Chromosome 14

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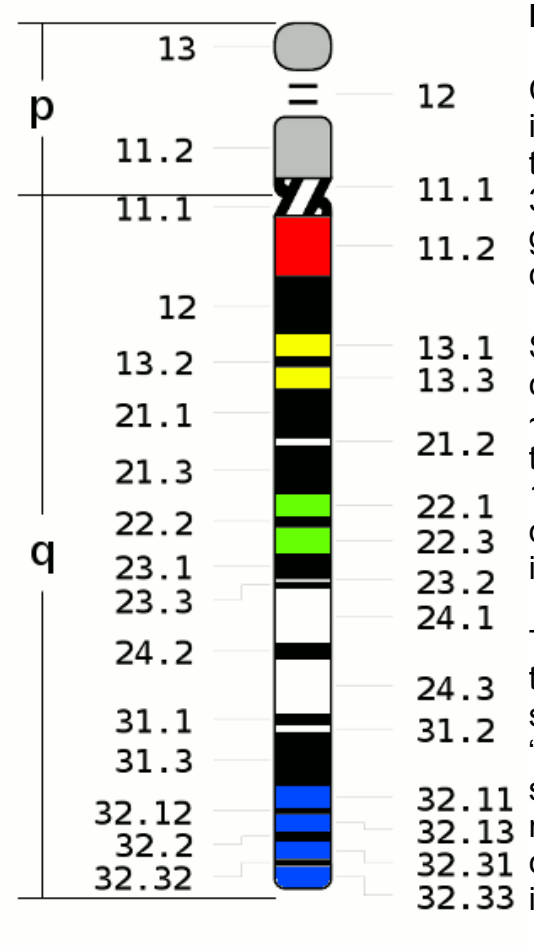

Introduction

Chromosome 14 is one of five acrocentric chromosomes in humans. All of its genes are located in the long arm of this chromosome. The length of 14q is 82 Mb. It is ~3–3.5% of the total human genome. There are ~900–1,200 genes on chromosome 14. It has 1.5 times as many as chromosome 13 has.

Structural defects of the long arm of chromosome 14 are considered to be relatively rare. Currently, there are ~550 patients with all kinds of structural imbalances for this chromosome and ~300 patients with deletions of 14q (including both deletions as a sole abnormality and deletions in association with another chromosomal imbalance).

There are at least five syndromes caused by deletions of the long arm of chromosome 14. Some of these syndromes basically are related with the deletion of one “alpha” gene in this particular area. Delineation of these syndromes became possible after wide usage of methods of molecular cytogenetics. Most likely, the clinical delineation of these syndromes will be improved in the nearest future.

Deletions of Chromosome 14

Chromosome 14 (as well as chromosome 13) is an acrocentric chromosome. Loss (or duplication) of the short arm of this chromosome does not lead to any clinical abnormalities. Only deletions of the long arm may cause clinical consequences. The genetic length of the long arm of chromosome 14 is ~82 Mb. There are ~200 reports of patients with deletions 14q as a sole abnormality.

The clinical syndromes associated with deletions of 14q (especially of the proximal part of 14q) became known only after the invention of methods of molecular cytogenetics, and delineation of these conditions has not been finished. One of these syndromes is caused by the deletion of 14q11.2 and another by the deletion of 14q12.

Deletion of 14q11.2

The tiny (less than 1 Mb) deletion within 14q11.2 causes an association of delay in psycho–motor development and a relatively unspecific complex of facial dysmorphias (widely spaced eyes, short nose with flattened nasal bridge, long philtrum, full lower lip, abnormal formation of helix). Not more than 10 patients having this deletion (without involvement of 14q12 or more distal segments of 14q) are reported. Two of them had heart defects: ventricular septal defect (VSD) and patent ductus arteriosus. Defects of other systems have not been reported so far.

Deletion of 14q12 and Rett Syndrome

Rett syndrome is a neurodegenerative disorder characterized by psycho–motor regression, delay in psycho–motor development, seizures, stereotypic hand movements, dyspraxia, gastro–esophageal reflux and constipation. Almost all patients with classic Rett syndrome are females. The majority of affected patients have mutations in two genes (MECP2 and CDKL5). A phenotype similar to Rett syndrome also was found in several patients with mutations of the FOXG1B gene, which is located at 14q12.

Deletions of the segment of 14q involving the FOXG1B gene also cause phenotypic manifestations similar to Rett syndrome. There are ~15 patients with this phenotype and deletions of the FOXG1B gene. At least one patient had a microdeletion downstream of FOXG1B, suggesting a misregulation of FOXG1B transcription.

The patients with deletions of 14q12 without the loss of the FOXG1B gene had a delay in psycho–motor development, but no Rett–like features.

Several patients with del 14q12 had hypoplastic corpus callosum. Some authors believe that this defect is another manifestation of the FOXG1B deletion, although participation of genes from the more distal segment of 14q cannot be excluded.

Deletion of 14q13

There are two clinical syndromes related to deletions of various areas of 14q13.

There is a strong association between this deletion and holoprosenecephaly (HPE). Ten children (or fetuses) with this deletion had obvious HPE (including cebocephaly and HPE with premaxillar agenesis). At least 15 more patients did not have overt HPE, but microforms of this defect, including microcephaly, single central incisor and median cleft lip and palate.

The gene responsible for this defect remains unknown, although the critical region for this [still] elusive gene, HPE8, is limited to 3 Mb. The genes EAPP and SNX6 are the most likely candidates.

The segment 14q13.3 contains the NKX2–1 gene. Mutations (as well as deletions of this gene) produce the so–called brain–lung–thyroid syndrome, which includes hypothyroidism, athetosis, chorea, and respiratory problems (multiple lung infections caused by a congenital defect of surfactant function). At least 10 reported patients having this deletion had various manifestations of this rare condition. Some of them (who had deletions involving HPE–8

locus) had manifestations of holoprosencephaly.

Deletion of 14q22

The segment 14q22 contains several genes important for normal development. Two neighboring genes, BMP4 and OTX2, seem to be the most significant. The OTX2 gene is responsible for the development of the eyes and the anterior part of the pituitary gland. The BMP4 gene is also involved in the development of the brain and eyes. The last gene also is responsible for digital anomalies, including polydactyly and syndactyly.

The deletion of these genes (which occurs in patients with deletions of 14q22) produce severe clinical manifestations, including anophthalmia (absence of eyeballs) or microphthalmia (small eyes), underdevelopment of the anterior hypophysis, sometimes in association with microcephaly, hypoplastic cerebellar vermis, partial agenesis of the corpus callosum, hearing impairment, syndactyly or polydactyly.

At least 15 patients having deletions of this region have been reported so far. The most common defect is anophthalmia (usually bilateral). Computer tomography in some patients showed undeveloped anlagen of the eyeballs. Some patients had microphthalmia or other eye defects (sclerocornea, glaucoma).

The most common clinical manifestation of the underdeveloped pituitary gland is hypothyroidism.

Anophthalmia and hypoplasia of the hypophysis may be attributed to the deletion of the OTX2 gene because some patients with mutations within OTX2 have both eye and pituitary defects.

Morphological brain defects (partial agenesis of the corpus callosum, microcephaly, hypoplastic cerebellar vermis), polydactyly and syndactyly are more likely caused by deletions of the BMP4 gene. However, it was shown that mutations of the BMP4 also may cause anophthalmia.

The intellectual status of patients with mutations (and an isolated deletion of the OTX2 gene) may be normal. Involvement of other genes, which is common for the patients with deletions, may cause a delay in psycho–motor development.

Some patients with del 14q22q23 had associated defects of the heart and kidneys caused by deletions of the genes within 14q23.

Isolated deletions of 14q23q24 are very rare. There is no syndrome associated with the loss of this segment of chromosome 14. At least two patients with deletions of 14q23.2q23.3 had spherocytosis (abnormal formation of the red blood cells, which causes anemia). Preliminary data shows that 14q23 may contain genes important for the development of the palate (several patients had cleft palate), heart and kidneys.

Deletions of 14q32

Deletions of the terminal segment of 14q are relatively frequent: at least 50 patients having these deletions have been reported. However, clinical manifestations in these patients are

relatively non–specific. It is too early to speak about this deletion as a recognizable syndrome.

Most patients were born at term with a relatively normal birth weight. Low muscle tone (hypotonia) may be evident from the first weeks of life. Facial abnormalities (broad forehead, epicanthus, short bulbous nose, flat nasal bridge, ptosis, low–set ears) are not constant. All of these manifestations cause suspicion of a chromosomal abnormality, but not any specific, condition. Feeding difficulties, including gastro–esophageal reflux are relatively common. Several patients had hearing problems caused both by narrow ear passages and by cochlear defects. These children may need a hearing aid.

Delay in psycho–motor development is a common finding, but in most patients this delay is relatively mild.

Heart defects are the most common form of visceral abnormalities. They were found at least in 25% of patients. Most of these defects are relatively mild (VSD, patent ductus arteriosus). Spontaneous closure of these defects was reported in some children.

Defects of other systems are relatively rare. However, recurrent appearance of craniosynostosis (3), colobomas (3), intestinal malrotation (2) and anal atresia (2) suggests that this part of 14q may contain genes involved in the formation of these systems. Several patients sharing a common tiny deletion (1.1 Mb) within 14q32.2 had pubertas praecox.

Seizures are not characteristic. It seems surprising because almost all patients with ring chromosome 14 (and loss of the same terminal segment of 14q) have seizures. Most likely, a mechanism of seizures in ring(14) patients involved not only the deletion of the distal part of 14q but some other factors.

Almost all interstitial deletions and most terminal deletions of 14q are sporadic events. However, a significant number of terminal deletions is caused by familial translocations with a relatively high recurrence risk for further children. Very small interstitial deletions may be inherited from one of the parents having minimal (if any) clinical abnormalities. Cytogenetic examination of the parents has to be a standard procedure in genetic counseling of affected families.

Ring Chromosome 14

Ring chromosome 14 is a relatively frequent type of ring chromosome. At least 110 patients with this abnormality have been reported. Seven of these patients had mosaicism with a secondary monosomic clone, five had mosaicism with a normal clone, three were mosaics with a clone partially trisomic for chromosome 14, and in one patient r(14) was accompanied by the deletion of the short arm of chromosome 5.

Because chromosome 14 is an acrocentric chromosome, loss of the short arm material does not have a clinical significance.

The most important and almost constant manifestations of ring chromosome 14 are seizures. Excluding several reports of r(14) in fetuses, there are only seven patients (out of more than 100) who did not have seizures (or at least seizures have not been reported). The mechanism of seizures remains unknown: the frequency of seizures in patients with distal deletions of 14q

is much less.

The second hallmark of a ring chromosome 14 syndrome is abnormal pigmentation of the ocular fundus, usually as grayish or dark yellow-whitish flecks. This abnormality was reported in 37 patients (~50% of all patients who had sufficient ophthalmological examination). Abnormal skin pigmentation with a linear pattern of hypo- and hyperpigmentation was found in ~10 patients.

At least 1/3 patients have microcephaly, usually relatively mild. Most patients do not have microcephaly upon birth: it became evident later. Various degrees of delay in psychomotor development is very common.

Other defects are relatively uncommon. Hydrocephaly, trigonocephaly, and scaphocephaly were reported in one patient, each. Structural defects of the eyes are more frequent: there are several reports of microphthalmia, cataracts, colobomas, corneal opacity, glaucoma. Several patients had blepharophimosis.

The most frequent skeletal abnormality is scoliosis, which was noted in 11 patients. Other defects (sacral dysgenesis, dislocated hips, dislocated knees, exostoses) were reported in 1-2 patients, each. No patient with r(14) had polydactyly or oligodactyly.

Heart defects were reported only in eight patients: one had tetralogy of Fallot, another had relatively mild defects: atrial septal defect, pulmonary stenosis etc. Defects of the kidneys (hypoplasia, pelvic kidney) are exceptionally rare. Vital prognosis is favorable, because defects of internal organs are very rare.

There are at least four families with direct transmission of r(14) from a parent to a child. Both mothers and fathers were the carriers in such families.

Partial Trisomies for Chromosome 14

Partial trisomies for the long arm of chromosome 14 (like partial trisomies for the long arm of chromosome 13) may be subdivided into three groups:

1) “proximal” trisomies (from centromere to 14q22),
2) trisomies for the “medial” part of 14q (where the 14q3 segment is not involved),
3) and “distal” trisomies (with an obligatory involvement of 14q3 segment).

None of these trisomies constitutes a recognizable syndrome.

The total number of known patients with pure partial trisomies for any part of 14q is ~135. This number is rapidly increasing because the wide application of molecular methods allows the discovery of numerous small duplications which could not be diagnosed by standard cytogenetic methods.

a. *Proximal Trisomy 14q*

Sixty patients with proximal trisomies 14q may be subdivided into two groups:
Patients having an additional marker chromosome, which includes the short arm of chromosome 14, its centromere, and part of the material of 14q (sometimes up to 14q22, but

usually limited to 14q13). Of course, these patients may be easily recognized by standard cytogenetic methods.

Patients with small duplications within 14q (up to 14q22): at least half of these patients could not be recognized by standard methods.

Generally patients with additional marker chromosomes have more severe abnormalities. It should be noted, however, that approximately 10 patients in this group had triplications of genetic material and therefore had four copies of the affected genes, not three copies (which is usual for trisomies).

There are no characteristic external manifestations for patients having proximal trisomies of 14q.

The most common finding is severe infantile seizures (the so-called West syndrome). The origin of this condition is related to the duplication of the FOXG1 gene, located at 14q12.

Other recurrent manifestations include cleft palate (six patients), heart defects (five patients, including one with tetralogy of Fallot and one with AVSD), microphthalmia (three patients), coloboma (three patients), craniosynostosis (three patients), hypoplastic corpus callosum (two patients), preauricular pits (three patients), hearing impairment (three patients), microstomia (two patients), camptodactyly (three patients), syndactyly of 2-3 toes (two patients), short hands or feet (two patients), kyphosis (two patients), and umbilical hernia (two patients). Several patients had autistic features or attention deficit disorder.

Some unusual abnormalities, including ectrodactyly, aplasia of tibial bones, postaxial polydactyly, omphalocele, and pelvic kidney were reported in one patient, each.

Small duplications in this area may be inherited from healthy or minimally affected parents.

b. *Trisomy for the "Medial" Part of 14q*

This group includes ~25 patients, which also may be subdivided into a small group of people with additional marker chromosome 14pter-q24 and a group of patients with trisomies (usually relatively small) within 14q22q24.

All patients with an additional marker have some degree of delay in psycho-motor development. Three (out of seven) had microphthalmia, two had cleft palate, two had heart defects, two had scoliosis, two had contractures, and two had umbilical hernia. Craniosynostosis, partial agenesis of the corpus callosum, choanal stenosis, absent thymus, narrow auditory canals, deafness, preauricular pits, renal agenesis, ectopic kidney, esophageal stenosis, and omphalocele were reported in one patient, each.

Manifestations in patients with duplications 14q22q24 are not severe, but four out of 17 had hearing impairment, three had seizures, three had non-life-threatening heart defects, two had microcephaly, and two had kyphoscoliosis. Cleft palate, coloboma, choanal atresia, anotia (the absence of a normally formed external ear), and preauricular tags also were sporadically reported in these patients.

c. *Trisomy for the Distal Part of 14q*

All 50 patients in this group have trisomy for the distal part of 14q, but proximal breakpoints may vary. Most patients have trisomies 14q24qter or 14q31qter, but there are patients with an involvement of more proximal segments, as well as patients with (sometimes small) trisomies within 14q31 or 14q32. Different sizes of duplicated segments partially explains the wide clinical heterogeneity in this group.

External manifestations in patients with distal trisomy 14q include cleft lip or palate (or cleft palate), which was reported in five patients. Four patients had macroglossia (a very large tongue), and three had preauricular pits or tags. Three patients had areas of skin hypopigmentation.

Abnormalities of the skull and brain include agenesis or partial agenesis of the corpus callosum (5), scaphocephaly (2), arhinencephaly, hydrocephaly, and even spina bifida.

Defects of the eyes are relatively uncommon, but there are reports of coloboma (2), cataract, microphthalmia, megalocornea, and stenosis of the lacrimal ducts.

Defects of the loco-motor system are rare and include three patients with contractures, two with shortening of femoral bones, and sporadic reports of polydactyly and the absence of the 12th ribs. There are reports of umbilical hernia (4) or inguinal hernia (2).

Heart defects are very common; they were reported in 19 patients. Some of these defects were life-threatening (truncus arteriosus, tetralogy of Fallot, AVSD). Defects of the gastro-intestinal system include intestinal malrotation (2), anal atresia, and omphalocele. The latter defect is caused by the duplication of 14q32. Absent thymus, diaphragmatic hernia, and sporadic abnormalities of the kidneys (hypoplastic kidneys, cystic kidney, and dilatation of the renal pelvis), and ambiguous genitalia were reported in one patient, each.

The patients with larger duplications have different degrees of psycho-motor retardation. People with a smaller amount of duplicated material may have normal psycho-motor development.

Trisomy 14

Trisomy 14 is a relatively frequent type of “uncommon” trisomies: there are ~60 reports about patients with this trisomy. Full trisomy 14 leads to intrauterine death of the fetus. There is only one report of full trisomy 14 in a liveborn child, but unrecognized mosaicism in that patient cannot be excluded. It is interesting that this girl had spina bifida. Two spontaneously aborted fetuses with full trisomy 14 also had neural tube defects, although neither of the live-born children had occipital encephalocele or spina bifida.

All other persons with trisomy 14 were mosaics, usually with a low percentage of trisomic clone. Most people with mosaic trisomy 14 have a “free” additional chromosome 14: 46,XX (or XY)/47,XX (or XY),+14. However, because chromosome 14 is an acrocentric chromosome, trisomy 14 may be result of iso-chromosome 14: 46,XX (or XY)/46,XX (or XY),i(14q) or the translocation of chromosome 14 onto the short arms of another acrocentric chromosome. Mosaicism 46/47,+14 was found in 41 out of 58 persons with mosaic trisomy 14. Seventeen

other patients had trisomy 14 due to iso-chromosome or translocation. There are no clinical differences between both sub-types of mosaic trisomy 14.

Patients with mosaic trisomy 14 show evident failure to thrive – a delay in physical and psycho-motor development. However, there is significant individual variability.

Most patients with mosaic trisomy 14 have facial dysmorphism, which includes broad nose, “dysplastic” low-set ears, macrostomia, micrognathia, and a short neck. However, all of these findings are not specific and may be found in numerous syndromes caused by chromosomal anomalies.

Morphologic abnormalities of the brain are relatively uncommon: microcephaly was found only in six patients. Four patients had arhinencephaly (the absence of olfactory bulbs). Holoprosencephaly, agenesis of the corpus callosum, Dandy-Walker anomaly, dilatation of cerebral ventricles, or hypoplastic cerebellum were reported in 1-2 patients each.

Defects of the eyes are generally uncommon. There are four reports of microphthalmia, three reports of corneal opacity, and sporadic reports of cataract, coloboma, or abnormal retinal pigmentation. At least four patients had ptosis, and two had blepharophimosis.

Hearing impairment was reported nine times. Several patients had stenotic auditory canals, microtia, or preauricular tags.

Cleft lip or palate is a common manifestation of mosaic trisomy 14. Ten patients had cleft palate, three had cleft lip and palate, and one had cleft lip only.

Abnormal pigmentation of the skin (usually as areas of hyper- and hypo-pigmentation along Blashko lines is very common (23/58)). These pigmentary defects may be absent at birth, but they appear in children of 1-2 months. Another common manifestation (13/58) is body asymmetry, when one side is larger than the other. However, both pigmentary anomalies and asymmetry of the body are not specific traits of mosaic trisomy 14, but reflections of the mosaicism itself. Similar defects may be found in other conditions when the patient has different clones of cells.

The most common and most significant visceral defects are heart defects, which were reported in more than half of the patients. The most serious defect, tetralogy of Fallot, was found in nine patients. Thirteen had ventricular septal defects, and eleven had atrial septal defects. Heart defects are the main cause of lethality in patients with mosaic trisomy 14. Gastro-intestinal defects are represented by omphalocele (3), intestinal malrotation (3), ventral ectopia of the anus (6). No patient, however, had anal atresia.

Two patients had diaphragmatic hernia. Abnormal lobation of the lungs was reported in two other persons.

Defects of the kidneys are not characteristic. There is no recurrent pattern of renal abnormalities in these patients.

Vital prognosis depends on the status of visceral organs, mainly the heart. The patients without heart defects may survive until adulthood, but they reveal an evident delay in psycho-

motor development.

Except one family when a child with mosaic trisomy 14 was born by the mother having the same mosaicism, all other patients with mosaic trisomy 14 were results of sporadic mutation with negligible risk of recurrence in future pregnancies.