Surviving a Genetic Code
Interprofessional Case Conference
October 23, 2009
Genes contain instructions for making proteins.

Proteins act alone or in complexes to perform many cellular functions.

U.S. DEPARTMENT OF ENERGY
ABO Blood Typing System in Humans

Gene has a “recipe” for an enzyme that adds sugars to a protein found on the surface of red blood cells

3 alleles

Type A

Type B

Type O
homozygous

heterozygous

Type A

Type B

Type O

Type AB
Sickle Cell Disease

• Gene contains the recipe to make the protein \( \beta \text{globin} \), part of the molecule hemoglobin.

• Hemoglobin in red blood cells transports oxygen from the lungs to cells throughout the body.
A mutation, or alteration, in the beta-globin gene results in a defective protein which causes the red blood cells to sickle, stick together, and clog up blood vessels.
The mutant form of the gene (a) is **recessive**, while the normal form of the gene (A) is **dominant**, so only individuals who are homozygous for the mutant form of the gene will have sickle cell disease. Individuals who are heterozygous for the gene are said to be **carriers** for sickle cell disease.

\[
\begin{align*}
    & AA & \rightarrow & \text{Normal} \\
    & Aa & \rightarrow & \text{Normal (carrier)} \\
    & aa & \rightarrow & \text{Sickle cell disease}
\end{align*}
\]
Father
Has sickle cell trait
One copy of sickle cell gene

Mother
Has sickle cell trait
One copy of sickle cell gene

Key
A  Normal gene
   Normal hemoglobin (A)
S  Sickle cell gene
   Abnormal hemoglobin (S)

Child
Does not have sickle cell anemia
Two copies of normal gene

Child
Has sickle cell trait
One copy of sickle cell gene

Child
Has sickle cell trait
One copy of sickle cell gene

Child
Has sickle cell anemia
Two copies of sickle cell gene

Child
Has sickle cell trait
One copy of sickle cell gene
Testing for sickle cell allele

[Genetic diagram showing family tree with alleles and DNA sequences for beta-S and beta-A genes, indicating the presence of the sickle cell allele (GTG) and its absence (GAG)].
Huntington Disease

- inherited brain disorder that causes uncontrolled movements, mental and emotional problems, and progressive loss of thinking ability (cognition)
- affects about 1 in 10,000 people
- caused by a dominant mutation in the HD gene
- normal gene encodes huntingtin protein
Inheritance of HD

hh x hh  All offspring hh (normal)

Hh x hh  50% chance of offspring being hh (normal)
          50% chance of offspring being Hh (HD)
What’s happening here?

- The mutation is a short DNA sequence which is abnormally repeated many times, called a CAG repeat expansion.
- As the altered HD gene is passed down from one generation to the next, the size of the CAG repeat expansion can increase.
<table>
<thead>
<tr>
<th>CAG Repeat Size</th>
<th>Median Age at Onset * (years) (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>66 (72-59)</td>
</tr>
<tr>
<td>40</td>
<td>59 (61-56)</td>
</tr>
<tr>
<td>41</td>
<td>54 (56-52)</td>
</tr>
<tr>
<td>42</td>
<td>49 (50-48)</td>
</tr>
<tr>
<td>43</td>
<td>44 (45-42)</td>
</tr>
<tr>
<td>44</td>
<td>42 (43-40)</td>
</tr>
<tr>
<td>45</td>
<td>37 (39-36)</td>
</tr>
<tr>
<td>46</td>
<td>36 (37-35)</td>
</tr>
<tr>
<td>47</td>
<td>33 (35-31)</td>
</tr>
<tr>
<td>48</td>
<td>32 (34-30)</td>
</tr>
<tr>
<td>49</td>
<td>28 (32-25)</td>
</tr>
<tr>
<td>50</td>
<td>27 (30-24)</td>
</tr>
</tbody>
</table>
Cancer “genes”

NORMAL CELL

FIRST MUTATION
Cell seems normal but is predisposed to proliferate excessively

SECOND MUTATION
Cell begins to proliferate too much but is otherwise normal

THIRD MUTATION
Cell proliferates more rapidly; it also undergoes structural changes

MALIGNANT CELL

FOURTH OR LATER MUTATION
Cell grows uncontrollably and looks obviously deranged
Two-hit hypothesis
Multifactorial inheritance

• characteristics due to interaction of multiple genes AND environmental factors
• conditions run in families, but not in a straightforward fashion
• empiric risks are used to predict the recurrence of a multifactorial disorder
• empiric risk is based on epidemiologic and population studies and on mathematical models
Risk perception

- Your lifetime risk of developing lung cancer is 1 in 9
- You have greater than a 88% of not developing lung cancer
- Your chance of developing lung cancer is twice as high as the general population
Unaffected male

Affected male

Unaffected female

Affected female

Person whose sex is not known

Marriage (mating)

Consanguinous marriage

vertical line = offspring (in this case, son)

A family of four brothers and sisters. The last two are non-identical twins

Identical twins

Pedigree

Key:
- □ male
- ■ affected male
- ✗ deceased male
- ○ female
- ● affected female
- ✗ deceased female