



Chromosome 4

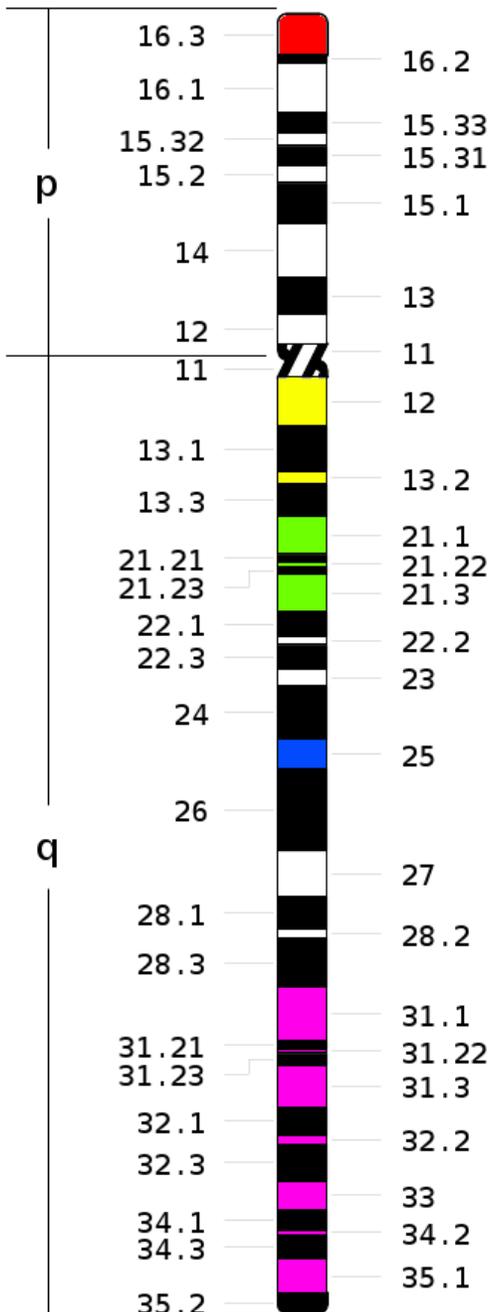
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David Adler.hum_04.gif



Introduction

The genetic size of this chromosome is ~190 Mb. It is almost 6.5% of the total human genome. The length of the short arm is ~40 Mb; the length of the long arm is ~150 Mb.

Different sources show various numbers of genes on this chromosome: from ~1,000 genes to ~1,500 genes. At least 10% of these genes are known to be involved in a variety of different functions in the body.

At least 2,200 patients with different structural abnormalities of chromosome 4 (as a sole abnormality or in association with another chromosomal imbalance) are known from the literature, including ~1,500 patients with deletions. Almost half of these reports, however, are related to one form of deletion of the short arm (Wolf–Hirschhorn syndrome). However, most forms of the long arm deletions are also well delineated. At least 20 patients with deletions of each segment of 4q are known from the literature.

The Wolf–Hirschhorn syndrome caused by a deletion involving 4p16.3 is the only well delineated syndrome of 4p deletion. Proximal deletions of 4p (not involving 4p16.3) are rare. There are at least 5 syndromes caused by deletions of the long arm: two of these conditions (del 4q13.3q21 and del 4q21) still are being delineated.

Deletions of Chromosome 4

The genetic size of chromosome 4 is ~190 Mb, where the short arm is ~40 Mb. Terminal deletions of the short

arm cause Wolf–Hirschhorn syndrome. Deletions of different segments of the long arm are responsible for several syndromes.

Deletions of 4p

Wolf–Hirschhorn Syndrome

The loss of the distal part of the short arm of chromosome 4 causes the Wolf–Hirschhorn syndrome. Historically it is the first syndrome of autosomal deletions found in humans. The first description of a patient with this condition was published almost 50 years ago — in 1961. This report by Hirschhorn and Cooper from New York appeared in “Human Chromosome Newsletter” — a semi–official journal, which was published in the USA by T.Hsu and distributed to the centers involved in cytogenetic studies. In 1965, in the same issue of “Humangenetik”, there were two official articles about this condition. One was written by the group of Wolf (Germany); another was an expanded version of a Hirschhorn and Cooper publication. The term Wolf–Hirschhorn syndrome (WHS) became widely accepted as a name for this entity.

More than 700 patients with WHS have been reported to date. Of course, it is only the tip of the iceberg. When any syndrome is a new entity, a description of each patient may bring some additional details about this condition. Usually, when 40–50 patients with the given syndrome have been already published, only patients with unusual clinical and cytogenetic characteristics are likely to be described. It is obvious that each cytogenetic group has several observations of WHS, which are unpublished. The groups specially involved in the study of this condition report about 30–40 “own” observations.

Although WHS is a very “old” syndrome, the clinical picture of the syndrome has been drastically changed for the last 5–7 years. New technologies showed that the main (or at least diagnostic) features of WHS are caused by a small deletion of 4p16.3 [the most terminal segment of 4p]. These small deletions could not have been detected without molecular technologies and remained unrecognized. Only patients with large deletions could be diagnosed by “standard” cytogenetics. Most of these patients had a complex of serious malformations, which determined the clinical image of WHS. At the same time, the patients with tiny deletions of 4p16.3 have some typical facial features, but usually do not have defects of the eye, heart and kidneys, typical for “classical” WHS. Typical clinical features include prenatal hypoplasia (low birth weight even for those born at term), severe growth delay, and hypotonia. The facial appearance is usually described as “Greek warrior helmet” of the nose with high forehead, prominent glabella, protruding eyes, epicanthus, micrognathia, low set ears sometimes with lobeless pinnae, preauricular tags and pits. Microcephaly is a common sign (~90%). Hearing impairment was reported in ~40% of patients, abnormal dentition in 50%. Seizures occur in 90% of patients, usually within the first 3 years of life.

Molecular studies showed that a critical segment for WHS is an area ~165 Kb located at 4p16.3, approximately 2 Mb from the telomere. Later, a second critical segment (a little bit closer to the telomere) was found. Deletions of the most distal 0.4–0.5 Mb of 4p are relatively innocent; these deletions may be found in completely normal individuals and considered as a familial variant.

Some data show that microcephaly occurs in patients having deletions of more than 2.2 Mb of 4p16.3 and cleft palate in patients with deletions of more than 2.5 Mb. Loss of at least 3.5 Mb is necessary for the origin of hypospadias, at least 5 Mb should be lost for the origin of heart defects, and at least 8 Mb for the origin of renal abnormalities.

From the clinical point of view, all WHS patients may be subdivided into 3 groups: patients with small terminal deletions (<3.5 Mb), patients with average deletions (4–18 Mb) and patients with large deletions (usually >20 Mb). Typical face, seizures, prenatal hypoplasia, delay in postnatal development, hypotonia, microcephaly and small skeletal defects occur in all 3 groups with the same frequency. All patients with large deletions manifest severe mental retardation; 76% of patients with small deletions have only mild mental retardation. The relative frequency of some other defects in patients with a different size of deletion is shown in the table (adapted from Zollino et al., 2008).

Occurrence of congenital defects in patients with different size of 4p deletion

Type of Defect	Small deletions	Medium deletions	Large deletions
Cleft lip and palate	8%	25%	44%
Coloboma and other eye defects	0%	30%	80%
Congenital heart defects	2%	52%	70%
Defects of kidneys	2%	37%	38%

Abnormalities of the eyes are frequent manifestations in WHS, especially in patients with medium or large deletions. A typical defect is coloboma iris and/or choroid. Multiple other defects (microphthalmia, cataracts, glaucoma, microcornea, corneal opacity) have been reported in several patients each.

Congenital heart defects are frequent, but usually not life-threatening. There is no typical type of heart defect in WHS. Most reported defects were atrial septal defects (ASD), ventricular septal defects (VSD), and stenosis of pulmonary artery.

Defects of kidneys, although not so frequent as heart defects, may be clinically very significant. Most patients have hypoplastic kidneys, sometimes with cystic lesions. Hydronephrosis, horseshoe kidney, and malposition of kidneys have been also repeatedly reported. Most boys have hypospadias. Bifid uterus is relatively frequent among affected girls.

Diaphragmatic hernia, ectrodactyly, and polydactyly have been reported in ~10 patients, each. However, these defects are rare (less than 2%) and certainly the patients with unusual defects are more likely to be published. Analysis of cognitive and behavioral characteristics showed that in patients with predominantly small deletions, the level of socialization was significantly higher than the level of communication.

WHS is a well known condition. There are several sources of detailed information regarding different aspects of this syndrome. Publications of Battaglia et al. (2008), Fisch et al. (2008) and Zollino et al. (2008) may be recommended for more comprehensive information about WHS.

From the genetic point of view, in a very large proportion of patients, the deletion was a result of a translocation. Most of these translocations could be detected only using contemporary methods of molecular cytogenetics. The most frequent translocations involve 4p and 8p.

Genetic prognosis depends on cytogenetic status of the parents: risk for the sibs will be negligible if the deletion occurred de novo. Risk will be high if one parent has a translocation or other structural chromosomal rearrangement.

There are 30–40 reports about interstitial deletions of 4p, not involving 4p16.3. Clinical presentations in the patients are not sufficient for delineation of a syndrome. Even patients having the same deletion are very heterogeneous. The only exception may be the presence of periventricular heterotopia (occurrence of nests of neurons in unusual places about brain ventricles) found in several patients with del(4)(p14p15.32). However, descriptions of syndromes caused by small deletions (discovered by molecular methods) are appearing every week, and it cannot be excluded that a syndrome caused by the interstitial deletion of the proximal segments of 4p will be described in the nearest future.

Deletions of 4q

The genetic size of the long arm of chromosome 4 is ~150 Mb. There are at least 300 reported patients with different deletions 4q without any additional imbalance. At least 200 more patients had associations of monosomy 4q with partial trisomies for other chromosomes (or for other parts of chromosome 4). Only the patients without additional imbalances will be analyzed here.

Deletions of 4q12q13

There are ~25 reports about patients with deletions within 4q12q13. The most common manifestation of this deletion (found in ~50% of patients) is piebaldism — an association of the white forelock and scattered areas of hypo- or hyperpigmentation of the body. Some patients may have hearing impairment. Most patients are delayed in psycho-motor development. The critical segment for piebaldism is limited to 11.5 Mb (53 Mb – 64.5 Mb) and contains the gene cKIT, which is responsible for the origin of piebaldism.

The main manifestations in another group of patients with del 4q12q13 are microphthalmia and coloboma. The critical segment for these defects is almost the same (53.2 Mb – 62.5 Mb). It is not known yet which deletion of which gene is responsible for the origin of microphthalmia and coloboma in these patients.

To date, all reported patients with del 4q12q13 and piebaldism did not have either microphthalmia or coloboma.

Deletions of 4q13.3q21

Four patients with deletions involving this segment of chromosome 4 had short tubular bones. The critical segment for this defect is a 14.4 Mb area in 4q13.3q21.3. It is not known which gene is responsible for this defect.

Deletion of 4q21

Very recently, a group of French geneticists proposed a syndrome caused by microdeletion 4q21. They believe that clinical manifestations of this microdeletion include severe mental retardation, absent speech and significant growth delay (between -3.5 SD and -6 SD).

Deletion of 4q25 and Rieger Syndrome

The so-called Rieger syndrome is an association of defects of the eye, teeth and umbilicus. Ocular manifestations of the syndrome include anterior displacement of Schwalbe's line (posterior embryotoxon), peripheral iris strands extending to Schwalbe's line, and thinning of the iris with atrophic "holes". These defects may lead to easily recognizable ectopia of pupils. Sometimes, however, the defects may be found only by eye exam. Glaucoma, which occurs in ~50% of patients with Rieger syndrome, is the most serious problem. Defects of the teeth may be seen as small teeth (microdontia), incomplete set of teeth (hypodontia), or an abnormal form of teeth. Redundant skin in the periumbilical area is the most common umbilical defect. Rieger syndrome is inherited as an autosomal-dominant trait with variable expressivity. Mutations of the PITX2 (or RIEG1) gene at 4q25 are the most common genetic base of this condition.

Deletions of 4q25 (with a deletion of the PITX2 gene) may also cause a phenotype of the Rieger syndrome. Out of 27 currently known patients with deletions involving 4q25, 13 had manifestations of Rieger syndrome. Some of these patients were developmentally delayed; mental development in others was normal. Associated deletions of more distal segments may cause some additional defects (cleft palate, hearing impairment, anteriorly placed anus). Possibility of microdeletion 4q25 should be considered when a patient with Rieger syndrome, dysmorphisms, or mental retardation does not have a family history and is negative for the PITX2 mutation.

Terminal Deletions of 4q

There are more than 100 reports about patients with terminal deletions of 4q with approximately equal representation of deletions 4q31qter, 4q33qter and 4q34qter. Clinical manifestations in these patients are relatively common: postnatal growth retardation (although almost all have a normal birth weight), relatively mild delay of psycho-motor development (some patients have almost normal development), facial dysmorphisms (hypertelorism, depressed nasal bridge, small defects of external ears, micrognathia), and very characteristic

anomalies of the 5th fingers. These fingers are short, incurved, with ankylosis of the distal interphalangeal joint, usually with a very thick nail. Sometimes, this finger is described as “pointed” and the nail as “ram’s horn–shaped”. ~2/3 patients have these defects of the 5th fingers. Microcephaly is relatively frequent; it may be found in 30–35% patients. Other frequent defects are cleft lip and palate (or cleft palate only) and different kinds of congenital heart defects, sometimes very serious (tetralogy of Fallot, atrio–ventricular communication). Hearing defects are found in ~15% patients. Numerous abnormalities of other systems have been reported in a small subset of affected patients.

Because most manifestations in the patients with del 4q31qter and 4q33qter are similar, there are contradictory opinions whether to consider all distal deletions of 4q as one or two syndromes). A significant number of reported observations allows comparing manifestations in these patients.

Table: Clinical Data of Patients with Terminal Deletions of 4q

Birth Defect	Del 4q31qter (n=35)	Del 4q33qter (n=38)	Del 4q34qter (n=30)
Cleft palate	14	11	2
Cleft lip and palate	8	2	0
Hearing impairment	5	5	0
Congenital heart defects	17	16	7
Abnormal corpus callosum	3	0	0
Duplication of collecting system in kidneys	4	0	0
Inguinal hernia	6	4	1
Hypospadias	2	2	0

These data show that cleft lip and palate occurs predominantly in patients with larger deletions. Patients with these deletions also have some rare defects (abnormal corpus callosum, microphthalmia, cervical ribs, duplication of the collecting system in kidneys), which have not been mentioned in patients with more terminal deletions.

Several reports of cleft lip and palate in patients with interstitial deletions 4q31.21q31.22 show that this area has to harbor at least one gene, which (when deleted) may cause this defect.

There are at least three reports of ectrodactyly (absence of 1–2 “central” fingers or toes) in patients with distal monosomy 4q. The finding of this defect in a person with interstitial deletion 4q31.1q31.3 allows the thinking that one of the genes in this segment sometimes causes ectrodactyly, although at least 90% of patients with this deletion do not have this defect. Another unusual limb defect in the patients with distal 4q deletions is the underdevelopment or absence of ulnar bones with absence of the 3rd–5th fingers. This defect was reported in three patients with “pure” 4q terminal deletions, one patient with association del 4q with partial trisomy 20p, and in two patients with interstitial deletions of 4q. Molecular

studies showed that this defect, virtually unique for patients with chromosomal syndromes is caused by the deletion of 4q34.1.

Diaphragmatic hernia and tracheo–esophageal fistula (TEF) are very rare manifestations of distal monosomy 4q, but each of these serious manifestations was reported in 3–4 patients each. The gene for TEF should be expected at the very terminal part of 4q. The position of the genes responsible for diaphragmatic hernia is uncertain. However, it should be noted that all of these defects (ectrodactyly, underdevelopment of ulnar structures, diaphragmatic hernia, TEF) are found in a very small proportion of affected patients. For some reason, these genes remain silent in 90% of patients. Therefore, deletions are necessary, but not sufficient, for the origin of these defects.

Most terminal deletions of 4q are sporadic events. However, a significant number of patients have associations of monosomy 4q with partial trisomy for another chromosomal segment (due to familial translocations) or with partial trisomy 4p (due to familial pericentric inversions). Recurrence risk is negligible for families with sporadic rearrangements. If one of the parents had translocation or inversion), risk (basically relatively high) will depend on the exact formula of rearrangement.

Ring Chromosome 4

This type of ring chromosome is relatively frequent: at least 66 patients with ring chromosome 4 have been reported so far. Six of these patients had mosaicism with a normal clone, three patients had translocations of the one of the broken segments to another chromosome, one patient was a mosaic with a 46,4p– clone, and one was a mosaic with a 46,4q– clone.

Approximately 15 of the known patients did not have any significant birth defects. Obvious manifestations of the Wolf–Hirschhorn syndrome were found in 10–12 children. Another patient had anomalies (e.g., microcephaly, cleft lip and palate, heart defects, absent or hypoplastic kidneys, hypospadias), which may be caused both by deletions of the distal segments of the short and long arms of chromosome 4.

At least 10 patients with ring chromosome 4 had absent or hypoplastic thumbs. In some patients, the absence of thumbs was accompanied by the absence of the radius or even both forearm bones. This defect is not characteristic either for the deletion of the short arm or for the deletion of the distal tip of the long arm. Most likely, these defects are caused by an interaction between some genes of 4p and 4q, which were lost (or rearranged) upon formation of the ring. Numerous other defects (trigonocephaly, microphthalmia, ectrodactyly, preaxial polydactyly, diaphragmatic hernia, anal stenosis, hypoplastic thymus) were reported in 1–2 patients each.

Familial transmission of ring chromosome 4 has not been reported so far.

Partial Trisomies for Chromosome 4

Partial Trisomies for 4p

Trisomy for the short arm of chromosome 4 is a relatively well-recognized condition known since the 1970's. More than 200 patients with various forms of trisomy 4p have been reported. Most of these patients, however, do not have a "pure" trisomy 4p, but trisomy 4p in association with partial monosomies for other chromosomes (due to translocations) or partial monosomy 4q (due to pericentric inversions). Another sub-type of partial trisomy 4p has been reported in recent years: there are ~15 observations, where a duplication of 4p was associated with a tiny deletion of the terminal segment of 4p. Because this segment contains genes responsible for most manifestations of Wolf-Hirschhorn syndrome, patients with this sub-type had mainly Wolf-Hirschhorn-related features. All of these "additional" imbalances can significantly modify clinical manifestations of "pure" trisomy 4p. Nevertheless, there are ~70 observations, which may be considered as "pure" trisomy 4p.

Prenatal hypoplasia is not characteristic: most patients have normal birth weight. However, postnatal growth retardation is typical. Most patients have a borderline head circumference (with microcephaly in ~20% of the affected persons) and multiple dysmorphic characteristics: relatively rough facial features, bulbous nose with prominent glabella, hypertelorism, micrognathia, pointed chin, high arched palate, abnormally shaped low-set posteriorly rotated ears, and short neck with low hairline. None of these findings is pathognomonic or specific: all of these abnormalities also may be found in numerous other forms of structural autosomal imbalance.

Abnormalities of skeletal system are very frequent: a significant number of patients have scoliosis, contractures, brachydactyly, camptodactyly, 11 pairs of ribs, hypoplastic 1st ribs, or dysplastic hips. Two patients had preaxial polydactyly (an additional digit on the side of the thumb or great toe). At least 2 patients with "pure" trisomy 4p had spina bifida.

A small sub-group of patients with trisomy 4p has structural eye defects, including microphthalmia and coloboma. [Several patients who had trisomy 4p in association with other defects even had anophthalmia]. The critical segment for eye defects is 4p15p16.

Heart defects were confirmed (or suspected) in 10 patients with "pure" trisomy 4p. In some patients, their defects were very serious, including single reports of truncus arteriosus, hypoplastic left heart, pulmonary atresia, or double outlet of the right ventricle. Other heart defects were relatively mild and not life-threatening.

Abnormalities of the respiratory system (choanal stenosis, hypoplastic lungs, hypoplastic larynx), digestive system (omphalocele, atresia ani) or kidneys (hypoplastic kidneys, hydronephrosis) were reported in 1-2 patients, each.

If defects of the eyes and internal organs are non-obligatory findings of trisomy 4p (most patients do not have any of these abnormalities), moderate delay in psycho-motor development is a constant manifestation. Some patients may have seizures.

Surprisingly, there is no correlation between the severity of the syndrome and the size of the duplication. Several patients with trisomy for the whole short arm of chromosome 4 did not have any defects of the internal organs and eyes. At the same time, there are severely affected patients with duplications limited to the distal part of 4p (4p15-pter). Most likely, duplication of 4p15 is critical for the clinical manifestations of this syndrome.

Partial Trisomies for 4q

The long arm of chromosome 4 is a large segment of chromosomal material. It contains more than 140 Mb: more than the whole chromosome 10. More than 280 patients with different kinds of trisomy 4q have been reported so far. However, at least 2/3 of these patients also had an additional imbalance, mostly as a result of translocations and inversions. "Pure" trisomy 4q occurs (or at least has been recognized) relatively rarely: there are only ~90 reports on such patients. Surprisingly enough, there are no recognized syndromes, associated with such trisomies.

"Proximal" trisomies 4q (trisomies 4q1)

At least 12 patients had trisomies limited to the proximal segment of 4q (from the centromere to 4q21). The most common manifestations in these patients are obesity and skeletal abnormalities (kyphosis, scoliosis). Coloboma iris, cleft palate, and preauricular fistula were reported in one person, each. Not a single patient had defects of the brain or heart. Intellectual development was normal in most patients.

Trisomies for the "medial" segment of 4q (4q2)

Trisomies limited to the 4q2 segment were reported in 15 patients. Clinical manifestations vary in different people, even with apparently the same duplication.

The most common abnormalities are heart defects (6/15), including patients with hypoplastic left heart and tetralogy of Fallot. Other heart defects were not life-threatening.

Other recurrent abnormalities include craniosynostosis (2), coloboma (2), cleft lip and/or palate (2), short neck (2), low set thumbs (2), short hands (2), and sacral dimple (2).

There is no common conclusion regarding psycho-motor development: some patients were intellectually normal (or subnormal), other revealed significant delay in psycho-motor development. It should be noted that several patients with very large trisomic segments involving mostly 4q2 (up to 70 Mb: much larger than the whole chromosome 19 or 20) did not have significant abnormalities.

Distal trisomies 4q (4q3)

This group includes ~60 reported patients with trisomies involving the distal third of 4q. The actual size of the duplication and the positions of the breakpoints were different in almost all persons.

A different degree of delay in psycho–motor development (usually relatively mild) is a common trait. Some patients with distal trisomy 4q developed epileptic seizures. Autism and autistic–like features seem to be uncommon, although some children had these manifestations.

Almost all patients had facial dysmorphism, but the dysmorphia is not characteristic or unique. Cleft lip and palate was reported only twice.

Structural abnormalities of the brain are not characteristic: several patients had microcephaly, two had partial agenesis of the corpus callosum. Defects of the eyes are represented by colobomas (3) and dacryostenosis (2). There are also reports of microphthalmia or even anophthalmia. However, the vast majority of patients with distal trisomy 4q do not have brain or eye defects. Hearing impairment was reported in 5 patients.

A significant number of children with this trisomy have muscular hypotonia. Umbilical and inguinal hernias are very common. Some patients had contractures, brachydactyly, dislocations of the hips.

Heart defects are the most common. They were reported in 14 patients, including 3 with tetralogy of Fallot, 6 with patent ductus arteriosus, and 4 with ventricular septal defect.

Hypoplastic kidneys were found in 4 patients, dilated ureters in 2. Two persons had Hirschsprung's disease [actually these patients had a triplication (not a duplication) of the 4q32 segment].

At least 10 patients with “pure” trisomy 4q3 (all having a common trisomic segment 4q31) had various abnormalities of radial structures: absent thumbs (2), hypoplastic or finger–like thumbs (5) or preaxial polydactyly (3). Surprisingly, not a single patient had postaxial defects (although generally postaxial polydactyly occurs more commonly than the preaxial one).

Analysis of patients having an associated imbalance for other chromosomes shows the same picture: absent thumbs were reported in 4 patients, hypoplastic or finger–like thumbs in 8, and preaxial polydactyly in 6. It is evident that both types of defects (underdevelopment of thumbs or development of an additional digit from the radial side) are controlled by the same duplicated segment. However, it is unclear which factors switch development to either of these opposite directions.

Relatively small duplications may be inherited from unaffected (or minimally affected) parents. Cytogenetic examination of the parents is absolutely necessary for counseling regarding further offspring in the families.

Trisomy 4

Trisomy 4 is also a very rare abnormality. Confined placental mosaicism was found in four out of 14 known reports on trisomy 4. Three out of four patients with confined placental mosaicism were completely normal, and one had microcephaly.

Nine of ten patients with trisomy 4 in their cells were mosaics, including two with unusual mosaicism: one had a normal clone, a clone with trisomy 4, and a clone with trisomy 6; another had a clone with trisomy 4 and a clone with monosomy 21.

Most persons with mosaic trisomy 4 have facial dysmorphism and very serious birth defects. Brain defects were reported three times: holoprosencephaly (2) and severe hypoplasia of the cerebellum.

Heart defects are almost constant. They were found in eight out of ten persons. Most heart defects were very serious: atrio-ventricular communication (2), monoventricular heart (1), tetralogy of Fallot (1), and truncus arteriosus (1).

Most patients have a remarkable spectrum of limb defects. Abnormalities of preaxial structures are especially common: three patients had absent thumbs, and two had preaxial polydactyly or triphalangeal thumbs. Similar defects may be found in patients with partial trisomies in the area of 4q28q31, but they occur with much lesser frequency. Other limb defects include partial syndactyly (4), underdeveloped toes, and camptodactyly. There are several reports of scoliosis, vertebral defects and rib abnormalities.

Gastro-intestinal defects include Hirschsprung's disease, anal atresia and anal ectopia. Two patients had renal defects: dystopia kidneys (kidneys in an unusual position) and dysplasia kidneys (an abnormal structure of renal tissue, usually with small cysts). Both known adult patients with mosaic trisomy 4 had delayed sexual development.

Psycho-motor delay is common for all patients with trisomy 4 who could be evaluated.