



Chromosome 13

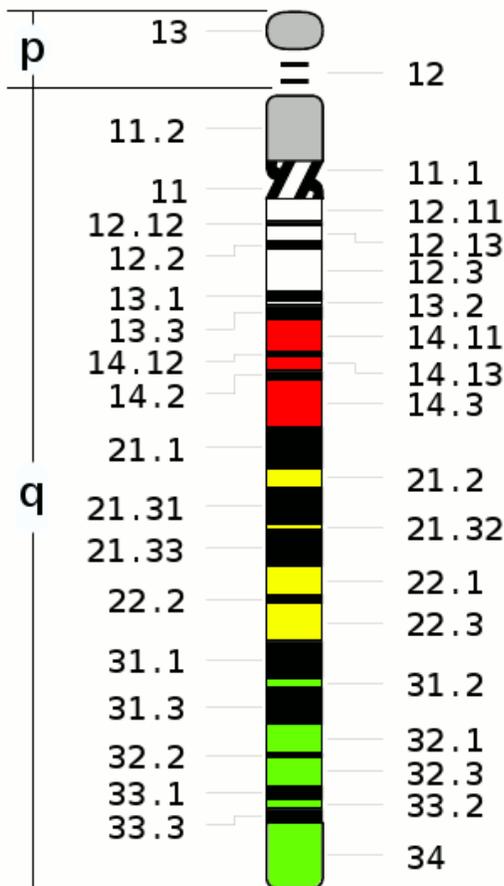
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David Adler.hum_13.gif



Introduction

Chromosome 13 (as well as chromosomes 14, 15, 21 and 22) is an acrocentric chromosome. Short arms of acrocentric chromosomes do not contain any genes. All genes are located in the long arm. The length of the long arm is ~95 Mb. It is ~3.5% of the total human genome. Chromosome 13 is a gene poor area. There are only 600–700 genes within this chromosome.

Structural abnormalities of the long arm of chromosome 13 are very common. There are at least 750 patients with deletions of different segments of the long arm (including patients with an associated imbalance for another chromosome).

There are several syndromes associated with deletions of the long arm of chromosome 13. One of these syndromes is caused by deletions of 13q14 and neighboring areas. The main manifestation of this syndrome is retinoblastoma. Deletions of 13q32 and neighboring areas cause multiple defects of the brain, eye, heart, kidney, genitalia and extremities. The syndrome caused by this deletion is well known since the 1970's. Distal deletions of 13q33q34 usually do not

produce serious malformations. Deletions of the large area between 13q21 and 13q31 do not produce any stable and well-recognized syndromes.

Deletions of Chromosome 13

Chromosome 13 (as well as chromosomes 14, 15, 21 and 22) belongs to the group of acrocentric chromosomes. Short arms of these chromosomes do not carry genes. Loss the short arm of an acrocentric chromosome is harmless. Only deletions of the long arm of acrocentric chromosomes have clinical significance. The genetic length of the long arm of chromosome 13 is ~95 Mb.

There are at least 450 reports on patients with deletions of 13q as a sole abnormality, and clinical conditions associated with these deletions are well-known.

Deletions of the very proximal segment of 13q (q11q13) occur very rarely. There is no stable phenotype associated with these deletions.

Scientists who studied deletions of 13q recommended subdividing all deletions into several groups: proximal deletions, involving 13q14; deletions of the “medial” part of 13q and deletions of the terminal part of 13q. Basically, this subdivision is still valid, although very terminal deletions 13q34 should be considered separately.

Deletions of 13q14 and Retinoblastoma

Retinoblastoma is a malignant tumor affecting retinoblasts (cells of the ocular retina). This tumor may be an autosomal dominant condition, caused by mutations of the Rb1 gene. This gene is located at 13q14.2. Deletions of this segment (involving Rb1 gene) may cause retinoblastoma.

Retinoblastoma occurs mainly in children at the age of 1–2 years. The first clinical sign of this tumor — leukocoria (a white spot on the eye as a reflection from the retina). Retinoblastoma may be unilateral or bilateral, but in patients with bilateral tumor, both eyes were not affected at the same time. Treatment of retinoblastoma (usually very successful) in patients with deletions 13q14.2 has to be provided by the standard protocols for treatment of this tumor.

Deletions of the segment 13q14.2 are found in 5–10% of all patients with retinoblastoma.

Retinoblastoma is the most frequent and most significant manifestation of this deletion. It was reported in 115 out of 160 known patients having a deletion of this segment. It does not seem, however, that ~30% of the carriers of the deletion are free of this tumor: many patients were described at a young age and development of retinoblastoma at the later age cannot be excluded. Methods of molecular cytogenetics showed that patients with relatively small deletions (~1.5 Mb) involving Rb1 and 4–5 neighboring genes have normal mental status and have no dysmorphism. Delay in psycho–motor development and dysmorphic features are typical for the patients discovered by “standard” methods, allowing recognition of much larger deletions. These features include brachycephaly, broad nasal bridge, bulbous tip of the nose, long philtrum, and large ear lobules. Although all of these abnormalities are unspecific, an association of retinoblastoma with mental retardation and dysmorphic features increases the probability of deletion. Normal development, however, does not exclude a small deletion.

Molecular studies showed that there are no favorite breakpoints; every patient has his/her own unique breakpoints on chromosome 13.

Deletions of the Medial Segments of 13q

The majority of patients with del 13q14.2, discovered by “standard” cytogenetics, also have deletions involving more distal parts of chromosome 13 — 13q21 and 13q22. These patients may have some additional abnormalities caused by the loss of more distal segments. There are ~25 patients with isolated deletions 13q21q22 (but not involving 13q31). The information about these patients shows that interstitial segments of 13q (13q21, 13q22) have to contain genes responsible for defects of the brain, eye, heart and gastro–intestinal tract.

At least five patients in this group had craniosynostosis (a minimal common area of deletion 13q14.1q21); five had agenesis of hypoplasia of the corpus callosum (common deleted area 13q14.11q21.1); two had hypoplastic optic nerve (common deleted area was 13q21.2q21.31); hydrocephaly was found in two other patients. Several patients had structural eye defects, including microphthalmia and coloboma. Two patients had manifestations of the Rieger syndrome including dysgenesis of the anterior eye segment. Therefore the segment 13q12q22 (the common deleted area in these patients) has to contain a gene leading to this anomaly.

Heart defects including tetralogy of Fallot (3), VSD (3) and patent ductus arteriosus (2) were found in 20% of patients.

At least 6 patients in this group had Hirschsprung's disease. It is evident that one of the genes responsible for this disease resides within the 13q21.1q22 area (which was deleted in all affected patients). Another unusual defect of the gastro-intestinal tract is atresia of duodenum (4), jejunum (2) or ileum (1). The common deleted segment (13q21.2q21.3) had to contain a gene responsible for these defects.

Four patients (with the common deleted area 13q14q21) had cleft palate. However, this defect is relatively common for many types of chromosomal imbalances.

Isolated deletions of 13q31 are very rare, although there are at least 50 patients who had deletions 13q31 together with more proximal segments of 13q. Most abnormalities reported in these patients (hypoplastic optic nerves, microphthalmia, Rieger's syndrome, duodenal stenosis, Hirschsprung's disease) should be attributed to deletions of more proximal areas of 13q. Some abnormalities, however, have not been reported in patients with deletions of 13q22 (without involvement of 13q31). Therefore, there are good reasons to believe that the segment 13q31 contains genes related to pigmentary retinopathy, hypopigmentation of iris (13q31.1), coloboma (13q31.1), hearing loss and cleft lip.

The vast majority of interstitial deletions 13q are sporadic events, although in some rare families these deletions were caused by familial insertions.

Distal Deletions 13q (Orbeli Syndrome)

Deletions of the distal part of chromosome 13 cause a well-known syndrome. Sometimes it is called Orbeli syndrome. Clinical delineation of the syndrome was done in the 1970's, and at least 195 patients with these deletions as a sole abnormality have been reported. At least 25–30 patients with clinically evident Orbeli syndrome were described before individual identification of chromosomes 13–15 became available. At that time, the syndrome was reported as "Dq-syndrome". Numerous patients having ring chromosome 13 also reveal the same phenotype.

The syndrome is unique because it affects numerous systems. Defects of the brain, skull, eyes, extremities, heart, lungs, kidneys, the gastro-intestinal tract and genitalia are typical, although not constant, manifestations of the syndrome.

Typically, the patients with Orbeli syndrome have significant prenatal hypoplasia. Almost all patients have a diminished head circumference (and significant delay in psycho-motor

development). Cranio–facial dysmorphism is relatively mild and non–specific: most patients have hypertelorism, flat nasal bridge, short philtrum, low–set malformed ears, and a short neck. A significant number of patients have trigonocephaly, but it is usually not as obvious as in Alfi syndrome (del 9p) or Jacobsen syndrome (del 11q).

Holoprosencephaly [HPE] (non–division or incomplete division of cerebral hemispheres) is a very common manifestation of the syndrome. It was reported more than 30 times. However, HPE in del 13q does not associate with severe facial defects (cyclopia, cebocephaly, premaxillar agenesis), which are typical for HPE caused by del 2p22, del 7q36, or del 18p11. Because obvious facial signs of HPE are absent, diagnosis of this defect became possible either by special investigations of the brain (MRI, CT) or at autopsy. Living patients who did not have special tests actually might have unrecognized HPE.

HPE is caused by the deletion of the ZIC2 gene, located at 13q32.2. Some authors consider microcephaly or cerebral dysgenesis found in patients with confirmed deletion of the ZIC2 gene as a micro–manifestation of HPE.

In very rare occasions, deletions of 13q were accompanied by even more severe brain defect — aprosencephaly, where actually all derivatives of the forebrain (prosencephalon) are absent, although derivatives of mesencephalon and metencephalon are well preserved. It is not clear whether aprosencephaly is the severest manifestation of the ZIC2 deletion or caused by other factors.

Defects of the neural tube (anencephaly, encephalocele or spina bifida) are also frequent. There are ~25 reports of these defects in patients with isolated distal 13q deletions (and many more when considering patients with a ring chromosome 13 or with associations of del 13q with partial trisomies for other chromosomes). The etiology of these defects remains unclear. Because a minimal deleted segment common for all of these patients is 13q33.2qter, there are good reasons to believe that the gene responsible for these defects should be located in this area. At the same time, analysis showed that the frequency of neural tube defects is much higher in persons who have a larger deletion (involving 13q22) than in persons with unaffected 13q22. This allows us to think that 13q22 may contain additional genetic elements somehow regulating the function of the gene at 13q33.2.

Dandy–Walker malformation is another frequent brain defect in persons with distal del 13q. It was reported more than 12 times. The smallest critical deletion region for this defect is 13q32.2q33.1, although the causative gene remains unknown. Hypoplastic cerebellar vermis (without other signs of Dandy–Walker malformation) was found in other 12 patients.

Abnormalities of the eyes are also very common. Microphthalmia was mentioned at least in 30 patients. Three patients had unilateral anophthalmia. The genes responsible for microphthalmia or anophthalmia are still unknown. The most likely location of these genes is 13q32.2. Approximately 20 patients had coloboma of the iris, choroid, or optic disc. Most likely, there are at least 2 genes (one at 13q31.1 and another one at 13q32.2) involved in the formation of this defect.

Distal deletions of 13q have very a characteristic pattern of limb defects, which is the hallmark of the syndrome. These defects include absent or hypoplastic thumbs (which occur in ~25% of patients) in association with syndactyly of 4–5 toes. X–ray examination shows Y–like

synostosis of 4–5 metacarpal (and metatarsal) bones. Absent or hypoplastic 5th fingers may be found in a small proportion of patients. Hypoplasia of the great toes with absent or hypoplastic 5th toes are less common. The critical segment for these defects is 13q32. Other defects of extremities are not characteristic.

Cleft lip and/or palate are not typical. Less than 10 patients had these defects.

Different heart defects were reported in ~30% of patients. Most of these defects are not life-threatening. The spectrum of heart defects does not show any particular pattern: Atrial septal defect and ventricular septal defect were reported in a dozen patients each; 5 patients had tetralogy of Fallot. Other forms of heart defects were found each in 1–2 patients.

Lung defects (hypoplastic lungs, abnormal lung lobation) are relatively frequent, but some types of lung defects may be diagnosed only at autopsy. In some patients, hypoplastic lungs may be secondary to hypoplastic or cystic kidneys.

The most characteristic defects of the gastro-intestinal tract are atresia, stenosis, or ventral ectopia of the anus reported in ~20% of patients. The critical segment for the origin of anorectal malformations is 13q33.3. Other defects (esophageal fistula, duodenal atresia or stenosis, intestinal malrotation) were noted in 2–3 patients, each. Surprisingly, the distal part of 13q contains another gene leading to Hirschsprung's disease: this gene should be located at 13q33. However, Hirschsprung's disease does not belong to characteristic manifestations of the syndrome.

Abnormalities of the kidneys are also relatively common. Hypoplastic kidneys are the most frequent defects, but some patients have an absence of one kidney, dysplastic kidneys, cystic kidneys, hydronephrosis, and other defects. Genital abnormalities are also very common. Many patients have ambiguous genitalia. Abnormal uterus has been found in several girls. Most boys have hypospadias. Recent studies showed that uro-genital defects are caused by the same gene (or group of the same genes) located at the distal part of 13q33.

As in proximal deletions, 13q molecular studies showed that there are no favorite breakpoints on distal 13q. Every person has a unique set of breakpoints on chromosome 13.

Although critical areas for numerous defects in Orbeli syndrome have been determined, the exact genes leading to these defects remain mainly unknown (as of today the ZIC2 gene causing HPE is the only exception).

The term Orbeli syndrome is a synonym for distal 13q deletion; however, the most distal segment of the long arm — 13q34 — does not harbor many “damaging” genes. There are ~20 reports of patients having isolated deletions of 13q34: these patients do not manifest any constant and significant abnormalities, except mild delay in psycho-motor development.

If the deletion at any level is a sporadic event, recurrence risk is extremely low. In practice, it has been shown that in 15–20% of children, distal deletions may be caused by familial translocations or inversions. Interstitial deletions may be caused by inherited insertions, but only in a very small percentage of families. Cytogenetic examination of the parents remains necessary for genetic counseling of the families.

Ring chromosome 13.

Ring chromosome 13 is one of the most frequent types of ring chromosomes. At least 180 patients with r(13) have been reported since 1962. It is the same number of patients as all known patients with ring chromosomes 6-12. Different forms of mosaicism were found in more than 20 patients: nine had mosaicism with a monosomic clone (45,-13), five had mosaicism with a normal clone, five had mosaicism with a clone with partially duplicated chromosome 13, and one patient had mosaicism with a deleted chromosome 13. At least two patients had two different types of ring 13 in their cells: a clone having a ring with a distal breakpoint and another clone with a more proximal 13q breakpoint.

Chromosome 13 is an acrocentric chromosome. Therefore, only the loss of the genetic material of the long arm may have clinical significance. From the clinical point of view, there are two main groups of patients with r(13). Basically, these differences depend on the location of the breakpoint of 13q. The patients with breakpoint on 13q32 or more proximal show all typical manifestations of the 13q- syndrome, including holoprosencephaly (sometimes even aprosencephaly, anencephaly or occipital encephalocele), microcephaly, trigonocephaly, microphthalmia, colobomas, absent thumbs and first toes, heart defects, atresia or ectopia of anus, hypoplastic kidneys, and hypospadias in boys. Of course, not each patient within this group has all these defects, but, generally, a spectrum of abnormalities in this group shows a close resemblance with typical 13q-syndrome. It should be noted that several patients in this group show some abnormalities typical for trisomy 13 or partial trisomy 13q, but not for 13q-syndrome (e.g. anophthalmia, polydactyly, cleft lip and palate).

The mechanism of occurrence for these abnormalities remained unclear for a long time. Molecular examination of several patients with ring chromosomes 13 in recent years showed that some patients had partially trisomic segments of 13q. These trisomic segments may explain the occurrence of trisomic traits in the monosomic patients.

If the 13q breakpoint is located in the area of 13q33 or 13q34, clinical manifestations are significantly milder. They include microcephaly, seizures, relatively mild heart defects (atrial or ventricular septal defects), short neck, hearing impairment, and hypogonadism.

Of course, molecular cytogenetics is the only reliable tool for the precise localization of breakpoints in persons with ring chromosomes. These methods were applied only to ~10% of all known patients. Therefore, the location of the distal breakpoints in most other published patients is relatively arbitrary.

Direct transmission of the ring chromosome 13 from a mother to a child has been reported in two families.

Partial Trisomies for Chromosome 13

Chromosome 13 (as well as chromosomes 14, 15, 21 and 22) is an acrocentric chromosome. The short arms of acrocentric chromosomes do not contain genes, and therefore trisomies (or deletions) of these areas do not have clinical significance. All clinically significant trisomies for these chromosomes are related to trisomies for the genetic material of the long arms.

Full trisomy 13 (Patau syndrome) is a frequent and well-known type of chromosomal

pathology. Main manifestations of trisomy 13 are arhinencephaly or holoprosencephaly (HPE) (~50%), trigonocephaly (~50%), microphthalmia (50-70%) or even anophthalmia, colobomas (25-30%), cleft lip and palate (70%), defects of the heart (65-70%), postaxial polydactyly (75%), and multicystic dysplastic kidneys (65-70%). Only a small proportion of patients with complete trisomy 13 survive one year. However, it is still unclear, which segments of chromosome 13 (when triplicated) are responsible for each of the abovementioned anomalies.

There are ~190 reports of patients with partial trisomies for different segments of 13q as a sole chromosomal abnormality, including 25 patients who had partial tetrasomy for chromosome 13 in part of their cells or in all cells. Twenty of these patients have relatively small duplications for different segments of 13q, which could not be recognized by standard cytogenetic methods.

a. *Proximal trisomy 13q*

There are ~25 patients who have “proximal” trisomy 13q – from the centromere to 13q21. Of course, these patients are very different both by the size of the duplication and by the location of breakpoints. Not a single phenotypic manifestation is common for all these patients. Most of them reveal a delay in psycho-motor development and complex abnormalities of different organs.

Congenital heart defects reported in six patients include two with tetralogy of Fallot, two with coarctation of aorta, and one with atrio-ventricular septal defect (AVSD).

Defects of the brain are represented by agenesis, or underdevelopment, of the corpus callosum (3); hydrocephaly (2); HPE (1); and microcephaly (1). Defects of the eyes are relatively common. Microphthalmia was reported in four patients. Two had colobomas; there are also reports of cataract and glaucoma. Three patients in this group had cleft lip and palate. One had cleft palate only. Three patients had preauricular tags or dimples. There are also reports of hearing impairment.

Three children had postaxial polydactyly. There are sporadic reports of micromelia (short extremities), scoliosis and kyphosis.

Several patients had abnormalities of the gastro-intestinal system (intestinal malrotation, and atresia ani) or kidneys (cystic dysplastic kidneys, doubling of the collecting system, and pyeloectasia).

Many of these abnormalities (HPE, microphthalmia, cleft lip and palate, colobomas, polydactyly, defects of the heart and kidneys) are typical for complete trisomy 13 and may be frequently found in patients with “distal” trisomy 13q. It shows that chromosome 13 includes several segments, which (when duplicated) may lead to the same type of abnormalities.

b. *Trisomies for the “Central” Part of 13q*

This group contains of ~40 patients with trisomies mostly involving the 13q2 segment. This area of chromosome 13 contains very few genes. As a result, most patients with these duplications do not have serious birth defects.

Reported abnormalities include microcephaly (2), short neck (2), hyperflexible joints (6), and congenital heart defects (4, including one report of tetralogy of Fallot). There are sporadic reports of cataract, choanal stenosis, esophageal atresia, and cystic kidneys. It is unclear, however, whether these defects were caused by trisomies 13q or trisomies for the small segment of 13q were discovered only by chance. In some families the same duplication of 13q was found in an affected child and in his/her unaffected parent.

Functional defects seem to be more frequent. Four patients in this group had seizures, four had hearing impairment, and two patients had autism.

Trisomies for this part of 13q do not constitute any recognizable syndrome.

c. Trisomies for the "Central" Part of 13q

There are numerous reports about patients with partial trisomies for the distal part of 13q, including ~115 patients where trisomy 13q was the only chromosomal imbalance. Generally, these patients have most symptoms of the full trisomy 13.

Almost all patients have a diminished head circumference, but HPE – the most serious and most common brain defect of trisomy 13 – was reported only in seven patients, most of whom had trisomies 13q21qter or 13q22qter. It sharply contrasts with the incidence of this defect in complete trisomy 13 (~ 50%). The most reliable explanation is that chromosome 13 contains at least two segments related to HPE, and genes in these areas have to act together to produce this brain defect. There is no strong indication that trisomy for the ZIC2 gene, located at 13q32 (and leading to HPE in patients with 13q deletion), is somehow related to HPE.

Trigonocephaly, however, was reported in 21 patients with distal trisomy 13q (~15%). Duplication of the segment 13q31.3q33.1 is a critical segment for the origin of this defect. Basically, the same area (dup 13q32q33) seems to be responsible for agenesis (or underdevelopment) or corpus callosum, although this defect is relatively common and there are numerous genes involved in the formation of this organ.

Serious eye defects are common. At least 16 patients had anophthalmia (absent eye) or microphthalmia (underdevelopment of the eyeballs) (three patients had bilateral anophthalmia, two had right-side anophthalmia in association with left-side microphthalmia, 11 had microphthalmia). The critical segment for these defects is dup 13q32.3q33.1. Segment 13q32 seems to be critical also for colobomas, which were reported in 11 patients with distal trisomy 13q (10%).

Cleft lip and/or palate were found in 15 patients with distal trisomy 13q. However, all patients having cleft lip had trisomies for 13q22qter (or larger), but reported patients with duplications of the more distal segments (13q31qter) had cleft palate only. It shows that there are at least two groups of genes on 13q, which may be involved in the formation of this defect.

Seven patients with distal trisomy 13q had preauricular tags or pits.

Postaxial polydactyly was reported in 47 patients. The most probable location of the gene(s) responsible for this defect is 13q31.

Many patients with distal trisomies 13q reveal defects of the internal organs. The most common are heart defects discovered in 25 patients, but only two of them had life-threatening abnormalities – hypoplastic right heart and tetralogy of Fallot. Others had not so severe defects, including dextrocardia (3), ventricular septal defects, patent ductus arteriosus, or aortal stenosis. Most likely, chromosome 13q has several segments, which (when duplicated) may lead to heart defects.

Abnormalities of the kidneys are less frequent than in patients with full trisomy 13. Severe kidney defects were reported only in 11 patients. The spectrum of these defects includes agenesis of one kidney (5) or cystic dysplasia. Other defects of the urinary system include hydronephrosis (6) and duplication of the renal pelvis and ureters (4).

Defects of gastro-intestinal tract are uncommon and presented by bowel malrotation (3) or ectopic anus and anal stenosis (narrowing of the anus) (2).

There are several reports of dysplastic or ectopic thymus (thymic tissue was found in the thyroid). Several patients had laryngeal stenosis, tracheal stenosis or abnormalities of the main bronchus. Inguinal and umbilical hernias are very common.

Delay in psycho-motor development is almost constant. The development of patients with mosaic forms of distal trisomy 13q (who have a normal clone) and patients with trisomy for the most distal segments 13q33q34 may be only minimally affected. Hearing impairment and seizures are common, especially for the patients with larger duplications.

From the genetic point of view, distal trisomies 13q may be caused by malsegregation of familial translocations or pericentric inversions or by de novo (sporadic) rearrangements (mostly duplications). Cytogenetic examination of the parents remains the gold standard for counseling regarding recurrence risk for future offspring.