Understanding Chromosome & Gene Disorders

2q13 microduplications

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2q13 microduplications

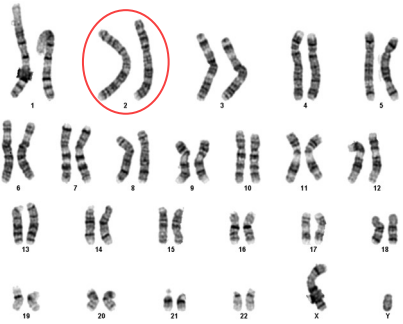
A 2q13 microduplication is a rare genetic condition caused by a small piece of extra genetic material from one of the body's chromosomes - chromosome 2. Duplications can vary in size but those that are too small to be visible under the microscope using standard techniques are called microduplications.

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

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 46 in total. 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.



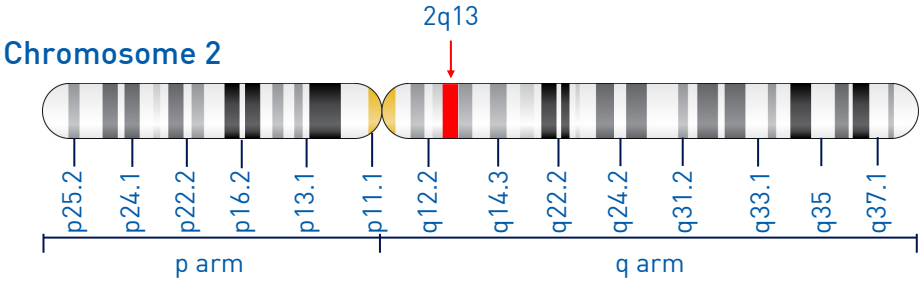
Chromosome pairs 1-22, X and Y (male)
Chromosome 2 pair circled in red

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 and/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.



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 duplication, the amount of duplicated 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 microduplication may have previously been told their standard chromosome analysis was 'normal'. A laboratory technique called FISH (fluorescence *in situ* hybridisation) enables sections of the chromosome to be analysed in more detail and can help detect a duplication. This technique uses fluorescently labelled pieces of DNA that match the DNA in specific places on a chromosome so this test will only be offered if there is a suspected abnormality in a specific region of a chromosome. The more commonly used test nowadays is called microarray comparative genomic hybridisation (array CGH) and allows DNA to be analysed in great detail. An array CGH test can detect very small duplications even when this diagnosis is not suspected, it will also identify a more precise position on the chromosome for the piece of DNA that has been duplicated but it cannot show if the new piece of DNA has moved to a different place on the same chromosome or to a different chromosome.

Sources

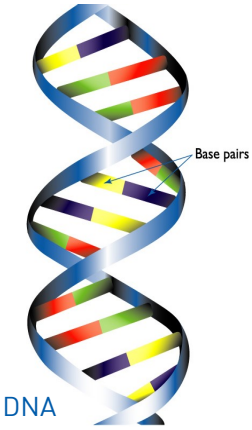
The information in this booklet is drawn from published medical literature and information from Unique members. The first-named author and publication date from articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed (http://www.ncbi.nlm.nih.gov/pubmed). 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 have told you which piece of genetic material has been duplicated and from which chromosome it originated. The information you are given will include any significant changes that are identified and which significant genes are included in the change. 2q13 microduplications 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) x3 dn



DNA

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 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)

x3 There are three copies of the piece of DNA specified. Since there should be 2 copies of chromosome 2, this shows that the DNA anomaly is a duplication

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

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

You may wish to compare your child's results with others who have the same or a similar microduplication to help understand your child's development. While this may help identify common consequences, it is important to remember that the same duplication can have very different effects on different people. Even siblings with the same parents and the same duplication 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 duplicated piece 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 and duplications 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 may 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 have new base pair numbers.

How common are 2q13 microduplications?

It is difficult to estimate the prevalence of 2q13 microduplications since many children will not have been diagnosed, and many of those who are diagnosed are not reported in the literature. To date (2016), very few people with a 2q13 microduplication have been reported in detail in the medical literature (Baris 2006; Szatmari 2007; Rudd 2009; Pinto 2010; Cooper 2011; Kaminsky 2011; Yu 2012; Dittwald 2013; Costain 2013 & 2014; Roberts 2014; Yasuda 2014; Riley 2015; Rees 2016; Kendall 2016). However, just under 150 cases have been noted in 'copy number variant' databases such as DECIPHER (DatabasE of genomiC varlation 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 microduplications have also been identified in the general population and it is assumed that people who provide such samples are not affected by their duplicated piece of DNA, however, some may be mildly affected but not have received a diagnosis (Kendall 2016). Two different recurrent 2q13 microduplications have been identified. The larger microduplication is infrequently reported in the general population and the smaller 2q13 microduplication is more frequently found. These microduplications can vary slightly in size and other less common microduplications have been reported. DNA samples collected from groups of

people with learning difficulties or intellectual disability and/or developmental delay show an increased prevalence of 2q13 microduplications (both the larger and smaller recurrent microduplication; Cooper 2011; Costain 2013).

Unique currently has 18 family members worldwide with a duplication that includes region 2q13. One of these families also has additional anomalies on other chromosomes and 9 families have large duplications that extend to other bands of chromosome 2 outside q13. It is only those with pure 2q13 microduplications (small duplications within band 2q13 and no other chromosomal anomaly) who will be considered in this guide since, for the others, the reason for their clinical features may be due to other chromosomal changes. This guide may however be of help to explain some of their features. Unique currently has 8 family members with a 'pure' microduplication; 4 families completed a survey in 2016.

Why did this happen?

2q13 microduplications are known to be either inherited from a parent or occur *de novo* (dn) which means the duplication has occurred as a new event in the child. The reason the duplication occurred in this specific region of chromosome 2 is due to the presence of lengths of DNA with a very similar sequence (discussed further on page 17). It is important to know that as a parent there is nothing you could have done to prevent the duplication from happening. No environmental, dietary or lifestyle factors are known to cause 2q13 microduplications. There is nothing that either parent did before, during or after pregnancy that caused the microduplication.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 2q13 microduplication or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 2q13 microduplication. This is called germline mosaicism and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the duplication.

In families where the 2q13 microduplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 2q13 microduplication rises to 50% in each pregnancy. However, the effect of the microduplication on the child's development, health and behaviour cannot be reliably predicted.

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

If your child with a 2q13 microduplication goes on to have children of their own, the chances of passing on the duplication to their child are 50%. We have not known about the condition for long enough to be certain if it affects fertility but given the number of 'healthy carriers' 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 microduplication may be more common than others. The following is a list of possible features:

- Low muscle tone (hypotonia)
- Difficulties with gross and fine motor control (e.g. walking and hand control)
- Smaller or larger head size
- Slightly unusual facial features
- Developmental delay
- Learning difficulties or Intellectual disability
- Speech and language delay or difficulties
- Autism spectrum disorder or other behavioural difficulties
- Anxiety

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 microduplication 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 duplication, as well as the unique genetic makeup of each person. Other less common features have also been reported in association with 2q13 microduplications and are discussed later in this guide.

Pregnancy and birth

Many mothers carrying babies with a 2q13 microduplication have reported an uncomplicated pregnancy and birth and their babies were born at or near their due date. To our knowledge, no Unique member experienced unusual observations during routine prenatal ultrasound scans but anonymous database entries have included nuchal translucency and intrauterine growth retardation (when a baby does not grow as expected while in the mother's womb during pregnancy) in association with a 2q13 microduplication. A genetic test during pregnancy may be suggested if there are concerns about fetal development or an anomaly is detected.

Newborn

Babies with a 2q13 microduplication are commonly reported as having a low birth weight. Some babies with an average birth weight are later described as 'failure to thrive' as their weight drops to below average (e.g. 3rd to 10th centile) in the first few months or more. Some babies with a 2q13 microduplication 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.

First signs

Since the outcome of having a 2q13 microduplication is so variable, babies and children are diagnosed at various stages of development. Those who are born with obvious physical problems such as a 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 an unusually small birth size or unusual facial features, fingers or toes. Some Unique members were identified as babies or toddlers due to concerns such as developmental delay, floppiness and feeding or breathing problems. However, some children are diagnosed later in childhood due to learning difficulties or a developmental disorder such as autism spectrum disorder.

Appearance

Children with a 2q13 microduplication may have subtle facial features such as a slightly larger space between the eyes (this is known as hypertelorism) or a flat or broad nasal bridge. Unique members and those described in the medical literature were identified as having various other features such as a high arched or cleft palate, misaligned or small teeth with dental crowding, a small jaw, an upturned or bulbous nose, eyes that slant downwards slightly towards the ears, or unusually formed ears. Some children may not have any unusual facial features and some features can be very subtle so children may not look very different to other children and may closely resemble their siblings or parents. Children with a 2q13 microduplication have been described as short, average and tall for their age but those who show intrauterine growth retardation or failure to thrive may be smaller than their peers.

Sleep

There are a few reports of sleep disruption in children with a 2q13 microduplication. One family informed Unique that their child had major sleep problems from birth to six years that later resolved. Another family mentioned that their child has never been a good sleeper and wakes early, another mentioned that their child sleepwalks. Sleep disruption can be observed in children with known chromosomal changes (for example children with a 2q13 microdeletion) but we don't have enough information yet to be sure if this is commonly observed in children with a 2q13 microduplication.

Sleep disruption can include finding it difficult to 'switch off' and fall asleep at night, not sleeping for long periods of time and waking repeatedly in the night, or waking far too early in the morning. Reasons for sleeping difficulties are not always 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 bedding that your child is comfortable on/in may help. Some Unique members favour the use of weighted blankets. 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. Blackout blinds/curtains may help a child to both fall asleep and not wake too early. Light therapy can also be used, 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. Some 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. The use of melatonin should first be discussed with a doctor.

Daytime exercise may also have an effect on your child's ability to sleep at night so it may help if your child is old enough and able to do some light exercise every day. 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 effect. 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, where feeds readily return up the food pipe from the stomach, or constipation can also have an effect on sleep. If necessary, reflux can be controlled with medication and feed thickeners as well as careful positioning. In older children, difficulties falling asleep at the end of the day may be associated with anxiety.

Feeding and growth

A few Unique families have mentioned feeding problems either as a baby or a child or both, whereas others have not reported any feeding issues. Babies with hypotonia (low muscle tone) may find breast feeding or bottle feeding very tiring and 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 not be able to maintain a healthy weight and are described as 'failure to thrive'. This was the case for two children with a 2q13 microduplication reported in the medical literature (Baris 2009). Such babies or children may require supplementation with a high energy formula.

Some babies may have reflux, or 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. Feeding difficulties may also be apparent if your child is tongue tied (when the tip of the tongue is anchored to the floor of the mouth) and/or lip tied (when the upper lip is tethered to the upper gum). Some children also experience feeding difficulties due to unusual tongue positioning and/or movement.

" He is behind in his feeding skills with no bilateralization of his tongue and chewing. **"** - Age 18 months

As children get older they may find it difficult to move onto puréed and then solid foods. This could be due to oral motor difficulties in tongue lateralisation (when the tongue moves from side to side to manipulate food) or chewing (the circular jaw motion necessary to grind food): it could also be due to sensory issues. If your child is experiencing feeding difficulties, a speech and language therapist may be able to help. If your child has a developmental disorder such as SPD (sensory processing disorder), OCD (obsessive compulsive disorder), ODD (oppositional defiant disorder) or ASD (autism spectrum disorder) they may have an aversion to certain foods. One Unique family mentioned their child with a 2q13 microduplication and a diagnosis of autism has extreme sensory issues that impact on their eating habits to the point of malnutrition.

" He has had 2 iron infusions and a few episodes of ketoacidosis requiring hospital admission as a result of starving himself and dehydration. **"** - Age 4 years

Another Unique member informed us their child had feeding issues in the first month and sensory related feeding issues at 7 years; another Unique member had breast milk intolerance as a baby. One Unique family mentioned their child has never experienced any feeding problems (the child is now 7 years old).

Children

Once your child has shown their individual pattern of development it will become easier to predict if they will have any longer term difficulties. Unique members have reported a range of difficulties in their children. Developmental delay has been described in most, ranging from mild to severe and is commonly mentioned in databases and the medical literature but, not all children with a 2q13 microduplication will have developmental delay or obvious difficulties.

Mobility

There is some evidence to suggest that a child's gross motor skills may be affected by a 2q13 microduplication (Baris 2009; Unique) and some children are affected by hypotonia (Baris 2009; Rudd 2009; Yu 2012; Unique). Some children are hence delayed in reaching their motor development milestones such as walking. Unique parents have also mentioned that their child has one foot or both feet that turn slightly inwards or outwards which may affect mobility and balance. One Unique member mentioned their child had short tendons and muscles in their legs which led to toe walking and an inability to put their toes flat. This was rectified by use of ankle foot orthoses (AFOs) that hold the ankles and feet in a straightened position and help control any abnormal movement. Another member mentioned that their child has hypermobile joints.

" Late walker at 20 months. Unable to do mobility transitions until his second year. " - Age 7 years (mobility transitions refer to changing body positions or actions such as getting up from a seated position to walk)

" Didn't walk until after 2, still has gross motor delays. " - Age 7 years

Fine motor skills and self care

Children with a 2q13 microduplication can have difficulties with their fine motor skills (Rudd 2009; Yu 2012; Unique). Two Unique children have been diagnosed as having dyspraxia (when brain messages are not accurately transmitted to the body and planning of movements and coordination are affected). Self care such as getting dressed alone and toilet training may be delayed (Unique).

" Significant fine motor delays (still can't write at age 7). Has both dysgraphia and dyspraxia diagnoses. Poor fine and gross motor strength, ability, and coordination. " - Age 7 years

" Dyspraxia. Poor hand dexterity and poor strength in hands. Muscle weakness in hands. " - Age 7 years

" With OT he is not as far behind in his fine motor skills any more " - Age 18 months

Ability to learn

Some children with a 2q13 microduplication described in the literature and members of Unique experience learning difficulties and Unique members have mentioned a strong link to language difficulties. Although developmental delay is more commonly observed, two members of the same family with a 2q13 microduplication were described in the medical literature as having a learning disability (Riley 2015) and one Unique member received a diagnosis of moderate intellectual disability. A large scale study of children with intellectual disability and/or developmental delay identified 118 children with a small recurrent 2q13 microduplication (that includes the NPHP1 gene, see page 18) and 8 with a larger recurrent microduplication (that includes the MERTK gene, see page 18; Cooper 2011).

Some children will attend a mainstream school and may or may not need a dedicated support worker and others may 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.

“ In a mainstream school and statemented. ” - Age 7 years

‘Statemented’ refers to a system previously used in the UK whereby a statement of special educational needs was issued to children with learning difficulties. This has recently been changed to an education, health and care plan (EHC plan) and is a document that legally binds the local education authority to ensure that the educational, health and social provisions stated in the plan are delivered to the child.

“ He is home schooled. We tried public school and had to pull him out. Even though he was in a Special Ed(ucation) classroom his needs were not being met and his anxiety was through the roof. We made the decision to pull him out and home school him a year and a half ago. He is thriving in home school. ” - Age 7 years

Speech and communication

The ability to learn is strongly associated with the ability to understand and use language. Children with a 2q13 microduplication may have delayed speech and/or other language difficulties such as word retrieval problems, difficulty understanding abstract concepts or an auditory processing disorder (the way the brain processes sounds). An assessment by a speech therapist should be able to identify if your child has a specific difficulty and if regular therapy sessions are advised, they should be tailored to your child’s specific areas of need.

“ At 4 yrs he is non verbal. He struggles to produce the correct sounds needed for speech. ” - Age 4 years

“ Slight speech delay; currently has problems with pragmatic language. ” - Age 7 years

Pragmatic language impairments have been related to developmental disorders such as autism and ADHD (attention deficit hyperactivity disorder) and have been observed in children with intellectual disability or learning difficulties. Children with pragmatic language impairments find it difficult to use language appropriately in social situations (pragmatic language) and to understand the meaning of what is being said (this is called the semantic aspect of language).

Behaviour

Not all children or adults with a 2q13 microduplication have behavioural difficulties, but some have been diagnosed with a behavioural, social or communication difficulty. 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. Children identified as having a 2q13 microduplication have received the following diagnoses (Baris 2009; Rudd 2009; Yu 2015; Unique):

- ASD: Autism spectrum disorder
- ADHD: Attention deficit hyperactivity disorder
- OCD: Obsessive compulsive disorder
- SPD: Sensory processing disorder
- Generalized anxiety disorder
- Social communication disorder
- Tourette's syndrome: Neurological condition characterised by tics
- PDD-NOS: Pervasive developmental disorder not otherwise specified

Other behaviours may include antisocial behaviour, aggressiveness, bad temper outbursts and autistic like behaviour. Some behaviours may be anxiety based due to other difficulties in areas such as comprehension and communication.

Depending on where you live, 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) 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, but 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.

Although large scale screening studies have identified numerous children and adults with 2q13 microduplications, very few details regarding possible difficulties have been described in the medical literature. It is hence difficult at this stage to estimate the percentage of children with a 2q13 duplication who will have an autistic spectrum disorder or other neurodevelopmental difficulty.

An occupational therapist may be able to help with some behavioural issues by giving your child tools to deal with their sensitivities if need be. Joining a social skills group may help a child with social difficulties to learn and practise important social skills. A parenting course for autism may also help parents to learn behaviour management skills and help to encourage communication and cooperative behaviour in their child to strengthen their emotional wellbeing.

❝ He is a very smart, friendly, and empathetic child. However, he has issues with emotional regulation and a need for routine, so he struggles daily. ❞ - Age 7 years (with generalised anxiety disorder and social communication disorder)

❝ Has a nervous and anxious personality but might be due to his testing over the years. Can become frustrated, can become angry if something is difficult to do. ❞ - Age 7 years

Medical concerns

Ears and Hearing

Although not many children have been described to date, permanent hearing problems do not appear to be associated with 2q13 microduplications. There is only one report of mild sensorineural hearing loss (a problem with the inner ear) in association with a 2q13 microduplication (Rudd 2009). No Unique member is known to have a hearing problem.

Eyes and Vision

Eye and vision problems have not been commonly reported in association with 2q13 microduplications but there are a few cases where an eye anomaly has been observed. Although no Unique member has mentioned problems with vision, one family mentioned their child was diagnosed as having downward ocular flutter, a rapid and involuntary movement of the eye.

One publication in the medical literature identified a child with a 2q13 microduplication and bilateral cataracts (a clouding of the lens in both eyes; Baris 2009). The duplication included the NPHP1 gene (see page 19) which has been linked to problems with eye movement as well as the fluid filled space between the iris and cornea (anterior chamber) if deleted. There is also an anonymous database report of oculomotor apraxia (deficiency in voluntary horizontal lateral fast eye movements) in association with this common 2q13 microduplication. In such cases, an inability to follow objects using eye movement is often compensated for by head movements.

Another report mentions a child with a 2q13 microduplication and retinitis pigmentosa (a degenerative abnormality of the retina that leads to progressive loss of vision; Rudd 2009). The duplicated piece of DNA in this case contains the MERTK gene (see page 19) which has been associated with retinitis pigmentosa when deleted. Another anonymous database report notes a pupil abnormality in association with this duplication but there is no further information.

Spine, Joints and Bones

There is one report in the medical literature of a child with a 2q13 microduplication and severe scoliosis (curvature of the spine; Rudd 2009). However, no Unique member with a 2q13 microduplication is known to have scoliosis. One report mentions mild hyperextensibility of the elbows and knees in association with a common 2q13 microduplication (Baris 2009) and one Unique member has mentioned their child has joint hypermobility (joints that easily move beyond the normal range). Another report describes joint contractures (a stiffness or constriction that restricts normal movement) involving hands, knees and ankles in a child with a 2q13 microduplication (Rudd 2009).

Teeth

It is not uncommon for children with genetic changes to have changes in their dentition. Reports of tooth anomalies in children with a 2q13 microduplication

include tooth anomalies such as dental crowding, small teeth, delayed tooth eruption or decay due to a malformed or structurally weak tooth (Rudd 2009; Baris 2009; Unique)

Hands and Feet

Although no Unique member has mentioned any unusual features in their child's hands, a few cases in the medical literature have been described. One child was identified as having both thumbs adducted (where the thumb is clasped in the palm of the hand; Baris 2009) and another was described as having 5th digit clinobrachydactyly (where the little finger is bent (clino-) towards the thumb and is shorter (brachy-) than expected; Rudd 2009).

One Unique member mentioned their child has high arches and bilateral foot overpronation (where the foot rolls inwards as weight is transferred from the heel to the forefoot). The child benefits from the use of SMO (Supra Malleolar Orthosis) ankle braces to control the hind foot. Another member mentioned their child had flat feet and turned in ankles. A publication in the medical literature describes one child as having partial cutaneous syndactly of the second and third toes (webbing) and another child with mild syndactyly of the second and third toes in association with 2q13 microduplications (Baris 2009).

Brain and Head Size

Both micro- and macrocephaly have been reported in the medical literature and databases. These are medical conditions in which the brain does not develop as expected which results in a smaller (micro) or larger (macro) than usual head. This may be present at birth or may develop over the first few years of life. No Unique member has reported either micro– or macrocephaly in association with a 2q13 microduplication. There is one anonymous database report of cerebral atrophy (loss of neurons in the brain) together with spastic paraparesis (nerve damage that leads to stiffness in limbs but can also affect sight, hearing and brain function) in association with a 2q13 microduplication. Another report mentions schizencephaly (abnormal clefts in the brain) and polymicrogyria (too many folds in the brain).

Seizures

There are no reports of seizures in association with 2q13 microduplications in the medical literature and no Unique member with a 2q13 microduplcation has mentioned seizures. However there are two anonymous database reports of seizures in association with a 2q13 microduplication.

Other features

Mitochondrial myopathy (neuromuscular disease caused by damage to the energy producing structures of cells) has been noted in an anonymous database report as has general neuropathy (nerve dysfunction). One publication in the medical literature describes a child with a 2q13 microduplication and congenital hypomyelinating neuropathy (CHN), which is a neurological disorder present at birth due to reduced amounts of myelin, the protective sheath that surrounds nerves (Riley 2015).

Although a heart condition is not commonly reported with duplications within 2q13, there is an anonymous database report of hypoplastic left heart (when the left side of the heart does not form correctly and blood flow is affected), and pulmonary hypoplasia (when the lungs do not form properly) was also noted in this case. One anonymous database report mentions a meningocele (incomplete closure of the backbone and membranes around the spinal cord usually with a sac of fluid at the gap in the spine) in association with a 2q13 microduplication.

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. However, Unique members who responded to the survey in 2016 noted that their child was in good general health. One report in the medical literature mentions a child with primary IgG2 deficiency and a 2q13 microduplication, which may increase susceptibility to infections.

Puberty

There is very limited information available on puberty in children with 2q13 microduplications. When this guide was written in 2016, the eldest Unique child with a 2q13 microduplication and no other known genetic change was 7 years old. No unusual findings relating to puberty have been reported in the medical literature or databases and puberty is expected to proceed as usual.

Adults

Adults identified as having a 2q13 microduplication are commonly unaffected or mildly affected parents of diagnosed children. Parents are commonly diagnosed as a consequence of their child's investigation and have otherwise been unaware of their duplication. Occasionally, more severely affected adults are identified in large scale screening studies of adults with intellectual disability or other developmental disorder but such adults have also been diagnosed with additional genetic changes (Costain 2013 and 2014; Yasuda 2015).

What is the outlook?

There appears to be no reason why people with a 2q13 microduplication 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 duplication.

What families say

“ I would say to never give up. It was really tough when he was first showing signs of delays. And while it is still difficult, things are easier. He is exactly who he was meant to be. **”** - Age 7 years

“ Let go of your expectations of what your child “should” be. Let them show you their own way. This life may be different than you planned, but it's still wonderful. **”** - Age 7 years

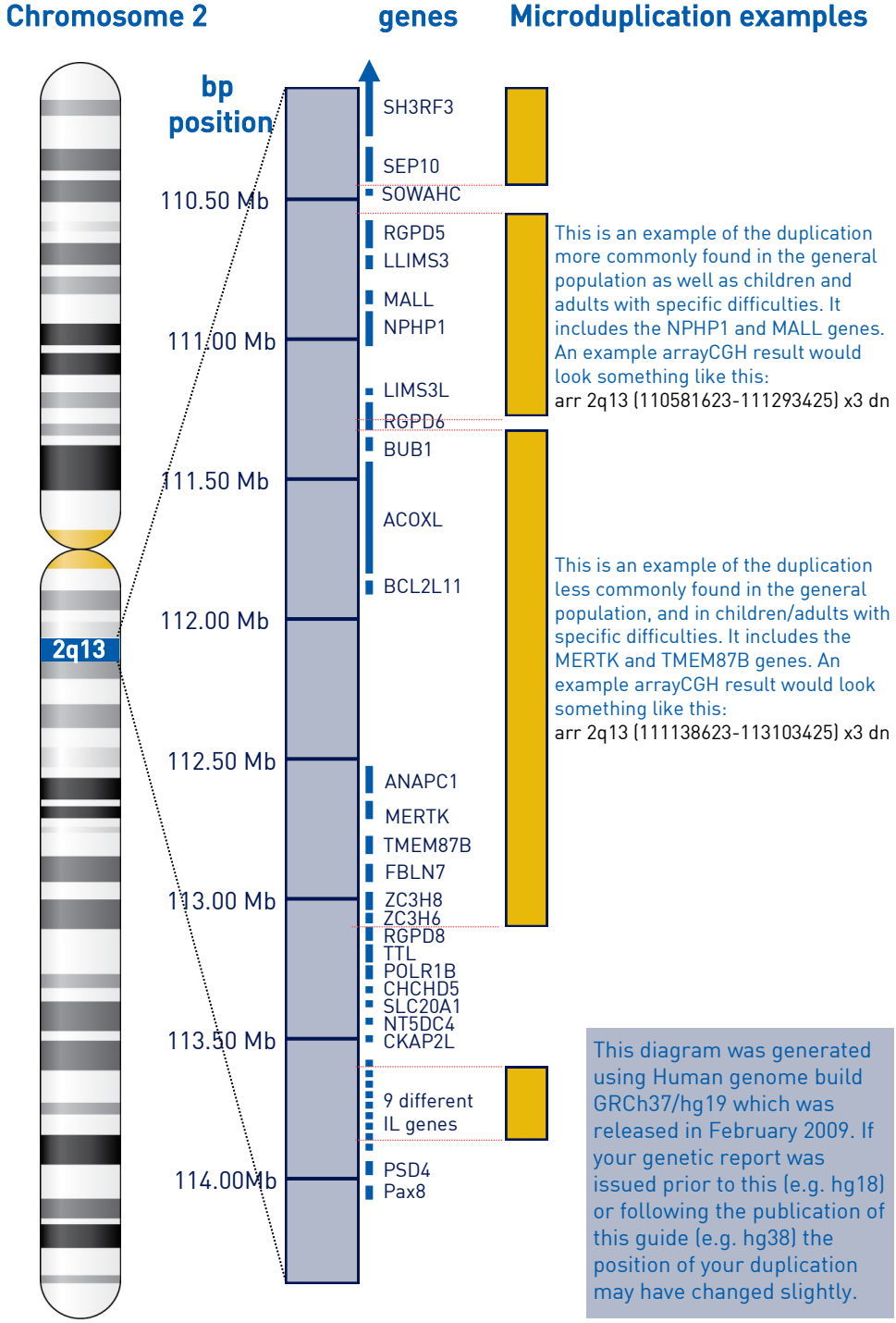
Research

The most frequently identified cases of 2q13 microduplications have occurred on one copy of chromosome 2. The other copy remains unaltered and hence should function as normal. It is believed that most of the clinical difficulties are probably caused by having three copies (instead of the usual two) of a gene or number of genes from the duplicated piece of DNA. We are still learning about the specific jobs or functions of the genes in this region.

A de novo 2q13 microduplication is caused by a genetic change 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 duplication of DNA is more likely to occur. This is why unrelated people have duplications in very similar positions in region q13 of chromosome 2. It is assumed that, in the majority of cases, the duplicated piece of DNA is placed next to the original copy on the same chromosome. However, in some cases, the duplicated DNA may be placed elsewhere on the same or a different chromosome. It may also be inverted (placed back-to-front on the chromosome). In such cases, one or more genes at the site of integration may be disrupted. This can only be confirmed by further genetic tests where chromosomes are visualised such as FISH (see page 3).

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 18, shows the most significant known genes in region 2q13 as well as the position of a few common example duplications. RNA genes (genes that do not have a protein product but may regulate other genes), pseudogenes (genes that have lost their ability to code for a protein but may have a regulatory roll) and other regulatory sequences are not shown. Occasionally these genes are described in genetic reports depending on the geneticist and in which country the test was performed. 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.

If your geneticists thinks that your child's difficulties cannot be fully explained by the duplicated piece of DNA from 2q13 alone, such as in cases when the child's difficulties are quite severe, they may suggest 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 to look for alterations that may have an effect. It may also have been suggested that you join the DDD project 'Deciphering Developmental Disorders' if you live in the UK.


Chromosome 2
genes
Microduplication examples
bp position
2q13
110.50 Mb
111.00 Mb
111.50 Mb
112.00 Mb
112.50 Mb
113.00 Mb
113.50 Mb
114.00Mb
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 duplication more commonly found in the general population as well as children and adults with specific difficulties. It includes the NPHP1 and MALL genes. An example arrayCGH result would look something like this:
arr 2q13 (110581623-111293425) x3 dn
This is an example of the duplication less commonly found in the general population, and in children/adults with specific difficulties. It includes the MERTK and TMEM87B genes. An example arrayCGH result would look something like this:
arr 2q13 (111138623-113103425) x3 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 duplication may have changed slightly.

Genes

A number of different duplications within 2q13 have been identified. Some appear to be more common than others and they vary in size as shown in the image on page 18. Each duplication 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 duplication is not always known. New information is constantly emerging and will help with further understanding of 2q13 microduplications. The possible roles of a few genes within 2q13 that are included in known duplications have been investigated, although outcomes are more often linked to gene mutations or deletions:

- NPHP1 Deletion of this gene has been linked to kidney and eye problems as well as Joubert syndrome (abnormal development of regions at the back of the brain). However, no link has been made to such problems when this gene is duplicated.
- 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. Higher levels of this gene product would be expected if this gene is duplicated and remains active.
- ANAPC1 This gene product is involved with neurodevelopment and has been linked to autism when duplicated (Costain 2013 & 2014).
- MERTK Linked to retinitis pigmentosa when deleted or mutated (Ostergaard 2011) and autism when duplicated (Costain 2013 & 2014).
- FBLN7 Associated with tooth formation and heart problems when deleted. It is expressed in cartilage and may be linked to craniofacial abnormalities (Russell 2014) and an eye problem called AMD (age related macular degeneration; Sardell 2016). 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) and learning disability (Yu 2012; Roberts 2014).
- ILs A group of cytokines that regulate immune/inflammatory reactions and also influence neurotransmission. Mutations to these genes could affect immunity/inflammation as well as psychosocial behaviour (Srinivas 2016).
- PAX8 mutations in this gene can affect the thyroid and may cause neurological, mental and motor damage if not treated early in life. There are detection methods and treatment is available.

* The DDD project, 'Deciphering Developmental Disorders' 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 closed but almost 14000 families joined and funding has been secured to continue to analyse results for the next five years.

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.