LETTERS TO THE EDITOR

Holoprosencephaly in deletions of proximal chromosome 14q

Recently, Chen *et al*[1] reported a patient with holoprosencephaly (HPE) and a proximal interstitial deletion of chromosome 14q. Since classical HPE was also present in two of the seven other patients with a deletion involving chromosome 14q13, they suggested that this region may harbour a gene for HPE.

The gene for thyroid transcription factor 1 maps to this region (TTF-1, MIM 600635), which is also known as thyroid specific enhancer binding protein (T/EBP) and as NKX-2A.[2] This protein belongs to the family of homeodomain containing transcription factors, and besides a role in thyroid and lung development and function, this transcription factor is also important for ventral brain and pituitary development. This was suggested by expression studies in rat and mouse embryos, where the TTF-1 gene was expressed in very restricted areas of the brain, that is, structures of diencephalic origin, including the neurohypophysis.[3 4] More recently, in knockout mice homozygous for the TTF-1 gene, extensive malformations were documented in the ventral region of the forebrain, including fusion in the midline of different structures.[4] These anomalies can be viewed as the mild end of the spectrum of malformations seen in HPE.[5]

Since the TTF-1 gene has not been precisely localised on chromosome 14q,[6] the potential role of the TTF-1 gene in HPE in the fetus reported by Chen *et al*[1] was investigated further by means of FISH, using a cosmid probe from the TTF-1 gene.[7] As shown in fig 1, a normal signal is detected on the normal chromosome 14, but not on the chromosome 14 with the interstitial deletion, indicating a deletion of the TTF-1 gene in this fetus.

Heterozygous TTF-1 knockout mice appear normal, in contrast to humans with a heterozygous chromosomal deletion of chromosome 14q13. This could be explained by the fact that the patients carry large deletions, which may involve many other genes important in brain development. On the other hand, haploinsufficiency for the Sonic hedgehog gene (Shh) in humans causes a wide spectrum of HPE, whereas HPE was found in homozygous but not in heterozygous knockout mice.[8 9] This points to important species specific modifying factors.

Not all interstitial deletions in proximal chromosome 14q are associated with HPE. One possible explanation is that the gene is not deleted in all these patients. Alternatively, the phenotypic expression of HPE is known to vary widely, even in those patients with the same mutation, and this probably depends on genetic background, environmental influences, or stochastic factors. In addition, mild malformations might remain undetected. For instance, Govaerts *et al*[10] recently reported another patient with del(14q11.2q13) who had diabetes insipidus, responsive to desmopressin. In view of the aforementioned findings, this might be caused by a developmental anomaly of the neuropituitary, which remained undetected on a routine cerebral CT scan.

Interestingly, three patients with a more distal deletion on chromosome 14q have been described who had anophthalmia and an absent or hypoplastic pituitary gland or hypogonadism.[11] This suggests that more distally, on chromosome 14q22, one or more genes are located that are equally important for pituitary gland development.

In conclusion, the TTF-1 gene may represent another candidate gene for HPE in humans. As a first step to resolving this question, more precise delineation of the deleted 14q region in the different patients with a del(14q) is warranted.

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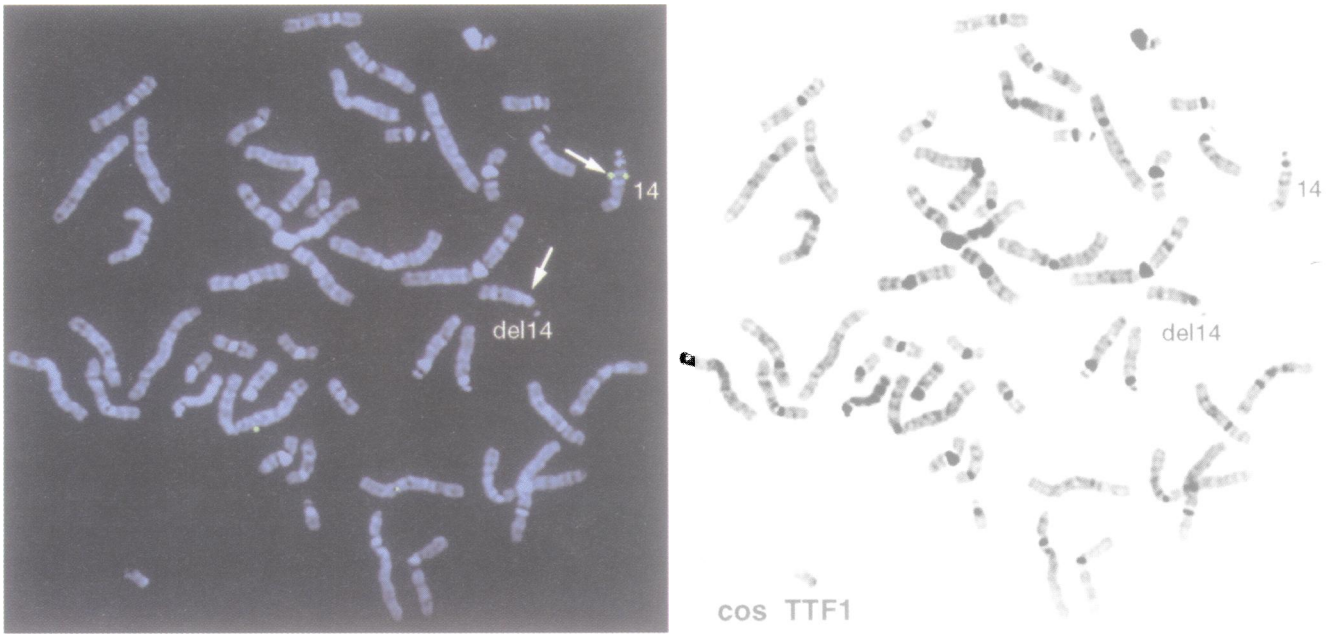

Figure 1 (Left) FISH using a cosmid probe from the TTF-1 gene. Note the absence of a signal on the chromosome 14 with an interstitial deletion 14q13-q21. Additional but weaker signals were consistently seen on chromosomes 6q and 2q, indicating the presence of closely related sequences at these positions. (Right) G banded chromosomes of the patient.