Understanding chromosome disorders

Unique

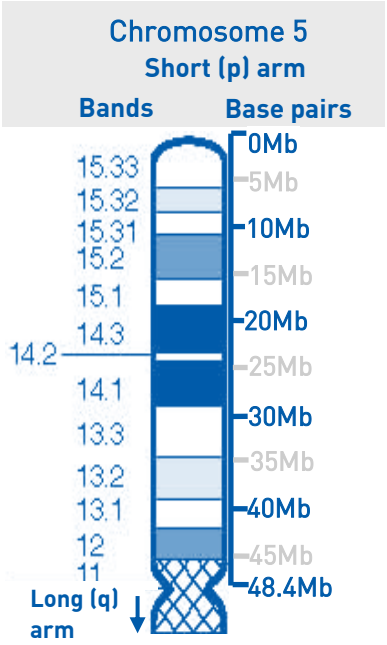
Trisomy 5p: Duplications of 5p15

rarechromo.org

"I wish we had known that we are not alone and that there are many others who have the same diagnosis, going through the same things"

Duplications of 5p15

Duplications of 5p are very rare genetic conditions in which there is an extra copy, called a duplication, of part of the genetic material (DNA) that makes up the body's 46 chromosomes. The extra copy is of part of the end of one of the chromosomes, chromosome 5. Like most other chromosome disorders, this usually affects development, and sometimes health and behaviour as well. But how much it affects individuals, and the ways in which it affects them, can vary a lot. The precise effects vary depending on how large the duplication 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.



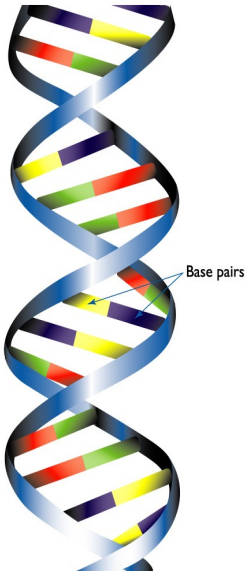
Chromosomes usually come in pairs, one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: two Xs for a girl and an X and a Y for a boy. The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22, approximately from largest to smallest, so chromosome 5 is a relatively large chromosome. Each chromosome has a short (p) arm (from petit, the French for small) and a long (q) arm (*See* Diagram, above).

In people with a duplication of 5p15, one chromosome 5 is normal but there is an extra copy of part of the top third of the short arm of the other chromosome 5.

Sources

The information in this guide is drawn partly from 2 reports in the medical literature (Sheen 2003). 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 8 members with a small duplication from the 5p15 band, one of whom has also been reported in the medical literature. The guide also contains information from 18 cases on the publicly accessible Decipher database (https://decipher.sanger.ac.uk). In all, 27 people are reported, aged between 3 and 30 years.

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. 5p15 is at the top of chromosome 5 in the diagram (where?) and is divided into 5 bands: 15.1, 15.2, 15.31, 15.32, and 15.33.

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 whole of chromosome 5 has about 181 million base pairs, shortened to 181Mb; the short p arm has around 48Mb; and the 5p15 bands have 18.4Mb. The position of each of the 900 or so genes on chromosome 5 is measured in base pairs. On the right of the diagram 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 often used to find the size and position of the extra DNA, helping to identify genes and pinpoint their location on chromosomes.

Genetic test results: three examples

A person's chromosome make-up is called their karyotype. Someone with a 5p15 duplication might have a karyotype that looks like one of these examples:

Example 1: 46,XY,dup(5)(p15.2p15.3)dn

This result tells you that the chromosomes were examined under a microscope. 46 chromosomes were seen, the correct number. The sex chromosomes were an X and a Y (XY), so this is a boy or man. A piece of extra DNA was seen on chromosome 5. The start point of the extra material was in band 5p15.2 and the end point was in band p15.3, so this could be quite a large duplication, although we are not told precisely how big it is. dn de novo (Latin for 'from the beginning') means that the chromosome change has not been inherited but has arisen 'anew' in that child for the first time.

Example 2: arr cgh 5p15.31(RP11-554C16++,RP11-32D12++)

The test was by array comparative genomic hybridization (arr cgh). 5p15.31 shows that a change was found in the 15.31 band of the short (p) arm of chromosome 5. RP11-554C16 and RP11-32D12 refer to fragments known as clones whose position on the chromosome is known. ++ means that there was an extra copy of each of them, that is, a duplication.

Test results example 3: arr(hg19) 5p15.1 (16396821-16930516)x3 mat

The test was by array comparative genomic hybridization (arr cgh). The results follow the Human Genome build 19 [hg19], which is the most up-to-date version of a kind of atlas of human chromosomes. Two break points were found, both in band 5p15.1. (16396821-16930516)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. (x2-3) would mean that there are some cells with 2 copies and some with 3. This is called mosaicism, and generally moderates the effects, but this can be hard to predict. 16396821-16930516 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 533,695 extra base pairs. This is about 0.5Mb, or a very small microduplication. mat means that the chromosome change has been inherited from the mother. pat would mean it was from the father.

How did this happen?

5p duplications can occur out of the blue for no obvious reason, 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 (*see* **Common Features**). At least 10 parents are known to have passed a 5p duplication on to their child. In the other families we know of, one of the parents has a rearrangement of their own chromosomes which has become unbalanced when eggs or sperm were created. In this situation, there is often a part missing (a deletion) from another chromosome as well as the 5p duplication.

If both parents have normal chromosomes, the 5p duplication is a new occurrence. The term that geneticists use for this is *de novo* (dn). A new 5p duplication 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 change or control this. In other words, there is nothing that either parent did before or during the pregnancy that caused the duplication.

"She is very tough but extremely sweet, super social and happy most of the time. She loves music, the outdoors and people, and has helped everyone in her circle realise that what is really important is life is family and friends, not the petty day to day junk."

5p15.2p15.1 duplication, 23 years

Common features

As explained in **How did this Happen?**, some people have a tiny duplication within 5p15 without any symptoms at all, and only find out when they have an affected child. But among those who do have some features, the most common are:

- Speech delay
- Behaviour difficulties. Autistic features
- Developmental delay
- Feeding difficulties
- Seizures
- Small size
- Learning difficulties
- Abnormal joints and limbs, low muscle tone. Sitting, moving, walking
- Heart problems
- Eye and vision problems
- Slightly unusual hands
- Slightly unusual facial features

(Sheen 2003; Decipher; Unique)

"He is a very intelligent, loving boy who seems to have a gift for learning things and retaining information which is sometimes astounding. Although he struggles with understanding the world at times he is happy and caring and his family have learned and understand what upsets him and frustrates him so we are able to help him to resolve his problems. He brings love, light and laughter to our lives, and our lives would be much darker without him." 5 years

Speech delay

The most consistent feature, affecting 6/6 Unique members and mentioned in 5/18 Decipher reports, is a delay in starting to talk – but there is a huge variation in how severe this is. From the detailed information we have on 6 Unique members there does not always appear to be a significant delay in a baby starting to smile (6 weeks-3 months), but babbling, joining two syllables together, can emerge late (4-12 months), and one child never babbled. First words can emerge on time or late (9 months to 2/3 years), and at this stage the development of communication can be helped by signing. Once talking, some children catch up completely: one child overcame an initial delay and was using fluent conversation by the age of 3. Other children continue to support their communication by using gestures, objects or pictures to show what they meant. One child's language flowered through music: she could sing songs, with words that she couldn't speak. Difficulties with pronunciation can persist: one child of 11 years has difficulty making *x, k, s* and *t* sounds, while another child of 13 years has a hearing loss and problems with her palate (velopharyngeal insufficiency), so that she cannot close off the air spaces at the back of her

mouth and nose as she talks, making her speech hypernasal so that it is hard to understand her and she has to use sign language, an interpreter, or both. When she tries to communicate by writing instead of speaking, she spells words as they sound to her rather than as they should sound, so making them unintelligible to others. All children bar two can hold conversations, although response speeds can interrupt the natural fluency of the exchanges. Children have generally been helped by speech and language therapy, and one of the most severely affected people, now an adult, also benefits from listening therapy. She has complex health needs, including epilepsy and brain surgeries, and is effectively non-verbal, as is another child who has had many seizures.

"He tends to use more complex sentences. For example he may say 'I was slightly disappointed that we are not going to be able to go to gymnastics after school. I think you should take us there so that we can have fun', whereas his twin will say 'I sad, I want to go to gymnastics after school' - a more typical sentence for her age." 3 years

"He can now sometimes say a sentence of 4 or 5 words which is a huge improvement for him. He can hold short conversations with people, but cannot always explain how he is feeling and finds it difficult to ask for help." (5 years)

"She loved the 'Is this the way to Amarillo?' song, and sang it constantly! Today, she talks and you can understand her. She did learn Makaton signing at school, but she didn't really need it." 11 years

"She has been attending a school for the deaf and hard of hearing since she was 6. Her sentences are typically somewhat shorter than normal, but she can carry on a full conversation when she has enough energy. Her conversations are also briefer, I think, from habit – most people don't have the time to wait for her to fully say what is on her mind." 13 years

"Currently no speech, she stopped saying the few words she could say during many years of severe seizures." 14 years

"She has had no speech since her 4th immunisation but relearned babbling after severe seizures. She uses some signing, gestures, vocal noises, reaching for and looking at what she wants, as well as a DynaMyte touch-screen communication device. She also does a lot of stimming, ie sitting on the floor and rapidly swinging her head from side to side to the point of dizziness. She also repeatedly pushes certain buttons on her cause and effect toys."

5p15.2p15.1 duplication, 23 years

Behaviour difficulties. Autistic features

Some children with a 5p15 duplication behave beautifully, others' behaviour is affected by their health, and others experience anxiety and frustration at their own difficulties. Problems vary from child to child, and there are too few detailed reports to be sure whether there are definite traits associated with the duplication. In particular, while there are 4/18 reports of autism on Decipher, and 4/6 children with autistic traits in Unique, the high prevalence of autism generally among Unique members means that this behaviour is not necessarily associated with this particular chromosomal duplication.

In addition to autism, behaviour difficulties reported on Decipher include hyperactivity, a short attention span, low tolerance of frustration and an unspecified behaviour/psychiatric abnormality. Within Unique, one child of 3 years is balanced, happy, easy-going, active and sociable. A girl of 13 years who has very serious heart problems that keep her in bed much of the time while she awaits a heart transplant has some difficulties with socialisation most likely caused by her health problems, but is otherwise organised, responsible and mostly cheerful.

> "She does not show a lot of affection, when she does, you feel like a king! She teaches us patience, if you stop what you are doing and give her enough time she will respond. You never know when things are going to get worse, so enjoy the happy moments."
> 5p15.1p15.3 duplication, 14 years

Children who do face difficulties include a child of 5 years who generally behaves well except when faced with changes in routine, frustration and anxiety; he dislikes crowds and struggles in social situations; he also has sensory problems such as disliking loud noises and having his hair washed or brushed, never mind cut. This child does have autistic features, and the family have had advice from a clinical psychologist to use visual prompts for changes in routine, and visual timers to encourage timed good behaviour or task completion. A girl of 11 years who also has autistic traits is very prone to anxiety around cars and dogs, struggles socially although she wants to be liked, and this makes her upset, and finds anything around her head hard to handle. She also has a very high pain threshold. A girl of 14 years is generally happy and content, but lacks initiative and needs reminders to move on when she starts to become mildly destructive. A 23 year old woman generally behaves well unless she is frustrated or feeling poorly. She has no autistic behaviour, and no sensory processing disorder. She is highly sociable, loving to be around other people

especially of her own age. On the down side, she does lack concentration, and sometimes she self harms.

"Socially, he is like a typical 3-year-old. He is very active at school, and has lots of friends he interacts with on a daily basis." 3 years
"He has lots of strengths but lots of weaknesses and this gap causes him much frustration. He has problems interacting socially and is very wary of other children. He spends much of his time alone unless he is encouraged to mix with other children with adult guidance. He lacks confidence and seems to find it difficult when children are being loud and running around him." 5 years
"She has autistic traits, but has too much empathy to be fully autistic." 11 years
"She is a perfectionist and has from time to time engaged in self harm when she is extremely frustrated. We have followed her lead and reduced stressful situations in school (reduced homework load). She has no diagnosis of a sensory processing disorder, but aversion to textures has been an ongoing issue." 13 years
"A little bit of a morning temper, but gradually in a better mood during the first hour. She is constantly making noises, which can be very stressful, but when she is silent (rarely) you miss it. She was not diagnosed with autism, but there are autistic elements in her behaviour. With people she knows she likes to try and get into their lap. She smiles and make happy noises." 14 years
"Very sociable – loves to be around other people, especially her peers." 23 years

Developmental delay

Developmental delay is mentioned as a feature in 7/8 Unique members and 2/18 Decipher reports. The extent of delay among Unique members varies widely, from mild, limited delays showing significant improvements by school age to a

"Our son is a loving, caring and compassionate boy who loves to give in many ways. For example, last year he grew and cared for tomatoes and we donated them to the homeless shelter. He has already asked about growing other vegetables to help people. He has shown us that no matter the obstacles, he can overcome them. We are amazed when this little boy who we were once told may not be able to hold his own head up is playing golf, riding bikes, participating and loving gymnastics, and other activities. He knows no limits! He has contributed by showing me that I can make a difference in the lives of other families and since his birth I have become a board member for a non-profit organisation that assists families who have children with a special need. Our son has contributed to my life by giving me a vehicle to voice my passion as an advocate for him and other children. He is so loving and just a joy. "
Mosaic form of 5p13.3 duplication, 3 years

profound level of global delay. The two profoundly affected Unique members share a duplication between 5p15.2 and 5p15.1, and each has severe epilepsy; her family believe that their daughter regressed significantly after immunisation. One Unique child with a tiny microduplication within the 5p15.33 band is not at all delayed: he is above average, testing at 4 years and 11 months for speech and vocabulary at the age of 2½, and with above average gross motor and fine motor skills.

Delay was first noticed by parents: a girl with a duplication between 5p15.2 and 5p15.1 was not sitting at 9 months; one girl with a large duplication between 5p15.3 and 5p15.1 had noticeably delayed speech at the age of 1 year, while another had delay in speech and eye contact, and never cried when she was hurt; and boy with a small microduplication at 5p15.33 raised concerns with his delayed speech and social skills by the age of 2 years.

"I knew something was the matter, but no one would listen."

Feeding difficulties

Information on feeding is available only on Unique members, where 3/7 had significant difficulty, 2 needed to be fed for a time by tube, and another needed calorie supplementation. However, one child, now aged 11 years, has always eaten completely normally, and another only had difficulty breastfeeding, needing to take breast milk from a spoon or cup. Three mothers at least partly breastfed their new babies: three babies had difficulty latching on and sucking due to low muscle tone in the face and mouth and in one baby dysfunction of the muscles of the mouth. One mother's milk dried up after three days, and her baby thrived better on formula; another fed very slowly and could not drink enough milk to meet his nutritional needs, so was supplemented by formula.

Two babies with significant health problems needing corrective surgery proved unable to breastfeed: one had complex heart problems, the other had a developmental anomaly of the digestive tract known as intestinal malrotation. After corrective surgery, this child developed eosinophilic esophagitis (an allergic inflammation of the food passage) and duodenal ulcers, as well as reflux, needing combined treatment with medications and food eliminations.

Three babies had gastro oesophageal reflux (GORD/ GERD), where part of a feed 'goes down the wrong way', or feeds aren't efficiently processed into the stomach but instead come back up the food pipe and can be inhaled. Careful feeding and positioning can help reflux as can feed thickeners and medication to inhibit gastric acid. Babies often grow out of reflux, especially when they start solids, although even on solids some children continue to bring back small amounts of food after meals. Reflux can be persistent, although most families can control it using prescription medication. Three babies had difficulty coping with different food textures once they were weaned, one spitting foods out and

preferring to drink milk or juice, another working on feeding therapy from birth to increase his range of foods and textures.

"In his first months, he would sleep through feedings, and was difficult to wake. We had to dream feed him often to ensure that he had sufficient intake, but he would not gain a lot of weight regardless of feedings. He eats most foods now, but still has some textural issues related to foods. We worked with the Nuk massage brush for oral motor stimulation prior to feeding, and this is still done through feeding therapy." 3 years

"He eats a range of foods including chicken nuggets, sausages, vegetables and fruit, but does not like lots of things especially dairy products, and is not keen on trying new foods." 5 years

"She had difficulty taking a bottle early on, and then had texture aversions, but did not have the feeding tube until her heart stopped during surgery at age 3. Her feeding tube was in place from age 3 until age 8. When she ate, she could not eat large bites: we would peel and cut a single grape into 16 pieces. She now eats by mouth, but has never been able to eat significant amounts of food at a single sitting." 13 years

"No feeding problems after the newborn period." 14 years

Seizures

Seizures appear to be common, affecting 5/8 Unique members, as well as two children reported in the medical literature (one of them a Unique member) and 1/18 at Decipher (Sheen 2003; Decipher; Unique). The information we have on seizures suggests that they are not all of the same type. One baby developed fever fits just after birth, with seizures only when she had a high temperature, which resolved by the age of 3 or 4 years. On Decipher there is a patient who had generalised tonic seizures (where the brain's abnormal electrical activity involves both sides of the brain at once, and causes a sudden stiffness) as well as seizures starting in only one part of the brain (focal).

Two Unique members with a 5p15.2p15.1 duplication each developed severe epilepsy around the same age, 18-20 months, one of them just after an immunisation booster. This epilepsy has proved very hard to treat, although one responded well to vagal nerve stimulation (repeated electrical stimulation of the left vagus nerve in the brain) until the stimulator had to be removed due to infection, and then responded well to the ketogenic diet (a high-fat, carbohydrate-restricted diet). In the other, despite every appropriate anti-epilepsy medication; the ketogenic diet; vagal nerve stimulation; and brain surgeries, including most recently a corpus callosotomy, an operation that divides the corpus callosum that connects the two sides of the brain, status epilepticus episodes (long seizures, or tailgating seizures with no recovery in-between) continue to occur at the age of 23 years, although less frequently than before the latest brain surgery.

Small size

6/10 children and adults are short. In some, the small stature was first noticed before birth, although most Unique babies were within the normal weight range at birth, averaging 3.165 kg at term (7lb), with a range of 2.44-3.885 kg (5lb 6oz-8lb 9oz). We only know the birth length of 4 babies, but this too was normal, averaging 49cm (20"). Later on, however, 4/5 are short, and two are very short: 91cm (36") at 3 years; 135 cm (4'5") at 13 years; 150cm (5') at 14 years; and 137 cm (4'6") at 23 years (Decipher; Unique).

Learning difficulties

Most children do need some support with their learning, but not all, and some only need a small amount of extra help. The range is broad, and only two Unique members have a severe or profound learning disability. Overall, 6/8 Unique members have a learning difficulty or disability, and this is mentioned in 10/18 Decipher reports.

5p15.2p15.1 duplication, 23 years

Among those who do have learning support, there is a boy of 5 years who can read books and magazines, instruction leaflets and signs; recite the alphabet and count up to 100; navigate a computer; remember well what he has learned at school every day; and write his name and other words. He does have difficulty concentrating, especially when he does not want to do something; and he tries to be independent, and then becomes frustrated and angry if he cannot do things by himself. There is a girl of 11 years who learns best through music, and by chanting songs. She is learning to read and write and is very proud of being able to count to 10 in French. A girl of 14 years has the intellectual capacity of a 7-month-old baby but has a lot of experience, so can appear more knowledgeable; she has a good sense of direction and is inquisitive; and she is highly motivated by music. The adult of 23 years has graduated from the life skills class for medically fragile children, and received total learning support throughout her education. She has an excellent memory, and is determined and sociable, both of which help her learning. Among those who need no learning support is a child of 3 years who is advanced for his age, and has a mosaic form of the 5p15 duplication. There is also a girl of 11 years who has never shown any cognitive delays.

"They use music a lot at school, and the children can choose the song to be sung by indicating it on a board with pictures. It is one of the rare moments when she

takes an initiative." 14 years

Abnormal joints and limbs. low muscle tone. Sitting, moving, walking

Six people have some abnormality of the joints or movement of their limbs. One Unique member has a rotation in the femur known as anteversion and in the shin bone known as torsion, that is in fact very common in the general population, and usually needs no treatment. Two Unique members have very stiff joints that need regular stretching to maintain their mobility, and two people have either marked weakness or paralysis on one side of the body. One child has dislocated hips, and two have certain extremely bendy (hyperextensible) joints (Sheen 2003; Decipher; Unique).

Additionally, 4 children have low muscle tone, including 3 Unique members. In one, there is also raised tone, creating stiffness in some parts of the body, and floppiness in others. The joint conditions and abnormal muscle tone affect mobility, which can also be delayed independently as part of a child's global developmental delay. 4/7 Unique members showed a delay in gross motor skills, and this was mentioned in 2/18 Decipher reports. Among Unique members with a delay in learning to sit and walk, babies first held their head up from around 4 months, sat from 7-10 months, got mobile from 9-12 months, in some cases bum-shuffling rather than crawling, and learned to walk from 13 months to 2 years, although one girl of 14 years cannot walk without support yet. Other Unique members learned to sit and walk on time, although one never crawled, and one, with a mosaic form of the duplication, was actually advanced in gross motor skills.

The effects of the motor delay and low tone can be subtle: a child of 3 years who could ride a bike with stabilisers at 18 months, fell over while walking and running until the age of 2 years; a child of 11 years only learned to ride a bike at the age of 10, and still walks up and down steps one at a time.

"Initially when he was learning to sit, stand and crawl you could tell that he was less stable when compared to his sister who does not have low muscle tone. He would wobble a lot, and was less steady." 3 years

"Walking was delayed slightly. Running was very delayed, and she still has trouble running and has never been able to skip. She has ongoing issues with muscle coordination." 13 years

"She is currently practising walking with a walker indoors and a wheelchair outdoors. She has difficulties when walking without orthoses." 14 years

"She can walk independently for short distances. She walks with ankle foot orthotics (supports) and some assistance for grade changes." 23 years

Heart problems

Five people with a 5p15 duplication have been born with a heart problem, and one has a heart murmur but no structural defect. Four of the duplications are not overlapping, suggesting that no particular gene underlies the heart defects.

Three babies were born with a hole between the upper or lower chambers of the heart, in each case as part of a more complex heart anomaly. One baby also had an unspecified malformation affecting the heart and the large blood vessels leading to and from it; another also had leaky heart valves that allowed the blood to flow backwards instead of pumping straight through the heart. The third child had a narrowing of the large blood vessel leading out of the heart to the rest of the body (coarctation of the aorta), a valve with only two flaps instead of 3, and an abnormal link between two major blood vessels leaving the heart (persistent ductus arteriosus, PDA), a defect that also occurred in another child but resolved naturally. The complex anomalies in the third child meant that by the age of 13 years, despite 5 open heart surgeries, she was in heart failure and was awaiting a heart transplant.

"She is currently in heart failure and is extremely fatigued much of the time. She is only able to attend school 1-2 hours per day, 3-4 days per week, and spends most of her time in bed. She has never had the stamina to run and play tag with others – her biggest wish. The heat is also difficult for her to tolerate." 13 years

"She is extremely fair minded and sticks up for what is right. She has a huge heart and an unbreakable spirit. She is steadfast in her interests and inspires others every single day: she inspired my co-workers to pitch in and send her to Paris for her 13th birthday, she convinced the heart transplant team to let her go. This girl knows how to make her dreams come true."
5p15.1 microduplication, 13 years

Eye and vision problems

Most children and adults with a 5p15 duplication appear to have normal eyesight, with no vision problems, but one Unique child and 4/18 Decipher cases have a difficulty with vision. Three children have a squint (strabismus), one is long-sighted, one short sighted, and one has the drooping upper eyelids known as ptosis.

"He is long sighted has a squint in his left eye with poor sight, but will only wear glasses at school and refuses to wear them at home." 5 years

Slightly unusual hands

6/7 Unique members have something unusual about their hands, but apart from generally small size, there is no common or recognisable pattern to the unusual features. Two children have somewhat small hands, in one with fewer layers of fat. One has stubby ('blunted') fingers and toes, another has long fingers, and another child has unusually-shaped thumbs that look more like a finger than a

thumb. This child also has very weak, flexible wrists. Finally, one child was born with two fused fingers (fingers 3 and 4) on each hand.

"Her hands are so small that she still eats with toddler-sized utensils. Her wrists overly flexible: her hands bend at an angle so that her pinky (little) finger nearly touches her forearm (keeping the palm and forearm flat on a table). She has difficulty opening jars, rotating her arm to hold her toothbrush, difficulty wiping after toileting, and she has a hard time carrying even light loads." 13 years

"The surgery to separate her fingers at 8 months was successful but stressful, and she was not able to use her hands for some time afterwards." 14 years

- Slightly unusual facial features

Some children look just like other members of their family, while others have one or two unusual facial features. There is absolutely no recognisable pattern to these facial features, but they include facial asymmetry or a triangular or abnormally shaped face, a high/low hairline, large eyes, short or otherwise abnormal eye slits, downslanting eyes, drooping eyelids, low-set ears, odd earlobes, a small chin, and a forward jutting jaw. Three Unique members with a duplication between 5p15.3 and 5p15.1 are all described by their family as essentially looking completely normal.

"Small face, large head, slanted eyes, uneven ears, one larger than the other, pointed chin, bone in forehead protrudes. While these sound drastic, we are told they are subtle. As he gets older we think they grow a little more subtle – or perhaps we get more used to it." 3 years

"She's beautiful: she looks perfect, with long blond hair." 11 years

Pregnancy, birth and the newborn baby

From the information we have on 7 families, pregnancy was typically entirely normal. Two babies were found to be small for dates during the pregnancy, and one mother had some light bleeding in the first three months which was treated with a progesterone injection. The exception to the general rule of an uneventful pregnancy is a mother with a twin pregnancy, one baby with normal chromosomes, the other with a mosaic 5p15 microduplication: this mother was extremely sick with hyperemesis gravidarum, and had multiple infections, one leading to a coma, and was catheter fed throughout the pregnancy. Her babies were born at almost 33 weeks into the pregnancy.

One other baby was also born early, at 34 weeks. Babies were generally in very good condition at birth, with top scores on the Apgar scale – a measure of physical wellbeing within minutes of birth – of 9 or 10. There were two exceptions to the picture of general wellbeing among newborns: a baby with breathing difficulties who spent her first day of life in an incubator, a baby with complex heart problems who had a seizure within hours of birth. Additionally, the twin with a mosaic form of 5p15 duplication had apnoea (episodes when he stopped breathing). The first signs that the baby might have an underlying

disorder were diverse: one baby had feeding difficulties, an asymmetric face when she cried, finger-like thumbs, and complex heart problems. Another was floppy, with low muscle tone, and a dysfunction of the muscles of the mouth when feeding. Another had fused fingers and toes. Otherwise, no problems were noted among new babies.

"She has the most loving nature but is very vulnerable, because she thinks that everyone loves her. She has made me realise that she's special in more ways than one."

5p15.1p15.3 microduplication, 11 years

General wellbeing

Generally, children and adults with a 5p15 duplication are fit. The exceptions are: a child with complex heart problems, who also developed serious infections following surgical procedures, has had severe nosebleeds throughout her life, and sometimes shows unusual blood clotting; and a child with epilepsy who also developed an infection after insertion of a vagus nerve stimulator; other people with epilepsy; and one other child, a twin aged 3 years, catches many more colds and respiratory infections than his twin or classmates, so that on average he needs time off school once a month. When he does have an infection, he is much more obviously ill than his twin sister and runs a high fever.

Head, brain, palate

Most Unique members have a normal head shape and size, but 3/7 Unique members have something unusual about the size of shape of their head, and this also figures in 3/19 reports in the medical literature and Decipher (Sheen 2003; Decipher; Unique). Two Unique children have an abnormally small head (microcephaly), while one child is reported to have a large head. Microcephaly is reported in 2 Decipher cases as well, and one case of hydrocephaly, where there is an abnormal build-up of fluid within the brain, leading to an enlargement of the head. Two children are reported with plagiocephaly, an unusual shape where the head is flattened at the back and longer from front to back on one side than the other.

We have information from brain scans on 9 individuals, 6 from Unique (one also reported in the medical literature), 2 in the medical literature, and 2 on Decipher. Of these, 4/6 MRI scans from Unique showed an essentially normal brain, one confirmed a diagnosis of epilepsy (see Seizures), and one showed – in addition to gliosis (central nervous system scarring) - extensive periventricular heterotopia (PH), where clumps of brain cells are found in the wrong place,

along the walls of the ventricles, the fluid-filled spaces within the brain. PH is also sometimes associated with seizures, as it was in this girl, and in another child with a 5p15 duplication. The question has been asked whether the chromosomal duplication in any way causes PH (Sheen 2003), but with so few cases this remains unanswered.

Linking the two hemispheres of the brain is a broad band of nerve fibres called the corpus callosum. This has been seen to be affected in 2 children, one on Decipher where the corpus callosum was missing, and one in Unique, where it was 'clipped'.

Interpreting brain scans is a matter for your child's neurologist in the context of their general health.

The palate (roof of the mouth) is formed in a fetus in early pregnancy from parts which start on opposite sides of the head, come round and join. When there is a mistake in this process, the result can be a cleft (gap) in the palate. Sometimes the palate forms without a gap, but is an unusual shape, most often high. Among the 27 cases here, one child has a cleft palate (Decipher) and 3 have a high palate (Unique).

Minor genital anomalies

Minor genital anomalies are relatively common among people, especially males, with a chromosome disorder. Among the 27 children and adults with a 5p15 duplication, one boy was born with an abnormally small penis and with undescended testicles (Decipher); another boy had a hernia in the groin, caused by a developmental failure linked to the descent of the testicles, that was surgically corrected (Sheen 2003); and a girl has uneven external labia, which will not need correction (Unique).

Feet

5/27 children were born with a foot anomaly or developed one over time. One was born with flat feet, another with club foot (equinovarus), affecting both feet, as well as an incurving little toe; another with overlapping toes; a fourth with two fused toes on each foot; and a fifth with a pronounced crease in the sole of each foot from toe to heel, so that each foot could almost be folded in half lengthways. This has not been treated (Sheen 2003; Decipher; Unique).

Teeth

Dental anomalies are somewhat more common among children with a chromosome disorder than among other children. In this group 4/27 children are affected. One has widely spaced teeth. Another has a wide gap (diastema) between her two front teeth, a misaligned jaw and one malpositioned molar tooth that is causing tooth grinding. A third had jutting out ('beaver') teeth corrected with a brace, and misaligned jaws because the lower jaw is very small, and getting smaller with age as the rest of her head grows. A fourth has very crowded teeth, and her milk teeth did not fall out when her permanent teeth

came through (Decipher; Unique).

"It is difficult to brush her teeth and she does not always let us tend to them. She receives dental care in a special clinic, and is mildly sedated when she has dental treatment, normally once a year." 14 years

Spinal curve

Three of the 4 oldest Unique members, aged 13, 14 and 23 years, have a sideways spinal curve known as scoliosis. In one, the scoliosis is mild and is not treated. In the second, the 13-year-old, the curve is monitored every 4 months and has reached 16%. In the third child, a girl of 14 years, wearing a corset for 20 hours a day has reduced her high grade scoliosis of 43% to 15% so that she may now not need corrective surgery.

Puberty

All Unique members who have reached or are near the age of puberty appear to have developed normally at the appropriate age. The adult had a successful endometrial ablation to lessen the length and discomfort of her periods.

"Normal spicy 13 year old behaviour as her energy allows."

Sleep

Sleep difficulties appear to be relatively common among children with a chromosome disorder. In this group, they have been found in 4 Unique members and one Decipher report. One child is a very light sleeper who wakes and demands attention frequently at night. Following a rigid bedtime routine has helped him to settle in the evening, but the frequent waking remains unresolved. A girl of 11 years has episodes of waking very early, being excitable and silly; she is treated with melatonin. Another girl had interrupted sleep while on multiple anti-epilepsy medication, but her sleep has improved on the ketogenic diet. The adult is also given melatonin on the infrequent occasions when she has trouble sleeping.

5p15.2p15.1 duplication, 23 years

Personal care and toilet training

Generally, children are more dependent on others for their personal care than a typically developing child would be – but the range among those with a 5p15 duplication is very broad. The child with a mosaic duplication has the normal personal care needs of a 3-year-old, and is naturally independent. A child of 5 years can dress himself, but is slow, needs prompting, gets easily distracted, and often puts clothes on the wrong way round. In addition he has sensory issues around washing and toothbrushing, disliking both. The 11 year old dresses and undresses, but slowly, and washes her own hair. The 13 year old has difficulties in rotating her hands, and in carrying even light loads, and her hands tire easily – so she needs help with many aspects of washing, toothcare, and dressing. The two members with severe epilepsy are both totally dependent on others for their care: what helps is consistency in activities such as entering and exiting the bathtub – sequentially doing the same steps each time; and a full range of aids and adaptations in the home. As for toilet training, all Unique members are dry during the day apart from those with severe epilepsy. Children were toilet trained in the day between 2 and 5 years. All Unique members still wet the bed at night apart from the boy with the mosaic duplication and the girl of 13 years.

"Able to complete most tasks himself, such as toileting, dressing, unzipping coat, putting on hat, gloves." 3 years, mosaic duplication
"We just follow a routine and generally we can overcome the refusals." 5 years
"Avoid clothes with zips and buttons!" 11 years

Notes

Unique asked families what they know now that they wish they had known when their child was first diagnosed with a 5p15 duplication. Here is what they said:

"I am thankful that I was a foster parent for children who have special needs prior to my son's birth, so we were educated and knowledgeable about services available to help our child be the best version of himself that he could be. I wish I had known how difficult it could be to feed him, and had others to talk to about it." 3 years

"Don't listen to what the doctors say: always believe your mother's instinct. As a mother you know best, so don't be put off. It took me 4 years to get the diagnosis even though it was it was blindingly obvious: the sooner you get a diagnosis, the better. Sometimes it's been ghastly. If you get a good paediatrician, cling on with all your might!" 11 years

"Until age 10, our daughter was misdiagnosed. I wish we'd had the correct diagnosis." 13 years

"All the help you were entitled to, but had to find out for yourself, like personal assistance, and the best treatments (like the ketogenic diet). Also that you are going to survive and grow with the challenge /adapt to the situation. It is very helpful to be in touch with others in a similar situation, exchanging experiences etc." 14 years

"To question doctors and get second opinions if I think they are not modifying the treatment plan to accommodate her developmental delays – e.g. she is not indicating that her stomach hurts because she can't, so don't rule out that symptom. She is so much tougher than she looks and if a doctor seems uncomfortable with her uniqueness, he isn't the doctor for her!" 23 years

Support and Information

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Unique is a charity without government funding, existing entirely on donations and grants. If you are able to support our work in any way, however small, please make a donation via our website at
www.rarechromo.org/html/MakingADonation.asp
Please help us to help you!

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