Chromosomes, Genes, Alleles and Mutations

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Your turn to be House.
A patient has arrived at the clinic with mystery symptoms. Your group needs to perform a series of tests and find the clues that point to his diagnosis.

Start at the patient history and then take each test in turn. Once they're all completed, move on to step 3: the diagnosis.

Read the history and start here:

Complete all of the tests. https://www.box.net/shared/0bt8jbp8vm

Adapted from:

The Mystery of the Crooked Cell
Chromosomes, Genes and Alleles

**Chromosome**
- made of DNA and protein
- contains **GENES**
  - heritable factors that control specific characteristics

**Alleles** are different forms of a specific gene

**Gene locus:**
- specific position of a gene on a chromosome

All individuals of a species carry the same genes at the same loci on the same chromosomes

i.e. they are **homologous**

Take a tour of the basics:

[Link to the basics tour](http://learn.genetics.utah.edu/units/basics/tour/)
What is the system for assigning gene loci?

The gene **TP53** (prevents tumours) is found at **17p13.1**.
*Mark its approximate location with an arrow.*
What is the system for assigning gene loci?

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What is the system for assigning gene loci?

Match the gene loci with the letters

16q13.2
11p13.1
17q1.1
What is the system for assigning gene loci?

Order a free, cool poster:
http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/chooser.shtml
Genome: the whole of the genetic information of an organism

Watch this introduction to the Human Genome Project:

http://www.youtube.com/watch?v=XuUpnAz5y1g

Great book:

http://www.amazon.com/Genome-Matt-Ridley/dp/0060932902
Chromosomes are structural units that are made up of DNA and proteins.

By coiling the DNA around the proteins many times, a large amount of information can be stored inside the nucleus.

All members of a species have the same number of chromosomes - each with the same genes in the same gene loci.

The number of chromosomes varies between species.
More about Chromosomes and DNA coiling:

How do we get a 2m strand of DNA to fit into one nucleus?

http://www.youtube.com/watch?v=N5zFOScowqo

http://www.scientenlinks.com/interactives/dna.swf

http://www.youtube.com/watch?v=AF2wwMReTf8
Transcribe and translate these sections of a gene:

**sense**

CCT GAG GAG
GGA CTC CTC

**anti-sense**

CCT GTG GAG
GGA CAC CTC

mRNA

amino acid
Sickle Cell Disease

A single base-substitution mutation occurs here

Chromosome 11

Normal

CCT GAG GAG

sense

anti-sense

transcription

translation


http://www.sicklecelldiseasejax.org/SickleCell.jpg
Sickle Cell Disease

A single **base-substitution mutation** occurs here

Chromosome 11

**Normal**

- CCT GAG GAG
- GGA CTC CTC

**transcription**

**mRNA**

- CCU GAG GAG

**translation**

- pro
- glu. ac
- glu. ac

**normal Hb**

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http://www.sicklecelldiseasejax.org/SickleCell.jpg
Sickle Cell Disease

A single base-substitution mutation occurs here

Chromosome 11

Normal

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GGA CTC CTC

↓

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mRNA

↓

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glu. ac
glu. ac

normal Hb

Mutant

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transcription

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GGA CTC CTC

sense

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translation

normal Hb

Mutant

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GGA CAC CTC

transcription

translation

sickle Hb


http://www.sicklecelldiseasejax.org/SickleCell.jpg
Comparing glutamic acid and valine

What differences in properties can we deduce from the structures?

How might this change the quaternary protein structure?
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How might this change the quaternary protein structure?

http://carnegieinstitution.org/first_light_case/horn/lessons/images/hemoglobins.GIF
Gene Mutations

A mutation is a permanent change in the base sequence of DNA.
It is unlikely to give you the power to control the weather, read minds, sprout adamantium claws, fly, shoot fire or lasers from your eyes, freeze things, heal fatal wounds, bend the will of others or absorb other mutants' powers.

However, it is the cumulative effects of millions of mutations and natural selection that have allowed all organisms to evolve from simpler ancestors.

Not all mutations cause disease (but some do)

Even though DNA replication is protected by base-pairing, mistakes can occur. This is more likely after exposure to mutagens, such as radiation and some chemicals. The mutation may cause a gene to be wrongly expressed - a genetic disease.
Base-substitution mutation

One base is substituted for another.
This may or may not result in the change of a single amino acid in the polypeptide.

What are the effects of these base substitution mutations?

DNA  AGCCCGTGA  AGCCCGGTG
mRNA  UCGGGCAAU  UCGGGCAAC
a.a.  ser  gly  asp  ser  gly  asp

This is a silent mutation:
The change in base sequence has had no effect on the amino acid produced.
Base-substitution mutation

What are the effects of these base substitution mutations?

DNA GGACTCCTC $\rightarrow$ GGACACCTC
mRNA CCUGAGGAG $\rightarrow$ CCUGUGGAG
a.a.

DNA GGAACCCCCTC $\rightarrow$ GGAACCTCTC
mRNA CCUUGGGAG $\rightarrow$ CCUUGAGAG
a.a.
Base-substitution mutation

What are the effects of these base substitution mutations?

DNA  GGACTCCTC  \rightarrow  GGACACCTC
mRNA  CCUGAGGGAG  \rightarrow  CCUGUGGGAG
a.a.  pro  glu. ac  glu. ac  pro  val  glu. ac

This is a missense mutation:
The change in base sequence has caused one different amino acid to be produced (e.g. sickle cell)

DNA  GGAACCCTC  \rightarrow  GGAACCTCTC
mRNA  CCUUGGGGAG  \rightarrow  CCUUGAGGAG
a.a.  pro  tryp  glu. ac  pro  STOP

This is a nonsense mutation:
The change in base sequence has caused a STOP codon to be produced, so the polypeptide produced is shortened. (e.g. cystic fibrosis)
Sickle cell disease

A single base substitution leads to the production of valine instead of glutamine.

This leads to production of abnormal red blood cells. People with one copy of the faulty gene produce some abnormal Hb, but are fine. Those with two faulty copies produce all abnormal Hb - this can be dangerous.

<table>
<thead>
<tr>
<th>HBB Sequence in Normal Adult Hemoglobin (Hb A):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleotide</td>
</tr>
<tr>
<td>Amino Acid</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBB Sequence in Mutant Adult Hemoglobin (Hb S):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleotide</td>
</tr>
<tr>
<td>Amino Acid</td>
</tr>
<tr>
<td></td>
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Malaria is a parasitic disease caused by a plasmodium cell. It is carried by the *Anopheles* mosquito and invades normal red blood cells.

The plasmodium invades red blood cells and causes them to lyse.

Common symptoms include fever, shivering, vomiting and anemia. Death is common, often due to kidney failure or severe anemia.

Malaria cannot infect sickle cells, so people with the sickle cell trait are resistant to the disease. As a result, sickle cell is more prevalent in areas where malaria is endemic.
The Evolution of Sickle Cell Disease

How is sickle cell an example of natural selection in humans as a result of a single mutation?

Evolution:
The cumulative change in the heritable characteristics of a population.

This is gradual - over many generations.

Natural selection occurs when there is variation within a species (as the result of a mutation). If the individual is benefited by the mutation, it may have greater reproductive success, thus passing on the mutation.

http://www.youtube.com/watch?v=1fN7rOwDyMQ
Inheriting Mutations

Try this activity to see how sickle cell is inherited and to see how researchers use genetic markers to trace inheritance patterns.

https://genographic.nationalgeographic.com/genographic-custom/atlas/spanish/dist/ax/_swfs/populationGenetics.swf
Frequently Asked Questions

1. What is sickle cell disease?
2. What causes sickle cell disease?
3. How is sickle cell inherited?
4. What is the sickle cell trait?
5. If sickle cell trait is not an illness, why are people tested?
6. What medical problems are caused by sickle cell disease?
7. What are the signs and symptoms of sickle cell disease?
8. How many people have sickle cell disease?
9. How long does a person with sickle cell disease live?
10. Can people with sickle cell disease live a productive life?
11. Are people of African descent the only group affected?
12. How is sickle cell disease treated?
13. Is there a cure?
14. What is the future of sickle cell treatment?
15. How is sickle cell disease detected?
16. How can a patient with sickle disease, as well as their family and friends be helped with coping?
17. Is it possible to detect sickle cell disease in an unborn baby?
18. What should future parents know?
haemoglobin gene

Hb^A  Allele for normal haemoglobin
Hb^s  Allele for sickle cells

mum

Hb^A  Hb^A
normal

dad

Hb^A  Hb^s
carrier (produces some sickle cells)

gametes:

Hb^A  Hb^A
Hb^A  Hb^s

cross:

Hb^A  Hb^A
Hb^A  Hb^s

F1 generation (offspring)

genotypes:

phenotypes:

punnet square
haemoglobin gene

Hb^A  Allele for normal haemoglobin
Hb^s  Allele for sickle cells

gametes:

Hb^A  Hb^A
Hb^A  Hb^S

cross:

Hb^A Hb^A
Hb^A Hb^S

F1 generation (offspring)

genotypes:

2Hb^A Hb^A : 2Hb^A Hb^S

phenotypes:

2 normal : 2 carrier
haemoglobin gene → Hb^A (Allele for normal haemoglobin) → Hb^S (Allele for sickle cells)

**F₀**
- **genotype:**
  - mum: Hb^A Hb^S
  - dad: Hb^A Hb^S
- **phenotype:** mum and dad are heterozygous (carrier) for sickle cell trait.
- **gametes:** Hb^A, Hb^S

**cross:**

**F₁ generation (offspring)**
- **genotypes:**
  - Hb^A Hb^A
  - Hb^A Hb^S
  - Hb^S Hb^A
  - Hb^S Hb^S
- **phenotypes:**
  - Hb^A Hb^A: Normal
  - Hb^A Hb^S: Heterozygous carrier
  - Hb^S Hb^A: Heterozygous carrier
  - Hb^S Hb^S: Sickle cell anemia

Both parents are carriers (protected against malaria but don't suffer from sickle cell)
**F₀**

**genotype:**

**phenotype:**

**gametes:**

**cross:**

**F₁ generation (offspring)**

**genotypes:**

1. Hbᴬ Hbᴬ
   - normal (no protection)
2. Hbᴬ Hbˢ
   - carrier (protected)
3. Hbˢ Hbˢ
   - sickle cell disease

**What's unusual about the notation of the alleles in this case?**

**punnett square**
Stem cells used in sickle cell treatment:

Thanks to a recent breakthrough in stem cell reprogramming, faulty genes in mice were 'repaired' and replaced.

Retroviruses were used to insert the corrected gene into the mouse's cells, which were then put back into the mouse and started to produce healthy red blood cells. Amazing.


http://www.youtube.com/watch?v=4EFab8-HIGc
For more help and animations, visit:

http://sciencevideos.wordpress.com