Understanding Chromosome & Gene Disorders

2q13 microdeletions

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2q13 microdeletions

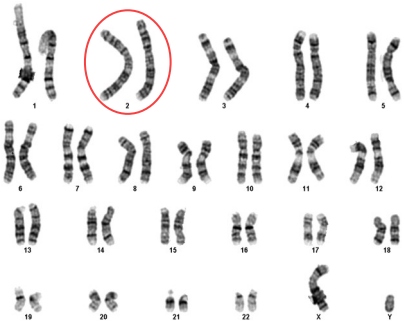
A 2q13 microdeletion is a rare genetic condition caused by a small piece of missing genetic material from one of the body's chromosomes - chromosome 2. Deletions can vary in size but those that are too small to be visible under the microscope using standard techniques are called microdeletions.

For typical and healthy development, chromosomes should contain the expected amount of genetic material. Like most other chromosome disorders, having a missing piece of chromosome 2 may affect the development and intellectual abilities of a child. The outcome of having a 2q13 microdeletion is very variable and depends on a number of factors including what and how much genetic material is missing.

Background on chromosomes

Our bodies are made up of different types of cells, almost all of which contain the same chromosomes. Each chromosome consists of DNA that carries the code for hundreds to thousands of genes. Genes can 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 to make a total of 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 usually have one X chromosome and one Y chromosome, and females usually have two X chromosomes.



Chromosomes pairs 1-22,
X and Y (male)
Chromosome 2 pair circled in red

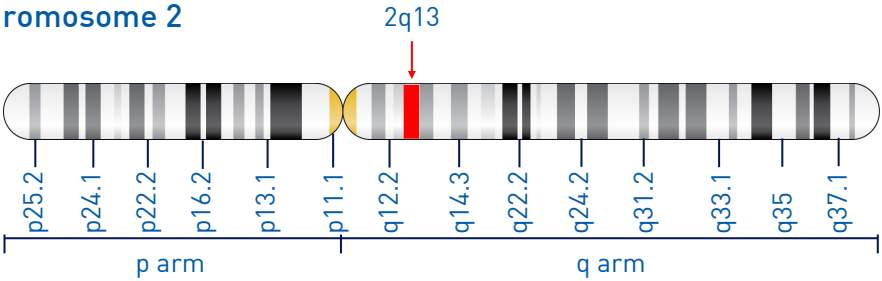
Chromosomal changes

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 are necessary for 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, duplicated and/or become rearranged. The effect of any chromosomal change varies according to how much genetic material is involved, and more specifically, which genes or regions that control genes are included.

Looking at 2q13

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 2 in the image below and on the previous page.

Chromosome 2



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 (coloured yellow in the image above). Region 2q13 is on the q arm of chromosome 2 in band 13 close to the centromere (highlighted in red and indicated with a red arrow in the image above).

With any deletion, the amount of missing DNA can vary. If the amount is small it may not be possible to see it under the microscope and many people who have a small deletion (microdeletion) 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 deletion. 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 change of DNA content in a specific region of a chromosome. A more 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 deletions even when this diagnosis is not suspected. An array CGH will also identify a more precise position on a chromosome where the DNA has been lost.

Sources

The information in this booklet is drawn from published medical literature and information from Unique members. The first-named author and publication date from articles in the medical literature 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.
The first Unique member survey was carried out in 2016.

Chromosome test results

Your geneticist or genetic counsellor will tell you where your child's chromosome has broken and which piece of genetic material has been lost. The information you are given will include any significant changes that are identified and which significant genes are included in the change. 2q13 microdeletions are usually identified using array CGH and the results are likely to read something like the following example:

Array CGH example:

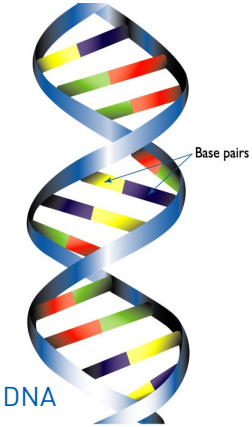
arr[hg19] 2q13(111392145-113094687) x1 dn

arr The analysis used microarray technology

hg19 This is the reference DNA sequence that the base pair numbers refer to, in this case Human Genome build 19. For more information, see page 5.

2q13 The analysis revealed a DNA anomaly on chromosome 2, region q13

(111392145-113094687) The DNA anomaly is identified by its base pair numbers (the exact points where the chromosomal change has occurred). In this example, the DNA anomaly lies between base pairs 111392145 and 113094687 (a region covering 1,702,542 base pairs)



DNA

x1 There is only one copy of the piece of DNA specified. Since there should be 2 copies of each chromosome, this shows that one copy of this piece of DNA is missing and the DNA anomaly is hence a deletion

dn The deletion occurred *de novo* (as a 'new event'). The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 2q13.

If the deletion is identified as *de novo*, it is very unlikely to have been inherited so the chance of the parents having another child with the deletion is very small. If the test result is followed by mat, the deletion has been inherited from the child's mother (maternal); if it is followed by pat, the deletion has been inherited from the father (paternal).

You may wish to compare your child's results with others who have the same or a similar microdeletion to help understand your child's development. While this may help identify common consequences, it is important to remember that the same deletion can have different effects on different people. Even siblings with the same parents and the same deletion can have different outcomes. 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 loss of DNA.

Genome Assemblies

The human genome project, an international effort to sequence the entire human genome and map all of its genes, was announced complete in 2003. However, there were many gaps in the sequence and mapping data, and scientists have since been working continuously to identify the missing information. When new sequence information is identified, the base pair numbers of each chromosome change slightly and hence the numbers for individual genes, deletions, and duplications and so on can shift.

Each new version of the genome is often referred to as an 'assembly'. Every few years a new assembly is released. The genetic information in this guide is based on the Genome Reference Consortium (GRC) human (h) genome assembly number 37 (GRCh37), which was released in 2009. You will often see the DNA sequence data for this assembly referred to as hg19 (human genome 19) on your child's genetic report.

The databases commonly used by clinical geneticists and Unique will soon move to a more recent assembly named GRCh38/hg38, which was released in 2014. Genetic reports will at some point also be altered, so genes and genetic changes may well have new base pair numbers.

How common are 2q13 microdeletions?

It is difficult to estimate the prevalence of 2q13 microdeletions since many children will not have been diagnosed, and many of those who are diagnosed are not reported in the literature. There are about 30 case reports in the medical literature to date (2016;Bisgaard 2007; Rudd 2009; Shen 2010; Cooper 2011; Brau Javier 2012; Yu 2012; Boone 2013; Costain 2013; Hoang 2013; Lindstrand 2014; Roberts 2014; Russell 2014; Vuillaume 2014; Haghighi 2015; Hladilkova 2015; Riley 2015; Shin 2015; Fry 2016; Wolfe 2016) and over 150 cases have been noted in 'copy number variant' databases such as DECIPHER (DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources; https://decipher.sanger.ac.uk). Such databases are used by geneticists and clinicians to report anonymised genetic conditions, with consent, so the possible outcomes of genetic changes can be shared amongst other professionals. This sharing of information helps to increase the knowledge and understanding of each genetic change which in turn helps to provide more information to those with the same or similar genetic changes. 2q13 microdeletions have also been identified in the general population and it is assumed that people who provide such samples are not affected by their deleted piece of DNA, however, some may be mildly affected but not have received a diagnosis (Kendall 2016). One recurrent 2q13 microdeletion is infrequently reported in the general population and a different and smaller 2q13 microdeletion is more frequently found. DNA samples collected from groups of people with learning difficulties or intellectual disability and/or developmental delay show an increased prevalence of 2q13 microdeletions (Cooper 2011; Costain 2013).

Unique currently has 44 members (32 families) worldwide with a deletion that includes region 2q13. Seven of these members also have anomalies on other chromosomes and 8 members have large deletions that extend to other bands of chromosome 2 outside q13. It is only those with pure 2q13 microdeletions (small deletions within band 2q13 and no other chromosomal anomaly) who will be considered in this guide. For the others, the reason for their clinical features may be due to other chromosomal changes but this guide may be of help to explain some of their features. Unique currently has 29 members (19 families) with such a microdeletion; 10 families completed a survey in 2016.

Why did this happen?

In about half of the children identified so far, the 2q13 microdeletion was inherited from a parent. The other half are *de novo* (dn) cases in which the deletion has occurred as a new event in the child. The reason the deletion occurred in this specific region of chromosome 2 is discussed on page 20. It is important to know that as a parent there is nothing you could have done to prevent the deletion from happening. No environmental, dietary or lifestyle factors are known to cause 2q13 microdeletions. There is nothing that either parent did before, during or after pregnancy that caused the microdeletion.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 2q13 microdeletion 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 2q13 microdeletion. 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 deletion.

In families where the 2q13 microdeletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 2q13 microdeletion rises to 50% in each pregnancy. However, the effect of the microdeletion 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.

If your child with a 2q13 microdeletion goes on to have children of their own, the chances of passing on the deletion to their child are 50%. We have not known about the condition for long enough to be certain if it affects fertility but it is likely that fertility will be normal. Your child's ability to look after their own child is very likely to be closely related to their own learning ability and behaviour.

Possible features

Features of any genetic change can vary considerably but some effects of having a 2q13 microdeletion appear to be more common than others. The following is a list of possible features:

- Low muscle tone (hypotonia)
- Smaller or larger head size
- Slightly unusual facial features
- Developmental delay
- Learning difficulties or Intellectual disability
- Speech and language difficulties
- Autism spectrum disorder or other behavioural difficulties
- Anxiety
- Heart problem
- Kidney problem

It is important to note that no one person will have all of the features listed in this information guide and each person will have different developmental and medical concerns. A number of people with a 2q13 microdeletion have none of the features while a few may have almost all of them. The outcome will also depend on the size and content of the deletion, as well as the unique genetic makeup of each person. Other less common features have also been reported in association with 2q13 microdeletions and are discussed later in this guide.

Pregnancy and birth

Many mothers carrying babies with a 2q13 microdeletion have reported an uncomplicated pregnancy and their babies were born at or near their due date. However, one Unique mother informed us that she had polyhydramnios, which is an unusually large amount of amniotic fluid and can lead to premature delivery. The baby was identified as having enlarged brain ventricles. Another mother mentioned an increased level of nausea. One Unique mother had an abruption (separation of the placenta from the wall of the womb) early on in her pregnancy and was put on medication to prevent early labour. A case report in the medical literature noted one mother had pre-eclampsia (high blood pressure).

A genetic test during pregnancy may be advised if there are concerns about fetal development or an anomaly is detected. To our knowledge, only one Unique member experienced unusual observations during routine ultrasound scans.

Newborn

Babies with a 2q13 microdeletion generally have a birth weight within the normal range. Some babies with a 2q13 microdeletion are described as 'floppy' in the newborn period. Professionals call this hypotonia and it can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Hypotonia can also result in delays reaching developmental milestones such as rolling, sitting, crawling and walking.


Newborn

First signs

Since the outcome of having a 2q13 microdeletion is so variable, babies and children are diagnosed at various stages of development. Those who are born with obvious physical problems such as a heart or kidney anomaly or hernia are more likely to be tested at birth (or during pregnancy if this is identified during routine screening). Others may be offered a genetic test if other unusual features are observed such as unusual facial features, fingers or toes. Some Unique members were identified as babies or toddlers due to concerns such as developmental delay, floppiness, feeding problems or lack of eye contact. Others were identified due to behavioural characteristics such as ADHD (attention deficit hyperactivity disorder) or ASD (autistic spectrum disorder). However, some Unique members were diagnosed later in childhood due to learning difficulties (one Unique child was diagnosed at 12 years).

Appearance

Children with a 2q13 microdeletion may have subtle facial features that are not obvious to a parent but can be identified by a paediatrician or clinical geneticist. Such features include a slightly larger space between the eyes (hypertelorism) or a flat nasal bridge. Unique members have mentioned their children were identified as having various anomalies such as a high arched palate, misaligned teeth, a low hair line, small jaw, an upturned nose, eyes that slant downwards slightly towards the ears, or unusually formed ears. However, facial features can be very subtle and children may not look very different to other children and may closely resemble their siblings or parents.

Sleep

All but one Unique family who completed a survey in 2016 remarked that their child has some form of sleep disruption. Families informed us that their children find it difficult to 'switch off' and fall asleep at night, some children do not sleep for long periods of time and wake repeatedly in the night, some wake far too early in the morning. The reasons for these sleeping difficulties are not yet well understood.

It can be challenging having a child who won't settle to sleep or who does not have sufficient undisrupted sleep, and it can be very difficult for parents to function well during the day if they have a continuous lack of sleep. Although there is little formal evidence that any of the following interventions work, some children may benefit from their use. First of all, it is strongly believed that a good routine, where your child goes to sleep at the same time in the same place every night (when possible) does help. Having a habitual 'going to bed' routine that is neither too long nor too short may also help. For very young babies, some families have found that white noise can help their baby to get off to sleep or playing relaxing music may help young children, although in some cases this can have the opposite effect. Some children with sensory issues may find a certain sheet or mattress particularly uncomfortable so, if possible, investing in a bed/bedding that your child is comfortable on/in may help. If your child still needs a daytime nap, it's best to avoid napping late in the afternoon. This may mean restructuring your day (if possible) to avoid car journeys or long walks in a pushchair/pram late in the afternoon.

Light is also very important since your child's body will naturally detect light and set its 'body clock' (circadian rhythm) according to any light stimulus (even when their eyes are closed). Blackout blinds/curtains may help a child to both fall asleep and not wake too early. One Unique family mentioned their child is using 'light therapy', which is when your child sits near a special light box for a certain amount of time each day to synchronise their 'body clock'. Light therapy uses visible light and filters out ultraviolet rays. Light rays regulate the brain cells that produce hormones that induce sleepiness and wakefulness. Other families favour the use of melatonin (a hormone naturally produced by the body in response to day/night cycles) to help synchronise their child's body clock.

Daytime exercise may also have an effect on your child's ability to sleep at night so it may help if your child is able to do some light exercise everyday, this will depend on their age and muscle tone. Certain foods and drinks may also affect your child's ability to sleep, and awareness of their eating habits during the

afternoon and evening may help to evaluate if what they are consuming is having an affect (e.g. sugar, caffeine and additives may have an unwanted effect - the caffeine in chocolate can remain in the body for many hours). It has also been suggested that certain food supplements may help with sleeping issues, you may be able to discuss suitability with your doctor. Some families also use aromatherapy, homeopathy and massage. Certain medical conditions such as reflux or constipation can also have an effect on sleep as can any pain or discomfort. In older children, difficulties falling asleep at the end of the day may be associated with anxiety.

Feeding and growth

A number of Unique families have mentioned feeding problems either as a baby or a child/adolescent or both. Babies with hypotonia (low muscle tone) may find breast feeding or bottle feeding very tiring. They may take a long time to feed or need to be fed more often. If a baby's nutritional needs cannot be met, they may require supplementation with a high energy formula or via a nasogastric tube (a tube leading to the stomach that is inserted via the nose to allow all feeds and medicines to be taken directly) or gastrostomy (a tube leading to the stomach is inserted through the abdomen wall).

Some babies may have reflux, where feeds readily return up the food pipe from the stomach. If necessary, this can be controlled with medication and feed thickeners as well as careful positioning. Some babies may be reluctant to feed since their sucking reflex is not developed or they find it difficult to co-ordinate sucking, swallowing and breathing. These difficulties may be exacerbated by palate anomalies. One Unique member mentioned feeding difficulties due to their child being tongue tied (when the tip of the tongue is anchored to the floor of the mouth) and lip tied (when the upper lip is tethered to the upper gum). Another member mentioned feeding difficulties due to their child's unusual tongue positioning and movement.

A case report in the medical literature identified a child with a 2q13 microdeletion as having pyloric stenosis. This is a narrowing of the opening from the stomach to the first part of the small intestine and causes projectile vomiting following a feed. Pyloric stenosis is of particular concern in the first few months after birth and may need surgical correction.

As children get older they may find it difficult to move onto puréed and then solid foods. If your child has a developmental disorder such as SPD (sensory processing disorder), OCD (obsessive compulsive disorder), ODD (oppositional defiant disorder), ADHD (attention deficit hyperactivity disorder) or ASD (autism spectrum disorder) achieving a balanced and healthy diet may be more demanding if they may have an aversion to certain foods. Some Unique parents have mentioned their child with a 2q13 microdeletion is a picky eater, reluctant to try new foods, very sensitive to different textures (will vomit easily) or will not eat food of a certain colour. Other parents have not experienced feeding problems with their child.

“ No feeding difficulties, loves food. ” - Age 10

“ Very sensitive to taste, even between brands. ” - Age 7

“ He will not eat anything that has been a little over cooked and that has turned a little dark. He will not eat anything that has black on it. He has texture issues. He will vomit as soon as peas touch his mouth. ” - Age 12

Children

Once your child has shown their individual pattern of development it will become easier to predict their longer term possibilities. Unique members have reported a wide range of difficulties in their children. Developmental delay has been described in most, ranging from mild to severe/global but less than half of the cases in the medical literature report developmental delay in association with a 2q13 microdeletion.

Mobility

There is little evidence to suggest that a child's gross motor skills are strongly affected by the 2q13 deletions discussed in this guide, although some Unique children were affected by hypotonia and a few parents mentioned balance issues in younger children. Some children were delayed in reaching their motor development milestones such as walking or riding a bicycle. A number of parents also mentioned that their child had one foot that turned slightly inwards or outwards and some children have 'flat feet' which may affect mobility and balance. One family mentioned their child had difficulties walking that may be related to poor vision.

Fine motor skills and self care

Fine motor skills appear to vary between children with a 2q13 microdeletion ranging from no problem to dyspraxia (when messages from the brain are not accurately transmitted to the body and planning of movements and coordination are affected). A few parents mentioned mild problems with buttoning clothes or tying shoe laces and others mentioned poor hand use and coordination. Otherwise self care was delayed but eventually achieved.

" Coordination slow but improved over time. " - Age 16

" Toilet trained himself at 20 months during the day however was in a night nappy until he was 5 years old. Dressing was late, still required assistance until he was 8 years old. Still needed help with washing himself until he was 12 years old. " - Age 21

Age 6

Ability to learn

Most children with a 2q13 microdeletion described in the literature and members of Unique experience learning difficulties and for some this may be compounded by hearing and vision problems. While some children are identified as having a mild learning difficulty, the learning abilities of others are more

severely affected and they are diagnosed as having intellectual disability. Some children will attend a mainstream school and may or may not need a dedicated support worker and others will attend a school specifically for children with special educational needs. If your child is diagnosed early enough they may benefit from early intervention programmes. Children may also benefit from speech and occupational therapy sessions. While developmental delay and learning difficulties are commonly observed, intellectual disability is less commonly reported (less than 10% of recent case reports in the medical literature and four Unique members).

❝ Difficulty in writing but good at numeracy. Emotional and behavioural immaturity. ❞ - Age 8

❝ At nearly 9 yrs he is 2.5 yrs behind in school. Has memory and auditory processing problems. He has no sense of time (yesterday, today, tomorrow) and rarely knows what day of the week it is. He doesn't remember his birthday. His short and long term memory is poor. If he is taught something in class he forgets it. Has difficulty with reading decoding, reading comprehension and maths. ❞ - Age 16

❝ Dyslexia. Dyscalculia and auditory processing disorder. He has supports in place at school and we work closely with him at home to manage his school work and some of the anxieties that come with these learning difficulties. ❞ - Age 13

❝ Severe learning disabilities. At a special school. Has ID. ❞ - Age 10

Speech and communication

The ability to learn is strongly associated with the ability to understand and use language. Unique members have commonly informed us that their child with a 2q13 microdeletion had or has delayed speech, word retrieval problems, difficulty understanding abstract concepts, long and short term memory

problems or an auditory processing disorder (the way the brain processes sounds). An assessment by a speech therapist should be able to identify your child's specific difficulties and regular therapy sessions should be tailored to your child's specific areas of need. One parent informed us that their child cannot coordinate language and movement.

❝ The OT has tried since he was 4 to get him to throw a ball back and forth and say his ABC's at the same time...he still can't. ❞ - Age 16

❝ Started to speak at 3.5 years. Much better now but frustration when constructing sentences, he often struggles and becomes upset. ❞ - Age 9

❝ Very little communication. Babbles and says 2/3 words. Uses photo exchange, picks up objects of reference. ❞ - Age 10

Behaviour

Not all children or adults with a 2q13 microdeletion have behavioural difficulties, but as a group, they appear to show a higher incidence of behavioural, social and communication difficulties. It is not yet known what causes this but a known vulnerability in this area means that children should be monitored and families offered early support. Diagnoses that have been associated with a 2q13 microdeletion are listed below.

- ASD: Autism spectrum disorder
- ADHD: Attention deficit hyperactivity disorder
- OCD: Obsessive compulsive disorder
- ODD: Oppositional defiance disorder
- SPD: Sensory processing disorder
- GAD: Generalised anxiety disorder

Other behaviours may include antisocial behaviour (including fear of other children), aggressiveness, bad temper outbursts, stubborn refusal to conform, autistic like behaviour and self harming. These behaviours may be anxiety based due to other difficulties in areas such as comprehension and communication.

From birth to at least 3 years of age, most children are routinely screened for developmental milestones. If there are any concerns about your child's development (either from the doctor or you as a parent or carer) they should be referred for developmental evaluation, which may include a hearing test and autism specific screening.

There is not a 'medical test' that can diagnose autism, children undergo an autism-specific behavioural evaluation usually carried out by a specially trained physician and psychologist. The evaluation may be multidisciplinary and include a speech and language therapist as well as an occupational therapist, it is also tailored to the age of the child. Depending on the outcome, further evaluation by a specialist such as a developmental paediatrician, neurologist, psychiatrist or psychologist may be offered.

Less than 10% of children identified in the medical literature are diagnosed with ASD. However, seven Unique members with a 2q13 microdeletion have received this diagnosis, 3 of whom also have ADHD, and one also has OCD and ODD.

An occupational therapist may be able to help with some behavioural issues by giving your child tools to deal with their sensitivities. One Unique member mentioned their child with an SPD has a particularly strong reaction to smells and an occupational therapist has prescribed a smell therapy to help to train the child's system not to overreact to smell stimuli. One parent mentioned their child with ASD had a compulsion to eat rubber. An appetite for non-nutritive substances has been observed in children with ASD and OCD.

Joining a social skills group may help your child with social difficulties to learn and practise important skills. A parenting course for autism may also help parents to learn behaviour management tools and help to encourage communication and cooperative behaviour in their child to strengthen their emotional wellbeing. Some parents have tried medication to help control their child's behaviour when it becomes of great concern (such as self harming or aggression).

If you think your child's anxiety has become difficult for them to cope with you could discuss with your doctor the possibility of seeing a child psychologist to help determine the roots of their anxiety and establish some tools to help them deal with their feelings.

❝ Very sensitive to touch, smell, texture of certain clothes and texture in food, does not like crowds or noisy places. ❞ - Age 13

❝ Has a sensory processing disorder, sense of smell is quite obvious. Has autistic like tendencies but not been diagnosed with ASD. ❞ - Age 13

❝ We do not give medicines for it even though it is significant. Since it will not change over time, we prefer he learns skills to adapt rather than long term use of medicines. ❞ - Age 16 (with ADD and ADHD)

❝ Due to the medication his behaviour is controllable during the day. However when he is not medicated or anxious he is in the flight/fright mode. ❞ Age - 20

Medical concerns

Kidneys

Kidney problems are not commonly reported by Unique members, although one member mentioned an unspecified kidney problem and another noted renal reflux. However, the NPHP1 gene (see page 21) known to be responsible for some kidney problems is included in one of the common 2q13 deletions (see page 18) so your child may be offered regular kidney checks. Kidney problems are more likely if both copies of this gene are deleted or altered in some way. 2q13 microdeletions are commonly found on one chromosome; in such cases, the other chromosome usually has a functional copy of this gene.

Heart

A congenital heart defect has been identified in about 10% of cases in the medical literature (Rudd 2009; Yu 2012; Riley 2015; Yu 2016). The gene thought to be responsible in these cases is TMEM87B (see page 21) which is found in a common 2q13 deletion. Since these reports highlight the possibility of heart problems, your child may be offered routine heart checks. Only two Unique members have reported a heart anomaly, both of which are relatively mild - one has a heart murmur, the other has a murmur with a benign small hole.

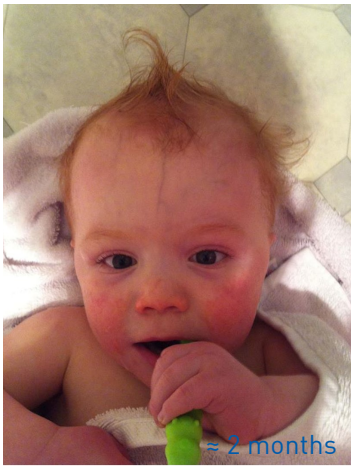
Ears and Hearing

Several Unique members have mentioned that their child with a 2q13 microdeletion suffered numerous ear infections when young. Having frequent ear infections can be annoying and painful for a child and commonly necessitates use of antibiotics. Children can be fitted with ear tubes to equalise the air pressure either side of the eardrum and to improve hearing. Glue ear (when the middle ear becomes filled with fluid) and the consequent effect on hearing at a stage crucial for language development can be frustrating for a child. Although permanent hearing problems are not commonly reported in association with 2q13 microdeletions, there is an anonymous database report of sensorineural hearing loss (a problem with the inner ear) and conductive hearing impairment (a problem with the middle and/or outer ear) in association with a 2q13 deletion. No Unique member is known to have a hearing problem other than that associated with an ear infection or glue ear.

Eyes and Vision

Although eye and vision problems are not commonly reported in association with 2q13 microdeletions, 7 Unique families have reported that their child has an eye or vision problem. One Unique member is longsighted and wears glasses, another had eye surgery to straighten a misaligned eye and has worn glasses since the age of two years. One Unique member has cortical blindness (blindness caused by damage to the brain), nystagmus (involuntary eye movement) and optic atrophy (damaged optic nerve), two members have a strabismus (misaligned eye). One Unique member has an astigmatism (blurred

vision that may be due to curvature of the cornea or lens) and is far sighted. Another member started wearing glasses at age 10. The MERTK gene (see page 21) found in a common 2q13 microdeletion has been associated with retinitis pigmentosa (an abnormality of the retina that leads to progressive visual loss) if both copies are deleted, which is not commonly the case with 2q13 deletions. The NPHP1 gene has also been linked to problems with eye movement and the fluid filled space between the iris and cornea (anterior chamber).



Spine, Joints and Bones

There are a couple of reports in the medical literature of scoliosis (curvature of the spine) in association with a 2q13 deletion and one Unique member is known to have scoliosis, while another has cervical spinal stenosis (narrowing of the spinal canal in the neck). Three Unique members mentioned hypermobility and joint pains and there is mention of accelerated skeletal maturation in an anonymous database report. One Unique member mentioned their child has muscle tightness and back and leg pains. The reason for these pains is unknown.

Hands and Feet

A single crease on the palm of the hand, extra fingers or toes (polydactyly), and fingers curved towards the thumb or toes curved towards the big toe (clinodactyly) have been identified in children with a 2q13 microdeletion. Children have also been described as having broad feet or flat feet and can have a foot that turns inwards or outwards; they may benefit from the use of special shoe inserts.

Brain and Head Size

Microcephaly (a small head and brain) has been found in 6/22 children reported in the medical literature (Yu 2012; Hladilkova 2015;Riley 2015;Yu 2016). However, in the same reports, two children with a 2q13 microdeletion were identified as

having macrocephaly (a larger head and brain). Micro– and macrocephaly are medical conditions in which the brain does not develop as expected. This may be present at birth or may develop over the first few years of life. Two Unique members mentioned their child had macrocephaly - one was identified by the geneticist, another was diagnosed at 8 months as being due to benign hydrocephalus (when there is an unexpected accumulation of cerebrospinal fluid in the brain) which prompted genetic testing. No Unique member has reported microcephaly in association with a 2q13 deletion. Pontine tegmental cap dysplasia (a non-progressive neurological disorder with cranial nerve dysfunction and malformation of the hind brain) has been identified in a man with a 2q13 microdeletion (Macferran 2010). Agenesis of the corpus callosum (when part of the brain that connects the left and right hemispheres does not develop as it should during pregnancy) has also been identified (Yu 2012).

Seizures

Reports in the medical literature have noted that some children with 2q13 microdeletions (4 out of 22) have seizures (Bisgaard 2007; Yu 2012; Riley 2015; Fry 2016). Three Unique members are known to have absence seizures and temporal night seizures were identified in one family. Another Unique member has reported that their child has epilepsy. There is also an anonymous database report of tonic-clonic seizures in association with a 2q13 microdeletion.

Other features

Children with chromosomal changes often show other features that may not be directly related to the specific piece of missing DNA. Such features described in children with a 2q13 microdeletion include: hernias (Yu 2012; Unique); mild anomalies of the genitalia or anus such as hypospadias in boys (where the opening of the urethra is on the underside of the penis; Riley 2015), small penis (microphallus; Yu 2012; Unique), undescended testis (Unique), shawl scrotum (Unique) bilateral scrotal hernia (Unique). An anal fistula (where a small channel

develops between the end of the bowel and the skin near the anus has also been reported (Unique)). A report in the medical literature identified a girl with a missing uterus (Müllerian agenesis; Ma 2014). An inability to control urination (enuresis) was noted in an anonymous database report (no age was recorded).

Sleep apnoea has also been reported (pauses in breathing or shallow breathing during sleep; Yu 2012; Riley 2015; Unique). Some children have their tonsils and adenoids removed which may aid breathing. Choanal atresia (blockage at the back of the nasal passage usually caused by abnormal bony or soft tissue due to failed nostril formation during fetal development) has also been described in association with a 2q13 microdeletion (anonymous database entry).

One anonymous database report identified microdontia (where teeth are smaller than usual) and a few Unique members have mentioned their child has a dental anomaly such as delayed or disordered tooth eruption, delayed loss of baby teeth, wide spacing between teeth or misaligned teeth, weak tooth structure or insufficient enamel and missing, crooked or discoloured teeth.

Hypoglycemia (low blood sugar) has been reported in one case (Yu 2012). There is also a link to obesity in an anonymous database entry, a publication in the medical literature (Vuillaume 2014) and in one Unique family.

One Unique member has an undiagnosed bruising problem and a few other members have mentioned their child bruises easily but there is no evidence as yet to this being related to a 2q13 deletion.

General wellbeing and allergies

Infections are common in childhood and some children with chromosome disorders seem particularly prone to them and to suffer more when they catch them. Ear infections seem to be particularly common and four Unique members with a 2q13 microdeletion are known to have asthma. Although allergies are not commonly reported, one Unique member is known to have several allergies (to fruits, nuts and grains) and requires regular medication. Another member has had two episodes of Henoch–Schönlein purpura (when blood vessels become inflamed typically resulting in a rash often with joint and abdominal pain). Otherwise, all members who responded to the survey in 2016 noted that their child was generally in good health.

Puberty

There is very limited information available on puberty in children with 2q13 microdeletions. When this guide was written in 2016, Unique had 6 family members with a child aged between 13 and 19 years, two of whom completed a survey (both boys). No unusual findings were reported and puberty is expected to proceed as usual.

Adults

Adults identified as having a 2q13 microdeletion are commonly unaffected or mildly affected parents of children recently diagnosed. Parents are commonly

diagnosed as a consequence of their child's investigation and have otherwise been unaware of their deletion. Occasionally, more severely affected adults are identified in large scale screening studies of adults with intellectual disability or a developmental disorder. One adult Unique member has been diagnosed with Asperger syndrome. Although he was aware of his difficulties throughout life he was not aware of his 2q13 microdeletion until his child was tested.

What is the outlook?

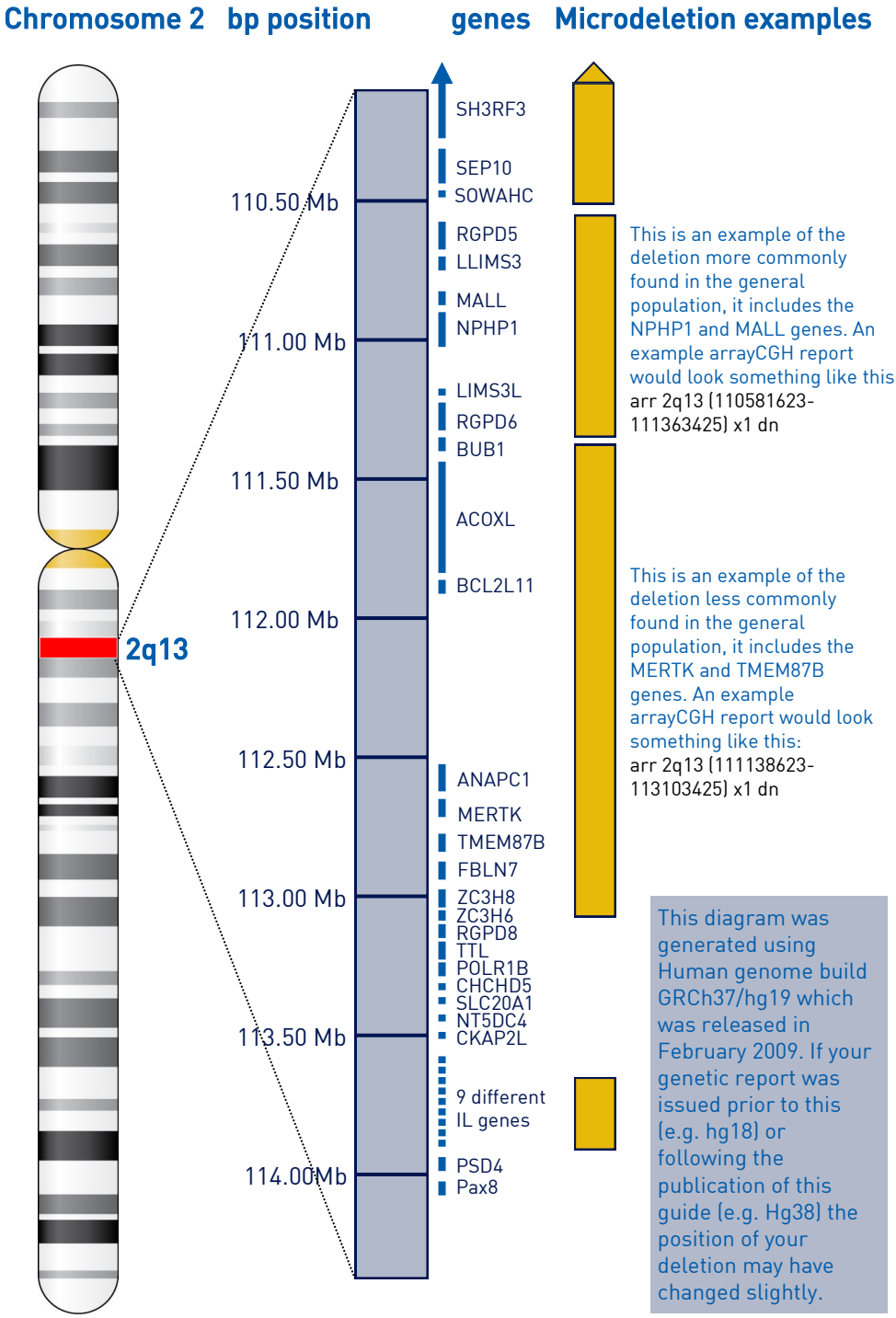
There appears to be no reason why people with a 2q13 deletion who are healthy should not enjoy a normal lifespan. Although it is not possible to predict any difficulties your child may have during adulthood, there are currently no late onset conditions commonly reported in the medical literature in association with a 2q13 deletion.

Genes and Research

The most frequently identified people with a 2q13 microdeletion have one intact chromosome 2, but a small piece from the long arm of the other copy is missing. Therefore it is believed that most of the clinical difficulties are probably caused by having only one copy (instead of the usual two) of a gene or number of genes from the missing piece of DNA. Occasionally people will have both copies missing (Betz 2000; Haghighi 2015) and rarely, people are identified with a missing piece of DNA in 2q13 on one chromosome and a mutation on a specific gene in the same region on the other chromosome (Betz 2000; Yu 2016). In both instances, the outcome is likely to be more severe and depends on the genes affected. We are still learning about the specific jobs or functions of the genes in this region.

A de novo 2q13 microdeletion is caused by a mistake that occurred when the parents' sperm or egg cell formed or in the very earliest days after fertilisation. During these processes, each chromosome pair comes together and swaps segments in order to generate a chromosome unique to each person. To pair up precisely, each chromosome 'recognises' matching or near-matching DNA sequences on its partner chromosome. The 2q13 region has an extremely complex structure that includes lots of very similar, repetitive blocks of DNA. It is at these sites of repetitive DNA that mismatches and consequent loss of DNA is more likely to occur. This is why unrelated people have deletions in very similar positions in region q13 of chromosome 2.

There are about 65 known genes in region q13 of chromosome 2 as well as other regions of DNA that may have some functional significance, such as regions that can control the expression of genes. The following image on page 21 shows the most significant known genes in region 2q13 as well as the position of some common example deletions. The base pair positions of DNA on this section of chromosome 2 are also shown as megabase pairs (1 Mbp = 1 million base pairs) if you wish to roughly map your child's deletion using the numbering on their arrayCGH report.


Chromosome 2
bp position
genes
Microdeletion examples
2q13
110.50 Mb
111.00 Mb
111.50 Mb
112.00 Mb
112.50 Mb
113.00 Mb
113.50 Mb
114.00 Mb
SH3RF3
SEP10
SOWAHC
RGPD5
LLIMS3
MALL
NPHP1
LIMS3L
RGPD6
BUB1
ACOXL
BCL2L11
ANAPC1
MERTK
TMEM87B
FBLN7
ZC3H8
ZC3H6
RGPD8
TTL
POLR1B
CHCHD5
SLC20A1
NT5DC4
CKAP2L
9 different IL genes
PSD4
Pax8
This is an example of the deletion more commonly found in the general population, it includes the NPHP1 and MALL genes. An example arrayCGH report would look something like this:
arr 2q13 (110581623-111363425) x1 dn
This is an example of the deletion less commonly found in the general population, it includes the MERTK and TMEM87B genes. An example arrayCGH report would look something like this:
arr 2q13 (111138623-113103425) x1 dn
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 deletion may have changed slightly.

Genes

A number of different deletions within 2q13 have been identified. Some appear to be more common than others, some are larger than others and some overlap with others as shown in the image opposite. Each deletion will include a different set of genes and other important regulatory sequences. The function of each gene and its relevance to the outcome for the person with the deletion is not always known. New information is constantly emerging and will help with further understanding of 2q13 microdeletions. The possible roles of a few genes within 2q13 that are included in known deletions have been investigated:

- NPHP1 If both copies of NPHP1 are deleted or altered, this can result in ocular motor apraxia (defective or absent horizontal voluntary eye movements) and has been linked to an abnormality of the anterior chamber of the eye. NPHP1 is also associated with kidney problems and Joubert syndrome (abnormal development of regions at the back of the brain). However, children with a 2q13 deletion usually have one unaffected chromosome 2 and hence a functional copy of NPHP1 (although this is not always the case; Betz 2000).
- BCL2L11 Lower levels of this gene product have been identified in individuals with autism spectrum disorder (Fatemi 2001; Araghi-Niknam 2003; Sheikh 2010). The gene product is involved with regulating the number of neurones in the developing nervous system.
- ANAPC1 This gene product is involved with neurodevelopment and has been linked to autism when the gene is duplicated (Costain 2013 &2014).
- MERTK Linked to retinitis pigmentosa when both copies are deleted (Ostergaard 2011) and autism when duplicated (Costain 2014).
- TMEM87B Associated with heart problems (10% of cases in th emedical literature) when deleted (Russell 2014; Yu 2016).
- FBLN7 Associated with tooth formation. It is also expressed in cartilage and may be associated with heart problems. It may be linked to craniofacial abnormalities (Russell 2014). A variant of this gene has been identified in the DDD project as a candidate for abnormality of the nervous system.
- ACOXL Involved in lipid metabolism and linked to obesity (Vuillaume 2014).
- CKAP2L Small mutations in this gene have been linked to Fillipi Syndrome which includes intellectual disability, microcephaly and syndactyly (when two or more fingers and/or toes are fused together (Hussain 2014).
- ILs A group of cytokines that regulate immune/inflammatory reactions and also influence neurotransmission. Changes to these genes could affect immunity/inflammation as well as psychosocial behaviour (Srinivas 2016). Chronic cutaneous pustulosis has been linked to a 2q13 microdeletion that includes a number of interleukin genes (Brau-Javier 2012).
- PAX8 Changes in this gene can affect the thyroid and can cause neurological and motor damage if not treated early in life. No Unique member is known to have a 2q13 deletion including this gene to date. There are detection methods and treatment is available.

Further DNA analyses

If your geneticists thinks that your child's difficulties cannot be fully explained by the deleted piece of DNA from 2q13 alone, perhaps if your child's difficulties are more severe than expected, they may suggest that your child's genome (DNA) is studied in more detail by further tests such as whole exome sequencing (WES). This test analyses the coding sequence of every gene in your child's genome to look for alterations that could have an effect on your child's development. In such cases, it may also have been suggested that you join the DDD project 'Deciphering Developmental Disorders' if you live in the UK. The DDD project aims to advance clinical genetic practice in the UK by offering families with children who have a developmental disorder, access to the latest DNA sequencing and microarray technologies. Recruitment for this project has now closed but analysis of all DNA samples will continue for the next five years (at least). One Unique child with a 2q13 microdeletion has been offered WES and another is taking part in the DDD study.

2q13 deletion family (father and children have the deletion)

What parent's say

" He is a lovely, cuddly affectionate boy who gets frustrated by his own limitations. Take each day as it comes, don't try to predict what will happen. **"**

Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom
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 Please help us to help you!

Facebook groups

Unique has a number of public and private facebook groups worldwide

https://www.facebook.com/groups/chromo2syndromes/ is a chromosome 2 disorder support group

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 information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This booklet was compiled by Unique in 2016 (AP) and reviewed Dr Nick Bass, Senior Lecturer at UCL Division of Psychiatry and Consultant Psychiatrist, and Kate Wolfe, MRC PhD student, UCL Division of Psychiatry.

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