



Chromosome 5

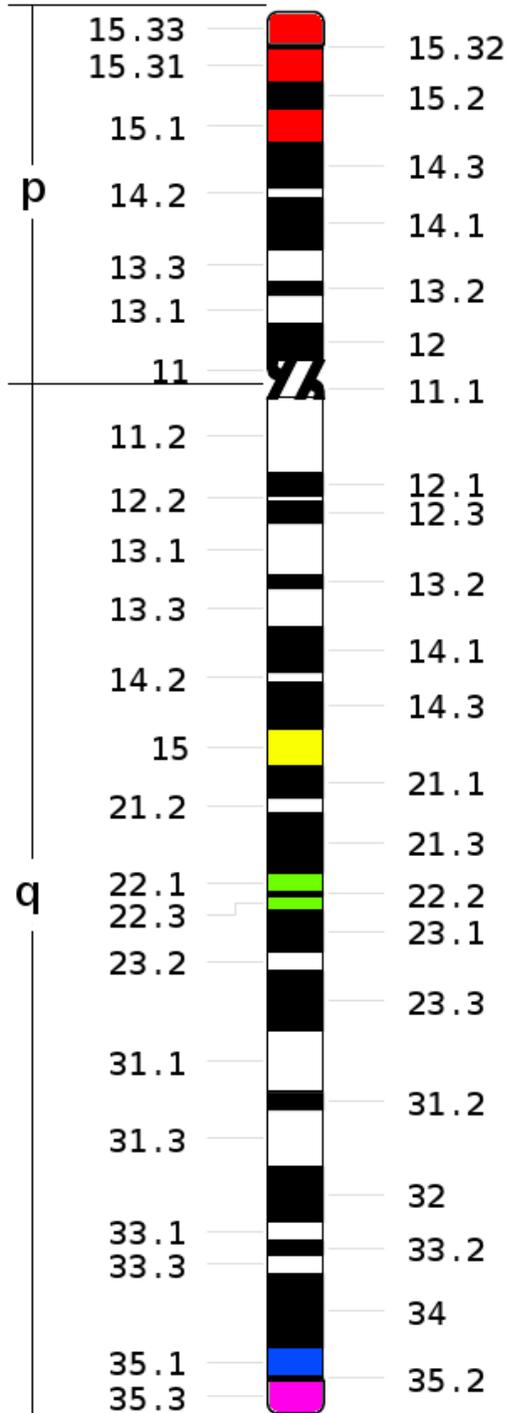
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Introduction

The size of chromosome 5 (180 Mb) and the ratio between the short arm (45 Mb) and the long arm (135 Mb) are very similar to those parameters for chromosome 4. Although chromosome 5 has ~6% of the total length of human genome, it has only ~900–1,000 genes (~3% of the total number of the human genes). Therefore, this chromosome has a low mean number of genes per unit of genetic material.

The total number of persons with structural abnormalities of chromosome 5 is ~1,200, including ~850 patients with different deletions. However, more than 600 of these patients had cri-du-chat syndrome. All other types of deletions of this chromosome are relatively rare.

Cri-du-chat syndrome, caused by deletions of the distal part of 5p, is known from the 1970's. This deletion has been studied in detail. Other types of deletions of 5p (del 5p13.2 causing rare instances of de Lange syndrome) and almost all deletions of the long arm are not well characterized yet. Some of these syndromes (del 5q14.3q15, del 5q35.1 or del 5q35.3) have been described only after the invention of molecular cytogenetics. It is obvious that further details about these syndromes, as well as clinical syndromes associated with the loss of relatively large segments between 5q22 and 5q35 will be delineated in the nearest future.

Deletions of Chromosome 5

The genetic size of the chromosome 5 is ~180 Mb, where the short arm is ~45 Mb. Deletions of the short and long arms cause several syndromes. "Cri-du-

chat” syndrome, caused by deletion of 5p15, is the most well-known syndrome caused by abnormalities of chromosome 5.

Deletions of 5p

“Cri-du-Chat” (or “Cat Cry” Syndrome)

“Cat cry” syndrome caused by a deletion of the distal part of 5p (5p15) is the most frequent (and probably most well clinically studied) syndrome, caused by a visible structural autosomal imbalance. The syndrome was described in 1963 by Lejeune et al. in three patients with a characteristic phenotype and a deletion of the short arm of one of the B-chromosomes. Later, it became clear that the B-chromosome deleted in these patients was chromosome 5 (deletion of the short arm of chromosome 4 causes Wolf-Hirschhorn syndrome).

The unusual name of the syndrome is caused by a very characteristic cry of infants with this condition, which is similar to mewing of a cat. “Cri-du-chat” syndrome (or its English equivalent “cat cry” syndrome) became commonly accepted terms. The syndrome occurs at least in 1 out of 40,000 newborns. Girls are more frequently affected (in an approximate ratio of 4:3).

The infants with cri-du-chat syndrome usually have prenatal hypoplasia (low birth weight after a normal 40-wk pregnancy), microcephaly, hypotonia, preauricular tags or fistulas, facial dysmorphisms (hypertelorism, epicanthus, down-slanted palpebral fissures, broad nasal bridge, micrognathia, and low-set ears). These findings, however, are not specific and (except for preauricular tags or pits) may be found in many conditions caused by a chromosomal imbalance. The characteristic meowing-like cry seems to be pathognomonic for this disorder. It should be noted, however, that this cry disappears in older children and usually cannot be heard in patient older than 2–3 years.

There are some other findings typical for newborns, which became less evident in older children and disappear in adults. For example, the frequently mentioned round face with full cheeks in infants became elongated with normal (or sunken) cheeks in teenagers and adults.

Microcephaly, which is an almost constant finding, causes significant cognitive, speech and motor delay.

The typical cry and microcephaly are hallmarks of the syndrome in infancy; microcephaly, facial dysmorphisms and psycho-motor retardation are main manifestations in children above 2–3 years.

There were several studies aimed to understand the mechanisms of the high-pitched cry in these children, but structural defects of the larynx (laryngeal hypoplasia, floppy epiglottis, asymmetric vocal cords) can give only partial explanation of this cry.

Most patients have short fingers, single palmar (simian) crease and some mild abnormalities of extremities (dysplastic hips, partial syndactyly 2–3 toes, hyperextensible joints).

Very common congenital heart defects are found in ~25% of patients. Most prevalent forms of the heart defects are atrial septal defects (ASD), ventricular septal defects (VSD), persistence

of ductus arteriosus, sometimes tetralogy of Fallot or other defects.

Cleft palate or bifid uvula is a frequent finding, but cleft lip is found in a very small proportion of the patients. Hearing impairment is noted in ~1/3 of patients. It should be noted that ~10 patients with cri-du-chat syndrome also had manifestations of Goldenhar syndrome (hemifacial microsomia [hypoplasia of one side of the face], epibulbar dermoid, and absence or severe hypoplasia of one ear). Some of these patients did not even manifest typical cri-du-chat syndrome features, although they had a typical 5p deletion. The reasons of this rare association remain unknown.

At least 1000 patients with this syndrome have been described, and the spectrum of associated defects in these patients is very wide. There are numerous descriptions of defects of the brain (Dandy-Walker malformation, encephalocele), gastro-intestinal system (megacolon, intestinal malrotation, anal atresia), and kidney defects (hypoplasia, hydronephrosis, horseshoe kidney). However, patients with unusual manifestations have a greater chance of being described. All of these defects may not be considered as typical (or frequent) manifestations of the syndrome.

Although heart defects and pneumonia may be deadly for some infants, most patients now survive to adulthood.

Association of mental retardation and serious behavioral problems are typical for the patients after 7-8 years of age. Aggression, hyperactivity, self-injurious behavior, and clumsiness seem to be typical for older patients. Autistic features, however, are not typical. Most patients have increased sensitivity to loud sounds (hyperacusia), which causes auditory discomfort.

Deletion of the distal part of 5p (5p15 segment) is a genetic basis of the syndrome. Almost 80% of patients have sporadic rearrangements (deletions or sporadic translocations); ~15% of patients may have an additional imbalance as a result of malsegregation of parental translocations or inversions. Patients with an additional imbalance may manifest some abnormalities not characteristic for "pure" deletions. A small group of patients has mosaicism (with a normal clone) or more complex rearrangements. There are reports of direct transmission of a deleted chromosome from a mildly affected mother, but the incidence of direct transmission is very low.

There were several attempts to map regions which cause the main clinical manifestations of the syndrome. There are at least two non-overlapping regions within 5p15 responsible for "cat's cry" (1.5 Mb within 5p15.31) and for dysmorphic features (2.4 Mb within 6p15.2p15.31). Patients with very distal 5p15.33 deletions may have only speech delay, but no other manifestations of the syndrome. A significant number of patients may have more proximal deletions also involving 5p14 or even 5p13. Most "atypical" findings may be attributed to these deletions, although del 5p15 is sufficient to produce a typical phenotype.

Genetic risk for the siblings of the affected child depends on parental karyotypes: it will be negligible if parental karyotypes are normal, relatively high (usually ~15-20%) if one of the parents has a translocation or inversion, and very high, if the mother has a deletion.

There are no satisfactory biochemical or ultrasound markers, which allow suspicion of cri-du-chat syndrome in a fetus. Cytogenetic study remains the only reliable test for identification of

the syndrome, but this study is performed only for the women in a “risk group”.

There are many sources of information about cri-du-chat syndrome and several support groups devoted to patients with this pathology.

Deletion of 5p13.2 and de Lange Syndrome

Cornelia de Lange syndrome is a complex of congenital malformations characterized by severe prenatal (and postnatal) hypoplasia, microcephaly, typical facial features, and, in many cases, underdevelopment of extremities (oligodactyly or monodactyly). In most patients, the syndrome is caused by mutations within the NIPBL gene. The genetic position of this gene is 5p13.2. Deletions (or disruptions) of this gene may also produce the de Lange syndrome phenotype. There are several reports on patients having proximal deletions of 5p (involving 5p13.2) who had all features of de Lange syndrome. In some other patients, the syndrome was caused by translocations with a breakpoint in 5p13.2 disrupting the NIPBL gene. However, these deletions and translocations are rare (less than 10 such patients have been reported so far), and deletions of 5p13.2 are not the cause for any significant number of de Lange syndrome.

There are several reports on other types of interstitial deletions 5p (not involving either NIPBL gene or regions responsible for cri-du-chat syndrome). Clinical characteristics of these patients are not specific and do not constitute any recognizable syndrome.

Deletions of 5q

The long arm of chromosome 5 is a very large segment of DNA; its genetic size is ~135 Mb. Nevertheless, deletions of 5q are relatively rare. The first report about deletion 5q was published in 1980 (at least 250 patients with deletions of 5p were described at that time). It can be explained not only by the absolute rarity of these deletions, but also by a character of banding of 5q: for example del(5)(q13q15) can be easily misinterpreted as del(5)(q15q22) and vice-versa. Naturally, the scientists were not inclined to publish reports without precise delineation of the deleted segment. Introduction of molecular methods of cytogenetic investigation produced several dozens of new reports of various 5q deletions. Some of these “new” deletions may constitute new syndromes.

Deletion of 5q14.3q15

In 2008–2009, three groups from Italy, Germany and France reported ~10 patients with deletions 5q14.3 (sometimes with involvement of 5q15). Several more patients were described by other investigators.

Severe psycho-motor retardation and muscular hypotonia are the common findings in all of these patients; almost all children have epilepsy or febrile seizures. Stereotypic movements are another typical manifestation. Dysmorphic features are relatively mild: most patients have high and broad foreheads, up-slanted palpebral fissures, short nose, and small chin. However, these features are non-obligatory and non-specific.

MRI of the brain reveals hypoplastic corpus callosum, periventricular heterotopias (clusters of neurons placed in unusual places along the lateral ventricles), and hypoplastic optic nerves.

Some scientists believe that these MRI–abnormalities are the most typical manifestation of this deletion.

Some patients had mild syndactyly of 2–3 toes; coloboma iris was found in two patients. Several more defects (polydactyly, absent distal phalanges on the foot, sub–sternal fistula) were found in one person each. Not a single patient had defects of the internal organs (heart, lungs, gastro–intestinal tract, or kidneys).

In all cases, deletions were sporadic. The size of deletions varied from ~1.5 Mb to 17 Mb, sometimes involving the proximal part of 5q15. Some authors think that the deletion of the gene GPR98/MASS1 is responsible for seizures in these patients; other scientists believe that haploinsufficiency for the gene MEF2C causes the main manifestations of this syndrome. Additional investigations are necessary both to delineate clinical boundaries of this syndrome and to find the genes responsible for its manifestations.

Deletion of 5q21q22 and Gardner Syndrome

Gardner syndrome is a familial adenomatous polyposis, which is an association of numerous polyps of the colon with soft tissue tumors (mostly in the brain and thyroid) and osteomas. If untreated, these polyps may result in the formation of colon cancer. Congenital hypertrophy of the retinal pigment epithelium, jaw cysts and sebaceous cysts are additional diagnostic manifestations of the syndrome.

Gardner syndrome is caused (usually) by mutations of APC gene, which is located at 5q21q22 (its position is from 112.1 to 112.2 Mb). The syndrome will also occur if this segment of 5q is deleted.

There are ~25–30 reports of Gardner syndrome as a result of deletions involving 5q21q22. Usually these patients have (above Gardner syndrome) mild developmental delay. The associated loss of more proximal or more distal genes may produce other abnormalities, both morphological (bifid uvula, dislocation of the hips, horseshoe kidney) and functional (deafness, seizures). One of these additional defects may not be considered as a frequent manifestation of the syndrome.

From the genetic point of view some patients inherited their deleted chromosome from one of the parents (also affected). In other families, deletions occurred de novo or resulted from insertion in one of the parents.

Other interstitial deletions within the 5q22 area do not constitute recognizable syndromes. It should be mentioned, however, there was one family with del (5)(q22q23.3) due to paternal insertion (10;5) where four affected siblings had arthrogyriposis, polydactyly and cleft palate (one of them also had spina bifida and horseshoe kidney).

Deletion of 5q35.3 and Sotos Syndrome

Sotos syndrome is characterized by macrosomia [large size of the body], advanced bone age, macrodolichocephaly [large skull elongated in antero–posterior axis], acromegalic features and pointed chin. Some patients may have seizures. Visceral abnormalities are uncommon. The finding of Sotos syndrome in a child with a balanced translocation t(5;8)(q35;q24.1) lead

to the discovery of the NSD1 gene, located at 5q35.3. Further studies showed that most patients with Sotos syndrome have intragenic mutations in the NSD1 gene, but a significant number of patients have cytogenetically recognizable deletions of the whole gene. Several dozen patients with Sotos syndrome caused by such deletions have been described in the literature. Association of Sotos syndrome with developmental delay should be an indication for cytogenetic study.

Most of these patients have a typical deletion of ~2.0 Mb (175.4–177.4 Mb), but some patients have both smaller and larger deletions. Patients with larger deletions may have some additional abnormalities.

Deletion of 5q35.1

There are ~15 reports of patients with deletions involving 5q35.1. Most of these children have very serious heart defects — tetralogy of Fallot, Ebstein anomaly, transposition of the great arteries, or double outlet of the right ventricle. Further studies showed that the deletion of the NKX2-5 gene, which is located at 5q35.1, is responsible for the origin of these heart defects. The critical segment is from ~172.0 to 172.7 Mb. The patients with deletions involving more proximal areas of 5q35.1 (to ~171.7 Mb) do not have heart defects.

Another frequent abnormality in these patients is microcephaly, which was noted at least in 1/3 patients. Other defects of the skull and brain (Dandy–Walker malformation, arhinencephaly, parietal foramina, hydrocephaly) and eyes (microphthalmia, hypoplastic optic nerves) have been also reported. One patient with holoprosencephaly had a deletion of the proximal part of 5q35.1 (170.5–171.76 Mb), and it is likely that the gene responsible for brain defects may reside in this area. Some patients had camptodactyly, syndactyly, agenesis of one kidney, hydronephrosis, cleft lip and palate (or bifid uvula), atresia ani or intestinal malrotation, but none of these abnormalities may be considered as frequent manifestation of this syndrome. Manifestations of Sotos syndrome also may be found if the deletion involves the 5q35.2 region.

Deletion of 5q35.3

Deletion of the subtelomeric region of 5q (5q35.3) seems to be a very rare condition. There are only several reports on patients having this deletion of the most terminal part of 5q (~3.5 Mb). These patients have lymphedema (which starts to develop prenatally), muscular hypotonia, short neck and multiple minor anomalies (frontal bossing, epicanthus, mild micrognathia, bell-shaped chest, short fingers, camptodactyly). However, the number of known patients is still too low to make a final conclusion about phenotypic manifestations of this condition. If the deletion also involved the 5q35.2 segment, clinical manifestations of Sotos syndrome may be expected.

The publication of Rauch and Dörr (2007) may give a more detailed description of subtelomeric deletions of 5q.

Ring Chromosome 5

Ring chromosome 5 occurs infrequently. Since 1965, there have been reports of only about 24 patients with this abnormality. Two of these patients were mosaics with the normal clone,

two others were mosaics with a 45,-5 clone. Most patients with ring chromosome 5 reported before 1990 had a clinical resemblance to cri du chat syndrome, including such manifestations as microcephaly, hypoplastic larynx, or preauricular tags. Most patients described after 1990 had very unspecific manifestations, including seizures, scoliosis, and ventricular septal defect.

Some patients who were studied in recent years had an actual loss of the genetic material either only from the short arm or only from the long arm. One patient did not lose any genes; only telomere sequences were lost upon formation of the ring.

Familial transmission of ring chromosome 5 from the mother was reported in one family; all other observations of r(5) were sporadic.

Partial Trisomies for Chromosome 5

Partial Trisomies 5p

In most patients, trisomy for the short arm of chromosome 5 is associated with partial monosomies for 5q (as a result of inversion), partial monosomies for other chromosomes (usually as a result of translocations), or with other forms of autosomal imbalance. This additional imbalance (especially partial monosomies) affects clinical manifestations in the patients. However, there are more than 100 reports regarding patients with “pure” trisomy 5p.

From the cytogenetic point of view, all of these patients may be divided into 4 groups: patients with a trisomy for a whole (or almost whole) 5p, patients with a trisomy for the distal half of 5p, patients with a trisomy for the distal segment of 5p (5p14–pter), and patients with tetrasomy 5p (these patients have 4 copies of the whole material of 5p). Surprisingly, none of these variants of trisomy (or tetrasomy) 5p constitutes a clinically recognizable syndrome.

Complete Trisomy 5p

Patients in this group have trisomy for the whole 5p, or for the segment 5p11–pter. Only 12 patients with such a variant of “pure” trisomy 5p have been reported so far.

Most of these patients have serious abnormalities of the brain and internal organs. The most common brain defect is hydrocephaly, reported in 4 out of 12 children. One more child had unusually wide cranial sutures.

Congenital heart defects were noted in 6 patients, including at least one person with a transposition of the great arteries. Heart defects in other patients were not so severe and included ventricular and atrial septal defects, stenosis of the pulmonary artery, or patent ductus arteriosus. Other defects include cataract, corneal opacity, abnormal larynx, branchial abnormalities, eventration of the diaphragm, and hydronephrosis. There is no typical pattern of facial dysmorphism, but some patients had narrow auditory canals, preauricular tags, macroglossia (enlarged tongue) and a short neck with redundant skin.

Vital prognosis depends on the severity of the defects of the brain and internal organs, which present in almost every person in this group.

Trisomy 5p13pter

There are ~45 patients having this type of trisomy 5p as a sole abnormality. Although the precise length of trisomic segment is different in different persons, roughly, the distal half of 5p is duplicated in all of these patients.

A significant number of the patients have defects of the brain and heart. The most common brain defects are agenesis or dysplasia of the corpus callosum (6), hydrocephaly (2), or hypoplastic cerebellum (2). There are sporadic reports of lissencephaly [smooth brain], pachygyria, craniosynostosis, Dandy–Walker anomaly, or “dilated brain ventricles”. At least 5 patients in this group had seizures. Reported eye defects include microphthalmia (2), coloboma (2), cloudy cornea and cataracts. Two children had cleft lip and palate.

Facial abnormalities include blepharophimosis (3), absent or reduced eyebrows (2), macroglossia (5), and preauricular pits (3). Hearing impairment was reported in 2 patients.

Defects of the extremities are usually mild and include hypoplastic 4–5 fingers (2), tapering fingers (2), long fingers (2), hip dislocation (2), postaxial polydactyly (1), and hypermobility of joints (1). Reported heart defects include ventricular septal defects (4), patent ductus arteriosus (2), atrial septal defect (1), and coarctation of the aorta (1). At least 3 patients in this group had laryngeal stenosis, and one had abnormal lobation of the lungs. Defects of the gastro–intestinal system (omphalocele, pyloric stenosis) or genitor–urinary system (hypoplastic kidneys, hydronephrosis, septate uterus) are uncommon.

Generally, the patients with this trisomy have relatively mild internal defects (if any), and vital prognosis is favorable. Most patients, however, have a delay in psycho–motor development, usually relatively mild.

Distal Trisomy 5p (5p14–pter or 5p15–pter)

Trisomy for the distal segment of 5p as a sole abnormality is known in 43 patients (including 2 children with tetrasomy for 5p14–pter). Differences in the length of the duplicated segment and in the position of the breakpoints are responsible for significant clinical variability in this group of persons. Some patients have facial dysmorphism, but others do not. Morphologic defects of the brain are occasional: craniosynostosis, microcephaly, hydrocephaly and hypoplastic cerebellum were reported in one patient, each. Four patients in this group had seizures.

Defects of the extremities are mild and also occasional: arachnodactyly (2), scoliosis (2), broad or proximally placed thumbs, syndactyly, brachydactyly, pectus excavatum. Heart defects were found in 5 patients, including atrial septal defects (3), ventricular septal defect, coarctation of aorta and small abnormalities of other blood vessels (some children had an association of several defects).

Abnormalities of the gastro–intestinal system and kidneys have not been reported. Genital defects include occasional reports of hydrocolpos, abnormal formation of Müllerian ducts and hypospadias. At least 2 patients in this group were obese.

Delay of psycho–motor development is usually mild; some patients are able to attend regular

classes. Three patients in this group had autism. Two children with tetrasomy for 5p14–pter had a much more severe phenotype: both had serious heart defects, contractures and seizures. One of these children also had eye defects (retinal dysplasia, coloboma of retina, and choroid), dysplastic kidneys, diaphragmatic eventration, and intestinal malrotation; another had cleft palate and scoliosis.

Tetrasomy 5p

There is a small group of patients with tetrasomy for the whole short arm of chromosome 5 as a result of an additional isochromosome 5p. The karyotype of this type of person has 47 chromosomes: a normal set of 46 chromosomes plus an additional metacentric chromosome, which consists of two short arms of chromosome 5 joined by the centromere. This mechanism is common for the short arms of chromosomes 9, 12 and 18 (where there are specific syndromes caused by isochromosomes 9p, 12p and 18p), and occurs rarely for the short arms of chromosomes 5 and 8. Because isochromosomes 5p occur mostly post–zygotically (i.e. after fertilization), almost all patients are mosaics: they have a normal clone 46,XX (or 46,XY) and a clone with an additional isochromosome 5p. Even if mosaicism was not reported, it is unclear whether the patient really does not have a normal clone or if a normal clone just has not been found. It should be taken into account that both arms of an isochromosome are completely genetically identical and, as a result, the affected person has 3 copies of the genes of 5p from one parent and only one copy of the 5p genes from another parent.

Clinical manifestations of tetrasomy 5p depend on the proportion of an abnormal clone and the distribution of cells with the additional chromosome in different tissues. It explains why at least 4 out of 14 reported patients with an additional isochromosome 5p did not have any birth defects or their phenotypic manifestations were limited to areas of skin hypopigmentation. However, in most patients, clinical manifestations are very serious. Congenital heart defects, including tetralogy of Fallot, atrio–ventricular communication and atresia of the pulmonary artery were reported in 5 patients. Two infants had diaphragmatic hernia or relaxation of the diaphragm. Hypoplastic lungs were reported even in patients without diaphragmatic defects. Three patients had kidney abnormalities. Other abnormalities include cystic hygroma of the neck (3), short neck (2), cleft palate (2), preauricular pits (2), and sporadic observations of hydrocephaly, hypoplastic cerebellum, macroglossia, omphalocele, atresia ani, hypospadias and uterus bicornis. It shows that the entire short arm of chromosome 5 harbors numerous genes involved in different areas of morphogenesis.

However, not a single group of trisomies 5p constitutes a clinically recognizable syndrome.

Partial trisomies 5q

The long arm of chromosome 5 is a very large segment of genetic material; its length is ~135 Mb. However, isolated trisomies 5q are relatively rare. There are just a little more than 100 reports on patients with this pathology. Of course, there are numerous reports on trisomy 5q (especially distal segments of 5q) in association with another imbalance (mostly deletions of other chromosomes due to translocations), but associated monosomies may significantly change phenotypic manifestations of trisomy itself.

All reports on trisomies 5q may be arbitrarily divided into three groups: trisomies for the

proximal part of 5q (5q11 or 5q12 until 5q22), trisomies for the “central” part of 5q (affecting mostly segments 5q21/22–5q31); and distal trisomies, involving 5q31 and more distal areas. Of course, each patient having any of the 5q duplications is unique both by the size of the duplicated segment and by exact breakpoints. This explains the very wide clinical heterogeneity, which may be found in each of the three main groups.

Proximal trisomies 5q

There are ~30 reports on patients having trisomies within the proximal segment (from the centromere until 5q22). Some patients have large duplications covering almost all this segment; others have relatively small duplicated segments, sometimes less than 1 Mb.

Facial dysmorphism is not characteristic. Microcephaly, abnormal corpus callosum, microphthalmia, and preauricular tags were reported in a few patients, but the vast majority of affected persons do not have these defects. At least 3 patients with such trisomies had craniosynostosis. There are sporadic reports of branchial cysts, cleft palate, and hearing impairment.

The most common internal defects are heart defects, reported at least in 9 patients, including some life-threatening conditions (hypoplastic aortic arch, transposition of the great arteries, atresia of pulmonary artery, and tetralogy of Fallot).

Several patients had kidney defects — cystic kidney, duplication of the kidney or ureters, nephroptosis, and atresia of the ureter. However, most patients did not have any kidney defects. Two patients had pyloric stenosis (critical segment 5q13); other defects of the gastro-intestinal system have not been found.

Abnormalities of the skeleton and extremities are usually mild and include partial syndactyly, scoliosis, lordosis, supernumerary ribs, and pectus excavatum. Primary hypogonadotropic hypogonadism reported in several adult patients is caused by the duplication of the 5q12.3q13.3 segment.

Most patients have a different degree of delay in psycho-motor development. Autism and schizophrenia have been also reported in several persons with proximal trisomy of 5q.

A wide spectrum of manifestations in patients with proximal trisomies of 5q does not allow a clinical recognition of this condition.

Trisomies for the “medial” segment of 5q

There are 24 patients who may be considered as patients with a trisomy for this segment of 5q. Broad clinical heterogeneity does not allow considering this trisomy as a recognizable entity. Manifestations in various patients are extremely different. Some do not have any serious defects and reveal only a mild delay in psycho-motor development. Other patients, however, show numerous abnormalities, including life-threatening defects.

The most common defects are heart defects, reported in 9 out of 24 patients. Although tetralogy of Fallot and double outlet right ventricle have been reported, most patients have relatively mild heart abnormalities.

Three patients with this kind of trisomy 5q had ectrodactyly (absence of one or several digits

where both the 1st and 5th digits are preserved). Ectrodactyly is a relatively uncommon birth defect, and there is no doubt that the occurrence of ectrodactyly in 3 patients having this trisomy provides strong evidence that duplicated segment includes one or many genes, involved in the formation of the distal limb. The critical segment for ectrodactyly is 5q21q31. Other defects of loco-motor system (hypoplastic tibia and fibula, brachydactyly, syndactyly, contractures, fusion of several ribs) cannot be considered as characteristic, because they were reported in 1–2 patients, each.

The same is true for brain defects (microcephaly, arhinencephaly, hypoplastic corpus callosum), cleft lip and palate, and defects of the kidneys (cystic kidney, hydronephrosis).

Several patients had abnormalities of skin pigmentations (café-au-lait spots, areas of depigmentation).

Most affected persons have a significant delay in psycho-motor development. At least 2 patients had seizures.

Distal trisomies 5q

There are ~50 patients with isolated trisomies for the distal segments of 5q. At least 80 more patients had distal trisomies of 5q in association with other types of chromosomal imbalances.

There is a strong association between very distal trisomy 5q (5q35-qter) and the so-called Hunter-McAlpine syndrome. The main manifestations of this syndrome include microcephaly, craniosynostosis, short stature, characteristic facial features (“almond-shaped” palpebral fissures, down-turned corners of the mouth) and mild or moderate delay in psycho-motor development. This syndrome was considered to be an autosomal dominant condition, but re-examination of the original patients and patients from some other families showed that they have small duplications of 5q35qter. Some patients studied by conventional cytogenetics and considered to have a normal karyotype could not be re-examined. Therefore, the possibility of a “cytogenetically normal” variant of the Hunter-McAlpine syndrome could not be excluded (at least so far). Numerous reports of microcephaly, craniosynostosis, brachydactyly or other mild defects of the fingers (partial syndactyly, camptodactyly, and tapering fingers) in patients with distal trisomy 5q may be attributed to the duplication of the most distal segments of 5q.

Many patients (both with and without Hunter-McAlpine syndrome features) have congenital heart defects. 13 out of 19 patients with heart defects had a ventricular septal defect; abnormalities in most other patients were also relatively mild. However, there are single reports of interrupted aortic arch, right-sided aortic arch, and double outlet of the right ventricle.

Two persons with distal trisomy 5q35.1-qter had anencephaly or occipital encephalocele. Other defects of the brain and eyes are not characteristic, although there are sporadic reports of holoprosencephaly, hypoplastic cerebellum and microphthalmia. At least 6 patients had seizures. Hearing impairment was reported in 4 children.

Defects of the gastro-intestinal system have not been found. Several children had various abnormalities of the genitor-urinary system (polycystic kidneys, duplex kidney, ureteral reflux,

hypospadias, uterus bicornis), but all of these defects were reported in one patient, each.

It should be mentioned that 3 patients with the commonly duplicated segment 5q35.1 had preaxial polydactyly (an additional digit on the side of the thumb). Surprisingly, absent thumbs were reported in the only known patients with tetrasomy for the more distal segment (5q35.2q35.3). Most likely, the distal area of 5q contains at least 2 genes, which, when duplicated or triplicated, may affect the development of the limbs.

It seems that the duplication of the material of 5q31q34 produces relatively mild abnormalities, but the segment 5q35 is critical for the occurrence of clinical manifestations.

Trisomy 5

Trisomy 5 (as well as trisomies 2, 3, 4) also occurs very rarely. There are 12 reports when cells with trisomy 5 were found only in placental tissue. All patients with confined placental mosaicism for this chromosome were clinically normal.

Only nine persons with trisomy 5 in their cells have been reported so far. All of them were mosaics.

The most common internal abnormalities are heart defects reported in seven persons. These defects included life-threatening interrupted aortic arch, atrio-ventricular communication, and hypoplastic aortic arch.

Defects of the brain included encephalocele (2), agenesis of cerebellum, microcephaly, and hydrocephaly.

Two patients had pre-auricular pits.

Abnormalities of the gastro-intestinal system were represented by intestinal malrotation, bowel atresia, anal atresia, and ventral ectopia of the anus.

Diaphragmatic eventration, duplication of the collecting system of kidneys, and preaxial polydactyly were reported in one person, each.