



## Chromosome 21

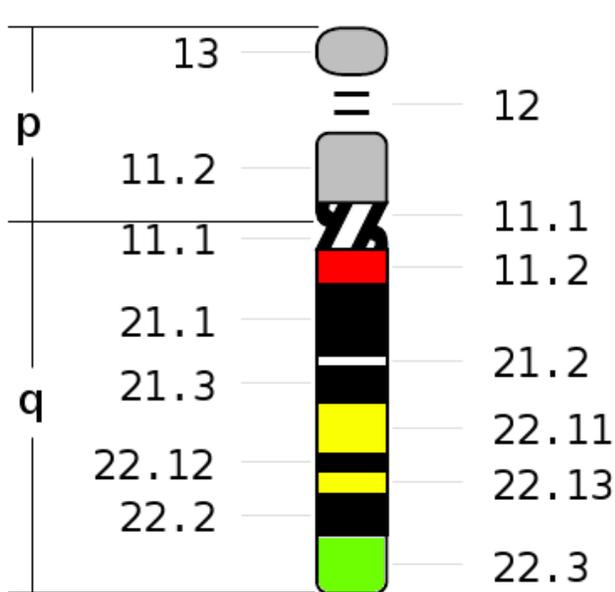
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### Introduction

Chromosome 21 is an acrocentric chromosome. It means that all of the genes are located in the long arm of this chromosome. The total length of chromosome 21 is 48 Mb, but ~19 Mb belongs to the short arm, which does not contain genes. The long arm (~29 Mb) is just above 1% of the total human genome. There are ~300–400 genes on this chromosome. Many of these genes are important both for the formation of body organs and for maintaining numerous functions of the organism.

Structural defects of the long arm of chromosome 21 are not very common. It should be noted, however, that precise diagnostics of

these defects became possible only after the usage of methods of molecular cytogenetics. As a result, the number of reported patients is rapidly growing. To date, there are ~650 patients with all kinds of structural imbalances for chromosome 21 and ~400 patients with deletions of 21q (including both deletions as an only abnormality and deletions in association with another chromosomal imbalance).

### Deletions of Chromosome 21

There are several reports regarding patients with full monosomy 21. This monosomy may be the only autosomal monosomy compatible with life. It may be explained by the relatively small size of this chromosome and the relative paucity of genes on this chromosome.

There are several groups of conditions caused by deletions of the long arm of chromosome 21. Deletions of the proximal area (21q11q21) or the very distal area (21q22.13–qter) do not constitute well-recognized syndromes. Deletion of the 21q22.1 section may be the first clinically recognizable conditions caused by deletions of chromosome 21.

### Monosomy 21

Monosomy is a condition when a whole chromosome is missing. It differentiates monosomy from deletion, where only a part of chromosome is missing. Monosomies for relatively large

chromosomes (except monosomy X) are not compatible with life. Monosomies for small chromosomes (21 and 22) have been reported in some patients. However, usage of sophisticated cytogenetic methods showed that most patients reported as having monosomy 21 in the 1970's–1980's actually had translocations with a previously unrecognized transfer of the part of chromosome 21 to another chromosome. However, there are ~20 reports regarding “monosomy 21” without any signs of translocation. Almost half of these patients are mosaics who had a clone with monosomy 21 and a clone with two normal chromosomes 21. These mosaics occur post fertilization when one of the chromosomes 21 becomes lost upon division of cells. In other reports, there was no indication for mosaicism. Of course, unrecognized mosaicism (with the presence of two chromosomes 21 in some unstudied tissues) cannot be excluded. Up until now, there is no final answer regarding the possibility of survival for the individual with complete monosomy for any autosome.

Phenotypic manifestations in reported patients with monosomy 21 vary from person to person. Generally, patients with a mosaic monosomy seem to be less affected than patients with full monosomy.

Reported persons with “monosomy 21” have a wide range of defects, including cleft palate (or cleft lip and palate) [in 6 patients], agenesis of hypoplasia of kidneys [4 patients], congenital heart defects [3 patients], holoprosencephaly [3 patients], arthrogryposis [3 patients], microphthalmia [2 patients], hypospadias [2 patients]. All of these manifestations are caused by monosomy for several genes important for development of body organs.

#### *Deletions of 21q11q21*

There are ~30 reports on patients with interstitial deletions of the proximal part of chromosome 21 (21q11q21) as a sole abnormality. It will be too early to speak about a syndrome associated with this deletion. Delay of psycho–motor development is common to these patients (as well as to the patients with almost all kinds of autosomal deletions). Most children have relatively mild defects of loco–motor system (contractures, kyphosis, scoliosis, short metacarpals). Several patients with such deletions had congenital heart defects (ventricular and atrial septal defects, aortal valve stenosis). Congenital malformations of other systems are not characteristic.

#### *Deletions of 21q22.1*

The segment 21q22.11q22.12 contains the RUNX1 gene. Mutations of this gene are related to thrombocytopenia and a predisposition to acute myelogeneous leukemia. The same effect may be found in patients with deletions of this area or chromosome 21. Of course, precise delineation of such small deletions became available only in the recent years when methods of molecular cytogenetics became available.

Currently there are ~15 reports on patients having small interstitial deletions of this area with thrombocytopenia. Only one patient developed leukemia; another one showed signs of myelodysplasia (pre–leukemic condition). It should be noted that 4 patients with deletions of this area did not have thrombocytopenia (at least it was not reported). Usually, these patients had psycho–motor delay, behavioral problems, obesity, deep–set eyes, downturned corners of the mouth, dysplastic ears and small chin. Other manifestations in these patients include seizures (5), microcephaly (5), dysgenesis of corpus callosum (4), various types of heart

defects (8, including two patients with very serious defects). All of these manifestations are caused by accompanied deletions of the neighboring genes because patients with mutations of the RUNX1 gene do not have such defects. At least two publications report patients with thrombocytopenia and deletions of 21q22, but with a preserved RUNX1 gene. The authors of one of these publications indicate the possible role of the DYRK1A gene. Most likely, this area of 21q has more than one gene involved in the formation of thrombocytes.

It should be noted that all known patients have a relatively small deletion in the areas between 30 Mb and 36 Mb, but not a single person had a deletion completely encompassing this region. The area between 30 Mb and 36 Mb (21q22.11q22.12) has ~80 genes. There is an opinion that embryos with a complete deletion of this area cannot survive.

### *Distal Deletions of 21q*

Deletions of the distal part of 21q (21q22.13–22qter) have been reported in ~35 persons with a very wide range of clinical manifestations. Some patients had multiple malformations incompatible with life. Other patients had delayed psycho–motor development and mild dysmorphic features. The most commonly affected systems are the brain, eyes and heart.

The area 21q13.3 contains one of the genes, responsible for holoprosencephaly (HPE). However, HPE was found only in two persons with such a deletion. However, six patients had agenesis or hypoplasia of the corpus callosum and two had lissencephaly. Microcephaly, hydrocephaly, micropolygyria also have been reported. At least four patients with distal deletions 21q had seizures. Different eye defects were noted in 10 patients, including 6 patients with microphthalmia and one with anophthalmia. The distal part of 21q has to contain a gene (or several genes) responsible for the development of the eye. There are also four reports of cloudy cornea and two reports of congenital glaucoma. Two patients had atresia of the auditory canal; one more patient had stenosis (narrowing) of this canal. Eleven patients had various types of heart defects, including three patients with very serious life– threatening conditions. Defects of the kidneys and gastro–intestinal tract are not characteristic. Almost all of the patients had small defects of the skeleton and extremities — contractures, pectus excavatum, 13 pairs of ribs, dysplastic hips, etc.

Further examinations are necessary to delineate clinical characteristics of the distal deletion of 21q.

### **Ring Chromosome 21**

Ring chromosome 21 occurs relatively frequently. At least 135 people with ring (21) have been reported in the literature. Mosaicism with a 45 chromosome,-21 clone was found in 21 people, and mosaicism with a normal clone in five people. Two patients had double ring (21) chromosome. Other types of mosaicism (mosaicism r(21)/del 21q, triple mosaicism with normal and monosomic clones, etc.) were reported five times.

Chromosome 21 is acrocentric; therefore, loss of the material of the short arm does not have any clinical significance. The small size of ring chromosome 21 facilitates the occurrence of secondary changes within the ring. As a result, ring chromosomes in some people contain some duplicated areas, and these patients became partially trisomic for some areas of chromosome 21. Molecular examinations in several patients showed the co-existence of

several trisomic and several monosomic areas of 21 within the same karyotype.

From the clinical point of view, ring 21 is a very heterogeneous condition. First, at least one-third of all reported persons with r(21) do not have any abnormalities or have very mild dysmorphism and almost normal intellectual development. There are ~15 families where r(21) was transmitted through two, three, or even four generations, and, in these families, most persons with r(21) were completely normal. Most of these families were ascertained when r(21) was found in a fetus upon prenatal diagnosis in woman above 35 years of age.

Further examinations showed that pregnant women, their previous children, siblings, and one parent (usually mother) also carry r(21). In six male patients, r(21) was found upon cytogenetic examination due to azoospermia or other types of male infertility. Presence of r(21), however, does not exclude male fertility: in rare instances r(21) was transmitted through male carriers. At least twice, r(21) was found in women having recurrent miscarriages.

Most patients with r(21), however, have abnormalities resulting from either the loss of genetic material of 21q, possible partial trisomies due to internal duplications frequent in r(21), and an unspecific influence of ring chromosome on cellular behavior. The most common abnormality is microcephaly, which was reported in 17 patients. Microphthalmia was found in six persons, corneal opacities in five, hypoplastic optic nerve in three, cataracts in three, and coloboma in two. Preauricular tags or pits were reported in four patients, and four more had hearing impairment. Cleft lip and/or palate were found in ten patients, and two more had bifid uvula.

Several patients had kyphosis, scoliosis, mild syndactyly, and hip dysplasia. These manifestations, however, are unspecific and may be found in almost any type of autosomal imbalance.

The distal area of 21 (21q22) contains one of the genes responsible for holoprosencephaly. The loss of this gene explains holoprosencephaly in five patients with r(21). Other morphological defects of the skull and brain occur very rarely.

Different forms of heart defects were reported in 19 patients with r(21). Three of these defects (interrupted aortic arch, single ventricle with atretic truncus pulmonalis, and tetralogy of Fallot) are life-threatening conditions.

Heart defects in other patients were relatively mild (ventricular and atrial-septal defects, aortic stenosis, etc.). Four more patients were suspected of having unspecified heart defects. Defects of the gastro-intestinal system, kidneys or genitalia are exceptionally rare.

As a result of “duplicated” ring 21 (or ring occurring from the i(21q) chromosome), several patients had the phenotype of Down syndrome.

There are at least six reports on patients with constitutional r(21) who developed leukemia. One more had myelodysplasia, and several more had thrombocytopenia (but did not have other blood defects). These blood defects may be explained by the deletion of the RUNX1 gene, located at 21q22. Other types of neoplasias in r(21) patients have not been reported.

*Partial Trisomies for Chromosome 21*

Partial trisomies of 21 as sole abnormalities are a very rare form of chromosomal disorders in humans. However, this group of patients have attracted the attention of specialists for decades. This is because complete trisomy 21 (Down syndrome) is the best known and most frequent form of chromosomal disorders. Clinical manifestations of Down syndrome include a significant delay in psycho-motor development, a characteristic pattern of facial dysmorphism (which causes the recognition of most patients just at a glance), and serious, often life-threatening, heart abnormalities, mostly endocardial cushion defects.

Many other defects (duodenal atresia or stenosis, Hirschsprung's disease, anal atresia, and preaxial polydactyly) occur in less than in 5% of patients with trisomy 21, but occur 30-100 times more frequently than in the general population.

The same is true for some forms of leukemia which are found in trisomy 21 patients 100 times more frequent than in children without trisomy 21.

The analysis of manifestations in patients with partial trisomy 21 may show which segment of 21q is responsible for each of the above-mentioned defects (or that there is one segment responsible for the whole complex of abnormalities, associated with trisomy 21).

The attempt to locate segments responsible for most abnormalities (first for the delay in psycho-motor development, cranio-facial dysmorphism, and heart defects) have been known since the 1970s. Of course, contemporary molecular methods of the precise location of breakpoints and the size and position of the trisomic segment allow the most accurate conclusion regarding the issue.

There is general agreement that the duplication of the segment 21q22 is critical for the manifestations of Down syndrome (DS). The scientists determined a ~3 Mb region (approximately between points "39 Mb" and "42 Mb") as critical for Down syndrome. Most patients trisomic for this segment have obvious manifestations of Down syndrome. No patient having only more proximal or more distal trisomies has a Down syndrome phenotype.

Using information about available patients with partial trisomy 21 and information about mouse models with segmental trisomies, it was concluded that the 1.77 Mb segment within the DS critical region is responsible for endocardial cushion defects (which occur in Down's syndrome 1000 times more commonly than in the general population). This segment contains several genes. One of these genes, DSCAM, seems to be the most important for the development of this type of heart defect.

Other characteristic manifestations of trisomy 21 are considerably more rare, and it is difficult to find an appropriate number of patients for the precise location of segments responsible for these defects. The segment related to the development of leukemia is an ~8.5 Mb area (between "35 Mb" and "45.5 Mb").

Approximately the same area seems to be critical for Hirschsprung's disease and anal atresia.

All patients with partial trisomies 21 may be subdivided into 3 groups:

- patients with trisomies for the "proximal" segments 21q (21cen-q22.1);
- patients with trisomies involving the Down syndrome critical segment;

- patients with isolated trisomies limited to the distal part of 21q22.3.

### *“Proximal” trisomy 21q*

There are less than 30 known patients having “proximal” trisomies 21q as a sole abnormality. These persons either have an additional marker chromosome which consists of a centromere and a “proximal” part of 21q or direct duplication within the “proximal” region.

These persons may have some mild delay in psycho-motor development and unspecific mild facial dysmorphism, but they do not have serious congenital abnormalities. Some of these persons are completely normal. There is no syndrome associated with “proximal” trisomy 21q. Partial trisomies involving the Down syndrome critical region

There are only 40-45 patients with pure partial trisomy 21, including the Down syndrome “critical region”. At least twice as many had trisomy for this segment in association with another chromosomal imbalance. Almost all known patients with a trisomy involving this area have a complete clinical picture of Down syndrome, including typical facial dysmorphism, brachydactyly, endocardial cushion defects, duodenal stenosis, and leukemia. The incidence of these abnormalities is basically the same as in patients with complete trisomy 21.

There are several reports about patients with a trisomy for the “critical region,” but without the typical picture of Down syndrome, although all had a delay in psycho-motor development and facial dysmorphism.

### *Distal (subtelomeric) duplications 21q*

There is a very limited number of patients having an isolated trisomy for the most distal part of 21q (21q22.3). Patients with these trisomies may have mild heart defects and a delay in psycho-motor development, but do not have either dysmorphism nor internal defects typical for Down syndrome. Some authors even consider very distal tiny duplications 21q22.3 as a benign chromosomal variant.