



Chromosome 8

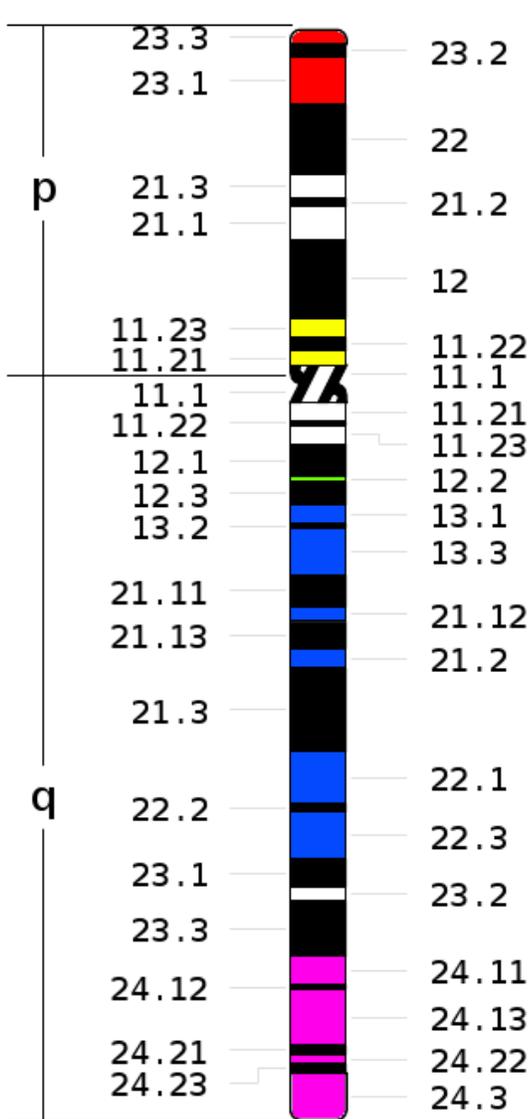
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David Adler.hum_08.gif



Introduction

The genetic size of chromosome 8 is 146 Mb. It is ~4.5–5% of the total human genetic material. The length of the short arm is 45 Mb; the length of the long arm is 101 Mb. Chromosome 8 contains less than 1,000 genes. Many of these genes participate in the development of body organs or are important for psycho-motor and neuro-cognitive development.

Numerous variants of structural abnormalities of chromosome 8 have been reported in at least 1,300 patients. Deletions of chromosome 8 (as a sole abnormality or in association with other chromosomal defects) are described in ~770 patients. However, distribution of these deletions is unequal. All types of deletions of the long arm (it is 100 Mb of genetic material) are reported only in ~250 patients, but deletions of the short arm (mostly in associations with partial trisomies for more proximal segments of 8p) are described more than in 500 patients.

There are 3 syndromes caused by deletions of the short arm (including 2 syndromes basically caused by deletions of the genes responsible for spherocytosis and Kallmann syndrome) and 3 syndromes caused by deletions of the long arm. Deletions of 8q21q23 remain virtually unknown, and the delineation of syndromes caused by the loss of this segment of 8q has to be expected in the nearest future.

Deletions of Chromosome 8

The genetic size of the chromosome 8 is ~146 Mb, where the short arm is ~45 Mb. There are at least three clinical syndromes caused by deletions of the short arm and at least three syndromes caused by deletions of the long arm of chromosome 8. Several more conditions

need further delineation.

Deletions of 8p

All deletions of the short arm of chromosome 8 may be subdivided into 2 groups: rarely occurring deletions of the proximal part of 8p and relatively frequent deletions of the terminal (or subterminal) regions of 8p.

Deletions of 8p11.2 and Spherocytosis

Segment 8p11.2 contains the gene ankyrin 1 (ANK1). This gene is responsible for the production of a protein necessary to support the bi-concave disk shape of the red blood cells. Deletions of this area lead to the deficiency of this protein. As a result, red blood cells (erythrocytes) become sphere-shaped. These blood cells may be destroyed by a spleen that leads to hemolytic anemia (usually, relatively mild). This condition is called spherocytosis.

There are ~15 observations of spherocytosis in the patients having deletions which involve 8p11.2. Other manifestations in these patients include cleft lip and/or palate, heart defects, and hearing impairment. The spectrum of associated defects depends mostly on the size of the deletion. Involvement of the segment 8q12 also may produce Kallman syndrome: at least 3 patients with spherocytosis caused by 8p deletions had Kallman syndrome as well.

Deletion of 8p12 and Kallman Syndrome

Kallman syndrome (KS) is an association of hypogonadotropic hypogonadism and anosmia. Hypogonadotropic hypogonadism is the underdevelopment of gonads (mainly testicles) caused by a defect of the central [pituitary] stimulation of their development. Anosmia is an absence of the sense of smell. KS is a genetically heterogeneous condition; this syndrome may be caused by mutations of several genes. The most common form of KS is caused by mutations (or deletions) of the KAL1 gene on chromosome X. The gene KAL2, located at 8p12, is responsible for ~10% of all patients with KS. Most persons with KAL2-related KS have mutations within the KAL2 gene. However, deletions of 8p12 (with loss of the KAL2 gene) also may produce clinical manifestations of this condition. Less than 10 patients with KS caused by deletions of 8p12 have been reported so far.

If the deletion also involves the more proximal part of 8p (8p11.2), the patients also may have spherocytosis. Associated cleft lip and palate, hearing loss and agenesis of the corpus callosum (not typical for KS) may be attributed to the loss of other neighboring genes.

Distal deletions of 8p

Distal deletions 8p are a relatively frequent type of chromosomal pathology. They have been reported in at least 400 patients, including ~150 where monosomy 8p was not associated with partial trisomies for more proximal segments of 8p, distal 8q or for parts of other chromosomes. Only patients with isolated distal monosomy 8p were taken into consideration for the analysis.

Most patients had terminal deletions of 8p, but, in some patients, the most terminal areas of 8p remained intact. However, all patients were monosomic for the segment 8p23.1, which is

crucial for the development of this syndrome.

External manifestations of the syndrome are relatively non-specific. Microcephaly, epicanthus, flat nasal bridge, microstomia, high-arched palate, low-set and/or deformed ears, short neck and broad chest were reported in ~50% of patients. Almost all patients have delay in psycho-motor development, usually relatively mild. Some patients have seizures. A significant number of boys have hypospadias.

Congenital heart defects are the most common and most clinically significant manifestations of the syndrome. These defects are found in ~3/4 of patients with distal deletions 8p.

Unfortunately, these defects are usually severe and life-threatening. They include hypoplastic left heart, double outlet right ventricle, atrio-ventricular septal defects (AVSD), tetralogy of Fallot (TOF), transposition of the great arteries, pulmonary atresia or stenosis, and hypoplastic right ventricle. Isolated atrial or ventricular septal defects and persistent arterial duct (most common in other chromosomal syndromes) occur rarely. Several investigations showed that most of these heart defects are caused by the deletion of the GATA4 gene — a transcription factor, which plays a critical role in heart development. All patients with distal deletions of 8p and heart defects had only one copy of this gene. Mutations of the GATA4 gene were found in numerous patients with isolated AVSD, TOF, and other forms of heart defects. These facts confirm the role of the GATA4 gene for heart development. It should be noted, however, that there are several reports of patients with a deletion of the GATA4 gene (especially with small deletions, not involving other genes) who did not have congenital heart defects. In this context, participation of other factors outside of GATA4 may be necessary (or at least important) for the origin of heart defects.

Congenital diaphragmatic hernias (CDH) are not so common, but they have been found at least in 18 patients (including several reports of CDH in fetuses with del 8p detected at prenatal testing). All persons with CDH (except one) also had congenital heart defects. Recent studies showed that CDH are caused by deletions of the same GATA4 gene, which is responsible for heart defects.

Several patients with distal deletions of 8p had some features of Cornelia de Lange syndrome (very low birth weight, hirsutism, long eyelashes, long philtrum). These features may be attributed to the loss of the TNKS (tankyrase 1) gene, also located at 8p23.1. This gene has been proposed as a further candidate for Cornelia de Lange phenotype.

Other abnormalities (hydrocephaly, hypoplastic cerebellum, defects of the corpus callosum, microphthalmia, intestinal malrotation, atresias of the ileum or jejunum) are relatively uncommon. Most of them were found only in 2–3 patients each. These defects may be caused by deletions of some neighboring genes or by individual characteristics of each patient unrelated to the deletion.

Deletions of 8q

Deletions 8q12 and CHARGE Syndrome

The CHARGE syndrome (or CHARGE association) is a complex of congenital defects, which includes coloboma of eyes (C), heart defects (H), atresia of choanae (A), growth retardation

(R), genitor–urinary defects (G) and ear abnormalities (E). Practically, most patients have only 3–4 main symptoms. This complex is etiologically heterogeneous. Mutations of the CHD7 gene, located at 8q12, are one of the causal factors of this association. The same phenotype may be produced by deletions involving this part of chromosome 8. There are ~12 patients with manifestations of the CHARGE syndrome caused by deletions of 8q12. Most of them had developmental delay, colobomas, heart defects and hearing problems (or ear defects). Choanal atresia/stenosis and genitor–urinary defects were not so common.

Some additional defects (hypoplastic cerebellar vermis, camptodactyly, absent gallbladder, femoral bifurcation with absent fibulae) may be caused by deletions of the neighboring genes.

Deletion of 8q13 and BOR Syndrome

Branchio–oto–renal (BOR) syndrome is an autosomal dominant condition, which affects branchial structures (usually manifested as fistulas on the neck), ears (preauricular sinuses or tags, hearing impairment) and kidneys (duplex kidneys, hypoplasia, etc). BOR syndrome is a genetically heterogeneous condition, which may be caused by mutations of several genes.

The EYA1 gene, located at 8q13, is responsible for the origin of the syndrome in ~65% of patients. Most of these persons have mutations of the EYA1 gene. A small group of patients has deletions of 8q13 (usually with the involvement of genes in neighboring areas — 8q12 or 8q21). Less than 10 patients with BOR–syndrome caused by del 8q13 have been described so far. At least two of these patients also had postaxial polydactyly.

Deletions of 8q21–q22 are rare and do not constitute any recognizable syndrome. Several patients with del 8q22 had diaphragmatic hernias as an isolated defect or in association with defects caused by deletions of more distal segments of 8q.

Deletions of 8q24 and Langer–Giedion Syndrome

Langer–Giedion syndrome is a complex of tricho–rhino–phalangeal syndrome (TRPS), multiple exostoses and psycho–motor delay. Sometimes, this condition is called tricho–rhino–phalangeal syndrome, type II (TRPS–II). The classical TRPS (or TRPS–I) is an autosomal–dominant condition, which is characterized by typical facial features (sparse slowly growing scalp hair, long nose with a bulbous tip, large protruding ears, long philtrum and thin lips) and cone–shaped epiphyses of fingers. Most patients have short stature. TRPS–I is caused by a mutation of the TRPS1 gene, located at 8q24.1.

Exostoses are additional benign bony structures, which grow from the tubular bones (humeral bones, femurs, phalanges) or from flat bones (pelvic bones, scapulae). Hereditary multiple exostoses are caused by a mutation of the EXT1 gene, also located at 8q24.1. There are 6 other genes, located between TRPS1 and EXT1, however no disease caused by mutations (or deletions) of these genes has been found so far.

The Langer–Giedion syndrome is caused by simultaneous deletions of TRPS1 and EXT1. Although an association of TRPS–II with deletions of 8q has been known for many years, the precise location of the deletion became clear only after the usage of molecular methods. Previous reports assigned the syndrome to the deletions of 8q23 or even 8q22. There are several reports of Langer–Giedion syndrome in the patients with an apparently normal

karyotype, but all of these persons had only a standard cytogenetic study. All patients studied by molecular methods showed a deletion.

Delay in psycho–motor development is usually mild. Most patients have a very friendly personality.

Approximately 35 patients with TRPS–II and deletions of 8q have been reported so far. Approximately the same number of patients was described (in the “old” literature) as having a normal karyotype or without any indication for cytogenetic testing. Several patients with a verified deletion of 8q24.1 had a phenotype of TRPS–I (did not have exostoses), at least one had exostoses, but did not have a phenotype of TRPS. The deletion of only one out of two “responsible” genes may explain such manifestations.

Involvement of more proximal genes (at 8q22 or 8q23) or more distal genes (at 8q24.2) may cause the occurrence of some additional anomalies reported in ~50% of patients. The most common associated defects are relaxation of the diaphragm, dislocation of the hips, umbilical hernias, syndactyly and cleft palate (or cleft lip and palate).

It should be noted that very unusual limb reduction defects (the absence of the tibiae and/or oligodactyly) have been reported both in patients with Langer–Giedion syndrome and in 5–6 patients with distal deletions of 8q without a Langer–Giedion phenotype. The common segment deleted in all of these patients is 8q23.3. Until now, there is no indication of which gene(s) may be responsible for these defects.

The most distal segment of 8q24.3 has to contain a gene responsible for coloboma, which was found in six patients with very distal deletions of 8q. From the genetic point of view, virtually all deletions of 8q and most deletions of 8p are sporadic events with a negligible recurrence risk. Sometimes, interstitial deletions of 8p and 8q may be caused by parental insertions. A small proportion of terminal deletions of 8p is caused by parental translocations. However, for the families planning further children, cytogenetic examination of the parents will be necessary.

Ring Chromosome 8

Ring chromosome 8 (r(8)) is one of the rarest forms of a ring chromosome. Only 12 patients with r(8) have been reported since 1973. Two of these patients were mosaics with a normal clone.

Exostoses — the hallmark of deletion 8q24 — were reported only once. Two patients had cleft palate and hydrocephaly. All other patients with r(8) had manifestations of a “ring chromosome syndrome”, but did not have any serious abnormalities. Neither one had heart defects, kidney defects, or defects of the gastro–intestinal system.

Direct transmission of ring chromosome 8 has not been reported.

Partial Trisomies of Chromosome 8

Trisomies of 8p

Trisomies for different segments of the short arm of chromosome 8 are relatively common. There are more than 350 reports on patients with such trisomies (including those with an associated imbalance for other chromosomes).

Basically, trisomies for the short arm of chromosome 8 may be subdivided into two main groups: trisomies for the large segment 8p12p23 (or 8p21p23) and trisomies for the most distal part of this chromosome (8p23). There are also two additional sub-groups, which also will be discussed: tetrasomy 8p and additional minute markers from the pericentromeric area of chromosome 8.

Trisomies 8p12p23 or 8p21p23

This kind of trisomy 8p is the most common. Formally “isolated” trisomies for this segment are reported in ~120 patients. From the cytogenetic point of view, almost all of these trisomies are duplications of the large (10–20 Mb) segment of 8p, and only a few are results of translocations to the short arm of acrocentric chromosomes. Very often duplications of 8p are associated with deletions of the most distal segments of 8p (8p23). There are more than 70 reported patients with such an association. These small deletions may remain unrecognized without special methods of cytogenetic examination. That is why many patients reported as “pure” trisomy 8p12p23 (or 8p21p23) actually may be patients having associated deletions. However, these tiny deletions do not change the basic manifestations of this condition (See the following table).

Comparison of clinical manifestations in patients with “pure” trisomy 8p and dup 8p with associated del 8p23.

	“Pure” dup 8p (n=117)	Dup 8p with del 8p23 (n=71)
Ageneis of corpus callosum	33	36
Hypoplastic corpus callosum	5	4
Dandy–Walker malformation or hypoplastic cerebellar vermis	12	6
Hydrocephaly	3	1
Cleft palate	3	1
Coloboma	3	1
All congenital heart defects (CHD)	22	17
Life–threatening CHD	11	7
Scoliosis	8	6
Kyphosis	3	4
Preaxial polydactyly	1	1
Absent gallbladder	1	1
Hearing loss	2	3

Seizures	9	11
Autistic traits	3	8

The most common brain defect is agenesis (or hypoplasia) of the corpus callosum, reported in at least 40% of patients (and in ~65% of patients who had examinations necessary to diagnose this condition). The critical segment for this defect is 8p21.3p22. Another frequent abnormality is Dandy–Walker anomaly in its full form or only as hypoplastic cerebellar vermis. The critical segment for Dandy–Walker anomaly is 8p22. Other brain defects (hydrocephaly, pachygyria, and microcephaly) are uncommon.

Another group of important manifestations of trisomy 8p is congenital heart defects (CHD), reported in 20–25% of all patients. At least half of these defects are life–threatening conditions (tetralogy of Fallot, transposition of the great arteries, atrioventricular septal defect, hypoplastic left heart, and interrupted aortic arch). The gene(s) responsible for these CHD are unknown. Duplication of the GATA4 gene (which causes heart defects in patients with deletions of 8p) does not seem to be causally related to CHD in patients with trisomy 8p.

A significant number of patients have defects of the vertebral column: kyphosis, scoliosis, and rib abnormalities. Polydactyly is exceptionally rare. Cleft palate, eye defects, and structural abnormalities of other systems (lungs, gastro–intestinal tract, kidneys) are very uncommon. All patients had delay in psycho–motor development, usually relatively mild. Other functional defects of the central nervous system (seizures, autistic behavior, and hearing loss) are relatively frequent.

Duplications of this area of 8p (both “pure” or in association with del 8p23) are sporadic events.

Trisomy 8p23

The group with isolated duplications of 8p23 is relatively large; ~100 people with such duplications have been reported. Most of them are either normal people (identified upon examination of the parents or other relatives of the probands) or patients with delay in psycho–motor development, autism (5), seizures (4) or obesity (4).

The most common structural defects are congenital heart defects (14), including several patients with hypoplastic left heart, aortic atresia, or atresia of the pulmonary artery. Defects of the brain (cerebellar aplasia, hypoplastic optic nerve), cleft lip and/or palate, scoliosis, radio–ulnar synostosis, hypospadias, or growth hormone deficiency are reported in 1–2 patients, each. However, it is unclear whether these defects are caused by duplication 8p23 or the duplication was found only by chance. The high frequency of the same duplication in phenotypically normal parents of affected children speaks in favor of a non–causal role of these small duplications. Actually, it is most likely that some (relatively small) sub–group of dup 8p23 is a pathogenic variant, causing clinical abnormalities, whereas the other (larger) sub–group represents a normal variation.

Isolated duplications of 8p23 are frequently inherited from phenotypically normal parents.

Additional Isochromosome 8p (Tetrasomy 8p)

Additional isochromosome 8p is a relatively rare condition. Only 22 patients with such an abnormality have been reported in the literature. As a result of this aberration, the patients have four copies of the genetic material of 8p (tetrasomy 8p).

The clinical picture of this condition is very heterogeneous — from a mild delay in psychomotor development to a complex of severe defects incompatible with life. Mosaicism with a presence of a normal clone, confirmed in 19 out of 22 patients, is the most obvious reason of such variability. There is no guarantee that three patients where mosaicism was not reported did not have a normal cell line in some tissues. A different proportion of the normal and abnormal clones in different tissues seems to be responsible for a great variability of manifestations. For instance, generally, there is no constant or specific form of facial dysmorphism.

Abnormalities of the brain, skeletal system, and heart are the most common findings in patients with this abnormality. The most common brain defect is agenesis of the corpus callosum reported in 14 out of 22 patients (one more child had hypoplastic corpus callosum). Most likely, a tetrasomy for the gene, which may produce this defect even in the trisomic form (see above) leads to the formation of this defect in almost all patients. Two infants had polymicrogyria.

Heart defects are also common: they were reported in half of the patients. Although most patients had ventricular septal defects or patent ductus arteriosus, which spontaneously closed in some children, there are reports of severe congenital heart defects (CHD) — such as a transposition of the great arteries, hypoplastic left heart, double outlet right ventricle, mitral or tricuspid atresia (there were several patients with combination of 2–3 forms of heart defects).

Most skeletal abnormalities are defects of the vertebral column and ribs. There are many reports of extra vertebrae; hemivertebrae; fusion of several vertebrae; additional, missing, or “fused” ribs; or scoliosis. Defects of the fingers and toes, however, are uncommon: only one fetus with +i(8p) had oligodactyly.

Defects of the gastro–intestinal system include gut malrotation (3), absent gallbladder, annular pancreas, and anorectal atresia. It should be noted that several affected infants had heterotopias (a condition when the tissue of one organ can be found in the tissue of another organ or in unusual positions within the same organ). There are reports of ectopic pancreatic tissue in the wall of the gut or in the spleen, ectopic renal tissue in the adrenals, and ectopic parathyroid glands in the thymus. Most likely, tetrasomy 8p predisposes to the origin of these heterotopias, whereas concrete genetic mechanisms of this phenomenon are still unknown.

An additional isochromosome 8p was the sporadic event in all reported families.

Additional Pericentromeric Markers of Chromosome 8

Additional micro–chromosomes consisting of a centromere and a small amount of the gene–containing DNA from both arms of the chromosome are known for all autosomes (of course, the precise attribution of such marker chromosomes to any specific chromosome usually

requires contemporary cytogenetic techniques). In most instances, however, the presence of these additional micro-chromosomes does not cause any specific phenotypic consequences: some patients with such chromosomes may reveal a degree of delay in psycho-motor development or birth defects; other persons with such chromosomes were found upon examination of patients with infertility, spontaneous abortions, or upon examination of normal parents having a child with an additional micro-chromosome in association with defects in physical or mental development.

Basically, this is also true for additional micro-chromosomes from chromosome 8, where 9 out of 24 persons with such an abnormality did not have any abnormalities, several had autism (3), obesity (1), isolated hypospadias (1), an additional nipple (1), short neck (1) or rib fusions (1), and four had multiple congenital abnormalities (different in all children). However, three patients with additional markers from chromosome 8 developed juvenile myelocytic leukemia (a specific and rare form of blood cancer). The area, duplicated in all three patients, was a 9.5 Mb stretch from 8p11.21 to 8q11.21. This region contains ~30 genes, both on the short and on the long arm of chromosome 8. Currently, it is not known, which of these genes is responsible for the predisposition to the leukemia (and whether this gene is on the short or on the long arm of chromosome 8). However, the presence of such a small marker should be considered as a risk factor for the development of this form of leukemia.

It may be noted that juvenile myelocytic leukemia (and other types of leukemia) were reported in ~20–25 patients with mosaic trisomy 8 syndrome, but the location of the gene, predisposing such patients to the development of blood malignancies, remained unknown for a long time.

Trisomies for 8q

All trisomies of 8q may be subdivided into 3 large groups: a) a pure trisomy of 8q; b) an association of trisomy 8q and partial monosomies for other chromosomes (mainly due to different translocations), and c) an association of distal trisomy 8q with a partial monosomy for the distal part of 8p. The last condition, known as San Luis Valley syndrome, is one of a very few known chromosomal syndromes caused by an imbalance of not one, but for two non-neighboring segments of the chromosome. Because this association forms a recognizable syndrome with definite clinical characteristics, it will be described as a very specific variant of trisomy 8q.

Pure Trisomies of 8q

Pure trisomies of 8q are relatively rare. There are only ~85 reported patients with different trisomies of 8q, including ~15 with tiny duplications (< 1Mb), whose etiologic role remains unclear. No single group of pure duplications 8q may be considered as a recognizable syndrome.

Duplications of 8q11.23

Tiny (< 0.6 Mb) duplications of 8q11.23 were reported in 10 patients. Some of these people had a delay in psycho-motor development; another had autism, seizures, or different birth defects (hypoplastic left heart syndrome, polydactyly). Further observations are needed to determine the significance of dup 8q11.23 in the origin of the above-mentioned

abnormalities.

Duplications of 8q12

There are only 5 reported patients with this duplication. All but one had a hearing impairment (caused by an abnormal development of the internal ear) and various heart defects (atrial and ventricular septal defects, pulmonary stenosis, patent ductus arteriosus). Three patients had Duane anomaly (a defect of the VI nerve, causing an inability to move the eye inward (to the nose) and/or outward (to the ear)). This defect is highly uncommon in patients with chromosomal pathology. Therefore, there are good reasons to believe that the segment 8q12 contains genes, which (when triplicated) may cause Duane anomaly, hearing impairment and heart defects.

Pure trisomies 8q13–8q21 do not cause any recognizable defects.

Duplications 8q21(q22)–q24(qter)

This variant of “pure” trisomy 8q was reported only in ~20 patients. The most common abnormalities in this group are heart defects (7/19), including one person with tetralogy of Fallot. At least four patients had deformities of the spine (scoliosis). Short neck was reported in four other patients. Two children had craniosynostosis and two had hydronephrosis. Several patients who shared a duplication of the 8q22.3q24.1 segment had seizures. The segment 8q22 may carry genes causing cleft palate and anteriorly displaced anus. Both have been reported in several patients with these trisomies.

Other defects of the eyes (microphthalmia, megalocornea), respiratory tract (choanal atresia), kidneys (cystic kidneys and megaureter) and loco–motor system (contractures, “curved” radial bones, syndactyly, and camptodactyly) were reported in one person each.

Distal Trisomies 8q (dup 8q23–q24)

Less than 20 patients with such abnormalities have been reported so far. At least half of them had a mild delay in psycho–motor development, hearing impairment, seizures, behavioral problems, or autism, but had no structural defects. Recurrent birth defects include contractures (3), camptodactyly (2), bifid uvula (2), and a short webbed neck (2). Microcephaly, diaphragmatic hernia, and polycystic ovaries were reported in one patient each. A significant (~13 Mb) duplication of this region may be asymptomatic (as found in one of the parents having an affected child).

San Luis Valley Syndrome

An association of distal trisomy 8q with partial monosomy for the most distal segments of 8p has been reported in the 1970's. This combination is caused by the recombination between a normal chromosome 8 and a chromosome 8 having pericentric inversion. Later the formula of this inversion was determined as inv(8)(p23q22). Although two different recombinants may be expected as a result of the exchange of genetic material between a normal chromosome 8 and inverted chromosomes 8, only one – involving trisomy 8q22qter with monosomy 8p23pter – was reported in all affected patients. The opposite variant (monosomy 8q22qter with trisomy 8p23pter) has never been described: most likely, all embryos with such an imbalance die

during early pregnancy.

The vast majority of known patients with this syndrome are people of Spanish background residing mostly in New Mexico or Colorado. There are reasonable beliefs that most patients have a common ancestor living in this area ~300 years ago. In that sense, this disease may be considered as an example of “founder effect”. However, there are several reports of the same (or very similar) chromosomal inversions in patients of very different ethnicity, for example, in Koreans. The genetic structure of 8p23 and 8q22 (with a large amount of tandem repeats) may facilitate the occurrence of the inversion. As usual, balanced carriers of this inversion are completely normal people, but they have a significant risk of having an affected child (the risk for female-carriers is about 8%; the risk for male carriers is around 5%). Clinical manifestations of the syndrome include delay in psycho-motor development, multiple dysmorphias, and very serious internal abnormalities.

Almost all patients have a relatively wide face, hypertelorism, infraorbital creases, a wide nasal bridge, anteverted nares, thin upper and thick lower lips, downturned corners of the mouth, an abnormal hair whorl (or the presence of several whorls), and a low posterior hairline. Redundant neck skin is reported in ~50% of affected patients. Muscle tone is low. Cleft lip and palate are found in ~20% of patients. Pectus excavatum, scoliosis, camptodactyly, and absent (or hypoplastic) patella may be found in one half of the patients. Deep plantar furrows (a typical sign of the patients with mosaic trisomy 8 syndrome) are almost constantly found.

Structural brain defects are uncommon. There are sporadic reports of Dandy-Walker anomaly, hydrocephaly, hypoplastic cerebellum or hypoplastic corpus callosum. Congenital heart defects (CHD) are, however, almost constant manifestations of the syndrome. Only seven out of more than 100 described patients did not have CHD. The defects are life-threatening and usually require surgical intervention. Successful heart surgeries may improve development of the patients. ~35% of patients have tetralogy of Fallot. There are also reports of truncus arteriosus or double outlet right ventricle. Most other patients have ventricular septal defects and stenosis of the pulmonary artery. Such a spectrum and frequency of heart defects are not characteristic either for pure monosomy 8p23pter or for pure trisomy 8q22qter. Most likely, the combined action of several genes (or the creation of a new genetic structure upon the formation of the recombinant chromosome) may be responsible for the origin of heart defects in patients with San Luis Valley syndrome.

The kidneys and the urinary system are also frequently affected. The most common defect is hydronephrosis, but many other forms of kidney defects (agenesis of one kidney, hypoplastic kidney, dysplastic kidneys, cystic kidney, doubling of the renal collecting system, and ureterovesical obstruction) are also reported. Abnormalities of the genitalia are relatively common: some boys have hypospadias. There are several reports of uterus bicornis in girl. Abnormalities of the gastro-intestinal system include agenesis of the gall-bladder, bowel malrotation, and an underdevelopment of the pancreas.

A delay in psycho-motor development is usually severe. All patients have a significant communication deficit. Their social-adaptive function seems to be much better than cognitive functions.

Almost all known patients inherited an abnormal chromosome from a parent-carrier of the

inversion.

Trisomy 8

Trisomy 8 is the most common of all "rare" trisomies. More than 300 patients with this condition have been reported in the literature. Actually, some patients with trisomy 8 were described in the pre-banding period as patients with "trisomy C". Later it was shown that most of them actually had trisomy 8. Some estimates show that the frequency of this condition among newborns is between 1:30,000 and 1:50,000.

Almost all patients with trisomy 8 have mosaicism with a normal clone. A small cohort of non-mosaics shows very serious abnormalities, mostly incompatible with prolonged survival. Most affected patients are males. Some authors report that the sex ratio among affected persons is 3:1.

Most infants have a normal birth weight and a normal head circumference. A large (sometimes asymmetric) skull or macrocephaly may be found in children and adults. Mosaic trisomy 8 is a clinically recognizable condition. Typical manifestations include prominent bulging forehead, long face, deeply set eyes, high palate (in 10% with cleft palate), micrognathia, and thick everted lower lip. The neck is usually short.

Characteristic abnormalities of loco-motor system include long narrow shoulders, pectus excavatum, accessory nipples, kyphoscoliosis, abnormally shaped vertebrae, and an abnormal number or position of the ribs. Gaps in the first ribs and abnormal clavicles may be typical findings upon X-ray examination. The pelvis is narrow. Coxa valga are found in a significant proportion of patients. Most patients reveal arachnodactyly, camptodactyly or clinodactyly. However, they have neither poly- nor oligodactyly. The most typical skeletal defect is the absence or severe hypoplasia of patellae. As a result, the range of motion in the knee joints may be limited. There are deep skin furrows on the palms and on feet. However, these diagnostically important findings are typical for infants and disappear in older children.

The most common brain defect is agenesis of the corpus callosum which is found in 25-30% of patients. Other brain defects are highly unusual, but there are several reports of Dandy-Walker anomaly or hydrocephaly. 50% of patients have strabismus. At least 7-8 patients had corneal opacities.

Heart defects are found in 10-15% of patients. However, almost all of these defects are relatively mild.

Urinary defects are common: hydronephrosis, hydroureter and vesico-ureteral reflux.

Generally the patients with mosaic trisomy 8 do not have life-threatening birth defects. A small subgroup of persons with full trisomy 8 reveals serious defects of the heart, kidneys and other organs. Morphologic examination of an embryo with complete trisomy 8 showed an absence of mesonephros (a precursor of kidneys) and a defective development of the heart. Almost all patients with mosaic trisomy 8 reveal a significant delay in psycho-motor development. Their IQ is usually between 50 and 80. Speech delay is especially obvious. Some patients may develop seizures. Teenagers and adults sometimes have personality disorders. There are several reports on schizophrenia and bipolar disorder, especially among

adult patients. Of course, intellectual development depends on the percentage and distribution of the trisomic cells. There are several instances when mosaic trisomy 8 was diagnosed basically by chance upon examination of donors or women with amenorrhea. It was shown that there is a growth advantage of normal cells vs trisomy 8 cells. If so, the proportion of trisomic cells may be decreasing in adult patients compared with newborns. However, almost all morphogenesis occurs before birth, and a diminishing proportion of trisomic cells hardly may improve the clinical condition of the patient.

Mosaic trisomy 8 may cause significant immunologic abnormalities. As a result, it may have a causative role in the development of embryonal childhood tumors and hematological malignancies (myelofibrosis, monocytic leukemia). There are at least 20 reports of such complications of trisomy 8.

Trisomy 8 (as an acquired anomaly) is found in 6-10% of persons with myeloid leukemia. Special investigations showed that in 15-20% of persons with "trisomy 8 positive" leukemia, trisomy 8 is actually not acquired but represents a previously unrecognized constitutional mosaicism.

Another serious complication of mosaic trisomy 8 is Bechçet syndrome (sometimes in patients with myelodysplasia, sometimes without it). The main manifestations of this condition are mucocutaneous changes (mostly oral ulcers, genital ulcers, and skin lesions). Both Bechçet syndrome and myelodysplasia are manifestations of the same immunologic defect caused by mosaic trisomy 8.