Interstitial duplication of the short arm of chromosome 2: report of a new case and review

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Abstract
An 18 month old girl was referred to us because of dysmorphic features and psychomotor and growth retardation. On physical examination, she was found to have microcephaly, open fontanelles, a prominent forehead, a flat occiput, hypertelorism, sparse eyebrows, a small nose with a depressed nasal bridge, a bulging philtrum, a thin upper lip, a high arched palate, low set and posteriorly rotated ears, a small mandible, a short neck with a low hair line, and eye malformations. High resolution chromosome analysis identified a de novo direct duplication of the 2p21.00→p24.2 region. The phenotype of de novo partial trisomy 2p is discussed. (J Med Genet 1997;34:783-786)

Keywords: dysmorphology; growth retardation; mental retardation; partial duplication 2p

Up to the present, approximately 30 patients with an interstitial duplication of the short arm of chromosome 2 (dup(2p)) have been reported. In most cases, the duplication results from an unbalanced product of a parental translocation involving the short arm of chromosome 2 and another chromosome. However, three patients presented a terminal duplication associated with a deletion of the short arm of an acrocentric chromosome.1,2 Only five cases reported carried a de novo interstitial duplication of the short arm of chromosome 2p3-7 and one a pure interstitial trisomy secondary to a malsegregation of a maternal balanced chromosomal rearrangement.8

Here, we report a new case of de novo interstitial duplication of the short arm of chromosome 2.

Case report
The proband, a newborn girl, is the fourth child of healthy, non-consanguineous Lebanese parents. At birth, the mother was 35 years old and the father 36. The father is a school teacher and the mother a housewife. The family history was unremarkable. Two previous pregnancies ended at 2 and 3 months of gestation for unknown reasons. Medical follow up during pregnancy was not performed. Delivery at term by cephalic presentation was normal, as was the amniotic fluid. Birth weight was 2100 g, length 46 cm (~3rd centile), and head circumference (OFC) 36.3 cm (~3rd centile). The Apgar score was not available. The baby was immediately breast fed and discharged from hospital on the third day.

At 18 months the child was referred to us because of dysmorphic features and psychomotor and growth retardation. Her weight was 7800 g, length 70 cm (~3rd centile), and OFC 42.2 cm (~3rd centile). She could stand and walk with support. On physical examination, the baby was microcephalic, the fontanelles were open, there was a large and prominent forehead, a wide glabella, a flat occiput, sparse hair, hypertelorism, a regular slant of the palpebral fissures, sparse eyebrows, a small nose with a depressed nasal bridge, a bulging philtrum, a thin upper lip, a high arched palate, and normal teeth. The ears were low set and posteriorly rotated with a prominent anhelix. A small mandible and a short neck with a low hair line at the back were also noted (fig 1). Dermatoglyphics on the fingertips and palms were unremarkable. Ophthalmological examination showed mild microcornea in both eyes, anisometropia, bilateral hypermetropic astigmatism, and left exotropia and amblyopia. There was no evidence of optic atrophy. No other malformation was present except mild pectus excavatum and widely spaced nipples.

Radiological examination of the skeleton, abdominal ultrasound, echocardiography, and a cerebral CT scan were normal. Complete blood count, blood glucose, urine analysis, amino acid studies of plasma and urine as well as liver and thyroid function studies were also unremarkable.

From birth to the time of examination, the clinical course was uneventful except for a serious episode of respiratory distress owing to infection at the age of 6 months, which was treated by antibiotics.
Figure 2  FISH using chromosome 2 painting on a metaphase of the proband. Note that both chromosomes 2 are completely coloured.

CYTOGENETIC STUDIES
High resolution chromosome analysis was performed using G and R banding after lymphocyte culture. An abnormal short arm of chromosome 2 was found in all 30 metaphases examined. In order to confirm the cytogenetic findings, in situ hybridisation using a chromosome 2 paint was performed and confirmed the chromosome 2 origin of the additional material (fig 2). In addition, three cosmids, cCI 2-111, cCI 2-10, and cCI 2-610, were used for FISH studies. Cosmids cCI 2-111 and cCI 2-10, which map in the 2p21 and 2p21-p22 region respectively, were duplicated. However, cosmid cCI 2-610, which maps in the 2p25.1 region, did not show any duplicated signal on the abnormal chromosome (fig 3A, B). Therefore, the karyotype of the patient was interpreted as 46,XX,del(2)(p21p24) (fig 4A, B).

The chromosome abnormality occurred de novo, as both parents had a normal karyotype. The possibility of non-paternity was ruled out by blood and HLA typing.

EBV transformed lymphocytes of the patient are available on request.

Discussion
The pertinent features and the rearrangement of the patient’s chromosomes reported here are compatible with the partial duplication of the short arm of chromosome 2 syndrome first defined by Francke in 1978. However, as partial monosomy of the derivative chromosome also influences the phenotype, a detailed study of carriers of de novo interstitial duplication of the short arm of chromosome 2 is very helpful in delineating the clinical phenotype associated with this chromosome aberration.
Besides our patient, we are aware of six other cases. Clinical findings in the present case and in the other published cases are summarised in Table 1. It is apparent that parental age does not seem to play a role in the appearance of the duplication and that the sex ratio is 1:1. However, the number of cases reported is small. Delivery occurred at term in all the reported patients with a mean birth weight of 2290 g (3rd centile), indicating prenatal growth retardation.

A prominent, large forehead, hypertelorism, a depressed nasal bridge, low set, posteriorly rotated ears, and mental and growth retardation with speech delay are the most common features. A flat occiput, open fontanelles, posterior low hair line, small mandible, long and hypextendible fingers, and pectus excavatum are less common and seem less specific (Table 1). In contrast to the dup(2p) patients resulting from an unbalanced product of parental translocation where upward or downward slanting palpebral fissures have been described, in de novo interstitial dup(2p) patients, the palpebral fissures are always in a normal position but sometimes narrow. Also microcephaly, which has been reported in almost all the dup(2p) cases was present among the patients with a de novo dup(2p) only in our proband.

Ocular malformations or clinical ophthalmic abnormalities are particularly frequent in de novo dup(2p) and must always be studied. The severity of the cardiopulmonary malformations determine life expectancy. Indeed, of the three patients who died within the first month of life two had this malformation. It is also important to be aware of respiratory complications as six of the seven reported cases had respiratory problems, one of whom died very early. Diaphragmatic hernia also seems to be a common complication of the dup(2p) syndrome as it has been reported in three patients with a partial dup(2p).

Delayed bone age was present in two patients.

Finally, dermatoglyphics are unremarkable but an excess of fingertip whorl patterns has been reported.

From a chromosomal point of view, it seems probable that in all the cases except the one reported by Sawyer et al., the germline events that may have led to these chromosomal aberrations were the result of (1) an unequal reciprocal translocation between two chromosomes 2 (interchromosomal duplication) or (2) chromatic exchanges during the first or second meiotic division (intrachromosomal duplication) yielding tandem duplication. The common duplicated region in all the patients except the one reported by Fryns et al is the 2p21→p22 region. This region might well be responsible for most of the clinical findings, as suggested by Parutti et al. In addition, it has been emphasised that severe malformation and poor life expectancy in the dup(2p) syndrome seem to occur more often in duplications involving the 2p1→2pter region than the 2p2→2pter region. However, in the de novo dup(2p) patients, we cannot be certain that the difference in duplicated region alters the characteristic clinical findings of the syndrome. Also, life expectancy is not related to the importance of the R or G banded chromosomal duplicated region but more to the association with a visceral malformation, as we can see by comparing our patient and the one reported by Say et al.

In conclusion, the dysmorphology of patients with duplications of different segments of the short arm of chromosome 2 varies most probably according to the duplicated region. In order to understand this rare entity better, it is important to report further cases with chromosome 2 duplication more accurately defined by using high resolution banding and FISH.
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