Huntington's Disease

"13"

Woody Guthrie

Arlo Guthrie

Huntington's Disease

- Degenerative disease
- Progressive
- **Fatal** (10 – 20 years)
- **Inherited** (Autosomal Dominant)
- Somewhat rare

Huntington's Disease

Gradual loss of

Motor coordination and

Mental function

What's in a Name ?

"**Chorea**" comes from the Greek word for "**dance**" and refers to the incessant quick, jerky, involuntary movements that are characteristic of **Huntington's Chorea**


TURNING POINT
SCOTLAND

Cognitive

- As Huntington's disease progresses, the ability to concentrate becomes more difficult
- May have difficulty driving, keeping track of things, making decisions, answering questions, and may lose the ability to recognize familiar objects.
- Over time judgment, memory, and other cognitive functions begin to **deteriorate into dementia**

Types of Symptoms

1. Movement
2. Cognitive
3. Psychiatric

* Chorea can become more intense when the person is anxious or upset

Psychiatric

- Early psychiatric symptoms of Huntington's disease are subtle, varied, and easily overlooked or misinterpreted

- **Depression** is the most common psychiatric symptom and often develops early in the course of the disease. Signs of depression include:

  - Hostility/irritability
  - Inability to take pleasure in life (anhedonia)
  - Lack of energy

Continued…

- May exhibit psychotic behavior:

  - Delusions
  - Hallucinations
  - Inappropriate behavior (eg unprovoked agression)
  - Paranoia

Complications

- Lack of physical activity, dietary problems, and eating and swallowing problems can cause constipation, incontinence, and **weight loss**

- Psychiatric and cognitive problems can lead to **social isolation** and **deep depression**

Pathophysiology

Destroys neurons in areas of the brain involved in the **emotions**, **intellect**, and **movement**

ATROPHY – Brain Cell Death

Which Explains…

- Jerking uncontrollable movement of the limbs, trunk, and face (chorea)
- Progressive loss of mental abilities
- Development of psychiatric problems

Characteristics

- Usually develops at age 35 – 45 (+ or – 17 years)
- 10% in children
- Men and women equally
- **Younger people** with Huntington's disease often have **more severe** case, and symptoms may progress more quickly

Cause and Risk Factors

- Having a parent with Huntington's **is** the risk factor. A child of an affected parent has a 50% chance of inheriting the disease

- The genetic mutation that occurs in gene IT-15, located on **chromosome 4,** alters the huntington protein, which is present in all human beings, and causes Huntington's disease. How the mutation of gene IT-15 alters the function of the protein is not well understood

Pre-Symptomatic Testing

A positive test result can have profound, unanticipated impacts on patients and their families

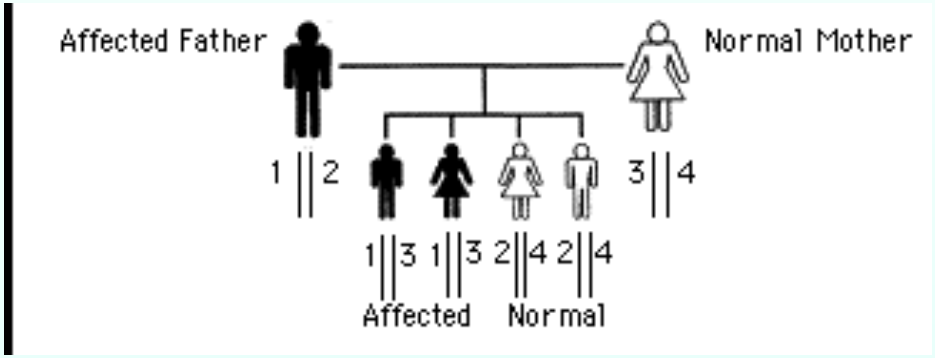
Clinical Features

- Huntington's disease is a rapidly progressive neurodegenerative disease that leads to dementia.
- Typically presents with alterations in mood as well as a change in character, defects in memory and attention.
- Progresses to a movement disorder consisting of involuntary, rapid motions.
- Usually not recognized until the patient is in their early 30's.

Genotype/Phenotype

- Huntington's is autosomal dominant.
  - This means that anyone with ONE abnormal copy of the gene will clinically have the disease.
  - There are no carriers for Huntington's.

- A parent with Huntington's will have a 50% chance of passing it on to their child.



Statistics:

- About 30,000 Americans have HD
- 150,000 more are at risk of inheriting the disease from a parent.
- There is a 50% chance that a child whose parent has Huntington's will have the disease.

Genomic Information

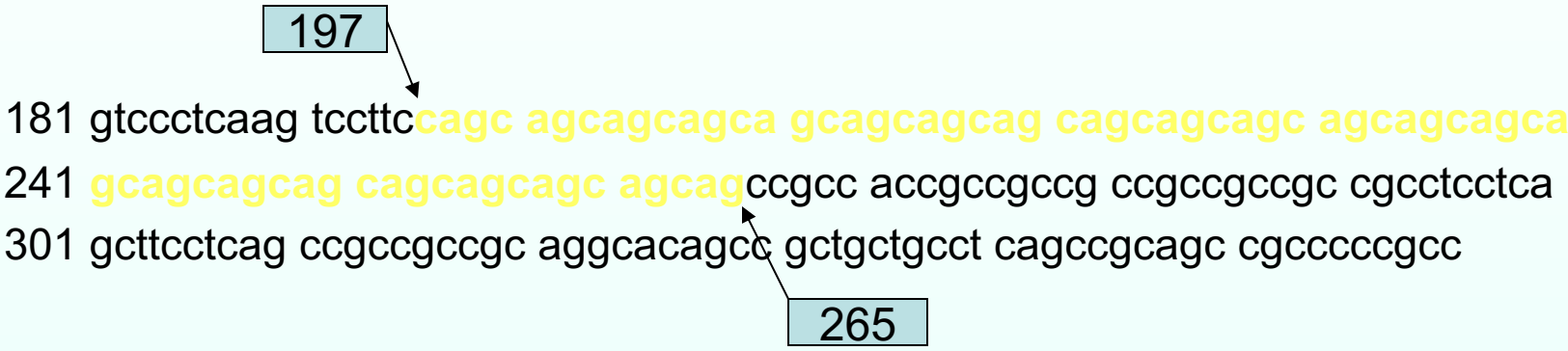
- The HD gene is located on chromosome 4, in the p-arm (4p16.3)
- It is a very large gene, consisting of 169,280 base pairs.
- Contains 67 exons, which are spliced together in the mRNA template.

mRNA information

- mRNA is 13,482 base pairs long
- Coding region of mRNA: 146…9580
- Would normally code for 3144 amino acids (very large protein!)
- Protein product of this gene is called Huntingtin (with an “i”)

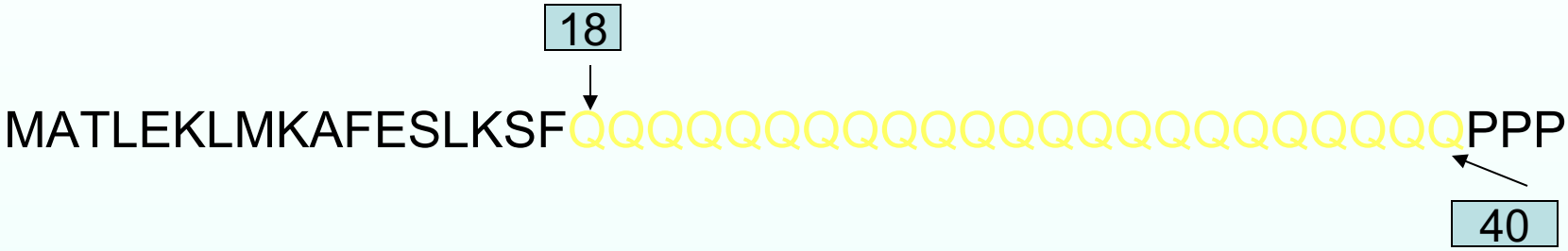
Where errors occur…

- The repeat region of CAG tri-nucleotide sequence from 197…265 is called the polyglutamine repeat. This sequence codes for 23 of the amino acid glutamine.



Protein Information

- There are 23 Q's (glutamine) in a repeating sequence in the normal protein. This is referred to as the 23Q repeat.



- The 23Q's in a normal Huntingtin protein are located as amino acids 18…40.

Pathological Protein Changes

- Expansion of this repeat region is what causes Huntington's disease. It translates to an unstable polyglutamine repeat in the protein product. Repeats in excess of 40 are considered to be pathological.

- The expanded ploy glutamine region of the pathological form of the protein causes impairment of the ubiquitin-proteasome system.

- This means that the dysfunctional protein is not removed and destroyed as it should be.

Pathology

- The accumulation of the abnormal Huntingtin protein is believed to be what causes neurological changes.

- The excess of the mutated protein interferes with neurotransmitters.

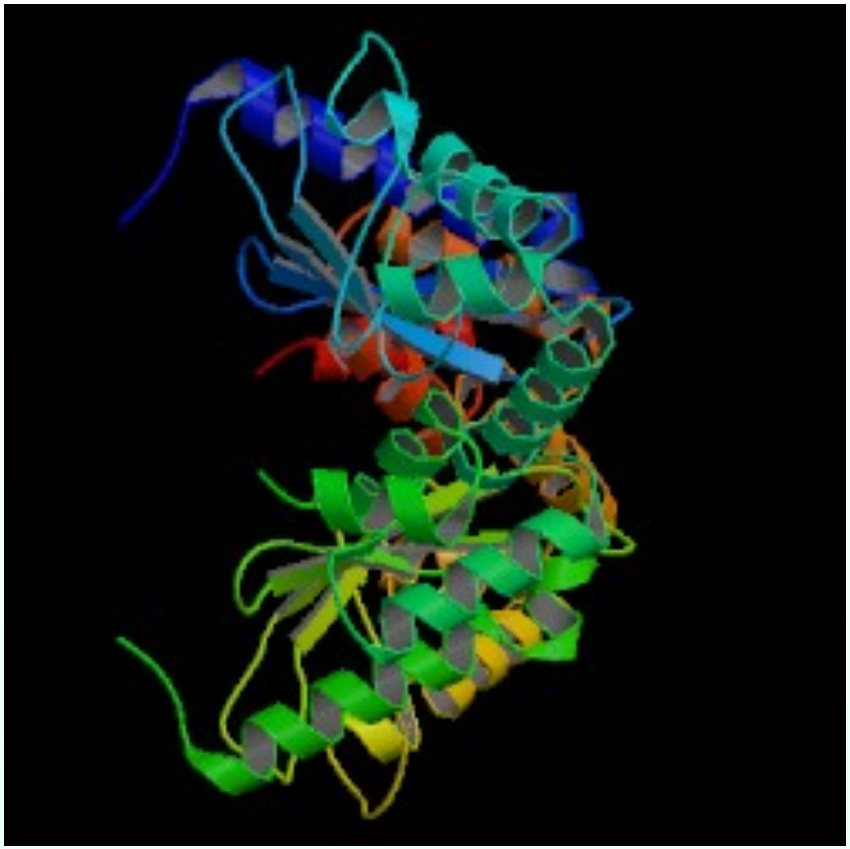
Ubiquitin-conjugating enzyme E2-25 kDa

- Also called “Huntington interacting protein 2”

•There are many ubiquitin-conjugating enzymes that attach a ubiquitin molecule to a specific protein.

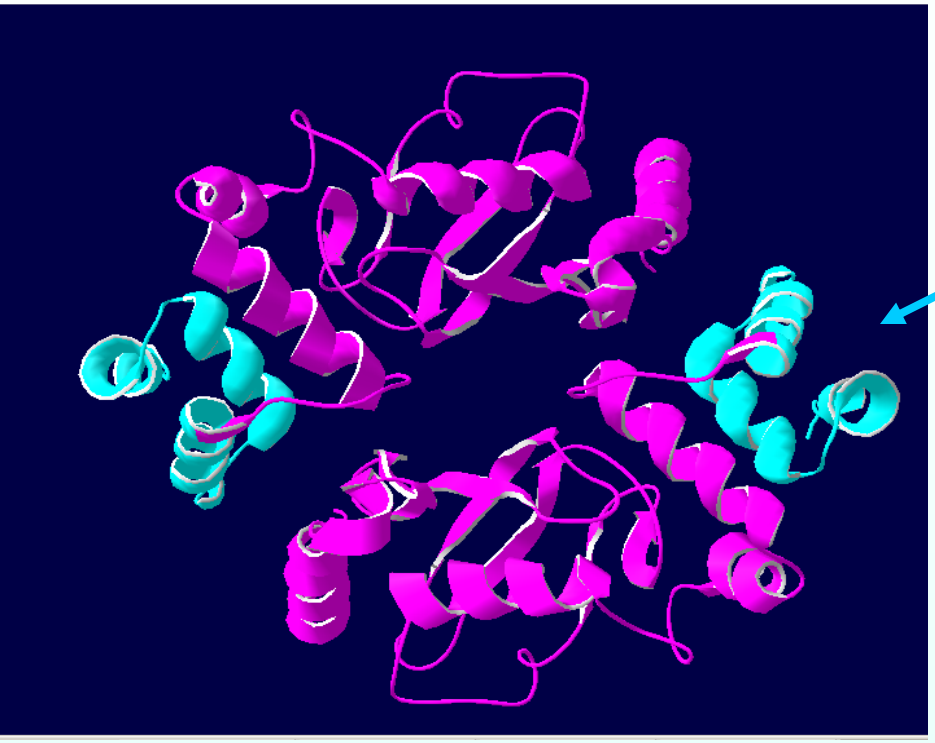
•This specific one attaches ubiquitin to huntingtin.

•This enzyme is directly related to the mutation because it is not able to perform it’s function when the HD protein has mutations in the 23Q region.



Different view with PDB viewer

It is made up of two identical subunits, A and B, and has a conserved domain (blue.)



This domain is found in many enzymes and proteins that bind to ubiquitin.

Pre-Symptomatic Testing

- Can be performed on adults, children, and even fetuses in the womb. Genetic testing of a fetus holds special challenges and risks, and some testing facilities choose not to do it

- At-risk couples wanting to have children may choose to undergo in vitro fertilization with pre-implantation screening. In this procedure, embryos produced from the couple's sperm and eggs are screened to identify one that is free of the HD mutation, which is then implanted in the woman's uterus

Genetic Testing

- Genetic testing may be required from a closely related affected relative, ideally a parent
- This helps **confirm the diagnosis** and is important if the family's history is in any way unclear, uncertain, or unusual
- Persons who test positive and are considering pregnancy are advised to seek genetic counseling before they conceive

Treatment

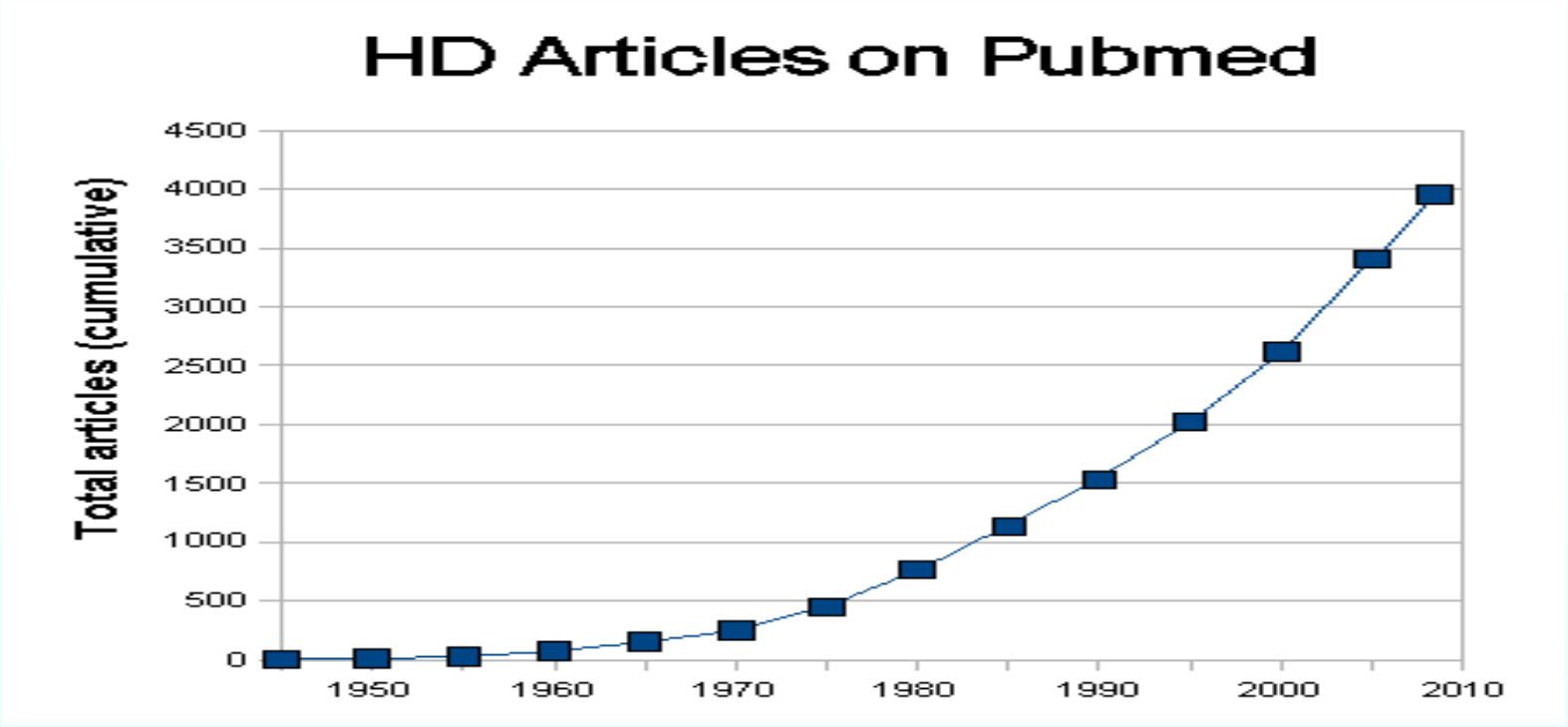
- There is **NO YET A CURE** for Huntington's disease

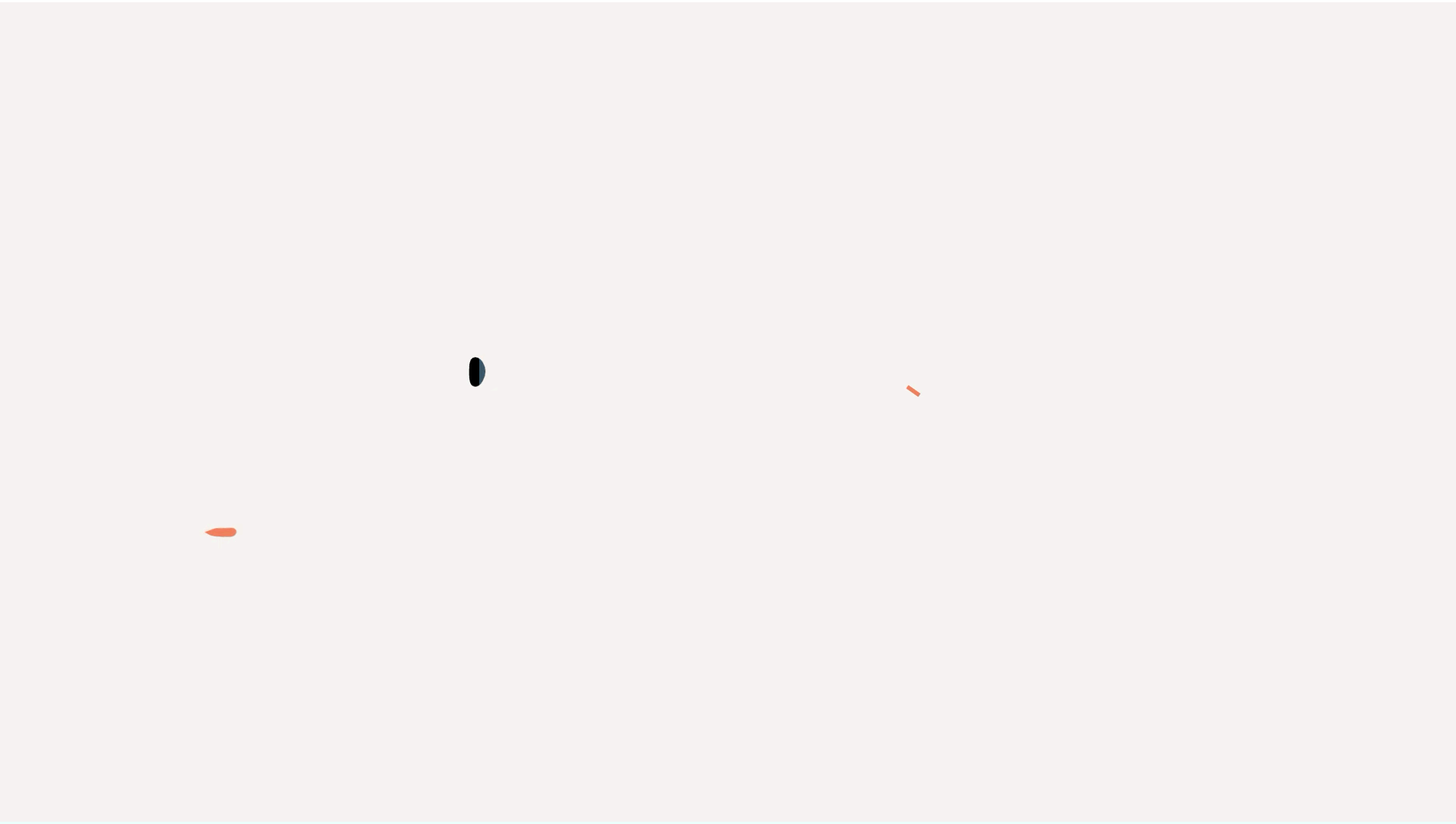
- Collaborative goals focus on:

  - Reducing symptoms
  - Preventing complications
  - Providing support and assistance to the patient and significant others

Medications

Medications are available to help **manage the signs and symptoms** of Huntington's disease, but treatments can't prevent the physical and mental decline associated with this condition





Nutrition

- Some HC patients need a lot of time for meals because the loss of coordinated movement makes it difficult for them to swallow or feed themselves

- **Minimize Risk of Choking**

  - **Cut food** into small pieces, softened, or pureed to make swallowing easier
  - **Swallowing therapy** can help if started before there is serious difficulty
  - **Avoid dairy** products because they tend to increase the secretion of mucus, which can increase the risk for choking

Continued…

- Important to consume enough **calories** to maintain adequate body weight

  - Number of daily meals may have to be increased
  - Vitamins and nutritional supplements recommended
  - If eating and dietary problems become severe, may need feeding tube

- Requires large quantities of **fluids** **(**especially during hot weather to avoid dehydration)

  - Bendable straws make drinking easier
  - Liquids may have to be thickened with additives to the consistency of syrup before drinking is possible

Physical Activity

- Should walk as much as possible, even if assistance is necessary
- Daily exercise promotes physical and mental well-being
- Falls are always a risk, keep surroundings free of hard, sharp objects
- Wearing special padding during walks helps protect against injury from falls
- Small weights worn around the ankles and sturdy, well-fitting shoes that slip on and off easily can improve a patient's stability

Social Activity

- Unless and until the disease's progression prohibits it, should participate in outside activities, socialize, and pursue hobbies and interests

- These activities also give family members and caregivers valuable time for themselves

Prognosis

- The bedridden patient in the final stages of Huntington's disease **often dies from complications** such as heart failure or pneumonia

- **Juvenile Huntington's** disease (16%) runs it course comparatively fast, with death typically occurring in about 10 years