Chromosome 15

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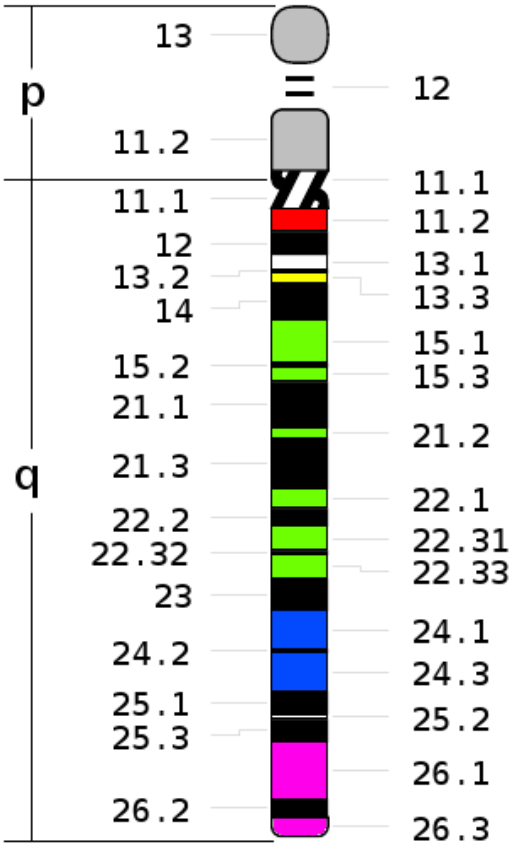

Introduction

Chromosome 15 (as well as chromosomes 13 and 14) is an acrocentric chromosome. Its short arm does not contain any genes. The genetic length of the long arm of chromosome 15 is 81 Mb. It is ~3% of the total human genome. The length of its short arm is ~20 Mb. Chromosome 15 contains from 700 to 1,000 genes. At least 10% of these genes are important for the development of the body plan and sustaining numerous functional activities.

There are 2 peculiar characteristics of this chromosome.

1. The structure of some regions of this chromosome (15q11.2 and 15q13.3) is predisposed to a relatively frequent occurrence of microdeletions and microduplications of these areas. Of course, diagnosis of these microanomalies is possible only using sophisticated molecular methods. An increasing amount of evidence regarding the clinical significance of these microanomalies shows that they make a particular niche between “standard” deletions (leading to some defects in all affected persons) and normal variants. Increased frequency of these microanomalies was found in patients with different types of pathology such as: schizophrenia, seizures, obesity, and autism. At the same time, many persons with these abnormalities (including many parents of affected persons) do not have any phenotypic abnormalities. Most likely, these microdeletions have to be considered as “risk factors”, but not the only cause of any type of pathology.

2. Deletions of the paternal and maternal segments 15q11q13 will lead to different clinical consequences. (Usually every individual has one copy of each chromosome inherited from the mother and one copy of this chromosome inherited from the father). The differences in the phenotypic picture of the paternal and maternal deletions are caused by the specific character of the genes in the deleted region. This phenomenon is called “genetic imprinting”.

The deletions of the proximal area of 15q are very common: there are more than 1,000 reports about such patients (including patients with microdeletions 15q11.2 and 15q13.3.

Deletions of more distal areas are not so common. There are two syndromes caused by deletions of the distal part of 15q: a well–known condition caused by a distal deletion, usually involving the deletion of the IGFR1 gene, and the recently described syndrome caused by del 15q24. This syndrome, delineated only by methods of molecular cytogenetics, has been reported so far only in a couple dozen patients.

Deletions of Chromosome 15

Chromosome 15 (as well as chromosomes 13 and 14) is an acrocentric chromosome. Loss of the short arm of chromosome 15 is not associated with any abnormalities. Deletions of the long arm may cause clinical consequences. The genetic length of the long arm of chromosome 15 is ~81 Mb. Loss of the genetic material of the long arm of 15q causes several clinical syndromes.

Deletions of 15q11q13

The situation regarding deletions of the segment 15q11q13 is unique, because clinical manifestations of this deletion are different depending on which chromosome 15 (maternal or paternal) is deleted. One chromosome 15 (as well as any other chromosome) in each diploid cell had a maternal origin (it came from an egg–cell), and another chromosome 15 had a paternal origin (it came from a sperm). If the segment 15q11q13 is lost from the paternal chromosome 15, the patient develops Prader–Willi syndrome. If the same segment is lost from the maternal chromosome 15, the patient will have Angelman syndrome. The phenomenon of the parent–specific function of the genes within any chromosomal segment is called genomic imprinting. There are some other examples of imprinting regarding manifestations of chromosomal pathology in humans (e.g. partial trisomy 11p15 will have different clinical consequences depending on the parent whose chromosome 11p is duplicated), but deletion 15q11q13 is the most frequent and best studied example of genomic imprinting in human chromosomal pathology.

The following are descriptions of the two syndromes caused by this deletion and genomic imprinting:

- *Prader–Willi Syndrome*

  The genetic basis of the syndrome is a loss (or un–expression) of the small group of genes within 15q11q13. The patient will have manifestations of this disorder only if the deletion (or the inactivation) occurred within the chromosome 15 inherited from the father.

  Clinically Prader–Willi syndrome (PWS) is known from the 1950's, but its etiology became known only in the early 1980's.

  PWS occurs relatively frequently. At least 1:20,000 live born infants will develop this condition.

  The patients with PWS usually do not have congenital malformations, but there is a complex of mostly functional defects, which allows the recognition of this syndrome even before cytogenetic examination. The babies are very floppy (hypotonic).

Sometimes reduced fetal movements are even mentioned during pregnancy. The newborn babies are very sleepy. Hypogonadism may be evident even in newborn boys. The infants continue to be floppy and sleepy. A delay of psycho–motor development may be noticed already at that stage: infants start sitting, standing, crawling, and walking later than healthy infants of the same age.

Delay in speech development is one of most common signs of PWS. Hyperphagia (over–eating, sometimes with insatiable appetite) becomes evident usually starting from 3–4 years. As a result of over–eating and relatively low physical activity, most children become obese. Scoliosis develops in a significant number of children. Facial characteristics of the syndrome include elongated face, prominent nasal bridge, thin down–turned lips.

Obesity persists in the adolescent period and in adulthood. Frequent striae are a direct result of obesity and soft skin.

Hypogonadism affects both sexes. While a small size of the testicles is evident even in small boys, hypogonadism in girls becomes obvious only in adulthood as late onset of menstrual periods or amenorrhea. Hormone replacement therapy may be necessary.

A delay in psycho–motor development in most patients is mild or moderate. Severe intellectual defects (as well as almost normal intellectual development) are relatively rare. A cognitive profile of these patients includes relatively good spatio–visual orientation, reading and vocabulary, but serious problems with spoken language. 5–10% of adult patients reveal hallucinations, paranoia or depression.

Deletions of the paternal copy of 15q11q13 are the most common. Other mechanisms include uniparental disomy (if both copies of the 15q11q13 region in a patient are maternal) or translocations with breaks in the area of 15q11q13. Clinical diagnosis of PWS has to be confirmed by cytogenetic examinations. It should be noted that patients with terminal deletions of 2p (2p25–pter) and with interstitial deletions of 6q16 may have very similar clinical manifestations.

- *Angelman syndrome*

Loss of the maternal copy of 15q11q13 leads to Angelman syndrome (AS). Prevalence of this syndrome is approximately the same as the prevalence of PWS: about 1:20,000 newborns. Although AS was described in the 1960’s, this condition was practically unknown until the 1980’s when cytogenetic examinations showed the deletion of 15q11q13 in patients with this condition. Basically, it was shown that the absence (or mutation) of the maternal UBE3A gene is crucial for the development of the syndrome.

Clinical manifestations of AS include intellectual disability, speech impairment and ataxia.

Developmental delay, in most patients very significant, is an obligate manifestation of the syndrome. The patients do not speak at all or have very limited use of words, although non–verbal communication is much better than verbal. All patients with AS have ataxia (disturbance of balance). Most children develop epilepsy and microcephaly

(usually after 2 years).

Severe delay in psycho–motor development, almost absent speech and ataxia are associated with a happy excitable demeanor, usually with frequent laughter, almost constant smiling, frequent hand flapping (when H. Angelman described this condition in 1965 he used a term “happy puppet syndrome. Now, this term is used in very rare publications).

External features: hypopigmented skin and eyes, strabismus, wide mouth and prominent mandible are common, but not characteristic enough to make a diagnosis by photo (as it can be done for many other syndromes). Sexual development is basically non–affected. Defects of internal organs are not characteristic.

Diagnosis is based upon an association of tremor, jerky limb movements, wide–based gait, frequent laughter and epilepsy. Only symptomatic treatment of seizures is possible.

Both variants of del 15q11q13 are relatively common. There are special support groups both for the families with PWS and for the families with AS.

Deletions of 15q11.2 and 15q13.3

The wide use of array–CGH helped find tiny deletions in two specific regions of chromosome 15 — 15q11.2 and 15q13.3. These microdeletions are relatively frequent. For the last 3–4 years, del 15q11.2 were reported in ~40 persons and del 15q13.3 in ~160. Both of these deletions share one common characteristic. Usually (at the molecular level), breakpoints in different patients with apparently the same deletion are different. This is not so for the above–mentioned deletions. Both of these deletions have preferential breakpoints, usually the same for the whole group. The consistency in location of the breakpoints may be explained by specific characteristics of the chromosomal structure in these regions. Homologous segmental duplications typical for 15q11.2 and 15q13.3 facilitate breakage of the chromosome at these specific regions.

Both of these deletions were found primarily in patients with dysmorphism and developmental delay. It is not surprising because these abnormalities are the most common indication for cytogenetic examination. Surprisingly, however, the same deletions were found in a significant number of clinically unaffected parents of studied children. It raised a question: are these deletions benign familial variants or do these deletions have pathological consequences?

Several large studies showed that the frequency of these deletions is sharply increased in patients with functional abnormalities of the nervous system, including autism, benign idiopathic epilepsy, and schizophrenia. However, it will be an oversimplification to consider these microdeletions as the only causes of these disorders. The calculations show that an overwhelming majority of carriers does not have any clinical abnormalities. Of course, these deletions are harmful, but some additional factors (genetic or non–genetic) may be necessary to produce clinically significant problems. One study showed that a significant number of patients with developmental delay have two microdeletions (not limited to microdeletions 15q11.2 and 15q13.3), and a proportion of persons with two microdeletions is higher than

could be expected by chance. The authors think that at least two hits are necessary to produce an abnormal phenotype, and any one microdeletion is only one of these hits. Taken together, all of these data allow us to consider the microdeletions 15q11.2 and 15q13.3 as risk factors or susceptibility factors, but not a direct and only cause of the found abnormalities.

Interstitial Deletions of 15q15–15q23

Interstitial deletions in the area 15q15–15q23 occur very rarely: there are ~20 reports of patients having deletions of this region (but not including 15q24). Clinical manifestations in these patients are different, and there is no clinical syndrome associated with these deletions. However, recurrent occurrence of several defects allows assigning craniosynostosis to a locus within 15q15q21, Marfan–like phenotype (joint hyperlaxity, scoliosis, mitral insufficiency) to 15q21.1q21.2, and hydronephrosis to 15q15.2q21.2.

Deletions of 15q24

The syndrome caused by isolated deletions of 15q24 started to be delineated in 2006–07. There are ~15 reports of patients with this deletion. Approximately the same number of patients had deletions of 15q24 in association with deletions of more proximal regions of chromosome 15 (15q22, 15q23) or with deletions of more distal regions.

The occurrence of a pure deletion of 15q24 (usually the size of the deleted segment is ~3.5 Mb) is facilitated by structural characteristics of this region (multiple copies of non–coding repeats).

Common clinical manifestations include relatively mild developmental delay, high anterior hair line, broad medial areas of eyebrows, hypertelorism, down–slanting palpebral fissures, epicanthus, broad nasal bridge, smooth philtrum, muscular hypotonia, joint laxity, hypoplastic genitalia and hypospadias in boys. All of these findings are non–specific and may be found in numerous other forms of autosomal imbalance. Some patients had autism, which may be caused by deletions of the proximal part of 15q24 (or even the distal part of 15q23).

Almost every reported patient also had defects in other systems. However, most of these defects were found only in 1–2 patients. The only exception is a diaphragmatic hernia, which has been reported in at least 3 patients with del 15q24 (without involvement of 15q26) (it should be noted that at least one other gene related to diaphragmatic hernia lies within 15q26). In several patients with diaphragmatic hernia and deletions encompassing both 15q24 and 15q26, diaphragmatic hernias could be caused by deletions of the “distal” genes. Among other defects found in persons with del 15q24 are growth hormone deficiency, hearing loss, microphthalmia, coloboma, bowel atresia, atresia ani, hypoplastic thumbs, and myelomeningocele. Further observations are necessary for a more detailed delineation of this deletion.

Deletion of 15q26

There are 2 clinical syndromes associated with the loss of 15q26. The main manifestations of one of these syndromes are severe congenital defects. This variant of del 15q26 has been reported in ~50 patients.

The most common and most serious defect is diaphragmatic hernia found in ~20 patients with "pure" deletions of 15q26 (as well as in patients with ring chromosome 15 with the loss of 15q26 and in patients with an association of del 15q26 with trisomies for other chromosomal segments). Some patients had hypoplastic diaphragm or diaphragmatic relaxation, which may be considered as mild manifestations of the same genetic defect. A significant number of patients also had heart defects. These defects tend to be severe, including hypoplastic left heart, interrupted aortic arch, transposition of the great arteries, stenosis of aortic isthmus, coarctation of aorta, and hypoplastic aorta. The tendency of predominant affection of the left heart and aortal structures is obvious. Renal defects are the third group of internal malformations. Hypoplastic kidneys and dysplastic kidneys are main types of renal defects in these patients.

The critical segment for diaphragmatic hernia, heart defects and defects of kidneys is 15q26.2. Nevertheless, two main questions remain to be open:

1. Are all of these defects caused by the loss of one gene responsible for all main manifestations, or is each type of main defects under its own control?
2. Which genes (or gene) are (or is) responsible for the defects?

Moreover, it is possible that the distal part of 15q harbors several genes, which may be responsible for the defects of the diaphragm and the heart.

If the "first" del 15q26–related syndrome is unusually severe, the "second" syndrome is relatively mild. The distal part of 15q26 (15q26.3) contains the IGF1R gene–receptor for insulin growth factor–1. The mutation (or deletion) of one copy of the IGF1R gene leads to significant intrauterine and postnatal growth failure. A significant delay in growth (usually with relatively mild delay in psycho–motor development) is the main manifestation of this deletion. Some of these patients are clinically similar to the patients with Silver–Russell syndrome. The patients may have a small head circumference (but the newborns do not have microcephaly), blepharophimosis, hearing loss or hyperextensible joints. It is not clear, however, whether these additional findings are caused by the deletion of the IGF1R gene itself or by deletions of some neighboring genes. Treatment with growth hormone may be necessary for these children.

Actually, the IGF1R gene is also lost in most patients with the "first" 15q26 deletion syndrome, but growth retardation is not the most striking problem for these persons with multiple life–threatening congenital abnormalities.

Ring Chromosome 15

Ring chromosome 15 is a relatively common type of ring chromosome. There are at least 113 reports about patients with this abnormality. Two patients had mosaicism with a normal clone, one had mosaicism with a clone with duplication 15q, and one had mosaicism with a monosomic clone. Chromosome 15 (like chromosomes 13 and 14) is an acrocentric chromosome. Therefore, loss of the material of the short arm does not have any clinical significance.

Most patients with ring chromosome 15 do not have significant physical abnormalities. Moreover, their intellectual development may be virtually normal. In typical form, these patients are small as babies with a delay in physical development and a relatively large head.

They may resemble the patients with Russell-Silver syndrome. At least 12 patients with r(15) were clinically diagnosed as patients with Russell-Silver syndrome. Deletion of the IGFR1 gene, responsible for the production of one of the growth factors, leads to this growth delay. This gene is located at the distal tip of 15q and almost all patients with r(15) are monosomic for this gene. However, there is a sub-group of patients (~15) who had obesity and even Prader-Willi-like phenotype.

Deletions of more proximal segments of 15q are responsible for the whole group of serious morphologic abnormalities. There is a syndrome caused by distal 15q deletion, which consists mainly of three groups of abnormalities: heart defects, diaphragmatic hernia and defects of the kidneys. All of these findings may be present in those r(15) patients who lost, not only the tip of 15q, but also more proximal segments (15q25-15q26).

Different heart defects were found in 23 patients, although in six of them, the precise form of heart defect was not specified. Most patients had relatively mild defects (ventricular septal defect and patent foramen ovale). However, one patient had atrio-ventricular communication and one had double outlet right ventricle. It should be noted that three patients with r(15) had myocardiopathy.

Diaphragmatic hernia was reported in seven patients (including antenatally diagnosed fetuses) with ring chromosome 15. Most of these patients also had heart defects. Abnormalities of the kidneys were reported in 11 patients with r(15). These abnormalities included bilateral renal agenesis, hypoplastic kidneys, polycystic kidney, ectopic kidney, etc.

Absent or hypoplastic thumbs were noted in five patients with r(15). Four had dislocations of the hips. Different forms of skin depigmentation (except for 17 patients with café-au-lait spots) were reported in six patients. Five boys had hypospadias. Defects of the brain (microcephaly, hydrocephaly, craniosynostosis), eyes (microphthalmia, cataract), gastro-intestinal system (pyloric stenosis, ectopic anus), and preaxial polydactyly were reported in 1-2 patients, each.

The vital prognosis is very favorable, except for the patients with serious kidney defects or diaphragmatic hernia.

There are at least three families, where children inherited r(15) from their minimally affected mothers.

Partial Trisomies for Chromosome 15

Chromosome 15 is an acrocentric chromosome. Therefore, isolated excess of the material of its short arm does not have any clinical significance.

There are more than 800 reports of patients with different variants of 15q trisomies. All these reports may be subdivided into 4 groups:

a. trisomy for the short segment of the near–centromeric area (15q11–q13);
b. trisomy for the “medial” part of 15q (15q14–q24);
c. trisomy for the distal part of 15q (15q24–qter);
d. tetrasomy for the paracentromeric area (isodicentric chromosome 15cen–q13).

Trisomy 15q11q13

There are more than 400 reports of people having trisomies for this relatively small segment of 15q. Recognition of such small trisomies became possible only using molecular methods of cytogenetic diagnosis. Cytogenetic basis of these trisomies is a duplication of the segment 15q11q13.

There is no general clinical picture for people having such duplications. Some of them have abnormal manifestations, both morphological (birth defects) and functional (like autism, seizures, or schizophrenia). Other people with the same duplications do not have any clinical abnormalities.

Discovery of dup 15q11q13 in several patients with epilepsy, psychoses, and autism induced a whole series of publications where results of cytogenetic examination in the large groups of persons with these diseases were compared with results of examinations of healthy individuals. The results were surprisingly similar for all studied conditions. For example, examination of 1000 patients with schizophrenia (with seizures, autism) revealed that 30 (3%) of these patients have duplications 15q11q13. At the same time, among 1000 healthy persons, the same duplication was found in 5 people (0.5%). In this context, dup 15q11q13 seems to be a strong risk factor for the development of schizophrenia (with epilepsy, autism). Let us assume, however, that schizophrenia affects 1% of the population. If so, out of 1,000,000 people, there will be 10,000 persons with schizophrenia and 990,000 persons without it. Among affected patients, we can expect 300 persons with dup 15q11q13. In the unaffected group, we can expect 4,950 persons with the same duplication. This simple calculation shows that, although dup 15q11q13 is a strong risk factor for schizophrenia (with autism, epilepsy), discovery of this duplication is in no way a guarantee that the person will be affected.

The mechanism of influence of dup 15q11q13 onto brain functions remains unclear.
Of course, there are dozens of reports of an association of 15q11q13 and various birth defects, including defects of the brain and eyes (hypoplastic corpus callosum, Dandy–Walker malformation, anophthalmia, microphthalmia, aniridia, megalocornea), defects of the heart (hypoplastic left heart syndrome, ventricular septal defect, pulmonary stenosis), abnormalities of the skeleton (kyphoscoliosis, syndactyly, brachydactyly, hip dislocation), abnormal skin pigmentation, defects of the gastro–intestinal system (esophageal atresia, intestinal atresia, intestinal malrotation) and hydronephrosis. However, etiologic significance of this duplication in the origin of these defects remains doubtful because:

a. reported malformations are very different;
b. in many reports, the same duplication was found in the affected child and his/her healthy parent.

Generally speaking, dup 15q11q13 is a strong risk factor for the wide range of functional brain defects, but this duplication cannot be considered as the only explanation of these defects.

Trisomies for the "medial" part of 15 (15q13q24)

There are only 30 reports of patients with isolated duplications within this region. These patients are different both for the size of duplicated segments and the position of breakpoints.

There is no recognizable clinical syndrome, associated with these duplications.

Most patients have relatively mild delay in psycho–motor development in association with dysmorphism and mild abnormalities of the loco–motor system.

Structural defects of the brain are rare, although there are 3 reports of microcephaly. “Abnormal neural tube”, craniosynostosis, dilatation of the brain ventricles, and agenesis of the corpus callosum were reported in one person, each. Defects of the eye are represented by 2 patients with blepharophimosis and 2 patients with macular degeneration. There are sporadic reports of cleft lip and palate, preauricular pits, hypothyroidism, tracheal defects and skin depigmentation.

There is a relatively broad spectrum of mild defects of the skeleton and extremities: kyphosis, scoliosis, camptodactyly, proximally placed thumbs, broad thumbs, tapering fingers, syndactyly 2–3 toes, joint hypermobility, but all these defects were found in 2–3 patients, each.

The most common visceral defects are heart defects, reported in 8 patients. Most of these defects are relatively mild. Only one defect(univentricular heart) was life–threatening.

Defects of the digestive tract have not been reported. One person had bilateral renal agenesis, another had vesico–ureteric reflux.

At least 3 patients with “medial” duplications 15q had autism.

Trisomies for the distal part of 15q (15q24qter)

Distal trisomy 15q as a sole abnormality was reported in 89 patients. This number includes 22 patients with tetrasomies for the distal part of 15q. Basically, patients with tetrasomies have the same spectrum of abnormalities as patients with trisomies.

There is a significant heterogeneity between patients having the same imbalance: some may have only minor dysmorphism, whereas others have a complex of significant birth defects.

The most common cranial defect is craniosynostosis, reported in 16 patients (including 8 with distal tetrasomy 15q). Approximately half of these patients had synostosis of the frontal bones (trigonocephaly), but synostosis of the temporal and parietal bones are also common. Other forms of brain defects are not characteristic, although there are 3 reports of hydrocephaly, 2 reports of Dandy–Walker abnormality and agenesis of the corpus callosum, and sporadic reports of hypoplastic cerebellum, and, even, anencephaly.

There were other defects. Cleft palate was found in 6 patients. Heart defects are relatively common (16/89, including 5/22 of those with tetrasomy), but mostly mild. One patient had common arterial trunk, another had Ebstein defect (abnormality of the tricuspid valve), and heart defects in other patients were not life–threatening.

Defects of the kidneys are surprisingly frequent. Hydronephrosis was reported in 7 patients (including 5 patients with tetrasomy 15q); 8 patients (including 3 with tetrasomy 15q) had horseshoe kidney. Other renal defects include cystic kidney, vesico–ureteric reflux, and renal

failure without evident morphologic defects of the kidneys. Two children (both with tetrasomy 15q) had Wilms' tumor.

Defects of the gastro–intestinal system are highly uncommon. There are only sporadic reports of pyloric stenosis and anal ectopia.

Numerous abnormalities of the skeleton and extremities are relatively mild. They include scoliosis (11), kyphosis (3), contractures (9), camptodactyly (6), hip dislocation (3), brachydactyly (2), 11 pair of ribs (2), and sporadic reports of pre– and postaxial polydactyly, syndactyly 3–4 fingers and pectoral deformities.

As a rule, physical development of a patient with distal trisomy 15q is normal or even above normal. "Overgrowth" is a typical manifestation of this condition reported in at least 11 patients. The distal tip of 15q contains the IGF1R gene — the receptor for insulin growth factor–1, participating in growth control. A deficit of this gene (in patients with deletions) leads to hypoplasia and a delay in physical development, excess of this gene (in patients with trisomy) causes excessive growth.

The psycho–motor development of patients with distal trisomy 15q varies, but, in most patients, the delay in psycho–motor development is not very serious.

Functional defects that accompany distal trisomy 15q include seizures (9), hearing impairment (9), autism (6), and schizophrenia (1).

Association of overgrowth, craniosynostoses, mild effects of the loco–motor system and kidney defects (horseshoe kidney, hydronephrosis) allows to us to speak about a clinical syndrome associated with distal trisomy 15q.

Tetrasomy for the paracentromeric area of 15q

There is a large group of patients who have a small supernumerary chromosome, consisting of the short arm, centromere, and proximal part of 15q on both sides of the centromere. Of course, such an additional chromosome is read by standard cytogenetics, although recognition of the marker as tetrasomy for 15cen–q11 (or 15cen–q13) requires special techniques. If trisomy 15q11q13 may be considered as an intermediary form between "normal" and "abnormal", there are no doubts that tetrasomy 15cen–q13 is a pathologic condition. Not less than 250 patients with an additional marker chromosome, dic 15q11 (or dic 15q13) have been reported so far.

The vast majority of patients with tetrasomy 15cen–q13 does not have major birth defects. Main manifestations of this tetrasomy are multiple developmental problems and functional brain abnormalities.

Most infants with tetrasomy 15cen–q13 are born at term with normal weight, but a significant number of affected patients has hypotonia. They begin crawling, sitting and walking much later. Cognitive delay became evident usually after 1 year. Speech of these children may be absent or they reveal very poor vocabulary. There are reports of defects of sensory processing that hampers the ability of the patient to adapt to daily challenges. More than 50

patients with tetrasomy 15cen–q13 have autism or autistic features. Actually, tetrasomy for this segment is the most frequent chromosomal abnormality in autistic patients.

All these developmental abnormalities, however, are not constant: there are at least 15 clinically normal persons with tetrasomy 15cen–q13, 6 more patients were discovered upon cytogenetic examination of patients with oligospermia or infertility.

A small sub–group of patients with tetrasomy 15cen–q13 has a typical Prader–Willi syndrome phenotype (hypotonia, obesity, hypogenitalism). In all of these patients, an additional chromosome has maternal origin: the presence of 3 copies of maternal genes in this area and only one copy of paternal genes produces imbalance, leading to Prader–Willi syndrome. There are not more than 20 published patients with this syndrome, caused by tetrasomy 15cen–q13. Only 1–2% of Prader–Willi syndrome patients have this additional chromosome.

Seizures are a very common manifestation of tetrasomy 15cen–q13. They were reported in ~30% of persons having this imbalance. There are several reports of hearing loss and ataxia, but each of these defects was found only in 6–7 patients.

Physical abnormalities are not as common as in most other types of autosomal imbalance. Mild dysmorphic features may be found in 15–20% of patients. Abnormalities of the loco–motor system include kyphosis (8), scoliosis (6), hip dysplasia (4), joint laxity (3), contractures (2) or brachydactyly (2).

Defects of the brain include hypoplastic corpus callosum (4) and sporadic reports of hydrocephaly, hypoplastic cerebellum, holoprosencephaly or even spina bifida. Cleft palate was reported in 5 children.

Congenital heart defects are rare (6/250), but they include very serious defects — tetralogy of Fallot (2), transposition of the great arteries and aplasia of the right atrium.
Defects of the gastro–intestinal system (pyloric stenosis, ventral ectopia of the anus) and kidneys (agenesis of one kidney, dilated renal pelvices) are very rare.

There are several reports of direct transmission of an abnormal chromosome from one of the parents. Therefore cytogenetic examination of the parents is necessary to determine the genetic risk in families that are planning to have more children.

Trisomy 15

Trisomy 15 seems to be very uncommon. There are only 18 reports about people with this pathology. Complete trisomy 15 is exceptionally rare: only three out of 18 patients had trisomy 15 in all cells; all other were mosaics.

Basically, mosaicism of any trisomy may occur through two opposing ways: 1) secondary non-disjunction in a primarily cytogenetically normal embryo; 2) “rescue” with elimination of one of the excessive chromosomes from the primarily trisomic embryo. Due to the latter mechanism, however, it is possible that the two remaining chromosomes will be identical (both maternal or both paternal). As a result, a “rescued” (or partially “rescued”) person will have uniparental disomy for one of his/her chromosomes. This mechanism was shown in

several patients with mosaic trisomy 15 who had two identical chromosomes 15 in a 46-chromosomes clone.

Trisomy 15 does not constitute a recognizable syndrome. External manifestations include cranio-facial dysmorphism with relatively common microstomia (5) or a short neck (3). Four patients had microcephaly. Other structural defects of the brain and eyes are not characteristic. There are only sporadic reports on hypoplasia of cerebellar vermis and retinal dystrophy.

The most common are heart defects reported in 12/18 patients. In some of them, defects were very serious, including double outlet of the right ventricle (2), hypoplastic left heart (1), and atrio-ventricular communication (1). At the same time, atrial septal and ventricular septal defects in some patients spontaneously closed without any medical intervention. Basically, the condition of the heart is the main factor determining the vital prognosis of such persons.

Sporadic skeletal abnormalities include kyphosis, 11 or 13 pairs of ribs, dislocation of the hips, camptodactyly, and, even, ectrodactyly.

Anterior position of the anus was reported in four patients. Diaphragmatic hernia, omphalocele, and cystic liver were found in one patient, each.

Asymmetry of the body and areas of hyperpigmented skin (strong evidence of mosaicism) are uncommon: hemihypertrophy was mentioned only twice, areas of hyperpigmentation was mentioned once.

Surviving children with mosaic trisomy 15 reveal an evident delay in psycho-motor development; two of them developed seizures.

The presence of two maternal chromosomes 15 in a 46-chromosome clone caused clinical manifestations of Prader-Willi syndrome in three patients, where the paternal chromosome 15 was randomly eliminated upon the “rescue” of trisomic cells.