Chromosome 20

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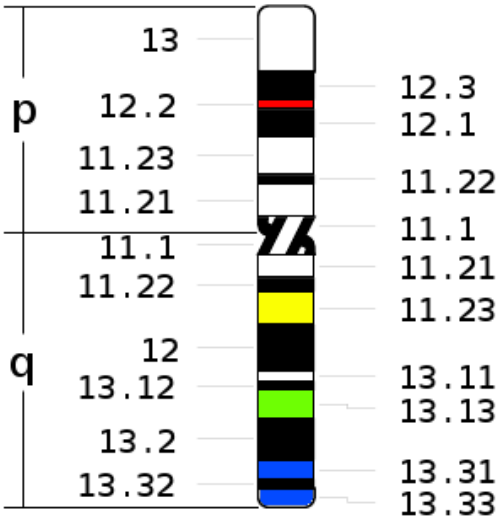

Introduction

Chromosome 20 contains about 2% of the whole genetic material. Its genetic length is ~63 Mb. The long arm (~36 Mb) is a little bit larger than the short arm (~27 Mb).

Chromosome 20 contains ~700–800 genes. Less than 10% of these genes are known to be related to human diseases. Deletions or duplications of these genes, which may be found in patients with chromosomal abnormalities, cause mostly functional defects, including a delay of psycho–motor development and seizures. Only a few genes may lead (when deleted) to structural defects of the heart, liver, extremities and other organs.

Deletions of Chromosome 20

There is a relatively small number of known conditions caused by deletions and duplications of various segments of chromosome 20. Almost all of these deletions and duplications became recognized after usage of molecular cytogenetics. Only a handful of reports on patients with these abnormalities were available only 10 years ago. Because these methods open wide an opportunity to examine abnormalities of this previously not–well studied chromosome, there are no doubts that some new syndromes caused by deletions (or duplications) of chromosome 20 will be delineated in the near future.

Currently, the most frequent forms of chromosome 20 deletions are deletions 20p12, involving the JAG1 gene and Alagille syndrome, and deletions 20q13.13q13.2, involving the SALL4 gene.

Deletions of 20p

There are more than 100 reports on patients with deletions of the short arm of chromosome 20. Most of these patients have interstitial deletions involving the area 20p12. This area contains the gene JAG1, responsible for the so–called Alagille syndrome, and all of these patients had different manifestations of this syndrome.

Alagille syndrome is an autosomal–dominant condition with variable expressivity, meaning that the effects of the condition can vary from person to person. This syndrome affects mostly the liver, heart and skeleton. Most patients have chronic cholestasis caused by a paucity of intrahepatic bile ducts, heart defects (usually peripheral pulmonary stenosis) and vertebral defects (usually butterfly–shaped vertebrae). Sometimes, the patients have posterior embryotoxon (a white opacity just anterior to the limbus) in the eyes. Facial manifestations are usually mild and include prominent forehead, broad nasal bridge and pointed chin. However, only a small number of affected patients have all of these abnormalities. Most patients have only hepatic defects or only heart defects. The clinical picture varies even within one family. Intellectual development of patients with “pure” Alagille syndrome is usually normal. Most affected patients have mutations within the JAG1 gene. Approximately 5% of patients with Alagille syndrome have complete deletions of this gene. Deletions may be very small (not affecting other genes) or relatively large involving some genes on both sides of the JAG1 gene). There are no preferential breakpoints: each patient has his/her own “unique” breakpoints. The JAG1 gene is located ~10 Mb from the telomere. It was shown that additional deletions of genes located within the areas of ~2.5 Mb proximal and ~2.5 Mb distal from the JAG1 gene do not cause any additional symptoms in the patients. Deletions involving more proximal or more distal areas of 20p are associated with some additional abnormalities not characteristic for Alagille syndrome itself.

Involvement of the PRKAG2 gene, located at 20p12.3 causes Wolff–Parkinson–White (WPW) syndrome — a specific disturbance of tachycardia with characteristic electrocardiographic findings. Some patients with this deletion have variable neurocognitive defects (language delay, learning disability).

It was shown that involvement of more proximal areas (20p11) is associated with microcephaly, cleft palate, preauricular pits, hearing defect, growth hormone deficiency or autism. It is not known which of the deleted genes (if any) causes these manifestations.

Distal Deletions of 20p

There are ~20 reports on patients having distal deletions of 20p (more distal than the JAG1 gene). There are some attempts to delineate a clinical syndrome associated with such deletions. The most common findings in such patients are large fontanels, ear abnormalities (ear pits, abnormal position) and seizures. Some patients with distal deletions also had hydronephrosis, hearing loss, obesity or autism. Trigonocephaly, chorio–retinal coloboma, cleft palate, patent ductus arteriosus, and coarctation of aorta also have been reported, but it is not clear whether these abnormalities are manifestations of the syndrome or just random findings.

Deletions of 20q

Isolated deletions of the long arm of chromosome 20 are relatively rare. There are ~30 reports on patients having such abnormalities.

All of these reports may be subdivided into 3 groups: a proximal deletion of 20q (del 20q11.2q12), deletion of the “central” part of 20q (del 20q13.13q13.2) and distal deletions (del 20q13.3–qter).

The patients with proximal deletions have intra–uterine and post–natal growth retardation, triangular face, large forehead, hypertelorism, hypoplastic alae nasi, esophageal reflux and increased tolerance to pain. Pyloric stenosis and hearing loss also have been reported in the patients with these provisional conditions.

Region 20q13.13q13.2 contains several genes, including the SALL4 gene. This gene (when mutated) caused the Okihiro syndrome: an autosomal–dominant condition, which manifests itself by an association of defects of the radial ray (hypoplastic radius, hypoplastic or low–inserted thumbs) and Duane anomaly (sort of limited eye abduction). Some scientists believe that acro–renal–ocular syndrome is allelic to Okihiro syndrome and also may be caused by defects of the SALL4 gene. The patients with acro–renal–ocular syndrome also have colobomas of iris and optic nerve and renal defects. Several patients with deletions of this region of chromosome 20 revealed an association of radial defects, renal defects (hypoplastic kidney, agenesis of one kidney), choanal atresia, hearing loss, and eye defects.

Deletions in all reported patients had different breakpoints. In all patients, these deletions involved several neighboring genes, both more distal and more proximal to the SALL4 gene. The patients with “pure” Okihiro syndrome have normal mental development. The patients with additional deletions of other genes have a different degree of developmental delay.

Terminal Deletions of the Long Arm of Chromosome 20

There are ~15 reports on patients with isolated terminal deletions involving the most distal segments of 20q (20q13.3–qter). All of these children have a delay in psycho–motor development, usually relatively mild, but most of them have very mild dysmorphism or do not have any. Defects of the brain (trigonocephaly) or heart defects have been reported. This segment of 20q contains two genes (CHRNA4 and KCNQ2) involved in the autosomal dominant forms of epilepsy. Deletions of these genes explain the origin of seizures in some (but not all) patients with terminal deletions of 20q13.3qter. The more distal SOX18 gene is involved in the development of hypotrichosis–lymphedema syndrome, but neither of the reported children with deletions of this gene had these symptoms. Most likely, the isolated deficiency of SOX18 is not sufficient for the occurrence of hypotrichosis and lymphedema.

Terminal deletions of 20q (as well as terminal deletions of 20p) frequently are caused by parental translocations. Interstitial deletions are mostly sporadic, although (especially for relatively small 1–2 Mb deletions) direct transmission from an unaffected (or minimally affected) parent should be considered.

Ring Chromosome 20

Ring chromosome 20 is one of the most frequent forms of ring chromosomes. There are at least 131 reported patients with this abnormality. More than 50% of all patients (73/131) have mosaicism with a normal clone.

Ring chromosome 20 is unique. The vast majority of patients with ring chromosome 20 are born at term with normal physical parameters (height, weight, and head circumference). Early development in most children is completely normal. But at the age of 2-3 years (sometimes earlier, sometimes later), they start to develop seizures. In most patients control of seizures either could not be achieved or had only limited success. Seizures are common (and in most

patients the only) clinical manifestation of ring chromosome 20. There are only 7 patients (out of 131) where seizures have not been reported. Microcephaly found in several patients is secondary: usually it develops after the patient suffers from seizures for several years.

Visceral abnormalities and facial dysmorphism are very rare. Only 3 patients had heart defects (ventricular or atrial septal defects). Hypoplastic cerebellum, hyperextensible joints, preauricular tags or pits, brachydactyly and areas of skin depigmentation were reported in two patients, each. There are single reports of microphthalmia, chorio-retinopathy, intestinal obstruction, pyloric stenosis, and hypoplastic corpus callosum.

Molecular examination of ring chromosome 20 in a large cohort of patients showed that there are two types of rings: in one group there is no loss of genes either from 20p or from 20q, only telomere sequences are lost upon the formation of rings. Clinically, patients of this group have seizures, but they do not have any phenotypic abnormalities. In another subgroup, there is a loss of several genes from 20p and/or 20q. These patients are more likely to reveal birth defects or facial dysmorphism.

The mechanism of seizures, common for both sub-groups and affecting both the patients with non-mosaic ring (20) and the patients with a normal clone remains unknown.

Direct transmission of r(20) from mothers was reported in three families.

Trisomy 20

All reports of trisomy 20 may be subdivided into two groups:
trisomy 20 found upon prenatal diagnosis based on the examination of amniotic fluid or placental tissues, but not confirmed upon examination of the fetus or child, and
trisomy 20 found in fetal tissues (after prenatal diagnosis of this abnormality in amniotic fluid or without any prenatal diagnosis).

In the first group (prenatal detection not-confirmed in fetal tissues) there may be two variants: prenatal diagnosis performed after finding some fetal abnormalities by ultrasonography, and prenatal diagnosis performed for other indications (maternal age, increased risk for trisomy 21, etc.).

Discovery of trisomy 20 (usually in mosaic form) upon cytogenetic examination of the morphologically abnormal fetus usually leads to the termination of the pregnancy. Reported defects in such cases include DandyWalker malformation, diaphragmatic hernia, sirenomelia, Pena-Shokeir syndrome (multiple contractures with hypoplastic lungs), and transposition of the great arteries. It is difficult to decide whether these abnormalities were caused by trisomy 20 or they were just randomly associated with trisomy 20. The problem is much more complicated if mosaic trisomy 20 is found upon examination of the fetus without visible morphologic abnormalities. If the family decided to continue the pregnancy, most children would be clinically normal, and trisomy 20 would not be found in fetal cells. However, there are several examples when the child showed a delay in psycho-motor development and/or had some morphologic abnormalities (despite the absence of trisomic cells in fetal tissues). An opposite situation occurs when the parents decide to terminate the pregnancy, but post-mortem examination shows the absence of any abnormalities in the fetus.

The second large group represents patients where mosaic trisomy 20 is found in fetal tissues (rarely in blood, more frequently in skin). There are ~35 such patients. Clinically this group seems to be the most important. Almost all of these patients are mosaics. One fetus with full trisomy 20 had multiple malformations (spina bifida, cleft lip and palate, omphalocele, and cystic kidneys). However two live-born children with reportedly full trisomy 20 did not have any serious morphologic abnormalities.

Out of 31 patients with mosaic trisomy 20 in fetal tissues, four were completely normal (although the percentage of trisomic cells in these patients was very low). All other patients had some morphologic or functional defects. It has to be mentioned that several children who had some structural abnormalities were intellectually normal. Conversely, some children with a delay in psycho-motor development did not have any morphologic defects.

Dysmorphic features are relatively uncommon (5/31) and non-specific. Sporadic abnormalities of the craniofacial area include microcephaly (1), cleft lip and palate (1), bifid uvula (1), preauricular pits (2), and short neck (1). One patient had hearing impairment.

The most common defect is abnormal pigmentation of the skin with streaks (or whirls) or hyperpigmented and hypopigmented areas. Such skin defects may be found in many other mosaic trisomies. In persons with mosaic trisomy 20, however, these pigmentary abnormalities may be the only manifestations of the disorder. Abnormal skin pigmentation was reported in 12 patients. Actually, the incidence of this defect may be higher because, in several patients, pigmentary skin abnormalities became evident only after 4-5 years of age, but some patients with mosaic trisomy 20 were much younger.

Defects of the loco-motor system are relatively mild. Kyphoscoliosis was reported in five patients. Other defects include 13 pair of ribs (2), hyperflexible joints (2) and sporadic reported of postaxial polydactyly, camptodactyly, and hip dysplasia.

Heart defects were found in five patients, including two with very serious abnormalities: transposition of the great arteries and hypoplastic left heart.

Two patients had anal defects (anal fistula and ventral ectopia of the anus). There are reports of hypoplastic kidneys (2), hydronephrosis (1), dilatation of renal pelvis (1) and bicornuate uterus (1).

Intellectual development in most patients was normal; only five showed delay in psycho-motor development. Seizures were reported in 3 persons.

Generally, patients with mosaic trisomy 20 have relatively small abnormalities, and their vital prognosis is almost the same as for cytogenetically normal children.

Partial Trisomies for Chromosome 20

Partial Trisomies for 20p

Patients with partial trisomies for the short arm of chromosome 20 are uncommon. There are only ~45 reports about such patients. All of these reports may be subdivided into 3 groups:

- trisomy for the whole or almost whole 20p (~20 reported patients);

- trisomy for the small interstitial segments of 20p (~20 reported patients);
- additional isochromosome 20p (5 patients).

Of course, there are more than 100 reports of trisomy 20p in association with deletion 20q (due to pericentric inversions) or partial monosomies for otherchromosomes (due to translocations).

Trisomy for the Whole or Almost Whole 20p

This form of trisomy is a clinically recognizable syndrome, although this conclusion was made analyzing all known reports of this trisomy (including patients with an additional imbalance).

The patients with trisomy 20p11pter usually reveal a mild delay in psychomotor development, sometimes microcephaly, and facial dysmorphism, which includes coarse hair, a round and flat face, hypertelorism, epicanthus, upslanted palpebral fissures, strabismus, short nose, anteverted nares, and malformed low set ears. Some patients have a short neck.

Although structural brain defects are uncommon, there are sporadic reports of acrocephaly, agenesis of corpus callosum, and even anencephaly.

Congenital heart defects are common (40% of all patients), but usually not life-threatening. The defects are ventricular and atrial septal defects with mild effects on hemodynamics). Only one patient had tetralogy of Fallot.

Renal defects are also common. There are reports of a double collecting system, dystopic, or even polycystic kidneys. One boy had hypospadias.

Abnormalities of the loco-motor system (vertebral defects, kyphosis, joint laxity, preaxial polydactyly or macrodactyly (unusually large fingers)) were reported in 1-2 patients, each.

Defects of other systems are uncommon, although there are sporadic reports of microphthalmia, cleft palate, pulmonary hypoplasia and ventral position of the anus.
Interstitial Duplications of 20p

There are twenty patients with interstitial duplications for relatively small (usually less than 1 Mb) segments of 20p. The clinical significance of these abnormalities remains uncertain, because, in many families, the same duplication was found both in the child with birth defects and in his/her unaffected parent. In one of such family, the child with dup 20p12.2 had hemifacial microsomia (microphthalmia of the right eye and right-side microtia (small ear) with pre-auricular fistula) and agenesis of the right kidney. In another family, the patient with dup 20p12.3 had tetralogy of Fallot, atrio-ventricular communication, rhizomelic shortening of the limbs, hearing impairment, and retinal detachment. In both families, the same duplications were found in unaffected mothers of the probands.

There is no clear picture of abnormalities related to interstitial duplications of 20p.

Additional Isochromosomes of 20p

Additional isochromosomes of 20p (resulting in tetrasomy for the whole short arm of

chromosome 20) were reported only five times. Three of these patients were mosaics with a normal clone.
All patients with an additional isochromosome 20p had very serious multiple defects, involving brain, heart, kidneys and locomotor system. Brain defects were presented by occipital encephalocele, Dandy-Walker malformation, and hypoplastic corpus callosum. Heart defects included double outlet right ventricle, pulmonary atresia. and ventricular septal defects. Two patients had pelvic kidneys, and one had bilateral renal agenesis. The latter defect is extremely rare in people with structural chromosomal abnormalities.

Two probands had multiple bone fractures, one of them was reported as having osteopenia (lowered bone mineral density). It should be mentioned that osteopenia also was occasionally mentioned in patients with trisomy 20p. Of course, not all reported patients had tests necessary to confirm or exclude this bone defect. There are no doubts that the short arm of chromosome 20 contains a gene controlling bone structure. Excessive dosage of this gene in people with trisomy 20p, and especially with tetrasomy 20p, significantly increases bone fragility.

Partial Trisomies for 20q

Trisomies for 20q (as the only abnormality) occur very rarely: there are only ~25 reports of patients with this abnormality. At the same time, there are at least 90 reports of patients having trisomy 20q is association with other forms of a chromosomal imbalance, mostly due to pericentric inversions or reciprocal translocations. Because of a limited number of available publications of “pure” trisomy 20q, information about patients with an associated imbalance may provide some additional details, which are necessary for delineation of the phenotypic picture.

Trisomies 20q11q12

There are only ~10 reports of patients having isolated trisomies of the “proximal” segment of 20q. Neither of these patients had significant anomalies: some of them had mild dysmorphism, some had peculiar behavior, or a mild delay in psycho-motor development. One of these persons was obese; two were reported as having “short hands”.

There are good reasons to believe that this area of 20q does not contain genes which (when triplicated) may seriously harm a fetus.

“Distal” Trisomies of 20q

This group includes patients having trisomies for the segment 20q13. There are only 14 patients with trisomy 20q13 but without the involvement of other chromosomal imbalances.

Dysmorphic features in these patients are relatively mild and unspecific. They include high forehead, epicanthus, large ears, protruding upper lip, and micrognathia. Hypoplastic nasal bones or “bifid nose” (a nose with a grooved septum) were reported in three patients. A short webbed neck was mentioned twice. Three patients had cleft lip and palate (a common duplicated segment for this defect was 20q13.2q13.3). Cleft lip and palate also was reported in many patients having distal trisomy 20q in association with another chromosomal imbalance. Two patients with dup 20q13.13 had isolated growth hormone deficiency; two had

hypothyroidism. Two others had hearing impairment.

Brain defects are uncommon. Several patients had hypoplastic or dysplastic corpus callosum. Other brain defects were not reported.

Skeletal defects are also rare. There are several reports of vertebral clefts, scoliosis, pectus excavatum, fused ribs, or hip dysplasia. Neither poly- nor oligodactyly was described in any patient with isolated distal trisomy 20q.

Congenital heart defects are common. They were reported in six patients. All six were trisomic for the 20q13.2 segment. Most defects were very serious and included single ventricle, hypoplastic left heart, dextrocardia, or an association of severe “mild” defects in one individual. The same spectrum of heart defects may be found in several dozens of patients who had trisomy 20q13 in association with another chromosomal imbalance.

Several patients with dup 20q13 had some unusual abnormalities: tracheal stenosis, diaphragmatic hernia, omphalocele, and branchial fistula. Because tracheal stenosis, diaphragmatic hernia, and omphalocele were reported in several patients with distal trisomy 20q in association with another chromosomal imbalance (where these defects are not typical), there are good reasons to believe that these abnormalities are causally related to trisomy 20q13. The question about branchial fistula remains open: this defect was not reported in other patients with either isolated or “associated” trisomy 20q.

Many patients with distal trisomy 20q, in association with another chromosomal imbalance, had hydronephrosis ,or a dilated collected system of kidneys, and dilated ureters. Neither of the reported patients with isolated distal trisomy 20q had this defect. However, because patients with these kidney defects had 1) various forms of associated imbalance, and 2) these forms of imbalance are not known as producing hydronephrosis, it is most likely that the above-mentioned renal defects are actually caused by trisomy 20q, but not by an associated imbalance.