



# Characterisation of chromosomal breakpoints in patients with hearing loss and microcephaly

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## Aim of the study

The aim of this study is to characterise the chromosomal breakpoints of two patients with microcephaly and hearing loss (Table 1). The breakpoints in both patients involve chromosome region 1q31, where respective loci for primary microcephaly and hearing loss have been described.

### Patient A

- hearing loss
- microcephaly
- mental retardation

### Patient B

- hearing loss
  - microcephaly
  - mental retardation
  - microphthalmia
- 46,XY, (1;16)(q31;q13) • 46,XX, t(1;4)(q31;q21), t(3,13)(p13;q34)

**Table 1.** We have studied two patients with a common breakpoint region 1q31, patient A and B. Both patients suffer from microcephaly and hearing loss, where patient B also have microphthalmia.

**Primary microcephaly** (MCPH) is a genetic disorder, used to describe patients with head circumference less than 3 SD below mean and without any other malformations. MCPH causes mental retardation and is usually inherited as an autosomal recessive trait. Five MCPH loci have been described and causative genes have been identified for the MCPH1 locus (microcephalin, 8p23)(1) and for the MCPH5 locus (Abnormal Spindle-like Microcephaly Associated (ASPM), 1q31)(2), while genes for three other loci MCPH2 (19q13.1-13.2), MCPH3 (9q34) and MCPH4 (15q15-q21) are yet unknown.

**Hereditary hearing impairment** affects about 1 in 1000 newborns. Genetic defects account for more than half of the cases and 70% of the genetic cases are nonsyndromic (3). In 1996 a new locus for autosomal dominant nonsyndromic hearing impairment (DFNA7) was linked to 1q21-q23, with a maximum LOD score of 9.68 between markers D1S426 and D1S416 (4).

## Methods

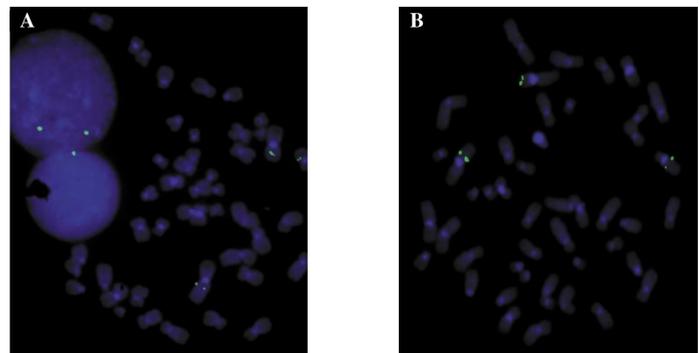
The 1q31 breakpoints were mapped using Fluorescence in situ Hybridisation (FISH) analysis with bacterial artificial chromosomes (BACs) as probes. The probes were received from the Max Planck Institute of Molecular Genetics, Berlin (Germany).

## Results

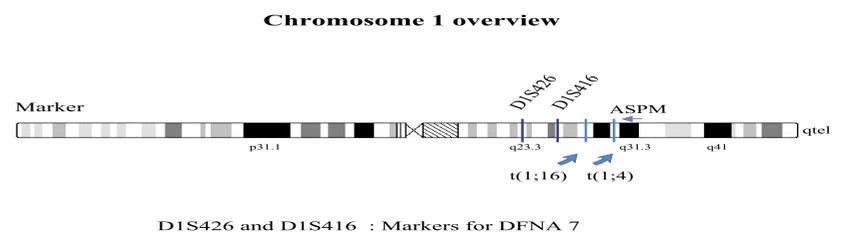
The breakpoints on chromosome region 1q31 have been mapped in patient A and B by FISH analysis to a region of 42 kb and 154 kb, respectively (Figure 1). The two breakpoints are more than 9 Mb apart and the breakpoint of patient A is more than 7 Mb distal to the deafness locus DFNA7 (Figure 2) while the breakpoint of patient B is more than 4 Mb proximal to ASPM (Figure 2). FISH analysis with a BAC covering the ASPM gene as a probe shows that ASPM is present in both patients (Figure 3). The ASPM gene will now be screened for mutations to reveal whether ASPM is involved in the abnormalities.

## Acknowledgements

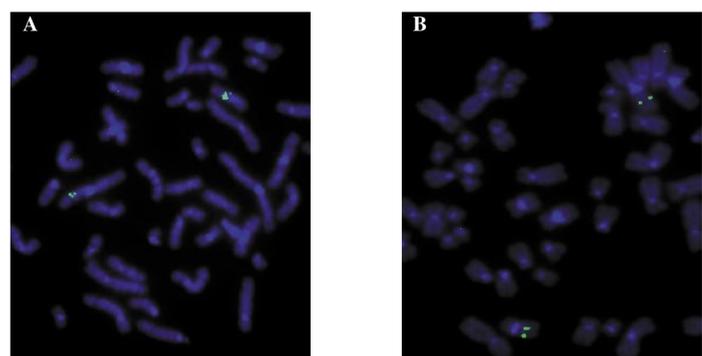
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**Figure 1.** FISH mapping of breakpoint regions. A) Spanning BAC (154 kb) breakpoint region t(1;4) B) Spanning BAC (42 kb) breakpoint region t(1;16)



**Figure 2.** Overview of chromosome 1 describing the genomic map of markers for the autosomal dominant deafness gene DFNA7, ASPM and the two breakpoints.



**Figure 3.** FISH analysis of A) breakpoint region t(1;4) and B) breakpoint region t(1;16) using a BAC covering the ASPM gene as a probe

## Discussion

MCPH5 is an autosomal recessive disease. Chromosomal breakpoints are usually observed in autosomal dominant or X-linked recessive diseases, but unmasking of heterozygosity (6) by a reciprocal translocation has recently been demonstrated in Alstrom Syndrome (7). Other translocation cases with MCPH and 1q31 breakpoints have been described (8), suggesting that such translocations may interfere with ASPM. In the present study we demonstrate that both 1q31 breakpoints were located more than 4-14 Mb from ASPM; we excluded gross deletions of ASPM and conclude that the microcephaly in the patients may be coincidental or caused by breakpoints on the other involved chromosomes. Furthermore, since the hearing impairment in the two patients was not related to DFNA7, one or more of the breakpoints involved may define additional deafness loci (5).

## References

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