



Chromosome 1

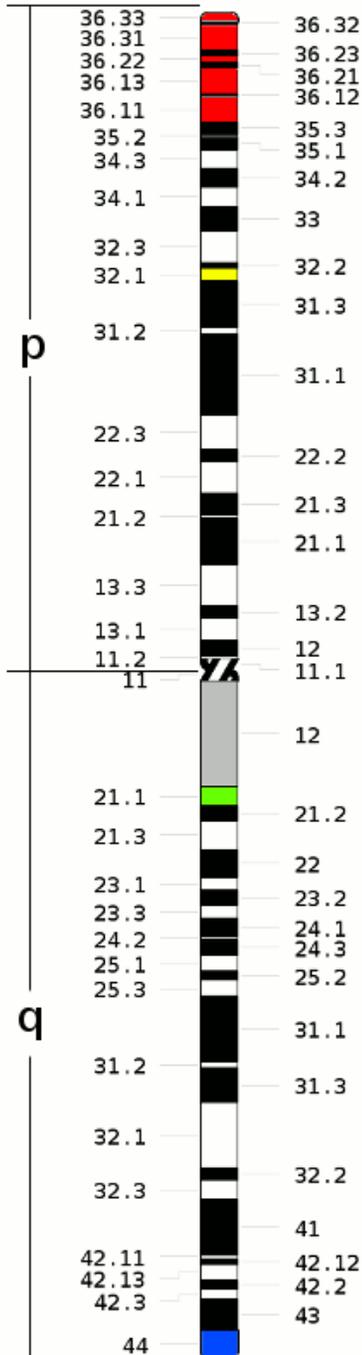
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Introduction

Chromosome 1 is the largest of the human chromosomes. It contains almost 8% of the whole genetic material. Its genetic length is ~246 Mb. The short arm and the long arm (~125 Mb) are almost equal in size. Chromosome 1 has ~3,000 genes. Many hundreds of these genes are related to mental development and the formation of body organs. Deletions or duplications of these genes can lead to numerous abnormalities, which can result in both physical (birth defects) and functional (eg, seizures, autism, and hearing impairment) anomalies.

Methods of molecular cytogenetics—namely, fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH)—are now available and allow recognition of very small deletions and duplications. As a result, many previously unknown microdeletion and microduplication syndromes have been delineated. Other new syndromes are emerging literally every month.

Deletions of Chromosome 1

There are numerous reports of different kinds of abnormalities of chromosome 1, including hundreds of reports of patients with chromosome 1 deletions. The most frequent chromosome 1 deletions are deletion 1p36 (almost 80% of all reported patients with deletions of 1p have this syndrome), deletion 1q21.1, and deletion 1q43q44. Although deletions of almost all other segments of 1p and 1q have been reported, these deletions are relatively rare and involve different (usually unique) combinations of deleted genes. It is therefore difficult to describe the medical problems associated with these unique occurrences.

Deletions of 1p

Deletion of 1p36

The whole 1p36 segment is relatively large (~ 28 Mb). However,

most patients have deletions of 3–4 Mb in the distal part of 1p36 (near the end of the chromosome). For example, the cytogenetic abnormality in patients tested using FISH or CGH might be written as del(1)(p36.2), del(1)(p36.22), or del(1)(p36.23). Such small deletions cannot be recognized using standard cytogenetic tests, which is why it was not recognized before 1990, despite the fact that this syndrome occurs relatively often. Some investigators believe that it affects ~1:5000 newborns.

Approximately 10% of patients have interstitial deletions, meaning the deletion occurs within the segment and preserves the most distal part of 1p36. The cytogenetic formulas in such children would be written as del(1)(p36.32p36.33), if the deletion involved 2 sub-bands, or del(1)(p36.33p36.33), if the deletion involved only one sub-band. Another 10–15% of patients have more complex rearrangements, sometimes involving other chromosomes.

Clinical studies have shown that patients with terminal and interstitial deletions of the distal part of 1p36 have very similar clinical manifestations. There is no strong correlation between the severity of the syndrome and the size of the deleted segment. Several investigators have reported that even children with non-overlapping deletions in this area can have the same set of abnormalities. This is possible in cases where the clinical manifestations are the result of a positional effect of rearrangement, and not the effect of missing genes. From a clinical standpoint, one can then analyze all cytogenetic variants as one entity under the name 1p36 deletion syndrome. There has been speculation that up to 1% of all patients with intellectual disability of unknown origin may have deletions within 1p36. It should be noted, however, that deletions affecting the proximal part of 1p36 (1p36.11–1p36.13) are currently unknown.

As a rule, babies with 1p36 deletion syndrome are born after uncomplicated and normal pregnancies. The ratio of females to males is approximately 2:1. Almost all infants are small for gestational age. Most children have brachycephaly (decreased head circumference in an antero-posterior direction). Microcephaly (small head) may become evident later. Typical facial abnormalities (deep-set eyes, broad nasal bridge, mid-face hypoplasia, and long philtrum), short digits and short feet may go unrecognized by the parents, but be apparent to a pediatrician or geneticist. The large anterior fontanel (soft spot) is usually late inclosing. The most frequent eye problems are anomalies of refraction or nystagmus; structural eye defects (cataract or coloboma) are relatively uncommon. Almost half of the patients have different hearing problems, either sensori-neural or conductive. Some children have skeletal abnormalities, most often scoliosis, and rib defects, which are recognizable upon X-ray examination. Cleft palate, although reported in several patients, is relatively uncommon.

Heart defects are the most common internal malformation. Almost two-thirds of patients have structural heart defects (septal defects, stenosis of aorta, or pulmonary artery) or cardiomyopathy, a disorder in which the ventricles become spongy and cannot pump enough blood to the organs. Renal abnormalities, although relatively uncommon (20%), include dilatation of the renal pelvis and ectopic kidneys. They usually do not affect the function of the kidneys but may predispose the person to urinary tract infections. Structural defects of the brain are uncommon, although hydrocephalus and polymicrogyria were reported in several patients. A significant number of patients with this syndrome were diagnosed with hypothyroidism.

More than half of children with 1p36 deletion syndrome develop different forms of seizures, which begin most often during the first year. In some cases, seizures may stop, and the

children can be weaned off anti-convulsive medications. In others, however, seizures can get worse over time. Although some children with infantile spasms have been treated with steroids, their use remains controversial; in most children, seizures did stop, but some developed severe epilepsy that was non-responsive to anti-epileptic drugs.

Intellectual and developmental delays are both significant and common in most children with 1p36 deletion syndrome. Milestones in gaining head control, sitting without support, and walk unaided are reached at a later age than normal. Expressive language is also commonly affected; some children may say several isolated words or short sentences, but others do not speak at all. Most children with 1p36 deletion syndrome have behavioral problems, as well, including fits of temper, self-biting of hands, and stereotypic mannerisms (eg, holding hands in front of face, hand flapping, or head shaking). Problems with both behavior and speech development usually improve with age.

Because the medical issues involved in 1p36 deletion syndrome pertain to various systems of the body, children should be followed by a team of specialists, including a cardiologist, urologist, neurologist, ophthalmologist, and sometimes a psychologist; all should have speech, physical, and occupational therapies.

The articles by Bahi-Buisson et al. (2009) and Battaglia et al. (2009), available from the CDO library, provide further details about 1p36 deletion syndrome.

Genetic Counseling

In ~15% of patients with apparent terminal deletions, one of the parents may be a carrier of a balanced translocation or inversion. Cytogenetic examination of both parents can determine if there is a genetic risk for further offspring of the couple. If the parents are cytogenetically normal, the recurrence risk is very low. If either one of the parents has a translocation or inversion, there is a 15%–20% recurrence risk, depending on the precise type of rearrangement. Although it is possible that an interstitial deletion could be caused by a chromosomal insertion in one of the parents, the probability is still very low; to date, in all described patients with interstitial deletions of 1p36, these aberrations have been sporadic (with negligible recurrence risk for further children).

Deletion of 1p32.1

Numerous new microdeletion and microduplication syndromes have been described since molecular cytogenetics became widely implemented. Some of these syndromes are common and relatively well recognized now. Another group of syndromes has not been well delineated yet, but reports of patients with similar deletions (or duplications) and similar clinical characteristics indicate that these syndromes will be officially recognized in the near future. Deletion 1p32.1 belongs to the last category of syndromes.

There are ~15 reports on patients having deletion 1p32.1, usually in association with the more proximal deletion 1p31.3 or the more distal deletion 1p32.2. The exact size of the deletion has been different in all reported patients. Abnormalities of the corpus callosum (the part of the brain connecting the two hemispheres) are the most common sign of this deletion. Hypoplasia or absence of the corpus callosum was found in all patients examined for this defect. Hydrocephaly and seizures were detected in two patients each. Congenital heart defects

were reported in 5 patients. Three children with this deletion had cleft palate. Premature fusion of the cranial bones (craniosynostosis) and an additional thumb-like digit (preaxial polydactyly) were found in one patient each, but their occurrence may be explained by involvement of additional segments of 1p. Further reports of deletion 1p32.1 are necessary for final delineation of this condition.

Deletions of 1q

Deletion of 1q21.1

As stated earlier, the genetic size of the whole chromosome 1 is ~246 Mb. The segment 1q21.1 occupies only ~4 Mb (from ~141.5 Mb to 145.9 Mb). Due to its small size, both deletions and duplications within this segment became recognizable only during recent years when molecular cytogenetic methods became available.

Surprisingly, there are two conditions related to deletions 1q21.1. One is a well-known syndrome called Thrombocytopenia–Absent Radius or TAR. The main manifestations of this entity are evident from its title. Thrombocytopenia (low blood platelet count) may be accompanied by leukopenia (low number of white blood cells). The characteristic defect of the extremities is an absence of radial bones with preservation of thumbs. (In most other syndromes when radial bones are absent, the thumbs are also absent.) TAR has been considered an autosomal–recessive condition. Molecular studies have shown a very small deletion of 1q21.1, measuring only ~350 Kb (from 144.1 Mb to 144.5 Mb) in all persons with this syndrome. This segment, although small, contains more than 10 genes, but it remains unclear which of these genes contributes to the occurrence of TAR syndrome. Although this deletion occurred de novo in most patients, in at least 25% of families, this same deletion was found in one of the healthy parents. From these data it was determined that the deletion is necessary but not sufficient for the occurrence of TAR syndrome, with researchers concluding that the development of clinical manifestations depend on the interaction between the deleted segment and at least one other (still unknown) factor.

The other condition related to 1q21.1 deletion is caused by a larger deletion of the more distal part of 1q21.1 (144.8 Mb–145.9 Mb). Sometimes this deletion is called the “distal 1q21.1 deletion” (to distinguish it from proximal or TAR-related 1q21.1 deletion). At first, this deletion was found in several patients with congenital heart disease. Later, it became evident that manifestations of this condition are very variable in that a valid clinical spectrum of this deletion could not be formulated because different groups had different criteria for selecting participants and no conclusions could be drawn.

Most patients do not have microcephaly, but, typically, the head circumference is near the lower end of the normal distribution. Facial features include frontal bossing, deep-set eyes and bulbous nose, although it is difficult to recognize distal 1q21.1 deletion solely upon clinical examination. Congenital heart disease is found in 30% of patients. Although most of the heart defects are relatively mild (bicuspid aortic valve, septal defects, and patent ductus arteriosus), some patients have very serious defects (interrupted aortic arch, arterial trunk, and transposition of great arteries).

Different types of polydactyly were found in ~15% of patients. Trigonocephaly, hydrocephaly, cleft palate, microphthalmia, and cataracts were often reported. There are isolated

descriptions of numerous other defects such as absence of one kidney, hydronephrosis, and pyloric stenosis. However, ~40% of patients with distal 1q21.1 deletion do not have any overt birth defects. Patients may also suffer from seizures. There are indications that the deletion may be associated with autism and schizophrenia, although in some cases the presence of autism and/or schizophrenia was a criterion for selection of patients for study.

The size of the distal 1q21.1 deletion may vary, but, typically, it is between 1.0 and 1.9 Mb. In some persons, the deletion also involves the TAR region, but it does not cause any additional abnormalities. (The deletion of the TAR region may produce abnormal findings only when accompanied by other (still unknown) genetic factors)

A real clinical picture of the distal 1q21.1 deletion will only become clear when it is possible a) to implement a common protocol for evaluating and describing these patients; b) to follow-up on the children who were too young at the time of the examination.

Most 1q21.1 deletions occur de novo. However, in almost 25% of families, the same deletion may be found in one parent who manifests mild manifestations, such as psychological problems, learning disability or minimal dysmorphisms, or are clinically normal. The normal phenotype in persons with microdeletions suggest that some microdeletions (including, but not limited to deletion 1q21.1) may cause abnormalities in that they reveal (unmask) certain mutated genes on the normal (non-deleted) chromosome.

Genetic prognosis will depend on the karyotype of the parents. The recurrence risk is negligible if the parental chromosomes are normal. However, if one parent has an asymptomatic deletion, the chance of passing this deletion onto offspring can be as high as 50% but its clinical significance remains unpredictable.

Deletion of 1q43–q44

Deletions of the distal part of chromosome 1q have been recognized for many years. However, reliable diagnosis of these conditions became available only after the advent of molecular cytogenetic methods. The segment 1q44 is the most distal part of the long arm of chromosome 1; its genetic size is ~6 Mb. The segment 1q43, which is approximately the same size, is the more proximal part of 1q. The cytogenetic variants of the distal deletions of 1q are numerous: terminal deletions 1q43qter, interstitial deletions 1q43q44, and deletions involving only the segment 1q44. The comparison of clinical findings between these groups did not show significant differences. The absence of genetic material of 1q44 is strongly associated with physical and/or development abnormalities; the additional absence of the genetic material from 1q43 does not appear to be clinically significant.

In deletion 1q43–q44, birth weight is usually less than normal, although in most babies prenatal hypoplasia is relatively mild. Postnatal growth of these patients is also delayed. Head circumference is usually below normal; many patients may have microcephaly. The typical pattern of recognizable anomalies includes sparse fine hair, round face, epicanthus, low set ears, short broad nose with flat bridge, downturned corners of the mouth, and microretrognathia (small chin). These features are found in ~80% of patients with the syndrome.

Approximately half of patients have small hands with tapering fingers or short curved 5th

fingers; more serious defects of the fingers or toes are rare. Some children have small pits or additional skin tags in front of their ears. Hearing impairment has been reported in ~15% of examined patients. Cleft palate or bifid uvula is also relatively common (~15%). Several children had coloboma of the iris. Although not common, underdevelopment of the thyroid gland was reported in several patients. Therefore, exclusion of hypothyroidism should be a part of the clinical examination.

Abnormalities of the brain and the clinical consequences of these abnormalities are the most characteristic (and most serious) features of deletion 1q43–q44. Microcephaly, which is found in ~90% of the patients, causes significant delay in psycho–motor development. Seizures are common (~80%). Small occipital encephalocles are found in ~10% of children. In 90% of examined patients, MRI of the brain shows absence or hypoplasia of the corpus callosum. There have been several attempts to find what gene is responsible for underdevelopment of the corpus callosum when it is deleted. The critical region has been narrowed down to a 360 Kb segment, which contains 4 possible candidate genes, but the responsible gene has yet to be determined. Another uncommon defect is Dandy–Walker malformation, an anomaly involving dilatation of the 4th ventricle in association with underdevelopment of the cerebellum and/or absent or hypoplastic cerebellar vermis. Because brain abnormalities are common findings in distal 1q deletions, MRI of the brain should be an integral part of an examination of these patients. Other consequences of abnormal brain development are floppiness (hypotonia), dysphagia and difficulties in feeding, and autonomic dysfunction (disturbances in function of the cardiac muscle, smooth muscles and various glands).

Heart defects (usually not life threatening) are the most common abnormality of internal organs and are found in ~30% of the patients. Absence of one kidney, hydronephrosis and an ectopic position of a kidney has been found in several patients each; however only a small number of children had examinations to exclude kidney defects. Some boys have hypospadias. Polydactyly, additional nipples, scoliosis, dislocation of the hips are uncommon. All of these findings are known as manifestations of “pure” distal monosomy 1q (as an interstitial or terminal deletion).

There are numerous descriptions of children with an association of distal monosomy 1q and partial trisomy for another chromosome (usually due to translocation). Patients with these associations may have additional abnormalities caused by partial trisomy.

Genetic prognosis depends on the type of rearrangement. Almost all interstitial deletions are sporadic. A significant number of terminal deletions may be a result of parental translocations; examination of parental chromosomes will help determine recurrence risk. Risk for further affected children of the couple will be very low if parental karyotypes are normal. If one of the parents has a translocation, the risk will depend on the exact type of rearrangement but will most likely be relatively high.

Ring Chromosome 1

Ring chromosome 1 or r(1) is the rarest type of ring chromosome. Since 1964, when the first patient with r(1) was reported, there have only been 7 other patients reported with this abnormality. Two of these patients had hypoplasia or dysplasia of the corpus callosum (most likely as a result of the loss of the distal segments of 1q), and two others had dislocated hips. One patient had atrial septal defect and dysplastic hypoplastic kidneys. Another developed

leukemia. Other abnormalities included hydrocephaly, preauricular and suprasternal sinuses, cleft palate, and hypoplastic thumb. The paucity of these clinical data precludes any discussion of manifestations related to any one syndrome. Familial transmission of ring chromosome 1 has not been documented.

Partial Trisomies for Chromosome 1

Partial trisomies for 1p

Partial trisomies for the short arm of chromosome 1 are very rare, especially as sole abnormalities. Although the genetic size of 1p is relatively large (120 Mb, it is larger than the whole chromosome 13), there are no well-delineated syndromes associated with these trisomies.

Trisomies for the proximal segment of 1p (1cen–1p22) are exceptionally rare. Several known patients have had different abnormalities, including Dandy–Walker malformation (critical region 1p13p21), cleft palate (critical region 1p11p13), rhizomelic shortening of the limbs (critical region 1p13p22), and autism (critical region 1p13.3p21.2). All other defects in the patients with proximal duplications 1p were reported one time each.

Trisomies for the “central” part of 1p (from 1p22 to 1p35) have been reported in ~30 patients. Most patients in this group have a complex of congenital defects, usually serious. These defects involve almost every system, including brain (hydrocephaly, absent or hypoplastic corpus callosum, microcephaly), eyes, heart, skeletal system, gastro–intestinal system, kidneys (hypoplastic kidneys, horseshoe kidney), and genitalia. However, since there is wide differences in the size of the trisomic segments, there is significant heterogeneity in the clinical manifestations. Analysis of abnormalities reported in several patients with these trisomies has led to linking hydrocephaly to the duplication of 1p31.2, hypoplastic (or absent) corpus callosum to the duplication of 1p13.3, and coloboma to the duplication of 1p34.1. At least 2 segments within this area are related to heart defects. If duplications of 1p31 cause relatively mild defects (types of ventricular septal defects), duplications of the more distal segment (1p34.1p34.3) may cause very serious defects, such as double outlet of the right ventricle, dextrocardia, and hypoplastic left heart.

Several patients with duplications involving 1p32.1p32.3 had a very unusual defect — sex reversal, in which phenotypically girls had an XY–karyotype. Other patients in this group had ambiguous genitalia. It is still unclear which duplication of which gene in 1p32 may cause these defects. Certain other defects—cleft palate, ptosis, preauricular pits, abnormalities of spinal segmentation— have been repeatedly observed in patients in this group, and are likely attributed to duplications of several genes because these defects were found in persons with non–overlapping duplications.

Distal trisomy 1p (trisomy 1p36)

“Pure” distal trisomy 1p36 is known only in ~25 patients. In 55–60 additional patients, this trisomy was accompanied by deletions of other chromosomes. Basically, clinical manifestations in patients with isolated trisomy 1p36 are relatively mild. Seven patients had various heart defects (mainly stenosis of the pulmonary artery and atrial septal defect); two had choanal atresia; two had stenosis of the naso–lacrimal duct; and two patients had anal

defects (stenosis, ventral ectopia). Functional defects are much more common. At least eight patients in this group had seizures, and three had sensori–neural hearing loss. A comparison of clinical manifestations and duplicated segments shows that the duplication of genes within 1p36.11p36.13 causes hearing loss, choanal atresia and stenosis of the naso–lacrima duct, whereas the distal segment 1p36.3 is responsible for the occurrence of heart defects and seizures.

Pericentromeric duplications of chromosome 1

Small additional marker chromosomes (structurally abnormal chromosomes with no identifiable part) have been known since the early 60's, but delineating the precise nature of these markers became available only in recent years when molecular methods in cytogenetic analysis became available. In at least 20 people, small additional marker chromosomes were found originating from the pericentromeric area (near the middle) of chromosome 1. In some patients, the marker included only the material of 1q (from centromere to 1q21); in others, the markers also involved small areas of 1p (up to 1p12). Several markers had the form of an additional ring chromosome; other markers had a rod structure.

There is no clinical syndrome associated with the presence of an additional marker from the pericentromeric region of chromosome 1. Nonetheless, three patients had a ventricular septal defect (in one, an association with pulmonary stenosis), two had cleft lip, and two had ptosis. Intestinal atresia, hydronephrosis, hypospadias, polydactyly, camptodactyly, knee dislocation, and scoliosis were reported in one patient each. In several families, however, the same marker chromosome was found in one of the phenotypically normal parents of the affected children. Therefore, it still remains unclear whether the above–mentioned defects were caused by the duplication of genes located at this area, or if these defects were only occasional findings, unrelated to the presence of a marker chromosome.

Partial trisomies for 1q

Partial trisomy 1q11(q12,q21)–qter

Trisomies for the whole (or nearly whole) long arm of chromosome 1 occur very rarely. There are ~30 reports regarding fetuses or newborns with this abnormality. Some of them had mosaicism, meaning only some of their cells had the extra material. For unknown reasons, at least six of these patients had associated monosomy for Yq12qter due to t(Y;1). Because this tiny deletion does not produce any significant morphological abnormalities, persons with this unbalanced t(Y;1) abnormality were considered to have “pure” trisomy 1q. Most born with whole or nearly whole trisomy 1q have multiple malformations usually incompatible with life. This is not surprising since the size of the duplicated segment is more than 110–115 Mb, and this segment contains more than a thousand genes.

The most common defects involve the brain, eyes, kidneys, and loco–motor system, although almost every defect known has been reported in some number of patients with these trisomies. The most frequent brain defects are hydrocephaly (7/30), hypoplastic cerebellum (5/30), and agenesis of the corpus callosum (4/30); anencephaly, encephalocele, polymicrogyria and trigonocephaly have also been reported. Eye defects include microphthalmia (6/30) and colobomas (3/30); anophthalmia, cryptophthalmos (“hidden eye”), and symblepharon (fusion of the upper and lower lid) have also been reported. Defects of the

kidneys include cystic dysplasia (3/30), hydronephrosis (2/30), and nephroblastomatosis (2/30). Kidney agenesis, malrotated kidneys, obstruction of ureter, and dilated renal pelvices have also been observed. Skeletal defects include syndactyly of fingers or toes (6/30), absent or hypoplastic thumbs (4/30), camptodactyly (6/30), contractures (4/30), and defects of vertebral segmentation (3/30). Preaxial polydactyly, ectrodactyly, low-set thumbs, thiphlangeal thumb, brachydactyly and rhizomelic shortness of limbs have also been reported.

Abnormalities in other organ systems have been more sporadic. Cleft palate (or cleft lip and palate) has been reported in 5 patients. Another 5 patients had diaphragmatic hernia; the critical segment for this defect has been isolated to 1q12q22. Omphalocele has been reported in 3 patients. Reported defects of the gastro-intestinal system include anal atresia (2) and intestinal malrotation (2). Although primary lung defects are relatively uncommon, abnormal lung lobation, hypoplastic epiglottis and pulmonary hypoplasia have been reported in patients with trisomy 1q. Surprisingly, heart defects are not typical, although three patients had atrial septal defects, three had ventricular septal defects, one had coarctation of the aorta, and one had bicuspid aortic valve (some patients had more than one heart defect). The more serious transposition of the great arteries with double outlet right ventricle was reported only once.

Unique to this group of patients is a very unusual tumor originating from embryonal tissues called a teratoma. Teratomas have been reported in 7 persons with the disorder and in several more patients whose trisomy 1q was associated with an imbalance in another chromosome. These teratomas can originate from neck structures (epignathus) or from the sacro-coccygeal area. The gene responsible for this tumor is most likely located within 1q21 because the tumor has not been found in any patient with more distal trisomies for 1q.

Although clinical recognition of the “whole” trisomy 1q (in the absence of teratoma) is not possible, this trisomy is one of the gravest conditions associated with structural autosomal abnormalities.

Trisomy 1q21.1

The genetic structure of the 1q21.1 region predisposes it to the formation of small deletions in this area, as well as to reciprocal duplications. As with other microdeletions and microduplications, identification of such small duplications became possible only with the use of molecular cytogenetics. Usually, duplications of 1q21.1 are relatively small (1.3–1.7 Mb or less).

So far, 55 persons with duplications of 1q21.1 as an isolated cytogenetic anomaly have been reported. There is no specific phenotype associated with this duplication. However, the prevalence of schizophrenia, autism, and seizures among persons with dup 1q21.1 is much higher than in persons with a normal karyotype; schizophrenia and autism were reported in seven persons each; seizures, in five persons. Existing data suggest that these duplications may be considered as risk factors for the development of these three conditions, but inclusion of other factors (environmental or genetic) is necessary to actually produce any one of them.

Structural defects are relatively uncommon. Four patients had heart defects (including one patient with a monoventricular heart and one with tetralogy of Fallot). Two patients had hypospadias. Hydrocephaly, hypoplastic corpus callosum, hypoplastic cerebellar vermis, bifid

uvula, cataract, and glaucoma were reported in one patient each. However, the identical duplications of 1q21.1 were reported in healthy parents of several patients. In that context, it is not clear whether these abnormalities are the direct result of duplications of 1q21.1.

Several patients had relatively large duplications of 1q21.1 (2.7–4 Mb); such a large size indicates that they were not normal or borderline variants. Patients having these larger duplications have a wide range of uro–genital anomalies (hypoplastic kidneys, uretral stenosis, utero–vaginal fusion), as well as other defects (eg, atretic ear canals and skin depigmentation). The direct transmission of such a large duplication as 1q21.1 has not been reported.

Trisomy for the “medial” segment of 1q

There are ~25 reports of persons with trisomies for the “medial” segment of 1q (from 1q23 to 1q41), although the actual size and location of breakpoints are different in almost all patients. As of now, it would be premature to describe these types of trisomies as a syndrome. However, analysis of known reports provides some inclination about clinical consequences of such trisomies.

The most common abnormalities are congenital heart defects and abnormalities of the eyes and extremities. Various heart defects are mentioned in half of the patients. However, none of these defects was life–threatening. The most common abnormalities were ventricular septal defect (8), patent ductus arteriosus (6), atrial septal defect (3), stenosis of the pulmonary artery (3). Some patients had more than one heart defect. Trisomy 1q31 appears to be a critical area for the origin of microphthalmia, which was reported in six patients. Segment 1q32 likely harbors gene(s) responsible for coloboma, which was reported in three patients. The most common defects of skeleton and extremities are contractures, camptodactyly, and scoliosis. Two patients trisomic for the 1q31q32 segment had preaxial polydactyly. Numerous other limb defects (absent toes, syndactyly, brachydactyly, proximally placed thumbs) were found in one patient each.

Three patients had cleft palate, one more had cleft lip and palate. Brain defects are relatively rare, although three patients had dilatation of the lateral ventricles, one had arhinencephaly, and one had Dandy–Walker malformation.

Two persons sharing trisomy for the segment 1q25q31.2 had diaphragmatic hernia. Lung defects (bilobed right lung and bronchial stenosis) and kidneys defects (cystic kidneys, hydronephrosis, ureteral reflux) were all reported in one person each. Generally, most patients with “medial” trisomy 1q do not have life–threatening defects. Delay in psycho–motor development is common for all patients in this group.

Trisomy 1q32–q44 (qter)

There are ~36 reports about patients with trisomies for the large segment of the distal part of 1q: 1q32qter (or 1q32q44). Generally speaking, phenotypic manifestations in these persons are relatively mild, especially since the trisomic region constitutes such a large segment (> 40 Mb); this is more than the whole long arm of chromosome 21 or 22).

All patients have varying degrees of psycho–motor developmental delays, but facial dysmorphism is mild. Brain defects are rare; there are two reports of hypoplastic cerebellum.

Trigonocephaly, megalencephaly (large-size brain) and agenesis of the corpus callosum were found in one patient, each. Several patients had seizures. Microphthalmia and coloboma were reported in two patients, each. Other sporadic eye defects include dysgenesis of the anterior segment, glaucoma, corneal opacity, and macular hypoplasia. Four patients were reported as having microstomia (small mouth), four had cleft palate (with associated cleft lip in two of them), and four others had short neck.

Congenital heart defects were found in 14 patients. Most of these defects were relatively mild (including atrial septal defect II in 5 patients), although the type of heart defect was not specified in 4 patients. Only one patient had life-threatening Ebstein's anomaly. Occasional (but different) defects of the gastro-intestinal tract (esophageal stenosis, duodenal obstruction, pyloric stenosis) were found in several patients. Hydronephrosis was reported in 3 persons; other kidney defects (eg, cystic dysplasia, agenesis of one kidney) were sporadic. Four boys had hypospadias; one female patient had ovarian failure.

Preaxial polydactyly was reported in 3 patients. Most likely, this defect is caused by a triplication of the gene located at 1q32. Other digital defects mentioned in 1–2 patients, each include brachydactyly, camptodactyly, mild syndactyly, sandal gap (wide space between the 1st and 2nd toes), proximally implanted thumbs, and other skeletal defects (11 or 13 pair of ribs, scoliosis, and pectus excavatum).

Clinical manifestations of trisomy 1q32–qter may be much more severe when it is associated with a partial monosomy of another chromosome (as a result of a reciprocal translocation) or with partial monosomy for 1p (as a result of an unbalanced pericentric inversion).

Distal trisomies for 1q

Most patients with “distal” trisomies 1q (1q41–qter or 1q42–qter) have an additional chromosomal imbalance as a consequence of familial translocations or inversions. The number of reported patients with pure trisomy for the distal 1q is very limited (only ~25).

Structural defects of the internal organs are very rare. Five patients had heart defects (atrial septal defect (2), patent ductus arteriosus (1), unspecified heart defects (2)). Three patients had microcephaly. Other brain defects (hydrocephaly, agenesis of the corpus callosum, trigonocephaly) were reported in one patient each. Most patients have mild defects of the skeletal system (arachnodactyly, brachydactyly, camptodactyly, mild scoliosis) and mild dysmorphism. Hirsutism was reported in 3 patients. Patients with a smaller size of the duplicated 1q42–qter segment have less structural defects.

Molecular studies of patients with autism and schizophrenia has shown that some of these patients had small trisomies of 1q42.2 (for autism) and 1q42.3 (for schizophrenia). It is unclear, however, whether these duplications were causal factors for these disorders or just accidentally discovered, unrelated abnormalities.

Trisomy 1

Full trisomy for chromosome 1 is known only in spontaneous abortions. Embryos having this trisomy cannot survive until birth.