6th Form Open Day

15th July 2015

“DNA is like a computer program but far, far more advanced than any software ever created.”

— Bill Gates

Welcome

to the Open Day event at the Institute of Genetic Medicine (IGM). We are a bunch of research and clinical scientists at Newcastle University and we are eager to share our enthusiasm in science and in particular, genetics. We would like to take you on a journey from the research bench, where we spend the majority of our time, to the patients’ bedside; and show you how the research done at the IGM can help develop future therapies and improve the life of patients. We hope that participating in today’s workshop will inspire you to pursue a career in biomedicine and show you how genetics can help in understanding the diseases and their mechanisms.

Thank you for coming along today, we hope you enjoy it!

Public Engagement Team

Institute of Genetic Medicine

Newcastle University

Agenda

IGM Open Day 15.07.15

Programme:

08:45-09:00 Arrival and registration

09:00-10:00 Short seminars (Institute of Genetic Medicine (IGM) seminar room)

09:00:09:05 Welcome

09:05-09:25 Mitochondria, the power house of the cell (Dr Gavin Hudson, IGM)

09:30-09:50 Mitochondrial conditions (Dr Michael Keogh, IGM/NHS)

10:00-12:30 From bedside to the lab - Hands on diagnostic workshops (IGM researchers)

1 meet the patient *(informal chat about everyday life with the condition, the impact of research on everyday life)*

2 DNA lab *(run a diagnostic agarose gel and identify the affected individuals in the family)*

3 genetic counselling lab *(draw a pedigree and identify the pattern of inheritance in the affected family)*

4 histopathology lab *(analyse tissues from affected and unaffected individuals, note specific disease features)*

5 animal models of human disease *(use of animal models in research; how they compare to human samples)*

12:30-13:15 Lunch (IGM seminar room)

13:15-14:30 Research at the IGM

13:15-13:30 Therapeutic avenues (Dr Louise Hyslop, NHS)

13:30-14:00 5 min PhD thesis (overview of IGM research)

14:00-14:30 Careers workshop (Dr Catherine Meplan, Faculty of Medical Sciences, Newcastle University)

14:30-14:40 Break

14:40-16:15 From lab to bedside – drug approval and clinical trials

14:40-15:10 The future of medicine, single cell and NGS (Dr Jonathan Coxhead, IGM)

15:10-15:40 From lab to pharmacy, how drugs get tested and approved (Robbie Brown, Newcastle Clinical Trials Unit)

15:40-16:15 Debate about clinical trials (Cathy Turner, IGM)

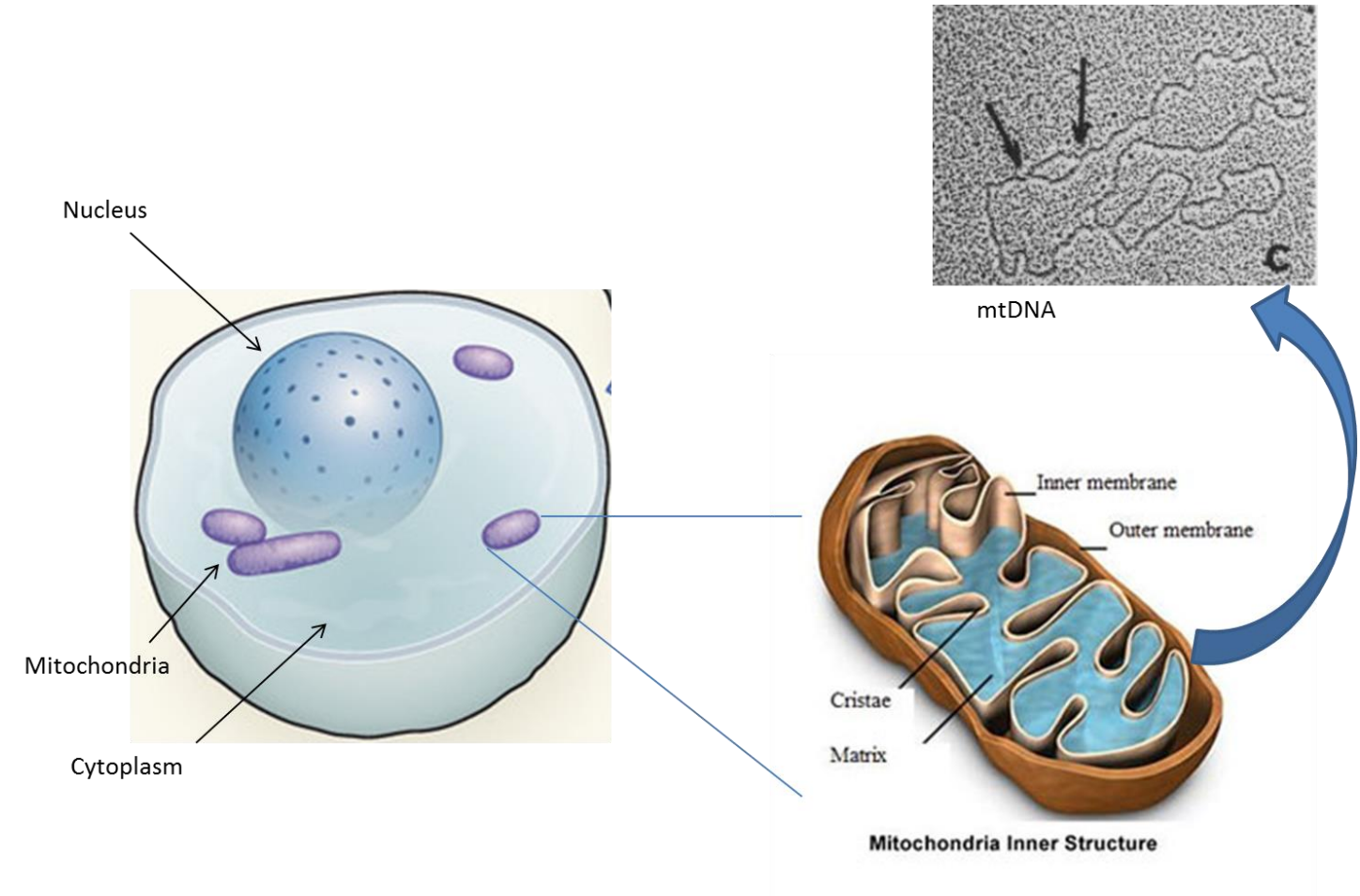
16:15-16:30 Closing remarks (Prof Michael Briggs, IGM)

Newcastle University

INSTITUTE OF Genetic Medicine

Mitochondria, the powerhouse of the cell

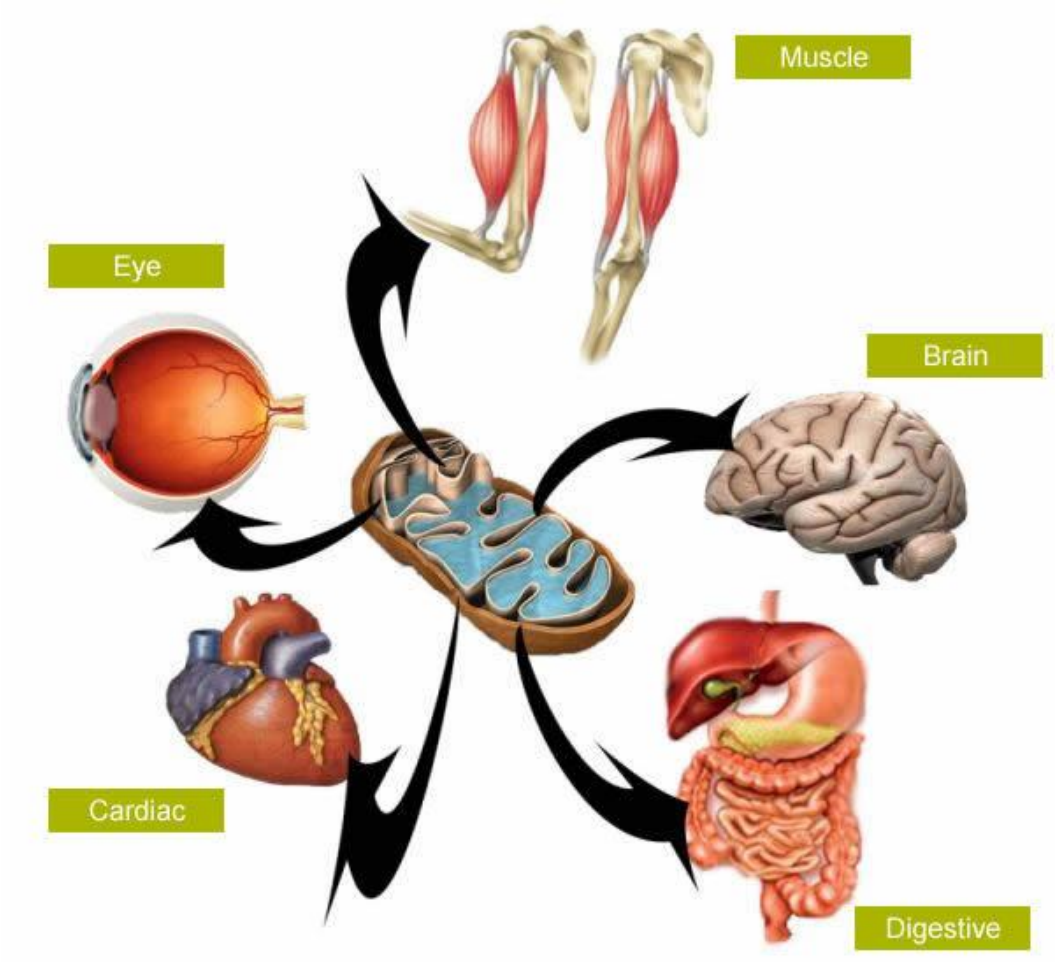
Mitochondria are one of the organelles present in a cell and produce all of the energy (ATP) needed for cellular function. Mitochondria also contain DNA molecules independent of the nuclear DNA.



Notes

Mitochondrial conditions

Mitochondrial disease affects tissues in the body which have a high energy demand such as brain, skeletal muscle and heart. These disorders can be clinically ‘heterogeneous’ meaning that patients often have many symptoms involving many tissues and organs. This makes them very difficult to diagnose and manage. Mitochondrial disorders can affect both children and adults.



Notes

Workshop 1

Meet the patient

Notes

Workshop 2

DNA lab

In this session, you will carry out a diagnostic technique known as DNA gel electrophoresis. This is used to separate DNA molecules according to their size and charge, and can help researchers identify the affected individual in a family.

Before you receive the DNA for this practical, it has undergone two biological techniques: PCR and RFLP.

1) PCR

Polymerase chain reaction (PCR) is used to amplify the DNA extracted from a patient, from few copies to thousands or millions of copies. This is achieved using a polymerase enzyme at alternating temperatures.

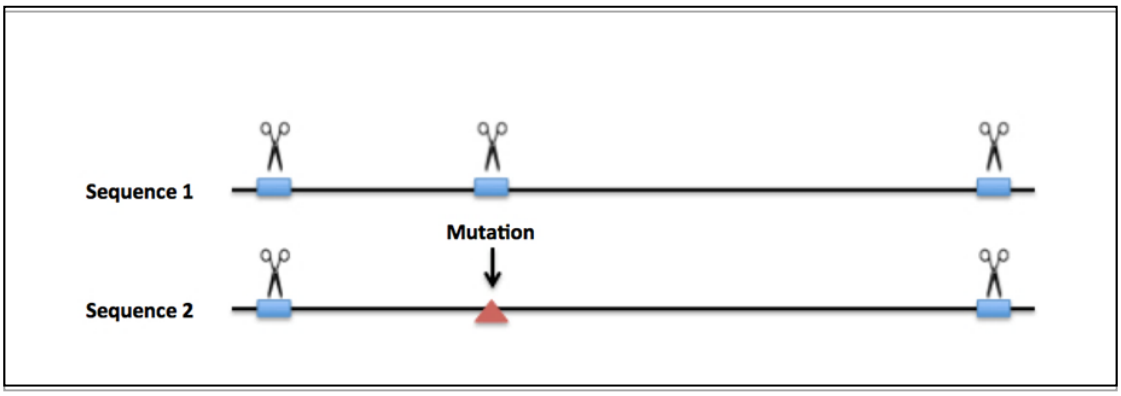
Q1. Why do we need to amplify the DNA first?

Q2. Why is temperature cycling necessary?

2) RFLP

Restriction fragment length polymorphism (RFLP) can be used to identify differences between DNA sequences. An enzyme called a restriction enzyme is used to cut the DNA wherever a specific sequence occurs. If the specific sequence contains a mutation, the enzyme will not cut the DNA, resulting in fragments of differing length.

Diagram 1

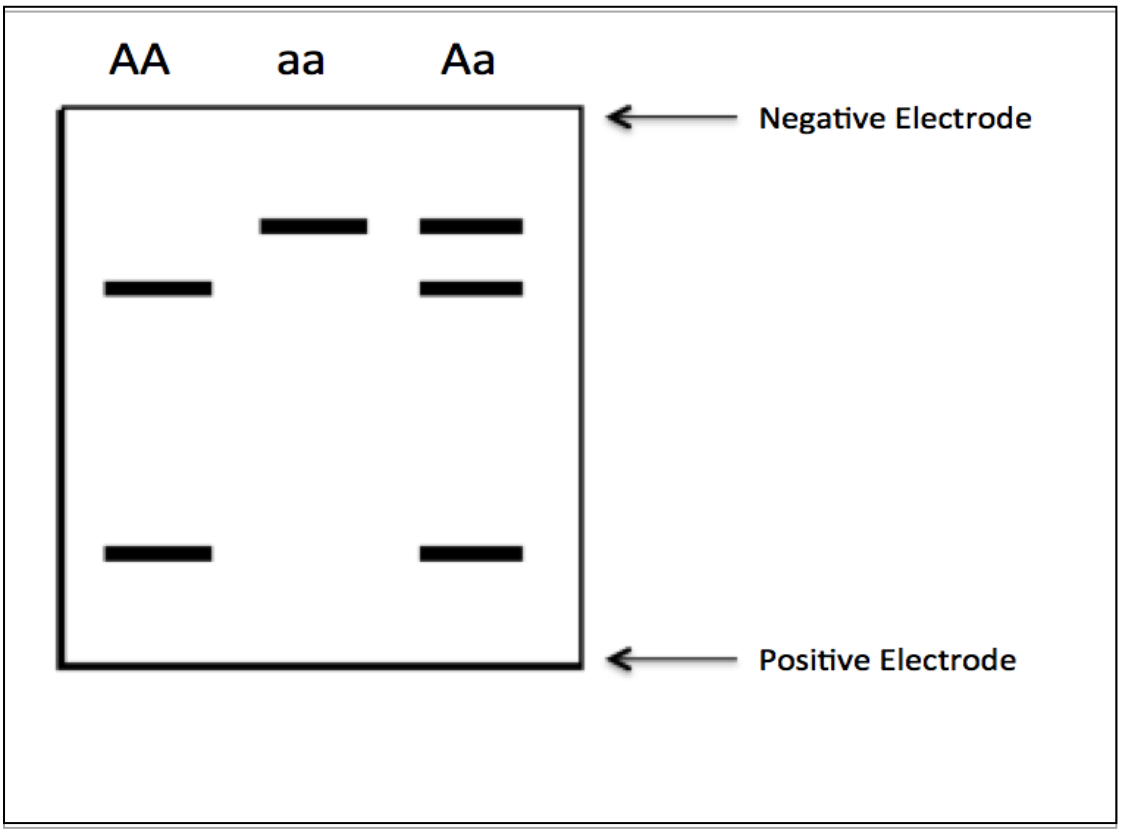


Q3. Explain how the situation in Diagram 1 allows us to differentiate DNA sequences containing a mutation.

3) DNA Gel Electrophoresis

DNA gel electrophoresis is used to separate DNA molecules according to their size and charge. An electrical field is applied to the DNA gel; since DNA is negatively charged, it moves towards the positive electrode. We can then view the gel under ultraviolet light to identify different genotypes.

Diagram 2



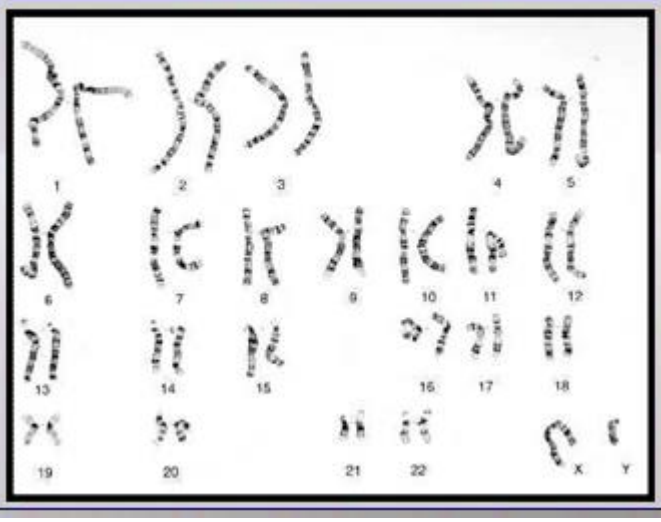
Q4. Make notes of the steps involved in carrying out DNA gel electrophoresis.

Q5. Do you have any questions about the techniques you have used in the DNA lab?

Workshop 3

Genetic counselling

Pictures of Chromosomes



Suppose the message coded by a particular gene is:

The big dog has one red eye.

Missense mutation → The sig dog has one red eye.

Nonsense mutation → The big dog has.

Suppose the message coded by a particular gene is:

The big dog has one red eye.

Frameshift mutation → The big dha son ere dey e.

In-frame mutation → The dog has one red eye.

Heterozygote and Homozygote

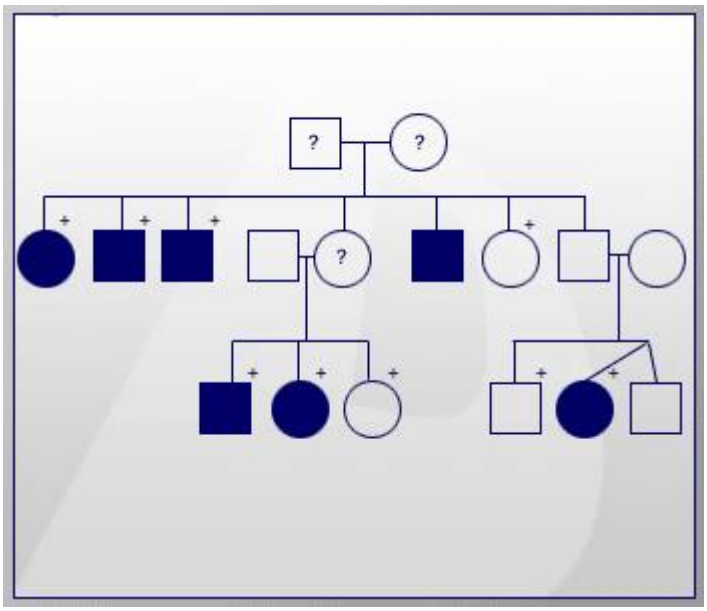
Heterozygote: Person with two different alleles at a marker

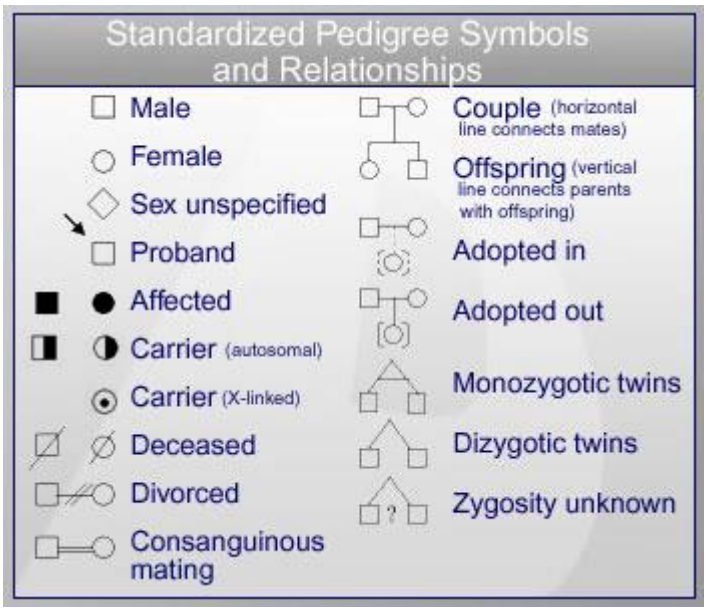
HBB genotype = AS

Homozygote: Person with two identical alleles at a marker

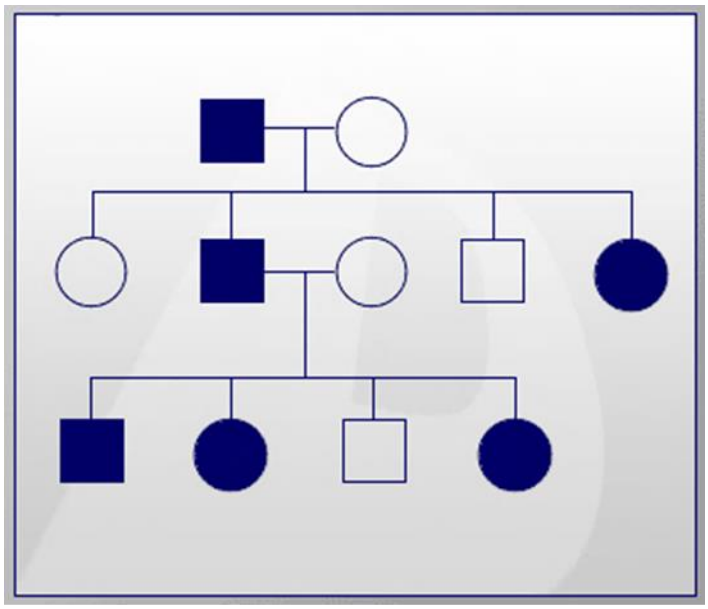
HBB genotype = AA or SS

Drawing a family pedigree

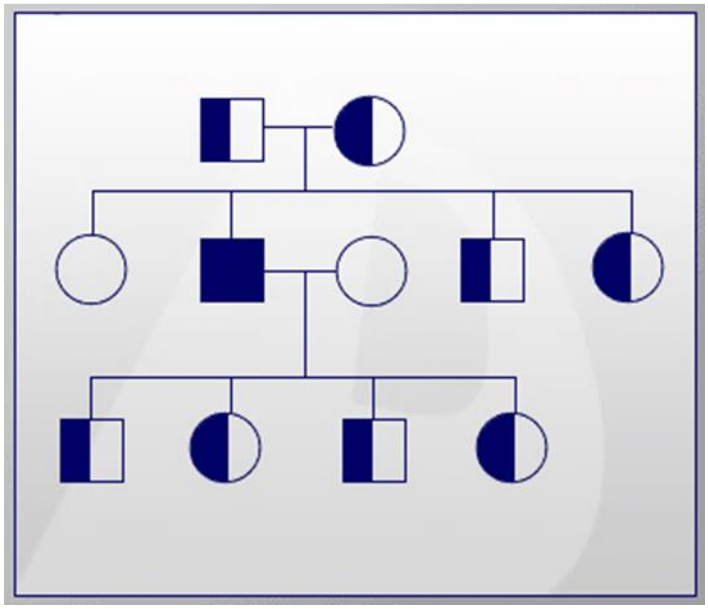




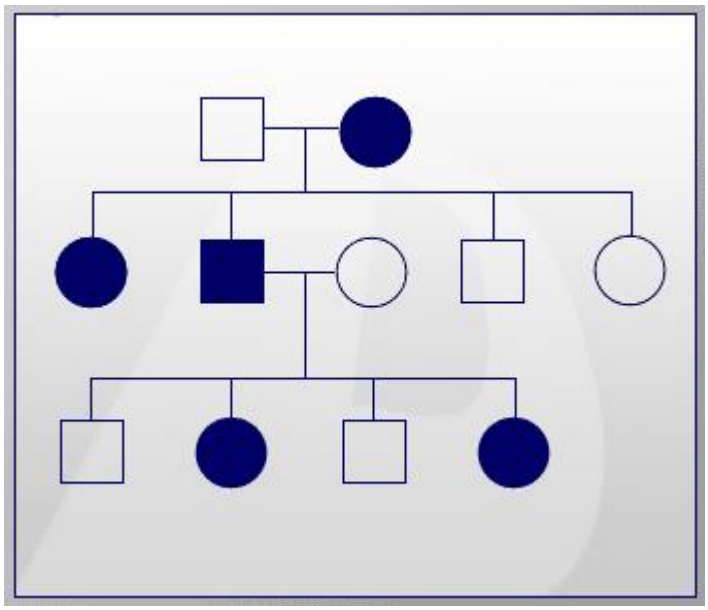
Modes of inheritance



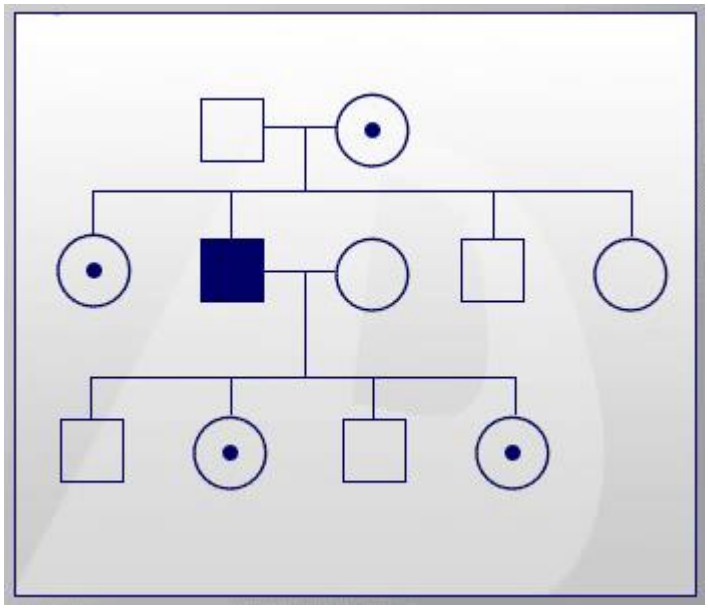
autosomal dominant



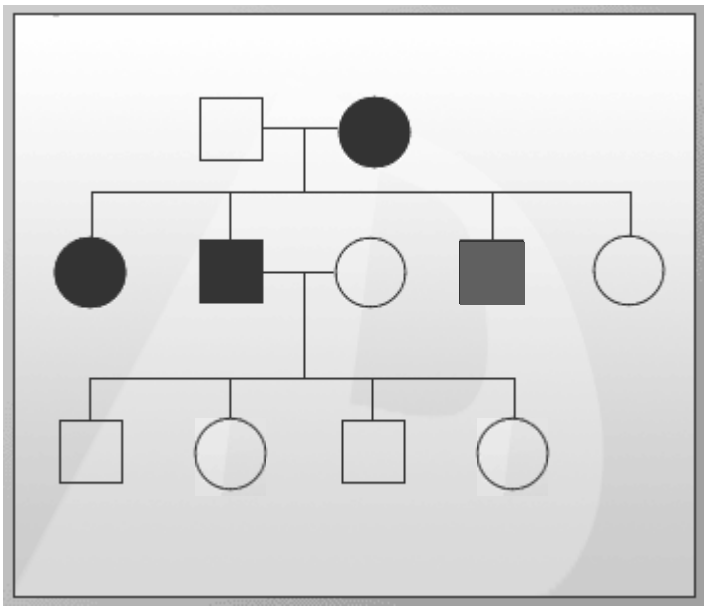
autosomal recessive



X-linked dominant

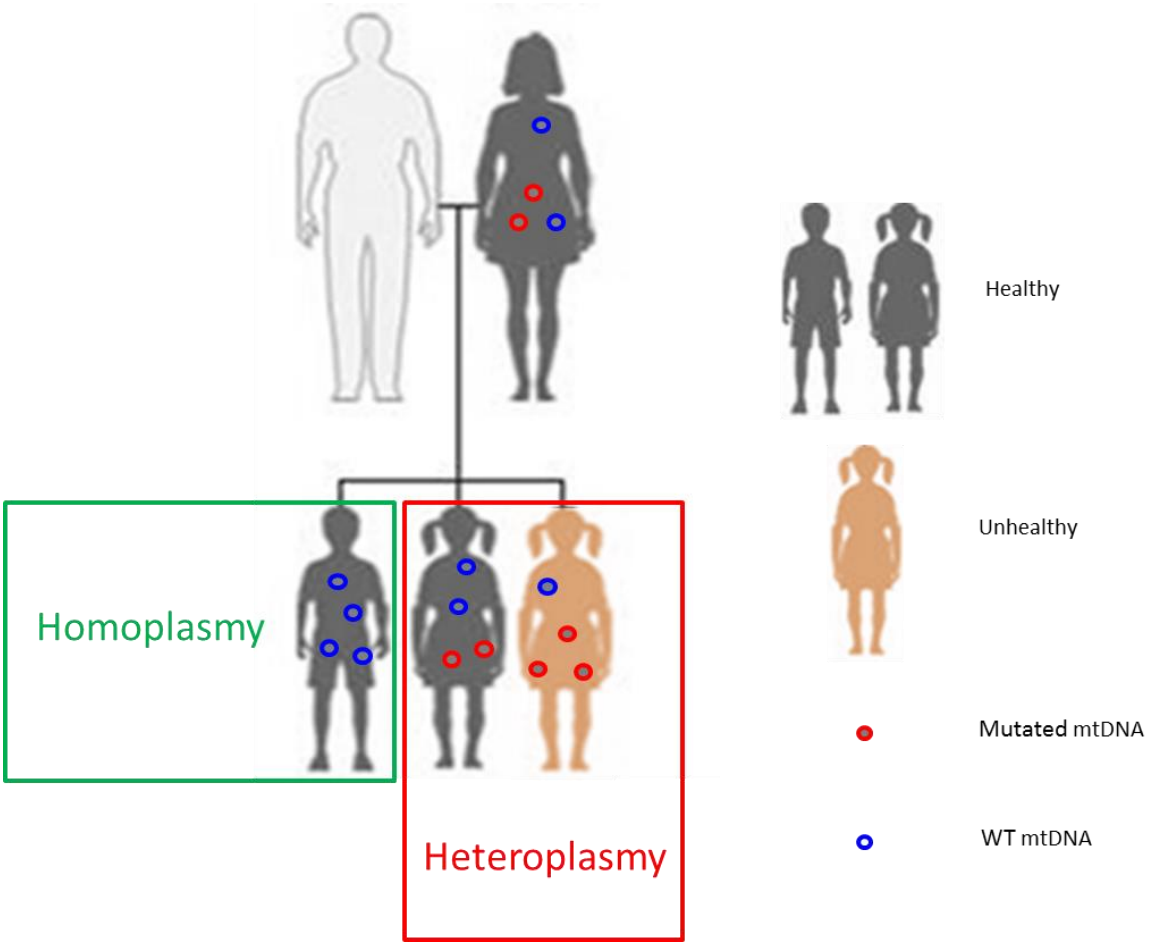


X-linked recessive



mitochondrial inheritance

Mitochondrial DNA is maternally inherited, meaning that all of your mitochondrial sequence comes from your mother and not your father. Mitochondrial DNA mutations can be transmitted to the next generation in different proportions.



- if all the copies of the mtDNA are the same it leads to a **homoplasmic** state

- if some molecules display a different nucleotide sequence the state will be **heteroplasmic**

Once it reaches a certain threshold, heteroplasmy leads to a pathological symptoms.

Draw the family tree of the patient from Workshop 2:

Workshop 4

Histology

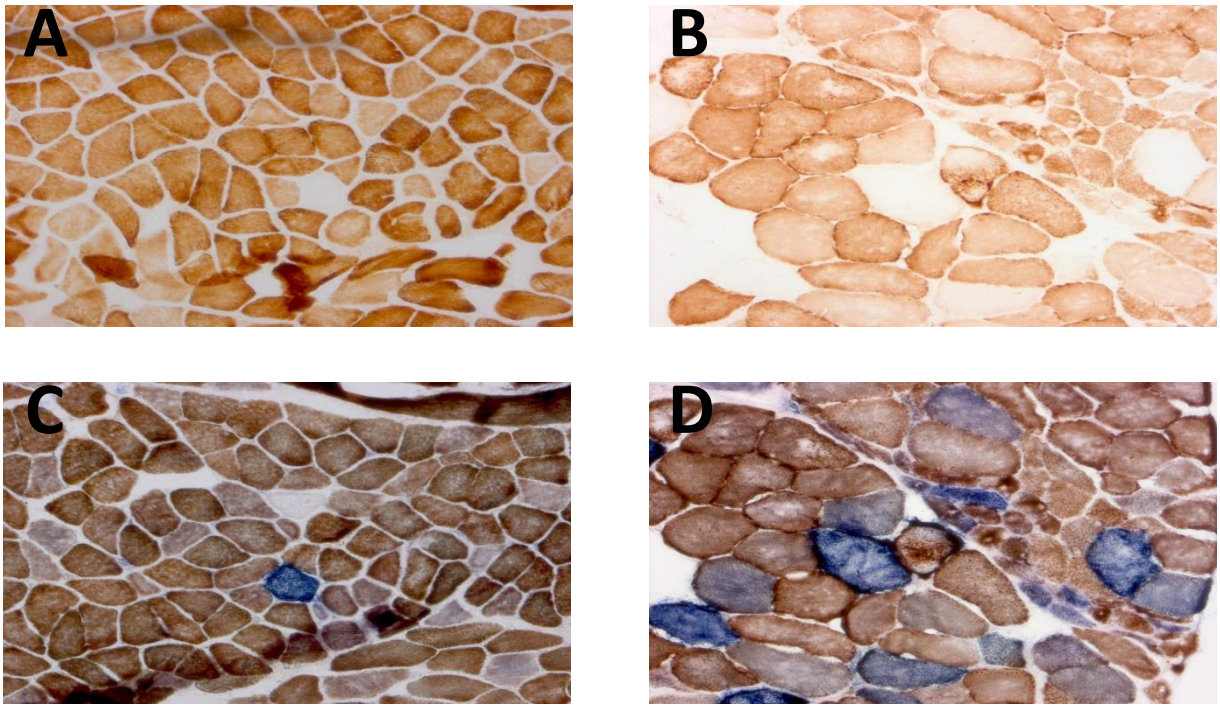
Human mitochondrial diseases can be caused by mutations in the mitochondrial DNA or in a nuclear gene encoding a mitochondrial protein. Such mutations will generally lead to malfunction of mitochondria. Mitochondrial diseases can affect many organs that are highly-dependent on mitochondria such as brain, liver and muscles.

It is possible to assess the severity of mitochondrial myopathies by sampling muscle biopsies from patients and assess mitochondrial health in their biopsies. Pathologists have developed biological assays to assess mitochondrial health in patients with mitochondrial diseases. It is possible to use an assay which will stain healthy mitochondria in brown but mal-functioning mitochondria will not stain and cell will remain transparent.

In some instances, although mitochondria are non-functional, they can accumulate as a compensatory effect. Using a specific blue dye, cells can stain deep blue if they have accumulated mitochondria compared to light blue in healthy cells. Both brown and blue stains can be used in combination for a complete assessment of mitochondrial health. Cells with healthy mitochondria will stain brown, whilst cells with malfunctioning mitochondria will stain blue.

Cells with unhealthy mitochondria will also look abnormal by varying in size, shape and mitochondrial localization within the cell.

Healthy | **Mitochondrial myopathy**



A and B: brown cells have healthy mitochondria, transparent cells have lost their function.

C and D: brown cells are healthy, blue cells have accumulated non functional mitochondria.

Choose a field of view and count the number of blue cells for each slide. Can you tell which is the control, which is a mitochondrial myopathy and which is another mitochondrial disease with myopathy as a secondary symptom?

Can you describe what other morphological features have the diseased cells in the patient with mitochondrial myopathy?

1

2

3

Following fertilisation, development from a single cell to a mutli-cellular, complex organism is orchestrated by the expression and regulation of both the nuclear and mitochondrial genomes. Alterations (mutations) to key genes necessary for normal devolvement can disrupt this tightly regulated network, which in turn, can alter the way in which the forming cells develop and communicate with each other. Sometimes this can have serious consequences for an individual who carries such a mutation.

Studies have shown that while over 90% of the protein coding genes are shared between humans and mice, the regulation and expression of these genes can vary significantly between the two species. Even though the mtDNA of both humans and mice encode for the same proteins and RNAs required for mitochondrial protein synthesis, comparison of human and mouse mtDNA DNA sequences has shown that while very similar, they are not identical.

Owing to the differences between human and mouse nuclear and mitochondrial genomes, both in structure and regulation, it is perhaps unsurprising that mouse models of human diseases do not always exactly mimic the phenotype of the human disease. Therefore, if we are to understand fully human genetic disease it is necessary to carry out research directly in human tissue.

Understanding both the anatomical and molecular biological differences between humans and mice during normal development is an important goal in not only being able to answer the key question *"what makes us human?"*, but can also provide insight into what extent we can extrapolate the data being generated by mouse models of genetic human diseases.

The most obvious differences in the physical appearance of two species are seen following birth; however, important phenotypic differences can be seen between human and mouse even at the very early stages of the developing embryos.

Can you identify which are the mouse and which are the human embryos from the histology slides and give a reason for your answer?

A

1

B

2

C

3

D

4

Workshop 5

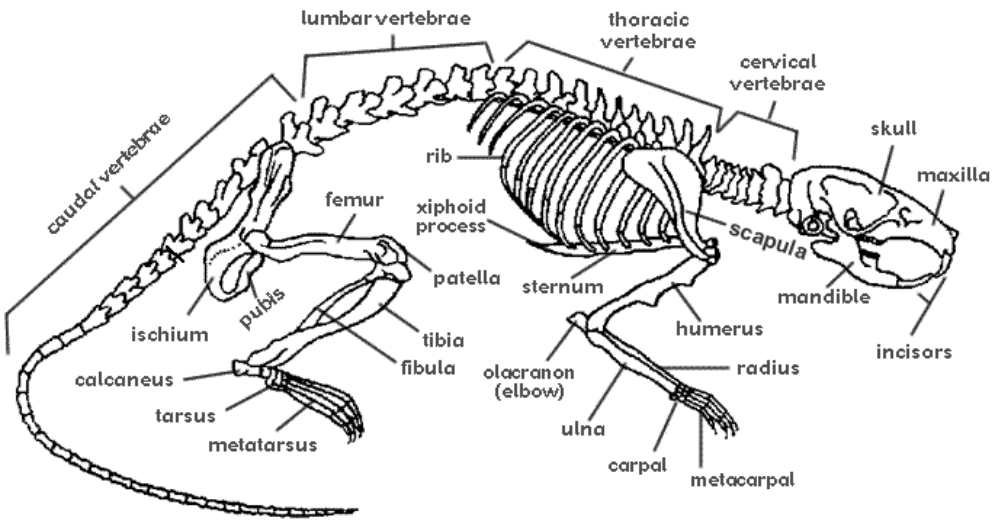
Animal models of disease

- What is an animal model?
- Why do scientists use them and how do they compare to humans?
- Which species would you choose for an experiment?

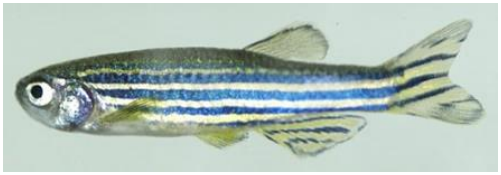
Mouse

- Genetically identical
- Fast lifecycle
- Sequenced genome/easy genetic manipulation
- Ideal for studying more complex body systems

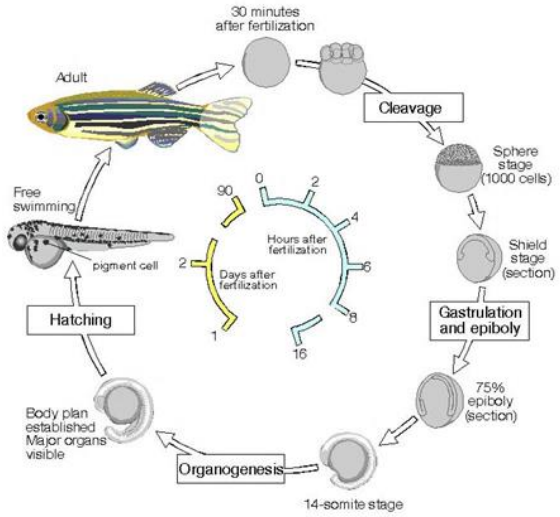
Activity 1 **Compare the 2 skeletons using the diagram below. What can you see?**



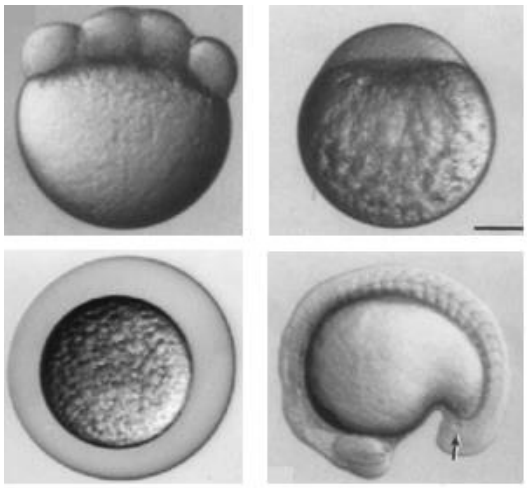
Zebrafish



- transparent embryos (ideal for microscopy)
- rapid development (outside the womb)
- 1 pair of adult fish will produce a large number of embryos
- drugs can be tested easily by adding them to the water



Activity 2 — Label the images in the correct order



A. zebrafish egg

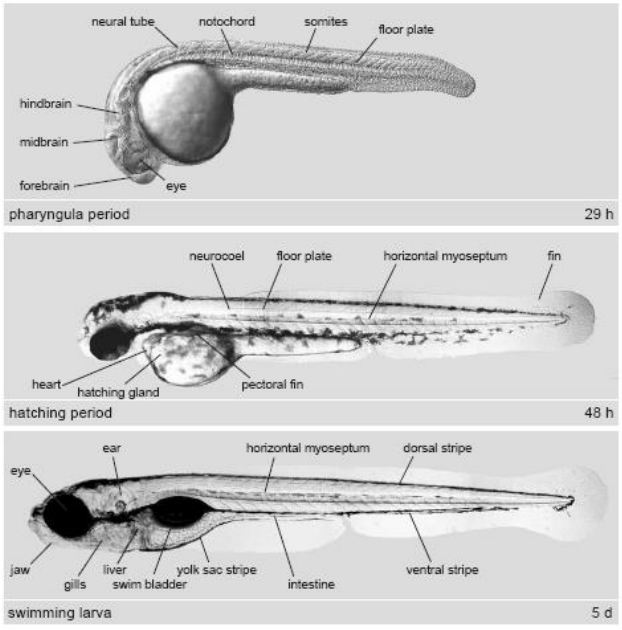
B. 1-cell stage (20 min)

C. 8-cell stage (1h 15 min)

D. 16h

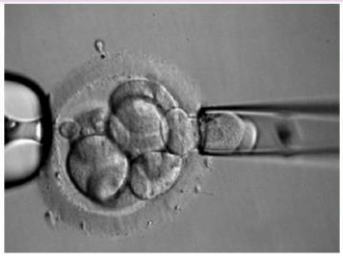
Activity 3 — Under the microscope

- Can you see the features of the embryos?
- Diseased vs healthy?
- How old is each embryo?



Therapeutic avenues

PGD can be used to detect mtDNA mutations



Single cell removed and sent to diagnostic lab for analysis

	Mutation level	Risk of developing mitochondrial disease
No mutation	0%	No risk
Low-level mutation	<30%	Lifetime risk extremely low
Intermediate-level mutation	31-70%	Risk rises with increasing mutation level
High-level mutation	>70%	High risk of severe disease

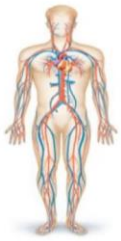
Notes

Careers

School of Biomedical Sciences:
Study with us……..

Newcastle University
UK | Malaysia | Singapore

- Biomedical Sciences
- Biomedical Genetics
- Biochemistry
- Physiological Sciences
- Pharmacology
- MSci Biomedical Sciences (4years)



- **New for 2015:**
  - Biomedical Sciences with an industrial placement year 4 years
  - Exercise Biomedicine

Careers:

Newcastle University

- Science and non-science related
- Further study:
  - PhD
  - Masters
  - Clinical degree (medicine/dentistry/veterinary/nursing)
- Pharmaceutical/biotech industry
- NHS Biomedical scientist
- Teaching
- Graduate training schemes
- And much more!

Further details

Newcastle University

- Entry offer: typically AAB
  - Based on academic performance
- Common stage 1 (3 semesters)
- Specialise 2nd semester of year 2
- Flexibility
- Range of modules to select
- 10 week lab-based research project in final year
- Study abroad
- Lab placements

NewcastleBiomedicalSciences

@biomedsciNU

http://www.ncl.ac.uk/biomed/

5 min PhD workshop

Notes

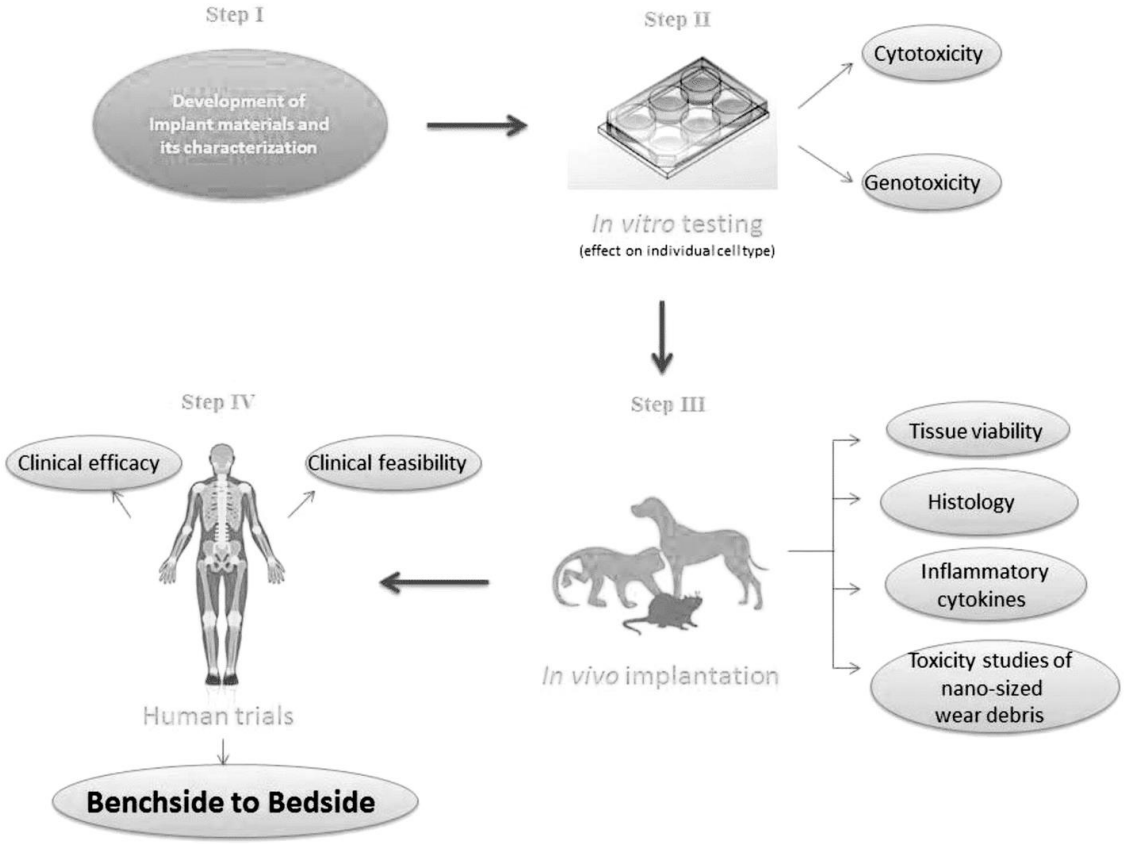
The future of medicine

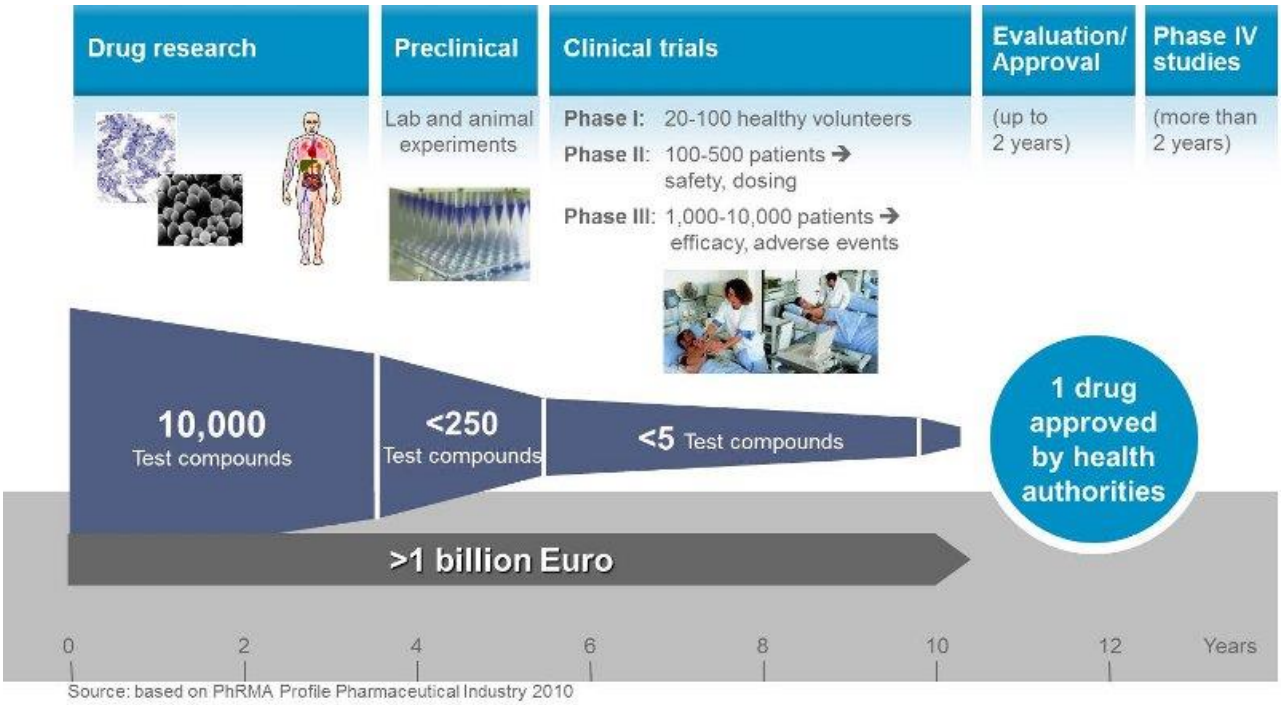
Single Cell Next-Generation Sequencing - everything you need to know in 20 minutes

A single cell is the fundamental unit of all living things. Advancements in technology in the last few years has given researchers the opportunity to look at the genomic (DNA), transcriptomic (RNA) and DNA methylation (epigenomic) status of individual cells. This brief overview will introduce some of the latest methods and technologies developed for single cell sequencing; areas of research where these developments are having the biggest impact; and finally, looking into the future for single cell studies and next-generation sequencing.

Notes

From bench to bedside (drug development and clinical trials)





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Debate

At the end of today, we will discuss why clinical trials are important to develop new medicines and some of the ethical issues raised when using experimental treatments on patients.

As you listen to lectures – especially in the final session – and spend time in workshops, think about what these issues might be.

You might find it useful to note some things down below.

Why do we need clinical trials?

Why do trials use a placebo?

Would you ever consider taking part in a clinical trial?

What factors would affect your decision?

Should trials be allowed to recruit children? Why?

What are the ethical issues about using a placebo?

What questions do you have about clinical trials?

Feedback form

Newcastle University

INSTITUTE OF Genetic Medicine

IGM Open Day

Wednesday 15th July 2015

09:00am – 4:30pm

What was your overall impression of the day?

☐Thought provoking ☐Useful ☐Informative ☐Waste of time

The length of the event was...

☐Just right ☐Too Long ☐Too short

The presentations... *(Tick all that apply)*

☐Answered many questions ☐Were useful

☐Covered material relevant to me ☐Were interesting

☐Were clear and well organised ☐Were inappropriate

☐Were uninteresting ☐Were hard to follow

Did attending the Open Day change your ideas about genetic research?

☐Yes ☐No ☐Not sure

How?

Did attending the Open Day help you decide about your future career path?

☐Yes ☐No ☐Not sure

How?

Any additional comments:

Name and email (optional):

Please leave your completed form with a member of staff


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Medicine