Chromosome 3

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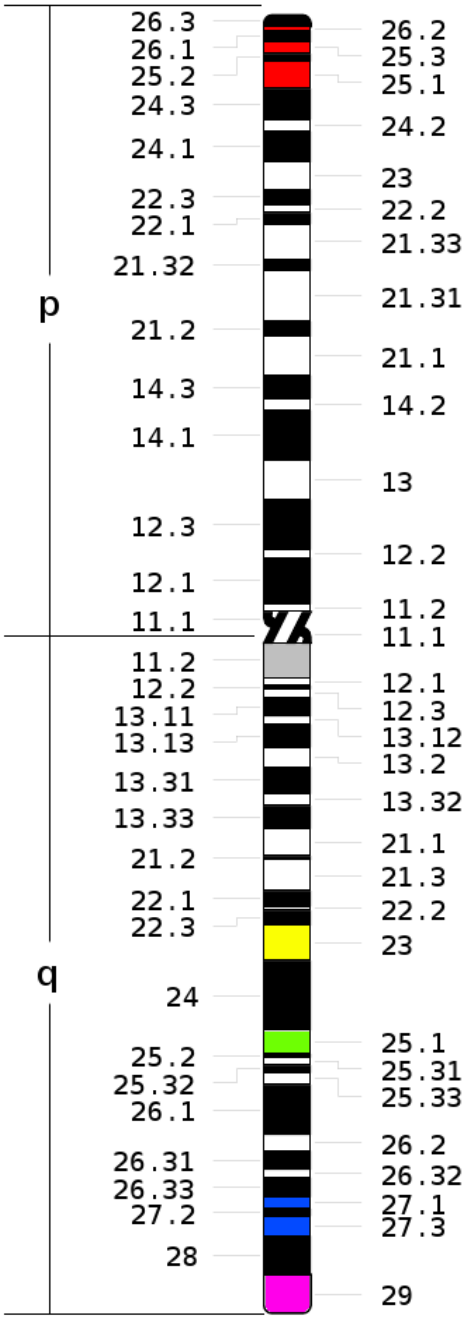

Introduction

The size of chromosome 3 is ~200 Mb. Within this chromosome, there are thousands of genes, many of which are necessary for normal intellectual development or involved in the formation of body organs.

Deletions of Chromosome 3

The length of the short arm of chromosome 3 is ~90 Mb. Most known deletions of 3p are caused by the loss of its distal 15 Mb segment (3p25–pter). Deletions of the more proximal segments are relatively rare; there are only ~50 reports on such patients. Therefore, it would be premature to talk about any syndrome related to deletions of the proximal part of 3p. The location of the breakpoints, size of deletion, and reported abnormalities are different in most described patients. However, recurrent aortal stenosis in patients with deletion 3p11p14.2, abnormal lung lobation in patients with deletion 3p12p14.2, agenesis or hypoplasia of the corpus callosum in patients with deletion 3p13, microphthalmia and coloboma in patients with deletion 3p13p21.1, choanal atresia and absent gallbladder in patients with deletion 3p13p21, and hearing loss in patients with deletion 3p14 are all indicators that the above–mentioned segments likely contain genes involved in the formation of these systems.

Deletions of 3p

Deletion of 3p25–pter

The most distal segment of the short arm of chromosome 3 is 3p26 and spans ~8 Mb. The more proximal segment 3p25 spans ~11 Mb. Each of these segments may be subdivided into three “sub–segments”. There are approximately 120 known patients who have sole

deletions of the distal part of 3p without any additional chromosomal imbalance. Since not all patients were described in detail, the clinical analysis here is based on only the 70–75 with full reports.

Patients with deletions involving only sub–segment 3p26.2–3p26.3 usually are affected very mildly. Ten known persons with such deletions were completely normal; their deletions were either found by chance or after the birth of a child with a similar deletion and some clinical abnormalities. These data show that the deletion of 3p25 (and possibly part of 3p26.1) is crucial for the typical manifestations of the 3p25–pter deletion syndrome. Most deletions are terminal; interstitial deletions (usually deletion 3p25.3p26.3) have been found in 10 patients.

Babies with this deletion usually are born at term (or almost at term), but the birth weight is usually low. Most individuals remain short and small. Head circumference is usually at the lower end of the norm at birth and remains so as the child grows. Approximately one-third of children over 6 months old are diagnosed with microcephaly. Babies have low muscle tone and suck weakly. Many develop gastro–esophageal reflux.

All patients with deletions involving 3p25-pter have developmental delay, but the severity of delay varies from person to person. Seizures have developed in ~20% of patients. Ptosis, blepharophimosis (short eye slits), brachycephaly, low–set ears, and micrognathia are the most characteristic facial features. Preauricular pits or sinuses are frequently reported and postaxial polydactyly was found in ~25% of patients. Another frequent manifestation of the syndrome is hearing impairment. The ATP2B2 gene is responsible for this symptom and is located within 3p25.3. (The particular study that identified this gene was performed with the participation of several CDO members.) Hypothyroidism has been found in several children, but only a small number had tests to diagnose (or exclude) this condition. The most likely location of the gene responsible for hypothyroidism is 3p26.1. The association of blepharophimosis, hypothyroidism, polydactyly and mental retardation was described in the 1980's as a separate syndrome, known as Yunis–Simpson syndrome. In 1995, Moncla et al reported on a patient who had all of these manifestations and a deletion of the distal part of 3p and, therefore, proposed that some patients reported as having Young–Simpson syndrome may actually have deletion 3p. In 2009, reexamination of one of the patients who was initially reported (in 1989) as having Yunis–Simpson syndrome showed that he did indeed have deletion 3p25-pter.

Although most patients with this syndrome do not have any defects of internal organs, 25% of patients do have congenital heart defects. The most common type of heart defect is atrio–ventricular septal defect, a condition in which there is a defect in the wall dividing the atria and ventricles. Some of the heart defects can be very serious and require surgical intervention. A gene responsible for heart defects has been narrowed down to 0.2 Mb within 3p25.3, but the genes known within this segment do not appear to be involved in heart development.

Defects of the kidneys are relatively common (~15%). Hypoplastic kidneys, cystic kidney, horseshoe kidney, and duplication of the collecting system were reported in several patients each. Five patients had atresia, ectopia or stenosis of anus. Some males have hypospadias. Most genes responsible for the clinical manifestations of 3p25-pter syndrome reside within the 3p25 segment, but; deletion of 3p26.1 appears to be responsible for the intellectual disability and hypothyroidism.

Because the syndrome affects many different systems, patients should be seen by a team of specialists (eg, cardiologist, endocrinologist, neurologist, ENT–specialist, urologist).

From the genetic point of view, cytogenetic investigation of the parents is needed for the genetic prognosis. There are 6 known families where the children inherited the deletion from their mothers who were either clinically unaffected or had only minimal manifestations. When parental karyotypes are normal, recurrence risk is negligible.

Deletions of 3q

The genetic size of the long arm of chromosome 3 is ~110 Mb. There are 35 reports of patients having “proximal” 3q deletions, from the centromere to 3q23. These patients are very heterogeneous in regard to clinical manifestations, size of the deleted segment, and position of the breakpoints. Based on observations of 12 patients with deletions involving (but not limited to) del(3)(q13.11q13.12), Simovich et al. (2008) found that prominent forehead, epicanthus, hypertelorism, flat nasal root, scoliosis, and developmental delay were recurrent features. However, since these manifestations are common for other syndromes caused by chromosomal rearrangements, the authors were unable to postulate a description for proximal 3q microdeletion syndrome as a unique entity. Many other abnormalities found in these patients were absent in patients with deletions limited to del(3) (q13.11q13.12); most likely, these abnormalities were caused by deletions of more proximal and/or more distal segments of 3q. Further observations are necessary to confirm (or reject) the existence of a syndrome associated with deletion 3q13.1.

From analysis of known publications, one can conclude that the proximal 3q segment contains genes responsible for these manifestations: 1) delayed cranial ossification (3q13.11); 2) seizures (3q13.2q13.31); 3) omphalocele, a condition in which the intestine is covered only by a thin membrane and protrudes outside the abdomen at the umbilicus) (3q13.2q21); cleft palate (3q21.3q22); holoprosencephaly (3q22); and diaphragmatic hernia (3q22). Furthermore, evidence indicates that the proximal part of 3q must harbor at least 2 genes involved in the development of the corpus callosum and at least 3 genes related to cardiac defects. However, it is premature to propose that any syndrome is associated with deletions of this part of 3q.

Deletions of 3q23 and Blepharophimosis–ptosis–epicanthus Inversus Syndrome

Blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) is a well known genetic disorder, and is described in terms of its symptoms: short narrow horizontal apertures of the eyelids, usually 5–7 mm less than normal (blepharophimosis); drooping of the upper eyelid (ptosis), and a small skin fold arising from the lower eyelid and running inwards and upwards (epicanthus inversus). These manifestations produce problems with vision and may require surgical intervention. Typically, patients with this syndrome do not have other abnormalities, although premature ovarian failure has been reportedly found in type I of BPES. The syndrome is inherited as an autosomal dominant trait and, in most cases, is caused by mutation of the FOXL2 gene, which has been mapped to 3q23.

Intragenic mutations, however, are not the only mechanism for the origin of BPES. Analysis of a large cohort of BPES patients showed that a significant number of these patients have chromosomal abnormalities — either deletions of 3q23 and its adjacent regions or balanced

translocations in which one of the chromosomes is broken within 3q23. According to the literature, these deletions have been observed in 50 patients with BPES. Usually, those patients with deletions lose not only the FOXL2 gene, but also some neighboring genes. As a result, most of these patients are developmentally delayed. Some of them have other eye defects, such as microphthalmia, microcornea, dislocated lens, optic atrophy, or alacrimia (inability to produce tears); these eye defects are not typical for those patients with intragenic mutations. Several other manifestations were repeatedly found in BPES patients with these deletions—namely, microcephaly, cleft palate, heart defects (ventricular or atrial septal defects, and bicuspid aortic valve), contractures, camptodactyly, dislocation of the hips, and inguinal hernias. These defects are usually not life–threatening.

From the genetic point of view, detailed examination of each family is necessary for a genetic prognosis. Almost all chromosomal rearrangements in BPES are sporadic, with minimal recurrence risk for further children of the couple. Most intragenic mutations are inherited, and therefore, the genetic prognosis is typical for that of other autosomal–dominant conditions.

Deletion of 3q24q25.1 and Dandy–Walker Malformation

Dandy–Walker malformation (DWM) is an association of hypoplastic cerebellar vermis and cystic dilatation of the 4th ventricle. Individuals with this defect usually exhibit ataxia, hypotonia (floppiness, delayed motor development, and sometimes, hydrocephaly). DWM may be caused by intragenic mutations or may by a component in syndromes caused by chromosomal defects.

DWM may be caused by deletions of two linked genes, ZIC1 and ZIC4, both of which reside in the distal part of 3q24 (very close to 3q25.1). Approximately 15 patients having deletions within 3q24q25.1 had this defect. In addition to the common manifestations of DWM, children are usually developmentally delayed, and some of them have microcephaly. The spectrum of associated defects depends on the length and content of other parts of 3q lost upon deletion. If the deletion involves 3q23 (and the FOXL2 gene), they may also have manifestations of BPES (four such patients are known). Other frequently associated defects are hydrocephaly and heart defects (most commonly ventricular septal defect). Some patients have microphthalmia, hypoplastic optic nerve, agenesis of the corpus callosum, hypoplastic kidneys, and politelia (additional nipples).

It should be noted that DWM is not an obligatory manifestation of deletion 3q24q25.1. There are several patients with this deletion (including those whose breakpoints were confirmed by molecular methods) who do not have DWM but do have seizures, microcephaly, and a defect of the scalp in the occipital area. Deletions in all reported patients in this group have been sporadic so far.

Deletion of 3q26.33q27 and Anophthalmia

Anophthalmia (complete absence of the eyeball) is very uncommon in patients with chromosomal rearrangements. The finding that several patients with anophthalmia also had deletions of the distal part of 3q or balanced translocations involving 3q27, led to the discovery that the SOX2 gene was involved in the origin of this defect. SOX2 is located at 3q26.33q27 and is critical for the development of the human eye. Further investigations showed that this gene is also responsible for anophthalmia–esophageal–genital (AEG)

syndrome. In fact, intragenic mutations of the SOX2 gene lead to complete manifestation of AEG–syndrome. AEG syndrome includes anophthalmia, esophageal atresia (usually with trachea–esophageal fistula), and hypospadias or cryptorchidism in males, as well as defects of the kidneys (hypoplasia, horseshoe kidney, or duplex kidney), and abnormal formation of the vertebral column (hemivertebrae and abnormalities of the ribs).. Mutations of the SOX2 gene were also found in a significant number (10%) of patients who had anophthalmia or microphthalmia, but no other abnormalities.

Because the SOX2 gene is located at 3q26.33q27, deletions of this region may produce an association of anophthalmia with some of these defects. Currently, there are 12 reports of patients having these abnormalities as a result of this deletion; several more have balanced translocations with breakpoints in the vicinity of the SOX2 gene. Some patients had bilateral anophthalmia; in several other children anophthalmia on one side was accompanied by microphthalmia on the other side. Bilateral microphthalmia was found in three patients. Esophageal atresia was found in only one patient, another two had 13 pairs of ribs, and one had laryngeal cleft.

Although not typical for AEG–syndrome, arhinencephaly, cleft lip and/or palate, choanal atresia, heart defects, and atresia ani are found in most of these patients as well and may be attributed to the neighboring deletion of 3q28. Generally, deletion of 3q26.33q27 is very rare. However, the possibility of a deletion involving the SOX2 gene should be considered in any child with anophthalmia or microphthalmia.

So far, all reported observations of this deletion were the result of a de novo chromosomal aberration.

Deletion 3q29 Syndrome

With implementation of molecular cytogenetics, it has been possible to delineate several new syndromes, including 3q29 deletion syndrome. In most patients, there was an almost identical loss of 1.5–1.6 Mb in 3q29 (197.3 Mb – 198.9 Mb), whereas the most distal area of 3q (~1 Mb) remained intact. Genetically, the structure of this segment of 3q predisposes it to such microdeletions (and reciprocal microduplications) due to non–allelic homologous recombination.

Approximately 40 patients with 3q29 deletion syndrome have been reported in the literature. Clinically, patients show a wide range of abnormalities, although genetically they are very similar. The most common manifestation is developmental delay, especially speech delay, which is found in all but three patients. However, in most cases, this delay is relatively mild. A significant number of infants had low birth weight; most patients have a short stature and a slim build. Autistic features were reported in five patients; some children had attention deficit hyperactivity disorder, and some adults had hallucinations.

Microcephaly is relatively frequent (~30%). Some patients have brachycephaly or trigonocephaly (triangular shape of the forehead as a result of premature ossification of the metopic suture). The nasal bridge is usually high and the philtrum is short; many patients have dysplastic ears. Widely set irregular teeth has been reported in several patients. Long tapering fingers, pectus abnormalities, and hypospadias also are relatively common findings.

Heart defects (pulmonary stenosis, patent ductus arteriosus, and stenosis of the mitral valve) have been found in seven patients and are usually mild. Numerous abnormalities (microphthalmia, cataracts, diaphragmatic hernia, pyloric stenosis, horseshoe kidney, and syndactyly of the third and fourth toes) were reported in one patient each. It is not clear whether these defects are rare manifestations of the syndrome or individual characteristics of the given patient not caused by 3q29 deletion.

A significant number of patients with deletion 3q29 inherited the deletion from one of the parents. There are seven known families where direct transmission of the deletion occurred; carriers of the deletion were found on both the maternal and paternal sides of the family. Usually the parent who was found to have a deletion had mild clinical manifestations (minor dysmorphic features, if any, and mild intellectual defect, sometimes only a learning disability).

Genetic prognosis for the parents of the affected child will depend on their karyotypes: it will be very low if parental karyotypes are normal and 50% if one of the parents has a deletion. The person with the deletion has a 50% risk of transmission of this deletion to his/her children.

Ring Chromosome 3

Ring chromosome 3 is one of the rarest types of ring chromosomes. Since 1966, when the first patient with ring chromosome 3 was reported, there have been only 13 more known patients with this anomaly. One of these patients also had a translocation of the part of the deleted segment onto another chromosome 3.

There is no syndrome associated with ring chromosome 3. Delay in psycho–motor development was the only abnormality common for all patients. Clinical manifestations are highly heterogeneous, and serious defects of the internal organs are uncommon. One patient had a heart defect (atrio–ventricular communication), and another had only one kidney and atresia ani; a third person had enlargement of the spleen (Banti syndrome), which had not been reported in either forms of chromosome 3 deletions. Four patients had hypospadias, and two had absent (or hypoplastic) thumbs. Other defects (coloboma, microcephaly, syndactyly, and hip dislocation) are reported in one patient each. Direct transmission of ring chromosome 3 from a parent to a child is not known.

Partial Trisomies for Chromosome 3

Partial Trisomies for 3p

Trisomy 3p1

There are only a couple dozen reports regarding isolated trisomies for the proximal segment of the short arm of chromosome 3. In almost all patients, the exact position of breakpoints and the size of the duplicated segments were different.

There is no recognized syndrome caused by the trisomy 3p1 segment. Some patients had a delay in psycho–motor development; others did not have any psychomotor or mental problems. However, at least five patients were obese.

Congenital abnormalities were reported in five patients and included microcephaly, agenesis of the corpus callosum, Dandy–Walker malformation, cleft palate, congenital heart defects, and a narrow auditory canal. All of these defects were noted in one patient each.

Several patients had behavioral problems, including attention deficit hyperactivity disorder. However, it is not clear whether these behavioral characteristics were causally related to their proximal 3p duplication.

Trisomy 3p21p24

Trisomy 3p21p24 is a well–recognized syndrome, although isolated trisomies for this segment of the short arm of chromosome 3 are very rare: While there are only 26 reports of such patients, more than 80 had a trisomy for this segment of 3p in association with a partial monosomy of another chromosome as a result of a translocation. Clinical manifestations in such persons will depend on the nature of both the trisomy 3p and the associated imbalance of the other chromosome. However, a comparison of manifestations in the group of patients as a whole allows for delineating the complex of symptoms caused by trisomy 3p.

Most patients with isolated trisomy 3p21p24 have a normal head circumference and normal weight at birth, but exhibit a relatively mild delay in psycho–motor development. Typical facial characteristics include brachycephaly, frontal bossing, hypertelorism, square–shaped face, short nose, prominent cheeks, down–turned mouth corners, micrognathia, low–set dysmorphic ears, and a short neck. Most patients also have significant defects of the internal organs and/or the brain. Out of the 26 known patients with isolated trisomy for this segment, only eight did not have these defects.

Patients with an association of trisomy 3p and a partial monosomy for other chromosomes have some additional abnormalities, but by analyzing this group as well, one can obtain more complete data on recognizing the phenotypic spectrum of this trisomy. Data regarding the main abnormalities in patients with isolated trisomy 3p21p24 and in those with an additional imbalance are presented in Table 3.1.

Table 3.1. Main Birth Defects in Patients with Trisomy 3p

	Isolated Trisomy 3p		“Associated” Trisomy 3p	
Birth Defect	3p21p24 (n=26)	3p25pter (n=23)	3p21p24 (n=82)	3p25pter(n= 44)
Congenital heart defects [total]	10	4	53	15
a. VSD	3	–	22	2
b. PDA	3	1	8	4
c. ASD	1	1	13	8
d. TOF	1	–	8	3
e. Pulmonary stenosis	1	1	6	–
f. DORV	–	–	3	1
g. TGA	–	–	2	–

h. Dextroposition of aorta	–	–	3	–
Cleft lip and palate	4	–	11	4
Cleft palate/bifid uvula	–	1	8	3
Holoprosencephaly	–	–	18	4
Spina bifida	–	–	4	1
Dandy–Walker anomaly	–	2	3	1
Microphthalmia	1	1	5	5
Diaphragmatic hernia	1	–	2	–
Esophageal atresia	1	–	1	1
Hydronephrosis	1	–	6	–

ASD — atrial septal defect; DORV — double outlet of the right ventricle; TGA — transposition of the great arteries; TOF — tetralogy of Fallot; VSD — ventricular septal defect.

The most common visceral defects in trisomy 3p2 are heart defects, which were found in 10 out of 26 patients with isolated trisomy 3p2 and in 53 out of 82 patients having an additional chromosomal imbalance. The increased incidence of heart defects in persons with an additional imbalance may be explained in two ways: 1) genetic material lost from other chromosomes contains some genes involved in the formation of the heart; 2) an additional imbalance increases activity of triplicated genes of the 3p segment. A spectrum of heart defects in persons with isolated trisomy 3p is typical for all chromosomal abnormalities. The vast majority of patients had ventricular or atrial septal defects or patent ductus arteriosus. Only one child had tetralogy of Fallot. Patients who have trisomy 3p2 in association with an additional imbalance have more serious heart defects; tetralogy of Fallot was diagnosed in eight patients, two had a transposition of great arteries, and three had double outlet of the right ventricle.

Cleft lip and palate was reported in four patients with an isolated trisomy 3p2 and in 11 patients having an additional imbalance. Eight additional patients had cleft palate or bifid uvula. Microphthalmia was found in one patient with an isolated trisomy 3p and in five patients with an additional imbalance. Other eye defects are non–characteristic.

While patients with an isolated trisomy 3p2 did not have serious brain abnormalities, such defects as holoprosencephaly (HPE), spina bifida, agenesis of corpus callosum or Dandy–Walker malformation, were repeatedly found in patients having trisomy 3p2 in association with other chromosomal defects.

HPE was reported in 18 out of 82 persons in the “associated” group. In patients with associated monosomy 7q36 or 13q32, this defect can be explained by the loss of HPE–related genes in these specific areas. However, HPE was also reported in patients who had an associated monosomy of 2q37, 3p26 or 4q35. None of these bands is known to be an HPE–related area. In that context, it is speculated that the short arm of 3p is an area that presumably contains the gene(s), which (when triplicated), can lead to HPE. The most likely location of this gene (or these genes) is 3p25, but the nature of the gene(s) remains unknown. There is strong evidence that the HPE–related gene(s) within 3p can interact with other HPE–related genes. For example, the SHH gene on 7q36 may be implicated since patients with

trisomy 3p in association with monosomy 7q usually have much more severe forms of HPE than patients with isolated monosomy 7q.

Four patients with trisomy 3p2 and an associated partial monosomy (different in all affected) had spina bifida. Therefore, the segment 3p23.2p26 (Deletion was common for all four patients.) has to harbor gene(s) leading to spina bifida. Other types of neural tube defects have not been reported in these patients. Several patients with trisomy 3p2 and an associated monosomy had Dandy–Walker malformation or agenesis of the corpus callosum. Consequently, there is good reason to believe that these two defects are also caused by genes within 3p2.

Defects in other systems are observed less frequently. One person with isolated trisomy 3p2 and two persons with the trisomy and an associated imbalance had diaphragmatic hernia. The critical segment for this defect is 3p24.3pter. Esophageal atresia was reported in one patient with an isolated trisomy 3p2 and in another with duplication of 3p2 in association with deletion 4q35. Other rarely reported defects include hydronephrosis, duplication of the ureter and hypospadias. Seizures and autism are uncommon, although several patients with these manifestations have been reported. All of these defects occur more frequently in patients with an associated imbalance.

Distal trisomy 3p (3p25p26)

As an isolated defect, trisomy of the distal part of 3p (3p25p26 or 3p25pter) has been reported in 23 patients. Trisomy for this same segment in association with a partial monosomy of other chromosomes has been reported in 44 patients.

External manifestations of patients with distal trisomy 3p are basically the same as manifestations in patients with trisomy 3p21p24.

Congenital heart defects were reported in four patients, none of whom had life–threatening abnormalities. Among the 44 patients who had distal trisomy 3p with an associated monosomy, 15 had heart defects including three with tetralogy of Fallot and one with double outlet of the right ventricle.

Cleft lip and palate was reported in four patients with an associated imbalance, but not in patients with isolated distal trisomy 3p. Cleft palate alone was reported in three patients having an associated imbalance but in only one patient with an isolated distal trisomy 3p.

Four patients with an associated imbalance had holoprosencephaly (HPE) (including one with an associated deletion of 4q35qter, an area not known to contain HPE–related genes). In that context, segment 3p25p26 is a likely location for HPE–related genes on 3p. Two patients with an isolated distal trisomy 3p had Dandy–Walker malformation (critical segment 3p26).

Unlike those with trisomy for the more proximal segments of 3p, patients with distal trisomy 3p did not have hydronephrosis, polycystic dysplastic kidneys, duplicated ureter, or diaphragmatic hernia. Comparison of manifestations in patients with isolated and associated variants of distal trisomy 3p is presented in the table 3.1.

Partial Trisomies for 3q

The long arm of chromosome 3 is very large and measures ~105 Mb. The whole long arm may be arbitrarily divided into three segments: segment 3q1 (~31 Mb), segment 3q21q26 (~50 Mb), and segment 3q27qter (~23 Mb).

Trisomies for the segment 3q1 are exceptionally rare. There are less than 10 reports about persons having such trisomies. Although some patients had serious defects (eg, HPE, microcephaly, and diaphragmatic hernia), these abnormalities were reported in only one patient each. Several patients with relatively large (20 Mb) duplications of 3q11q13 did not have any serious defects. The clinical significance of duplications of this segment remains basically unknown.

Trisomies for the segment 3q21q26 (or part of this segment) have been reported in 22 patients. More than half (13) had a delay in psycho–motor development, but none had serious morphological abnormalities.

The most common internal anomalies were heart defects, reported in six patients. These defects included tetralogy of Fallot and endocardial cushion defect. Heart defects in other children were not life–threatening.

Two patients had cleft lip and palate and two others had cleft palate only. Hearing impairment was reported in four persons. Other defects reported were agenesis of the corpus callosum (2), coloboma (2), brachydactyly (2), and hypoplastic or proximally located thumbs (2). All other abnormalities were found in one patient each.

The existing data is not sufficient to consider trisomy 3q21q26 as a recognizable syndrome.

Distal trisomy 3q

Trisomy for the distal segment 3q26q29 (or 3q26qter) is a well–known syndrome. There are 60 published reports of patients having this trisomy as a sole abnormality. Actually, this group includes 12 patients with a triplication (not duplication) of 3q, although most patients with tetrasomy were mosaic. Most patients had a trisomy for a larger segment (usually 3q23qter or 3q25qter), but trisomy 3q26q29 (or 3q26qter) was present in all of these patients.

More than 110 patients had a trisomy for this segment in association with monosomy 3p (as a result of pericentric inversion) or with a monosomy for another chromosome (as a result of translocation). A sufficient number of patients with an isolated distal trisomy 3q exists to analyze this syndrome without additional data on manifestations in those patients with an associated imbalance. Nevertheless, this latter group is useful for localizing the segments of 3q responsible for some abnormalities.

Typical manifestations of distal trisomy 3q syndrome include a severe delay in psycho–motor development, prenatal hypoplasia (low birth weight in babies born at term), microbrachycephaly, short limbs, excessive growth of hair (hirsutism), short upturned nose, low–set ears, and synophrys (meeting of the medial eyebrows in the midline). Since all of these findings are also typical for Cornelia de Lange syndrome, it was thought that the syndrome was caused by a small duplication within 3q. However, a significant difference

between trisomy 3q and Cornelia de Lange syndrome exists, and that theory has been disbanded. It is now known that Cornelia de Lange syndrome is caused in most instances by mutations of the NIPBL gene within 5p13.2 (or deletions of this area of 5p).

Almost all patients with distal trisomy 3q have multiple defects of the brain, eye, internal organs and extremities. Seven patients had craniosynostosis, five had neural tube defects (four had spine bifida and one had encephalocele). Dandy–Walker malformation was reported in seven patients and agenesis of the corpus callosum in two others.

The most common eye defects were cataracts and glaucoma, reported in four patients each. Cataracts are relatively frequent in a structural autosomal imbalance, but glaucoma is a very rare manifestation. Two children had microphthalmia. Numerous other eye defects were found in one person each. Only one patient had cleft lip, but four had cleft palate and five others had bifid uvula. Seven patients had preauricular dimples.

The most frequent internal abnormalities were heart defects, reported in 22 patients. However, life–threatening defects (interrupted aortic arch, tetralogy of Fallot, single ventricle, double outlet of the right ventricle) were uncommon.

Reported kidney defects include cystic kidneys (5), hydronephrosis (4), duplication of the renal collecting system (4), and ureteral reflux (3).

Four patients with a pure distal trisomy 3q had omphalocele, a defect not generally observed in chromosomal syndromes.

Defects of the loco–motor system include proximally placed thumbs (9), postaxial polydactyly (4), hip dysplasia (5). Brachydactyly, contractures, syndactyly and preaxial polydactyly were also noted.

Abnormal skin pigmentation, usually manifesting as streaks of hypopigmented areas, was reported in 10 patients, some of whom had mosaicism.

Vital prognosis depends on the severity of the internal defects and the brain abnormalities. The additive effects of these defects in one person leads to a significant limitation in life span.

While neural tube defects, craniosynostosis, glaucoma, omphalocele, post– and pre–axial polydactyly were all uncommon findings in distal trisomy 3q, they were reported more frequently in patients with trisomy 3q in association with 3p monosomy (as a result of inversion) or with other chromosomes (as a result of translocation). Comparison of minimal trisomic segments in persons with isolated and “associated” trisomies [Table 3.2] may help in localizing chromosomal segments responsible for the origin of these defects. Absence of these defects in patients with trisomies 3q28qter or 3q29qter indicates that the segment 3q26q27 harbors genes, which (when duplicated), might cause all of these abnormalities.

Table 3.2. Comparison of critical segments responsible for some manifestations of trisomy 3q.

Birth Defect	Isolated distal trisomy 3q (n=59)		“Associated” distal trisomy 3q (n=110)	
	Number of	Common duplicated	Number of	Common duplicated

	patients	segment	patients	segment
Neural tube defects	5	3q26.2q29	7	3q25.1q27
Craniosynostosis	7	3q27q28	8	3q27qter
Glaucoma	4	3q26.2qter	8	3q26qter
Omphalocele	4	3q26qter	10	3q27.3qter
Postaxial polydactyly	4	3q26.2qter	9	3q26.1qter
Preaxial polydactyly	1	3q12qter	3	3q21qter

Trisomy 3q29

Over the last several years, at least 30 patients with isolated duplications of 3q29 have been identified, thanks to the use of molecular methods of examination. Seven of these patients had congenital defects. Four of them had congenital heart defects, including one patient with tetralogy of Fallot; two had cleft lip and palate. Microcephaly, craniosynostosis, esophageal atresia, anal atresia, and kidney agenesis were reported in one person each. Other patients were examined due to diabetes, ataxia or dysmorphic features. At least half of all known persons with duplication 3q29 do not have any abnormalities, but were examined because of clinically affected relatives. Currently, the real significance of isolated duplication 3q29 has yet to be clarified.

Trisomy 3

Trisomy 3 is an extremely rare condition. In five out of 15 known cases the trisomy was found only in placental cells. All children with confined placental mosaicism were clinically normal, and nine of ten patients who had trisomy 3 in their cells were found to be mosaic. Usually, trisomy 3 is found only in a small proportion of cells.

Facial dysmorphism was observed in four patients. Two males had cleft lip and palate. Defects of the eyes include cataracts (4), microphthalmia (2), and coloboma and cataracts (one each). Hearing impairment was reported in two patients.

Brain defects are rare. There are sporadic reports of microcephaly and hypoplastic cerebellum.

Four patients had congenital heart defects, including one patient with tetralogy of Fallot and another with dextrocardia and pulmonary isomerism.

Defects of the gastro-intestinal tract include ventral ectopia of anus (1) and intestinal malrotation (1). One child had hepatoblastoma (tumor of the liver), but the child also had a clone with a deletion of chromosome 21.

Defects of the loco-motor system include scoliosis (2), dislocation of hips (2), vertebral anomalies, pectus excavatum, and syndactyly of second and third toes.

Two patients had failure to thrive despite not having any serious morphologic abnormalities. Delay in psycho-motor development is common, but the severity of delay depends on the percentage and distribution of trisomic cells.