



Chromosome 9

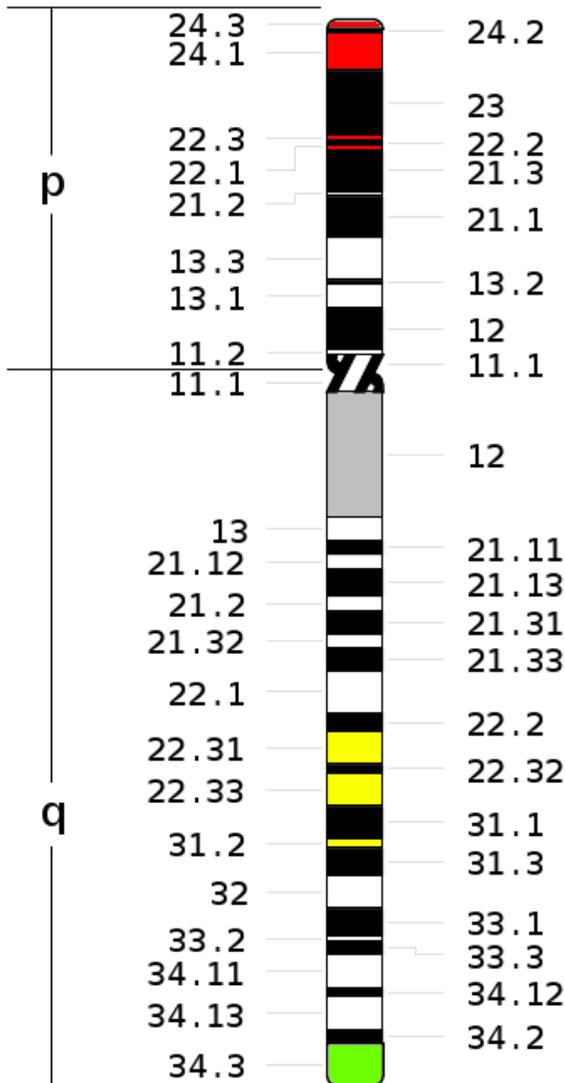
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David Adler.hum_09.gif



Introduction

The genetic size of chromosome 9 is ~140 Mb. It is ~4.5% of the total human genome. The length of the short arm is ~41 Mb; the length of the long arm is ~99 Mb.

Chromosome 9 contains between 900 and 1,200 genes. Many of these genes play a crucial role in the development of body organs and sustaining functional activities.

At least 2,300 persons having different structural defects of chromosome 9 have been reported so far. For this chromosome, the number of persons with partial trisomies is higher than the number of persons with deletions. Although the long arm of chromosome 9 is twice as long as the short arm, the total number of known patients with deletions of the short arm (~600) is much larger than the number of known persons with deletions of the long arm (~250). [Both patients with deletions of chromosome 9 as the only abnormality and patients with an associated imbalance for other chromosomes were taken into consideration for these estimates].

Surprisingly enough, there is only one well-known syndrome caused by deletions of the distal part of 9p (Alfi syndrome). Clinical manifestations of this condition depend on the size of the lost genetic material. Isolated

deletions of the proximal part of 9p are very rare and are not considered to be a syndrome.

There are two syndromes caused by deletions of the long arm: Gorlin syndrome caused by the deletion of 9q22.3 and a syndrome caused by a distal deletion of 9q34.3. Deletions of the large (~40 Mb) segment between 9q22.3 and 9q34.3 do not constitute any currently recognizable syndrome. Most likely, new techniques of chromosome study in the nearest

future will allow delineation of these conditions.

Deletions of Chromosome 9

The genetic size of chromosome 9 is ~147 Mb, where the short arm is ~41 Mb. Although it is a relatively large chromosome, there are only three clinical syndromes caused by deletions of this chromosome: one syndrome caused by the deletion of the short arm and two syndromes caused by deletions of the long arm.

Deletions of 9p

The only well-known syndrome caused by a deletion of the short arm of chromosome 9 sometimes is called Alfi syndrome because the first description of this condition was made by Alfi et al. in 1973. At least 320 patients with 9p deletion syndrome have been described, including ~150 patients where the deletion of 9p was not accompanied by duplications of other chromosomal segments. Only the patients with “pure” deletions of 9p will be the object of clinical analysis.

Most patients who were described in the 1980s–1990s had relatively larger deletions with breakpoints at 9p22 or 9p23. The new methods introduced in the 2000s allowed recognizing smaller deletions (with breakpoints within 9p24).

The major manifestations of the syndrome are trigonocephaly and a complex of relatively unspecific manifestations, including delay in psycho-motor development, facial abnormalities (hypertelorism, epicanthus, flat nasal bridge, midface hypoplasia, anteverted nares, long philtrum, malformed and posteriorly angulated ears, micrognathia), short neck and hypotonia. Trigonocephaly (a V-shaped abnormality at the front of a skull), which is a result of the premature fusion of the frontal bones, is a hallmark of this syndrome. It was reported in 50% of patients. Other types of craniosynostosis in del 9p are rare. The above-mentioned dysmorphic features are found in almost all patients, but usually a single patient has only some of these abnormalities. Cleft palate or bifid uvula are found in 10% of patients.

Congenital heart defects are reported in 15% of patients. Almost all of these defects were relatively mild and non-life-threatening. Some patients have hypoplasia of the corpus callosum, narrow auditory canals and impaired hearing. At least 20% of patients have inguinal or umbilical hernias. Choanal atresia was noted in several patients. Omphalocele is not a common sign (it was found in 5 out of 150 patients with isolated deletions of 9p), but it is much more common than in patients with most other chromosomal deletions.

A significant number of patients with del 9p have a wide spectrum of disorders of sex development. These abnormalities may be manifested as complete gonadal dysgenesis (normal external female genitalia in persons with an XY karyotype), ambiguous genitalia or hypospadias. Some female patients have hypoplastic uterus.

It should be noted, however, that most patients with severe abnormalities of sexual development do not have trigonocephaly. Conversely, most patients with trigonocephaly have normal development of sex organs.

Genetic Background of Two Main Defects of the 9p Deletion Syndrome

Trigonocephaly and genital abnormalities were objects of special studies. However, to date, there is no final answer regarding the mechanisms of these defects. Most authors believe that trigonocephaly is caused by a deletion of a small region within 9p22.3 (~ 15 Mb from the telomere). At the same time, trigonocephaly was found in several patients with more distal deletions. It may be caused either by the second critical region in 9p24.1 or by positional effects affecting the expression of genes responsible for trigonocephaly.

The genes responsible for abnormalities of genital development are also unknown, although three DMRT genes, located at 9p24 are the most likely candidates. All of these genes are involved in pathways of sex determination. A very distal location of these genes explains the frequent absence of trigonocephaly in patients with 9p-related genital abnormalities.

Deletions of 9p are very frequently associated with duplications of other segments of 9p [such associations are usually sporadic] or with the duplication of other chromosomal segments caused by translocations [mostly inherited].

There are ~20 reports on patients with “proximal” interstitial deletions of 9p (mainly 9p12–9p22). All of these patients had different manifestations, and no syndrome associated with “proximal” interstitial deletions of 9p has been delineated so far.

Deletions of 9q

Deletions of the proximal part of 9q (9q11–9q21) are rare. There are not more than 15 reports about deletions of this area. Some patients in this group did not have significant clinical abnormalities. The manifestations in other patients are heterogeneous and do not allow delineation of any syndrome.

Deletions of 9q22.3 and Gorlin Syndrome

Gorlin syndrome (or basal cell nevus syndrome) is an autosomal dominant condition. The main manifestations of this syndrome are multiple tumors, involving mostly the skin (basal cell carcinomas) and the brain (medulloblastomas). Another typical manifestation is multiple anomalies of the skeleton (anomalies of cervical and thoracic vertebrae, bifid or fused ribs, pectus excavatum, syndactyly, short 4th metacarpals). Some patients have macrocephaly, coarse facial features, frontal bossing or hypertelorism. The syndrome is caused by mutations of the PTCH gene, located at 9q22.3. Mental development of the patients with Gorlin syndrome, caused by mutations of the PTCH gene, is usually normal. Small children do not have any tumors, and most patients are diagnosed in the second or third decade of life.

Clinical manifestations of Gorlin syndrome also may be found in patients with deletions of 9q22 involving [but not limited to] the PTCH gene. There are some patients with deletions of 9q22 without manifestations of Gorlin syndrome. This may be caused by several reasons: 1) the deletion did not involve the PTCH gene; 2) patients were too young for typical clinical manifestations; 3) the syndrome did not occur despite the deletion of the PTCH gene. At least 42 patients having deletions involving 9q22 have been reported in the literature. 21 of them (50%) had typical manifestations of Gorlin syndrome, including multiple tumors. Seven patients had facial and skeletal manifestations of the syndrome, but did not have tumors (at least at the moment of description). Fourteen patients did not have any signs of Gorlin syndrome.

Deletions in almost all patients also involved more proximal segments of 9q (mostly 9q21) or more distal segments of 9q (9q31). As a result, most patients also had abnormalities atypical for Gorlin syndrome. Different forms of craniosynostosis were mentioned in 9 patients (including 6 with trigonocephaly), 9 had hydrocephaly, 5 had postaxial polydactyly. Cleft palate (or cleft lip and palate) were noted in 5 patients. Hydronephrosis, dilated renal pelvices or hydroureter were reported at least 6 times. Seven patients had various heart defects. Some patients had seizures, agenesis of the corpus callosum, hearing loss, cataract, retinal detachment, inguinal and umbilical hernias.

Craniosynostosis, heart defects, hearing loss and cleft palate are most likely caused by involvement of 9q31, because these abnormalities were reported in several patients with del 9q31 (without loss of 9q22).

Clinical manifestations in the group of patients having deletions 9q31–9q33 are not characteristic enough to delineate any syndrome. It should be noted, however, that the deletion of 9q33.3 (involving the NR5A1 gene) may cause XY–sex reversal: occurrence of female external genitalia in patients with a male (XY) set of sex chromosomes.

Deletion of 9q34.3 Syndrome

This syndrome, caused by the loss of the distal segment of 9q (9q34.3), became known only during the last several years. It is not surprising because “standard” cytogenetics is not sensitive enough to find such small deletions. More than 100 patients with this syndrome have been reported, including ~75, where deletions 9q34.3 were “pure” (not accompanied by partial trisomies for other chromosomes, which may affect phenotypic manifestations).

The patients usually have normal weight, length and Apgar score at birth, but hypotonia is obvious, usually in the first months of life. Delay in psycho–motor development is typical, but the severity of the delay may vary significantly between children. Most patients have an absolute or relative microcephaly, although head circumference at birth is usually normal. Typical facial manifestations include flat face, hypertelorism, synophrys or arched eyebrows, short nose with depressed nasal bridge, protruding (sometimes large) tongue. Not a single feature is obligatory, but most patients have at least several of these dysmorphic features.

Some patients have brachydactyly, clinodactyly or partial syndactyly. Others have tapering fingers.

Hearing impairment is very common. It was reported in ~20% of patients (and some children were too young for hearing testing).

Heart defects were found in 29 of 70 patients, but most had relatively mild defects, including ventricular septal defects (14), atrial septal defects (13), patent ductus arteriosus (6), pulmonary stenosis (4) [several patients had a combination of several defects, e.g. atrial and ventricular septal defects]. In some children, ventricular septal defect and patent ductus arteriosus closed spontaneously. Only 3 children had tetralogy of Fallot (2) and a double outlet right ventricle (1).

Hypospadias was noted in 5 boys.

Some authors reported obesity as a typical manifestation of the syndrome. Actually, however,

it was mentioned only in 5–6 patients.

Malformations of the brain, intestinal tract and kidneys are not typical, although there are sporadic reports of hydrocephaly, agenesis of the corpus callosum, pyloric stenosis, diaphragmatic hernia, omphalocele, agenesis of one kidney, etc.

A significant number of patients develop seizures, usually well–controlled by medications. Many patients with del 9q34.3 have antisocial or autistic behavior (although a number of known patients were found during a study of children with autism).

The clinical manifestations are relatively non–specific. All (or almost all) patients were referred for cytogenetic examination due to developmental delay and facial dysmorphism, not to rule out deletion 9q34.3.

The publications by Stewart and Kleefstra (2007) and Kleefstra et al. (2009) may provide further details about this condition.

Most clinical features of the syndrome are caused by a deletion of the EHMT1 gene, located at 9q34.3. The role of this gene in development remains not very clear, but absence of this gene produces all manifestations of 9q34.3 deletion syndrome. It was shown that a “tiny” 0.4 Mb deletion involving the EHMT1 gene is sufficient to cause a clinical picture of the syndrome. Loss of 3–4 Mb of the more proximal area of 9q34 does not produce additional symptoms. Some patients may have interstitial deletions; others have terminal deletions. Loss of the EHMT1 gene seems to be critical. Several patients with mutations within the EHMT1 gene had the same phenotype as the patients with deletions. On the other hand, patients with interstitial deletions 9q34 where the EHMT1 gene was preserved did not have typical features of the syndrome.

From the genetic point of view, almost all interstitial deletions are sporadic. At least 25% of del 9q34.3 (and at least 50% of deletions 9p) are caused by parental rearrangements, which have to be excluded (or confirmed) for decision about further genetic prognosis.

Ring Chromosome 9

Since 1970, ring chromosome 9 has been reported in 50 patients. Two of these patients were mosaics with a normal clone, one was a mosaic with a 9p– clone, one was a mosaic with an add 9p clone (unknown additional material on the short arm of chromosome 9), and one had r(9) in association with a small duplication of 4q.

Only 8 of 50 patients did not have serious structural defects. Other patients had numerous abnormalities, including trigonocephaly (13 patients), ambiguous genitalia or XY–sex reversal (6 patients), or hypospadias (5 patients). Both trigonocephaly and sex reversal (or ambiguous genitalia) are the hallmarks of the 9p– syndrome (Alfi syndrome). Other manifestations of Alfi syndrome (e.g., exomphalos or choanal atresia) also have been reported in r(9) patients.

Two other groups of abnormalities — cleft palate and heart defects — may be attributed both to the loss of 9p and to the loss of 9q. Congenital heart defects were found in 16 patients, including tetralogy of Fallot (3) and ventricular septal defects (8). Cleft palate was reported in 8 patients. Numerous other defects (microcephaly, hypoplastic corpus callosum, cloudy

cornea, hearing impairment, hypothyroidism, deficiency of growth hormone, absent thumbs and radial structures, micromelia (shortened limbs), preaxial polydactyly, pyloric stenosis, hydronephrosis, and single kidney) were also reported in several patients.

Direct transmission of the r(9) from a parent to a child is not known.

Partial Trisomies of Chromosome 9

Trisomies of 9p

Trisomy for the short arm of chromosome 9 is a well known condition. The syndrome was described in 1970 by Rethore et al., and sometimes this condition may be reported as Rethore syndrome.

Trisomy 9p exists in several cytogenetic variants: a) pure trisomy for the whole (or almost whole) short arm of 9p; b) pure trisomy for the distal part of 9p (9p21–pter); and c) trisomies for 9p in association with an imbalance for 9q or for other chromosomes. Because an imbalance for another chromosome may change the clinical picture of the syndrome, this group will not be analyzed here. There are two other sub–types specific for 9p. One is tetrasomy 9p, when the patient has four copies of the short arm of chromosome 9 as an additional metacentric chromosome. The mechanism of the origin of such an additional chromosome is similar to the mechanism for the origin of an additional iso–chromosome 8p (and for iso–chromosomes 12p and 18p, which will be analyzed later). Another sub–group — the formation of dicentric chromosome 9 — is unique for this chromosome.

The total number of reported patients with all variants of trisomy 9p is ~500. It was shown that a partial trisomy for the distal part of 9p (9p22–pter) causes all typical (or basic) symptoms, and trisomy (or tetrasomy) for additional segments of 9p may produce additional clinical manifestations.

Trisomy 9p is a well recognized entity. Clinical diagnosis in most patients with this syndrome is possible upon physical examination of the patient, and cytogenetic testing is necessary basically for the confirmation of clinical diagnosis and genetic prognosis for further pregnancies. It does not mean, however, that some patients with this syndrome may not have atypical phenotypes. At the same time, the diagnosis is based not on some unique manifestations, but on the complex of dysmorphic features, each of whose may be found in patients with numerous other syndromes.

Distal trisomy 9p

Trisomies for the distal part of 9p are known in at least 68 patients (excluding numerous reports of distal trisomy 9p in association with partial monosomies for other chromosomes as a result of different translocations).

Prenatal hypoplasia is not typical; most patients are born at term with normal length, weight and head circumference. However, almost all children are shorter than healthy children of the same age, and 60–65% will have a head circumference below normal. Typical facial abnormalities include high broad forehead, brachycephaly, downward slanting of palpebral fissures, deep set eyes, hypertelorism, strabismus, bulbous nose, high arched palate, large

mouth with downward corners, short philtrum, and large and poorly lobulated low set ears. Short neck (sometimes with excessive skin folds) is also common.

Abnormalities of the loco-motor system are a second important group of clinical findings. Usually (in 80–90% of patients), the hands and feet are relatively short. The distal phalanges of the fingers and toes are especially hypoplastic (or may be completely absent). The nails are usually hypoplastic or may be even absent on some fingers and toes. These manifestations are found in 65–70% of the affected patients. At least 50% of the patients have scoliosis or hyperlordosis. Dislocations of the hips and other large joints are relatively uncommon: they were reported in three out of 68 patients with pure distal trisomy 9p.

Almost all patients have a significant delay in psycho-motor development, but most of them are relatively minor. Seizures are uncommon. Several patients in this group had hearing impairment. Cleft lip and palate were found in four patients in this group.

Structural abnormalities of the brain, eyes, and internal organs are relatively rare: two patients in this group had cerebellar hypoplasia, two others had Dandy-Walker anomaly (DWM) (an association of hypoplastic cerebellar vermis and cystic dilatation of the fourth ventricle). The critical segment for DWM is 9p21.2. Macrocephaly and hydrocephaly were found in one patient each. Three patients had microphthalmia.

Defects of the heart were reported only twice in this group: one child had ventricular septal defect (VSD), another had cardiomyopathy. Three patients had abnormalities of the urinary system (one had dysplastic kidneys and two had abnormalities of the ureters).

Complete Trisomy 9p

There are almost one hundred reports on patients with complete pure trisomy 9p. The basic difference between this group and distal trisomy 9p is the presence of additional material from the proximal part of chromosome 9 (cen-p22 or p11-p22). These patients have all manifestations of distal trisomy 9p and may have some additional symptoms.

There are no significant differences in intellectual development between patients with complete trisomy 9p and distal trisomy 9p.

Cleft lip and palate were reported in five out of 97 patients. Three children had hearing impairment. Hydrocephaly was found in three patients. Structural eye defects are a little bit more common and more severe than in patients with distal trisomy 9p: three patients had microphthalmia; there are sporadic reports of anophthalmia, coloboma, eccentric pupil, ectopia lentis; and five patients had high myopia.

Congenital heart defects were found in ten out of 97 patients, including VSD (3), stenosis of the pulmonary artery (2), patent ductus arteriosus (2), patent foramen ovale, coarctation of aorta, and Ebstein anomaly (a condition, when the opening of the tricuspid valve is displaced toward the apex of the right ventricle). Most likely, the proximal segment of 9p (p11-p22) contains genes, which, when duplicated, may lead to heart defects.

Dislocations of the large joints (7/97) seems to be more common than in patients with distal trisomies. These include dislocations of the knees and elbows, which are relatively

uncommon forms of limb defects.

Basically, the group with complete trisomy 9p is very similar to the group with distal trisomy 9p. Only dislocations of large joints and congenital heart defects seem to be more common.

Tetrasomy 9p

There is a significant group of patients who have an additional metacentric chromosome which comes from two copies of the short arm of chromosome 9. Both arms of the iso-chromosome are genetically identical. As a result, the patients have four copies of all of genes of the short arm, including one copy of the genes from one parent and three copies of the genes from another parent.

All patients with an additional iso-chromosome 9p may be subdivided into non-mosaics (with an additional iso 9p chromosome in all cells) and mosaics (who have both cells with an additional iso 9p and cells with a normal karyotype). Out of 55 known patients with iso-chromosome 9 — 27 were mosaics and 28 were non-mosaics. Mosaicism may be caused by 1) a post-zygotic origin of the iso-chromosome, or by 2) the loss of an additional iso-chromosome upon cellular division. In any case, clinical manifestations in patients with mosaicism are less severe.

Basically, the patients with iso-chromosome 9p have the same spectrum of birth defects. However, all of these defects occur much more frequently than in the patients with trisomy 9p.

Structural defects of the brain are very common for patients with non-mosaic tetrasomy 9p: seven of them had DWM, five had agenesis of the corpus callosum, and two had hydrocephaly. Cleft lip and palate occur in more than 50% of patients with complete tetrasomy 9p. Heart defects are also very common (12 out of 28), including three life-threatening defects (tetralogy of Fallot, transposition of the great arteries, hypoplastic left heart). At least three patients had persistence of the left superior vena cava (PLSVC) — this defect usually does not produce significant hemodynamic disturbances, but occurs relatively rarely in persons with other chromosomal defects). Dislocations of the large joints (shoulders, elbow, hips, knees) were reported in ten out of 28 patients. Defects of the kidneys were found in 11 persons, including dysplastic kidneys (3) and hydronephrosis. Two patients had sternal tag — pedunculated skin and subcutaneous tissue originating from the sterna area. As PLVSC, this defect is a very rare manifestation of chromosomal disorders, although it is not clinically significant. Detailed characteristics of patients with complete tetrasomy 9p are presented in Table 1.

Table 1: Main characteristics in patients with iso-chromosome 9p and dicentric chromosome 9

Abnormality	Iso-chromosome 9p		Dicentric chromosome 9 (n=45)
	Complete (n=28)	Mosaics (n=27)	
Hydrocephaly	2	2	9
Dandy-Walker malformation	7	1	10

Aggenesis of corpus callosum	5	–	3
Defects of cerebellar vermis	4	–	–
Craniosynostosis	–	1	2
Cleft lip/palate	15	4	11
Microphthalmia	1	–	5
Stenosis of auditory canals	–	2	3
Deafness	–	–	2
Heart defects, total	12	4	20
Life-threatening defects	3	2	3
VSD	1	1	10
ASD	3	1	4
PDA	2	1	4
PLSVC	3	–	4
Contractures	5	–	6
Dislocation of large joints	10	1	11
Colon malrotation	1	–	4
Hirschsprung's disease	–	–	2
Abnormal lung lobation	1	–	3
Pigmentary defects	–	3	2 (mosaics)
Kidney defects	11	1	12
Hydronephrosis	3	–	5
Horseshoe kidney	–	–	3
Dysplastic kidney	4	–	1
Polycystic kidney	–	–	1
Double ureter	1	–	1
Other	3	1	1
Sternal tag	2	–	1
Ambiguous genitalia	2	–	–

The patients with mosaicism (n=27) have the same spectrum of defects, but they occur with significantly lesser frequency. Detailed information about the forms or distribution of these defects may be found in Table 1.

Dicentric Chromosome 9

There is a group of patients who have tetrasomy, not only for the short arm, but also for the proximal segment of the long arm of chromosome 9. This may occur if chromosome 9 breaks in the area of 9q11, 9q12 or even 9q21 and forms an additional centromere. As a result, the chromosome has two centromeres (this explains the term dicentric), although only one centromere remains functionally active. Of course, the person with a dicentric chromosome will have tetrasomy not only for the whole short arm, but also for the segment between the original centromere and a neo-centromere (that is, tetrasomy for the segment 9cen-q11(q12, q21)).

These patients (there are at least 45 reports on such patients) have manifestations of tetrasomy 9p. Only any additional symptoms may be attributed to tetrasomy for the proximal segments of 9q. Basically (see Table 1), the patients with dicentric chromosome 9 have the same spectrum of brain defects (hydrocephaly, DWM, agenesis of the corpus callosum), cleft lip and palate, congenital heart defects (with the same proportion of life-threatening forms, but actual forms of pathology included truncus arteriosus and hypoplastic left heart), dislocations of large joints, and defects of the kidneys. The only abnormalities described in patients with dicentrics (but not mentioned in the patients with iso-chromosome 9p) were Hirschsprung's disease (noted in two patients with dicentrics) and horseshoe kidney (reported in three patients with dicentrics). However, these defects occur too rarely to be attributed to the tetrasomy for the proximal region of 9q.

Two patients with pigmentary abnormalities and dicentric chromosome 9 were also mosaics (as well as three patients with mosaic iso-chromosome 9p). Most likely, these pigmentary defects are caused by mosaicism itself, but not by the genetic content of duplicated chromosome.

As a result of the frequent occurrence of significant defects of the brain, heart, and kidneys, vital prognosis for most patients with dicentric chromosome 9 and non-mosaic tetrasomy 9p is very serious.

In all families, pure trisomy 9p, iso-chromosome 9p, and dicentric chromosome 9 were results of sporadic mutations. Therefore, the prognosis for future pregnancies in such families is favorable. It is not so for the families with partial trisomy 9p in association with another chromosomal imbalance caused by translocations, where prognosis will depend on the type or translocation and sex of the carrier.

Trisomies for 9q

Proximal trisomies 9q

Information about the phenotypic consequences of pure trisomies for the proximal segment of 9q is very scanty. 5-6 reported patients with such abnormalities do not show any pattern of anomalies. In that context, the best way to evaluate the clinical significance of these trisomies

is to compare pure trisomy for the whole 9p and trisomy for the whole 9p in association with trisomy for the proximal segment of 9q.

There are many reports on patients with an additional chromosome that consists of the whole 9p, the centromere, and part of 9q. In most of these patients, only small a part of 9q (up to 9q13) is duplicated. Analysis of this sub-group (there are 53 patients with trisomies 9p + a region of 9q through 9q13) shows that they reveal the same spectrum and the same frequency of abnormalities as patients with pure trisomy for the whole 9p. Above typical (for trisomy 9p) cranio-facial and skeletal manifestations, they reveal cleft lip and palate (3/53 vs. 5/97 in patients with pure trisomy 9p), congenital heart defects (5/53 vs. 10/97 in pure trisomy 9p), and single reports of hydrocephaly, DWM, agenesis of the corpus callosum, and horseshoe kidney. Basically, it means that trisomy for the segments 9q11–q13 does not cause additional abnormalities.

A smaller group of patients (n=27) have trisomies for 9p in association with a more significant segment of 9q (usually to 9q21 or 9q22, but seven of these patients have trisomies for 9cen–q31, 9cen–q32, or even 9cen–q33). Surprisingly, these patients have basically the same spectrum of abnormalities, but all defects occur much more commonly. Congenital heart abnormalities were reported in 9/27 patients, cleft lip and palate in 9/27, DWM in 4/27, dislocations of large joints (including elbows, hips and knees) in 11/27, etc. An additional trisomy for this segment of the long arm does not cause additional types of defects, but somehow facilitates manifestations of genes located on the short arm.

There are ~20 reports on patients with tiny “pure” duplications in the area of 9q13, 9q21, and 9q22. These patients show different manifestations, including autism, seizures, and other functional disturbances. The etiological role of 9q duplication in some of these patients remains doubtful. There is no stable pattern of dysmorphism or congenital abnormalities in these patients.

Trisomy for the “Medial” segment of 9q

This group consists of 32 patients with duplications of different segments of 9q. All of these patients were trisomic for the whole 9q2 segment, although both proximal and distal breakpoints were different in all patients.

There is no clear or stable pattern of dysmorphism associated with a trisomy for this segment. Usually, patients show a moderate delay in psycho-motor development. Microcephaly is reported in 30% of the patients. Four of them had hypoplastic cerebellum, and two had abnormalities of the corpus callosum. Other structural brain defects are not typical. A significant group of patients have eye defects, including microphthalmia (5), colobomas (3), blepharophimosis (2), microcornea (1), or myopia (1). Cleft palate was found in four children (but cleft lip was not reported). Some patients have a short neck with excessive skin. Defects of the loco-motor system include contractures (4), camptodactyly (4), hip dislocation (4), and sporadic reports of arachnodactyly or additional ribs. Three patients had hearing loss, three had hypothyroidism (with the common trisomic segment dup 9q22.1q33), and one had goiter. Congenital heart defects were reported in 9 patients, including two life-threatening conditions — tetralogy of Fallot and truncus arteriosus.

At least eight patients had pyloric stenosis: this defect is relatively rare in other chromosomal

conditions. All patients with pyloric stenosis had trisomy for the 9q22.1q31.3, which had to contain a gene responsible for this defect. Other gastro–intestinal defects (esophageal atresia, ventral ectopia of anus, and omphalocele) were reported in one person each.

All other defects were sporadic.

Distal Trisomy 9q (dup 9q34)

There is a relatively small group of patients with a “pure” trisomy for the distal part of 9q (9q34, sometimes involving 9q33). The number of reports on such patients has markedly increased in the last 2–3 years because molecular methods allowed the detection of very small duplications. Currently, there are 28 patients with dup 9q34 available for phenotypic analysis.

Usually, these patients have borderline or even normal psycho–motor development. There is no characteristic pattern of facial dysmorphism; moreover, at least half of patients do not have dysmorphic features. Some patients have the so–called “marfanoid habitus” — an elongated trunk, long extremities, and sometimes arachnodactyly. There are at least three reports of the fusion between several cervical vertebrae. Some patients have scoliosis, contractures, camptodactyly, radio–ulnar synostosis, and dislocations of hips or other joints.

Three patients had epilepsy, but structural defects of the brain have not been reported. There is a report of a brain tumor, which developed in a patient with dup 9q34.

Congenital heart defects (all non–life–threatening) were described in six patients. Microphthalmia was found in three patients, ptosis in two, and one person had a cataract. Defects of the urinary system include hydronephrosis (2), agenesis of one kidney, and vesico–ureteral reflux. Defects of other systems have not been reported.

Trisomy 9q34 does not constitute a clinically recognizable syndrome. It may be diagnosed only after cytogenetic examination.

Some small duplications of 9q34 may be inherited from clinically normal (or almost normal) parents. Therefore, cytogenetic examination of the parents is a prerequisite for the decision regarding further offspring.

Trisomy 9

Trisomy 9 is relatively common among the so-called “rare” trisomies. Approximately 180 cases of trisomy 9 in humans have been reported (excluding several reports on trisomy 9 in spontaneously aborted fetuses). Mosaic trisomy 9 and complete trisomy 9 are found with the same frequency. Among 172 cases where individual characteristics of the patient (or fetus) are described, there were 85 with a complete trisomy and 87 with mosaic trisomy. Of course, in some cases, the conclusion was made upon examination of only one tissue, and actually unrecognized mosaicism cannot be completely excluded in some persons reported as having full trisomy 9.

Trisomy 9 has been known since 1973. Almost all patients reported in the 1970s–80s were diagnosed after birth. Currently, however, trisomy 9 is usually recognized during pregnancy

based on ultrasound examination (where some morphological abnormalities are found) or cytogenetic examination performed on the basis of maternal age or abnormal biochemical screening.

Complete trisomy 9 usually manifests itself by a complex of very serious morphological abnormalities, significantly limiting vital prognosis. There are only 2-3 publications where patients reported as having non-mosaic trisomy 9 were alive after 1 year. Unrecognized mosaicism is a very likely explanation.

The situation with mosaic trisomy 9 is different. Of course, these patients may have serious structural abnormalities. However, the individual prognosis depends on the frequency of trisomic cells and distribution of these cells in different tissues. There are many reports on patients with mosaic trisomy 9 who were above 10 years of age.

Most patients with trisomy 9 are born after normal pregnancies. Usually their birth weight is a little less than normal. A typical complex of dysmorphic features is similar to the patients with trisomy 9p and includes brachycephaly, high forehead, down-slanting palpebral fissures, deeply set eyes, hypertelorism, bulbous nose, high palate, downward corners of the mouth, and short philtrum. Many patients have a short neck.

Abnormalities of the loco-motor system include camptodactyly, contractures, "clenched" hands, dislocations of the hips, knees and elbows. There are several reports of hypoplastic thumbs, syndactyly, polydactyly or oligodactyly, but the defects were found only in 2-3 out of almost 200 patients. Some persons reveal kyphosis or scoliosis. Additional ribs may be found upon X-ray examination of the chest.

Morphological defects of the brain include mostly Dandy-Walker malformation (30/172) and hydrocephaly (13/172), but there are several reports of holoprosencephaly (4/172) or agenesis of the corpus callosum (6/172). At least seven instances of open spina bifida are reported in fetuses with full trisomy 9 (two more neural tube defects were found in spontaneously aborted fetuses with this pathology). There are no doubts that there is a causal relationship between these neural tube abnormalities and trisomy 9.

Microphthalmia is a typical and relatively common eye defect (23/172). Colobomas and corneal clouding were reported in 4-5 patients, each.

Cleft lip or palate is a relatively frequent manifestation: it was found in 34 patients (~20%). A very rare defect – underdevelopment (or complete absence) of the tongue was reported five times.

The most common visceral abnormalities are heart defects found at least in 50% of patients. These defects include very serious abnormalities (truncus arteriosus, hypoplastic left heart, monoatrial heart, double outlet of the right ventricle, and atrio-ventricular communication). Most patients, however, have ventricular septal defects (37) or atrial septal defects (26), which may be associated with other defects of the heart and large vessels. Dextroposition of the heart (as an isolated defect or in association with heterotaxy of the internal organs) was reported six times.

A very frequent lung abnormality – incomplete lobation (it was reported at least 16 times) is

not clinically very significant. Of course, this defect may be recognized only upon pathomorphological examination or upon heart surgery. Diaphragmatic hernia was found in 12 patients: several of them survived surgery to repair this defect.

Abnormalities of the kidneys are common. They include hydronephrosis (23), cystic dysplasia (18), fusion of the kidneys (usually as horseshoe kidney, reported in 12 patients), and hypoplastic kidneys (11). Unilateral agenesis, however, is very rare; bilateral renal agenesis has not been reported. Other defects of the kidneys are infrequent.

Defects of the gastro-intestinal system however are common. The most frequent defect was incomplete gut rotation (15/172), which may cause intestinal obstruction. There are several reports of hypoplastic biliary ducts, hypoplastic or absent gallbladder, annular pancreas, and hypoplastic pancreas. Atresia ani or rectal stenosis was reported in eight patients. Gastro-esophageal reflux was found in eight patients.

A complex of abnormalities in the brain, heart, and kidneys determines unfavorable life prognosis for persons with complete trisomy 9. Patients with mosaic trisomy 9 have better life expectancy. However, their psycho-motor development is usually severely delayed, and most of them are bedridden. Only a small percentage of patients with a low percentage of trisomic cells may acquire the necessary skills or visit special classes. Seizures are uncommon, but they are reported in a small percentage of patients with mosaic trisomy 9.