



Chromosome 19

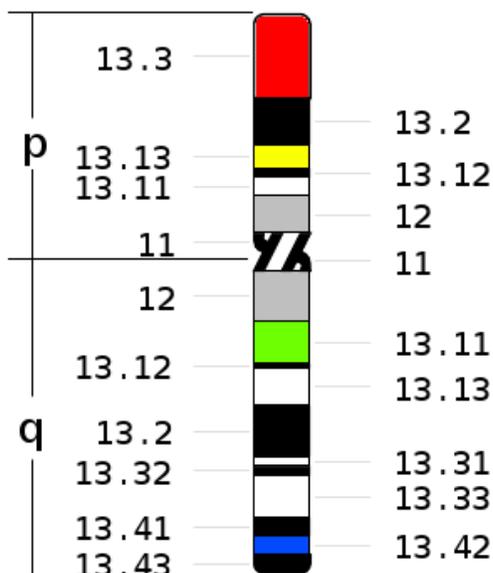
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Introduction

The genetic size of chromosome 19 is 59 Mb. It is ~2.5% of the total human genome. Its short arm is 29 Mb; its long arm is 30 Mb. Chromosome 19 is a very gene-rich area. It contains ~1,400–1,600 genes. It is ~25 genes per 1 Mb, the highest number of genes per unit among all chromosomes. Many genes on chromosome 19 are involved in either the formation of body organs or maintain numerous functional activities.

There is a very limited number of known reports about patients with structural abnormalities of chromosome 19. Including persons with an associated imbalance for other chromosomes, there are not more than 170 persons with all forms of structural imbalance for chromosome 19 and ~100 persons with deletions of the

short arm (~50) and the long arm (~50).

Not a single syndrome caused by deletions of chromosome 19 had been known until methods of molecular cytogenetics allowed recognition and detailed characterization of breakpoints in small deletions within this chromosome. Currently, there are at least three syndromes caused by deletions of the short arm (del 19p13.12, del 19p13.13 and del 19p13.3) and three syndromes caused by deletions of the long arm. All of these syndromes are very new. There are no doubts that clinical characterization of each of these conditions will become much clearer when additional patients with these abnormalities will be reported.

Deletions of Chromosome 19

The genetic size of chromosome 19 is ~59 Mb. Deletions of chromosome 19 seem to be very rare. The total number of known patients with isolated deletions of the short arm of chromosome 19 is ~35; the total number of known patients with isolated deletions of 19q is approximately the same. At least two reasons explain such a situation: 1) chromosome 19 is a very gene-rich chromosome, and loss of several of these genes may lead to early embryonic death; 2) the banding pattern of chromosome 19 makes recognition of chromosome 19 deletions (using traditional cytogenetic methods) very difficult: sometimes not only the localization of breakpoints within 19p or 19q, but even the differentiation between 19p and 19q may be difficult. And when scientists are uncertain about breakpoints, they hardly

publish these observations. Molecular methods, however, do not have such limitations. Wide usage of these methods caused a rapid increase in the number of publications about deletions of chromosome 19 in recent years. At least 28 out of 34 reports on deletions of 19p were published in 2009–2010. There are no doubts that this number will increase in the next couple years because it will be necessary to delineate syndromes caused by these deletions.

Deletions of 19p

Generally, almost all deletions of 19p are interstitial. There are no preferential breakpoints: every patient has his/her own “unique” breakpoints. All currently known deletions of 19p were sporadic.

From the clinical point of view, all deletions of 19p may be subdivided into 3 groups: a) deletions 19p13.12; b) deletions 19p13.13; c) deletions 19p13.3. Of course, in some patients, deletions involve part of 19p13.12 and part of 19p13.13.

Psycho–motor and language delay, hyperactivity, brachycephaly, hearing loss, anteverted nares, synophrys (abundant hair between the eyebrows), hypodontia (absence of several teeth) and short neck are the most constant manifestations for the patients with del 19p13.12. Involvement of more proximal areas leads to the occurrence of mild heart defects (patent ductus arteriosus, incompetence of aortic valve). Each of the known patients had some unique manifestations: trigonocephaly, hypoplastic corpus callosum, microcephaly, cleft palate, or cervical sinus. Further observations will show whether some of these manifestations are components of the 19p13.12 deletion syndrome.

Deletions of 19p13.13 were reported in ~10 patients. These patients have the tendency to overgrow. Usually they have macrocephaly, hypoplastic optic nerves, arachnodactyly and seizures. Involvement of more distal areas leads to the occurrence of atrial septal defect and craniosynostosis.

Deletion 19p13.3 and Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an autosomal dominant syndrome, which is characterized by the association of intestinal polyposis and deposits of melanin in the lips, buccal mucosa and digits. The patients with Peutz–Jeghers syndrome have a significantly increased risk of developing cancer of the stomach, thyroid, pancreas or reproductive organs. The genetic background of the syndrome is a mutation of the STK11 gene, which is located at 19p13.3. Deletions of the part of 19p13.3, which includes the STK11 gene, will produce the same phenotype. New studies showed that ~25–30% of all patients with Peutz–Jeghers syndrome have deletions of the gene. Some of these deletions are relatively mild and involve a small number of neighboring genes. Patients with “small” deletions typically do not have any additional defects. Patients with larger deletions in 19p13.3 may also have heart defects and kidney defects (unilateral agenesis, pelvic kidney).

Deletions of 19q

All of these deletions may be subdivided into 3 groups: deletions of 19q13.11, which may be considered as a “true” chromosomal syndrome, and deletions of 19q13.2 and 19q13.42, which manifest themselves as already known clinical conditions (Diamond–Blackfan anemia

and retinitis pigmentosa).

Deletions of 19q13.11

Deletions involving this area of 19q are known in ~12 patients. Almost all reports of these patients were published in the last couple years. Typically, these patients have pre- and post-natal growth retardation, significant feeding difficulties, microcephaly, ptosis or blepharophimosis, and additional nipples. Most boys have hypospadias. Some patients have signs of ectodermal dysplasia: thin and sparse hair, eyebrows and eyelashes, dry skin and dysplastic nails. All patients with this deletion had areas of aplastic skin, mainly in the occipital area. This abnormality occurs in other syndromes very rarely. Aplasia or hypoplasia of the femur is another unique (but not constant) manifestation of the syndrome. At least 2 patients had defects of kidneys (multicystic kidneys, kidney failure); 2 patients had heart defects. Cataract, deafness, preauricular tags, central median incisor, pyloric stenosis also have been reported, but it is still unclear whether these abnormalities are important components of the syndrome or random findings.

The size and distribution of breakpoints were different in all known patients. All deletions were interstitial; all occurred de novo. The minimal common deleted area (~ 3 Mb) contains more than a dozen genes. The individual role of these genes in the origin of symptoms is not known.

Deletion 19q13.2 and Blackfan–Diamond Syndrome

Blackfan–Diamond syndrome (or inherited erythroblastopenia) is anemia caused by a significant decrease of the production of red blood cells. Genetically determined defects of erythroblasts (bone marrow cells responsible for the production of erythrocytes) are the primary reasons for this anemia. Some patients may have anomalies of the upper extremities, heart defects, cleft palate and other abnormalities. It was shown that one of the genes (and probably a leading gene) responsible for this condition is the PRS19 gene which lies within 19q13.2. Most patients with Blackfan–Diamond syndrome have mutations of the PRS19 gene, but there is a subgroup of patients where Blackfan–Diamond anemia is caused by deletions of 19q13.2 (as well as translocations in this area).

Most likely, additional defects in patients with Blackfan–Diamond anemia are caused by deletions of some other genes surrounding the PRS19 gene.

As for 19q13.11 deletions, all known 19q13.2 deletions have different breakpoints, unique for each patient.

Deletions of 19q13.42 and Retinitis Pigmentosa

Retinitis pigmentosa is a group of genetically determined conditions associated with light blindness and the progressive loss of the visual field. One of the genes related to retinitis pigmentosa is the PRPF31 gene, which is located at the distal tip of 19q — 19q13.42. Recently, it was shown that in some families, this form of retinitis pigmentosa is not caused by mutations within the PRPF31 gene, but deletions of the whole gene. Deletions of some additional genes in these patients did not produce any additional abnormalities.

Almost all deletions of chromosome 19 (except tiny deletions of the PRPF31 gene) are sporadic with very low recurrence risk for further offspring.

Ring Chromosome 19

Ring chromosome 19 is one of the rarest forms of ring chromosomes. Only 16 patients in 13 families have been reported so far. Ten patients were mosaics with a normal clone; one was a mosaic with a monosomic clone.

Nine persons with r(19) did not have any anomalies. Seven other patients revealed a delay in psycho-motor development. Three patients had microcephaly. Two patients had heart defects (pulmonary stenosis in one child with hypoplastic right ventricle). Syndactyly in 1–2 toes, eventration of the diaphragm, Wilms tumor, hearing loss, joint contractures, and areas of skin hypopigmentation were reported in one patient, each.

Direct inheritance of r(19) was found in 3 families: mothers were the carriers in all of these families.

Partial Trisomies for Chromosome 19

Partial trisomies for 19p

Partial trisomies for the short arm of chromosome 19 are very rare. There are only 40 reports about patients with such trisomies as the only chromosomal imbalance. Most patients have trisomies for the most distal segment of 19p — 19p13; only 3 reported patients had trisomies limited to 19p11 and/or 19p12.

Clinical manifestations of trisomy 19p vary from one patient to another. There is no syndrome associated with this chromosomal anomaly.

Almost all patients have a mild delay in psycho-motor development, as well as a mild and unspecific complex of facial dysmorphism. Microcephaly was reported in 4 patients; other brain defects have not been reported at all.

Congenital heart defects were found in 10 patients, including one with heterotaxy and two patients with endocardial cushion defects (and non-overlapping duplications of 19p that means that there are a minimum of two segments within 19p13 related to the formation of this very serious heart defect). Heart defects in other patients were not life-threatening.

Abnormalities of the kidneys (agenesis of one kidney, pyeloectasia, vesico-ureteral reflux) were found in one patient, each.

There are sporadic reports of cleft lip and palate, preauricular pits, choanal stenosis, laryngeal cleft, hearing loss, pituitary tumor, syndactyly and arthrogyriposis. However, it is not clear whether these defects are causally related to trisomy 19p.

Five patients from one family with an inherited 2 Mb duplication in the 19p13.2 had a Sotos-like phenotype (excessive physical growth, macrocephaly, protrusive forehead, large hands and feet).

At least 6 patients with partial trisomy 19p had seizures. There are also reports of schizophrenia (2) and pervasive developmental disorder.

Almost all patients had duplications of the small segments of 19p. In such situations, there is a significant probability that this duplication may be inherited from one of the parents. Therefore, cytogenetic examination of the parents is necessary for families planning further children.

Partial trisomies for 19q

Partial trisomy for the long arm of chromosome 19 (as a sole defect) is a rare condition. Only 50 patients with different forms of 19q trisomy have been reported so far. Almost all of these patients were trisomic for the distal part of 19q (19q13); only two patients have trisomies limited to more proximal areas.

Most patients were reported over the last several years because “standard” cytogenetics may be not sufficient for the precise location of the breakpoints on 19q.

There is no recognizable syndrome of trisomy 19q. However, almost all patients have a delay in physical and psycho–motor development (sometimes without evident dysmorphism). Most patients trisomic for 19q13.1–19q13.3 have defects of the internal organs. As a rule, the patients with very distal trisomies (19q13.3) do not reveal serious structural congenital abnormalities.

Defects of the brain include agenesis or hypoplasia of the corpus callosum (6), hypoplastic cerebellum (2), craniosynostosis (2), and macrocephaly (2). Microcephaly and cortical dysplasia were reported in one patient, each. Defects of the eyes and ears are not characteristic. Six patients had cleft palate (not a single had cleft lip). Short neck with redundant skin was found 9 times. There are sporadic reports of choanal stenosis, ptosis, hypertrophic gums and hypothyroidism.

Different abnormalities of the loco–motor system include pectus excavatum (3) and sporadic reports of kyphosis, joint laxity, hip dislocation, contractures, preaxial polydactyly, and camptodactyly.

Congenital heart defects are relatively common (9), including 2 patients with tetralogy of Fallot and one with hypoplastic right heart. Duplication 19q13.3 seems to be responsible for the origin of tetralogy of Fallot. Heart defects in other patients were not life–threatening (ventricular and atrial septal defects, patent ductus arteriosus, stenosis of the pulmonary artery).

Two patients were found having bilobed right lung. Of course, this defect may be more frequent, because it may be diagnosed only upon visual examination of the lungs.

Seven patients had defects of the kidneys, including cystic kidneys (3) and hydronephrosis (3). Duplication of the 19q13.2 area seems to be responsible for these kidney abnormalities. Three boys had hypospadias. Three other patients had inguinal hernias.

Defects of the gastro–intestinal tract include hypoplastic gallbladder (3) and cystic liver (1).

Two reports of obesity seem to be caused by duplication 19q13.1q13.2.

Most duplications of 19q are sporadic. Very small duplications (usually less than 1 Mb) may be inherited from one of the parents.

Trisomy 19

Trisomy 19 is an extremely rare type of chromosomal pathology. It was reported only four times; all four patients were mosaics.

All of the infants had many dysmorphic features, but they did not have life-threatening structural malformations. One boy was still-born, and one child died at the age of 13 days. The two surviving patients showed a significant delay in psycho-motor development.

The stillborn boy had microcephaly, microstomia, short neck, and shortening of the long bones. The boy with hypoplastic corpus callosum, pachygyria, and thrombocytopenia died from pulmonary hemorrhagia.

Abnormalities in the surviving patients included subglottic stenosis and hydronephrosis in one child and microcephaly, microphthalmia, absent lens (aphakia), leucocoria, and persistence of the oval window in another one.