

# Xp11.2 duplications



## Sources and references

The information in this guide is drawn from what has been published in medical articles or on publicly available databases about around 60 babies, children and adults with a duplication of Xp11.2. 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

([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)). If you wish, you can obtain most articles from *Unique*. The guide also draws on information from the Decipher database (<http://decipher.sanger.ac.uk>) and from *Unique's* database. At the time this guide was published in 2012, *Unique* had 12 members with an Xp11.2 microduplication (Bonnet 2006; Froyen 2008; Marshall 2008; Giorda 2009; Hunter 2009; Argiropoulos 2010; Holden 2010; Honda 2010; Edens 2011; El-Hattab 2011; Decipher; *Unique*).

## What is special about my child

“ P is so sweet and loving. She brightens up our life. She loves people, and when she is happy she is a joy to be around. ” 16 months

“ L is very lovely, and most of the time very happy. We love him very much. ” 4 years

“ M is sweet and happy and adorable. Everyone that knows her loves her. When she lights up when she sees you, it is like a gift. ” 4 years

“ A has an incredible enthusiasm for things as simple as seeing a hawk in the sky or planting tulip bulbs or finding a mushroom. ” 6 years

“ I love K to death! She is the most compassionate, loving child you will ever meet and blesses my life every day. I am so thankful for her. I wouldn't have it any other way. ” 9 years

“ D is the life and soul of the party, and loves to socialise. He is very sweet-natured and affectionate. He has taught us patience and strength we didn't know we had. ” 10 years

## What is an Xp11.2 duplication?

An Xp11.2 duplication is a genetic variation caused by having an extra copy of a small piece of one of the chromosomes. The extra piece is part of one of the sex chromosomes, called chromosome X. The duplication is found near the middle of the chromosome at a place called p11.2.

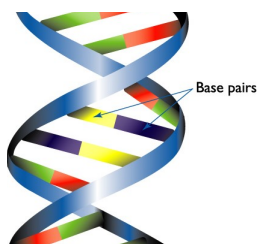
At the moment, information is available in medical articles, on publicly available databases or at *Unique* on only 60-70 or so people with an Xp11.2 duplication. This means that there is still much to learn. But this guide contains the best information we have to date.

The features of people with an Xp11.2 duplication vary, even among members of the same family. Speech delay and difficulty speaking clearly are common and many people need support with their learning. Some children have seizures and a recognisable brain wave pattern when assessed by EEG (electroencephalogram).

## What does Xp11.2 duplication mean?

Chromosome X is one of the 23 pairs of chromosomes in the cells of the body. The top bit down to the pinched point in the diagram (right) is known as p, and is the short arm of the chromosome. The bottom bit is the long arm, called q.

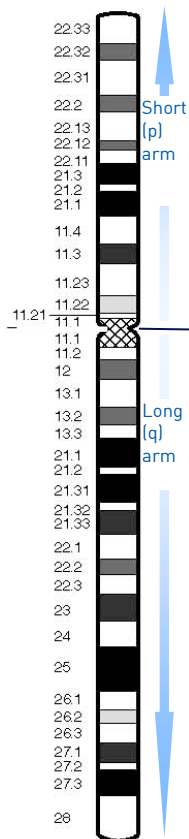
People have 22 pairs of chromosomes numbered 1 to 22 and one pair of sex chromosomes. Men and boys have one X chromosome and one Y; girls and women have two X chromosomes. In men and boys, the extra bit of Xp11.2 is part of their X chromosome. In girls and women, there is an extra bit of just one of their X chromosomes. The other X chromosome is usually unaffected. As you can see in the diagram, the Xp11.2 band is divided into three smaller bands: Xp11.21, Xp11.22 and Xp11.23.



Chromosomes are made up of DNA, which contains the genetic instructions we need to develop and function properly. DNA has a ladder-like structure, with the ladder's rungs formed from chemicals known as base pairs. If the genetic diagnosis of an Xp11.2 duplication has been made after examining chromosomes with a technique known as microarrays (array CGH), the size of the extra

bit of Xp11.2 is often stated in base pairs. There are millions of base pairs on a chromosome, so the numbers can be shortened. One million base pairs is called a megabase, and written 1 Mb.

The part of the short arm of the X chromosome known as Xp11.2 is rich in genes. It is also prone to chromosome rearrangements (Giorda 2009; Edens 2011).



X Chromosome

## Chromosome X: active or inactive?

Boys and men have just one X chromosome, while girls and women have two. Do females really need two X chromosomes? The answer is a qualified no. In girls and women, only one X chromosome is usually active. In each of the cells of their body, one X chromosome is active, while the other one is mostly silenced and plays little or no role in development or functioning. This is called X-inactivation, and when it occurs, around the second week after conception (when a baby is made), it is usually random, so there is an equal (50: 50) chance of either of the two X chromosomes being active in any particular cell.

In most girls and women with an X chromosome duplication, the X chromosome with the extra bit is usually inactivated, so the active X chromosome is the normal one. If the normal X chromosome is the active one, you wouldn't expect any effect on development, health or functioning. But with an Xp11.2 duplication, there is a puzzle. In girls and women with an Xp11.2 duplication, inactivation seems to be either random (around 50: 50), or it is skewed (as much as 96: 4 in one girl) in favour of the X chromosome with the extra bit. No-one is sure yet why this is so, but it may be

because in females, cells containing an active chromosome X with an additional copy of one of the genes in the extra bit of Xp11.2 have some sort of advantage (maybe they grow faster) over cells carrying an active normal chromosome X (Giorda 2009; Holden 2010).

### Chromosome X Activation



Part 1 shows usual situation, with two X chromosomes, one of them inactivated



Part 2 shows normal situation with a duplication on the X chromosome, ie dup X is inactivated



Part 3 shows situation with an Xp11.2 duplication, ie normal X is inactivated, leaving X + the active chromosome

There is another puzzle as well. You might expect people with more cells with the duplicated X chromosome to be especially severely affected, but when one group of researchers examined families with this question in mind, it didn't seem to be the case (Giorda 2009).

### Are there people with an Xp11.2 duplication who have developed normally and have no speech, behaviour, learning or health difficulties?

Yes, there are. The Xp11.2 duplication can be 'silent' – or at least, there may be no signs or symptoms that make a person stand out from the rest of their family. We know this because at least two parents of children with a small Xp11.2 duplication have the same duplication as their children but do not have any obvious unusual features or delayed development – at least, not to the point where they have needed medical or educational help (Giorda 2009; Honda 2010).

### In your family, is the Xp11.2 duplication inherited or not?

Xp11.2 duplications can be passed down from parents to children. In one study, 3/8 people with the duplication had inherited it from their mother (Giorda 2009).

Xp11.2 duplications can also occur ‘out of the blue’, for the first time in a family. The genetic term for this is *de novo* (dn), which is Latin for ‘new’. A new Xp11.2 duplication arises when the sperm or egg cells are formed, or in the very earliest days after fertilisation. In one study which looked at whether girls with a new (de novo) Xp11.2 duplication had the extra bit on the X chromosome they inherited from their father or mother, the extra bit was on the X chromosome from the father in all cases. But numbers in the study were very small, so this doesn’t prove that all de novo cases come from the father’s X chromosome (Giorda 2009; Holden 2010). The only way to be certain if the Xp11.2 duplication is inherited or not is to check the chromosomes of both parents, even if they are themselves completely healthy. If you check a blood sample and find that one parent has the same duplication as the child, we can assume that it has been passed from parent to child.

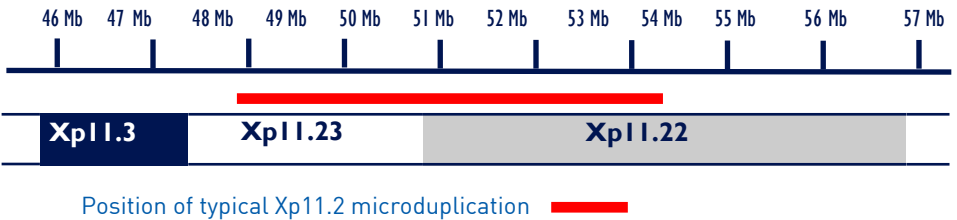
As a parent there is certainly nothing you did to give your child the Xp11.2 duplication and nothing you could have done to prevent it. No environmental, dietary, workplace or lifestyle factors are known to cause Xp11.2 duplications (or other chromosomal conditions, for that matter). There is nothing that either parent did before or during pregnancy that caused the duplication: so no one is to blame and there is no reason for anyone to feel guilty.

**If one person in a family with the Xp11.2 duplication is mildly affected, will others in the same family also be mildly affected?**

Not necessarily. There is some variation between different members of the same family who have the same duplication. We know that if one person is mildly affected, or not affected at all, others may be more severely and obviously affected (Giorda 2009).

**Does everyone with an Xp11.2 duplication have the same extra bit of the chromosome?**

No, they don’t. So far, people have been found with an extra bit that ranges in size from 0.5 to 55Mb. That means that the extra bit is 110 times bigger in some people than in others. The bit that is most often duplicated measures about 4.5Mb.



You can discover the size and position of the Xp11.2 duplication in your child or family by asking the geneticist or by checking the base pair numbers on the laboratory report. This is important to know if you are going to read medical literature describing other people with an Xp11.2 duplication, because there can be subtle differences in the size and position of the duplication along the chromosome, and this means that different genes are affected.

## How common is it to have an Xp11.2 microduplication?

It's difficult to be certain how common Xp11.2 duplications are. Among people who need support with their learning, at least three per cent are believed to carry the duplication (Giorda 2009).

## Is there an Xp11.2 duplication syndrome?

That depends on how you define 'syndrome.' Typically geneticists define a syndrome as a group of characteristics that are common to all or most individuals with a particular genetic anomaly. However, that definition is changing now that we can detect very small chromosome differences, because the signs and symptoms are more variable, and less well-defined.

By the 'old' criteria, we cannot yet say for sure that there is a specific 'syndrome' related to having an Xp11.2 duplication. But it may be that a syndrome is emerging for people who have a similar duplication of around 4.5 Mb.

## What does that mean? Some possible genetic test results

**Example 1:** [46,X,dup\[X\]\(p11.22p11.3\)](#) This result shows that the expected number of chromosomes [46] were found. It also shows that two X chromosomes were found, so this is a girl or woman. The first [X] is a normal X chromosome. The second has a duplication [[dup \[X\]](#)]. [\[p11.22p11.3\]](#) shows the bands in the chromosome where break points were found: the first was in band Xp11.22 and the second in band Xp11.3. This means that in this girl or woman, the extra bit stretches from Xp11.22 to Xp11.3. The extra material may lie directly beside the original location (known as 'in tandem'), or may have been inserted somewhere else (such as on another chromosome, or further away on the same chromosome).

**Example 2:** [arr\[hg19\] Xp11.23p11.22\(47946245-52639304\)x3](#) This result shows that a technology known as array comparative genomic hybridization [[arr](#)] revealed an extra copy [[x3](#)] – remember the normal copy number is 2 in women but only 1 in men] of part of the bands known as [Xp11.23](#) and [Xp11.22](#). The first extra base pair known to be present is [47,946,245](#) and the last extra base pair is [52,639,304](#). By taking the first number from the second, you can work out that there are 4,693,059 extra base pairs, or about 4.7 Mb of extra material. [hg19](#) tells you which version of the human genome sequence was used to make these measurements. At present, hg19 is the latest version.

## Main features

- Need for support with learning. The extent of any learning difficulty varies widely, from borderline to severe
- Speech delay
- Early puberty
- Significant weight problems
- Anomalies of the legs and/ or feet
- Unusual pattern of electrical activity in the brain in children
- Minor facial features

## ■ Need for support with learning. The extent of any learning difficulty varies widely, from borderline to severe

A baby born with an Xp11.2 microduplication is likely to need learning support. Not enough people are known about to be sure whether there is a distinctive type of learning difficulty linked to the duplication. We do know that the range of learning difficulty is quite broad. At one end are children who need a small amount of extra help in a mainstream (regular) school but go on to lead normal, productive working lives. At the other end of the spectrum and less common are people with a severe learning disability. This makes it difficult to predict an individual child's learning ability in advance. Having said that, members of the same family, all with the same Xp11.2 microduplication, have generally similar learning profiles. Children with the smallest duplications of just 0.5-1.3Mb seem to have only a mild learning difficulty; others with the typical duplication of around 4.5 Mb generally have a borderline, mild or moderate learning disability; and one child with a very large duplication indeed, of 55 Mb, has a severe intellectual disability (Marshall 2008; Giorda 2009; Eden 2011; El-Hattab 2011; Decipher).



A child with a 1.3Mb duplication that only partly overlaps the typical 4.5Mb duplication showed severe delay in visual and motor skills, making it very hard for him to copy figures (El-Hattab 2011).

Difficulty concentrating is common and a few children have been diagnosed with attention deficit hyperactivity disorder (ADHD), which lessens the ability to concentrate for long enough for learning to take place. In one child, very poor understanding of speech was believed to underlie the ADHD. In any child with speech delay learning will obviously be affected (El-Hattab 2011; *Unique*).

Among *Unique*'s membership, children ranging in age from a 16-month-old baby to a boy of 15 years are generally considered to have a borderline to moderate learning disability. One boy has difficulties classed as severe. One girl who has a larger duplication of 7.6Mb slightly closer to the tip of the chromosome than the typical duplication has a possible, but not confirmed, learning disability at 6 years; her lack of speech makes it hard to assess her cognitive abilities. Measurements in other children suggest IQs in the 60s or perhaps above.

Some children are reading with support and writing, albeit not yet neatly or clearly, by the age of 6; drawing basic images and stick figures by 9 or 10 years; and at 10 years one boy is reading factual books such as cook books or I-spy books and writing his name and a range of common words. This will not be possible for all.

Children are generally sociable and this is a learning strength, as they attract support from other children, as well as wanting to please adults. Parents say that their children are also determined learners. They recommend other parents to use visual tools such as picture schedules to reduce anxiety about what is coming next;

to be patient; to keep on pushing their children; to use repetition and games; and to be very consistent. One family of a 4-year-old strongly recommends the home programme developed by Applied Behaviour Analysis. Memory is a strong point for some children, particularly for places and routes, as well as for people.

Children usually have a statement of educational need or an individual educational plan. Most children are educated in a regular (mainstream) school, with substantial (1:1, 2:1) learning support. They usually join their peers for art, music, physical education etc but are taught academic subjects separately.

“ M is very happy and loves to participate with other children. ” 4 years

“ A is good at visual recognition, but finds certain concepts hard. She is not reading yet on her own but can read simple books if asked and can write all the letters and numbers, although not clearly. She also has trouble writing small and spacing words on a page. ” 6 years

“ C is not able to read yet. She is at the stage of drawing vertical and horizontal lines and circles. ” 6 years

“ K likes maths and can read, but does not work well independently and needs a lot of assistance. ” 9 years

“ D can read but finds maths very difficult. He is helped to learn by loving to please people; giving him jobs also helps, as he likes to feel useful. He has an excellent memory and draws basic pictures such as a person or house and writes own name and basic words, although his writing is large and messy. ” 10 years

### ■ Speech delay

Speech is very commonly affected, and speech delay may occasionally be the first sign that anything is wrong. Both understanding and speaking seem to be affected, but not necessarily to the same extent. While some children understand more than they can express, testing in one *Unique* child revealed that understanding was at three per cent of the expected level, while speaking (expression) was far better, at 63 per cent.

Both children and adults frequently have difficulty in speaking clearly: as ever, there is a range of severity, with people talking a little unclearly at one end of the spectrum and, at the other, people whose speech is so unclear that it's hard to understand what they say. In one family, three brothers were diagnosed with dysarthria— a difficulty in making the sounds of speech; all three also had low facial muscle tone and an open mouth. Some children have difficulty making particular sounds of speech; others leave out words or make grammatical errors. One girl has a distinctly nasal voice; at least two others have a hoarse voice.

Communication milestones were generally delayed among *Unique* members: babies generally started to smile between two and four months, although one baby first smiled at nine months. Babbling emerged between a few months of age and one year, followed by first recognisable words between 12 months and four years. However, one baby stopped babbling and has yet to say any words at four years. Another four-year-old has yet to start to speak. One girl of 14 had a vocabulary of 10-20 single words and rarely used two-word phrases. Some children learn to sign to support their communication; others use communication devices. Families have



found speech therapy very helpful, as well as regular contact with verbal children (Froyen 2008; Marshall 2008; Giorda 2009; Edens 2011; Decipher; *Unique*).

“ Presley uses mainly vocal noises and leaning towards what she wants, as she can’t communicate verbally and has no speech yet. ” 16 months

“ Molly does not speak yet, but is very adept at using vocalizations to let someone know when she is happy or unhappy, and reaches for things she wants. She can sign *Please* to indicate that she wants something. We have started using Proloquo to Go on the iPad, limiting it to two to four choices. She will make choices of a snack or an activity she would like. She is starting to identify things using this program as well. It has a lot of room for growth and we are optimistic that it will help her communicate her needs, wants and feelings. ” 4 years

“ Abby uses complete, complex sentences, but with errors in verb tenses and certain letter sounds. ” 6 years

“ Camryn uses some words, signs and gestures but doesn’t have fluent conversation yet. She uses a mix of one to four word phrases such as *Mom, What’s that?, Daddy’s here or Want to go outside*. She can understand a lot more than she can express. ” 6 years

“ Krista talks in broken (incomplete) sentences of around five or six words. She has difficulty with *r, l* and *y* sounds. ” 9 years

“ Declan talks, although it can be difficult for strangers to understand him. He uses eight to ten word sentences, although he frequently misses out words and mixes them up. ” 10 years

### ■ Early puberty

Early puberty had occurred in 8/10 children or adults, with two girls starting periods at the age of nine. Early puberty is sometimes treated by an endocrinologist with hormone therapy known as GnRH (gonadotrophin releasing hormone), a synthetic equivalent of the body’s natural hormones. GnRH agonist analogues are usually given by monthly or three-monthly injection. A nasal spray is also available. Growth and hormone levels will be regularly monitored in any child on GnRH therapy and they can expect to be under the care of an endocrinologist (Giorda 2009; Decipher).

Puberty started early in the three *Unique* members for whom we have information. First signs were noticed in a girl at the age of 7½, and by the age of nine, she had some breasts and secondary hair, but no periods yet. In a boy, first signs of puberty were seen at the age of 8½; he had hormone (leuprolide acetate) injections from the age of nine and then a histrelin acetate hormone implant. In a further *Unique* boy, puberty was complete by the age of 13 (*Unique*).

### ■ Significant weight and height changes

We have information on weight and height in 20 people with an Xp11.2 duplication, including seven from *Unique*. It shows a mixed picture.

The information from the medical literature shows that 5/13 people (that is, one in three, both adults and children) are very short, as small as the shortest three per cent of the population. One boy was 20 centimetres (8 inches) shorter than his expected family height. At the same time, half are in the top 10 per cent of the

population for weight. So there is a distinct tendency to be overweight, and sometimes significantly so (Bonnet 2006; Giorda 2009; Edens 2011).

Among seven *Unique* children aged between 16 months and 10 years, a much more varied picture emerges. Five children are tall for their age: some of them in the top one per cent of the population for height. The others are of average height; none are short. Three children are overweight, including two who are very tall. One girl of nine, who is overweight, started putting on weight very rapidly from the age of four. The others are 'about right', apart from two other tall children, both boys, who are under weight and who have both had significant feeding difficulties. One of them had low muscle strength in the mouth and only a feeble ability to suck; as a baby he 'failed to thrive', meaning that he wasn't able to meet his own nutritional needs, although he was eating well at the age of 10. The other underweight boy, who has other chromosome changes as well as the extra bit of Xp11.2, was unable to suck either from breast or bottle as a baby, and as a toddler took all his liquids through a gastrostomy tube direct to the stomach. At four, he is a picky, slow eater with a small appetite; he also has food intolerances to gluten and casein (*Unique*).

### ■ Anomalies of the legs and/ or feet

Researchers have drawn attention to the fact that anomalies of lower limbs or feet are common in people with an Xp11.2 duplication, affecting 10/14. The unusual features included flat feet (in five — severe enough in one 12-year-old girl to require leg supports); arched feet (3); clubfoot (talipes) (3); narrow feet (2); webbed or joined toes (2); and underdevelopment of the fifth toe (1) (Giorda 2009; Decipher).

Among *Unique* children, positional foot anomalies are also common, affecting six out of seven children, with four needing foot or leg supports at some point in early childhood. In two children, the ankles lean markedly inwards and two children naturally tend to walk on their toes. One of these children has had heel cord lengthening to loosen the tendons in her legs.

Other unusual features affect one child only: small or very narrow feet; extremely flat, broad feet, with 'weird' fifth toes; and large big toes (*Unique*).

### ■ Seizures and/or an unusual pattern of electrical activity in the brain in children

Researchers have identified a typical pattern of electrical activity in the brain in children, which they described as 'subclinical seizures': that is, anomalies in brain electrical activity that are not strong or widespread enough to manifest as seizures. During sleep, these anomalies are longer-lasting and easier to document.

As for seizures, eight out of 11 children experienced seizures, starting at different ages between six months and 12 years. In two further children, seizures only occurred with a high temperature. In three children the seizures proved resistant to drug treatment; one of these had tonic-clonic seizures, occurring as often as daily or weekly, although she could go for a month without seizures when on anti-epilepsy drugs; in another, complex partial seizures occurred twice a month, usually in the morning, and lasted for less than five minutes. Four of the children had episodes where they appeared to be distant or disconnected from the world around them ('subclinical absences'). Children generally outgrew their tendency to seizures, in

one case by the age of 2½, and it is currently believed that seizures in people with an Xp11.2 duplication are confined to childhood (Froyen 2008; Giorda 2009; Holden 2010; Edens 2011).

The *Unique* experience is that three out of eight children aged up to 13 years have had seizures. Two further children have abnormal brainwave patterns on an EEG (electroencephalogram); seizures may start 'at any time' in one of them, their neurologist says. In one child, seizures started at 7½ months and continued until the age of one. The seizures were treated with levetiracetam (Keppra) and now aged four, it is three years since the child had one. EEGs showed no unusual activity.

In a second child, with other chromosome changes and the Xp11.2 duplication, myoclonic (jerky, shock-like) seizures started at a few weeks old. He started treatment with anti-epilepsy drugs at 18 months and a variety of drugs as well as the ketogenic diet have been tried. At four years, he still has daily seizures and abnormal EEG recordings when awake and asleep. A third child had 'mild' seizures (*Unique*).

### ■ Minor facial features

While many children and adults with an Xp11.2 microduplication simply look like other members of their family, others have some unusual facial features. Overall, there doesn't appear to be a recognisable pattern, so children and adults don't look especially like each other. A survey of 11 children and adults shows that the most common unusual features are a short or flat groove between the nose and upper lip, known as the philtrum (7/11); a large, high or deep nasal bridge, at the point where the nose joins the forehead between the eyes (6/11); bushy eyebrows that sometimes join in the middle, a feature known as synophrys (6/11); and thin lips (5/11) (Giorda 2009; Edens 2011).

These features are not commonly seen among *Unique* members, however, although one child does have eyebrows that join, almost creating a 'mono-brow'. Other facial features seen among seven *Unique* children are deep set eyes (1), a small fold of skin across the inner corner of the eye (an epicanthic fold) (3), lower eyelashes growing towards the eye (1), downturned eyes (1), a small nose (1), ears set unusually low on the side of the head (2), fused ear folds (1), widely spaced teeth (1), a downturned mouth (1), and a small lower jaw and chin (1).

## Development

Having an Xp11.2 microduplication increases the likelihood of developmental delay, but does not necessarily lead to it. Some people with the duplication have never experienced a significant delay in any area of their development and since these are usually adults only discovered during family testing after the duplication has been found in one of their children, we don't know how many of them there could be. Developmental delay in children with an Xp11.2 duplication is typically mild-to-moderate and responds well to early intervention and therapy. However, the severity of delay cannot be predicted from the chromosome diagnosis.

## Sitting, moving, walking (gross motor skills)

From the medical literature, we have information on seven children with the Xp11.2

duplication. This shows a really quite variable picture, even among children with exactly the same size duplication. Some children are late to roll over, sit, become mobile and walk – but others are not. The age at which children start walking is generally between 12 and 22 months, but one child walked at 34 months, another at three years and another did not walk until she was four years old (Edens 2011; Holden 2010; Giorda 2009).

Within *Unique*, babies with the Xp11.2 microduplication learned to roll over between five and 14 months (average eight months); they sat up between six and 24 months (average nine months); they became mobile, usually by crawling but in some cases by bottom-shuffling, scooting, rolling or bunny-hopping, between seven and 18 months (average 13 months); and they were generally up and walking between 12 months and 2 years 3 months (average 19 months). One child of four years was not walking yet, while another was just taking his first steps alone (*Unique*). Low muscle tone (hypotonia), making children feel floppy, was found in 5/15 children and adults in the medical literature and 6/7 in *Unique*, and can be significant. In *Unique*'s experience, it is an important feature, with far-reaching consequences for mobility, early feeding and speech. Two children in *Unique* and one described in the medical literature have a spinal curve, which may also result from low muscle tone. Hypotonia tends to gradually improve with age and physiotherapy is helpful (Marshall 2008; Giorda 2009; Edens 2011; *Unique*).

“ P is not yet walking, but cruises furniture. She most enjoys swinging and water activities. Physical therapy has been most useful. ” 16 months

“ M is still unable to stand, crawl, or walk. She does roll and scoot and is able to move herself to where she wants to be. Right now aquatic therapy seems to be helping her because it reduces the strain her weight puts on her body. ” 4 years

“ L crawls most of the time. He walks on his knees and sometimes gets up, holding on to things, and might try a few steps. But he is very wobbly and would fall over after some time. He has a larger buggy, a walker that he does not like and an adapted tricycle. ” 4 years

“ A gets around easily with no supports or aids. She enjoys swimming and swinging on her swingset. Physical therapy has been most useful. ” 6 years

“ C walks and runs, although not fast and a bit awkwardly. She wears orthopedic inserts in her shoes to provide an arch and support. She most enjoys playing outside on the playground equipment, riding her bike and going for walks. ” 6 years

“ K has normal mobility. She wears a shoe lift as her right leg is an inch longer than her left. Her favourite physical activities are walking and running. ” 9 years

“ D walks normally, although he is clumsy and not very well coordinated. He most enjoys the trampoline and basketball. Physical therapy has been most useful for his hypotonia. ” 10 years

## Using their hands (fine motor skills)

Babies are likely to experience some delay in using their hands purposefully and in coordinating hand use with eye use. They are likely to be slow to grasp, hold, pinch

and drop objects, to pass them from hand to hand and to develop the later skills of feeding themselves and scribbling, drawing and writing. Babies and children will benefit from play therapy as well as occupational therapy and some children - but not all - will entirely overcome these initial delays by 8-11 years (Holden 2010; El-Hattab 2011).



*16 months old*

The evidence from *Unique* amplifies these findings: at 12 months, one child is unable to hold her feeding bottle and at 16 months is operating more like a baby of 10 months; at four years, one girl still has a loose grip, but can manipulate small toys; a boy of four with additional chromosome changes which likely intensify his difficulties can hold a cup or fork of food when interested and get it to his mouth unless he is holding it with a pincer grip, and cannot yet press a button. By the age of six, children have made considerable progress, but one girl still has difficulty using a pincer grasp, and with writing and drawing specific shapes and letters; another girl can eat, drink, hold objects, and make puzzles but remains severely delayed in writing and drawing. At 10, one child still has poor motor planning and remains obviously clumsy (*Unique*).

## Personal care

The difficulties with fine motor skills mean that children will be late to learn how to undress, dress, and wash themselves.

The *Unique* experience shows that by the age of four, some children can help with dressing and undressing by lifting their arms, holding out a leg or arm or stepping into trousers with help, but cannot dress or undress themselves. By six, some children can wash their hands and put on and take off easy clothes, while others can only pull clothes up or down. Difficulties with motor planning and concentration make personal care a challenge for a boy of 10; he is helped by picture schedules to keep him on task.

Toilet training is also delayed and in most children significantly so. One girl was dry by day and night at the age of three, another was dry by day with accidents at six and a boy was dry by day at six, but many children were not dry at night and most are not yet dry by day. Training to be clean was a particularly long process for one child, whose family was supported by a behavioural specialist at school.

*“ He loves being bathed and gets wild in there with joy, but we have to lift him into the tub and out again. ” 4 years*

*“ She knows the toileting routine but sometimes needs assistance with making sure that her underwear and clothing are pulled back up correctly and comfortably. We brush her hair and teeth for her still. ” 6 years*

## Behaviour

It is not yet known whether any particular behaviour is associated with having an Xp11.2 microduplication but there is a distinct impression from the *Unique* evidence that children are happy, with a loving, sociable temperament. The evidence from published research is mixed, with no consistent pattern identifiable. Negative behaviour traits noted among seven children include being unusually shy; unusually

stubborn, strong willed and aggressive; emotional instability; high anxiety levels; and temper tantrums.

More positively, one 11-year-old boy was described as having a happy temperament and being affectionate, although he had difficulty with impulse control, and preferred the company of children younger than himself (El-Hattab 2011).

Among *Unique* children, six out of seven showed a clearly sociable temperament, enjoying the company of others. One 15-year-old boy showed autistic-like behaviour, including little eye contact and little interaction with other children; another child showed repetitive behaviour; two further girls of 3 and 14 years were diagnosed with autism, one of them refusing to be cuddled and being described as a 'loner'; a further 15-year-old boy was diagnosed with autistic-like behaviour and hyperactivity; and a further child had been diagnosed with autism by the age of three. The evidence from *Unique* on autistic-like behaviours is more mixed: three out of 10 children have a diagnosis of autism, two of them boys. One boy was assessed for autism but his overall sociability, empathy and eye contact ruled the diagnosis out and it was felt that his behaviour could be better explained by his delay and learning difficulties. Two girls of 11 and 12 years in this group had episodes of compulsive eating; both were significantly overweight (Bonnet 2006; Marshall 2008; Giorda 2009; Edens 2011; Decipher).

"P is very high maintenance: she wants to be held a lot, is very social and likes to play, but gets worn out easily. She sometimes gags by putting her entire hand down her throat and scratches at people. Advice received is: take one day at a time." 16 months

"L loves people's company and attention but is still displaying severe autistic behaviours. He is starting to play with different objects than his Frisbee, but not very meaningfully yet. He also loves to play physically with his therapists and his parents." 4 years

"M is mostly happy and cooperative. When she is tired or hungry she may be a little more vocal. When she is not getting what she wants, she is starting to throw her body around to get the point across. Socially, she makes eye contact and smiles and loves her twin sister. Her favourite toy is a Cookie Monster that eats plastic cookies: she likes to manipulate the cookies in her hand, put them in and take them out of his cookie jar, push his hand down so he asks for cookies, and putting them in his mouth. We love the Upside Down Show and Noddy Cartoon and she also loves music. M loves interacting with her family and with her teachers and classmates." 4 years

"C likes to be around other people and with her friends and classmates. She loves being outdoors: playing on her slide/swingset, riding her bike and going for walks. She enjoys listening to music and action songs and has just started to show an interest in watching television. She likes looking at books and listening to stories. She likes building with her blocks and playing with her younger brother." 6 years

"A is usually excited about what is happening that day or coming up. She wants to talk about what is or has happened and is very excited to see friends. She does have difficult behaviour, and this includes: loudness, impulsivity, hitting, spitting,

scratching, and throwing toys, and she has been diagnosed with impulsivity; a short concentration span; immaturity; and anxiety. A behavioural specialist in kindergarten helped manage her negative behaviour at school and when she was four, a child psychologist recommended using social stories to help her with certain situations. She does not have a diagnosis of autism but her neurologist thought some behaviours (pushing cars around a table) were within the autistic spectrum.” 6 years

“ K is a very happy child: she gets no special treatment and everything is the same as for her typically-developing sisters. Overall she is very pleasant and loving, though she hates waking up early and has occasional emotional breakdowns. She absolutely loves routine: if it's messed up, it's not good. She can also be aggressive at times, and scratches herself when she gets mad. Advice received is: take time to let them cool down; chill out; lots of love.” 9 years

“ D has inappropriate social skills, poor eye contact, perseveration and a diagnosis of PDD-NOS/Autism as well as severe attention deficit hyperactivity disorder, for which he takes dexamethphenidate (Focalin). He also has Applied Behavior Analysis therapy. He is normally very talkative, excitable and hypersensitive to noise, so he comments on every sound. So he is mostly happy but busy. But he is also restless, impulsive and anxious. He is very sociable but inappropriately so. He understands personal space, but poor impulse control means he touches people's face, hands etc. When a stranger responds positively to him, he latches on to them and won't stop talking to them.” 10 years

## First signs

The first sign in most babies was that they were late to reach early developmental milestones, such as lifting their head up or rolling over. One child raised concern because of unusual facial features at birth, low muscle tone, feeding problems and slow growth. In a minority, first concerns were not raised until their second year when they were slow to talk. Epilepsy added to the concerns but was not the first sign in any *Unique* child (Froyen 2008; Giorda 2009; *Unique*).

“ I noticed that she wasn't meeting her milestones: specifically that she wasn't able to lift her head off the ground when lying on her tummy or push up with her hands or arms.”

## Sleep

*Unique* records show that 4/7 children had sleep-related problems, and these appeared to be related to seizure activity in only one child. Other children showed a variety of apparently unconnected sleep problems. One child wakes frequently at night and is awake for the day very early; melatonin helped her to get to sleep but not to stay asleep, and other medications have left her wakeful. Another child takes a soother to bed to chew, and often calls out and rolls around in her sleep; she sometimes wakes in the middle of the night and stays awake supervised for a couple of hours before falling back to sleep. Finally, a child with attention deficit hyperactivity disorder has trouble getting to sleep, for which he takes melatonin.

## Pregnancy, birth and the newborn period

We have some information on 11 pregnancies from the medical literature and eight from *Unique*. Among the *Unique* pregnancies, five were entirely uncomplicated; one baby moved little and there was little amniotic fluid; in a second there was unnoticed placental failure by the end of the pregnancy and the baby was born in poor condition. A third *Unique* pregnancy was a twin pregnancy, with the other twin having normal chromosomes. The twin with the Xp11.2 duplication was larger and had more amniotic fluid at the 20 week ultrasound; she moved less in the womb than her twin.

Eight babies were delivered before term and six were premature (born at 37 weeks or before); only one was delivered after 40 weeks. In one pregnancy, the membranes broke early with loss of amniotic fluid. Two babies were born breech and one was delivered by emergency Caesarian for unnoticed placental failure.

There was no consistent effect of the duplication on size, weight or head size at birth: some babies were tiny, others average, and others large.

In the newborn period, about half the babies had no problems at all: they fed well, needed no particular treatments and went home at the expected time. Three babies had significant feeding difficulties - sucking poorly and having difficulty coordinating sucking and swallowing. Three further babies had laryngomalacia, where the structural framework of the larynx (the voicebox) is soft and limp. Mild laryngomalacia may cause no problems, but if the soft, limp tissues of the larynx collapse while a baby breathes in, you may hear noisy breathing (stridor).

Laryngomalacia can also interfere with feeding (Bonnet 2006; Giorda 2009; El-Hattab 2011; *Unique*).

## Feeding

There is some information on feeding in nine babies and children. More than half the babies and children had no feeding issues, breast- or bottlefed well, and went on to have a healthy and varied diet. Four children had some difficulty with feeding, but this was only significant in two of them. One baby sucked weakly from birth, and had difficulty moving food and liquids around his mouth; he was diagnosed with failure to thrive, meaning that he couldn't meet his own nutritional needs, but by the age of 10 was eating a normal, healthy diet. A baby with additional chromosome changes faced particular feeding difficulties and was fitted with a gastrostomy tube for feeding direct to the stomach.

Three babies had swallowing difficulties or reflux, probably related to their underlying low muscle tone. In reflux, feeds and stomach contents return into the gullet and are often vomited or may be inhaled, raising the risk of chest infections - known as aspiration pneumonia. There are many simple measures to control reflux, including positioning semi-upright for feeds and using a cot with a raised head end, and your doctor can prescribe medication to help feeds stay down and counteract any effect of acidity on the food passage. If this is not enough, a surgical operation called a fundoplication can improve the action of the valve that normally prevents reflux from the stomach.

Generally, the babies with swallowing difficulties or problems with low muscle tone in the face, mouth and throat were late to wean onto solid foods and took puréed



foods for longer than typically developing babies. The general difficulties with hand use and hand-eye coordination meant that they were also late to feed themselves: but they got there in the end and generally did not need adapted cutlery.

Three children had chronic constipation, needing treatment with stool softeners and medicines to stimulate bowel movements. Two babies had food allergies (milk and soy) or intolerances (gluten and casein) (*Unique*).

“Hypotonia causes swallowing difficulties and aspiration. P eats puréed foods and a special formula.” 16 months

“M eats everything! She feeds herself finger foods and will put foods placed on a fork in her mouth and pull out the fork. She is still using a high chair and we are currently looking for a new seating system. We are working on using a universal cuff to help her hold her spoon or fork.” 4 years

## Head and brain

Babies will have their head measured as part of routine care and babies and children with an Xp11.2 duplication are likely to have tests of the electrical activity in the brain because of the known link with abnormal patterns.

Some people with an Xp11.2 duplication have a small head, some large, and most average. In some children, the head grows at a very rapid rate after birth, so from being small or average at birth, it becomes proportionately large; in other children the growth rate appears to be similar before and after birth; in others, the growth of the head is slower after birth than before, so the child has a proportionately small head (Giorda 2009; Edens 2011; *Unique*).

Out of 13 children whose brain scan outcomes are known, five had normal results; one had a relatively thin cerebral cortex (the outer layer of the brain, consisting of grey matter) and three others may also have had a thin cortex, while one had a thickened cortex. It has been suggested that a thin cerebral cortex, or one of abnormal thickness, may be typical for people with an Xp11.2 duplication.

Two children had enlarged fluid-filled spaces within the brain; one had a wasting away and decrease in size of the grey matter in the front and top (frontoparietal) parts of the brain; one had a delay in the natural process of insulating the nerves, known as delayed myelination; and one had an area of slight hyperintensity in a particular region at the front of the brain. Areas of hyperintensity show up as light or white areas on an MRI scan; they are normal in ageing and also occur in people with neurological disorders. A further child with additional chromosome changes has a very small cerebellum vermis: a structure at the back and bottom of the brain that plays an important role in movement and co-ordination (Giorda 2009; Holden 2010; Edens 2011; *Unique*).

## General wellbeing

Once any early feeding difficulties are overcome, children and adults with an Xp11.2 duplication are generally healthy. They usually have strong hearts, lungs and kidneys, and good vision and hearing. As children they are as vulnerable to common infections, including chest and ear infections, as typically-developing children, but they outgrow this tendency in the normal way. Conditions that occur more commonly in children with chromosome disorders, such as minor genital anomalies, are seen,

but not frequently. An exception here is teeth: dental anomalies seem common, as they are in other children with chromosome disorders (see below). Children do have regular follow-ups with more doctors than typically developing children, and children with early puberty see an endocrinologist while those with epilepsy see a neurologist, but this is part of the special care they receive, and most children spend little time in hospital. The most common reason for hospital admission is to have tubes placed in the eardrums to improve hearing after repeated ear infections. Some children also have surgery to correct a squint (strabismus) (Giorda 2009; El-Hattab 2011; Decipher; *Unique*).

Inevitably, individuals have particular medical conditions, which we list here, although they may have no connection with the Xp11.2 duplication. One adult has ulcerative rectocolitis, an inflammatory condition affecting the rectum and colon (Giorda 2009); another has Wegener's granulomatosis, an inflammatory condition affecting the lining of the nose, sinuses, throat or lungs and blood vessels as well as thrombophilia, a condition where the blood has an increased tendency to form clots (Giorda 2009); a 14-year-old girl has low thyroid levels and raised insulin levels; she also has scant periods (Giorda 2009); a 13-year-old girl has cyclical vomiting (Giorda 2009). Two boys were born with hypospadias, where the hole usually at the tip of the penis is on the underside; one also had hernias in the groin, which were surgically corrected; and another boy had enlarged testicles (Froyen 2008; *Unique*). One girl was born with multicystic dysplastic kidneys, so only one kidney works and the other consists of cysts (*Unique*). Two babies were born with a split in the soft part of the back of the top of the mouth, known as a submucous cleft (Froyen 2008; *Unique*). At the age of 55, one man developed a condition known as amyloidosis, where particular proteins accumulate in organs or tissues, in his case causing kidney damage (Froyen 2008).

“ P seems very frail. ” 16 months

“ M is a pretty healthy kid. We do deal with constipation and she is on medication to hopefully prevent another asthma-triggering illness. Other than that, she is doing pretty great. ” 4 years

“ Besides his seizures, L is well and very happy. ” 4 years

“ For the most part C is healthy, though she gets colds and viruses like any other child. She was admitted to hospital for various day surgeries - tubes placed in her ears, tongue clipped, adenoids removed, heel cords lengthened – but was released the same day. ” 6 years

“ K gets a lot of headaches. ” 9 years

## Eyesight

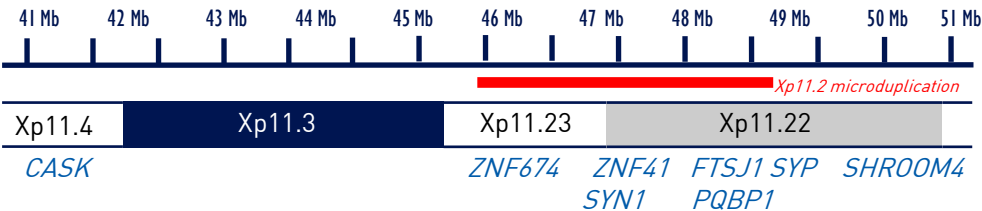
Babies and children with a chromosome disorder or developmental delay usually have a careful eye examination to ensure that any problem with vision is addressed early. Among 10 children and adults, two sisters each have long sight and an astigmatism, where the front of the eye has an abnormal curve; and one has repeated episodes of uveitis: swelling and irritation of the middle layer of the eye (Giorda 2009). One *Unique* child had a severe strabismus (squint), corrected

surgically at the age of 11 months; she also has the involuntary eye movements known as nystagmus (*Unique*).

## Teeth

In *Unique*'s experience, children with a chromosome disorder generally have a higher rate of dental problems than typically-developing children. This may be due to a number of problems: unusual dental development; unusual size of the jaws, leading to overcrowding or widely spaced teeth; feeding difficulties and delayed eating and chewing activity; tooth grinding, wearing down the enamel; unavoidable side effects of necessary prescribed medications; or dislike of tooth brushing and going to the dentist. Teeth may emerge late and milk teeth may be late to fall out. Extra teeth may be found and either milk or adult teeth may be missing. The unusual combination of potential problems means that children and adults with an Xp11.2 microduplication may need sensitive and specialist dental care. Among 43 children and adults in the medical literature, six are known to have some special feature affecting their teeth: one has widely-spaced teeth, two have a wide gap between the two top front teeth, one has unusually placed upper canines, and one has unusually small milk teeth (Froyen 2008; Giorda 2009; Holden 2010; Edens 2011; El-Hattab 2011). The rate of dental anomalies is much higher among *Unique* families, with 6/7 families reporting a problem. The problems are, however, quite varied: very thin enamel, possibly caused by early medications; late emergence of milk teeth; tooth grinding; a large number of cavities; and overcrowded teeth (*Unique*).

## Genes in the Xp11.2 region



A candidate gene for seizures in children with an Xp11.2 duplication is the synaptophysin gene *SYP*. Loss or mutation of this gene has been associated with seizures (Tarpey 2009; Holden 2010).

Many genes in the duplicated bit have been linked to learning difficulties: these include the *CASK* gene; *ZNF674*, *ZNF41* and *ZNF81* genes; *SYN1*; *FTSJ1*; *PQBP1*; *SYP*; and *SHROOM4*. But while we know that losing one of these genes or having a defective copy of one of them is linked to learning disabilities, we don't know whether having an extra copy of one of the genes is linked to learning difficulties (Holden 2010).

*SYN1* encodes synapsin 1, a protein associated with the membranes of small synaptic vesicles which is predominantly expressed in the brain and plays a key role in the regulation of neurotransmitter release, axonogenesis and synaptogenesis. Mutations are linked with learning difficulties (El-Hattab 2011).

*GRIPAP1* encodes *GASP1* protein and may be a cause of autism in females with the duplication.

*PQBP1* may be the cause of a large head (Honda 2010).

# Inform Network Support



Understanding Chromosome & Gene Disorders

## Rare Chromosome Disorder Support Group

The Stables, Station Rd West, Oxted, Surrey. RH8 9EE

Tel: +44(0)1883 723356

[info@rarechromo.org](mailto:info@rarechromo.org) | [www.rarechromo.org](http://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/donate](http://www.rarechromo.org/donate)

Please help us to help you!

This 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. The information is believed to be the best available at the time of publication. It was compiled by *Unique* and reviewed by Dr Roberto Giorda, Molecular Biology, Bosisio Parini, Italy and by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK and chief medical advisor to *Unique* (PM, 2012). Version 1.1

Version 1.1.1 (CA, 2022)

Copyright © Unique 2022