Single-Gene Disorders

Oral Histology | Kristine Krafts, MD
Objectives

• Explain how hemophilia is inherited, and describe its most common clinical features.

• Describe the inheritance pattern of neurofibromatosis, and explain two things about the NF-1 gene that are non-Mendelian.

• Describe the most common clinical features of neurofibromatosis, and list a few things you might see in a patient in dental clinic.

• Define anticipation as it applies to trinucleotide repeat diseases, and explain why it happens.

• Describe the main clinical features of Huntington disease.

• Explain (in a general way) what happens to the brain in patients with Huntington disease.
Single-Gene Disorders

- Hemophilia
- Neurofibromatosis
- Huntington disease
Hemophilia

- X-linked recessive (70%) or new mutation (30%)
- 1 in 5000 people
- Follows Mendel’s laws
- Defect in gene for coagulation factor VIII or IX
- Massive hemorrhage following trauma, bleeding into joints
Queen Victoria’s Kindred with Hemophilia

[Family tree diagram with details of Queen Victoria's direct descendants, including those with hemophilia]
Married Nicholas II, Russian Czar

Desperately sought help for Alexis’ severe bleeding
Rasputin
Romanov family executed in Ekaterina in 1918
Normal knee

Knee of patient with hemophilia
Neurofibromatosis

- Rare autosomal dominant disease
- Near-complete penetrance but variable expressivity
- Loss-of-function mutation in NF-1 gene (which encodes a protein that keeps cell growth in check)
- Multiple neurofibromas (benign tumors of nerve sheath cells) and other abnormalities
Joseph Merrick, age 27, the year of his death
Small neurofibroma
Innumerable neurofibromas
Disfiguring neurofibromas
Neurofibromatosis: Other Features

- Pigmented skin lesions ("café-au-lait spots")
- Eye tumors
- Brain tumors
- Lisch nodules
- Skeletal abnormalities
Café-au-lait spots
Lisch nodules
A Kindred with Neurofibromatosis

- Café-au-lait spots
- Eye tumors
- Brain tumors
Huntington Disease

- Inherited neurodegenerative disease
- Early symptoms: lack of coordination, unsteady gait
- Later: chorea (random, involuntary movements), psychiatric symptoms, dementia
- Usually begins in 30s-40s; slow progression over 10-20 years.
Huntington disease is inherited in an autosomal dominant pattern.

But... in each subsequent generation, the disease starts earlier and is more severe!
Here’s the explanation.

- It is autosomal dominant – but there’s a twist.
- The normal HTT gene has a bunch of trinucleotide repeats.
- The mutated HTT gene has more repeats than normal.
- The more repeats, the earlier the onset and the worse the symptoms.
- The mutated gene is unstable! As it passes from parent to child, the number of repeats increases.
- So in each successive generation, the disease starts at a younger age and is more severe (“anticipation”).
- Diseases like this are called “trinucleotide repeat diseases.”
Huntingtin protein
26 or fewer CAG repeats

Normal huntingtin gene

Normal huntingtin protein

Normal neuron

36 or more CAG repeats

Mutated huntingtin gene

Mutated huntingtin protein

Degenerating neuron
The exact number of repeats matters!

<table>
<thead>
<tr>
<th># of repeats</th>
<th>Designation</th>
<th>Affected?</th>
<th>Transmit mutation?</th>
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<tbody>
<tr>
<td>26 or fewer</td>
<td>normal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>27 - 35</td>
<td>intermediate</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>36 - 39</td>
<td>reduced penetrance</td>
<td>Maybe</td>
<td>Maybe</td>
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<tr>
<td>40 or more</td>
<td>full penetrance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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The greater the number of repeats, the earlier the onset of disease.
A Kindred with Huntington Disease

O = age of onset
R = number of repeats

O = 45
R = unknown

O = 40
R = 45

O = 39
R = 47

O = 31
R = 51

O = 26
R = 55

O = 28
R = 57

O = 22
R = 60

O = 16
R = 68

O = 18
R = 70
Huntington Disease: Pathogenesis

• Loss of neurons in basal ganglia
• Spiny striatal neurons dampen motor activity
• Lose these, and you get increased motor output (manifests as choreoathetosis)
• Cognitive changes related to neuronal loss from cortex
Normal brain (L) and brain in HD (R)
Read this story about Katharine and her family: