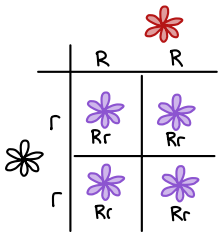
Chapter 6 ~ Alleles at a Single Locus

Introduction:



Mendelian Inheritance describes patterns that obey 2 laws:
1. Law of Segregation
2. Law of Independent Assortment

Simple mendelian inheritance involves a SINGLE gene with 2 different alleles and alleles which display a simple dominant / recessive relationship

Locus → specific section of a chromosome
- Term gene and locus often used interchangeably
  - Locus is limited to defining the position along a chromosome
- Each locus has an allelic form
  - specific DNA sequence

Genotype
- Complete set of alleles at all loci in an individual

Phenotype
- The visible / detectable effect of alleles on the structure or function of that individual
- ex:
  - Hair colour
  - Disease susceptibility
  - Behaviour

IF two alleles are present in an individual as is the case w/ diploid organisms, then various interactions b/w them MAY influence their expression in the phenotype

Somatic v.s Gremline Mutations

Haploid vs Diploid

Haploid organisms, have only 1 copy of a gene, thus a mutation will directly affect the organisms phenotype
- Phenotype can be used to directly infer the genotype of the organism

Diploid organisms have two copies of each gene. The phenotype depends upon an interaction b/w the 2 alleles
- Any mutations may not have a direct impact on the organisms phenotype
- Interaction b/w 2 alleles can show complete dominance, incomplete dominance, co-dominance or recessiveness
  - Inferring genotype based on phenotype is NOT as simple in diploids

Mutations:
- Occurs in the DNA of a single cell
- Single-cell organisms
  - That mutation is passed on directly to it's descendants, typically through the process of mitosis
- Multicellular animals
  - There is a partitioning early in development into Somatic cells which form the body cells & germline cells, which form form the gametes for the next generation
- Mutations may be passed on to somatic cells via mitosis and to gametes via meiosis.
- In plants
  - Somatic / germline seperation occurs later in the cells that form the flower

Somatic Mutations:
- Somatic cells form the tissues of the organism and are not passed on as gametes
- Any mutations in somatic cells will only affect the individual in which they occur, not its progeny
- If mutations occur in somatic cells, its mutant descendants will exist alongside other non-mutant (wild type) cells
- If the mutation occurs at every stage of development, the mutation will be present in more cells
  - This gives rise to an individual composed of two or more types of cells that differ in their genetic composition
  - Such an individual is said to be a "Mosaic"

Germline Mutations:
- Germline cells are those that form the eggs or sperm cells (ovum or pollen in plants) and are passed on to form the next generation
  - Mutations in germline cells will be passed on to the next generation but won't affect the individual in which they occur
- In animals
  - Somatic cells are segregated from germ line cells
- In plants
  - Somatic cells become germline cells; so somatic mutations can become germline mutations

Alleles: Hetero-, Homo-, Hemizygosity

Mendel's 1st Law: Segregation of Alleles
- Remarkable b/c his observation & conclusions w/o knowing about the relationship b/w genes, chromosomes and DNA

We know...
- Why more than one allele of a gene can be present in an individual
  - Most eukaryotic organisms ARE DIPLOID and have at least two sets of homologous chromosomes
  - Organisms that are predominantly diploid (Humans & peas) chromosomes exist as pairs, w/ one copy inherited from each parent
    - Diploid cell, therefore, can contain 2 different alleles of each gene, w/ one allele part of each member of a pair of homologous chromosomes
    - IF BOTH alleles of a particular gene are the same (indistinguishable), the individual is said to be HOMOZYGOUS at the gene / locus
    - If alleles are DIFFERENT (can be distinguished) from each other, the genotype is HETEROZYGOUS

In cases where there is only one copy of a gene present, for example if there is a deletion of the locus on the homologous chromosome we use the term HEMIZYGOUS

ex: Single X-chromosomes in X/Y males, where almost all the loci on that chromosome are HEMIZYGOUS

While a single diploid individual can have at MOST two different alleles of a particular gene, many more alleles CAN EXIST in a population of individuals

- In natural population the most common allelic form is usually called "Wild type"
- In many populations there can be multiple variants at the DNA sequence level that are visibly indistinguishable as ALL EXHIBIT a normal, wild type apperance
- There can also be various MUTANT alleles (in wild populations and in lab strains) that vary from wild type in their appearance, each w/ a different change at the DNA sequence alleles
- The many different mutations (alleles) at the SAME locus are called an "allelic series" for a locus

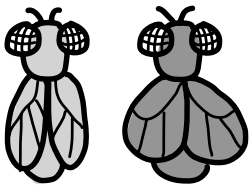
Pleiotrophy v.s Polygenic Inheritance

*There is usually NOT a one-to-one correspondence b/w a gene and a physical characteristics
- Often a gene is responsible for SEVRAL phenotypic traits and is said to be pleiotropic

Pleiotropy

- Occurs when one gene influences two or more seemingly unrelated phenotypic traits
  - Such a gene that exhibits multiple phenotypic expression is called a pleiotropic gene
  - ex: Mutations in vestigial gene (vg) in Drosophila results in an easily visible short wing phenotype. However, mutations in this gene also affects
    - ↳ # of egg strings
    - ↳ position of the bristles on scutellum
    - ↳ lifespan

vg gene = pleiotropic in that it affects MANY different phenotypic characteristics

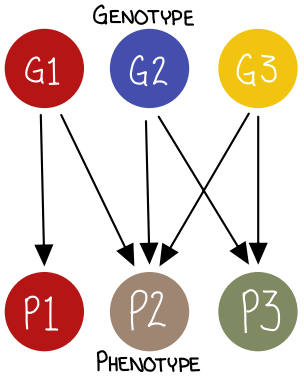


In his studies...

- He made several interesting observations regarding the colour of various plant components

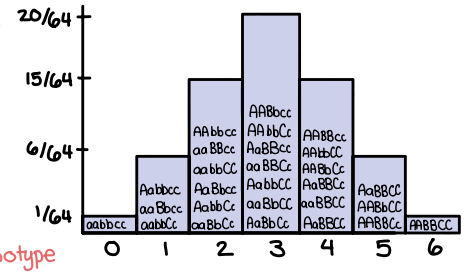
SPECIFICALLY he noticed...
- Plants w/ coloured seed coats always had coloured flowers and coloured leaf axils
  - Axils are the parts of the plants that are attach leaves to stems
- Pea plants w/ colourless seed coats ALWAYS had white flowers & NO pigment on their axils

Seed coat colour was ALWAYS associated w/ specific flower & axil colours



Now we Know...
- These results were due to pleiotropy or the phenomenon in which a single gene contributes to multiple phenotypic traits

*Single characteristics can be affected by mutations in multiple, different genes ← Implies that MANY genes are needed to make each characteristics
- ex: Drosophila wings
  There are LOTS of genes that when mutant alter the normal shape of the wing (NOT just the vg locus)
  Many genes are needed to make normal wings
  mutant to any one causes an abnormal, mutant phenotype

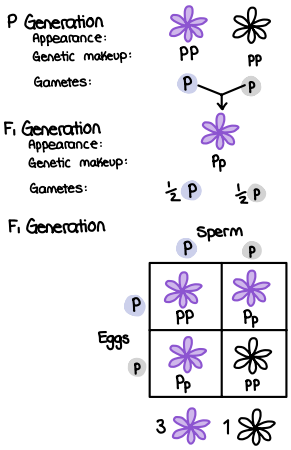


Type's of Dominance

Complete Dominance

- ex: Flower colour
  1 allele as a homozygous = ✿
  other allele as homozygous = ✿

what about heterozygous individual w/ 1 purple & 1 white allele?
- Can be determined experimental observation



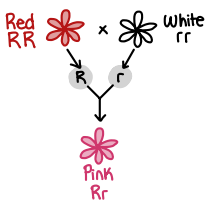
*From observation:
- Heterozygous individuals = ✿
  ↑
  purple allele = dominant
  Therefore white allele = ✿

Incomplete Dominance

- Both alleles affect the trait additively and the phenotype of the heterozygote shows a typically intermediate b/w the homozygotes which is often referred to as blended phenotype

- ex: alleles for colour in carnation flowers exhibit incomplete dominance

Allele for red petals = RR ✿
Allele for white petals = rr ✿
Allele for pink petals = Rr ✿



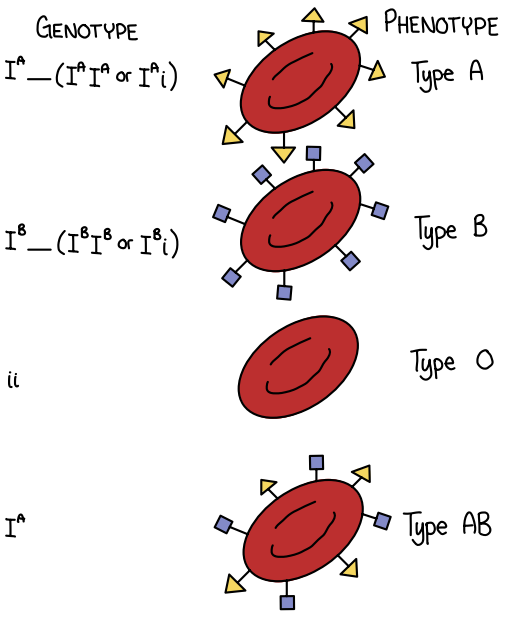
Co-Dominance

- Heterozygous individual expression expresses the phenotype of both alleles simultaneously

- ex: ABO blood group of humans has 3 alleles
  I^A
  I^B
  i

People homozygous for
I^AI^A = A type antigens = A type blood
I^BI^B = B types antigens = B type blood

People heterozygous
I^AI^B = A & B types antigens = AB type blood

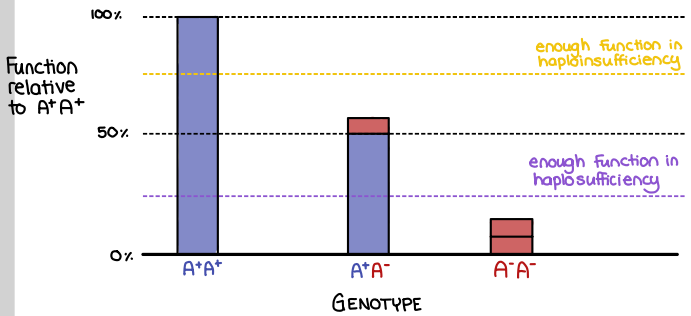


Examples	Interpertations
A & a	Uppercase letters represent dominant alleles and lowercase letters indicate recessive alleles. Mendel invented this system but it is NOT commonly used b/c not all alleles show complete dominance & many genes have more than 2 alleles
a^+ & a^-	Superscript or subscripts are used to indicate alleles. For wild type alleles the symbole is a superscript +
AA or A/A	Sometimes a forward slash is used to indicate that the 2 symbols are alleles of the same gene locus but on homologous chromosomes

Biochemical Basis of Dominance

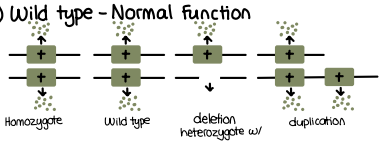
- Majority of genes studied, the normal (ie wild type) alleles are haploid sufficient. So in diploids, even w/ a mutation that causes a complete loss of function in one allele, the other allele - a wild type allele - will provide sufficient normal biochemical activity to yield a wild type phenotype ∴ thus be dominant and dictate the heterozygote phenotype

- Some biochemical pathways, a single wild-type allele is NOT enough protein and MAY be haplo-insufficient to produce enough bio-chemical activity to result in a normal phenotype, when heterozygous w/ a non-functioning mutant allele. In this case, the non-functional mutant allele will be dominant (or semi-dominant) to be wild-type allele

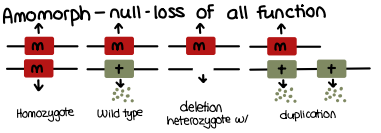


Identifying Muller's Morphs

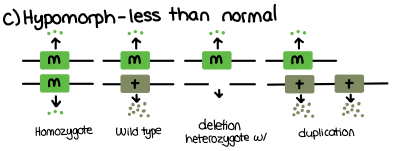
a) Wild type - Normal function



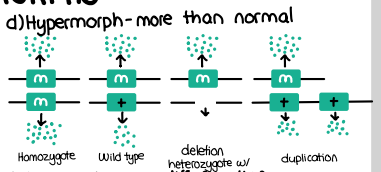
b) Amorph - null - loss of all function



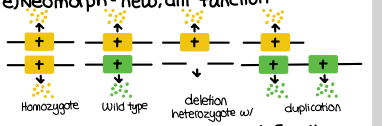
c) Hypomorph - less than normal



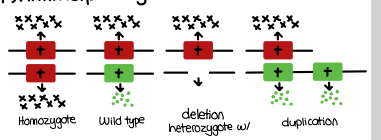
d) Hypermorph - more than normal



e) Neomorph - new, diff function



f) Antimorph - against normal function



Loss of Function

- Haplo-insufficient
  - loss of function dominant mutation
- Null mutations
  - loss of function mutation that remove the activity of the gene product

Hypomorphic mutations
- Decreased activity of the gene product - loss of function mutant phenotypes can be due to partial or complete elimination of the activity of a gene's encoded product

Gain of Function

- Hypermorph
  - mutation that produces more gene activity per gene does than wild-type
- Neomorph
  - Mutation that produces some novel gene activity that is not characteristic of the wild-type

Muller's Morph

Amorph

- Amorphic alleles have a complete loss-of-function
- They make no active product - zero function
- They are known as a "Null" mutation or a "loss of function" mutations

Molecular explanation: Changes in the DNA basepair sequence of an amorphic allele may cause one or more of the following

1. Gene deletion - The DNA sequence is removed from the chromosome
2. Gene is present, but is NOT transcribed b/c of a sequence change in the promotor or enhancer / regulatory elements
3. Gene is present, but the transcript is aberrantly processed. There is normal transcription but base pair changes cause the MATURE mRNA to incorrectly splice introns, therefore the translated amino acid sequence would be altered ∴ non-functional
4. Gene is present and a transcript is produced but no translation occurs - changes in the base pair sequence would preclude the mRNA from binding to the ribosome for translation
5. Gene is present and transcript is produced and translated but non-functional protein product is produced - the mutation alters a key amino acid in the polypeptide sequence producing a completely non-functional polypeptide

Allele combination	Result
w^+/w^+	Wildtype
w^+/w^-	Wildtype
w^-/w^-	Mutant

Allele combination	Result
M^+/M^+	Wildtype ∴ long bristled
M^+/M^-	Wildtype ∴ short bristled
M^-/M^-	Dead, recessive allele

Hypomorph

- Alleles show only a partial loss-of-function
- These alleles are sometimes referred to as a "leaky" mutations, b/c they provide some function, but NOT complete, normal function

Molecular explanation: Changes in the DNA basepair sequence of the hypomorphic allele may cause one or more of the following, w/ the gene still present

1. Reduce transcription - changed DNA sequence in the promoter or enhancer / regulatory elements can reduce the level of transcription
2. Increased translation - changes in the basepair sequence would increase the efficiency of the mRNA binding to the ribosome for translation
3. Increased function protein product - normal transcription, processing, translation, but base pair changes alter certain amino acids in the polypeptide sequence, so its function is normal but increased in amount

Genetic / phenotypic explanation: Hypomorphic mutations of most genes usually act as dominant to wild type since they are a gain of function. The classic hypermorph is a gene duplication

Allele combination	Result
w^+/w^+	Wildtype
w^+/w^a	Wildtype
w^a/w^a	Mutant

Antimorph

- Antimorph alleles are rare ∴ have a new activity that is dominant and opposite to the wild type function
- These alleles usually interfere w/ the function of the wild type allele
  - Often lose their normal function too
- New function works against the normal expression of the wild type allele
  - Can happen at the transcriptional, translational or later level of expression
- When an antimorphic allele is hetero-zygous w/ wild type, the wild type allele function is reduced / prevented
- At the molecular level, there are many ways this can happen
  - ↳ Simplest model to explain an antimorphic effect is that the protein acts as a dimer (or any multimer) and the inclusion of a mutant subunit poisons the whole complex, thereby preventing / reducing its level of function
- Antimorphs are also known as "dominant-negative" mutations b/c they are usually dominant and act negatively against the wild type function

Neomorph

- Neomorphic alleles produce a product w/ a new, different function, something that the wild type allele does not do

Molecular explation: Changes in the DNA basepair sequence of the neomorphic allele may cause one or more of the following, with the gene still being present

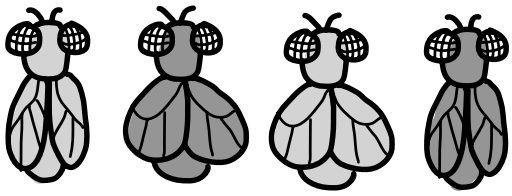
1. New transcription - changed DNA sequence in the promoter or enhancer / regulatory elements that makes new transcription either temporally or in a tissue-specific manner
2. New function protein product - normal transcription, processing, translation but base pair changes alter certain amino acids in the polypeptide sequence so it aquires a new function (activity) that is different from the normal function

Genetic / Phenotypic explanation: Most neomorphic mutations act dominant to wild type since they are gain-of-function. The classical neomorphic mutation is a translocation that moves to a new regulatory element next to a gene promoter so it is expressed in a new tissue or at a new time during development. Such mutations are often produced when chromosome breaks are re-joined and the regulatory sequence of one gene are juxtaposed next to the transctiptional unit of another = chimeric gene

Classification of Mutants

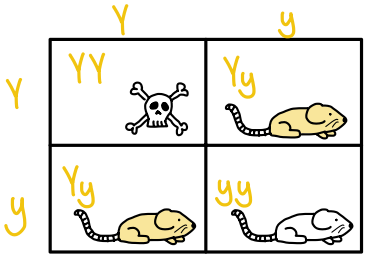
Morphological Mutants

- Mutations that cause changes in the visible form of the organism as they rise to altered forms of a trait e.g (change in size, shape, colour, #, etc...



Lethal Mutants

- Mutations cause the premature death of an organism
- Are usually recessive so both copies of a gene MUST be lost for premature death to occur
- Heterozygotes, which have one leathal allele and one wild type allele, are typically variable
- ex: leathal mutation in Drosophila results in death during the embryonic, larval or pupal stage



Biochemical Mutants

- Auxotrophic mutants can be derived from prototrophic parents.
- This type of mutation blocks a step in a biochemical pathway for the arg- mutants of Beadle & Tatum
- Such biochemical mutations are a specific type of the conditional mutation class
- Biochemical mutants result in the inability to carry out a specific biochemical pathway

Mutant	Growth of mutant on MM supplemented w/:				
	Nothing	Ornithine	Citrulline	Arginino-Succinate	Arginine
Arg^+	+	+	+	+	+
$ArgE^-$	–	+	+	+	+
$ArgF^-$	–	–	+	+	+
$ArgG^-$	–	–	–	+	+
$ArgH^-$	–	–	–	–	+

Conditional Mutants

- Relys on concept of: phenotype = genotype + environment + interaction
- Organisms w/ this mutation express a mutant phenotype, BUT only under specific environmental conditions
- Ex: Temperature-sensitive pigmentation of Siamese cats
  - Siamese cats have temp sensitive fur colour
    - ↳ Unpigmented (light colour) in ↑ temp
    - ↳ Pigmented (dark colour) in ↓ temp
  - Colour is seen in PERIPHERAL regions of the feet, snout & ears
  - In warm temp the enzyme for melanin pigment synthesize becomes non-functional

Restrictive Conditions

- Express mutant phenotype

Permisive Conditions

- Express wild type phenotype