

Support and Information



Understanding Chromosome & Gene Disorders

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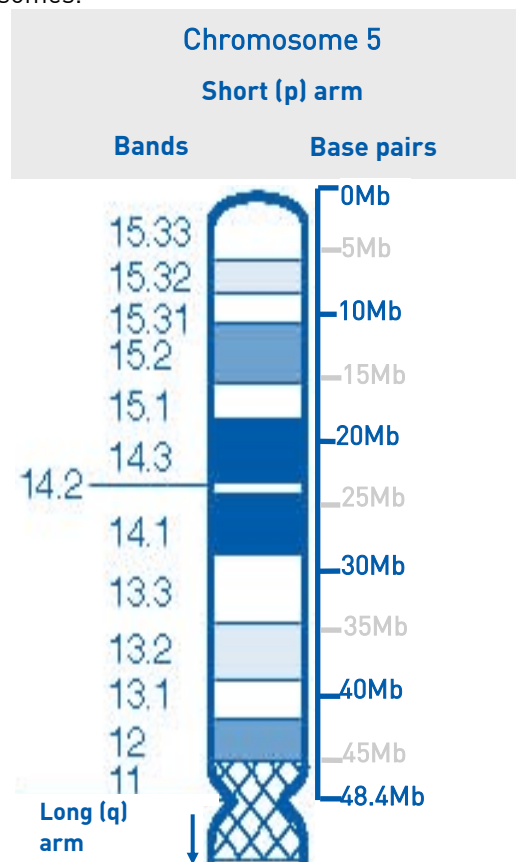
Understanding Chromosome & Gene Disorders

Trisomy 5p: Microduplications of 5p13 & 5p14

5p13 and 5p14 microduplications

A 5p duplication is a rare genetic condition that occurs when there is an extra copy of part of the genetic material (DNA) in one of the 46 chromosomes – chromosome 5. An extra copy of a portion of DNA is known as a duplication, but when it is very small amount, it is called a microduplication. People have 2 copies of chromosome 5 in most of their body cells. However only one of the copies of chromosome 5 in each cell will have the microduplication and the other will have the usual amount of DNA.

This can affect development, health, behaviour or all three, or there can be no discernible effect. How much a microduplication affects an individual, and the ways in which it affects them, can vary quite a lot. The precise effects vary depending on how large the microduplication is, how many genes it contains and what those genes do. The effects may not be limited to the genes within the duplicated piece of chromosome because these genes may interact with other genes on chromosome 5 or other chromosomes.



How did this happen?

5p microduplications can occur for the first time in the affected person, or they can be inherited from either the mother or the father. The only way to be certain is to check both parents' chromosomes from a blood test. If one parent has the same duplication, it has almost certainly been inherited, even if the parent is apparently unaffected. If both parents have normal chromosomes, the 5p duplication is a new occurrence. Geneticists call this a *de novo* (dn), change, meaning that it has not been inherited but has arisen 'anew' in this person for the first time. A new 5p microduplication has been caused by a mistake that either occurred when the parents' sperm or egg cells were formed, or during the formation and copying of the early cells after the egg and sperm joined.

As a parent you could have done nothing to cause or control this. In other words, there is nothing that either parent did before or during the pregnancy that caused the duplication.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 5p13 or 5p14 microduplication or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 5p microduplication. This is called **germline mosaicism** and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the duplication.

In families where the 5p microduplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 5p13 or 5p14 microduplication rises to 50% in each pregnancy. However, the effect of the microduplication on the child's development, health and behaviour cannot be reliably predicted.

Your genetics centre should be able to offer counselling before you have another pregnancy.

Can my child have children of their own?

Theoretically, anyone with a 5p13 or 5p14 microduplication has a 1:2 (50 per cent) chance in each pregnancy of passing it on.

■ Large head (macrocephaly)

A larger than normal head is a distinctive feature of Trisomy 5p, where an extra copy of most or all of the short arm of chromosome 5 is present. In people with a microduplication of 5p15, a large head is also occasionally found. It was observed in 2 adults and a child, all with microduplications of 5p13.2, although 11 others also with a 5p13.2 microduplication are not known to have a large head.

Sometimes the head is also a somewhat unusual shape: it may be unusually long (dolicocephaly); tower-shaped (turricephaly), or short from front to back (brachycephaly). The unusual shape may occur because some of the bony plates that make up the skull have fused too early (craniosynostosis), and if necessary, these can be released to allow the brain more room to grow and assume a more normal shape (Yan 2009; Oexle 2011; Romero 2012; Unique).

“Normal head size, but a prominent forehead. I believe if his forehead was normal, then his head size would be on the small side.” 5p14.2p14.3 microduplication

■ Unusual limb features

There is something unusual about the legs of four people. Two children, with microduplications at 5p13.2, have bendy, mobile joints, and one has an abnormal right knee position, in which the knee is turned outwards. More seriously, a baby with a tiny microduplication in 5p13.1 was born with quite deformed legs, but this may not be related to the microduplication (Yan 2009; Romero 2012; Decipher).

■ Seizures

Seizures have been reported in 3 babies or children with a 5p13 or 5p14 microduplication, and a further young child showed an abnormal pattern of electrical activity in the brain, without any seizures. There is detail on only one young boy, who first had seizures at 2½ years, and went on to develop a type of epilepsy that was somewhat resistant to medication although anti-epilepsy drugs did make his seizures less frequent (Yan 2009; Kluger 2012; Novara 2013).

■ Other issues

Health problems occurring in only one or two people cannot be attributed to the 5p microduplication without further evidence. Among those we know about are: one missing kidney; underdevelopment of the muscles in the abdominal wall; one undescended testicle; underactive thyroid; diabetes; spinal curve; high blood pressure; lymphoedema with swelling of the lower legs and feet; abnormal positioning of the feet at birth; squint (strabismus); hearing disorder; missing teeth; dry skin that bruises easily and takes a long time to heal. In each of these cases, the microduplication is within the 5p13.2 band.

Feeding difficulties are common in babies with chromosome disorders, and in this group included a baby who would not breast feed but took good feeds from a bottle, and a baby with a 5p14.2p14.3 duplication who has marked feeding difficulties and at 2 years is fed by gastrostomy tube direct into the stomach; he also has gastro-oesophageal reflux; and mild hypothyroidism, treated with thyroid hormone replacement (Yan 2009; Oexle 2011; Romero 2012; Decipher; Unique).

Genes and chromosomes

Our bodies are made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes; the genetic information they carry tells the body how to develop, grow and function. Genes are carried on chromosomes. Chromosomes usually come in pairs, and we inherit one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: two Xs for a girl and an X and a Y for a boy.

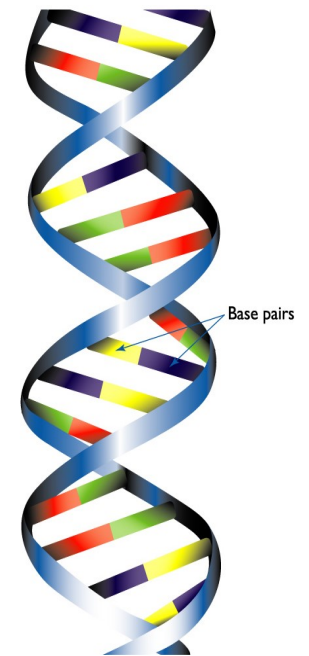
The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22, approximately from largest to smallest, so chromosome 5 is quite a large chromosome. Each chromosome has a short (p) arm (from petit, the French for small) as well as a long (q) arm (see diagram on page 2).

Looking at chromosome 5p

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. 5p13 and 5p14 are bands in the middle and lower half of the short arm of chromosome 5. You can see in the diagram that 5p13 consists of 3 bands: 5p13.1, 13.2 and 13.3. 5p14 also has 3 bands: 5p14.1, 14.2 and 14.3.

Each band of each chromosome contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. The short arm of chromosome 5 has about 48.4 million base pairs, shortened to 48.4Mb; the 5p13 bands have 13.6 Mb; and the 5p14 bands have 10.5 Mb. The position of each of the 900 or so genes on chromosome 5 is measured in base pairs. On the right of the diagram on page 2 you can see how the base pair numbers relate to the chromosome bands.

Looking at chromosomes under a microscope, it may be possible to see a large piece of extra genetic material. However, changes smaller than 5Mb are very hard to identify, and sometimes even 10Mb changes are hard to see. Because of this, if the extra piece is very small, the chromosomes can look normal under a microscope. New techniques, particularly one known as array CGH, are now usually used to find the size and position of the extra DNA in the microduplication, helping to identify genes and pinpoint their location on chromosomes.



Sources

The information in this guide is drawn partly from 9 people reported in the medical literature with microduplications of 5p (Yan 2009; Oexle 2011; Romero 2012; Kluger 2013; Novara 2013). The first-named author and publication date are given to let you look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain most articles from Unique. In addition, this guide draws on a survey of members of Unique conducted in 2014, referenced Unique. When this guide was compiled, Unique had 5 members with a pure 5p13 or 5p14 microduplication not involving any other chromosome arm. The guide also contains information from 10 more cases on the publicly accessible Decipher database (<https://decipher.sanger.ac.uk>). In all, 23 people are included, from babies to adults.

Has everyone with a 5p13 or 5p14 microduplication got the same amount of extra DNA?

No. People have different - but always small - amounts of extra DNA, and different extra genes.

Genetic test results: an example

A person's chromosome make-up is called their karyotype. Someone with a microduplication of 5p13 or 5p14 might have a karyotype that looks like this example:

arr[hg19] 5p13.3 (31278306-32890231)x3 pat

The test was by array comparative genomic hybridization (arr). The results follow the Human Genome build 19 [hg19] which is the most up-to-date 'atlas' of human chromosomes.

5p13.3 shows that the microduplication was in band 5p13.3. (31278306-32890231)x3 shows that three copies of the material between the break points was found (x3). The normal number of copies is 2, so this means there is an extra copy. 31278306-32890231 are the start and end points of the extra copy, measured in base pairs. Take the first long number from the second and you find that there are 1,611,925 extra base pairs. This is about 1.6Mb.

pat means that the chromosome change has been inherited from the father. mat would mean it was inherited from the mother.

I wish I had known

"That he will progress on his own time and therapies might not speed that along."

■ Growth, height and build

Generally speaking, babies with a 5p13 or 5p14 microduplication are an average or above average birth weight and length. The average birth weight at term among 8 babies was 3.3kg (6lb 13oz), with most babies weighing above 3kg (6lb 10oz). Just 3 babies were light and short at birth, all with similar microduplications within 5p13.2.

Growth in babyhood and childhood continues this trend, with children and adults generally a similar height to the rest of their family. Three children differ in this, one a baby born very small who remained very small at 8 months; another girl born an average weight who was in the bottom three per cent of the population for height by the age of 5; and a third girl who is very tall, measuring 5' 5" (165cm) at 12 years. Among the others, one girl, born very tiny, had grown to a normal height by the age of 6; a toddler of 2¾ years was 88cm (2' 10") tall, well within normal limits; while an adult woman measured 163cm (5'4") and an adult man 175cm (5'9").

One noticeable feature is that 2 of the 4 adults, a man and a woman, are obese, one with a body mass index of 40 (the normal range is 18.5-25), and the other in the top 5 per cent of the population for weight. We don't know when the woman started to gain weight, but the man put on weight as an adolescent (Yan 2009; Oexle 2011; Romero 2012; Kluger 2013; Novara 2013).

■ Changes in the structure of the brain

In the 7 cases where the brain has either been imaged or examined, a change was found to the usual brain structure.

The changes are quite varied, with the corpus callosum (the broad band of nerve fibres linking the brain's two halves) most often involved, either small or malformed, or missing altogether. In each case involving the corpus callosum, the microduplication involved a similar region in the 5p13.2 band. In 2 people, there were further anomalies, in one, asymmetry in the cortex, the outer grey matter of the brain; in the other, areas of high intensity around the fluid-filled spaces within the brain viewed on a magnetic resonance imaging (MRI) scan, as well as widespread incomplete myelination. Myelination is the deposition of an insulating layer around nerve fibres, which then carry signals faster. In addition, this child and one other had abnormal brain wave patterns on an electroencephalogram recording, although only one had experienced any seizures. Another child had unspecified white matter growth delay at 10 months. Finally, one young boy had an arachnoid cyst, a collection of spinal fluid between two of the three membranes that cover the brain and spine.

If a brain scan reveals anomalies, interpreting them is a matter for your child's neurologist or paediatrician (Yan 2009; Romero 2012; Kluger 2013; Novara 2013; Decipher; Unique).

Oexle 2011; Romero 2012; Novara 2013; Unique). One child from Unique, described below, held his hands in fists for almost the entire first year of his life.

“As an infant he was tightly fisted and would only hold things if you prised open his hands. At 22 months he started to hold toys, shake them, and throw them. Now, at 2 years, he does not have great coordination and will not take toys from your hand: they have to be placed in front of him. He cannot self feed and hates hand-over-hand, so you can't help him. His hands have always been very sensitive and he doesn't like them being touched. He is becoming less sensitive, but still has issues. He can use his pincer grasp to grab his diaper, but not in other situations.” 2 years

■ Hypotonia

Low muscle tone, which can mean a baby feels floppy to hold, is known to affect at least 6 children and adults, and was one of the first signs that something was wrong in at least 2 babies. Low tone may not affect the entire body, or may not affect the whole body equally, so that tone may for example be different in the trunk to the arms and legs. It can also affect the muscles of the mouth and face, causing feeding difficulties and drooling (dribbling). The low tone is often obvious in a newborn baby, and can be persistent, making it harder for babies and children to learn head control, to sit up straight, crawl and walk. Physiotherapy and exercises are very helpful, but in at least one adult the low tone has persisted (Yan 2009; Oexle 2011; Romero 2012; Novara 2013; Unique).

“The doctors say that he does have low muscle tone, but he seems to be very strong. He just can't use his muscles in a productive way.” 2 years

■ High palate (roof of the mouth)

The main concern about the palate in a baby with a chromosome disorder is whether there is a split in it (cleft palate). There is no evidence of this in babies with a 5p13 or 5p14 microduplication. A lesser concern is whether the palate has a high arch like a church roof, because this, together with low muscle tone in the mouth and face, can mean that when babies are weaned onto solid food, they have difficulty moving the food from their mouth down into the throat and food passage, and as a result store food at the top of the mouth. If this happens, the child needs enough fluid to wash food down as s/he eats. If the palate is also narrow, and it often is, it may lead to overcrowding of the teeth. Other possible problems associated with a high palate include disrupted sleep caused by obstruction of the nasal passages, and speech problems. A high palate has been seen in 4 children, and an unusually narrow one in another (Yan 2009; Oexle 2011; Novara 2013).

Common features

It is not yet known what the most common features are of specific microduplications within 5p13 and 5p14. This is because the microduplications are very rare and there are still only a small number of reported cases in the medical literature and genetic databases. As more people are diagnosed, it may be possible to identify the most common features of specific microduplications. The list that follows shows the most common features of any microduplication within the 5p13 or 5p14 bands. They are:

- Learning disability
- Unusual facial features
- Developmental delay
- Speech delay
- Autism or autistic spectrum disorder (ASD)
- High arched or unusually shaped palate
- Unusual hands
- Hypotonia
- Short stature
- Changes in the structure of the brain
- Behaviour or psychiatric concerns
- Large head
- Feeding difficulties
- Unusual limb features
- Epilepsy

■ Learning disability, usually mild to moderate

15/16 children old enough to go to school have needed support with their learning, but the amount varies, with the level of learning difficulty usually ranging from mild to moderate. A child of 12 years has problems with her working memory and is very slow to process information, while her father, who has the same microduplication in the 5p13.2 band, has an honours degree. A young man of 23 years with a microduplication between 5p13.1 and 5p13.2 attended a mainstream (regular) school, but needed support to gain a professional qualification (Oexle 2011; Decipher; Unique).

“She seems to do well at maths but can't spell, and receives extra time in tests. She has a terrible memory for some things, amazing for others. She reads books like Tracy Beaker, and is very good at art.” 5p13.2 duplication, 12 years

■ Unusual facial features

Your child may look like the rest of your family, but he or she may also have some facial and other features that are unusual in your family but can sometimes be seen in others with 5p duplications. The most obvious feature is a large head, but in order of frequency, others include: ears set low on the side of the head; an unusually long or short groove between the nose and the upper lip; a prominent forehead; small eyes; a broad base to the nose; somewhat

unusually formed ears; and a small lower jaw. Many other slightly unusual facial features have been observed in one or two children by trained geneticists, but these features may be very subtle (Yan 2009; Oexle 2011; Romero 2012; Novara 2013; Decipher; Unique).

■ Developmental delay

Developmental delay is not inevitable, but it does appear to be common. In 10 babies and children, some level of developmental delay has been reported, but the degree of delay varies, as does the most obviously affected area of development. The mother of one baby was aware that there might be problems with development by the age of 4 months; by 6 months she sought early intervention to help; her son could first sit by 12 months, but then lost this ability, and regained it by 20 months when he also started using his hands to play with toys; at 18 months he learned to roll over, and kept the ability to roll from tummy to back, but lost the skill of rolling from back to tummy; at just over 2 years he has very good head control but still cannot sit up on his own from lying down, crawl or walk. Another boy developed normally up to the age of 2½ years, when he developed seizures that were hard to treat, and his development then slowed. A girl of 2¾ years had 'significant' delay; and another child was diagnosed with apraxia, a neurological disorder characterised by an inability to carry out skilled movements and gestures, despite having the physical ability to perform them.

The developmental delay has an inevitable impact on how a child learns to care for himself, and an adult of 23 years with a relatively large 3.7Mb microduplication between 5p13.1 and 5p13.2 remains dependent on his family's support for all of his personal care. Toilet training is also affected, with one child only becoming dry at almost 3 years (Yan 2009; Oexle 2011; Kluger 2013; Novara 2013; Decipher; Unique).

["He loves to bounce when sitting on the couch by throwing his back on the back of the couch. He loved his jumperoo when he had it. He still likes it when you spin him and bounce him around."](#) 2 years

["She took a long time to crawl and walk, and remains slow compared with others her age. Her favourite physical activity is swimming."](#) 12 years

■ Speech delay

Speech delay is almost as common as developmental delay, but the severity is quite variable. At one end of the spectrum, a boy of 2 years with a microduplication between 5p14.2 and 5p14.3 cries, but is not yet making simple sounds with discernible meaning, saying words or communicating non-verbally, for example by pointing. By contrast, a girl with a 5p13.2 microduplication smiled and talked early and at the age of 12 communicates fluently. Another child with a microduplication in

5p13.3 was late to smile and to talk, but was smiling by 3 months and talking by 2 years; a girl of 2¾ years had language delay, but better non-verbal communication; another boy didn't start talking until he was 4 years old; and a child of 5½ years was communicating using signs and a handful of words. A further young boy had a mild language delay, and another child had echolalia, automatically repeating words or phrases either immediately after hearing them, or later. Echolalia can be a symptom of autism, and this child did also have stereotypic behaviour (repetitive movements) (*see below* Autism) (Oexle 2011; Romero 2012; Novara 2013; Decipher; Unique).

["He loves singing, kisses, and the show 'Wheel of fortune'."](#) 2 years

["She babbled and spoke early, and speaks normally in fluent conversation. However, she cannot express how she feels and wants us to guess or just know."](#) 5p13.2 duplication, 12 years

■ Autism and other behavioural concerns

While some children are engaging and communicative, a diagnosis of an autism spectrum disorder or of full autism has been made in 9 children or adults, many of them on the Decipher database.

One Unique child with an inherited 5p13.2 microduplication has a diagnosis of atypical autism, where her behaviour fits most but not all of the criteria for typical autism. Her microduplication was found after reasons for her 'bad behaviour' were sought. Another 2 year old boy has a diagnosis of autism, but also has developmental delay. Many Unique members have said that a diagnosis of autism was more helpful to their child in accessing services than the diagnosis of a chromosome disorder. Five other people have a diagnosis of some mental health or behaviour difficulty, including hyperactivity, difficulty concentrating, having obsessive thoughts and compulsive behaviour (OCD/obsessive compulsive disorder), as well as self harm (Oexle 2011; Decipher; Unique).

["She swings from calm to aggressive very quickly, and can be angry and stubborn. She hates playing and tries to stop her brother from playing too. She hates using her imagination and only wants to use a computer."](#) 5p13.2 duplication, 12 years

■ Unusual hands

Your child's hands may be subtly unusual. The feature noticed most often is long fingers. Other unusual features include large hands; short 5th (little) fingers; and thumbs held in a fist position after around the age of 7 months. The palm creases may also be unusual: two types have been observed - a single palm crease, and a 'hockey stick crease' that runs across the palm from the little finger side, then widens and turns upwards to end between the index and middle fingers (Yan 2009;