



Chromosome 17

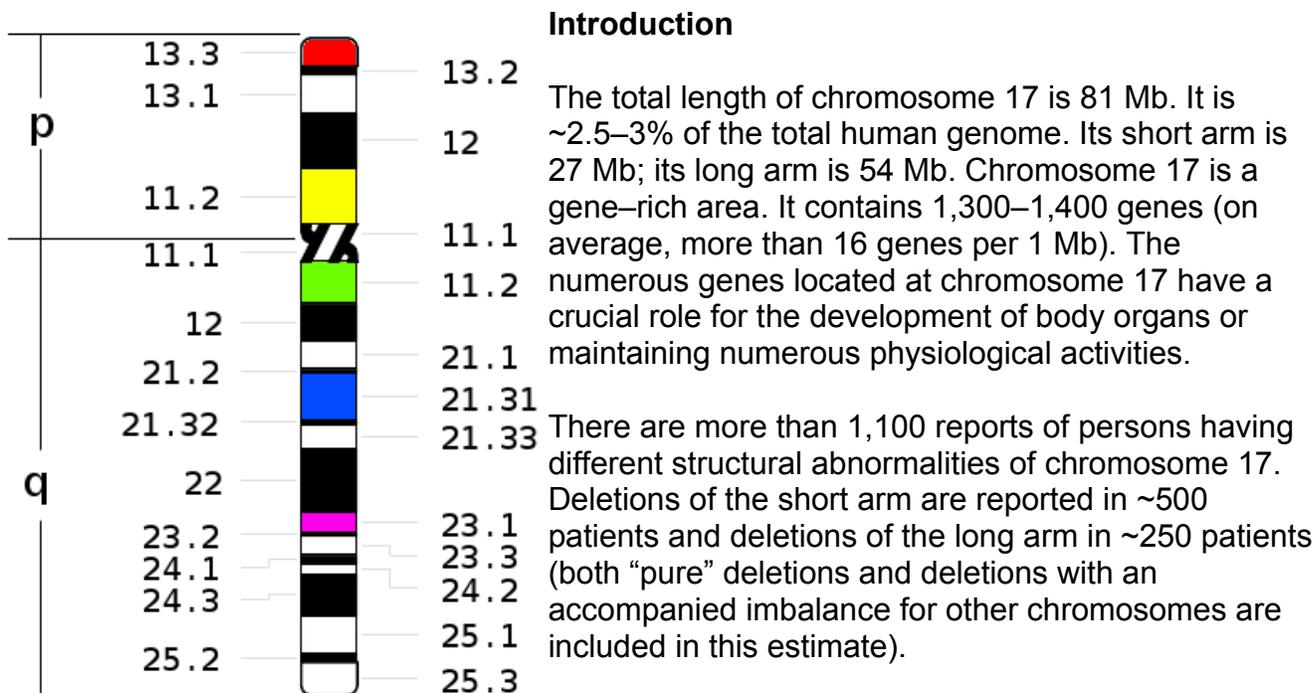
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David Adler.hum_17.gif



There are two well-known syndromes caused by deletions of the short arm. Distal deletions involving the PAFAH1B1 (LIS1) gene produce Miller–Dieker syndrome. Interstitial deletions of 17p11.2 are the genetic basis for the Smith–Magenis syndrome. Both of these syndromes have been known for decades. Syndromes caused by deletions of the long arms are not as well-known. Basically, all of these conditions became known in recent years when wide usage of molecular methods became available. Some of these syndromes caused by deletions of the “alpha”-genes for these areas produce a phenotype of monogeneous conditions (neurofibromatosis I, generalized hypertrichosis, campomelic dysplasia). Another group seems to be “real” chromosomal syndromes, where a phenotypic picture is caused by deletions of several consecutive genes or disturbed interactions between retaining genes caused by deletions.

Deletions of Chromosome 17

The genetic size of the chromosome 17 is ~81 Mb, where the short arm is ~27 Mb, and its long arm is ~54 Mb.

Deletions of 17p

There are two well-known syndromes (Miller–Dieker syndrome and Smith–Magenis syndrome) caused by deletions of 17p, and one syndrome, which started to be delineated only in 2009–2010.

Miller–Dieker Syndrome

Several publications in the 1960's described a highly unusual defect of the brain — lissencephaly (“smooth brain”). In this condition, the brain does not have normal fissures and gyri: in extreme variants, upon external examination (or on MRI films) of the brain, which normally has a walnut-similar structure, resembles an egg. In not so extreme (and much more frequent) variants, only some areas of the brain appear to be smooth or where plump gyri are divided by very shallow fissures.

There are several syndromes associated with lissencephaly. One of these syndromes (Miller–Dieker syndrome) is caused by the deletion of the distal part of chromosome 17p — 17p13.3. Although a structural abnormality of the short arm of chromosome 17 was mentioned in one of the originally described patients, the chromosomal etiology of the syndrome became obvious only 15 years later when it was found that the deletion of 17p13.3 is necessary and sufficient for the origin of this condition.

Miller–Dieker syndrome is a well-studied disorder: at least 200 patients have been reported. Later, it was shown that this area of 17p contains a gene, PAFAH1B1 (formerly the gene was called LIS1). Deletions (as well as mutations) of this gene are able to produce lissencephaly. Lissencephaly is the main, but is not the only, manifestation of the syndrome. Almost all patients have decreased head circumference, a significant delay in psycho-motor development and seizures. There is a characteristic complex of cranio-facial dysmorphism: most children have a prominent forehead, bitemporal hollowing, short nose with upturned nares, thickened upper lip, low-set ears and small jaw. Some may have cleft palate, cystic or ectopic kidneys, omphalocele, or heart defects. However, visceral defects may be considered as “additional” findings (probably caused by concomitant deletions of the neighboring genes). Facial dysmorphism is so typical that a clinical diagnosis may be suspected even before cytogenetic examination.

Deletions (and mutations) of the PAFAH1B1 gene are responsible for the isolated lissencephaly. In that context, there is a question: which genes are responsible for cranio-facial dysmorphism in Miller–Dieker syndrome patients? Several recent investigations showed that there is a relatively small group of patients with small deletions of the very distal part of 17p13.3, but not affecting the PAFAH1B1 gene. Delineation of this new syndrome caused by a deletion of the most distal part of 17p13.3 became possible only using methods of molecular cytogenetics. The patients with this condition usually have a mild delay in psycho-motor development, prominent forehead, broad nasal root, low-set ears, and thick upper lip. Some of them had eye defects (coloboma), “mild” heart defects (patent ductus arteriosus), “small” structural abnormalities of the brain, but do not have either lissencephaly or microcephaly. The tiny segment deleted in all of these patients contains the YWHAE gene. It is possible that Miller–Dieker syndrome is caused by concomitant deletions of both of these genes: YWHAE is responsible for cranio-facial dysmorphias and PAFAH1B1 is responsible for lissencephaly.

Miller–Dieker syndrome and “distal” 17p13.3 deletion syndrome are caused by deletions of

the terminal segments of 17p. In a very high proportion of families, these deletions may be due to familial translocations. Therefore, both parents of an affected child have to be tested before planning any further pregnancies.

Smith–Magenis Syndrome

This syndrome was first reported in 1986. Smith and Magenis were the first and the last authors of the original publication. The syndrome is relatively frequent. At least 300 patients with this condition have been reported. The prevalence of Smith–Magenis syndrome was estimated as 1:25.000. Although it may be an overestimation, there are no doubts that this is a very common form of chromosomal deletion.

The genetic background of the syndrome is an interstitial deletion in the segment 17p11.2. There are no “preferential” breakpoints, but, in most patients, the size of the deletion is less than 4 Mb. Larger deletions are relatively rare; most patients with larger deletions exhibit some additional manifestations. Some patients have smaller deletions, but all affected persons have deletions of the RAI1 gene, which is considered to be the main “player” determining clinical manifestations. The persons with mutations of the RAI1 gene (but without a deletion) have the most clinical manifestations of the syndrome. However, other genes within 17p11.2 also may be involved in the clinical picture.

Smith–Magenis syndrome is manifested mainly by an association of relatively mild cranio–facial and skeletal abnormalities, delay in psycho–motor development and a characteristic pattern of behavioral abnormalities. Congenital malformations are relatively uncommon. The most external manifestations are relatively unspecific. Sometimes fragile X syndrome, Angelman syndrome or autism may be initially suspected in some of the patients. A clinical diagnosis of Smith–Magenis syndrome should be confirmed by cytogenetic examination.

The birth weight is usually normal. Most infants have brachycephaly (the skull is diminished in the antero–posterior direction), a hypoplastic middle part of the broad face, deep set eyes, everted upper lip, and hoarse voice. Most patients are shorter than children of the same age. Short broad hands and feet are very common. A significant number of patients have hearing impairment, which may be caused (at least partially) by ear infections. Velo–pharyngeal insufficiency, tracheo–bronchial problems (with frequent lung infections) and scoliosis are other common manifestations of the syndrome. Systematic ophthalmologic investigations showed frequent strabismus, microcornea, myopia and retinal detachment. Almost all newborns have hypotonia, weak cry and decreased babbling. Motor skills (both gross and fine) are delayed. Seizures are observed in 20–25% of patients, although epileptiform patterns of brain activity are found in 50% of patients.

The most significant manifestation in older children is neuro–behavioral problems, which include hyporeflexia, signs of peripheral neuropathy, self–injurious behavior (usually after 2 years of age), hyperactivity, stereotypic behaviors and sleep disturbance. The stereotypic behavior includes compulsive picking or tearing at the nails and inserting foreign bodies into ears or other body orifices (the latter obsession is unique for Smith–Magenis syndrome).

Sleep problems are a very characteristic manifestation of the syndrome. The patients have a tendency for awakening at night and increased sleepiness at daytime. Usually, the patients sleep 1–2 hr less per 24 hr than other children of the same age. Shortened fragmented sleep

cycles and prolonged nocturnal awakening cause serious problems for the caregivers. This specific pattern of sleep disturbances is caused by an inverted pattern of melatonin secretion. Typically, the day–time level of melatonin is low, and the nighttime level of melatonin is high. The patients with Smith–Magenis syndrome have the opposite pattern: their daytime level of melatonin is high and their nighttime level is low. There are attempts to treat these sleep disturbances by β 1–adrenergic antagonists to suppress morning melatonin secretion and by melatonin in the evening.

At least 1/3 of the patients have abnormalities of thyroid function (low thyroxine), but this defect can be easily treated. More than 50% have an increased level of cholesterol.

Cleft palate (in rare occasions with cleft lip) is found in less than 10% of patients. A special study showed that patients with cleft palate usually have deletions extending the average size. This observation suggests the role of additional genes in the origin of this defect.

There are ~25 patients with this syndrome having congenital heart defects, including 6 patients with tetralogy of Fallot and 7 patients with ventricular septal defect (VSD). Special urologic investigations showed some kidney defects (mostly duplication of collecting system) in a small group of patients. However, only a few patients had clinical problems related with kidney defects.

Because patients usually do not have life–threatening abnormalities, they may have an almost normal life expectancy.

From the genetic point of view, almost all deletions are sporadic, and recurrence risk for further children is negligible.

Deletions of 17q

Deletions of the long arm of chromosome 17 may be subdivided into 2 groups. There are several genetic disorders (usually) caused by mutations of the genes residing on chromosome 17. Deletions of small areas of 17q may cause the same clinical consequences as mutations of these genes. There are at least four genetic conditions, which are sometimes caused by deletions of the causative genes. Deletions of other areas produce clinical abnormalities not previously known as being caused by a specific mutation. In these cases, there are losses of several contiguous genes, and these deletions should be considered as specific chromosome 17q deletion syndromes.

Neurofibromatosis I

Neurofibromatosis I is an autosomal dominant condition, which manifests itself by an association of abnormalities of skin pigmentation (multiple café–au–lait spots in children), freckles in the underarm and groin areas, and neurofibromas (benign tumors) developing under the skin and in nerves. This disease is caused by mutations of the NF1 gene located at 17q11.2. Very rarely, neurofibromatosis I may be caused by deletions of 17q11.2. If the deletion expands beyond the NF1 gene, the patients may have some additional abnormalities, including heart defects, imperforate anus, and pyloric stenosis.

Deletion 17q12

Hepatocyte nuclear factor-1 β (HNF-1 β) is a gene which plays a critical role in the tissue-specific regulation of gene expression in different organs, including the kidneys and pancreas. This gene (which resides at 17q12) is the main genetic cause of the autosomal dominant form of the maturity onset diabetes of the young, type 5 (MODY5). However, mutation studies showed that not all patients with clinically obvious MODY5 have mutations within the HNF-1 β gene. It was shown that ~1/3 of all MODY5 patients had deletions of the whole HNF-1 β gene. In most patients, these deletions also involved several neighboring genes. Approximately at the same time, the HNF-1 β gene was shown to be related to a wide diapason of kidney defects — from hyperechogenic kidneys in fetuses to evident renal abnormalities, including renal agenesis, multicystic kidney disease or hypoplastic kidneys. Also, in this group, at least 50% of patients had deletions of the whole gene. However, the methods used by this group of scientists do not allow one to judge whether HNF-1 β was the only deleted gene or if it was a deletion involving several genes. Invention of molecular cytogenetics showed that a large group of patients with a broad spectrum of kidney abnormalities (mostly cystic or hypoplastic kidneys) have a relatively small (~ 1.5 Mb) deletion involving HNF-1 β , as well as 4–5 neighboring genes. At least 35 such patients have been reported for the last 3–4 years. Clinical manifestations in the patients with del 17q12 were very polymorphous — from almost normal renal function to significant renal problems. Only 3–4 of these patients also had MODY5. It is not surprising, however, because MODY5 develops usually in young adults, and the most studied patients were children. Several patients with del 17q12 had absent uterus and vagina. Defects of genital organs also are considered a result of the deletion of the HNF-1 β gene, but other deleted genes also may be involved.

Developmental delay, cognitive impairment and seizures reported in patients with del 17q12 show possible involvement of other deleted genes. The LHX1 gene seems to be the most suspicious. Several patients with del 17q12 showed an association of kidney pathology with autism or were reported as having autism or pervasive developmental disorder (an autism-like condition) without any indication for a pathology of kidneys. All of these data show that deletions of 17q12 may be involved in neurological problems, including autism and epilepsy.

Coarctation of aorta found in two patients with del 17q12 is a direct indication of the involvement of other genes because the HNF-1 β gene does not express itself in the developing heart.

Congenital generalized hypertrichosis

This rare condition is characterized by excessive hair growth (sometimes with gingival hyperplasia). Although this disorder has been known since the 19th century, its etiology remained unclear. Very recently, it was shown that (at least in three studied Chinese families) this autosomal dominant condition was caused by a small deletion within 17q24.3q24.3. The minimal common segment deleted in all 3 families was ~550 Kb and included 4–5 genes. This deletion is more proximal than the SOX9 gene. Not a single known patient had an association of congenital generalized hypertrichosis with other congenital defects.

Congenital hypertrichosis is genetically heterogeneous: analysis of an Irish family showed no linkage to 17q24.

Campomelic dysplasia

Campomelic dysplasia is a complex of severe skeletal defects (shortness of limbs, especially legs, bent bones of the lower extremities, dislocation of hips, sometimes 11 pairs of ribs instead of 12), genital defects (ambiguous genitalia or apparently normal female genitalia in association with male karyotype), relatively large head, and Pierre Robin complex (a combination of cleft palate, small lower jaw and glossoptosis, when a tongue is placed further back than normal). Most persons with this disease have mutations in the SOX9 gene located at 17q24.3. Some patients may have balanced translocations in the vicinity of the SOX9 gene that indicated involvement of some regulatory elements located on both sides of the SOX9 gene in the origin of the syndrome. Very rarely, the syndrome may be caused by the deletion of 17q24.3. There are ~10 reports on patients with campomelic dysplasia caused by the deletion of this segment.

Deletion of 17q21.31 Syndrome

In 2006, three independent groups described several patients with a small deletion within 17q21.31. The size of the deletion (~ 0.6 Mb) was remarkably similar in all patients, although precise breakpoints were not the same. Of course, these deletions could be detected only using array-comparative genomic hybridization. Currently, there are at least 100 reported patients with this tiny deletion. However, it is virtually impossible to determine the precise number of known patients, because most reports are prepared by a collaborative efforts of scientists from different countries, and it is possible that the same patient may be counted in different publications more than once. Individual analysis is possible for ~70 patients: others were reported only as groups.

Most known chromosomal syndromes (Williams-Beuren, Miller-Dieker) were first delineated as clinical entities, and their chromosomal etiology became known later. The situation with del 17q21.31 was the opposite: first, patients with this deletion were found. As the second step, a comparison of clinical characteristics of the known patients allowed clinical delineation of the condition.

The most consistent features are global developmental delay (mild to severe) and hypotonia. Almost all patients have facial dysmorphism, which includes high forehead, elongated face, epicanthus, upward slanting palpebral fissures, long prominent ears, and everted lower lip. The facial features became coarser in adults. Dislocations of the hips, long slender fingers, and slender lower limbs are also common. Ectodermal structures such as hair, teeth and skin are frequently affected. Some patients have dry skin, eczema, ichthyosis, or missing teeth. Hearing impairment is relatively common.

Epilepsy was mentioned in ~50% of patients. At least 5 patients with del 17q21.31 had craniosynostosis. Heart defects (usually ventricular septal defect, atrial septal defect (ASD) or stenosis of pulmonary artery) were found in 15% of patients, but these defects are relatively mild and not life-threatening. Spontaneous closure of ASD was reported in several children. Agenesis or hypoplasia of the corpus callosum was found in 5-6 patients. There are several reports of hydronephrosis and doubling of renal pelvis and ureters. These defects have minimal clinical significance.

Frequent paracentric inversion in 17q21.3, which is generally considered to be a benign

variant, facilitates the occurrence of the deletion in this particular area. The critical segment of ~440 Kb, which is missing in all affected patients, involves 5 genes. The significance of the loss of each gene is still unknown.

In all patients, deletions are sporadic. Insertions and mosaicism, which theoretically can cause familial cases, have not been reported so far.

Deletion of 17q23.1q23.2

The syndrome caused by the deletion within 17q23.1q23.2 started to be delineated in 2010. There are less than 12 patients having this deletion of usually ~2.2 Mb. A peculiar chromosomal structure (large segmental duplications on both sides) facilitates the origin of deletions (as well as duplications) of this particular segment.

Clinical manifestations of the syndrome include mild developmental delay (especially delay in speech), microcephaly, postnatal growth retardation. Facial dysmorphism is not common; there are no specific facial findings which may facilitate recognition of this condition. Several patients had hearing loss, scoliosis, contractures, club foot, mild syndactyly. Mild heart defects (ASD, patent ductus arteriosus, valvular defects) were reported in one half of known patients. All of these data should be considered as preliminary. Characteristics of the syndrome will be clearer when other patients are reported.

Deletions of TBX2 and TBX4 genes, located at this segment of 17q are considered to be responsible for its clinical manifestations.

Other forms of the deletion of 17q have not been considered as known syndromes. It has to be mentioned, however, that at least 4 patients sharing deletion 17q22q23.3 had esophageal atresia. It is evident that one of the genes involved in the formation of this defect lies in this 6 Mb area of 17q.

Ring Chromosome 17

Ring chromosome 17 is a relatively rare form of ring chromosome. Only 32 patients with r(17) have been reported so far. Three of these patients had mosaicism with a normal clone, and one had mosaicism with a clone with a deletion of the short arm of this chromosome.

The gene, PFAH1B1, responsible for lissencephaly (and Miller-Dieker syndrome) is located on the distal part of the short arm of 17p. Loss of this gene caused lissencephaly and other manifestations of the syndrome (hypoplastic corpus callosum and seizures). At least six known patients with r(17) had lissencephaly.

The patients with deletions not involving the PFAH1B1 gene usually do not have serious birth defects. One patient had an association of diaphragmatic hernia, ventricular septal defect, the absence of the lobe in one lung, and duplex vagina. Morphological abnormalities in other patients were mild and sporadic: microcephaly, cataracts, exostoses, preauricular fistula, scoliosis, polysplenia (additional spleens), pyelo-ureteral duplication, and lymphedema were reported in 1-2 patients, each.

Most patients with ring chromosome 17 have a delay in physical and psycho-motor

development and seizures (16 patients in addition to patients with lissencephaly). 17 patients had multiple café-au-lait spots, and three had other types of abnormal skin pigmentation. This association is typical for neurofibromatosis 1 (NF-1). At least three patients were diagnosed as having NF-1. Occurrence of NF-1 manifestations in patients with r(17) is difficult to explain: the gene NF1 is located at 17q11.2, and this area should not be deleted in patients with ring chromosome 17.

Five patients were reported as having yellowing flecks or spots on the retina: actually this abnormality may be more frequent, because ocular fundus was not examined in all reported patients.

In one family, the patient inherited r(17) from the father.

Partial Trisomies for Chromosome 17

Partial trisomies 17p

The short arm of chromosome 17 is a relatively small part of the total human genome (~26 Mb), but duplications of different segments of 17p are responsible for several genetic conditions. Surprisingly, even 20 years ago, there was less than a dozen reported patients with trisomy 17p (including patients with an associated imbalance). Today, however, there are at least 400 reports of patients with various (mostly submicroscopic) duplications of 17p.

a) *Duplication 17p13.3 and Ectrodactyly*

Ectrodactyly is a defect of the hands and/or feet where one (or several) central digits are missing. Sometimes this defect is described as “split hand/split foot” malformation. The term “lobster claw” defect may be found in older literature. Ectrodactyly may affect only the hands or only the feet, may be unilateral or bilateral, may be associated with the underdevelopment of the long bones (a tibial defect or underdevelopment of radial or ulnar bones) or may be limited to the hands and feet.

Ectrodactyly is a genetically heterogeneous condition. It means that this defect may be caused by various chromosomal abnormalities (del 2q31, del 7q21, or dup 10q24 among others) or mutations of some genes (e.g., TP63). In 2011, the group of Canadian and American scientists reported three unrelated families with ectrodactyly and microduplication of the small segment within 17p13.3 (~1 Mb from the telomere). Later, the same American-Canadian group and another (mostly European) group decided to study the prevalence of dup 17p13.3 in the large cohorts of patients with ectrodactyly. Both groups have studied patients from 86 families with sporadic or inherited ectrodactyly and found that, in 20 of these families, ectrodactyly was caused by submicroscopic 17p13.3 duplication. Therefore, microduplications of 17p13.3 are one of the most frequent causes of ectrodactyly. The size of the duplication was different in all examined families (from 55 Kb to 394 Kb), but the only gene which was duplicated in all affected patients was the BHLHA9 gene. This tiny gene (~ 12 Kb) plays an important role in the development of the apical ectodermal ridge.

Analysis of manifestations in patients with dup 17p13.3-related ectrodactyly shows that underdevelopment of the long tubular bones (most frequently tibial defects) was found

in 17 out of 23 known families. However, patients in six families had no signs of involvement of the long bones.

Because only a small number of genes is duplicated in each affected person (the largest known duplication was less than 0.6 Mb), all reported patients are intellectually normal and do not have any associated defects. Of course, additional abnormalities may be expected in patients with significantly larger duplications.

Duplication of the critical segment of 17p13.3 does not guarantee that this person will have ectrodactyly. In several families, there were people with a duplication of the critical segment but without any clinical abnormalities.

b) *Duplication 17p13.3 (YWHAE-PAFAH1B1 Region)*

Deletions of the segment 17p13.3 produce the well-known Miller-Dieker syndrome. The main manifestations of this syndrome depend on the loss of the two genes – YWHAE and PAFAH1B1 – both located within this segment. There are ~20 reports of patients having duplications of this region of 17p13. Some scientists subdivide these duplications into 2 classes: class I (where the patients have a duplication of YWHAE, but not PAFAH1B1) and class II (where the PAFAH1B1 gene is also involved). Clinical analysis, however, does not show significant differences between these classes.

The main clinical manifestations in both groups are a delay in speech, delay in motor development, and autism. Overgrowth was reported in half of the patients in both groups. Patients with larger duplications more likely have microcephaly, dysplastic corpus callosum, heart defects, or dislocation of the hips.

It should be mentioned that at least 5-6 patients with duplication of this area also had duplications of the BHLHA9 gene, responsible for ectrodactyly (see above). However, neither patient in this group had ectrodactyly or long bone underdevelopment. Most likely, a duplication of the BHLHA9 gene is necessary for the origin of ectrodactyly, but not sufficient to produce an abnormality without the influence of some additional factors.

c) *Duplication of 17p12 (PMP22)*

Charcot-Marie-Tooth disease type 1A (CMT1A) is a very common inherited polyneuropathy. The main manifestations of this condition are abnormal velocity of nerve conduction, weakness of distal muscles, muscular atrophy, and sensory loss. This condition was considered to be an autosomal dominant trait.

Approximately 20 years ago, it was shown that the vast majority of patients without a familial history of the disease actually has small duplications within 17p12. Later it was shown that a duplication of the PMP22 gene within this area is responsible for 80-85% of sporadic cases of CMT1A.

Clinically, however, CMT1A does not seem like a “chromosomal” pathology. Treatment of this condition is usually provided by neurologists.

d) Duplication 17p11.2 (Potocki-Lupski Syndrome)

The structure of the short arm of chromosome 17 predisposes it to a specific kind of rearrangement (nonallelic homologous recombination), which may lead to reciprocal deletions and duplications for the same segment. When this mechanism was found in the majority of patients with deletion 17p11.2 (Smith-Magenis syndrome), it was proposed that some persons should have a duplication for the same region of 17p11.2. Therefore, existence of this condition was predicted before detection of the actual patients. The first patients with dup 17p11.2 were described several years later. The clinical condition associated with such duplication is called Potocki-Lupski syndrome after the names of the scientists who anticipated, and later reported, this entity. Currently, there are ~100 reports of patients with this condition, although the level of clinical and genetic examination varies from one publication to another. The Texan group (which includes L.Potocki and J.Lupski) is a leading team, collecting and reporting the large number of uniformly (and carefully) tested patients.

It was shown that ~65% of patients have a “standard” 3.7 Mb duplication, whereas others may have both larger and smaller duplications. Of course, people with larger duplications may reveal some abnormalities atypical for the usual Potocki-Lupski syndrome phenotype.

The vast majority of syndromes caused by autosomal duplications and deletions produce different forms of facial dysmorphism. Even if this dysmorphism is not specific enough to diagnose any specific condition, it serves as an indicator allowing a pediatrician to suspect a chromosomal abnormality in a child and refer him (or her) for cytogenetic examination. This is not so for Potocki-Lupski syndrome where the patients (or at least the vast majority of patients) do not have any dysmorphic features.

The main manifestations in these patients are disturbances of brain functions. Most patients have low muscle tone as infants causing difficulties in feeding, among others. Developmental delay, and especially speech delay, became obvious in patients at 2-3 years. Older children may reveal hyperactivity or symptoms of autism. Unlike patients with Smith-Magenis syndrome, who have serious sleep problems, parents of Potocki-Lupski syndrome children do not report sleep apnea or other sleep disturbances in their children. Oropharyngeal dysphagia and problems with swallowing may contribute to a delay in physical and intellectual development.

Microcephaly, cleft uvula, or bifid uvula were each reported in 8% of patients.

The heart is affected in many patients with Potocki-Lupski syndrome. Special studies showed that 40% of the patients have structural heart defects (atrial or ventricular septal defects or bicuspid aortic valve). At least two patients had a very serious defect – hypoplastic left heart syndrome.

Less than 10% of patients have structural defects of the kidneys, including hypoplastic kidneys and cystic dysplastic kidneys. It was shown that the critical segment for abnormalities of kidneys is limited to a 0.285 Mb region, containing the FLCN gene. However, not every patient having a duplication of this gene has kidney defects.

There are no reports about structural defects of the brain (except microcephaly), eyes, diaphragm, gastro-intestinal system, genital organs, or extremities in patients with this syndrome.

A standard 3.7 Mb duplication involved many genes. Examination of the patients with lesser deletions (but having virtually the same phenotype as patients with a “standard” duplication showed that the duplication of only one gene, RAI1 (retinoid acid inducible 1), causes all characteristic manifestations of the syndrome. A deletion of the same gene may explain most findings in Smith-Magenis syndrome.

Therapeutic measures may include speech therapy for verbal problems, occupational therapy to increase muscle tone, and behavioral therapy.

Almost all patients have sporadic duplications. However, there are at least three reports of a direct transmission of a duplicated chromosome 17 from the (usually mildly) affected parent. Therefore, examination of the parents is necessary for all families planning having further children.

Partial trisomies 17q

Wide usage of molecular methods in cytogenetics caused the discovery of numerous (mostly relatively small) duplications involving different segments of 17q. Clinical significance of these findings remains mainly uncertain, because most published patients have duplications of different sizes, and reported clinical manifestations vary from one patient to another. There are, however, two groups of microduplications which may be described separately. And there is an “old” syndrome of 17q trisomy, caused mainly by large duplications of 17q23q24.

a) Duplication 17q12

There are ~35 reports of patients with duplication 17q12. At least 14 of them did not have any clinical abnormalities (they were mostly parents or siblings of clinically affected children with the same duplication).

The most common manifestations were seizures, reported in six patients. Some congenital abnormalities (cortical dysplasia, esophageal atresia, hypodysplasia of kidneys, and syndactyly) and functional defects (autism and aggression) were reported each in two patients. Numerous other defects (choanal atresia, microcephaly, exencephaly, anal atresia, persistent foramen ovale, and hypoplastic thumbs) were also mentioned in patients with dup 17q12. It is not clear, however, whether the above-mentioned defects were causally related to dup 17q12 or if dup 17q12 was only randomly found in persons with unrelated abnormalities.

b) Duplication 17q23.1q23.2 and Club Foot

Sometimes club foot is inherited as an autosomal dominant condition. Molecular cytogenetic examination of several families where club foot was traced through 3-4 generations showed that affected persons have a small duplication in the 17q23.1q23.2 area. Currently, the critical region for this defect is limited to 0.36 Mb. This area includes three genes, and it is not known yet which of these genes is responsible for this defect.

The patients have normal psycho-motor development and do not have any other structural abnormalities. At least two carriers in affected families did not have club foot, and one person had dysplasia of the hip, but no foot defects. At the same time, there is a significant number of patients with large duplications involving the 17q23.1q23.2 area who did not have club foot. Most likely (as it can be seen in relation to ectrodactyly and dup 17p13.3), duplication 17q23.1q23.2 is necessary to produce club foot, but not sufficient to do it without action of other genetic factors.

c) *Trisomy for Distal 17q*

Trisomy for the distal part of 17q (17q22-qter) is considered to be a recognizable condition. However, the vast majority of known observations were caused by unbalanced translocations between 17q and other chromosomes. Therefore, most of the known patients have an additional imbalance. There are only ~30 observations of “pure” distal trisomy 17q, mostly recognized by “standard” cytogenetics.

These patients have a significant delay in physical and psycho-motor development. Facial dysmorphism is almost constant, but not specific for recognition of the syndrome. Hirsutism, blepharophimosis, short neck, and excessive neck skin are relatively common. Cleft palate (sometimes with cleft lip) was found in four patients with “pure” distal trisomy 17q.

Two main groups of defects, typical for this syndrome, are skeletal abnormalities and defects of the brain.

Microcephaly is very common. Some patients have craniosynostosis (2), hypoplastic corpus callosum (2), hypoplastic cerebellar vermis (2), Dandy-Walker malformation, or hydrocephaly. Epilepsy was reported in several patients, but relatively uncommon. Microphthalmia and colobomas are found only sporadically.

Different abnormalities of the skeletal system are the hallmarks of the syndrome. The most common is rhizomelic shortness of the limbs (shortening of the proximal limbs), which is highly unusual for other types of chromosomal imbalances. This abnormality is reported in ~30% of patients with “pure” trisomy 17q (and in ~50% of patients with an additional imbalance). Another characteristic defect is postaxial polydactyly (20% of patients with “pure” distal trisomy 17q and ~40% of patients with an additional imbalance). Polydactyly may affect both hands and feet. Preaxial polydactyly also has been reported, although not so frequently. Other skeletal abnormalities are not so specific. They include scoliosis (5), short metatarsal bones (4), hypermobile joints (3), dysplastic hips (2), contractures (2), bifid vertebrae (2), fused or supernumerary ribs (2), proximal position of thumbs, syndactyly, or absent distal phalanges of the toes.

Abnormalities of internal organs are relatively uncommon. Five patients had congenital heart defects (four had ventricular heart defects and one had double outlet of the right ventricle). Defects of other organs (intestinal malrotation, gastro-esophageal reflux, anteriorly placed anus, duplex kidney, and ambiguous genitalia) are very rare and were found in one patient, each.

The most typical abnormalities of the syndrome (rhizomelic shortness of the

extremities and post-axial polydactyly) are caused by a duplication of the segment 17q22q23. However, the precise size and location of the “critical” segment and genetic content of this segment are still unknown.

Trisomy 17

Full trisomy 17 does not occur in humans. There are ~20 reports on “mosaic trisomy 17” where trisomic cells were found only in placental tissues. Of course, these patients cannot be considered as patients with mosaic trisomy 17. True mosaic trisomy 17, where trisomic cells were present in the tissues of the child (or fetus), was reported only in 11 patients. In all of these patients, trisomic cells were found in the skin or other tissues, but not in lymphocytes. Dysmorphic features were noted in five patients. Structural defects of the brain seem to be common. At least five patients had hypoplasia of the cerebellar vermis. Microcephaly was reported twice, and one patient had hydrocephaly. Hearing impairment was reported in four children.

Heart defects were found five times, including reports of truncus arteriosus and tetralogy of Fallot.

Asymmetry of the body (3) and hypomelanosis (1) may be considered as relatively unspecific manifestations caused by mosaicism.

Numerous other abnormalities (cataract, polydactyly, ectrodactyly, joint laxity, dislocation of the hip, duodenal atresia, intestinal malrotation, pelvic kidney, and hydronephrosis) were reported in 1-2 patients, each.

The vital prognosis depends on the status of the internal organs. Without serious abnormalities of the brain, heart and other internal organs, patients may survive into adulthood. All surviving children with true mosaicism 17 show evident psycho-motor delay.