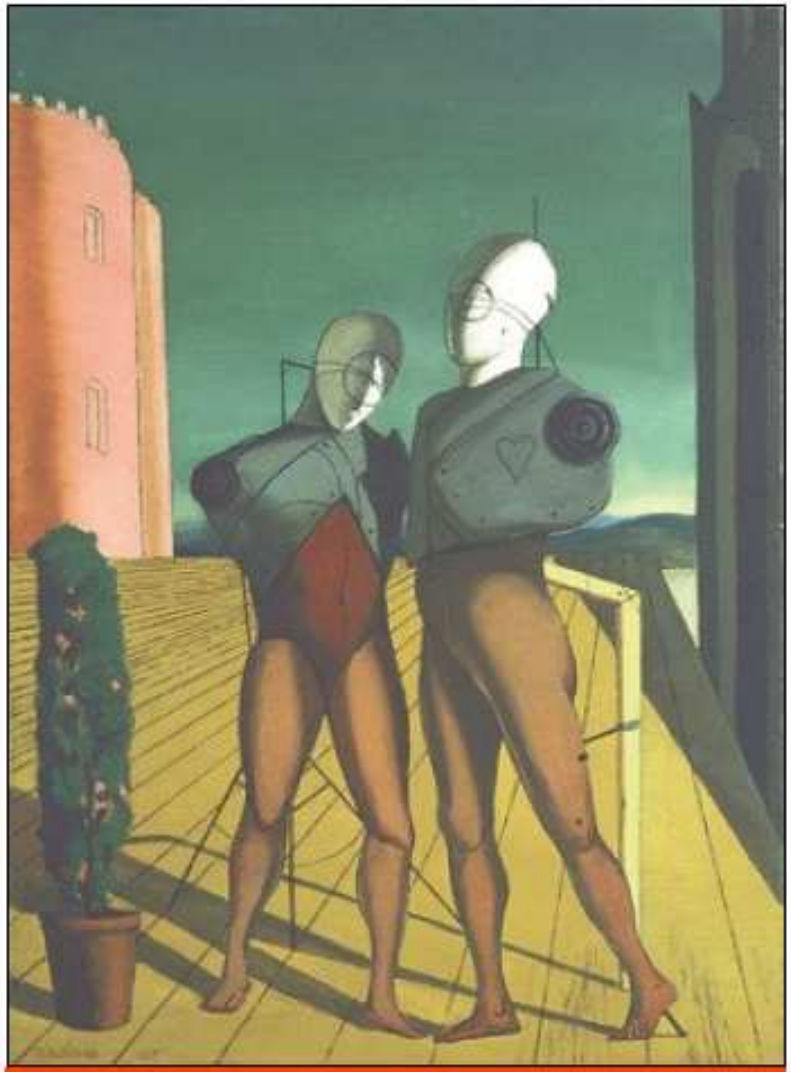


La consulenza genetica e i test genetici nella pratica clinica

Indicazioni, percorsi e interpretazioni

Siena, 28 settembre 2009

LA CONSULENZA GENETICA E I TEST GENETICI NELLE MALATTIE NEUROLOGICHE

15.00 - *Corea di Huntington*

Francesca Mari, Genetica Medica, AOUS

Corea di Huntington

George Huntington (1850-1916)

THE

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 15, 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 char-

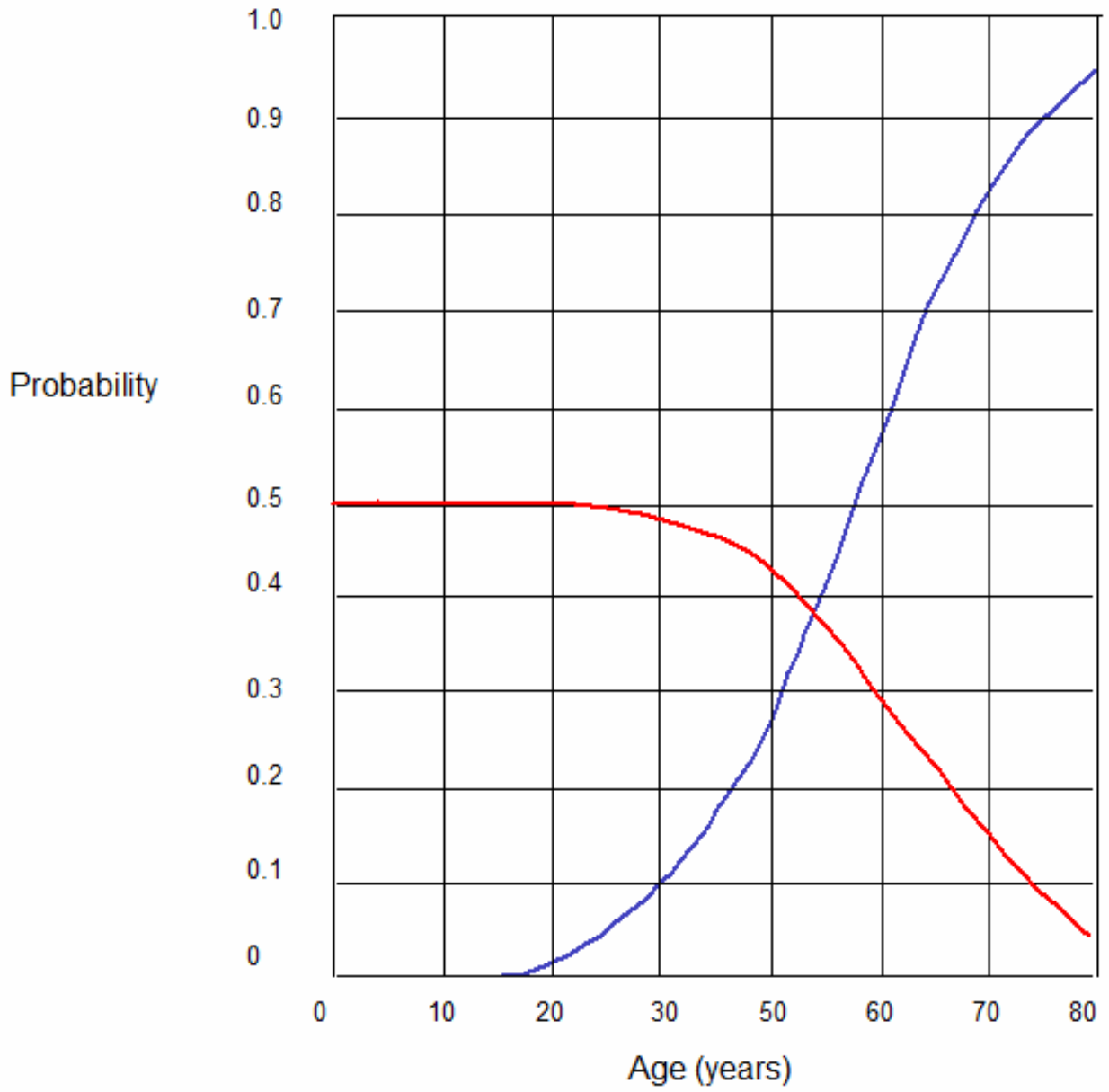
The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

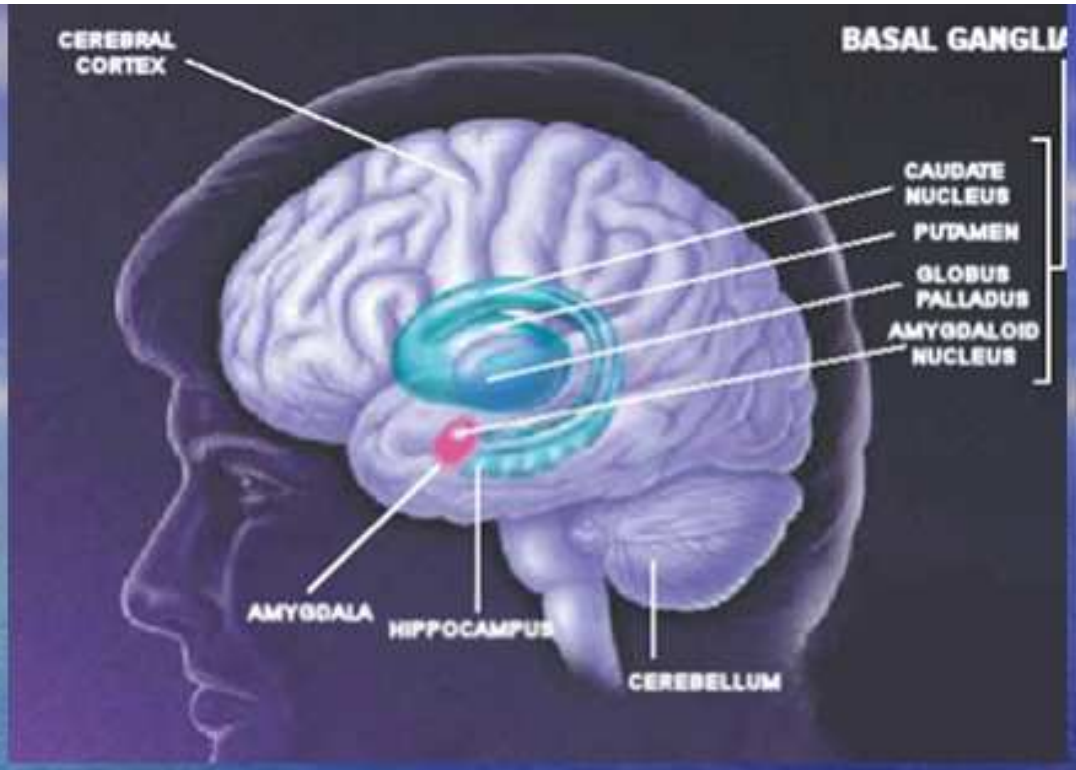
If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete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

Huntington G, 1872. On chorea. Medical and Surgical Reporter 26:320-321.

Corea di Huntington

- Disturbo del movimento (corea)
- Declino cognitivo
- Disturbi della personalità/depressione
- Non esiste al momento una cura risolutiva
- Prevalenza di circa ~1/15000
- Esordio
- Progressione


Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
50
60
70
80
Age (years)

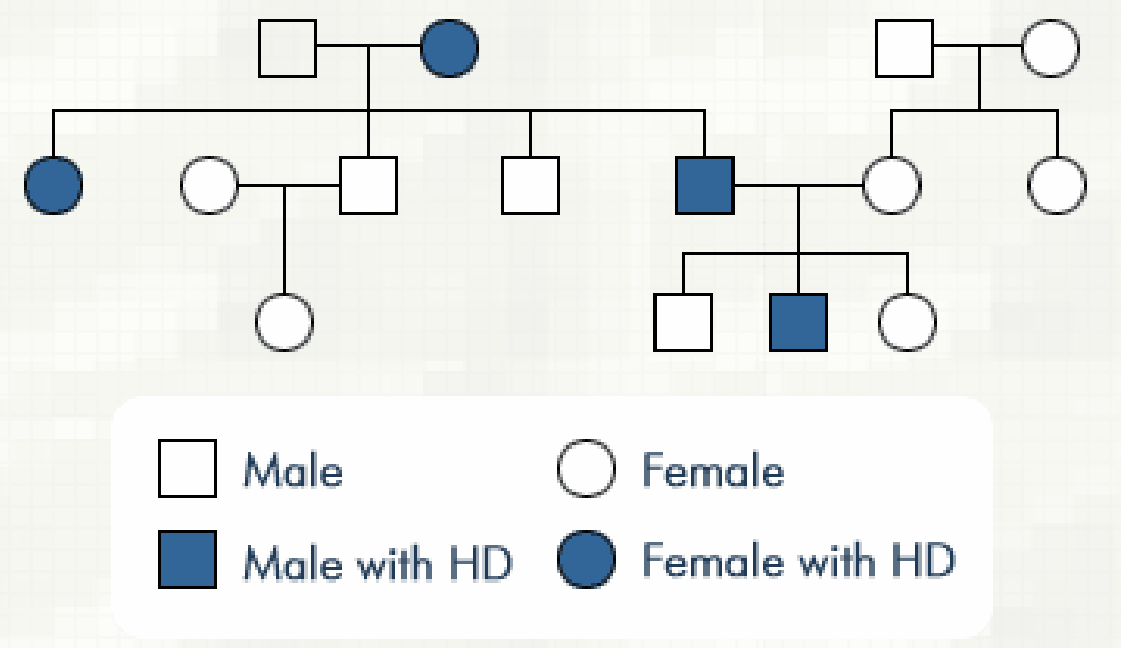


Normal Basal Ganglia vs. HD Basal Ganglia

The basal ganglia of the human brain, showing the impact of HD on brain structure in this region. Note especially that the brain of a person with HD has bigger openings due to the death of nerve cells in that region.

Corea di Huntington

- AD
- anticipazione
- 1993: gene HD, 4p16.3

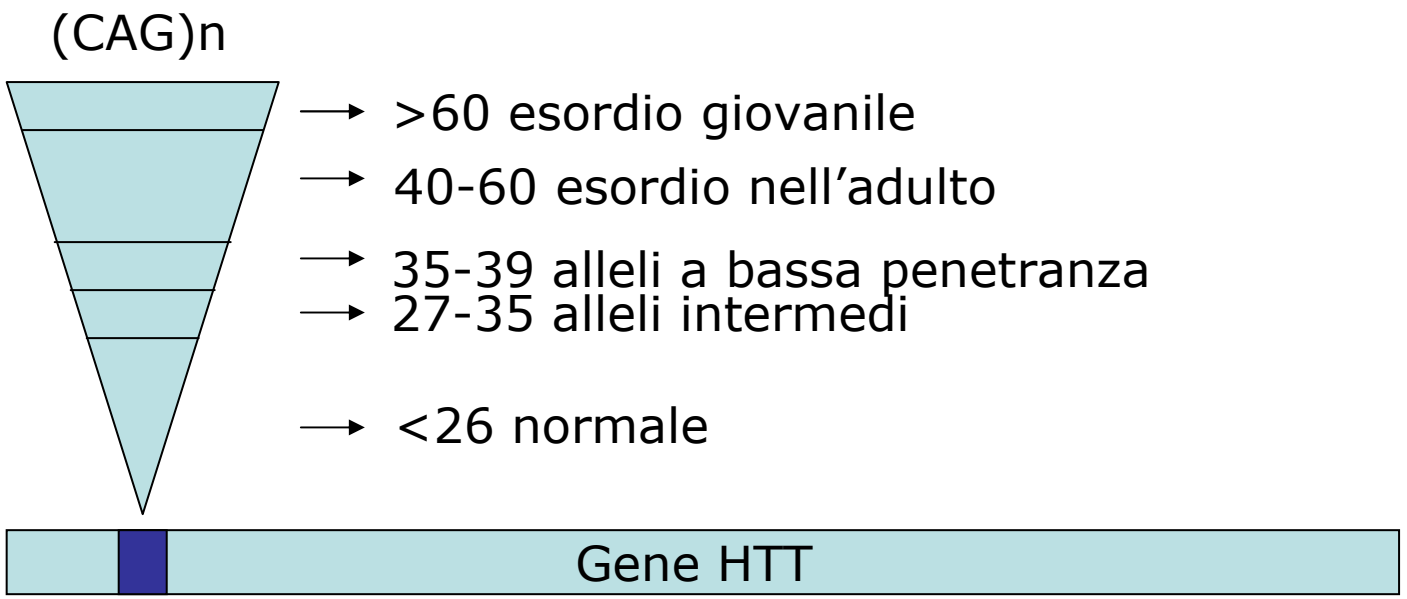


Corea di Huntington

- Ripetute CAG
- normalmente < 35 ripetute (15-25)
- affetti > 40 ripetute
- ”zona grigia” 35-39

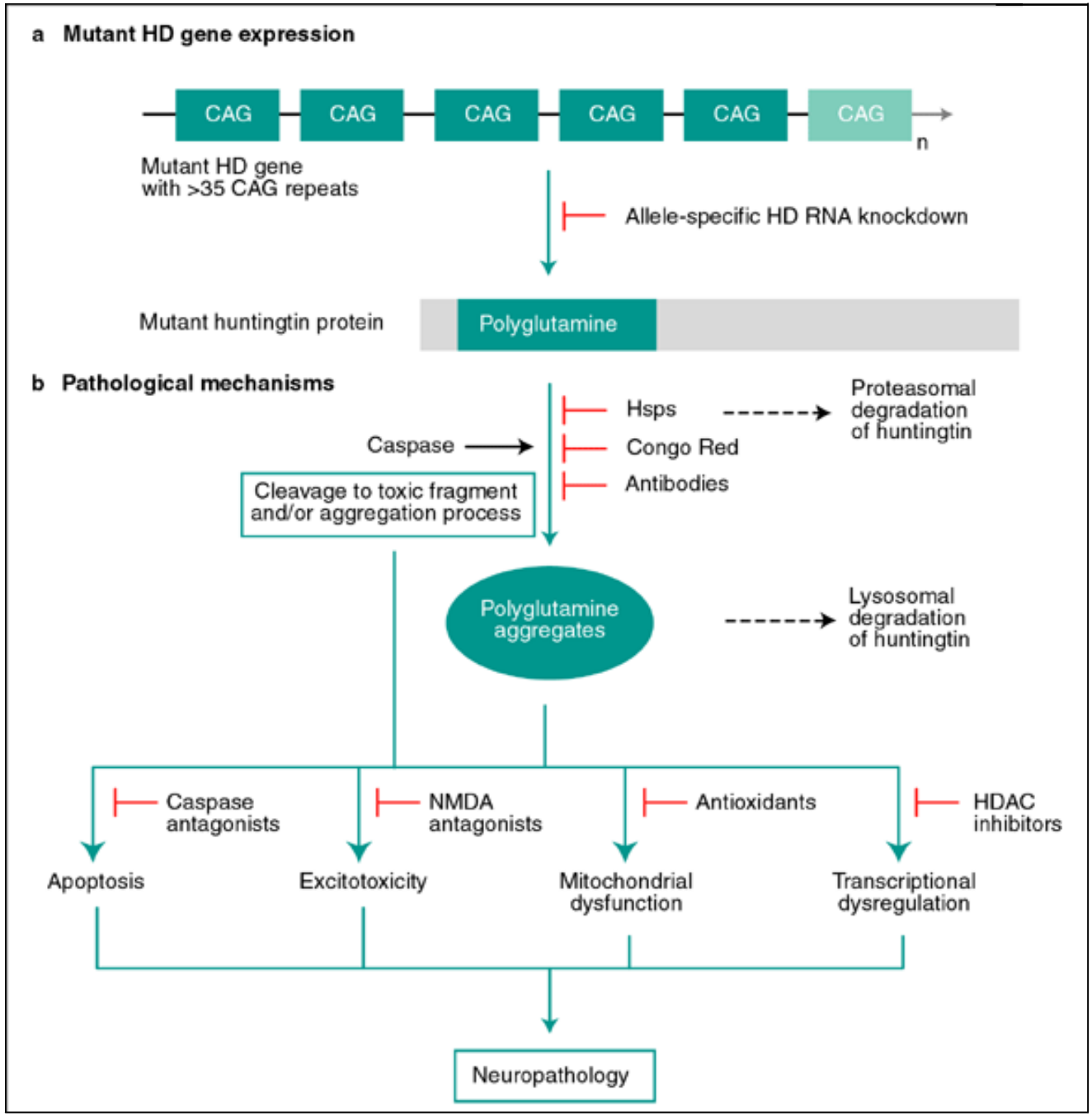
- L’età d’esordio dei sintomi correla con il numero delle ripetute
- La mutazione è instabile alla meiosi maschile

Gene *HTT – IT15*



-67 esoni
-200 kb
-4p16.3

Meccanismo dominante negativo e possibili target terapeutici



- Il numero di ripetute CAG influenza per il 70% la variabilità di insorgenza della malattia, il restante 30% è dato da altri fattori genetici

- I pazienti omozigoti per hanno un'età di esordio simile agli eterozigoti ma presentano una più accelerata progressione della malattia

Uses of Molecular Genetic Testing

- **Medical care**
  - Diagnostic
  - Predictive with a treatment
- **Personal decision-making**
  - Predictive without a treatment
  - Carrier
  - Prenatal

Test genetico per Huntington

- **Test diagnostico**

- **Test presintomatico**

- **Test prenatale e diagnosi genetica preimpianto**

Special issues of communication

Families need psychological support while decision-making

May never be a “right” decision, simply a more appropriate decision

Iter diagnosi presintomatica

- Consulenza multidisciplinare: genetista, psicologo, neurologo
- Almeno 4 incontri prima della diagnosi
- Necessità di follow-up
- Trial clinici in fase presintomatica o sintomatica

Ethics Lesson

Why do predictive testing when no cure exists?

Personal decision-making

- Education
- Employment
- Life experiences
- Family planning

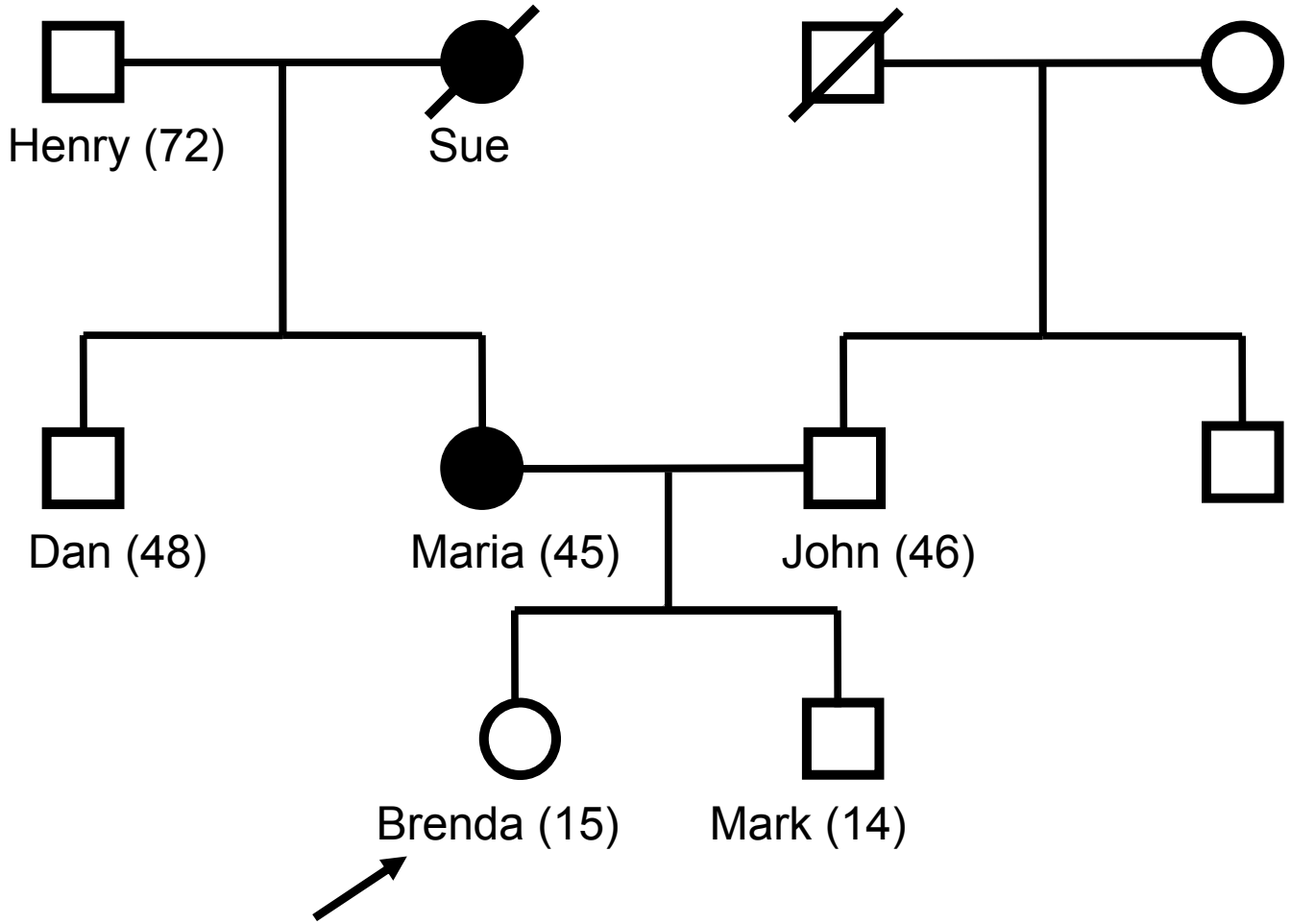
When: ≥ age 18 years

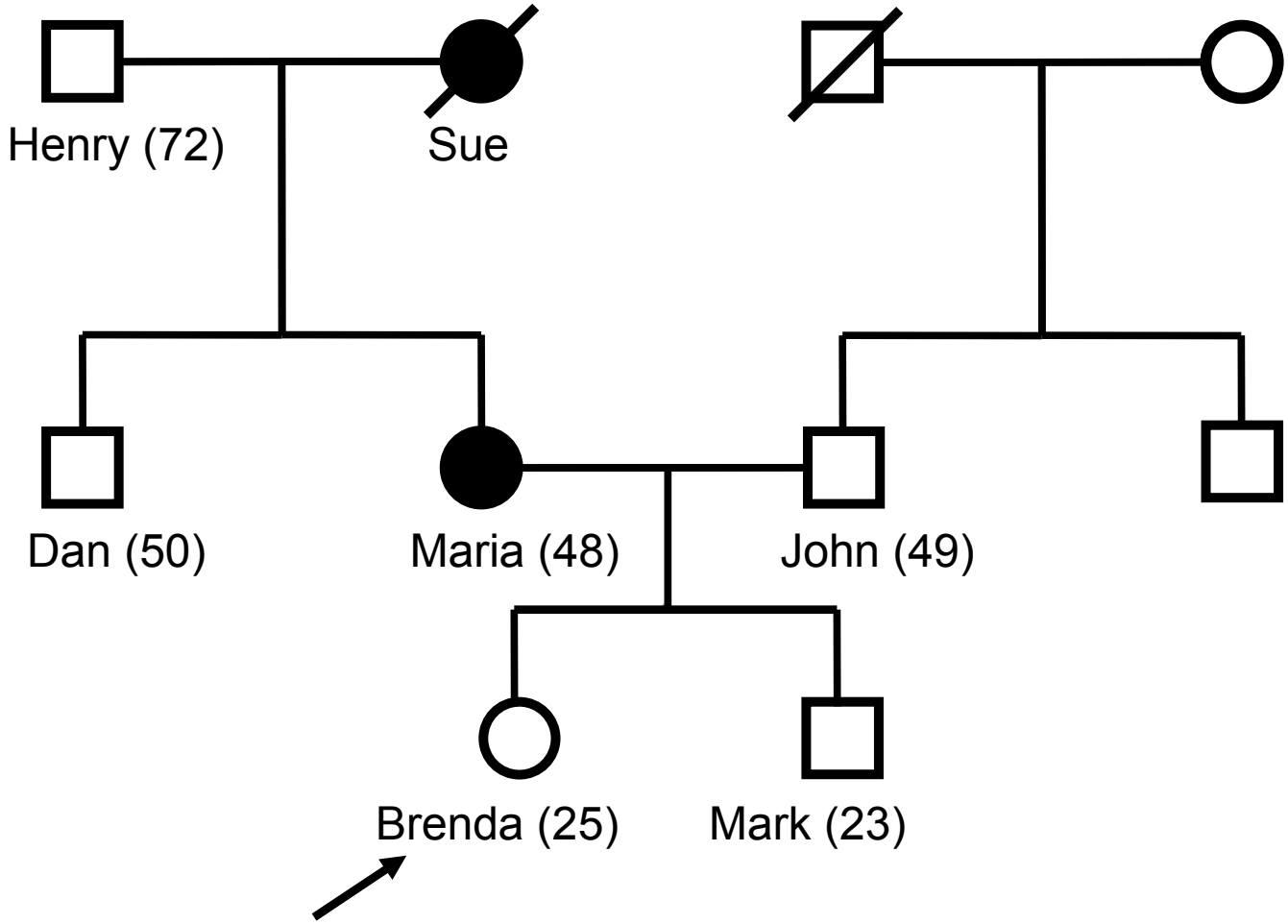
- Informed decision

Why not test children who are < age 18 years?

- Social stigma (family, education, relationships)
- Deprives individual of the right to choose to know versus not know

Testing Children for Huntington's disease: the Child's Request



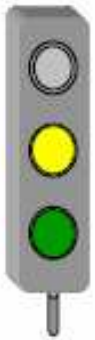

Henry (72)
Sue
Dan (50)
Maria (48)
John (49)
Brenda (25)
Mark (23)

Testing Strategy = Science Lesson

Many inherited conditions mimic each other; therefore, the diagnosis must be secure before predictive testing is used.

Conclusion: Must confirm the diagnosis in an affected relative first

Testing and Genetic Counseling Strategy

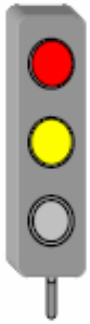


Test Mom

Mutation detected

- Direct testing useful
- Proceed with
  - Genetic counseling
  - Genetic testing of at-risk adult relati
    who choose to be tested

Testing and Genetic Counseling Strategy

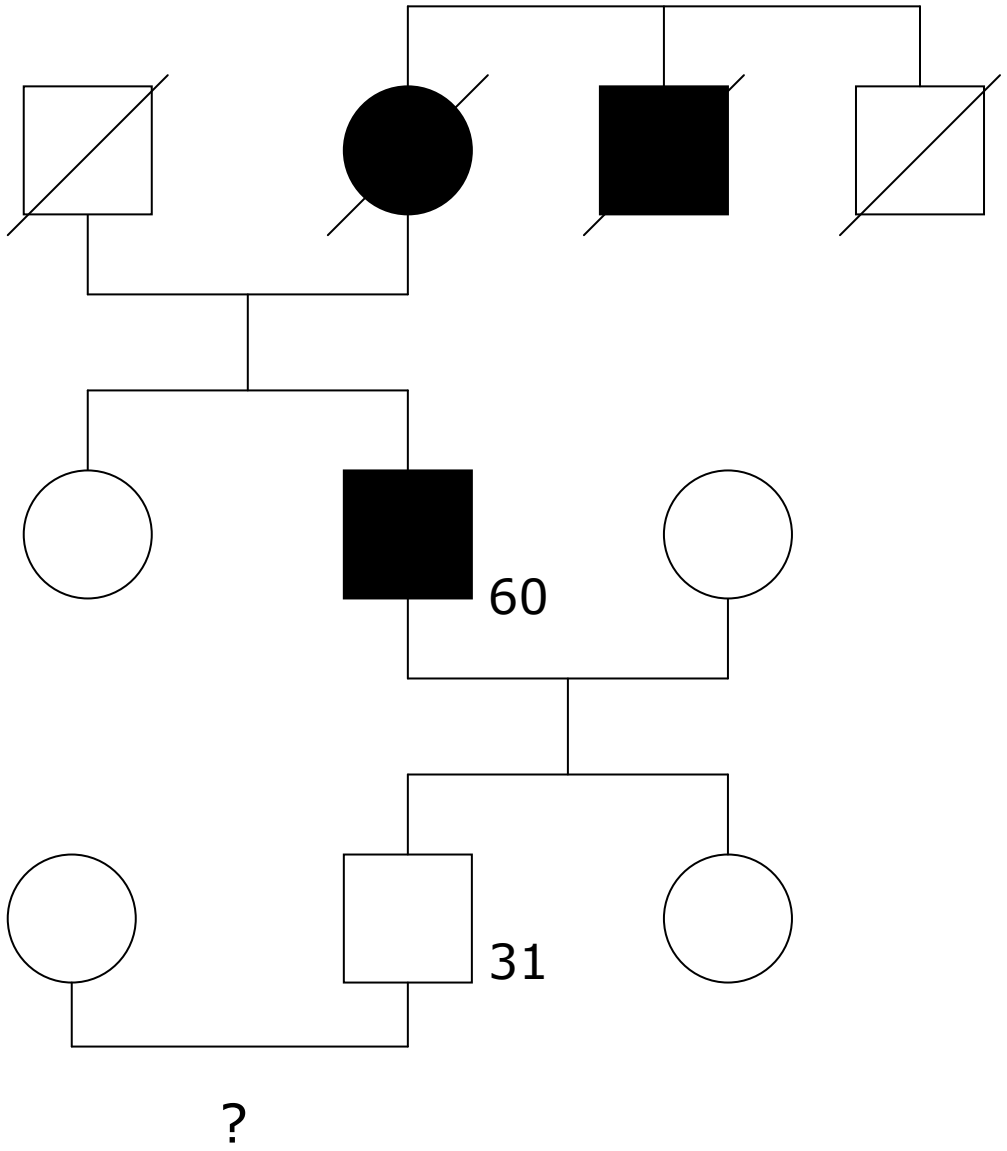


Test Mom

No mutation detected STOP

- **Diagnosis not known**

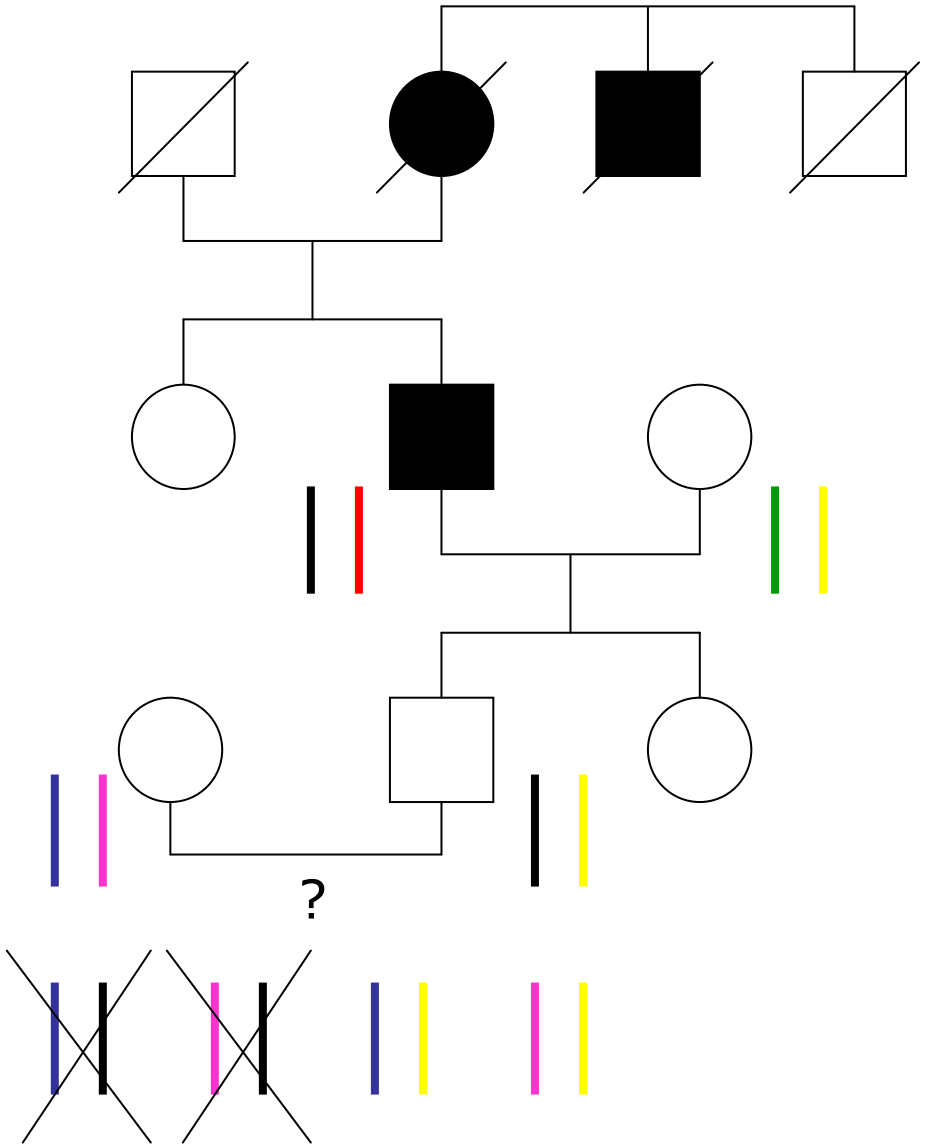
Pre-conceptional counselling and prenatal diagnosis for Huntington's disease



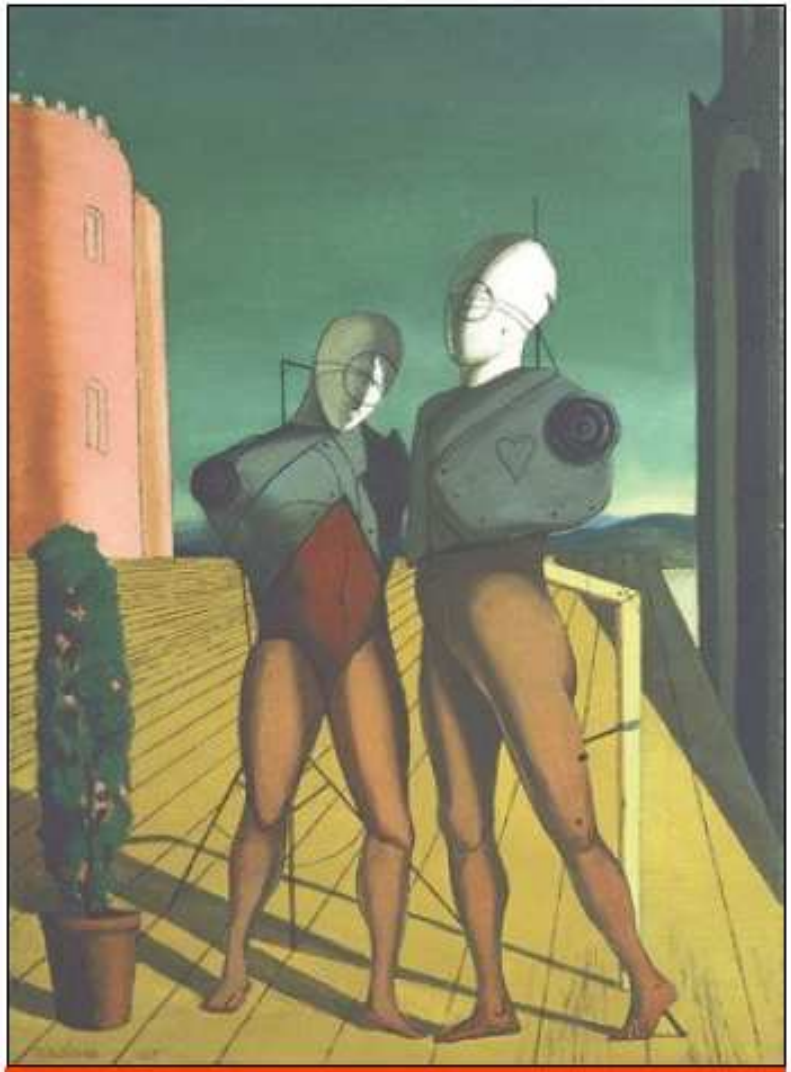
- Diagnosi presintomatica sul soggetto/consultando

- Diagnosi di esclusione su feto

Diagnosi di esclusione su feto



- Diagnosi genetica preimpianto - PGD



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