta_i) + 2\sum_{i=1}^{p_1}\sum_{i=1}^{p_2} X_i\,\mathrm{Cov}\,(\gamma_i,\delta_i)$$

$$+2\sum_{i<i'}\sum \mathrm{Cov}\,(\beta_i,\beta_{i'}) + 2\sum_{i<i'}\sum \mathrm{Cov}\,(\gamma_i,\gamma_{i'}) + 2\sum_{i<i'}\sum \mathrm{Cov}\,(\delta_i,\delta_{i'})\ ,$$

History of HD in America

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

By George Huntington, M. D.,

Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 13, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not af-

Huntington G. (1872) *The Medical and Surgical Reporter* 26(15)

What was notable about Dr. Huntington's description?

- Published when he was only 22 years old!
- His only medical publication.
- Drew on 78 years of records from his family's medical practice on long island
- Accurate description of the hereditary nature of the disease
  - Gregor Mendel had only described dominant and recessive patterns of inheritance in 1865 (using peas!)

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).

While we understood the inheritance pattern for many years, we did not have the necessary tools to find the actual gene:

- Important groundwork from the 20th century
  - The discovery of DNA
  - Formation of patient advocacy groups
    - Most notably the contributions of the Wexler family.

1979- The US-Venezuela HD Collaborative Research Project

Why look for genes?

- Understand the mechanism of disease
- Potential treatments
- Answers for families
- Scientific curiosity

Why Venezuela?

- Lake Maracaibo region of Venezuela has the highest incidence of HD in the world.
- All cases can be traced to a single European ancestor.
- This founder has ~18,000 descendants.

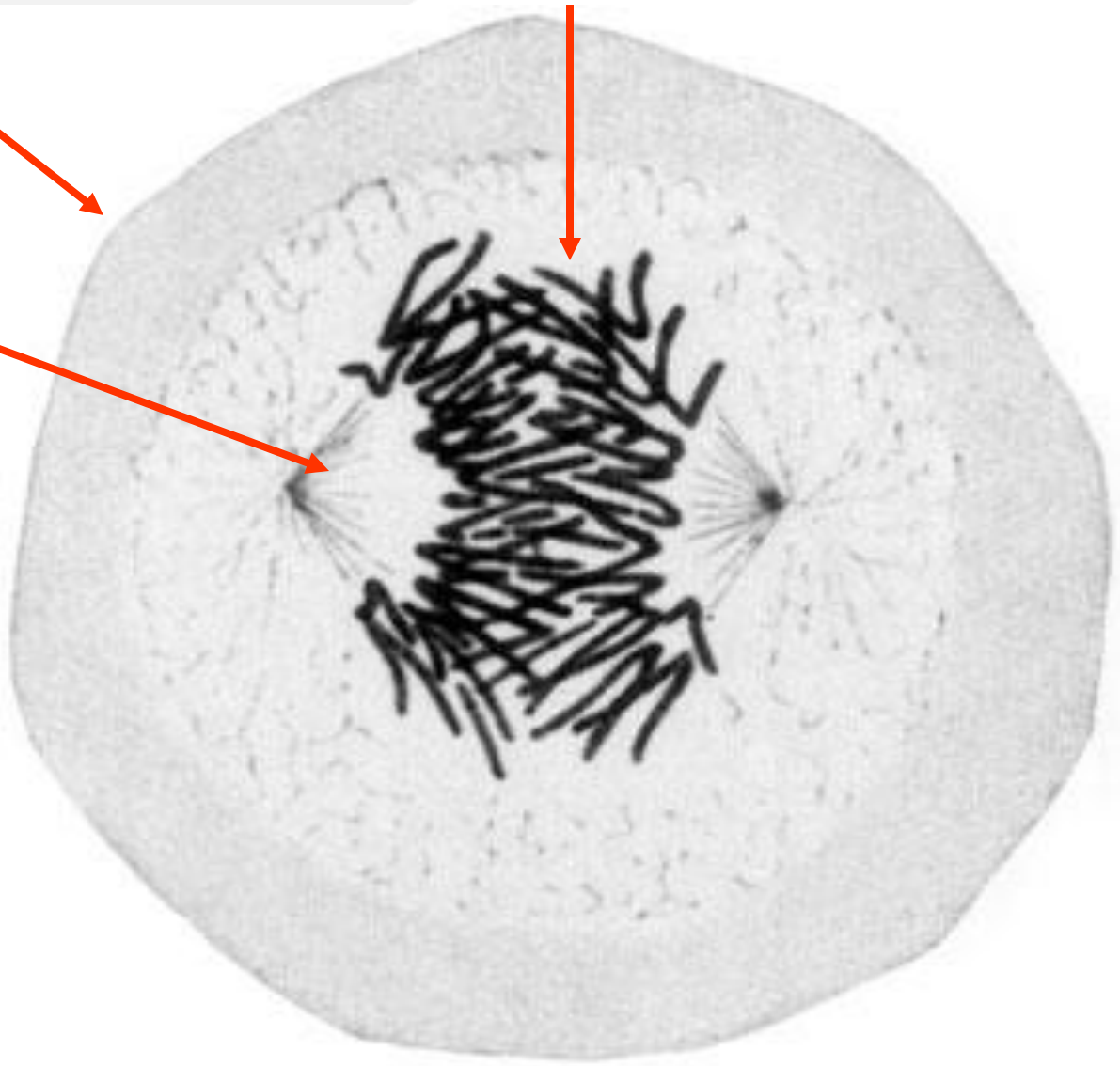
Searching for genes- A brief detour to define genetic terms.

Where is our genetic information stored?

Chromosomes

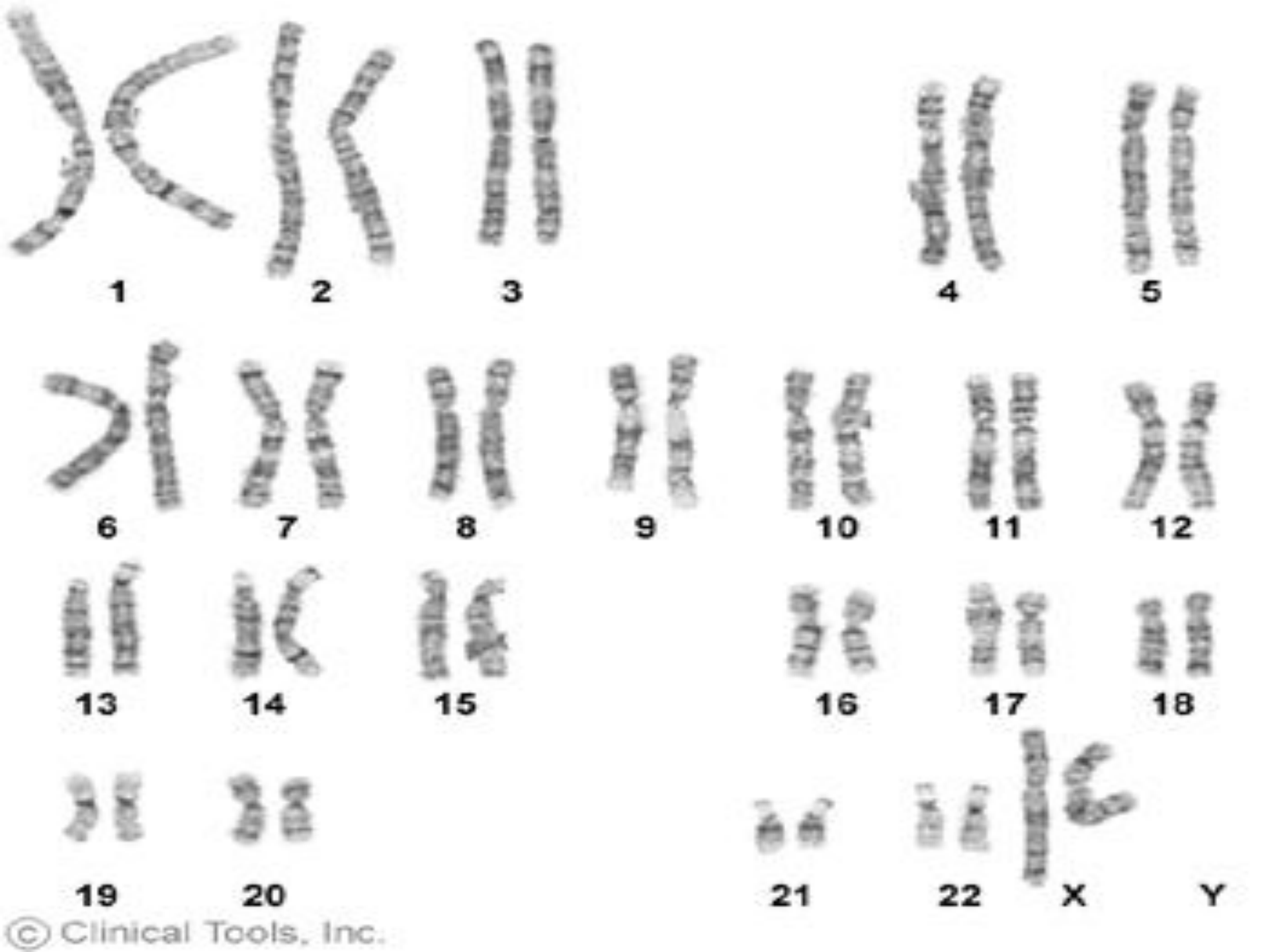
Cell

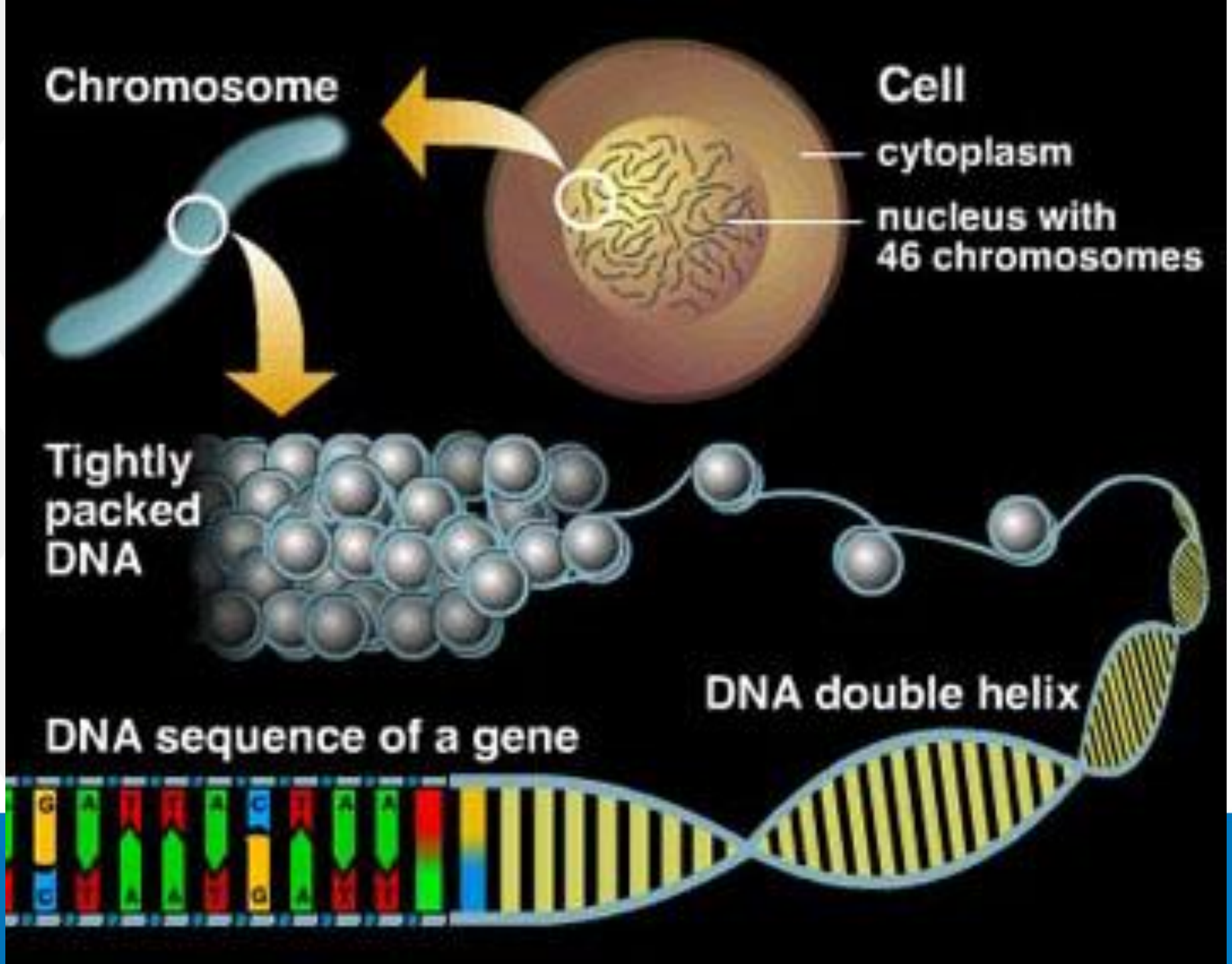
Nucleus



What are chromosomes ?

- Packages of genetic information
- We have two copies of each chromosome (one from mom and one from dad)




Chromosome
Cell
cytoplasm
nucleus with
46 chromosomes
Tightly
packed
DNA
DNA double helix
DNA sequence of a gene

What is a gene?

- A gene is a series of genetic letters (A, C, G, T) that spells out a specific instruction for the body.
- Genes encode proteins.
- The Huntington disease gene tells the body how to make “Huntingtin protein”-nobody knows the function of this protein.

The HD story- finding the gene

Perspective:

In 2011, finding the HD gene would be a relatively simple undertaking.

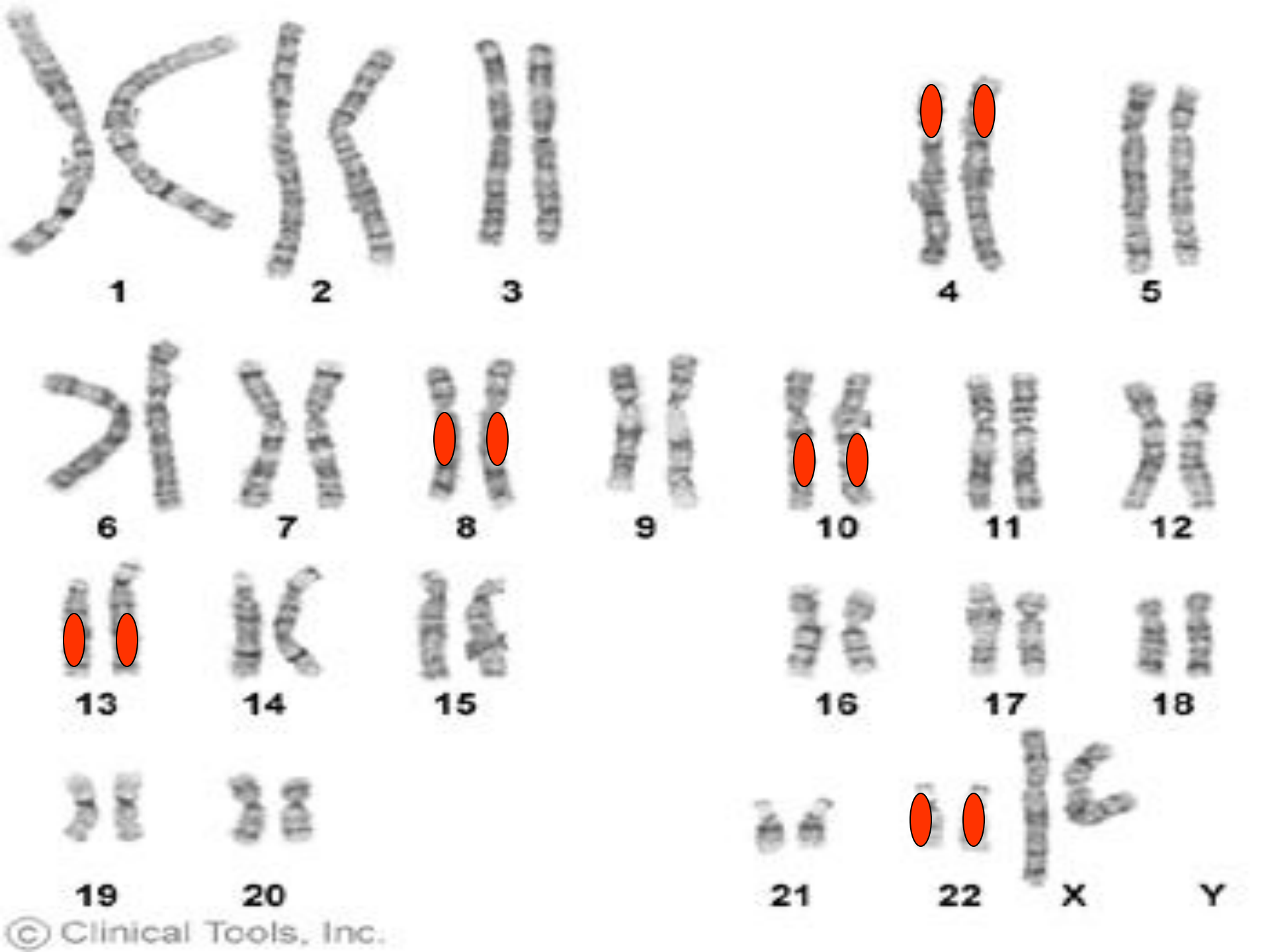
The HD story- finding the gene

1979

- No modern scientific techniques
- No human genome sequence
- No catalogs of normal variants to use for mapping
- No clues from the normal structure or function of the gene product.
- Late age of onset- difficult to assign individuals to “Affected” or “unaffected” groups

How do you map a gene?

- You need large families who are willing to be clinically evaluated and to give a blood sample.
- Researchers then look for parts of chromosomes that are shared by family members affected with the condition.
- Conversely- exclude areas of the genome that are not shared by affected individuals.
- Initial results usually highlight several areas of interest (see next slide)



What comes next?

- Researchers try to hone in on which of these regions actually contains the gene.
- Larger families (and a little luck) are needed for more precision.
- In 1983, researchers pinpoint the approximate location of the HD gene on chromosome 4.

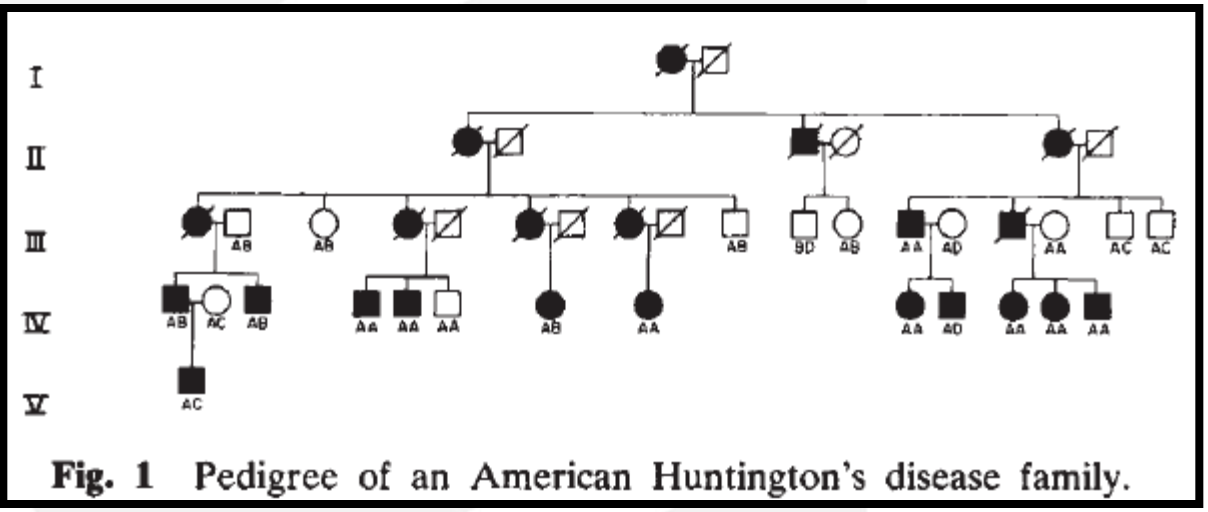


Fig. 1 Pedigree of an American Huntington's disease family.

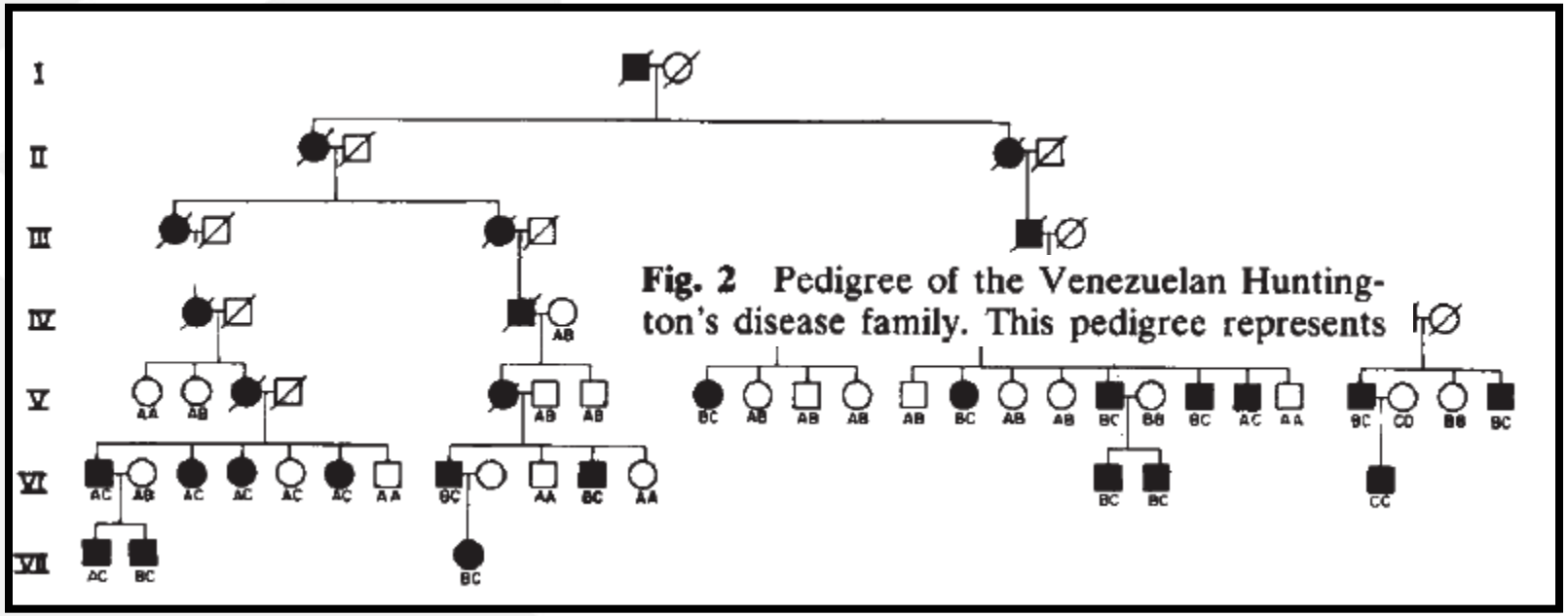


Fig. 2 Pedigree of the Venezuelan Huntington's disease family. This pedigree represents

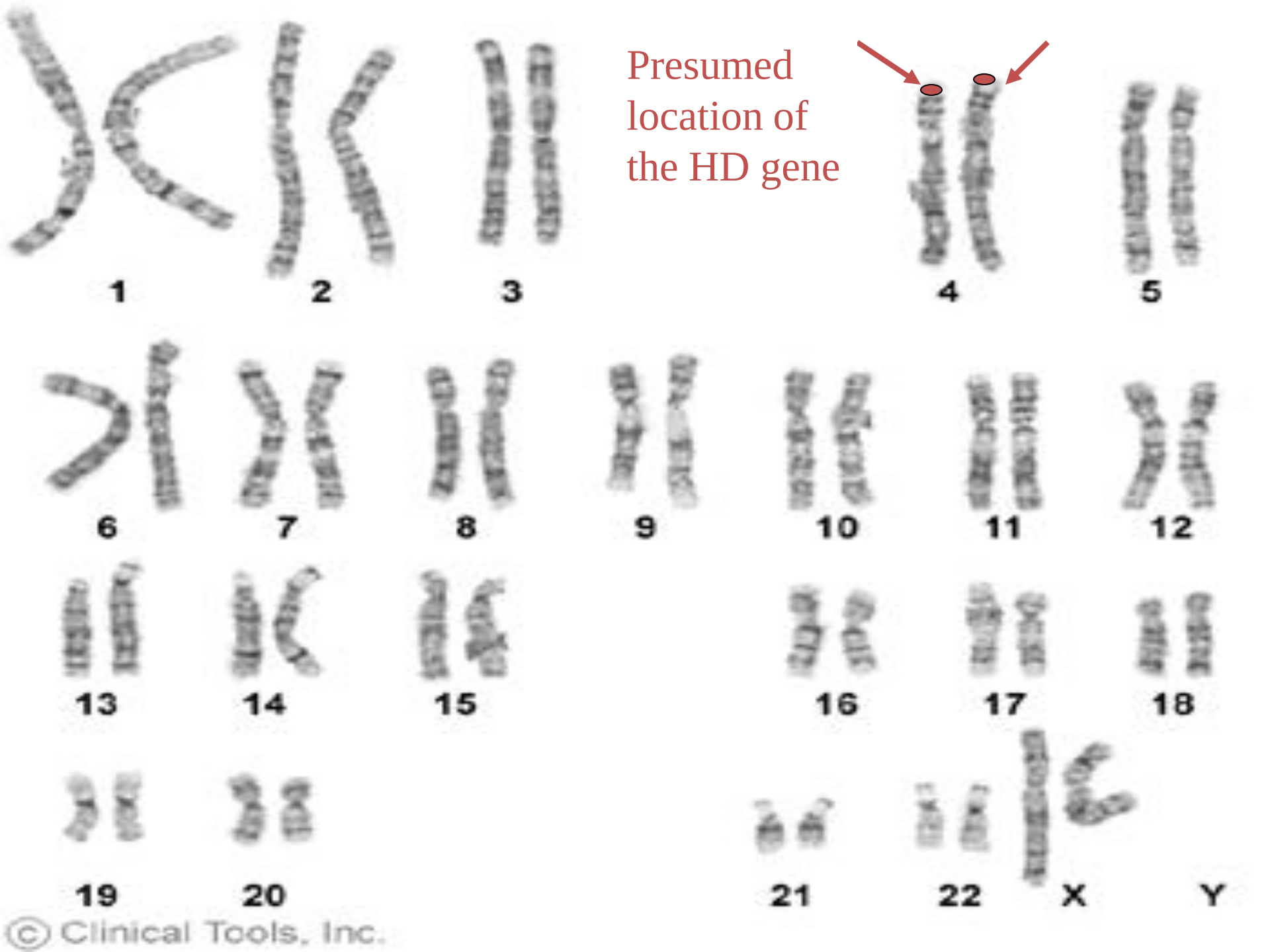
Gene location is mapped to 4p16.3

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#

Nature 306(5940);


Presumed
location of
the HD gene
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y
© Clinical Tools, Inc.

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

Success!

Display AbstractPlus Show 20 Sort By Send to

All: 1 Review: 0

1: Cell. 1993 Mar 26;72(6):971-83.

Comment in:
Cell. 1993 Mar 26;72(6):817-8.

A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group.

[No authors listed]

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PMID: 8458085 [PubMed - indexed for MEDLINE]

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Francis S. Collins, M.D., Ph.D.
NIH Director

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At NIH, we are dedicated to improving the health of Americans by conducting and funding medical research.

We also train scientists, and communicate medical and health sciences information to patients, their families, health care providers and the general public.

NIH guides America's efforts in medical research. Our goal is to uncover new knowledge that will help prevent, detect, diagnose, and treat disease and disability, from the common cold to the rarest genetic disorder.

Our investment in understanding such diseases as AIDS, diabetes, heart disease and cancer returns dividends in longer, healthier, and safer lives.

We continue to make major inroads in fighting humanity's most enduring illnesses. And we are working to confront new threats to our health and safety, like bioterrorism.

We encourage you to explore the wealth of medical research on the NIH Web site

Huntington's Disease Society of America

Discovering the HD gene

- The HD gene was called “IT15”
- The gene contained a repeated series of letters- a CAG repeat.
- Affected individuals from 75 different families consistently had > 40 CAG repeats
- Unaffected individuals consistently had <30 repeats
- “Intermediate” range of 30-40 repeats- uncertain significance
- **Please note, these repeat ranges are not currently accurate!!!!**

Discovery of HD gene opened the door for accurate predictive testing

Rather than a “probability” of being affected based on sharing genetic information, individuals received their own “CAG” repeat number

Discovery of HD gene opened the door for accurate predictive testing

1: Neurology. 1994 Aug;44(8):1533-6.

Guidelines for the molecular genetics predictive test in Huntington's disease. International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea.

[No authors listed]

PMID: 8058167 [PubMed - indexed for MEDLINE]

Predictive Testing Guidelines
Key Points- Autonomy

"2. The decision to take the test is the solely choice of the individual concerned. No requests from third parties - family or otherwise - shall be considered."

"2. The individual must choose freely to be tested and must not be coerced by family, friends, partners or potential partners, physicians, insurance companies, employers, governments, or others."

Neurology (1994) 44(8) 1533-1536.
Journal of Medical Genetics (1994) 31(7) 555-559

Predictive Testing Guidelines
Key Points- Juveniles

"2.1 The test is available only to individuals who have reached the age of majority (according to the laws of the respective country)."

Neurology (1994) 44(8) 1533-1536.
Journal of Medical Genetics (1994) 31(7) 555-559

Predictive Testing Guidelines
Key Points- Setting

"2.9 The counselors should be specifically trained in counseling methods and form part of a multidisciplinary team."

"2.9 Such multidisciplinary team should consist of, e.g.., a geneticist, a neurologist, a social worker, a psychiatrist and someone trained in medical ethical questions."

Neurology (1994) 44(8) 1533-1536.
Journal of Medical Genetics (1994) 31(7) 555-559

Lessons from 15 years of predictive testing

<u>Uptake of predictive genetic testing</u>– What percentage of the "at-risk" population chooses to have predictive genetic testing.

• Prior to the availability of predictive testing, 60-85% of at-risk individuals said they would use a predictive test.

•Large study of Canadian experience reflected worldwide trends that only 10-20% of at-risk individuals have chosen to have predictive testing.

Creighton et al (2003) *Clinical Genetics* 63(6) 462-475

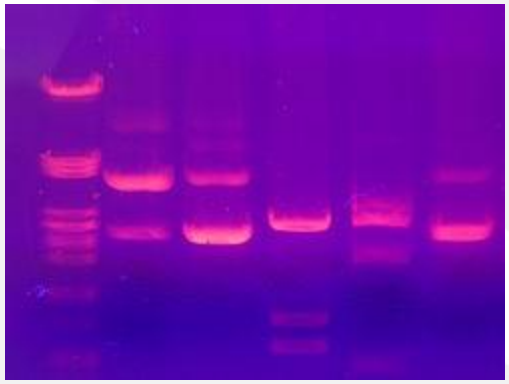
Lessons from 15 years of predictive testing

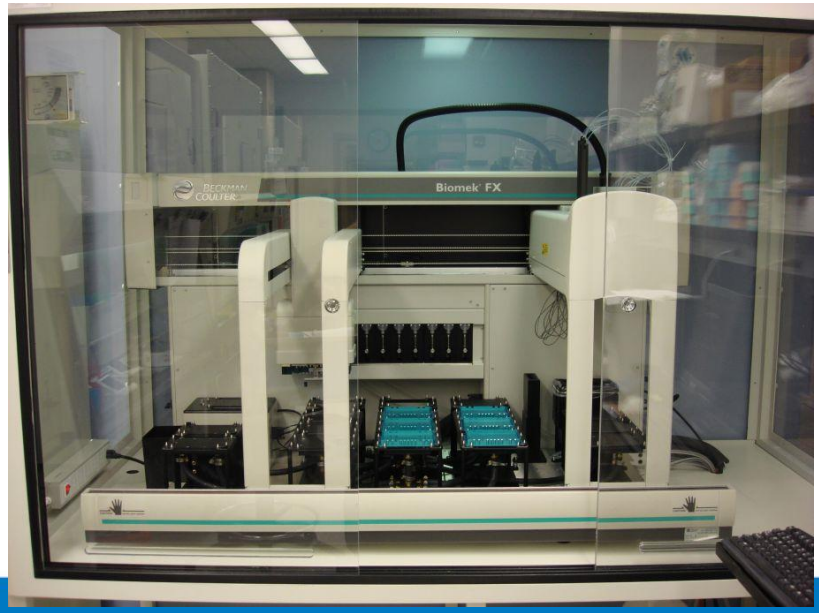
Who uses predictive testing?–

- Females tend to outnumber males 2:1
- Average age in two studies (37-39)

Creighton et al (2003) *Clinical Genetics* 63(6) 462-475.

Life in a Molecular Diagnostics Lab





My life in a Molecular Diagnostics Lab

Life in a Molecular Lab

- The molecular lab at the University of Minnesota performs testing for hospitals throughout the country
- >4000 tests have been performed since the 1990's

Receiving the sample

- Most of our testing is done with blood samples.
- We occasionally test other tissue from autopsy (skin, brain).
- Testing can be performed on any tissue containing DNA (no hair or fingernails…sorry CSI fans).

Receiving the sample

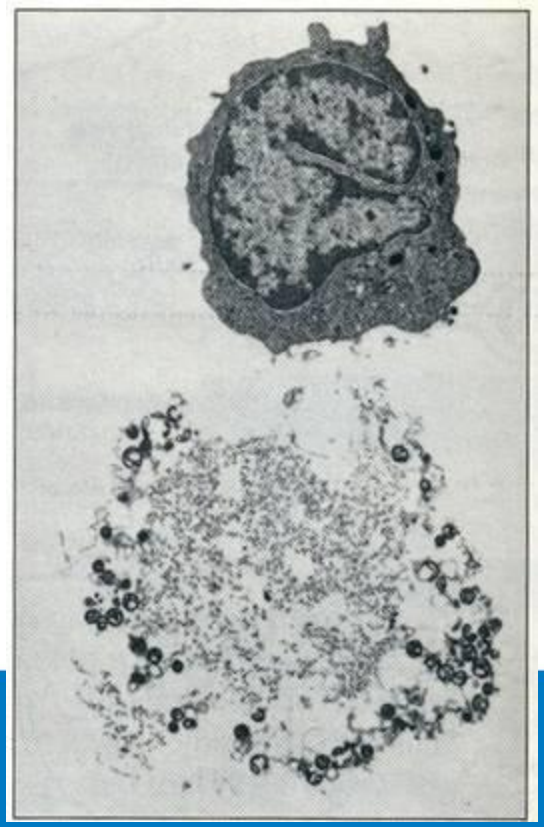
- One of the most important steps is identification of the sample.
- 2 identifiers must be matched-usually name and date of birth.
- Samples are assigned a unique number which is used to track it through the testing process.


CAUTION
RADIOACTIVE MATERIALS

Cell Lysis- A controlled explosion!

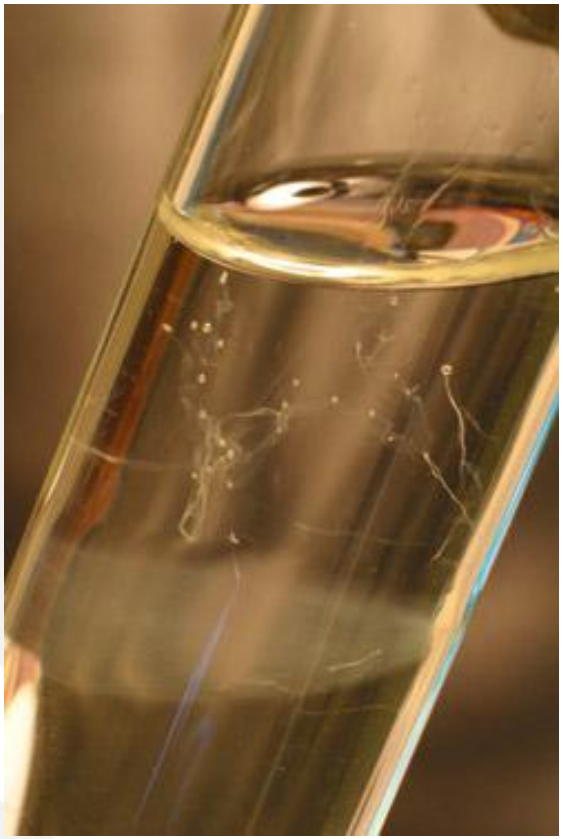
Before lysis

After lysis



DNA precipitation-

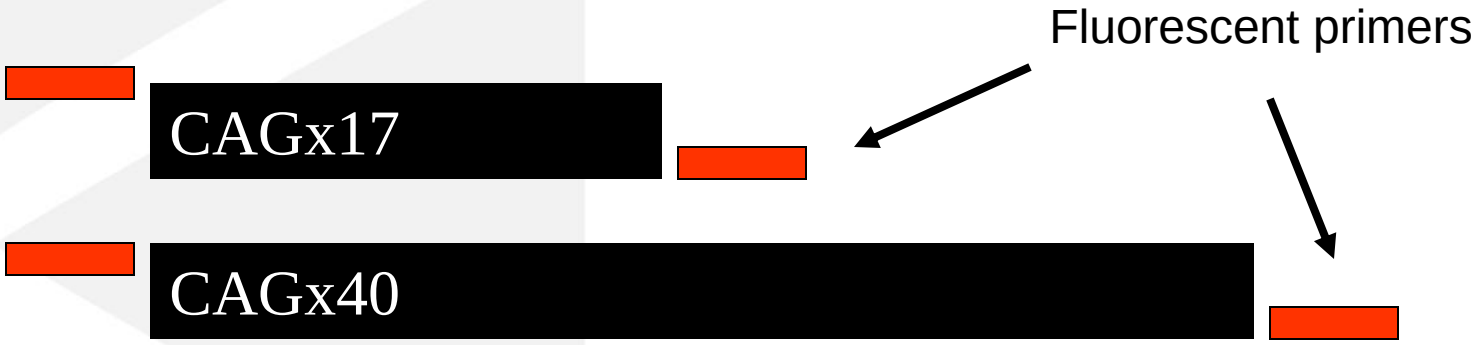
DNA is “pulled out” of the solution by using alcohol



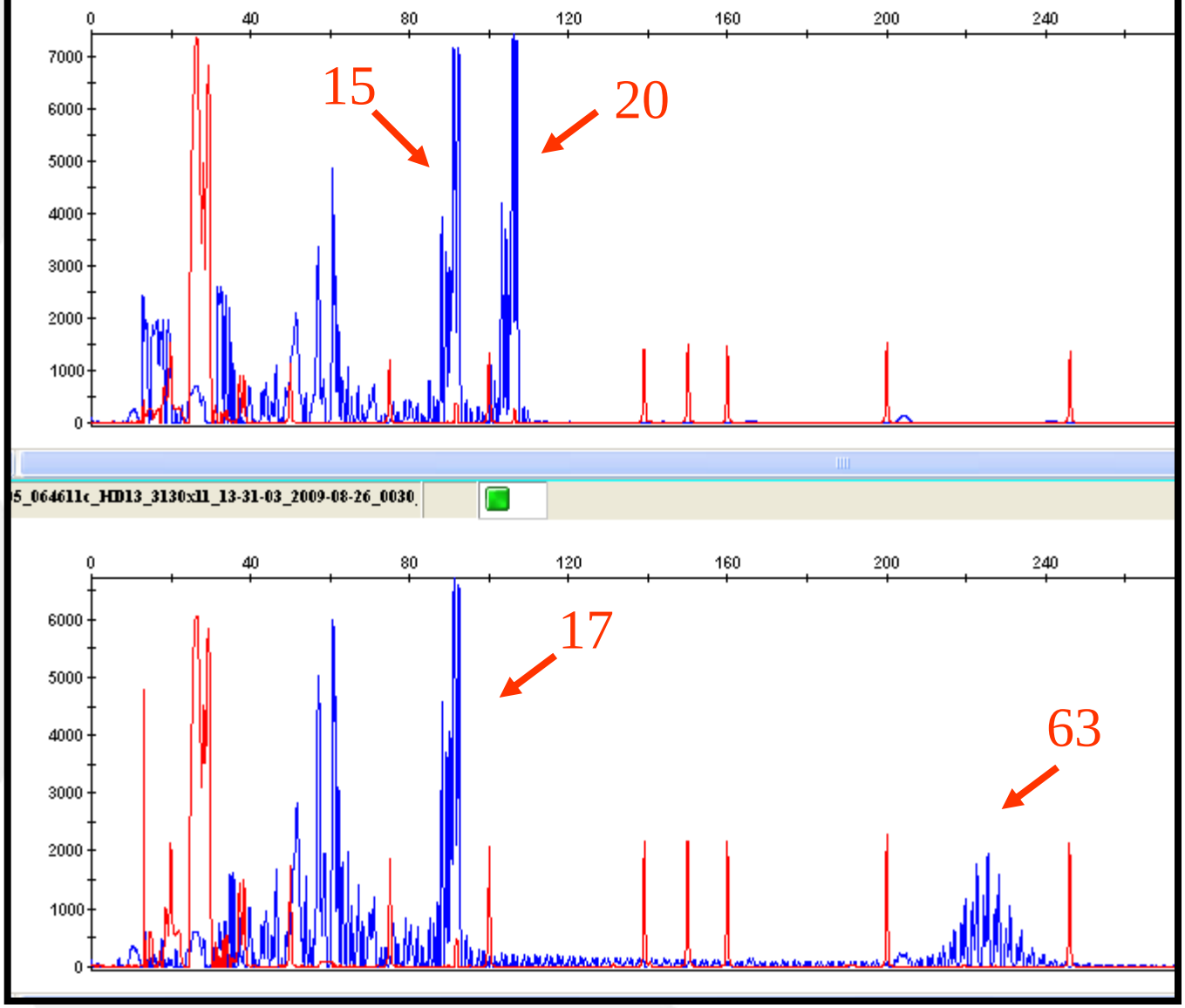
Question- How can we visualize 2 tiny pieces of DNA?

Answer-Make millions of fluorescent copies!

PCR- molecular “xeroxing”



PCR – Molecular Xeroxing



15 and 20 CAG repeats

17 and 63 CAG repeats

FAIRVIEW

Fairview Diagnostic Laboratories
D293 Mayo, MMC 198
420 Delaware Street SE
Minneapolis, MN 55455-0374
Phone: 612-273-7838

Patient: **PT-CAP, MGL2-15 2010B**

Case #: G10-14356

Fairview ID: U547-893

Collected	10/12/2010 00:00	Client:	Cytogenetics Lab, PT		
Received:	10/12/2010 14:36	Submitting Location:	U547 (B)	Other ID:	{None}
Reported:	10/15/2010 14:19	Billing Number:	B024234403	DOB:	01/01/1900
		Encounter Number:	B024234403	Sex:	Unknown
Ordering Phy:	PHYS NON-STAFF		MDL Accession#: 10-14761		
Additional Phy(s):	{None}				

MOLECULAR DIAGNOSTICS REPORT

TEST(S) REQUESTED:
Huntington Disease Molecular Analysis

SPECIMEN DESCRIPTION:
DNA

CLINICAL COMMENTS:
CAP

RESULTS:
PCR:
CAG Repeat Sizes:
Allele 1 18
Allele 2 59

METHODOLOGY: Total cellular DNA was extracted from the above patient's sample and was subjected to amplification using primers specific for regions flanking the CAG trinucleotide repeat segment of the HTT(previously named *IT15*) gene. The PCR fragments were analyzed on an ABI 3130xl Genetic Analyzer and results were analyzed using Genemapper software. Repeat sizes are accurate +/-2 repeat units.

INTERPRETATION:
There is an expansion of an *HTT* allele to a size greater than 35 CAG repeats. These results indicate that this individual has the *HTT* CAG repeat expansion that causes Huntington disease. Genetic counseling regarding these results is recommended.

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Technical results- "CAG" repeat numbers

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DNA

CLINICAL COMMENTS:
CAP

Interpretation- what does the technical result mean for the patient?

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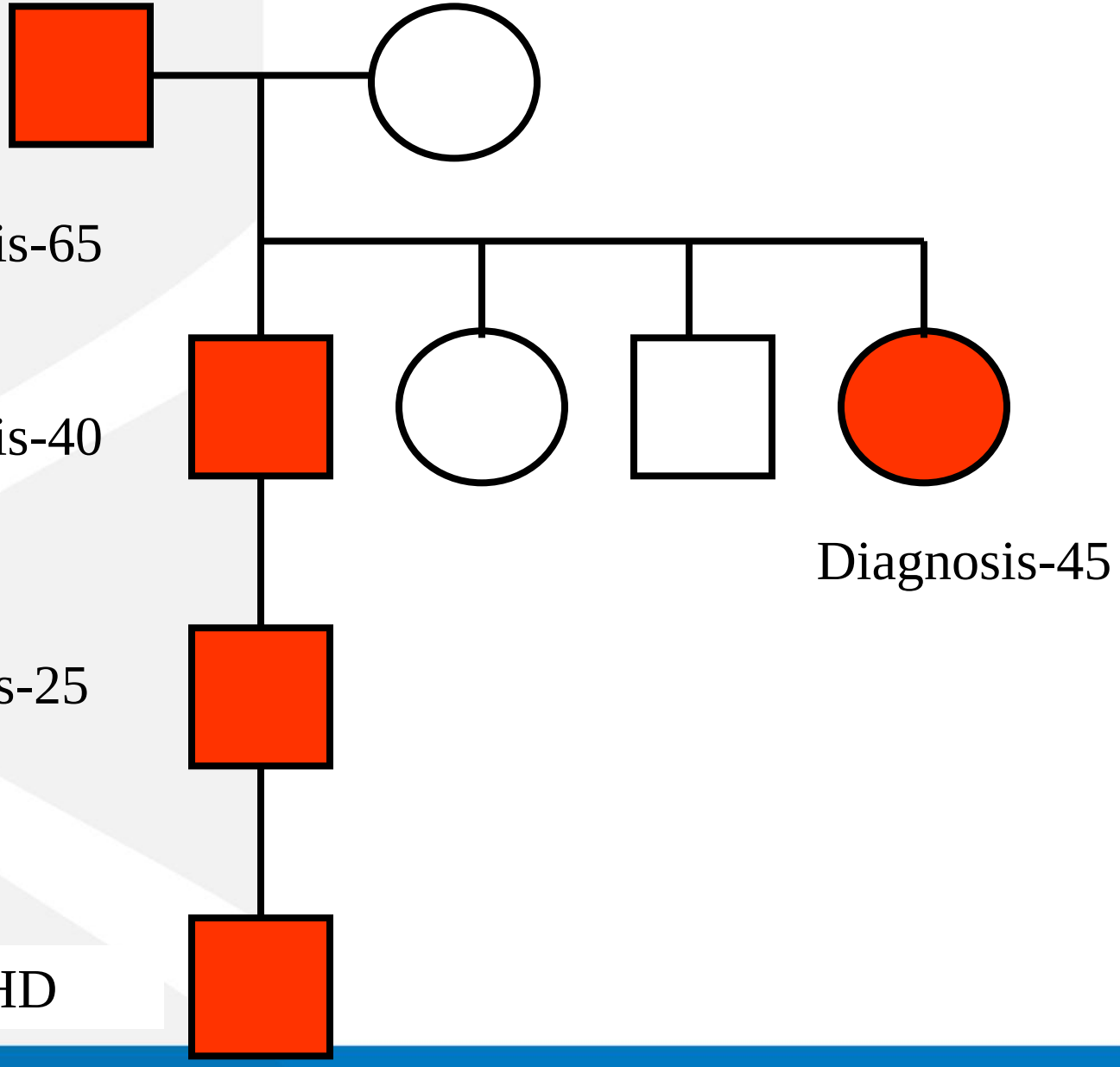
Official repeat ranges for HD

- **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

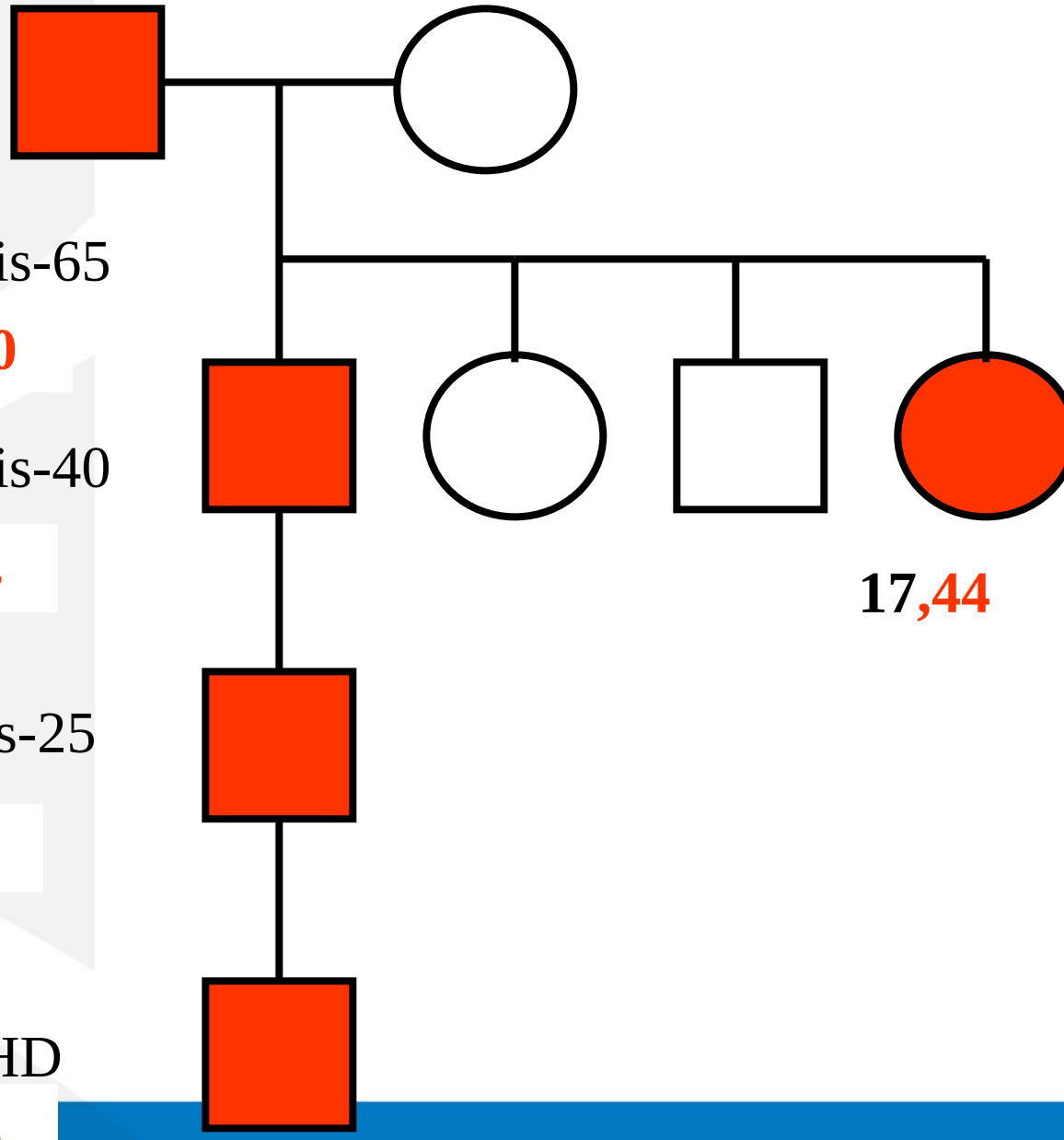
Potter et al. (2004) *Genetics in Medicine* 6(1) 61-65.
ASHG (1998) *American Journal of Human Genetics* 62(5) 1243-1247.

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.


Diagnosis-65
Diagnosis-40
Diagnosis-45
Diagnosis-25
Juvenile HD

CAG repeats explain anticipation



Diagnosis-65

17,40

Diagnosis-40

17,44

17,44

Diagnosis-25

17,50

Juvenile HD

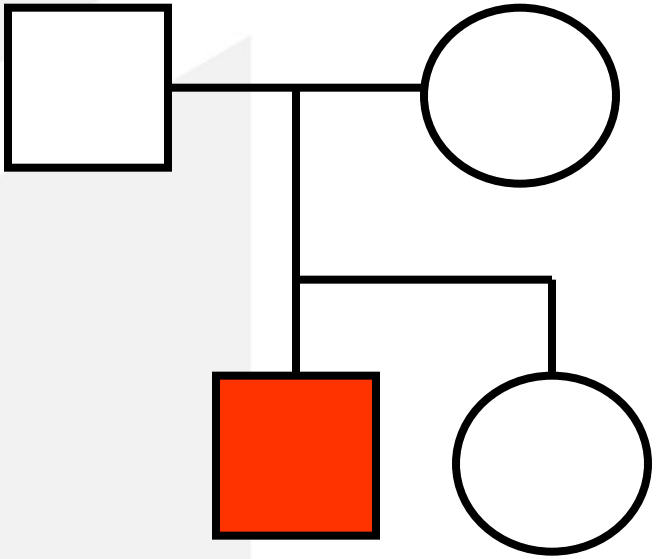
17,68

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.
- Some genes are more stable than others

HD without a family history-

as many as 20% of cases

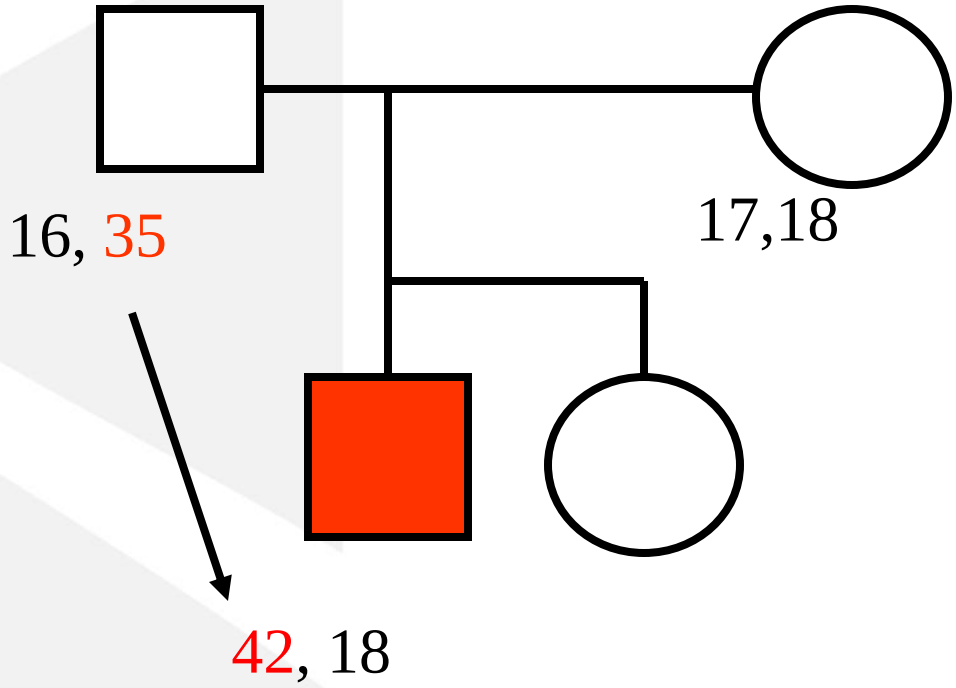


HD-Diagnosed
age 45

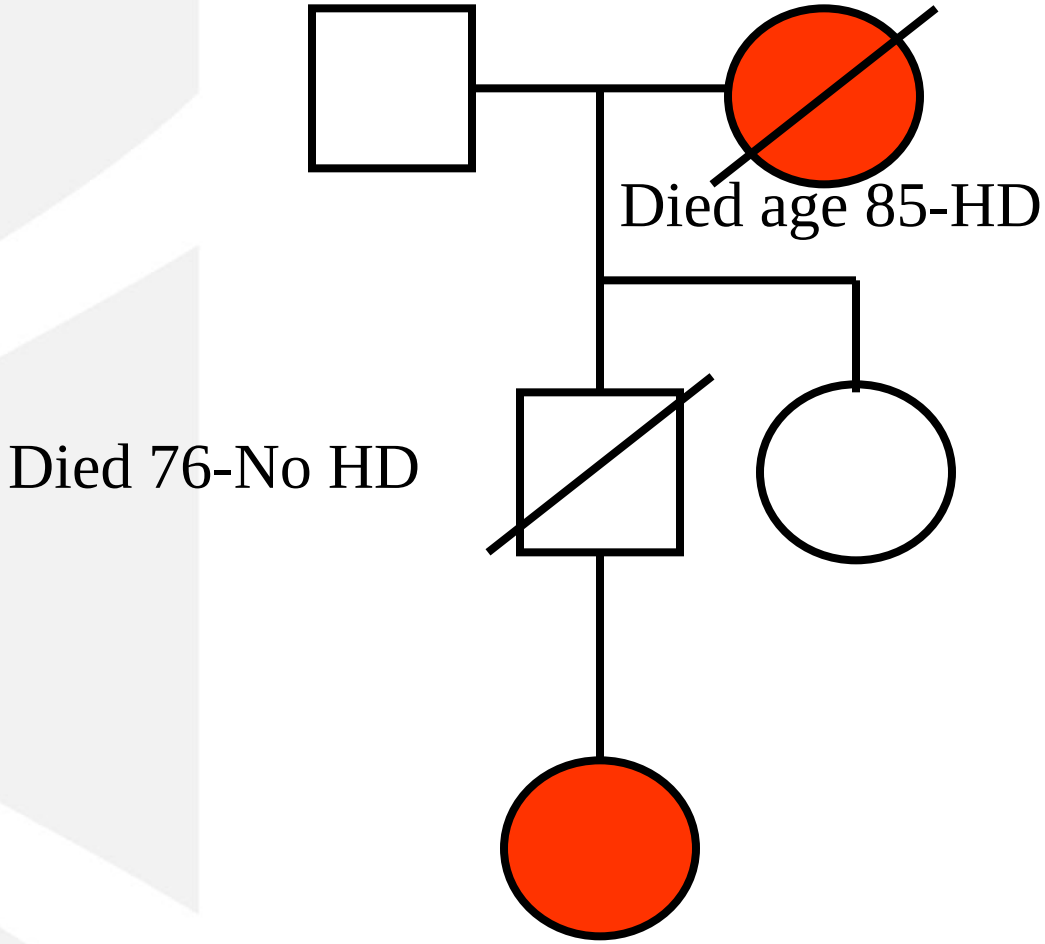
HD without a family history

A molecular explanation:

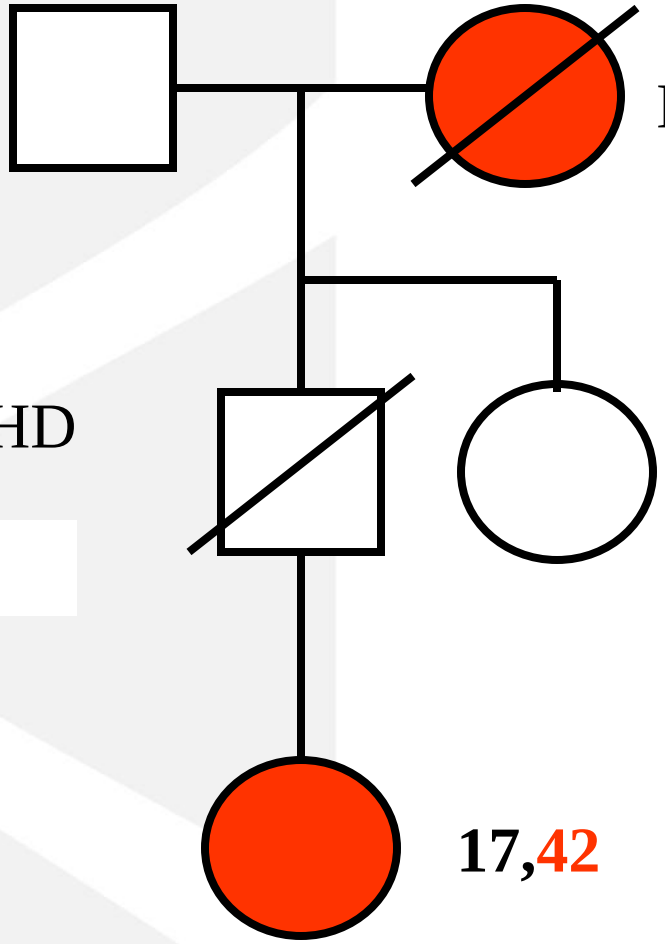
- Expansion of an intermediate repeat number



HD “skips generations”



HD “skips generations”



Died age 85-HD

17,37

Died 76-No HD

17,37

17,42

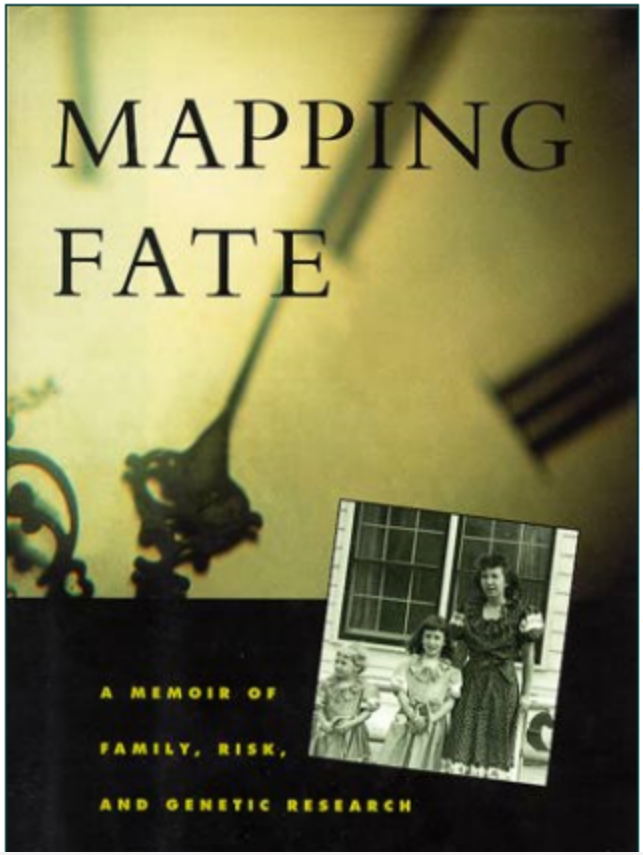
HD diagnosed age 44

A “Reduced penetrance” mutation explains this family history

Alice Wexler

Mapping Fate

A Memoir of Family, Risk, and Genetic Research.



In *Mapping Fate*, Alice Wexler tells the story of a family at risk for a hereditary disease, once called Huntington's chorea. That her mother died of the disease, that her own chance of inheriting it was fifty-fifty, that her sister and father directed much of the extraordinary biomedical research to find the gene and a cure, make Wexler's story both astonishingly intimate and scientifically compelling.

Recording her own emotional odyssey, Wexler sifts through memories, dreams, and her mother's beloved books and letters to find the personality of the woman Huntington's stole away. Despite such painful circumstances, Wexler writes with clarity and depth about mothers and sisters, about the nature of living at risk, and how her family was alternately driven apart and flung together by this destiny they could not escape.

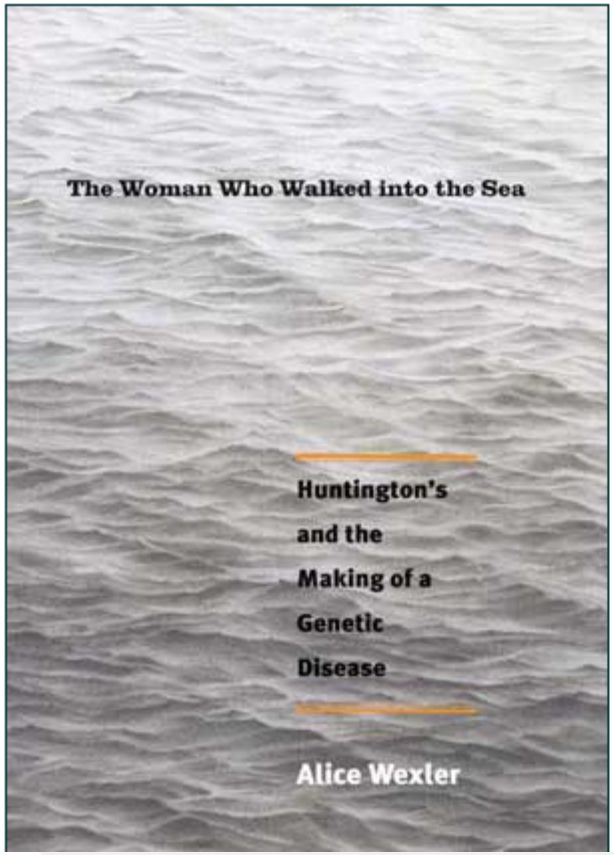
In later chapters, she explores how her father, Milton, and sister, Nancy, developed innovative methods to stir up science. Nancy, like Alice, living at risk, helped organize the effort that led to the stunning discovery in 1983 of a genetic marker for Huntington's, decades before most scientists thought possible. She then

Alice Wexler

The Woman Who Walked into the Sea

Huntington's and the Making of a Genetic Disease

Foreword by Nancy S. Wexler



When Phebe Hedges, a woman in East Hampton, New York, walked into the sea in 1806, she made visible the historical experience of a family affected by the dreaded hereditary disorder of movement, mind, and mood her neighbors called St. Vitus's dance. Although East Hampton is known more for its celebrities than its contributions to medical science, this book shows how local families and a community helped to shape new medical knowledge and define the clinical entity known initially as Huntington's chorea—today called Huntington's disease—after the East Hampton physician George Huntington who described it in 1872.

Starting with the life of Phebe Hedges, Alice Wexler uses Huntington's as a lens to explore heredity, disability, and medical knowledge among lay people as well as scientists and physicians. She addresses these themes through three overlapping stories: the lives of nineteenth century families who, despite "that disorder," were integrated and sometimes prominent in their community; the emergence of Huntington's chorea as a new paradigm of heredity;