



Chromosome 18

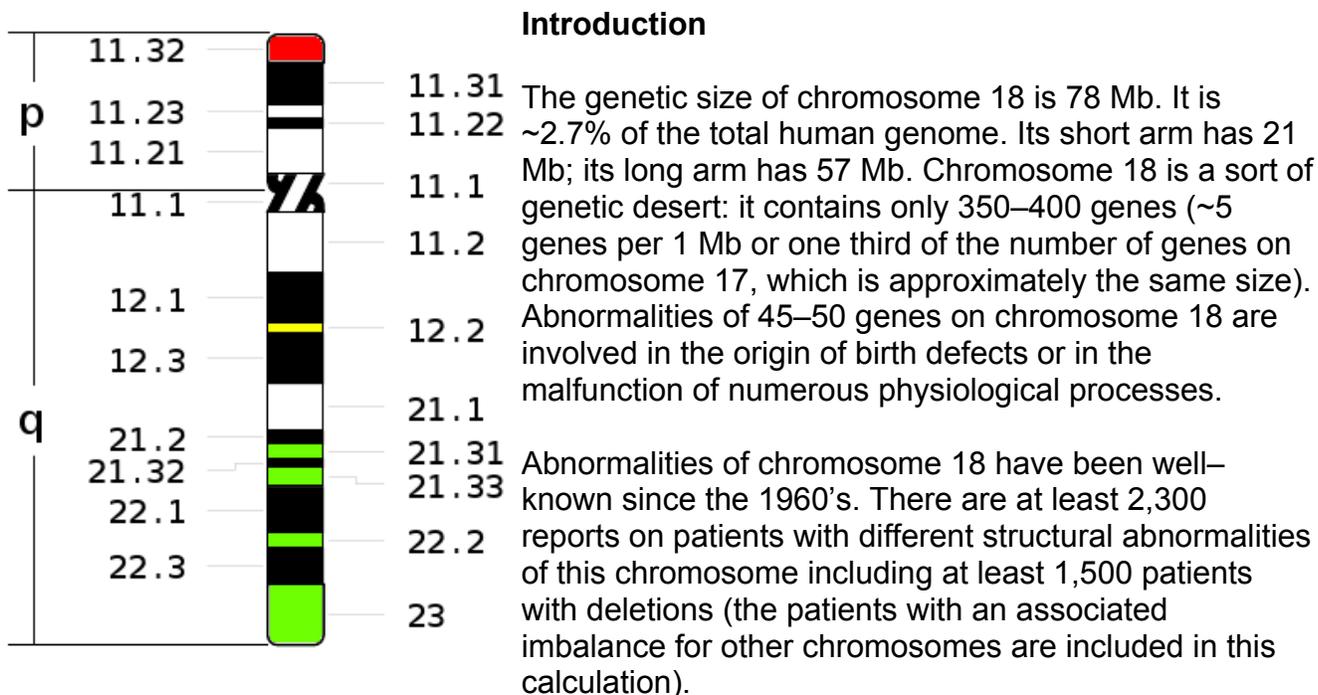
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David Adler.hum_18.gif



There is one syndrome caused by the deletion of the short arm (~600 reported persons). Most patients with deletions of the long arm have distal deletions of 18q, which forms a well-known syndrome. During recent years, it was shown that several patients with Pitt-Hopkins syndrome have not only mutations of the TCF4 gene, but deletions of the whole area of 18q21.2, which contains this gene. The clinical picture of persons with proximal deletions of 18q (18q11–18q21) is not characteristic enough for a delineation of any syndrome.

Deletions of Chromosome 18

The genetic size of chromosome 18 is ~78 Mb, where the short arm is ~21 Mb, and its long arm is ~57 Mb.

Deletions of 18p

Deletions of the short arm of chromosome 18 (or monosomy 18p) have been known since the early 1960's. Actually, it was one of the first conditions which was found to be caused by a structural autosomal imbalance. More than 300 patients with this deletion (as a sole abnormality) have been reported, at least 150 more patients had partial monosomy 18p in

association with partial trisomies for other chromosomes (mainly as a result of translocations) or with partial trisomies of 18q (as a result of inversions).

The size of the deletion varies. Most patients reported in the 1960s–1980s had deletions of the whole short arm (this kind of deletion can be diagnosed easily). Most patients reported more recently have relatively small deletions affecting only the distal part of 18p (18p11.3). Almost all deletions of 18p are terminal.

Some authors believe that this syndrome may be found in 1:50,000 newborns. However this number seems to be too high.

If many syndromes caused by chromosomal deletions (Wolf–Hirschhorn syndrome, cri–du–chat syndrome, Alfi syndrome (del 9p), etc.) can be diagnosed upon clinical examination of the child, a clinical picture of monosomy 18p is not so clear, and its clinical diagnosis needs to be confirmed by cytogenetic examinations.

Clinically there are two sub–types of monosomy 18p: del 18p with holoprosencephaly (HPE) and without HPE. The distal part of 18p (18p11.3) contains the gene TGIF, which is one of the HPE–related genes. Deletion of this gene may lead to HPE — abnormal development of the brain, which is non–divided (or incompletely divided) into hemispheres. Severe forms of HPE may be associated with facial abnormalities, including cyclopia, cebocephaly, or HPE with premaxillar agenesis (in this form of HPE, the patients have medial cleft of the upper lip, cleft palate, underdeveloped nasal bridge and hypotelorism — an unusually small distance between the eyes). Milder forms of HPE manifest itself by microcephaly, single central incisors or some “mild” brain anomalies, which can be observed only upon MRI or CT–examination. HPE (in severe forms) is a life–threatening condition. Although the TGIF gene is missing in all (or almost all) patients with monosomy 18p, HPE is found in a relatively small proportion of patients (5–10%). The reasons of this phenomenon are not clear. Most likely, TGIF is a relatively “weak” HPE–related gene, and some additional factors (genetic or environmental) are needed for development of HPE even in persons with only one copy of the gene. In this context, it may be noted that, in patients with iso–chromosome 18q (when monosomy 18p is associated with trisomy 18q), the incidence of HPE is ~35–40%, although trisomy 18q itself does not produce HPE. It shows that the participation of other genes is a necessary condition for the formation of HPE after the loss of the TGIF gene.

The vast majority of patients with monosomy 18p do not have any signs of HPE. Clinical manifestations in this group of patients include expressionless round face, ptosis (usually bilateral), wide mouth with short philtrum, high palate, irregularly set teeth, large floppy ears, and short neck. Microcephaly is not a typical sign of the syndrome. The hands are relatively short and wide. Most patients with monosomy 18p have short stature. Some of these patients have growth hormone deficiency: treatment with growth hormone may be beneficial. The combination of short stature and the above–mentioned external characteristics can resemble patients with Turner syndrome.

Defects of internal organs are not characteristic. Different types of heart defects are mentioned in ~10% of patients. Defects of the lungs, kidneys, gastro–intestinal tract are exceptionally rare. Because visceral malformations are absent, the vital prognosis is good and most patients (without HPE) survive until adulthood.

Some patients may have juvenile diabetes, thyroiditis, rheumatoid arthritis and other auto-immune disorders. Small subsets of persons with monosomy 18p have alopecia or other rare skin disorders (keratosis pilaris).

There are several reports of dystonia (a movement disorder when involuntary muscle contractions cause twisting or repetitive movement). This condition, which may be caused by the deletion of the DYT7 gene, is found mostly in patients above 20 years of age.

Mental development is affected in all patients, but the degree of impairment may vary from severe delay to borderline normal intellect. The average IQ is about 50. There are several reports on women with del 18p and borderline mental development who had their own children (and became diagnosed after deletion 18p was found in their children or upon prenatal diagnosis).

Behavioral problems (autism, depression) are uncommon, although they are found in significantly higher numbers than in persons with a normal karyotype.

There were several attempts to map various clinical manifestations to the areas of 18p. It was found that ptosis and short neck are related to the loss of the proximal part of 18p, whereas a round face may be caused by the deletion of the most distal regions of 18p.

Genetic counseling regarding further children requires cytogenetic examination of the parents: not only for inherited translocations and inversions, which are responsible for 10–15% of deletions, but also direct transmission from minimally affected parents should be taken into consideration, as these individuals have a 50% chance to pass the deletion on to each of their children.

Deletions of 18q

Deletions of the proximal part of 18q are relatively rare. There is no clinical syndrome associated with such deletions. However, it should be noted that several of these patients had cleft palate (with the common deleted area of 18q12.1q12.3), seizures (with the common deleted area of 18q12.2q12.3), obesity (with the common deleted area of 18q12.2q21.1) and autism (with the common deleted area of 18q12.2q21.1). Most likely, this part of 18q contains genes determining cleft palate and is involved in the development of seizures, obesity and autism.

Pitt–Hopkins Syndrome

In 1978, Pitt and Hopkins described two patients with a significant delay of psycho-motor development, postnatal microcephaly and an unusual breathing pattern, when paroxysms of hyperventilation may be followed by apnea. This complex of abnormalities, called Pitt–Hopkins syndrome, is considered to be an autosomal-dominant condition.

Clinical manifestations of the syndrome include coarse face, deep-set eyes, broad nasal bridge, wide mouth with everted lower lip, and widely spaced teeth. Epileptic seizures are a frequent (but not obligatory) manifestation of this condition. Attacks of hyperventilation are not associated with epileptic changes but may be increased by fatigue. Malformations of internal organs are not characteristic.

The delay of psycho–motor development is usually serious; speech is most severely affected. At the same time, most patients have a happy disposition. An association of psycho–motor delay, happy disposition and coarse facial features may resemble Rett syndrome or Angelman syndrome.

Several years ago, it was found that this condition is caused by mutations of the TCF4 gene located at 18q21.2. Deletions involving 18q21.2 (with the loss of the TCF4 gene) produce the same clinical picture. At least 20 patients with Pitt–Hopkins syndrome caused by deletions of 18q21.2 are currently known. However, at least 10–12 patients with this deletion were described as having Rett–like syndrome or an unspecified association of microcephaly, coarse facial features and seizures. The size of the deletion varies in different patients; each had a unique localization of breakpoints.

Some data shows that “large” deletions (affecting the whole TCF4 gene) are responsible for ~35% of all patients with Pitt–Hopkins syndrome. Other children have mutations or small deletions within the TCF4 gene. Clinical manifestations are almost identical in both groups, although seizures seem to be more frequent in patients having mutations within the TCF4 gene.

To date, all reported observations of the syndrome deletions were sporadic.

“Distal” deletions 18q

Usually the deletions affecting 18q21.3 or more distal segments of 18q are considered “distal” deletions. The descriptions of the syndrome may be found also under the names “monosomy 18q” or “de Grouchy syndrome” (Jean de Grouchy was the French geneticist who published the first “official” report about this condition). The syndrome caused by the distal deletions is well–known. Since the early 1960’s, when first observations of this syndrome were noted, there have been at least 350 patients found with this deletion.

The syndrome is relatively frequent: some estimates show that about 1 in 40,000 babies are born with this condition. In 15–20% of patients, the deletion is associated with trisomies for other chromosomes (due to translocations), trisomy 18p (due to pericentric inversions) or with some other types of imbalance. Only patients with distal deletions as a sole abnormality will be the object of this analysis.

Children with this syndrome are usually born at term after normal pregnancies. Although the mean birth weight is slightly bit less than normal, prenatal hypoplasia is not typical. Postnatal development is significantly delayed: most babies have hypotonia (low muscle tonus) or poor reflexes. Typical facial abnormalities include hypoplastic mid–third of the face, low–set ears, “carp–like” mouth (when the mouth turns down at the corners), but these abnormalities are usually noticed by a pediatrician or geneticist. MRI studies showed a delay of normal myelination (myelin is a substance that covers the nerve cells). The beginning of myelination is delayed in children with del 18q, and they never achieve normal levels. Poor reflexes and tremor may be caused by these defects of myelination. Post–natal microcephaly is relatively common.

Vision may be affected in some patients. Most of them have squint or nystagmus. Structural defects of the eyes (colobomas) or abnormalities of the optic nerve are uncommon.

Approximately 15% of patients have cleft palate, sometimes in mild form (bifid uvula). Cleft lip, however, is uncommon.

Abnormalities of the ears and hearing defects are typical. In almost 50% of patients, the auditory canals are narrow or even closed. These findings are relatively specific for distal deletions of 18q: atresia (abnormal closure) of auditory canals occurs very rarely in patients with other chromosomal deletions. As a result, most patients have different degrees of hearing impairment. In some patients, hearing loss may be severe.

Anomalies of the hands are usually very mild. Many patients have tapering fingers and/or a proximal position of the thumbs with shortened first metacarpal bones. Postaxial polydactyly is uncommon, although it was found in several patients with del 18q. Many infants are born with clubfoot or “rocker–bottom” feet. Later in life some patients may develop scoliosis. Orthopedic treatment may be necessary for the patients having these problems.

Defects of genital development are basically mild, although most boys have hypoplastic penis and/or cryptorchidism. Girls may have hypoplastic labia minora, but pubertal development in the girls is almost normal. There were several reported when mildly affected females with del 18q had their own children (of course, 50% of these children have a chance of being affected).

Different types of heart defects are found in 25–30% of patients. Although most of these defects are relatively mild, some children may have tetralogy of Fallot or other serious abnormalities that require surgical treatment and affect life expectancy.

Defects of the kidneys (mostly dilation of ureters or vesico–ureteric reflux) are reported in ~10% of affected persons. Defects of the gastro–intestinal tract are uncommon. Life expectancy is almost normal (at least for patients without life–threatening heart defects).

Most children and adults with del 18q have short stature. The level of growth hormone in these patients is usually less than normal. Treatment with growth hormone may be beneficial for these patients. Another common endocrine problem is hypothyroidism, which may be found in 15–20% of patients.

Delay in psycho–motor development is very common, but the degree of this delay varies. Although 70% patients have an IQ < 70, some persons have only mild learning disability.

Seizures are reported in ~25% of patients with distal deletions. They occur mostly in small children and are usually well–controlled by medications. Recent publications showed that children with distal 18q deletions are more likely to be autistic than children with a normal karyotype.

Children with del 18q are predisposed to different infections. It may be caused by a decreased level of immunoglobulin A (IgA) — an antibody that normally resists the occurrence of infections. Another problem is a frequent occurrence of asthma and other allergies.

There are many studies about the mapping of various clinical abnormalities to different segments of 18q. It was shown that the segment 18q21.33 is critical for the formation of

microcephaly; underdevelopment of the ear canals depends on the genes located at 18q22.3. Delayed myelination and growth hormone deficiency are caused by the genes located at the distal tip of 18q. Generally, the patients with larger deletions are more severely affected, and vice versa.

Prognosis for further children depends on parental karyotypes. The risk is negligible if the deletion occurred “de novo”. The risk will be 50% for the woman who has del 18q (there are no reports about male patients having their own offspring). If one of the parents has a translocation or inversion risk, it will depend on the type of rearrangement and sex of the carrier. Prenatal diagnosis in such families allows making decisions by knowing the fetal karyotype.

Ring Chromosome 18

Ring chromosome 18 is the most frequent form of ring autosome. There are at least 210 reports of patients having this chromosomal abnormality. Seventeen of these patients had mosaicism with a normal clone, five had mosaicism with a monosomic clone, five had mosaicism with a 18p- clone, one with 18q- clone, and six had other forms of mosaicism. Actually, the situation is even more complicated: molecular examination showed the existence of partially duplicated areas of chromosome 18 even in some patients with r(18).

The clinical pictures in patients with r(18) are very heterogeneous. The main reason is the involvement of different sizes of deletions of the genetic material from 18p and 18q.

A delay in physical and psychomotor development is common for almost all patients with r(18). Clinical manifestations of the deletion of the long arm (microcephaly, narrow or atretic (closed) auditory canals, coloboma of the iris and choroid, and heart defects) are more visible than the possible effect of the loss of the short arm (a short neck, for example). The only exception is holoprosencephaly, caused by the deletion of the TGIF gene on 18p11.3. However, holoprosencephaly is relatively rare even in patients with del 18p and a confirmed loss of the TGIF gene. There are only ~12 patients with holoprosencephaly among persons with r(18). The presence of often unrecognized partial trisomies for 18p (or 18q) may provide some additional findings, not typical for deletions of 18p or 18q. As a result, there are numerous reports of patients with r(18) with clinical manifestations not characteristic for deletions of the short or long arms of chromosome 18 (hydrocephaly, cloverleaf skull, cataract, cleft lip, hypoplastic thymus, lip fistulas, choanal atresia, Chiari malformation, abnormal lobation of the lungs, etc.).

Familial transmission of r(18) has been reported in seven families. In these families, the abnormal chromosome was inherited from mildly affected mothers.

Partial Trisomies for Chromosome 18

Partial trisomies 18p

Reports of partial trisomy 18p in association with another chromosomal imbalance are numerous, but the number of known patients with “pure” trisomy 18p is very limited. There are only 50 people with such trisomies, including those who did not have any abnormalities but were investigated as parents or siblings of children with partial trisomy 18p and clinical

abnormalities.

There is no recognizable syndrome associated with trisomy 18p.

Basically patients with partial trisomy 18p show a relatively mild delay in psychomotor development, mostly without significant facial dysmorphism. Microcephaly, as well as macrocephaly, which are reported in several patients, are not typical manifestations of this condition. There are sporadic reports of microphthalmia, coloboma, preauricular tags and microtia (i.e. very small ears).

No patients had cleft lip or palate. Defects of extremities are sporadic, and they include joint laxity, brachydactyly, and osteoporosis (two patients, each), preaxial polydactyly, and camptodactyly. Two more patients had unspecified foot anomalies and unspecified abnormalities of the extremities.

Six patients out of 50 had congenital heart defects, but all of these defects were mild and not life-threatening. Defects of the gastro-intestinal system were reported twice – one patient had anal atresia and the one had pyloric stenosis.

Defects of the kidneys are also rare: hydronephrosis (2) and horseshoe kidney (1). At least two girls had abnormalities of the uterus. Three patients were obese.

Epileptic seizures were reported in 5 out of 50 patients (10%). There also are reports of autism and schizophrenia in people with pure trisomy 18p.

Duplications of 18p (especially relatively small ones) may be inherited from healthy parents. Therefore, cytogenetic (including molecular cytogenetic) examination is necessary for families planning further children.

Partial trisomies 18q

Trisomy 18 is a well known syndrome. Affected patients have severe prenatal hypoplasia, microcephaly, characteristic craniofacial dysmorphism, and multiple congenital anomalies, including, almost constantly, defects of the heart and frequent defects of kidneys. A significant number of patients with trisomy 18 has esophageal atresia, omphalocele, and underdevelopment of the radial bones and thumbs.

There are multiple facts evidencing that trisomy 18q plays a decisive role in the origin of the above-mentioned defects. For example, many patients with isochromosome 18q (who have trisomy for the whole 18q in association with monosomy for the whole 18p) have typical manifestations of trisomy 18. In that context, partial trisomies of 18q could be considered as anomalies, which may be helpful to assign some morphological defects to specific areas of 18q. However, the real situation is much more complicated.

Pure partial trisomies of 18q are relatively rare: there are only ~83 reports of patients having trisomy 18q as the only chromosomal abnormality. This number includes all trisomies – from trisomies for the whole long arm of 18 to very small trisomies (< 1 Mb) recognizable only using methods of molecular cytogenetics.

The clinical manifestations depend both on the size of the duplicated segment and on the individual characteristics. The same duplication may be found in several people in the family: one with a significant abnormality and another without this defect (and sometimes a completely normal phenotype).

It seems very difficult to give any general characterization of the patients with trisomies of 18q.

A small subgroup of patients with trisomy for the whole 18q (18cen-qter) or with almost a whole 18q trisomy (18q11qter) have many congenital defects typical for trisomy 18. Manifestations in patients with trisomies for smaller segments of 18q usually are not as severe.

Facial dysmorphism (consistent in patients with larger trisomies) may be absent in persons with small duplications.

Heart defects are the most common. They were found in 21 out of 83 patients. Most defects are not life-threatening. Ventricular septal defects (as an only heart defect or in association with other heart abnormalities) is especially common (15 patients). Nine patients had patent ductus arteriosus, four had atrial heart defects, and coarctation of the aorta was reported three times. Heart defects are much more common in patients with trisomies involving 18q11 or 18q12 (14/35) than in patients with more distal trisomies (7/48).

The same is basically true for kidney defects (absent kidney, pelvic kidney, pyeloectasia, and vesico-ureteral reflux) which were found in eight patients. Most of them had trisomies involving 18q11 or 18q12 (6/35), and only two were trisomic for the more distal areas of 18q.

Not a single reported person with trisomy 18q had esophageal atresia. Two patients (both with trisomy for 18q11.2) had anal atresia.

Two persons with radial defects also had trisomies for the proximal part of 18q. Out of three patients with omphalocele, two had trisomies 18q12.1, and one had trisomy 18q23. It means that 18q has to include at least two areas which, when duplicated, may produce this defect.

Both patients with holoprosencephaly had trisomy for the whole 18q. Three patients had Dandy-Walker malformation: the critical segment for this defect is 18q23. Most other defects were reported sporadically and do not provide sufficient information about the possible location of genes responsible for these abnormalities.

Generally, it is most likely that the segment 18q11q12 contains most genes responsible for phenotypic manifestations of trisomy 18. This conclusion, however, has to be confirmed by further investigations.

Tetrasomy 18p

The first reports of patients with a small additional metacentric chromosome, now recognized as isochromosome 18p, were published in the 1960's. For the past 20-25 years, an additional isochromosome 18p is considered to be a clinical syndrome.

There are at least 170 reported patients with this condition. Almost all patients have an additional isochromosome 18p in all cells, whereas almost all patients with an additional isochromosome 12p and a significant number of the patients with an additional isochromosome 9p are mosaics (and have some cells without the isochromosome).

The patients with an additional isochromosome 18p are born at term. The mean birth weight is 2,500 g (between the 3rd and 10th percentile). The newborns usually have growth retardation, problems with neonatal feeding, muscular hypertonia, and abnormal deep reflexes.

A delay in psychomotor development is a constant manifestation of the syndrome. These children usually began to roll from side to back, crawl, sit, walk, or speak considerably later than other children. Special studies showed, for example, that the mean age for independent sitting is 16 months (six months is more typical), the mean age for independent walking is 33 months (12 months is more typical). All developmental milestones are affected approximately to the same degree.

Microcephaly is reported in ~50% of affected patients. However, the vast majority have "borderline" microcephaly. Severe microcephaly is not typical.

Facial dysmorphism includes low set ears, high arched palate, small mouth (microstomia), and sometimes a small chin. The neck may be short and webbed. However, these dysmorphic features are neither constant nor specific. Cleft palate or bifid uvula is reported less than in 5% of the patients (7/170).

Mild defects of the loco-motor system are much more common. They include scoliosis or kyphosis (35% of patients), contractures, camptodactyly, and hip dislocation. There are sporadic reports of arthrogryposis, limb shortening, cervical ribs, fused ribs, and proximally inserted or adducted thumbs. However, no patients had polydactyly or ectrodactyly.

Congenital heart defects are the most common internal abnormalities. They are found in ~20% of patients. The vast majority of these defects are mild and usually do not require surgical treatment. A life-threatening defect (interrupted aortic arch) was reported only once.

The most common gastro-intestinal defect is pyloric stenosis reported in eight patients. Other defects are exceptionally rare, although there are reports of esophageal atresia (1) and anal ectopia (2).

Defects of the urinary system include hydronephrosis (2), horseshoe kidneys (5), and vesico-urinary reflux (2), but there are no cystic or dysplastic changes.

Structural brain defects are uncommon. There are several reports of hypoplastic corpus callosum (4) or hypoplastic cerebellum (2). Surprisingly, at least eight patients had myelomeningocele (spina bifida), but there are no reports of anencephaly or encephalocele. Spina bifida is a relatively rare manifestation of chromosomal abnormalities, although it may be found in trisomy 18.

Approximately 20% patients develop seizures. Anxiety or psychosis is reported in at least five patients with tetrasomy 18p.

In all reported families, an additional isochromosome 18p was a result of a new mutation.