Chromosome 11

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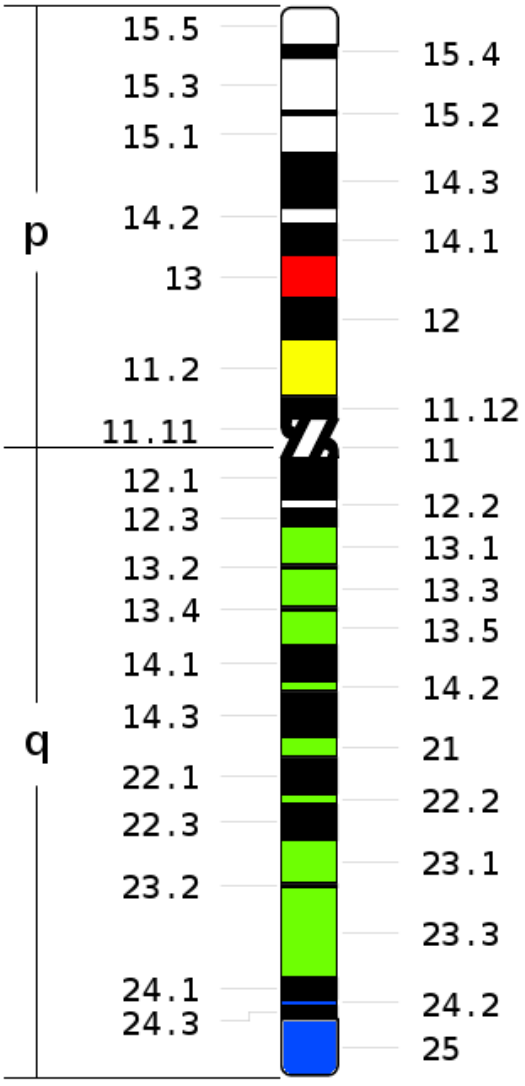

Introduction

The genetic size of chromosome 11 is ~134 Mb (almost the same as the size of chromosome 10). It is ~4–4.5% of the total human genome. The length of its short arm is ~50 Mb; the length of its long arm in ~84 Mb. Chromosome 11 is a very gene–rich area. It contains ~1,500 genes. Mutations of ~200 of these genes are known to cause birth defects or some functional abnormalities. The short arm of chromosome 11 contains a region which is known to be imprinted. As a result duplications of this region will have different manifestations depending on the sex of the parent responsible for this defect. Phenotypes of persons with duplications of the maternal origin will be different from the phenotypes of the persons with a paternal duplication of the same area.

There are ~1,400 patients with different structural abnormalities of chromosome 11 as the only abnormality or in association with abnormalities for other chromosomes. At least 800 of these patients had different deletions of chromosome 11. Deletions of the short arm have been reported in ~250 patients (including those with an additional imbalance); deletions of the long arm have been described in ~550 patients.

There are two syndromes caused by deletions of the short arm (both of these syndromes have been known for several years) and one well–known syndrome caused by distal deletions of the long arm (Jacobsen syndrome). Deletions of the large segment of the long arm (between 11q11 and 11q23), although reported in more than 60 patients, do not constitute any known syndrome.

Deletions of Chromosome 11

The genetic size of the chromosome 11 is ~134 Mb, where the short arm is ~50 Mb. There

are two well–characterized syndromes caused by deletions of the short arm of chromosome 11 (WAGR syndrome, caused by the deletion of 11p13 and Potocki–Shaffer syndrome, caused by the deletion of the proximal part of the short arm (11p11.2p12)), and one syndrome caused by the deletion of the distal part of the long arm (Jacobsen syndrome).

Deletions of 11p

WAGR–syndrome

WAGR — acronym for the main manifestations of this condition — Wilms tumor (W), aniridia (A), genitor–urinary anomalies (G) and mental retardation (R). An association of aniridia and Wilms tumor was known since the 1960's, but the chromosomal etiology of this condition became evident only since 1978, when the small interstitial deletion of 11p was found in several patients with this syndrome. Further studies showed that the deletion of the 11p13 segment is responsible for WAGR syndrome. Although the deletion of 11p13 is sufficient to produce all manifestations of WAGR syndrome, most patients have larger deletions also involving 11p14 or 11p12.

The syndrome is well known: in the literature there is information on ~185 patients with this condition, although ~40 of them were presented as "WAGR–syndrome" without a detailed description of phenotypic manifestations. The detailed clinical picture is known for the remaining 145 patients. There are ~20 more patients with WAGR–phenotype who did not have a cytogenetically visible deletion but apparently had balanced translocations with one of the breakpoints within 11p13.

The main (and more constant) manifestation is aniridia: absence or severe underdevelopment of the iris. It was found in 139 out 145 patients. In some studies, however, aniridia was a prerequisite for the selection of patients for cytogenetic examination. Aniridia is frequently predisposed to other defects of the eye, including cataract and glaucoma. Cataracts were reported in 46 of these patients, glaucoma in 23 (the actual frequency of these defects may be higher, because not every report contained a detailed description of the eyes). As an isolated defect, aniridia may be inherited as an autosomal dominant trait. The genetic basis of aniridia is the deletion of the PAX6 gene, which is located at 11p13. This gene is necessary for normal development of the eyes.

Wilms tumor affecting the kidneys is a second leading manifestation of the syndrome. This tumor was reported in 61 out of 145 patients. Special analysis showed that the risk of development of Wilms tumor in a patient with aniridia and del 11p13 is ~45%. It shows that 1) development of the Wilms tumor is not obligatory; 2) periodical urologic examination is necessary for all patients with aniridia and del 11p13. Treatment of the patients with Wilms tumor should be performed under regular protocols for treatment of this tumor.

The deletion of the gene WT1 also located within 11p13 is the genetic background for Wilms tumor. The same gene is considered to be responsible for a wide range of genitor–urinary defects. Different abnormalities of the genital system (from hypospadias to complete sex reversal) were mentioned in ~20% of patients. At least 4 patients had gonadoblastoma — another type of tumor affecting gonadal tissue.

Defects of the kidneys (cystic kidneys, ectopic kidneys, double collecting system etc.) were

reported in 17 patients. Of course, the real frequency of renal defects is higher because not every patient had an adequate urologic examination.

Delay in psycho–motor development is an unspecific but almost constant manifestation of the syndrome. Neither the deletion of PAX6 nor the deletion of WT1 causes this delay: a small group of patients with tiny deletions encompassing PAX6 and WT1, but not affecting other genes, had normal intellectual development. The most likely explanation of the delay in psycho–motor development is involvement of other genes.

Obesity is typical for a significant proportion of patients. Some authors even recommend to add a character “O” (obesity) to the acronym WAGR and use the acronym WAGRO. The genetic reasons for the obesity in this syndrome remain unknown.

Abnormalities of other systems are infrequent. Congenital heart defects (all non–life–threatening) were reported in seven patients; two more had hypertrophic cardiomyopathy. Four patients had agenesis of the corpus callosum; four had postaxial polydactyly; four more had preaxial polydactyly. At least 3 patients had diaphragmatic hernia. Several patients had chronic pancreatitis. All of these defects are caused by deletions of other genes because, in most patients, deletions are not limited to 11p13, but involve 11p14 or 11p12. At least two patients with del 11p12p14.3 had colobomas but neither aniridia nor Wilms tumor. Most likely, colobomas in these children were caused by the deletion of the same PAX6 gene, although other possibilities cannot be completely excluded. Rare patients, where deletions involved the 11p11.2 region, had symptoms of Potocki–Shaffer syndrome (exostoses, parietal foramina).

Systematic and repeated examinations to exclude Wilms tumor (or to find its earliest stages) is a necessary precaution regarding patients with del 11p13 and aniridia.

Potocki–Shaffer Syndrome

Potocki–Shaffer syndrome (PSS) is a classical example of a contiguous gene deletion syndrome because the main manifestations of this condition are caused by simultaneous deletions of two neighboring genes located at 11p11.2. PSS was delineated in the 1990’s, mainly by the works of Potocki and Shaffer. At least 45 patients with PSS have been described so far.

This syndrome consists of several non–specific manifestations (delay in psycho–motor development, craniofacial dysmorphism) and two very specific defects — exostoses and parietal foramina, which are hallmarks of PSS.

The patients with PSS usually have normal birth weight; most of them have brachycephaly. Other facial dysmorphias — epicanthus, sparse eyebrows, broad or depressed nasal tip, hypoplastic nares, short philtrum, down–turned mouth — are common, but these features may be found in many other forms of autosomal imbalance. Almost all patients show significant delay in psycho–motor and intellectual development.

The exostoses (additional benign bony structures, which grow mostly from the tubular bones) usually became evident after 3 years of age. These exostoses are caused by the deletion of the EXT2 gene, located in the 11p11.2 region. Mutations of this gene cause hereditary multiple exostoses but no other abnormalities.

Parietal foramina are caused by delayed ossification of cranial bones. Sometimes these defects may be suspected upon physical examination, but they should be confirmed by X–ray examination. In other patients, defects of cranial ossification became evident only upon X–ray examination. The deletion of the gene ALX4, located just proximal to the EXT2 gene, is considered a primary cause of these defects of ossification. Several patients had defects in other cranial bones (frontal, occipital).

There are no preferential breakpoints: every patient has unique breakpoints, both proximal and distal. The patients with tiny interstitial deletions involving only 2 neighboring genes, EXT2 and ALX4, may have normal intellectual development. Involvement of more distal genes (11p12p13) causes additional abnormalities, which may be found in some patients.

Hypoplasia (or aplasia) of the corpus callosum and hypoplastic cerebellar vermis are reported in ~25% of patients. Several patients had myopia, hearing defects or seizures. Other defects are very rare: only two patients with PSS had heart defects (VSD); two had hypospadias; one had anal atresia. Very large deletions involving 11p14.1 may cause symptoms of WAGR syndrome, including aniridia and Wilms tumor.

The publication by Swarr et al. (2010) may be useful for detailed characterization of this condition.

Deletions of 11q

Interstitial Deletions of 11q

There are at least 60 reports on patients with various interstitial deletions of 11q (from 11q13 to 11q23). These patients show numerous abnormalities, sometimes in very unusual associations. However, until now, there is not a single syndrome caused by interstitial deletions of 11q. At the same time, recurrence of several abnormalities in patients with similar deletions allows one to think that the segment 11q14.3 contains a gene causing cleft palate, the segment 11q14.1q23 may harbor a gene leading to neuroblastoma, and the segment 11q14.2q23 has a gene leading to retinal dysgenesis. There is strong evidence for a coloboma–related gene within 11q22.3. Several patients with deletions of 11q22.2q22.3 were obese. The segment 11q22.3q23 may contain a gene causing Ebstein anomaly — a heart defect with the abnormal formation and displacement of the tricuspid valve. The segment 11q23.1q23.3 has the recessive gene, PLZF, causing (in patients with the deletion or mutation of the homologous gene on another chromosome 11) the complex of microcephaly, hypoplastic radii, absent thumbs and preaxial polydactyly of the foot.

Distal Deletion of 11q (Jacobsen Syndrome)

The distal deletion of 11q is a well–known entity: this syndrome was described in 1973 by P.Jacobsen et al. The term “Jacobsen syndrome” is frequently used as a synonym to the term “distal deletion 11q syndrome”. At least 350 patients with this syndrome have been described, but ~140 of them had an associated imbalance caused by different translocations or inversions. Several out of ~210 patients with “pure” distal monosomy 11q have not been described in detail. Therefore ~200 patients with “pure” deletions were used for the analysis

Most patients with Jacobsen syndrome are females; some authors suggest that the male to

female ratio is ~1:2. The reason of this phenomenon remains unknown.

Most children have a relatively low birth weight, but severe prenatal hypoplasia is uncommon. The spectrum of dysmorphic features is wide, but relatively non–specific. Most patients have high prominent forehead, ptosis, epicanthus, hypertelorism, sparse eyebrows, short nose with anteverted nares, low–set posteriorly rotated ears, rethognathia, short neck. These features may be found in numerous other syndromes caused by chromosomal imbalance.

Trigonocephaly, however, may be a hallmark of the syndrome. It was reported in 72 out of 200 patients. In a patient with trigonocephaly, the skull has a triangular appearance (if the head is seen from above). Trigonocephaly is caused by the premature closure of the metopic suture and, by definition, is a variant of craniosynostosis. Other variants of craniosynostoses, however, are very rare: there are only 7–8 reports of patients with a premature fusion of other skull bones.

Microcephaly is a very rare feature. Moreover, a significant number of patients may have moderate macrocephaly. Delay in myelination or an abnormal pattern of myelination became frequently reported in patients who had an MRI of the brain. It is unclear, however, whether these defects are specific for 11q deletion or just common manifestations of many chromosomal syndromes.

Thrombocytopenia (a small number of thrombocytes) is another hallmark of the syndrome. It was reported in 82 out of 200 patients. Actually, however, the prevalence of this defect is even higher because, in most “old” reports about Jacobsen syndrome, there is no indication regarding the presence or absence of hematological anomalies. In some patients, thrombocytopenia was associated by leucopenia and anemia. Although thrombocytopenia may be transitory and the number of thrombocytes in older patients may be normal, structural (and functional) defects of thrombocytes persist. This form of pathology is called the Paris–Trousseau syndrome, which is unique (and diagnostic) for a distal deletion of 11q. As a result, patients have abnormalities of blood coagulation. Most likely a gene responsible for Paris–Trousseau syndrome is within 11q24.3, but data about the exact character of that gene are still contravening.

Approximately 10 patients with Jacobsen syndrome had transverse limb reduction defects — underdevelopment of the distal regions of the hands and feet. Generally, such defects are not characteristic for chromosomal pathology. Some authors believe that these defects are casually linked to intrauterine hemorrhages caused by defective blood coagulation.

Congenital heart defects are very common. At least 50% of the patients have different heart defects. Unfortunately, in a significant number of the patients, these abnormalities are very serious. Many patients need surgical treatment or at least support of cardiac function by medications. The spectrum of heart defects is rather specific with a significant preponderance of the so–called “left heart defects” including hypoplastic left heart (frequently a lethal abnormality), aortal stenosis, coarctation of aorta, hypoplastic aortic arch, defects of aortal and mitral valves. At least 2 patients had a very rare defect — aneurysm of interatrial septum. All of these defects may be caused by the deletion of a gene on the boundary of 11q24.2 and 11q24.3, although an exact character of this gene remains unknown. It is possible that the distal part of 11q contains more than one gene involved in heart formation.

Abnormalities of the eyes are relatively common. Colobomas of iris, choroid or optic nerve were noted at least in 16 patients. Other eye defects (microphthalmia, retinal dystrophy, cataract, optic atrophy, glaucoma), although repeatedly reported, are not so frequent.

Hearing impairment was described in at least 8 patients.

Gastro–intestinal defects are generally uncommon. However, 9 patients had pyloric stenosis and 7 patients had anal atresia or anal stenosis. The deleted segment of 11q has to contain genes responsible for these defects. More than 10% of affected patients have defects of the kidneys: absence of one kidney, cystic kidney, hypoplastic kidney, hydronephrosis. Inguinal hernias and hypospadias are also relatively common.

Skeletal anomalies (except maybe the above–mentioned transverse limb reductions) are relatively mild (camptodactyly, contractures, partial syndactyly, dislocation of the hips) and uncommon. These defects do not seem to be clinically significant.

Delay in mental development, neurocognitive impairment, and behavioral defects are typical for the patients with a distal 11q deletion. It was shown that patients with the loss of the larger segments of 11q have more severe problems than patients with smaller deletions. The BSX gene may be (at least partially) responsible for defects of neurocognition.

Almost all manifestations of the syndrome are related to deletions within 11q24.2 and 11q24.3. The patients with extremely rare isolated deletions 11q25 do not have typical manifestations of Jacobsen syndrome.

There are no favorite breakpoints. Almost each patient has his/her own unique breakpoint within 11q. The vast majority of deletions are terminal. Some patients, especially recently reported (when methods of molecular cytogenetics were used to determine breakpoints) have interstitial deletions of 11q23q24 or 11q23q25 (with preserved telomeric region). There are several reports of mosaicism with the coexistence of the deleted and normal clones. Direct transmission of a deleted chromosome from a mother to a child seems extremely rare: usually mothers of such patients have mild mental retardation or learning disability.

Cytogenetic examination of the parents remains a prerequisite for evaluation of the genetic risk.

The article by Mattina et al. (2009) may give further details about this syndrome.

Ring Chromosome 11

Ring chromosome 11 is a rare type of chromosomal pathology. There are only 18 reported patients having this abnormality. One of these patients had mosaicism with a normal clone. Molecular examination of the ring chromosome in another patient showed concomitant duplication of part of the 11p material.

Five patients with r(11) mainly had manifestations of the distal deletion 11q (Jacobsen syndrome), including trigonocephaly, heart defects, thrombocytopenia, or pancytopenia. Wilms tumor found in two patients strongly suggests the deleterious effect of the lost genes of 11p (surprisingly enough not a single patient with r(11) had aniridia or serious genital

abnormalities).

The patients with r(11) who did not reveal strong evidence of Jacobsen syndrome or WAGR syndrome had microcephaly (5), multiple café-au-lait spots (5), hypothyroidism, hypoplastic thenars, uterus bicornis. There is one report of direct transmission of r(11) from a mother to a child.

Partial Trisomies of Chromosome 11

Trisomies of 11p

Partial trisomy 11p as a sole abnormality is a relatively rare condition. Excluding patients with tiny duplications of uncertain clinical significance, there are less than 80 persons having partial trisomy 11p. All of these patients may be divided into two main groups: patients with duplications not involving the terminal segment 11p15.5 (this group may be designated as “proximal” 11p duplication) and patients with duplications involving 11p15.5.

“Proximal” duplications 11p

There are ~35 persons with such duplications. Some patients really have proximal duplications (11p12p13 or 11p12p14). Others have larger duplications, but without the involvement of the most distal segment of 11p.

Patients with “proximal” duplications do not reveal any recognizable syndrome. Most of them have various degrees of delay in psycho-motor development in association with facial dysmorphism and mild anomalies of the extremities.

Rare structural brain abnormalities include absent or hypoplastic corpus callosum, hypoplastic cerebellum (11p15.2 is the critical segment for these defects), and hydrocephaly. Eye abnormalities include hypoplastic optic nerve, microphthalmia, hypoplastic iris and stroma, blepharophimosis, ptosis and cataract. However, all of these defects were reported in 1-2 patients, each. Cleft lip and palate (or bifid uvula) was found in 6 patients. Most skeletal defects are mild (scoliosis, arachnodactyly, contractures, and dysplastic hips). However, absent thumbs were found in one child. Inguinal hernias (5) and umbilical hernias (3) are relatively common.

Four patients had heart defects: ventricular septal defect (2) and atrial septal defect (2). One boy had hypospadias; one child suffered from ureteral reflux. Defects of the lungs, diaphragm or gastro-intestinal system have not been reported.

Several patients had seizures.

Although most “proximal” duplications were sporadic, there are several reports of direct transmission of duplication from parent to child.

Duplications 11p15.5

This group of patients has to be analyzed separately, because a clinical picture will depend on the origin of the duplicated segment. The patients with duplications 11p15.5 inherited from

the father will have very different manifestations in comparison with patients having duplications 11p15.5 of maternal origin. This phenomenon known as genetic imprinting has been known since the 1980's, when it was shown that mice with the same chromosomal defects of different parental origin will have opposite results regarding their growth. In humans, the imprinting effect is shown only for the limited number of chromosomal segments. The distal part of 11p15 is one such areas. Detailed mechanisms of this phenomenon regarding 11p15.5 (differential methylation of the imprinting controlling genes) are out of the scope of this chapter).

From the clinical point of view, two opposite syndromes are caused by maternal and paternal duplications of 11p15.5.

Maternal duplication produces the so-called Silver-Russell syndrome (SRS). This syndrome is characterized by pre- and post-natal growth retardation, relatively large head with a triangle face, hypotonia, and normal or only slightly delayed psycho-motor development. The syndrome is relatively common and etiologically heterogeneous. Maternally inherited trisomy 11p15.5 is responsible only for 4-5% of all patients with SRS. The clinical differentiation between SRS caused by dup 11p15.5 or by other factors is negligible. Of course, if the patient has a maternal duplication not limited to 11p15.5, but involving also more proximal segments of 11p, that person may have additional clinical manifestations. Currently there are ~20 patients with SRS caused by the duplication of 11p15.5.

Paternal duplication of the same segment causes clinical manifestations of Beckwith-Wiedemann syndrome (BWS). The infants with BWS have relatively high birth weight. They have macrosomia; macrocephaly; macroglossia (large tongue, frequently too large for the oral cavity); coarse facial features; frequently, small pits on earlobes; omphalocele; or umbilical hernia. Some patients with BWS have polydactyly. Internal organs (kidneys, liver) of such patients are also unusually large. Most children have a relatively mild delay in psycho-motor development. The patients with BWS have a predisposition to childhood tumors, which may be found in 10-15% of such patients.

The typical picture of BWS may be found in patients with paternal duplications of 11p15.5. As in any situation with maternal duplications, an additional imbalance for the more proximal segments may cause additional defects, not typical for BWS.

In the literature there are ~15 reports of patients with BWS caused by a paternal duplication of 11p15.5. Of course, paternal duplication 11p15.5 is responsible only for a tiny proportion of all persons with BWS. Some dup 11p15.5 patients were reported as having macrosomia, macroglossia, and tumors (e.g., Wilms tumor) without direct indication for BWS. There are reports that the same duplication caused BWS in the mother but SRS in her daughter. In another family, a healthy brother and sister had the same balanced translocation, and their children had the same imbalance, but the brother's child had BWS and the sister's child had SRS.

Trisomies 11q

Trisomies for the long arm of chromosome 11 may be subdivided into trisomies for the proximal segment (till 11q22) and trisomies for the distal segment (11q23-11qter).

Proximal trisomies 11q

Trisomies for this part of 11q are relatively rare: only 33 patients with such duplications (as a sole abnormality) are known from the literature. The size of the duplicated segment and location of breakpoints were different in almost all reported families. There is no clinically recognizable syndrome associated with these duplications.

Reported patients have different degrees of delay in psycho-motor development, mild (if any) facial dysmorphism, and relatively mild defects of loco-motor system.

Brain defects include craniosynostosis (2), hypoplastic corpus callosum (2), microcephaly, and polymicrogyria. Two patients had preauricular pits or tags. Atrophy of the optic nerve, cleft palate, short neck, or redundant neck skin was reported in 1 patient, each. Defects of the skeletal system include scoliosis (3) and excessive joint laxity (3). Three patients had inguinal hernias, and two had umbilical hernias. Congenital heart defects were found in 6 patients, including two with life-threatening conditions (endocardial cushion defect, tetralogy of Fallot). Two patients had kidney defects. Functional abnormalities were relatively common. Three patients had attention deficit disorder, three had seizures, and three had depression. One child had hearing impairment.

In some families, these duplications (especially relatively small duplications) were inherited from the parents.

Distal trisomies 11q

Pure distal trisomy 11q is uncommon: there are only 36 patients having such trisomies as a sole abnormality. At the same time, distal trisomy 11q in association with trisomy for the proximal part of 22q is extremely common: this association forms a well known clinically recognizable syndrome known as Emanuel syndrome. However, the question of which manifestations of Emanuel syndrome are caused by trisomy 11q, which by trisomy 22q and which by the combined effects of these trisomies has not been analyzed. The comparison of clinical manifestations in patients with “pure” trisomy 11q and with Emanuel syndrome may facilitate this analysis. Moreover, there is large group of patients who have associations of trisomy 11q with an imbalance for other chromosomes (except dup 22q). Comparison with this group may further show the role of distal trisomy 11q in the origin of some phenotypic abnormalities.

“Pure” distal trisomy 11q

These patients show mostly a mild delay in psycho-motor development, non-specific forms of facial dysmorphism, cleft palate (3/36), short neck (4/36), redundant neck skin (3/36), dysplastic hips (9/36), and inguinal hernia (4/36). Two patients had colobomas. Only one child had preauricular pit, and one had hearing impairment.

Heart defects, however, were very common (19/36), including atrial septal defects (10), coarctation of aorta (4), patent ductus arteriosus (4), stenosis of pulmonary artery (3), and only single observations of tetralogy of Fallot and endocardial cushion defect (See the Table 1).

Table 1: Spectrum and distribution of heart defects in patients with different types of 11q trisomy.

Type of heart defects	‘‘Pure” distal trisomy 11q (n – 36)		Emanuel syndrome (n – 198)		Distal trisomy 11q with other abnormalities (n-93)	
	number	%	number	%	number	%
TOTAL	19	53	100	50	41	44
Atrial septal defect	10	28	49	25	23	25
Ventricular septal defect	3	8	28	14	12	13
Patent ductus arteriosus	4	11	17	9	9	10
Endocardial cushion defect	1	3	8	4	3	3
Tetralogy of Fallot	1	3	4	2	-	-
Coarctation of aorta	4	11	7	3	2	2
Pulmonary stenosis	3	8	21	11	8	7
Aortal stenosis	1	3	5	2.5	3	3

Abnormalities in other systems, however, were rare: defects of the epiglottis, hypoplastic kidneys, and anal atresia were reported only in one patient, each. Three patients had seizures. Morphologic abnormalities of the brain, diaphragmatic hernia, and Hirschsprung’s disease has not been reported to date in these patients.

Emanuel syndrome

Translocation t(11;22)(q23;q11) (with a small deviation of the formula in different families) is the most common non-Robertsonian translocation in humans. In almost all families, this imbalance is caused by the so-called “segregation 3:1”. If a person has a balanced reciprocal translocation, during meiosis, four chromosomes (two involved in a translocation and their normal homologues) form a figure called a “quadrivalent”. Usually upon division of this quadrivalent, two chromosomes move to one pole, two others go to another pole. In such cases there is segregation 2:2. Both gametes (egg-cells, if this occurs in female meiosis, or sperm-cells, if this occurs in male meiosis) will have 23 chromosomes. More rarely, three chromosomes move to one pole (and form a gamete with 24 chromosomes) and one chromosome goes to another pole (forming a gamete with 22 chromosomes). Fertilization of

the gamete with 24 chromosomes by a normal gamete will lead to an embryo (fetus, child) with 47 chromosomes: 46 normal chromosomes plus an additional chromosome consisting of parts of two chromosomes involved in the translocation. In the particular case with t(11;22)(q23;q11), almost all children with an imbalance have 47 chromosomes and an additional chromosome consisting of the distal part of 11q and proximal part of 22q.

Although segregation 3:1 may occur in many translocations, Emanuel syndrome, caused by simultaneous trisomies for parts of chromosomes 11 and 22, is the only clinically recognizable syndrome caused by an imbalance, not for one, but for two different chromosomes.

Emanuel syndrome is very common; almost 200 patients with this condition are available for phenotypic analysis.

Generally these patients have a significant delay in psycho-motor development, microcephaly, and facial dysmorphism, which includes prominent forehead, epicanthus, down-slanting palpebral fissures, flat nasal bridge, long and prominent philtrum, and microretrognathia. Preauricular tags or pits are very common (106/197). Hypoplastic ears (microtia) or atretic or stenotic external ear canals are also common (16/197). Many patients have hearing impairment. It should be mentioned that when children become older, their facial features became coarser. Cleft palate is extremely frequent; it was found in more than half of the patients. However, not a single patient was reported as having cleft lip. Some patients have short neck (12/197) and redundant neck skin (16/197).

Structural defects of the brain (above microcephaly) are relatively common: 11 patients had agenesis (or hypoplasia) of the corpus callosum, ten had cerebellar defects (hypoplastic cerebellar vermis, hypoplasia or dysplasia of cerebellar hemispheres), and eight had Dandy-Walker malformation. Trigonocephaly and other forms of craniosynostosis were found in five persons. Arhinencephaly was reported three times (but not a single patient had holoprosencephaly). One patient had spina bifida.

Defects of the eyes are relatively uncommon and include microphthalmia (4), coloboma (3), atrophy of the optic nerve (3), retinal defects (2).

The most frequent skeletal abnormalities are congenital hip dysplasia or subluxation (50/197). Additional ribs (13), contractures (15), kyphoscoliosis (16) are also common. Several patients have tapering fingers, proximally placed thumbs, small vertebral defects, radio-ulnar synostosis, or short forearms. At least 20 patients had inguinal hernias.

Multiple defects of the internal organs are typical for the patients with Emanuel syndrome. The most common are heart defects, which were found in half of all patients (100/197). The most common type of heart defects were atrial septal defects (49), ventricular septal defects (28), stenosis of the pulmonary artery (21), patent ductus arteriosus (17), endocardial cushion defects (8), coarctation of aorta (7), and tetralogy of Fallot (4). (A significant number of patients has more than one heart defect). The spectrum and distribution of heart defects in patients with this syndrome is basically the same as in patients with pure distal trisomy 11q (Table 1).

At least 25 patients (out of 197) had diaphragmatic hernia. Only patients with deletions 15q26 and tetrasomy 12p have compatible incidence of this defect.

Defects of the throat (laryngeal dysplasia) were reported twice.

Gastro-intestinal defects are also common. 30 patients had different kinds of defects of the rectum and anus: anal atresia (19), anal stenosis (7), or anal ectopia (4). In the latter case, the anus is placed too close to the vagina (or scrotum). Correction of these defects may require surgical intervention. Different forms of intestinal malrotation were reported in eight patients (of course, such defects may remain unrecognized and its actual incidence may be much higher). Atresia of the bile ducts and Hirschsprung's disease were reported in four patients, each. Esophageal atresia, cirrhosis of liver, hypoplastic pancreas, and absent gallbladder was found in 1-2 patients, each.

Many patients with Emanuel syndrome have serious abnormalities of the kidneys. Unilateral renal agenesis was reported in 16 patients; hypoplastic kidneys in 14. Of course, it is the minimal estimate, because these defects cannot be recognized without special examinations. Hydronephrosis was diagnosed in five children. There are several reports of dysplastic kidneys, ureteral stenosis or unspecified renal abnormalities.

Genital abnormalities, however, are relatively uncommon. There are six reports of hypospadias, two descriptions of ambiguous genitalia, and sporadic reports of hypoplastic uterus, duplicated uterus, or septate vagina.

Some defects of the heart, diaphragmatic hernia, and abnormalities of the gastro-intestinal system and kidneys are very serious, and life expectancy for the newborn with Emanuel syndrome is much less than for healthy newborn.

Almost all patients with Emanuel syndrome inherit their chromosomal abnormalities from their parents. Recurrence risk is ~7% if the mother carries a balanced translocation t(11;22)(q23;q11), and ~2% if a father is a carrier.

Comparison of the incidence and structure of heart defects, defects of the neck, hips and hernias allows the attribution of these defects mainly to distal trisomy 11q, whereas most defects of the brain, cleft palate, problems with hearing, and defects of gastro-intestinal system most likely are caused by trisomy for the proximal part of 22q. However, analysis of the group of patients having distal trisomy 11q in association with other autosomal abnormalities (except dup 22q) shows that the situation with defects of the neural tube, defects of the throat (larynx, pharynx), diaphragmatic hernia and kidney defects is a little bit more complicated.

Distal trisomy 11q in association with defects of other chromosomes

There are 93 patients who had distal trisomy 11q in association with defects of other chromosomes (mostly partial monosomies for other autosomes due to familial translocations). Clinical manifestations in these patients are caused both by effect of distal trisomy 11q and by effect of the accompanying imbalance.

The spectrum and distribution of heart defects in these patients (Table 1) is very similar to the spectrum in "pure" distal trisomy 11q. However, only 15/93 patients had cleft palate (vs. 102/197 in the patients with Emanuel syndrome).

Anal defects in this group occur rarely.

Neural tube defects are relatively rare in persons with structural autosomal imbalance. However, spina bifida was reported in five patients in the group “distal trisomy 11q with associated imbalance”, two more patients in this group had occipital encephalocele, two more fetuses had anencephaly (Table 2).

Table 2. Distribution of several abnormalities in patients with different types of 11q trisomy.

Type of defects	“Pure” distal trisomy 11q (n – 36)		Emanuel syndrome (n – 198)		Distal trisomy 11q with other abnormalities (n-93)	
	number	%%	number	%%	number	%%
Cerebellar defects	-		10	5	10	11
Defects of corpus callosum	-		11	6	14	14
Dandy-Walker malformation	-		8	4	6	6
Neural tube defects	-		1	0.5	9	10
Defects of the throat	1	3	2	1	6	6
Diaphragmatic hernia	-		25	13	5	-
Kidney agenesis	-		16	8	7	8
Hypoplastic kidneys	1	3	14	7	5	5
Hirschsprung’s disease	-		4	2	1	1
Anal atresia	1	3	19	10	2	2
Anal stenosis and ectopia	-		11	6	2	2

An unusually high incidence of these defects shows that the distal part of 11q has to contain the gene(s) that somehow facilitate the origin of neural tube defects. The same is true for abnormalities of the throat (defects of epiglottis, laryngeal dysplasia), which are extremely rare in the patients with a structural autosomal imbalance, but were found in 6/93 patients in an “associated” group. Here again, there is a good evidence for the role of duplication 11q in the origin of these defects. The incidence of agenesis of kidneys or hypoplastic kidneys is

almost the same in the patients with Emanuel syndrome (30/197 or 15%) and in patients in an “associated” group (13/93 or 14%). Most likely, 11q contains some genes involved in the origin of these defects of the kidneys.

Analysis of an “associated” group allows a more complete recognition of the role of thedistal part of 11q in the formation of vital organs.

Trisomy 11

Mosaic trisomy 11 occurs very rarely. Except several reports when cells with trisomy 11 were found only in placental tissues, there are only three reports of mosaic trisomy 11 in fetal cells. One fetus was an acardiac-acephalus twin. Another fetus had bilateral renal agenesis with some secondary defects caused by oligohydramnios.

The only liveborn child had facial dysmorphism, abnormal position of the fingers, a wide gap between the first and second toes, 11 pair of ribs, sacral dimple, and hypopigmented areas. Surprisingly, this girl did not have abnormalities of the internal organs.