Support and Information

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

11q Research and Resource Group
www.11qusa.org

Chief Medical Advisor Paul Grossfeld, MD
pdgmd@aol.com

Unique
Rare Chromosome Disorder Support Group,
PO Box 2189,
Caterham,
Surrey CR3 5GN,
UK
Tel/fax: +44 (0) 1883 330766
info@rarechromo.org
www.rarechromo.org

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 and has been verified by Dr Paul Grossfeld MD, paediatric cardiologist, University of California and by Professor Maj Hultén BSc, MD, PhD, FRCPath, Professor of Medical Genetics, University of Warwick, 2005. Revised 07/09.

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11q deletion disorder: Jacobsen syndrome

Version 1 of this leaflet is also available in Spanish, Dutch, German and French
11q terminal deletion disorder: Jacobsen syndrome

11q terminal deletion disorder is a rare genetic disorder. 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 leaflet, both the names 11q terminal deletion disorder and Jacobsen syndrome are used.

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 this chromosome disorder, one chromosome 11 is intact but the end of the long arm of the other has been lost.

The genes lost from the end of the long arm of chromosome 11 determine most of the effects of Jacobsen syndrome. In most people, the chromosome has broken in the bands called 11q23 or 11q24 and the end is missing. Some people have lost a part of this area of the chromosome and they are expected to have some of the typical features but not all. The geneticist or paediatrician can tell you where your child’s 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.

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. This is called a coloboma, is a developmental defect and so long as the inner structures of the eye are not involved does not affect eyesight.

- Infections and ear infections

Ear and sinus infections are very common, as they are in other children with chromosome disorders. However, researchers have found no evidence that children with Jacobsen syndrome have low levels of natural immunity and they should be immunised at the same age as other children. 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.

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.

Reading

Heart conditions
Around half of Jacobsen syndrome babies are born with a heart condition that may well need surgical repair. The most common heart defects involve a hole between the two 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. It is strongly recommended that all babies with 11q terminal deletion disorder should have a cardiac evaluation and be monitored every three years as some less severe conditions can develop over time.

Genitals
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.

Pyloric stenosis
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 develop between two and six weeks of age and requires immediate surgery.

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
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 babies is a very unusual finding in a small minority of

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. This will show more precisely which chromosome segments have been lost and helps in predicting the effects.

Why did this happen? Can it happen again?
To answer this question, the parents’ chromosomes need to be examined. In the great majority of families – over 90 per cent in the largest group of 110 people studied - 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 child with Jacobsen syndrome is the only person in the family known to be affected.

A de novo deletion will usually have occurred during the formation of the egg or the sperm and may perhaps be caused by a fragile site on the chromosome. Whatever the reason, nothing that either parent did caused it to happen and there was nothing they could have done to prevent it.

In a few families - under 10 per cent in the large group study - 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 when you are thinking about another pregnancy.

An unusual situation: mother and son have the same 11q24.2 deletion
How can I know how this disorder will affect my child?

Jacobsen syndrome is one of the most thoroughly and recently studied rare chromosome disorders. Drawing on a large study published in 2004 that looked at the effects on 110 people, its general effects and natural history can be described fairly accurately. All the same, this is still a small number and it is quite possible that as more people with this disorder are identified, new features will emerge that affect only a minority of people.

It is also very likely that people who have lost a smaller amount of chromosome material from 11q are less obviously affected and may not have been diagnosed. For these families, the description in this leaflet probably paints too bleak a picture.

On the other hand, babies with the syndrome who have very serious heart disease, particularly hypoplastic left heart syndrome where the chambers and valves on the left side of the heart are severely underdeveloped, may in the past not have survived, so this description would be too encouraging. Overall, it is the best picture that can be drawn at the moment.

Feeding and weight gain

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

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%); individuals with Angelman syndrome (25%); and individuals 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.

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

All children with 11q terminal deletion disorder are considered to have a bleeding disorder known as Paris Troussseau syndrome. This makes them liable to bruise easily or bleed copiously if any blood is taken and puts them at risk of internal bleeding. Even a nosebleed can cause heavy blood loss.

The problem is two-fold – at birth babies have a low level of the platelets in the blood that help to form blood clots (thrombocytopenia). 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.

This means that 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.
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.

**Behaviour**
The first formal study of behaviour in 11q terminal deletion disorder is under way. Until it is completed, 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). A few children attract a diagnosis of autism and 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.

**Sleep**
Families of 43 individuals aged 1-25 years with 11q terminal deletion disorder have taken part in a sleep survey. 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 5am), 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%).

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.

**Growth and appearance**
Most children are short for their age, and many are in the lowest five per cent of the population for height. Some of the very short children have a shortage of a type of growth hormone called IGF-1 (insulin 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 low set ears, a pointed forehead (caused by early joining of the plates of bone in the skull at the central metopic seam, and known as trigonocephaly), wide set eyes (hypertelorism), a broad bridge to the nose, down turned corners to the mouth, hooded or drooping eyelids (ptosis), a small lower jaw, folds of skin across the
inside corner of the eyes (epicanthic folds) and a small head.

Most of these features are no more than 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

Most children with Jacobsen syndrome learn more slowly than their classmates in a mainstream class, and typically they have mild to moderate learning difficulties. A few children learn at a normal pace and a link has been suggested between the size of the deletion and learning ability. There is a very varied picture and it means that children with 11q terminal deletion disorder 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.

As of 2009, Dr Paul Grossfeld’s team has recently performed comprehensive cognitive assessments on 14 children with Jacobsen syndrome who have 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 megabases (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 megabases 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 patients with larger deletions have.

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 speak 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