



Understanding Chromosome & Gene Disorders

# Xq28 duplications



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## Xq28 duplications and microduplications

An Xq28 duplication means that the cells of the body have an extra amount of genetic material from one of their 46 chromosomes – the X chromosome. These duplications can be variable in size but those that are too small to be visible under the microscope are called **microduplications**.

For typical and healthy development, chromosomes should contain just the right amount of genetic material – not too much and not too little. Like most other chromosome disorders, having an extra part of chromosome X may increase the risk of birth defects, developmental delay and intellectual disability. However, the outcome is variable and depends on what and how much genetic material is duplicated and whether the affected person is male or female.

## Background on chromosomes

Our bodies are made up of different types of cells, almost all of which contain the same chromosomes. Each chromosome contains hundreds to thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information that tells the body how to develop, grow and function. Chromosomes (and hence 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, 44 are grouped in 22 pairs, numbered 1 to 22. The remaining two are the sex chromosomes that determine biological sex. Males have one X chromosome and one Y chromosome, and females have two X chromosomes.

Early in embryonic development in females, one of the two X chromosomes (either the one inherited from the mother or the one inherited from the father) is randomly and permanently inactivated (switched off) in all cells of the body (other than egg cells). This phenomenon is called **X-inactivation**. Since the inactivation is normally random, some cells in the female body may have an inactive X chromosome inherited from the father, while other cells may have an inactive X chromosome inherited from the mother.

## Chromosome duplications

When the sperm and egg cells join they form a single cell and this cell must continuously make copies of itself (and all its genetic material) in order to produce the billions of cells that form during human growth and development. Sometimes during the formation of the egg or sperm cells or during this

complicated replication process, parts of a chromosome are lost or duplicated and/or become rearranged. The effect of any duplication varies according to how much DNA (genetic material) is duplicated (more specifically which genes are included) and how many times it is duplicated. The effect of an Xq28 duplication, like other X chromosome anomalies, also varies if the child is a boy or a girl.

In general, duplication of Xq28 has a milder effect, or no obvious effect in girls since girls have two X chromosomes and the chromosome with the duplication is usually the one that is switched off. As a result, the extra genetic material plays little or no role in development. This is known as [skewed X-inactivation](#), which means the chromosome that is switched off is not chosen randomly. However, in some girls with an Xq28 duplication, the X chromosome with the duplication is not inactivated. Instead, the unaffected X chromosome is inactivated in some or all cells which means the girl's development is more likely to be affected. Occasionally the duplicated genetic material is relocated onto another chromosome. When this happens, it is called a [translocation](#). If the genes on this piece of duplicated DNA remain active they may affect development (Lachlan 2004; Sanlaville 2005; Makrythanasis 2010; Bijlsma 2012; Shimada 2013; Fieremans 2014; Novara 2014; Scott Schwoerer 2014).

Boys have only one X chromosome and it is active. The duplicated part of a boy's X chromosome is also fully active, so an effect is commonly observed in boys.

Recent advances in technology have allowed the development of DNA tests that can reveal the exact amount and location of the DNA that is duplicated in each person, as well as the genes included in the duplication. It is believed that most of the clinical features of Xq28 duplications, such as effects on learning and physical development, are caused by having extra copies of one or more of these genes. Since the duplicated regions of DNA vary in size, different people can have different genes (or no genes) included in their duplication. We are still learning more about the specific jobs or functions of the genes in this region (see [Ongoing Research involving Xq28](#) on page 20).

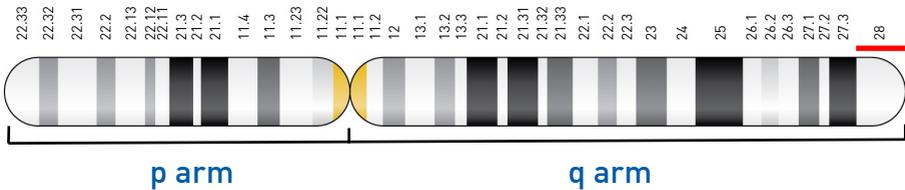
## Sources

The information in this booklet is drawn from published medical literature and from information from Unique members. The first-named author and publication date from articles in the medical journals 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. Unique member surveys were carried out in 2009 and 2015.

## Looking at Xq28

Chromosomes can't be seen with the naked eye but if cells are prepared in a specific way, the chromosomes can be stained and viewed under a microscope to show a distinctive pattern of light and dark bands. You can see the banding pattern for chromosome X in the diagram below.

## Chromosome X banding pattern



Each chromosome has a short (**p**) arm and a long (**q**) arm. Bands are numbered outwards starting from where the short and long arms meet, at a point called the centromere (the area coloured yellow in the diagram above). Region q28 is at the bottom end of the long arm of chromosome X (marked with a red bar in the diagram).

With any duplication, the amount of duplicated DNA can vary. If the amount is small it may not be possible to see under the microscope and many people who have a small duplication may have previously been told their standard chromosome analysis was 'normal'. A laboratory technique called FISH (fluorescence *in situ* hybridisation) enables sections of the chromosome to be analysed in more detail and can help detect a duplication. This technique uses fluorescently labelled pieces of DNA that match the DNA in specific places on a chromosome so this test will only be offered if there is a suspected abnormality in a specific region of a chromosome. The most recent test now available that allows DNA to be analysed in great detail is called microarray comparative genomic hybridisation (array CGH). An array CGH test can detect very small Xq28 duplications even when this diagnosis is not suspected.

Duplications can be either **terminal duplications**, in which the duplication stretches to the end of chromosome X or **interstitial duplications**, in which a segment of DNA that includes q28 (or part of q28) but not the end of the X chromosome is duplicated. The duplicated DNA is called a **translocation** if it has been moved to a different region of chromosome X or onto a different chromosome. A translocation can only be diagnosed using a standard chromosome analysis or FISH since the chromosome needs to be visualised.

Large duplications of Xq28 (more than 10Mbp) may extend to region Xq27 or Xq26 and so include a large number of different genes. These are visible under the microscope (Sanlaville 2004; Van Esch 2005; del Gaudio 2006).

Small duplications may only have an effect if they include a gene. The Xq28 region is very gene-rich and the most commonly identified symptom causing gene in this region is called **MECP2 (methyl CpG binding protein 2)**. This is why an Xq28 duplication is sometimes called **MECP2 duplication syndrome** (Ariani 2004; Meins 2005; Van Esch 2005; del Gaudio 2006; Friez 2006; Madrigal 2007; Smyk 2008).

In extremely rare cases, cells with a normal chromosome make-up are found as well as cells with extra DNA from Xq28. This is called **mosaicism** and can, in some cases, lessen the effects of the extra chromosomal material.

## Chromosome test results

Your geneticist or genetic counsellor will tell you about the point(s) where your child's chromosome has broken and the extra genetic material has been added. The information you are given will depend on the method used to test your child's chromosomes. If the duplicated piece of DNA was identified when your child's chromosomes were observed under a microscope following a basic staining technique, the results (called a karyotype) may read something like the following example:

### Karyotype example

#### 46,XY,dup(X)(q28)dn

- 46** The total number of chromosomes in each cell
- XY** The two sex chromosomes: XY indicates a male, XX indicates a female
- dup** A duplication means that there is an extra amount of DNA
- (X)** The duplication consists of DNA from chromosome X
- (q28)** The chromosome has broken in one place, q28, and material from this point to the end of chromosome X (q arm) is included in the duplication
- dn** The duplication occurred *de novo* (as a 'new event'). The parents' chromosomes have been checked and no duplication or other chromosome change has been found at Xq28.

If the duplication is identified as *de novo*, it is very unlikely to have been inherited so the chance of the parents having another child with the duplication is very small. If the karyotype is followed by **mat** the duplication has been inherited from the child's mother (maternal); if it is followed by **pat** the duplication has been inherited from the father (paternal), although duplications are rarely inherited from the father since a man is likely to be affected by his duplication.

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

## FISH example

### 46,XY,dup(X)(q28).ish dup(X)(RP11-119A22++)

46 The total number of chromosomes in each cell

XY The two sex chromosomes: XY indicates a male, XX indicates a female

dup A duplication means that there is an extra amount of DNA

(X) The duplication consists of material from chromosome X

(q28) The chromosome has broken in one place, q28, and material from this point to the end of chromosome X (q arm) is included in the duplication

ish The analysis was by FISH

dup A duplication means that there is an extra amount of DNA

(X) The duplication consists of DNA from chromosome X

RP11-119A22++

A region of DNA known as RP11-119A22 has been detected in two copies instead of the usual one copy

## Array CGH example

### arr[hg19] Xq28(152,940,458-153,016,382)x3

arr The analysis used microarray technology

hg19 Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new 'builds' of the genome are made and the base pair numbers may be adjusted

Xq28 The analysis revealed a duplication of DNA on chromosome X, region q28 (152940458-153016382)

The duplicated fragment is identified by its base pair position (the exact points where the chromosome has broken and duplicated).

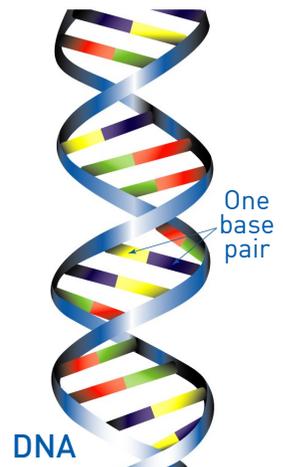
In this example, the extra piece of DNA is from 152,940,458 bp to 153,016,382 bp

(see diagram on page 7, the duplication is shown as a yellow bar)

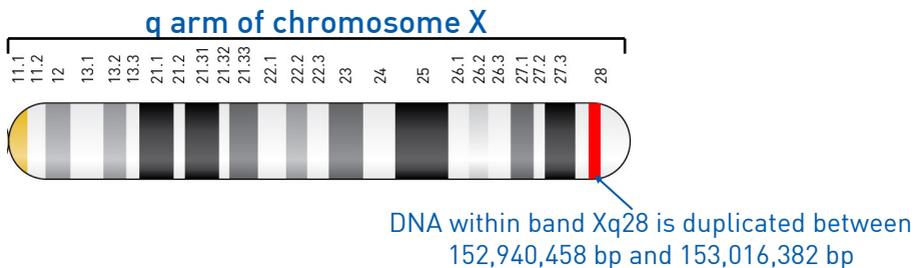
This means that about 75,924 base pairs are duplicated. This is usually expressed as 75.9 Kb (1 Kb = 1,000 base pairs)

x3 There are 3 copies of this section of DNA

The normal copy number of chromosome X is 2 in women but only 1 in men



## Xq28 duplication: an example



You may wish to compare your child's results with others who have the same or a similar duplication to help understand your child's development. However, it is important to remember that the same duplication can have different effects on different people, even siblings with exactly the same genetic change can have a very different outcome. A child's other genes, environment and unique personality help to determine their future development, needs and achievements. 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 or a similar duplication.

### How common are Xq28 duplications?

Duplications of Xq28 are considered quite rare but now that more specific laboratory techniques are available, the frequency of diagnoses is increasing. At the time of updating this booklet in 2015, over 100 male and almost 100 female cases of Xq28 duplication had been reported in DNA variation databases used by the clinical community, and just over 100 of these included a duplication of the MECP2 gene. The actual number of people with an Xq28 duplication will be much greater than anything recorded since not everyone will have their DNA tests published or put in a database and not everyone will have been diagnosed. In 2014 it was estimated that 150 boys had been reported as having an MECP2 duplication (Van Esch 2014).

To date (end of 2015), Unique has 63 families with at least one child or adult with an Xq28 duplication, just under half of whom have a duplication that is known to include the MECP2 gene. These members range in age from a child of two years to an adult aged 46 years.

Unique members who do not have a 'pure' Xq28 duplication i.e. have a loss or gain of material from another chromosome as well as an Xq28 duplication are not considered in this guide since the reason for their clinical features may not be explained by the duplication from Xq28 alone. However, if your child has been diagnosed as having a chromosomal rearrangement that includes an Xq28 duplication this booklet may help to explain some of your child's symptoms.

## Common features

### Boys with an Xq28 duplication

Boys with an Xq28 duplication are, in the majority of cases, more severely affected by the duplicated DNA than girls. Every boy with an Xq28 duplication is unique and so each child will have different medical and developmental concerns. If the duplicated DNA does not contain a gene or other important information there may be no apparent effect on development (Unique has one adult male member who is not affected by his duplicated piece of DNA). However, there is usually an effect, and a gene is usually involved, which is why a genetic test is carried out. The gene most commonly identified as the cause of developmental or medical concerns is MECP2. Unique has 42 members who are boys or men with an Xq28 duplication (6 of whom also have a loss or gain of genetic material from another part of chromosome X or another chromosome). They range in age from less than a year to 36 years old, roughly half of whom have a duplication that is known to include the MECP2 gene.

Common features of Xq28 duplications in boys are as follows:

- Hypotonia (floppiness or low muscle tone) in babies and infants
- Delayed, limited or absent speech and language
- Learning (intellectual) disability
- Epileptic seizures
- Progressive spasticity (muscles are continuously contracted which causes tightness and stiffness and may interfere with walking and moving)
- Recurrent respiratory infections

Boys may also have other symptoms such as difficulty swallowing, reflux (when the contents of the stomach return up the food pipe), extensive dribbling (which may be due to hypotonia), and they may find it difficult to maintain a healthy weight. Some boys also display autistic behaviour (including anxiety, stereotypic hand movements, and decreased sensitivity to pain/temperature). Some boys show mild facial features such as a flat head, small midface, large ears or low nasal bridge. Other less common features include microcephaly (a neurodevelopmental disorder characterised by a small head), growth retardation and effects on urinary or genital organs.

### Girls with an Xq28 duplication

In the majority of cases, girls with an Xq28 duplication are not obviously affected by the duplicated DNA due to skewed X-inactivation (see [Chromosome duplications](#) on page 2-3). Although, neuropsychiatric symptoms including depression, anxiety, and autistic features have been described in carriers (those who have the duplicated DNA on the X chromosome that is switched off) who have normal intellectual abilities [Ramocki 2009].

Girls who are affected by their Xq28 duplication normally show milder and more variable symptoms than affected boys (Lachlan 2004; Sanlaville 2005; Makrythanasis 2010; Bijlsma 2012; Shimada 2013; Fieremans 2014; Novara 2014; Scott Schwoerer 2014).

However, over the last few years an increase in diagnoses of girls affected by an Xq28 duplication has emerged and more severe cases are being reported. In one family, twin sisters showed severe but varying intellectual disabilities, seizures, hypotonia, limited/absent speech and severe motor disabilities (Schwoerer 2013).

Unique now has 28 affected female members, aged between 2½ and 30 years as well as 8 apparently unaffected carriers, less than half of whom are known to have duplicated DNA that includes the MECP2 gene. Twelve members also have duplicated, deleted or rearranged DNA in other regions of chromosome X or on other chromosomes. It is difficult to describe common features of Xq28 duplications in girls with non-skewed X inactivation since symptoms vary enormously. When this booklet was first written, girls who were diagnosed with an Xq28 duplication were thought to be mildly affected in areas such as learning, language and motor skills (and a few were reported to have seizures). In more recent years, a few girls with Xq28 duplications have been reported with more severe symptoms similar to those observed in boys (see page 8).

“ We were concerned about her development, when at 18 months she hadn't started speaking, and also that she was not developing and progressing at the same rate as her peers. This led to a referral to Speech and Language, then to a Paediatrician who eventually suggested genetic testing. ”



8 years old

## What is the outlook?

The outlook for a boy or girl with an Xq28 duplication depends on what part of chromosome Xq28 has been duplicated and how this has disrupted early development. Those with a large Xq28 duplication are more likely to have more symptoms. Occasionally, two extra copies of all or part of Xq28 are present, which is known as a triplication. When this happens, the effects are likely to be more severe (del Gaudio 2006; Tang 2012).

As far as we know the oldest person affected by their Xq28 duplication (i.e. not a female carrier) that includes MECP2 is a 45 year old man (Friez 2006; see [Adults with an Xq28 duplication](#) page 19). One paper reported that six out of 11 boys with an Xq28 duplication died (from secondary recurrent respiratory infections or pneumonia) before 25 years of age (Friez 2006). In this report the boys also had severe functional problems of the bowel and/or bladder which are thought to have affected respiration by restricting lung capacity. Unique has seven adult members older than 18 years. As far as we are aware, only one Unique member with an Xq28 duplication has died. He had pulmonary hypertension and underdeveloped lungs, and his family believe that otherwise his chromosome disorder was manageable.

**“ Kaleb was an extremely contented, happy little boy despite everything he went through medically. I am proud to say I can count the ‘bad days’ on one hand they were never ‘days’, they were half hours. ”**

## Pregnancy and birth

Mothers carrying babies with an Xq28 duplication do not usually experience problems during pregnancy. They usually have a normal delivery and only discover their baby is affected after the birth. Of the 11 Unique families who told us about their pregnancy experiences, 7 mentioned they experienced no difficulties. Two babies were born at 37 weeks, one of which was born with a low birth weight, the other was diagnosed with IUGR (intrauterine growth restriction which means poor growth as a fetus) at 34 weeks. One baby was born at 33 weeks following a pregnancy complicated by pre-eclampsia and one mother had 3 false labours. There are no reports in the medical literature of pregnancy or birth complications.

## Newborn

Typically babies who are affected by their Xq28 duplication are floppy (hypotonic) in the newborn period. This can result in delays reaching developmental milestones such as sitting, rolling, crawling and walking, and may also cause feeding problems.

## Growth and feeding

Babies with an Xq28 duplication generally have a normal birth weight. The range of birth weights (at or near term) at Unique and in the medical literature was 2.1 kilos (4lb 10oz) to 4.3 kilos (9lb 8oz). Six Unique babies of the 17 for whom we have a record of their birth weight had a low birth weight (below 2.6 kilos or 5lb 12oz), although two were born early and one was a twin. Feeding difficulties are however a major area of concern for families. Some babies are 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 an Xq28 duplication can lead to difficulties with sucking and

swallowing, and/or latching onto the breast. One study reports that more than 50 per cent (15/29) of boys have severe feeding problems. One baby in the medical literature benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat) and two babies at Unique needed a gastrostomy tube (a G-tube) in order to meet their nutritional requirements (Vasquez 1995; Goodman 1998; Lammer 2001; Van Esch 2005; Friez 2006; Echenne 2009; Sanlaville 2009).

Hypotonia can also affect the food passage and contribute to gastroesophageal (GO) reflux (feeds return readily up the food passage). 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 surgical intervention such as fundoplication (a procedure on the stomach) (Friez 2006; Sanlaville 2009).

Boys with a duplication of Xq28 usually have normal growth and are of normal height and weight. Although there are reports in the medical literature of boys who have growth retardation, this has been associated with a larger chromosomal duplication (Sanlaville 2009; Van Esch 2014). Unique girls with an Xq28 duplication have been described as tall, short and of normal height for their age.



## Appearance

Children with a duplication of Xq28 sometimes have specific facial features, the most common of which is large ears. They may also have a flat nasal bridge. Facial hypotonia can result in an inverted V-shaped ('tented') upper lip, an open mouth and dribbling. Microcephaly (an unusually small head) has been reported in a minority of boys (3 Unique members), however, most children have a normal head size. Facial features can be very subtle and children may not look very different to other children and may closely resemble their siblings or parents (Van Esch 2005; Friez 2006).

## Learning

Intellectual disabilities affect boys with an Xq28 duplication, with most children severely affected and a small minority profoundly affected. One boy described in the medical literature who has a very small duplication has a moderate learning disability. Girls may also show learning difficulties which can vary considerably. Children will need support and may benefit from early intervention programmes and thrive best in a special learning environment (Madrigal 2007; Echenne 2009).

“Great progress in communication in the past 2 years, he really has an interest and great coping skills” – 10 years

“He has a good memory and loves music and TV” – 4½ years

“His memory is not good” – 16 years

## Speech and communication

Speech is delayed or absent in boys with an Xq28 duplication. Some children use sign language to help to communicate their needs and wants, and many children have long term speech therapy to help their communication skills. Children use gestures, facial expressions and vocal noises to indicate their needs and express their feelings. One Unique child with no formal speech is very expressive with his eyes and smiles (Van Esch 2005; Friez 2006).

“He does not use words but screams and points” – 4½ years

“He has no speech” – 16 years



Girls may show delays or impairments in speech and language acquisition and difficulties appear to vary quite considerably. There are many reasons for the absent or delayed speech, 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 can also affect the development of speech.

## Development: gross motor skills

### (Sitting, moving, walking)

Boys with an Xq28 duplication are typically slow to reach their developmental motor milestones, as are some girls. The evidence in the medical literature and at Unique is that boys with an Xq28 duplication sit between 7 months and 4 years (average 19 months); crawl between 14 months and 6 years (average 31 months) and walk between 14 months and 3 years (average 26 months). Independent walking is not possible for all boys. The effect can be milder for girls and gross motor skills may not be affected. Some children need support (such as a standing frame, walking frame, wheelchair and/or support boots) while learning to walk. Many children have **ataxia** which is a disorder affecting their balance and/or coordination. People with ataxia have problems with co-ordination so often walk unsteadily or clumsily (Van Esch 2005; Echenne 2009).

There are several reasons for these motor delays including hypotonia, and physiotherapy and occupational therapy can be beneficial. Hypotonia often improves as children mature, however, it can progress to spasticity in later childhood or adolescence and usually affects the legs more than the arms (Van Esch 2005; Friez 2006; Echenne 2009).



## Development: fine motor skills

### (Hand-eye co-ordination and dexterity)

There is little detailed information on the fine motor skills of boys with an Xq28 duplication. However, these skills do appear to be affected in some boys. Hypotonia may influence this and children may take longer to reach their developmental milestones. The three families who responded to our 2015 survey about their daughter mentioned that their child had difficulties or delays with fine motor skills. Occupational therapy may help improve these skills.

## Medical concerns

### ■ Immunity and respiratory infections

While there is little evidence of decreased immunity or increased respiratory infections in less severely affected girls, an increased susceptibility to infection seems to be common in boys with a duplication of Xq28. Recurrent respiratory infections are especially common. In one study almost all of the 18 individuals had needed mechanical ventilation on at least one occasion, and four of the five who were aged over 15 years had a tracheostomy. A tracheostomy is a surgical procedure in which an opening is created in the front of the trachea (windpipe). A tracheostomy tube is inserted through the opening and into the trachea. If a person's airway (the tube that connects the mouth and nose to the lungs) is blocked or unusable, the opening that is created during a tracheostomy allows them to breathe freely. As well as helping someone to breathe, a tracheostomy can also be used to remove unwanted fluids produced by the lungs or throat. By contrast, a different study of five boys with an Xq28 duplication revealed that none had frequent infections (Friez 2006; Echenne 2009). Thirteen Unique members mentioned that their child suffered recurrent respiratory infections and six members are known to have had pneumonia. It is possible that muscle weakness may also play a role in respiratory problems. Five members mentioned recurrent ear infections and six members informed us that their child had glue ear (this is when the middle ear fills with fluid and it may affect hearing). Early detection of infection and the use of antibiotics is recommended (del Gaudio 2006; Friez 2006).

Tonsillectomy (surgical removal of the tonsils) and adenoidectomy (surgical removal of the adenoids) are commonly reported in case reports. Four Unique members informed us that their child had had their adenoids and tonsils removed and three further children were reported as having frequent tonsillitis.

“ Because of his muscle problem, he has difficulty coughing mucus out by himself. Adenoidectomy, tonsillectomy and CPAP helps his sleeping. He sleeps less during the day, more concentration and more energetic. We noticed that he recovered from his cold faster than before. ”

“ I was told during one of his hospitalizations that his constipation may cause breathing problems, one of the X-rays showed the possibility that his stool in his intestine occupied space for him to breathe. ”

“ Scoping into his respiratory prior to adenoidectomy, doctor told us that he noticed his muscle is weak which may cause him difficulty trying to clear congestion when he has cold. ”

“ Getting the chest infections under control is very important. It can be difficult as even if you tackle the unsafe swallow sometimes they still get unwell. ”

It has also been reported by Unique members and in the medical literature that severe constipation may restrict lung capacity. Nine Unique members reported that their child has problems with constipation.

The increased susceptibility to infections seen in some boys with an Xq28 duplication could be explained in part by contributing factors such as reflux and swallowing difficulties. Another explanation is that low levels of an infection-fighting antibody, IgA (immunoglobulin A) have been found in some boys with an Xq28 duplication. IgA plays an important role in defending the body against infection that invades the body through the mucous membranes, such as the nose, eyes, lungs and intestines. Therefore, people with low IgA are more susceptible to infections and colds. However, a low level of IgA is also frequently found in typically developing children. A recent study showed that an increased susceptibility to infection in people with an Xq28 duplication that included MECP2 can be associated with IgA/IgG2-deficiency. The children in the study were also found to have a lower concentration of antibody against pneumococci (a bacterium known to cause pneumonia) and a change in their body's early defence system to infection (Bauer 2015). One Unique member is also known to have low pneumococcal antibody levels. Vaccination against common pathogens is recommended.

## ■ Seizures

It has been estimated that approximately 50% of boys with an Xq28 duplication that includes the MECP2 gene have seizures (Van Esch 2014) and this value may increase as children reach adolescence. The onset of seizures varies widely from very early childhood to post teenage. Medication has shown to be effective at controlling seizures, although for some, seizures have become resistant to medication (Sanlaville 2009; Vignoli 2012). Seven Unique families have reported that their child (five boys and two girls) has seizures.

## ■ Genital anomalies

Minor anomalies of the genitals are common in boys with chromosome disorders. Cryptorchidism (undescended testes) has been noted in a number of boys with an Xq28 duplication. The testicles can be brought down by a straightforward surgical operation if they do not descend of their own accord in time. Hypoplastic (underdeveloped) genitalia have also been reported. Hypospadias (where the hole usually situated at the end of the penis is on the underside instead) and micropenis (a small penis) have also been described in the medical literature (Vasquez 1995; Goodman 1998; Lammer 2001; Meins 2007). To our knowledge there are no genital anomalies in girls.

## ■ Brain

Brain imaging has shown that a number of boys with an Xq28 duplication have brain anomalies. Some boys have delayed myelination. Myelin is the substance

that covers nerve cells (much like the plastic coating covering the wire in an electric cable). Myelination, the formation of myelin, is an ongoing process that starts in the womb and continues after birth and into middle age, and in some boys with an Xq28 duplication the myelination process seems to normalise.

A recent study (Chehadeh 2015) used brain magnetic imaging (MRI) to analyse the brains of 30 people with Xq28 duplications that included MECP2. Twenty-eight out of the 30 people studied showed brain abnormalities, but the size of the DNA duplication could not be correlated to specific abnormalities. A recent article also identified brain anomalies in a female patient (Shimada 2013) and a further article described cystic lesions in three male and one female patient (Shimada 2012). Non-specific neuroradiologic findings on brain MRI, including hypoplasia (underdevelopment) of the corpus callosum (the band of nerve fibres that connects the left and right hemispheres of the brain), enlarged ventricles, non-specific changes in the white matter, and cerebellar hypoplasia (under development of the part of the brain (cerebellum) that controls motor skills) have been observed (Friez 2006; Philippe 2013). Two Unique boys had hydrocephalus (a build-up of fluid in the brain) which resolved with no intervention. One Unique member is known to have delayed myelination, a thin corpus callosum and subtle loss of volume in white matter. Two further members have abnormalities in the grey and white matter of their brain.

## ■ Digestion

Constipation is a common feature in boys with an Xq28 duplication. Dietary changes and/or medication can help to manage the problem. One report of a series of boys with Xq28 duplications described severe functional problems of the bowel from the newborn period onwards. In several children regular enemas were necessary and dilatation of the bowel affected respiratory function (Goodman 1998; Clayton-Smith 2009). Nine Unique families have informed us that their son or daughter has problems with constipation.

## ■ Vision

The vision of boys and girls who have a duplication of Xq28 seems to be largely unaffected. One Unique boy had a squint (strabismus, where one or both eyes can turn inwards, outwards or upwards). Another Unique boy had Horner's syndrome (a disruption in the nerves that supply the eye) in his right eye. One boy in the medical literature had mild long sight (hypermetropia) (Meins 2007).

## ■ Hearing

Like vision, hearing appears to be largely unaffected in children with an Xq28 duplication. One boy in the medical literature had bilateral (affects both ears) deafness. Another boy in the medical literature had glue ear, where there is a build-up of fluid in the middle ear. Glue ear usually resolves as children get older but if this does not happen, the child may need a grommet (small ventilation tube) inserted into their eardrum.

## ■ Heart problems

Heart (cardiac) conditions do not appear to be a common feature of an Xq28 duplication. Only one Unique member (a girl) had a heart problem. She had a heart murmur, an ASD (atrial septal defect in which blood flows between the upper chambers of the heart) and the right atrium and ventricle were mildly enlarged. Two boys in the medical literature had problems associated with their aorta, which is the main artery that supplies oxygenated blood to the circulatory system (Madrigal 2007).

## ■ Feet

The feet of children with an Xq28 duplication are often not affected. However, some foot anomalies have been described both at Unique and in the medical literature. These anomalies include high arches, flat feet, puffy feet and/or feet that turn inwards. Some children may require special insoles or inserts in their shoes or special supportive footwear (Friez 2006).

## ■ Teeth

Generally speaking, children with chromosome disorders appear to have more dental problems than their peers, so high quality treatment and frequent dental appointments are recommended (del Gaudio 2006; Unique). There have been no reports of specific dental anomalies in children with Xq28 duplications.



## ■ Other concerns

Scoliosis (curvature of the spine) has been reported in one Unique boy and a girl in the medical literature. Three boys in the medical literature had inguinal hernias (where a bulge of tissue from the intestines is located in the lower abdomen (groin)). An inguinal hernia may require surgery. One boy at Unique had kidney (vesico-ureteral) reflux (where the urine flows upwards from the bladder back to the kidney, potentially damaging the kidneys). A few boys in the medical literature suffered from frequent urinary tract infections (Vasquez 1995; Goodman 1998; Lammer 2001; Friez 2006).

## Behaviour

Children with an Xq28 duplication are typically pleasant, calm and sociable. However, they are as vulnerable to frustration as other children with a communication difficulty and temper tantrums and aggression can present carers with challenges. Behaviour within the autistic spectrum has been reported both in the published medical literature and in a number of Unique children with an Xq28 duplication. Some children do not have a diagnosis of autistic spectrum disorder (ASD) but show some autistic tendencies or traits. The autistic tendencies that have been noted include a limited range of facial expressions, decreased eye contact, repetitive behaviour, self-stimulating behaviour and repeating movements like head shaking or wringing their fingers. A recent article studying the behaviour of 10 boys with an Xq28 duplication that includes the MECP2 gene (aged between 3 and 10 years) states an over expression of this gene (which commonly occurs when the gene is duplicated) is related to core features of autistic spectrum disorder (Peters 2013). This article also described 9 out of 10 of the boys as having a decreased responsiveness to pain and temperature, this is known as sensory hypo-responsiveness and the authors suggest this may be a common feature. 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 (Meins 2005; del Gaudio 2006; Friez 2006).

Aggressive behaviour or mood disorders have been described in a small minority of boys. One boy described in the medical literature showed autistic features at the age of 4 years which disappeared two or three years later. Between the age of 15 and 20 he developed a mood disorder and had oppositional behaviour, but these disappeared by the age of 20 years (Meins 2005; Van Esch 2005; del Gaudio 2006; Echenne 2009).

“ He is happy but has some behavioural problems ” – 4½ years

“ Has plenty of behavior issues and is going to a special school for that, he also has moderate to severe intellectual delay ” – 10½ years

## Puberty

Unfortunately, there is very little information available on puberty in children with an Xq28 duplication, either at Unique or in the medical literature. One Unique member who responded to our survey mentioned she had noticed her son had 'more meltdowns' as he enters puberty (10½ years). Another mother mentioned that her son was more aggressive and frustrated (15½ years). Two parents at Unique mentioned that their sons' seizures were worse during puberty. One mother of a Unique girl mentioned that her daughter went through typical female changes but entered puberty early and menstruated from 10 years.

## Adults with an Xq28 duplication

We do not have a lot of information about adults with an Xq28 duplication. This is partly due to the fact that years ago, chromosome analyses were not precise enough to detect small duplications and many people remain undiagnosed. As an example, two men in their 40's were recently diagnosed as having an Xq28 duplication, and both men have severe intellectual disabilities (Prof. Van Esch, personal communication). Another reason for not having much information may be that not everyone survives into adulthood.

Unique has 7 adult members affected by their Xq28 duplication (3 male and 4 female). The eldest male member is now 36 years old, he loves music, his memory is not good and he has ASD. He has no speech, needs full time care and uses a wheelchair (*Unique*). Another member in his twenties is quite severely affected by his duplication and a 20 year old member has severe learning difficulties. The two younger female adult members have developmental delay, one has learning disabilities, visual impairment and hearing loss, the other has epilepsy. The two older female members are mothers with mild symptoms.

Two brothers of 25 years and 33 years have been described in the medical literature. Both had swallowing difficulties and one had a feeding tube. Due to recurrent pneumonia both had had a tracheostomy. A 24-year-old man is also described in the medical literature. He has a profound learning disability.

A 26-year-old man was described as having a low IQ but his learning disability has not worsened over time. He was diagnosed with ASD as a child but these characteristics were lost over time. He has mastered walking and the ataxia he had when younger has lessened over time. He has epilepsy. His 20-year-old nephew is also described: he is not affected by autism but suffers from epilepsy, albeit less severely than his uncle (Van Esch 2005; Friez 2006; Echenne 2009).

## Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the Xq28 duplication occurred. In the majority of cases a boy inherits the Xq28 from his mother (a carrier) who is either not at all affected or only mildly affected by the duplication. In some cases the Xq28 duplication occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* Xq28 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 Xq28 duplications are accompanied by a loss 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.

In a few people, the cells containing the chromosome with an Xq28 duplication exist alongside cells with a normal chromosome number and arrangement. This is known as **mosaicism** and typically arises after fertilisation. Mosaicism may 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 or did not do to cause the Xq28 duplication and nothing you could have done to prevent it from occurring. 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, there is no reason for anyone to feel guilty.

## Can it happen again?

The possibility of having another pregnancy with an Xq28 duplication depends on the parents' chromosomes. If neither parent is found to have the duplication when their blood cells are tested, the duplication is very unlikely to happen again. However, if the mother is a carrier, the risk in each pregnancy of having another affected boy is 25 per cent and the risk of having a carrier girl is 25 per cent. Since carrier girls generally have skewed inactivation resulting in the Xq28 duplication being inactivated, girls are more often than not unaffected by the duplication. If a parent has a chromosome rearrangement involving Xq28, the possibility is greatly increased of having other affected pregnancies. It is very unlikely that the father will carry the duplication since, in most cases, he will be affected by his duplication. In the case of *de novo* duplications, the possibility exists that the mother can have mosaicism and therefore only carries the duplicated X chromosome in her ova or egg cells (or only in some of these cells). Because this type of mosaicism cannot be ruled out in *de novo* cases, the risk to subsequent pregnancies in *de novo* cases is considered to be between one and two per cent. To date, no cases of men transmitting a duplication containing the MECP2 gene have been reported. This is because, as far as we know, all boys/men who have the duplication have MECP2 duplication syndrome.

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. For an Xq28 or MECP2 duplication a specific test known as MLPA (multiplex ligation-dependent probe amplification) can be carried out to determine whether the baby carries the duplication. Testing is generally very accurate, although not all of these tests are available in all parts of the world.

## Ongoing research involving Xq28

Region q28 of chromosome X is known for its gene density (it contains over 100 genes) and has been studied for over 30 years. A large number of X-linked syndromes (syndromes known to be caused by a change in DNA content of chromosome X) have been mapped to this region and the genes responsible for the syndromes have been identified. The use of molecular techniques such as array CGH and FISH has allowed detection of microduplications that were previously undetectable using older techniques. This has enabled more accurate definition of chromosomal breakpoints (where the DNA change has occurred) which has in turn enabled researchers to identify regions on the chromosome that correlate with the different clinical features of different conditions. The size and position of duplicated pieces of DNA from Xq28 identified so far varies enormously, from a small duplication of 4.88 kb (4880 base pairs) to a larger duplicated region of 155.27 Mb (1Mb is equivalent to 1,000,000 base pairs). Looking at the latest genome databases, many different Xq28 duplications have been identified, over 100 of which contain the [MECP2](#) gene.

Although a lot of research is being carried out relating to the [MECP2](#) gene, there are a number of other genes known to be included in larger duplications which may contribute to varying symptoms (see diagram on page 22). Duplication of the gene [RAB39B](#) has been associated with learning difficulties and/or intellectual disability as well as behavioural difficulties (Vanmarsenille 2014; Giannandrea 2010; El-Hattab 2011 & 2015). [GDI1](#) has also been identified as a gene responsible for learning disabilities (Bienvenu 1998; Clayton-Smith 2009; Vandewalle 2009), but the consequence(s) of a duplication of [GDI1](#) is not yet known. [IKBKG](#) has been linked to a variety of distinct syndromes, including immunodeficiency but not intellectual disability. [L1CAM](#) (L1 cell adhesion molecule) has been identified as a gene linked to intellectual disability and spasticity (an unusual tightness of muscles; del Gaudio 2006; Stumpel 2015). Boys who also have duplication of the [FLNA](#) (Filamin A) gene have been shown to be at risk for intestinal pseudo-obstruction (a disorder of the digestive system that affects the movement of food through the intestines).

There are reports of a small duplication that includes genes [H2AFB](#), [F8A](#), [FUNDCC2](#), [MTCP1NB](#), [MTCP1](#), [BRCC3](#), [VBP1](#), [RAB39B](#) and [CLIC2](#) (but not [MECP2](#)) that has been identified in males with learning difficulties and/or intellectual disability who share behavioural difficulties and characteristic facial features. Females are thought to be affected to a lesser extent (El-Hattab 2015).

[AFF2](#) and [FMR1](#) (a gene just at the border of Xq28 within the adjacent band Xq27.3) are both associated with fragile X syndrome when a mutation occurs in either of these genes. Children with fragile X syndrome may have learning difficulties and/or intellectual disability, autism and in some cases seizures. The possible effects of having a duplication of either of these genes are not yet well understood.

# Chromosome X



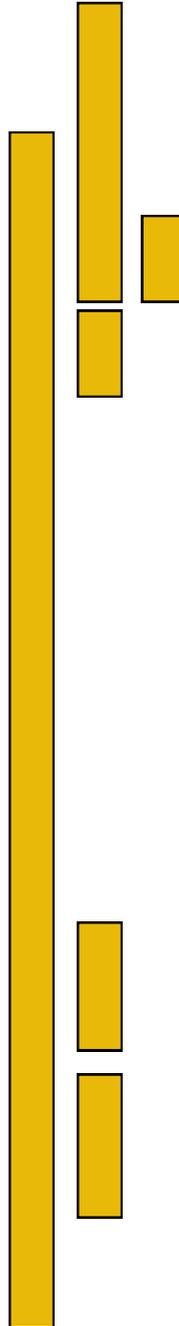
bp position

148 Mb  
149 Mb  
150 Mb  
151 Mb  
152 Mb  
153 Mb  
154 Mb  
155 Mb

## genes

FMR1  
AFF2  
IDS  
TMEM185A  
MAMLD1  
MTM1  
HMGB3  
VMA21  
NSDHL  
L1CAM  
**MECP2**  
FLNA  
GDI1  
IKBKG  
DKC1  
H2AFB  
F8  
FUNDC2  
MTCF1  
BRCC3  
VBP1  
RAB39B  
CLIC2  
TMLHE

## example duplications



This diagram was generated using Human genome build GRCh37/hg19 which was released in February 2009. If your genetic report was issued prior to this (e.g. hg18) or following the publication of this guide (e.g. hg38) the position of your duplication may have changed slightly. Not all genes are shown.

It is important to remember that while identifying the gene(s) responsible for certain features of an Xq28 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 more than the expected copy number 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.

## Recent advances in research

Recently, a research article describing the reversal of MECP2 syndrome in adult symptomatic mice using gene therapy was published (Sztainberg 2015). Mice were shown to have a reduction of the MECP2 protein to normal levels following treatment. Seizures stopped and symptoms of hypoactivity (decreased activity), anxiety and abnormal social behavior were resolved. Gene therapy on cells taken from MECP2 syndrome patients also corrected MECP2 levels. This research has shown promising initial steps towards the future possibility of reversing neurological dysfunction after symptoms set in.

In another very recent study, stem cells derived from skin samples of patients with an Xq28 duplication including MECP2 were generated and differentiated into neurons. These cells showed clear abnormalities in their appearance and functional behavior. The abnormalities were reversed following treatment with a compound that alters gene activity (Nageshappa 2016).

## Other families

Some families find it helpful to join support groups so they can get information and advice or just chat with other families who have a child with an Xq28 duplication or similar learning, social or medical issues. You will find information regarding these groups on the back page of this booklet. Unique also runs a private Facebook 'café'.

## Comments and advice from our members

“ Stay positive and focus on the good days. Try and get respite to recharge your batteries. ”

“ It is a very long journey. One person will have to not work and care for the child 24/7 with going to a doctor's office or the hospital at least once a week. ”

“ It can be quite scary reading all of the information and stories and you often worry about what may or may not happen to your child, but it is important to keep focus on the achievements that your child is making and celebrate them. Each child is unique – even if they have been given a diagnosis. ”

“ The information is extremely useful but most of all be guided by your child. While certain traits are associated, others may not be. Comparison can be dangerous. Never stop speaking up for your child, parents know best what their child needs. Enjoy all the moments big and small, and try not to get bogged down medically. ”

## Support and Information



Understanding Chromosome & Gene Disorders

### Rare Chromosome Disorder Support Group

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

Tel: +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/donate](http://www.rarechromo.org/donate)

Please help us to help you!

### Support groups and websites

<https://mecp2duplicationuk.org.uk>

[www.mecp2duplication.com](http://www.mecp2duplication.com)

<https://mecp2d.org/>

A US-based family-founded foundation providing support for the MECP2 duplication syndrome community and a syndrome-specific registry.

<https://www.facebook.com/groups/mecp2families>

An MECP2 Duplication Syndrome Family Talk Facebook Group that connects hundreds of family members of children and adults with MECP2 Duplication Syndrome.

<https://mecp2.wordpress.com>

<http://www.facebook.com/Blake-McMillan-Mecp2-Duplication-Syndrome-226615617485039/>

[www.vanwrightfoundation.org](http://www.vanwrightfoundation.org)

<http://www.reverserett.org.uk>

[www.rsrt.org](http://www.rsrt.org)

<https://curemds.com>

<http://www.duplication-mecp2.fr>

<http://duplicacionmecp2.es>

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it. This leaflet 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. In 2010 it was compiled by Unique and reviewed by Dr Damien Santaville, Hospices Civils de Lyon, France; Professor Dian Donnai, University of Manchester, UK and by Professor Maj Hultén BSc, PhD, MD, FRCPath, Professor of Reproductive Genetics, University of Warwick, UK. In 2016 it was updated by Unique (AP) and reviewed by Professor Hilde Van Esch, Centre for Human Genetics, University Hospital Leuven, Belgium. Version 1 2010 (SW), version 2 2016 (AP).

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