Lecture 1: What is genetics?

Inheritance as we observe it

- Offspring resemble parents in broad terms i.e. same species
- Offspring often share more similarities with their parents than with non-related individuals
- But they are not identical to either parent or to their siblings (except in the case of identical twins)
- What is the mechanism that ensures both this continuity of inheritance and this variation?
- Genetics aims to answer this question

Inheritance and development

- Organisms are not born mature/complete: whatever is inherited has to go through a process of development to get from egg/sperm to mature individual
- The inherited material i.e. genes, guide development but do not entirely determine it
- There are other factors acting throughout the organism's lifetime

Organism and environment

- What is the environment? Internal vs external
- Complex interaction between genes and environment
- Examples of traits affected by inheritance and by environment

a) Organisms with the same inheritance can develop in very different ways depending on the environment
    - In social insects like bees and ants queens and workers are genetically identical but morphologically very different due to different feeding as larvae
        - All larvae are fed on royal jelly for three days, but workers-to-be are then moved onto pollen and nectar, while queens-to-be continue on royal jelly

b) Organisms in the same environment can develop differently under the influence of different genes
    - Leptin is a hormone that is involved in appetite regulation and metabolism
    - *ob* mutation affects function of leptin and causes mice to be abnormally obese – they both overeat and metabolise food less efficiently

Internal environment

In the womb:

- congenital anomalies affect approx. 1 in 33 babies (WHO)

- 50% cases due to genetic/environment/infectious factors, including:
    - Infections: rubella
    - Chemicals: pesticides, heavy metals (lead, mercury etc)
    - Radiation
    - Medicines: thalidomide; retinoic acid (acne medications)
    - Recreational drugs
    - Alcohol
    - Smoking
    - Maternal nutrition: folic acid; iodine
- 50% cases have no identified specific cause

In the egg:

- provides the environment for the very first cell divisions in development
- e.g. proteins laid down during the production of the Drosophila egg (before fertilization) determine body axis formation in the embryo

Terminology:

Phenotype
An observable character or characters in an organism; may refer to structural or functional characters e.g. blood group, hair colour

Genotype
The genetic make-up of an individual with respect to a given characteristic(s) e.g. an individual with the phenotype blood group O has the genotype OO. Remember that genes interact with one another and with the environment so that individuals with the same genotype do not necessarily have the same phenotype e.g. honey bee queen vs worker, and vice-versa

Haploid
Describes a cell or individual with a single copy of each chromosome e.g. an egg or sperm cell

Diploid
Describes a cell or individual with two copies of each chromosome e.g. a normal human somatic cell

Gene
A sequence of DNA that affects a given characteristic of an organism by producing a protein or RNA molecule e.g. a sequence on human chromosome 9 produces the ABO antigens.

Genome
The complete genetic make-up of an individual or species (for all characteristics)

Locus
The position of a gene on a chromosome: for ABO blood group the locus is chromosome 9, 9q34.1-q34.2

Allele
One or more alternative variations of a particular gene that can exist at that gene locus e.g. A, B, and O alleles for blood groups

Homozygote
A diploid individual with two identical alleles at a given locus e.g. (in ABO blood groups) AA or BB

Heterozygote

A diploid individual with two different alleles at a given locus e.g. AO or AB

So, for the ABO blood group:

- The A allele causes the production of A antigens
- The B allele causes the production of B antigens
- The O allele causes the production of a non-functioning protein so no antigens are produced

Genotype	Phenotype
AA or AO	Blood group A
BB or BO	Blood group B
AB	Blood group AB (universal recipient because the individual does not produce either anti-A or anti-B antibodies to attack the donated blood cells)
OO	Blood group O (universal donor because the RBCs contain no antigens to be attacked by the recipient's immune system)

- Variant alleles can have different kinds of effects – in this case, the O allele leads to a protein that doesn't function at all, in other cases there might be a protein product that has a different function, or one that blocks the activity of the normal version (more on this later)

"Genes for" cardiovascular disease

(see final slide in PowerPoint presentation)

Required readings:

Richard Lewontin, "Genes, Environment, and Organism", in *Human Diversity*, New York: Scientific American Library, 1982, pp.14-28 (pdf available on the VLE)

Steven Pinker, "My Genome, My Self". Available online at:
http://www.nytimes.com/2009/01/11/magazine/11Genome-t.html

As you read these pieces bear in mind that Lewontin and Pinker have been on opposite sides of the debate over biological determinism for many years. Lewontin has often been labelled as a Marxist critic of biological determinism while Pinker is often interpreted as a strong biological reductionist. See what you think when you've read these.

Other resources:

WHO factsheet on congenital anomalies: http://www.who.int/mediacentre/factsheets/fs370/en/

British Heart Foundation website on CVD: http://www.bhf.org.uk/heart-health/conditions/cardiovascular-disease.aspx

A glossary of genetic terms: http://www.genome.gov/glossary/

Lecture 2: Basic Development

Development = one cell to many cells

- As discussed in the last lecture, organisms do not appear in the world complete and fully formed
- The organism has to undergo a process of development from a single cell to a multi-celled organism
- In humans: from 1 cell → 50-70 trillion cells
- Around 200 different cell types: nerve, bone, skin, liver, retina etc. etc. etc.

Development begins at fertilization

- Haploid GAMETES (also known as GERM CELLS) i.e egg and sperm each have a single copy of each chromosome – 23 in humans (all other cells in the body are diploid and are called SOMATIC CELLS)
- Gametes fuse to form a diploid ZYGOTE or fertilized egg
- Note that the sperm cell is much smaller than the egg and contains little cytoplasm, so the cytoplasm of the zygote is largely from the egg i.e. maternally derived

Genomic equivalence

- Because all of the cells of the organism derive from the zygote by cell division, they all contain the same set of genetic material or genome
- Each cell (or cell-type) expresses a certain sub-set of this genome
- Cells do not lose the genes they do not express but retain the potential (in the right circumstances) to express any or all of the genes in the genome
- “House-keeping” genes are expressed in most or all cells as they are necessary for basic processes of metabolism, cell division etc.
- Other genes are expressed only in certain cell types e.g. ABO blood antigens (see Lecture 1)
- Some genes have multiple functions depending on the cell type, location in the organism and time e.g. sonic hedgehog

Evidence for genomic equivalence

- Genomic equivalence was demonstrated by cloning
    - Removing the haploid nucleus from an unfertilized egg cell and replacing it with a diploid nucleus from a somatic cell of another individual
    - Given the right conditions the egg will develop into a genetic “copy” of the original organism, showing that all of the original genome has been retained

Cell potentials

- TOTIPOTENT cells can develop into any embryonic structure and into extra-embryonic structures (chorion i.e. embryonic part of the placenta)
- PLEURIPOTENT cells can become any embryonic cell type – which is why ICMs are favoured for stem cell research – but not extra-embryonic structures
- UNIPOTENT cells can only replicate themselves (in normal circumstances)

Cell differentiation depends on communication

- Cell differentiation depends on cells receiving and responding to signals (by turning genes on and off)
    - from the maternal cytoplasm
    - from the cell's own genes
    - from other cells around them
    - from the environment

Maternal gene effects to zygotic gene effects

- products of maternal genes in the cytoplasm of the egg guide the early stages of development e.g. axis formation in *Drosophila*. This is known as maternal effect
- at the MID-BLASTULA TRANSITION the zygotic genome begins to be expressed
- the maternal gene products activate the first zygotic genes, which in turn signal other zygotic genes to turn on etc. e.g. segmentation in *Drosophila*

Environmental effects on development

- developmental effects can be perturbed by environmental effects
    - e.g. in sea urchins, water condition – salinity, temperature, pH levels etc. – can alter embryonic development
    - in vertebrates, neural tube closure (essential for proper development of the brain and spinal cord) is highly dependent on dietary factors
        - 1 in 1000 live human births are affected by spina bifida – failure of the neural tube to close fully
        - This incidence can be cut by 50% by supplementation with folic acid

Chance in development

- **White spotting**
    - Melanocyte migration in black and white cats
        - The pigment cells originate in the neural crest on the dorsal side of the embryo and migrate around the developing body to the ventral side
        - Certain genes interfere with this migration so that the pigment cells do not make it all the way around the body – hence black cats with white feet and white bellies
        - The specific gene has not been identified in cats (though there is a known gene in mice that has similar effects)

        - There appears to be a gene with two alleles – S and s
            - Homozygous ss have no white markings
            - Heterozygous Ss have minor/medium white markings
            - Homozygous SS have extensive white makings
    - Within this broad pattern, it is not possible to predict the extent or distribution of the white markings

- **X-inactivation**
    - Female mammals (and many other organisms) have two X chromosomes (XX) while males have only one (XY)
    - In order for the dosage of products of genes on the X chromosome to be similar in both males and females, there is a process of dosage compensation
        - In each cell of the female, one of the two X chromosomes is inactivated
        - This happens randomly for each cell, so that it is not possible to predict whether the maternal or paternal chromosome will be inactivated
    - X-inactivation occurs early in development and is irreversible – so if the maternal X chromosome is inactivated in a particular cell, all the daughter cells will also have the maternal X turned off
        - E.g. tortoiseshell cats
        - There is a gene on the X chromosome with red and black alleles for coat colour
        - Males are XY so will have only EITHER a red allele OR a black allele and will always be either all red or all black
        - Females are XX so they could be:
            - X^{black}/ X^{black}, in which case, whichever X chromosome is inactivated, the female will still be all black
            - X^{red}/ X^{red}, and whichever X is inactivated, the female will still be all red
            - X^{black}/ X^{red} : if the X carrying the black allele is inactivated in a cell, that cell and its descendants will produce red pigment; if the X carrying the red allele is inactivated in a cell, that cell and its descendants will produce black pigment
        - The resulting cat will be a mosaic of red and black colours, arranged at random

Developmental noise

- Cell differentiation and specification, developmental signalling and cell migration can all be affected by chance fluctuations in levels of signalling chemicals, or by a minor environmental change that affects the chemical properties of a signalling molecule etc.

Required readings:

For more information on stem cells: http://stemcells.nih.gov/info/basics/Pages/Default.aspx

In preparation for next week: On the structure and function of DNA read this guide at Scitable: http://www.nature.com/scitable/ebooks/essentials-of-genetics-8/6913802#bookContentViewAreaDivID (Please be sure to read all the sections: 1.1–1.6)

Other resources:

Developmental biologist Scott Gilbert with more on the evidence for genomic equivalence: http://9e.devbio.com/article.php?ch=2&id=297

A chance to explore the debate about the ethics of stem cell research in more depth: http://www.nature.com/scitable/spotlight/stem-cells-6969855

Gap genes and pair rule genes in *Drosophila* at the Interactive Fly: http://www.sdbonline.org/fly/aignfam/gapnprl.htm#dafka

The genetics of calico cats: http://www.bio.miami.edu/dana/dox/calico.html

For more on cloning and X-inactivation http://learn.genetics.utah.edu/content/tech/cloning/cloningmyths/ (and check out the additional resources)

Lecture 3: How does it all work?

Genes are necessary but not sufficient to create an organism

The search for the genetic material

The genetic material…

- must be capable of **accurate reproduction** – to explain the continuity we observe in inheritance
- must be capable of **change** – to explain the variation we see in inheritance (and evolution)
- must be able to encode a great deal of **information** – because living organisms are extremely complex

Chromosomes behave consistently with hereditary factors

- germ cells have half the number of chromosomes that somatic cells do

Chromosomes are made largely of **protein** and **nucleic acids** (deoxyribonucleic acid or DNA and ribonucleic acid or RNA)

- protein was a better candidate for the genetic material, because it has a more complex chemical composition than nucleic acids

Griffith's transforming principle (1928)

- genetic material from a heat-killed, lethal smooth strain of bacteria somehow transforms the non-lethal rough strain, making it lethal

Avery *et al.* (1944): DNA is the transforming principle

- If you destroy the RNA in the bacterial preparation, it can still transform rough cells into smooth cells, but if the DNA is destroyed, the transformation no longer happens – therefore the DNA must be the transforming principle

Further support for DNA as the genetic material

- DNA is localised in the nucleus (and we know that the nucleus is crucial in reproduction)
- Germ cells contain half the amount of DNA that somatic cells do (and we know that the germ cells contain half of the hereditary material)
- DNA is highly stable, where RNA and protein are not (we know that the hereditary material must be stable, in order to ensure continuity in inheritance)

Structure of DNA

Any proposed model for the structure of DNA has to fulfil certain requirements:

- Must explain how DNA can be accurately replicated
- Must explain how DNA can encode a huge amount of information
- Must be made of sugar + nitrogenous bases (adenine, cytosine, guanine, thymine) + phosphate group, all in equal quantities
- Must obey Chargaff's rules
    - Quantity of adenine (A) = quantity of thymine (T)
    - Quantity of cytosine (C) = quantity of guanine (G)
    - In humans:
        - A = 31%
        - T = 31%
        - C = 19%
        - G = 19%
    - Ratios differ in different organisms but always A = T and C = G
- From X-ray diffraction studies
        - Must have a helical structure with 10 nitrogenous bases for each turn of the helix

Jim Watson and Francis Crick, in Cambridge, in 1953, synthesized all this data to produce their model of the double helix (see PowerPoint slide)

DNA replication

Watson and Crick's model suggested a way that DNA could replicate accurately:

Semi-conservative replication

- Each strand of the double helix can serve as a template for a complementary new strand, with A-nucleotides binding to T-nucleotides and C-nucleotides binding to G-nucleotides
- Each new double-stranded molecule has one original strand and one new strand

A number of enzymes are essential for this process:

- DNA helicase unwinds the double helix to allow replication to proceed
- DNA primase forms a short RNA primer to intiate DNA replication
- DNA polymerase adds complementary nucleotides to create the new DNA single strand

Each of these enzymes is encoded by a gene and also requires certain environmental factors in order to function properly

Transcription: DNA → RNA

- DNA is "read off" by RNA polymerase to create RNA (ribonucleic acid)
- Only one strand of DNA is transcribed

Structure of a gene

- Within a gene there are sub-sequences which have different functions:
  - **Promoter** = regulatory site where RNA polymerase binds to initiate transcription
  - **Exon** (EXpressed sequence) = protein coding
  - **Intron** (INtervening sequence) = non-coding
  - **Terminator** = regulatory site that signals end of transcription
  - **Transcription factors** are proteins that can bind to the DNA to enhance or repress transcription
- The primary RNA transcript is **spliced** to remove the introns, leaving the protein-coding sequences joined up to create the **mRNA**

There are different types of RNA:

- **Messenger RNA (mRNA)**: translated into amino acid sequence of proteins

Some RNAs are not translated into proteins – they are functional in themselves

- **Ribosomal RNA (rRNA)**: makes up the **ribosome** on which mRNA is translated to produce proteins
- **Transfer RNA (tRNA)**: brings **amino acids** to the ribosome during translation
- **Small nuclear RNA (snRNA)**: involved in RNA processing (**splicing**)

Translation: mRNA → protein

Amino acids are the building blocks of protein molecules

- In translation, the mRNA acts as a template for a chain of amino acids
- See above for the function of rRNAs and tRNAs in translation

The genetic code

- With 4 bases (A, U, C, G) there are **64 possible triplets**, known as **codons**
- 61 of these combinations encode the 20 amino acids found in living organisms (these are known as **sense codons**)
- a particular triplet of bases encodes each amino acid e.g. aaa = lysine
- the code is **degenerate** – with 2 exceptions (AUG for methionine and UGG for tryptophan) there is more than one triplet encoding each amino acid
- the code is **continuous** – no nucleotides are missed
- the code is **non-overlapping** – the mRNA is read in successive, discrete groups of three nucleotides
- the code is (almost) **universal** – with a very few exceptions, the code is the same in all organisms
- there are 3 **stop codons** to indicate the end of translation (known as **nonsense codons**) and one to initiate the **start** (AUG, which also encodes the amino acid methionine)

The amino acid string goes through several levels of **folding** to create the final, functional protein molecule (see PowerPoint slide)

Required readings:

On the role that small non-coding RNAs play in gene expression:
http://www.nature.com/scitable/topicpage/small-non-coding-rna-and-gene-expression-1078

On the role of the environment in regulating gene expression: http://www.nature.com/scitable/topicpage/Environmental-Control-of-Gene-Expression-Sex-Determination-982

On epigenetics: Nessa Carey, *The Epigenetics Revolution*, Icon Books, 2011, Introduction and Chapter 4 (paper copies provided).

Other resources:

A fantastic Lego animation of DNA replication: http://video.mit.edu/watch/dna-replication-with-legos-10133/

For more information on transcription factors: http://www.nature.com/scitable/topicpage/transcription-factors-and-transcriptional-control-in-eukaryotic-1046

James Watson's idiosyncratic but entertaining account of the discovery of the structure of DNA, *The Double Helix*, is available in the library (bear in mind that this is Watson's personal perspective and not everyone agrees with his portrayal of other people involved).

Watson and Crick's 1953 paper is available in the *Nature* archive at http://www.nature.com/nature/dna50/archive.html, together with several other relevant papers from the time.

An animated guide to protein folding: http://www.wiley.com/college/boyer/0470003790/animations/protein_folding/protein_folding.htm

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Lecture 4: How does it all work 2

Mutations (changes in the DNA sequence)

Spontaneous mutations

- Chemical changes in bases
    - Minor chemical changes in bases can lead to e.g. C changing to U or T, or loss of bases leaving a gap in the DNA sequence, which is then filled randomly by any of the 4 bases
- Replication errors
    - Replication is balanced between speed and accuracy

        - Human genome = 3 billion base pairs
        - Complete replication in c. 8 hours (replicating at multiple sites)
        - Replication rate = 33 base pairs per second
    - DNA polymerase can accidentally insert the wrong base
    - Proof reading mechanisms normally correct the errors, but not always

Point mutations: mis-sense and nonsense

- The result of a replication error (or a chemical change in a base) is a point mutation i.e. a single base change – these affect a single codon but can still have significant effects on the protein product, depending on the exact nature of the change and whereabouts in the DNA sequence it occurs
    - **Silent point mutation**
        - a base is replaced such that the resulting new codon encodes the same amino acid as the original i.e. Lysine is encoded by either AAG or AAA
    - **Nonsense point mutation**
        - a point mutation leads to a STOP codon so that the protein is truncated prematurely. The resulting protein will have limited or no function depending on where the STOP occurs
    - **Mis-sense mutation**
        - **conservative**: the new codon gives an amino acid that has similar chemical properties to the original
        - **non-conservative**: the new amino acid has very different chemical properties to the original
            - this could result in a non-functional protein, or in one that does something quite different to the original = a **new phenotype**

Frameshift mutations

- spontaneous **deletion** or **insertion** of bases leads to a **frameshift**
- see slides for examples
- Frameshifts affect every codon after the mutation

Induced mutations

- Caused by environmental factors
- May be **chemical mutagens** (see slides for diagrams)

a) Base-modifying agents

- Make chemical changes to a single base in the DNA sequence
    - e.g. nitrous acid changes cytosine to uracil – leading to a change from CG-TA pair
- chemical mutagens are often used to induce mutations in model organisms for experimental purposes
    - e.g. ENU is known as a "supermutagen" because it induces point mutations at a very high rate throughout the genome
        - used in the Nobel Prize winning zebra fish screening programme in the mid-1990s
        - 49 male fish were treated with ENU, causing random DNA point mutations in their sperm cells
        - over 1000 different mutant strains were identified in their descendants

b) Base analogs

- chemically similar to normal bases and replace them during DNA replication
- base analogs can spontaneously change chemical state
    - e.g. 5-bromouracil (5BU)
        - In one state, 5BU pairs with A in place of T
        - When 5BU changes its chemical state it pairs with G instead
        - Result (after subsequent DNA replication) is that an A-T pair is replaced with a C-G pair
        - And the reverse can happen if the 5BU is in its G binding state when it is incorporated

c) Intercalating agents

- e.g. acridine
- insert themselves between bases in the strand, creating a gap that is complemented at random during DNA replication, with any one of the 4 bases
- results in an **insertion** and therefore a **frameshift**

Mutations can also be induced by **radiation**

- **High energy radiation** (X-rays, gamma radiation) causes breaks in the DNA strand
    - Subsequent repair/replacement of missing bases can lead to mutations
- **UV exposure** causes formation of **thymine dimers**
    - Adjacent T bases on the DNA strand develop a chemical bond which distorts the DNA helix, interfering with normal DNA replication and/or transcription
        - This can happen up to 50-100 times per second in a cell exposed to UV

- Normally the cell's repair mechanisms can deal with these
    - However, if you are over exposed the number of dimers that form is too much for the repair processes to deal with and the cell is damaged and will die
    - leads to symptoms of sunburn
- Thymine dimers form at random in the genome
    - If they occur in genes involved in regulating cell division (e.g. p53 tumour suppressor), and are not repaired, they can interfere with gene expression and this can lead to uncontrolled, abnormal cell division i.e. cancer
- Note that this is a statistical phenomenon
    - UV exposure doesn't entail the development of cancer, but the more exposure, the more thymine dimers will form, the less chance they will be repaired, and the greater chance they will occur in a crucial gene

Consequences of mutations

- A stable mutation leads to a variant allele
- **Haplophenotype** is the phenotype associated with a single allele
    - If the mutation is silent, or conservative, the phenotype will be normal
    - Mis-sense, non-conservative or frameshift mutations can lead to non-functioning, malfunctioning or differently functioning proteins
- So an individual **heterozygous** for the mutant allele could have one of a number of phenotypes
    - If the product of a single copy of the 'normal' allele is sufficient for normal function (i.e. **haplosufficient**) the mutation will have no effect on the individual i.e. phenotype will be normal
    - If the normal allele is *not* haplosufficient, the phenotype will be mutant e.g. individual may suffer a disorder
        - Severity depends on how much the function of the mutant protein is affected
- An individual **homozygous** for the mutant allele will suffer more severe symptoms than a heterozygote

Epigenetics

- Molecular mechanisms that alter the way genes are expressed, therefore alter the phenotype (without changing the DNA sequence)
- Can be mediated by environmental factors (but not always)
- Can be passed on to offspring (but not always)

DNA methylation

- **Methylation** = the addition of a **methyl** group (1 carbon and 3 hydrogen atoms) to a C base at a **CpG motif** (i.e. C followed by G in the DNA sequence)
- CpGs tend to cluster at promoter regions
- Methylated C binds **MeCP2** which in turn binds other proteins that shut down transcription of the gene, by preventing RNA polymerase from binding
- This process is more or less permanent
    - e.g. In neurons, which cease division after differentiation
    - In skin cells, which pass on the methylation to their daughter cells so that skin cells only ever produce more skin cells
- Rett Syndrome is a disorder of DNA methylation
    - Affects 1 in 10,000 females
    - Develop normally for up to 18m, then develop a range of symptoms, including:
        - Intellectual impairments
        - Slow growth
        - Small head
        - Seizures
- Most cases are due to a mutation in *MECP2*, which means that cells cannot recognize and respond to the methylated C bases, so they can't shut down transcription of certain other genes
- Most cases are *de novo* (new) mutations i.e. the mutation wasn't present in the somatic cells of the parents but occurred during the production of an egg or sperm cell of a parent
- over 300 different mutations in the *MECP2* gene have been identified in cases of Rett Syndrome
- Why females? – *MECP2* is on the X chromosome – so females, having 2 X-chomosomes, one randomly inactivated in each cell, might have up to 50% of cells with a working copy of the gene, whereas males have only 1 X, so no functioning protein, therefore die during development or in very early infancy

Histone acetylation/methylation

- DNA is packaged around groups of **histone** molecules (each cell has around 2m of DNA and this packaging is necessary to fit it into the cell nucleus)
- 15 years ago, the story about histones would have ended here but today it brings us to the cutting edge of genetic research
- Histones have **amino acid tails**

- **Methylation** or **acetylation** (addition of an acetyl group – $COCH_3$) of these tails can modulate gene expression – either increasing or decreasing it
- In the example on the slide, acetylation of the amino acid tail of the histones reduces the affinity of the histones for DNA
    - "weakens the bond", loosening the structure and making the DNA more accessible for transcription.

- This process is generally reversible
    - allows gene expression to be altered in response to circumstances
- Kabuki Syndrome
    - Affects 1 in 32,000 live births. Symptoms include:
        - Developmental delay
        - Intellectual impairments
        - Small stature
        - Seizures
        - Characteristic facial features
- 50-75% cases due to mutations in the *MLL2* gene on chromosome 12
    - Mainly *de novo* mutations
- Non-functioning MLL2 → failure to activate certain genes via histone modification

X-inactivation is an epigenetic process

- The inactive X chromosome (Xi) produces Xist non-coding RNA
    - This ncRNA binds to Xi, wrapping it up
- This in turn leads to histone changes and repressor recruitment
- Xi becomes tightly "wound up" so that no transcription (other than Xist) can take place
- These modifications are passed on to daughter cells at cell division

Inherited epigenetic effects

- In the Dutch Hunger Winter (Nov 1944 - May 1945), due to a combination of blockades preventing food supplies getting through and very severe weather conditions, reducing local supplies, widespread malnutrition in Netherlands. 20K people died of starvation
- Good medical record keeping means that we can study the effects.
- Looking at women who were pregnant during the Hunger Winter:
    - If they were malnourished in the 1st trimester, and then ate normally for the rest of the pregnancy, their babies were normal weight at birth

- If they ate normally in the first stages of the pregnancy, but were malnourished in the last trimester, their babies were born small (this is to be expected because most growth takes place in the last trimester).

- But the effects seem to pass on to the next generation
  - the children of the normal babies (whose mothers had been malnourished in the 1st trimester) were likely to be heavier than average, even though their mothers ate normally during their pregnancies.
- Related effects have been observed in male lineages:
  - In an isolated region of northern Sweden in the late 19th and early 20th centuries, there were periodic serious food shortages, interspersed with periods of plentiful food supply – so you would eat a lot when you got the chance!
    - Men who went through a period of food shortage in their slow growth period (the years just before puberty, around 9-12) had sons with a decreased risk of CVD
    - Men who had plentiful food during SGP had grandsons with an increased risk of diabetic diseases

Evidence for inherited epigenetic effects

- We don't yet fully understand the mechanisms of these phenomena in humans but there is some evidence from studies of animal models
- For example, (in a particular inbred strain of mice)
  - When males are fed a low protein, high sugar diet, and females are fed normally, the offspring show abnormal patterns of expression in genes involved in metabolism, and changes in epigenetic modifications in the liver
  - When pregnant female rats are exposed to high doses of a fungicide called vinclozolin (used in wine making) at a certain point in pregnancy, their male offspring are born with defects in development of the testicles and reduced fertility AND 90% of males are affected for the next 3 generations
- A later study showed that exposure to vinclozolin leads to unusual patterns of DNA methylation (suggesting it's an epigenetic effect)

Required readings:

David S. Moore 'Current thinking about nature and nurture', in *The Philosophy of Biology: a Companion for Educators*, ed. Kostas Kampourakis, Springer, 2013, pp. 629-652. This reading brings together the theme we started with, about the interaction between genes and environment, with epigenetics, and also some discussion of heritability, which ties in to the blog task from last week.

Some short readings on Scitable about the cell cycle and cell division (don't worry they really are all short!):
http://www.nature.com/scitable/content/the-eukaryotic-cell-cycle-47739
http://www.nature.com/scitable/definition/cell-division-47
http://www.nature.com/scitable/definition/meiosis-88
http://www.nature.com/scitable/topicpage/meiosis-genetic-recombination-and-sexual-reproduction-210 (you only need to look at Figure 1 on this web page – I'm sorry but there is no way to link directly to it!)

Other resources:

More detail on DNA repair mechanisms: http://www.nature.com/scitable/topicpage/dna-damage-repair-mechanisms-for-maintaining-dna-344

A short animation on thymine dimer formation and repair
http://highered.mcgraw-hill.com/olcweb/cgi/pluginpop.cgi?it=swf::535::535::/sites/dl/free/0072437316/120082/micro18.swf::Thymine%20Dimers

A very short, easy piece about thymine dimers and skin cancer:
http://theoncologist.alphamedpress.org/content/6/3/298.full

Nessa Carey demonstrating epigenetic modifications to DNA with sweeties – this is only a few minutes long but is one of the best representations to help you get the idea of epigenetic changes:
http://www.youtube.com/watch?v=1BwHXcOXCRo

A popular article on epigenetics: http://www.telegraph.co.uk/science/10369861/Epigenetics-How-to-alter-your-genes.html

An excellent BBC documentary on the discovery of epigenetics*: Horizon: The Ghost in your Genes*
http://www.youtube.com/watch?v=ga-twTFWdNs

Royal Society Lecture on Genetics, Epigenetics and Disease:
http://www.youtube.com/watch?v=SHpfkNRscOc

Professor Steve Jones on "Nature, nurture or neither? What we do not know about genetics"
http://www.youtube.com/watch?v=zmCjIydEf1I

Lecture 5: Chromosomes, linkage and genetic maps

Human Karyotypes and Chromosome Structure

Karyotype = diploid chromosome profile as seen in somatic cells

- all the pairs are matched up and arranged in order

Remember from Lecture 1:

Haploid

Describes a cell or individual with a single copy of each chromosome e.g. a human egg or sperm cell contains **23** chromosomes

Diploid

Describes a cell or individual with two copies of each chromosome e.g. a normal human somatic cell contains **46** chromosomes (22 pairs of **autosomes** and 1 pair of **sex chromosomes**: XX or XY)

Each pair of chromosomes (e.g. the copy of chromosome 1 inherited from the father and the copy of chromosome 1 inherited from the mother) is called a **homologous pair**

Within the chromosome:

- the strand of DNA is wrapped around groups of histone proteins
- the complex formed by the DNA together with the proteins is called **chromatin** (meaning "coloured matter" because of the way it takes up certain chemical stains and shows up under the microscope)
- the packaging process continues, winding the chromatin tighter and tighter in the chromosome, in preparation for cell division
- Each chromosome has:

- A short arm = **p arm**
- A long arm = **q arm**
- A **centromere** = a specialized region of the chromosome, important in the movement of the chromosome within the cell during cell division

- Prior to cell division, the chromosome duplicates to form **sister chromatids** (e.g. 2 copies of the chromosome 1 inherited from the father) which remain connected at the **centromere**
  NOTE: it is essential that you do not confuse homologous pairs of chromosomes with pairs of sister chromatids, so make sure you are clear on the definitions above

Cell cycle

- **M phase**
  - both nuclear division and cell division (**cytokinesis**) take place in M phase
  - chromosomes are visible only during this period
- **I (interphase)**
  - chromatin is unravelled to allow transcription and replication take place so the chromosomes not visible during this phase
  - Sub-phases of interphase:
    - G1 = Pre-synthesis gap (growth)
      - cells that are transcribing and producing proteins necessary for their function but not dividing
      - cells that do not divide (e.g. neurons) usually arrest in G1
    - S = synthesis of DNA
      - DNA is replicated
    - G2 = Post-synthesis gap (growth)
      - Proteins necessary for cell division are produced
    - G0 = resting phase
      - e.g. stem cells become quiescent or dormant and don't divide until needed
      - aging or damaged cells can be pushed into G0 to prevent them dividing and hence propagating errors in DNA replication etc.

Mitosis

- occurs in somatic cells during growth and development e.g. in embryos, and in cell types with a quick turnover e.g. skin cells, lining of intestine
- **1 diploid cell → 2 diploid cells** identical to the original

- Chromosome number: **2n → 2n**
- Chromosomes duplicate and line up on the **mitotic spindle**
    - This is a network of protein fibres in the cell that are crucial for directing the movement of the chromosomes in cell division
- Spindle contracts, the centromere breaks, and the individual chromatids are pulled to opposite poles of the cell
- the cell then divides into two, each of which contains 1 of the chromatids
- see slide

Meiosis

- occurs ONLY in the production of germ cells
- **1 diploid cell → 4 haploid germ cells**
- Chromosome number: **2n → n**
- DNA replicates and chromosomes condense
- **Meiosis 1**
    - chromosome replication, without cytokinesis
    - the centromeres do not split when the spindle contracts, so the chromatids travel to the cell poles in their sister pairs
- **Meiosis 2**
    - sister chromatid pairs separate and one of each pair travels to each cell pole
    - Products are haploid cells – which combine with other haploid germ cells to form diploid zygote
- See slide

Recombination

- The products of meiosis are a large source of variation in organisms without requiring any changes in DNA sequence
- With 2 chromosomes (n = 2) there are 2^2 (=4) possible products of meiosis i.e. 4 different kinds of egg or sperm
- With 23 chromosomes (n = 23), there are 2^{23} = 8,388,608 possible products

Crossing over

- another source of huge variation in inheritance, again without any changes in the DNA sequence
- In meiosis 1, the homologous chromosomes exchange sections as they line up together on the spindle

- crossing over is reciprocal i.e. there is no loss or gain of genetic material because exactly corresponding sections of homologous chromosome are exchanged
- As the homologous pairs line up and come into contact a section is exchanged between the paternal and maternal copy
- The point of crossing over is called the **chiasma**
- In the resulting products of meiosis we have both **parental** products (identical to either the original maternal or paternal chromosomes) and also new, **recombinant** chromosomes, which contain combinations of alleles not seen in either parent
- See slides
- this crossing over can take place on any and all of the chromosomes, and anywhere along the length of the chromosome
- massively increases the range of possible chromosome/ allele combinations in the gametes

Linkage and mapping

- We can use the frequency of crossing over to map where genes are on the chromosome (relative to one another)
    - the closer together, the less likely they are to be separated by crossing over
- For two loci on a chromosome: probability of crossing over approx. = distance between them
- E.g. if A and B are at opposite ends of the chromosome, they are more likely to be separated in crossing over than C and D, if C and D are extremely close together
- If we count the number of crossing over events in a large number of offspring, we can calculate the relative positions of the loci

Errors in meiosis

- Meiosis doesn't always work correctly
- problems arise when chromosomes (either homologous pairs or sister chromatids) do not line up properly on the spindle and so fail to separate at the appropriate time
    - i.e. **nondisjunction**
- See slide
- nondisjunction leads to **aneuploidy**
    - the number of chromosomes is not an exact multiple of the haploid number i.e. one or more chromosomes has missing or extra copy(ies)
- Incidence of aneuploidy
        - 1-2% sperm cells
        - 20% egg cells

- 20% pre-implantation embryos (implantation occurs around day 7)
- 35% miscarriages
- 4% still births
- 0.3% lives births

Consequences of aneuploidy

- **Trisomy** = three copies of a particular chromosome
- Most trisomies are embryonic lethal but a few are compatible with survival
    - E.g. Down Syndrome (trisomy 21)
    - 1 in 1000 live births
    - Symptoms can include:
        - Characteristic facial features
        - varying degree of intellectual impairment
        - small stature
        - intestinal and heart problems
        - early onset Alzheimer's disease
- **Monosomy** = only one copy of a particular chromosome
- Autosomal monosomies are always embryonic lethal but we do see monosomy in the sex chromosomes
    - E.g. Turner's Syndrome (monosomy X)
    - 1 in 2500 live births (but only about 1% XO zygotes survive)
    - Symptoms include:
        - short stature
        - neck webbing
        - bone and joint deformities
        - failure of ovaries to develop, hence infertility
        - reduced secondary sexual characteristics e.g. breast development

Changes in chromosome structure

- As well as changes in the number of chromosomes, there can be changes in the structure of chromosomes too
    - E.g. deletions, duplications, isochomosomes, ring chromosomes, inversions, translocations (see http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/structuralchanges for details)
- Effects of these changes depend on whether or not genetic material is lost or gained
    - E.g **Cri du Chat Syndrome**

        - Incidence = 1 in 20k to 1 in 50k
        - deletion of part or all of p5 (short arm, chromosome 5)
        - Usually de novo
        - Symptoms include:
            - Small size
            - Respiratory problems/ Abnormal larynx
            - Small head/ Round face, small chin
            - Heart defects
            - Hearing or sight problems
            - Intellectual impairment
    - **Ring Chromosome 20 syndrome**
        - Incidence = not clear – 60 cases have ever been noted
        - Symptoms include:
            - Seizures
            - Small stature/ Small head
            - Intellectual impairment
    - Some cases of **acute myeloid leukemia** are caused by an inversion in chromosome 16
    - Some cases of **Down Syndrome** are caused by a translocation which means that the individual has three copies of the long arm of chromosome 21 (2 normal copies of 21, plus the long arm of 21 attached to a different chromosome)
- Structural abnormalities in chromosomes are almost always de novo i.e. they have occurred in the formation of sperm/egg in one parent (as opposed to being a change the parent was born with)

Required readings:

More on meiosis and recombination: http://www.nature.com/scitable/topicpage/meiosis-genetic-recombination-and-sexual-reproduction-210 Note: you do not need to know the detail of the different stages of meiosis but you do need to be able to summarise the events of meiosis 1 and meiosis 2.

http://www.nature.com/scitable/topicpage/chromosomal-abnormalities-aneuploidies-290
Vanessa Heggie (2013) 'Subjective sex: science, medicine and sex tests in sport', forthcoming in *Routledge Handbook of Sport, Gender and Sexuality*, ed. Jennifer Hargreaves and Eric Anderson.

Other resources:

A short video on meiosis: http://www.youtube.com/watch?v=6xMXKU7JnMQ

A helpful tutorial on meiosis:
http://hihg.med.miami.edu/code/http/modules/education/Design/Print.asp?CourseNum=1&LessonNum=5

More resources from Scitable on mitosis/meiosis and aneuploidies:
http://www.nature.com/scitable/topicpage/chromosomal-abnormalities-aneuploidies-290
http://www.nature.com/scitable/topicpage/mitosis-meiosis-and-inheritance-476

Lecture 6: Sex determination and sex-linkage

Environmental sex determination

- In some organisms, sex determination is entirely governed by the environment
- Crocodilians and some turtles have no sex chromosomes and sex is determined by egg incubation temperature
    - E.g. *Trachemys scripta elegans* (Red Eared Slider Turtle)
    - Incubation @ 26C = all ♂
    - Incubation @ 31C = all ♀
    - Incubation @ 29.2C = 50:50 ratio
    - There are temperature sensitive molecules involved in the sex determination process – certain ones are active at higher temperatures, others at lower temperatures

Genotypic sex determination

- Sex is determined by the genetic (chromosomal) makeup
    - Homogametic sex = two similar sex chromosomes e.g. XX
    - Heterogametic sex = two different sex chromosomes e.g. XY
- Mammals
    - XX = female
    - XY = male
    - Sex determined by presence of Y (Y present = male, Y absent = female)
- Birds
    - ZZ = male
    - ZW = female
- *Drosophila*
    - XX = female
    - XY = male
    - Sex determined by no. of X chromosomes (1 X = male, 2 X = female)
- Hymenopterans (bees, ants etc.)
    - Diploid (fertilized egg) = female

- Haploid (unfertilized egg)= male

Drosophila sex determination

- Females = XX Males = XY
- Y carries genes for sperm formation i.e. specific to males, but is not involved in sex determination
- Sex determined by number of X chromosomes
- See slide
    - Based on concentration of certain genes on X which activate a gene called *sex lethal* (*Sxl*)
    - Two copies of activating genes on X = high levels of Sxl protein = female development
    - Single copy of activation genes on X = no Sxl protein = male development

Mammalian sex determination

- Based on presence of Y chromosome
- Two stages:
    - **Primary sex determination** = formation of the **gonads** (♂ testes and ♀ ovaries)
    - **Secondary sex determination** = action of **hormones** produced by the gonads to produce external sexual characteristics, development of genitalia, changes at puberty etc.
        - Main (but not only) hormone in testes = testosterone
        - Main (but not only) hormone in ovaries = oestrogen
- See slide
- In **males**, the gonads develop into **testes**, the **Wolffian duct** (green) becomes the **vas deferens**, and the Mullerian duct disappears
- In **females**, the gonads become **ovaries**, the **Mullerian duct** (yellow) becomes the **oviduct** and the Wolffian duct disappears

Primary sex determination

- in humans ♂ and ♀ identical til week 7 of embryonic development
- *Wt1, Wnt4, Sf1, Lhx9, GATA4* are expressed in the **bipotential gonad**: failure of any of these genes will prevent development of the gonads in either direction
- If **XY**:
    - ***Sry*** (on Y chromosome) activates ***Sox9***

  - Sox9 protein both **inhibits** expression of **β-catenin** (thereby inhibiting ovary-formation) and **activates AMH** (which causes the Mullerian duct to degenerate) and other testis-forming genes
  - (Mutations in the *AMH* gene lead to development of both testes and ovaries [true hermaphroditism])
- If **XX**:
  - Continued expression of ***Wnt4*** and activation of ***Rspo1*** in the developing gonad increase β-**catenin** expression
  - β-catenin both **inhibits** *Sox9* (thereby inhibiting testis formation) and **activates** *Follistatin* and other ovary-forming genes

Note: that most of the genes involved in this process are not on the sex chromosomes, and that mutations in these genes often have effects on other systems as well as on sex determination (i.e. the sexual phenotype relies on many genes, not just one, and each gene has more than one function)

Hermaphroditism

- True hermaphrodite has both testis and ovary tissues (either separate or mixed)
- This can arise in several ways:
- **Mutations in *Sry* causing late expression**
  - there is only a short period of time in development when Sry can act – if its activation is delayed, even by a few hours, development will follow the female path, and the gonads will become ovaries (partially or totally, depending on how delayed *Sry* expression is)
- **Sex reversal**
  - Rarely, due to a translocation, an XX individual has the *Sry* gene on one X chromosome (and will become an XX male, or a mosaic, due to X-inactivation)
  - or an XY individual lacks the *Sry* gene due to a deletion on the Y chromosome (and will become an XY female)
- **XX/XY chimera**
  - Two separate zygotes – 1 male and 1 female – become fused into a single embryo during early development
  - The resulting embryo has some cells that are XX and some that are XY

Sex chromosome aneuploidies

Aneuploidy of sex chromosomes is better tolerated than that of autosomes for two main reasons

- Y chromosome carries largely genes involved in male fertility and no genes essential for survival
- X inactivation happens to all but one X chromosome in a cell, however many copies there might be
- See table on slide

Triploidy X

- Normal sexual development and fertile
- Female phenotype
- Increased risk of learning disabilities and delayed development of speech/motor abilities but very variable
- 10% suffer kidney problems and/or seizures

XYY

- 1960s and 70s there was a significant body of thought that these individuals would be "hypermasculine" and therefore more prone to aggression, violence, sexual offences
- used as a defence in some criminal cases
- No clear evidence to support this and now discredited
    - a recent study (link below) shows a slight increase in criminal activity (which could be explained by social circumstances) but it applies equally to XYY and XXY

Kleinfelter Syndrome: XXY

- Affected individuals tend to be tall and thin
- Can have intellectual impairments
- Infertile to some degree
- Male phenotype but can have female characteristics e.g. lack of facial/body hair or breast development
- More X chromosomes = more severe symptoms

48, XXYY

- Similar to Kleinfelter but more extreme symptoms
- Also prone to type 2 diabetes, autism spectrum, dental problems, DVT and other problems

NOTE: as with other aneuploidies we talked about last week, the symptoms can be very variable in all of these conditions

Pseudohermaphroditism

- Problems in **secondary sex determination**
- Normal sex chromosomes but abnormal hormone levels (or non-functional receptors)
- E.g. **Kallmann Syndrome**
    - 1 in 10-86,000 (mainly male)
    - Insufficient/ Insensitivity to GnRH (GnRH is a “master” hormone that controls the production of several other hormones in sexual development before in the womb and during puberty)
    - Affected males are born with under-developed genitals
    - Females may appear unaffected at birth
    - Both sexes have absent/incomplete or delayed puberty
    - No sense of smell
    - Other symptoms can include: Cleft lip/palate, hearing loss, abnormal tooth development
- **Androgen Insensitivity Syndrome**
    - Affects 1 in 20-50,000
    - Affected individuals are genetically male: XY
    - Androgen receptors do not function so body cannot respond to “male” hormones such as testosterone etc.
    - Most cases due to mutation in the *AR* gene on X chromosome
    - Phenotype is variable depending on degree of insensitivity
- **Congenital adrenal hyperplasia**
    - Affects around 1 in 15,000
    - Adrenal glands normally produce androgens (male hormones similar to testosterone)
    - In CAH, excess androgens are produced
    - Affected females have normal ovaries but ambiguous genitalia
    - Experience early “male” puberty: voice breaking, facial and body hair

Environmental effects on sexual development

- **Atrazine** (most widely used weedkiller in the world) has been proven to have effects on sexual development in frogs
    - male frogs develop as hermaphrodites (with gonads that produce both sperm and eggs)
    - they may fail to develop secondary sexual characters (so are unable to mate normally)
    - adult male frogs can be affected, with the testes changing into ovaries
- Atrazine causes testosterone to be converted into oestrogen
    - Male frogs exposed to Atrazine have testosterone levels similar to, or lower than, normal females
- Happens at very low concentrations in the water
- Concerns that this effect could extend to humans (though not proven) have led to Atrazine being banned in several countries (France, Germany, Italy, Norway, Switzerland, Sweden)
- **Freemartin cattle**
    - Female calves with a male twin become masculinized via transfer of foetal cells and male hormones in the womb → infertile XX/XY chimeras
    - Occurs in ~90% of male/female twin pregnancies in cattle
- **Twin testosterone hypothesis**
    - a highly contested hypothesis that claims similar effects in humans
    - i.e. female twins may be behaviourally masculinized *in utero* due to exposure to testosterone from the male twin

Required readings:

A review of sex determination: http://www.nature.com/scitable/topicpage/genetic-mechanisms-of-sex-determination-314

Celeste Michelle Condit (1999) *The Meanings of the Gene*. Wisconsin: University of Wisconsin Press. Chapter 6: Genetic Counseling (PDF available on the VLE)

Other resources:

For more on environmental sex determination: http://www.ncbi.nlm.nih.gov/books/NBK9989/

Drosophila sex determination: http://www.sdbonline.org/fly/gene/sexlthl1.htm

And on mammalian sex determination: http://www.ncbi.nlm.nih.gov/books/NBK9967/

Kallmann syndrome: http://ghr.nlm.nih.gov/condition/kallmann-syndrome:

Androgen Insensitivity Syndrome: http://ghr.nlm.nih.gov/condition/androgen-insensitivity-syndrome

Congenital Adrenal Hyperplasia: http://www.nlm.nih.gov/medlineplus/ency/article/000411.htm

A basic guide to intersex conditions for parents and patients:
http://www.nlm.nih.gov/medlineplus/ency/article/001669.htm

Recent study on criminality in XYY and XXY men: http://bmjopen.bmj.com/content/2/1/e000650.full

Report on declining fertility in men and possible causes: http://www.sciencemediacentre.org/wp-content/uploads/2012/12/Sharpe12-EMBO-Reports.pdf

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Lecture 7: Patterns of Inheritance

Patterns of inheritance of traits

- If we want to understand something about a trait we observe in a human population (whether this is a normal characteristic or a disease condition), start by asking ourselves some questions about what we observe e.g.:
    - Who is affected?
    - What do the affected individuals have in common?
        - Shared environment? Shared experience? Shared ancestry?
    - Does the trait run in families?
        - Does it appear more frequently amongst related individuals than amongst non-related?
    - Does it affect males and females equally?
        - If not, what are the proportions affected?
    - Does the trait appear in every generation?
    - Do affected individuals always have affected parents?
    - Do affected parents always have affected children?
    - In this lecture we are focussing on single-gene traits i.e. differences that are dependent on a single gene

- We know that such traits are relatively rare, because genes generally interact with one another and with the environment BUT, especially with respect to human genetic disorders, single gene traits are the easiest to analyse
- Don't let the fact that we can identify and explain lots of single gene disorders make you think that this is the most common sort of disorder – it's just the one we have most easily been able to explain so far!

Model organisms

- Model organisms allow us both to make observations of inheritance on a large scale and to experiment and test our hypotheses about whether/how a trait is inherited.

Qualities of good model organisms:

- Short generation time so that we can see the results of experiments quickly
    - e.g. *Drosophila* has a generation time of 30 days
- Should produce many offspring for each mating
    - more offspring = bigger sample which allows us to observe statistical effects that we would not see in a smaller sample
    - e.g. *Drosophila* lay c. 500 eggs from a single mating
- Should be easy and cheap to keep so that we can maintain large populations
- Should be easy to induce mutations by chemical mutagenesis or radiation
- Similarity to humans
    - The qualities that make a good model organism also bring limitations, because they are very unlike humans, so we try to approximate to humans as far as we can
    - E.g. Zebra fish are vertebrates, therefore much closer to us than insects but still fulfil most of the requirements for a good model organism
    - Though mice have a much longer generation time than either *Drosophila* or zebra fish, they are mammals and so that much nearer to humans
    - Model organisms are not like animals outside the laboratory but are engineered to facilitate the study of genetics
        - inbred for many generations, so that individuals are almost genetically identical except for the particular gene being studied, so reducing variation in gene interactions
        - kept in identical environments, so there is little or no variation in environment
        - allows us to attribute any differences that are observed more accurately
- Model organisms allow us to observe and experiment in ways that would be neither practical nor ethical in humans, and the results from these organisms can help to elucidate what is

happening in human genetics BUT remember the special conditions that model organisms are raised and kept in and that those conditions are NOT like the "real world"

Reminder from Lecture 1 that each gene lies on a particular LOCUS on the chromosome and that there are often different variants of the DNA sequence of the gene, called ALLELES, that can occupy that locus e.g. ABO blood groups

Dominance and recessiveness

- If allele A is haplosufficient the protein product of a single copy is enough for normal function so the heterozygote will show the normal phenotype, while the homozygote will show the mutant phenotype
    - In this case allele A is said to be **dominant** to allele B, which is **recessive** to A (in this context)
- If A is haploinsufficient the protein product of two copies is required for normal function so the heterozygote will show the mutant phenotype
    - In this case A is said to be **recessive** to B, which is **dominant** to A (in this context)
- A mutant allele can also show dominance over the normal allele if the protein product of that mutant allele competes with the normal protein product e.g. the non/malfunctioning protein binds to the sites where the normal protein should bind, thereby blocking the function of the normal protein
- OR gain-of-function mutations where the product of the mutant allele has a new and different function to the original gene product
    - e.g.in the ABO blood group case, if allele A was the original allele, then mutant allele B is a gain-of-function mutation, while allele O is loss-of-function
    - A and B are described as co-dominant
- Remember that dominance and recessiveness are properties of the relationship between two alleles – NOT inherent properties of the allele itself
    - allele A can be dominant to B but recessive to C, for example, or only dominant to B in certain environmental conditions, or in the presence of allele D etc.

Just a word of caution – if you look at examples on the internet or in text books, you'll often see genotypes notated as e.g. Bb, where the upper case letter denotes the dominant allele, and lower case the recessive allele (so the homozygotes would be BB or bb and the heterozygotes Bb or bB). I've avoided this notation because it does suggest that dominance and recessiveness is an absolute property of the alleles and I don't want you to lose sight of the fact that it is contextual.

Autosomal dominant inheritance

- If one parent has the mutant allele, there are 4 possible outcomes of segregation in the germ cells and fertilization (see slide)
- In autosomal dominance this would give us a 1:1 ratio of normal to affected phenotypes in the offspring
    - note that this ratio is statistical – if we had a huge population of flies and thousands of offspring resulting from such a cross, we would expect to see approx. 50:50 normal to affected phenotypes but human families are much too small to necessarily see this ratio
    - AND the odds are the same for each individual offspring – even if you had 10 affected children, the odds for the next one would still be 50:50
- In autosomal dominant inheritance (e.g. achondroplasia) we usually see:
    - Every affected person has at least 1 affected parent
    - The trait rarely skips a generation
    - Every child of an affected person has a 50/50 chance of being affected
- Complications arise if the condition is late onset e.g. Huntington's disease (a progressive and ultimately fatal degeneration of the nervous system) because the symptoms would not manifest until after people had already had children (Huntington's symptoms generally start in late 30s-40s)
- Where genetic tests are available (and one is for Huntington's) people can, if they wish, find out whether or not they carry the disease allele and make reproductive decisions on that basis

Autosomal recessive inheritance

- See slides
- Here the normal allele is haplosufficient, so heterozygotes are unaffected and of normal phenotype
    - This means that we can have heterozygous **carriers** – individuals with a single copy of the mutant allele – but because they have a normal phenotype we can't necessarily identify them without testing of some sort
- (statistically) 2 carriers will produce offspring in the ratio 1 homozygous normal (normal phenotype): 2 heterozygous carriers (normal phenotype): 1 homozygote mutant (affected phenotype)

- In autosomal recessive inheritance (e.g. cystic fibrosis) we tend to see:
    - Most affected individuals have two unaffected parents
    - Statistically, two heterozygous parents will have normal:affected children in a 3:1 ratio (although we rarely, if ever, see this ratio in human families)
    - Phenotypically normal children have a 2:1 chance of being a carrier
    - Two affected parents will have all affected children

Y-linked inheritance

- Because the Y chromosome does not carry essential genes, we see very few Y-linked disorders
- One example is Y-chromosome infertility due to deletions of genes for sperm production and function on Y
    - Where the phenotype is complete infertility this will never be inherited (without some kind of assisted reproductive technology) but some mutations cause reduced fertility rather than complete infertility and this will be passed on to male children
- Characteristics of Y-linked inheritance:
    - Only males are affected NEVER females
    - All the male offspring of an affected male will be affected
    - Every affected male has an affected father

X-linked dominant inheritance

- See slides
- Only a few X-linked dominant disorders are known
    - e.g hereditary enamel hypoplasia (faulty and discoloured tooth enamel)
- Characteristics of X-linked dominant disorders:
    - Females more frequently affected than males
    - Symptoms usually milder in females than males (because of X-inactivation)
    - Affected females will have 50/50 affected and unaffected children of both sexes
    - Affected males will have all non-affected sons and all affected daughters

X-linked recessive inheritance

- See slides
- affects mainly BUT NOT ONLY males (because males have only a single copy of all genes on X)
- we only see affected females if they inherit an affected copy of the gene from both parents.
    -

    - Since many of these disorders are very severe, affected males may not survive to have children, therefore affected females are relatively rare
- If a female is affected, all of her sons will be affected and half of her daughters will be carriers
- The daughter of an affected male (a carrier) will have 50/50 affected sons (and 50/50 carrier/normal daughters)
- Affected males NEVER transmit the condition to their sons
- Some X-linked recessive disorders appear to affect only females because males with only a single affected copy of the gene do not develop
- Examples of X-linked recessive inheritance include:
    - Some forms of colour blindness
    - Duchenne Muscular Dystrophy
    - haemophilia (see slide for pedigree of haemophilia in the Royal Family)

Required readings:

Peter J. Russell (2006) *iGenetics*: a Mendelian Approach. Pearson, pp. 30-33 plus problems 2.26 and 2.27 (PDF available on the VLE)

In preparation for next week: http://www.nature.com/scitable/topicpage/phenotype-variability-penetrance-and-expressivity-573

Other resources:

A short(ish) online lecture and tutorial on pedigree analysis:
http://ocw.mit.edu/courses/biology/7-01sc-fundamentals-of-biology-fall-2011/genetics/pedigrees/
including a video of a worked problem in pedigree analysis:
http://www.youtube.com/watch?v=qY0ixUWJx0g

Andrew Douch has a useful set of tutorials on pedigree analysis, starting here:
http://www.youtube.com/watch?v=HbIHjsn5cHo

If you really want practice your pedigree analysis, there are lots of examples here:
https://www.msu.edu/course/zol/344/Elsea/Pedigrees/

Some more pages from Scitable to help consolidate what we covered in this lecture:

http://www.nature.com/scitable/topicpage/mendelian-genetics-patterns-of-inheritance-and-single-966

http://www.nature.com/scitable/topicpage/Genetic-Dominance-Genotype-Phenotype-Relationships-489

Lecture 8: Factors Affecting Patterns of Inheritance

Pleiotropy

- a single gene having multiple phenotypic effects
- e.g. Phenylketonuria (PKU)
    - PKU is due to a mutation in the phenylalanine hydroxylase gene (PAH) on chromosome 12
    - PAH is required to metabolize the amino acid phenylalanine (Phe) from the diet into tyrosine (Tyr)
    - Phenylalanine is an essential amino acid i.e. it is required for normal function but cannot be synthesised in the body
    - Phe is found in most high protein foods: meat, fish, dairy, eggs, soy products, some nuts and seeds
        - Some dietary Phe is used for protein synthesis (creating new proteins in translation)
        - In normal circumstances, excess Phe is converted, by PAH, to tyrosine
        - Mutation in the PAH gene means that the excess Phe cannot be converted into Tyr, leading to a Tyr deficit (we also get Tyr from our diet, but not in sufficient quantities)
        - Tyrosine is a very important precursor of several important compounds in the body: thyroxin, adrenaline (epinephrine), dopamine/melanin
        - Low tyrosine levels → low levels of these compounds
            - Low melanin levels → pale skin, hair and eyes, cataracts
            - Low adrenaline levels → impaired stress response
            - Low thyroxine levels → slow growth and development
- As well as these effects, excess Phe accumulates in the body and can be converted into phenylpyruvic acid, which is thought to interfere with the energy metabolism of cells in the brain

- Excess Phe also saturates the blood-brain barrier, which protects the brain from major fluctuations in blood chemistry, and from some infections – most bacteria cannot cross the barrier, nor can anti-bodies and most antibiotics, but there are mechanisms to transport biological molecules needed for brain development and function across the barrier (see PowerPoint slide)
- These pleiotropic effects combine to give a wide and severe range of symptoms in those affected, if not treated ((Source: OMIM, http://omim.org/entry/261600)). These include:
    - **Neurological symptoms:**
        - Mental retardation/ Infantile irritability/ Peculiar gait and posture/ Seizures/ Defective myelin formation
    - **Behavioral/ Psychiatric Manifestations:**
        - Psychosis/ Hyperactivity/ Autistic symptoms/ Aggression/ Self-mutilation
    - **Other**
        - Mousy odour
        - Eczema
- Untreated, the disease often leads to early death.
- Even with treatment, affected individuals can still suffer attention deficit disorder, social sensitivity, Obsessive-compulsive disorder, Depression/ Anxiety disorders
- **Treatment**
    - In developed countries all new-borns are tested in first week of life
    - Careful control of Phe in the diet, from shortly after birth greatly reduces (but doesn't eliminate) the effects of classic PKU
        - breast milk and normal formula milk both contain high levels of Phe, so it's important to identify the disease quickly and change the diet
    - Supplementation with other amino acids further alleviates the effects, allowing normal development
- So, in a sense, we could also describe PKU as an environmental disorder, since the phenotype can be largely over-ridden by the appropriate environment
- More than 500 different mutations in the *PAH* gene have been identified
- Different mutations have different effects
    - some make PAH completely non-functional (or nearly so) = classic PKU
    - Others reduce the activity of the protein leading to milder symptoms: variant PKU or non-PKU hyperphenylalaninemia
- There is another potential level of modulation of the phenotype, because some studies have suggested that the relationship between levels of Phe in the blood and in the brain is not

consistent in all individuals i.e. in some people, it seems the blood-brain barrier is better at resisting the saturation effects of excess Phe, and so the neurological symptoms of those people are less severe than in some other affected individuals

Penetrance

- Penetrance is a statistical measure of how often a particular phenotype at a given locus will lead to the expected phenotype
- If less than 100% of individuals with the genotype in question display the related phenotype = **incomplete penetrance**
- Penetrance is most commonly observed in dominant conditions
    - probably because the presence of the product of the normal allele in the heterozygote modulates the effects of the product of the mutant allele
    - e.g. osteogenesis imperfecta
        - a disorder caused by a dominant mutation
        - symptoms include weak bones and teeth, joint problems, bluish colouration to the whites of the eyes
        - some heterozygous individuals show no symptoms at all
        - it is impossible to predict whether any specific individual will or will not express the phenotype

Age-related penetrance

- In some disorders the symptoms do not appear until later life
- E.g. Huntington Syndrome (a neurological disorder)
    - Affects 4-7 per 100,000 individuals
    - Symptoms of Huntington's
        - progressive chorea
        - Rigidity
        - Dementia
        - May be a phase of mild psychotic and behavioral symptoms preceding full symptoms by up to 10 years
    - age of onset commonly around 30-40 years (but there is a juvenile form which has onset before 20 years)
    - Death typically happens 10-20 years after onset of symptoms (quicker for juvenile forms)
    - See PowerPoint slide for graph
        - At age 20 penetrance = 0% but at age 70 penetrance = 100%

- See http://www.omim.org/entry/143100?search=huntington&highlight=huntington for a very good example of the complicating factors that affect the phenotypic expression of even such a relatively well understood condition

Expressivity

- where individuals sharing a particular genotype at a specified locus show the related phenotype in differing degrees
- Also largely seen in dominant conditions
- e.g. Waardenburg Syndrome
- consider also the variable symptoms of Down Syndrome (see http://genomebiology.com/content/pdf/gb-2007-8-5-r91.pdf)

Incomplete penetrance/ variable expressivity can be due to

- presence of another allele which modulates the effects of the mutant allele
- specific genes at other loci
- environmental effect
- chance

Epistasis/ effects of multiple genes

- Where the phenotypic expression of one gene is affected by the activity of another gene/genes
- e.g. cystic fibrosis (CF)
    - one of the most common monogenic diseases
    - Caused by mutations in the *CFTR* gene on chromosome 7 (more than 1000 different mutations have been identified)
    - Individuals homozygous for one of these mutations will express the CF phenotype, which includes a range of symptoms, but the exact phenotype is affected by the presence of certain alleles at other loci
    - See PowerPoint slide

Lethal mutations

Recessive lethals

- Can make a condition look like an autosomal dominant e.g. homozygotes for achondroplasia do not survive to birth. This lethal phenotype is recessive, but the physical phenotype is autosomal dominant

Dominant lethals

- Can only persist in the population if effects are either age-related (e.g. Huntington Syndrome) so that affected individuals may have children before the lethal effects appear, OR if penetrance is incomplete, so that some individuals do not show the phenotype
    - NOTE: this failure to express the phenotype is not necessarily passed on with the allele i.e. if your father carries the disease allele, but is unaffected, and you inherit the allele from him, it does not necessarily follow that you will not express the phenotype either

Conditional lethals

- The lethal phenotype is only significant under certain environmental conditions e.g. TPMT (see PowerPoint slide)
    - TPMT is a metabolic enzyme
    - Individuals with low levels/non-functioning TPMT cannot metabolize the immuno-suppressant drug azathioprin, which is used in organ transplant cases and treatment of auto-immune diseases
    - 6 alleles of *TPMT* gene: 1 normal, 5 mutant
    - Administration of the full dose of azathioprin in an individual homozygous for nonfunctioning alleles causes life-threatening myelosuppression (loss of activity in bone marrow hence no production of new blood cells)
    - Prospective patients are tested for phenotype (enzyme levels) or genotype (presence of mutant alleles) before treatment begins so the dose can be adjusted accordingly

Locus heterogeneity

- In some instances, mutations in genes at different loci, but leading to similar phenotypes, can complicate pedigree analysis
- This is often seen in disorders affecting complex functions, where many different genes may be involved
    - e.g. different forms of congenital hearing loss
- the example in the PowerPoint slides shows two families, each of whom has an autosomal recessive disorder
- if the mutations were at the same locus, we would expect all the children in generation 3 to have hearing loss (as they would all be homozygous for the mutant allele) but, because the parents actually carry mutations at different genes, the children are heterozygous for two different hearing mutations, therefore have normal hearing

Imprinted genes

- Some genes have different effects depending on which parent they are inherited from
- E.g.:
    - Prader-Willi Syndrome
        - 1 in 20,000 live births
            - Low birth weight
            - Floppy muscles
            - Failure to thrive in early infancy
            - Severe over-eating from early childhood on
            - Mild/moderate mental impairment
        - Caused by a specific deletion on chromosome 15
        - ONLY IF THE DELETION IS ON THE COPY OF 15 INHERITED FROM THE FATHER
    - Angelman Syndrome
        - 1 in 12-20,000 live births
            - Severe mental retardation
            - Small brain
            - Little speech
        - Caused by a specific deletion on chromosome 15
        - ONLY IF THE DELETION IS ON THE COPY OF 15 INHERITED FROM THE MOTHER
- See PowerPoint slide
- Imprinting is an epigenetic process – certain genes are normally methylated and deactivated on either the paternal or maternal chromosome and these epigenetic changes are carried through the germline to offspring

Required readings:

T. Strachan and A.P. Read (1999) Human Molecular Genetics. 2nd edition. New York: Wiley-Liss, Chapter 3 'Genes in Pedigrees'. Available online at: http://www.ncbi.nlm.nih.gov/books/NBK7573/?redirect-on-error= HOME #A286.
NOTE: You only need to read up to and including Section 2.6.

T. Strachan and A.P. Read (2010) Human Molecular Genetics. 4th edition. Garland Science, Chapter 9 'Organization of the Human Genome'. Available online at: http://www.garlandscience.com/res/pdf/9780815341499_ch09.pdf

Ariel Bleicher (2012) 'Perils of newborn screening'. *Scientific American*, July, pp. 30-31. Available online at: http://www.scientificamerican.com/article.cfm?id=perils-of-newborn-screening. NOTE: the article has 3 pages, please make sure you read them all.

Other resources:

http://www.nature.com/scitable/topicpage/mendelian-ratios-and-lethal-genes-557

http://www.biomedcentral.com/content/pdf/1471-2407-8-155.pdf BRCA penetrance

http://ghr.nlm.nih.gov/handbook/inheritance/penetranceexpressivity

http://www.phgfoundation.org/tutorials/penetrance/index.html

http://www.nature.com/scitable/topicpage/epistasis-gene-interaction-and-phenotype-effects-460

Lecture 9: What does it all mean?

Course recap

- What we've seen throughout the course is that genes are essential BUT other factors are just as important

Human Genome Project (this section was not included in the lecture due to lack of time)

- started in 1990 and was completed in 2003
- produced the full DNA sequence of the complete full haploid set of human chromosomes (including both sex chromosomes)
- Used DNA from a number of volunteers from diverse ethnic/racial backgrounds
    - A composite human genome
- Has moved on from sequencing to analysis of functional and non-functional sequences of the genome via the transcriptome and the proteome
- The HapMap project aims to identify the range of variation in the genome by sequencing the genomes of a larger number of individuals from several widely divergent populations (see link to the HapMap project in the reading list below)
- See PowerPoint slide for summary of the content of the genome

Comparative genomics

- The genomes of many different organisms have now been sequenced
- See PowerPoint slide for table of comparative genome sizes
- While the overall of size of the genome relates broadly with the complexity of an organism, the number of protein-coding genes does not

- The single-celled *T. vaginalis*, for example, has around 60,000 protein coding genes, while humans have only around 1/3 that number
- And the Marbled Lungfish has c. 60 times the amount of DNA that humans have (we don't yet know the number of genes)
- So we cannot rely on the amount of DNA, or on the number of genes, to predict the complexity of an organism

500,000 proteins from 20,000 genes?

- At the start of the human genome project, the estimated number of genes was around 100,000 but it turns out there are about 20,000
- How is this enough to account for the complexity of the human organism which comprises approximately half a million different proteins?
- There are several ways by which one gene can contribute to more than one protein
    - Alternative splicing
        - The exons of a gene can be spliced in different combinations
        - E.g. the mRNA for the protein tropomyosin is spliced differently in different tissue types, to give five different forms of the protein (see PowerPoint slide)
    - Trans-splicing
        - Exons from two (or more) genes can be spliced together
    - Tandem chimerism
        - The mRNAs of two genes can be spliced together into a single mRNA for translation
- Here's a point to consider about the future of genetics. It's often speculated that we will eventually be able to engineer genes to cure disorders etc. But what if we could change the sequence for a gene that produced a mutant protein in one cell type so that we could "repair" the protein in that cell type, but that change interfered with alternative gene products in other cell types?

Genetic testing

- Many genetic tests are based on **DNA polymorphisms**
    - two or more alternative forms of an allele at a locus, not necessarily (and not usually) in a protein coding region
- Forms of DNA polymorphism:
    - SNPs (single nucleotide polymorphisms): a difference in a single base pair at a specific site

- STRs (short tandem repeats): 2-6 base pair DNA sequences repeated from several to around 100 times e.g. CAG.
    - Expanded repeats may or may not have phenotypic effects, depending on whether they occur in a protein coding region or not
- VNTRs (variable number tandem repeats): similar to STRs but longer – from 7-c.50 base pairs long
- RFLPs (restriction fragment length polymorphisms) – see PowerPoint slide
- SINES: dispersed repeated DNA, sequences 1-400 bp long
- LINES: dispersed repeat sequences 1000s of bp long

Techniques in genetic testing

Gel electrophoresis

- Fragments of DNA are placed on a gel and an electric current passed through
- This causes the DNA to move through the gel
- Smaller fragments travel faster than larger, so they will travel further in a given time period
- By using a scale of fragments of known length, we can calculate the length of each fragment
- See PowerPoint slide

Restriction enzymes

- See PowerPoint slide

DNA (RNA) hybridisation

- Identify target sequence e.g. DNA sequence of mutated allele
- Make a complementary probe, which is labelled with a dye or a fluorescent molecule, so that we can see the probe
- Mix the probe with the sample DNA. If the target sequence is present, the probe will bind to it, and the label will allow us to see that it is present

Microarray testing

- Biochip or microarrays allow a DNA sample to be tested for many different sequences at once e.g. for several different conditions or for possible different mutations that cause a particular condition

Whole genome sequencing

- We can sequence an entire genome and search it for known mutant sequences

Types of genetic testing

Diagnostic testing

- often more effectively done via non-genetic means e.g. the sweat test for CF, testing levels of TPMT enzyme (see Lecture 8)
- Also the presence of “the gene” does not always confirm the cause of symptoms
- The individual may not be expressing the phenotype for that mutation but the symptoms may have some other cause

Carrier testing

- some mutations can have effects in carriers e.g. carriers of the sickle cell trait can be unaffected under normal conditions but may experience problems under severe physical stress and there are currently debates in the US over whether high performance sports people and military personnel should be tested, so that potential problems can be avoided

Pre-natal testing

- can be done via amniocentesis or chorionic villus sampling, potentially giving parents the option of termination of an affected foetus

Pre-implantation genetic diagnosis

- using IVF techniques, unaffected embryos can be selected for implantation or, in an X-linked female embryos can be chosen
- this can avoid some of the ethical concerns some people might have about pre-natal testing and termination but is not without such issues itself e.g. what to do with surplus embryos
- also an expensive and complicated technique and not without risks

Commercial testing/sequencing services

- these are currently raising concerns about how the public deal with health-risk results, in the absence of proper individual advice/counseling
- see slide about 23andMe

Should you have a test?

Can anything be done?

- If early treatment or preventative measures can reduce risk or improve quality of life, testing may be an attractive option e.g. Angelina Jolie and breast cancer
- If there is no such benefit to pre-symptomatic identification of the condition, people may prefer not to know e.g. Huntington Disease

Incidental results

- what should we do if we have tested for condition X, but find results regarding condition Y?
    - if the patient has consented to/asked for information about X, should we tell them about Y?
- tests can also raise issues of paternity, since it might show that it is not possible for the male parent to actually be the biological father (this could also apply to the "mother" though this is less likely)

Should children be tested?

- See reading from last week about the perils of new born screening
- See also example on slide of a child with CF mutation but no symptoms (remember last week we looked at mutations outside the CFTR gene which modulate the CF phenotype – this child could, for example, have another, unknown mutation which is protecting her from the CF phenotype)
    - This child and her parents have to live with the worries raised by the "diagnosis", without knowing if/when the symptoms might appear

How might a diagnosis affect family relationships?

- Families don't always react in the ways we might expect
    - e.g. Some will feel guilt that they have passed the mutation on to their child, some feel relief that it's not their fault because it came from the other parent, some blame the parent carrying the mutation etc.
- Some feel excluded when the attention switches to the other parent as the carrier – as if their own contribution to the child isn't relevant any more
- Hence genetic counselling, to help people deal with the issues

A "new eugenics"?

- There are concerns that selection against certain alleles/traits/conditions is a kind of eugenics and is the start of the slippery slope
- If we think that we should prevent the birth of babies with condition X, what does that say about our attitudes towards people who have that condition?

"Designer babies"

- A term usually used to describe selection FOR traits seen as positive (high intelligence, sporting ability, aspects of appearance etc) rather than against negative traits, like diseases
- We currently do not have the technology to do this to any great extent but some believe it is only a matter of time
- Also consider "state" or more formal selection

- E.g. the BGI project to find "genes for" intelligence and concerns about "an army" of engineers, scientists etc.

- Especially when we consider issues such as intelligence, the main difficulties with these sorts of claims centre on the issue of **heritability** (see slide)
- Even if we can reasonably attribute some part of the variation in intelligence across a population, we cannot control all aspects of the environment, or test the idea in all possible environments
    - e.g. Suppose we were to send underachieving black children from deprived urban areas to a top public school, and they still didn't achieve the same level of academic success as most of the other pupils there. We might argue that this proves that the difference is genetic, because both groups are in the same environment BUT is the environment at the school really the same for the urban, black children as for the children of aristocrats and wealthy families? What about earlier experiences, parental support and expectations? How will the black children be treated at the public school?

"Genes for….."

- Think about the examples shown in the PowerPoint slides. To what extent do you think they support the idea of "genes for" characteristics such as criminality, political allegiance etc.?
- Autism database (http://autism.mindspec.org/autdb/submitsearch?selfld_0=GENES_GENE_SYMBOL&selfldv_0=&numOfFields=1&userAction=viewall&tableName=AUT_HG&submit2=View+All)
    - Over 400 genes listed here – does this mean that there are 400+ "genes for" autism?
    - This is freely available on the internet – what would a concerned parent, with no education in genetics, make of this?
- How does the labelling of a characteristic as "genetic" affect individual and social attitudes towards that characteristic?

Further reading:

More from Scitable on genomic complexity: http://www.nature.com/scitable/topicpage/eukaryotic-genome-complexity-437

In case you ever need a reliable source of numbers on biological topics to solve arguments at the pub quiz: http://bionumbers.hms.harvard.edu/default.aspx

More on mRNA splicing: http://www.nature.com/scitable/topicpage/regulation-of-mrna-splicing-by-signal-transduction-14128469

On some of the ethical problems around genetic testing: http://www.nature.com/scitable/topicpage/ethics-of-genetic-testing-medical-insurance-and-651

An interesting radio programme about the ethics of genetic testing in children

- http://www.bbc.co.uk/programmes/b038hhs7: Inside the Ethics Committee: Genetics Testing in Children (radio)

An article on testing for sickle cell trait in sports people:
http://asheducationbook.hematologylibrary.org/content/2013/1/632.full.pdf

A couple of popular articles on genetics and intelligence:

- http://www.wired.com/wiredscience/2013/07/genetics-of-iq/

- http://www.wired.com/opinion/2013/05/so-you-know-that-10000-hours-makes-an-expert-rule-bunk/

A more detailed explanation of heritability: http://www.nature.com/scitable/topicpage/estimating-trait-heritability-46889