

Duplications of 17p



17p duplications

A 17p duplication means that the cells of the body have a small but variable amount of extra genetic material from one of their 46 chromosomes – chromosome 17. For healthy development, chromosomes should contain just the right amount of genetic material (DNA) – not too much and not too little. Like most other chromosome disorders, having an extra part of chromosome 17 may increase the risk of birth defects, developmental delay and learning (intellectual) disability. However, the problems vary and depend on what and how much genetic material is duplicated.

Background on Chromosomes

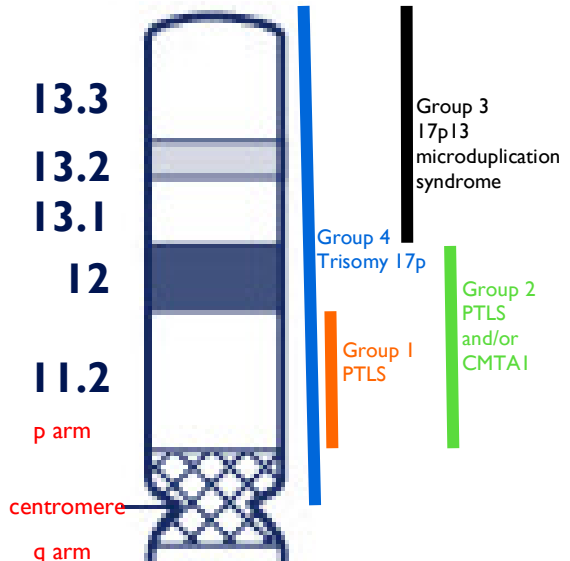
Chromosomes are structures which contain our DNA and are found in almost every cell of the body. Every chromosome contains thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information telling the body how to develop, grow and function. Chromosomes (and genes) usually come in pairs with one member of each chromosome pair being inherited from each parent. Most cells of the human body have a total of 46 (23 pairs of) chromosomes. The egg and the sperm cells, however have 23 unpaired chromosomes, so that when the egg and sperm join together at conception, the chromosomes pair up and the number is restored to 46. Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Chromosome 17 is a medium-sized chromosome and contains around 1500 genes. Each chromosome has a short or petit (p) arm (shown at the top in the diagram opposite) and a long (q) arm (the bottom part of the chromosome).

Chromosome Duplications

A sperm cell from the father and an egg cell from the mother each has just one copy of each chromosome. When they join together they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make the many billions of cells that form during human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes break off or become arranged differently than usual. People with a 17p duplication have one intact chromosome 17, but the other copy of chromosome 17 has an extra piece of the short arm. Although the exact numbers and types of genes that are included in the duplication are often not known, the extra copies of some genes usually have an effect on a person's learning and physical development. Therefore it is believed that most of the clinical difficulties are caused by having three copies (instead of the usual two) of a number of genes. We are still learning about the specific jobs or functions of the genes in these regions (see [Ongoing Research involving 17p](#) on page 24). Also, it is important to keep in mind that a child's other genes, environment and unique personality help to determine future development, needs and achievements.

Looking at 17p

Chromosomes can't be seen with the naked eye but if they are stained and magnified under a microscope it is possible to see that each one has a distinctive pattern of light and dark bands that look like horizontal stripes under a microscope. You can see these bands in the diagram. They are numbered outwards starting from where the short and long arms meet (the [centromere](#)). By looking at your child's chromosomes in this way, it is possible to see what material is duplicated, if the duplicated piece is large enough. The duplicated piece can be small or large. When the duplication includes all or most of the short arm, it is sometimes called a [trisomy](#). A smaller duplication will include just part of 17p.



Duplications can be at the tip of the chromosome (called [terminal](#) duplications) or somewhere in between the two ends (called [interstitial](#) duplications). Because the amount of material duplicated is often small and impossible to see on a routine chromosome test, your child may have been told their chromosome analysis was normal. In fact, many individuals with duplication 17p are not diagnosed. A technique in the laboratory, called FISH can help detect a duplication, but only if the person ordering the test actually suspected that there was an abnormality of a specific region of chromosome 17p. The newest test now available for patient care is called an array CGH or microarray test. A microarray can detect a 17p duplication from a single blood sample even when the doctor ordering the test does not even suspect this diagnosis.

Sources

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>). If you wish, you can obtain most articles from *Unique*. In addition, this leaflet draws on information from two surveys of members of *Unique* conducted in 2004 and 2008/9, referenced *Unique*. When this leaflet was written *Unique* had 39 members with a pure 17p duplication without loss or gain of material from any other chromosome. These members range in age from a child of one year to an adult aged 33 years.

Many more people, described in the medical literature and 11 members of *Unique*, have a loss or gain of material from another chromosome arm as well as a 17p duplication, usually as a result of a chromosome change known as a translocation. As these people do not show the effects of a 'pure' duplication, they are not considered in this leaflet. *Unique* holds a list of the cases described in the medical literature and the karyotypes of those in *Unique*; this is available to members on request.

In some people, cells with a normal chromosome make-up are found as well as cells with extra material from chromosome 17p. This is called **mosaicism** and can, in some cases, lessen the effects of the extra chromosome material.

Generally, people with a 17p duplication fit into one of four groups (see diagram, page 3):

Group 1: People who have an extra copy of the short arm band 17p11.2. This is called **dup(17)(p11.2p11.2) syndrome** or **Potocki-Lupski syndrome (PTLS)**. There are at least 50 people in the published medical literature and 20 registered at *Unique* who have PTLS.

Group 2: Those harbouring a larger duplication that encompasses both 17p11.2 and 17p12 are more likely to be more severely affected. They will often have the features of PTLS but with additional features. Duplications that include the peripheral myelin protein (*PMP22*) gene have **Charcot Marie Tooth type 1A (CMT1A)**. A number of people have been described in the medical literature with a duplication that includes the 17p12 band; in the majority the duplication includes the *PMP22* gene (Lupski 1992; Upadhyaya 1993; Roa 1996; Fernandez-Torre 2001; Moog 2004; Potocki 2007; Doco-Fenzy 2008).

Group 3: People who have an extra copy of the short arm band 17p13. This is called **17p13 microduplication syndrome** and may be an interstitial duplication of part of the 17p13 band, or a terminal duplication that also includes the tip of chromosome 17. There are nine people described in the medical literature with a pure duplication of 17p13 and six registered at *Unique* (Bi 2009; Roos 2009).

Group 4: People who have a complete or almost complete extra copy of the short arm. This is called **trisomy 17p**. Complete trisomy 17p is very rare, having been reported in only two people in the published medical literature. However a number of other people, including ten registered with *Unique*, have an almost complete copy of 17p, often called partial trisomy 17p (Paskulin 2007).

Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point(s) where the chromosome has broken in your child. You will almost certainly be given a karyotype which is shorthand notation for their chromosome make-up. With a 17p duplication, the results are likely to read something like the following example:

46,XY,dup(17)(p11.2p13.1)dn

| | |
|--------------|---|
| 46 | The total number of chromosomes in your child's cells |
| XY | The two sex chromosomes: XY indicates a male |
| dup | A duplication means that there is an extra amount of DNA |
| (17) | The duplication consists of material from chromosome 17 |
| (p11.2p13.1) | The chromosome has broken in two places. The first break is at p11.2 and the second break is at p13.1 so these are the ends of the duplicated section |
| dn | The duplication occurred <i>de novo</i> (or as a “new event”). The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 17p11.2p13.1. The duplication is very unlikely to be inherited so the risk for the parents to have another child with the duplication is very small (less than 1 per cent) |

46,XX,dup(17)(p11.2pter)

- 46 The total number of chromosomes in your child's cells
- XX The two sex chromosomes: XX indicates a female
- dup A duplication means that there is an extra amount of DNA
- (17) The duplication consists of material from chromosome 17
- (p11.2) The chromosome has one breakpoint in band p11.2.
- pter Material from the breakpoint to the end of the short arm (pter) is duplicated

In addition to, or instead of a karyotype you may be given the results of molecular analysis such as FISH or array-CGH for your child. In this case the results are likely to read something like the following example:

46,XX,dup(17)(p11.2p11.2).ish dup(17)(LSI SMSx3)

- 46 The total number of chromosomes in your child's cells
- XX The two sex chromosomes, XY for males; XX for females
- dup A duplication means that material has been repeated
- (17) The duplication consists of material from chromosome 17
- (p11.2p11.2) The chromosome has broken in two places, both in band p11.2 so the duplicated section is band p11.2
- ish The analysis was by FISH
- dup A duplication
- (17) The duplication consists of material from chromosome 17
- (LSI SMSx3) A region of DNA called LSI SMS is present in three copies (instead of the usual two)

You may wish to compare your child with others with the same duplication. It's important to remember that the same duplication can have different effects on different people and there will be differences, between your child and others with an apparently similar karyotype. It is very important to see your child as an individual and not to rely on direct comparisons with others who appear to have the same karyotype. After all, each of us is unique.

Breakpoints in Unique families

Bracketed numbers show numbers of families on the *Unique* database (2009).

| Duplication of 17p11.2p11.2 (PTLS) | Larger duplications that include 17p11.2 plus additional material (that may or may not include PMP22) | 17p13 microduplication syndrome | Complete or partial trisomy 17p |
|--|---|--|------------------------------------|
| 17p11.2p11.2 (11) 17p11.2p11.2 (mosaic) | 17p10p11.2 (mosaic) 17p10p12 17p11.2p12 (3) 17p11.2p13.1 | 17p13.3 - pter (2) 17p13.1p13.1 17p13.1p13.2 17p13.1p13.3 17p13.3p13.3 | 17p11.2 - pter (9) 17p12 - pter |

Most common features of a duplication of 17p

Every person with a 17p duplication is unique and so each person will have different medical and developmental concerns. Additionally, no one person will have all of the features listed in this leaflet. However a number of common features of the various duplications of 17p have emerged:

PTLS

- Growth delay both in the womb and after birth leading to lower than average weight and height
- Feeding difficulties
- Hypotonia (floppiness or unusually low muscle tone) in newborn babies
- Behaviour difficulties such as hyperactivity and autistic features
- Speech and language delay
- Characteristic facial features
- Learning (intellectual) disability. All children with PTLS should have a developmental assessment so their educational program can be tailored appropriately
- Heart defects at birth and/or widening of the aorta with age
- Scoliosis
- Sleep apnoea

Charcot-Marie-Tooth type 1A

Children whose duplication includes the *PMP22* gene develop a condition known as Charcot-Marie-Tooth type 1A (CMTA1) (Roa 1996). Your child's geneticist or paediatric specialist will tell you if the *PMP22* gene is duplicated or not. This condition is characterised by peripheral neuropathy which is a progressive wasting and weakness in the legs, feet and hands. Children often also have an unusual walk. However, the condition can be highly variable, even within the same family (see [Ongoing Research involving 17p](#) on page 24 for further information on *PMP22*).

17p13.3 microduplication syndrome

- Hypotonia in newborn babies
- Speech and language delay
- Characteristic facial features
- Some children will need support with learning. The amount of support needed by each child will vary
- Some children are unusually tall

Trisomy 17p

Those with trisomy 17p may have a duplication that includes some, or often all, of the three duplicated regions described above. Therefore children with trisomy 17p may have any of the features described for these three groups. However, the features that have been most often associated with trisomy 17p include:

- Growth delay both in the womb and after birth leading to short stature
- Feeding difficulties

- Hypotonia in newborn babies
- Characteristic facial features
- Learning (intellectual) disability. Many children will need support with learning. The amount of support needed by each child will vary
- Microcephaly (an unusually small head)

How common are 17p duplications?

Duplications of 17p have been rarely detected and only around 50 people have been reported in the published medical literature. However, it is thought that there are many more people with PTLs or 17p13 microduplication syndrome who have not been diagnosed. Deletions of the same regions of 17p have been reported much more frequently. Deletions of the region of 17p that is duplicated in PTLs give rise to Smith-Magenis syndrome (SMS) and deletions of the region of 17p that is duplicated in 17p13 microduplication syndrome result in Miller-Dieker syndrome (MDS). Individuals with SMS and MDS usually have a more distinctive physical appearance, and may be more likely to have their chromosomes tested. Also, a deletion of a chromosome is much easier to see under the microscope than a duplication, so until array CGH is more widely used the number of persons diagnosed with deletions will be greater than the number of those diagnosed with duplications. However, we now know that the frequency of the duplication and the frequency of the deletion should be about equal and we expect that more individuals with dup17p will be diagnosed as physicians in the community become more familiar with the array CGH test.

Are there people with a 17p duplication who are healthy, have no major medical problems or birth defects and have developed normally?

In many children with a 17p duplication, no major internal organs are affected so children are often healthy and without major medical problems. However, all those so far reported with a 17p duplication have some degree of learning difficulties and/or motor delays. However, since duplications of 17p11.2p11.2 (PTLS) and 17p13 microduplications are likely to be under-reported, it is certainly possible that there are many people with small duplications of 17p who are mildly affected by the duplication and who therefore have never been identified or reported by the medical profession.

What is the outlook?

The outlook for any baby or child depends on what segment of chromosome 17 has been duplicated and how this has disrupted early development in the womb. Since most of those who are known to have a 17p duplication are children, long term follow-up is necessary. However, in many children no major internal organs are involved and for them the outlook seems good. There are two babies in the published medical literature with complete trisomy 17p who have died before the age of one following surgery for complex heart conditions (Martsof 1988; Paskulin 2007).

“ He is a very healthy child who last year had a 97% attendance record at school!
– 8 years with a 17p11.2p13.1 duplication

Pregnancy and birth

Many mothers carrying babies with 17p duplications experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, of the 17 families who have told us about their pregnancy experiences, four babies were small for gestational age or were described as having intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed resulting in babies that are smaller than expected for the number of weeks of pregnancy. Two babies showed little fetal movement while in the womb. A number of parents also had unusual findings when undergoing ultrasound scans: one baby with a 17p11.2p11.2 duplication was shown to have an echogenic bowel (the bowel looks white rather than grey and speckled, on the scan); another baby (with a 17p10p12 duplication) had enlarged ventricles (fluid filled regions of the brain), although at the upper limit of the normal range, at a 20-week scan, although a subsequent scan at 28 weeks was normal. One baby with a 17p12pter duplication was shown to have a cleft palate and possible kidney and brain anomalies. This baby was born at 34 weeks after induced labour due to loss of amniotic fluid and the mother had pre-eclampsia (causing a sudden increase in blood pressure and the presence of excess protein in the urine). If left untreated, pre-eclampsia can have serious complications for both mother and baby (*Unique*).

There is only one case in the published medical literature where a duplication of 17p was diagnosed prenatally. A duplication of 17p11.2pter was detected after amniocentesis was performed due to multiple anomalies and IUGR were picked up on a prenatal ultrasound scan (Kulhaya 1998).

Three mothers in the published medical literature had prenatal screening results that suggested an increased risk of Down syndrome. Prenatal chromosome analyses were performed for two of these mothers but the results were interpreted as normal despite their babies later being diagnosed as having a 17p11.2p11.2 duplication. Prenatal diagnosis was undertaken for a further mother (because of parental anxiety) which also failed to detect a 17p11.2p11.2 duplication. In yet another case, an amniocentesis performed after multiple anomalies were found on a prenatal ultrasound scan failed to detect a 17p13.3pter duplication. Standard chromosome analysis performed after amniocentesis is likely to be normal if the duplication is small, however an array CGH analysis will detect these chromosomal duplications 100 per cent of the time (Potocki 2007; Doco-Fenzy 2008; Roos 2009).

Newborn

Typically babies with a duplication of 17p are floppy (hypotonic) in the newborn period. This can result in delay reaching the baby developmental milestones (such as sitting, rolling, crawling and walking) and also cause feeding problems. Babies with PTLs or trisomy 17p often also have feeding difficulties. Many babies with PTLs experience spells of apnoea (pauses in breathing) and some may need extra oxygen within the newborn period (*Unique*).



4 months with a
17p10p12 duplication

Growth and feeding

Babies are often, but not always, small and underweight at birth. Regardless of the region of 17p that is duplicated, birth weights recorded at *Unique* show a considerable variation with an average of 3.088 kilos (6lb 13oz). Around 15 per cent of the *Unique* babies had a low birth weight (below 2.6 kilos or 5lb 12oz) at term (*Unique*).

Range of birthweights at *Unique* (at or near term):

2.381 kilos (5lb 4oz) to 4.223 kilos (9lb 5oz)

For those with a duplication of 17p, feeding difficulties are a major area of concern for families, particularly as babies usually start out small and underweight. After birth, babies tend to grow more slowly than their peers, with a small minority of babies described as “failure to thrive”. This term is used to describe a baby who has poor weight gain and physical growth failure over a period of time. The hypotonia that is common in babies with a 17p duplication (regardless of the part of 17p that is duplicated) can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft or high palate can also find the action of sucking and swallowing difficult. Many babies have a small appetite and struggle to finish a feed. Eleven of the 16 mothers surveyed by *Unique* attempted to breastfeed their babies, although only four established successful breastfeeding. However, a number of babies were bottle-fed expressed milk. Four out of 26 *Unique* babies benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat). As some of these babies matured enough to suck effectively, the NG-tube could be removed and breast or bottle feeding established. A further three babies who initially benefited from temporary NG-tubes later needed gastrostomy tubes (a G-tube, feeding direct into the stomach) in order to meet their nutritional needs (*Unique*).

The hypotonia can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). In the *Unique* survey, almost a third of babies had reflux. This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (*Unique*).

As children grow many develop normal eating habits and eat a wide variety of foods. However, a minority continue to have feeding difficulties. Some older babies and toddlers have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers and the start of finger feeding may be delayed. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems. Two *Unique* children needed food to be liquidised until the age of 4. Another had food aversions as a toddler and still has a limited diet at the age of 7½. As a result of these feeding difficulties a number of families have consulted a dietician and/or nutritionist (*Unique*).

Children with a duplication of 17p are often of small stature. However, there are some reports of those who have 17p13 microduplication syndrome who are unusually tall.

The evidence at *Unique* is mixed: 3/5 of those with 17p13 microduplication syndrome are described as small or tiny, and 2/5 are described as tall (Roos 2009; *Unique*).

“ She is very tall and very thin – 2 years with a 17p13.1p13.3 duplication

“ He had feeding problems as a baby but by the age of one he was fine. He eats all sorts now and has a good appetite – 4½ years with a 17p11.2p11.2 duplication

“ As a newborn he had difficulties latching onto the breast. There were no problems with switching to the bottle. He started having real food aversions as a toddler. We attended a 12 week feeding program when he was 4 years of age with no real progress. He still has an extremely limited diet – 7½ years with a 17p11.2p11.2 duplication

Appearance

Children with a duplication of 17p sometimes have facial features in common. Some babies (irrespective of their duplication) have a small head (microcephaly) with large low set ears. They may have a triangular face with a broad forehead, full cheeks and a thin upper lip or small mouth. They may have widely spaced eyes (hypertelorism) with down-sloping eyes (palpebral fissures) a broad nasal bridge. Those with trisomy 17p or 17p13 microduplication syndrome may have a short neck. However, these facial features can be very subtle and children look little different compared to other children and may closely resemble their siblings or parents (Paskulin 2008; Roos 2009; *Unique*).

Learning

Learning difficulties and intellectual disabilities are common in children with a 17p duplication, with most children mildly or moderately affected and a very small minority severely affected. As always, there is individual variation, and a few children have borderline learning difficulties. However, many children will need support and benefit from early intervention programmes and may thrive best in a special learning environment. Around half of *Unique* children attend mainstream school, often receiving some learning support or 1:1 help in the classroom with the other half benefiting from a special education school (*Unique*).

A study carried out in the USA assessed the learning difficulties of children with a 17p11.2p11.2 duplication and found that all had mild to moderate learning difficulties with the exception of two who were borderline (Potocki 2007). A recent study assessed 15 children with a 17p11.2p11.2 duplication and found that 13/15 had an intellectual disability (Treadwell-Deering 2010). Those children with 17p13 duplication syndrome have so far also been shown to have mild to moderate learning difficulties (Roos 2009). There is less information in the published medical literature about those with trisomy 17p but evidence seems to suggest that they may be more likely to be severely affected (Martsolf 1988).

Typically children are persistent and hard-working and this helps them to reach their full potential. Some children learn to read and write. The *Unique* experience is that those who master reading do so between the ages of 5 and 8 years (with an average of 6 years and 10 months). Those mastering writing do so between the ages of 5 and 7 years (with an average of 6½ years). For some children, hypotonia can make writing or drawing difficult and many children find using a keyboard to write easier than a pencil or pen. This level of achievement is not possible for all children and a number do not master reading or writing, although some can recognise their own name and make

simple drawings. Children generally have a good memory. A number of children are hyperactive or described as being easily distractible or having a short attention span which can make learning more of a challenge (see [Behaviour](#) page 20) (*Unique*).

“ He seems to have a good memory and loves music. He has good visual matching skills. He cannot read but can pick his name out from all of his classmates' names – 4½ years with a 17p11.2p11.2 duplication

“ She wants to learn and tries very hard. She needs 1:1 at all times – 4½ years with 17p13.1p13.2

“ He has a wonderful memory and a wonderful fun personality! He is a visual learner and does a lot by memory. He reads very basic books and can write his name and draw basic figures – 6 years with a 17p13.3p13.3 duplication

“ He receives minimal assistance (1 hour/day) with writing and maths. His reading is slightly above grade level. He has an excellent memory if it involves his preferred subjects. It requires lots of repetition if it's something he doesn't care about – 7½ years with a 17p11.2p11.2 duplication

“ He has a great memory. He can sound out all the alphabet and can put two and sometimes three letters together. He can draw simple people and can write out all his letters - 8 years with a 17p11.2p13.1 duplication

“ We believe he has a good memory. He recognizes people and things that he hasn't seen in a very long time. However, when learning new tasks he struggles and needs a lot of repetition. He does not like paper and pencil tasks but learns better with things he can do with his hands – 11 years with a 17p12p12 duplication

“ She has an excellent memory. She is interested in history and can remember the queens of Henry VIII. She enjoys most subjects and remembers facts well. She has poor reading but can read at least 20 key words and is improving each week. At a recent parents evening the teachers were very pleased with all areas of learning. She is making excellent progress! – 12 years with a 17p11.2p11.2 duplication

“ He enjoys school but lacks confidence in his work. He is looking forward to going to college soon. He has a very good memory. He loves to read Dr Who magazines. He is confident at writing and writes at the level of a 10-year-old. He needs a calm environment and lots of adult supervision in order to learn well – 16 years with a 17p11.2p12 duplication

“ She is quite good at art and likes to read simple books. She can write and draw – 19 years with a 17p11.2p11.2 duplication

*12 years with a
17p11.2p11.2 duplication*



Speech and communication

Speech is almost always delayed in those with a 17p duplication with first words emerging between the ages of two and six years. Many children use sign language and/or PECs (picture exchange communication system) help to communicate their needs and wants. Often, as speech is mastered, they find they no longer need these aids. Evidence in the literature, which is also backed up at *Unique*, suggests that many children have better receptive language than expressive language: they understand more than they can express. Many children have articulation difficulties. Speech therapy has proved extremely beneficial to many children and children can go on to speak in complex sentences and have a very large vocabulary, although the articulation difficulties may remain. However some children do not master language and continue to use gestures, facial expressions and vocal noises to indicate their needs and express their feelings (*Unique*).

The evidence in the published medical literature reflects these observations at *Unique*. All ten children who participated in one study in the USA had articulation problems and difficulties with motor planning and/or sequencing sounds within words. Three out of ten used augmentative communication such as signing and PECs (Potocki 2007). A boy with a 17p13.3 microduplication had four words at age 2 but after speech therapy he had good verbal skills at the age of 14 (Roos 2009).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which in addition to insufficient sucking, can also affect the development of speech. Those with a cleft or high palate may also have specific difficulty with certain sounds (*Unique*).

“ He has about 80 Makaton signs. His speech started around the age of 4 and has made good progress since starting the Nuffield dyspraxia programme. He tries very hard – 4½ years with a 17p11.2p11.2 duplication

“ She has 75-100 signs and about 20 spontaneous words. She will mimic speech. She uses one to two word sentences – 4½ years with 17p13.1p13.2

“ She speaks in full sentences – 6 years with a 17p13.3pter duplication

“ He uses speech and signing. He speaks in three or four word phrases but his articulation is bad – 6 years with a 17p11.2p11.2 duplication

“ His speech was very delayed and he only had about 12 words at the age of 3. Now he doesn't stop talking and is using new words every day. He uses full sentences but does get words mixed up. His speech is very clear although he finds some words difficult – 8 years with a 17p11.2p13.1 duplication

“ He has limited speech which is developing slowly. He learns in fits and starts – 9 years with a mosaic 17p11.2p11.2 duplication

“ He has very strong receptive language. He has some limited signs and tries to vocalise with speech, mostly single words. He does try to put two or three words together to form a sentence. Speech is very limited and most words do not contain the first syllable – 11 years with a 17p12pter duplication

“ She speaks in long sentences but with a stutter. She has ongoing speech therapy. She did use some signing but found it difficult because of poor fine motor skills – 12 years with a 17p11.2pter duplication

“ She uses noises, gestures and has limited PECs in order to communicate – 14 years with a 17p10pter duplication

“ He has good communication skills now, and we never thought that would happen! His speech is appropriate for his age although it can be immature at times – 16 years with a 17p11.2pter duplication

“ She speaks normally although sometimes she has difficulty saying certain words – 19 years with a 17p11.2pter duplication

Development: sitting, moving, walking (gross motor skills)



*4½ years with a
17p11.2p11.2
duplication*

Children with a 17p duplication are typically slow to reach their developmental motor milestones.

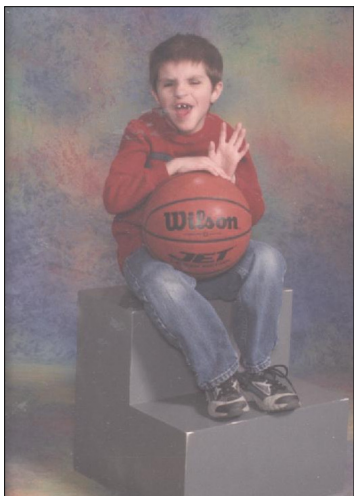
The medical literature reports that children with PTLs walk on average at age 31 months (range 18 months to 5 years). The *Unique* experience is that babies start to roll between 4 months and 20 months (average 7½ months); sit between 6 months and 3 years (average 11 months) and crawl between 8 months and 4 years (average 18 months).

Some children, however, do not crawl but instead move around by bottom shuffling. Independent walking was mastered between 14 months and 5½ years (average 26 months). Some children need support (such as a standing frame, walking frame, wheelchair, support boots and/or a supportive Lycra ‘second skin’) while learning to walk. Most children go on to walk, climb stairs and run, although they can be unsteady with poor balance and co-ordination. Some children walk with a wide gait and trip easily (Potocki 2007; *Unique*).

Children and adults with CMT1A are affected by a slow progressive muscular weakness that usually begins between the ages of 5 and 15 years. The first sign is often difficulties walking due to picking up the feet and a high arched instep. After many years the weakness may spread upwards in the lower limbs to affect the calf muscles, knees and thighs. The hands may also become weak. Some people with CMT1A may have a loss of sensation in their hands and feet. As a result of this weakness children may need special footwear and there may be some impairment of mobility for adults in middle life.

There are several reasons for these motor delays including the hypotonia that affects 90 per cent with PTLs, 60 per cent of those children with a 17p13 duplication and 80 per cent who have trisomy 17p. Hypotonia often improves as children mature; nonetheless, early physiotherapy and occupational therapy can be beneficial. Physical activities enjoyed by some children at *Unique* include swimming, riding a tricycle, bicycle

or scooter, playing football, basketball, gymnastics, dancing, trampolining and horse-riding. Due to the possibility of heart conditions in children with a 17p duplication, it is advisable for these children to have a cardiac examination before undertaking any strenuous physical activity (Paskulin 2008; Roos 2009; *Unique*).



*6 years with a
17p12pter duplication*

“ She crawled at 19 months and sat at 12 months. She is not walking yet but uses a standing frame. She can bear weight but is not steady – 2 years with a 17p13.1p13.3 duplication

“ She walks but gets tired very easily due to her weakness. Her right leg is a fair bit weaker than her left. She is able to climb stairs one at a time because her right leg is too weak to push up on. She loses her balance very easily and will trip over anything that is on the ground – 4 years with a 17p11.2pter duplication

“ She did not walk unaided until 5½ years – 6 years with a 17p13.3pter duplication

“ His mobility is now very good although he still has a few problems with balance and so he is careful – 6 years with a 17p11.2p11.2 duplication

“ He can run, jump, climb, gallop, ride a bike with training wheels and throw a ball. He still cannot skip or catch a ball – 7½ years with a 17p11.2p11.2 duplication

“ He has no mobility problems – 8 years with a 17p11.2p13.1 duplication

“ She moves around very well. She is still unable to catch a ball very well and needs a little help going down very steep steps. She swims 50 metres, rides a horse and has learned to ride a bike without stabilisers [trainer wheels] – 12 years with a 17p11.2p11.2 duplication

“ She was unable to sit unaided until 3 years old and did not walk until 4½ years

“ She still needs help on stairs – 14 years with a 17p10p12pter duplication

“ He moves around well but has a tendency to walk into things or bang his elbows or legs going through doorways – 16 years with a 17p11.2pter duplication

“ She moves around normally – 19 years with a 17p11.2p11.2 duplication

Development: hand-eye co-ordination and dexterity (fine motor skills) and self care

Hypotonia can also affect fine motor skills in children with a 17p duplication and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups

with handles and cutting up food have helped some children. Some children with a 17p duplication also have lax, excessively mobile joints that can make tasks that involve fine motor skills (such as holding a pen or using scissors) a challenge. For those children who have problems holding and controlling a writing implement, mastering a keyboard or touch screen computer can often be easier. Many children have occupational therapy in order to help improve these skills (*Unique*).

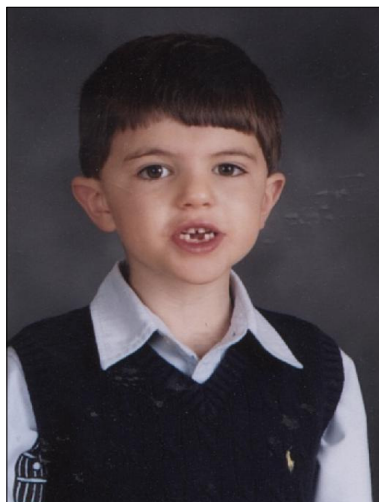
As a result of these difficulties, children are likely to continue to need help with dressing and undressing. They will also require assistance in tasks such as brushing teeth and washing. Toilet training is also likely to be delayed. The information at *Unique* shows that consistent toilet training was mastered between 2½ years and 11 years (average 4½ years) (*Unique*).

“ She has great fine motor skills – 2 years with a 17p13.1p13.3 duplication

“ He wears nappies at night-time but has been toilet trained since 3½ years. He tries to put on his clothes and has been successful so a new skill is developing. He will wash parts of his body when asked – 4½ years with a 17p11.2p11.2 duplication

“ He still only uses one hand and it is difficult for him to grasp items between the thumb and forefinger – 6 years with a 17p11.2p11.2 duplication

“ He can dress himself but still needs help with buttons and zips. He is left-handed and his writing is illegible. He has difficulties with scissors but can type very well – 7½ years with a 17p11.2p11.2 duplication



5 years with a
17p13.3pter duplication

“ He was clean during the day at 19 months and at night by 3½ years. He is able to brush his teeth and get dressed but he often puts his clothes on round the wrong way and finds socks hard to put on – 8 years with a 17p11.2p13.1 duplication

“ His fine motor skills are delayed but he gets there in the end. He can hold a pen and write his name clearly but was 8 years old before he drank from a cup! – 9 years with a mosaic 17p11.2p11.2 duplication

“ He was toilet trained at 8 years but still wears pull-ups at night-time – 11 years with a 17p12pter duplication

“ She has very good independence skills. She dresses herself, washes, makes a sandwich and is very organised – 12 years with a 17p11.2p11.2 duplication

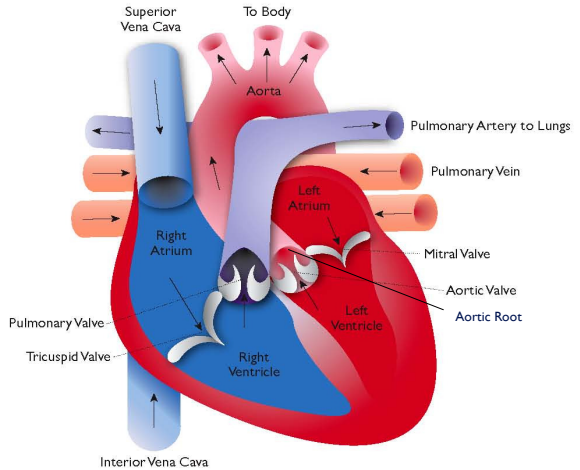
“ She could not hold a spoon to feed herself until she was 5½ years old. She is not interested in holding a pen – she has hand-over-hand assistance at school – 14 years with a 17p10p12pter duplication

Medical concerns

■ Heart problems

Heart (cardiac) conditions have been reported in the medical literature to affect up to half of all babies born with PTLS and around two thirds of those with trisomy 17p. However, heart conditions are reported less frequently among *Unique* members with around a quarter of children with a PTLS or trisomy 17p affected. (The reduced frequency may be due to a number of children not having had a cardiac examination.)

The most common heart problems are holes between the upper or lower chambers of the heart (ventricular septal defects (VSD) or atrial septal defects (ASD)). In many children these defects heal (close) naturally without surgery. Other reports at *Unique* and in the medical literature are a bicuspid aortic valve (the valve that regulates blood flow from the left ventricle into the aorta has two flaps instead of the usual three); mitral valve regurgitation (leakage of blood from the left lower chamber of the heart through to the left upper chamber), dilated aortic root (the aortic root, see diagram, becomes enlarged which can result in leakage of blood back through the aortic valve) and hypoplastic left heart (the left side of the heart is underdeveloped). There have been no reports in the medical literature of children with a 17p13 duplication with a heart condition, although one member of *Unique* with a 17p13 duplication had mitral valve regurgitation on a heart scan performed at birth (Potocki 2007; Paskulin 2008; *Unique*).



■ Vision

A squint (strabismus), where one or both eyes can turn inwards, outwards or upwards, is the most common vision problem noted by *Unique* families. Many squints are convergent (the eyes cross) and many children need surgery to re-align the eyes.

However, researchers have reported that long sight (hypermetropia) is the most common vision problem in those with PTLS with as many as 60 per cent affected (the evidence at *Unique* is that around a third are affected). Short sight and astigmatism (the cornea, the clear cover over the iris and pupil, is abnormally curved resulting in blurred vision) have also been reported in the medical literature and at *Unique* to affect those with a 17p duplication. These problems are often mild and can be corrected with glasses (Potocki 2007; *Unique*).



9 years with a mosaic duplication of 17p11.2p11.2

A number of other vision problems have been reported more rarely. Three children at *Unique* (one with a 17p12pter duplication and two with PTLs) are very sensitive to light; one *Unique* child with PTLs has nystagmus (rapid, uncontrolled eye movements) and difficulties with depth perception (*Unique*).

■ Hearing

More than half of *Unique* children surveyed reported excessively sensitive or acute hearing and an exaggerated response to loud noises. Some children appear to outgrow this problem although for others it remains a problem (*Unique*).

Hearing impairment is common in children with chromosome disorders and has been reported in around a quarter of *Unique* children with a 17p duplication. The most common cause of hearing impairment is glue ear, where there is a build-up of fluid in the middle ear. Glue ear usually resolves as children get older and the ear tubes widen and become more vertical resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear and glue ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum. Two *Unique* children (one with a 17p11.2p11.2 duplication and one with a 17p13 duplication) have a slight bilateral (affects both ears) high frequency hearing loss (*Unique*).

■ Seizures

Seizures are not a major feature of 17p duplications. Two of the 16 children who took part in the *Unique* survey had suffered from at least one seizure. One was a child with PTLs who suffered one seizure at age 2 and another age 4. The second child, with a 17p13 duplication, developed a seizure disorder at the age of 3½ years which was well controlled with medication at 4½ years. In one study in the published medical literature, none of the ten children with PTLs reported seizures. However, all of those who underwent an electroencephalogram (EEG) examination (a recording of the brainwave patterns from the continuous tiny electrical signals coming from the brain) had unusual findings (Potocki 2007: *Unique*).

■ Feet

The feet of those with a 17p duplication are often not perfectly formed. Anomalies include talipes (clubfoot), overlapping toes, high arches, flat feet and/or feet that turn inwards. Some children who have clubfoot may need surgery to correct the unusual positioning of their feet, although for other children plaster and splints may be sufficient. Generally the foot anomalies may mean that children require special insoles or inserts in their shoes or special supportive footwear (Morelli 1999; Roos 2009; *Unique*).

■ Hands

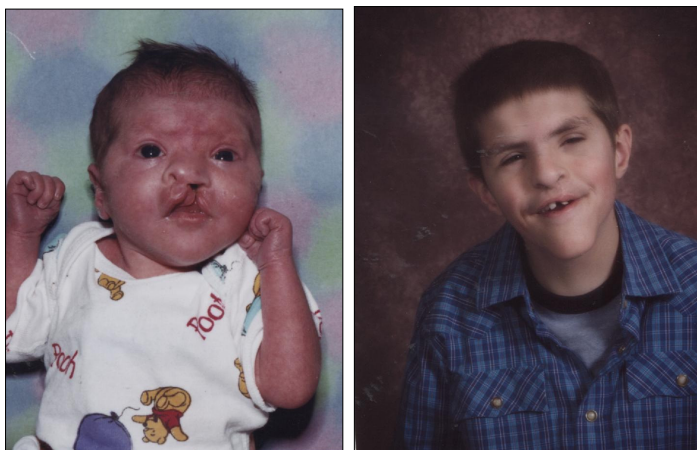
Some children with trisomy 17p, PTLs and 17p13 microduplication syndrome have unusual hands including an incurving little finger (clinodactyly), single palmar crease, extra palmar crease or unusually long fingers. Two *Unique* children (one with PTLs and one with trisomy 17p syndrome) have fingers that do not fully straighten; one child wears splints at night to help straighten the fingers. In general, the hand anomalies do not greatly affect the function of the hands, although they can lead to problems with fine motor skills (Paskulin 2008; Roos 2009; *Unique*).

■ Genital anomalies

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. Cryptorchidism (undescended testes) has been noted in boys with trisomy 17p syndrome, PTLS and 17p13 microduplication syndrome. The testicles can be brought down by a straightforward surgical operation if they do not descend of their own accord in time. Hypospadias (where the hole usually sited at the end of the penis is on the underside instead) has also been seen in a boy with trisomy 17p syndrome. Micropenis (a small penis) has been seen in a boy with 17p13 microduplication syndrome (Paskulin 2008; Roos 2009; *Unique*).

■ Palate

A cleft palate (opening in the roof of the mouth resulting from the palate not forming correctly during development) has been reported to affect some children with a 17p duplication. The evidence at *Unique* is that a cleft affected only one of those who participated in the *Unique* survey: a child with a 17p12pter duplication. Cleft palates have also been reported in one person with a 17p11.2p11.2 duplication and in two babies with trisomy 17p in the published medical literature (Martsolf 1988; Kulharya 1998; Potocki 2007; *Unique*).



A boy with a 17p12pter duplication as a baby and at 9 years

A small number of children (2/16 at *Unique*, both with PTLS; two in the medical literature with trisomy 17p and one with 17p13 microduplication syndrome) are reported to have a high palate. Cleft and high palates can contribute to the early feeding difficulties seen in children and may also make speech more difficult (Paskulin 2008; Bi 2009; Roos 2009; *Unique*).

■ Digestion

One problem is chronic constipation which affects over half of *Unique* children with a 17p duplication and has also been reported in the medical literature. Dietary changes and/or medication can help to manage the problem (Shaw 2004; *Unique*).

■ Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers. One study suggests that as many as 60 per cent of children with a duplication of 17p have dental anomalies. Dental problems seen at both *Unique* and in the medical literature include crooked, crowded, small and irregular teeth and teeth that are either slow to erupt or erupt particularly early. One *Unique* child with a 17p12pter duplication had very little enamel on the teeth, missing teeth and a tooth that has turned 180 degrees. A *Unique* child with a 17p11.2p11.2 duplication has an overbite – the bottom teeth overlap the top teeth (Doco-Fenzy 2008; *Unique*).

■ Spine

Scoliosis (curvature of the spine) has been reported in 30 per cent of children with PTLs in one study and 60 per cent in another (Potocki, personal communication). Additionally, one child with 17p13 microduplication syndrome has been reported in the published medical literature to have scoliosis. However, *Unique* has no reports of scoliosis in children with PTLs, although one child with a duplication of 17p13 has a possible curvature which is currently being monitored. The variations in the numbers of people affected are likely to be due to the fact that the number of people with a 17p duplication in each study is very small so the percentages can change significantly when just a few more extra people are included (Potocki 2007; Bi 2009; *Unique*).

■ Breathing

Sleep apnoea (pauses in breathing) can affect children with PTLs. In one study in the USA more than 80 per cent of children with PTLs were affected. This was not the case at *Unique* where only one child with a 17p11.2p11.2 duplication had sleep apnoea. Two children with a 17p13 duplication suffered from sleep apnoea but both outgrew it. Asthma and frequent respiratory tract infections have also been reported in one child with a 17p13 duplication (Potocki 2007; Roos 2009; *Unique*).

■ Brain

One child with 17p13 microduplication syndrome and two with trisomy 17p (one in the medical literature and one at *Unique*) were shown to have agenesis of the corpus callosum (ACC) on brain imaging. The corpus callosum is the largest connective pathway in the brain. It is made up of more than 200 million nerve fibres that connect the left and right sides (hemispheres) of the brain. ACC is a birth defect in which the corpus callosum is partially or completely absent, resulting in poorly connected or disconnected brain hemispheres. Each hemisphere of the brain is specialised to control movement and feeling in the opposite half of the body, and each hemisphere specialises in processing certain types of information (such as language or spatial patterns). Thus, to co-ordinate movement or to think about complex information, the hemispheres must communicate with each other. The corpus callosum is the main, although not the only, connector that allows that communication (Paskulin 2008; Roos 2009).

■ Other concerns

Low cholesterol was seen in a third of those with PTLs who participated in one study. Very fine hair and bald patches have also been reported in the medical literature (Potocki 2007).

An inguinal hernia (a bulge located in the lower abdomen or groin that consists of tissue from the intestines) has been reported in three children with 17p13 microduplication syndrome and two with trisomy 17p syndrome. An inguinal hernia should always be reviewed by a doctor as it can strangulate (compromise the blood supply) (Morelli 1999; Roos 2009).

Behaviour

Children with a 17p duplication are typically happy, sociable, loving and affectionate. A number of families describe their children as having a great sense of humour. However, a significant number of children – although not all – show a similar pattern of behavioural difficulties. They are often easily frustrated and children with both PTLS and trisomy 17p have been shown to be compulsive and impulsive (Potocki 2000). They tend to be hyperactive which can make learning more challenging (Potocki 2000; *Unique*). A number of children with PTLS and 17p13 microduplication syndrome have been diagnosed with attention deficit hyperactivity disorder (ADHD) which is characterised by restlessness and a short attention span. Some families report that their children with PTLS and trisomy 17p syndrome are overly affectionate and show inappropriate friendliness and have no understanding of personal space.



4½ years with a
17p11.2p11.2 duplication

Standard discipline techniques such as rewarding good behaviour and ignoring unwanted behaviour have proved effective for many families. Behavioural management techniques have helped many families, but for some children medication has been shown to be the only effective treatment (Potocki 2000; Fernandez-Torre 2001; Doco-Fenzy 2008; Bi 2009; *Unique*).

Sensory issues affect some children. Over half of those surveyed had sensitive hearing and were hypersensitive to noise, although some children outgrew this. A number of *Unique* families say that their children can become anxious and worry a lot and one family have used Bach flower remedies in order to calm and soothe their child (*Unique*).

Features of autism are very common in those with PTLS and trisomy 17p syndrome. Behaviour within the autistic spectrum has been reported both in the published medical literature and in a number of *Unique* children. Some children do not have a diagnosis of autistic spectrum disorder (ASD) but show some autistic tendencies or traits. In the USA study of children with PTLS all except one child displayed autistic tendencies. A recent study looking at the behavioural characteristics of children with PTLS noted that 10/15 met the diagnostic criteria for autistic spectrum disorder (Treadwell-Deering 2010). The autistic tendencies that have been noted include decreased eye contact, motor mannerisms or posturing, sensory hypersensitivity, repetitive behaviours, lack of appropriate functional or symbolic play and failing to recognise social cues, self-stimulating behaviours and repeating movements like head shaking or wringing their fingers. A diagnosis of autism can be extremely helpful in accessing services and tailoring

the educational and behavioural therapy to meet the specific needs of a child with autism (Moog 2004; Potocki 2007; Doco-Fenzy 2008; *Unique*).

“ She is very special, very sociable and loves to laugh, but she cries so much! If she is not completely stimulated by something she'll cry. When she is mad, she pulls her hair out and eats it. She'll try to bang her head and her body thrusts. She flaps her hands when she is excited – 2 years with a 17p13.1p13.3 duplication

“ She is always joyful and happy and cares about others. She will inappropriately invade other kids' personal space or touch them
– 4 years with a 17p11.2pter duplication

“ He is very loving and happy – 4½ years with a 17p11.2p11.2 duplication

“ She is kind, lovable and social. She has difficulties with transitions – 4½ years with 17p13.1p13.2

“ He loves music and riding a bicycle. He has attention deficit disorder and hyperactivity – 6 years with a 17p11.2p11.2 duplication

“ He is a very friendly guy but is lacking in social skills. He can dominate a conversation. He loves attention so managing his behaviour has always been easy. Negative behaviour was ignored as much as possible (the worst consequence in the world for him!). Positive behaviour got him the attention that he craved. He has more anxieties than anger. He is beginning to see that he's different from his peers and that can also cause anxiety – 7½ years with a 17p11.2p11.2 duplication

“ He is an enjoyable, fun-loving little boy. He is always happy and keeps himself busy. He can swim 10 metres. He loves gymnastics, dancing and music lessons, but his favourite activity is being in the garden digging the earth and making a lot of mess but having great fun! – 8 years with a 17p11.2p13.1 duplication

“ He is very well behaved. He is very sensitive and will cry if someone is upset about something. He is polite and friendly to everyone. He hugs everyone which can be inappropriate at times but he is oblivious to the dangers of strangers – 9 years with a mosaic 17p11.2p11.2 duplication

“ He is funny, happy and easy-going – 10 years with a 17p11.2pter duplication

“ He loves to listen to country music and recognises a very large number of songs within the first few notes. He is very personable and friendly. He displays some obsessive and compulsive behaviours – he has to have his pillow in a certain position before going to bed and he is very particular about fabrics and shoes. He is very active and very stubborn. He often displays anger in the form of hitting and pushing when he is frustrated. However, he is very loving and loves attention. He is a great joy and a challenge all at the same time – 11 years with a 17p12pter duplication

“ She is very funny and has a good sense of humour. She has a big personality and is loving and fun. She is generally very good especially at school. When she is tired she can



*4 years with a
17p13.1p13.2 duplication*

be challenging – 12 years with a 17p11.2p11.2 duplication

“ She has a happy disposition. She is passive most of the time although she does have times she does things for attention (pinches or scratches). She is easy-going when she sets the agenda – she can become overwrought if pushed to do something she doesn't want to do – 14 years with a 17p10p12pter duplication

“ He is very special. He has funny little sayings. For example, if he is hot he will say ‘I'm as hot as a pancake!’ He gets nervous every day at school. He worries about whether the minibus will turn up on time although it has never been late in 12 years! He likes a routine to be stuck to, which can be difficult in holiday times. He gets hyperactive after particular foods so his eating has to be monitored. Time out is used to calm him down – 16 years with a 17p11.2pter duplication

“ She has a great sense of humour and is a sweet girl who is very good with younger children. She likes routine and it can annoy her if it is changed – 19 years with a 17p11.2p11.2 duplication

Sleep

Many children go to bed easily at bedtime and sleep well. However, sleep problems are common in children with 17p duplications, irrespective of the duplication. Almost 50 per cent of those who took part in the *Unique* survey reported sleep problems. Some children find it hard to settle at bedtime, while others wake up often during the night and need re-settling. Others seem to have a diminished need for sleep. A number of families use melatonin to help with the sleep problems (*Unique*).

“ He has a hard time staying asleep. He normally wakes up after 3 or 4 hours. He used to have problems going to sleep but currently OK – 6 years with a 17p13.3pter duplication

“ He has always had a problem falling asleep. His brain is always going a-mile-a-minute. But once he falls asleep, he's out for 12 hours. Melatonin has been a saviour! – 7½ years with a 17p11.2p11.2 duplication

“ She had sleep problems when she was younger but improved from about the age of 7 or 8 and she now loves to stay in bed in the mornings! – 12 years with a 17p11.2p11.2 duplication

“ She appears to only need 5 or 6 hours sleep a night. She is happy in bed awake but often will be awake from midnight or 1am and stays awake all night and goes to school tired – 14 years with a 17p10p12pter duplication

“ She has no sleep problems – she loves her sleep – 19 years with a 17p11.2p11.2 duplication

Puberty and Fertility

There is limited information available on puberty in both males and females with 17p duplications. There is some evidence both at *Unique* and in the medical literature that puberty may proceed early in girls with a duplication of 17p. One girl with PTLS underwent puberty at 8 years of age. A girl with a duplication of four small segments of 17p also showed signs of precocious puberty at the age of 8. Two *Unique* girls (one with a 17p10p12 duplication and one with PTLS) had early development of pubic hair (at 7 and 9 years respectively) but full puberty developed at the usual age (Shaw 2004;

Vissers 2007; *Unique*).

Adults with a 17p duplication

To date, there are very few adults known to have a 17p duplication. *Unique* has three adult members between the ages of 19 and 33 years, only one of whom took part in the *Unique* survey. A 19-year-old girl with PTLS has moderate learning difficulties and can write and draw and read a simple book. She has good visual skills and is quite good at art. She loves playing with dolls, listening to CDs and texting on her phone. She belongs to a special Olympics club. She is very sweet and very good with younger children and does weekly volunteer work at an early childhood centre. Her speech is good although she sometimes struggles with certain words.



16 years with a
17p11.2p11.2 duplication

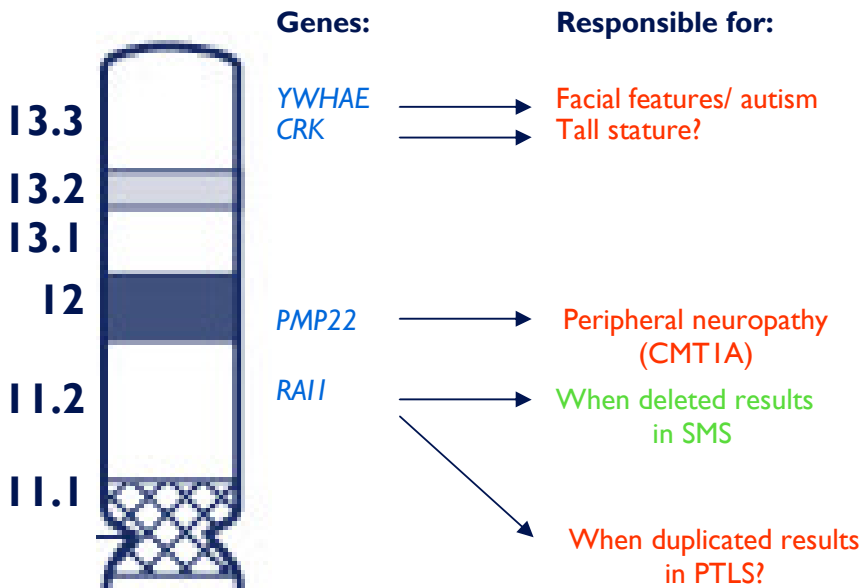
Only two adults have been described in the medical literature. A 41-year-old man with PTLS has mild learning difficulties and is hyperactive. After puberty he developed short stature and as an adult had obesity. An adult woman with a 17p13 microduplication had ADHD and seizures and passed the duplication on to her son (Potocki 2000; Bi 2009).

Ongoing research involving 17p

The features of a 17p duplication are likely to be a result of the extra copies of a number of different genes found in this region. The size and position of the duplicated region found varies widely, ranging from a small interstitial duplication of 0.24 megabases (one megabase or Mb= one million base pairs of DNA) of band 17p13.3 to much, much larger ones involving the whole of the short arm (about 22Mb).

The increasing use of molecular techniques such as array CGH and FISH in the research laboratory enables more accurate definition of the breakpoints. This, in turn, enables researchers to study more accurately which parts of the chromosome are missing and attempt to correlate certain regions with the different clinical features of the condition.

If the region involved in PTLS is deleted (missing) instead of being duplicated, the resulting syndrome is called Smith-Magenis syndrome (SMS). In SMS the critical gene responsible for the features has been shown to be the retinoic acid inducible 1 gene (*RAI1*). Further studies are needed to determine whether *RAI1* is also the gene that when present in three copies instead of the usual two is responsible for the features of PTLS. However, the person with the smallest duplication of 17p11.2 has three copies of *RAI1* and also shows the clinical and behavioural features of PTLS suggesting that this gene could play a role. It is also interesting to note that this person does not have abnormal EEG findings or long sight which suggests that *RAI1* or other genes in this region are not responsible for these features. The role of *RAI1* in PTLS is supported by experiments in mice which have a duplication of the mouse equivalent region of 17p11.2. These mice show many of the features of PTLS (including abnormal behaviour) and have three copies of the *RAI1* gene. If the level is reduced down to the normal level



of two copies, the mice no longer have the features of PTLIS (Walz 2006; Potocki 2007; Molina 2008; Carmona-Mora 2009).

Since behavioural problems seem to be a common feature affecting those with PTLIS there have been efforts to identify the gene(s) responsible. Studies have shown that a gene involved in hyperactivity is likely to be located on 17p11.2 (Arcos-Burgos 2004).

Duplications of the *PMP22* gene result in CMT1A (Roa 1996). *PMP22* contains the coded instructions to the body to produce the peripheral myelin protein (PMP22). When there is a third copy of this gene, a defect occurs in the insulating sheath known as myelin that wraps around the peripheral nerves in the legs and arms. Although the exact role of the protein within the myelin is not known, abnormal myelin means that messages travel very slowly between the limbs and the brain. Studies have shown that mice that have a duplication of the *PMP22* gene developed peripheral neuropathy closely similar to that seen in human CMT1A (Huxley 1996).

A number of children with 17p13 microduplication syndrome have tall stature, all of whom have a duplication that includes the *CRK* gene. It has been hypothesised that *CRK*, which is involved in growth regulation, may be responsible for the overgrowth seen in these children (Bi 2009; Roos 2009).

A study of those children with 17p13 duplications has also shown that the facial features associated with this duplication were not present in those individuals whose duplication did not include the *YWHAE* gene suggesting that this gene may contribute to the unusual facial features that often accompany a 17p13 duplication. This finding has been backed up by another recent study involving five people with a 17p13.3 microduplication. This study also suggested that the *YWHAE* gene may also be responsible for the autism seen in these duplications (Bi 2009; Bruno 2010).

It is important to remember that while identifying the gene(s) responsible for certain features of a 17p duplication is interesting and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is present in three copies instead of the normal two it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

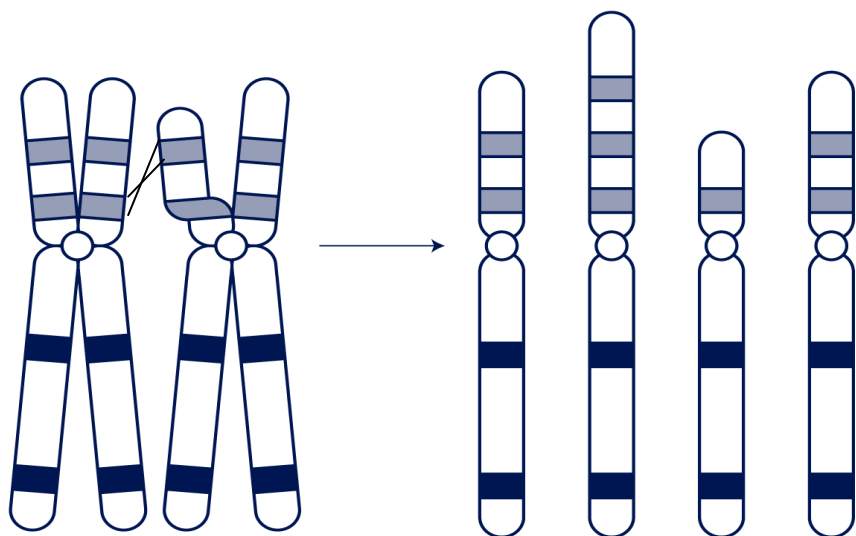
Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 17p duplication occurred. In the majority of cases the 17p duplication occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 17p duplications are thought to be caused by a change that occurred when the parents' sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined.

Some 17p duplications are accompanied by a gain of material from another chromosome. This can be a *de novo* change or it can be a result of a rearrangement in one parent's chromosomes. This is usually a rearrangement known as a balanced translocation in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. Balanced translocations involving one or more chromosomes are not rare: one person in 560 has one, making a total world population of over 12 million balanced translocation carriers.

In a few people, the cells containing the 17p duplication chromosome exist alongside cells with a normal chromosome number and arrangement. This situation, known as mosaicism, typically arises after fertilisation and can lessen the impact of the duplication.

Whether the duplication is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 17p duplication and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary, workplace or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault and there is no reason for anyone to feel guilty.



One way that a deletion and a duplication could theoretically arise during the formation of egg or sperm cells. On the left are two matching chromosomes, each split to the centromere and ready to pair and exchange segments. The shaded bars show similar sequences of DNA in the chromosome that enable correct pairing. But just above the centromere mispairing has occurred. When the chromosomes separate (right), the mispairing has given rise to two normal and two abnormal chromosomes, one with a deletion and one with a duplication.

Can it happen again?

The possibility of having another pregnancy with a 17p duplication depends on the parents' chromosomes. If both parents have normal chromosomes when their blood cells are tested, the deletion is very unlikely to happen again. However, if either parent has a chromosome rearrangement involving 17p, the possibility is greatly increased of having other affected pregnancies.

Parents should have the opportunity to meet a genetic counsellor to discuss their specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all of these tests are available in all parts of the world.

Can my child have similarly affected children?

To our knowledge, there are only two people who have been known to pass a 17p duplication on to their children. A mother with passed a small 17p13 microduplication on to her son. However, as advances in technology, especially the use of microarrays, uncover smaller microduplications, the possibility will increase of discovering families where the duplication has been passed from generation to generation.

Theoretically, someone with the deletion would have a 50 per cent chance of passing it on and a 50 per cent chance of having an unaffected child (Bi 2009; Potocki, personal communication; *Unique*).

Growing up with a 17p10p12 duplication



4 months



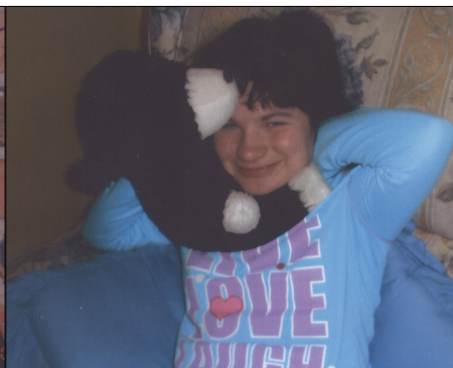
2 years



4 years



7 years



13 years

Support and Information



Rare Chromosome Disorder Support Group,

G1, The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel/Fax: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

POTOCKI-LUPSKI



The genetic key to a life full of possibilities.

Potocki-Lupski Syndrome Outreach Foundation,

PO Box 250245, Plano, Texas 75025-0245, USA

info@PTLSFoundation.org | www.ptlsfoundation.org

There are two Facebook groups for families affected by Potocki-Lupski syndrome:

- PTLS Family Support
 - PTLS Families with Teens and Above
- www.facebook.com

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Dr Lorraine Potocki, Texas Children's Hospital, USA, Dr Laura Roos, Kennedy Center, Denmark and by Professor Maj Hultén BSc PhD MD FRCPATH, Professor of Reproductive Genetics, University of Warwick, UK 2009; 2013. [SW]

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