MACQUARIE University

BIOL3120 –Human Genetics and Evolutionary Medicine

Faculty of Science and Engineering

Lecturer profile

DR OLIVER GRIFFITH

Dr Oliver Griffith

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Faculty of Sciences and Engineering

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My path to Macquarie

Bachelor of Engineering UNSW
(dropped out after 2 years)

Bachelor of Science at Usyd
- Biology Major

PhD at Usyd – evolution of pregnancy in reptiles

Postdoc at Yale University – marsupial pregnancy
Postdoc at University of Melbourne
- Maternal-fetal communication

Lecturer at Macquarie – Evolutionary Genomics Lab

Human Genetics

With great power comes great responsibility

- Human Genome Project
- Next Generation Sequencing
- Genetic Testing
- Pre-implantation screening
- Genome Wide Associated Studies
- Personalised Medicine
- Genome Editing

BIOL3120 –Human Genetics & Evolutionary Medicine

LEARNING OBJECTIVES

On successful completion of this unit, you will be able to:

- **ULO1:** Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources.
- **ULO2:** Interpret and demonstrate understanding of the primary scientific literature.
- **ULO3:** Explain the importance of new techniques in human genetics for understanding human disease.
- **ULO4:** Explain the principles of evolutionary biology and their role in human health and disease.
- **ULO5:** Learn basic bioinformatic skills, including handling of genetic sequence data.

BIOL3120 –Human Genetics & Evolutionary Medicine

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BIOL3120 Unit Information

Welcome to Human Genetics and Evolutionary Medicine. This online space is your virtual classroom, where we can work together to enhance your learning and experience in the unit. Embracing this online space is an important part of this unit. There are a number of things that contribute to online community building and one of them is establishing a visual online presence. Please take the time (if you haven't already) to setup your iLearn profile and include a photograph of yourself (or an avatar if you like!) that way we can bring a little personality into this online space. Here's a guide to help.

We'll be running this unit on a Flipped Classroom model. Therefore, it's really important that you watch the online lecture content *before* attending your practical class. You'll get much more out of the unit this way and we can answer your specific questions in class. We'll also be available on zoom during your scheduled lecture slot to answer all of your questions. Please see the timetable information for the zoom link.

This unit has the following Learning Outcomes. On completion of this unit you should be able to:

1. Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources

2. Interpret and demonstrate an understanding of the primary scientific literature

3. Explain the importance of new techniques in human genetics for understanding human disease

4. Explain the principles of evolutionary biology and their role in human health and disease

5. Learn basic bioinformatic skills, including handling of genetic sequence data

Week	Lectures	Practical Class	Assessments	Unit Learning Outcome
1	Introductory Lecture and Overview Intro to Evolutionary Medicine	No Practical Classes in Week 1		Explain the principles of evolutionary biology and their role in human health and disease
2	Oliver's Research Problem solving in genetics	No Practical Classes in Week 2		Interpret and demonstrate understanding of the primary scientific literature

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Timetable: Lectures and Practicals

Activity	Day	Time	Location	Lecturer/Tutor
Lecture	Released Monday Morning	Watch before tutorial	iLearn	Oliver, Emily, or a Guest Lecturer
Drop In Session	Wednesday	1-2 pm	Zoom	Oliver
Practical 1	Wednesday	9-11 am	14 Sir Christopher Ondaatje Ave - 163 Active Learning Space	Erin
Practical 2	Thursday	3-5 pm	01CC 103 Active Learning Space	Oliver
Practical 3	Thursday	12-2 pm	01CC 214 Active Learning Space	Oliver
Practical 4	Wednesday	2-4 pm	01CC 218 Active Learning Space	Callum
Practical 5	Wednesday	11 am - 1 pm	Zoom	Erin

Last modified: Wednesday, 16 February 2022, 12:23 PM

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Announcements

Open all Close all

BIOL3120 Unit Information

Communications

Please don't discuss problem sets which are still open, as they are worth marks. I will open discussion forums for problem sets after they close.

- Unit administration and general information discussion
- Lecture and unit content discussion
- Exam revision discussion

BIOL3120 –Human Genetics & Evolutionary Medicine

What to expect?

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Assessments

	Type of Assessment	Value	Due	Learning Outcome
AT1	Problem Sets and Practical Classes	25%	Internal Students Problem Set 1 (Week 3, Sunday 13th March) Problem Set 2 (Week 4, Sunday 20th March) Problem Set 3 (Week 5, Sunday 27th March) Problem Set 4 (Week 6, Sunday 3rd April) Problem Set 5 (Week 7, Sunday 10th April)	Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources Interpret and demonstrate understanding of the primary scientific literature Explain the principles of evolutionary biology and their role in human health and disease Learn basic bioinformatic skills, including handling of genetic sequence data

BIOL3120 –Human Genetics & Evolutionary Medicine

Assessments

	Type of Assessment	Value	Due	Learning Outcome
AT2	Literature Review	25%	Week 13 (11:59 pm, Friday 3rd June)	Interpret and demonstrate understanding of the primary scientific literature Explain the importance of new techniques in human genetics for understanding human disease
AT3	Final Exam	50%	Exam Period	Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources Interpret and demonstrate understanding of the primary scientific literature Explain the importance of new techniques in human genetics for understanding human disease Explain the principles of evolutionary biology and their role in human health and disease Learn basic bioinformatic skills, including handling of genetic sequence data

What’s next?

BIOL3120 –Human Genetics & Evolutionary Medicine

What's next?

Week	Lectures	Practical Class	Assessments	Unit Learning Outcome
1	Introductory Lecture and Overview Intro to Evolutionary Medicine	No Practical Classes in Week 1		Explain the principles of evolutionary biology and their role in human health and disease
2	Oliver's Research Problem solving in genetics	No Practical Classes in Week 2		Interpret and demonstrate understanding of the primary scientific literature
3	The Human Genome Modes of Inheritance and Population Genetics	Problem Set 1	Problem Set 1 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources
4	Heritability and Polygenics Chromosomal Mutations	Problem Set 2	Problem Set 2 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources

Flipped Classroom

BIOL3120 –Human Genetics & Evolutionary Medicine

A week in the life of a BIOL3120 student

Week 1 content

Welcome to Week 1 of Human Genetics and Evolutionary Medicine. This week we're going to start slowly by introducing the unit and the concept of evolutionary medicine. Whilst we don't have practical classes this week, we've included a module on genetics that you may wish to review to check your background knowledge. Please don't hesitate to get in touch if you have some questions for us, either via the forums for general knowledge or via email for private matters.

Lecture Material

- Lecture 01 -Introductory Lecture and Overview Recording -being updated
- Lecture 01 -Introduction and Overview Slides -being updated 3.6MB PDF document
- Lecture 02 -Introduction to Evolutionary Medicine Recording
- Lecture 02 -Intro to Evolutionary Medicine Slides 13.4MB PDF document

Practical Class Preparation and Resources

Whilst we don't have practical classes this week. You may wish to review this genetics module to check your background knowledge.

- Assumed Genetics Knowledge -being updated

Your Feedback is Important to Us

Hidden from students

- Unit Difficulty

BIOL3120 –Human Genetics & Evolutionary Medicine

A week in the life of a BIOL3120 student

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Introduction to Evolutionary Medicine

BIOL3120 – LECTURE 2

What is evolutionary medicine?

- Uses evolutionary biology to understand, prevent, and treat disease
- Evo Med, uses the knowledge that we and our pathogens are the product of evolution, to understand how we were put together, how we work, and how disease manifests

Book recommendation

- Accessible book that looks at human evolution and how it impacts on human health

- Great read if you have some down time through the semester

Evo Med – ted talk

Ultimate vs. proximate understanding of disease

Some evolutionary principles

- Natural selection acts slowly
- There are limitations to what evolution can produce
- We are optimized for reproductive success, not health

Constant arms race with pathogens

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Evolution, Medicine, and Public Health [2018] pp. 13–23
doi:10.1093/emph/eox025

ORIGINAL RESEARCH ARTICLE

EVOLUTION, MEDICINE, & PUBLIC HEALTH

Core principles of evolutionary medicine

A Delphi study

Daniel Z. Grunspan,[1,2] Randolph M. Nesse,[1,2] M. Elizabeth Barnes[2] and Sara E. Brownell*[1,2]

Topic	Core principle
Types of explanation (question framing)	Both proximate (mechanistic) and ultimate (evolutionary) explanations are needed to provide a full biological understanding of traits, including those that increase vulnerability to disease.
Evolutionary processes (evolution I)	All evolutionary processes, including natural selection, genetic drift, mutation, migration and non-random mating, are important for understanding traits and disease.
Reproductive success (evolution I)	Natural selection maximizes reproductive success, sometimes at the expense of health and longevity.
Sexual selection (evolution I)	Sexual selection shapes traits that result in different health risks between sexes.
Constraints (evolution I)	Several constraints inhibit the capacity of natural selection to shape traits that are hypothetically optimal for health.
Trade-offs (evolutionary trade-offs)	Evolutionary changes in one trait that improve fitness can be linked to changes in other traits that decrease fitness.
LHT (evolutionary trade-offs)	Life history traits, such as age at first reproduction, reproductive lifespan and rate of senescence, are shaped by evolution, and have implications for health and disease.
Levels of selection (evolution II)	Vulnerabilities to disease can result when selection has opposing effects at different levels (e.g. genetic elements, cells, organisms, kin and other levels).
Phylogeny (evolution II)	Tracing phylogenetic relationships for species, populations, traits or pathogens can provide insights into health and disease.
Coevolution (evolution II)	Coevolution among species can influence health and disease (e.g. evolutionary arms races and mutualistic relationships such as those seen in the microbiome).
Plasticity (evolution II)	Environmental factors can shift developmental trajectories in ways that influence health and the plasticity of these trajectories can be the product of evolved adaptive mechanisms.
Defenses (reasons for vulnerability)	Many signs and symptoms of disease (e.g. fever) are useful defenses, which can be pathological if dysregulated.
Mismatch (reasons for vulnerability)	Disease risks can be altered for organisms living in environments that differ from those in which their ancestors evolved.
Cultural practices (culture)	Cultural practices can influence the evolution of humans and other species (including pathogens), in ways that can affect health and disease (e.g. anti-biotic use, birth practices, diet, etc.).

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Core principles of evolutionary medicine

- Evolutionary understanding is required to fully understand traits including disease susceptibility
- Evolutionary processes shape traits and disease
- Natural selection maximises for reproductive success not health
- Evolution has trade offs
- Many signs and symptoms of disease are useful defenses (e.g. fever)

Darren Naish

Evolutionary understanding is required to fully understand traits including disease susceptibility

- Our bodies are the product of evolution, so to truly understand health, we must know how we were put together

- Ultimate vs. proximate

- Type II Diabetes
  - **Proximate cause**: fat and muscle become insulin resistant and pancreas can't produce enough insulin
  - **Ultimate cause**: changes in diet and exercise regime after agriculture and industrialisation of society

Evolutionary processes shape traits and disease

Natural selection maximises for reproductive success not health

- No where is this more evident than in the brown antechinus

- Males live for just 1 year
- They can re-produce in a short 2 week breeding season each year
- During the breeding season males spend all their time fighting to gain access to females
- This produces so much stress hormones that their body gives up the ability to fight disease and otherwise function
- At the end of the breeding all males in the population die

Evolution has trade offs

- Fitness advantages often come at a cost in other areas of our physiology

- Loss of melanin leads to greater vitamin D synthesis in cooler climates, but leads to increased susceptibility to skin cancer

Many signs and symptoms of disease are useful defenses (e.g. fever)

- Tissue damage and infection results in pro-inflammatory signals
- Inflammation recruits the immune system, leads to swelling, and fever
- Inflammation is painful and uncomfortable
- Managing inflammation is often done to decrease discomfort
- Inflammation is a necessary part of immune system to promote healing and eliminate pathogens

Tools of evolutionary biology

Population genetics

Phylogenetics & ancestral state reconstruction

Evo-Devo
Evolutionary developmental biology

Applications of evolutionary tools

Phylogenetics

- Identify evolutionary relationship of species
- Identify the timeline of evolutionary processes
- Required to evaluate animal models
- Identify the evolutionary relationship of pathogens

Applications of evolutionary tools

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Population genetics

- Field of genetics that identifies frequency of genes within and between populations
- Required to identify genes associated with disease phenotypes
- Identify difference in disease susceptibility between populations

Applications of evolutionary tools

Evo devo

- Compares developmental process between organisms, to identify how development has shaped our evolutionary history
- Vulnerabilities of development
- Understand vestigial structures
- Understand quirks of human anatomy

SARS-CoV-2

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Phylogenetics

Population genetics

Evo-Devo

Complexities of implantation:
a case for evolutionary medicine

Oliver Griffith

@oligriffith

Implantation failure

- 75% of pregnancies are lost at implantation
- If implantation is imperfect, this can lead to complications further in pregnancy
- While gains in IVF success rates have been made, these are predominantly in increasing embryonic growth, and screening embryo developmental success

Implantation in infertile couples

About 60% of Embryos Fail to Implant in Young Women

Source: www.sart.org (US National IVF Registry)

We need a better understanding of the endometrial changes that support implantation so we can better characterize, diagnose, and treat implantation disorders in women.

Biology is complex

Biology is complex

Biology is complex

Evolutionary comparisons allow us to understand how things were put together

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- We can identify changes associated with the evolution of a trait
  - Identify candidates genes that underpin the process

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- We can identify conserved components of a process
  - Most critical components for the physiological outcome

Evolutionary comparisons allow us to understand how things were put together

- We can identify changes associated with the evolution of a trait
  - Identify candidates genes that underpin the process
- We can identify conserved components of a process
  - Most critical components for the physiological outcome
- We can identify how different animals do things differently
  - Alternative strategies for treatment

Pregnancy and the immune system

The immune system has been widely thought of as being dangerous for pregnancy, because it may ‘reject’ the fetus as foreign tissue for containing, foreign, paternal genetic material.

Controlling the immune system during implantation

About Fertility | Fertility Treatment | Success Rates | Specialists & Clinics | About Us | Fees | Resources

Home > Fertility Treatment > Fertility Treatments

- Getting Started
- Fertility Treatments
  - Ovulation Cycle Tracking
  - Ovulation Induction (OI)
  - Artificial Insemination/IUI
  - IVF Treatment
  - ICSI Treatment
  - IMSI Procedure
  - Frozen Embryo Transfer

Natural Killer Cell Testing

Immune cells in the uterus are important in the early detection and elimination of foreign cells, such as infections or cancer. These immune cells are normally present in every person as part of their immune system.

'Natural Killer cells' (NK Cells) play an important role in the immune system responses to viral infections as well during implantation. Some women who have fertility problems, and specifically **recurrent miscarriage** or failed IVF, are more likely to have higher levels of activity of these NK cells than other women. What this means for treatment is still not clear, but a number of different treatments are being trialled.

- WHAT IS NATURAL KILLER CELL TESTING?
- HOW DO I GET THE NATURAL KILLER CELL TEST?
- MORE ABOUT NATURAL KILLER CELLS

The inflammation paradox

The inflammation paradox

The inflammation paradox

The inflammation paradox

The inflammation paradox

The inflammation paradox

Why is inflammation used to regulate normal physiological processes when it is also the biggest threats to pregnancy during most of development?

Talk outline

- An evolutionary model of inflammation in pregnancy

Talk outline

- An evolutionary model of inflammation in pregnancy

- Hypothesise about the role of inflammation in maternal recognition of pregnancy?

Talk outline

- An evolutionary model of inflammation in pregnancy
- Hypothesise about the role of inflammation in maternal recognition of pregnancy?
- Interrogating the model, how can we learn more about our own pregnancy?

The first mammals laid eggs

- Major transition in therian mammals was the shift from egg laying to producing live young

Phylogeny of mammals

Phylogeny of mammals

Eutherians

Marsupials

Monotremes

Phylogeny of mammals

Eutherians

Marsupials

Monotremes

Phylogeny of mammals

Eutherians

Marsupials

Monotremes

Marsupials share features with both monotreme and eutherian reproduction

- Monotreme like:
  - Embryonic development is short
  - Very precocious young
- Eutherian like:
  - Viviparous
  - Formation of a placenta

Embryonic development of marsupials

Sellwood & Wooley Reproduction 1991

Eggshell is lost on day 12 of a 14 day pregnancy

Day 11.5

Eggshell is lost on day 12 of a 14 day pregnancy

Day 11.5

Day 12.5

Eggshell is lost on day 12 of a 14 day pregnancy

Day 11.5

Day 12.5

Day 13.5

Late gestation is morphologically similar to implantation in eutherian mammals

Hildenbrand et al. (2006) *Fertil. Sterility*

What is implantation?

- Apposition
- Attachment
- Invasion

Is term pregnancy in marsupials similar to implantation at the molecular level?

Grey short tailed opossum

- Found in south America
- Typical marsupial mode of pregnancy

Is term pregnancy in opossum similar to implantation at the molecular level?

- Inflammation
- Transcriptome wide similarities

Central Dogma of Biology
'Omics
DNA
Genomics
Transcription
RNA
Transcriptomics
Translation
Protein
Proteomics

Transcriptomics of the endometrium through the reproductive cycle

Not pregnant

Pre-attachment

Post-attachment

n = 3

Griffith et al. (2017) *PNAS*

Non-pregnant vs pre-attachment

Griffith et al. (2017) *PNAS*

Non-pregnant Vs pre-attachment

- 1358 Upregulated genes
- Gene ontology:
  - Transport
  - Biosynthesis
  - Metabolism
- NO immune related terms
  - - inflamation
  - - immune
  - - cytokine

Griffith et al. (2017) *PNAS*

Pre-attachment vs post-attachment

Griffith et al. (2017) *PNAS*

Pre-attachment Vs post-attachment

- 2056 genes higher in late gestation

- Gene ontology:
  - Transport
  - Biosynthesis
  - Metabolism

- Immune related terms (11 GO terms)
  - Immune system process (~250 genes)
  - Acute immune response
  - Inflammatory response

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Griffith et al. (2017) *PNAS*

Up-regulation of cytokines

- Pro-inflammatory cytokines
  - IL17A
  - IL1A
  - IL19
  - TNF
- Anti-inflammatory cytokine
  - IL10

How does the expression of inflammatory markers temporally correlate with the attachment reaction?

Griffith et al. (2017) *PNAS*

How does the expression of inflammatory markers temporally correlate with the attachment reaction?

Griffith et al. (2017) *PNAS*

COX2
Opossum
not pregnant

COX2 Opossum post-attachment

Shell coat is eroded by the embryo

Day 11.5

Embryo produces proteases that degrade shell and then potentially irritate the uterine lining

Day 14.5

DAPI
PRSS8

Inflammation is an important component of implantation in eutherians

Inflammation is an important component of implantation in eutherians

In opossums inflammation is spatially and temporally correlated with the attachment reaction but precedes birth

Transcriptome wide similarity with human implantation

Transcriptome wide similarity with human implantation

Look at uterine biopsies either within or outside implantation window

Transcriptome wide similarity with human implantation

Comparison with uterine biopsies either within or outside implantation window

Transcriptome wide similarity with human implantation

Comparison with uterine biopsies either within or outside implantation window

Transcriptome wide similarity with eutherian implantation

Rabbit vs. opossum comparison

Song et al. (2002) *Development*

Inflammation paradox

Inflammation paradox

Hypothesis:
Inflammation was an early mechanism for recognising pregnancy

1) Inflammation is a direct consequence of exposure of the uterine epithelium to the yolk-sac membrane following breakdown of the eggshell barrier

Hypothesis:
Inflammation was an early mechanism for recognising pregnancy

1) Inflammation is a direct consequence of exposure of the uterine epithelium to the yolk-sac membrane following breakdown of the eggshell barrier

2) Inflammation results in endometrial changes that are advantageous to the developing fetus
   - angiogenesis
   - vascular leakage
   - oedema

Hypothesis:
Inflammation was an early mechanism for recognising pregnancy

1) Inflammation is a direct consequence of exposure of the uterine epithelium to the yolk-sac membrane following breakdown of the eggshell barrier

2) Inflammation results in endometrial changes that are advantageous to the developing fetus
   - angiogenesis
   - vascular leakage
   - oedema

3) Inflammatory signalling may have further supported the parturition reaction which occurs shortly after the recognition of pregnancy in the opossum and likely the common ancestor of today's therian mammals

Inflammation as an early form of maternal fetal signalling in mammals

Inflammation as an early form of maternal fetal signalling in mammals

Inflammation as an early form of maternal fetal signalling in mammals

Inflammation as an early form of maternal fetal signalling in mammals

Are eutherians the only mammals with an extended period of placentation?

Are eutherians the only mammals with an extended period of placentation?

How do wallabies contribute to understanding implantation?

Molecular changes through pregnancy in the wallaby

Pattern of inflammatory gene expression

Pattern of inflammatory gene expression

Pattern of inflammatory gene expression

Wallaby pregnancy uses inflammatory signalling in a dynamic way through placentation

Consistent with a derived state of maternal-fetal interaction

Hopefully I have convinced you

- Inflammation at implantation is a modified maternal response to the presence of the embryo
- The extension of pregnancy has involved the modification of this inflammatory pathway perhaps to support derived aspects of pregnancy
- We can use this evolutionary framework to identify key aspects of implantation biology

Why is an evolutionary perspective important?

- Narratives drive research agendas
- This explanation re-frames our understanding of inflamation
  - Shifting from “dangerous due to paternal genetic material” to a normal outcome of maternal-fetal interaction

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Lecture 4:

Modes of Inheritance and Population genetics

Some terms/ideas to recall

- **Gene** = many different meanings depending on context.
  - In genetics we might talk about the gene for a specific trait. i.e. The gene associated with red hair.
  - In genomics we talk about genes as being a part of the genome associated with a specific transcribed unit of genetic information
  - In evolutionary biology we talk about genes as a unit of inheritance

- **Locus** = specific, fixed position on a chromosome where a particular gene or genetic marker is located

- **Allele** = a variant of a particular gene locus

Some terms/ideas to recall

- **Dominant** = Having one copy of particular allele will show this condition/trait

- **Recessive** = Need two copies of recessive alleles for condition/trait to show

- **Genotype** = the alleles (versions of gene) you have at a particular gene or locus (genetic location)
  - Often shown with upper and lower case letters
  - A = dominant allele
  - a = recessive allele
  - Humans have two copies of most genes: AA or Aa or aa

- **Homozygote** = having two copies of the same allele at a particular gene/locus
- **Heterozygote** = having two different alleles at a particular gene/locus
  - AA is homozygous dominant genotype
  - aa is homozygous recessive genotype
  - Aa is heterozygote genotype
  - Homo = same, hetero = different, zygote = things coming together

More terms/ideas to recall

Autosomal = on a ‘normal’ chromosome (chromosomes 1-22)

- ie not X or Y chromosomes which determine your sex
- Generally affects males/females equally

Sex-linked = on the X or Y chromosome

- Will affect males/females differently
- Female karyotype = 22*2 + XX
- Male karyotype = 22*2 + XY

Inheritance in humans

1. Autosomal dominant inheritance
2. Autosomal recessive inheritance
3. X-linked recessive inheritance
4. X-linked dominant inheritance
5. Y-linked inheritance
6. Mitochondrial inheritance

Human pedigree key

Autosomal dominant inheritance

- One faulty copy of gene causes the condition/trait
- 50% chance of passing on to each child

- An affected person has at least one affected parent
- Approximately half the offspring of an affected parent will be affected
- Affects both genders evenly

Autosomal dominant inheritance

- If this woman has children with an unaffected man, what are the chances of their first child being affected?

- Her genotype Aa, therefore 50% chance child would be affected

Autosomal dominant inheritance

Exceptions to autosomal dominant pattern of inheritance:

Incomplete penetrance

- When person carries mutant gene but does not show signs of disease
- Example: mutations in BRCA1 gene → 80% risk of breast cancer
- Pedigrees show skipping generations

Variable Expression

- Severity and manifestations of phenotype vary between individuals
- Example: mutation in FBN1 gene → Marfan syndrome is highly variable (disorder of connective tissue)

Other situations that might not look dominant

- De novo (new) mutation: sporadic cases without affected parents
- Delayed onset: appears to skip a generation, consider an early death

Autosomal recessive inheritance

Who else's genotype can we figure out?

- Two copies of gene required for the condition/trait (homozygous recessive)

- Can skip generations
- Two unaffected parents can have an affected child (indicates parents are carriers)
- Affects genders equally

Autosomal recessive inheritance

- If this person has a child with a carrier woman, what are the chances their child would be affected?

- If both parents carriers
  - ¼ of offspring affected aa
  - 2/4 of offspring carriers Aa
  - ¼ of offspring normal AA

	A	a
A	AA	Aa
a	Aa	aa

Allelic heterogeneity =
Usually many mutations in a gene which can cause a condition

Cystic fibrosis = autosomal recessive genetic disorder

- Caused by mutations in CFTR gene (cystic fibrosis transmembrane conductance regulator)

- over 2,000 mutations in the CTFR gene associated with cystic fibrosis disease
- varying degrees of frequency within the disease carrying population
- different mutations produce varying degrees of disease phenotypes
- can also work in combinations to produce additive phenotypic effects.

Molecular defect	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Functional abnormality	Protein is not synthesized	Folding defect	Channel opening defect	Ion transport defect	Decreased protein synthesis	Decreased half-life of the protein
Main mutations	Gly542X Trp128X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Compound heterozygote

- The presence of two different mutant alleles at a particular gene locus

- Both are ‘recessive’

Quick revision of sex determination

- Mothers always pass on one of their two X chromosomes

- Fathers pass on:
  - Y to sons
  - X to daughters

X-linked recessive inheritance

- Males hemizygous (only one copy) = affected or not, can't be carriers
  - Males more often affected by X-linked conditions
  - Males get their X from mother, so affected males have carrier mothers

- Females can be carriers, affected females much lower frequency since two copies of X

- Carrier mothers pass on either healthy X or mutant X
  - 50% of sons of carrier mothers will be affected
  - 50% of daughters of carriers mothers will be carriers

- Affected fathers pass on either X or Y
  - Y = boy – affected males can't pass condition onto a son
  - X = girl – all daughters of affected males will be carriers

X-linked recessive inheritance

End result of all this:

- Only / mostly males affected
- Can skip generations

X-linked recessive inheritance

- Sometimes dots or circles used to indicate carrier women in X-linked
- But don’t assume you will get this information

X-linked dominant inheritance

- No male-to-male inheritance since Y being passed on

- Affected males transmit to 100% of daughters but 0% of sons
- Affected females transmit to 50% of their offspring, regardless of sex
  - ratio = 2 affected females : 1 affected male

Y-linked inheritance

- All sons of an affected father are affected
- Very rare for expressed traits
- Only males can be affected
- Dominance is irrelevant

- Far fewer Y-linked genetic disorders compared to X-linked
- Y chromosome smaller and fewer genes compared to X
- The SRY (sex determining region of the Y-chromosome) develops the testes and can be associated with Y-linked disorders

Mitochondrial inheritance

- Mitochondrial genome (16,569 base pairs) encodes genes of mitochondrial oxidative phosphorylation pathway and mitochondrial tRNAs
- Mutations can cause structurally and functionally abnormal mitochrondria
- Usually maternally inherited (mitochondria in egg cell, not sperm cells)
- Rare evidence of father passing on mitochondrial disease

- Theoretically: every child of affected mother is affected

Reality: Mitochondrial heteroplasmy

- Heteroplasmy = having a mix of mitochondrial genomes within cells/organism

- Heteroplasmy levels vary for each child of affected mum

MELAS: Mitochondrial Encephalopathy, Lactic acidosis and Stroke-like episodes

- m.3243A>G in majority of affected people

- Can be a ‘threshold level’ before disease onset
- Severity and age of onset often vary with heteroplasmy level

Mitochondrial Replacement Therapy

This is a simplified diagram outlining two methods for mitochondrial donation – maternal spindle transfer (prior to fertilisation) and pronuclear transfer (after fertilisation).

- Nuclear DNA removed from a fertilised egg of affected mother
- Transplanted into the fertilised egg of a female donor whose nuclear material has been removed
- Legal in UK from 2018, legal in Australia soon?

Multiple modes of inheritance for same disease:

Kallman syndrome / normosmic isolated gonadotrophin-releasing hormone deficiency

	Gene [1, 2]	% of IGD Attributed to Pathogenic Variants in This Gene [3]
X-R	*ANOS1* (*KAL1*)	5%-10% (KS)
AD	*CHD7*	5%-10% (KS or nIGD)
AD	*FGFR1*	~10% (KS or nIGD)
AD or AR	*GNRHR*	5%-10% (nIGD)
AR	*IL17RD*	2%-5% (KS or nIGD)
AR	*PROKR2*	~5% (KS or nIGD)
AD	*SOX10*	2%-5% (KS)
AR	*TACR3*	~5% (nIGD)

Pedigrees help on a family by family basis, not necessarily a disease by disease basis

General pedigree tips

- If you know the mode of inheritance, you know the genotype of anyone who is affected
  - You might be able to infer the genotypes of an affected person‘s parents

- You may be able to rule out a particular mode of inheritence
  - Father passing onto son = can‘t be X-linked (though mum may be a carrier)
  - Two affected people having an unaffected child = can‘t be recessive
  - Try to genotype everyone assuming a particular mode of inheritence – it just won‘t work for some modes

Population genetics: Hardy Weinberg equilibrium

$$p + q = 1$$

Allele	A	a
Frequency	p	q

$$p^2 + 2pq + q^2 = 1$$

Genotype	AA	Aa	aa
Frequency	p^2	2pq	q^2

Assumptions of Hardy-Weinberg equilibrium

1. Large population (avoids random chance having a big impact on allele frequencies).
2. No selection (ie no allele is necessarily more likely to get passed on than another)
3. Mating is random (ie any individual has an equal chance of mating with any other individual).
4. Mutation either does not occur or is in equilibrium.
5. Immigration and emigration do not occur.

The consequences of abiding by the Hardy-Weinberg Law are that allele frequencies remain constant from generation to generation, so we can calculate allele/genotype frequencies

Do these assumptions fit for humans?

Hardy Weinberg equilibrium

$$p + q = 1$$

Allele	A	a
Frequency	p	q

$$p^2 + 2pq + q^2 = 1$$

Genotype	AA	Aa	aa
Frequency	p^2	2pq	q^2

In Caucasian populations, approximately 1 in 2,500 people are affected with cystic fibrosis

Theoretically, what is the carrier rate in this population?

$q^2 = 1/2500$
q = square root 1/2500 = 0.02
p = 1– q = 0.98

Carrier rate = 2pq = 2 * .02 *.98 = .0392

One more…

d	0.05	0.01	0.001
1	3.841	6.635	10.828
2	5.991	9.210	13.816
3	7.815	11.345	16.266
4	9.488	13.277	18.467
5	11.070	15.086	20.515
6	12.592	16.812	22.458
7	14.067	18.475	24.322
8	15.507	20.090	26.125
9	16.919	21.666	27.877

Consider two alleles A and a for sickle cell disease

	AA	Aa	aa
Observed:	25,374	5,482	67

Allele frequencies p = 0.91 and q = 0.09

Expected:	25,562	5,106	255

Chi-squared = 167.7, p-value < 0.001 (very significantly different)
Excess of heterozygotes, deficiency of homozygotes

Why might this population be so different from HWE?

Positive selection in humans

AA – no sickle cell, but relatively susceptible to malaria
Aa – sickle cell carrier, not clinically important
aa – die early because of sickle cell anaemia

in equatorial Africa, up to 40% of people are carriers of this mutated gene

Read a recent paper to find out more:
http://science.sciencemag.org/content/334/6060/1283.full

MACQUARIE University

The Human Genome

BIOL3120 Human Genetics and Evolutionary Medicine

The Human Genome

LEARNING OBJECTIVES

At the end of this lecture you should be able to:

- Define the terms used to describe the human genome
- Understand the structure of chromosomes
- Understand the coding regions of the human genome

The human genome

- First draft sequence February 2001
- Complete draft 2003
- Cost ~ 2.7 billion USD

Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017

The human genome

- First draft sequence February 2001
- Complete draft 2003
- Cost ~ 2.7 billion USD

- Sequence determined but little understanding of its meaning

Quick overview

- 3.2 billion basepairs x 2
- Over 23 chromosome pairs
- ~20,000 protein-coding genes

Junk DNA?

- Historically, non-coding DNA referred to as junk DNA

- ENCODE project (2012):
  - “The vast majority (80.4%) of the human genome participates in at least one biochemical RNA- and/or chromatin-associated event in at least one cell type”
  - (think about gene definition)

  - https://www.nature.com/articles/nature11247

National Human Genome Research Institute

ENCODE

Example genome sizes

Terms used to describe the human genome

Chromosomes

Chromosome related nomenclature

- Chromatin: the material of which chromosomes are made.
  - complex of DNA, and proteins (histones and non-histones)
- Chromatid: one of the two copies of a chromosome
  - joined at the centromere
  - two homologous chromatids are called sister chromatids.
- Centromere is DNA normally in a heterochromatin state
  - Site of spindle attachment to chromosomes (important in meiosis)

Chromosome parts

- Heterochromatin:
  - More condensed
  - Silenced genes (methylated)
  - Gene poor (high AT content)
  - Stains darker
- Euchromatin:
  - Less condensed
  - Gene expressing
  - Gene rich (higher GC content)
  - Stains lighter

DNA & Gene parts

- Enhancers: genomic DNA (gDNA) which can alter the expression of a gene
- Promoters: gDNA region where transcription factors bind to initiate transcription of a gene
- Exons: gDNA that is the coding regions of a gene
- Introns: a portion of a gene that does not code for an amino acid
- Gene: a sequence of nucleotides in DNA that codes for a molecule that has a function

The Structure of Chromosomes

Chromosome numbering

- 1-22 Arranged in order of decreasing size
- q = long arm; p = short arm

G-banding example: Chromosome 4

- Giemsa stain
  - darker on heterochromatin (AT rich) regions, less accessible
  - Lighter on euchromatin (GC rich) regions, more accessible and active
  - 92% of genes in euchromatin in humans

Chromosome numbering

- 1-22 Arranged in order of decreasing size
- q = long arm; p = short arm
- Black and white stripes are because of staining: G-banding
- ‘Bands’ have the same appearance on homologous chromosomes so identification became easier
- Banding allows:
  - Unequivocal identification of each human chromosome
  - Detection of rearrangements (e.g. translocations)

Chromosomes

Telomeres

- protect functional regions (containing genes) by capping the ends with a ‘buffer’ sequence
- Telomeres consist of variable numbers of a repetitive sequence (TTAGGG)
- Telomere length is reduced every time a cell divides
- average telomere length declines from ~ 11 kilobases at birth to less than 4 kilobases in old age, decline greater in men
- Marker of cell age – signal for apoptosis (cell self-destruction)
- **“telomeric** DNA is **lost** at an **average rate** of '25.7–27.7 base pairs' per year

Telomeres

- Various premature ageing disease characterised by critically short telomeres
- Cancer cells often do not show telomere length shortening - telomerase protein not normally active has become active in many cancer cell types
- Telomerase and telomere-binding proteins are potential targets for anti-cancer and anti-ageing therapies

Pseudoautosomal regions on X & Y chromosomes

- Homologous regions at ends of X and Y chromosomes
  - Allows pairing during meiosis
  - Regions tend not to be silenced in X-inactivation
  - Inherited in an autosomal manner
  - These regions are called PAR1 and PAR2

Number of genes on each chromosome

Chromosome	Length (mm)	Base pairs	Variations	Protein-coding genes	Pseudo-genes	Total long ncRNA	Total small ncRNA	miRNA	rRNA	snRNA	snoRNA	Misc ncRNA	Links	Centromere position (Mbp)	Cumulative (%)
1	85	248,956,422	12,151,146	2058	1220	1200	496	134	66	221	145	192	EBI	125	7.9
2	83	242,193,529	12,945,965	1309	1023	1037	375	115	40	161	117	176	EBI	93.3	16.2
3	67	198,295,559	10,638,715	1078	763	711	298	99	29	138	87	134	EBI	91	23
4	65	190,214,555	10,165,685	752	727	657	228	92	24	120	56	104	EBI	50.4	29.6
5	62	181,538,259	9,519,995	876	721	844	235	83	25	106	61	119	EBI	48.4	35.8
6	58	170,805,979	9,130,476	1048	801	639	234	81	26	111	73	105	EBI	61	41.6
7	54	159,345,973	8,613,298	989	885	605	208	90	24	90	76	143	EBI	59.9	47.1
8	50	145,138,636	8,221,520	677	613	735	214	80	28	86	52	82	EBI	45.6	52
9	48	138,394,717	6,590,811	786	661	491	190	69	19	66	51	96	EBI	49	56.3
10	46	133,797,422	7,223,944	733	568	579	204	64	32	87	56	89	EBI	40.2	60.9
11	46	135,086,622	7,535,370	1298	821	710	233	63	24	74	76	97	EBI	53.7	65.4
12	45	133,275,309	7,228,129	1034	617	848	227	72	27	106	62	115	EBI	35.8	70
13	39	114,364,328	5,082,574	327	372	397	104	42	16	45	34	75	EBI	17.9	73.4
14	36	107,043,718	4,865,950	830	523	533	239	92	10	65	97	79	EBI	17.6	76.4
15	35	101,991,189	4,515,076	613	510	639	250	78	13	63	136	93	EBI	19	79.3
16	31	90,338,345	5,101,702	873	465	799	187	52	32	53	58	51	EBI	36.6	82
17	28	83,257,441	4,614,972	1197	531	834	235	61	15	80	71	99	EBI	24	84.8
18	27	80,373,285	4,035,966	270	247	453	109	32	13	51	36	41	EBI	17.2	87.4
19	20	58,617,616	3,858,269	1472	512	628	179	110	13	29	31	61	EBI	26.5	89.3
20	21	64,444,167	3,439,621	544	249	384	131	57	15	46	37	68	EBI	27.5	91.4
21	16	46,709,983	2,049,697	234	185	305	71	16	5	21	19	24	EBI	13.2	92.6
22	17	50,818,468	2,135,311	488	324	357	78	31	5	23	23	62	EBI	14.7	93.8
X	53	156,040,895	5,753,881	842	874	271	258	128	22	85	64	100	EBI	60.6	99.1
Y	20	57,227,415	211,643	71	388	71	30	15	7	17	3	8	EBI	12.5	100
mtDNA	0.0054	16,569	929	13	0	0	24	0	2	0	0	0	EBI	N/A	100
total		3,088,286,401	155,630,645	20412	14600	14727	5037	1756	532	1944	1521	2213			

https://en.wikipedia.org/wiki/Human_genome

Chromosome size vs number of genes

Gene size in humans

- Titin gene (TTN)
  - 365,719bp total gene size (including introns)
  - Exons: 80,781bp across 365 exons

- DMD gene (Duchenne muscular dystrophy)
  - 2,220,390 bp including introns
  - ~14kb mRNA

- Average gene size ~8kb

Coding Regions Human Genome

Human genome summary

- 3.2 billion base pairs x 2 across 23 chromosome pairs
- ~20,000 protein coding genes, but other functional molecules
- Only 1-2% codes for protein, but up to 80% of genome regulatory function

How many genes?

What is a gene?

- Classically, region of DNA which codes for a protein
- Nowadays:
  - a sequence of nucleotides in DNA that codes for a molecule that has a function
  - This might code for a protein, or just be transcribed into RNA e.g. t-RNAs, non-coding RNAs

What is a gene?

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Exons and introns

- Exon: part of a gene that will encode a part of the final mature RNA
- Intron: any nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product
- 1.1% of the genome is spanned by exons, whereas 24% is in introns, with 75% of the genome being intergenic DNA

Multiple transcripts / alternate splicing

- Exons can be alternatively arranged to create different proteins from the same gene

- Different types of cells often use different transcripts more/less frequently

The Human Genome

LEARNING OBJECTIVES

At the end of this lecture you should be able to:

- Define the terms used to describe the human genome
- Understand the structure of chromosomes
- Understand the coding regions of the human genome

MACQUARIE University
SYDNEY·AUSTRALIA

Solving genetic problems

BIOL3120 – LECTURE 6

Where to find the problem sets?

iLearn!

In the assessments tab

AT1

PROBLEM SET ASSESSMENT

1. What is the *most likely* mode of inheritance for the condition shown in the above pedigree? Why?

a) Autosomal dominant
b) Autosomal recessive
c) X-linked dominant
d) X-linked recessive

Special considerations

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Student wellbeing / special considera...

If you experience events or conditions that adversely affect your academic performance, please visit the special consideration page.

Visit the the Student Support webpage to see a range of services available to students at Macquarie University.

If you feel you are struggling with studies or have had disruptions in your personal life, you can speak to a trained professional at Campus Wellbeing.

Your job as geneticists is to work out which tools you can use

You already know all the tools to solve genetic problems

- Using family trees to infer inheritance patterns
- Hardy-Weinberg equilibrium
- Punnett squares to find expected phenotypes
- Simple probability

Using family trees to infer inheritance patterns

- Useful for inferring inheritance patterns
- Useful for inferring individual's genotype

Hardy-Weinberg equilibrium

Hardy-Weinberg equilibrium

- Assumptions of Hardy-Weinberg equilibrium

1. Large population (avoids random chance having a big impact on allele frequencies).
2. No selection (ie no allele is necessarily more likely to get passed on than another)
3. Mating is random (ie any individual has an equal chance of mating with any other individual).
4. Mutation either does not occur or is in equilibrium.
5. Immigration and emigration do not occur.

Punnett squares to find expected phenotypes

Punnett squares to find expected phenotypes

Homozygous
Alleles are same

Heterozygous
Alleles are different

Hemizygous
Only one allele
(e.g. XY)

Simple probability

- If you need to think about a probability problem, draw a probability tree

Solving genetic problems

LEARNING OBJECTIVES

At the end of this lecture you should be able to:

- List the tools available to solve genetic problems
- Think about which tools may be useful in certain circumstances
- Be prepared to work through genetic problems in week 3 and beyond

MACQUARIE University

BIOL3120 –Human Genetics and Evolutionary Medicine

Heritability and Polygenic Inheritance

BIOL3120 –Heritability and Polygenic Inheritance

LEARNING OBJECTIVES

On successful completion of this lecture, you will be able to:

- Discuss factors that indicate a possible genetic basis for a condition
- Define heritability & understand it's limitations
- Discuss polygenic inheritance and polygenic risk scores

Terms

- Monogenic inheritance
  - Caused by variation in a single gene
  - Striking familial inheritance patterns
  - Sickle cell anaemia, cystic fibrosis, Huntington disease, Duchenne muscular dystrophy
- Polygenic inheritance
  - Caused by the combined action of more than one gene
  - Hypertension, coronary heart disease, diabetes
- Environmental factors
  - Complex diseases occur as a result of many genomic variants, paired with environmental influences

Monogenic inheritance

Polygenic inheritance

Human height.
There is great variation in human height between different individuals.
Jane Ades/National Human Genome Research Institute.

Complex disorders

Genetic and environmental **risk factors**

CAUSES AND DISEASE MECHANISMS / MND RESEARCH

Steps to understanding MND

AUGUST 3, 2018 NICKJAMESCOLE 2 COMMENTS

THE OFFICIAL BLOG OF THE mnda motor neurone disease association

Al-Chalbi *et al* Lancet Neurol; 13: 1108–13, 2014
Chio et al Neurology :e1-e8, 2018

How to tell how 'genetic' a disease is: Relative risk ratio

$$\lambda_r = \frac{\text{Prevalence of the disease in the relatives of an affected person}}{\text{Prevalence of the disease in the general population}}$$

TABLE 8-2 Risk Ratios λ_s for Siblings of Probands with Diseases with Familial Aggregation and Complex Inheritance

Disease	Relationship	λ_s
Schizophrenia	Siblings	12
Autism	Siblings	150
Manic-depressive (bipolar) disorder	Siblings	7
Type 1 diabetes mellitus	Siblings	35
Crohn disease	Siblings	25
Multiple sclerosis	Siblings	24

Value of 1 = no more likely to develop condition if you have an affected relative

Value higher than 1 = relative of affected person more likely to develop the condition

How to tell how ‘genetic’ a disease is: Family history case-controlled studies

- Multiple sclerosis (MS) study example: 3.5% of first-degree relatives of people with MS also had MS themselves.
- Compared to 0.2% of first-degree relatives of people without MS
- 3.5 / 0.2 = 17.5
- The odds of having a first degree relative with MS were 17.5x higher amongst MS patients than controls.
- Suggests genetic factors underlying

Problem:

- People who are related tend to have environmental factors in common.

- How do we tease apart genetic vs. environmental influences?

Heritability

- Define heritability & understand it's limitations

What is Heritability?

- A measure of how well differences in people's genes account for differences in their traits
  - Popularly referred to as 'nature versus nurture' debate

- Heritability is a statistical concept that describes how much of the variation in a given trait can be attributed to genetic variation

- Used in reference to the resemblance between parents and their offspring. In this context, high heritability implies a strong resemblance between parents and offspring with regard to a specific trait, while low heritability implies a low level of resemblance.

- An estimate of the heritability of a trait is specific to one population in one environment, and it can change over time as circumstances change.

What is Heritability?

- Heritability estimates range from zero to one.

- A heritability close to one indicates that almost all of the variability in a trait comes from genetic differences, with very little contribution from environmental factors.
  - Many disorders that are caused by mutations in single genes, such as phenylketonuria (PKU), have high heritability

- A heritability close to zero indicates that almost all of the variability in a trait among people is due to environmental factors, with very little influence from genetic differences.
  - Characteristics such as religion, language spoken, and political preference have a heritability of zero because they are not under genetic control.

- Most complex traits in people, such as multifactorial diseases, have a heritability somewhere in the middle, suggesting that their variability is due to a combination of genetic and environmental factors.

Heritability limitations

- Heritability does not indicate what proportion of a trait is determined by genes and what proportion is determined by environment.
  - a heritability of 0.7 does not mean that a trait is 70% caused by genetic factors; it means than 70% of the variability in the trait in a population is due to genetic differences among people.

- Heritability does not determine which genes/loci are involved in the trait/disease.

- Estimating Trait Heritability

Heritability
Khan Academy

Polygenic Inheritance

- Discuss polygenic inheritance and polygenic risk scores

Polygenic inheritance

- Caused by the combined action of more than one gene
  - Height, skin colour
  - Hypertension, coronary heart disease, diabetes
- The inheritance of polygenic traits does not show the phenotypic ratios characteristic of Mendelian inheritance, though each of the genes contributing to the trait is inherited as described by Gregor Mendel.

Diagram based on similar diagram by W. P. Armstrong[3].

Genetic susceptibility to complex disease

- **Complex disease**: Most medical problems such as heart disease, diabetes, obesity, Alzheimer's disease, asthma, Parkinson's disease, multiple sclerosis, osteoporosis, and sporadic MND, do not have a single genetic cause—they are likely associated with the effects of **multiple genes** in combination with **lifestyle and environmental factors**. These are called complex or multifactorial disorders.

- **Susceptibility (risk) alleles**: an allele, usually inherited, that increases the likelihood of developing a complex disease. The combination of multiple susceptibility alleles and environmental factors may be additive or synergistic, leading to disease.

- On their own, they are neither necessary nor sufficient to cause disease

Polygenic Risk Score

- "a substitution of a single nucleotide that occurs at a specific position in the genome, where each variation is present to some appreciable degree within a population (e.g. > 1%)" (Wikipedia)

- 4-5 million per person ~ every 1,000bp on average

Hall A, Bandres-Ciga S, Diez-Fairen M, Quinn JP, Billingsley KJ. Genetic Risk Profiling in Parkinson's Disease and Utilizing Genetics to Gain Insight into Disease-Related Biological Pathways. *International Journal of Molecular Sciences*. 2020; 21(19):7332. https://doi.org/10.3390/ijms21197332

BIOL3120 –Heritability and Polygenic Inheritance

LEARNING OBJECTIVES

On successful completion of this lecture, you will be able to:

- Discuss factors that indicate a possible genetic basis for a condition
- Define heritability & understand it's limitations
- Discuss polygenic inheritance and polygenic risk scores

BIOL3120 –Human Genetics and Evolutionary Medicine

Chromosomal Mutations

3	The Human Genome Modes of Inheritance and Population Genetics	Problem Set 1	Problem Set 1 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources
4	Heritability and Polygenics Chromosomal Mutations	Problem Set 2	Problem Set 2 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources
5	Nucleotide Mutations Human Genetic Diversity and Evolution	Problem Set 3	Problem Set 3 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources

BIOL3120 –Chromosomal mutations

LEARNING OBJECTIVES

On successful completion of this lecture, you will be able to:

- Explain the different types of chromosomal mutations
- Use this knowledge to solve problems in human genetics relating to heritability, polygenic inheritance and chromosomal mutations

1
2
3
4
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16
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18
19
20
21
22
X
Y

Chromosomal mutations overview

- Mosaicism
- Aneuploidy / other euploidies
- Uniparental disomy
- Translocations + Robertsonian translocations
- Changes within a chromosome

Chromosomal mutations

- Mosaicism
- Aneuploidy / other euploidies
- Uniparental disomy

Mosaicism

- Mosaicism = two sets of genomes in an organism
- Somatic mosaicism refers to the occurrence of two genetically distinct populations of cells within an individual, derived from a postzygotic mutation.
- In contrast to inherited mutations, somatic mosaic mutations may affect only a portion of the body and are not transmitted to progeny.
- These mutations affect varying genomic sizes ranging from single nucleotides to entire chromosomes and have been implicated in disease, most prominently cancer.

What cell is a mutation happening in, and when?

Mosaicism = two sets of genomes in an organism

Aneuploidy

- Aneuploidy = abnormal number of chromosomes in a cell

- Aneuploidy usually caused by nondisjunction
  - Failure of homologous chromosomes to separate properly during cell division

Normal meiosis

Nondisjunction

Can occur during mitosis, but only gets passed onto offspring if occurs during meiosis

Aneuploidy usually caused by nondisjunction

- Nondisjunction in meiosis 1 = pass on two different copies of chromosome
- Nondisjunction in meiosis 2 = pass on two same copies of chromosome

Why/how does non-disjunction happen?

- Happens more frequently in oocytes (egg cells)
  - Oocytes initially form before birth (at 3-4 months)
  - Arrested in prophase 1
  - Resume rest of meiosis after puberty as eggs are released
  - Cohesin which holds chromosomes together wears down over time?
  - Fewer crossover events in oocytes?
  - Spindle/centromere breakdown?

Male sex chromosome nondisjunction

- Also occurs in males:
  - 1 in 1,000 boys are XYY = nondisjunction had to occur in sperm

Aneuploidy = abnormal number of chromosomes in a cell

- Monosomy = 1 copy of a chromosome
  - Monosomy X (XO) = Turner syndrome
  - Short stature, delayed puberty, infertility, heart defects, learning disabilities
  - 1 in 2,000-2,500 live female births

- Trisomy = 3 copies of a chromosome
  - Trisomy 21 = Down syndrome
  - Distinct facial appearance, intellectual disability, developmental delays
  - Maybe: thyroid/heart issues

- Others:
  - Trisomy X = Triple X syndrome 1 in 1,000 female births
  - XXY = Klinefelter syndrome = 1 in 500-1,000 males
  - XYY = XYY syndrome = 1 in 1,000 males
  - Trisomy 13 = Patau syndrome
  - Trisomy 18 = Edwards' Syndrome

Generally: deletion is more severe than duplication

Triploidy

- 1-2% of all conceptions
- Usually early miscarriages but can survive to birth
- Euploid = an exact multiple of the haploid number of chromosomes
  - Monoploidy
  - Diploid
  - Triploidy
  - Tetraploid
  - etc

Uniparental disomy

- When two copies of a chromosome are inherited from the same parent
- **Heterodisomy** = inherited both of one parent's chromosomes
  - Error in meiosis I
- **Isodisomy** = inherited two identical copies of a chromosome from one parent
  - Error in meiosis II

Uniparental disomy – how?

a) Errors in meiosis from both parents
(isodisomy or heterodisomy)

b) Trisomy rescue
(isodisomy or heterodisomy)

c) Duplication of single chromosome
(isodisomy only)

Abnormalities of Chromosome Structure

- Translocations + Robertsonian translocations

- Structural varients

Translocations

- Structural rearrangements of the chromosome

- Balanced
  - Normal complement of chromosomal material
- Unbalanced
  - Additional or missing material

- 1 in 375 newborns, most unaware until they try to have children

- Naming: **t(8;14)(q24;q32)** indicates a translocation between chromosomes 8 and 14
  - recombination points at 8q24 and 14q32

- Many specific translocations are seen more often, many linked with cancers

Meiosis with balanced translocations?

Fertilization with balanced translocations?

Trisomy A Monosomy B	Trisomy B Monosomy A	Normal chromosomes	Balanced (like parent)	Trisomy B Monosomy A	Trisomy A Monosomy B

Robertsonian translocations

- Chromosomes 13, 14, 15, 21, 22 have only one functioning ‘arm’
- Robertsonian translocation = two of these chromosomes joining up into one chromosome, containing the long arm of both
- Balanced
- Individuals will have 45 chromosomes

Robertsonian meiosis/fertilization

If one parent is a Robertsonian translocation carrier

Mother has 13;21, 14;21, 15;21 or 21;22	10-15% risk of a baby with translocation Down's.
Mother has 13;14, 13;15, 13;21 or 13;22	1% chance of having a baby with trisomy 13.
Mother has 14;15, 14;22 or 15;22	Almost certainly no risk of having a baby with a trisomy, but possible risk of miscarriage or UPD.
Father with any Robertsonian combination	Low risk, below 1%, of any child being affected.

Images from rarechromo.org

Notes on translocations

- A small number (~5%?) of down syndrome is caused by Robertsonian translocation.

- Some balanced translocations are causes of or associated with cancer types in **somatic** mutations (not germ line)

- Mechanism still under investigation, but happens more frequently at some known ‘breakage points’. Requires:
  - Double-stranded break
  - Non-homologous end joining

Structural variation (SV)

Jenn Fifita

What is it?

- Large genomic alterations affecting stretches of DNA >1000bp
- Affects chromosome structure
- Most prominent source of variation in the human genome
- Effects gene dosage and gene expression

How to find it?

- Traditionally detected using laborious cytogenetic techniques
  - Multiplex ligation-dependent probe amplification (MLPA) or microarrays
- Recent development of bioinformatic tools for SV detection in NGS data now make high-throughput SV analysis possible

Relevance to ALS?

- Implicated in other neurodegenerative diseases
  - *incl. Parkinson's disease, Kennedy's disease, Spinocerebellar ataxias, Duchenne muscular dystrophy*
- ALS pathogenic *C9orf72* expansion is a similar phenomenon to copy number variation and is similar in size to SVs at up to 27,000bp long

Smaller/non-specific chromosome changes

- Insertion/Inversion similar to translocation
  - Maybe problems if gene interrupted, and in meiosis

- Duplications/deletions 5Mb or larger
  - <5Mb = microdeletion / microduplication
  - Can cause copy number variant (CNV)
  - Missing a gene copy more likely to cause problems than extra gene copy

Copy number variants (CNVs)

- In healthy population (Itsara et al., 2009):
  - 5-10% of people at least one del/dup larger than 500kb
  - 1-2% of people at least one del/dup larger than 1Mb

- What makes a CNV cause problems?
  - How many genes does it include? More = more likely to cause problem
  - Does it interrupt a gene?

- Extremely variable, even within same family

- Developmental delay / intellectual disability
  - 30% of unexplained cases had pathogenic duplication or deletion (2018 study)

- Many CNVs linked with Autism Spectrum Disorders (ASD), neurocognitive problems

Summary

- Mosaicism = mutation early in embryo development – person will have mutation in a certain % of their cells
- Aneuploidy = abnormal number of one chromosome set
  - Most trisomies/monosomies aren't survivable
- Uniparental disomy = both copies of a chromosome from one parent
- Translocations + Robertsonian translocations
- Changes within a chromosome = copy number variants
  - Deletions/duplications

- Next lecture: nucleotide mutations

BIOL3120 –Chromosomal mutations

LEARNING OBJECTIVES

On successful completion of this lecture, you will be able to:

- Explain the different types of chromosomal mutations
- Use this knowledge to solve problems in human genetics relating to heritability, polygenic inheritance and chromosomal mutations