TEACHING OUTREACH RESOURCE

Inheritance and Pedigree Analysis

Brought to you by

Genetics
Mātai Ira
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University of Otago
Te Whare Wānanga o Otāgo
New Zealand

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GO BEYOND WITH GENETICS…

__Explore__ the origins and mechanics of life. __Discover__ causes of disease and their cures. __Solve__ the problems facing our agriculture and natural heritage. __Understand__ the past. __Create__ a better future. __Master__ the world of genetics…

WELCOME...

...to this Genetics teaching resource, created by Genetics Otago and the Genetics Teaching Programme at the University of Otago.

Our aim is to engage young minds with Genetics and to do this we have developed a range of resources that include information, worksheets and activities or experiments that will help you to plan exciting Genetics classes for your students.

Where possible we have endeavoured to align and link the content of the resources to the New Zealand Curriculum.

If you have any questions relating to the content of the resources or would like to organise an onsite teaching session on one of our topics please contact us at go@otago.ac.nz.

Contents

Overview

A number of traits and diseases are passed on through generations of a family in a Mendelian manner, this is what we know commonly as inheritance. In this resource we provide background information, instructions and worksheets necessary to provide a basic understanding of inheritance and pedigrees. Students will be given the opportunity to work through a series of exercises to understand the concepts before testing the inheritance of cystic fibrosis through a small family using gel electrophoresis (electrophoresis kits are available on request).

OBJECTIVES

- Successfully follow a scenario through a logical set of steps to reach an informed conclusion.
- Understand the laws of Mendelian Inheritance, including the different modes of inheritance.
- Appreciate that the use of a pedigree can simplify the description of a family and be able to draw one from a given description.
- Interpret the results of an electrophoresis gel and apply the results to a pedigree.

SECTIONS

Part A: Mendelian Inheritance

- Activity One – Punnett Squares (**Blood Type Analysis**)

Part B: Pedigrees

- Activity Two – Pedigrees (**Draw a Pedigree**)

Part C: Case Study

- Activity Three – Family X (**Family X Diagnosis**)
- Activity Four – Gel electrophoresis interpretation (**Family X Diagnosis**) including an optional practical component.

CURRICULUM LINKS

This module is designed to feed into the following curriculum areas at Level 6+, but could be adapted to suit younger students:

- **Nature of science**
  - *Understanding about science* **–** working in groups, working with current scientific theories, collecting evidence and developing a logical argument.
  - *Investigating in science* **–** *c*arrying out investigations, using models and working scientifically with multiple variables.
  - *Communicating in science* **–** Using science vocabulary and relating science understanding to scientific texts.
  - *Participating and contributing* **–** develop an understanding of socio-scientific issues and draw evidence based conclusions.

- **Living World**
  - *Evolution* **–** Explore the patterns of inheritance of genetically controlled characteristics.

PART A

Mendelian Inheritance

Inheritance

Mendelian inheritance describes the pattern of biological inheritance applied to single gene traits. This model is based on the work of Gregor Mendel in 1865, where through the breeding of sweet peas he proposed three laws of inheritance.

Law of Segregation: During the formation of gametes, the parental alleles for each gene are separated, at random, so that each egg or sperm only contains one of the parental gene pair. By this mechanism offspring will inherit one copy of each gene from each of their two parents.

Law of Independent Assortment: To be inherited in a Mendelian fashion genes must be discrete to allow the inheritance of one trait independent of all others (this is why this model of inheritance cannot be applied to complex diseases).

Law of Dominance: Where an organism inherits alternate alleles for a gene, the dominant allele will always be expressed when present.

KEY TERMS

- **Allele** – Variant form of a gene. Humans have two alleles for each gene inheriting one from each parent.
- **Gene** – Basic unit of heredity both physically and functionally.
- **Dominant** – A version of an allele that will produce a phenotype regardless of the presence of alternate alleles
- **Recessive** – A version of an allele that must be homozygous to be expressed as a phenotype
- **Genotype** – The chemical composition of the DNA giving rise to a certain phenotype.
- **Phenotype** – The physical expression of a gene.
- **Homozygous** - Where both copies of a gene have identical alleles, they can be dominant or recessive.
- **Heterozygous** – Where each copy of a gene has a different allele with one being dominant over the other.
- **Gamete** - Reproductive cells i.e. sperm and egg or ova.

Punnett Squares

Punnett squares provide a graphical representation of Mendelian inheritance and as such are a useful tool to predict the possible genotypes of the offspring from a particular mating. The creation of a Punnett square requires that the genotypes of both parents is known. The different possible combinations of these genotypes are then recorded in tabular form.

It is possible to use a Punnett square for single gene and double gene crosses, with anymore alleles the method becomes cumbersome and other methods are more effective. From the Punnett square it is possible to determine the percentage of offspring with each genotype.

SINGLE GENE CROSS

Seed colour in sweet pea plants is determined by a single gene and has two phenotypes, Green or yellow. The yellow phenotype Y is dominant over the green phenotype y. Below is a monohybrid cross between a plant that is heterozygous yellow and one that is green.

	y	***y***
Y	*Yy*	*Yy*
y	*yy*	*yy*

This cross shows that 50% of the offspring will produce yellow seeds (have at least 1 dominant Y allele) and 50% will produce green seeds (2 recessive y alleles).

DOUBLE GENE CROSS

The sweet pea seeds can have either a wrinkled or round appearance. The round phenotype (R) is dominant over the wrinkled phenotype (r). Below is a Punnett square showing a cross between two plants that are both heterozygous for both seed colour and texture.

	RY	Ry	rY	ry
RY	RRYY	RRYy	RrYY	RrYy
Ry	RRYy	RRYy	RrYY	Rryy
rY	RrYY	RrYy	rrYY	rrYy
ry	RrYy	Rryy	rrYy	rryy

This cross shows a 9:3:3:1 ratio of phenotypes. With 9 (~56%) being round and yellow, 3 (~19%) being each of round and green or wrinkled and yellow and 1 (~6%) being wrinkled and green.

Activity One: Have the students complete the worksheet '**Blood Type Analysis**'

ANSWERS

Ao
x
Bo

	A	***o***
B	*AB*	*Bo*
o	*Ao*	*oo*

Phenotypes:
25% Blood type A (Ao)
25% Blood Type B (Bo)
25% Blood Type AB (AB)
25% Blood type O (oo)

AB Rh^+Rh^-
x
oo Rh^- Rh^-

	o Rh-	**O Rh-**	**O Rh-**	**O Rh-**
A Rh+	Ao+-	Ao+-	Ao+-	Ao+-
B Rh+	Bo+-	Bo+-	Bo+-	Bo+-
A Rh-	Ao--	Ao--	Ao--	Ao--
B Rh-	Bo--	Bo--	Bo--	Bo--

Phenotypes:
25% A^+: Ao+-
25% B^+: Bo+-
25% A^-: Ao--
25% B^-: Bo--

PART B

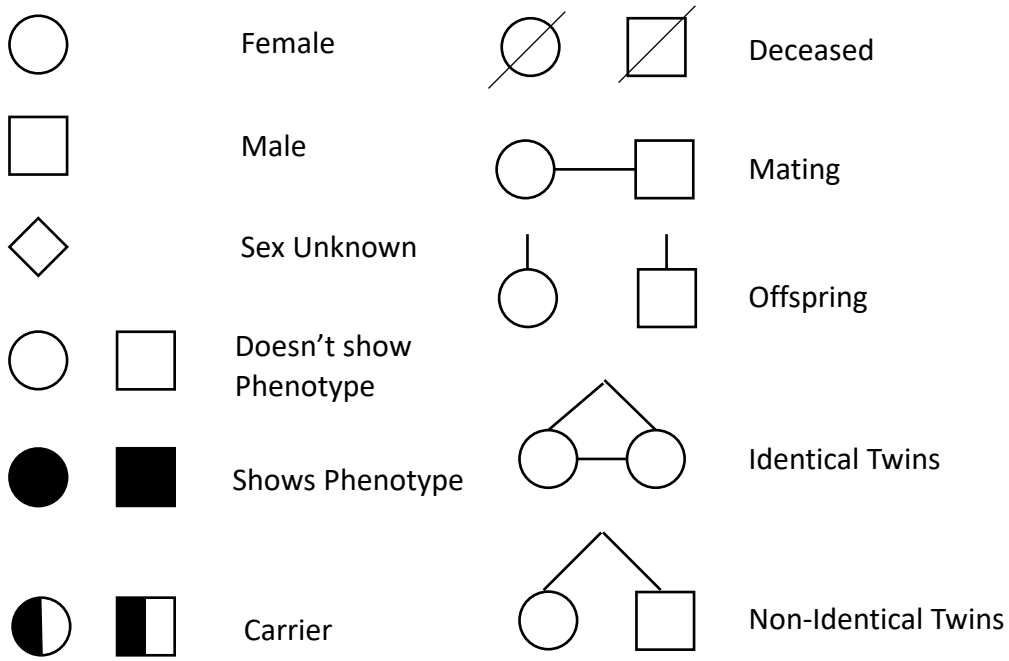
Pedigrees

Pedigree Basics

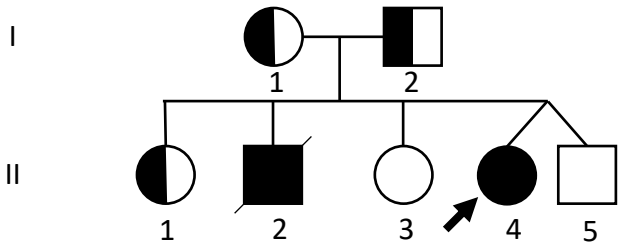
A written or verbal description of a family group quickly becomes complicated and difficult to follow. A pedigree (family tree) is a simple way of taking all of this information and presenting it in a visual manner that is quick and easy to interpret. Pedigrees are often used in medical genetics as they are a useful way to decipher the mode of inheritance of a particular disease, i.e. is it dominant or recessive, mitochondrial, autosomal or sex linked? Pedigrees are also useful for tracing parentage in breeding programmes for agriculture or conservation genetics.

To make pedigrees as simple as possible there are a universally accepted set of symbols and conventions that are used.

PEDIGREE SYMBOLS

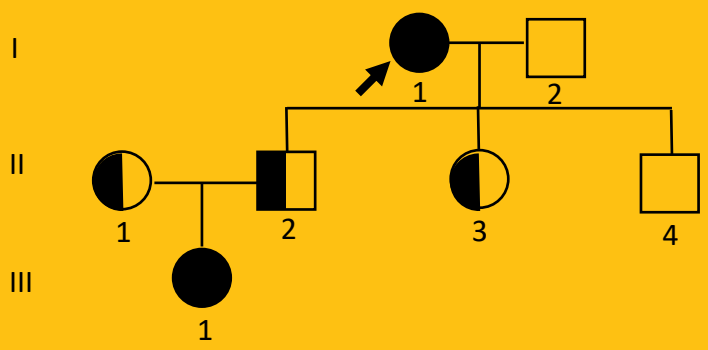


The proband (individual from who the analysis was initiated) is indicated by an arrow. Pedigrees are also numbered, each generation receives a number using roman numerals and each individual within each generation receives a numerical value. This numbering system aids in patient confidentiality and avoids confusion where two members of a family share a name. In the example below the proband would be referred to as individual II4.



Activity Two: Have the students complete the worksheet '**Drawing a Pedigree**'

ANSWERS



1. *Jane, Tom, Kate, Sarah and Lisa can all have children with the disease.*
2. *They would all need to have partners who carried the disease to pass it on to their children*
3. *25% of the offspring of two carriers will be affected (the students may need to draw a Punnett square to work this out).*

PART C

Case Study

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by the presence of a non-functional variation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene. This gene is involved in the production of bodily fluids including sweat, mucous and digestive fluid. When *CFTR* is non-functional these fluids become much thicker than normal, making it difficult to move the fluids and for them to undertake their normal functions.

Health problems associated with cystic fibrosis include lung congestion, salty sweat, digestive issues, sinus problems, nasal polyps, gallstones, abnormal pancreas function and infertility. These lead to symptoms such as poor growth, liver problems, poor weight gain, weakened bones, intestinal blockage, clubbing of fingers and toes, cystic fibrosis-related diabetes and frequent infections. There is no cure for this disease but a number of treatment options are available including antibiotics to treat underlying infections, pancreatic enzyme replacement and lung transplants.

The vast majority of deaths related to cystic fibrosis are caused by problems with breathing or infections of the lungs due to the accumulation of mucus which provides a perfect breeding ground for bacteria. Where medical intervention is available, the life expectancy of individuals with cystic fibrosis is ~45 years.

The *CFTR* gene is located on the q (long) arm of chromosome 7. There are over 1500 variations to this gene that lead to cystic fibrosis but approximately 70% of cases worldwide are caused by the ΔF508 variant which is the deletion of a single amino acid (three base pairs) from the CFTR protein sequence.

Only one functional copy of *CFTR* is needed to produce adequate CFTR protein to prevent cystic fibrosis. This means that individuals with one copy of their CFTR gene affected by a non-functional variant will not show symptoms of the disease but they are able to pass on the disease to any children they may have. Individuals with two copies of the gene affected will have cystic fibrosis – this is the autosomal recessive inheritance model.

Cystic fibrosis is very common in people of European descent with approximately 1 in 25 being a carrier of the disease. It is slightly less common in Caucasian Americans at 1 in 30 and even less common in Hispanic (1 in 46), African (1 in 65) and Asian (1 in 90) populations.

The fact that the variant forms of the *CFTR* gene have persisted through evolution despite the lethality of the disease suggests that there is some benefit to carrying one copy of the variant. Some suggestions are resistance to cholera, typhoid, diarrhoea or tuberculosis (TB), but these are all unconfirmed hypotheses.

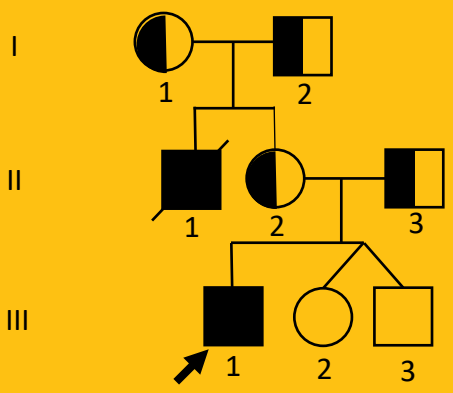
Family X

The oldest child in Family X has presented to their doctor with diagnosed Cystic Fibrosis and his parents who do not exhibit any symptoms of cystic fibrosis are worried that the child's twin sister and brother may also develop the disease. The boys mother tells the doctor that she had an older brother that died of cystic fibrosis when he was 33, but neither of her parents were affected.

The doctor orders a genetic test looking for a deletion in the *CFTR* gene. If the deletion is present the PCR product from the test will be smaller than expected, this can be visualized by running the samples on an electrophoresis gel.

Activity Three: Have the students complete the first question on the worksheet '**Family X Diagnosis**'

ANSWERS



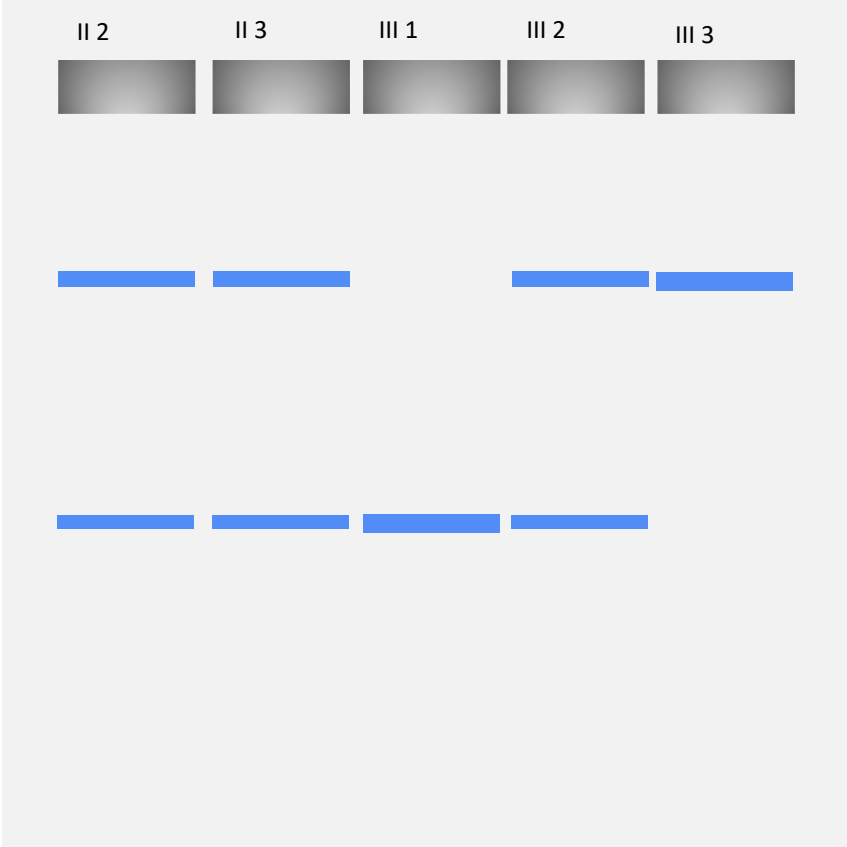
The proband is individual III 1

Activity Four: Draw the following gel diagram on the board before having the students answer the rest of the '**Family X Diagnosis**' worksheet.

DO NOT do this if you plan to run the practical experiment, the students will use the results from the experiment to complete the worksheet.

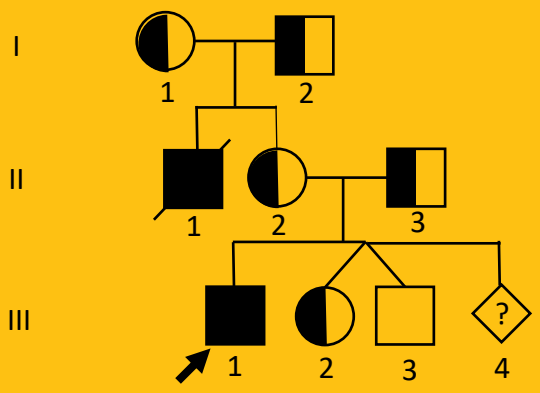
ELECTROPHORESIS KITS

This final identification step can be done as a practical exercise using the Genetics on the GO kits available from us. In this case the students will make and pour an agarose gel that they will then load 'DNA' samples into and analyse the results to decide which individuals are affected by the disease and which are carriers. For this exercise we supply dye samples as the DNA to eliminate the need for staining of DNA meaning that the exercise can be done in a single lesson. If you would like to borrow one of these kits please contact us at go@otago.ac.nz.



The results show that both the parents are heterozygous for the recessive allele, i.e. are carriers for the recessive allele (large band and smaller band). This explains why the parents have not developed cystic fibrosis, but their child has. The oldest child (III 1) is homozygous recessive and has developed cystic fibrosis (one smaller band). Individual III 2 is heterozygous for the recessive allele and will not develop cystic fibrosis but is a carrier of the disease allele (large band and smaller band). Individual III 3 is homozygous dominant and will not develop the disease (one large band) nor be able to pass it on. Note that the bands are brighter in the homozygous samples as there are two copies of the gene in the same place.

ANSWERS



We have now confirmed the status of II2 and II3 as carriers and III1 as affected, we also know that III2 is a carrier and III3 is not. The unborn baby is added as a diamond (sex is unknown) and its carrier status is untested so could include a ?.

Advice to II2 on her pregnancy would be that any future child where II3 is the father will have a 25% risk of having cystic fibrosis and if they are not affected they have a 50% chance of being a carrier.

The genotypes are: II2 Cc, II3 Cc, III1 cc, III2 Cc and III3 CC (any letter can be used).

Individual III3 can not have children with cystic fibrosis no matter who his partner is because his dominant allele will be protective.

Blood Type Analysis

There are eight different blood types in humans, these are determined by the ABO and Rh systems. In the ABO system there are three alleles A, B and O, these can combine to give A, B, AB and O blood types. A and B are both dominant over o. In the Rhesus system there are two alleles + and -, where + is the dominant allele.

Fill in this Punnett square for parents who are heterozygous type A and heterozygous type B and write down the percentage of offspring that will have each phenotype.

A =
B =
AB =
O =

Now try this square with one parent being heterozygous AB and heterozygous rhesus + and the other parent being type O and rhesus -. What percentage of the offspring will be each phenotype (complete blood type)?

Phenotypes: _____

_____

_____

_____

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Drawing a Pedigree

Jane discovers she has disease X an autosomal recessive disorder, her family are all tested to check their status. Her partner John is found to not carry the disease. Of their children Tom is a carrier, Kate is a carrier and Ben is not a carrier. Tom's partner Sarah is also a carrier and their baby Lisa is affected by disease X.

Draw a pedigree for the described family:

1. Which family members could have children with the disease?

_____

2. What will need to happen for these children to have the disease?

_____

3. What is the chance of two carriers having a child who is affected?

_____

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Family X Diagnosis

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Draw a pedigree for the described family including all information you currently know:

What is the identifier given to the proband? _____

1. Add any additional information you have gained from the gel to your pedigree.

2. Individual II 2 has just found out that she is pregnant (II 3 is the father) and wants advise on how likely it is that her unborn baby will be affected. What would you tell her?

_____

3. Add the baby be added to the pedigree

4. Write the genotypes for individuals II2, II3, III1, III2 and III3

_____

5. Can individual III3 have children with cystic fibrosis? _____

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