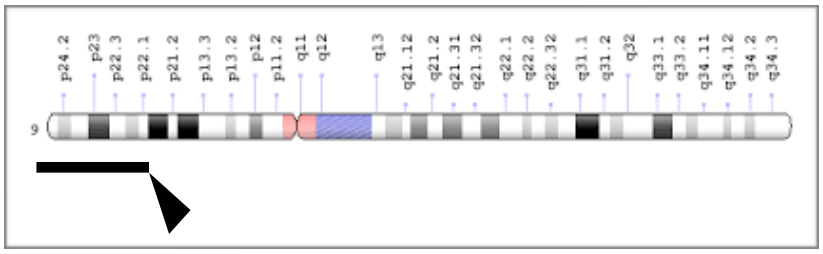
Deletions of the Distal Segment of 9p: Alfi Syndrome

The syndrome caused by the deletion of the distal segment of 9p was delineated in 1973 by Alfi et al. Sometimes this condition is reported as Alfi syndrome. This syndrome is a well known entity: not less than 400 patients with distal 9p deletion have been reported so far. At least 40% of these patients have an additional chromosomal imbalance, but even in these cases manifestations of distal 9p deletion have the main role in the clinical picture.



Although patients may lose different segments of 9p – from 9p22 to 9p24, contemporary methods show that the loss of the most distal segment 9p24 is sufficient to produce the complete picture of the syndrome.

From the clinical point of view this syndrome causes an association of delay in psychomotor development, characteristic defects of the skull and complex facial abnormalities. The most typical sign of distal 9p deletion syndrome is trigonocephaly – a keel-shaped abnormality of the skull, which occurs due to premature fusion of the frontal bones[1,2]. In 9p deletion syndrome the premature fusion of other cranial bones occurs relative rarely.

Facial dysmorphism includes hypertelorism, epicanthus, midface hypoplasia, anteverted nares, elongated philtrum, microstomia (small mouth), and abnormally formed ears. The neck is usually short, especially in small kids.

The association of these features and trigonocephaly allows one to suspect Alfi syndrome even before a cytogenetic examination. Cleft palate occurs in ~10% of patients, cleft lip is

exceptionally rare. Choanal stenosis or atresia and glaucoma (relatively rare manifestations in other chromosomal syndromes) were repeatedly found in patients with distal 9p deletion.

Usually small children reveal hypotonia (low muscle tone). Motor development of such children is behind their healthy peers[3]. Seizures are uncommon, but may be present in some patients.

At least 10-15% children with distal deletion 9p have congenital heart defects, but in most cases these defects are relatively mild.

Hypoplasia of the corpus callosum may be found upon special examination. 20-25% of patients have inguinal or umbilical hernias.

The most common defect of the gastro-intestinal system is omphalocele (defect of the abdominal wall, when intestines remain outside of the abdomen). Other gastro-intestinal abnormalities are very rare. However, gastro-esophageal reflux and constipation are relatively common. Defects of the kidneys are uncharacteristic.

A significant number (up to 20%) of patients with distal 9p deletion have disorders of sex development: hypoplastic male genitalia, hypospadias, ambiguous genitalia or even complete gonadal dysgenesis. In the latter case normal female external genitalia may be found in patients with an XY set of sex chromosomes. Dysgenetic tumors of the gonads (mainly gonadoblastoma) may occur in patients with complete gonadal dysgenesis. It has been shown that a deletion of the *DMRT1* gene is responsible for the production of genital abnormalities[4]. The *DMRT1* gene is located at 9p24.3 (the most distal part of 9p) and therefore deleted in virtually every patient with distal 9p deletion. However genital defects occur only in some patients. It has been shown that genital defects are more frequent in patients who have deletion 9p along with an additional chromosomal imbalance. In that context it has been proposed that the deletion of the *DMRT1* gene per se is necessary but (in most cases) not sufficient to produce defects of the genital organs[5]. It may be true also for glaucoma, choanal atresia and omphalocele: all these defects are more frequent among patients having an additional chromosomal imbalance.

The vital prognosis is relatively favorable, especially in patients without serious heart defects.

There is no cure for this syndrome. Patients may need neurosurgery for correction of the skull defect, and rarely - heart surgery. They must be observed and treated by occupational therapists, speech therapists and psychologists.

In most patients the syndrome is the result of a sporadic chromosomal mutation, but in ~15% of families it is caused by balanced abnormalities (usually translocations) in one of the parents. That is why parental cytogenetic examination is necessary especially for families planning to have more children.

There is another syndrome caused by the deletion of more proximal part of 9p (9p21.3). This segment contains the *CDKN2A-B* genes. Deletion of these genes causes various types of tumors including melanomas, astrocytomas, breast cancer etc. This condition is unrelated to the syndrome of the distal 9p deletion (Alfi syndrome).

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