

The Genetics of Beckwith Wiedemann Syndrome (BWS)

Introduction

Beckwith Wiedemann Syndrome (BWS) is an overgrowth disorder caused by changes in the activity of growth promoting and growth suppressing genes. The genetics of BWS are complex, but the effects of the genetic changes are to cause increased activity of growth promoting genes or reduced activity of growth suppressing genes.

What is a gene and how does it work?

Your body is made up of cells. All the information necessary to make up your body is contained in your genes. There are about 30 000 genes in the human body. Genes are made out of DNA. They are arranged on strand like structures called **chromosomes**. In every cell in the body there are 46 chromosomes: 23 are inherited from your mother and 23 are inherited from your father (Figure 1). People with BWS have changes on chromosome 11.

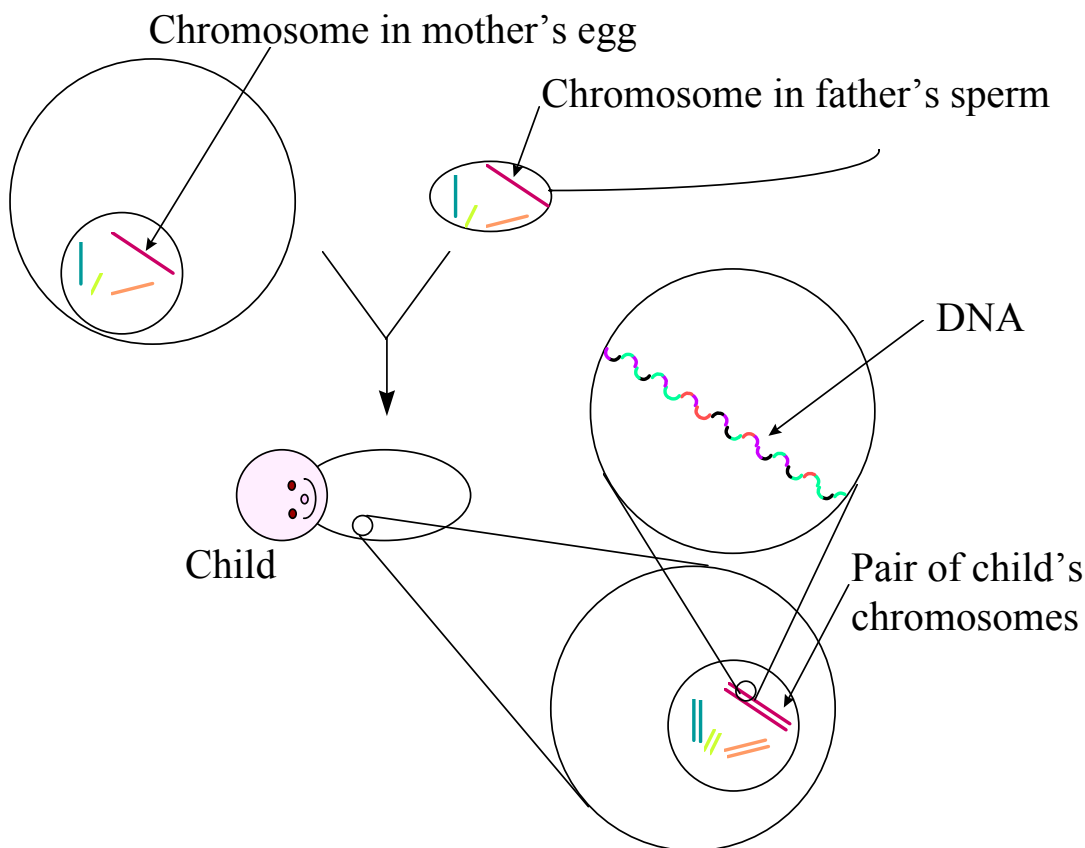


Figure 1: A sperm and an egg each containing 23 chromosomes (only 4 are shown in this figure for simplicity) join and make a baby in whom every cell contains 23 *pairs* of chromosomes (46 chromosomes in total). Each chromosome is made of DNA, and the information encoded in the DNA makes genes.

The job of every cell in your body is to convert the information contained in your genes into the many different chemicals (proteins) that your body needs in order to work efficiently. Not all the possible jobs are done at once, and thus not all genes are active at the same time. For example, the genes that cause hair to grow on chins (beards) need to be active (**expressed**) in men but not in boys

or in women. Sometimes gene expression must be restricted to different parts of the body *e.g.* the genes responsible for sight must only be expressed in your eyes. Gene activity is controlled by chemical switches.

As we have discussed, you inherit two copies of each gene: one copy from your mother (maternal) and one from your father (paternal). For most genes, both copies are active (expressed). However, the part of chromosome 11 that is involved in BWS is special. Some of the genes in this region are **imprinted**. This means that *either* the maternal *or* the paternal copy should be active. In the next section we will see how errors on chromosome 11 are thought to be responsible for BWS.

Causes of BWS

The region of chromosome 11 involved in BWS contains many genes. For simplicity we will concentrate on two genes that have been implicated strongly in BWS:

- A growth suppressing gene **CDKN1C** (active from the maternal chromosome, and sometimes called p57^{KIP2}).
- A growth promoting gene Insulin-like Growth Factor II (**IGF2** which is active from the paternal chromosome).

It can be predicted that genetic changes that result in reduced activity of **CDKN1C** or increased activity of **IGF2** (or both!) would cause overgrowth.

The activity of both of CDKN1C and IGF2 is regulated by chemical switches; CDKN1C is controlled by **KvDMR1** and IGF2 is controlled by **H19 DMR**. These switches are turned ON and OFF by undergoing a process called **methylation**. CDKN1C and IGF2 will only be active if their corresponding chemical switch is in its methylated form, and therefore turned ON.

Usually it is not known why errors in the KvDMR1 and H19 DMR1 have occurred, but there is some evidence from the UK and the USA that in vitro fertilization techniques (IVF, “test tube babies”) may increase the risk of such errors.

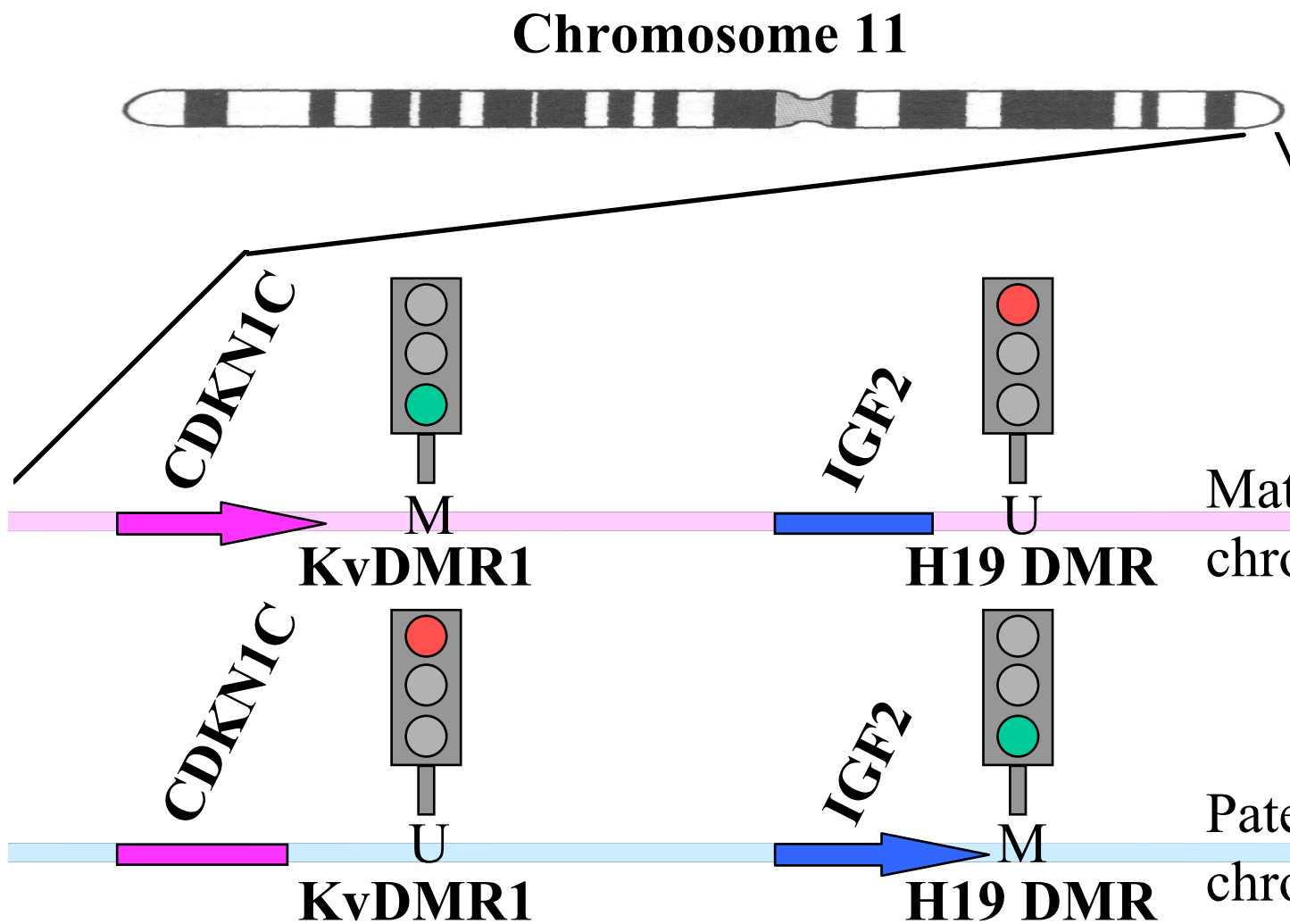


Figure 2: A diagram of the BWS region; the pink line represents the maternal chromosome from which CDKN1C is active and the blue line represents the paternal chromosome from which IGF2 is active. U represents an unmethylated switch (the red traffic light shows that the gene is off). M represents a methylated switch (the green traffic light shows that the gene is on).

Most children born with BWS do not have any relatives with BWS, and there are five known causes of BWS:

- IGF2 can be over-active because both chromosomes 11 have been inherited from the father, this affects one fifth (20%) of patients with BWS. This phenomenon is called paternal uniparental disomy (UPD). These children will have increased IGF2 and reduced CDKN1C expression (because IGF2 is expressed from the paternal chromosome and CDKN1C is not).
- BWS is very occasionally caused by other chromosomal abnormalities. These may be inherited from their parents or may be caused by a mistake occurring in the foetus during pregnancy.
- Mistakes (mutations) in their copy of CDKN1C inherited from the mother are found in roughly one in twenty (5%) children with BWS (although mistakes in CDKN1C are found in one half of families with several members with BWS).

- Reduced levels of CDKN1C due to incorrect methylation of KvDMR1 affects 40-50% of children with BWS (in some cases this can also increase expression of IGF2).
- Increased levels of IGF2 due to incorrect methylation of H19 DMR1 occurs in 5-10% of children with BWS

In some children with BWS none of these 5 mechanisms appears to be present and so there are additional causes for BWS that have not yet been defined !!!

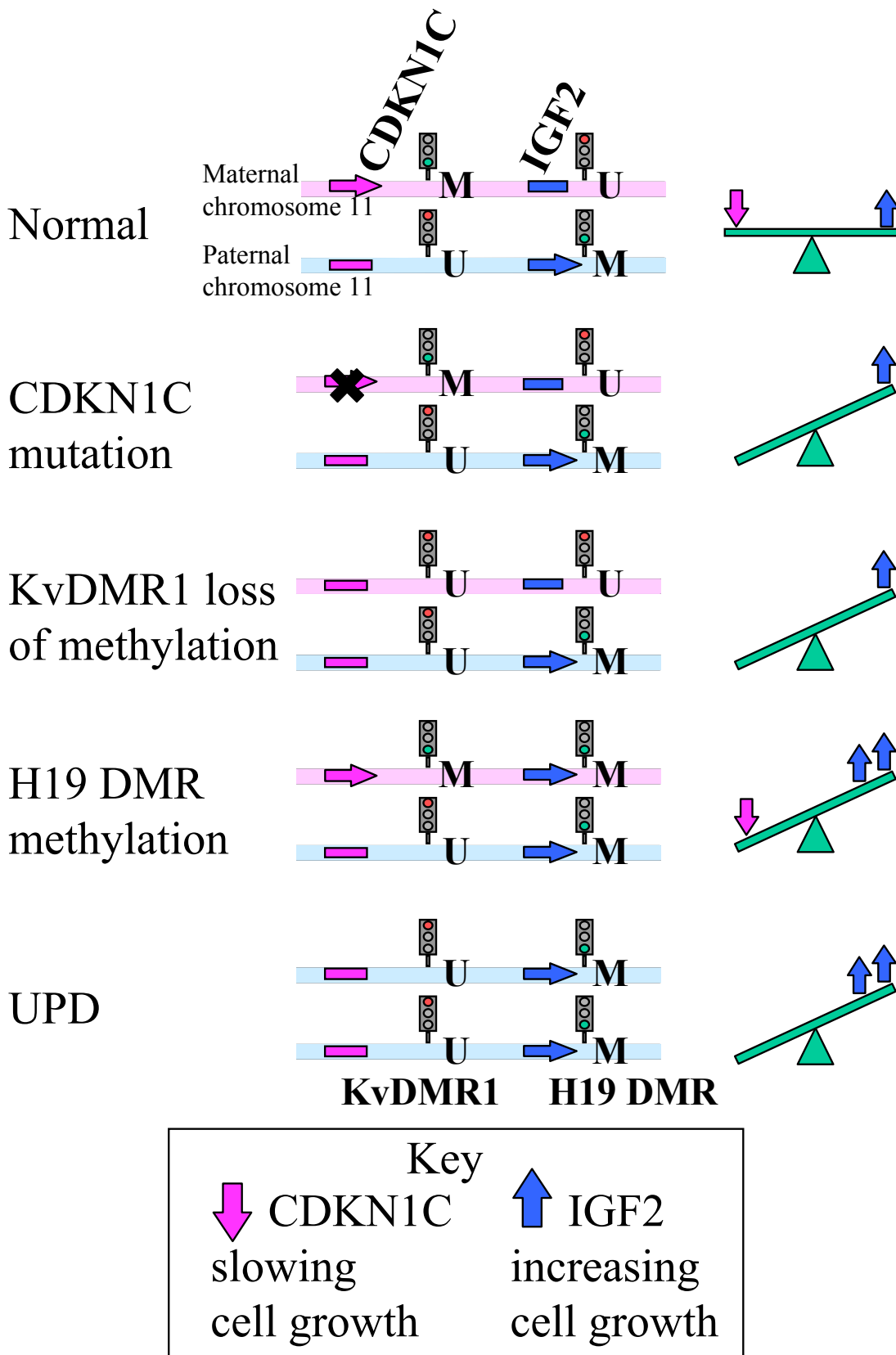


Figure 3: The four most common causes of BWS, and how they cause overgrowth. The pink line represents the maternal chromosome 11 and the blue line represents the paternal

chromosome 11. U represents an unmethylated switch (the red traffic light shows that the gene is off). M represents a methylated switch (the green traffic light shows that the gene is on).

How does the genetic cause of BWS correlate with the symptoms of BWS?

Both reduced CDKN1C activity and increased IGF2 activity can cause symptoms of BWS, but there are subtle differences according to the precise genetic cause. For example BWS children with a mutation in CDKN1C or a reduction in CDKN1C activity are more likely to have **exomphalos** than children with uniparental disomy or H19 DMR methylation change. Children with UPD are often born with one side of their body larger than the other (**hemihypertrophy**). Children with UPD, and those with a methylation error at the H19 DMR switch, have been suggested to be at a higher risk of developing a tumour than other children with BWS.

Testing for BWS

Not all genetic tests for BWS are available – even on a research basis! However NHS testing is available in Birmingham Genetics Centre for 3 tests:

1. Chromosome analysis
2. Testing for uniparental disomy
3. Testing for methylation at the KvDMR1 switch

If these tests are negative it does not disprove the diagnosis of BWS, as there are other causes of BWS that will not have been tested for and other causes that cannot yet be tested for!

Risks to future pregnancies

In the vast majority of cases the risk of a second child affected with BWS is very low if no one else in the family has had BWS. However specific genetic advice should be sought for accurate predictions. If uniparental disomy is found in a child with BWS, the risk to siblings appears to be minimal.

The special nature of imprinted genes helps us to explain the unusual inheritance pattern of BWS where inheriting a mutated copy of CDKN1C from your father has little effect, as the gene is not active from your paternal chromosome 11. Thus a woman with a faulty copy of the CDKN1C gene is at risk of having children affected with BWS. When such a woman has children she will either pass on her normal copy of this gene or the faulty copy. There is therefore a 50% chance of her child inheriting a mutated maternal copy of this gene and thus having BWS. Because CDKN1C is switched off when inherited from the father, a man with a fault in the CDKN1C gene has a low risk of having a child with BWS. Inheritance of familial BWS is complicated and is best discussed with a doctor who is specially trained in clinical genetics.

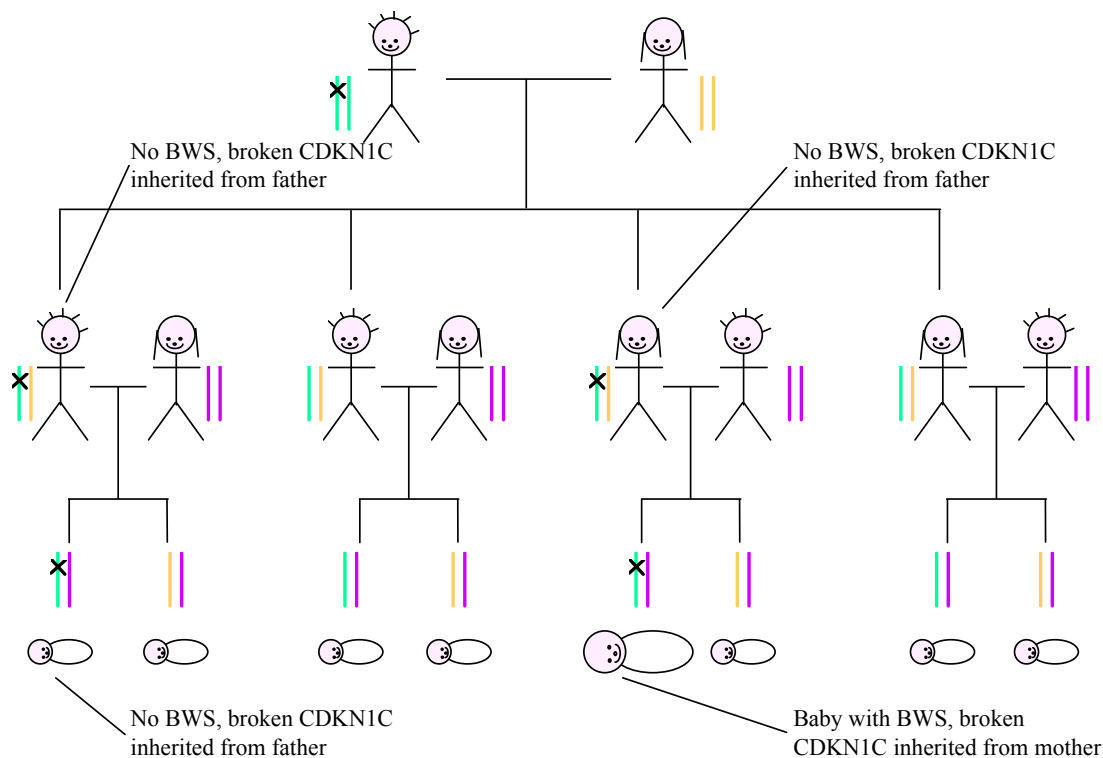


Figure 4: An example of how a mistake in CDKN1C can be inherited.

Summary

Table 1: The genetic causes of BWS

%	Cause	Effect	Test	Symptoms
5	Mistake in CDKN1C	No functioning CDKN1C	Not routine	Increased risk of exomphalos
40-50	KvDMR1 loss of methylation	Reduced CDKN1C expression	Routine testing on NHS	Increased risk of exomphalos
5-10	Methylation of maternal H19 DMR	Overexpression of IGF2	Under development	Increased risk of tumours?
20	UPD	No CDKN1C Overexpression of IGF2	Routine testing on NHS	Increased risk of tumours
1	Chromosomal abnormality	Variable	Testing available on NHS	Variable
Rest	Unknown		Diagnosis by a doctor based on clinical features	

BWS is a difficult disease to understand, but we are beginning to make progress in understanding the cause in the majority of patients. This should allow the clinical diagnosis to be confirmed in most people, and will hopefully lead to a better prediction of which children are at highest risk of developing a tumour, so that they can be closely monitored.

We would like to thank all of the children and their parents who have helped and who are continuing to help with our research.

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Glossary

CDKN1C (previously known as p57^{KIP2}) a chemical made from the maternal chromosome 11 that slows cell growth.

Chromosome a long string of helical DNA that carries genetic information in the form of genes.

Diastasis recti failure of the two rows of abdominal muscle to properly fuse together.

DMR (differentially methylated region) a region of DNA that is methylated on the chromosome inherited from one parent, but not on the copy from the other parent.

DNA (deoxyribose nucleic acid) the thread-like chemical that genes and chromosomes are made from.

Exomphalos failure of the two rows of abdominal muscle to properly fuse together, allowing the abdominal contents protrude, covered only by a membrane.

Expressed a gene is said to be expressed when it is actively producing its chemical product.

Gene a sequence of chemical "words" that performs a particular function. A gene is made from the chemical DNA.

H19 DMR the DMR that probably controls expression of IGF2.

Hemihypertrophy asymmetrical over-growth of one region of the body.

Hepatoblastoma a particular type of tumour of a child's liver.

IGF2 (insulin-like growth factor II) a chemical made from the paternal chromosome 11 that increases cell growth.

Imprinted genes genes where *either* the maternal *or* the paternal copy should be active. Sometimes genes are described as maternally imprinted or paternally imprinted this means that respectively the maternal or paternal copy is turned off.

Inherited passed on from parents to children.

KvDMR1 the DMR that controls expression of CDKN1C.

Macroglossia an enlarged tongue.

Methylation a chemical modification of DNA that switches genes on or off. CDKN1C is active from the methylated (maternal) copy, and IGF2 is active from the methylated (paternal) copy.

Mutation an alteration in a gene that affects its function.

Neonatal hypoglycaemia difficulty regulating the blood sugar in the first few weeks after birth.

Omphalocele American for exomphalos, failure of the two rows of abdominal muscle to properly fuse together, allowing the abdominal contents protrude, covered only by a membrane.

p57^{KIP2} the original name for CDKN1C.

Umbilical hernia failure of the two rows of abdominal muscle to properly fuse together allowing a small section of gut protrudes through the gap.

UPD (uniparental disomy) an absence of maternal chromosome 11 and two copies of paternal chromosome 11.

Wilms' tumour a particular kind of tumour of a child's kidney (named after the doctor who first described it), also known as a nephroblastoma.