



Chromosome 22

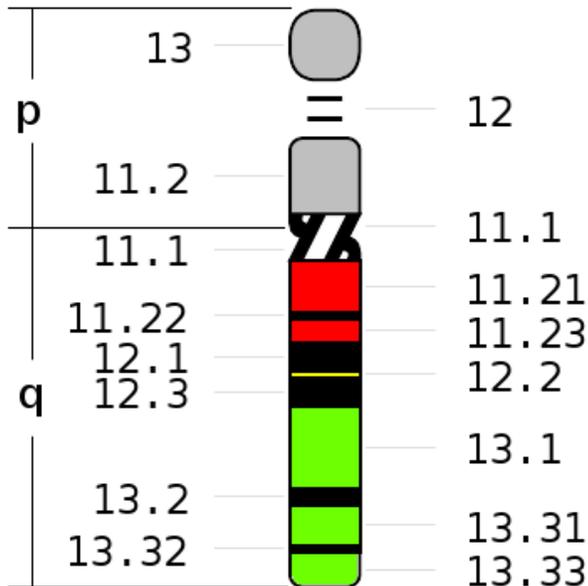
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David Adler.hum_22.gif



Introduction

Chromosome 22 (as well as chromosome 21) is an acrocentric chromosome. All 500–800 genes of this chromosome are located in its long arm. At least ~100 genes of chromosome 22 participate in the development of the body plan and maintain numerous functional activities. The total length of chromosome 22 is 51 Mb, and the length of the long arm is 36 Mb (~1.5% of total human genome).

It should be noted that chromosome 22 is a little bit larger than chromosome 21. In the early 1960's, it was decided that Down syndrome is caused by a trisomy for the acrocentric chromosome arbitrarily designated as "chromosome 21". Later, it was shown that the

chromosome involved in Down syndrome is the shortest chromosome of the human genome. However, to avoid confusion, it was decided to continue to designate the smallest chromosome as 21, and another chromosome in that group as 22.

Structural defects of chromosome 22 are very frequent. Deletion of the small segment within 22q11.2 is the most frequent form of structural chromosomal pathology in humans. Other forms of structural imbalance of this chromosome are not so common, but there are more than 400 reported patients with distal deletions (22q13), and hundreds of reports of patients with partial trisomies for chromosome 22 or ring chromosome 22. At the same time, there is a very limited number of reports regarding deletions of the "central" part of chromosome 22 (22q12) and just a handful of reports on monosomy 22.

Deletions of Chromosome 22

Monosomy 22

Monosomy 22 (as well as monosomy 21) has been reported in several patients since the 1970's. However, re-examination of these patients with more sophisticated cytogenetic methods showed that, as a rule, there were formerly unrecognized translocations with a

transfer of material of chromosome 22 to another chromosome. There are only ~10 reports that still can be considered as “monosomy 22”. Half of these patients were mosaics with co-existence of a monosomic clone and a normal diploid clone.

Several of these patients had manifestations of DiGeorge syndrome (see deletion 22q11.2). Clinical manifestations in other patients did not constitute any recognizable condition.

Deletion of 22q11.2

In the early 1980's, it was reported that some patients with partial monosomy for the proximal part of 22q (as a result of translocations between chromosome 22 and another chromosome) have manifestations of DiGeorge syndrome (DGS). DGS is a condition where the patients have an association of heart defects (usually very serious conotruncal defects), underdevelopment of parathyroid glands and absent or hypoplastic thymus. Several years later, when fluorescent in situ hybridization (FISH) became widely available, it was shown that a relatively small (up to 3 Mb), previously unrecognizable deletion within 22q11.2 is responsible for this phenotype. Thousands of patients with heart defects, immune defects or hypoparathyroidism have been examined (or re-examined), and it was shown that many of them have del 22q11.2.

From a cytogenetic point of view, most patients have a relatively small (2.5–3 Mb) deletions, but breakpoints are different in almost all of them. Some patients have deletions of a smaller size (~1.5 Mb). Larger deletions are relatively uncommon and may produce some additional manifestations. A very small proportion of patients may have very small deletions, which may remain unrecognized using standard FISH-probes.

It was found that the deletion of 22q11.2 is a very frequent form of pathology. Some estimates show that its frequency among newborns may be 1:5,000. Even taking into account that some infants with serious heart defects may not survive, the prevalence of this condition in the general population should be ~1:6,000. It means that ~50,000 persons with del 22q11.2 may live in the USA.

Clinical manifestations of this condition are so variable that several clinical conditions, which have been considered as separate syndromes (DiGeorge syndrome, Shprintzen syndrome, Caylor cardio-facial syndrome, Sedlackova syndrome, velocardiofacial syndrome) were found to have a common genetic basis — deletion 22q11.2.

Almost all reports on patients with del 22q11.2 are biased by the selection of patients. It is not surprising that the frequency of different manifestations among patients reported by cardiologists is different from the same characteristics in the patients reported by psychiatrists.

The most serious and most frequent manifestations are heart defects. Different forms of heart defects are found in 75% of children with this deletion. Some estimates show that ~10% of all congenital heart defects in the pediatric practice are caused by del 22q11.2.

The most common and most serious defects are interrupted aortic arch, tetralogy of Fallot and truncus arteriosus. The total share of these life-threatening defects is ~50% of all heart defects reported in del 22q11.2. Other patients have a large variety of more common defects,

less significant for hemodynamic processes. Up to 25% of patients do not have any heart defects.

Defects of the palate are found in ~70% of pediatric patients with del 22q11.2. Cleft palate or bifid uvula are reported in ~16% of the patients. Approximately the same percentage of patients has velopharyngeal incompetence, where the palate is short and functionally weak. Cleft palate, however, occurs very rarely.

Although classical DiGeorge syndrome includes aplasia of thymus, serious problems with the production of T-cells are relatively rare. At the same time, most patients have some degree of immunodeficiency, usually mild. This defect becomes even less obvious in school-age children.

Underdevelopment of parathyroid glands leads to hypocalcemia. This symptom is easily treated. In most patients, with age, metabolism of calcium becomes normal.

Cranio-facial manifestations include hypertelorism, malar flatness, hooded eyelids, tubular nose with round tip, low set ears with overfolded helices. Many children exhibit facial asymmetry when crying. Some patients may have craniosynostosis, which, however, rarely has clinical significance.

Ocular examination showed frequent posterior embryotoxon (70% in patients with del 22q11.2 and ~20% in controls) and tortuous retinal vessels. Hypoplastic optic nerve and amblyopia ("lazy eye") are found in ~6%, each.

Most patients have a mild delay in psycho-motor development, usually as a learning disability. Seizures, especially in infants, may be caused by hypocalcemia (as a result of hypoparathyroidism). However, unprovoked seizures are also reported in 4–5% of patients.

Urologic examination reveals abnormalities of the kidneys and urinary tract in 30% of patients. These defects include hypoplastic kidney, single kidney, horseshoe kidney, hydronephrosis, ureteral reflux. However, most of these defects found upon specialized study of persons with this deletion do not produce any clinically significant problems.

There are numerous descriptions of all kinds of defects of the brain, extremities, gastro-intestinal system etc. among persons with del 22q11.2. It is not surprising. If the geneticist or clinician has several patients of a relatively frequent condition with a "standard" clinical picture, he/she does not have the intention to publish these observations [unless he/she has plans to perform a special study regarding the given pathology]. However, if one of patients has unusual manifestations, such a person may be preferentially reported. It is true not only for del 22q11.2, but also for all relatively frequent deletions or duplications.

Del 22q11.2 is a predisposing factor to numerous autoimmune disorders. Idiopathic thrombocytopenic purpura occurs in persons with del 22q11.2 200 times more frequently than in the general population; juvenile rheumatoid arthritis occurs 20 times more frequently. The incidence of hyperthyroidism, vitiligo, autoimmune neutropenia etc. is also increased.

Psychiatric abnormalities seem to be a very serious problem. Many children show impulsiveness; others tend to be shy. Attention deficit disorder and anxiety also occur with

increased frequency.

There is a strong association of del 22q11.2 with schizophrenia. Cytogenetic examinations of the large groups of persons with schizophrenia showed that 1–2% of all these patients have del 22q11.2. Most of them do not have heart defects or other “typical” manifestations of this deletion. Therefore, persons with del 22q11.2 have ~10% probability to develop schizophrenia.

The segment deleted in patients with del 22q11.2 contains at least 35 genes (in patients with a 1.5 Mb deletion) or ~60 genes (in persons with a 3 Mb deletion). Typical manifestations (heart defects, underdevelopment of thymus and parathyroid glands) are considered to be caused by the deletion of the TBX1 gene. Susceptibility to autoimmune diseases and psychiatric abnormalities are caused by other genes. The precise role of each of these genes is still unknown.

Diagnostic of del 22q11.2 requires hybridization of the patient’s chromosomes with specific commercially available probes. This test give the results of “deleted/non–deleted”. It is sufficient for diagnosis (if “deleted”), but does not give a detailed localization of breakpoints, which can be obtained by array–comparative genomic hybridization (array–CGH). However, array–CGH is not absolutely necessary for diagnosis. If the patient has typical manifestations of DiGeorge syndrome, but does not have a deletion detectable by FISH, array–CGH may be necessary to detect an unusually “short” deletion (non–detectable by standard FISH probes) or to find other chromosomal abnormalities, which may be responsible for the patient’s phenotype.

In 93–94% of patients, del 22q11.2 is a sporadic event. However, 6–7% of patients inherit deletions from their parents, usually with minimal phenotypic manifestations, if any. Therefore, cytogenetic examination of the parents is absolutely necessary for genetic counseling regarding further children. The risk will be negligible for the families with sporadic deletions but 50% for the families where one of the parents has a deletion. Of course, prenatal diagnosis allows detection of a fetus with a deletion.

Deletion of 22q12

There are ~15 reports on patients with deletions 22q12 (not involving 22q11 or 22q13). It is too early to speak about a syndrome associated with this deletion. However, at least five of these patients had cleft palate or bifid uvula, five had sensori–neural deafness, and four had various heart defects. Areas of hypopigmentation were found in three patients. Preaxial polydactyly, cataract, Hirschsprung’s disease also have been reported. Further observations are necessary to delineate a clinical picture associated with this deletion.

Deletion of 22q13.3 syndrome

Deletion of the distal part of chromosome 22 (also known as Phelan–McDermid syndrome) was reported in 1994. More than 400 patients with this condition have been reported so far. The frequency of this deletion is unknown. Some estimates show that its overall incidence may be as high as 1:11,000–1:15,000.

Most common manifestations of this syndrome are significant global developmental delay,

hypotonia (weak muscles) and severe delay in speech development. At the same time, the growth of children is normal or even accelerated.

Dolichocephaly, full brow, long eyelashes, prominent dysplastic ears, puffy eyelids and cheeks, ptosis, bulbous nose, wide nasal bridge, relatively large fleshy hands, sacral dimple and decreased sensitivity to pain are mentioned in more than 50% of the known patients. All of these manifestations are non-specific, but, according to specialists in this disorder, they prompt to suspect the diagnosis. At least 25% of patients have vomiting, gastro-esophageal reflux, lymphedema, seizures and renal abnormalities. Approximately 20% of patients have problems with hearing.

Behavioral characteristics of this syndrome include poor eye contact, stereotypic movement, decreased socialization. Deletion 22q13.3 may predispose to autism.

All patients have terminal deletions of 22q, which usually involves 3–5 Mb of the distal part of 22q13. Some patients may have larger or smaller deletions. Usually, the size of deletion does not allow its recognition upon “standard” cytogenetic examination. FISH and especially array-CGH are able to detect the deletion and to exclude the translocation between 22q and other chromosome. The deleted segment contains many genes. Most scientists believe that the loss of the SHANK3 gene (which codes a protein necessary for the connection of ion channels and receptors in post-synaptic membrane) determines the main clinical manifestations of the syndrome.

There are a couple of reports of fulminant hepatic failure in patients with Phelan–McDermid syndrome. This autoimmune pathology may be caused by the loss of the PIM3 gene, although there are several other genes (NCAPH2, CYP2D6) within 22q13, which may be related to immune response.

Deletions in most persons with del 22q13 are sporadic. However, at least in 10% of the patients, deletions are caused by familial translocations. Therefore, cytogenetic examination of the parents is necessary to determine the genetic risk for further pregnancies.

Ring Chromosome 22

Ring chromosome 22 is one of the most frequent forms of ring autosome. It has been reported at least in 157 patients. Mosaicism is relatively uncommon: eight patients had mosaicism with a normal clone, one had mosaicism with a monosomic clone, and one had mosaicism with a clone with del 22q13. Double, or dicentric, rings were reported in three patients.

Chromosome 22 is an acrocentric chromosome, and a loss of genetic material of the short arm does not have a clinical significance. The small size of chromosome 22 facilitates secondary changes. As a result (as shown by molecular studies in several patients), some areas may be partially duplicated. That explains some “trisomic” features in several patients. From the clinical point of view, there are two main groups of patients with r(22).

The segment 22q12 contains the gene NF II, which is responsible for neurofibromatosis type II. The main manifestations of this condition are benign tumors of neural tissues (meningiomas, schwannomas, and neurinomas). The loss of this gene can produce a

phenotype of neurofibromatosis II in patients with r(22). At least 16 patients with r(22) and neurofibromatosis II have been reported so far. Some of them had hearing loss secondary to vestibular schwannomas (tumors affecting hearing-related structures in the brain). It was shown that gross rearrangements within chromosome 22 may produce neurofibromatosis II even if the NF II gene itself is not deleted. Most patients, however, do not have neurofibromatosis II.

Typically patients with r(22) have normal (or almost normal) physical development with few, if any, birth defects. However, the mental development in most of these patients is severely affected. Frequently, a delay in psychomotor development is the first manifestation, which causes the parents to see a geneticist. Most patients have relatively mild facial dysmorphism. Microcephaly has been reported in 18 patients. Defects of the eyes are rare: colobomas in several patients may be explained by partial trisomies for 22q. At least four patients revealed ptosis, four had cleft palate (but no cleft lip), and four more had preauricular pits or tags. Some patients had a short neck, brachydactyly, mild syndactyly, hyperextensible joints, scoliosis, kyphosis, contractures, and inguinal or umbilical hernias.

Abnormalities of the corpus callosum are uncommon: three had agenesis of the corpus callosum, one had dysgenesis of this organ, and three had hypoplastic corpus callosum. Hydrocephaly was found in two patients. Neither patient with r(22) had an open neural tube defect, holoprosencephaly, or arhinencephaly.

Nine patients had hearing defects, but, in several of these patients, hearing impairment was caused by schwannomas. Heart defects were reported in ten patients, including two patients with truncus arteriosus, one with right aortic arch, and one with tetralogy of Fallot. A concomitant deletion of 22q11.2 was responsible for some of these anomalies.

Defects of the gastro-intestinal system are not typical. Kidney defects, however, are relatively frequent. Cystic dysplasia of kidneys was reported in seven patients. There are sporadic reports of hydronephrosis, horseshoe kidney, or vesico-ureteric reflux.

In the absence of life-threatening defects of the brain and internal organs, the vital prognosis for the patients with r(22) is relatively good.

There are at least three families with a direct transmission of r(22) from mothers and from fathers.

Partial Trisomies for Chromosome 22

There are at least four (or even five) conditions related to partial trisomies 22. The first group is trisomy for the proximal part of 22q (from the centromere to 22q12). The second group is an isolated duplication of 22q11.2 (not involving the centromere). The third group is represented by patients with trisomy for the distal part of 22q (22q13). Patients with tetrasomy for the proximal part of 22q form the so-called "cat eye" syndrome. The fifth condition is closely related to partial trisomy 22 is Emanuel syndrome, where the trisomy for the proximal part of 22q is associated with a trisomy for the distal part of 11q. Emanuel syndrome was analyzed in the chapter about partial trisomies of chromosome 11.

Proximal trisomy 22q

This group includes 37 patients having a trisomy for the proximal part of 22q (from the centromere to 22q12) without another chromosomal imbalance. The main manifestations of this condition are colobomas, preauricular pits or tags, heart defects and atresia (or stenosis) of the anus. Preauricular tags or pits were reported in 15 patients, and colobomas in seven patients. Other defects of the eyes include microphthalmia (2), cataract (2), hypoplastic cornea (1), hypoplastic iris (1), glaucoma (1), and ptosis (1). Cleft palate was reported in five patients (but none had a cleft lip). Defects of the ears include atresia/stenosis of the auditory canals (six patients), microtia (small external ears) in two patients, and hearing impairment (1).

Heart defects were found in eight patients; two of these defects were life-threatening (Ebstein anomaly and cor triatriatum). One patient had total anomalous pulmonary veins return (a condition where none of the four veins taking blood from the lungs is attached to the left atrium).

Anal atresia or anal stenosis is reported in eight patients. There are sporadic reports of biliary atresia, Hirschsprung's disease and stenosis of the colon.

Defects of the kidneys were found in six patients, including two with polycystic kidneys, two with abnormalities of the collecting system, and one with unilateral renal agenesis.

There are sporadic reports of hydrocephaly, spina bifida, choanal atresia, costo-vertebral dysplasia, contractures, and additional ribs.

Most patients with proximal trisomy 22 reveal an evident delay in psycho-motor development, although the degree of this delay varies from one patient to another.

There are several reports of the direct transmission of proximal trisomy 22 from one mildly or minimally affected parent.

Duplication 22q11.2

Deletion 22q11.2 is the most frequent form of a structural autosomal imbalance. The genetic structure of this part of chromosome 22 shows that reciprocal duplications of the same region of 22q11 occur very frequently. However, only molecular genetic methods allow us to recognize the rapidly increasing number of patients with this duplication.

Currently, at least 425 reported persons with dup 22q11.2 are available for phenotypic analysis. This duplication occurs so often that sometimes there is a question whether dup 22q11.2 is a definite pathology, a factor predisposing to pathology, or a benign copy number variant.

The first problem is that there is no recognizable phenotype associated with this duplication. The second problem is that there is a frequent occurrence of the same duplication in a patient with congenital abnormalities (or functional disturbances) and in one of his/her completely normal parents.

Usually this duplication is relatively small (2-3 Mb) and involves a segment between 17 Mb and 20 Mb. However, there are significant variations regarding both the size of the duplication and the position of breakpoints.

All persons with dup 22q11.2 may be subdivided into a) persons with some physical abnormalities (~210 patients); b) persons with functional abnormalities (seizures, autism, etc.), but without any physical defects (66 persons), and c) healthy persons (150). The latter group consists mainly of parents and other relatives of the affected patients, but several persons with dup 22q11.2 were found upon examination of control groups taken for comparison with patients having some phenotypic abnormalities. There is no doubt that the proportion of healthy persons will be higher if both parents of the affected child were examined in all instances.

There is no typical pattern of dysmorphism for the patients with dup 22q11.2. Most of them do not have any dysmorphic features. A delay in psycho-motor development was noted at least in half of the patients. Defects of the brain are relatively rare. Microcephaly was found less than in 10% of the patients with dup 22q11.2; macrocephaly was found at least in six patients. Three children had trigonocephaly. Aplasia or hypoplasia of the corpus callosum was reported in eight patients.

Ocular defects include colobomas (8), microphthalmia (3), and sporadic reports of optic atrophy, microcornea and atresia of lacrimal ducts. Cleft palate (or lip and palate) are relatively common: they were reported at least in 25 patients.

Preauricular pits or tags were found in 23 patients. Twenty-six had hearing impairment. There are several reports of atresia of the auditory canals.

Heart defects are the most common type of internal abnormalities. They were reported in 70 patients. In 19 of them, the type of heart defect was not specified. At least 20 out of 51 with a specified character of heart defects had very serious abnormalities, including tetralogy of Fallot (7), hypoplastic left heart (3), atrio-ventricular septal defects (3), interrupted aortic arch (2), truncus arteriosus (2), etc. However, dup 22q11.2 is so common that it can be found in patients with almost any type of abnormality. The scientist studying chromosomal defects in people with cleft lip and palate will certainly find several patients with dup 22q11.2 in the examined group. In that sense, the high frequency of tetralogy of Fallot, for example, may be explained by the fact that somebody tested patients with this form of heart defect, whereas patients with patent ductus arteriosus (PDA) were not tested. It cannot be excluded that, if persons with PDA were the objects of examination, we could see higher a proportion of PDA among patients with heart defects accompanying dup 22q11.2.

Anal atresia or stenosis is the most common form of gastro-intestinal defects among patients with dup 22q11.2. They were found in 11 patients. Four patients were reported having gastro-esophageal reflux. Other defects of the system (trachea-esophageal fistula, pyloric stenosis, hypoplastic bowel) were found in one person, each.

Defects of the kidneys are basically rare. They are represented by the absence of one kidney (2), hypoplastic kidneys (4), hydronephrosis (6), duplication of collecting system (2), and vesico-urinary reflux (8). The only exception is bladder exstrophy – a very rare abnormality when part of urinary bladder is present outside the body. There are 15 patients with bladder

exstrophy who were found having dup 22q11.2. This duplication is the only chromosomal abnormality with a non-random occurrence of this exceptionally rare birth defect. Duplication of the segment 22q11.21 is responsible for this defect. Of course, there is a question why some patients with this duplication do develop bladder exstrophy, but others do not. Most likely, some additional (and yet unknown) factors are necessary for realization of the harming effect of triplicated genes within 22q11.21.

Defects of the loco-motor system are infrequent. The most common – contractures – was found in nine patients. Six patients had scoliosis, and six other had brachydactyly. Numerous other defects (pre- and postaxial polydactyly, syndactyly, hip dysplasia, hyperlaxity of joints) were found in 2-3 patients, each. There are sporadic reports of hypoplastic thumbs, radio-ulnar synostosis, oligodactyly and ectrodactyly, but most likely these defects were independent from dup 22q11.2.

The second group of persons with dup 22q11.2 are patients with some functional abnormalities of the nervous system, but without any physical abnormalities. Seizures were reported at least in 28 patients. Autism was diagnosed in 18 persons. Psychoses (most of all schizophrenia) and attention deficit hyperactivity disorder were diagnosed in seven persons, each. It is still unclear whether these data show pathologic effects of dup 22q11.2 or they reveal that patients with these conditions were the objects of several special investigations.

The vast majority of healthy persons were found upon examination of parents or other family members of patients with dup 22q11.2 and phenotypic abnormalities. A detailed examination of these persons shows that many of them had learning disabilities in childhood, although several were completely normal, had a college education and performed professions jobs.

Of course, dup 22q11.2 may cause heart defects, cleft lip and palate, and other phenotypic abnormalities. However, it is most likely that some additional factors are necessary to reveal a pathologic effect of this small duplication.

Distal trisomy 22 (22q13)

There are more than 70 reports on patients with distal trisomy 22q (trisomy 22q13). The majority of these patients were described in the last 3-4 years when molecular cytogenetics became widely available. Almost all patients had a duplication (direct or inverted), and only a small proportion had other kinds of abnormalities effectively resulting in trisomy 22q13.

There is no typical size or position of the duplicated segment. It varies from 14 Mb (in patients where the segment 22q12 was also involved) to very small duplications (< 0.1 Mb). There is no characteristic phenotype allowing a classification of dup 22q13 as a recognizable syndrome.

Except for a mild delay in psycho-motor development, there are no common manifestations in people having this trisomy. Microcephaly was reported in less than 20% of patients. Other (sporadic) abnormalities of the cranium and brain include trigonocephaly (2), craniosynostosis (1), hypoplastic or absent corpus callosum (2), hydrocephaly (1), polymicrogyria (1), and agenesis of the cerebellar vermis (1).

Facial dysmorphism is not typical. Although most patients do not have any dysmorphic

features, there are sporadic reports of blepharophimosis (2), ptosis (2), preauricular pits (2), macrostomia (2) or microstomia (1). There are six patients with cleft lip and palate, and three more patients had cleft palate only. At least eight patients (out of 71) had hearing impairment.

Abnormalities of loco-motor system are also uncommon. Reported defects include dislocation of the hips (6), brachydactyly (3), vertebral defects (2), syndactyly, contractures, and proximally placed thumbs (all in one person, each).

Some patients were obese.

The most common internal defects are congenital heart defects, reported in 13 patients. Three of them had life-threatening conditions (tetralogy of Fallot, truncus arteriosus and hypoplastic aortic arch).

Defects of other systems are not common, although there are two reports of diaphragmatic hernia (with common duplicated segment 22q13.31q13.33), two reports of anal stenosis or ectopia, and sporadic reports of Hirschsprung's disease, intestinal malrotation, hydronephrosis, ectopic kidney, and ureteral stenosis. Three boys had hypospadias.

Functional abnormalities seem to be relatively common. At least seven patients had seizures. Autism was diagnosed in seven patients, and schizophrenia in two. There are sporadic reports of bipolar disorder and attention deficit hyperactivity disorder.

As opposed to dup 22q11.2, where a large percentage of patients had unaffected or minimally affected parents with the same duplication, direct transmission of dup 22q13 is not typical.

Cat eye syndrome (tetrasomy 22cen-q11)

As a clinical entity, cat eye syndrome has been known since 1965, when it was shown that a specific phenotype was associated with an additional small marker chromosome. However, the origin of an additional marker was unclear until the beginning of the 1980s when new methods allowed one to conclude that this chromosome is actually an iso-chromosome for the segment 22cen-q11. More than 100 patients with this syndrome have been reported since 1980.

Coloboma of the iris is one of most common manifestations of the syndrome. As a result, the eye of a patient may resemble an eye of a cat. The syndrome was described in 1965 – two years after the description of the deletion of the short arm of chromosome 5, which was coined as “cat cry” syndrome. By the analogy with “cat cry” syndrome, this condition was published as “cat eye” syndrome.

There are many descriptions of cat eye syndrome reported between 1965 and 1980. However, it would be incorrect to include these reports in clinical analysis. It is easy to attribute an additional marker chromosome as iso-chromosome 22cen-q11 in typical cases, but an attribution of the marker in patients with an atypical phenotype will not be as certain. As a result, the clinical picture will be shifted in the direction of typical (and clinically more severe) cases. That is why only patients with cytogenetically confirmed markers were taken for clinical analysis. Since, in several reports, a detailed description of the patients was not given, only 88 reports were selected for further analysis. The phenotypic picture of the

syndrome includes four main groups of defects: coloboma (which gave the syndrome's name), preauricular pits or tags, congenital heart defects, and anal atresia or stenosis. It is obvious that the same abnormalities are the main manifestations in patients with proximal trisomy 22 (the difference is that patients with cat eye syndrome had four copies of the genes in the 22cen-q11 area, but patients with proximal duplications 22q had three copies of these genes). Numerous other defects are less common.

Some patients have microcephaly, but usually the head circumference is normal. Brain defects are not characteristic, although there are sporadic reports of cerebral hypoplasia, hydrocephaly, or hypoplastic corpus callosum.

The most common ocular defects are colobomas, reported in 42% of patients (37/88). In many patients, coloboma of iris was associated with colobomas of choroid, retina, and optic nerve. As a result, the visual acuity of patients is significantly reduced. Other eye defects include microphthalmia (5), cataract (2), hypoplastic optic nerve, and blepharophimosis. At least five patients had the so-called Duane anomaly (an inability of eye abduction caused by damage of the VI cranial nerve).

Defects of the ears are the second group of typical manifestations of the syndrome. Preauricular tags or pits were reported in ~75% of patients (64/88). Some patients have a diminished size of the external ear (microtia) or even the absence of an external ear (anotia). Seven patients had atresia or stenosis of the auditory canals. Hearing impairment can be found in ~10% of affected persons. Five patients had cleft palate, but cleft lip has not been reported.

A delay in psycho-motor development (usually mild or moderate) is typical. Many patients have decreased vision and hearing impairment. Seizures, reported in several patients, are basically uncommon.

Skeletal defects are uncommon and unspecific. The most common is scoliosis (~10% of patients). Other abnormalities (contractures, syndactyly, triphalangeal thumbs, additional lumbar vertebra, and underdevelopment of ribs) are reported in 1-2 patients, each.

Defects of the heart are the most frequent and most clinically important manifestations of the syndrome. Different types of heart defects were reported in ~60% of patients (52/88). These defects include very serious abnormalities – hypoplastic left heart syndrome (3), interrupted aortic arch (2), tetralogy of Fallot (2), and atrio-ventricular septal defect. Other defects include atrial septal defects (14), ventricular septal defects (9), or patent ductus arteriosus (9) (usually in association with other heart defects). A significant number of patients (15) had total anomalous pulmonary vein return (TAPVR) – a condition where pulmonary veins have no connection with the left atrium. This defect is not very significant for hemodynamics. However, TAPVR is a relatively rare defect (including patients with other types of chromosomal imbalance). Therefore, TAPVR may be regarded as a “hallmark” of the cat eye syndrome.

Anal atresia or stenosis is the fourth main abnormality. This defect was found more than in 60% of patients (54/88). It is a much higher than the percentage of anal defects in patients with other syndromes caused by chromosomal abnormalities. Several patients had other defects of the gastro-intestinal system, including incomplete intestinal rotation (7), biliary atresia (4), or Hirschsprung's disease (3).

Defects of the kidneys are not as common but can be found in a significant percentage of patients. These defects include hydronephrosis (5), agenesis of one kidney (4), hypo- or dysplastic kidneys (4), cystic kidneys (2), and unspecified renal anomalies (2). At least four patients had vesico-ureteral reflux.

Abnormalities of other systems are not typical. New investigations showed that tetrasomy for the relatively small (less than 2 Mb) para-centromeric area 22q11 is sufficient to produce all of the basic manifestations of the syndrome.

Parental karyotypes in most families with a cat eye syndrome child are normal. However, there are several reports when an additional microchromosome was inherited from the mildly affected parents (usually mothers). Such parents may have a mild delay in psycho-motor development, preauricular pits, facial dysmorphism, and sometimes colobomas, but usually do not have serious defects of the internal organs. Cytogenetic examination of the parents remains a gold standard upon genetic counseling of families having a child with cat eye syndrome.

The comparison of the incidence of some manifestations in proximal trisomy 22 and cat eye syndrome (See the following table) basically shows that almost all defects (heart defects, anal abnormalities, coloboma, and preauricular pit/tags) are more frequent in people with cat eye syndrome. These results are not surprising, because the effect of the extra copy of genes produces some additional damage to the developing embryo. The comparison of the incidence of manifestations in proximal trisomy 22q and Emanuel syndrome reveals some unexpected results. The increased percentage of heart defects or cleft palate among patients with Emanuel syndrome may be explained by the influence of additional genes from a triplicated (in Emanuel syndrome) distal part of 11q. At the same time, neither patients with proximal trisomy 22 nor patients with cat eye syndrome have diaphragmatic hernia, Dandy-Walker abnormality, or other cerebellar defects which are relatively common in Emanuel syndrome. These defects are not typical for pure distal trisomy 11q either. Therefore, the interaction of different genes (or genetic systems) both from proximal 22q and distal 11q is necessary to produce the above-mentioned birth defects. Colobomas in proximal trisomy 22q are much more common (> 18%) than in Emanuel syndrome (1.5%). Therefore, an additional trisomy 11q somehow saves an embryo from colobomas and genes (or other genetic systems) from 11q interact with excessive 22q genes, diminishing, in some situations, their influence on the phenotype.

Type of defects	Proximal trisomy 22q (n=37)		Cat eye syndrome (n=88)		Emanuel syndrome (n=197)	
	number	%%	number	%%	number	%%
Colobomas	7	18.9	37	42	3	1.5
Microphthalmia	2	5.4	5	5.7	4	2
Preauricular pits or tags	15	40.5	64	72.7	106	53.8

Micro/anotia, narrow auditory canals	8	21.6	12	13.6	16	8.1
Cleft palate	5	13.5	5	5.7	101	51.3
Heart defects	8	21.6	52	59	100	50.8
Incl. TAPVR	1	2.7	15	17		
Anal anomalies	8	21.6	54	61.4	30	15.2
Biliary atresia	1	2.7	4	4.5	4	2
Hirschsprung's disease	1	2.7	3	3.4	4	2
Kidney defects	6	16.2	20	22.7	43	21.8

Trisomy 22

Trisomy 22 actually is not very rare. Reports about patients with trisomy 22 have been known since the 1970s. However, methods of chromosome identification at that time were not very accurate, and some patients with partial trisomy 22 or the presence of additional acrocentric chromosome similar to chromosome 22 could be erroneously reported as people with trisomy 22. Nevertheless, there are ~150 patients where trisomy 22 was confirmed by adequate cytogenetic examination.

All patients may be subdivided into two large groups: patients with the full trisomy 22 (n – 104) and patients with mosaic trisomy 22 (n – 43). People with the full trisomy may be subdivided into a prenatally diagnosed trisomy 22 (n – 33) and children with a full trisomy 22 (n – 71).

Sometimes, trisomy 22 was diagnosed upon the cytogenetic examination of fetuses with structural defects found by ultrasonography. In other cases, karyotyping was undertaken for other reasons (e.g. maternal age). If prenatal diagnosis shows complete trisomy 22 in a fetus, almost all parents are inclined to terminate the pregnancy. Morphologic examination of aborted fetuses allows complete recognition of internal defects typical for trisomy 22. Of course, these fetuses are not informative for analysis of functional abnormalities (e.g. seizures or hearing impairment) or defects occurring later in life (e.g. Hirschsprung's disease, abnormal skin pigmentation, etc.).

The vital prognosis for those born with trisomy 22 is grave. Almost all infants do not reach their first birthday. There are only ~10 patients with reportedly complete trisomy 22 who survived more than a year. However, only one type of tissue was studied in almost all these children, and unrecognized mosaicism seems very likely.

Almost all patients with full trisomy 22 have significant pregnant hypoplasia. Hydrothorax (liquid in the pleural cavity), ascites (liquid in the abdominal cavity), or total edema are relatively common, especially in fetuses with full trisomy 22 detected prenatally (7/33). These defects are caused not by structural abnormalities, but by immunological problems.

Full trisomy 22 is characterized by a complex of very severe morphologic abnormalities involving all systems.

Facial dysmorphism is frequent in all subgroups (see the following table). It includes high nasal bridge, bilateral epicanthus, apparent lateral displacement of the orbits, hypoplastic supraorbital ridges, ptosis, micrognathia, and low set deformed ears.

Cleft palate (or cleft lip and palate) are very common in persons with full trisomy 22: they occur in half of the patients. In patients with mosaic trisomy 22, this defect occurs less frequently. Preauricular sinuses or preauricular skin tags are very common: this anomaly is reported in one-third of patients with mosaic trisomy 22 and in 40% of infants with full trisomy 22. Sometimes, the patients have both tags and sinuses. Defects of the external ear (small ear (microtia) or even anotia) are relatively frequent. Some patients had atresia of the external auditory canals. As a result, hearing impairment is relatively frequent. Microcephaly is not as common (21/71 in children with full trisomy 22 and 8/43 in patients with mosaic trisomy 22). Other defects of the central nervous system include arhinencephaly (10), holoprosencephaly (7), agenesis of the corpus callosum (7), hydrocephaly (5), Dandy-Walker anomaly (5), craniosynostosis (2) and spina bifida (1).

TABLE. MAIN MANIFESTATIONS OF TRISOMY 22

	Full trisomy (prenatal group) (n – 33)	Full trisomy (postnatal group) (n – 71)	Mosaic trisomy (n – 43)
Dysmorphism	7	25	18
Microphthalmia	2	13	1
Coloboma	-	13	1
Anotia or microtia	1	9	2
Preauricular tags and/or pits	1	31	13
Hearing impairment	...	5	10
Cleft lip and/or palate	11	40	6
Short webbed neck	5	25	6
Microcephaly	2	21	8
Arhinencephaly	1	9	...

Holoprosencephaly	3	2	-
Hydrocephaly	1	4	-
Dandy-Walker anomaly	4	1	-
Heart defects	20	53	25
Tetralogy of Fallot	1	3	1
Defects of tricuspid Valve	2	5	4
Endocardial cushion Defects	4	5	-
Double outlet of the right ventricle	-	5	-
Anal atresia/ectopia	2	19	5
Hirschsprung's disease	...	4	3
Contractures	2	10	2
Proximal position of the thumbs	3	7	-
Kidney: agenesis	8	10	2
Kidney: hypoplasia	6	14	1
Cystic kidneys	1	9	2
Seizures	...	6	2

Abnormalities of the eyes include microphthalmia (15/104 in full trisomy 22, but only 1/43 in mosaic forms), colobomas (13/104 in full trisomy and 1/43 in mosaic forms), retinal dysplasia (4) and sporadic reports of corneal clouding and glaucoma.

The most frequent and most significant abnormalities are heart defects common in all variants of trisomy 22 (Table). In persons with full trisomy 22 (both in pre- and post-natal groups), these defects are usually complex and include very serious abnormalities: double outlet of the right ventricle, endocardial cushion defects, tetralogy of Fallot, defects of tricuspid valve, transposition of the great arteries (2), and truncus arteriosus (3). Cardiac insufficiency is one of the main reasons of death in infants with full trisomy 22.

Abnormalities of the lungs are surprisingly frequent. Of course, these defects may be recorded only by autopsy (or – in rare instances – upon thoracic surgery). At least six patients had hypoplastic lungs (except hypoplastic lungs secondary to oligohydramnios caused by renal agenesis). Several other infants had abnormal segmentation of the lungs (usually as hyposegmentation or a complete absence of lobation of the lungs). Diaphragmatic hernia was reported five times.

The most common defects of the digestive tract are atresia or ectopia of the anus. These abnormalities were reported in ~20% of persons with full trisomy 22. Other defects include intestinal malrotation (14), atresia of the extrahepatic biliary ducts (3), esophageal atresia (2), hypoplastic pancreas, (2) or pancreatic cysts (2). Agangliosis of the colon (Hirschsprung's disease) was diagnosed in seven patients (including three with mosaicism). It is obvious that this defect could not be diagnosed in fetuses, stillborns, or infants who died in first days after birth.

Defects of the kidneys and genitals are very common. At least twenty people had agenesis of one kidney (18) or even bilateral renal agenesis (2). Hypoplastic kidneys (21), cysts in the kidneys (12) or ectopic kidneys (10) are also common. Ambiguous genitalia were reported in seven patients. Abnormalities of the uterus and ovaries (usually the absence of one uterine horn or uterus didelphus (bifid uterus)) were found in fourteen girls. At least fifteen boys had hypospadias.

Abnormalities of the loco-motor system, although frequent, are relatively mild and non-specific. They include contractures (14), proximal position of the thumbs (10), dislocation of the hips (7), shortening of the long bones (7), partial syndactyly (4) and sporadic reports of polydactyly or ectrodactyly. Significant hypoplasia of the nails is typical for patients, especially with full trisomy 22. Two children (both with mosaic trisomy 22) had transverse limb defects. The etiologic role of trisomy 22 in the origin of these defects remains questionable.

Vital prognosis for full trisomy 22 is generally very serious. Several reports of long survival are not very trustworthy because only one tissue (usually blood) was used for cytogenetic examination.

Mosaic trisomy 22 shows a very wide spectrum of manifestations. Some patients have actually the same defects as persons with full trisomy 22. Other have much milder manifestations. Patients in the third subgroup may have only mild dysmorphism, a mild delay in psycho-motor development, and Turner-like phenotype (low height, wide short neck, scoliosis, and cubitus valgus). Most likely, differences between patients with mosaic trisomy 22 will depend on the percentage of trisomic cells and distribution of trisomic cells in different tissues.

There are two manifestations which may be found only in patients with mosaic trisomy 22, but not with a full trisomy. First is asymmetry of the body, when one size is a little bit bigger than another. Such asymmetry was found in eleven children with mosaic trisomy. Second is an abnormal whirl-like or linear pigmentation defect (similar to those in mosaic trisomy 20). This anomaly (basically an indication to mosaicism not specific for any concrete disorder) was mentioned in eight children with mosaic trisomy 22. These skin defects usually appear in children after five years of age.

Patients with mosaic trisomy 22 usually have a delay in psycho-motor development, although the severity of this delay varies in different children. There are even a couple reports of normal psycho-motor development in children with mosaic trisomy 22. Several patients may develop seizures.