Jacobsen Syndrome

Description
Jacobsen syndrome is a rare chromosomal disorder that affects multiple aspects of physical and mental development. The estimated incidence of Jacobsen syndrome is 1 in 100,000 newborns. More than 200 affected individuals have been reported. More females than males have the disorder with 70–75% of cases being females. The life expectancy of people with Jacobsen syndrome is unknown, although affected individuals have lived into adulthood.

The syndrome derives its name from Dr. Petra Jacobsen, who first described an affected child in 1973. It is also known as 11q deletion syndrome or partial 11q monosomy syndrome because a specific region of one copy of chromosome 11 is missing. It is the loss of these genes that leads to the multiple problems found in Jacobsen syndrome.

Genetic profile
The loss of genetic material from a specific segment of chromosome 11q, which at least includes the critical region at band 11q24.1, leads to the manifestations of Jacobsen syndrome. There are several ways in which this portion of chromosome 11 can be deleted. In at least two-thirds of cases there is a partial chromosome 11q deletion (a terminal deletion) that begins at band q23 and extends through the end of the chromosome. The remainder of cases are attributed to the loss of this chromosome 11q genetic material due a deletion within, but not including the end of the chromosome (an interstitial deletion), or due to a chromosome rearrangement such as an unbalanced chromosome translocation or a ring chromosome. The size of the deletion varies with most affected people missing from about 5 million to 16 million DNA building blocks. In almost all affected people, the deletion includes the tip of chromosome 11. Larger deletions tend to cause more severe signs and symptoms than smaller deletions.

Most cases of Jacobsen syndrome are not inherited. They result from a chromosomal deletion that occurs as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family, though they can pass the chromosome deletion to their children.

Between 5 percent and 10 percent of people with Jacobsen syndrome inherit the chromosome abnormality from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation, in which a segment from chromosome 11 has traded places with a segment from another chromosome. In a balanced translocation, no
genetic material is gained or lost. Balanced translocations usually do not cause any health problems; however, they can become unbalanced as they are passed to the next generation. Children who inherit an unbalanced translocation can have a chromosomal rearrangement with some missing genetic material and some extra genetic material. Individuals with Jacobsen syndrome who inherit an unbalanced translocation are missing genetic material from the end of the long arm of chromosome 11 and have extra genetic material from another chromosome. These chromosomal changes result in the health problems characteristic of this disorder.

**Signs and symptoms**
The features of Jacobsen syndrome are related to the loss of multiple genes on chromosome 11. Depending on its size, the deleted region can contain from about 170 to more than 340 genes. Genes in this region appear to be critical for the normal development of many parts of the body, including the brain, facial features, and heart. Symptoms of Jacobsen syndrome are variable and the prognosis for an affected child depends on the presence of life-threatening birth defects or medical problems.

Those with Jacobsen syndrome have a distinctive physical appearance. The face is characterized by wide-spaced eyes, droopy eyelids (ptosis), redundant skin covering the inner eye, a broad or flat nasal bridge, a short nose with upturned nostrils, downturned corners of the mouth, a small chin, low-set ears, and a thin upper lip. Approximately 90–95% have a malformation of the skull, which may result from premature closure of one of the cranial sutures. Microcephaly is found in over one-third of cases. Affected individuals often have a skull abnormality called trigonocephaly, which gives the forehead a pointed appearance. Prenatal growth retardation occurs about 75% of the time. A newborn is usually small at birth and continues to have delayed growth and subsequent short stature. Feeding problems that can result in failure to thrive are also common.

Children with Jacobsen syndrome usually have some degree of developmental delay or mental retardation, ranging from mild to severe. Nearly all are either hypotonic or hypertonic as well as having fine and gross motor delays. Occasionally, brain abnormalities are present. Most also have cognitive impairment and learning difficulties. Behavioral problems have been reported, including compulsive behavior, a short attention span, and easy distractibility. Many have been diagnosed with attention deficit-hyperactivity disorder (ADHD).

Congenital heart disease is present in about half of affected children and, if severe, can pose a significant health problem. Other common internal abnormalities include pyloric stenosis, undescended testes, inguinal hernia, kidney defects, and urinary tract abnormalities. Craniofacial abnormalities such as strabismus, ptosis, colobomas, a high-arched palate, and
external ear anomalies are frequent. Orthopedic problems, mainly joint contractures and abnormalities of the fingers and toes; have been described in some cases.

In addition to congenital defects, there are a variety of other health problems found in individuals with Jacobsen syndrome. Illnesses including recurrent respiratory infections, sinusitis, and otitis media occur more frequently in children with Jacobsen syndrome. Gastrointestinal problems such as gastroesophageal reflux and chronic constipation may occur.

More than 90 percent of people with Jacobsen syndrome have a bleeding disorder called Paris-Trousseau syndrome. This condition causes a lifelong risk of abnormal bleeding and easy bruising. Paris-Trousseau syndrome is a disorder of platelets. Blood disorders such as thrombocytopenia and pancytopenia are often seen in childhood and may improve with time.

**Diagnosis**
Diagnosis usually occurs after birth. It is usually made through genetic testing of blood in an infant or child who has mental retardation and atypical facial appearance. The karyotype will show a deletion or rearrangement of the longer segment, known as the q arm, of one copy of chromosome 11. Jacobsen syndrome can also be diagnosed before birth through amniocentesis after an ultrasound demonstrated one or more fetal abnormalities. Another technique, known as FISH (fluorescent in-situ hybridization), may be used to further define the chromosome 11q deletion breakpoints; this is being done on a research basis to identify the disease-causing genes in the Jacobsen syndrome critical region.

**Treatment and management**
There is no cure for Jacobsen syndrome nor is there a therapy that can replace the missing genes from the deleted segment of chromosome 11. In addition to routine pediatric exams, there are management strategies and treatments that aim to prevent or minimize some of the serious health consequences associated with Jacobsen syndrome.

At the time of diagnosis a series of evaluations should be undertaken in order to appropriately guide medical management. Pediatric specialists in genetics, cardiology, orthopedics, ophthalmology, and neurology should be consulted, especially since some problems can be treated if caught early. Important tests may include a karyotype, a cardiac echocardiogram, a renal sonogram, a platelet count, a blood count, a brain imaging study, hearing and vision screenings, and a dental exam.

A neurodevelopmental evaluation should be initiated at the time of diagnosis with implementation of age-appropriate early intervention services such as speech therapy, occupational therapy, and physical therapy. An ear, nose, and throat specialist may be needed
to treat problems such as otitis media. Craniofacial and neurosurgery consults may be indicated if trigonocephaly or other forms of craniosynostosis are present.

Some children may require a gastroenterology specialist to evaluate problems such as failure to thrive, chronic constipation, and/or severe gastroesophageal reflux, some or all of which may require surgical intervention. Boys with Jacobsen syndrome should be examined for undescended testes, a problem found in half of males and one that often requires surgery.

**Prognosis**

Approximately 25% of affected children die before two years of age mainly from cardiac defects, a tendency to bleed, or infection. Except for respiratory infections, the remainder of children are usually healthy. Little is known about the course of this syndrome in adulthood, and the life expectancy for those who live beyond age two is unknown.

**References**


