Chromosome 12

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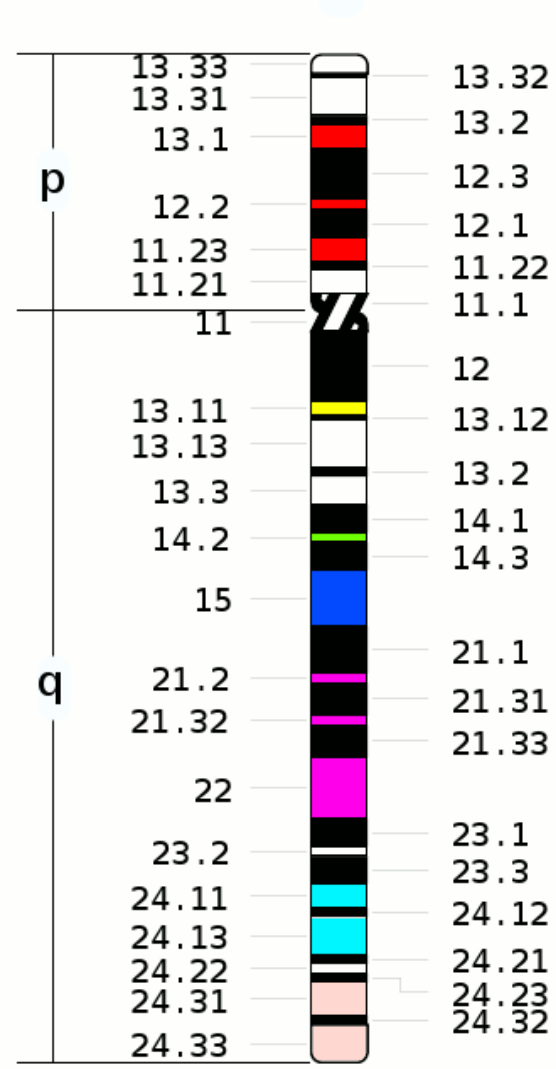

Introduction

The genetic length of chromosome 12 is ~132 Mb. It is ~4–4.5% of the total human genome, approximately the same size as chromosomes 10 and 11. The length of the short arm is ~35 Mb; the length of the long arm is 97 Mb. Chromosome 12 contains ~1,300 genes. Some of these genes control the development of body organs or participate in maintaining body functions.

Structural abnormalities of chromosome 12 are relatively rare. There are only ~150 reports on patients with deletions of the short arm and approximately the same number of persons with deletions of the long arm (in both cases, including patients having an additional imbalance for another chromosome).

Surprisingly enough, there are no clear–cut syndromes caused by deletions of chromosome 12 (except, maybe, patients with tiny deletions 12q12 having Buschke–Ollendorf syndrome). More precise determination of breakpoints and a clinical comparison of patients having similar well–characterized deletions may lead to a description of a new syndrome caused by deletions of chromosome 12.

Deletions of Chromosome 12

Deletions of 12p

The genetic size of the chromosome 12 is ~132 Mb, where the short arm is ~35 Mb. Deletions of this area are relatively rare: there are only ~50 reports of patients with “pure” deletions of the short arm. Until now, there are no syndromes caused by such deletions. At the same time, several birth defects were repeatedly found in patients with various deletions of 12p.

Reports of brachydactyly E (a form of brachydactyly, where short digits are caused by the predominant shortening of metacarpals and metatarsals) in patients having deletions of the small segment 12p11.22p11.23 lead to pinpointing the gene, PTHLH, responsible for this abnormality (and mutated in several cytogenetically normal patients with brachydactyly E).

At least 3 patients with deletions involving 12p12 had craniosynostosis; two children with deletions 12p12p13.1 had shortening of the limbs; two other patients sharing deletions 12p13.1p13.2 had ectrodactyly. The genes responsible for these defects are still unknown.

Deletions of 12q

Deletions of the long arm of chromosome 12 are also rare. In the world literature, there are only ~70 reports about different deletions of 12q as a sole anomaly. However, the number of reported patients significantly increased after methods of molecular cytogenetics became available: almost half of the patients have been reported after 2008.

There is a syndrome caused by the deletion of 12q14 (with ~20 patients), and ~50 patients having deletions of other areas of 12q, which do not constitute any syndrome.

Deletion 12q14 Syndrome

In 2007, Menten et al. reported three patients with an association of severe prenatal hypoplasia, failure to thrive in infancy, short stature, mild delay in psycho–motor development and signs of Buschke–Ollendorf syndrome [an association of osteopoikilosis with lenticular dermatofibrosis]. Osteopoikilosis is a term for multiple areas of dense calcification causing a mottled bone appearance. X–ray examination is necessary to diagnose this condition. Lenticular dermatofibrosis is characterized by cutaneous lesions of the limbs, trunk and sacral area. These painless lesions are slightly elevated and flattened yellowish papules grouped into plaques. All three patients had various deletions of 12q14 with a common deleted region of ~3.5 Mb. This region contains 12 genes, including the gene LEMD3, which was previously shown to be responsible for autosomal–dominant Buschke–Ollendorf syndrome.

An association of low birth weight (although most children were born at term), significant delay in weight and height, proportional short stature and almost normal mental development is typical for the Russell–Silver syndrome. Several patients with del 12q14 were found upon cytogenetic examination of patients suspected of having Russell–Silver syndrome. Smaller deletions with an intact LEMD3 gene were found in several patients who had no signs of osteopoikilosis or lenticular dermatofibrosis. All patients, however, shared a common deleted segment of 2.6 Mb, which included the gene HMGA2. It was shown that the deletion of this gene is responsible for prenatal hypoplasia and short stature.

Several patients with larger deletions had kidney defects (hypoplasia, ectopia) and heart defects (ventricular septal defect (VSD), patent ductus arteriosis (PDA)), but the number of reported patients is still too low to make a conclusion about the prevalence of visceral defects.

Because phenotypic manifestations, especially for patients with smaller deletions, are relatively mild, direct transmission of a deletion from the mildly affected parents can be expected.

“Other” Deletions of 12q

Deletion 12q14 is the only known syndrome, caused by deletions of 12q. Recurrent observations of some abnormalities in patients with other forms of del 12q give good reasons to assign a gene related to the formation of cleft palate to 12q12q13.12, a gene for cleft lip and palate to 12q15q21.1, and genes for pyloric stenosis and hydronephrosis to 12q21.2q22. The segment 12q24.1q24.2 is harboring one or two genes involved in the formation of the limbs (deletions cause aplasia of the radius or ulna, hypoplastic humeri). The most distal end of the chromosome (12q24.3) contains a gene, which (when deleted) may cause oesophageal atresia.

Ring Chromosome 12

Ring chromosome 12 is one of the rarest types of ring chromosomes. Since 1973, there have been only 13 reports on patients having this abnormality. One of these patients had mosaicism with a normal clone. Molecular examination of a ring chromosome in another patient showed concomitant duplication of 12p.

At least seven patients with r(12) did not have significant morphological defects, except for short neck and café-au-lait spots. Abnormalities in other patients included craniosynostosis, hypothyroidism, cardiomyopathy, atrial septal defect, scoliosis, hydronephrosis, hypospadias and uterine leiomyoma. All of these defects were found in one person, each. Ring chromosome 12 does not constitute any syndrome.

Direct transmission of ring chromosome 12 has not been reported.

Partial Trisomies for Chromosome 12

Marker chromosome 12

There is a group of patients that has an additional, usually very small, marker chromosome (a chromosome different from all other human chromosomes). As a rule, this marker chromosome includes a centromere and a small amount of genetic material from pericentromeric areas of both arms of any chromosome. For many years, the origin of such marker chromosomes could not be traced. Contemporary techniques, however, allow precise characterization of these markers.

Currently there are ~10 reports of patients having additional markers originated from chromosome 12. These markers include part of the short arm, centromere, and part of the long arm. Five patients were mosaic, having a clone with a marker chromosome and a normal clone. Mosaicism is relatively common for the patients with additional marker chromosomes, because small markers can be easily lost during cellular division.

There is no typical complex of facial dysmorphism, but almost all patients have different abnormalities of the skeletal system and internal organs. Two patients had cleft palate, two had hearing impairment.

The most common skeletal abnormality – postaxial polydactyly – was reported four times. There are patients with sacral agenesis, fused ribs, contractures, dislocation of the hips and

proximally placed thumbs.

Three patients had heart defects (atrial septal defects, persistent ductus arteriosus). Abnormalities of uro-genital system include hydronephrosis (2), absence of one kidney (1), and hypospadias (1). There are sporadic reports of alopecia (baldness), coloboma of the optic disc, omphalocele and unspecified “anorectal” malformation (1).

There are good reasons to believe that most of these defects are caused by a trisomy for the material of the short arm of chromosome 12.

Trisomies 12p

There are more than 90 reports of patients having trisomies for different segments of 12p as a sole chromosomal abnormality. Ten more patients had tetrasomy for the part of 12p (except numerous reports of patients with tetrasomy for the whole 12p – see below). From the clinical point of view, all patients may be subdivided into two groups: patients with trisomy for the whole (or almost whole) 12p and patients with trisomy for the distal part of 12p (12p12-pter or 12p13-pter).

a) Trisomy for the Whole 12p

   There are 45 patients with trisomy for the whole (or almost whole) 12p. Six of these patients had tetrasomy for a significant part of 12p.

   Usually these patients have normal or increased birth weight. Most of them have turricephaly (towered skull), high forehead, relatively flat face, broad eyebrows, epicanthus, hypertelorism, broad nasal bridge, short nose with anteverted nostrils, large philtrum, thin upper lip, broad everted lower lip, and a prominent chin. These manifestations, however, are not specific, and a clinical recognition of trisomy 12p is hardly possible. Some children have bifid incisors. Short neck is relatively common (10/45).

   Three patients with complete trisomy 12p had microphthalmia. Other eye defects are not characteristic. Cleft palate or bifid uvula was reported in nine patients (in one child, in association with cleft lip). Areas of alopecia were noted in three patients and areas of skin hypopigmentation in two. Four patients had hearing impairment. At least eight patients in this group had politelia (additional nipples).

   Polydactyly was found in four children: two had postaxial polydactyly (additional digits on the side of the 5th digits). Two other had preaxial polydactyly (additional digits on the side of the 1st digits).

   Heart defects were reported in seven patients, including three with patent ductus arteriosus and two with ventricular septal defects. Not a single heart defect in these patients was life-threatening. Two patients with complete trisomy 12p had diaphragmatic hernias. One more was reported as having a “diaphragmatic cyst”. Three patients had anal defects – atresia (2) or ectopia. Patients with complete (or almost complete) trisomy 12p usually have a serious delay in psycho-motor development. Some patients suffer from seizures.

b) Trisomy for the Distal Part of 12p

This group consists of ~60 patients (including four with partial tetrasomy for the distal part of 12p). These infants are also born with normal or increased weight. Most facial dysmorphias in these patients are the same as in patients with complete trisomy 12p. However, these patients usually have a relatively mild delay in psycho-motor development.

Polytelia and cleft palate have not been reported in patients with distal trisomy 12p. Therefore, there are good reasons to think that the segment 12p11 contains genes, which, when triplicated, may lead to these abnormalities. Other defects in patients with distal trisomy 12p are basically the same as in patients with complete trisomy 12p, but almost all these defects are not so common as in the group of persons with complete trisomy 12p. Short neck was reported in seven patients in this group. Three patients had hearing impairment. Microphthalmia, areas of alopecia, postaxial polydactyly and diaphragmatic hernia were found in one patient, each. Anal anomalies were reported twice (atresia ani in one person and anal stenosis in another one). Two patients had hydronephrosis (this defect has not been reported in patients with complete trisomy 12p).

Tetrasomy 12p (Pallister-Killian Syndrome)

Pallister-Killian syndrome (called by the names of physicians who first described this condition) is the most common type of chromosomal pathology involving chromosome 12. There are ~300 persons with this condition reported in the scientific literature.

The syndrome is unique in some aspects. First of all, it is the most common condition caused by the presence of an additional isochromosome. There are more reports of isochromosome 12p than for isochromosomes 5p, 8p, 9p and 18p combined. Second, and the most important aspect, is that, in all other chromosomal syndromes, cytogenetic examination of the patient's lymphocytes (blood cells) is sufficient for diagnosis. The situation in Pallister-Killian syndrome (PKS) is very different: 1) almost all patients with this syndrome are mosaics with a normal clone; 2) a clone with an additional isochromosome 12p is invariably present in fibroblasts (usually obtained by a skin biopsy), but may be absent (or present in a very low proportion) in blood cells. Therefore, cytogenetic examination of the blood cells is not sufficient to exclude diagnosis of this syndrome. There are no doubts that may persons who were reported as cytogenetically normal after examination of chromosomes only in lymphocytes had unrecognized PKS. Retrospective analysis showed that PKS was a real diagnosis for some patients formerly evaluated as "mosaic trisomy 20". There is no strong correlation between the severity of clinical manifestations and a proportion of cells with an additional isochromosome 12p. There are a few observations where additional isochromosome 12p was present in all studied cells, but unrecognized mosaicism in these patients cannot be excluded.

Basically, PKS is a complex of severe congenital anomalies involving virtually all organs and systems. From the clinical point of view, all observations may be subdivided into two large groups: prenatal and postnatal. A large proportion of fetuses with PKS is recognized upon prenatal diagnosis based on unusual presentations upon ultrasonographic examination (and consequent cytogenetic analysis of the amniotic cells having the same characteristics as skin fibroblasts) or by chance (for example, upon cytogenetic examination of the amniotic fluid in

pregnant women above 35 years of age). After the discovery of an additional isochromosome 12p, many couples decide to interrupt pregnancy. There are several dozen reports of manifestations of PKS in these fetuses. Analysis of manifestations in fetuses with PKS detected based on maternal age showed that most of these fetuses have defects, incompatible with life or causing severe disability. The defects in the postnatal group of patients are not so severe (because fetuses with most severe abnormalities have been partially eliminated).

Babies with PKS are born usually at term and their birth weight is basically normal. Almost all newborns have severe hypotonia causing difficulties with breathing and feeding. Most infants have a characteristic complex of facial dysmorphism, which includes coarse face, high forehead, short nose with a broad nasal bridge, hypertelorism, low-set ears, wide mouth, and a large tongue. A significant number of patients has sparse hair, especially in temporal areas; sometimes the hair in some areas is absent. Choanal atresia, stenosis of external auditory canals, microtia (small ears), or preauricular pits are not characteristic, but reported in 2-5 patients, each. Isolated cleft palate, however, is very common (32 out of 299 analyzed reports). Two more persons had cleft lip and palate. Some children have multiple frenula between the lip and the alveolar ridge.

Short neck with excessive skin folds was reported in 79/299 patients (the actual incidence may be even higher because not all reported patients were described in details). Many patients had additional nipples (politelia): this defect was reported in 22 patients (but not all reported patients were reported in detail).

Streaks or patches of skin that are darker (or lighter) than the surrounding skin is another hallmark of the syndrome. Such defects were reported in 25% (again, it is a minimal estimate). However, areas of hypo- or hyperpigmentation are very common for other patients having different clones of cells. In that context, it is not clear whether these pigmentary defects reflect the presence of mosaicism itself or are specific for mosaic tetrasomy 12p.

External examination reveals multiple other defects: shortened extremities (micromelia) were reported in 53 patients. Preaxial and postaxial polydactyly were equally frequent: 15 patients had preaxial polydactyly and 14 had postaxial one. Other defects of the skeletal system include contractures (18), scoliosis (12), hip dislocation (11), camptodactyly (9), brachydactyly or partial syndactyly. At least 10 patients had 11 pairs of ribs. A characteristic finding of the syndrome is a sacral appendage (sometimes tail-like structure) observed in 12 patients. Deep sacral dimple was reported six times. Umbilical hernias (27) or inguinal hernias (11) are also common.

Morphological defects of the skull and brain include hypoplastic or absent corpus callosum (12), hydrocephaly (9), micropolygyria (7), hypoplastic cerebellum (4), Dandy-Walker malformation (3), craniosynostosis (3). Eye defects are relatively rare. They include microphthalmia (5), cloudy cornea (4), abnormal retinal pigmentation (4), and hypoplastic optic nerve (3).

Most persons with PKS have severe defects of the internal organs. The most common defect is diaphragmatic hernia, which was reported in 94 out of 299 persons with this syndrome. No other chromosomal syndrome has a higher incidence of diaphragmatic hernia. Of course, prenatal diagnosis of this defect is the main reason to terminate a pregnancy. As a result, the

incidence of diaphragmatic hernia among newborns with PKS is much less. However, most patients with this defect do not survive surgery.

Heart defects are also common. At least 57 patients had various heart defects, including 15 patients with atrial septal defects, 14 with patent ductus arteriosus, ten with a ventricular septal defect, five with tetralogy of Fallot, and three with hypoplastic left heart syndrome. Ebstein anomaly, aortal stenosis, stenosis of the pulmonary artery, and cardiomyopathy were reported in two patients, each. Many of these defects are life-threatening. Absence or defects of the pericardium (exceptionally rare congenital defects) were reported in three patients with PKS.

Abnormal lobation of the lungs or primarily hypoplastic lungs (not caused by a diaphragmatic hernia) were found in eight affected persons.

The most common gastro-intestinal defects are anal defects (atresia, stenosis, or ectopic position of the anus). These abnormalities were reported in 35 patients. Different forms of intestinal malrotation were found in 16 affected patients. Five patients had omphalocele.

Defects of the kidneys are not so common. However, nine patients had hydronephrosis. Dysplastic kidneys were reported in seven persons, two more infants had hypoplastic kidneys.

Polysplenia (the presence of additional small spleens) was found five times.

Diaphragmatic hernia, heart defects, defects of the kidneys and gastro-intestinal system are life-threatening conditions. The patients who do not have these defects (or survive surgeries to restore abnormalities of the heart and intestinal tract) usually have a severe delay in psycho-motor development. Many of them have seizures. Hearing impairment was reported in 22 patients.

From the genetic point of view each instance of tetrasomy 12p is a result of a sporadic mutation. There is no report of recurrent birth of affected children in the same family.

Trisomies 12q

Partial trisomy for the long arm of chromosome 12 as a sole abnormality occurs rarely. There are ~55 patients with all kinds of such trisomies. All these patients may be subdivided into three groups: trisomies 12q13 (~15 reported patients), distal trisomies 12q (~20 reported patients), and all other types of trisomy 12q.

a) Trisomy 12q13

   Trisomy 12q13 (as well as distal trisomy 12q) does not constitute a recognizable syndrome. The most common abnormality in these patients is trigonocephaly, reported four times. Cleft palate, redundant neck skin, congenital heart defects, pectus carinatum (protrusion of the sternum) and inguinal hernia were found two times, each. Two patients were reported as having a Noonan-syndrome-like phenotype (short stature, pectus excavatum, and webbed neck). All other abnormalities (ptosis, corneal opacity, obstruction of lacrimal ducts, accessory nipple, relaxation of the diaphragm,

intestinal malrotation, megacolon, hypospadias) were also reported in these patients.

In some families, duplication of 12q13 may be inherited. Therefore, molecular cytogenetic examination of the parents is necessary for a prognosis for further pregnancies.

b) Distal trisomy 12q

This group includes ~20 patients having trisomy 12q24qter or 12q23qter. All patients have a delay in psycho-motor development. Facial dysmorphism does not seem to be characteristic. Brain defects are not typical; reported defects include microcephaly, hypoplastic corpus callosum (2), hypoplastic cerebellar vermis (1) hydrocephaly (1), Dandy-Walker abnormality (1).

A short webbed neck was noted in six patients. Coloboma and choanal atresia also have been reported. There is a very wide spectrum of defects of the skeleton and large joints: scoliosis (3), dislocation of the hips (3), camptodactyly (2), pectus excavatum (2), and loose joints (2). Arthrogryposis, shortened humerus, absent ribs, additional ribs, syndactyly, radio-ulnar synostosis (a fusion between radial and ulnar bones of the forearm), and a proximal position of the thumbs were reported in one person, each.

Congenital heart defects were found in six patients. All six had ventricular septal defects in association with atrial septal defects (3) or coarctation of the aorta (2). Anal atresia or ectopia was reported twice. One patient had pyloric stenosis.

There are two reports of chylothorax – an accumulation of lymphatic fluid in the pleural cavity (leading to inability to breathe normally). This defect is unique for distal trisomy 12q: there are good reasons to believe that 12q24 contains gene(s) which impair lymphatic circulation.

Functional defects in patients with distal trisomy 12q include hearing impairment, seizures, autism and attention deficit disorder.

Trisomy 12

There are two groups of reports about mosaic trisomy 12. In the first group, cells with an additional chromosome 12 were found in placental tissues, but were not found in fetal cells. If these pregnancies were terminated, fetuses did not have any visible abnormalities. If pregnancies were not terminated, the infants revealed normal development. All of these observations could not be considered as true trisomy 12 mosaicism.

The second group consists of 20 observations when trisomy 12 was discovered in the blood or other tissues of the liveborn infants. In all observations (except one), the patients were mosaics with a usually relatively small proportion of trisomic cells. The only known person with non-mosaic trisomy 12 had abnormalities of the brain (arhinencephaly, hypoplastic corpus callosum, and hypoplastic cerebellum), hypoplastic kidneys, hypoplastic larynx, hypoplastic lungs with an incomplete lobation of the right lung, 11 pairs of ribs, preaxial polydactyly on the feet, and some small abnormalities.

Clinical manifestations in liveborn patients with mosaic trisomy 12 vary from one patient to

another. There are no features allowing clinical recognition of this trisomy.

Dysmorphic features are relatively frequent (~25%), but unspecific. Defects of the brain are rare; there are only sporadic reports of microcephaly, ectopic pituitary and neuronal heterotopy. Ptosis, macrostomia, bifid uvula, hearing loss, and short neck have been reported in 1-2 patients, each. Defects of the eyes have not been reported.

Heart defects are found in half of the patients, including reports of interrupted aortic arch, transposition of the great arteries, hypoplastic left heart and myocardiopathy.

Abnormal skin pigmentation (streaks of hypo- and hyper-pigmented skin) was found in five out of 19 patients. In some children, their pigmentary defects became visible at the age of 1-2 months.

There are sporadic reports of hypoplastic or atretic gallbladder, intestinal malrotation, anteriorly placed anus, hypoplastic kidneys, pyeloectasia, tracheal web or bilobed right lung.

Two adult patients with mosaic trisomy 12 were found upon examination of infertile men.

The individual prognosis of each patient depends on the percentage of trisomic clone and the status of internal organs.