Chromosome 7


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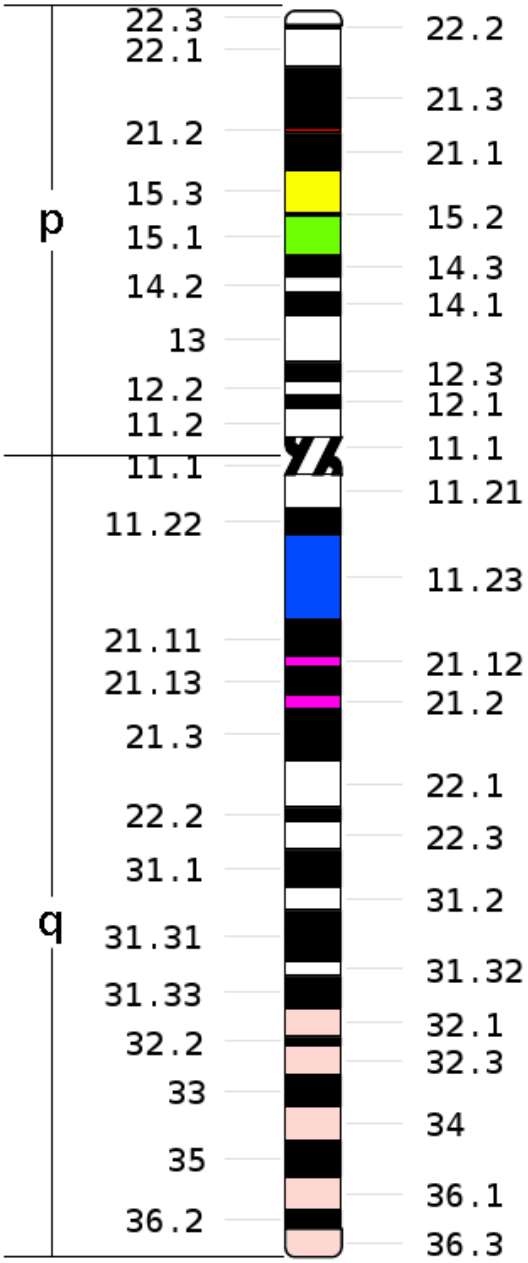


## Introduction

The genetic size of this chromosome is 159 Mb. It is 5–5.5% of the total genetic material. The length of the short arm is 60 Mb; the length of the long arm is 99 Mb. Chromosome 7 has ~1,150 genes. At least 150 of these genes are either related to the development of body organs or necessary for the performance of body functions.

There are numerous reports about patients having different abnormalities of chromosome 7. The most common is Williams syndrome caused by del 7q11.23. Excluding patients with Williams syndrome, there are ~1,500 reports on patients having partial trisomies or deletions of chromosome 7 as the only abnormality or in association with another chromosomal imbalance. Deletions of the short arm are reported in ~250 patients; deletions of the long arm (excluding del 7q11.23) are reported in ~600 patients.

There are at least 3 syndromes caused by deletions of the short arm and several syndromes caused by deletions of the long arm. The introduction of molecular cytogenetics allows the medical community to delineate del 7q31 syndrome, but it basically does not cause many changes in our understanding of conditions caused by deletions of this chromosome.

## Deletions of Chromosome 7

The genetic size of chromosome 7 is ~159 Mb, where the short arm is ~60 Mb. There are several syndromes caused by deletions of the short and long arms of chromosome 7. Several more conditions need further delineation.

## Deletions of 7p

*Deletion of 7p14.1 and Greig Cephalopolysyndactyly Syndrome*

Greig cephalopolysyndactyly syndrome (GCPS) is an autosomal dominant condition characterized by limb defects (pre– and post–axial polydactyly of the hands and feet, syndactyly, wide great toes, advanced bone age) and a spectrum of cranio–facial anomalies (macrocephaly, hypertelorism, high forehead, frontal bossing, hypertelorism, broad base of the nose). Mental development in most familial observations of GCPS is usually normal. The syndrome is caused by mutations in the GLI3 gene, located at 7p14.1.

Deletions of the short arm of 7p involving 7p14.1 also may cause GCPS. There are ~30 reports of patients having GCPS as a result of deletions, and several more apparently had balanced translocations with a breakpoint within 7p14.1. Some patients have small deletions recognizable only using molecular methods. Most of these patients have a “typical” GCPS phenotype. Another group has larger deletions, which involve not only the GLI3 gene, but several other genes. These larger deletions usually produce additional phenotypic manifestations: delay of psycho–motor development, seizures, dysgenesis of corpus callosum, inguinal and umbilical hernias, heart defects (ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosis (PDA)). Several patients have omphalocele. All of these defects are most likely caused by deletions of other genes within 7p13 and 7p14.

Band 7p15.1 is harboring the HOXA–13 gene, which is responsible for the hand–foot–genital syndrome. This syndrome causes shortening of the thumbs, hypoplasia of the feet, synostosis of bones in the wrists and ankles. Most patients have abnormalities of ureters (causing urinary tract infections) and hypospadias. Very rarely, some manifestations of the hand–foot–genital syndrome are found in patients with deletions involving the HOXA–13 gene.

*Deletion of 7p15.3 and Saethre–Chotzen Syndrome*

Autosomal dominant Saethre–Chotzen syndrome (SCS) is characterized by craniosynostosis, facial asymmetry, low frontal hairline, ptosis, small ears, maxillary hypoplasia, and cutaneous syndactyly of fingers and toes. The gene TWIST responsible for this syndrome is located within 7p15.3. Deletions involving 7p15.3 may produce phenotypic abnormalities, typical for SCS. More than 40 patients with this syndrome having deletions involving 7p15.3 have been reported. Patients with small deletions detected only by molecular methods show a typical SCS phenotype. Patients with larger deletions, usually involving 7p15.1 or 7p22, may show additional anomalies. Various (mostly relatively mild) heart defects (VSD, ASD, PDA, abnormalities of large vessels) were found in 12 patients. Lacunae in cranial bones, microphthalmia, stenosis of lacrimal ducts, choanal stenosis, vesico–ureteral reflux were repeatedly found in patients with larger deletions.

The patients may have various types of craniosynostoses, which seems to be more severe than in patients with SCS caused by mutations of the TWIST gene. The occurrence of craniosynostoses in persons with deletions more proximal to the centromere (but not involving 7p15.3) and in persons with more distal deletions suggest that this part of 7p may harbor several other craniosynostosis–related genes (within 7p14 and 7p21.3). Simultaneous loss of one of these genes and the TWIST gene, which happened in larger deletions, may explain the severity of craniosynostosis in patients with larger deletions of 7p.

*Deletions of 7p21p22*

Clinical manifestations in ~20 known patients with isolated deletions of the distal part of 7p do not yet allow the delineation of a syndrome. Distal deletions occur rarely. Most patients with these deletions were reported many years ago. Standard cytogenetic methods used to determine the breakpoints in these persons may be insufficient to produce accurate results. That is why the possibilities of clinical comparison of these patients are limited.

Frequently found craniosynostosis may be caused by the deletion of 7p21.3, which has to contain a gene responsible for this condition. Some patients have cleft palate (or cleft lip and palate). Tetralogy of Fallot (observed at least in 3 patients with distal 7p deletions) and ventricular septal defect (in 4 other patients) may be traced to a deletion within 7p22.2p22.3. At least 7 patients with distal deletions had anal atresia or malposition of the anus. All of these patients share the deletion of 7p21.2p21.3. Therefore, this segment has to contain a gene responsible for this defect.

**Deletions of 7q**

*Williams Syndrome*

Most syndromes caused by chromosomal deletions were delineated after comparison of phenotypic manifestations of several patients having this particular deletion. In very rare cases, however, non–monogenic syndromes were known far before the discovery of their chromosomal etiology. Williams syndrome (WS) belongs to this group. Williams syndrome (or Willams–Beuren syndrome) was identified in 1961. The main clinical manifestations of WS are: 1) characteristic facial appearance; 2) characteristic developmental delay with unusually well–developed language skills; 3) supravalvular aortic stenosis; and 4) transient hypercalcemia.

WS usually is easily recognizable even while viewing the picture of the patient. The characteristic face includes broad forehead, puffiness around the eyes, short nose with a broad tip, wide mouth with full lips, and full cheeks. The teeth are widely spaced; some teeth may be missing. A Star–like appearance of the iris is rather common. Most patients are short with a long neck, sloping shoulders and limited joint mobility.

The patients with WS have a very specific cognitive profile. They have a strong ability in language, music and memory (especially short term memory). At the same time, they have obvious weakness in the skills requiring writing, drawing or assembling puzzles. Typically, the patients are very friendly, overly sociable, and have an extreme interest in other people. Sometimes their personality had been characterized as a “cocktail party” type personality. However, attention deficit disorder, problems with anxiety and phobias (especially hyperacusis and phonophobia) are very common.

A frequent manifestation of WS is supravalvular aortic stenosis — narrowing of the aorta, which may cause shortness of breath and heart failure. Hypercalcemia is frequent in infancy, but older patients have a normal level of blood calcium. Malformations of other organs are not typical.

WS is relatively frequent. It affects ~1:10,000–1:20,000 newborns.

A genetic basis of WS was established only in the 1990's, when it was shown that almost all of the patients with WS have a relatively small deletion within 7q11.23. Most patients have a deletion of 1.55 Mb of 7q11.23 which includes ~25 genes. The molecular structure of this region of 7q facilitates formation of this deletion (as well as a reciprocal duplication). There are good reasons to believe that the deletion of the ELN gene is responsible for aortic stenosis. A smaller proportion of WS patients have a slightly larger deletion (1.84 Mb). Very rarely, involvement of more distal regions of 7q may produce a more severe phenotype, including infantile spasms (not characteristic for a typical WS).

*Deletion of 7q21*

At least 60 patients with deletions involving 7q21 have been reposted so far. The most remarkable manifestation in these persons is ectrodactyly, reported in more than 30 patients. Clinically, it is a typical ectrodactyly with the absence of 1–2 central digits. Sometimes, ectrodactyly is unilateral; sometimes, it is bilateral. The upper and lower limbs are affected with approximately the same frequency. Some children have not typical ectrodactyly, but aplasia of several nails. In other patients, the long bones of the lower extremities are also affected.

Using molecular cytogenetic analysis, it was shown that a loss of segment 7q21.3 was common for all of these patients. However, the primary genetic cause of ectrodactyly in these patients remains unclear. It should be noted that ~25 other patients had ectrodactyly due to apparently balanced rearrangements involving 7q21.3, and a very large proportion of these rearrangements were complex rearrangements involving 3–4 breaks of chromosomes. These data provide indirect support to the idea that the primary cause of ectrodactyly is not a deletion itself but some secondary disturbances in the regulation of gene function.

Microcephaly and developmental delay are usual for all of these patients. Another very characteristic manifestation is deafness, caused by the abnormal development of the internal ear. Hearing impairment was reported at least in 10 out of 30 patients (as well as in some patients with del 7q21 without ectrodactyly). Another typical finding is cleft palate, which was found in 25% of patients with ectrodactyly and del 7q21.3. Different heart defects were mentioned 5 times (ASD – 2, VSD – 2, tetralogy of Fallot – 1). Several patients had hypospadias and inguinal hernias. Defects of other systems are not characteristic and may be caused by associated deletions of other areas of chromosome 7.

A small subgroup of patients with del 7q21 have myoclonus dystonia — a condition, which is characterized by the association of myoclonic jerks of the neck and upper extremities and dystonia. This disorder (usually inherited as an autosomal dominant trait) is caused by the mutation of the epsilon–sarcoglycan gene (SGCE) on chromosome 7q21.3. Deletions of this gene also may cause a clinical picture of myoclonus–dystonia. This gene is located proximal of the region critical for the occurrence of ectrodactyly.

*Deletion of 7q31.1 and Oro–motor Dyspraxia*

Dyspraxia is a condition when a person is unable to initiate and perform an action. Oro–motor (verbal) dyspraxia is an inability to correctly pronounce sounds and words. This condition depends upon defects in central regulation, whereas muscles of the face, tongue or lips remain normal.

Oro–motor dyspraxia is caused by a defect of the FOXP2 gene located at 7q31.1. Deletions (as well as mutations) of this gene may cause this condition. There are ~15 reports of patients with this deletion and oro–motor (or linguo–facial) dyspraxia. If the deletion is relatively small, the patients have a Silver–Russell–like phenotype, but they do not have defects of the internal organs. Larger deletions involve many additional genes, which may cause defects of the eyes, heart and kidneys. In one study, it was shown that oro–motor dyspraxia is caused exclusively by deletions of paternal genes. Maternal isodisomy [a rare condition when both homologous chromosomes or a part of these chromosomes in an individual are inherited from one parent] for this region of chromosome 7 may produce the same effect, whereas children with paternal isodisomy do not have oro–motor apraxia.

*Distal Deletions of 7q*

Deletions 7q32q33, 7q32q34, 7q33q34 and 7q33q35 have been reported in several dozen patients, but clinical manifestations in these persons are heterogeneous and there is no clinical syndrome associated with these interstitial deletions. The terminal segment of 7q (as well as terminal segments of almost all chromosomes) is a gene–rich area. Deletions of 7q36 (or association of del 7q36 with deletions of more proximal segments [7q32, 7q33, etc.]) cause specific phenotypic manifestations.

Distal deletions of 7q have been reported in more than 270 patients. Almost half of them had distal monosomy 7q in association with partial trisomies for other chromosomal segments. Only 140 patients with “pure” distal monosomy 7q were analyzed to delineate a clinical syndrome associated with this deletion.

The phenotype of the patients with distal deletions of 7q depends mostly on two genes located at the distal end of 7q36 — SHH and MNX1 (the latter gene is a little bit closer to the telomere).

The SHH gene controls the normal development of the forebrain. Deletions (or mutations) of this gene cause holoprosencephaly (HPE) — a defect of the brain when cerebral hemispheres are not separated (alobar HPE) or only partially separated (semi–lobar HPE). In many cases, HPE may cause severe defects of the facial structures. Usually, it is an association of hypotelorism, flat nasal bridge and central cleft of the lip and palate (this complex is called a premaxillar agenesis). Overt HPE was reported in 27 out of 140 patients. However, most patients have the so–called “microforms” of HPE, which include the association of microcephaly and a single central incisor (reported in at least 10% of patients). Some investigators are inclined to consider agenesis or hypoplasia of corpus callosum (11/140) or colobomata (9/140) as other microforms of HPE. Taken together, ~50% of patients with distal deletions of 7q have HPE (in the complete form or as a microform). Some persons (even with a confirmed deletion or mutation of the SHH gene) do not have any manifestations of HPE.

The absence of the MNX1 gene (sometimes called also the HLXB9 gene) causes underdevelopment of the caudal end of the body. Underdevelopment or absence of the sacrum is the most remarkable manifestation of this defect. It should be noted that, although HPE may be found not only in del 7q36, but in many other forms of autosomal deletions (including 2p21, 14q13, 18p11) and duplications, sacral ageneses is virtually unique for del 7q36. This defect is not known as a frequent manifestation in any other deletion or

duplication. Sometimes caudal regression may be obvious by external examination; in other patients, it becomes evident only after X–ray examination of pelvic bones.

Defects of the kidneys (usually as hydronephrosis/hydroureter or hypoplastic kidneys), stenosis (or atresia) of the anus and dilated colon are other manifestations of caudal regression. At least five patients had presacral myelomeningocele — another result of the abnormal development of the caudal region of the vertebral column. It should be noted that 3 patients having deletions 7q32qter had anencephaly or encephalocele. These defects have not been reported in patients with more distal deletions. Most likely, the segment 7q32 may contain a gene, which in rare occasions, may cause neural tube defects.

Some defects found in patients with distal 7q deletions cannot be explained either by the deletion of the SHH gene or by the deletion of the MNX1 gene. A significant number of patients (~20%) have heart defects, but life–threatening types of heart defects are uncommon. Cleft lip and palate is another frequent manifestation (18/140), although some of these patients actually could have premaxillary agenesis. Microphthalmia, hearing impairment, choanal atresia or stenosis have been reported in several patients each. Incomplete lobation of the lungs was reported at autopsy at least 5 times, but, actually, this abnormality may be more frequent. Hypospadias was reported in ~20% of boys having this deletion. Some unusual (but repeatedly reported) defects of del 7q36 are situs viscerum inversum (with serious heart defects and asplenia) and ectrodactyly.

Developmental delay is a constant manifestation of distal 7q monosomy, although the degree of the delay depends on the presence (and severity) of brain defects. Seizures and autistic features were reported in rare occasions.

From the genetic point of view, most interstitial deletions are sporadic events with a negligible recurrence risk. A significant number of distal deletions may be caused by parental translocations and inversions. Cytogenetic examination of the parents remains a gold standard for every couple that plans on having future children.

**Ring Chromosome 7**

Ring chromosome 7 is a relatively rare form of ring chromosomes. Only 25 patients have been reported since 1973. Two of these patients were mosaics with a normal clone; one patient was a mosaic with a monosomic clone.

Craniosynostosis — a hallmark of the distal 7p deletion — was reported only once. Three patients had holoprosencephaly as a result of the loss of the SHH gene on 7q36. Other defects caused by distal 7q deletions (atresia ani, sacral agenesis, cystic kidneys) were reported in three more patients.

Four reported heart defects (including one person with an interrupted aortic arch and one with a transposition of the great arteries) may be attributed both to the loss of 7p and 7q.

Most other patients have neither of these defects, but most of them have unusual abnormalities of skin pigmentation: multiple naevi (12 patients), café–au–lait spots (7 patients), and areas of skin depigmentation (3 patients). Some patients have an association of several skin abnormalities. One patient developed melanoma. Pigmentary skin defects are

not typical either for distal deletions 7p or for distal deletions 7q. The origin of these defects remains unknown. The combined effects of the distal loss of 7p and 7q cannot be excluded as explanation of this phenomenon.

Familial transmission of ring chromosome 7 has not been reported.

**Partial Trisomies for Chromosome 7**

*Partial trisomies 7p*

More than 120 patients with trisomies for different segments of the short arm of chromosome 7 have been reported so far. Some of them have an associated imbalance for other chromosomes as a result of translocations or inversions. Almost 75 patients may be considered as patients with “pure” trisomy 7p. This number includes ~10 persons with tiny duplications of 7p where the etiological role of duplications in the patient’s phenotype is not clear.

Basically, the severity of the clinical manifestations depends on the size of a duplicated segment. Patients with trisomy for the whole (or almost whole) 7p have more severe abnormalities; the vital prognosis of such patients is much worse. However, there is no segment that may be considered as a critical segment for trisomy 7p syndrome.
Most patients have a significant delay in psycho–motor and a less severe delay in physical development. There is no characteristic pattern of facial dysmorphism. A significant proportion of infants have an unusually large anterior fontanel: this defect (with a critical segment 7p21.3p22.3) was reported in at least 11 children. A wide and short neck or neck with redundant skin was found in 10 patients. Three patients had not only redundant neck skin (pterygium colli), but also an axillary pterigyum (a wing–like triangular membrane between the torso and upper arm in the armpit area). These patients shared a duplication for 7p13p22.3. Cleft lip and palate was reported twice; one patient had a bifid uvula. Three patients had choanal atresia or stenosis. The critical segment for choanal defects is 7p21.1p21.3. Preauricular pits were reported twice.

Defects of the musculoskeletal system are relatively mild. They include camptodactyly (6), brachydactyly (5), scoliosis (5), dislocation of the hips (5), arthrogryposis (2), and postaxial polydactyly (an additional digit on the side of the 5th finger or 5th toe), partial syndactyly (2), and dislocated thumbs (1).

Defects of the brain are represented by hydrocephaly (3 patients), hypoplastic corpus callosum (3 patients), and Dandy–Walker malformation (4 patients). The critical segment for Dandy–Walker malformation is 7p21.1p22.2. “Aplasia” of the cerebellum and macrogyria (diminished number and increased size of the brain’s sulci) were reported in one patient, each.

Congenital heart defects are frequent (19 patients). The most common forms of heart defects are atrial septal defects (10), stenosis of the pulmonary artery (5), and ventricular septal defect (4) (some patients had an association of several defects). Except for one child having a heart with a single ventricle, all other heart defects were not life–threatening. Gastro–intestinal defects are represented by intestinal malrotation (3 patients), omphalocele (1) or absent gallbladder (1). The most common abnormality of the uro–genital system is hydronephrosis

reported in 5 patients. Other kidney defects (dysplastic kidneys, cystic kidney, and ureteral stenosis) were found in one patient, each. Two boys had hypospadias; two girls had uterine abnormalities (double uterus or absent uterus).

Five patients with trisomy 7p had autism; two had epilepsy. In one study, nine patients with a 3 Mb duplication of 7p15.2p15.3 had attention deficit hyperactivity disorder.
Small duplications of 7p may be inherited from an unaffected parent. All larger duplications 7p were sporadic.

*Partial trisomies 7q*

There are more than 350 patients having partial trisomies for different segments of 7q. More than 160 of them had an additional chromosomal imbalance, mainly due to various translocations and inversions. The remaining ~190 patients who did not have other imbalances except 7q trisomy form a very heterogeneous group, which may be subdivided into 4 sub–groups: duplication 7q11.23, duplications of the area between 7q21 and 7q32, distal duplications 7q, and a specific cohort of patients with an isolated 7q36.3 duplication.

*Duplications 7q11.23*

The well–known Williams–Beuren syndrome is caused by a ~1.5 deletion within 7q11.23. The origin of this deletion is facilitated by the genetic structure of this region of 7q, allowing a recombination (exchange) between low copy repeats flanking the deleted region. The same genetic structure has to lead to reciprocal duplications of this region. This theoretical suggestion was recently confirmed when new methods allowed recognition of small duplications. At least 70 persons with duplications limited to 7q11.23 have been reported to date. This number includes 2 patients with triplication of this region.

Generally, clinical manifestations of 7q11.23 duplication are much milder than clinical manifestations of the 7q11.23 deletion. Psychiatric and neurological problems are main symptoms in these people. At least 15 affected patients have autism or autistic features. Nine patients have seizures. Schizophrenia was diagnosed in 3 patients, attention deficit hyperactivity disorder in 2. However, it is still unknown whether the duplication itself is responsible for these problems or if duplication serves as a trigger for other genetic factors, facilitating their action.

Morphological abnormalities are relatively uncommon. Most patients do not have any facial dysmorphic features. Two had cleft lip and palate; one had cleft palate only. The most common cranial defect observed in 6 patients is craniosynostosis (mainly metopic craniosynostosis causing trigonocephaly). Three patients have hypoplastic (or absent) corpus callosum. Hydrocephaly was mentioned twice. Other brain defects (polymicrogyria, encephalocele, cortical dysplasia, hypoplastic cerebellar vermis, simplified gyral pattern, dysplastic hippocampus) were reported in one patient, each.

Relatively mild heart defects were found in 5 patients; 3 of them have patent ductus arteriosus. Defects of the kidneys or gastro–intestinal tract have not been reported.

The reported abnormalities of the loco–motor system are mild. They include increased joint laxity (5 patients), partial syndactyly (2), and pectus excavatum (2). Other defects were

sporadic.

It should be noted that at least 18 (out of 70) persons with duplication 7q11.23 do not have any physical and psychical abnormalities: most of them are parents or siblings of the affected patients. Therefore, findings of this duplication cannot be a 100% guarantee of any pathological features.

*Duplications 7q21–q32*

This group includes ~30 patients with different duplications within this region. The exact position of breakpoints and size of duplicated segment were different in different patients. There is no clinical syndrome associated with duplication of this region.

Almost all patients reveal a delay in physical and psycho–motor development. Defects of the skull are not characteristic, but 2 patients had unusually large fontanels. Cleft palate, microphthalmia, blepharophimosis, retro–auricular tags, narrow ear canals, and lobulated tongue were reported in one patient, each. Hearing impairment was mentioned twice.

The most common internal defects are heart defects, reported in 5 patients. They include two life–threatening conditions: interruption of the aortic arch and truncus arteriosus. Several patients show significant kidney abnormalities, including dysplastic kidneys (2), absence of one kidney, hydronephrosis, and dilated renal pelvis. Two patients with the same small duplication of 7q21.13 have diaphragmatic hernia.

Psychical abnormalities are not typical: only one patient had autism and one had schizophrenia.

Direct transmission of trisomy for this area of 7q from unaffected parents has not been reported.

*Distal duplications 7q*

This group includes 56 patients with isolated duplications of the distal segments, mostly distal to 7q32. However, patients with duplications from 7q22 to 7qter or from 7q31 to 7qter were also included in this sub–group. The size of the duplicated segments and the position of the breakpoints were different in almost all patients.

These patients have a serious delay in psycho–motor development, although a delay in physical development was not so obvious. Cleft palate was found in 7 patients (with cleft lip in one of them). A short neck was reported in 11 patients.

Abnormalities of the brain are relatively common. The most frequent defect is hydrocephaly (7 patients). Six patients have abnormal corpus callosum (with hypoplasia in five of them). Other brain defects include arhinencephaly, hypoplastic cerebellum, hypoplastic cerebellar vermis, holoprosencephaly and agyria. Two patients (both with duplication of the 7q32q34 segment) revealed a hypoplastic optic nerve – defect uncommon for patients with a chromosomal imbalance.

Congenital heart defects were diagnosed in 7 patients, but none of these defects was life–

threatening. Defects of the respiratory system include hypoplastic lungs (2), trilobed left lung (normally the left lung has two lobes) and hypoplastic epiglottis. Defects of the gastro–intestinal tract (gut malrotation, Hirschsprung's disease, and an anterior position of the anus) were found in one patient, each.

Defects of the musculo–skeletal system are relatively mild. They include scoliosis (8), dislocation of the hips (5), and 11 pairs of ribs (3). Other abnormalities ("missing fingers", finger–like thumbs, camptodactyly, contractures, short 1st toes) were reported in one patient, each.

Two patients reveal hearing impairment. Three patients reportedly have seizures. Autistic features were found only once.
In total, distal trisomy 7q does not constitute a clinically recognizable syndrome.

*Duplication 7q36.3 (ZRS duplication)*

The distal part of 7q contains the SHH gene, important for the development of different systems, including extremities. This gene itself is under the control of another genetic unit — the ZRS (a regulator sequence of the zone of polarized activity). Physically the ZRS structure is ~1 Mb away from the SHH gene. It is known that several forms of preaxial polydactyly are linked to 7q36. Further analysis shows that some forms of the pathology are caused by mutations of the ZRS unit, whereas other related forms are caused by tiny duplications of this area. There are ~10 pedigrees with apparently dominantly inherited forms of preaxial polydactyly (isolated or with other limb defects) where it was shown that these defects were caused not by mutations, but by microduplications of the ZRS unit. These patients have only limb defects, but their intellectual development is normal and they do not have other abnormalities. Defects of the extremities include triphalangeal thumbs, preaxial polydactyly, and sometimes complex polysyndactyly. These defects affect mostly upper extremities, but involvement of the lower limbs is also reported. Clinically pathology caused by the ZRS duplications may be described as Haas type polysyndactyly (I) and preaxial polydactyly with triphalangeal thumbs (II). In some families, however, some patients had phenotype I and others had phenotype II.

In all studied families, patients without limb defects did not have the ZRS duplications and, all patients with the ZRS duplications were clinically affected.

The severity of clinical manifestations does not depend on the size of the duplication. The patients with 0.7 Mb duplications involving the ZRS have the same manifestations as the patients with 0.1 Mb duplications of this area. One question, however, remains to be open.

There are ~40 patients with pure duplications of large segments of distal 7q, including the area of the ZRS unit, and >100 patients with these duplications in association with other chromosomal pathology who did not have limb defects. Most likely, the duplication of the ZRS unit is a necessary, but not the only, factor for the development of limb defects in these patients.

**Trisomy 7**

Trisomy 7 occurs more often than trisomies 2-6. There are at least 35 patients who had

trisomic cells in their tissues (above ~10 observations of trisomy 7 confined to placental tissues). Most known patients were mosaics, but five patients had trisomy 7 in all examined cells.

All persons with full trisomy 7 had severe birth defects. Potter sequence (absent or severely dysplastic kidneys) was reported in two of them. Another had “single eye”, abnormal anterior chamber of the eyes, cleft palate, tetralogy of Fallot, pyloric stenosis, omphalocele, atresia ani, scoliosis, ambiguous genitalia, and persistent Müllerian ducts. It should be noted that cystic kidneys (and other manifestations of Potter sequence) were found in two fetuses with non-mosaic “trisomy C” reported before individual identification of chromosomes became possible. Most researchers believe that these fetuses actually also had trisomy 7.

Abnormalities of the kidneys were found also in five persons with mosaic trisomy 7: three had very serious defects (bilateral renal agenesis, polycystic kidneys), and two had relatively mild defects (hydronephrosis, pyeloectasia).

Most patients with mosaic trisomy 7 however do not have serious defects of the brain or internal organs.

The most remarkable manifestations in these patients are streaks of hypo- and hyperpigmented areas on the skin, located along the so-called Blaschko’s lines. Some patients with it were diagnosed as having hypomelanosis of Ito, and others as pigmentary mosaicism or swirly hypopigmentation. Independently of the name of this condition, all affected patients basically have the same defect in the skin pigmentation. Pigmentary anomalies were reported in 50% of all patients with mosaic trisomy 7.

Cerebellar defects (cerebellar hypoplasia, Dandy-Walker malformation) were found in 3 patients. Two more patients had microcephaly.

Facial dysmorphism is relatively common, two patients had preauricular pits. Cleft palate or bifid uvula was found 3 times; one child had cleft lip and palate. Hearing loss was reported twice. In most patients the delay in psycho-motor development is relatively mild.
Heart defects (all non-life-threatening) were found in 3 patients. There are sporadic reports of hypoplastic radial bone, rhizomelic shortness of long bones, camptodactyly, or short thumbs. In the absence of cystic kidneys vital prognosis for the patients with mosaic trisomy 7 is very good.

The origin of a normal cell line in persons with mosaicism sometimes is caused by the “rescue” mechanism when an additional chromosome became lost from the trisomic cell. As a result, however, a cell with the normal chromosome number may have two identical homologous chromosomes from the same parent. Such phenomenon is known as uniparental disomy.

Uniparental disomy 7 may be one of causes of Silver-Russell syndrome, which is characterized by intrauterine and postnatal growth retardation, triangular face, relative macrocephaly, and truncal asymmetry. There are four patients with mosaic trisomy 7 and manifestations of Silver-Russell syndrome. All of these patients had maternal uniparental disomy in cells with 46 chromosomes.