Support and Information

European Chromosome 11 Network
www.chromosome11.eu
Comprehensive information in English, Dutch, German, French, Spanish, Italian and Danish

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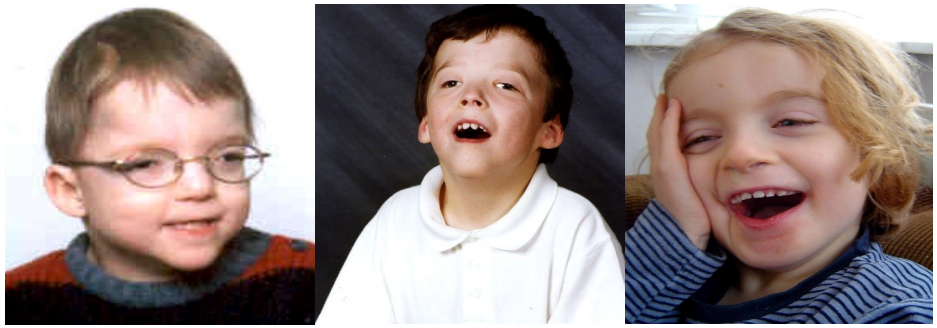
Rare Chromosome Disorder Support Group
Registered in England and Wales
Charity Number 1110661
Company Number 5460413

Understanding Chromosome & Gene Disorders

11q deletion disorder: Jacobsen syndrome



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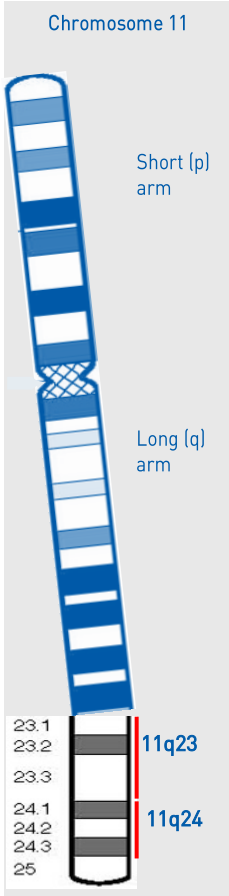
11q terminal deletion disorder: Jacobsen syndrome

11q terminal deletion disorder is a rare genetic disorder. About 1 baby in 100,000 is born with Jacobsen syndrome. The chromosome disorder is twice as common in girls as in boys (Mattina 2009). It is known as a terminal deletion disorder because it is caused by the loss of genes from the end (terminus) of chromosome 11. It is also called Jacobsen syndrome (JS) after the Danish researcher who first identified it in 1973. In this guide, both the names 11q terminal deletion disorder and Jacobsen syndrome are used.

People have Jacobsen syndrome if the bit missing from11q (from the middle or the end of the chromosome) includes at a minimum the following genes: *BSX, NRGN, ETS-1, FLI-1* and *RICS* (*ARHGAP32*). People who have lost a smaller part of 11q - and so fewer genes - have what is known as partial Jacobsen syndrome (Favier 2015).



Since the first report by Jacobsen more than 200 people with Jacobsen syndrome have been described in the medical literature (Favier 2015).11q terminal deletion disorder has been thoroughly studied and the clinical features are well known. Multilingual family support networks exist in Europe and North America, so there is no need for any family with a newly diagnosed child to feel isolated.

Chromosomes are the microscopically small structures in the nucleus of the body's cells that carry genetic information.They are numbered in size order from largest to smallest, from number 1 to number 22. We have two of each of these chromosomes, one inherited from our father and one from our mother, in addition to the sex chromosomes X and Y. Each chromosome has a short (p) and a long (q) arm. In most people with Jacobsen syndrome, one chromosome 11 is intact but the end of the long arm of the other has been lost. Chromosomes are made up of DNA and are the structures that carry genetic information (known as genes), telling the body how to develop, grow and function.

In most people the chromosome has been broken from band 11q23.3 and the end is missing (see figure). The size of the deletion differs from 7 to 16 Mb (7 to 16 million base pairs – DNA consists of base pairs) (Favier 2015).

The doctor who gives you the diagnosis - usually your geneticist, genetic counsellor or paediatrician - can tell you where the chromosome has broken.

In most people with Jacobsen syndrome, one chromosome 11 in each cell has the deletion but a few people have a mixture of cells with normal chromosomes. This is called mosaicism and usually makes the disorder less severe.

and less wrinkled than expected (pachygyria); the natural process of insulating the nerve fibres (myelinisation) is delayed (Mattina 2009).

Bones and limbs

Apart from early fusion of the bone plates of the skull (craniosynostosis), 14% of people with Jacobsen syndrome have been reported to have other anomalies affecting their bones. These may involve the spine: the hidden form of spina bifida (where one or more of the bones which form the backbone fails to form properly) has been observed, as has abnormal formation of part of the bones that form the backbone (vertebral body anomalies). Other anomalies involve the chest, and include an unusual number of ribs. Limbs may be short, and there may be additional fingers or toes. Around 20% of babies, children or adults have hip dislocation, a spinal curvature (scoliosis), flat feet or club feet (Mattina 2009).

Infections and ear infections

It is recommended to check the immune system of all children with Jacobsen syndrome. Contrary to what was previously thought, a recent Dutch study showed 6 children with Jacobsen syndrome were born immunodeficient. Features of the immunodeficiency are a reduced level of B and T lymphocytes (white blood cells involved in the immune system) and NK (natural killer) cells, also involved in immunity. The deficiency may be caused by the absence of the *ETS1* or *FLI1* genes. Further research is underway (Dalm 2015).

Ear and sinus infections are very common, (found in 42 out of 78 tested children, a rate of 54%), as they are in other children with chromosome disorders. The repeated infections may cause some measure of temporary hearing loss and many children need grommets (ear tubes). A few children will also have a degree of permanent hearing loss.

Hormonal aspects

A shortage of thyroid stimulating hormone (TSH), as well as a shortage of IGF (see Growth and appearance, pages 5-6) has been described in children with Jacobsen syndrome. It is important to test the *IGF1* and TSH levels in children with Jacobsen syndrome (Mattina 2009).

Adolescence

What little information exists suggests that puberty proceeds normally. Girls can have particularly heavy periods as a result of their underlying bleeding disorder and families should consult an endocrinologist.

As adults

There is little information available but it suggests that adults with 11q terminal deletion disorder can lead happy, semi-independent, fulfilling and worthwhile lives. Unique has members doing part-time voluntary and paid work in the community and living away from their families in supported independent housing.

Genitals and kidneys

Baby boys have an increased risk of being born with undescended testicles (testes). If the testicles do not come down naturally in time, they can be brought down and anchored in the scrotum with a small surgical operation.

Around one child in 10 has kidney problems. These include: a single kidney, double ureters (tubes leading from the kidneys to the bladder), hydronephrosis (swelling) and multiple cysts in the kidneys (Mattina 2009). These possibilities make it important to perform an ultrasound of the kidneys in children with Jacobsen syndrome.

Pyloric stenosis and other problems of the gastrointestinal tract

The risk of developing pyloric stenosis is much higher than in other babies. Babies with pyloric stenosis vomit forcefully and repeatedly because of a narrowing or blockage at the outlet from the stomach to the intestines. The condition tends to occur between two and six weeks of age and requires immediate surgery.

Other reported gut conditions include a small, narrow or blocked anus, or one that is located towards the front rather than the back of the body (anterior anus), intestinal obstruction caused by a missing part of the gastrointestinal tract (duodenal atresia), or by pancreas tissue encircling the gut (annular pancreas) as well as abnormal positioning of the gut (malrotation) (Mattina 2009).

Constipation

Constipation has been found in almost half of children with 11q terminal deletion disorder. Constipation is extremely common in babies and children with other chromosome disorders and is likely to be due in part to low levels of activity. If the remedies for other children (more fluid, more fibre, more exercise) are impractical, prescribed medication is needed.

Eye disorders

It is recommended that children with Jacobsen syndrome are seen by an ophthalmologist. The most common vision problems are an outward squint (strabismus) and either long or short sight, both of which can be corrected. A very unusual finding in a small minority of children is contorted blood vessels supplying the retina at the back of the eye, but this does not affect eyesight and it is uncertain what it means. Some children also have a 'keyhole' shape to the iris, called a coloboma, is a developmental defect and so long as the inner structures of the eye are not involved does not affect eyesight. Some children have cataracts (Mattina 2009).

Brain

Examination of the brain by ultrasound, CT or MRI scan or by autopsy has shown that 65% of people with Jacobsen syndrome have some structural abnormality of the brain. These include: enlarged ventricles with or without spinal involvement; brain atrophy (shrinkage); missing band of nerve fibres that link the right and left sides of the brain (agenesis of corpus callosum); the brain's surface is smooth

How is this disorder detected?

Magnified chromosomes can be seen under a microscope. Chromosomes from cells prepared from a blood sample are stained, giving them a 'barcode' appearance, then magnified as much as 900 times and examined. The broken chromosome 11 can normally be seen but to determine the breakpoint(s) more precisely, a molecular analysis such as FISH or microarrays is needed. Nowadays most people with Jacobsen syndrome are diagnosed by a technique involving microarrays. This shows more precisely where the chromosome has broken, and which genes are missing.

Genetic testing

Techniques that are commonly used include FISH and microarrays:

- Fluorescence *in situ* hybridisation (FISH) uses fluorescent dyes to visualise under a microscope the number of copies of small sections of chromosomes. Unique publishes a separate guide to FISH

However, rare chromosome disorders may be caused by subtle changes in the chromosomes that are too small to see using a microscope.

- Microarray comparative genomic hybridisation (array CGH) is a sensitive technique which shows gains (and losses) of tiny amounts of DNA throughout the chromosomes. Array CGH identifies duplicated, disrupted or absent DNA.

Why did this happen? Can it happen again?

To answer this question, the parents' chromosomes need to be examined. In 85% of families both parents have normal chromosomes. The 11q deletion has then happened as a one-off event and it is very unlikely that anyone else in the family will be affected. The technical term for this is de novo, meaning that the parents' chromosomes have been checked and no deletion or other chromosome change has been found at 11q23 or 11q24. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child. In this situation the possibility of having another child with Jacobsen syndrome is very small.

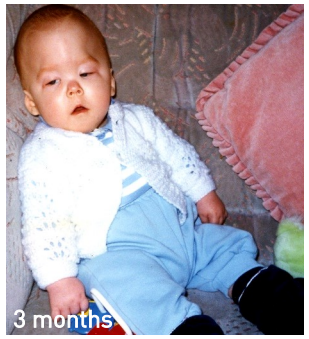
An unusual situation: mother and son with the same 11q24.2 deletion

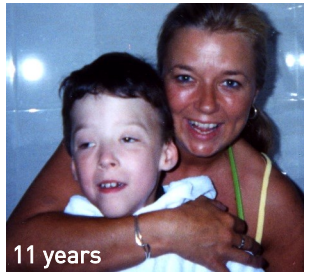
In 15% of families, one parent has a structural rearrangement of their own chromosomes. This is usually balanced so that all the genes and chromosome material are present and the parents are entirely healthy. However, in these families the risk of having another affected child is higher. Your genetics service can offer you an appointment to discuss your personal situation and chromosome testing when you are thinking about another pregnancy.

Whatever the reason, nothing that either parent did caused the chromosome change.


9 months


12 years


3 months


11 years

What are the most common features?

The most common features of Jacobsen syndrome in a child are:

- growth delay during pregnancy and later
- delay in development
- some typical facial features
- abnormal number and function of platelets in the blood
- sometimes an unusual number of blood cells
- deficient immune system
- developmental anomalies affecting the heart, kidney, gastrointestinal tract, genitals, central nervous system and skeleton
- problems with vision, hearing, hormones and the immune system (Mattina 2009).

Pregnancy and birth

Jacobsen syndrome can be diagnosed in pregnancy. An early pregnancy ultrasound scan showing for example nuchal thickening (at the back of the neck) may raise concerns, and later anomaly scans may show heart or kidney problems. A low level of amniotic fluid (oligohydramnios) has also been found (Mattina 2009). Non-invasive prenatal testing/screening (NIPT/S), using a blood sample from the mother, may be able to detect an increased chance of a fetus carrying an 11q deletion but an invasive testing procedure such as CVS (chorionic villus sampling) or amniocentesis is recommended for confirmation of the genetic change. A geneticist, or genetic counsellor can provide further advice regarding possible options for prenatal genetic testing.

Information on more than 200 people reported in the medical literature and a group of more than 60 people with Jacobsen syndrome shows that more than half (60%) of babies are born around the expected date of delivery. One baby in 10 is born after the expected date, and around 1 in 3 babies (30%) are born premature, that is, before 37 weeks of pregnancy (Mattina 2009).

In around half of pregnancies, there are no complications of delivery, but in just under half (46%) one of the following complications occurs: there is premature rupture of the membranes; the baby has problems; there is failure to progress during labour. Around 65% of babies are born by vaginal delivery, and 35% via Caesarean section. Birth weight is normal in 60% of babies. In around 1 in 3 (37%) birth weight is below the10th percentile - that is, the lowest 10% of the population - and in a very small number, around 3%, birth weight is above the 90th percentile - that is, the top 10% of the population.

Many babies need to stay in hospital because of feeding, heart or bleeding problems (see page 9).

Hand use and hand-eye co-ordination (fine motor skills) develop late but with early intervention and consistent occupational therapy, the great majority of children learn to feed and dress themselves, to write and to use a computer.

Medical concerns

Bleeding disorders

88.5% of children are born with a bleeding disorder known as Paris-Trousseau syndrome (Mattina 2009). This makes them liable to bruise easily or bleed copiously if any blood is taken and puts them at a raised risk of internal bleeding. Even a nosebleed can cause heavy blood loss. This is caused by deletion of the *FLI1* gene (Favier 2015). Deletion of the *ETS1* gene also seems to play a part in the development of thrombocytopenia (Carpinelli 2015).

The problem is two-fold – at birth babies have a low level of the platelets in the blood that help to form blood clots. Additionally, even when platelet levels rise to normal as they usually do during childhood, an abnormality in platelet function remains. The severity of the dysfunction is highly variable – it may be scarcely detectable or life-threatening – but Jacobsen syndrome children have a lifelong risk of heavy bleeding.

It is important to perform a coagulation test in children with Jacobsen syndrome. Further, platelets should be available to transfuse children with Jacobsen syndrome undergoing surgery; they should not take common medicines that interfere with platelet function, including ibuprofen; and they should be prescribed a desmopressin/vasopressin nasal spray (Desmospray, DDAVP) as this can speed clotting if heavy bleeding starts.

Heart conditions

Just under half of babies with Jacobsen syndrome are born with a healthy, normal heart, but a little over half of Jacobsen syndrome babies (56%) are born with a heart condition that may well need surgical repair (Mattina 2009). It is strongly recommended that all babies with Jacobsen syndrome should have a cardiac evaluation and be monitored every three years as some less severe conditions can develop over time.

The most common heart defects involve a hole between the left and right lower chambers of the heart (ventricular septal defect, VSD) or abnormalities on the left side of the heart (from which blood travels around the body), frequently affecting the aorta, the main artery leading from the heart. Hypoplastic left heart syndrome, an underdevelopment of the chambers and valves on the left side of the heart, is the most severe form. Hypoplastic left heart syndrome is found in 5% of babies with Jacobsen syndrome, making it 250 times more common than in other babies (Mattina 2009). These heart conditions may be caused by a missing *ETS1* gene. Further studies are underway (Favier 2015). Sadly, around 20% of babies with Jacobsen syndrome die before the age of 2 because of serious heart conditions and coagulation problems (Mattina 2009).

Behaviour

In the absence of published studies, information comes from families' experiences. Within a quite varied picture, these show a vulnerability in some children to behaviour disorders. Some children have challenging behaviour and have a tendency to be attention-seeking. Some children have spectacular tantrums, but these and any aggression usually lessen once language develops. Some children develop compulsive behaviour (such as shredding). Many are diagnosed with attention deficit hyperactivity disorder (ADHD). Overall, children appear to function better in a structured environment and there is a suggestion that they relate better to adults than to children of their own age. Families should seek early support if they are concerned, if their child starts hitting or biting others or shows any obsessive behaviour.

A recent study including 5 boys and 12 girls with Jacobsen syndrome (aged between 3 to 21 years old) showed that 8 of 17 children exhibited behaviour consistent with an autism spectrum disorder diagnosis. This means that it is important to check for any symptoms so early support can be offered. The size of the deletions ranged from 8.7 to 14.6 Mb. No link was found between the size of the deletion and the presence of autism. (Akshoomoff 2015).

Sleep

Families of 43 individuals aged 1-25 years with Jacobsen syndrome have taken part in a sleep survey (Maas 2008). This showed that the great majority (77%), including all six adults in the survey, did **not** have a current sleep problem. Around a quarter of individuals did have a sleep problem (occurring at least one night a week) and in some this was severe (occurring three or more nights a week). The most common problem was frequent night-waking, followed by early waking (before 5 am), and settling difficulties. Parents reported that over half the children (54%) had a sleep problem now or in the past. These problems lasted at least a year in most children.

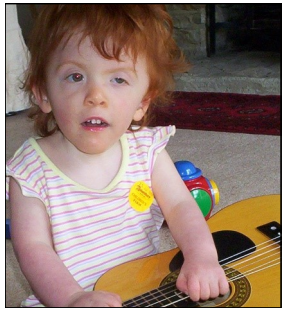
Other characteristics included restless sleep (60%), unusually high levels of daytime activity (41%) and insisting on having another person with them to settle or stay asleep (25%).

The percentage of children who have restless sleep (60%) is higher than in other disorders such as children with a severe intellectual disability (41%); children with any intellectual disability (21%); children with autistic spectrum disorders (45%); people with Angelman syndrome (25%); and people with Cri-du-chat syndrome (24%). Restless sleep may indicate a poor quality of sleep.

Development of motor skills

Children with Jacobsen syndrome will reach their developmental milestones somewhat later than other children – but they will reach them. Both the large group study and Unique's records show that all children learned to walk. Most children overcame hypotonia (floppy muscles, low muscle tone) to do so and some children also needed specific orthopaedic interventions to deal with problems such as talipes (club foot) and tight foot and calf muscles.

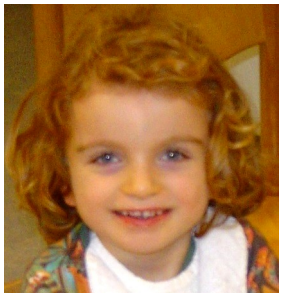
Feeding and weight gain



2 years
A surgical procedure can correct ptosis

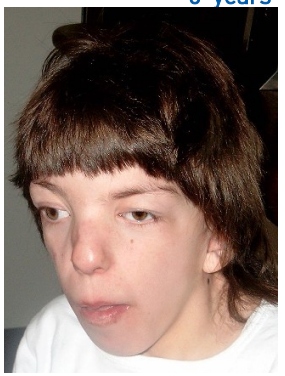
Many babies are reluctant to suck and find it hard to co-ordinate sucking with swallowing. Some babies also have reflux, when the contents of the stomach flush back up the food pipe. Most of the feeding difficulties are a result of low muscle tone and immature co-ordination and improve both with age and after heart surgery for babies with a cardiac problem. Babies with severe reflux that cannot be managed with careful positioning for feeds, sleeping with a raised cot-head and prescribed medication can be considered for a fundoplication, a surgical operation to improve the action of the valve at the lower end of the food pipe. Many babies and toddlers with Jacobsen syndrome benefit from a G-tube (a gastrostomy tube through which they can be fed direct into the stomach) as a temporary solution.

Around 1 in 3 children (34%) are a typical weight for their age. More than half (58%) weigh less than the 10th percentile (the lightest 10% of the population), and 8% weigh above the 90th percentile (the heaviest 10% of the population) (Mattina 2009).



5 years

Growth and appearance



13 years

Most children (75%) are short for their age, and many are in the lowest ten per cent of the population for height (Mattina 2009). Some of the very short children have a shortage of a type of growth hormone called IGF1 (insulin-like growth factor 1). All children with Jacobsen syndrome are recommended to have an evaluation of hormone levels by a paediatric endocrinologist. If your child is found to be deficient in this growth hormone, discuss the pros and cons of treatment with your child's endocrinologist.

Most children have slightly unusual facial features and you may notice similarities with other children with Jacobsen syndrome.

Some of the features that have been pointed out most frequently are:

Face: unusual skull shape (pointy forehead (trigonocephaly) and large skull); high, prominent forehead; asymmetric face

Head: a small head (microcephaly) in around 25%; an unusually large head (macrocephaly) in around 20%; a normal head size in around 50%

3 years

11 years

14 years

Eyes: wide set eyes (hypertelorism); a drooping upper eyelid (ptosis); small skin folds across the inner corners of the eyes (epicanthal folds); downslanting eyes (palpebral fissures)

Nose: the bridge of the nose is low and flat at first, but becomes raised and prominent with time; a short nose; a prominent columella (the visible part of the nose between the nostrils)

Ears: low set, and angled backwards (posteriorly rotated); unusual shape; small or underdeveloped lobes

Mouth: long or flat philtrum (the groove between the nose and the upper lip); V-shaped mouth; a thin upper lip

Jawline: the lower jaw is set back (retrognathia)

Neck: short and sometimes webbed, with a skinfold down the sides to the shoulders

Hands: some fingers joined by skin or tissue (syndactyly); thin fingers; unusual palm creases

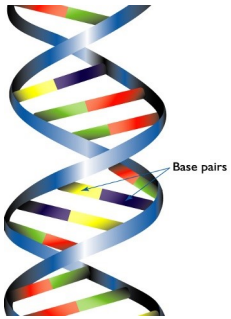
Feet: stubby, flat feet; large, long big toes; second and third toes joined by skin or tissue (syndactyly); crowded toes (Mattina 2009).

Most of these features are cosmetic but severe trigonocephaly can be relieved by a surgical operation to open the plates of the skull (craniotomy) and eyelids that obscure the pupil can be raised to ensure that vision develops properly.

Learning

A few children (3%) learn at a normal pace, but most children with Jacobsen syndrome (more than 97%) learn more slowly than their classmates in a mainstream class. Typically they have mild to moderate learning difficulties (Mattina 2009). A link has been suggested between the size of the deletion and learning ability (Mattina 2009), but in a recent article this link could not be confirmed (Fisch 2014). There is a very varied picture and it means that children with Jacobsen syndrome are recommended to have a detailed educational assessment to identify and build on their strengths. One factor that may undermine achievement is children's typically short attention span and easy distractibility, particularly in an unstructured learning environment. A recent study shows that some people with Jacobsen syndrome have behaviour consistent with an autism spectrum disorder diagnosis. This may be caused by absence of the *RICS* (*ARHGAP32*) gene (Akshoomoff 2015). This may have an effect on learning.

As of 2009, Dr Paul Grossfeld's team performed comprehensive cognitive assessments on 14 children with Jacobsen syndrome who had variable size deletions. The deletion sizes were categorised into small, medium, and large. All nine children who had a deletion size of at least 12.1 Mb (million base pairs of DNA, or about 7% of chromosome 11 missing), had significant, global cognitive impairments, whereas all children whose deletion was 11.8 Mb or less had much less severe impairment. This suggests that there might be a critical gene for brain development and/or function residing in the 0.3 megabase region that separates the smaller from the larger deletions. Interestingly, there are only three genes in this region. One of these genes, *BSX-1* (Brain-Specific Homeobox Protein) is a gene that is involved in the development of the brain. Dr Mathias Treier at the European Molecular Biology Laboratory in Heidelberg is the world's expert on this gene. In collaboration with Dr Grossfeld, he is studying the role of this gene in cognitive development. It is likely that this gene contributes to the more significant impairments that people with larger deletions have.



Base pairs and megabases

The curling blue bands in the image are DNA. The red-green and blue-yellow bands are the bonds between base pairs. The DNA is coiled up tightly into chromosomes. Your chromosomes contain about 3 billion base pairs. One million base pairs are called a megabase (Mb). One thousand base pairs are called a kilobase (kb).

1 base pair = bp 1,000 base pairs = 1kb

1,000,000 base pairs = 1Mb

Even tiny parts of missing chromosome are measured in hundreds of kilobases (hundreds of thousands of base pairs). A 12 megabase loss (12 million base pairs) is quite large.

Speech

Speech emerges late and children need support in using alternative means of communication (such as pictures and signing) until they can express their needs and feelings. The great majority of people with Jacobsen syndrome do learn to talk and some become fluent. However, this is not possible for all and many children understand (receptive language) at a higher level than they can talk (expressive language). In a small survey of 11 individuals, aged from 2½ to 26 years, researchers identified a number of features of the speech and language difficulties that they face. As four individuals were not yet speaking, the total number of responses to some questions was seven. Generally the nature and severity of difficulties varied considerably between individuals, with 7/11 having some speech and 4/11 communicating non-verbally. Most people (5/7) had difficulty in pronouncing all the sounds in their mother tongue and even more (6/7) had difficulty pronouncing those sounds as part of a word, so that words were typically simplified. Most (5/7) were hard or impossible to understand and only one individual always spoke intelligibly. While most (4/7) had a normal-sounding voice, in others the voice could sound too low, hoarse or loud and two individuals had difficulties with resonance. Two individuals were not fluent in the sense that they held on to a sound for too long, usually at the start of a word. Hearing loss was common, caused by glue ear due to frequent ear infections in 9/11 individuals.