

Huntington's Disease 101

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Huntington's Disease Society of America

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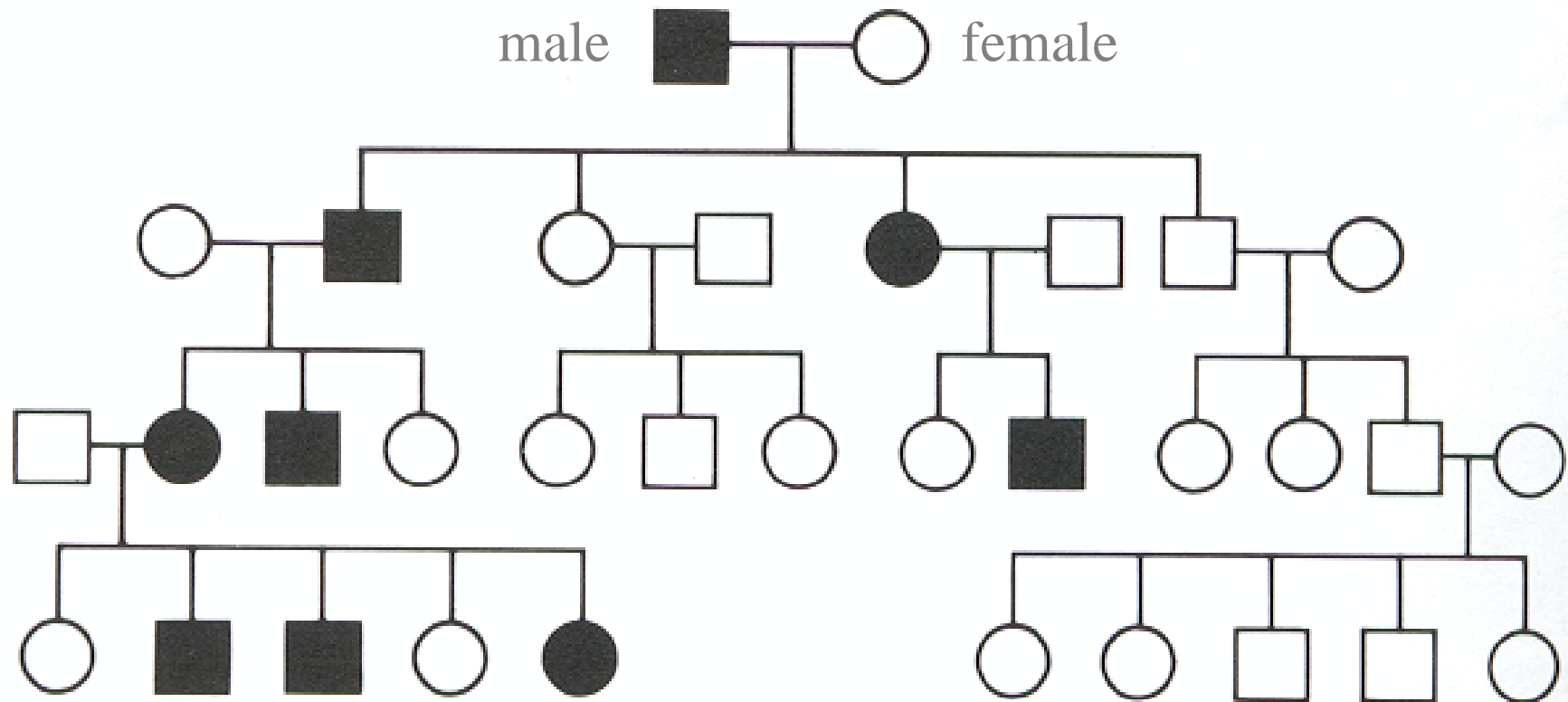
Huntington's disease

- Adult onset
- Juvenile onset
- Diagnosis and treatment
- Basic science breakthroughs
- Translational research

HD Basics

- Autosomal dominant --- there is a 50/50 chance of a child getting the disease if a parent has it.
- HD does not skip generations--If a person with an affected parent escapes the disease, so will all of their children.

Genetic chart (example)



HD Basics

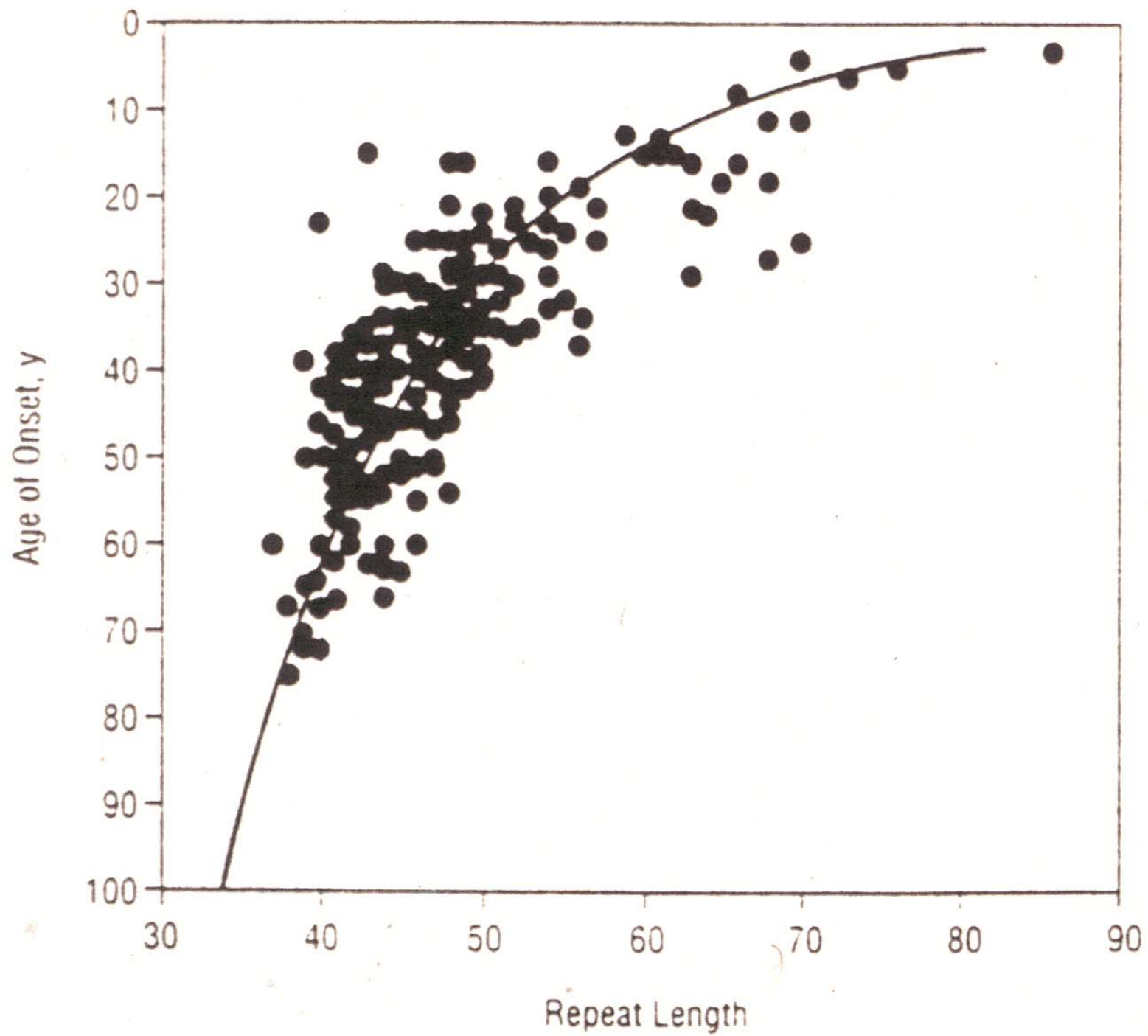
- **HD is a trinucleotide repeat disorder.**
(other repeat disorders include: Fragile X, Myotonic dystrophy, Kennedy's, SCA I, Machado-Joseph, etc)
- **Individuals with > 37 CAG (poly glutamine) repeats express the HD phenotype.**
- **Repeat sizes from 27-36 are considered unstable for future generations. There is a tendency for “anticipation” when the gene is transmitted by the father.**
- **There is a rough correlation between repeat size and age of onset.**

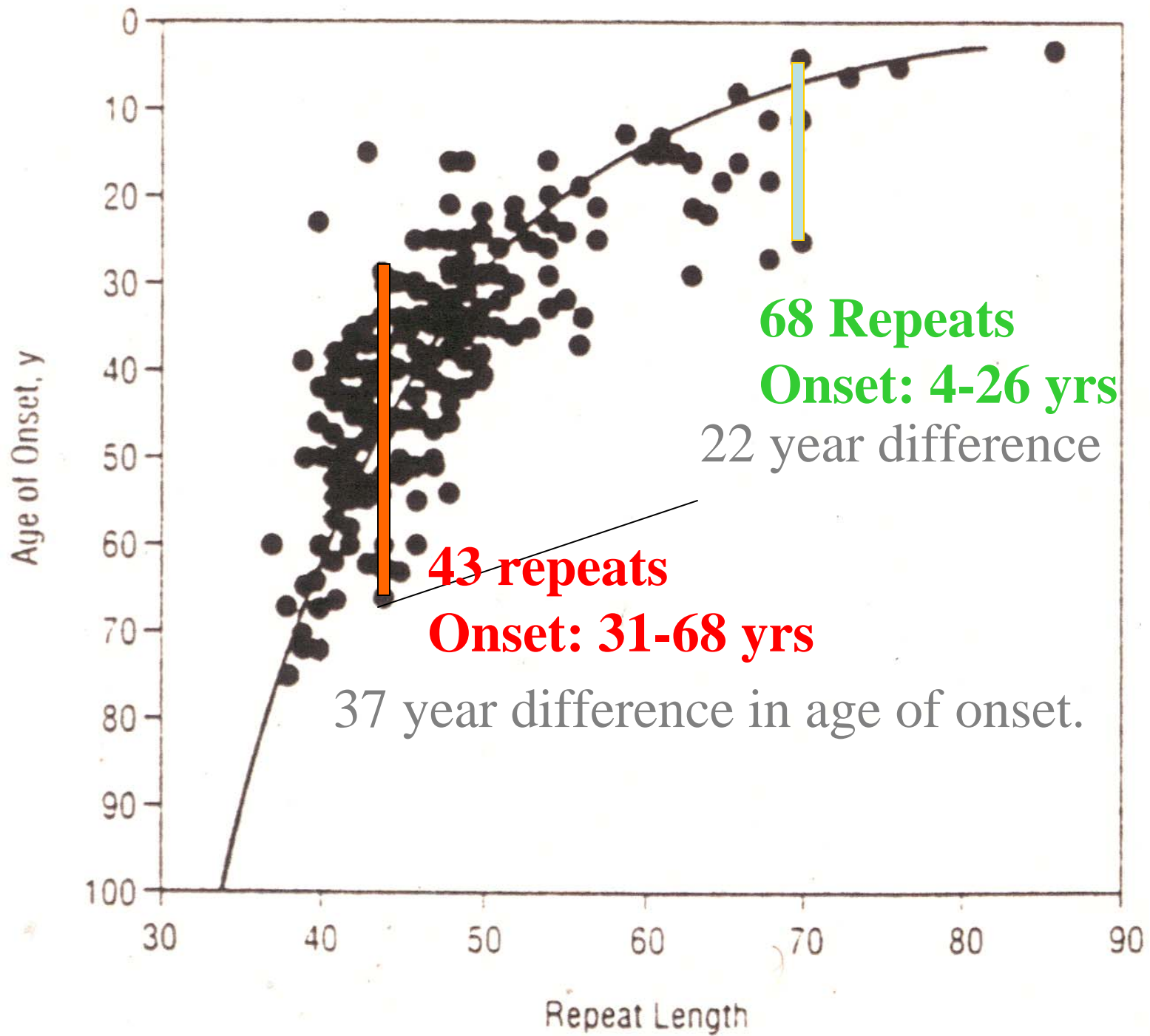
Normally < ~ 10-27 CAG repeats

TAC--TTA--TAG--GAG--GTA--ATA—TAT--GCC--CCT--GGT--CAG—TAC-TTA-TAG-
GAG-GTA-ATA-TAT-GCC-CCT-GGT-CAG--TTA--TAT—CAG—CAG—CAG—CAG—
CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG--TAC-
TTA-TAG-GAG-GTA-ATA-TAT-GCC-CCT-GGT-CAG-TAG-CGT-TAC-TTA-TAG-
GAG-GTA-ATA-TAT-GCC-CCT-GGT-CAG-TAG-CGT-TAC-TTA-TAG-GAG-GTA-
ATA-TAT-GCC-CCT-GGT-CAG-TAG-CGT

In HD there are more than 36 repeats

TAC--TTA--TAG--GAG--GTA--ATA—TAT--GCC--CCT--GGT--CAG—TAC-TTA-TAG-
GAG-GTA-ATA-TAT-GCC-CCT-GGT-CAG--TTA--TAT—CAG—CAG—CAG—CAG—
CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—
CAG—CAG-- CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—CAG—
CAG—CAG—CAG—CAG—CAG-- CAG—CAG—CAGCAG—CAG—CAG—CAG—
CAG—CAG—CAG—CAG—CAG-- TAC-TTA-TAG-GAG-GTA-ATA-TAT-GCC-CCT-
GGT-CAG-TAG-CGT-GGT-CAG-TAG-CGT-TAC-TTA-TAG-GAG-GTA-ATA-TAT-
GCC-CCT-GGT-CAG-TAG-CGT-TAC-TTA-TAG-GAG-GTA-ATA-TAT-GCC-CCT-
GGT-CAG-TAG-CGT





HD Basics

- **The disease starts insidiously and progresses continuously.**
- **Symptoms include changes in:**
 - **Behavior**
 - **Motor function**
 - **Cognitive function**

In Adults Motor Symptoms Include:

Chorea

Motor impersistence

Oculomotor changes

Impaired fine motor control

Balance and gait disorder

Dystonia

Speech/swallowing problems

Behavioral Symptoms Include:

Obsessive compulsive disorder

Depression/mood swings

Poor impulse control

Psychosis

Anxiety

Intellectual Difficulties In HD

- Completing complex tasks
- Organizing and prioritizing
- Adapting to change
- Problem solving
- Creative thinking
- Word finding
- Memory

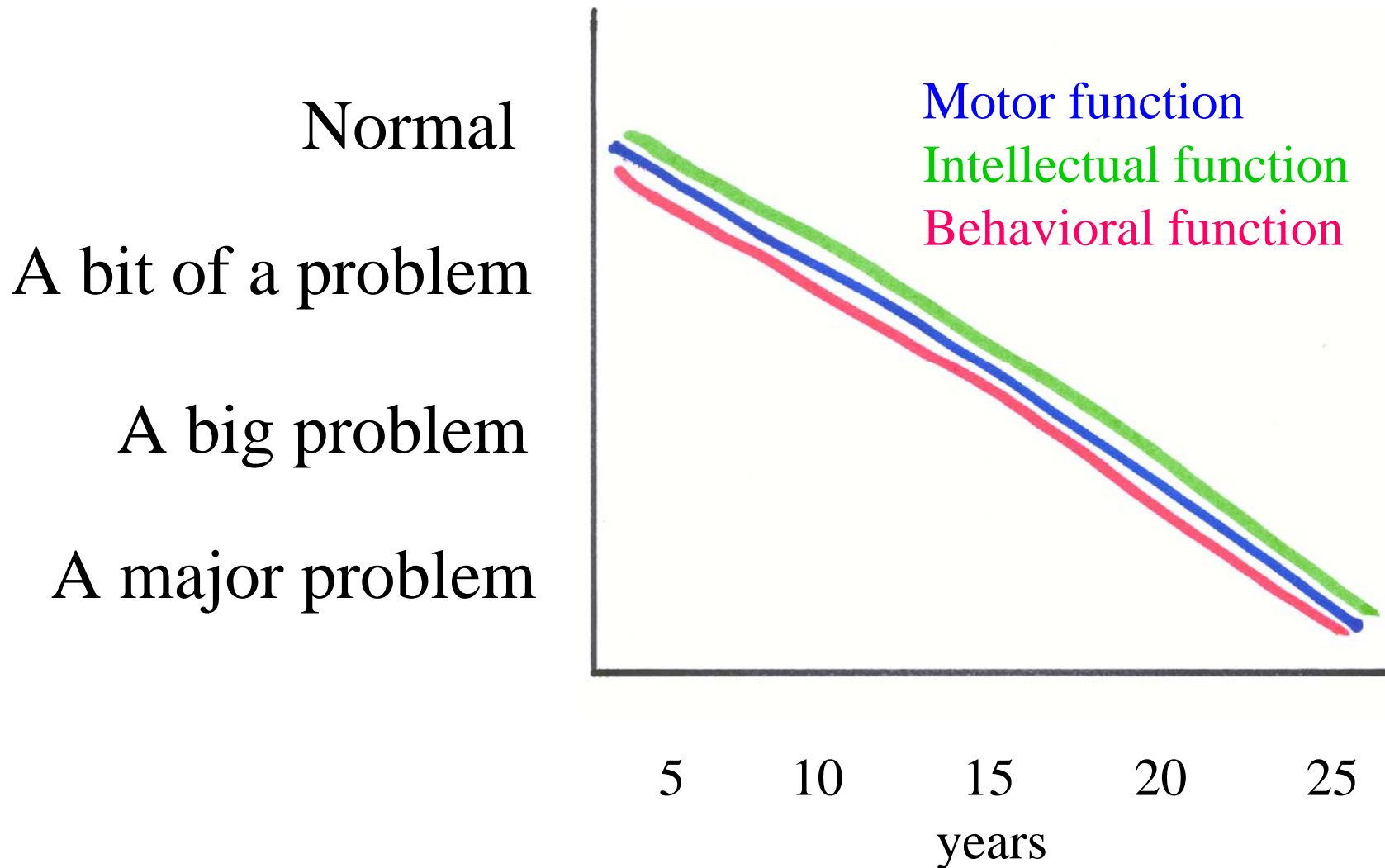
HD is a progressive
neurological disorder

Be prepared to adapt.

HD affects many aspects of how a person functions.

However, it does not do so to the same degree and at the same rate in every person.

It's not going to progress predictably like this!



Being Prepared.

Establish a relationship with a physician and/or support group and/or therapist early on. Build a local community support network.

Lifestyle Adaptations

- Changes in job performance.
 - Move to lower level, less stressful positions
 - Part-time work
 - Volunteer positions
 - Expand hobbies

Lifestyle Adaptations

- Driving.
 - Safety is the first priority
 - Alternate forms of transportation
 - Plan ahead when relocating.
 - Near bus routes
 - Near community assistance

Lifestyle Adaptations

- Finances.
 - Plan ahead
 - Power of attorney
 - Long-term care plans

Lifestyle Adaptations

- Environment and Domestic Issues.
 - Simplify
 - Limit distractions
 - Avoid visual and auditory clutter
 - Establish routines
 - Household aides
 - Assisted living

Caregiver Survival

- Team Approach. The more help the better.
- Schedule time for yourself.
 - Make this a priority.
 - Make this a routine and stick to it.
- Arrange for a backup caregiver on a regular basis.
- Use Humor.
 - Rent funny movies.
 - Laugh at yourself and HD.
- Change your expectations for success.
- Relaxation techniques.
 - Yoga, Hot Baths, Meditation, Old Movies, Whatever works for you.

(Adapted from: Jane Paulsen, Understanding Behavior in HD 1999)

Juvenile HD

- Usually a family history of relatively young onset HD.
- Often inherited from the father. (~80 %).
- CAG repeat size usually greater than 60.

Juvenile HD symptoms

- Stiffness of legs. Scissoring gait.
- Walking on toes.
- Clumsiness of arms and legs.
- Decline of mental ability and milestones.
- Changes in behavior.
- Seizures (~ 25 % of children with HD).
- Swallowing and speech difficulties.
- Bradykinesia.
- Cerebellar signs.

A functional scale for assessing juvenile-onset HD

- A. School attendance.
- B. Academic/developmental performance.
- C. Chores.
- D. Activities of daily living.
- E. Residence.

Dangers of premature testing

- Incorrectly blaming symptoms on HD.
- Discrimination (insurance, future employment).
- Negative psychological and social effects.
- Testing of children is discouraged.

Genetic testing choices.....

When to get tested and why...or why not...



Genetic counseling and making well informed decisions.

HD Treatment:

This is a progressive disorder. Treatment plans need to be regularly reviewed.

- Currently no medicine or specific treatment advised for everyone.
- Symptomatic treatment
 - Chorea. Benzodiazapines, amantadine, neuroleptics, valproate, tetrabenazine
 - Spasticity/rigidity. PT/OT, benzodiazepines, baclofen, dantrolene, tizanidine.
 - Speech/swallowing and dental care issues.
 - Behavior. Depression, Aggression, OCD, Impulse control
 - Gait and balance issues. Canes and Walkers often problematic.
 - Seizures rare in adults but can be relatively drug resistant.

Gait and balance disorders.

Very little data on type of gait disorders, rate of progression or effectiveness of interventions.

Commonly recommend repetitive exercises, Tai Chi, Yoga.

Problems learning new skills (also OCD)

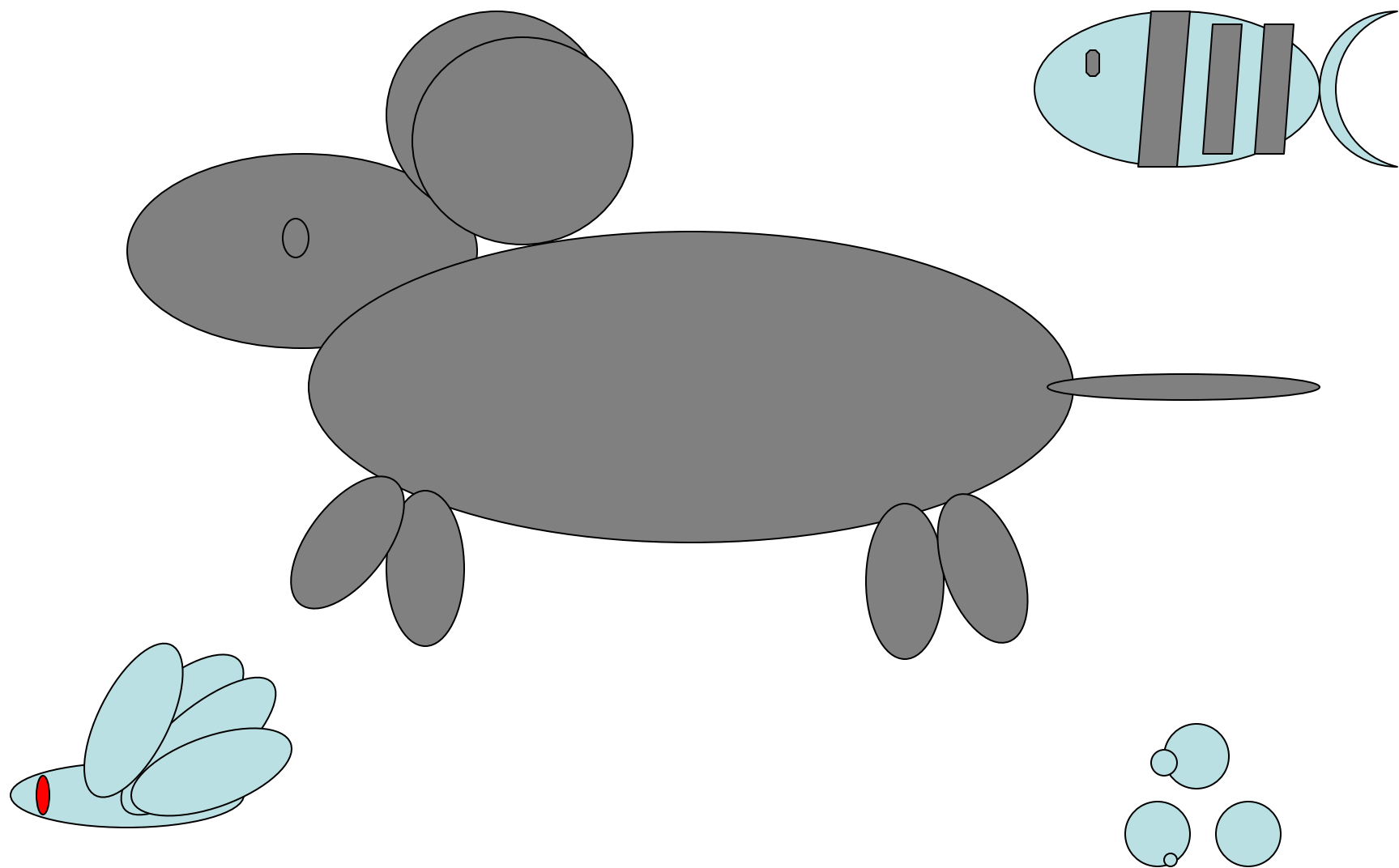
Often have difficulty with canes and walkers.

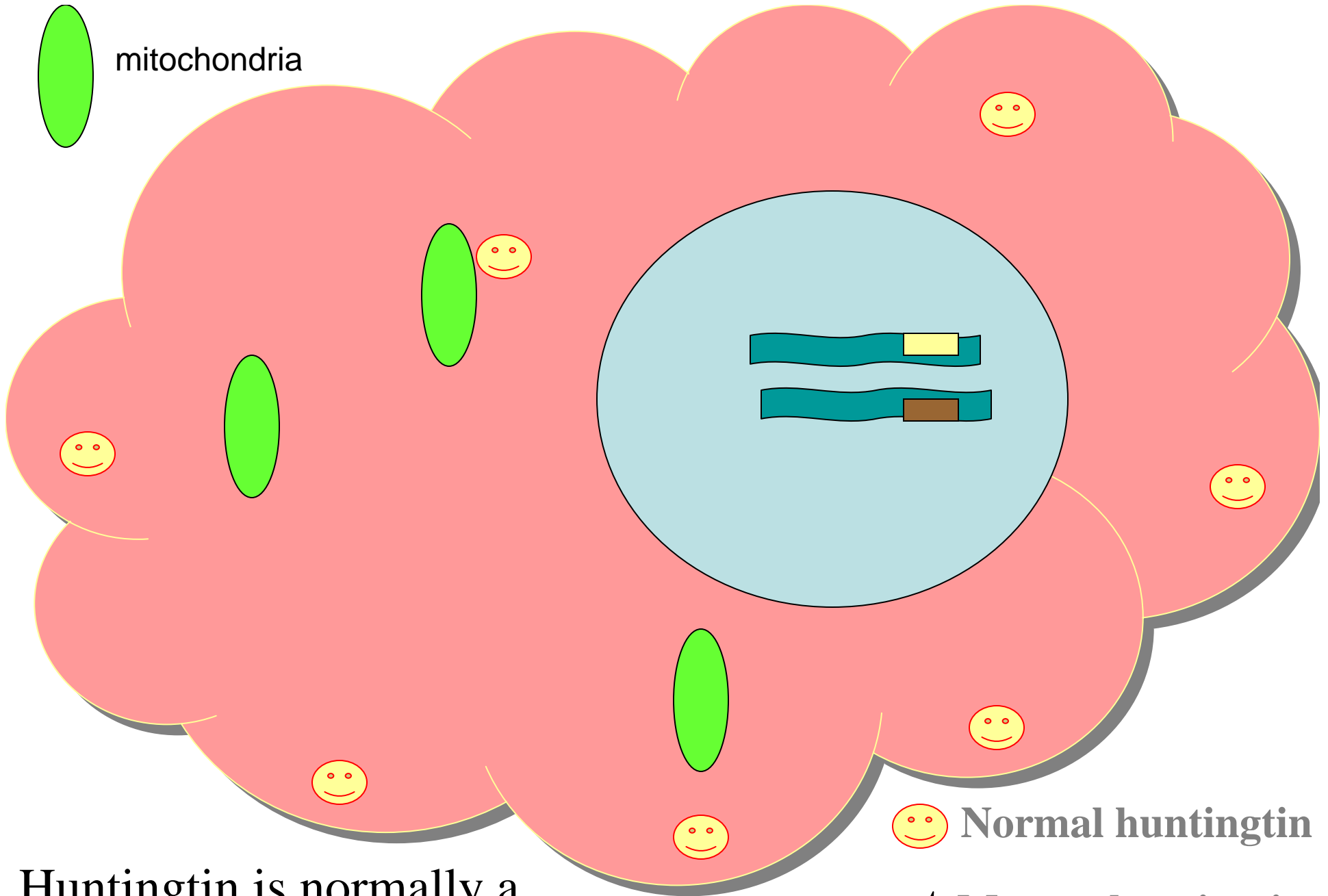
Problems with motor impersitence.

(Reverse hand brakes or regular hand brakes)

Research Advances in Huntington's Disease

- **A...Laboratory research:**
 - **Animal models of HD (mice, zebra fish, fruit flies).**
 - **Cell culture studies.**
 - **High through-put studies.**
- **Results of recent clinical trials.**
- **B....Ongoing Clinical trials:**
 - **Observational**
 - **Interventional**
 - **Symptomatic treatment**
 - **Neuroprotective, restorative.**



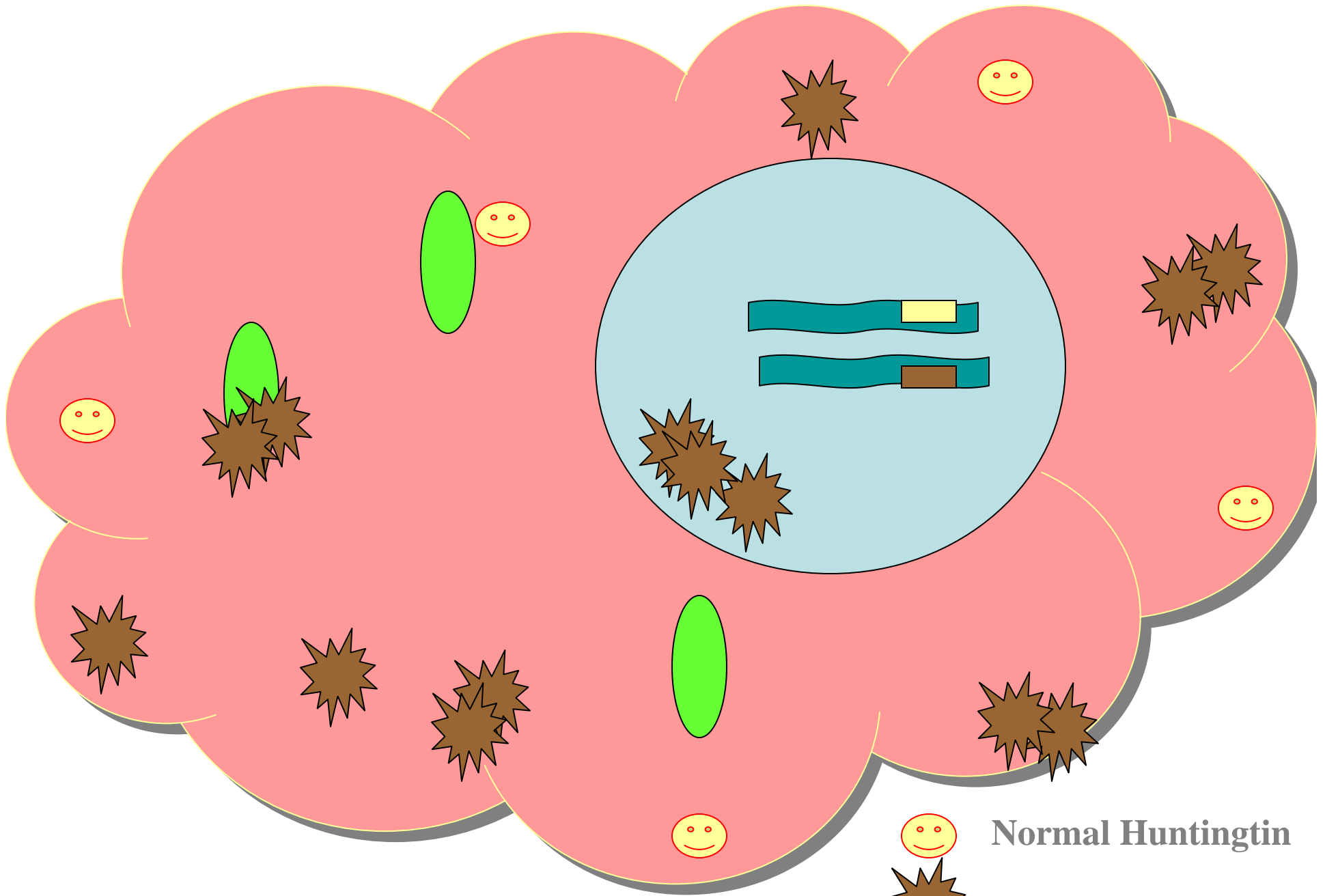


mitochondria

Huntingtin is normally a cytoplasmic protein

😊 Normal huntingtin

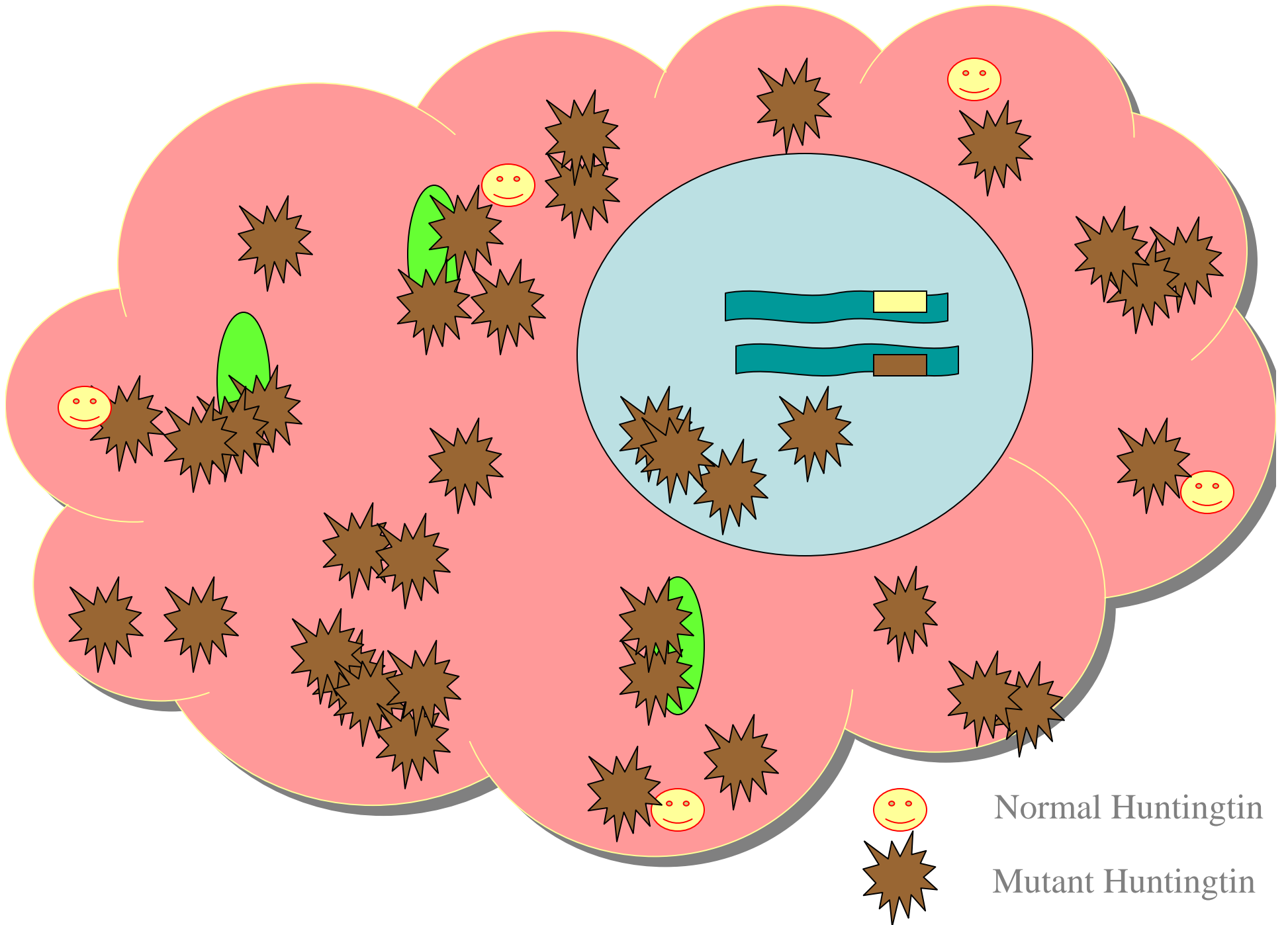
★ Mutant huntingtin



Normal Huntingtin



Mutant Huntingtin



Normal Huntingtin

Mutant Huntingtin

Some promising agents.

- Coenzyme Q10
- Ethyl-EPA
- Trehalose
- Minocycline
- Creatine

Examples of some of the numerous recent advances in HD basic science research.

Trehalose alleviates polyglutamine-mediated pathology in a mouse model of Huntington disease. Tanaka et al. *Nature Medicine*. Volume 10, February 2004

Allele-specific silencing of dominant disease genes

Victor M. Miller^{*†}, Haibin Xia[‡], Ginger L. Marrs^{*†}, Cynthia M. Gouvion^{*}, Gloria Lee[‡], Beverly L. Davidson^{*†‡§}, and Henry L. Paulson^{*†¶}

^{*}Department of Neurology, [†]Graduate Program in Genetics, and Departments of [‡]Internal Medicine and [§]Physiology and Biophysics, University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City, IA 52242

Edited by Charles M. Radding, Yale University School of Medicine, New Haven, CT, and approved April 9, 2003 (received for review February 17, 2003)

PNAS 100: 2003

Molecular Medicine for the Brain: Silencing of disease genes with RNA interference. Davidson and Paulson, March 2004
Lancet Neurology

Completed CLINICAL TRIAL:

Neurology 57:397-404, 2001

Expedited Publication

**A randomized, placebo-controlled trial of
coenzyme Q₁₀ and remacemide in
Huntington's disease**

The Huntington Study Group*

Coenzyme Q10

**(antioxidant and cofactor in mitochondrial
function)**

Remacemide

(noncompetative NMDA receptor antagonist)

347 HD patients followed for 30 months

Four treatment groups:

Coenzyme Q 10 (300 mg twice a day)

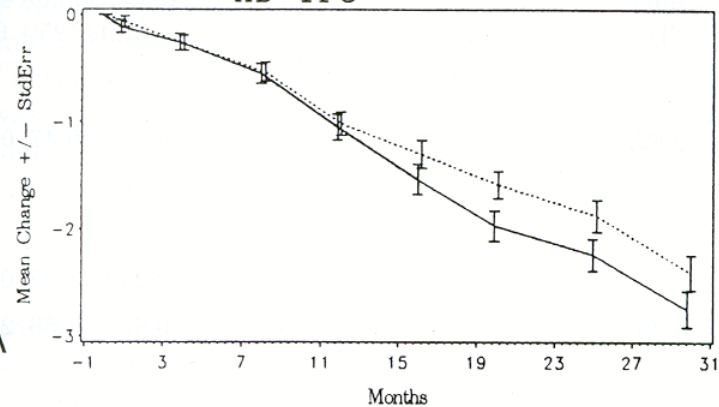
Racemide

Coenzyme Q10 + Racemide

Placebo

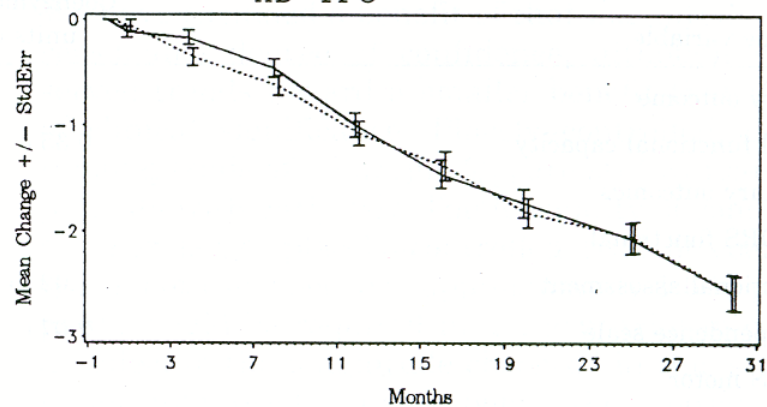
Coenzyme Q10

HD TFC

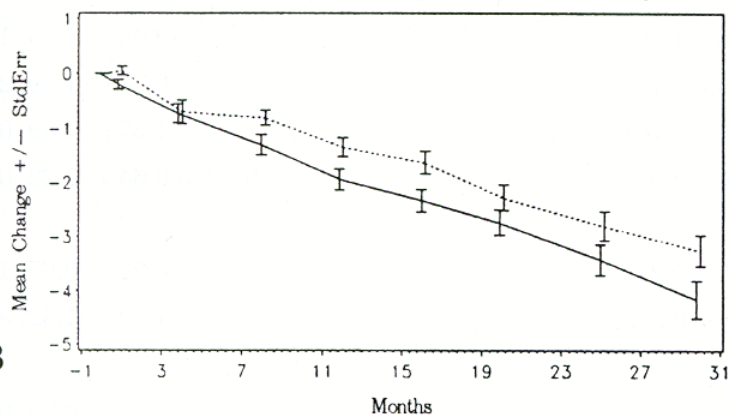


Remacemide

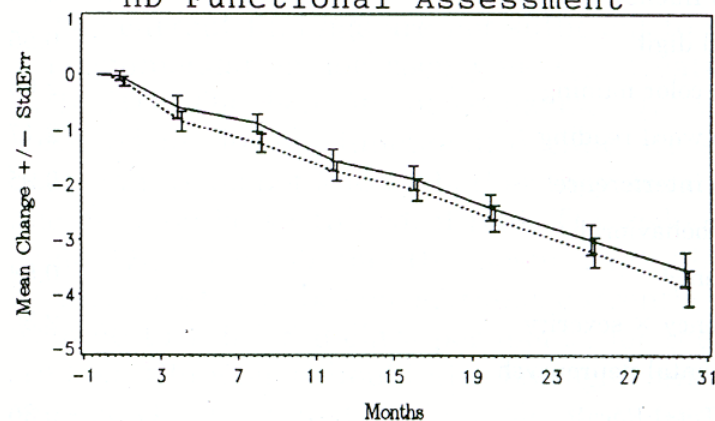
HD TFC



HD Functional Assessment



HD Functional Assessment



Conclusions: Neither treatment significantly altered decline, however Coenzyme Q10 showed a trend towards slowing of disease progress. BUT..... (HSG, Neurology, 2001)

Other potential beneficial agents

- Prozac (fluoxetine)
- Depakote (valporic acid)
- Lithium
- Namenda

- Physical exercise (may increase BDNF) and mental exercise.

Research Advances in Huntington's Disease

- **Laboratory research:**
 - Animal models of HD (mice, zebra fish, fruit flies).
 - Cell culture studies.
 - High through-put studies.
- **Clinical trials:**
 - **Observational**
 - **Interventional**
 - **Symptomatic treatment**
 - **Neuroprotective, restorative.**

Why participate in a clinical trial?

- **Advance medical science. HD is a rare disease. We have so many new therapies coming up, we need everyone to help us find the best.**
- **Earlier access to new therapeutic interventions.**
- **Free medications.**
- **Increased interactions with specialists and support staff.**

Types of Trials

- **Observational**-- learning more about the disease.
- **Interventional** -- trying to slow the disease process down and searching for a cure.

Disadvantages of participating in clinical trials

- **You might get the placebo.**
- **Potential risks of new and untried therapy.**
- **Time commitment.**

The number of potential treatments keeps growing.....

Coenzyme Q10

Stem Cells

Chocolate

Gene Therapy

Caspase -6
Inhibitors

Phenyl Butarte

BDNF
GDGF
CNTF

Trehelose

siRNA

Dimebon

Exercise

Creatine

Ampakinis

Ethyl-EPA

Memantamine

SSRIs

Ursodiol
(bile acid)

Curcumin

Minocycline

On the path to a cure.....



Resources for patients and families

www.HDSA.org

www.huntingtonproject.org

www.huntington-study-group.org

www.hdlighthouse.org