



Chromosome 2

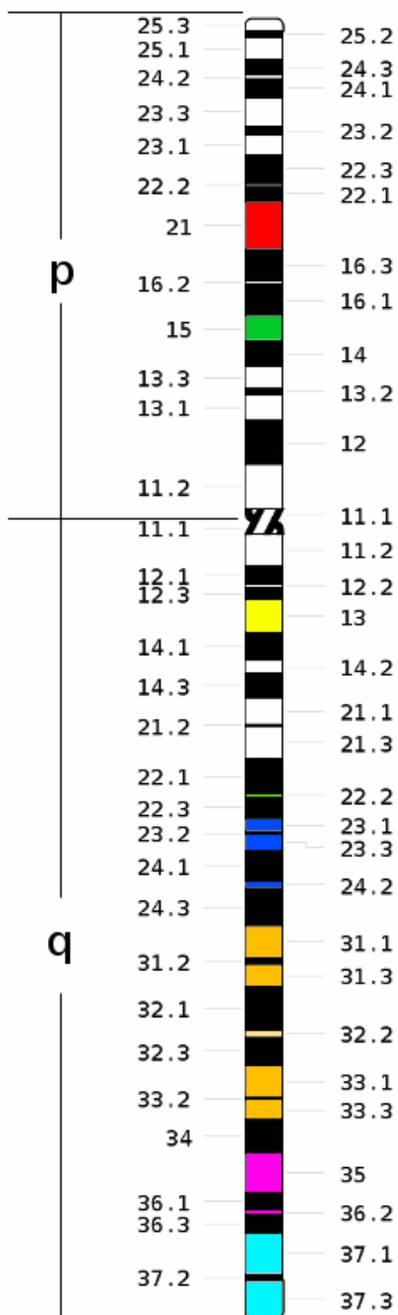
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Introduction

The genetic length of chromosome 2 spans ~237 Mb. It is ~8% of the whole human genetic material. The length of the short arm is ~89 Mb; the length of the long arm is 148 Mb. Chromosome 2 contains ~1500 genes. At least 200 of these genes are related to different kinds of genetic pathologies. Many of these genes are associated with structural defects of the organs, and others, to functional defects.

The numerous structural abnormalities of chromosome 2 had already been reported before methods of molecular genetics gained wide usage. Currently there are ~1,500 reports on patients with varying structural abnormalities of this chromosome, including ~1,000 reports on patients with deletions. Deletions have been reported in at least 10–15 patients for each segment of chromosome 2.

There are ten known syndromes caused by deletions of chromosome 2, including three syndromes related to deletions of the short arm (p). Some of these syndromes have been known for many years; others (del 2p15p16.1, del 2q23q24, and del 2q32) have been delineated only in the last couple of years.

Deletions of Chromosome 2

Different types of chromosome 2 deletions have been described in numerous publications and may be subdivided into 3 groups:

- Deletions that are “harmless” variants (usually familial)
- Unique deletions that have not been categorized as a syndrome yet
- Deletions that are considered a syndrome

Deletions of 2p

Deletion of 2p15p16.1

This syndrome, first described in 2007, is rare; only ten patients have been described to date. The characteristic features of this syndrome are microcephaly, postnatal growth retardation, developmental delay, joint subluxation, and camptodactyly (deformed fingers with limited range of motion). Typical facial abnormalities include telecanthus, ptosis, short palpebral fissures, everted lower lip, large low-set ears, and a high palate. MRI of the brain shows pachygyria (unusually wide ridges of the cerebral cortex) and hypoplasia of the cerebellum and brainstem. Most patients have hypoplastic optic nerves. Abnormal kidneys, such as cystic kidneys and hydronephrosis, are the most common visceral defects and usually can be detected during urological examination.

In two studies, autism was reported in half of the patients, but the significance of this remains unclear because autism was a selection criterion for participation. The size of the deletion and breakpoints were different in all patients; however, it was found that a 1.8 Mb deletion from 59.800 Mb to 61.600 Mb is needed to produce a typical phenotype. The only known patient with a smaller deletion (0.58 MB) had some characteristic facial features, but did not have microcephaly, optic hypoplasia, kidney defects, or autism.

Deletions of 2p21 and 2p24.1

The vast majority of syndromes caused by chromosomal deletions belong to a group called continuous deletion syndromes. This means that different clinical manifestations in the patient are caused by deletions of consecutive genes. For example, deletion of gene "A" might be responsible for microcephaly, deletion of gene "B", for hearing impairment, and deletion of gene "C", for cleft palate.

In some cases, however, the clinical spectrum of the syndrome depends on the deletion of one gene. There are numerous genetic conditions in which the clinical picture in the patient is caused by the mutation of one gene. When a mutated gene does not work properly, this generally leads to negative consequences (e.g., seizures or polydactyly). This same scenario occurs when the gene is absent (deleted). Clinical manifestations in some small deletions may be caused by the deletion of one "critical" gene because 1) distribution of the genes for the length of the chromosome is very unequal, and 2) not all genes are necessary for development. In that sense, there may be no significant difference between a small deletion and a mutation.

The segment 2p21 contains the SIX3 gene. Mutations of this gene cause holoprosencephaly (HPE), a birth defect in which the developing brain is not divided into two hemispheres or this division is incomplete. Manifestations of HPE can be very different, ranging from very severe defects of the brain and face to relatively mild forms, and may include pronounced hypotelorism (a diminished distance between the eyes), single central upper incisor, or hypoplastic philtrum. Head circumference is below normal even in patients with mild manifestations. Sometimes eye colobomas are considered a micromanifestation of HPE. The same clinical consequence can occur with deletion of the 2p21 segment. There are 15 reported patients with different types of HPE caused by cytogenetically identifiable deletions of chromosome 2. Without laboratory testing, it is not possible to distinguish between the

deletions and mutations of the SIX3 gene. An additional deletion of 2p22 may also produce defects of the heart and kidneys.

The segment 2p24.1 contains the MYCN gene. It has been shown that mutations of this gene cause Feingold syndrome (oculo–digito–esophago–duodenal syndrome). Patients with this syndrome have mild learning disabilities, microcephaly, short palpebral fissures, and various digital anomalies (eg, slightly hypoplastic thumbs, curved 5th fingers [clinodactyly], and partial syndactyly of 2–3 or 4–5 toes). The most remarkable manifestations of Feingold syndrome are duodenal and esophageal atresias, which occur in nearly 50% of patients. Defects of the heart and kidneys occur relatively frequently, but usually are not life–threatening. Patients who lack the 2p24.1 segment due to deletion have the same clinical manifestations, including, in some cases, duodenal and esophageal atresias.

Distal deletions of 2p (2p25–2pter) do not constitute any recognizable entity. Obesity is the only recurrent feature in these patients.

Deletions of 2q

At ~148 Mb, the long arm of chromosome 2 is the largest arm of all human chromosomes. There are numerous reports regarding clinical manifestations in persons with different 2q deletions. Some of these deletions cause phenotypic abnormalities; others are considered normal variants.

Deletions of 2q13 and 2q14.1

The segment 2q13 is ~4.5 Mb long (from 110.2 Mb to 114.6 Mb). The deletion involving a 1.62 Mb segment of 2q13 (from 111.158–112.927) is relatively common and is considered a familial variant because it is frequently found in unaffected family members. Despite this, there are reports of various defects found in persons with deletion 2q13, but the exact location of the deletion was not able to be determined using molecular technologies. It has been speculated that these deletions may involve more proximal or more distal regions of 2q13, which could mean there are deletions of several genes outside of the “common” deletion segment, or the defects in the patient were unrelated to the deletion. Small deletions within 2q14.1 also may be familial variants.

Patients who have deletions involving 2q14.3 do not exhibit recurrent clinical manifestations; craniosynostosis (premature fusion of cranial bones), which can affect normal growth of the developing brain, may be the only exception.

Deletion of 2q22 (Mowat–Wilson Syndrome)

An association of microcephaly, congenital heart defect (CHD), and Hirschsprung’s disease (agangliosis of the bowel, when absence or underdevelopment of the enteric nerves hampers normal peristalsis) was reported in 1994 in a child with deletion 2q22q23. Several years later, Mowat and coworkers found the same complex of abnormalities in several children with normal karyotypes and in one child with a balanced translocation t(2;11)(q22;q21). Further studies showed that the segment 2q22 contains the gene ZFAX1B (or ZEB2), which, when deleted, broken or mutated, leads to this complex of abnormalities, currently known as Mowat–Wilson syndrome (MWS). In most patients, MWS is caused by different mutations of

the ZEB2 gene, but a significant number of patients (~10%) have deletions within 2q22 (sometimes with the involvement of the more proximal segment 2q21 or the more distal segment 2q23). Again, as in the case of Feingold syndrome, the phenotype of MWS was first recognized in a child with a chromosomal deletion, and, only later, did it become evident that the deletion or mutation of only one gene (ZEB2) within 2q22 is enough to produce this syndrome. Since then, there have been reports of 40 patients whose MWS was caused by such a deletion. Clinical manifestations in the patients with MWS, whether caused by mutation or deletion, are basically the same, although some patients with deletions may have additional abnormalities caused by deletions of other genes.

Typical facial features include large eyebrows that are sparse in the middle, round face that becomes elongated with age, high forehead, frontal bossing, deep-set eyes, hypertelorism, broad nasal bridge, and round nasal tip; patients tend to smile with a mouth that is usually open. Scalp hair is usually fine and sparse and there is excessive skin on the back of the neck.

The association of Hirschsprung's disease and developmental delay is the primary criterion for clinical diagnosis of MWS. At least half of MWS patients have Hirschsprung's disease; chronic constipation is typical for other patients. All children have some degree of developmental delay (moderate or severe); 75% of patients have microcephaly. Seizures are also very common (75%–80%). Half of the patients have agenesis (or hypoplasia) of the corpus callosum; other structural brain defects are very uncommon. Congenital heart disease (CHD) is also common (50%–55%); in most patients, CHD is relatively mild and only a small number of those affected have serious clinical manifestations (ie, hemodynamic problems). Defects of the kidneys and extremities are highly unusual, although males frequently have hypospadias. Most patients have a happy, sociable personality. A more detailed description of MWS may be found in the review by Garavelli et al. 2009.

Deletions of 2q23q24

In the literature, there are reports on 30 patients with deletions solely within 2q23q24 (excluding patients who also had more proximal deletions of 2q22 causing MWS or more distal deletions involving 2q31). The comparison of these patients is difficult because different (sometimes not very precise) techniques were used to determine the breakpoints. In the patients who were examined using contemporary techniques, the size of the deletion and position of the breakpoints were different. The existing reports show a wide spectrum of abnormalities, including microcephaly (~30%), cleft palate (~20%), and various CHDs (~30%). Microphthalmia, colobomas of the iris, hearing loss, and small limb defects were noted in two to three patients each.

The most significant clinical manifestation in these patients is severe myoclonic epilepsy (also known as Dravet syndrome). Children with classic Dravet syndrome suffer from recurrent and prolonged seizures, which usually begin after 6 months of age in previously healthy infants. Investigations have shown that the cause of Dravet syndrome in most patients is mutation of the SCN1A gene which is located at 2q24.3 and encodes the voltage-gated sodium channel. Complete deletion of this gene causes the same clinical picture. If the deletion is relatively small and does not involve surrounding genes, patients exhibit a phenotype of classic Dravet syndrome. Larger deletions involving other genes may lead to additional defects (eg, microcephaly, cleft palate, and CHD).

Deletion of 2q31q33

Only 20 patients with deletions of 2q31q33 have been described in the literature. Several other patients had additional deletions of a more proximal segment (2q24) or a more distal segment (2q31). Genetic analysis shows that most manifestations of this entity are caused by the deletion of 2q31, whereas loss of genetic material of 2q32 and 2q33 is less significant.

Microcephaly is the most common manifestation and occurs in two-thirds of patients. There are no specific facial features which allow for clinical recognition of the condition, except for eye abnormalities such as blepharophimosis, ptosis and short eye fissures. The size of the eyeballs is also frequently diminished; microphthalmia was reported in at least one-quarter of patients and is likely due to the deletion of 2q31.1. Other eye defects include colobomas and corneal opacities. Cleft palate (usually without cleft lip) can be found in 50% with this condition.

Abnormalities of the extremities are an almost universal manifestation of deletion 2q31q33. Some patients have relatively mild defects, such as partial syndactyly of the second and third toes, sandal gap (wide distance between the 1st and 2nd digits), and camptodactyly. However, these types of limb defects are frequently found in patients with various other chromosomal deletions or duplications and are not specific to deletions of 2q31q33. Other patients may have more severe defects, including ectrodactyly (or “cleft” hand or foot). Most patients with ectrodactyly have intact 1st and 5th rays, but one or two “central” digits are missing. Sometimes the absence of digits on one hand or foot is accompanied by syndactyly of fingers/toes on another hand/foot. The upper and lower extremities are affected with the same frequency. In some cases, the defect may present as monodactyly (one single digit), with absence of bones in the forearms or forelegs. Most scientists believe that these defects of the extremities are caused by the deletion of the HOXD genes. This group of genes is located within the 2q31 segment. However, it was shown that a deletion of the most “centromeric” part of this group (HOXD9–HOXD13) leads to polysyndactyly, but not to ectrodactyly. Therefore, it is most likely that participation of other genes in this area is necessary to cause ectrodactyly.

Hydrocephaly, hypoplastic cerebellum, and hypoplastic optic nerve have been reported in several patients each. Craniosynostosis is relatively common and is attributed to two genes, one within 2q31 and another within 2q33. Visceral defects have also been reported. Forty percent of patients have various types of congenital heart disease (CHD) and several patients have hypoplastic kidneys or defects of the liver. Atresia (or ventral ectopia) of anus was also reported. Some males had hypospadias, others had a shawl-like scrotum. It should be noted that three patients had XY-reversal, a condition in which a child with an XY karyotype has apparently normal female external genitalia. While the gene, responsible for this defect is known to reside within 2q31.3q32, it has not yet been identified.

Deletion of 2q32

Isolated deletions of 2q32 are uncommon. In most patients, the deletion involves not only 2q32 but also more proximal (2q31) or more distal (2q33) segments. The most common birth defect, cleft palate, is found in half of the patients. Congenital heart disease has been reported in 10%–15% of patients. Most other presentations (sparse hair, small mouth, short

eye slits, tendency to microcephaly, and developmental delay) are very common in other chromosomal deletions and duplications. Some authors suggest that deletion 2q32 causes a specific syndrome. However, more patients with isolated deletion 2q32 would need to be reported to come to the conclusion that the deletion was a syndrome.

Deletions of 2q34–2q36

There is no clinical syndrome caused by deletions within the 2q34–2q36 segment. Different positions of the deleted segments and the presence of additional imbalances in ~30% of patients with these deletions limit possibilities for an accurate comparison of clinical findings.

Several patients with deletion 2q35q36 had manifestations of Waardenburg syndrome, specifically, white hair forelock, areas of hypopigmentation, heterochromia irides (different colored eyes), and sensori–neural hearing loss. The gene PAX3, which causes Waardenburg syndrome, when deleted or mutated, is located within 2q35.

Defects of the neural tube (including spina bifida) are relatively uncommon manifestations of chromosomal syndromes. However, several patients with deletion 2q36 had spina bifida, indicating that one of the genes responsible for this defect may be within 2q36.

The third defect, which was found in several patients, is Dandy–Walker malformation (DWM). This anomaly includes underdevelopment of the cerebellar vermis, increased space between the cerebellum and the medulla, and a cyst on the internal base of the skull. There is strong evidence that one of multiple genes responsible for DWM resides within 2q36.1. However, 50% of patients with deletions 2q34q36 did not have Waardenburg syndrome, spina bifida or DWM, meaning that the deletion is necessary but not sufficient alone to cause these defects.

Deletion of 2q37

Deletion of the distal segment 2q37 is the most common defect among all deletions of 2q. More than 260 patients with the deletions have been reported. Although ~40% of them had associated imbalances for other chromosomes, analysis of those with “pure” deletions allows for delineation of the typical phenotype. Because the main clinical manifestations in patients with deletions of the whole 2q37 segment and in those with deletions of the most distal sub–segment 2q37.3 are the same, it is evident that loss of 2q37.3 is critical for the origin of the syndrome.

Developmental delay (usually relatively mild) is a common manifestation of the syndrome. Approximately 50% of patients also have short stature, a tendency to obesity, short fingers and toes (caused by shortness of metacarpal and metatarsal bones), and a large space between the 1st and 2nd fingers or toes. Because the association of these skeletal defects with developmental delay resembles Albright hereditary osteodystrophy, the term “Albright hereditary osteodystrophy–like (AHO–like) syndrome” was coined to describe this condition in patients with deletion 2q37. Attempts to find a gene responsible for the AHO–like phenotype were unsuccessful, although a critical region was narrowed down to ~2MB (240.6 Mb–242.7 Mb) within 2q37.3.

Most patients with deletion 2q37 have facial dysmorphisms which include prominent forehead, round face, sparse hair, bushy arched eyebrows, deep–set eyes, and short nose

with narrow nares. The palate is usually high, but cleft palate is uncommon. Eczema is another frequent manifestation, especially in small children. In several patients, hearing impairment was caused by atresia of the auditory canals or defects of the internal ear. Other patients with hearing loss had no morphologic abnormalities of the ear. The most common malformations of internal organs are congenital heart defects (CHDs), which occur in 10%–15% of patients with isolated deletions. Most of these defects are relatively mild and do not usually require surgical intervention. Numerous defects in other systems occur in a very low percentage of patients (less than 3% each) and include craniosynostosis, holoprosencephaly, agenesis of corpus callosum, esophageal atresia, duodenal atresia, anal atresia or dystopia, situs inversus, horseshoe kidney, and dysplasia of the kidneys. At least 2 patients with deletion 2q37 had Wilms' tumor. Rare (but repeated) occurrence of these defects suggests that the lost 2q37 segment contains genes important for the morphogenesis of the above-mentioned systems, but that most likely the responsible genes produce a harmful effect only in the presence of other genetic or non-genetic factors.

Aside from developmental delay, the most common neurodevelopmental problems in deletion 2q37 are seizures and autism, each of which occurs in approximately one-third of reported patients. However, in some studies, the presence of seizures and/or autism was a selection criterion for participation. Typically seizures respond to the usual medications. Manifestations of autism include poor social contact, lack of eye contact, hyperactivity, and repetitive behavior. Attempts to find the genes responsible for seizures or autism in patients with deletion 2q37 have been unsuccessful so far. A more detailed description of deletion 2q37 may be found in the review by Falk and Casas (2007).

Genetic counseling

From the genetic point of view, all deletions of chromosome 2 may be subdivided into interstitial deletions and terminal deletions. A significant number of terminal deletions (up to 20%) are caused by chromosomal rearrangements (mostly translocations) in one of the parents. The recurrence risk is very low if parental chromosomes are normal and relatively high (up to 25%) for families having translocations or inversions.

Interstitial deletions are sporadic in at least 95% of patients. Rarely, one of the parents will be a carrier of an insertion (with subsequent high risk for further offspring). Some small deletions (recognizable only using molecular methods) may be either benign familial variants (as was described for deletion 2q13 and 2q14.1) or inherited from a parent having very mild manifestations of the disorder. Cytogenetic examination of both parents is necessary to determine genetic risk (and a tactic regarding further pregnancies) in all families having a child with any chromosomal deletion (or duplication).

Ring Chromosome 2

Since 1972, there have been only 18 reports of patients with ring chromosome 2, two of which had mosaicism with a normal clone, and another, mosaicism with a clone trisomic for the distal part of 2q.

At least half of the patients with ring chromosome 2 did not have any significant anomalies, other than generalized delays in physical and psycho-motor development and mild dysmorphism. Five patients had heart defects (four with ventricular septal defect and one with

tetralogy of Fallot). Four patients had craniosynostosis. Retinal dystrophy, preaxial polydactyly, hip dislocation, lymphedema, and hypospadias were mentioned in one patient each.

Familial transmission of ring chromosome 2 has not been reported.

Partial Trisomies for Chromosome 2

Partial Trisomies for 2p

There are approximately 90 patients with trisomies for different segments of the short arm of chromosome 2 as a sole abnormality. At least 120 more have trisomy 2p in association with a partial monosomy for other chromosomes. All observations of partial trisomy 2p may be arbitrarily divided into 3 groups: a) trisomies for the proximal or near-centromeric area of 2p; b) trisomies for the "medial" segment of 2p (from 2p12 to 2p23), and c) trisomies for the distal segments, involving the segments of 2p24 and 2p25.

Proximal duplications of 2p

Through molecular examination of small additional marker chromosomes, it was possible to detect in 12 patients that these marker chromosomes originated from the paracentromeric area of chromosome 2. At least half of these patients did not have any significant defects. Other patients had serious malformations, including craniosynostosis, situs inversus, diaphragmatic hernia, microphthalmia, and dysplastic kidneys. However, all of these malformations were found in one patient each. In that context, it is unclear whether the abnormalities found were causally related to an additional marker containing a minimal duplication of 2p (usually 2cen-p11 or 2cen-p13) or whether these markers were just randomly discovered chromosomal defects unrelated to the phenotype of the patient.

Trisomy for the medial segment of 2p

There are ~27 patients who are thought to have this type of trisomy 2p. Some of these patients had minimal abnormalities, whereas others had severe defects, some of which were not compatible with life. Because many patients had different breakpoints and a different size of trisomic segment, it is very difficult to compare their phenotypic manifestations.

The most common abnormality for this group was Pierre Robin complex (cleft palate, small chin and microglossia). This defect was found in at least 7 patients. Duplication of the segment 2p14p15 appears to be critical for the origin of Pierre Robin complex.

Brain defects were generally non-characteristic, but three patients with a common duplication of 2p16.1p16.3 had polymicrogyria. However, not every patient was examined for this abnormality. Hydrocephaly, macrocephaly, microcephaly, and partial agenesis of the corpus callosum were reported in one to two patients each.

The most common defects of the internal organs were heart defects, reported in seven patients. Three patients who had a common trisomic segment of 2p13p16.3 had pulmonary stenosis, and two who had a common trisomic segment of 2p13.2p16.1 had coarctation of aorta. It is not clear whether pulmonary stenosis and coarctation are different manifestations

of the same duplicated gene or whether this area harbors several genes involved in the formation of the heart and great arteries.

Anal stenosis was reported in three patients, all having a trisomy for a 2p21 segment. Absence of some teeth (adontia) or small teeth (microdontia) were reported in three patients trisomic for 2p21p23.

Three patients who all had a trisomy for the segment 2p14p21 had syndactyly, and three others had proximally implanted thumbs. Other defects of the skeletal system included pectus excavatum, kyphoscoliosis, and dislocation of the hips.

Defects of the eyes and ears are not characteristic, although there are isolated reports of microphthalmia, atresia of the auditory canal, and preauricular pits.

Two patients had hypoplastic kidneys. Two additional patients had incomplete intestinal rotation. Three males were found to have hypospadias.

There are reports of seizures or attention deficit disorder in several patients with this type of 2p trisomy.

Almost all cases of “medial” trisomy 2p are sporadic.

Distal trisomy 2p

Distal trisomy 2p as a sole abnormality is relatively rare; there are only 30 reports of patients with this pathology. Another 110 patients with distal trisomy 2p had additional imbalances, most of which were partial monosomies for other chromosomes due to familial translocations. Although only patients with “pure” trisomy will be used for the analysis of the phenotypic picture, additional information on persons with a more complex imbalance will be used for more precise localization of the segments responsible for various clinical manifestations.

All patients have a relatively mild delay in psycho–motor development. Facial dysmorphism is characteristic; most show a high prominent forehead with a frontal upsweep of hair, hypertelorism, short broad nose, narrow palate, maxillary hypoplasia, and small low–set ears (micrognathia) The most common eye defects are atrophy of the optic nerve (the common duplicated segment is 2p24.1p25) and microcornea (the common duplicated segment is 2p21p24.2). Minor defects of the trunk and limbs are common and include dolichostenomelia (unusually long limbs), long tapering fingers, and a “fan–like” position of the toes.

However, most patients do have serious defects of the brain and/or internal organs. Four of the 30 patients with “pure” distal trisomy 2p had neural tube defects (NTDs); two had anencephaly and two had spina bifida. It should be noted that NTDs (anencephaly, exencephaly, occipital encephalocele, and spina bifida) were also reported in 13 patients who had a distal trisomy 2p associated with a partial monosomy for a different chromosome. Generally, defects of the neural tube are very rare manifestations of structural autosomal imbalances. The critical segment containing the gene(s), which (when duplicated) lead to the formation of a NTD has been narrowed down to within 2p25. The wide spectrum of NTDs observed in patients with trisomy 2p indicates that all these defects may be caused by a

duplication of the same gene (or the same group of genes), although the gene(s) responsible for these defects have not been identified yet.

Heart defects have been reported in nine patients with “pure” trisomy 2p. In two patients, these defects were caused by an underlying situs viscerum inversum — a general defect of lateralization of internal organs. The critical segment for the gene(s) leading to situs viscerum inversum has been narrowed down to 2p23.2p24 (taking into consideration those patients with trisomy 2p and an associated imbalance). Another unusual heart defect, hypoplastic left heart, is caused by the genes within 2p24.2p25.1.

Two patients (including one with trisomy 2p and an associated imbalance) had lung agenesis — an extremely rare defect, especially among persons with chromosomal abnormalities. Both of these patients were trisomic for the very large segment 2p21p25.

Two patients with “pure” trisomy 2p (and two others with an associated imbalance) had diaphragmatic hernia. The critical segment for diaphragmatic hernia is the distal tip of 2p (2p25.3).

One patient with “pure” trisomy 2p (and at least six other patients with an associated imbalance) developed neuroblastoma — a tumor originating from cells of the sympathetic nervous system, usually in the adrenal glands. This tumor is caused by the duplication of the tiny MYCN gene, located at 2p24.3.

Postaxial polydactyly was found in three patients with “pure” trisomy 2p and in nine patients with trisomy 2p in association with another imbalance. The critical segment for postaxial polydactyly can be narrowed down to 2p24.2.

Ambiguous genitalia (XY–karyotype in persons with female external genitalia) were reported in several patients, including those with “pure” trisomy and in trisomy 2p in association with another imbalance. The critical duplicated segment for this defect is 2p23.2.

Generally, there is significant heterogeneity in clinical manifestations; some persons with the same duplication have numerous serious defects, while others only have facial dysmorphism and mild psycho–motor delay. This heterogeneity occurs even between affected siblings, although the size of the duplicated segment in such families must be exactly the same. Despite this, the distal part of 2p contains several genes, which (when duplicated) cause very serious defects of different organs. However, this does not mean that every child having a triplication of these genes will be affected.

Duplications and Trisomies of 2q

“Proximal” duplications of 2q

There is a small group of patients having duplications of the proximal, near–centromeric part of 2q, mainly from 2q11 to 2q21. Some of these trisomies were found upon cytogenetic examination of patients with various birth defects; others were randomly found upon examination of the family members of affected patients or after prenatal diagnostics. Surprisingly, 11 out of 28 known persons with such trisomies either have only mild dysmorphism or do not have any abnormalities. Other patients had a relatively wide spectrum of birth defects, but almost all abnormalities were reported in only one or two persons each. It

should be noted that four patients in this group had a triplication (not duplication) of the proximal 2q segment.

Repeatedly reported abnormalities included microcephaly (critical segment 2q13.3), agenesis of the corpus callosum (both reported patients had a triplication of the segment 2q11.2q21), glaucoma (critical segment 2q11.2q12), cleft palate (critical segment 2q11.2), hearing impairment (critical segment 2q12.3q13), cystic kidneys (both affected patients had a triplication of the segment 2q12.3q13), and hip dislocation (both reported patients had a triplication of 2q11.2q13). Two patients with a common duplication of 2q11.2q13 had epilepsy. Generally speaking, clinical manifestations in patients with triplications are more severe: all 4 patients had multiple abnormalities involving different systems.

Direct transmission from one of the parents was reported in several families with proximal duplication 2q. Therefore, cytogenetic examination of the parents is a necessary step for genetic counseling regarding further progeny.

Duplications of the “medial” part of 2q

Duplications of the “medial” part of 2q are uncommon; there are only 32 reports of patients in this group. The size of the duplicated segment and the precise boundaries of these duplications were different among patients. Generally, persons with such duplications have a complex of abnormalities in different systems. Only six patients who had duplications of relatively small segments or had mosaicism had no serious birth defects.

The most common defects involve the heart and kidneys. Congenital heart defects were reported in 11 patients. The spectrum of these defects varied from relatively mild abnormalities (eg, patent ductus arteriosus) to life-threatening defects (eg, tetralogy of Fallot, hypoplastic left heart, or dextrocardia with right-sided aortic arch). Most patients had a combination of several heart defects. All 11 patients with heart defects had trisomy for the segment 2q21q22.

Defects of the kidneys were reported in ten patients. The spectrum of these defects was highly unusual in that most patients had ectopia or dystopia of the kidneys, sometimes in association with a horseshoe kidney) or with the absence of one kidney. No patients had cystic kidneys or hydronephrosis, which is also unusual because these types of kidney abnormalities are common in patients with a structural chromosomal imbalance. The critical segment for kidney defects in these patients was 2q21q22.1, demonstrating that this segment must harbor a gene which, when duplicated, causes these defects of the kidneys.

Five patients in this group had cleft palate. The common duplicated segment for this defect again was 2q21q22. Postaxial polydactyly of the toes was reported in two patients sharing the duplication of 2q22q23. This same critical segment was common for three males who had hypospadias. Defects of the brain are uncommon; two patients had Dandy-Walker abnormality (common duplicated segment 2q21q31.1). Some patients had microcephaly, agenesis (or hypoplasia) of the corpus callosum, or diplomyelia. Numerous other abnormalities were reported in one patient each and include those of the eyes (microphthalmia, cataract), lungs (hypoplasia, anteriorly placed larynx), skeleton (scoliosis, hemivertebrae) and genitalia (uterus bicornis, vaginal atresia)

Several patients developed seizures, including four patients with a trisomy for a 1.5 Mb segment of 2q24.3. (Other patients with seizures did not have a trisomy for this segment.) Therefore, the “medial” part of 2q contains several segments, which (when present in three copies) can lead to the development of seizures.

There is one complex of symptoms— cleft palate, heart defects, and kidney defects —that is now designated a specific syndrome. This syndrome is caused by the duplication of the 2q21q22 segment. It is not clear, however, whether the syndrome depends on the duplication of one gene alone or on several genes, each responsible for a specific defect.

Trisomy for the distal segment of 2q

Trisomy for the distal part of the long arm of chromosome 2 (sometimes called 2q3 trisomy) is a well recognized entity. At least 60 patients are reported to have a trisomy for this segment as a sole abnormality, and ~100 have a distal trisomy 2q in association with a partial monosomy due to a translocation or inversion. Patients with distal trisomy 2q have growth retardation, delay in psycho–motor development, and a complex of cranio–facial abnormalities that allows for clinical recognition of the disorder in these patients. Most infants have a normal head circumference upon birth, but microcephaly is relatively common among children above three. Cranio–facial manifestations include prominent forehead, hypertelorism, short nose with a broad nasal bridge and anteverted nares, prominent nasal tip, long philtrum, thin upper lip, low–set large ears and micrognathia. Later in life, the nose becomes beaked. Small defects of the skeleton (eg, camptodactyly, partial syndactyly, brachydactyly) are very common.

Although patients present with a wide range of structural defects of the brain and internal organs, these abnormalities have been reported only in one to two patients each. Morphological defects of the skull and brain include trigonocephaly (critical segment 2q32.1q35) and craniosynostosis (critical segment 2q34qter).

Twelve patients had various heart defects; serious defects of the ascending aorta may be related to the duplication of 2q33.1q33.3, and ventricular septal defects, to the duplication of 2q36. Three patients sharing dup 2q32q33 had ventral ectopia of the anus. Numerous other defects, including those of the eyes, gastro–intestinal system, kidneys, and genitalia, were reported in one patient each.

There are 2 families (13 persons) in which isolated duplication of a ~1Mb segment within 2q31.1 produced a specific type of skeletal dysplasia (Kantaputra–type of mesomelic dysplasia). This dysplasia was caused by isolated duplications of the HOXD gene cluster. It should be noted that these patients were not included in the analysis of the “distal” 2q trisomy. In fact, no patient with a cytogenetically evident distal duplication 2q had this form of skeletal dysplasia.

Trisomy 2

Trisomy 2 is an exceptionally rare pathology. There are several reports of trisomy 2 being found only in placental tissue when the fetal tissues had a normal karyotype. This can happen if abnormal cell division occurs early in embryonal development (at the blastocyst stage), meaning that only placental tissue (or cells which will become placental tissue) have a

trisomic clone. Even when trisomy 2 cells are limited to the placenta, there is significant growth retardation in the fetus. One such fetus had an omphalocele. Fetuses with trisomy 2 may be subdivided into fetuses with full trisomy 2 (all cells have trisomy 2) and mosaics (some cells have trisomy 2, other cells have a normal karyotype).

Full trisomy 2 has been reported only four times: three of these fetuses were acardiac twin fetuses (with cytogenetically and clinically normal twins). One non-mosaic fetus with trisomy 2 had encephalocele, spina bifida, hypoplastic left heart, and fused kidneys. Full trisomy 2 is not compatible with life.

There are 10 reports of mosaic trisomy 2. This group includes both aborted fetuses (pregnancy terminated after prenatal diagnosis) and newborns who were diagnosed after birth. Phenotypic manifestations depend on the percentage of trisomic cells and their distribution. All fetuses and children had various birth defects.

Microcephaly was reported twice. There are reports of hypoplastic corpus callosum, micropolygyria, pachygyria (unusually thick convolutions of the cerebral cortex), and delayed myelination. Two fetuses had spina bifida (neural tube defects also were found in a fetus with non-mosaic trisomy 2). Two patients had cleft palate or cleft lip and palate. Live-born children have facial dysmorphism and an obvious delay in psycho-motor development.

Additionally, heart defects were found in two children. Diaphragmatic hernia was reported three times. Defects of the urinary system are relatively common and include agenesis of one kidney, cystic kidneys, hydronephrosis, and ureteral reflux. There are sporadic reports of uterus unicornus and ovarian cyst. Defects of the gastro-intestinal tract include duodenal atresia, Hirschsprung's disease, absent gallbladder, and incomplete intestinal rotation. Some children had multiple defects. Others had isolated abnormalities, including polymicrogyria and hypomelanosis of Ito (streaks and whorls of depigmentation on the skin).