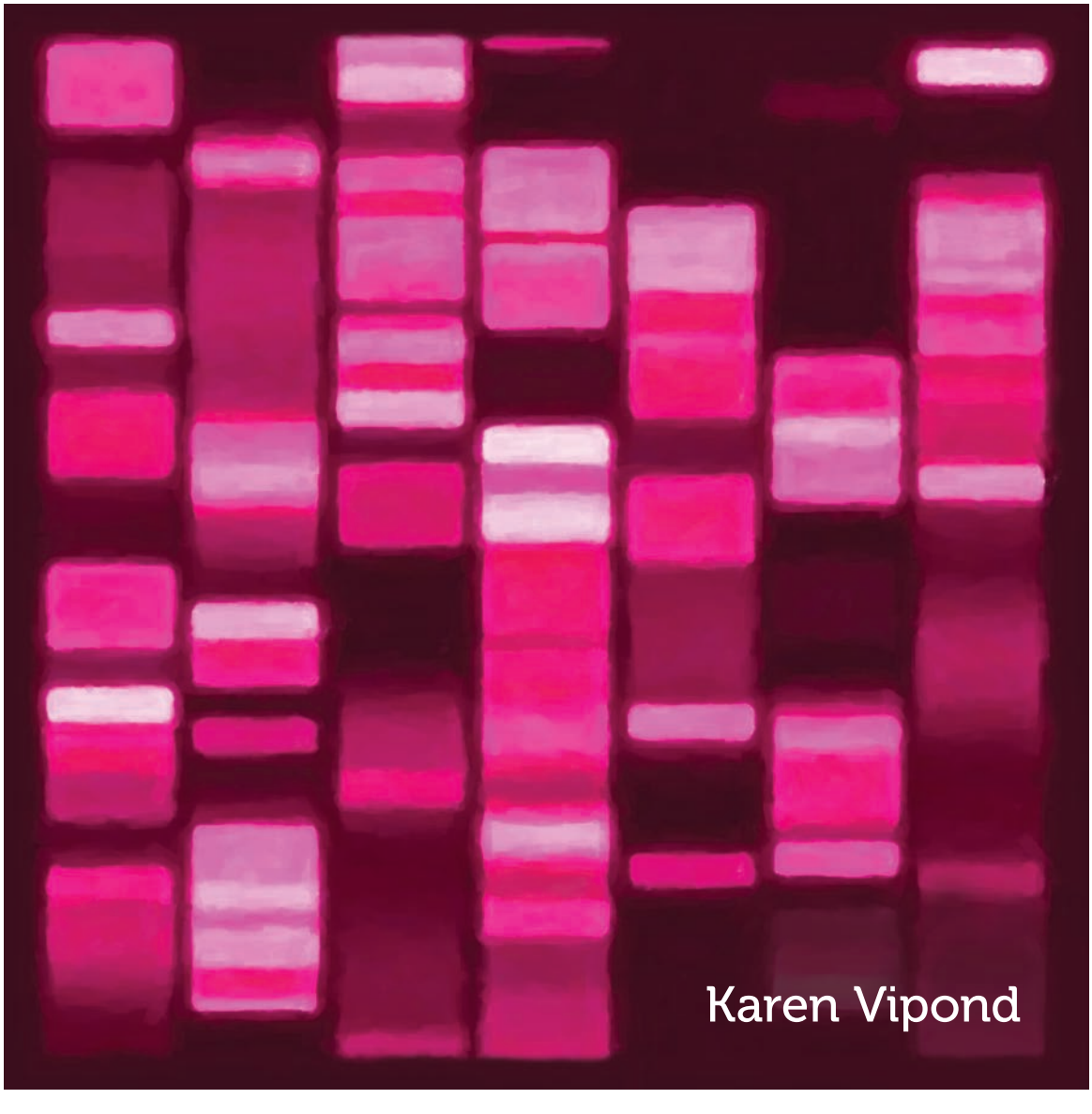
REVISED EDITION

Genetics

A Guide for Students and Practitioners of Nursing and Health Care



Karen Vipond

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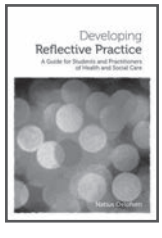

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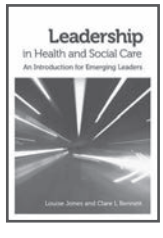

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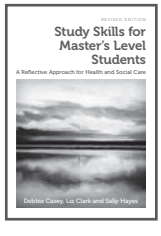

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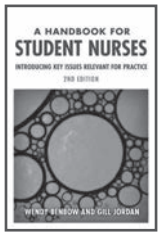

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CONTENTS

	Foreword	vii
	Introduction	ix
1	Basic Cell Biology	1
2	Inheritance	21
3	Autosomal Recessive and Dominant Inheritance	41
4	Sex-linked Inheritance	65
5	Two or More Genes	85
6	Mutations	109
7	Pedigree Analysis	131
8	Clinical Applications	149
9	Cancer Genetics	165
10	Genetic Counselling	181
	Answers to the Activities	207
	Glossary	219
	Index	227

03

AUTOSOMAL RECESSIVE AND DOMINANT INHERITANCE

LEARNING OUTCOMES

The following topics are covered in this chapter:

- autosomal recessive inheritance;
- autosomal dominant inheritance;
- variations in dominance;
- classification of gene action;
- co-dominance;
- multiple alleles;
- lethal alleles.

INTRODUCTION

In Chapter 2 the main principles of inheritance were explained. This chapter focuses on the inheritance of autosomal single gene disorders. Over 10,000 human diseases are due to single gene alterations and, although rare, they affect one per cent of the human population. Single gene disorders are also known as monogenic disorders. Genetic disorders are caused by abnormal genes. Alleles that become altered over time can be passed on to future generations. These altered alleles can result in the production of a non-functioning protein. An altered allele is a mutated allele.

The inheritance pattern of an altered gene depends on whether the gene is situated on an autosome (chromosomes 1 to 22) or on one of the sex chromosomes (XX in females, XY in males), and whether the alleles of that gene are either recessive or dominant. Genetic conditions arising from a single gene can be inherited in one of four ways:

1. autosomal recessive;
2. autosomal dominant;
3. X-linked recessive;
4. X-linked dominant.

Only the inheritance patterns of genes on the autosomal chromosomes will be explained in this chapter. X-linked inheritance is discussed in Chapter 4.

When the DNA coding within a gene becomes altered in any way, the resulting gene product may also be affected. The production of an altered or non-functioning gene can give rise to a genetic condition that affects health and development. These altered or mutated genes can be inherited in a recessive or dominant fashion.

AUTOSOMAL RECESSIVE INHERITANCE

Two copies of the altered allele must be present for an individual to be affected by a recessive disorder. That individual would be classified as homozygous recessive for that disorder. Heterozygous individuals who only possess one altered allele and a normally functioning allele will not display the effects of the altered allele in their phenotype but are classified as carriers of the altered allele. Carriers are not affected by the recessive allele but are able to pass that affected allele on to the next generation. Individuals need both alleles to be in the recessive form for the expression of the recessive phenotype.

Most individuals carry a small number of recessive alterations within their genes that cause no symptoms. Recessive diseases are single-gene disorders arising from two malfunctioning alleles (mutant alleles) and appear in homozygous individuals. Most affected individuals have two heterozygous parents who are unaffected because they have one altered and one normal allele and are carriers of the disorder.

Rules of autosomal recessive inheritance

- Both males and females are equally affected.
- Gene expression can 'skip' several generations as carriers do not express the gene.
- Affected children can be born to non-affected parents.
- If both parents are affected, all children will also be affected.
- Affected individuals with homozygous non-affected partners will usually have normal children.

Inheritance patterns

Affected individuals (homozygous recessive) are produced via one of three different types of mating:

1. Two heterozygous parents: **Aa x Aa** (both parents are carriers) (see Figure 3.1).

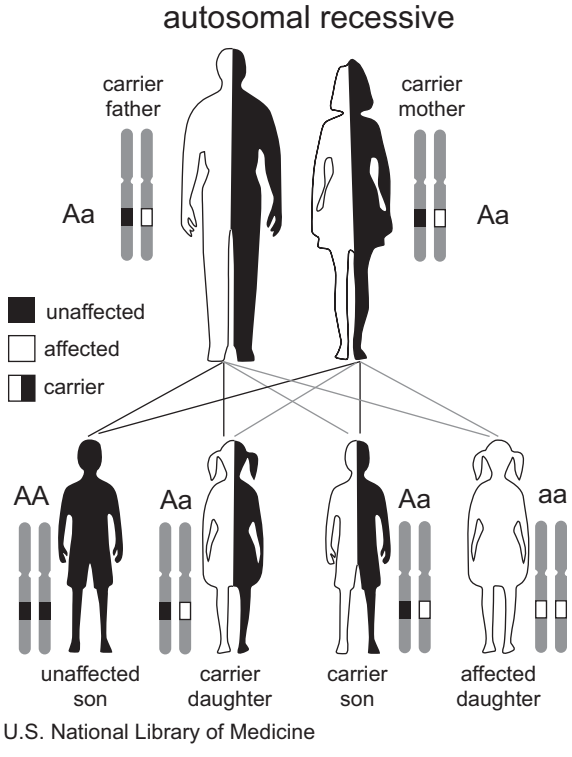

Figure 3.1 *Two heterozygous parents*
Key: **A** *= normal allele,* **a** *= affected recessive allele*

This is by far the most common type of mating that produces an affected offspring. The estimation of risk for an affected offspring from this type of mating is 25 per cent.

	A	**a**
A	**AA**	**Aa**
a	**Aa**	**aa**

Figure 3.2 *Estimation of risk from two heterozygous parents*

Offspring have a:

- 1 in 4 chance or 25 per cent risk of being an unaffected non-carrier (**AA**);
- 1 in 2 chance or 50 per cent risk of being a carrier (**Aa**);
- 1 in 4 chance or 25 per cent risk of being affected (**aa**).

2. Recessive Homozygote x Heterozygote **aa x Aa** (affected parent with a carrier parent) (see Figure 3.3).

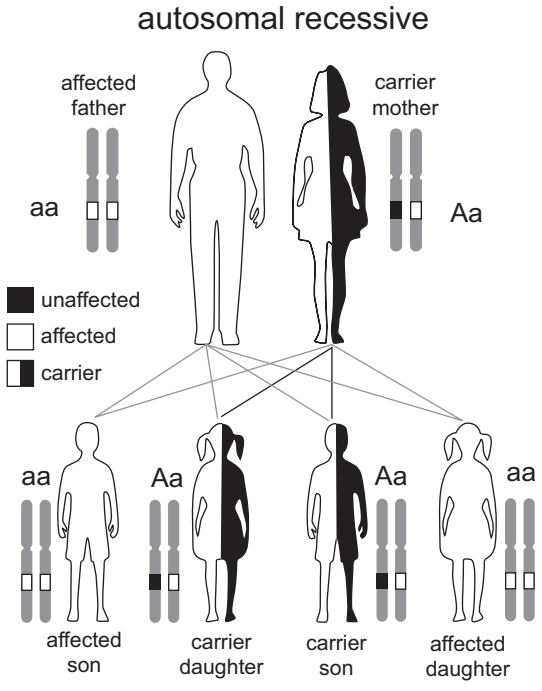

Figure 3.3 *Recessive homozygote x heterozygote parent*

The estimation of risk for an affected offspring from this type of mating is 50 per cent (Figure 3.4).

	A	**a**
a	**Aa**	**aa**
a	**Aa**	**aa**

Figure 3.4 *Estimation of risk from a recessive homozygote and heterozygote parent*

Offspring have a:

- 1 in 2 chance or 50 per cent risk of being a carrier;
- 1 in 2 chance or 50 per cent risk of being affected.

3. Two recessive homozygotes: **aa x aa** (both parents are affected) (see Figure 3.5).

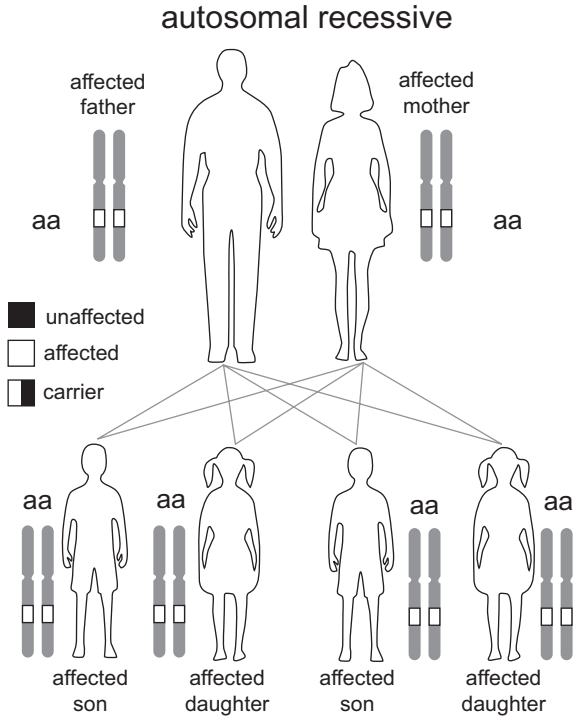

Figure 3.5 *Two recessive homozygote parents*

The estimation of risk for an affected offspring from this type of mating is 100 per cent (Figure 3.6).

	a	**a**
a	**aa**	**aa**
a	**aa**	**aa**

Figure 3.6 *Estimation of risk from two homozygote parents*

Offspring have a:

- 1 in 1 chance or 100 per cent risk of being affected.

Affected individuals who are homozygous recessive are usually the offspring of one of the above three matings.

There are thousands of autosomal monogenic recessive conditions. Table 3.1 contains a few examples of the most common conditions.

Table 3.1 *Common autosomal monogenic recessive conditions*

Condition	Chromosome	Gene	Effect
Adenosine Deaminase Deficiency	20q	ADA	Severe combined immunodeficiency
Batten Disease	16p	CLN3	Progressive disorder resulting in neuronal death within the brain
Congenital deafness	11p	USH1C	Deafness
Cystic Fibrosis	7q	CFTR	Defective chloride ion transport leading to thickened mucus production
Galactosaemia	9p	GALT	Developmental delay as a result of inefficient metabolism of galactose
Gaucher Disease	1q	GBA	Build-up of fatty deposits on liver, spleen, lungs and brain; anaemia and joint problems
Hereditary Haemochromatosis	6p	HFE	Iron overload due to too much iron being absorbed from the small intestine
Maple syrup urine disease	7q	DLD	Metabolic disorder leading to seizures, failure to thrive and developmental delay

(*Continued*)

Table 3.1 *(Continued)*

Oculocutaneous Albinism	11q	TYR	Lack of pigment in hair, skin and eyes
PKU	12q	PAH	Increased levels of phenylalanine leading to brain damage
Sickle Cell Anaemia	11p	HBB	Abnormal haemoglobin. Sickle-shaped red blood cells, which lead to the blocking of small blood vessels
Spinal Muscular Atrophy	5q 11 20	SMN1 IGHMBP2 VAPB	Progressive loss of function of motor neurones leading to atrophy of muscles
Tay-Sachs	15q	HEXA	Build-up of fatty deposits in the central nervous system, leading to death

Additional risks

Everyone carries several 'faulty' recessive genes that have no impact on their health. There are many different forms of faulty genes within a population but, because genes are inherited from parents and grandparents, family members will have more similarity within their genes and shared 'faulty' genes.

Consanguinity

The risk of developing an autosomal recessive genetic condition is increased in offspring of consanguineous relationships. The term **consanguinity** derives from the Latin prefix con-, meaning 'together', and the word *sanguis* which means 'blood'. It describes the marital relationship between two individuals who share a common ancestor. The most common form of consanguinity is the marriage between first cousins, which is encouraged in some cultures.

The children of unrelated parents are at low risk of inheriting two copies of the same faulty or altered allele. The risk of having a child with a birth defect is between 2 and 3 per cent, some of which will be due to a genetic condition. Children of parents who are blood

relatives have an increased risk of having a genetic defect. The risk is doubled for parents who are cousins (5 to 6 per cent).The risk of inheriting the same faulty gene from both parents is increased the closer the relationship is between the parents (i.e. the more genes that they have in common) (see Table 3.2).

Table 3.2 *Relationships between blood relatives*

Relationship to each other	Brothers/sisters Parent/child	Uncles/aunts Nephews/nieces Grandparents Half-brothers Half-sisters	First cousins Half-uncles Half-aunts Half-nephews Half-nieces
Relationship type	First-degree relatives	Second degree	Third degree
Proportion of genes that they have in common	Half 50 per cent	Quarter 25 per cent	Eighth 12.5 per cent

The risk of having an affected child is much higher than 5 to 6 per cent in some families, because parents who are first cousins might also have grandparents who are themselves related.

ACTIVITY 3.1

a. A child who has a recessive genetic condition has two unaffected parents. If the child's genotype for this disorder is bb, what are the genotypes of the parents?

b. Why do recessive conditions appear to 'skip' generations?

AUTOSOMAL DOMINANT INHERITANCE

Autosomal dominant single gene disorders occur in individuals who have a single altered copy of the disease-associated allele. An alteration in only one of the alleles within a gene is enough to cause the disorder. The mutated disease-causing allele can be inherited from either parent.

Alleles encode for the production of a specific protein. When one allele is altered, in that the specific protein is no longer produced, the remaining functioning allele will still continue to encode for the specific protein. In autosomal dominant disorders, the amount of protein being encoded for by the functioning allele is not enough for the body to function normally.

In these cases the faulty allele causes a problem for the individual as it is dominant in its effect over the functioning normal allele.

In individuals who possess both alleles in an altered form (homozygous dominant), the disease symptoms are generally more severe. Dominant disease allele homozygotes are quite rare as many conditions appear lethal in the homozygous dominant form.

Rules of autosomal dominant inheritance

- Both males and females are equally affected, and can transmit to both sons and daughters.
- Most affected individuals will have an affected parent. The disease does not 'skip' generations.
- In affected families, where one parent is affected, the risk of transmitting the trait to the offspring is 50 per cent.
- If both parents are unaffected, none of the children will be affected.

Inheritance patterns

Affected individuals, who possess a dominant allele, are produced via one of three different types of mating.

1. Two homozygous dominant parents: **AA x AA** (both parents are affected) (see Figure 3.7).

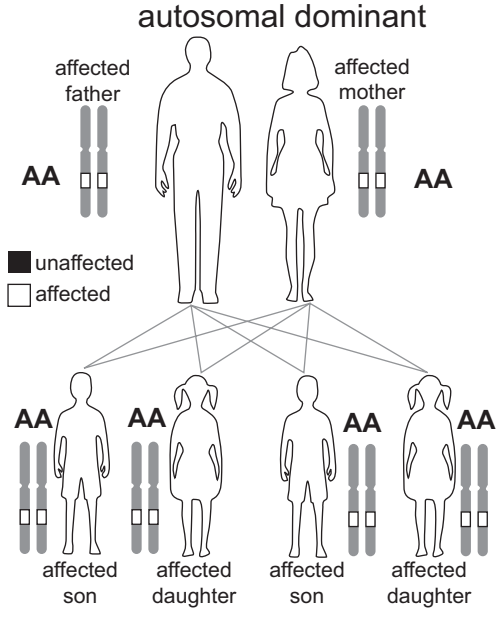

Figure 3.7 *Two homozygous dominant parents*
Key: **A** = dominant affected allele, **a** = recessive normal allele.

The estimation of risk of an affected offspring is 100 per cent (see Figure 3.8).

	A	A
A	AA	AA
A	AA	AA

Figure 3.8 *Estimation of risk from two homozygous dominant parents*

Offspring have a:

- 1 in 1 chance or 100 per cent risk of being affected.

2. Two heterozygous parents: **Aa x Aa** (both parents are affected) (see Figure 3.9).

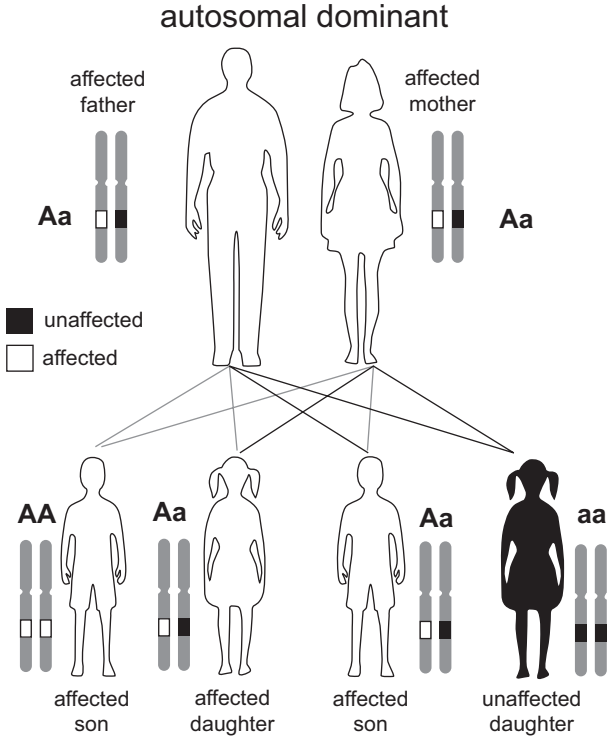

Figure 3.9 *Two heterozygous parents*

The estimated risk of having an affected child is 75 per cent (Figure 3.10).

	A	a
A	AA	Aa
a	Aa	aa

Figure 3.10 *Estimation of risk from two heterozygous parents*

Offspring have a:

- 3 in 4 chance or 75 per cent risk of being affected;
- 1 in 4 chance or 25 per cent risk of being unaffected.

3. Heterozygous x Homozygous recessive: **Aa x aa** (one affected parent and one unaffected parent) (see Figure 3.11).

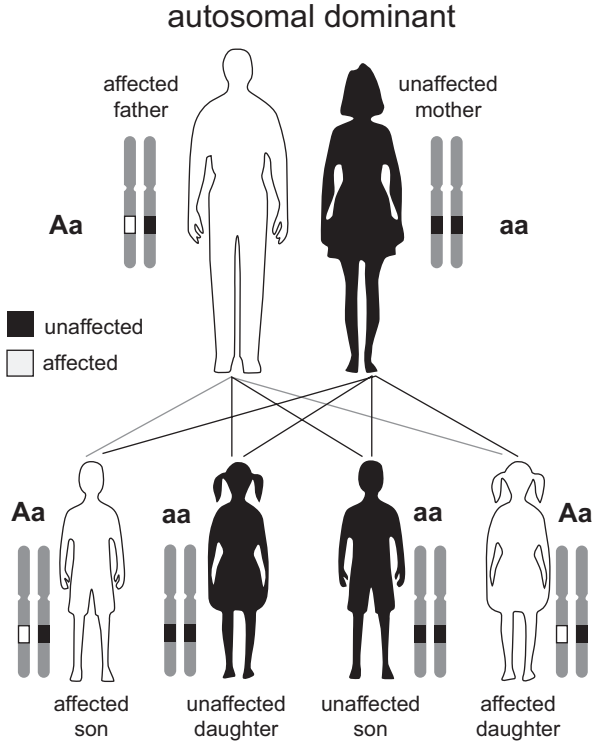

Figure 3.11 *Heterozygous x homozygous recessive parents*

Estimation of risk for this type of mating is 50 per cent (see Figure 3.12).

	A	a
a	Aa	aa
a	Aa	aa

Figure 3.12 *Estimation of risk from heterozygous recessive x homozygous recessive parents*

Offspring have a:

- 1 in 2 chance or 50 per cent risk of being affected;
- 1 in 2 chance or 50 per cent risk of being unaffected.

There are thousands of genetic conditions that are monogenic autosomal dominant. Table 3.3 gives some examples of the most common single gene dominant disorders.

Table 3.3 *Common monogenic autosomal dominant conditions*

Condition	Chromosome	Gene	Effects
Achondroplasia	4p	FGFR3	Dwarfism caused by severe shortening of the long bones of the limbs; lumbar lordosis and flattened bridge of the nose
Brachydactyly	9q	ROR2	Abnormally short phalanges (distal joints) of the fingers and toes
Huntington's disease	4p	HTT	Progressive brain disorder, involuntary movements and loss of cognitive ability
Hypercholesterolaemia	19p	LDLR	High blood cholesterol leading to increased risk of cardiovascular disease
Marfan Syndrome	15q	FBN1	Tall stature with elongated thin limbs and fingers; high risk of heart defects
Myotonic Dystrophy	19q	DMPK	Progressive muscle wasting

(*Continued*)

Table 3.3 *(Continued)*

Neurofibromatosis Type 1	17q	NF1	Growth of tumours along nerves in brain and skin; changes in skin colouration; increased risk of hypertension
Polycystic Kidney Disease Type 1	16p	PKD1	Fluid-filled cysts on enlarged kidneys and other organs, can lead to kidney failure
Polycystic Kidney Disease Type 2	4q	PKD2	Effects are the same as Type 1 but Type 2 has a later onset and symptoms are less severe
Porphyria Variegata	1q	PPOX	Inability to synthesise haem (essential for haemoglobin in red blood cells)

There are many more dominant traits than recessive traits recognised in humans. The reason for this is that a recessive trait can be 'hidden' by carriers whereas a dominant trait is always expressed. An individual with a dominant trait has a higher chance of having an affected child (a 50 per cent risk) compared with carriers of a recessive condition (a 25 per cent risk for two carriers).

ACTIVITY 3.2

a. Autosomal dominant conditions do **not** appear to 'skip' generations in the same way as autosomal recessive conditions. Explain the reasons for this.

b. What is the risk for two heterozygous dominant parents of having a child with the same condition?

c. Could a homozygous dominant affected individual and a homozygous recessive unaffected individual have an unaffected child?

For questions b) and c) you might need to draw a Punnet square (see page 31) to clarify your answers.

Variations in dominant inheritance

The way that dominant and recessive alleles behave is not always so straightforward. There are a few exceptions to the simplistic Mendelian inheritance patterns of dominance, even though the inheritance of these genes still follows Mendelian principles of inheritance.

1. New alterations

Most affected individuals with a dominant condition will have an affected parent. Some alterations in the chromosomal DNA can occur spontaneously either in the egg or sperm, or even early in embryonic development. Individuals may develop certain genetic conditions in this way. These individuals are affected by an altered allele, but their parents are not affected. The altered allele can be inherited by future generations. In some disorders the proportion of cases arising from new mutations is high. For example, 80 per cent of children born with achondroplasia do not have an affected parent but have developed the mutated allele either in early embryonic development or via a new arising mutated allele within the egg or sperm.

2. Late onset

Some autosomal dominant conditions are not expressed phenotypically until adulthood (e.g. Huntington's disease). This makes it difficult to predict risk when making reproductive choices.

3. Variable expressivity

The severity of symptoms of a dominant condition can vary between members of the same family, especially if the altered allele codes for a protein that is needed for different functions within the body. This makes it sometimes difficult to identify the condition and to track it through the generations of the family. Marfan syndrome has variable expressivity between members of the same family.

4. Incomplete penetrance

Usually a dominant allele will be phenotypically expressed. When an allele is always expressed it is said to be 100 per cent penetrant. There are some dominant conditions that do not follow this rule in that they have reduced penetrance. Retinoblastoma, an eye tumour, is an example of a genetic condition where the altered allele (allele RB on chromosome 13q) has variable penetrance. The susceptibility of developing the tumour is a dominant trait, but 20 per cent of individuals who have the altered allele do not develop the condition. The retinoblastoma gene therefore has an 80 per cent penetrance.

CLASSIFICATION OF GENE ACTION

Dominance usually occurs when a functioning allele is paired with a non-functioning allele. This usually arises from a mutation that alters the DNA structure within the allele, rendering it non-functional. An individual who has two altered alleles will generally display a distinctive phenotype as a result of the missing or altered protein produced by the altered alleles. It is not the lack of function that makes the allele recessive but the interaction of that allele with the alternative allele in the heterozygote. There are three main allelic interactions.

1. Haplosufficiency

This is when a single functional allele is able to encode for a sufficient amount of protein in order to produce a phenotype that is identical to that of the normal phenotype. If each allele encodes for 50 per cent of the amount of protein (100 per cent from both functioning alleles) and the normal phenotype can be achieved with only 50 per cent of the protein, then the functioning allele is considered dominant over the non-functioning allele. For example, the GALT gene on chromosome 9p that normally encodes for an enzyme needed for the breakdown of galactose shows haplosufficiency in the presence of one altered gene.

2. Haploinsufficiency

This is where a single functioning allele is unable to produce enough protein. Essential levels of protein must be over 50 per cent in cases of haploinsufficiency. The phenotype in haploinsufficiency resembles the homozygote for the non-functioning allele. This is rare in humans as deficiency usually results in a case of incomplete dominance.

3. Incomplete dominance

With a small number of alleles there is a lack of complete dominance. A heterozygous individual will have an intermediate phenotype compared with the two different homozygous individuals. The phenotype of the heterozygote becomes an intermediate or a 'blend' of the two different alleles. A simple example of incomplete dominance in humans can be seen with the gene for curly hair. An individual who has inherited a curly hair allele from one parent and a straight hair allele from the other parent will have wavy hair. In humans the 'blend' of the curly hair allele and the straight hair allele gives rise to wavy hair.

Most genes that display patterns of incomplete dominance have arisen from alleles in which a 'loss of function' has occurred. In a gene composed of one functioning allele and a non-functioning allele, only half the required amount of protein is encoded for by that gene. The genetic condition of familial hypercholesterolaemia demonstrates incomplete dominance in that individuals with one faulty or non-functioning allele will have raised blood cholesterol levels, while individuals who have two non-functioning alleles will have much higher cholesterol levels.

ACTIVITY 3.3

The straight hair allele (s) and the curly hair allele (c) show incomplete dominance in humans. Individuals with straight hair are homozygotes (ss), as are individuals who have curly hair (cc). Heterozygotes for this trait have wavy hair as they have one straight hair allele and one curly hair allele (sc). Note that the two different traits are represented by different letters.

a. Complete a Punnet square for a mating between a curly hair individual and a wavy hair individual.

b. What is the predicted offspring from this mating?

c. Is it possible for these individuals to have a straight hair child with each other?

d. Complete a Punnet square to determine the possible genotypes of the offspring of two wavy hair individuals.

e. Could two wavy hair parents have a child with straight hair?

f. Could the same wavy hair parents have a child with curly hair?

Whether an allele is classified as dominant or incomplete dominant depends on the individual's phenotype. However, the phenotype can be measured in different ways. Take, for example, the genetic condition of Tay–Sachs disease. Tay–Sachs disease is a degenerative condition that affects the nervous system. Affected individuals are born healthy but start to lose acquired skills at around the age of six months, gradually becoming blind, paralysed and unaware of their surroundings. It is a lethal condition with an average life expectancy of around five years. Affected individuals have two altered alleles in the HEXA gene on chromosome 15. A functioning HEXA gene is vital for development of the nervous system. Without the specific enzyme that this gene encodes for, fatty deposits build up in the brain, which then leads to neuronal damage. An affected individual has two non-functioning HEXA alleles. A heterozygote individual who has one functioning copy of the gene will be able to produce half the normal amount of the HEXA protein, which is enough to prevent damage from occurring. Heterozygotes are therefore carriers of Tay–Sachs disease. The healthy functioning copy of the HEXA allele is therefore classified as dominant to the non-functioning HEXA allele as the heterozygote individual displays no symptoms of the condition. However, if enzyme levels were measured, only half the usual amount of the HEXA enzyme protein would be discovered. In Tay–Sachs disease half the enzymatic levels are sufficient for health. At the biochemical level, the heterozygous individual displays incomplete dominance but complete dominance at the whole body level.

All the examples so far have demonstrated one allele being dominant or recessive over its partner allele. There are some conditions in which different versions of the same allele demonstrate equal dominance to each other. This is called **co-dominance.**

CO-DOMINANCE

Co-dominance is quite similar to incomplete dominance, in that neither of the two alleles is dominant or recessive to each other. However, there is no 'blending' in the offspring as both

allelic products are expressed. Both parental traits are expressed in the offspring with co-dominant alleles. The biggest difference between incomplete dominance and co-dominance is that in co-dominance both alleles still encode for a functioning protein. The different proteins may have a slightly different function.

Most co-dominant alleles are thought to have arisen from a 'gain in function' mutation, where the alteration to the DNA structure within the allele has resulted in a different functioning protein being encoded for.

The MN blood group

An example of a co-dominant gene in humans is the gene that encodes for the MN blood group. The MN system is a type of blood grouping that is formed by the presence of specific antigens on the surface of the red blood cells. Two co-dominant alleles were originally identified for this blood group, termed M and N. The MN system is under the control of the MN gene located on chromosome 4. As both M and N alleles are co-dominant to each other there are three possible genotypes and phenotypes that can arise from the MN blood grouping system (see Table 3.4).

Table 3.4 *The MN blood grouping system*

Genotype	Phenotype
MM	MM blood group
NN	NN blood group
MN	MN blood group

There is distinct expression of both alleles in the MN blood group system, which is a characteristic of co-dominant inheritance.

ACTIVITY 3.4

In which of the following does the 'blending' of traits occur – incomplete dominance or co-dominance?

MULTIPLE ALLELES

The genetic inheritance patterns discussed so far have been limited to two alleles. The maximum number of alleles within a gene is two, one inherited from each parent. However, different forms of alterations in alleles can occur within populations, leading to numerous different forms of the same gene. When three or more forms of an allele exist for a single gene

the term 'multiple alleles' is used. Note that multiple alleles can only exist in a population as an individual can only carry a maximum of two alleles within a gene.

Symbols used for multiple alleles

Multiple alleles also act in a dominant or recessive fashion, so capital and lower case letters are also used for multiple alleles. In addition, superscripts are used to aid identification within multiple alleles. The superscripts identify which form of the allele is present rather than its recessive or dominant action.

The ABO blood system

An example of multiple alleles in humans is the ABO blood system, in that there are three different types of alleles present in the population: A, B and O. An individual will only have two of these alleles within their individual genome, their blood group being dependent on the combination of the two alleles present.

In the ABO blood group system the possible blood groups that an individual might have are A, B, AB or O. This is determined by the expression of two out of the three possible alleles. As there are three different types of possible alleles, the gene for the ABO blood group is termed a 'tri-allelic' gene. This does not mean that the gene has three alleles, but has two alleles out of a possible three forms.

The alleles control the production of antigens on the surface of the red blood cells. Two of the alleles (A and B) are co-dominant to one another. The third allele (allele O) is recessive to the two co-dominant alleles as it does not encode for any antigens (acts as a 'loss of function' allele). The phenotype of an individual is determined by which antigens are present on the surface of their red blood cells (see Figure 3.13).

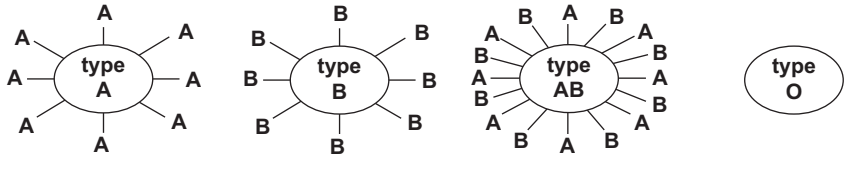

Figure 3.13 *Red blood cell antigens*

The symbols commonly used for the ABO blood system are: I for the representation of the allele (I for the dominant allele and i for the recessive allele). The letter I is used as it stands for isoagglutinogen, which is another term for antigen. The superscripts ^{A} and ^{B} are used to represent the encoded antigen (^{O} is not used as it does not code for any antigens).

- Allele I^{A} encodes for antigen A (blood group A).
- Allele I^{B} encodes for antigen B (blood group B).
- Allele i does not encode for any antigens (blood group O).

With three alleles, there is a higher number of possible combinations in a genotype (see Table 3.5).

Table 3.5 *Genotype combinations and phenotypes for blood group*

Genotype	Phenotype
$I^A I^A$	Group A
I^A i	Group A
$I^B I^B$	Group B
I^B i	Group B
$I^A I^B$	Group AB
i i	Group O

There are six different genotypes and four different phenotypes for the ABO blood system. The only homozygous recessive genotype is for blood group O.

Inheritance of blood group occurs following the Mendelian principles, taking into account the co-dominance of A and B and the dominance of A and B over O (see Figure 3.14).

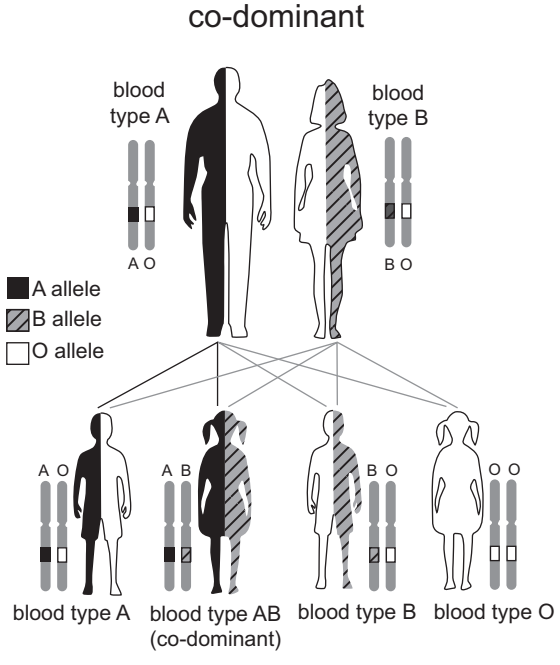

Figure 3.14 *The inheritance of blood group*

From a heterozygous mating between blood group A and blood group B individuals (AO x BO) the resulting offspring could be blood group A, B, AB or O (Figure 3.15).

	I^B	i
I^A	I^AI^B	I^Ai
i	I^Bi	i i

Figure 3.15 *Blood groups for the offspring of mating between individuals of groups A and B*

Offspring have a:

- 1 in 4 chance or 25 per cent risk of being group AB;
- 1 in 4 chance or 25 per cent risk of being group A;
- 1 in 4 chance or 25 per cent risk of being group B;
- 1 in 4 chance or 25 per cent risk of being group O.

The ABO blood group in humans is an example of co-dominance as well as being a multi-allelic trait.

ACTIVITY 3.5

The ABO blood group system in humans gives rise to four different types of blood; type A, type B, type AB and type O.

a. The A and B alleles are co-dominant with each other but dominant over the O allele. An individual with an AA or AO genotype will have type A blood.

i) List the possible genotypes that a person with type B blood could have.
ii) What is the genotype of an individual with type O blood?

b. Complete a Punnet square for a mating between a person with type AB blood and a person with type O blood.

i) From this mating is it possible to have a child with type AB blood?
ii) From the same mating is it possible to have a child with type O blood?

c. Complete a Punnet square for a mating between a heterozygous type A blood group individual and an individual who is heterozygous for type B blood. From this mating, is it possible to have a child with:

i) type AB blood?
ii) type O blood?

d. A mother who is blood group A has a blood group O child. The biological father of the child could be either of two men. One man has type B blood and the other has type AB. Who is the child's biological father?

e. Three babies have been 'mixed up' in the nursery on the maternity unit where they were born. Blood tests have revealed the blood types of the three babies and of their parents.

- Baby 1: type AB Parents 1: A and B
- Baby 2: type O Parents 2: AB and O
- Baby 3: type B Parents 3: AB and B

Work out which baby belongs to which set of parents.

LETHAL ALLELES

Any combination of alleles within a gene that results in the death of that individual is termed a lethal gene. Many of the proteins encoded for by different genes are essential for life. If one gene fails to 'work', the outcome might result in death. Death from a genetic disorder can occur at any stage of life. However, in terms of population genetics, a lethal gene results in the death of an individual before that individual has reached reproductive age. This prevents the gene from being passed on to future generations. The alleles of lethal genes can act in a dominant or recessive fashion.

Recessive lethal alleles

If the absence of a protein encoded by a gene results in death, it normally arises by a mutation leading to 'loss of function'. One allele that still encodes for the vital protein will often produce enough protein to compensate for the loss of function from the partner allele. If both alleles have mutated, resulting in total loss of function, then death occurs. Homozygous recessive individuals for a recessive lethal allele will not survive. The time of death varies according to when the normal gene product is essential for development. This could be at the embryonic stage, childhood or even adulthood. Gaucher Disease (perinatal form) and Tay-Sachs disease are both examples of genetic conditions with recessive lethal alleles.

Dominant lethal alleles

The presence of only one functioning allele in some genes will not be able to encode for a sufficient amount of vital protein for development. The non-functioning allele in this instance behaves in a dominant fashion as its loss of function will be displayed in the

individual's phenotype and results in death. The genetic condition of Huntington's disease has a lethal dominant allele.

Sometimes a double dose of a dominant allele that causes a genetic disorder will result in an individual's death. For example, the altered allele that causes achondroplasia (dwarfism) behaves in a dominant fashion. A heterozygous individual will display the effects of the altered gene and will have the phenotypic characteristics of achondroplasia dwarfism. However, inheriting two altered achondroplasia alleles is rarely compatible with life. In this case the altered allele is dominant for the condition but acts as a recessive lethal allele.

ACTIVITY 3.6

Achondroplasia is a form of dwarfism. It is an autosomal dominant condition in that individuals only need the presence of one altered allele for this condition. Most individuals are heterozygous for this condition (Aa) as a 'double dose' of the altered allele (AA) is lethal.

Construct a Punnet square for a mating between two individuals who have achondroplasia.

a. Is it possible from this mating to have a child of normal height?
b. What are the risks for this couple in having a baby who will die from this condition?
c. What is the risk (in percentage form) of a father with achondroplasia and a normal height mother having a child with achondroplasia?

Many genetic conditions or diseases in humans are classified as either dominant or recessive. This, however, tends to be an oversimplified view of genetics. Recent estimates have put the number of protein-coding genes in the human genome at 25,000, of which approximately 1,800 are thought to be linked with single-gene disorders (monogenic disorders). Only a small proportion of these monogenic disorder genes have, as yet, been linked to specific diseases. Most of the common genetic disorders in humans arise from mutations in a number of different genes that interact closely together (polygenic disorders). Single-gene disorders (monogenic) are relatively rare compared with multiple-gene disorders (polygenic). Common genetic disorders tend to exhibit complex patterns of inheritance that involve interactions between a number of different genes, as well as having an environmental influence in the expression of the disorder.

SUMMARY

- Recessive genetic conditions are single-gene disorders arising from two malfunctioning alleles. Two copies of the altered alleles must be present in recessive conditions.
- Heterozygotes with one normal allele and a recessive non-functioning allele are carriers of the non-functioning allele. They are not affected by the altered allele.
- Recessive disorders can 'skip' generations as carriers are not affected by the recessive, disorder-causing, altered allele.
- The risk of being affected by a recessive condition is increased in offspring of consanguineous mating.
- Autosomal dominant disorders are caused by the presence of only one altered allele. Dominant disorders do not 'skip' generations as most individuals will also have an affected parent.
- Dominant alleles can arise from new mutations, have a late onset, variable expressivity and/or incomplete penetrance.
- Classification of whether an altered allele is dominant or recessive depends upon whether the partner allele of the non-functioning allele can produce enough gene product at a sufficient level for health and development. A lack of enough levels for health indicates that the normal allele is haploinsufficient. If enough protein is produced then the allele is haplosufficient.
- Incomplete dominance results in the 'blending' of traits.
- Co-dominance occurs when both alleles code for a different protein of which both are expressed.
- Multiple alleles can exist within a population of which an individual can have two varieties of that allele.
- Lethal alleles result in the death of the individual. They can act in a recessive (two copies needed for lethality) or dominant (one copy is lethal) fashion.

FURTHER READING

Bennett, R.L., Motulsky, A.G., Bittles, A., Hudgins, L., Uhrich, S., Doyle, D.L., Silvey, K., *et al*. (2002) 'Genetic counseling and screening of consanguineous couples and their offspring: Recommendations of the National Society of Genetic Counselors'. *Journal of Genetic Counseling*, 11(2), 97–119

This article sets out recommendations for genetic counsellors when working with blood-related couples of second cousin status or closer.

Cummings, M.R. (2008) *Human heredity: Principles and issues*. USA: Brooks Cole Publishing

This is a well-written text, which has a good chapter on the transmission of genes from generation to generation (pages 44–69)

Harper, P. (2004) *Practical genetic counselling*. London: Arnold

This is an excellent text, which provides good detail on the different modes of inheritance.

The National Genetics Education and Development Centre, which is part of the NHS, has a few web pages that outline the main principles of inheritance. These pages can be found at:
www.geneticseducation.nhs.uk/learning-genetics/patterns-of-inheritance.aspx

This site also provides a lot of other resources that you may find useful in practice.

Statistical information on the number of genes detected and identified within the human genome can be found through the statistical pages of the Online Mendelian Inheritance in Man website, which is hosted by the Johns Hopkins University:
www.ncbi.nlm.nih.gov/omim

Further information on the conditions mentioned in this chapter can also be found on this website.