Important points

- It is increasingly clear that translation of the genetic code into proteins is not the only way that our genes influence our growth, development and health and that changes in the genetic information are not the only factors that influence the expression of health problems. For example, environmental factors interact with the information in the genes
- Another system of influence on the expression of genes is referred to as ***epigenetics*** that works in addition to the direct translation of the genetic information: a system that switches the genetic information on and off
- One example of an epigenetic system is where the information in certain genes is active only when it passes to a child through the sperm or the egg. This system of being 'stamped' according to the paternal or maternal origin of a gene copy is called ***'genetic imprinting'***
- It is thought that there are a number of mechanisms whereby the gene may be 'stamped' so that the expression of the inherited genetic information is modified according to whether it is passed to a child through the egg or the sperm. This modification determines whether the information contained in the gene copy is expressed or not
- Even though both imprinting of a gene and a mutation in a gene prevent the gene copy from coding for the gene product, a mutation changes the coded information in the gene permanently. The imprinting modification process is reversible in the next generation
- When a gene is faulty due to a mutation, if it is also subject to imprinting, the expression of that gene is further influenced
- Genetic imprinting occurs in the ovary or testis early in the formation of the eggs and sperm. Imprinting will then occur again in the next generation when that person produces his or her own eggs or sperm
- Evidence for the concept of imprinting: some gene copies inherited from the father control the supply of nutrients to the developing baby through the placenta while some gene copies passed through the egg from the mother are important for fetal development

Epigenetics

The cells of the body contain the genes or set of instructions for the cell to make all the necessary products for our bodies to grow and work normally (see Genetics Fact Sheet 1). The information in the genes is in the form of a genetic code that the cells translate into products such as proteins.

If the information in a gene (ie. the sequence of letters in the DNA) is changed so that it does not work properly, the gene is described as being faulty (ie. there is a gene *mutation* present). The result is that either a protein is produced that is faulty, produced in limited quantity or is not produced at all (see Genetics Fact Sheets 4 & 5).

It is, however, increasingly clear that translation of the genetic code is not the only way that our genes influence our growth, development and health and that changes in the genetic information are not the only factors that influence the expression of health problems. Genetics Fact Sheet 11 discusses the interaction of environmental factors with the information in the genes.

Another system of influence on the expression of genes is referred to as ***epigenetics*** that means 'on top of genetics'.

In other words, it is a system, in addition to the direct translation of the genetic information that switches the genetic information on or off.

To date several epigenetic systems in humans have been described:

- ***X chromosome inactivation*** is the epigenetic system where 'stamping' of the genetic information enables men and women to have equal expression of the genes carried on the X chromosome; despite the fact that women have two X chromosome copies and men have only one -in addition to a Y chromosome (see Genetics Fact Sheet 14)
- This Fact Sheet discusses the epigenetic system of 'stamping' the genetic information that occurs according to whether it is inherited from the mother or the father. This system is called ***'genetic imprinting'***

What is 'imprinting' of genes?

As described in Genetics Fact Sheet 1, each copy of a gene contains an individual and specific instruction for a particular task to be carried out in the cells of the body. These instructions, in the form of a genetic code made up of a sequence of letters in the DNA, tell the cells to produce a protein, for instance a hormone.

There are two copies of every gene carried on the chromosomes numbered 1-22 in each cell of the body:

- One copy comes from the mother (the ***maternal*** copy of the gene on the chromosome copy inherited from the mother)
- One copy comes from the father (the ***paternal*** copy of the gene on the chromosome copy inherited from the father)

Usually, the information contained in both the maternal copy of the gene and the paternal copy is used by the cells to make protein products.

- Both the maternal and paternal genes are usually active or 'expressed' in the cells
- The expression, however, or activity of a small number of the 20,000 or so genes in the cells is dependent on whether the gene copy was passed down from the father or the mother
- This process, whereby the expression of a gene copy is altered depending upon whether it was passed to the baby through the egg or the sperm, is called ***imprinting***

The term ***'imprinting'*** refers to the fact that some chromosomes, segments of chromosomes, or some genes, are stamped with a 'memory' of the parent from whom it came: in the cells of a child it is possible to tell which chromosome copy came from the mother (maternal chromosome) and which copy was inherited. from the father (paternal chromosome).

This expression of the gene is called a 'parent of origin effect' and was first described by Helen Crouse in 1960.

How does imprinting occur?

It is thought that there are a number of mechanisms whereby the gene may be 'stamped' so that the expression of the inherited genetic information is modified according to whether it is passed to a child through the egg or the sperm. This modification determines whether the information contained in the gene copy is expressed or not. Genetic imprinting (or *genomic imprinting*) is the name given to this modification process.

As shown in *Figure 15.1*, if the gene copy is modified, it will be turned off in that person and the cells will not produce any product from that imprinted gene copy.

It is important to remember that this process is not a mutation as described in Genetics Fact Sheet 4 & 5 since the genetic sequence of 'letters' is unchanged.

- Even though both imprinting of a gene and a mutation in a gene prevent the gene copy from making the appropriate gene product *(Figure 15.1),* a mutation is a more permanent change than an imprinting difference
- The imprinting modification process is reversible in the next generation as described below
- When a gene is faulty due to a mutation, if it is also subject to imprinting, the expression of that gene is further impacted

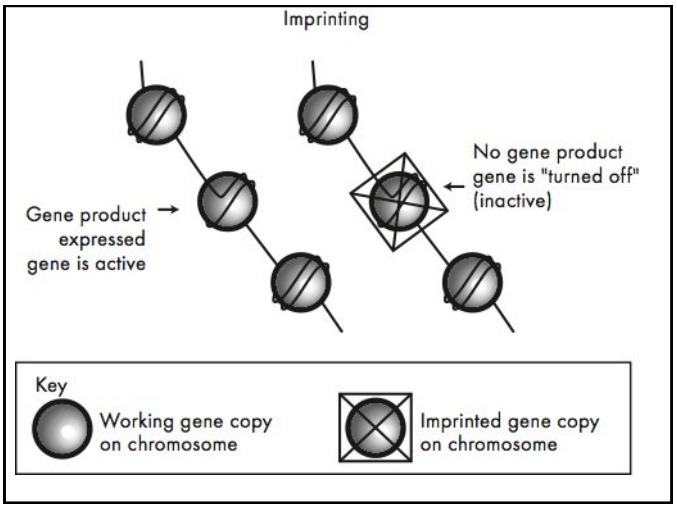

Figure 15.1: *Imprinted genes do not produce any product (they are inactive) depending upon whether they are passed on to the child from the egg or sperm.*

Examples of imprinting

In *Figures 15.2a* and *15.2b*, the inheritance patterns of two different faulty genes that are subject to imprinting are illustrated. These are hypothetical families.

(a) A maternally imprinted gene is 'switched off'

In *Figure 15.2a*, the gene copy inherited by a child from their mother (through the egg) that is causing the condition is always 'switched off' (imprinted). The gene copy remains active when passed to the baby through the sperm.

Joan (in Generation I) has a genetic condition caused by a faulty gene copy she inherited from her father.

- Only the faulty message translated from her father's faulty gene copy is expressed by Joan's cells
- The working copy of the gene, inherited from her mother, is switched off as it passed to her through her mother's egg
- Two of Joan's children, Mary and Jim in Generation II, inherited the faulty gene copy from Joan
- They also received a working copy of the gene from their father but neither of them have the condition. This is because this gene copy is 'switched off' (inactive) when inherited from the mother (passed down the maternal line)
- Thus the only copy of the gene which is active in Jim and Mary is the working copy which they inherited from their father: they are therefore unaffected by the condition

Importantly, both Jim and Mary have, in each of their cells, a faulty, inactive copy of this imprinted gene (inherited from their mother) and a working, active gene copy (inherited from their father). Therefore, Mary and Jim have a 50% chance of passing the faulty gene on to their children.

When **Mary's egg cells** develop, half of her cells will contain the working copy of the gene and half will contain the faulty copy.

- When the faulty gene is passed down to a child through the egg, however, it is switched off
- Therefore, none of Mary's children (Generation III), even those who inherit the faulty copy of the gene, will be affected by the condition, **because the gene is always switched off when passed through the mother**

When **Jim's sperm cells** develop, half of his cells will contain the working copy of the gene and half will contain the faulty copy.

- If the faulty gene copy is contained in the sperm, it remains active ie. it is not switched off
- Thus, any of Jim's children who inherit the faulty gene copy from him will have this gene copy active in their cells **because the gene always remains active when passed through the father**
- Jim's children will be affected by the condition because the faulty gene copy is the only active one: the working copy they received from their mother (Jim's partner) will be switched off

This same pattern of inheritance, where the gene is switched off as it passes through the maternal line, but remains active when it is passed through the paternal line, will occur in the next generation.

- Ben, Jim's affected son, can also have affected children if they receive the faulty gene copy from Ben because it will not be switched off
- On the other hand, Claire, Jim's affected daughter, will not have children with the condition as the gene copy will not be active when passed to the children through Claire's egg

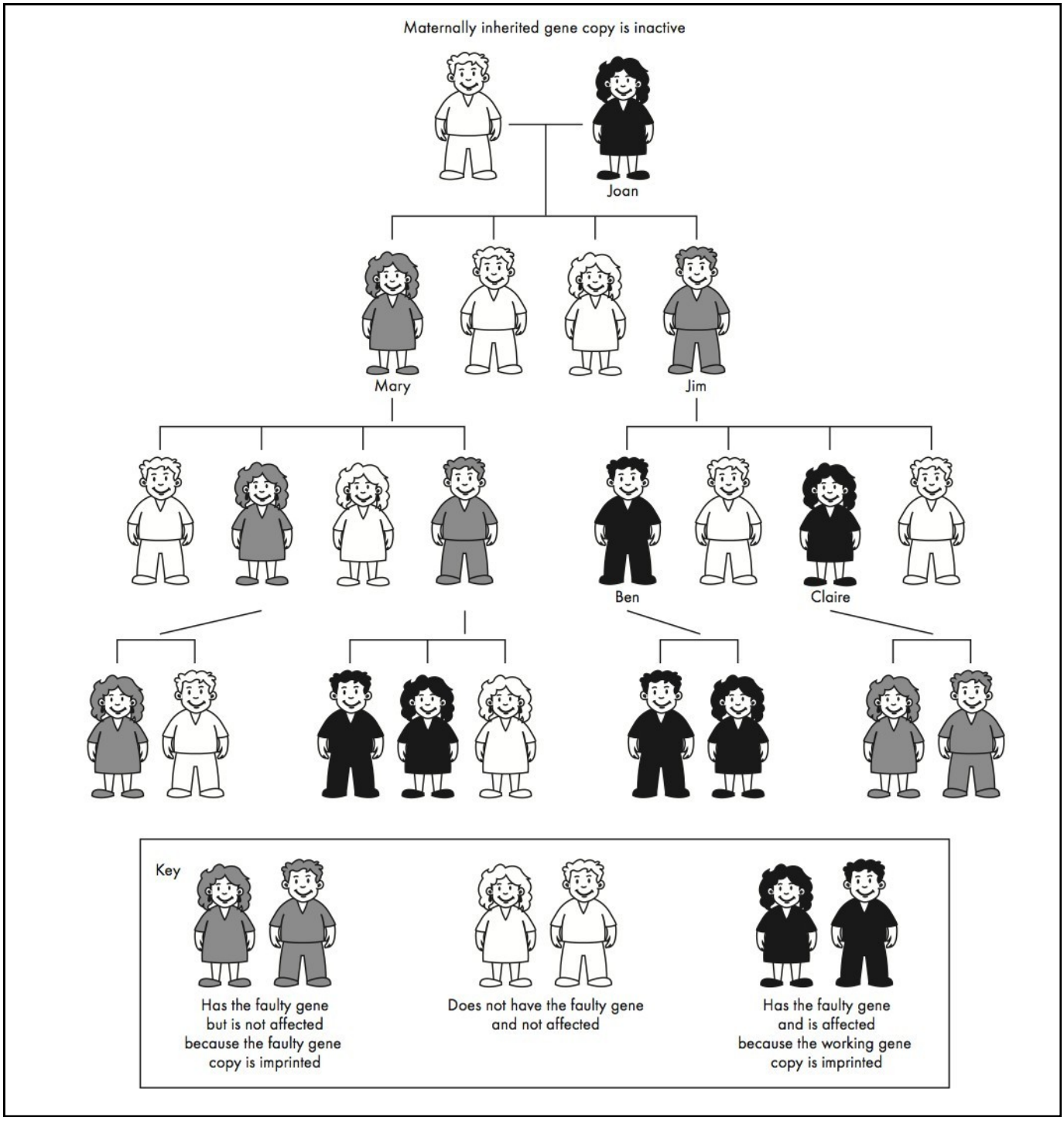

Figure 15.2a: *The faulty gene copy causing the condition is always 'switched off' (imprinted) when it passes to the baby through the egg. It remains active when passed to the baby through the sperm.*

(b) A paternally imprinted gene is 'switched off'

Other genes are imprinted so that they are inactive when they are passed through the paternal line; that is, when they are passed to children in the sperm.

This is shown in *Figure 15.2(b)* where the gene copy is switched off if it passes from father to child and remains active when passed by the mother to her children.

Even though both Anne and Tom inherited the faulty gene copy from their father, Michael, neither Anne nor Tom is affected by having the faulty gene copy.

- As the faulty gene copy is passed to Anne and Tom through Michael's sperm, the faulty gene is 'switched off'
- The only copy of the gene that is active in their cells is the working copy of the gene they received from the mother
- Anne, however, has passed the faulty gene copy to two of her children and they have the condition, as the gene copy remains active when passed to a baby through the egg
- Again, the 'switching off' (imprinting) of the faulty gene copy occurred when it was contained in Tom's sperm. Tom could not have affected children even though two of his children have inherited the faulty gene copy

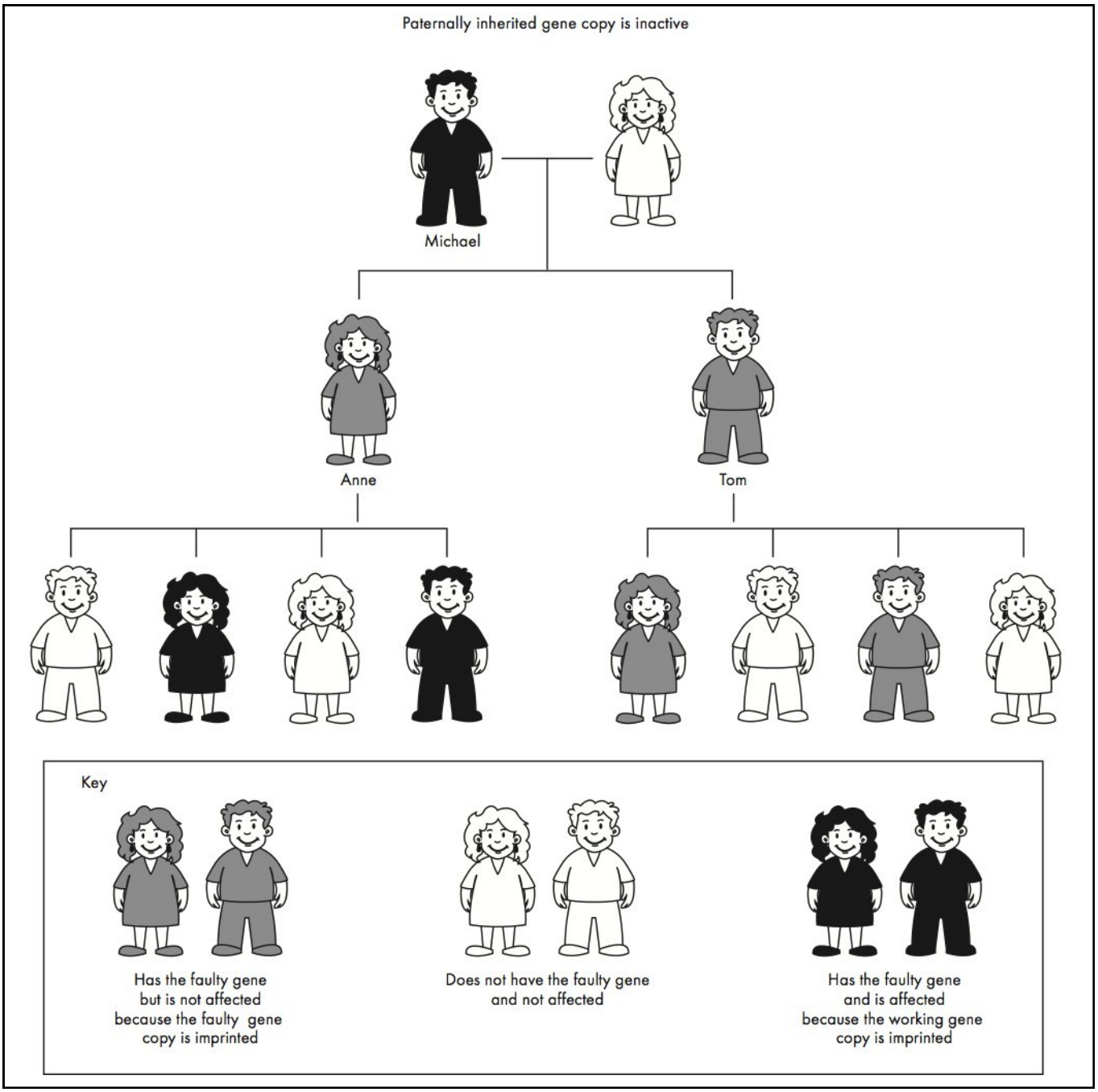

Figure 15.2b: *The faulty gene copy causing the condition is switched off when it is passed from the father to the baby through the sperm and remains active when passed by the mother, to her children, in the egg.*

When does genetic imprinting occur?

Genetic imprinting occurs in the ovary or testis early in the formation of the eggs and sperm.

Some genes are imprinted so that they are switched off or inactive only if they are passed down through an egg cell; others will be inactivated only if they are passed down through a sperm cell.

Imprinting will then occur again in the next generation when that person produces his or her own sperm or eggs.

Are all genes imprinted?

Some chromosomes do not contain imprinted genes. While imprinting is not a common epigenetic mechanism controlling gene expression in humans, it is an important one and provides interesting new insights into the mechanisms of gene expression.

By examining genetic conditions in which problems with growth are a feature, it may be possible to uncover more imprinted genes, and in fact this approach has led to the conclusion that there is an imprinted gene(s) on the long ('q') arm of chromosome 7 (7q). Other imprinted genes are found on the short ('p') arm of chromosome 18 (18p) and the long ('q') arm of chromosome 15 (15q).

More knowledge of imprinted genes and an understanding of the role that these genes play will become available as further information is generated from the completed Human Genome Project (Genetics Fact Sheet 24).

Evidence that genes are imprinted

Genetic imprinting provides a form of control or regulation of the expression of a gene. While it may not be clear to us why this is necessary, there may have been some advantage to survival in the past. It is thought that the imprinting of certain genes provided some regulatory mechanism on growth, particularly on the growth of the baby during pregnancy, which was beneficial to the development of the baby.

This is suggested from studies of some pregnancies that resulted in a miscarriage, in particular, where babies had inherited three copies of every chromosome instead of the usual two copies (is triploid -see Genetics Fact Sheets 1 & 6).

- Usually a baby receives one copy of each chromosome from its mother and the other copy from its father
- In the cases where the babies inherited two copies of each chromosome from their father, and one copy from their mother, the placenta was large and the baby was small
- In the cases where the babies inherited two copies of each chromosome from their mother, and one copy from their father, the baby was large and the placenta was small

These findings gave rise to the theory that some gene copies inherited from the father control the supply of nutrients to the developing baby through the placenta while other gene copies passed through the egg from the mother are important for fetal development.

Uniparental disomy

Uniparental disomy (UPD) occurs when an individual receives both copies of a chromosome from one parent only. Therefore the child inherits some of the genes from one parent only (*uniparental*) rather than the usual situation where one copy of each gene is inherited from the father, and the other from the mother (*biparental inheritance).*

Where the chromosome involved in the UPD is imprinted, there may be implications for that individual. For instance, if there is UPD for chromosome 15, there are different possible outcomes:

- If both copies of chromosome 15 are inherited from the mother (*maternal UPD*), a genetic condition called Prader Willi syndrome occurs
- If both copies of chromosome 15 are inherited from the father (*paternal UPD*) a different genetic condition called Angelman syndrome occurs

These two distinctly different conditions have features including intellectual impairment and characteristic facial features. Different conditions result from the UPD being maternal or paternal, since the effect of imprinting causes different genes to be switched off in each case. Other conditions that may be caused by UPD and imprinting effects include Beckwith-Wiedemann syndrome (an overgrowth condition) and Russell-Silver syndrome (featuring growth delay).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 4, 5, 6, 11, 14, 24