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A LEVEL

Delivery Guide

BIOLOGY A

H420
For first teaching in 2015

Manipulating Genomes

Version 2

www.ocr.org.uk/biology

Introduction

A LEVEL *BIOLOGY A*

Delivery guides are designed to represent a body of knowledge about teaching a particular topic and contain:

- Content: A clear outline of the content covered by the delivery guide;
- Thinking Conceptually: Expert guidance on the key concepts involved, common difficulties students may have, approaches to teaching that can help students understand these concepts and how this topic links conceptually to other areas of the subject;
- Thinking Contextually: A range of suggested teaching activities using a variety of themes so that different activities can be selected which best suit particular classes, learning styles or teaching approaches.

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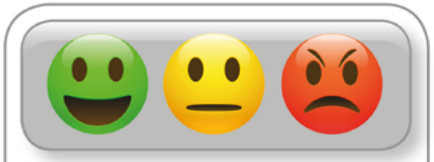

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Curriculum content

Genome research and manipulation is one of the fastest-growing fields of modern biology but the topic provides a number of specific challenges for teachers. These include:

- inspiring students with enthusiasm for the potential medical, agricultural and societal benefits of being able to readily sequence DNA and introduce new alleles into organisms
- developing in students a balanced view of the potential problems of generating stored information about individuals' DNA and of creating transgenic organisms
- helping students to visualise events at the molecular level and to encourage interest in what may seem to be very abstract concepts
- supporting students with less background in the physico-chemical sciences to understand complex technologies relying on molecular properties, electric current and attraction and laser detection of fluorescence
- keeping abreast of developments in a fast-moving field and deciding where to pitch the teaching between the traditional content of text books and the newest ideas and advances.

Two contrasting routes through the specification content are suggested over the following pages. They are:

- Molecular Route
- Applications Route

	Learning outcomes	Additional guidance
(a)	the principles of DNA sequencing and the development of new DNA sequencing techniques	To include the rapid advancements of the techniques used in sequencing, which have increased the speed of sequencing and allowed whole genome sequencing e.g. high-throughput sequencing. HSW7
(b)	**(i)** how gene sequencing has allowed for genome-wide comparisons between individuals and between species	
	(ii) how gene sequencing has allowed for the sequences of amino acids in polypeptides to be predicted	
	(iii) how gene sequencing has allowed for the development of synthetic biology	With reference to bioinformatics and computational biology and how these fields are contributing to biological research into genotype–phenotype relationships, epidemiology and searching for evolutionary relationships. **PAG10** HSW7, HSW9
(c)	the principles of DNA profiling and its uses	To include forensics and analysis of disease risk. HSW9
(d)	the principles of the polymerase chain reaction (PCR) and its application in DNA analysis	
(e)	the principles and uses of electrophoresis for separating nucleic acid fragments or proteins	Opportunity for practical use of electrophoresis. **PAG6** HSW4
(f)	**(i)** the principles of genetic engineering **(ii)** the techniques used in genetic engineering To include the isolation of genes from one organism and the placing of these genes into another organism using suitable vectors.	To include the use of restriction enzymes, plasmids and DNA ligase to form recombinant DNA with the desired gene and electroporation. HSW2
(g)	the ethical issues (both positive and negative) relating to the genetic manipulation of animals (including humans), plants and microorganisms	To include insect resistance in genetically modified soya, genetically modified pathogens for research and 'pharming' i.e. genetically modified animals to produce pharmaceuticals **AND** issues relating to patenting and technology transfer e.g. making genetically modified seed available to poor farmers. HSW10
(h)	the principles of, and potential for, gene therapy in medicine.	To include the differences between somatic cell gene therapy and germ line cell gene therapy. HSW9, HSW12

Curriculum content

Molecular Route

This works up from the basics step by step, building on previous knowledge and leading on from the techniques of genetic engineering and sequencing to their applications and relevance to society. It would suit able students with a good background in biochemistry and an ability to clearly visualise events at the molecular level.

Teaching Aims Content Outline	6.1.3 learning outcomes/links
Revise the structure of DNA	2.1.3 (a) - (d)
Introduce restriction enzymes and DNA digestion	(f) (ii)
Explain how electrophoresis separates DNA fragments of different lengths	(e)
Show examples of how electrophoresis gel results can be useful in different areas such as criminal forensics and ecological research	(c)
Show an example of how combining gel electrophoresis with hybridisation of a single-stranded probe can be used to identify disease alleles	(c)
Consider how DNA is obtained, to lead onto how PCR amplifies DNA samples	2.1.3 (d) 6.1.3 (d)
Stress the second benefit of PCR as a way of selecting desired DNA	(d)
Explain how electrophoresis and PCR are both integral to DNA sequencing	(a)
Teach the Sanger dideoxynucleotide chain termination method of DNA sequencing using fluorescent tags and laser detection	(a)
Explain how this generates sequence data on a single gel in contrast with the older technique of running four gels read in parallel	(a)
Present images of modern high throughput sequencing machines and specimen computer data print-outs as 'next generation sequencing' or 'massively parallel sequencing'	(a)
Mention third generation sequencing developments such as pyrosequencing and contrast whole genome and whole exome sequencing	(a)
Consider how genome wide comparisons between species reveal phylogenetic (evolutionary) relationships with contextual examples	(b)
Consider how genome-wide comparisons between human individuals can diagnose genetic disease	(b)
Revise levels of protein structure, protein synthesis and the genetic code	2.1.2 (k)(m) 2.1.3 (f)(g)
Explain how obtaining DNA sequence data also provides protein primary sequence data	(b)
Compare the rate of progress in reading DNA sequences and generating accompanying models of protein structure and function	(b)

Curriculum content

Teaching Aims Content Outline	6.1.3 learning outcomes/links
Consider electrophoresis of proteins, highlighting how charge as well as mass is significant	(e)
Illustrate the principle of genetic engineering with examples	(f)
Outline the techniques of genetic engineering	(f)
Discuss how genetic engineering is applied to humans in gene therapy	(h)
Provide a forum for ethical discussion about applications of genetic engineering	(g)

Curriculum content

Applications Route

This starts by exciting students with the potential of genetic engineering and sequencing, engages their judgement by looking at ethical dilemmas and only then goes deeper into solving the technical problems of how we achieve sequence data and the creation of transgenic organisms. It would suit students with a humanities background who are more likely to engage if the content relevant to society is presented first, and the nitty-gritty detail follows, as they then have more reason to want to engage with understanding the technological processes.

Teaching Aims Content Outline	6.1.3 learning outcomes/links
Illustrate the principle of genetic engineering with a range of examples	(f)
Revise the structure of DNA	2.1.3 (a)(d)
Introduce restriction enzymes and DNA digestion	(f) (ii)
Outline the techniques of genetic engineering	(f)
Discuss how genetic engineering is applied to humans in gene therapy	(h)
Show an example of how combining gel electrophoresis with hybridisation of a single-stranded probe can be used to identify disease alleles	(c)
Provide a forum for ethical discussion about various applications of genetic engineering	(g)
Show examples of how electrophoresis gel results can be useful in different areas such as criminal forensics and ecological research	(c)
Explain how electrophoresis separates DNA fragments of different lengths	(e)
Consider how DNA is obtained to lead onto PCR as a tool for amplifying small samples of DNA	2.1.3 (d) 6.1.3 (d)
Stress the second benefit of PCR as a way of selecting desired DNA	(d)
Consider how genome wide comparisons between species reveal phylogenetic (evolutionary) relationships with contextual examples	(b)
Consider the implications of genome-wide comparisons between human individuals for medicine	(b)
Teach the Sanger dideoxynucleotide chain termination method of DNA sequencing using fluorescent tags and a laser	(a)
Explain how the processes of electrophoresis and PCR are both integral to DNA sequencing	(a)
Explain how fluorescence and a laser allows sequence data to be displayed on a single gel and presented on a computer, in contrast with the older technique of running four gels which were read in parallel	(a)
Present images of modern high throughput sequencing machines and specimen computer data print-outs as 'next generation sequencing' or 'massively parallel sequencing'	(a)

Curriculum content

Teaching Aims Content Outline	6.1.3 learning outcomes/links
Mention third generation sequencing developments such as pyrosequencing and contrast whole genome and whole exome sequencing	(a)
Revise levels of protein structure, protein synthesis and the genetic code	2.1.2 (k)(m) 2.1.3 (f)(g)
Explain how obtaining DNA sequence data also provides protein primary sequence data	(b)
Compare progress in reading DNA sequences and generating models of protein structure, and function and uses of these models	(b)
Consider electrophoresis of proteins, highlighting how charge as well as mass varies (in comparison to DNA electrophoresis)	(e)

Curriculum content

Content-based teaching materials

DNA Manipulation Techniques (DNA Learning Centre, Cold Spring Harbor Laboratory) 6.1.3a
http://www.dnai.org/b/index.html

In the Manipulation module choose Techniques to access a range of animation and video resources detailing the cutting and pasting, transferring and storing, large scale analysis, sorting and sequencing and amplifying of DNA, plus a section on genetic model organisms. The animations are non-narrated and ideal for individual study. Accompanying activities should involve written summaries or translating the information into another form such as flow charts or diagrams in order to cement learning and understanding.

PCR animated tutorial (Sumanas, Inc.) 6.1.3b
http://www.sumanasinc.com/webcontent/animations/content/pcr.html

The molecular processes occurring in the Polymerase Chain Reaction are explained in a narrated or step through format.

This animation can be used in class teaching or by individual students with access to a computer in a class or private study setting.

To consolidate learning students could summarise the events that occur at 95, 60 and 72°C in the PCR cycle, list the ingredients in the PCR mixture and could calculate how many copies of the target DNA will be present after 5 and 10 cycles of PCR.

The Human Genome animated tutorial (Sumanas, Inc. and Pearson Prentice Hall, Inc.) 6.1.3b
http://www.sumanasinc.com/webcontent/animations/content/humangenome.html
This link does not work on Google Chrome

Methods of mapping chromosomes and using computers to assemble whole chromosome DNA sequences are explained.

This animation can be used in class teaching or by individual students with access to a computer in a class or private study setting. On completion of studying the information students should be able to summarise the difference between map-based and shotgun sequencing of whole genomes and to explain why shotgun sequencing was a later and improved development.

DNA Sequencing Technologies review article (Nature Education) 6.1.3b
http://www.nature.com/scitable/topicpage/dna-sequencing-technologies-690

A 2008 review of the development of sequencing technologies. If utilised online, students can use hyperlinks for more information if needed.

Students could summarise the main steps in the development of sequencing techniques or could present the changes as a flow chart or as a time line.

High Throughput Sequencing animated tutorial (Sinauer associates, W.H.Freeman & Co. and Sumanas Inc.) 6.1.3a-b
http://www.sumanasinc.com/webcontent/animations/content/highthroughput2.html

A third generation pyrosequencing (454 sequencing) technique is described in a narrated or step-through format, with a follow-up quiz activity.

Activity: This animation and quiz can be used in class teaching or by individual students with access to a computer in a class or private study setting. The main differences between this technique and the automated Sanger method should be identified by discussion and then the contrasting features of each method listed in two columns.

Thinking conceptually

Approaches to teaching the content

The molecular and applications routes highlight the distinction between two very different types of content: the technical detail of processes in molecular genetics, and the open-ended range of its applications and the ethical judgements accompanying its regulation. Detail, precision and rigour are necessary to fully understand the processes, but imagination and maturity are necessary to appreciate the applications and their relevance to society. Freedom to innovate and explore are encouraged in the interactive contextual resources provided.

Common misconceptions or difficulties students may have

Understanding the technical processes of PCR and sequencing is made much easier if students have a firm grasp of DNA structure, to include the anti-parallel orientation of the two strands, and the concept of the 5′ (terminal phosphate) and 3′ (terminal deoxyribose) ends.

The ethical dimension to decision-making about applications of DNA sequencing, profiling and creation of transgenic organisms often finds students unprepared in exams. It is important that students have a clear understanding of the idea of ethical as meaning morally right, and that they are used to assessing moral rights and wrongs without resorting to clichés. The OCR Lesson Element: Hoop Jump - Right or Wrong addresses this.

The other major difficulty students encounter is not appreciating the different ways in which standard techniques like PCR and electrophoresis can be used and combined, for example modified PCR and capillary electrophoresis in automated sequencing. This is specifically addressed in both teaching routes set out above.

Conceptual links to other areas of the specification – useful ways to approach this topic to set students up for topics later in the course.

Teaching of this topic should be firmly bedded in an understanding of the structure of DNA, 2.1.3(a)–(d) and proteins, 2.1.2(k)-(m). A secure grasp of the genetic code and protein synthesis, 2.1.3(f)-(g), is also needed. The concepts learnt in 6.1.3 are relevant to the following areas of the syllabus and links could be made back to the older topics and the 6.1.3 material re-introduced in the later topics in order to prepare students for synoptic questions.

4.2.1(e)	Measuring genetic diversity (detection of polymorphic alleles by electrophoresis)
4.2.2	Classification and evolution (whole genome comparisons)
5.2.2(b)	Mitochondrial DNA (sequencing to discover maternal line kinship)
6.1.1(a)	Genes and mutation (creation of sequence variability)
6.1.1 (b)	Gene regulation
6.1.1 (c)	Hox gene comparison
6.1.2(b), (f)	Relate sequence markers and DNA fingerprint profiles to classical genetics and population genetics
6.2.1(e)	Use of (GM) microorganisms in biotechnology
6.3.1(b)	Applying GM in agriculture (manipulation of biomass transfer)
6.3.2(e)	Use of sequence and profiling data in assessment of populations and detection of wildlife smuggling for conservation (management of environmental resources).

Thinking contextually

Interactive materials detailing the use of DNA profiling and sequencing techniques are listed below. A useful broad context in which to begin to understand the impact of genome manipulation is to consider the discovery of the structure of DNA in 1953 using the BAFTA award winning drama *Life Story* from BBC Horizon. The historical context sharpens students' appetites for discovering if the early promise of DNA has been fulfilled.

The Human Genome provides a context for exploring whole chromosomes and relating their structure to their DNA sequences, using resources from Cold Spring Harbor Laboratory. The GeneBoy tool on this site allows students to perform their own analysis of sections of sequence so they can understand how enormous sets of data are made sense of.

The context of who should have access to DNA sequence data allows students to explore the concept of what is ethical using three published resources.

The case study applications context provides interesting scenarios where DNA has been used to solve criminal justice and historical mysteries such as the fate of grand Duchess Anastasia of the Russian Romanov dynasty.

An activity involving an up to date summary of case studies in genetic engineering can be found in the OCR Lesson Element: Genetically Modified Organisms Dating Game.

Activities

Learner Activity 1
Discovery of DNA
BBC Horizon film 'Life Story' also re-named 'The Race for the Double Helix' (BBC, 1987)

https://vimeo.com/179934156

The drama is an hour long but provides a fascinating context for revision of DNA structure and a look at how scientific research and universities operate, which will be of particular interest to year 13 students. The clash of personalities and politics in Life Story show science as personal and intense, and the excitement over the potential of DNA builds throughout.

A worksheet listing the main characters is provided in the learner resources section within this document, to help students follow the drama and link their understanding of this story to names they may have encountered in physics and chemistry. A suggested follow-on activity is included in the learner resource section of this guide (groups or a class collaborate in obtaining print-outs of photographs of these scientists and plotting them onto a map with the scientific discoveries of each person bullet-pointed below).

Learner Activity 2
Exploring the human genome 6.1.3f
Genome (DNA Learning Centre website, Cold Spring Harbor Laboratory).
http://www.dnai.org/c/index.html

Select the Tour option for a narrated flyover of the tip of chromosome 11 including the globin genes, for interactive fluorescent in situ hybridisation searches of centromeres, telomeres and key genes, for a tour of the X chromosome moving from chromosome banding pattern to sequence code, and to hear a narrated animation of chromosome coiling.

A suggested creative activity after exploring the resources is to characterise some of the human chromosomes (eg 11 and X) in the form of a travel advertisement, highlighting features of the 'landscape' and 'attractions' of each.

Learner Activity 3
Making sense of sequence data 6.1.3b
GeneBoy (DNA Learning Centre website, Cold Spring Harbor Laboratory)
http://www.dnai.org/geneboy/

This interactive DNA sequence analysis tool is easy and fun to use and helps students see how long sections of code are made sense of. Students can transform the code into mRNA and amino acid sequences, can search for genes by looking for start and stop codons in three different reading frames and can search for a variety of restriction sites.

A worksheet to summarise their findings could be drawn up as a table with columns for 'percentage of each base', 'number of genes' and 'number of restriction sites' for example. If different students analysed different sequences the class results could be pooled, as individuals or groups.

Learner Activity 4
DNA Testing – Who, Why and Why Not? 6.1.3c
Policy statement on the clinical applications of genomic sequencing (American College of Medical Genetics and Genomics).
https://www.nature.com/articles/gim201274

This contains useful definitions of whole genome, whole exome and next generation sequencing and considers the uses to which genetic information about individuals should be put.

Policy information relevant to the UK healthcare setting can be found in: Whole Genome Sequencing: Clinical impact and implications for health services (PhG foundation).
http://www.phgfoundation.org/file/10365/

Activities

Learner Activity 5
Direct to consumer testing' researcher interviews (Wellcome Trust Sanger Institute) 6.1.3b
http://www.yourgenome.org/stories/direct-to-consumer-testing

Four short video clips investigating the pros and cons of unregulated DNA tests accessible online.

Activity: Students should divide into groups of four. One pair should scan the American policy document and one the PHG document (found above). The whole group should then watch the first two researcher interview videos. Based on what they have found out, the group should collaborate to prepare a flyer for a DNA testing laboratory. On it they should provide a two-column list, firstly of clinical situations where they agree to sequence an individual's genome, and secondly of types of screening that they will not carry out for ethical reasons. They should also outline their laboratory's policy on disclosing secondary findings of the DNA sequencing.

Extension Activity: The four students then assume the roles of a genetic counsellor and three clients: a person with an undiagnosed disease that is possibly genetic in origin, a person with a strong family history of a late onset genetic disease and a parent concerned that her unborn baby might have a congenital disease. Students role-play dialogue between the counsellor and client covering whether to proceed with testing, what results might reveal, patient consent and patient directions on secondary findings.

Learner Activity 6
Case study applications of DNA testing 6.1.3c
Applications (DNA Learning Centre, Cold Spring Harbor Laboratory)
http://www.dnai.org/d/index.html

This includes a step by step interactive tutorial on unravelling the mystery of the Romanovs by DNA evidence plus scenarios involving forensic identification (Human identification, Murder and Innocence), medical molecular genetics and the phylogenetic origin of humans. These resources are ideally suited to individual study with students working at their own pace, with options to try matching DNA profiles for themselves and to check answers to questions as they work.

A follow-up activity to reinforce learning could be to write a short newspaper article on one of the scenarios. If students were assigned scenarios the collected articles could be put together as a display or 'DNA Mysteries' magazine.

Learner Activity 7
Genetically Modified Organisms Dating Game 6.1.3g
OCR Lesson Element

This activity is designed to introduce students to a range of applications of genetic engineering and stimulate discussion and decision-making on the positive benefits and the negative risks of GMOs.

The activity can be run in two ways or a combination of the two:

- Blind Date involves selected students taking turns playing the game in front of their peers. It takes longer but everyone hears all the interactions.
- Speed Date involves all students simultaneously interacting and will more quickly produce results for the worksheet.

Learner Activity 8
Hoop Jump - Right or Wrong 6.1.3g-h
OCR Lesson Element

This fun activity is designed to help students develop skills in judging the ethical implications of applications of Biology and learn to write evaluations referring to both benefits and harms.

Learner Resource 1

Life story worksheet

'Life story' checklist of Scientists

Name	Most famous discoveries	Nobel prize winner?
Rosalind Franklin		
James Watson		
Francis Crick		
Maurice Wilkins		
John T. Randall		
Sir Lawrence Bragg		
Sir William Henry Bragg		
Max Perutz		
Linus Pauling		
Peter Pauling		
John Kendrew		
Raymond Gosling		

Group challenge:
Obtain print-outs of photographs of these scientists and plot them onto a map of either the UK or the world with the major scientific contributions of each person bullet-pointed below.

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