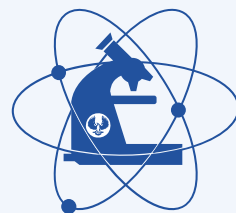


# Clinical Aspects of Genetic Testing for Huntington Disease

*Dr Liz Thompson  
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SA Pathology  
Women's and Children's Hospital*



SA PATHOLOGY



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 18, 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in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete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

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# What is Huntington disease?

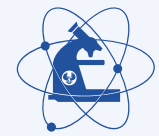
- Neurodegenerative disorder
- Involuntary movements (chorea)
- Cognitive decline
- Psychiatric disturbances
- Begins 30-50 years (range child-80s)
- Median survival 15-18 years after onset



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# Huntington disease

- Treatment is symptomatic: no cure
- Affects 5-7 people per 100,000 in populations of Western European descent
- Less frequent in Japan, China, Finland and among African blacks
- The frequency of HD in Japan is between 0.1 and 0.38 per 100,000



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# Genetic basis of HD

- Autosomal dominant
- CAG repeat expansion in *huntingtin* gene on chromosome 4p16.3 (linkage 1983, gene 1993)
- Normal:  $\leq 35$  CAG
- HD range:  $\geq 36$
- Low penetrance HD: 36-39
- Mutable normal (intermediate): 27-35
- Anticipation: expansion of CAG when passed to offspring (pat>mat) → earlier age of onset

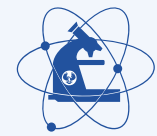


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# Mutable normal (intermediate) alleles CAG 27-35

Semaka et al., Am J Med Genet 2009

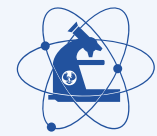
- 51 Canadian HD families
- 181 parent/child transmissions where parent had CAG 27-35
- 54 (30%) unstable on transmission
  - Expansions 37, contractions 17
- 25/181 (14%) went to HD range
- 10/25 originated from CAG 35
- Larger CAG is more likely to expand
- Data consistent with new mutation rate ~10%
- No reports of expansion to HD range if mother is transmitting parent



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# Differential diagnosis

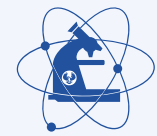
- Non-inherited chorea eg cerebrovascular disease
- HD-like disease 1: specific mutation in prion protein gene (PrP), *PRNP*, on chromosome 20p (AD)
- HD-like disease 2: CTG/CAG repeat expansion in the junctophilin-3 (*JPH3*) gene (mainly in Africans, AD)



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# Differential diagnosis

- Chorea-acanthocytosis (AR)
- McLeod neuroacanthocytosis syndrome (XL)
- SCA17 (AD)
- Dentatorubral-pallidoluysian atrophy (DRPLA, AD)
- Benign hereditary chorea (AD)
- Hereditary cerebellar ataxia
- Creutzfeld-Jakob disease (prion disease)
- Early-onset familial Alzheimer disease (AD)
- Familial frontotemporal dementia with parkinsonism - 17 (FTDP-17, AD)



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# HD Unit of South Australia, Flinders Medical Centre

Established 1986

**Senior social workers:** Barbara Singaram, Irene Scott (work full time on HD)

**Scientists:** Prof Pamela Sykes, Lesley Snell, Duncan Holds and Naomi MacMillan

**Psychiatrist:** Prof Ross Kalucy

**Genetic counsellors (at WCH)** Anne Baxendale, Hayley Salvemini, Lara Fitzgerald

**Clinical geneticists (at WCH):** Eric Haan, Lesley McGregor, Jan Liebelt, Chris Barnett (genetic fellow), Liz Thompson



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# Functions of HD Unit

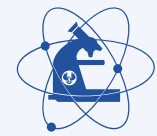
New diagnosis of HD: offer general support and genetic counselling

Predictive tests for asymptomatic individuals “at risk” of having inherited HD

Prenatal tests

Information about pre-implantation genetic diagnosis (IVF + genetic test of embryo)

Follow up and general support including home visiting by the social workers



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# Predictive Test Programme

Predictive (pre-symptomatic) test vs diagnostic test

Aim is to meet the needs of people wishing to have a predictive test or who just want information

Allow people to make an informed decision about choosing to test or not test

Foster emotional insight to aid adjustment to the result

Follow ethical principles of respect for the person's autonomy, confidentiality

Equality of access to the service (country clients)



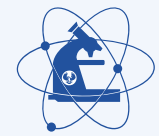
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# Clinics, Team Meetings and Referrals

Predictive test clinics held monthly at  
Flinders Medical Centre

HD Unit staff meet before each clinic

No financial cost to client



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# Predictive test: what happens?

Process follows international guidelines (1994)

Referral received

**1<sup>st</sup> appointment** with social worker

**2<sup>nd</sup> appointment** with clinical geneticist

**3<sup>rd</sup> appointment** with psychiatrist

Consent form signed, blood sample taken

Sample tested in laboratory

**Result appointment**

Takes 6-8 weeks (Flexibility for country clients)

Follow up



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# Role of the social worker

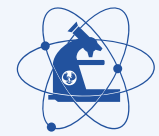
Meet client at FMC or home

Provide information about test process

Discuss with client reason requests test:

- Reproductive decisions
- “Need to know”
- Career and future planning
- Financial matters

Ensure client is requesting test voluntarily



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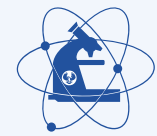
# Role of the social worker

Consider possible impact on client and family of positive or negative result

- Positive (abnormal) result: health and well-being, impact on life insurance, employment
- Negative (normal) result: changes in family's social interactions

Assess client's coping skills, history of mental illness, supports

Provide counselling and support



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# Role of the social worker

Consider the partner: distress often significant

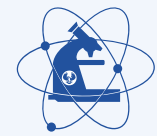
Provide written information to client about HD

Make all appointments for client

Accompany client to all appointments

Encourage client to bring support person to appointments

Write report



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# Role of the clinical geneticist

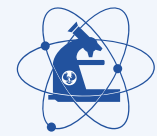
Confirm family history of HD

Confirm laboratory result in at least one relative if possible

Give information about HD

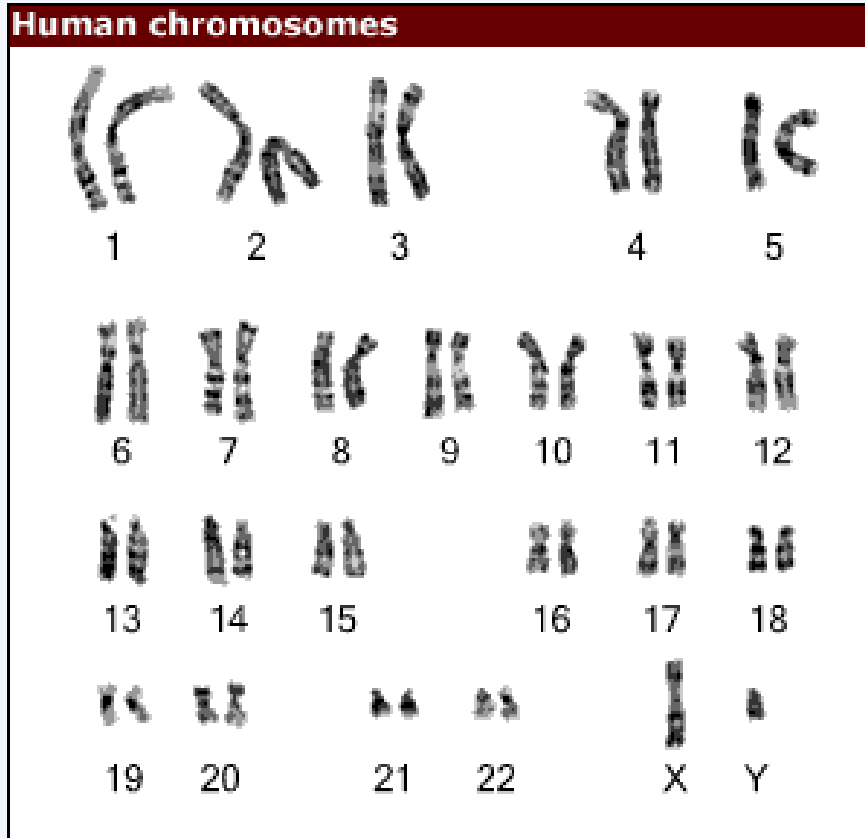
Review family tree, assess client's chance of having inherited HD:

In most cases is 1 in 2 (50%), as client's parent has or had HD



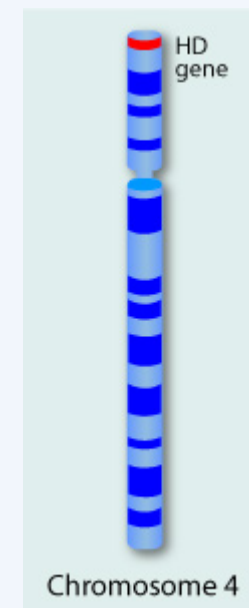
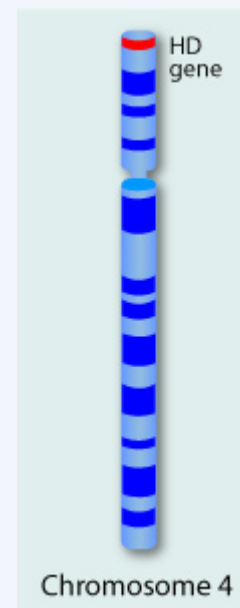
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# Visual aids



Normal

Abnormal



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# What does the result mean?

**Normal:**  $\leq 35$  CAG (negative or normal result)

**HD:**  $\geq 40$  CAG (positive or abnormal result)

BUT unable to predict accurately

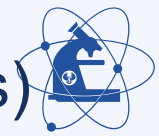
- age of onset (tables)
- severity, type of symptoms
- rate of progression

**Reduced penetrance:** 36-39 CAG (positive or abnormal result)

Onset may be late, milder condition, may not get HD at all

**Mutable normal:** 27-35 CAG

Not HD but may expand into HD range in future generations (?6-10% risk when transmitted by males)



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# Onset of symptoms with low penetrance gene (CAG 36-39)

Multicentre study

Quarrell et al., 2007

(175 anonymous samples)

At least:

40% chance asymptomatic at 65 years

30% chance asymptomatic at 75 years



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# Role of the clinical geneticist

Potential for result to alter risk of relatives, usually children

May alter risk of parent eg 40 year old man diagnosed with HD

- No family history of HD
- Parents offered predictive testing
- 80 year old father had CAG 38
- Mildly slow gait, mentally normal

Useful? Inform his siblings & their offspring



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# Role of clinical geneticist

Highlight difference between positive genetic test result and having symptoms of HD

Explain that client may withdraw from test at any time

- Recognise ambivalence to being tested
- Increased appreciation of impact on self or family
- Anxiety or depression may need treatment first

Counselling will be offered again if 6 months elapse (learnt from experience)



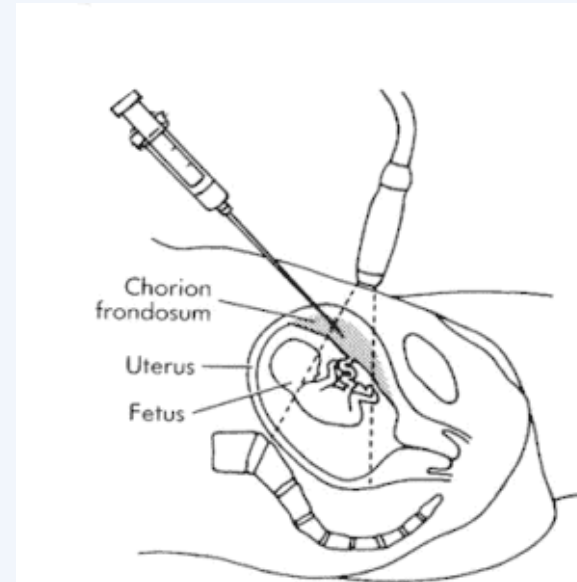
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# Role of the clinical geneticist

Discuss testing in pregnancy by CVS, if relevant

Discuss pre-implantation diagnosis

Send the client a summary letter



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# Role of the psychiatrist

Risk of severe adverse reaction, suicide

Current depression may need treating before proceed

Rarely do we say a client may never be tested

Be aware:

Not always bad news that causes adverse reaction eg

- Severe depression in a young man who had a normal result but sibling affected (survivor guilt?)
- Person who has focused heavily on HD finds it hard to adjust to normal result



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# Blood sample and laboratory practice

Consent form signed

Blood sample taken at Flinders Med Centre

“Chain of evidence”: client checks name on bottle,  
social worker takes sample to lab

Lab adheres to national/international standards of  
practice

Samples tested twice

Samples accepted for predictive test from HDU  
staff only



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# Result appointment

Clinical geneticist gives the result

Discuss again the CAG numbers and what they mean

Impact on support person, especially spouse or partner

Follow up by social workers in day or so after and a few weeks later

Offer of psychiatry follow up at 6 weeks

Neurology appointment may be requested

Ongoing follow up arrangements



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# HD predictive testing in SA

First predictive test 1987 (linkage)

Direct gene testing from 1993

| Predictive tests in last 16 years    | Negative CAG <27 | Negative CAG 27-35 | Positive CAG 36-39 (low penetrance) | Positive CAG >39 |
|--------------------------------------|------------------|--------------------|-------------------------------------|------------------|
| 321 tests<br>F 55%<br>M 44%<br>NR 1% | 165<br>(51%)     | 17<br>(5%)         | 18<br>(6%)                          | 121<br>(38%)     |



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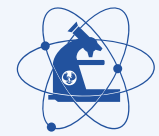
| <b>Predictive tests</b>                           | Negative CAG <27 | Positive CAG >39 | Mutable normal & 36-39<br>ie 27-39 |
|---------------------------------------------------|------------------|------------------|------------------------------------|
| Australia<br>1994-2003<br>(Tassicker et al, 2006) | 56%              | 38%              | 6%                                 |
| SA                                                | 51%              | 38%              | 11%                                |



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# Clinical scenarios

- Recent discovery of family history of HD
- The “man in the middle” does not want to know....
- Predictive testing of children and young adults
- Pregnancy when at risk parent’s carrier status is unknown
- Exclusion prenatal testing



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# Person has learnt recently a relative has HD

Many clients have known for long time about risk of HD

- Incorporated it into their identity
- Thought long and hard about having a genetic test

To suddenly discover a relative has HD may engender great anxiety in family members

May then request (demand) immediate test

Can feel frustrated and angry about counselling & the time it all takes

But can be the very ones who “take it hard”

We recommend waiting (?6 months) before testing

But will of course meet them to give information and negotiate timing of the test in the meantime



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# Grandparent of client has HD but parent does not wish to know

If client receives a positive result, implies parent  
also has the HD gene: an ethical dilemma

Whose information is it?

Encourage client to discuss with parent

If parent continues to not want testing, test cannot  
be denied to client

Plan of how to manage the result needs to be  
established

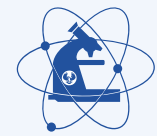
Often negative result (75% chance)



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# Predictive testing in children

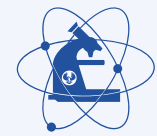
- Avoid any genetic testing in asymptomatic children unless medical benefit
- Particularly for HD because:
  - Adult onset, untreatable
  - Many adults at risk do not request testing
  - Employment and insurance issues
  - Child may think is already ill
  - Altered perception of child by family
- This focuses on **harms testing may cause**



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# Predictive testing <18yr

- BUT little evidence re whether better not to test or to test
- Duncan et al. (2007) interviewed 8 young people who had predictive test for HD (ages 17-25 yr at time of test)
- For some, uncertainty about carrier status was a barrier to moving forward in life
- “For 19 years I felt like I’ve held my breath...”
- Led to anti-social or risk-taking behaviours
- Regardless of result, were able to move forward (“start living again”) and make significant behavioural changes
- This focuses on **alleviating harms of not testing**
- (We don’t offer test to young children)



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# Pregnancy in which man or woman is “at risk” and carrier status unknown

Person at risk requests urgent test

Wants to know if baby has inherited HD

Requires urgent appointments to discuss all aspects

Urgent predictive test on the client will be done if:

- they are fully informed
- want to test the pregnancy if positive result

In some cases, if client has positive result, they do not go on to have test on the pregnancy

(Richards and Rea, 2005 + our experience)

Highlights benefit of predictive test programme



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# Exclusion prenatal testing

Person at risk does not wish to know if has HD gene

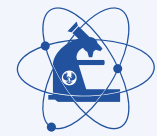
But wants to avoid passing HD to child

Family linkage study to see if fetus inherits gene from unaffected grandparent

If so, fetus at low risk of HD

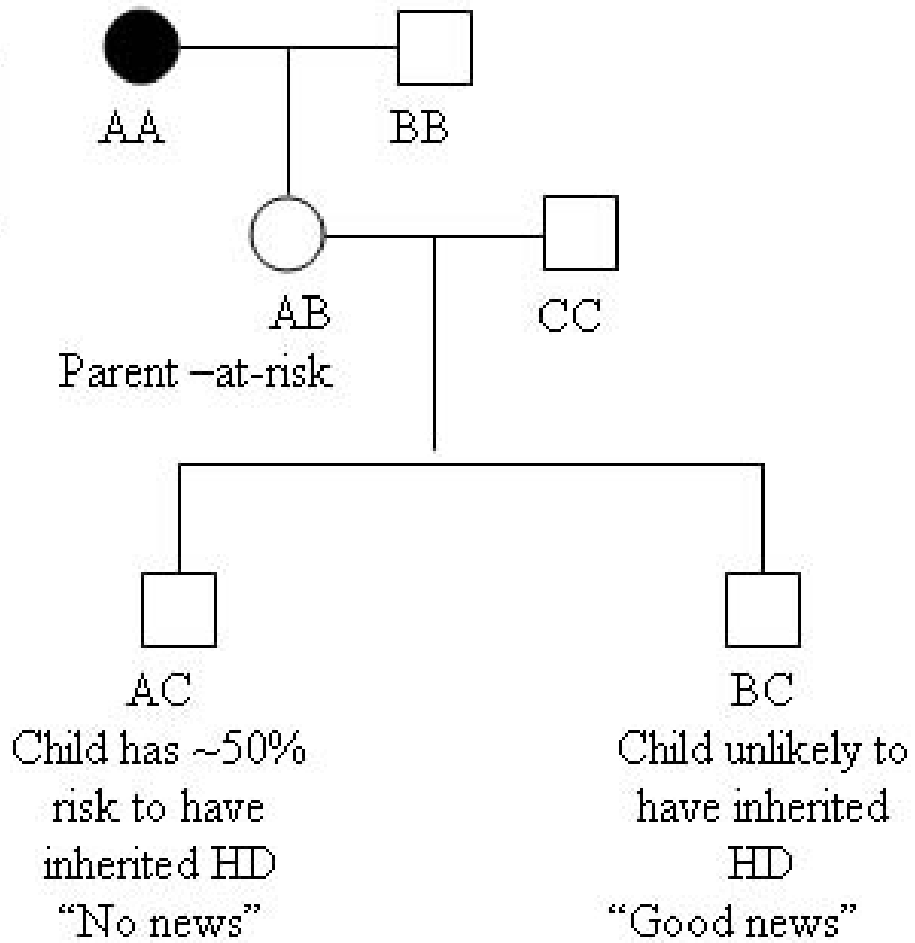
If not, is at 50% risk like parent

Need blood samples from various relatives



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Exclusion Testing



# Post-test adjustment

- Many people with positive result maintain or even improve psychological well-being
- Some individuals experience significant distress in 1<sup>st</sup> year and beyond: probably under-reported
- Require expert counselling and support
- Most, but not all, with negative result report great relief
- We remain committed to the predictive test protocol but recognise need for individual flexibility



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