Chromosome 16

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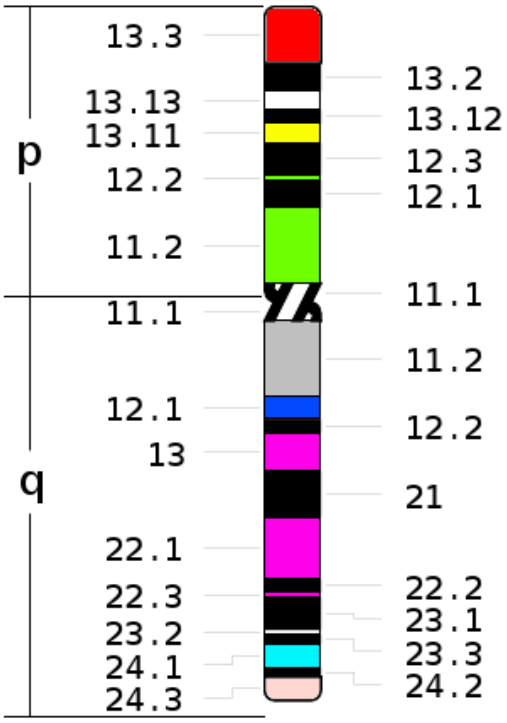

Introduction

The length of chromosome 16 is 90 Mb. It is ~3% of the total human genetic material. The length of the short arm is ~35 Mb; the length of the long arm is 55 Mb. Chromosome 16 is extremely gene rich. It contains at least 1,100–1,150 genes, including more than 150 genes related to genetic diseases in humans.

The genetic structure of the short arm of chromosome 16 has two areas (16p11.2 and 16p13.11), which (similar to 15q11.2 and 15q13.3) are predisposed to an unusually frequent origin of microdeletions and microduplications. These microanomalies were completely unknown before the invention of molecular cytogenetics. Several studies over recent years show that these microanomalies should be placed in a special position between completely normal variants and 100%–deleterious abnormalities. These microanomalies should be considered as relatively unspecific “risk factors”. The presence of these microdeletions significantly increases the risk of the development of autism, obesity or attention deficit disorder, but neither of these deletions should be viewed as the sole and only factor leading to these pathologies. Numerous reports show a considerable prevalence (frequency) of these microanomalies among control patients as well as among unaffected parents of affected individuals.

The distal part of 16p (16p13.3) contains several genes responsible for well–known and relatively frequent genetic disorders. Deletions of 16p13.3 have been reported among patients with tuberous sclerosis, Rubinstein–Taybi syndrome and alpha–thalassemia. Including microdeletions, deletions of the short arm of chromosome 16 have been reported in ~350 patients. Deletions of the long arm of 16 are not as common. There are ~150 patients with deletions of 16q (including persons having an associated imbalance for other chromosomal material). There are several genetic syndromes caused by deletions of the long arm. One of these syndromes is caused by deletions of the Townes–Brocks–related gene. Two other syndromes (del 16q24.1 and del 16q24.3) seem to be caused by the deletions of several contiguous genes.

Deletions of Chromosome 16

The genetic size of the chromosome 16 is ~90 Mb, where the short arm is ~35 Mb.

Deletions of 16p

Deletions of 16p13.3

The telomeric end of the short arm is a very gene–rich area. As a result, there are at least 3 clinical syndromes caused by deletions of this segment. The following are the three known clinical syndromes:

- *ATR–16 Syndrome*

  The most telomeric part of 16p is occupied by a cluster (group) of genes responsible for the production of α–globin. Mutations of these genes may cause α–thalassemia–blood disease, which manifests itself by microcytic hypochromic anemia with normal levels of iron. When α–thalassemia is caused by a mutation of α–globin genes, mental development of patients is normal. When this disease is caused by deletions of these genes with involvement of some other genes important for intellectual development, the patients show delay in psycho–motor development. The complex of α–thalassemia and psycho–motor delay caused by the deletion of the tip of 16p is called ATR–16 syndrome (Alpha–Thalassemia — Retardation (caused by the deletion of chromosome) 16).

  Because the deletion involves only the most distal part of 16p13.3 (0.7–0.8 Mb), detection of “pure” deletions of this area became available only after the invention of molecular techniques. Most patients reported in the “pre–molecular” period are persons with unbalanced translocations, where del 16p13.3–pter is associated with partial trisomies for other chromosomes.

  Typically the patients do not have other abnormalities, except a delay in psycho–motor development and α–thalassemia. Because clinical manifestations of α–thalassemia are relatively mild, most known patients were found not upon examination of persons with blood problems, but upon examination of persons with developmental delay.

- *Del 16p13.3, Tuberous Sclerosis and Polycystic Kidney Disease*

  Tuberous sclerosis (TS) is an autosomal dominant disease, which is characterized by an association of seizures, learning disability and hamartomas (mainly in brain and kidneys). One of the genes responsible for TS lies within 16p13.3 (~2 Mb from telomere). The vast majority of TS–patients have mutations within the TSC2 gene (or within the TSC1 gene located at 9q34).

  The gene responsible for the autosomal dominant polycystic kidney disease is located tail to tail with the TSC2 gene. Clinical manifestations of adult polycystic kidney disease occur usually in the 4th decade of life. Deletions of 16p13.3 affecting this area produce both of these conditions in the same person. Although well–known, this association is not frequent: not more than 15 patients with this complex have been described. These deletions may be both interstitial and terminal. If deletions are

terminal, the group of α–globin genes also will be affected (with a clinical picture of α–thalassemia). If deletions involve other (more distal from the telomere) genes, the patients may show other manifestations.

- *Del 16p13.3 and Rubinstein–Taybi Syndrome*

  The main manifestations of the Rubinstein–Taybi syndrome (RTS) are mental retardation, characteristic facial features and broad deviated thumbs (and halluces). The main genetic causes of RTS are mutations of the CREBBP–gene, located at 16p13.3 (~4 Mb from the telomere).

  In a small subgroup (~10% of RTS patients), the syndrome is caused by the deletion of the area that harbors the CREBBP–gene. There are ~20 reports when interstitial deletions of this area caused a phenotype of RTS. All of the deletions are heterogeneous in size and in position of the breakpoints. If the deletion affects only the CREBBP gene, the affected patients will have typical manifestations of RTS. If the deletion involves other (more distal or more proximal) genes, the patients may have other defects including polydactyly, dysgenesis of the corpus callosum and Chiari I malformation (herniation of cerebellar tonsils below the level of the foramen magnum).

Deletions of 16p11.2p12.2

For the last few years, several patients with interstitial deletions of 16p11.2p12.2 had been reported. The authors try to delineate a syndrome caused by this deletion. Of course, these data should be considered as preliminary, because not more than 10 such patients have been described.

The affected children have mild facial dysmorphism (flat face, deep set eyes, epicanthus, downslanting palperbral fissures), low–set ears with increased susceptibility to ear infection, gastro–esophageal reflux, muscular hypotonia. All children show delay in motor development and development of speech. Two patients had heart defects. Other abnormalities of the internal organs are not characteristic. Neither of these patients had autism.
All deletions were interstitial with various breakpoints. The size of the deletion varied from 7.1 to 8.7 Mb.

Microdeletions 16p11.2 and 16p13.11

Wide application of molecular methods showed relatively large groups of persons having microdeletions 16p11.2 and 16p13.11. Both deletions arise in areas rich in segmental duplications that facilitate the breakage of chromosomes at these regions. At first, both of these deletions were found in patients with mental retardation, autism, facial dysmorphism and wide (but variable) internal malformations. It is not surprising because these defects are main indications for cytogenetic examination. However, it was shown that, in some families, the same microdeletions were found in healthy parents of affected patients. Later, several groups of scientists studied the prevalence of each of these microdeletions in the large cohorts of patients with schizophrenia, autism, abnormal behavior, obesity, etc. All of these studies showed similar results. Microdeletion 16p11.2 was found relatively frequently among patients with obesity, autism and pervasive developmental disorder. The prevalence of this deletion in these groups was 10–20 (or even 100) times higher than in the control population.

However, simple calculations show that most persons with del 16p11.2 microdeletion should not have any phenotypic abnormalities. Likewise, del 16p13.11 shows strong association with obesity and epilepsy.

Both of these microdeletions (16p11.2 and 16p13.11) should be considered as risk factors or susceptibility factors, but not as a sole cause of clinical abnormalities. Most likely, some other factors (genetic, environmental or both) are necessary to produce an abnormal phenotype. There are data showing that the occurrence of two microdeletions in the same person (for example, 15q13.3 and 16p11.2) significantly increases the risk of being affected.

Deletions of 16q

Isolated deletions of the long arm of chromosome 16 are relatively uncommon. Less than 100 patients with all types of 16q deletions have been reported. All of these deletions may be subdivided into: a) proximal deletions (involving 16q12.1), b) deletions of the "central" part of 16q; c) deletions involving 16q24.1, and d) very terminal deletions 16q24.3.

"Proximal" Deletions of 16q

There are ~35 reports on patients with deletions of the "proximal" part of 16q (16q11–16q13). Clinical analysis of this group shows a frequent occurrence of ear defects (sometimes with deafness), abnormalities of distal extremities preaxial polydactyly, syndactyly), defects of the kidneys and anal abnormalities (atresia, stenosis or ectopia). Although these defects seemed to be typical for the whole group, each individual patient could have only 1–2 of these anomalies. For many years, "proximal" deletions have not been considered as a clinical syndrome. Only several years ago, it was found that the segment 16q12.1 harbors the SALL1 gene — a zinc finger transcription factor responsible for the Townes–Brocks syndrome. Clinical manifestations of this syndrome are the above–mentioned renal, anal, ear and limb anomalies.

Later, it was shown that the majority of patients with Townes–Brocks syndrome have mutations within the SALL1 gene. A relatively small number of patients have deletions of this area of chromosome 16, and these deletions produce the same phenotype as mutations of the SALL1 gene. Involvement of other (more distal or more proximal) genes may cause an occurrence of some additional defects of the eyes, brain and heart, which are not typical for Townes–Brocks syndrome.

The patients with Townes–Brocks syndrome usually have normal intellectual development. Developmental delay in patients with deletions should be explained by deletions of other neighboring genes.

The patients usually have an abnormal shape of the external ear with folded helix, preauricular tags and fistulas, and hearing impairment. Preaxial polydactyly (typical for Townes–Brocks syndrome) was reported only in 3 patients. Others had "triphalangeal thumb", proximally placed thumbs or syndactyly of some toes. Anal defects were found in 10 patients (~1/3 of known patients with del 16q12.1). Most of them had ventral ectopia ani. Atresia ani was reported only twice. Renal defects include agenesis of one kidney or hypoplastic kidneys. The frequency of renal defects is not clear, because not all patients had a urological examination.

The absence of a SALL1 mutation in a patient with a Townes–Brocks–like phenotype should be an indication for cytogenetic examination.

Deletions of the "Central" Part of 16q

There are ~25 reports on patients having deletions with proximal breakpoints in 16q13 (or more distal) and distal breakpoints in 16q23 (or more proximal). Clinical manifestations in this subgroup are too heterogeneous to delineate any syndrome. However, analysis of known patients shows that the segment 16q13 has to have a gene causing (when deleted) shortness of limbs, the segment 16q22.3q23 has to harbor a gene for coloboma, and the segment 16q23 has to include a gene causing polycystic or hypoplastic kidneys. The segment 16q22.1 has to include a gene related to the occurrence of cleft palate. The central area of 16q has to harbor at least two genes important for defects of the aorta and pulmonary artery because deletions of this area produce coarctation and stenosis of aorta, pulmonary atresia and stenosis of pulmonary artery. One of the genes causing hydrocephaly has to be sitting within 16q22. The area of 16q21q22 may harbor a gene for occipital encephalocele.

The nature of all of these genes will become more obvious when patients with deletions of these areas are studied using contemporary molecular techniques.

Deletions of 16q24.1

The syndrome caused by the deletion of 16q24.1 is a very new entity: it was delineated by Stankiewicz et al. in 2009. They found that small interstitial deletions of this area are capable of producing a recognizable pattern of congenital malformations. Not more than 12 infants having this deletion have been reported so far, but there is no doubt that usage of molecular techniques for examination of suspected persons will increase this number.

The main manifestations of the syndrome is an alveolar capillary dysplasia — a grave defect of the lungs, which includes diffuse thickening of alveolar walls with capillaries located away from alveolar basement membranes, increased muscular layer in small intra–acinar arterioles, and abnormal location of pulmonary veins. Of course, such conditions of the lungs excludes the capability of their normal function. All infants with this defect cannot survive more than several days. Not a single other (so far known) syndrome caused by a chromosomal effect has such a grave lung pathology. Alveolar capillary dysplasia seems to be a very common sign of del 16q24.1: there is only one patient with this deletion who did not have this form of lung defect.

Deletions in the affected infants had different breakpoints and different sizes, but all involved a small group of FOX–genes, including FOXF1 and FOXC2. Later, it was shown that alveolar capillary dysplasia (and other manifestations of the syndrome) may be found in persons with mutations within the FOXF1 gene. It means that this gene is the main contributor of the defects in this syndrome. Moreover, several persons with a similar phenotype had small mutations upstream of FOXF1 (but not involving the gene itself) suggesting a position effect.

Defects of the lungs are the main, but not only, manifestations of the syndrome. All affected infants (except one) had heart defects, including hypoplastic left heart (in 5 persons), atrio–ventricular communication, interrupted aortic arch, and tetralogy of Fallot.

Most infants revealed serious abnormalities of the gastro–intestinal tract: duodenal atresia (sometimes with annular pancreas), esophageal atresia, anal atresia, intestinal malrotation. Defects of the urinary tract are common but, usually, they do not affect the structure of renal parenchyma. The described abnormalities include hydronephrosis (4), dilated renal pelvices (3) or dilated ureters (3). Some persons had skeletal defects such as butterfly vertebrae and fused ribs. Defects of the brain are rare (only one person had Chiari I malformation).

Because affected persons may have malformations of the esophagus, heart, anus, kidneys and vertebral defects, some of these persons may have been misdiagnosed as having VACTERL–association (although defects of distal limbs have not been reported so far in persons with del 16q24.1).

Distal Deletions of 16q24.3

Small distal deletions of the distal tip of 16q — 16q24.2 and 16q24.3 (without involvement of other chromosomes) do not cause grave defects of internal organs. The most characteristic finding in this group of patients (less than 10 persons with these deletions have been reported so far) is autism in association with seizures, hypoplastic corpus callosum and relatively mild defects of the mitral valve. The genes ANKRD11 and/or ZNF778 are considered as main candidate genes for autism in this small group of patients.

Ring Chromosome 16

Ring chromosome 16 is one of the rarest types of ring chromosomes in humans. There are only eight reports of patients with this pathology. One of them had mosaicism with a monosomic clone.

All abnormalities (autism, cataracts, patent ductus arteriosus, double collecting system of kidneys, microstomia, hypoparathyroidism, shortening of one arm and one leg, pectus excavatum, and scoliosis) were reported in one patient, each.

Familial transmission of ring chromosome 16 is not known.

Partial Trisomies for Chromosome 16

Partial Trisomies for 16p

For a long time trisomies for the short arm of chromosome 16 were considered to be very rare forms of chromosomal abnormalities. The application of molecular methods, however, showed that within 16p there are two relatively frequent microduplications – dup 16p11.2 and dup 16p13.1. Currently, there are ~250 reports of people with different types of duplications of 16p, including almost 100 reports of dup 16p13.1 and 70 reports of dup 16p11.2.

a) *Duplication of 16p13.1*

   This duplication is relatively small by size, usually 1-1.5 Mb. It affects an area between 15 Mb and 16.5 Mb.

   Because this microduplication was found in several patients with autism,

schizophrenia, or hyperactivity disorder there were several studies aiming to compare the incidence of this and other microanomalies among patients affected by these conditions and in healthy persons. The results were remarkably similar: microduplication 16p13.1 was found significantly more frequently in each of the studied groups. However, the same microduplications also were found in healthy people or in the parents of the affected children. Currently, there are reports of 15 patients with dup 16p13.1 and schizophrenia, 15 patients with autism, 12 patients with hyperactivity disorder, and four patients with epilepsy. These data suggest that dup 16p13.1 should be considered to be a strong risk factor for the development of all of the above-mentioned conditions, but it does not mean that every person having this duplication will have one of these disorders.

The patients with dup 16p13.1 do not have a consistent type of facial dysmorphism. Structural brain and skull abnormalities include microcephaly (six patients), craniosynostosis (two patients), and sporadic reports of lissencephaly, agenesis of the corpus callosum, cortical dysplasia, or absent septum pellucidum. Cleft palate, narrow auditory canals, microstomia (small mouth), macroglossia, and vocal cord palsy were found in one patient, each. Three patients had hearing impairment.

It should be mentioned that one patient (having an atypically large 3.4 Mb duplication involving the area 15.0-18.4 Mb, which is usually not affected in people with dup 16p13.1) had an association of choroid coloboma, choanal atresia, aplasia of semicircular canals, atrial septal defect, and unique kidney (typical manifestations of the CHARGE syndrome). The same phenotype was reported in one patient with a little bit larger duplication, also involving the area of 16p12.3. Most likely, the segment 16.5-18.5 Mb contains gene(s) which (when duplicated) may lead to the CHARGE phenotype.

Congenital heart defects are common; a significant number of them are very serious. There are reports of monoventricular heart (3), hypoplastic left heart (2), tetralogy of Fallot (2), and transposition of the great arteries (1). Four other heart defects were relatively mild and, in four patients, the type of heart defects was not specified.

Defects of the loco-motor system are represented by increased joint laxity (4), scoliosis (2), polydactyly (2), and sporadic reports of syndactyly, thiphalangeal thumb, unspecified radial ray deficiency, arachnodactyly, femoral hypoplasia, and shortness of the arms and legs.

Defects of other system are not characteristic, but there are sporadic reports of Hirschsprung's disease and unspecified defects of the kidneys. It is not clear, however, whether these defects are caused by the duplication of 16p13.1 or that this duplication was randomly found in people having these abnormalities unrelated to dup 16p13.1.

The role of dup 16p13.1 as a risk factor for autism, schizophrenia, epilepsy, or hyperactivity and a wide spectrum of heart defects is undeniable, although the mechanism of realization of a potentially harming factor into an abnormal phenotype remains unknown.

b) *Duplication of 16p11.2*

There are ~70 reports on persons with this relatively small duplication (usually less than 1 Mb) located between 29 Mb and 30 Mb. This duplication is reciprocal to the deletion in this area.

From the clinical point of view, duplication 16p11.2 is very similar to duplication 16p13.1. Dup 16p11.2 is a strong risk factor for autism (found in 16 out of 71 reported patients), schizophrenia (13), seizures (15), and pervasive developmental disorders (5). There are reports of this duplication in the patients with bipolar disorder or attention deficit hyperactivity disorder. Of course, dup 16p11.2 also was reported in 13 healthy persons, but the incidence of this duplication among patients with the above-mentioned conditions is ~10 times higher than in the normal population.

There is no recognizable pattern of facial dysmorphism for dup 16p11.2 patients.

Structural defects of the brain and eyes are represented by microcephaly (five patients), agenesis of the corpus callosum (three patients), and sporadic reports of cerebellar hypoplasia, polymicrogyria, microphthalmia, and coloboma. Cleft palate was reported in three patients.

Out of four patients with heart defects, only one had a life-threatening transposition of the great arteries. One patient had diaphragmatic hernia.

Reported defects of the loco-motor system are mild and include scoliosis (2), pectus excavatum (2), syndactyly, or contractures.

c) *"Other" Duplications of 16p*

Outside of patients with microduplications of 16p13.1 and 16p11.2, there is a relatively large and highly heterogeneous group of patients having duplications of other areas of 16p. Some of these patients have large duplications involving all (or almost all) of the short arm of chromosome 16, others have smaller duplications. Of course, duplications in some of these patients may involve areas of microduplications of 16p11.2 and 16p13.1, but they always extend beyond these segments and involve many other genes. The genetic basis in most of these patients is direct duplication.

If microduplications 16p11.2 and 16p13.1 are basically risk factors – conditions between completely normal and completely abnormal – there are no doubts that all other duplications of 16p are pathological conditions with serious clinical consequences.

A delay in psycho-motor development is common for actually all of these patients, although the degree of this delay varies in different people. There is no characteristic complex of facial dysmorphism, but 19 patients (out of 94) had cleft palate (or cleft lip and palate). Fifteen patients had a short neck or webbed neck. Other craniofacial abnormalities include macrostomia (large mouth) (6), ptosis (4), preauricular tags (4), synophrys (2), and bifid nasal tip (2).

The most common brain defects are hypoplastic or absent corpus callosum (six

patients), microcephaly, and craniosynostosis (three). A wide spectrum of other brain abnormalities was reported in 1-2 patients, each. These defects include nodular neuronal heterotopia, cerebellar hypoplasia, lissencephaly, holoprosencephaly, or even encephalocele. Abnormalities of the eyes are uncommon and include microphthalmia (3), coloboma (3), blepharophimosis (2), and sporadic reports of microcornea, cataract, and optic atrophy. At least five patients had hearing impairment.

Heart defects are common (21/94), but mostly not life-threatening. Only two patients had hypoplastic left heart and tetralogy of Fallot.

Loco-motor defects are relatively mild. At least ten patients had camptodactyly, and seven had contractures. At the same time, four patients had increased joint laxity. The proximal position of the thumbs was reported in 13 patients (six of them had hypoplastic thumbs), and one child had preaxial polydactyly. Other defects of the fingers include syndactyly (6), brachydactyly (4), tapering fingers or hypoplastic distal phalanges (7), sandal gap (5), or hypoplastic toes (3). Scoliosis (6) and pectus excavatum (5) are also reported. Inguinal hernias were found eight times.

Several patients had skin abnormalities, including hypopigmentation (2), cutis marmorata (1), or alopecia (1).

Although four children had diaphragmatic eventration, diaphragmatic hernias have not been reported.

Except for gastro-esophageal reflux (four patients), defects of the gastro-intestinal system are uncommon: there are only sporadic reports of pyloric stenosis, pancreatic insufficiency, and anterior position of the anus.

Abnormalities of the genitor-urinary system are more common and include the absence of one kidney (2), hydronephrosis (3), pelvic kidney (1), hypoplastic kidney (1), vesico-ureteral reflux (6), and hypospadias (1). Premature ovarian failure or pubertas praecox were reported in one person, each.

Functional brain disturbances are common. At least 15 patients with this kind of 16p trisomy had seizures, 13 patients had autism, and two patients had anxiety. Also, there are sporadic reports of schizophrenia, uncharacterized psychosis, pervasive developmental disorder, or verbal dyspraxia. Part of these abnormalities may be explained by the involvement of microduplications 16p11.2 and 16p13.1, but all defects of this kind also were found in patients with duplications of other areas of 16p.

Although trisomy 16p does not constitute a recognizable syndrome, frequent cleft palate, short webbed neck, heart defects, proximal position of the thumbs, camptodactyly, contractures, and functional brain defects (autism and seizures) may be considered as hallmarks of this trisomy.

Partial Trisomies for 16q

Trisomies for the long arm of chromosome 16 are relatively rare forms of chromosomal anomalies. There are only ~85 reported patients with all kinds of 16q trisomies without an

associated imbalance. Of course, there are many reports of patients with distal trisomy 16q in association with partial monosomies for 16p (as a result of inversions) or partial monosomies for other chromosomes (as a result of translocations), but an additional imbalance may influence clinical manifestations in the patients.

"Pure" trisomies 16q may be arbitrarily divided into three groups: proximal trisomy 16q (trisomies limited to 16q11q21), "medial" trisomies 16q (involving segments 16q22q23, but not involving 16q24) and distal trisomies (involving 16q24).

a) *Proximal Trisomies of 16q*

From the genetic point of view, almost all partial trisomies in this group were duplications. Out of 27 persons with proximal trisomies, only 16 had morphological abnormalities. Another 11 were completely normal parents of affected children or had some delay in psycho-motor development but without any significant dysmorphism. There is no syndrome associated with proximal trisomies of 16q.

Clinical manifestations in patients are very heterogeneous. The most common finding was obesity, reported in five patients. Short neck and hyperopia were found in four patients, each. Three children had "stubbed" thumbs. Blepharophimosis and hip dislocation were reported in two patients, each.

Defects of the brain and internal organs are very rare. Three heart defects included hypoplastic left heart syndrome (1), aortic stenosis (1), and ventricular heart defect (1). One child had microcephaly and hypoplastic cerebellar vermis, another had horseshoe kidney.

There is a significant risk of direct transmission of a proximal duplication of 16q from an unaffected (or minimally affected) parent. That is why cytogenetic (or molecular cytogenetic) examination of the parents is necessary for the families planning to have more children.

b) *"Medial" Trisomies of16q.*

This group consists of 30 patients having trisomies for the segment 16q22q23, although some of these patients also have trisomies for the more proximal segments of 16q. As in the "proximal" group, 30% of reported patients with "medial" trisomies were completely normal (parents or siblings of affected patients) or had some degree of delay in psycho-motor development, but no recognizable structural abnormalities.

Generally patients in this group have more serious abnormalities than patients with proximal trisomies of 16q.

There is no stable pattern of facial dysmorphism. Reported defects include preauricular pits (3), ptosis, and atresia of lacrimal ducts. One child had cleft palate. Hearing impairment was reported twice.

Abnormalities of the loco-motor system include postaxial polydactyly (with the critical segment 16q22.1), brachydactyly, tapering fingers, kyphosis, scoliosis, and partial rib agenesis.

At least seven patients had heart defects (including two with atrial septal defects, two with ventricular septal defects, and three with other non life-threatening conditions). Defects of the brain included microcephaly or even spina bifida. One patient had cystic dysplasia of kidneys, another had vesico-ureteral reflux.

As for the proximal group, cytogenetic examination of the parents is necessary, because some duplications (especially small ones) may be transmitted from one of the parents.

c) *Distal Trisomy of 16q.*

There are less than 30 reported patients with distal trisomy 16q as a sole abnormality. All of these patients share trisomy for the segment 16q24, although some of them also have trisomies for more proximal segments of 16q. Taking into account numerous (> 150) reports on patients with distal trisomy 16q in association with another chromosomal imbalance, there are good chances to give a sufficient clinical characterization of this condition.

Generally, distal trisomy 16q is significantly more serious condition than the proximal of “medial” trisomies 16q. Almost all infants with trisomy involving all of 16q24 (but not small sub-segments within this area) show muscular hypotonia and a significant delay in physical development. Their height and weight is lower than in the healthy peers. A delay in psycho-motor development is also obvious.

A wide spectrum of dysmorphic features includes prominent forehead, small palpebral fissures, downward slanting of eyes, epicanthus, strabismus, hypertelorism, broad nasal bridge, thin upper lip, micrognathia, and dysplastic low-set ears. However, all of these abnormalities are unspecific: they allow suspicion of a chromosomal imbalance but are not sufficient for a clinical diagnosis. There are two reports of cleft palate and one report of choanal atresia.

Morphological defects of the brain are rare: there are only sporadic reports of trigonocephaly, hypoplastic corpus callosum, hypoplastic cerebellar vermis, or dilated cerebral ventricles. Defects of the eyes include several reports of colobomas, microphthalmia, and even anophthalmia (the critical segment for these abnormalities is 16q22.1q24; therefore the genes responsible may be located outside of the 16q24 segment).

Heart defects are very common (13/28) and include life-threatening conditions (“D” atrial malposition, interrupted aortic arch, hypoplastic left ventricle, transposition of the great arteries, and double outlet right ventricle). The incidence and spectrum of heart defects are in a strong contrast with these defects in patients with “medial” trisomies 16q. Therefore, specific genes within 16q24 should be involved in the origin of these defects.

At least seven patients with isolated distal trisomy 16q (and many patients with distal trisomy 16q in association with other imbalance) had anal atresia or ventral ectopia ani. Distal trisomy 16q seems to have one of the largest percentages of anal defects among all kinds of chromosomal imbalances. The critical segment for anal defects lies

within 16q24.

Reported abnormalities of uro-genital system include megacystis (giant urinary bladder])(2), vesico-urinary reflux (2), and sporadic reports of ureteral stenosis, pelvic kidney or fetal lobulation of the kidneys. Four boys had hypospadias. There also are reports of ambiguous genitalia and hypoplastic uterus.

Defects of the extremities are rare, but reports of an aplastic hand with rudimentary fingers and ectrodactyly shows that 16q24 may contain genes involved in the formation of digits. Other abnormalities include camptodactyly, contractures, kyphosis, and scoliosis.

Basically, the segment 16q24 has to contain multiple genes critical for normal development.

Trisomy 16

Trisomy 16 is a very common anomaly among spontaneous abortuses. The data about trisomy 16 in children are a bit controversial. Frequently, mosaic trisomy 16 is found upon prenatal cytogenetic examination of the tissue of chorion or in amniotic fluid. Sometimes, infants born after the prenatal discovery of mosaic trisomy 16 in non-fetal tissues are reported as patients with mosaic trisomy 16 without confirmation that fetal cells also contain a clone with an additional chromosome 16. As a result, a significant group of children described as having mosaic trisomy 16 actually are cytogenetically normal children where trisomic cells were limited to non-fetal tissue. Because most of these children have neither physical defects nor problems with psycho-motor development, inclusion of this group of patients causes a distorted image of consequences of mosaic trisomy 16. To avoid this controversy, only people having trisomy 16 in fetal tissues were taken for analysis of manifestations of this pathology.

Actually, almost all known peoples with trisomy 16 are mosaics having trisomy 16 in a small percentage of their cells. Complete trisomy 16 was reported only in 4-5 persons. All of them had multiple abnormalities: cleft palate (or cleft lip or palate), choanal atresia, malformations of the brain (microcephaly, arhinencephaly, and agenesis of corpus callosum), heart, extremities (ectrodactyly, aplasia or radial bones, and rhizomelic shortness of limbs), kidneys (cystic kidneys), digestive tract (omphalocele, absent pancreas, intestinal malrotation, and anal atresia), diaphragmatic hernia, and numerous other defects. None of the people with full trisomy 16 survived the neonatal period.

Patients with mosaic trisomy 16 can survive into adulthood.

In most people, mosaic trisomy 16 was discovered upon prenatal diagnosis, and only less than ten patients were diagnosed after birth. In total, 36 patients with mosaic trisomy 16 in their cells are available for analysis of clinical manifestations.

Facial dysmorphism is relatively common (9/36), but there are no manifestations typical for this condition. Defects of the brain and skull (microcephaly, craniosynostosis, hypoplastic cerebellum) were reported in one patient, each. Abnormalities of the eyes (microphthalmia, coloboma, glaucoma, and corneal clouding) were found in 1-2 patients. Cleft palate, preauricular pits, microstomia, and hearing loss are reported in small percentage of patients.

Asymmetry of the body and areas of hypo- or hyper-pigmentation (relatively unspecific manifestations of mosaicism) were reported in six patients, each. Three patients revealed the absence or hypoplasia of one nipple.

The most common internal defects are heart defects found in almost half of the patients (17/36). Life threatening abnormalities (ectopia cordis, hypoplastic left heart, double outlet of the right ventricle) are however uncommon.

Some patients revealed shortness of all of the extremities or of some specific bones (bones of the forearm and femur). Other defects of the extremities included hypoplastic thumbs (3), polydactyly (2), syndactyly (2), camptodactyly (2), bifid humerus, hypoplastic phalanges, butterfly vertebrae, or scoliosis.

Anal atresia was found twice; one patient had gallbladder agenesis. Defects of the uro-genital system are also uncommon. They include sporadic reports of hypoplastic kidneys, horseshoe kidney, doubling of ureters, and sexual ambiguity. Three boys had hypospadias. Inguinal hernia was reported in four patients.

Almost all patients with mosaic trisomy 16 had some structural defects. In that context, it is surprising that at least seven patients had normal intellectual development. Actually, the percentage of people with normal mental development is even higher because, in some of the 36 people whose intellectual development was analyzed, they could not be assessed. Other patients usually have a moderate delay in psycho-motor development. Only one patient with mosaic trisomy 16 had seizures. Autism or other psychiatric problems have not been reported.