Understanding Chromosome & Gene Disorders

Idic(15)

rarechromo.org

Idic(15)

Idic(15) is a rare chromosome disorder where people have extra genetic material (DNA) from one of their chromosomes - chromosome 15. For healthy development, chromosomes should contain just the right amount of genetic material – not too much and not too little. Like most other chromosome disorders, having extra material from chromosome 15 may increase the risk of developmental delay and learning difficulties.

Background on Chromosomes

Chromosomes are structures found in the nucleus of the body's cells. Every chromosome contains thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information telling the body how to develop, grow and function. Chromosomes (and genes) usually come in pairs with one member of each chromosome pair being inherited from each parent. Humans have 23 pairs of chromosomes giving a total of 46 individual chromosomes. Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes (XX) and males have one X chromosome and one Y chromosome (XY). The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest in size.

Each chromosome has a short or petit (p) arm (shown at the top in the diagram opposite) and a long (q) arm (the bottom part of the chromosome).

In idic(15) people have a small additional chromosome derived from chromosome 15, as well as the two normal chromosome 15s. This means that there are 47 chromosomes instead of the usual 46. The extra piece of chromosome 15 has been duplicated end-to-end like a mirror image (see diagram) and is referred to as isodicentric 15 [idic(15)], inverted duplication 15 (inv dup 15), tetrasomy 15q or supernumerary marker 15 [SMC (15)]. Occasionally, a person may have two extra idic(15) pieces (48 chromosomes) or three extra idic(15) pieces (49 chromosomes) in all or some of their cells. Alternatively, some people are born without an extra chromosome but have a segment of duplicated material within chromosome 15, called an interstitial duplication [int dup(15)]. This is, most often, the same section that makes up the extra chromosome in idic(15). For this reason, people with int dup(15) and those with idic(15) often share similar characteristics and collectively these two disorders are often referred to as chromosome 15q duplication syndrome. Although the exact numbers and types of genes that are duplicated are often not known, the extra genes can have an effect on a person's learning and physical development. Therefore it is believed that most of the clinical difficulties are probably caused by having extra copies of a number of genes. We are still learning about the specific jobs or functions of the genes in these regions. Also, it is important to keep in mind that a child's other genes, environment and unique personality also help to determine future development, needs and achievements.

The first published description of a person with idic(15) was in 1977. There have since been over 160 cases reported in the medical literature worldwide. No-one really knows how many people have it because a lot of older people may not have been diagnosed. However, the best estimate suggests that one baby in every 30,000 has this extra chromosome. The disorder occurs as often in males as in females (Van Dyke 1977; Battaglia 2008).

Looking at chromosome 15

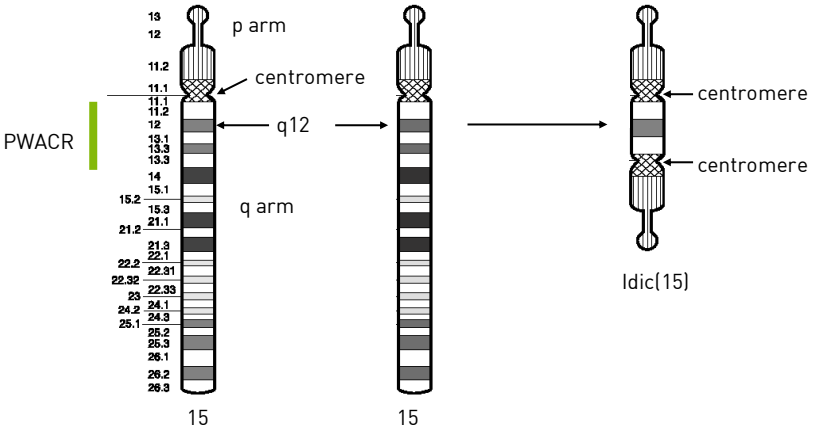
Chromosomes can't be seen with the naked eye but if they are stained and magnified under a microscope it is possible to see that each one has a distinctive pattern of light and dark bands that look like horizontal stripes under a microscope. In the diagram of chromosome 15 below the bands are numbered outwards starting from where the short and long arms meet (the centromere). By looking at your child's chromosomes in this way, it is usually possible to see the extra chromosome.

Extra genetic tests called FISH (fluorescent *in situ* hybridisation) or array-CGH can confirm idic(15) by identifying that the extra chromosome is derived from chromosome 15 and can give much greater precision about the points where the chromosome has broken.

Prader-Willi and Angelman critical region (PWACR)

There is a region of chromosome 15 close to the centromere at bands 15q11-q13 with its own name – PWACR, meaning Prader-Willi and Angelman Critical Region. (Prader-Willi and Angelman syndromes are caused by losing one copy of this region).

If the extra copies of chromosome 15 do not include this region [often called small inv dup(15)], people rarely face any particular problems and their idic(15) is usually just a harmless family trait. Idic(15) causes more problems if the duplicated fragment contains all or part of this critical region. The FISH or array-CGH test very importantly also shows whether the extra chromosome 15 contains one or, as is commonly the case, two copies of the PWACR. This leaflet describes the effects on children who have extra copies of chromosome 15 that do include all or part of this region.



Sources

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date 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*. In addition, this leaflet draws on information from two surveys of members of *Unique* conducted in 2004 and 2009, referenced *Unique*. When this leaflet was written *Unique* had 134 members with idic(15). These members range in age from a one-year-old to an adult aged 37 years.

Diagnosis and results of the chromosome test

Many doctors will not consider a chromosome test important unless a child looks unusual. Most babies with idic(15) have no obvious external physical features to suggest they might have a chromosome disorder, although they might have low muscle tone, seizures or extra skin at the corner of the eye that prompts chromosome testing in infancy. Concerns usually only arise after they miss their developmental milestones and even then other conditions may be considered first. This means that families have tended to receive a diagnosis quite late, in many children not until they were three or four years old and in some cases even later.

You will almost certainly be given a karyotype which is shorthand notation for your child's chromosome make-up. The karyotype will show how much extra chromosome material your child has. With idic(15), the results are likely to read something like the following example:

47,XX,idic(15)(q11)dn

47	The total number of chromosomes in your child's cells; 47 instead of the usual 46
XX	The two sex chromosomes, XY for males; XX for females
idic(15)	An isodicentric chromosome 15
(q11)	Both segments of chromosome 15 have breakpoints in q11
dn	The rearrangement occurred *de novo* (or as a 'new event'). The parents' chromosomes have been checked and no extra chromosome 15 has been found. The idic(15) is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

47,XX,+psu dic(15)(q11q13)

47	The total number of chromosomes in your child's cells; 47 instead of the usual 46
XX	The two sex chromosomes, XY for males; XX for females
+	There is an extra chromosome
psu dic (15)	A pseudodicentric chromosome 15. The extra chromosome 15 has two centromeres (see page 3); one of which is inactivated
(q11q13)	Of the two asymmetrical segments of chromosome 15, one has a breakpoint in band q11 and the other in q13

47,XY,+inv dup(15)(q13q13)

47	The total number of chromosomes in your child's cells; 47 instead of the usual 46
XX	The two sex chromosomes, XY for males; XX for females
+	There is an extra chromosome
inv dup(15)	There is an inverted duplication of chromosome 15 (which is the same as idic(15))
(q13q13)	Both segments of chromosome 15 have breakpoints in q13

In addition to, or instead of a karyotype you may be given the results of molecular analysis such as FISH for your child. In this case the results are likely to read something like the following example:

arr[hg19]15q11.1q13.3 (20688219-32889529)x4

arr	The analysis was by array (arr) comparative genomic hybridisation (cgh)
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted
15q11.1q13.3	The chromosome involved is 15. The chromosome has two breakpoints, one in band 15q11.1 and one in band 15q13.3, and material between these two breakpoints is extra (contained in the Idic(15) chromosome)
20688219-32889529	The base pairs between 20688219 and 32889529 have been shown to be duplicated (extra). Take the first long number from the second and you get 12,201,310 (12.2Mb). This is the number of base pairs that are extra
x4	This means there are 4 copies of these base pairs, not two – one on each chromosome 15 – as you would normally expect

There is a broad range of ability and achievement in children with idic(15). But does knowing the karyotype of your child predict your child's likely future? This is a question that both families and researchers are keen to answer and is an area of active and exciting research.

At present, three things are known for sure:

- If the extra material from chromosome 15 that does not contain the critical region 15q11q13 (PWACR) the duplication does not normally cause any problems at all
- Most children with idic(15) have four copies of the critical 15q11q13 region. Children with three copies (such as an int dup(15)) show much milder effects.
- Children with five or six copies tend to be more severely affected (Robinson 1993; Browne 1997; Roberts 2002; Huang 2003)
- Children who have the extra chromosome 15 in only a proportion of their cells (known as a mosaic form of idic(15)) also tend to show milder effects, but these could range from complete normality to significant problems (Dennis 2006)
- Paternally derived duplications often are not associated with developmental problems. It is the maternally derived copies that are associated with the developmental problems

People with idic(15) have varying breakpoints and the breakpoint may be different on each of the extra copies of the critical region (see diagram on page 3), so they have two additional copies of most of the genes in the PWACR but one extra copy of some of the genes furthest down the chromosome (Wang 2008). This variability may possibly help to explain some of the wide variations in children's abilities, but this is not certain.

3½ years

Most common features

Every person with idic(15) is unique and so each person will have different medical and developmental concerns. Additionally, no one person will necessarily have all of the features listed in this leaflet. However, a number of common features have emerged:

- Hypotonia (floppiness or unusually low muscle tone) in newborn babies
- Delay in reaching baby 'milestones'
- Variable disabilities in learning and motor development. Children will often need support with learning although the amount of support needed by each child will vary
- Absent or delayed speech
- Unusual behaviour, often including behaviour on the autistic spectrum
- Seizures are present in over 50 per cent of individuals with a duplication of 15q. Seizure onset, seizure type and responsiveness to treatment varies widely.

What is the outlook?

Most babies with idic(15) are born perfectly healthy. Dup 15q alliance has many family members around the world affected by idic(15) and can provide further information (https://dup15q.org). The most usual effects of the condition are on behaviour and learning and the only serious medical condition encountered is usually seizures. There are several adults reported in the medical literature and *Unique* has 14 adult members (see Adults with idic(15) page 23).

While the outlook depends on a child's individual progress it is likely that most children with idic(15) will continue to need support throughout their lives. However, over time it seems that children demonstrate improvement in social interactions and a decreased occurrence of withdrawal behaviour. Their fine and gross motor skills together with communication abilities and comprehension of language also seem to improve (Battaglia 2008).

Pregnancy and birth

Many mothers carrying babies with idic(15) experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. Of the 57 families who have told us about their pregnancy experiences, twelve babies showed little fetal movement while in the womb. Two babies had intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed resulting in babies that are smaller than expected for the number of weeks of pregnancy. In one of the cases the placenta had stopped functioning properly and the mother was hospitalised. In a further four babies growth slowed in the last few weeks of pregnancy. Two babies were shown to have brain anomalies at the 20 week scan. Three (out of 117) *Unique* babies were born prematurely, but that is as you would expect in any group of babies in the general population (*Unique*).

As far as we know, none of the *Unique* families discovered their baby had idic(15) before their baby was born. There are two examples in the medical literature of prenatal diagnosis of idic(15). In the first case, prenatal diagnosis was performed due to advanced maternal age. At 16 months old the child had delayed development and severe learning difficulties. In the second case, prenatal diagnosis was performed after IUGR and polyhydramnios (an unusually high volume of amniotic fluid) were observed at 30 weeks (Miny 1986; Robinson 1993; *Unique*).

Newborn

Typically babies with idic(15) are floppy (hypotonic) in the newborn period. This can result in delay reaching the baby developmental milestones (such as sitting, rolling, crawling and walking) and also cause feeding problems. Babies are often very placid and sleepy, frequently needing to be woken up for feeds. They may also be less responsive than typical babies, not responding appropriately to social cues (*Unique*).

Growth and feeding

Birth weights recorded at *Unique* show a considerable variation with an average of 2.76 kilos (6lb 1oz). Four (out of 117) *Unique* babies had a low birth weight (below 2.6 kilos or 5lb 12oz) at term (*Unique*).

Range of birthweights at *Unique* (at or near term):

2.438 kilos (5lb 6oz) to 4.649kilos (10lb 4oz)

The *Unique* experience is that new babies tend to feed slowly and breastfeeding may be hard to establish. The hypotonia that is common in babies with idic(15) can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft or high palate can also find the action of sucking and swallowing difficult. Many babies have a small appetite and struggle to finish a feed. Thirty-one of the 53 mothers surveyed by *Unique* attempted to breastfeed their babies, although only about half established successful breastfeeding. However, a number of babies were bottle-fed expressed milk. Four out of 55 *Unique* babies benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat). As some of these babies matured enough to suck effectively, the NG-tube could be removed and breast or bottle feeding established. Four babies needed gastrostomy tubes (a G-tube, feeding direct into the stomach) in order to meet their nutritional needs (Dennis 2006; *Unique*).

The hypotonia can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). In the *Unique* survey, almost a third of babies had reflux. This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage. Two *Unique* babies have benefited from this procedure (*Unique*).

Hypotonia can also have an impact on the gastrointestinal tract, slowing down bowel movements, resulting in constipation. Almost a third of those who took part in the *Unique* survey suffered from constipation although most children outgrew it (*Unique*).

4 years

Many older babies and toddlers with idic(15) have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers and the start of finger feeding may be delayed. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems. Children with a high palate (around a third of those surveyed) may also struggle with solid food – food can become trapped in the high palate (*Unique*).

The *Unique* experience is that feeding problems improve and many children have a good appetite, eating a good and varied diet. However, a number of children seem to lack the sensation of fullness and their children want to eat all of the time. Some children (7/55) overfill their mouths until they choke and need parents to be vigilant while they are eating, measuring food in small quantities (*Unique*).

Growth and height are usually normal for children with idic(15). However, around three quarters of parents describe their children, regardless of height, as slim or thin despite their children eating well. Conversely, those that lack the sensation of fullness may overeat and can become overweight (*Unique*).

"She had feeding problems and would take a long time to drink from her bottle. She would not latch on to the breast but had expressed milk in a bottle. She now eats a wide and varied diet and has learned to chew and eat finger foods." – *1 year*

"She was breastfed for 8 months with no problems. Her chewing is still poor and food needs to be relatively soft and small." – *4 years*

"He has vitamins every day and no artificial additives. He eats fresh fruit and vegetables every day. Everything has to be mashed or blended." – *5½ years*

"He took a while to learn to chew and swallow solids but now he eats almost everything." – *7½ years*

"He is a very messy eater and does not chew at all – all food must be finely mashed. Since the onset of epilepsy he has been less interested in food and so takes a dietary supplement." – *15 years*

"She tends to overeat." – *17 years*

5 years

Learning

Learning difficulties and intellectual disabilities affect all children with a duplication of 15 q (both those with idic(15) and those with an interstitial duplication), with most children moderately or severely affected and a small minority profoundly affected.

As always, there is individual variation, however most children will need support and benefit from early intervention programmes and may thrive best in a special learning environment. Indeed the vast majority of *Unique* children attend a special education school, although a small number attend mainstream school, often receiving 1:1 help in the classroom. In a recent study, of 17 children aged 5-16, three were attending mainstream schools with additional help (one was mosaic for idic(15)).

Most children with idic(15) also have a diagnosis of autism or autistic spectrum disorder (ASD) and a number have thrived in schools specialising in autistic programmes. Most children benefit from a 1:1 aide at school to help with focus and to help them communicate their needs (see Behaviour) (Rineer 1998; Dennis 2006; *Unique*).

A small minority of children learn to draw simply and write their own name and other simple words. However, the hypotonia can make holding a writing or drawing implement difficult and many children find using a keyboard easier to master.
Because of this, computers (including touch-screen computers) are used by many children both at school and at home. A number of children who do not master independent writing do learn over-writing (tracing words over 'dotted' letters). A few children learn to recognise their name and a small minority master reading. Many children, including those who do not master reading, love looking at books and listening to stories and a number especially love looking at catalogues.

Children generally have a good memory. A number of children are hyperactive or described as being easily distractible or having a short attention span which can make learning more of a challenge. Autism, which is common in children with idic(15), can also impact the way in which children learn. Some families utilise ABA (Applied Behavioural Analysis), a method of working with children with autism and other learning difficulties, which can help compensate for the child's learning difficulties by analysing and changing their behaviour. Learning for most idic(15) children is best achieved in small groups in a structured environment which is quiet and calm (*Unique*).

Many families report that their child particularly loves water and/or sand play.
Children with idic(15) seem to share an exceptional ability and love of music and singing with many families describing their child's perfect pitch or ability to recognise/hum a melody after only hearing it once (*Unique*).

> **"** Her memory is very good in areas. She can repeat melodies and songs very fast and correctly. She can't read but loves books. **"** – *4 years*

> **"** He has moderate learning difficulties. His strengths are his personality, music, helpfulness and phenomenal memory. He can read 3-4 letter words. **"** – 5 years

> **"** At the computer he can recognise numbers and letters and points to them when asked. **"** – *5½ years*

> **"** She loves music and can sing songs after hearing them once. She has a very good memory and can draw circles and straight lines. **"** – *7 years*

> **"** He has a great 'ear' – he can hum tunes he has heard only once or twice, pitch perfect and accurate. **"** – *9½ years*

> **"** She knows some letters and has a very good memory (for things and events). She is not strong in maths. **"** – *11 years*

> **"** He loves computer games and despite his poor dexterity, he can use a mouse and keyboard. We use games recommended by school to develop his skills as well as games designed for younger children covering a range of activities from counting to learning about being with friends. He responds well to these games and his vocabulary and some skills have noticeably improved through these. **"** – *11 years*

❝ She reads at about a 7-year-old level. She can draw a basic person and copy write her first name. ❞ – *13 years*

❝ She remembers the tunes of nursery rhymes. She learns better when her epilepsy is well-controlled. ❞ – *14½ years*

❝ He has severe and complex learning difficulties. His memory is good and he remembers where he lives, where his Nan lives and he knows certain places and people. ❞ – *15 years*

❝ She has severe learning difficulties but has an amazing memory! She learns best in small groups with a known teacher and 1:1 assistance. ❞ – *18 years*

❝ He loves music and can pick up on pitch very Easily. ❞ – *18 years*

❝ He has a good memory for music and sings well. He also has a good memory for places and doesn't forget where he has Been. ❞ – *19 years*

6 years

Speech and communication

Speech problems are common in children with idic(15). Speech is very often delayed. Children with idic(15) often have speech that is echolalic (they repeat words or phrases spoken by another person) and so they often 'echo' sentences or phrases rather than form them themselves. In a review of the speech abilities of 33 people aged between 2 and 57, researchers found that all except five used at least some words. The average age at which children started to speak was 27 months. One child, with a mosaic form of idic (15), understood language and spoke normally and nine others could conduct a simple conversation. Five more used short sentences, six used short phrases and six children only used single words. Another, ongoing study carried out by Dr Carolyn Schanen in the USA looking at 41 children has shown that 14 children had their first word by the age of 5 years, two began using words between the ages of 5 and 10 years and one acquired words after the age of 10 (Battaglia 1997; Battaglia 2005; Dennis 2006; *Unique*).

The evidence at *Unique* of those members aged over 5 shows a scattered range of abilities. On average *Unique* children first spoke at 3 years and 5 months. Seventeen people speak in sentences, but these are often short simple sentences and are not always clear or easy for people outside the family to understand. Ten used single words or had some speech. Seven children had no speech but had mastered signing and/or PECs (picture exchange communication system). However, this level of achievement is not possible for all and 14 children use no words and do not use signing or PECs. These children continue to use gestures, facial expressions and vocal noises to indicate their needs and express their feelings. They will often point or lead an adult to what they want.

A very small minority appear to have little need or intention to form communication with others (*Unique*).

One *Unique* child spoke fluently and in sentences until seizures began at age 7 and her speech regressed and she now does not speak. This regression of speech has also been described in the medical literature (Battaglia 1997; *Unique*).

Evidence at *Unique* suggests that some children refer to themselves in the third person rather than using 'I' or 'me'. Although children often learn to speak in simple sentences and communicate their needs and/or wants they may not have the ability to hold a conversation or respond and answer questions (*Unique*).

7 years

Some children use sign language, PECs and/or computer-based approaches to help to communicate their needs and wants. Evidence in the literature, which is also backed up at *Unique,* suggests that many children have better receptive language than expressive language: they understand more than they can express. Speech therapy has proved beneficial to many children (Battaglia 2008; *Unique*).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which in addition to insufficient sucking, can also affect the development of speech. Those with a cleft or high palate may also have specific difficulty with articulation of certain sounds (*Unique*).

"She communicates by speech, pushing/pulling and noises. She is able to form sentences with up to 6 words. She had a hip operation at 2 years and 8 months, and spent 2 months in a cast and her speech improved dramatically." – *4 years*

"He started using words at 2½. He has a large vocabulary and can name lots of objects. He will copy a lot of words he hears but he can't really hold a conversation or answer questions. He picked up lots of words from his Vtech™ toys as he likes repetitively pressing the buttons so hears the words lots of times." – *4½ years*

"He has only one word, 'cake', which he loves! He can sign 'more' and is starting to respond to PECs. He understands more than he can express." – *5½ years*

"He uses speech and signing. He understands well but finds it difficult to express his needs and gets frustrated. He uses a touch screen computer at school." – *7 years*

"He understands simple commands and although he has no words he growls when eating something he likes!" – *7½ years*

"Her first words were at 3 years and she used full sentences from 5 years. She uses a touch-screen computer." – *10 years*

"She speaks normally." – *11 years (mosaic idic(15))*

"She uses words but she cannot express her feelings." – *11 years*

"He has an increasingly large vocabulary which he uses appropriately for the most part. Speech is an area where he has shown vast improvement only in recent years and can now express simple needs. He cannot converse though and does not respond to questions." – *11 years*

“ She chooses not to engage in any communication. ” – *15 years*

“ He started using PECs two years ago and he reacted in such a positive way we could not believe it! ” – *15 years*

“ She talks but it is very echolalic. She understands simple language and needs plenty of time to process words, signs or symbols. ” – *17 years*

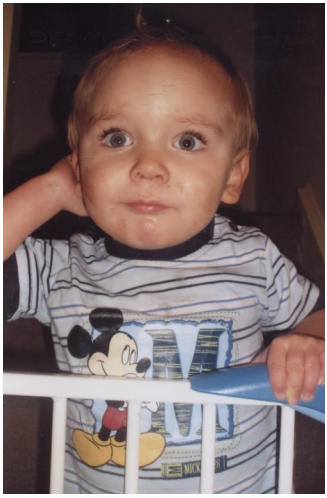
“ She uses 5-6 word sentences and is very vocal. She also uses Makaton [sign language] and PECs. Phonic computers have been very useful. ” – *18 years*

“ She understands almost everything but her speech is slurred and she finds it difficult to express herself. ” – *26 years*

Development: sitting, moving, walking (gross motor skills)

Children with idic(15) are typically slow to reach their developmental motor milestones. Reports in the published medical literature suggest that sitting is achieved between ten and 20 months of age, and walking between 2 and 3 years. The *Unique* experience is that babies start to roll between 3 months and 30 months (average 9 months); sit between 4 months and 3½ years (average 13 months) and crawl between 5 months and 5 years (average 16 months). Independent walking was mastered between 13 months and 7 years (average 3½ years). Some children need support (such as a standing frame, walking frame, support boots, a supportive Lycra ‘second skin’ and/or leg braces) while learning to walk. Most children go on to walk, climb and run, although they can be clumsy and unsteady with poor balance and co-ordination. Many children walk with a clumsy or wide gait and trip easily.

5 years



22 months

Spatial awareness is a problem for a number of children which results in trouble negotiating stairs (they cannot judge the depth of the stairs) and they may walk into objects in their path. Due to this clumsiness a few *Unique* children wear a helmet to protect their heads when they fall down. There is some evidence at *Unique* that children’s clumsiness improves and they get better at avoiding walking into objects and/or tripping over. Two *Unique* children walk on tiptoes. For many children, endurance is a problem and they tire easily, so for some children a wheelchair may be necessary at times or for long journeys. Although the majority of children master independent walking, this is not possible for a small number of children with idic(15) (Robinson 1993; Battaglia 1997; *Unique*).

There are several reasons for these motor delays including the hypotonia that affects around 70 per cent of children with idic(15). Hypotonia often improves as children mature; nonetheless, early physiotherapy and occupational therapy can be beneficial. A small number of children have loose or lax ligaments which can contribute to the mobility difficulties. The epilepsy that is common in children with idic(15) can also lead to problems.
Those children who have 'drop' attacks may need to have support while walking or use a wheelchair.

21 years

Behavioural problems, particularly in children who have no sense of danger or those who sometimes 'refuse' to walk, may result in using a wheelchair when out and about. However, many children with idic(15) seem to feel the need to move all the time and find it difficult to stay still – many families report that their children run everywhere rather than walk and love to climb anything and everything!

Swimming seems to be a particularly popular activity and many children have a love of any kind of water play. Other physical activities enjoyed by some children at *Unique* include riding a tricycle, bicycle or scooter, roller-skating, horse-riding, playing football, trampolining and dancing (*Unique*).

"He crawls well indoors. Walking is delayed because he is unable to support his weight due to hypotonia." – *2 years*

"He had a lack of strength in his trunk. He never crawled and toe-walked until a year ago" – *5 years*

"She moves around mostly by crawling but can cruise around the furniture. She can walk with a walker or aided and has taken some independent steps." – *5½ years*

"She is very fast and very clumsy. She climbs everything." – *10 years*

"He has poor spatial awareness and sitting can be a problem – he needs chairs with a back-rest and ideally arms so he does not fall off. He has problems on uneven ground and stairs as he cannot judge the depth of the stairs. He will run into things and is very clumsy." – *11 years*

"He crawls or uses a wheelchair." – *12 years*

"He no longer has any problems with gross motor skills. He walks for pleasure every day and gets angry if no-one will go outside for a walk with him. He also runs, climbs, goes up and down the stairs. It seems as though he needs to move." – *15 years*

"He walks on tiptoes. He is very unbalanced and falls regularly and cannot walk up and down stairs independently." – *17 years*

"He moves well. He swims, cycles and runs, but with an awkward gait." – *18 years*

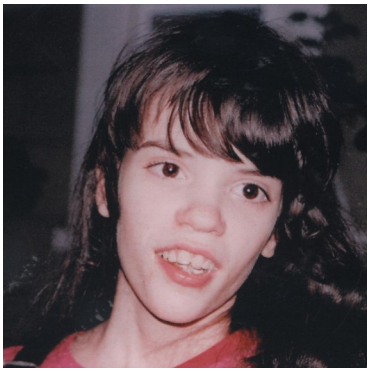
"She has good motor skills." – *22 years*

Development: hand-eye co-ordination and dexterity (fine motor skills) and self care

Hypotonia can also affect fine motor skills in children with idic(15) and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles and cutting up food have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard or touch-screen computer can often be easier. Many children have occupational therapy in order to help improve these skills (*Unique*).

An example of the fine motor skills of a 15-year-old girl with idic(15). She can thread the beads but not tie the knots

As a result of these difficulties, children are likely to continue to need help with dressing and undressing. They will also require assistance in tasks such as brushing teeth and washing. Toilet training is also likely to be affected. The information at *Unique* shows that consistent toilet training was mastered between 2½ years and 14 years (average just over 6 years). One study by the team at IDEAS (The isodicentric 15 education, advocacy and support group) has shown that bladder control was achieved by nine out of 41 children by the age of 6½ years, and bowel and bladder control achieved by eight (out of 41) by the age of 7 years. However this level of training has not been possible for all children (*Unique*).



15 years

“ Her hand movements are clumsy. She can bring the spoon to her mouth but still cannot fill the spoon herself. She is in nappies day and night and requires help to brush her hair and teeth. She might try to wash her hands but requires help. She cannot dress herself but will put her arm through a T-shirt when asked. She is very good at taking off shoes with Velcro fasteners. ” – *4 years*

“ He still has an immature grip and lack of co-ordination and has difficulty with small things such as raisins. ” – *7½ years*

“ She can do most personal hygiene things, but often chooses not to! ” – *11 years (mosaic idic(15))*

“ He has a severe delay in fine motor skills. He has only a simple grip – no pincer grip. ” – *15 years*

“ She is in nappies at night for bowel movements. She needs assistance and guidance with dressing and personal hygiene. ” – *18 years*

“ He has trouble with fine motor skills. He still has lots of trouble with forks and spoons and can only scribble roughly with a crayon. ” – *19 years*

Medical concerns

Seizures

Seizures are a common feature of idic(15), affecting around three quarters of children in the *Unique* survey. A recent report in the published medical literature found that seizures affected two thirds of the 33 people with idic(15) in the study (Dennis 2006). The evidence both at *Unique* and in the published medical literature suggests that children have a wide variety of types of seizure and individual children may experience more than one type. Onset is between birth and 18 years, although more than half had their first seizure before the age of one. Seizures may be occasional or frequent, short or prolonged. The most common type of seizures affecting *Unique* members are infantile spasms, a seizure that brings on a cluster of jerks or twitches and is most common in babies between the ages of three and ten months. Absences, where children stare into space for 5 seconds to 2 minutes, were also common. Other types of seizures seen in *Unique* members (and those in the medical literature) include jerks (myoclonic), 'drop attacks' (atonic), stiffening (tonic) or repeated jerking (clonic). 'Grand mal' seizures (tonic-clonic, where the child falls unconscious and then shakes all over) only affected two older teenage members, although they are reported in the literature in younger children. A small number of children had experienced odd episodes that might have been seizures but had normal electroencephalograms (EEGs). An EEG is a test that gives you a picture of the electrical activity inside the brain (Bingham 1996; Battaglia 1997; Elia 1998; *Unique*).

Seizures can often be well controlled by medication, although five children out of 67 have seizures that have not been completely controlled by medication. Some families have used a ketogenic (high fat and low carbohydrate) diet to attempt to control seizures. A number (3/35) of children who have epilepsy that has not been possible to control with medication have had vagus nerve stimulation (VNS) therapy. VNS is a treatment for epilepsy where a small generator is implanted under the skin below the left collar bone. This is connected to a lead with three coils at one end. These coils are wrapped around the vagus nerve in the left side of the neck in a small operation. The VNS stimulates the vagus nerve at intervals to reduce the frequency and intensity of seizures. In a few children whose epilepsy was hard to control, parents experimented with a variety of alternative treatments. These included yoga, oxygen therapy, craniosacral therapy (also known as cranial osteopathy) and homeopathy (*Unique*).

Two *Unique* children and four in the published medical literature have Lennox-Gastaut syndrome, a type of epilepsy which is often of early onset and resistant to medication. The published medical literature also describes mild, adult-onset epilepsy (Battaglia 1997; Chifari 2002; Battaglia 2008; *Unique*).

The epilepsy disturbs the sleep of many children (14/35). Children who are affected by seizures during the night may be excessively tired the following day and need to nap during the day. A number of families also report that the epilepsy medication makes their child drowsy or excessively tired (*Unique*).

Children who suffer from 'drop attack' seizures should wear a helmet to protect their heads when they experience seizures.

Some families report that seizures increased in number around the start of puberty (*Unique*).

There has been a suggestion that there is a correlation between seizures and learning difficulties but a recent study found no link (Dennis 2006).

Heart problems

Heart (cardiac) conditions are rare in those with idic(15). Only two of the 53 children surveyed had a heart condition. One had a heart murmur and was waiting for further tests and the other had a small hole between the two lower chambers of the heart (a ventricular septal defect or VSD) which healed (closed) naturally without surgery. It is not known whether heart rhythm disturbances are present in children or adults with idic(15), so it is recommended that children have an electrocardiogram to evaluate their heart rhythms (*Unique*).

Vision

A squint (strabismus), where one or both eyes can turn inwards, outwards or upwards, is the most common vision problem affecting around a third of *Unique* families and reported in 40 per cent in a recent published review. Many squints are convergent (the eyes cross) and many children need surgery to re-align the eyes (Dennis 2006; *Unique*). Other problems reported were long sight, short sight and astigmatism (the cornea, the clear cover over the iris and pupil, is abnormally curved resulting in blurred vision). These problems are often mild and can be corrected with glasses. Five *Unique* children had a cortical visual impairment (the visual systems of the brain do not consistently understand or interpret what the eyes see). Nystagmus (rapid, uncontrolled eye movements) has been observed in the published medical literature and at *Unique* (Huang 2003; *Unique*).

10 years

A number of other problems have been reported in only one child. One *Unique* child had no depth perception and another had entropion (the eyelids fold inwards) which was surgically corrected (*Unique*).

Hearing

Hearing impairment is common in children with chromosome disorders and has been reported in almost a third of *Unique* children with idic(15). The most common cause of hearing impairment is glue ear, where there is a build-up of fluid in the middle ear. Glue ear usually resolves as children get older and the ear tubes widen and become more vertical resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear and glue ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum (Dennis 2006; *Unique*).

Minor genital anomalies

Minor genital anomalies affected seven boys (out of 25) who took part in the *Unique* survey. Four had cryptorchidism (undescended testes). The testicles can be brought down by a straightforward surgical operation if they do not descend of their own accord in time. Cryptorchidism has also been reported in the published medical literature.

One *Unique* child has very small testicles; one had paraphimosis (the foreskin becomes trapped behind the 'head' of the penis) and one had hypospadias (the hole that is usually at the end of the penis is on the underside instead). Both paraphimosis and hypospadias can be corrected by a straightforward surgical procedure.

Micropenis (a small penis) and an imperforate anus (a malformed anus) have also been reported in the medical literature, although as far as we are aware have not be observed in any children known to *Unique.* In females, abnormal development of the ovaries has been identified in one case (Robinson 1993; Grosso 2001; *Unique*).

5 years

Palate

A cleft palate (opening in the roof of the mouth resulting from the palate not forming correctly during development) has been reported to affect some children with idic(15). A cleft palate only affected one baby (out of 55) who participated in the *Unique* survey. The low incidence of cleft lip and palate in children with idic(15) may indicate that the two are not necessarily connected (*Unique*).

Around a third (16/53) of children were reported to have a high palate (*Unique*). Both cleft and high palates can contribute to the early feeding difficulties seen in children. A cleft or high palate may also make speech more difficult.

Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers. Two *Unique* children have one or more teeth missing and one child had teeth that were slow to erupt. A small minority of children have oral hypersensitivity or a hypersensitive mouth resulting in an aversion to brushing teeth and visiting the dentist; one child required a general anaesthetic for dental treatment. There have been reports in the published medical literature of irregularly shaped or positioned teeth and hypertrophy (overgrowth) of the gums (Robinson 1993; *Unique*).

Spine

A small proportion (around 20 per cent in the *Unique* survey) have scoliosis (curvature of the spine). In most cases the scoliosis is mild and has not, at present, required surgery. Two *Unique* children had severe scoliosis which necessitated surgery (*Unique*).

Skin

Eczema is a type of allergic reaction that affects around a quarter of children with idic (15). In mild forms the skin is dry, hot and itchy, whilst in more severe forms the skin can become broken, raw and bleeding. Parents have found that gentle moisturising creams and emollients can help keep it under control, with steroid cream employed in more severe cases. Eczema is often worse during the summer months and many children outgrow it (*Unique*).

Behaviour

Babies and young children tend to be quiet and undemanding and do not respond to social cues, although their ability to respond usually increases with maturity. Children with idic(15) are often happy, sociable, full of enthusiasm, loving and enjoy life. However, as children grow up and leave the passive stage of babyhood behind, they may display sudden and extreme changes of behaviour, with outbursts of aggressiveness and destructive behaviour. This behaviour can be directed at themselves and others and include hair pulling, hitting, biting and kicking. A small minority have been known to be self-destructive or self-harm. They are often easily frustrated and can be impulsive. They tend to be hyperactive with poor concentration, a short attention span and are easily distracted, all of which can make learning more challenging.

21 years

Three of the 53 (6 per cent) who took part in the survey have been diagnosed with attention deficit hyperactivity disorder (ADHD) which is characterised by restlessness and a short attention span. There are also reports of ADHD in the published medical literature. Some families report that their children are overly affectionate and show inappropriate friendliness and are hyperverbal (talk too much). Strategies that families have used to help manage behaviour include firm discipline and very clear boundaries, trying to ensure that their child does not become overstimulated and if necessary moving the child to a quiet place to calm them. Singing and music are often successfully employed to calm and soothe children. Some families have had success with rewarding good behaviour using a star chart. Behavioural management techniques have helped many families, but for some children medication has been shown to be the only effective treatment. Other strategies employed by families include dietary manipulation such as a gluten-free diet, a low sugar diet, added fish oils or no food dyes (see the *Unique* leaflet on Behaviour) (Battaglia 1997; Maggouta 2003; *Unique*).

4 years

By contrast, sensitivity, anxiety and insecurity are concerns for some families. Children may show extreme anxiety on separation and be easily hurt by other children. Some become extremely anxious when too much is demanded of them and they may hurt themselves (usually biting their wrists or hands) as a result (*Unique*).

Behaviour within the autistic spectrum has been noted in more than 20 reports in the published medical literature and in almost half of *Unique* children. Some children do not have a diagnosis of autistic spectrum disorder (ASD) but show some autistic tendencies or traits.

Autistic tendencies may include stereotyped behaviour (repetitive behaviour such as wringing hands), no speech or echolalia. Echolalia is an unconventional verbal behaviour that is common among children with autism spectrum disorders. Echolalia occurs when the child repeats verbal information stated by others (for example people's conversational exchanges, videos, books read aloud, songs, etc.) (see section on Speech and communication page 10).

14 years

Other features of the autistic-like behaviour in children with idic(15) include struggling with changes in routine, avoiding eye contact and a lack of appropriate social interactions. A significant number of children have no awareness of danger. However, children with idic(15) are generally much more sociable than is common in children with autism, and many children learn to handle sustained eye contact and social responses more consistently. Families report that children thrive best in a calm, structured environment. A consistent routine helps children feel safe and secure (Battaglia 1997; Rineer 1998; Wolpert 2000; Borgatti 2001; *Unique*).

Two *Unique* children have a formal diagnosis of pathological demand avoidance (PDA), a disorder related to, but separate from, autism and Asperger's syndrome. For more information, contact the PDA syndrome contact group (www.pdacontact.org.uk).

Sensory issues affected more than half of those who took part in the *Unique* survey. Another report suggests that around half of those children with idic(15) are hypersensitive to noise, and almost two thirds have other sensory aversions at one time or another. Children may be either sensory defensive, for example they may display tactile sensitivity, disliking the touch of certain objects or textures, and/or have oral hypersensitivity. Conversely they may display sensory dormancy (they are under-responsive to sensory input or lack sensation and awareness).

12 years

Almost three quarters of those who took part in the *Unique* survey reported that their children had an increased tolerance to pain, often not noticing when they had been quite badly hurt. There are several activities and strategies that can be applied to increase body awareness and promote better sensory awareness.

These include ankle and/or wrist weights or a weighted vest or blanket, all of which help to increase body awareness; pushing/pulling activities such as furniture moving, carrying books, tug of war; resisted creeping and rolling games; deep tissues massage; body brushing; controlled jumping and falling games; climbing stairs and general core strengthening activities to improve muscle tone through trunk (Rineer 1998; Schanen 2006; *Unique*).

13 years

"She is constantly moving and requires an additional safety harness on her car seat to keep her sitting down. She has a weighted blanket to calm her and restrict her movements when going to bed." – *4 years*

"He has no sense of danger – he once burned himself on the hob and is still not wary of it. He has autism and needs to be spoken to very literally. It is important to recognise when he has been overstimulated and needs some space. He is a real comic and very affectionate. He seeks out sensory stimulation all the time and cannot play alone. He has strong separation anxiety and is overfriendly with everyone." – *5 years*

"She hates cold food and is tactile defensive on her hands and feet. Her therapists are working on hand holding." – *5 years*

"She is a very content and placid child and does not cry much. She is very affectionate but has no sense of danger." – *5 years*

"He loves playing in the garden, especially touching the plants to see their movement. His behaviour is better during term-time when he is more stimulated than in the holidays. Giving him lots of exercise helps (for example going on the trampoline or going for a walk)." – *5 years*

"He has a high tolerance to pain. He likes touching hot things, licking hot radiators and doesn't cry easily when he falls or hurts himself." – *5½ years*

"She is a very relaxed and mellow child as a general rule but under certain circumstances she will get very anxious and start shrieking uncontrollably – mostly when at the doctors or anywhere new or strange." – *5½ years*

"She is very restless: she moves around all the time and is constantly doing something." – *6 years*

16 years

15 years

“ He can be very happy and then upset in quick succession. He sometimes goes up to strangers and wraps his arms around their leg (he loves cuddles). He is not very good at staying still. ”
– *7½ years*

“ She is happy with no behavioural issues to deal with. She has her moments of unhappiness just like any other child. She LOVES bath-time. She entertains herself very well. She loves music – it has always comforted her. ” – *8 years*

“ She has ADHD and gets frustrated easily – she may hit or push if someone isn't listening to her or doesn't understand. She loves to be around other kids but doesn't understand personal space issues. She is sensory seeking – she always needs to hold something that is squishy or rubbery. ” – *10 years*

“ He is a lovely little chap who is generally happy and easy going. He can be a bit distant and in his own little world. He has a high pain threshold and no sense of danger. He loves climbing on furniture and is very attracted to water. He is very sociable and loves to be around people but does not like noisy environments unless he is making the noise! ” – *11 years*

“ She is generally a happy, healthy young lady who enjoys reading, videos and shopping (in many ways a typical teenager!) but she does have episodes of difficult behaviour. She used to be very sensitive to noise (such as lawn mowers, vacuum cleaners, air conditioning) but has slowly overcome her anxiety by familiarity. ”
– *14½ years*

“ She is extremely passive; she dislikes confrontation and will go anywhere to be alone. She hates trucks but loves loud music! Her hands, feet and head are sensitive to touch. ” – *15 years*

“ He likes to lick things and he also likes to touch different surfaces. He does not like clothes and shoes and if he had his way he would always be naked! ” – *15 years*

“ He is noisy at times but that is just his way of speaking. He has pica [eating non-food items]. He has always been hyperactive but has become less so as he has gone into his teenage years. ” – *15 years*

“ She can have difficulty with transition and often cries when leaving the house. However, we use PECs/objects to let her know where we are going and she does much better. ” – *15½ years*

“ As a baby he was very sensitive to noise and would jump at loud noises. ”
– *now 18 years*

“ She is kind, thoughtful and helpful. She sometimes suffers from mood swings. ”
– *26 years*

“ He is placid and unassuming. ” – *37 years*

Sleep

Sleep problems are not uncommon in children with idic(15), however most families report that their child's sleep patterns improved as they grew up. Some children find it difficult to 'switch off' and fall asleep needing someone to hold them or lie down next to them until they fall asleep. Evidence at *Unique* seems to suggest that children outgrow this need and eventually learn to fall asleep by themselves. A number of families report that their child only sleeps for small amounts of time with night wakefulness. Others have children who are consistently early risers. One family uses camomile drops in their child's drink to calm him and help relax him before bedtime. Melatonin has been used by a number of families (7/53) with some success, although for others it has not appeared to be of any benefit. One *Unique* child has periods when she is in a manic, frantic state and does not sleep for days. This is followed by a period of lethargy (*Unique*).

> "She power naps for 10-15 minutes and then awakens and is as bright as a button. At night-time she has always woken up at 4am and will play for 2-3 hours before going back to sleep. She has just received a weighted blanket and she slept for 12 hours for the first time!" – *1 year*

> "She has not had trouble going to sleep but struggles to stay asleep. Now she is becoming more mobile she is wearing herself out more and so the sleep is getting somewhat better." – *2½ years*

> "She finds it difficult to go to sleep. She is unable to switch off and stop moving. I [Mum] lie down with her and hold her tight to stop her legs moving and she will usually fall asleep within 45 minutes." – *4 years*

> "In the past he's had trouble going to sleep. He needs a very dark room so there are no distractions. His anti-convulsant medication sends him to sleep now." – *7½ years*

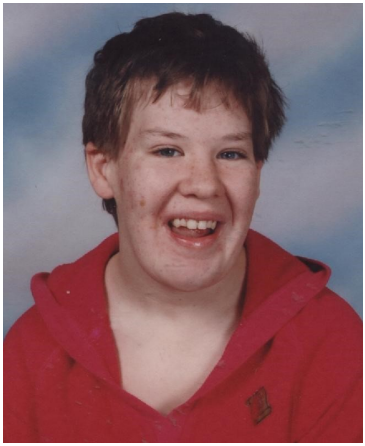
> "He tires easily so sleeps well at night and has two naps during the day." – *12 years*

> "For many years, she has had disturbed nights but although she still wakes she tends to stay in her room and potters about and then puts herself back to bed." – *14½ years*

Puberty and Fertility

There is limited information available on puberty in both males and females with idic(15); however, it appears that in many cases puberty proceeds as normal at the usual age, although there have been reports of precocious (early) puberty in girls. Two *Unique* girls had hormone injections to halt premature puberty. Two girls in a recent review and two girls at *Unique* started their periods normally but then experienced scanty or no periods afterwards (Grosso 2001; Dennis 2006; *Unique*).

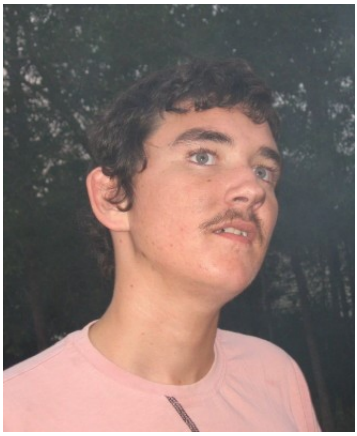
As far as we are aware, the only individuals with idic (15) who have had children had idic(15) in the mosaic form. There are several reports in the medical literature of mosaic mothers who are relatively mildly affected passing on the extra chromosome 15 to children who were non-mosaic and more severely affected (Van der Smagt 1996; Dennis 2006).



17 years

Adults with idic(15)

Unique has 14 adult members between the ages of 18 and 37 years, six of whom took part in the *Unique* survey.



18 years

A 37-year-old man has learning difficulties and uses gestures to communicate. He is placid and unassuming, loves music and swimming, and lives at home. He is medically fit but needs help with personal care.

A 26-year-old woman loves shopping and having her hair and nails done. She loves music and although she cannot read or write she can over-write. She has speech although it is slurred and she sometimes struggles to express herself. She left school at 19 years to attend a college (to study general studies) and now attends a day centre. She lives in a supported home with five others. A 22-year-old woman likes riding her tandem bike, swimming and walking. She loves music and easily learns melodies and plays small pieces on the piano occasionally. She was diagnosed with autism at the age of 3, but it has improved as she has grown older. She has simple speech and uses hand gestures to communicate.

A 19-year-old boy has moderate to severe learning difficulties but loves music and singing. He cannot read or write but can recognise logos (such as shop names). He has used speech since he was 6 years old and also uses PECs. He has autism and ADHD. He attends a day activity centre twice a week and lives at home.

An 18-year-old girl with severe learning difficulties has an amazing memory, can use a computer and over-write her name (although she cannot read or write). Her family describe her as very loving with a great sense of humour but she has some challenging behaviour. She loves being outside playing football or trampolining. In the past few years her sleep patterns have improved and she now sleeps all the way through the night. She has poor fine motor skills and still needs her food to be cut up. She wears nappies at night-time. She speaks very well in short sentences.

21 years

An 18-year-old boy has moderate to severe learning difficulties and lives in a community school. He loves music and can pick up on pitch very easily. He also has a very good memory and loves looking at pictures in books, although he cannot read. He has autistic tendencies and likes routine and a calm, relaxed environment. His speech mainly involves single words and short sentences. He can dress himself but needs some help brushing his teeth. He loves trampolining, swimming and biking (*Unique*).

A number of adults have been reported in the published medical literature.

A 31-year-old woman has seizures which are difficult to control and severe learning difficulties. She has never acquired social imitative play or appropriate eye contact.

An 18-year-old man has aggressive and hyperactive behaviour; he lives in an institution for males with learning difficulties and behavioural problems.

A 19-year-old girl has suffered from tonic seizures that have been difficult to control since she was 12 years old (Robinson 1993; Battaglia 1997; Takeda 2000).

Ongoing research on idic(15)

Chromosomes carry genes that control the physical development and behaviour of every individual. The features of idic(15) are likely to be a result of the duplication of one or a number of different genes found in the duplicated part of chromosome 15. The fact that those people who have four copies of the PWACR (and therefore four copies of all of the genes in the PWACR) are generally more severely affected than those who have three copies (as in interstitial duplications), suggests that there is a gene dosage effect for a gene or genes in this region. Genes contain the instructions for the manufacture of proteins which are required for the structure, function and regulation of the body's cells, tissues and organs.

The PWACR is gene rich, containing at least 20 genes. Genes, like chromosomes, come in pairs (one copy inherited from the father and one copy inherited from the mother). For most genes both copies are active or 'expressed' with each copy of the gene manufacturing the protein product. However, for some genes (and/or regions of the chromosome) only one copy of the gene is expressed (and therefore manufacturing protein), while the other copy has been 'switched off' and is not expressed. For certain genes the expressed gene may be the paternal copy (the one inherited from the father) whereas for other genes, the expressed gene may be the one inherited from the mother (maternal). The PWACR includes genes that are expressed from both maternal and paternal chromosomes as well as genes that are only expressed from either the maternal or the paternal chromosome. The published medical literature suggests that those people who have interstitial duplications inherited paternally (from the father) are not affected at all or may be only mildly affected. Therefore, because maternally (from the mother) derived chromosome 15 duplications are associated with developmental problems there is a lot of scientific interest in the two known maternally expressed genes called *UBE3A* and *ATP10A*:

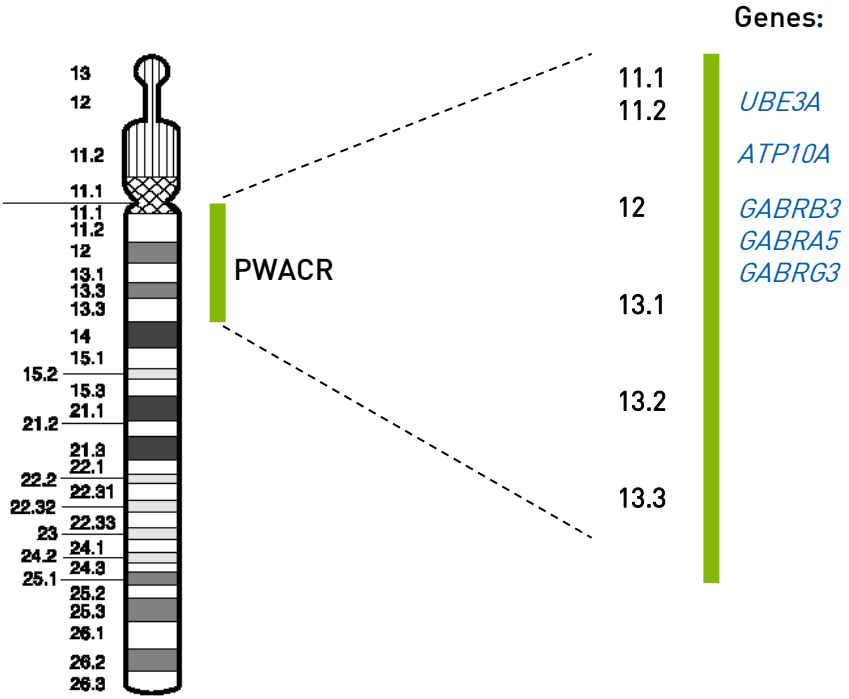
The *UBE3A* gene provides instructions for making a protein that is involved in targeting other proteins to be broken down (degraded) within cells. Protein degradation is a normal process that removes damaged or unnecessary proteins and helps maintain the normal functions of cells. Both copies of the *UBE3A* gene are active in most of the body's tissues. In the brain, however, only the copy inherited from a person's mother (the maternal copy) is normally active. This gene is present in four copies in most children with idic(15). Further studies are needed to determine the implication of having extra copies of this gene (Herzig 2002).

The *ATP10A* gene (also known as *ATP10C*) makes a protein that is thought to be involved in moving molecules in and out of cells. It is expressed in the brain and again only the maternal copy is usually active. Most people with idic(15) have four copies of this gene, instead of the usual two, although the implication of having these extra copies is not known. Further studies are needed.

There are two lines of evidence that point to the region of chromosome 15q11q13 as a good candidate for harbouring a gene(s) involved in epilepsy. The first is that loss of the maternal copy of this region results in Angelman syndrome which is associated with epilepsy. The second is the observation that extra copies of this same genetic region, in the form of idic(15), are also often associated with seizures.

Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature. Therefore, it seems that both reduced and increased copies of a gene or genes in the 15q11q13 region appear to be involved in epilepsy.

The *GABA* (gamma-amino butyric acid) gene makes proteins that are neurotransmitters in the brain: they carry messages between nerve cells. The overall effect of GABA and its interacting receptors (GABA receptors) is to stabilize the activity of nerve cells. The region 15q11q13 that is duplicated in idic(15) harbours three GABA receptor genes, known as *GABRB3*, *GABRA5*, and *GABRG3*. Studies in mice have shown that over-expression of individual components of GABA receptors often leads to seizures. They are therefore good candidates for being related to seizures because of both their location and their function, but further studies are needed. The *GABA* gene has also been linked to autism (Cook 1998; Buxbaum 2002; Shao 2003; Ma 2005).



There is also a very recently announced mouse model for dup15q. This is an extremely important and promising new development in the research efforts (Nakatani 2009).

It is important to remember that while identifying the gene(s) responsible for certain features of idic(15) is interesting and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is duplicated it does not always mean that the associated feature(s) will be present.

Why did this happen?

In the majority of cases idic(15) occurred sporadically, and no other family member is affected. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* idic(15) is a result of a change that occurred when the parents' sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined.

There are two regions on chromosome 15 that have been identified that are prone to breakage or genomic instability due to the presence of repeated DNA elements in the region: one region is more proximal (close) to the 15 centromere which produces small inv dup(15) without the PWACR (and no clinical features) and the others are more distal (further away from the centromere), which creates the larger inv dup(15) which includes the PWACR and are the ones that this leaflet focuses on. Because there are so many potential regions for rearrangements to occur, there are often subtle differences at the DNA level among people with idic(15) and int dup(15) chromosomes that cannot be detected by simply looking at the chromosomes under the microscope. This may also account for the wide variability in symptoms.

The extra chromosome 15 has in all but one case been found to come from the mother suggesting that an extra copy from the father is either a rare occurrence, or interferes with the function of the sperm cell and keeps it from functioning properly at fertilization or has no effect and therefore goes undetected. Maternal duplications are associated with epilepsy, speech delay and autism (similar to idic(15)), whereas individuals who inherit the same duplication from their father appear to be unaffected or more mildly affected. Advanced maternal age (as in other chromosome disorders such as Down's syndrome) may lead to a slight increased risk of having a baby with idic(15) (Browne 1997; Cook 1997; Mohandas 1999).

What is certain is that as a parent there is nothing you did to cause idic(15) in your child and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault.

Can it happen again?

The possibility of having another pregnancy with idic(15) depends on the parents' chromosomes. If both parents have normal chromosomes when their blood cells are tested (as in the vast majority of cases), it is very unlikely to happen again.
Very occasionally, a mother who has experienced none of the problems associated with idic(15) may be mosaic for idic(15), and then the chance of having another affected child will be significantly raised.

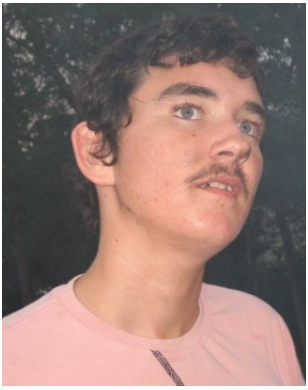
The type of idic(15) where the extra chromosome material does not contain the critical 15q11q13 region is passed down through families, often unknowingly as it does not cause any problems. The only known concern is a possible link with infertility in men.

Parents should have the opportunity to meet a genetic counsellor to discuss their specific recurrence risks and options for prenatal and possibly preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all of these tests are available in all parts of the world.

Growing up with idic(15)

3 months

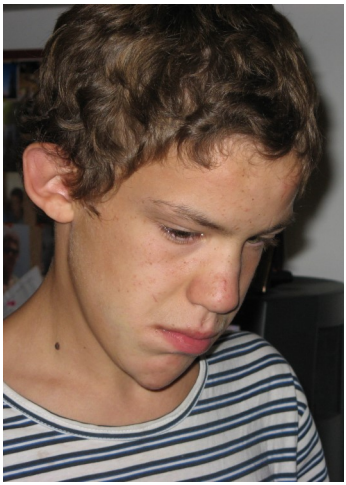
7 years



18 years

2 years

5 years



15 years

Inform Network Support

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The Stables, Station Rd West, Oxted, Surrey. RH8 9EE, UK
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Websites and FaceBook Groups

http://www.dup15q.org
Dup15q Alliance provides family support and promotes awareness, research and targeted treatments for chromosome 15q11.2-13.1 duplication syndrome.

UK www.facebook.com/groups/1436105923301221/
www.facebook.com/groups/201770003266536/
www.facebook.com/groups/youkmowyouhaveakidwithidic15/?fref=ts
Parents of Idic 15 adults www.facebook.com/groups/255127651274011/
(secret group, please email marion@rarechromo.org to request to join)

USA BigTent: www.bigtent.com/groups/dup15q
Facebook: www.facebook.com/groups/434813163252172/

France www.idic15france.fr

Germany www.facebook.com/groups/1724557007821374/

Italy www.idic15.it/

Spain www.idic15q.com/
https://www.facebook.com/pg/idic15-invdup15-España-189248794453964/

Australia www.facebook.com/Dup15qAustralia/

Australia and New Zealand www.facebook.com/groups/229118593766651/

Canada www.idic15canada.ca
Facebook page www.facebook.com/Idic15Canada

South Africa www.facebook.com/groups/idic15sa/

Norway www.facebook.com/groups/851458564881875/

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!

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by *Unique* and reviewed by Nicole Cleary, IDEAS Board Chair, USA, Dr N Carolyn Schanen, University of Delaware, USA and by Professor Maj Hultén, University of Warwick, UK. 2005, 2009, 2014

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