Chromosome 6

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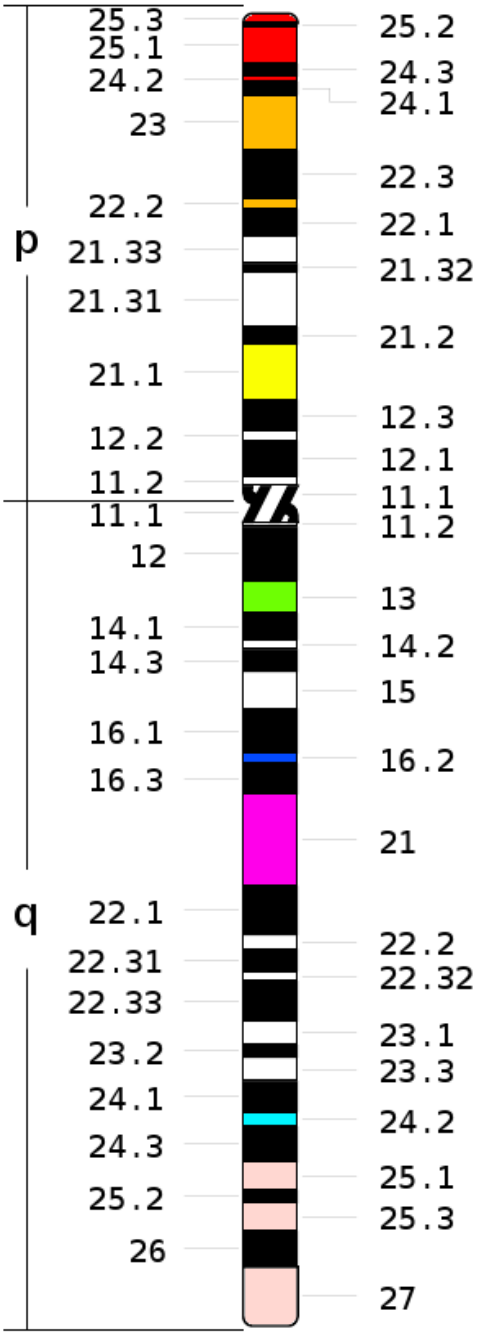

Introduction

The genetic size of chromosome 6 is ~170 Mb: its short arm is ~60 Mb, and its long arm is ~110 Mb. Chromosome 6 has ~5.5–6% of the total genetic material in humans. It contains ~1,300–1,400 genes. Many of these genes are involved in the formation of body organs (and malfunction of these genes cause birth defects). Other genes are involved in numerous functional characteristics, including occurrence of seizures, delay in psycho–motor development, or obesity.

There are ~1,300 reports of patients having different structural abnormalities of chromosome 6, including ~800 reports of patients with deletions of chromosome 6 as a sole abnormality or in association with other chromosomal abnormalities.

There are 3 syndromes caused by deletions of the short arm and at least 5 syndromes caused by deletions of the long arm. All of these syndromes were known before wide usage of molecular cytogenetics. New methods, however, allow a more precise image of these conditions and pinpoint the genes responsible for specific manifestations in each of these syndromes.

Deletions of Chromosome 6

The genetic size of chromosome 6 is ~170 Mb, where the short arm is ~60 Mb. Deletions of the short and long arms cause several syndromes. Some syndromes are relatively well–known; others have been delineated only recently.

Deletions of 6p

Deletions of 6p12.3p21 and Cleido–cranial Dysplasia

Cleido–cranial dysplasia (CCD) is a hereditary condition characterized by the absence (or hypoplasia) of clavicles, delayed closure of the fontanels, and dental anomalies. Mutations in the RUNX2 gene (the transcription factor necessary for maturation of osteoblasts and differentiation of chondrocytes) are responsible for CCD in the majority of patients with this disorder. This gene maps to chromosome 6p12.3p21, and deletions involving this area are shown to be responsible for CCD in a group of patients. Currently, deletions in this area were found in ~10 patients with CCD. Associated deletions of neighboring genes may lead to some additional abnormalities: heart defects, hearing impairment, choanal atresia.

Patients with CCD, especially with some additional defects and without familial history (CCD is usually inherited as an autosomal–dominant trait), should be tested to exclude deletions in this area.

Interstitial deletions of 6p22p24

Interstitial deletions involving (at least partially) the segment 6p22p24 have been reported in ~20 patients, although some of these patients were described before the invention of the precise methods to localize the breakpoints. There are several attempts to delineate a syndrome caused by these deletions. The most common findings in these patients are developmental delay, hypotonia, short neck, small abnormalities of extremities (clinodactyly, partial syndactyly 2–3 toes), hearing impairment, and abnormalities of the kidneys. Several patients had defects of the brain (hypoplastic cerebellum, hypoplastic corpus callosum, hydrocephaly). ~50% of patients with this deletion have heart defects, usually relatively mild (ventricular septal defects, patent ductus arteriosus). However, there are also reports of cardiomyopathy and interrupted aortic arch (IAA).

The critical segment, responsible for this condition, may be narrowed down to 2 Mb within 6p22.3.

Terminal deletions of 6p

Terminal deletions of 6p are much more common than interstitial deletions of 6p22p24. Different variants of terminal deletions as a single anomaly were reported in ~75 patients. This group may be subdivided into 2 subgroups: ~30 patients with terminal deletions involving 6p24 and ~45 patients with terminal deletions limited to 6p25. Eighty more patients had associations of distal deletions of 6p with partial trisomy 6q (as a result of inversion) or with partial trisomy for another chromosome (as a result of translocation).

There is a clinically recognizable syndrome associated with terminal deletions of 6p. Four main groups of abnormalities: defects of the brain, eye, heart, and hearing impairment are typical for these patients.

External manifestations are relatively unspecific. They include down–slanting palpebral fissures, hypertelorism, ptosis, flat nasal bridge, abnormal form, and position of the ears. The most common brain defect is Dandy–Walker malformation (DWM) — association of hypoplastic cerebellar vermis and cystic dilatation of the 4th ventricle. In this syndrome, DWM is usually associated with hydrocephaly. Different variants of DWM are found in ~60% of patients who had examinations of the brain necessary for diagnosis of this condition. Molecular studies showed that the deletion of the FOXC1 gene located at 6p25.3 (~1.5 Mb

from the telomere) is a major contributor for the origin of this defect. Some patients had other rarely occurring brain defects (holoprosencephaly [HPE], agenesis or hypoplasia of corpus callosum, trigonocephaly).

Most ocular defects are variants of Rieger (or Axenfeld–Rieger) anomaly, which consists of defects of the anterior segment of the eye, including posterior embryotoxon, corectopia, hypoplastic iris, corneal opacity, sclerocornea or megalocornea. These abnormalities may lead to glaucoma, which was reported in several patients. Basically, the Axenfeld–Rieger anomaly is etiologically heterogeneous: it may be caused by mutations of the PITX2 gene (or deletions of 4q25), deletions of 13q14, etc. In patients with terminal deletions of 6p, Axenfeld–Rieger anomaly is caused by the deletion of the same gene, FOXC1, which is responsible for DWM.

Other structural eye defects, found in patients with distal del 6p, include microphthalmia and coloboma. However, these defects occur rarely.

Hearing defects were reported in ~50% of evaluated patients.

Different heart defects (mostly patent ductus arteriosus, ventricular or atrial septal defects, abnormal aortal valves) were found in about half of the patients. It should be noted, however, that at least 3 out of 18 patients with heart defects in the subgroup of the deletion involving 6p24 had interrupted aortic arch (IAA) — a very rare and very serious type of heart defect. Not a single person (out of 20 having heart defects) with deletions limited to 6p25 had this defect.

A significant number of patients with deletions involving 6p24 (11/30) have cleft lip and palate, although this defect was not reported among patients with more distal deletions. The same is true for kidney abnormalities (cystic kidney, hydronephrosis, which were found in 10 out of 30 patients with larger deletions, but not in the patients with deletions limited to 6p25.
Most likely, 6p24 harbor some genes, which (when deleted) may lead to cleft lip and palate, IAA and defects of the kidneys.

Defects of other systems are not typical for patients with distal deletions of 6p.

There is some similarity between clinical manifestations of distal 6p deletions and the so–called cranio–cerebello–cardiac (or Ritscher–Schinzel syndrome). However, most patients with this syndrome have colobomas, but not defects of the anterior segment of the eye. There is one report of an isolated deletion of 6p24.3 in a family with branchio–oculo–facial syndrome. This syndrome includes cervical cysts, eye defects (microphthalmia, colobomas, cataract), cleft lip and palate. Analysis showed that this syndrome is caused by a mutation of the TFAP2A gene, located at 6p24.3. Deletions of this region (involving the deletion of the TFAP2A gene) may produce a similar phenotype. It cannot be excluded that the deletion of this gene was responsible for structural eye defects and cleft lip and palate in patients with terminal deletions involving 6p24. However, neither of the previously reported patients with deletions 6p24 had cervical cutaneous abnormalities or dermal thymus.

Deletions of 6q

The genetic size of the long arm of chromosome 6 is ~110 Mb. Several hundreds of patients

with different deletions of 6q have been described in the scientific literature. To date, several syndromes caused by 6q deletions have been delineated.

Deletions of 6q11q14

There are ~30 reports about patients having deletions of the most proximal area of 6q. Most of these patients have hypotonia, relatively mild delay in psychomotor development, short stature, complex of cranio–facial anomalies (hypertelorism, epicanthus, short nose, broad nasal tip, thin upper lip, low set dysplastic ears), short neck, mild syndactyly, hypermobile joints, and umbilical hernia. Most these abnormalities, however, are frequent manifestations in numerous other chromosomal deletions or duplications. At least two patients with these deletions had craniosynostosis (premature fusion of cranial bones). Mild defects of kidneys (hydronephrosis, ectopic kidney, vesico–ureteral reflux) are also common, but defects of the brain, heart or gastro–intestinal tract are not typical.

Association of kidney defects and hypermobility of joints may be considered as hallmarks of this condition.

Deletions of 6q16

Deletions of 6q16 (sometimes with deletions of 6q15 or 6q21) have been reported in ~40 persons. Clinically, these patients are similar to the patients with Prader–Willi syndrome. Mild developmental and language delay, obesity, hyperphagia, behavioral problems (temper tantrums, stereotypic movements, sometimes autistic features) are the most characteristic features of this deletion. Cranio–facial abnormalities are mild and non–specific: some patients have macrocephaly, low–set ears, microretrognathia. Defects of the internal organs are not typical (at least in patients without associated deletions of 6q21).

The breakpoints of these deletions are different in all patients, but all patients with obesity and a Prader–Willi–like phenotype lack the segment between 100 and 101 Mb. The deletion of the gene SIM located in this area seems the most reliable explanation of these abnormalities.

Deletion of 6q21

Deletions involving the loss of the 6q21 segment have been reported in ~70 patients. However, clinical manifestations in these patients are very different, and the syndrome, associated with this deletion, has not been delineated so far.

Most patients with deletions involving 6q21 have serious defects of the limbs and the heart. Some of them also have defects of other systems.

At least 10 children with these deletions had ectrodactyly of the hands (absence of 1 or 2 central fingers), sometimes in association with the absence or underdevelopment of ulnar bones. In some patients, ectrodactyly on one hand was accompanied by monodactyly (presence of only one finger) on another hand. Central polydactyly, triphalangeal and finger–like thumbs have been reported in several children.

Different heart defects were mentioned in ~30 patients in this group, and at least 10 of them had tetralogy of Fallot. These heart defects may be life–threatening. Most other patients had

atrial or ventricular septal defects or patent ductus arteriosus.

Defects of the brain (hydrocephaly, hypoplastic cerebellum, agenesis of corpus callosum) have been described in several patients, but most reported patients did not have any structural abnormalities of the brain. At least three patients had microphthalmia; four had cleft palate. Defects of the gastro–intestinal system are uncommon, but duodenal atresia and abnormal position of anus have been noted in two patients each. Abnormalities of kidneys, different in all patients, were found in 6–7 children. There are numerous reports of very uncommon abnormalities: laryngeal cleft, diaphragmatic hernia, spina bifida, aplastic thymus, and pigmentary retinitis. However, all of these defects were reported in one patient each and their relationship with deletions remains unclear.

The primary genetic reasons for the origin of ectrodactyly and tetralogy of Fallot remain unknown, but the role of deletion 6q21 in their origin is undeniable.

Deletion of 6q24

Methods of molecular cytogenetics widely used in the last years allow precise characterization of breakpoints in patients with different deletions. As a result, it became possible to describe many new syndromes caused by deletions. Clinical descriptions of several of these “new” syndromes are based on several reports. Deletion of 6q24 belongs to this group.

There are less than 10 reported patients having this deletion. These patients have intrauterine and postnatal growth retardation, developmental delay, short up–slanted palpebral fissures, intraorbital folds, dysplastic low–set ears, anteverted nares and thin upper lip. Most of them have different types of heart defects. Defects of other systems are not typical. All of these manifestations are caused by the deletion of the sub–segment 6q24.3. Involvement of more distal segments (6q25.1) may produce other abnormalities not typical for 6q24 deletion. Moreover, it cannot be excluded that clinical manifestations in the patients who lost a segment of the paternal chromosome 6 may be different from the patients who lost a segment of the maternal chromosome 6. Further observations are needed for answering these questions.

Terminal Deletions of 6q

Terminal deletions of 6q are relatively well–known. In the literature, there are descriptions of ~100 patients with isolated terminal deletions of 6q; ~70 or more patients had associations of deletions 6q with partial trisomy for another chromosome. The patients with isolated terminal deletions may be sub–divided into four “sub–groups”: patients with deletions 6q25–qter (36 reported patients), with deletions 6q26–qter (13 reported patients), with deletions 6q27–qter (17 reported patients) and 31 patients where deletions were characterized as 6qter.
Most (80%) patients with isolated deletions have microcephaly in association with characteristic facial features (broad nasal bridge with a bulbous tip, large malformed ears, “fish–like” mouth, micrognathia, high arched palate). Psycho–motor retardation and hypotonia are common signs, found in 75–80% of the affected persons. More than 30% of the patients had seizures. These findings are common for all “sub–groups” of patients.

A significant number of the patients have serious structural brain defects, mostly

hydrocephaly or absent (or hypoplastic) corpus callosum. Other defects of the brain found in persons with distal 6q deletions are cerebellar hypoplasia, large cysterna magna or polymicrogyria (small abnormally oriented gyri of the brain). Special studies showed that the distal part of 6q has a locus responsible for polymicrogyria. Traditionally, the distal part of 6q is not considered as a locus for (holoprosencephaly) HPE. However, there are ~10 reports of HPE in patients with distal deletions of 6q, including 6 reports in persons with isolated distal deletions of 6q. Most likely, this part of 6q contains a gene, which [in rare cases] may lead to HPE.

Heart and large vessels is another system which is frequently affected in patients with distal deletions of 6q, especially involving segment 6q25. The patients may have various forms of congenital heart defects, but usually these defects are not life–threatening. A significant number of patients, especially with deletions involving 6q25, have cleft palate, hearing impairment, preauricular sinuses, defects of vision (retinitis pigmentosa or macular degeneration), defects of the gastro–intestinal system (duodenal stenosis, dolichocolon, atresia ani) and kidneys. Several children with deletions 6q25qter had a cartilaginous tail–like appendix of the coccyx. It should be noted, however, that almost all of these defects (except heart defects) occur exclusively or predominantly in patients with del 6q25–qter. The patients with more distal deletions usually do not have cleft palate, defects of kidneys or gastro–intestinal systems. The relative frequency of these abnormalities in different sub–groups of patients with distal del 6q is shown in the table.

Interstitial deletions of chromosome 6 are mainly sporadic events, although some of these deletions may be caused by parental insertions. A significant number of terminal deletions of 6p and 6q may be caused by parental translocations or inversions (with a significant recurrence rate in a case of familial chromosomal rearrangement). Cytogenetic testing of the parents is a prerequisite for genetic counseling regarding further children in the family.

Table: Different Defects in Four "Sub–groups" with Distal Deletions of 6q

Type of Defect	Number of known patients in different sub–groups			
	q25–qter (n=36)	q26–qter (n=13)	q27–qter (n=17)	qter (n=31)
Hydrocephaly	10	3	2	3
Defects of corpus callosum	8	3	2	3
Holoprosencephaly	4	1	1	–
Other brain defects	5	3	–	6
Seizures	5	9	4	11
Congenital heart defects	21	1	–	3
Cleft palate	6	–	–	–
Preauricular sinuses/pits	4	–	–	–
Pigmentary retinitis	2	1	–	–

Macular degeneration	2	–	–	–
Hearing impairment	5	–	–	–
Kidney defects	7	–	–	–
Cartilagenous appendix on the coccyx	3	–	–	–
Stenosis of duodenum	2	–	–	–
Dolichocolon	2	–	–	–
Atresia ani	2	–	–	–

Ring Chromosome 6

Ring chromosome 6 is a relatively common type of ring chromosomes. At least 46 patients with r(6) have been reported so far. Only one of these patients had mosaicism with a normal clone, one had mosaicism with terminal deletion 6q27, and 8 had mosaicism with a clone without chromosome 6. However, in such patients, the origin of the monosomic clone is caused by the loss of r(6) upon cellular division, and we do not know at that stage of development that this loss has occurred.

Most patients with ring chromosome 6 have serious abnormalities. Only 15 patients did not have serious defects or had only mild abnormalities (short neck — 4, hearing impairment —2, scoliosis — 2, café–au–lait spots, umbilical hernia etc.). Other patients had abnormalities predominantly affecting the brain and eyes.

Hydrocephaly is the most common brain abnormality; it was reported in 16 patients with r(6). Agenesis or hypoplasia of the corpus callosum was found in 8 patients, cerebellar hypoplasia in 3. This group of brain defects is most likely caused by deletions of the genes of the short arm (hydrocephaly and cerebellar hypoplasia are common in patients with distal 6p deletions), although influence of the genes of the long arm cannot be excluded.

Holoprosencephaly and arhinencephaly reported in 3 patients with r (6) are almost certainly caused by the loss of the distal segments of the long arm. The occurrence of microcephaly may be the result of the loss both 6p and 6q genes.

Microphthalmia has been reported in 8 patients with r(6); 4 patients had retinal defects. Glaucoma, aniridia, optic atrophy and embryotoxon were found in 3 patients, each. Hypoplastic iris, Peters' anomaly, egalocornea and coloboma were also reported (most patients had more than one eye defect). These manifestations are caused by the loss of the genes of the short arm, which are responsible for eye development.

Cleft palate was found in 3 persons. At least 3 other patients had hearing impairment.

Heart defects were reported in 10 patients: only one of these patients had tetralogy of Fallot, and one had double outlet of the right ventricle. Defects in other patients (ventricular septal defect, patent ductus arteriosus, dysplastic or hypoplastic valves) were relatively mild.

Atresia ani reported in four patients with r(6) was most likely the result of the loss of the 6q genes. The same may be true regarding hypoplastic kidneys, hydronephrosis or horseshoe kidneys, found in five patients with r (6).

As a whole, analysis of manifestations in r(6) patients shows a mixture of very mild manifestations (which may be attributed to “ring chromosome” syndrome) and serious defects, caused by the loss of the genes both from the short and long arms.

Familial transmission of the ring 6 chromosome has not been reported.

Partial Trisomies for Chromosome 6

Partial trisomies 6p

The total number of reported patients with partial trisomies for the short arm of chromosome 6 is relatively large, but the vast majority of these patients also have partial monosomies for other chromosomes as a result of translocations, partial monosomy 6q due to inversions, or an association of duplication 6p with deletions of its distal part. Associated partial monosomies produce some additional manifestations. That is why reports of patients with additional imbalances were not taken into consideration.
Less than 90 patients who had “pure” partial trisomies of 6p were objects of the analysis.

“Proximal” trisomies 6p

There is a very small group of patients with duplications involving only proximal segments of 6p (6p11, 6p12 and 6p21.1). No clinical syndrome is associated with such duplications. Almost all of these patients had various degrees of delay in psycho–motor development. Some of them had hearts defects (atrial or ventricular septal defects), microcephaly, or shortened clavicles. Other did not have any manifestations. Not a single clinical feature seems to be characteristic for this group of patients.

Trisomy 6p22–pter (“6p trisomy syndrome”)

The largest group of patients with trisomy 6p (~60) have “pure” duplications for either the region 6p21.3–pter or 6p22–pter. At least 120 patients have this trisomy in association with another chromosomal imbalance. Many scientists believe that trisomy for this region of 6p constitutes a clinically recognizable syndrome. Conversely, if you read about “6p trisomy syndrome”, it means that the patient had either trisomy 6p21.3–pter or 6p22–pter.

Most patients have moderate prenatal hypoplasia, microcephaly (usually of postnatal onset), high prominent forehead, short palpebral fissures, blepharophimosis or blepharoptosis [the most frequently reported facial abnormality in this trisomy], low–set ears (usually of abnormal form), high nasal bridge, bulbous nose, microstomia, and micrognathia. This complex of dysmorphias is not sufficient for clinical diagnosis, but it raises suspicion about the possibility of 6p trisomy.

At least 7 patients with isolated trisomy 6p had craniosynostosis. The critical segment for this defect is 6p21p22 (patients that have more distal trisomies do not reveal this abnormality).

Other structural brain defects — hydrocephaly, arhinencephaly, and hypoplastic corpus callosum, hypoplastic cerebellum were reported in 1–2 patients, each.

A significant number of patients with trisomy 6p syndrome have structural eye defects — microphthalmia, microcornea, colobomas, pigmentary dystrophy of the retina, retinal clouding and/or visual impairment. Hearing impairment was reported at least in 5 patients. Four children (and at least 10 more patients with an additional imbalance) had choanal atresia. The critical segment for this defect lies within 6p21.3p22.

The most common visceral defects are heart defects found in 12 patients. Only one child had tetralogy of Fallot; most others had ventricular or atrial septal defects, patent ductus arteriosus, or stenosis of aorta or pulmonary artery.

Ten patients had different defects of the kidneys — absence of one kidney, hypoplastic kidneys, hydronephrosis, double pelvices and ureters, glomerular fibrosis, vesico–urinary reflux, or renal failure.

Defects of the gastro–intestinal tract (pyloric stenosis, omphalocele, atresia ani) were found only once, each. Defects of the extremities include short limbs, mild syndactyly, scoliosis, and brachy– or camptodactyly. Defects of the lungs and the genital system are not characteristic.

At least 7 patients had seizures. Most patients have a mild–to–moderate delay in psycho–motor development.

From the genetic point of view, most “pure” trisomies 6p in this group are sporadic events. It should be noted, however, that small 1–2 Mb duplications within this region may be inherited from a clinically unaffected parent.

Distal trisomy 6p (trisomy 6p25)

The genetic architecture of the 6p25 segment predisposes it to structural rearrangements in this area, both to deletions and duplications. These segmental duplications are relatively small (~0.5 Mb) and may be diagnosed only using molecular methods. The 6p25 segment contains several genes, including the FOXC1 gene. Duplication of this gene leads to complex eye defects, mainly iris hypoplasia and glaucoma. These patients have normal psycho–motor development and do not have other birth defects. Such small duplications may be inherited as a dominant trait, and, in several families, these duplications were diagnosed upon molecular cytogenetic examination of the families, which were considered having autosomal–dominantly inherited glaucoma and hypoplastic iris. Therefore, examination of the parents of the patient with isolated dup 6p25 is absolutely necessary for a decision about the prognosis for further children.

It is noteworthy that the deletion of the same 6p25 segment, containing the FOXC1 gene, produces the same or very similar ocular abnormalities.

Partial trisomies 6q

Approximately 130 patients with “pure” trisomies for different segments of the long arm of chromosome 6 have been reported so far. Many more patients have trisomy for the distal part

of 6q in association with partial monosomies for 6p (as a result of pericentric inversions) or with partial monosomies for other chromosomes (as a result of translocations).
All observations of trisomy 6q may be arbitrarily divided into 3 groups: duplications of the proximal segment (from the centromere to 6q23), a very specific condition caused by the duplication of 6q24, and duplications of the distal segment (from 6q24 to the telomere).

Trisomies for the "proximal" segments of 6q

This group consists of 33 people having duplications of various segments. Duplications of these areas do not constitute any recognizable syndrome, and clinical manifestations in most of these patients are relatively mild. Some patients reveal a delay in psycho–motor development; others have almost normal intellectual development.

Six patients had congenital heart defects or were suspected of having these defects, but, in all people, these abnormalities were mild (atrial or ventricular septal defects, pulmonary stenosis, thickened tricuspid valve). Defects of the gastro–intestinal or uro–genital systems are not characteristic.

There are 3 reports of autism in children with these trisomies, but the etiologic role of dup 6q in the origin of autism in these patients is not clear.

Trisomy 6q24

It was noted that some patients with the so–called transitional neonatal diabetes (TND) have duplications of 6q24.

TND is a relatively rare condition when a newborn child has very low or an undetectable level of insulin at birth. As a result, these neonates need a short period of insulin treatment. From the etiological point of view, TND in ~25% of patients is caused by mutations of genes on chromosome 11p15. In most other patients, TND is related to defects in 6q24. These defects may be of three kinds: duplications of the paternal 6q24, maternal hypometilation of 6q24, and paternal uniparental disomy (UPD) 6 (a condition, where the patient has two copies of the paternal segment 6q24, but no maternal segment). Only cytogenetic duplications of 6q24 will be the object of this analysis.

The total number of reported patients with TND caused by duplications of 6q24 is ~30 (several more patients with distal 6q duplications, involving this particular segment, had TND in association with other abnormalities, caused by duplications of more distal segments of 6q).

Comparison of sizes of the duplicated segment in known patients with TND showed that all patients have a common duplicated segment of ~170 Kb (144.285–144.458) on 6q24. This segment contains two genes: PLAGL1 and HYMAI. It is still unknown, which of these genes (or both genes together) are responsible for the occurrence of TND.
The patients with small duplications of this area do not have other clinical manifestations. Involvement of more distal (or more proximal) segments leads to additional abnormalities.
It should be underlined that only duplications of paternal DNA in 6q24 may lead to NTD. Duplications of maternal 6q24 do not cause this condition.

Distal trisomy 6q

Distal trisomy 6q is a relatively well–known condition. The first reports on patients with distal trisomy 6q appeared in the 1970's (almost all patients with proximal 6q duplications were reported in 2000's). The total number of known patients with "pure" distal trisomy 6q is ~65. Approximately the same number of persons has distal trisomy 6q in a complex with various partial monosomies.

Most children have significant growth retardation, microcephaly, prominent forehead, hypertelorism, almond–shaped palpebral fissures, relative exophthalmos, flat nasal bridge, anteverted nares, tented upper lip, "carp–shaped" mouth, low–set or malformed ears, or unusual cutaneous dimples. At least 8 patients had a cleft palate. A significant delay in psycho–motor development is a typical manifestation of this syndrome.
Most patients have a short webbed neck. Many also have pterygium colli (a wing–like triangular membrane between the chin and neck) and/or axillary pterygia (a wing–like triangular membrane between the torso and upper arm in the armpit area). Even patients without obvious pterygia have contractures and camptodactyly (a limited range of motion in large joints or in the joints of fingers). An association of characteristic facial abnormalities and defects of the loco–motor system allows one to suspect distal trisomy 6q.

The most common brain defect (except microcephaly) is agenesis of the corpus callosum, which was reported in 10 patients. Polymicrogyria was found in 4 patients (although not every child had examinations necessary to diagnose this condition). Trigonocephaly, occipital encephalocele, and hypoplastic cerebellum were also occasionally reported in these patients.

Eye defects (hypoplastic iris, glaucoma, megalocornea, and keratoconus) were reported in one patient, each.

Congenital heart defects are very common: they were confirmed (or suspected) in 19 patients. Many of these patients had serious complex defects of the heart, including Ebstein malformation (the displacement of the tricuspid valve towards the apex of the right ventricle) and tetralogy of Fallot. The most common defects are atrial septal defects and stenosis of the pulmonary artery.

The most common gastro–intestinal malformation is anal atresia (5 patients). The critical segment for this defect is 6q22.3q25. Other defects (omphalocele, absent gallbladders, and Hirschsprung's disease) were unique. Defects of the kidneys and the genital system (different in each person) were reported in 5–6 patients.

Other defects of distal trisomy 6q include hearing loss (4), umbilical, inguinal or hiatal hernias (8), and obesity (4).

Analysis of patients with an additional imbalance shows approximately the same complex of symptoms (with the presence of some additional characteristics).

Trisomy 6

Trisomy 6 is one of the rarest trisomies reported in humans. In six cases, trisomic cells were found only in placental tissues. Most of these patients were completely normal or revealed

mild abnormalities – dysmorphism, macroglossia, or shortening of the limbs.
There are only seven reports when trisomic cells were found in fetal tissues. All these fetuses or infants were mosaics. One of them had an additional clone with trisomy 4.

The persons with mosaic trisomy 6 reveal specific pattern of limb defects: oligodactyly or deep cleft between fingers or toes. Basically this is ectrodactyly or its equivalents. Such defects were found in five out of six affected patients (one patient with double mosaicism revealed an absent right thumb); one person with mosaic trisomy 6 did not have limb defects. These digital abnormalities are accompanied by syndactylies or (more rarely) by low implanted thumb or campomelia (slightly bent long bones). Other skeletal defects include scoliosis and arthrogryposis. A characteristic pattern of abnormalities of the hands and feet may be considered as a hallmark of this rare condition.

Heart defects were reported in five persons. At least two of them had very serious defects (atrio-ventricular communication and Ebstein anomaly).

Two patients had dystopia of kidneys; a dilatation of the pyelo-calyceal system and uterus bicornis were also reported. Holoprosencephaly, microphthalmia, deafness, abnormal pulmonary segmentation, accessory nipple, omphalocele, intestinal malrotation and ventral ectopia of the anus were found in one person, each.