

## Directly inherited partial trisomy of chromosome 6p identified in a father and daughter by chromosome microdissection

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### Abstract

**Cytogenetic analysis of a 4 year old girl with developmental delay and dysmorphic features showed extra chromosomal material of unknown origin on 20p (46,XX,add(20)(p13)). Familial chromosome studies showed direct inheritance of add(20)(p13) from the father, who had a similar, albeit milder, phenotype. Fibroblast chromosome studies of the father showed no karyotype mosaicism. The additional material could not be identified on the basis of the G banding pattern owing to its small size and ambiguous banding pattern. Chromosome microdissection of the unknown material was performed, the DNA was amplified and labelled using degenerate oligonucleotide primed polymerase chain reaction (DOP-PCR) and reverse painted to the proband's cells to show the karyotype 46,XX,der(20)t(6;20)(p23;p13), conferring partial trisomy 6p and presumed partial monosomy for 20p. Chromosome microdissection has made possible the first reported case of directly inherited partial trisomy 6p.**

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Partial trisomy of chromosome 6p was first described in 1971,<sup>1</sup> although a case was reported in 1962,<sup>2</sup> but the karyotype of that person was not known until 20 years later.<sup>3</sup> The proximal breakpoint varies from p11<sup>4</sup> to p25.<sup>5</sup>

The phenotype is a characteristic one with hypotelorism, blepharophimosis, and blepharoptosis with the eyes often closed. The nose appears short with tiny nares and the nasal bridge is prominent. The mouth is small with thin lips. The chin is small and pointed and the forehead is often bossed. Intellectual disability is generally considerable<sup>6</sup> and in all 33 cases previously reported significant psychomotor retardation was present.<sup>7-13</sup> Additionally, this chromosome anomaly is associated with a reduced life span, the oldest reported survivor being 23 years old.<sup>14</sup> No case of partial trisomy 6p previously reported has been directly inherited.

Direct inheritance of a chromosome abnormality is rare and in most reported cases the abnormality has been a deletion,<sup>15</sup> possibly because duplication, which should be better tolerated, is not so easily identified. Chromo-

some microdissection and reverse painting is an efficient means of positively identifying chromosome imbalance where additional material is involved that has not resulted from a known balanced translocation.

We present here a case of partial trisomy of 6p which was inherited in an unbalanced form from the proband's father who is only mildly affected, and in which the additional chromosomal material was identified by chromosome microdissection and reverse painting.

### Case report

A 4 year old female was referred because of dysmorphic features and developmental delay. The child was born at term with a birth weight of 2415 g, which is well below the 3rd centile. At birth she was found to be microcephalic with a head circumference of 32 cm. She was noted to have a left dislocated hip which was managed with harnessing, as well as blepharophimosis and blepharoptosis. She had surgery for her blepharoptosis at 3½ years of age. The proband is the first of two children born to non-consanguineous parents. The second child, a 20 month old girl, has normal psychomotor development and growth, is of unremarkable appearance, and was therefore not subjected to karyotype analysis.

The proband, at the age of 3½ years, was assessed by a behavioural psychologist to be at the global developmental level of approximately a 2½ year old. She walked late at 2 years, and at 4 years was only saying single words. She was not toilet trained when most recently seen at 4 years and significant behavioural problems were reported.

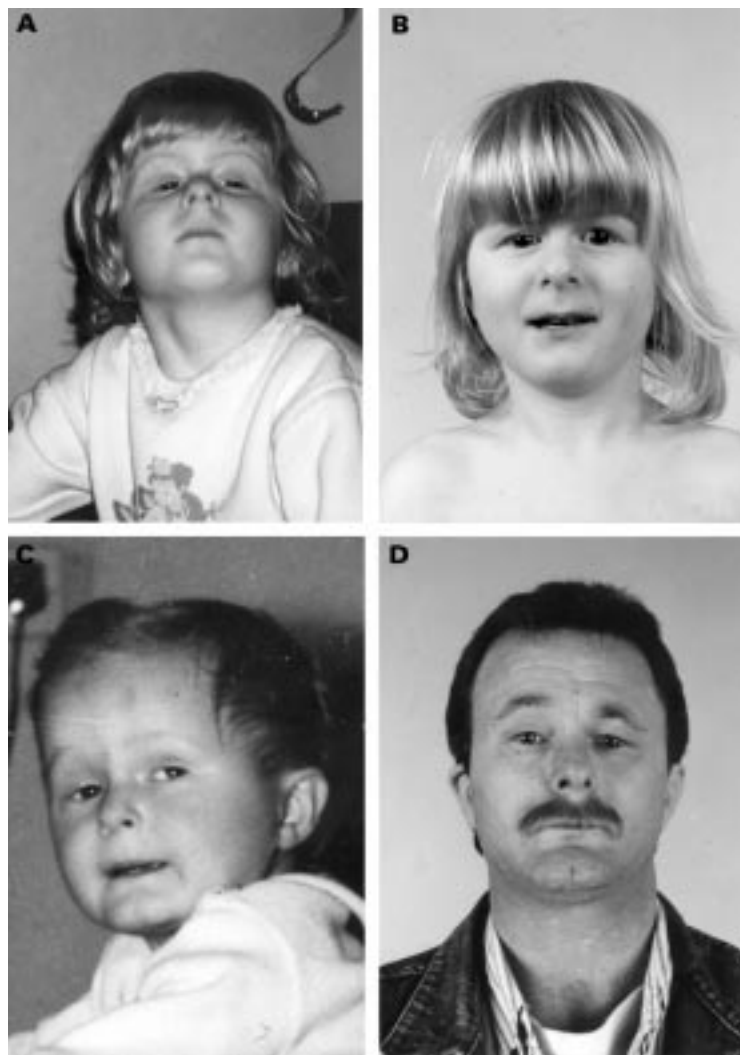
On examination, the proband had short palpebral fissures (2.2 cm, <3rd centile), mild residual ptosis, and hypotelorism (inner canthal distance 2 cm, <3rd centile). The palpebral fissures sloped downwards. Her height (100 cm) and weight (14.3 kg) were around the 25th centile, while her head circumference of 46 cm was just above the 2nd centile. She had a broad nasal tip, a prominent forehead, and hair which extended down onto her forehead. Her mouth was small and she had a pointed chin (fig 1A, B).

The child's father was not seen by us until after his karyotype had been ascertained. His birth weight was approximately 2700 g (10th centile). At presentation, he was 36 years old and his appearance was very similar to his daughter's (fig 1C, D). He had a height of 171.8 cm (10th-25th centile), his weight was 71 kg (50th centile), and head circumference

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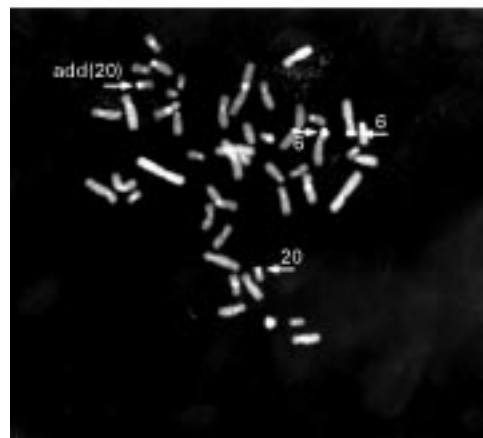
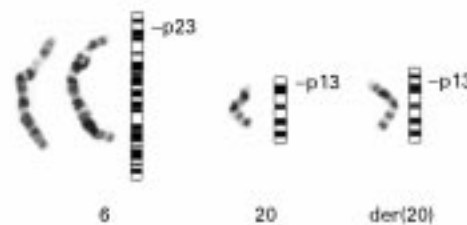
**Figure 1** (A) The proband before eye surgery showing severe ptosis, blepharophimosis, hypotelorism, thin lips, bulbous nose, high forehead, and prominent chin. (B) The proband after eye surgery. (C) The proband's father as a child showing a similar phenotype to his daughter. (D) The proband's father with residual ptosis and low set, cupped right ear.

54 cm (25th centile). He had residual ptosis having had surgery for this in childhood. His palpebral fissures were 2.6 cm (<3rd centile) and he had hypotelorism (inner canthal distance 2.5 cm, <3rd centile). He had a small mouth, thin lips, and an upturned nasal tip. His ears were low set and his right helix was malformed despite having had plastic surgery for this in the past. Mild clinodactyly was present, extra skin creases were present over some phalanges bilaterally, and there were areas of depigmentation on his trunk and arms. In addition to eyelid and ear surgery, he required surgery as a child for a squint and for undescended testes.

With regard to intellect, the father of the proband had "just passed" intermediate high school and was working as a dispatch supervisor and inventory controller where he was in charge of three people. He was able to use a computer for monitoring stock movement.

#### Cytogenetic studies

The blood karyotype from the proband was studied by conventional means. The karyotype was found to be 46,XX,add(20)(p13) on GTL



**Figure 2** (A) Partial karyotype from the proband's father after GTL banding showing chromosome 6, the normal 20 and der(20). (B) Reverse chromosome painting of the microdissected region showing hybridisation to chromosome 6p which identifies the additional material on add(20p).

banding. Parental studies showed the mother to have a normal karyotype, 46,XX, while the paternal karyotype showed the same abnormal 20 as seen in the proband (46,XY,add(20)(p13)) (fig 2A). The abnormality in the proband is thus apparently directly inherited from her father. The paternal grandparents' karyotypes were normal. The unbalanced abnormality is thus de novo in the father. In view of his milder phenotype, skin biopsies from the father were taken from an area of depigmented skin as well as from normally pigmented skin for skin fibroblast culture and cytogenetic analysis. All cells examined from both specimens were 46,XY,add(20)(p13) (70 cells from depigmented skin and 45 cells from normally pigmented skin).

#### Molecular cytogenetic studies

Chromosome microdissection was carried out as described by Meltzer *et al.*<sup>16</sup> Ten cuts of the additional material on 20p were microdissected from paternal cells. The material was amplified by DOP-PCR and biotin labelled in a 2<sup>o</sup>PCR. The labelled DNA was used as a probe and reverse painted to the paternal karyotype by fluorescence in situ hybridisation. The dissected material hybridised to the terminal region of the short arm of both copies of chromosome 6 as well as to the abnormal and normal short arms of chromosome 20 (fig 2(B)). Therefore, the paternal karyotype is 46,XY,add(20)(p13).rev ish der(20)t(6;20)(p23;p13) and that of the proband 46,XX,der(20)t(6;20)(p23;p13)pat.

The derivation of the additional material on 20p was confirmed using a commercially prepared chromosome 6 specific paint (Cambio, Cambridge) (results not shown). The deletion of 20pter was confirmed using a 20p telomeric probe (Oncor) (results not shown).

### Discussion

In the case presented here, chromosome microdissection and reverse chromosome painting has defined a directly inherited 6p duplication that is de novo in the father.

The facial appearance of the proband and her father was typical of patients with 6p duplication. The significant intellectual disability described in all other cases reported with 6p duplication was also present in the proband, but the father has had milder learning difficulties and was functioning normally within society. The milder intellectual disability seen in the father might be the result of mosaicism with a karyotypically normal cell line present. This has been previously seen in trisomy 6p<sup>7</sup>; however, in that case significant developmental delay was present. Skin depigmentation is frequently associated with chromosomal mosaicism,<sup>17</sup> but no evidence of mosaicism was found in the father in fibroblast cultures of skin biopsies from pigmented or depigmented areas. Although no mosaicism was found in the tissues studied, it is possible that mosaicism was present in other tissues, such as the brain.

The milder intellectual disability seen in the father compared with previously reported cases of partial trisomy 6p has a number of possible explanations apart from mosaicism. It may be the result of biased ascertainment. People with milder intellectual deficits are less likely to have a karyotype study undertaken than those more severely affected. Another possible explanation is that the breakpoint in 6p is more proximal than in some other cases, although de Grouchy and Turleau<sup>6</sup> state that the size of the trisomic segment does not appear to modify the phenotype. The cases reported where the subject presented is old enough for the authors to be able to comment on intellectual function do not convincingly show any difference between those with larger duplications and those with smaller ones.<sup>3 5 7-9 14 18</sup> Scarbrough *et al.*<sup>9</sup> have suggested that 6p25 is the critical band in the phenotypic features of partial 6p, an opinion supported by Wauters *et al.*<sup>9</sup> The size and chromosomal origin of the associated deleted segment might be also expected to contribute to the phenotype. In the subjects presented here, only the very terminal end of 20p appeared to be deleted. These arguments would not, however, account for the difference in intellectual functioning between the father and the child assuming that the translocation was unchanged in transmission between father and daughter (that is, that unequal crossing over in the paternal meiosis leading to an increase in duplicated/deleted material did not occur). This case indicates that the phenotype associated with 6p duplication (as well as a terminal deletion of 20p) can

be sufficiently mild to allow normal functioning within society.

In addition to the difference in intellect, the father also differed from other reported cases in that his height, weight, and head circumference were in the normal range. Other published cases were all below the 3rd centile for height and weight and most (11/13) had head circumferences below the 3rd centile.<sup>7-9</sup> This is further evidence for occult mosaicism. Of interest is the observation that the proband's height and weight were in the normal range although she was microcephalic. In terms of facial appearance, however, both the proband and her father closely resemble others with 6p trisomy.

Of 33 patients with partial trisomy 6p previously reported, 26 were inherited from a parental balanced translocation<sup>8-13</sup> and three from a pericentric inversion,<sup>9</sup> while only four have been de novo.<sup>7 9 12</sup> It is possible that other de novo cases have not been definitively diagnosed owing to the difficulty of identifying additional chromosomal material in the absence of a parent having a balanced translocation or inversion allowing identification of that material. The ability to microdissect and reverse paint such additional chromosomal material allows definitive answers to be reached regarding the aetiology of the unbalanced karyotype. This can be very helpful for families as they can then be provided with an exact diagnosis for their child's problems and can receive specific information about others with the same chromosomal duplication.

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