Deletion (2)(p14p15) in a child with severe neurodevelopmental delay

EDITOR—Cases with pure short arm deletion of chromosome 2 are rare. Among these cases chromosomal deletions within the region 2p21 to 2p23 have been associated with holoprosencephaly. Five cases with multiple anomalies, including microcephaly, have been reported to have more distal deletions within the region 2p23 to 2pter. Four cases have been reported with more proximal deletions involving segments 2p11-p21, 2p13-p15, 2p11-p13, and 2p11.2-p13. Patients in these cases were dysmorphic with psychomotor retardation. Wengen and McPherson reported a fifth case of a dysmorphic infant with del(2)(p11.2p13) who died at the age of 2 months. We report a case of a girl with severe neurodevelopmental delay associated with a small short arm interstitial deletion of chromosome 2, 46,XX,del(2)(p14p15). Two reported cases with larger interstitial deletions overlapping the segment 2p14p15 are reviewed for comparison.

The proband, a 30 month old girl, was born at term by spontaneous vaginal delivery with Apgar scores of 9 and 9 at one and five minutes, respectively. The mother was gravida 2, para 1. The first child is a normal, healthy, 5 year old girl. The pregnancy was uneventful. At the birth of the proband, the mother and father were aged 22 and 27 years, respectively. The parents were consanguineous and of Arabian origin. Both parents were phenotypically normal. There was no known family history of congenital anomalies or mental retardation.

At birth, the proband had a weight of 3180 g (50th centile) and a length of 47 cm (25th centile) and presented with microcephaly and a head circumference of 30 cm (<5th centile). Dysmorphic features noted at birth were abnormal sloping of the forehead, hypertelorism, micrognathia, bulbous nose, thin lips, long, shallow philtrum, widely spaced nipples, a single simian crease on the left hand, long halluces, and bilateral talipes equinovarus (fig 1). Ophthalmological examination showed normal bilateral eye segments. Both fundus appeared incurred with no angiulation, which is a normal eye variant. Inborn errors of metabolism screening (tandem MS test) for amino acids, urea cycle defects, and organic acidosis was normal. Serum ammonia and lactic acid were within normal limits. MRI scan of the brain showed normal intracranial structures. During early infancy, the proband had gastro-oesophageal reflux that cycle defects, required medical therapy. Clinical evaluation at 7 months of age showed that the head growth was very slow and continued to be below the 5th centile (head circumference 36 cm). Physical growth was also retarded with a poor weight gain (weight 5.8 kg and length 61 cm, both <5th centile). The baby also showed marked developmental delay. She could not sit, roll over, reach for objects, transfer objects from one hand to the other, or follow moving objects. She showed significant hypotonia with spasticity in all limbs. Follow up of the patient at 30 months of age showed severe microcephaly (head circumference 39.5 cm, <5th centile) and growth delay (weight 8.3 kg and length 78 cm, both <5th centile). She was spastic with generalised hyperreflexia. There were no seizures. Her right sided hearing was impaired owing to conductive deafness caused by chronic suppurative otitis media. She had bilateral decrease of visual acuity and left exotropia but no nystagmus. She started to sit without support by 28 months of age, but could not stand, walk, or talk.

Chromosomal studies on peripheral lymphocyte cultures showed a small interstitial deletion in the short arm of one homologue of chromosome 2, 46XX,del(2)(p14p15), in all 20 cells examined. The breakpoints of the deleted segment were determined by standard GTG banding at a high banding resolution (>850 banding level, fig 2). This deletion was concluded to be de novo since blood karyotypes of the parents were normal. To investigate whether or not other chromosomes were involved in this abnormality, fluorescence in situ hybridisation (FISH) using a painting probe specific for the whole of chromosome 2 was performed. The painting probe hybridised to the entire length of both homologues of chromosome 2. There was no hybridisation signal from any other chromosome.

To our knowledge there are two published cases that report pure 2p deletions encompassing bands p14-p15. However, in both of these cases the 2p deletion was larger than in our patient and encompassed other adjacent bands. The first case reported from Belgium by Fryns et al was a boy who had a deletion of the segment 2p11p21 and an extra small acentric fragment. The acentric fragment has been found by fluorescence in situ hybridisation (FISH) to be derived from the deleted 2p segment. Consequently, this patient does not have full monosomy for 2p11p21 and monosomy for the segment 2p14p15 cannot be ascertained. Therefore, comparison between this case and ours should be treated with caution. The second case reported from Romania by Duca et al was a girl who had a deletion of segment 2p13p15. The second patient therefore had...
monosomy for the segment 2p14p15 as is the case in our patient. Clinical findings of these two cases and the present case are listed in table 1 for comparison. As indicated in table 1, many clinical features of our patient have also been reported in one or both of the other two patients. These include psychomotor retardation, growth delay, feeding difficulties, abnormal facial features, widely spaced nipples, long halluces, axial hypotonia, and limb spasticity. Chest and spine anomalies, which are reported in the other two cases, are not present in our patient but may develop at a later stage. Of the anomalies found in our patient and not reported in the other two cases, microcephaly is the major one. Microcephaly was also not reported in three other cases with proximal 2p deletions within region 2p11.2p13.10–12 Microcephaly, however, has been reported in cases with more distal chromosome 2p deletions within the region 2p21 to 2pter.17–20

The association in our patient of a small chromosomal deletion, which involved two chromosomal bands, with dysmorphic features, axial hypotonia, spasticity, microcephaly, and developmental delay is suggestive of a contiguous (microdeletion) gene syndrome. Contiguous gene deletions cause dysmorphic features, organ malformations, and mental deficiency by haploinsufficiency,
deletion of imprinted genes, and unmasking of recessive mutations. Unmasking of recessive mutations is inevitably more relevant to our patient, who has consanguineous parents, than to the two patients reported by Duca et al and Fryns et al, who have non-consanguineous parents. Consanguineous parents are more likely to share similar genes in the heterozygous form than non-consanguineous ones and this increases the probability of unmasking recessive mutations in their offspring in the event of a chromosomal deletion. The unmasking of deleterious recessive mutations may have increased the severity of neurodevelopmental delay in our patient and resulted in microcephaly, which is not present in the two patients reported by Duca et al and Fryns et al. It is also possible that our patient may have an independently inherited autosomal recessive disorder that caused or contributed to the severity of the phenotypic features. One of these disorders is autosomal recessive microcephaly that has been reported to be common among Arabs. Molecular DNA family studies may help to clarify whether or not the chromosomal deletion per se was responsible for all or some of the phenotypic malformations of the patient. They will also be useful in defining the extent of the chromosomal deletion and the parent of origin.

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