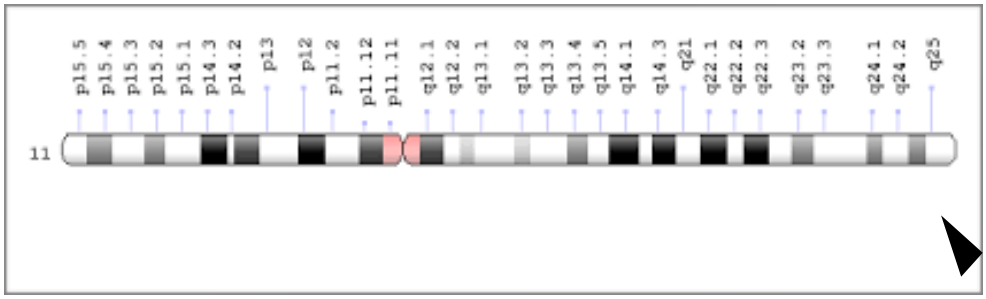
Jacobsen Syndrome

Jacobsen syndrome is a complex of abnormalities caused by the deletion of the distal segment of the long arm of chromosome 11. The syndrome was first reported by Danish scientist Petrea Jacobsen and her colleagues in 1973.



Jacobsen syndrome is a relatively frequent condition. At least 500 patients with this syndrome have been reported so far (including ~160 patients who had an additional chromosomal imbalance, mainly due to familial translocations). However, in at least 85% of patients the syndrome is a result of a sporadic mutation[1]: patients with an unusual cytogenetic picture (or with an unusual phenotype) are being preferentially published.

The clinical picture of this syndrome includes problems with psychomotor development, a complex of birth defects and facial dysmorphism (this triad is common for almost all syndromes caused by an autosomal imbalance) as well as hematological abnormalities and immunodeficiency. The last two conditions are specific for Jacobsen syndrome.

The clinical picture of the syndrome includes prenatal hypoplasia, postnatal growth delay and a complex of facial dysmorphic features: high prominent forehead, hypertelorism, downslanting palpebral fissures, epicanthus, ptosis, short nose with anteverted nares, small low set ears – sometimes with hypoplastic earlobes, thin upper lip and micrognathia[1]. Some patients may reveal more serious eye defects: iris coloboma or cataract. Most newborns have short necks, sometimes with webbing. Brachydactyly and partial syndactyly of 2-3 toes are common. However, serious defects of the extremities are rare. Microcephaly is a rare manifestation of the syndrome.

A relatively common abnormality is trigonocephaly, a result of the premature closure of the metopic suture causing a triangular shaped forehead. This abnormality may be found in 25-30% of patients. Sometimes treatment of trigonocephaly requires surgery. Surprisingly, other forms of craniosynostosis are exceptionally rare.

Structural defects of the internal organs are very common. More that 50% of patients have heart defects. Although most of these defects are not life-threatening at least 5% patients reveal hypoplastic left heart syndrome (HLHS) – a very serious condition which may be lethal. Although HLHS may be sporadically found in other chromosomal disorders, the incidence of this form of heart defect in Jacobsen syndrome is unusually high.

Abnormalities of the gastrointestinal tract which occur in ~25% of thoroughly examined patients include pyloric stenosis and ano-rectal defects (mainly anal stenosis or anal ectopia).

Defects of the kidneys are also common. They are reported in more than 10% of patients. These defects may be serious (cystic or dysplastic kidneys) but most patients have double urethers and mild hydronephrosis.

Delay of psychomotor development is virtually an obligate characteristic; 97% of patients show differing degrees of retarded development. It was shown that there is a direct correlation between the degree of psychomotor delay and the size of the deletion: larger deletions lead to more severe delay. Behavioral problems include attention deficit hyperactivity disorder and autism.

At least 85% of patients with this syndrome reveal a low number of platelets (thrombocytes) – thrombocytopenia or an association of thrombocytopenia with a low number of other white cells in the blood (pancytopenia). Although neonatal thrombocytopenia may be resolved in older children, the functional disability of platelets usually persists. This form of platelet disorder is called the Paris-Trousseau syndrome. There are reports of increased intracranial hemorrhages in patients with Jacobsen syndrome[2].

Detailed examination of patients shows that many have immune deficiency which may predispose them to serious infections[3]. This defect of antibody production is one of consequences of deletion 11q.

The vital prognosis of patients depends basically on the condition of their heart, immune system and hematological picture. If a patient has reached 2-3 years of age the vital prognosis is relatively favorable.

Surprisingly the syndrome occurs in females more often than in males.

The application of molecular methods shows that the loss of 8-12 Mb of distal 11q is necessary to produce all the characteristic manifestations of the syndrome. At the same time an isolated loss of 2-3 Mb of terminal 11q25 does not cause its full picture. Most likely the 11q24 segment may be critical. However even very sophisticated methods can not yet provide precise information about the etiology of each symptom. The gene ETS1 seems to be a good candidate for left-sided heart defects, but existing studies cannot definitely confirm its role[4]. The loss of the FLI1 gene is considered responsible for thrombocytopenia[4], but other scientists do not confirm this finding[5].

Developmental delay is likely caused by the combined action of several genes because patients with larger deletions as a rule reveal more severe developmental delay.

The deletion of an area of 4 genes (including the gene ARHGAP32) seems to be responsible for the development of autism[6].

Generally there is no strong correlation between the size of the deleted segment, the position of the breakpoints and the severity of the clinical consequences: sometimes patients with smaller deletions reveal more severe defects than patients with larger deletions.

Although Jacobsen syndrome is considered to be a result of a terminal deletion there is no doubt that interstitial deletion del 11q24q25 may cause the same manifestations even if the terminal 2-3 Mb of 11q is preserved.

In most cases deletions are sporadic. However, up to 15% of patients may have an imbalance caused by parental translocations or inversions. That is why cytogenetic examination of the parents is necessary to calculate the recurrence risk of the syndrome in further children and to make reproductive decisions.

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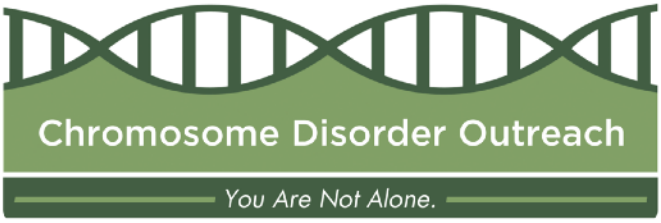

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