Idiopathic hypoparathyroidism in two patients with 22q11 microdeletion

Recently, Scire *et al*¹ reported the presence of haploinsufficiency in chromosome 22q11 in two patients with hypoparathyroidism. We wish to report two further cases in which we analysed 22q11 deletion by FISH.

The two patients were ascertained through their idiopathic hypoparathyroidism. The table shows their main clinical features and laboratory findings. All probes used for FISH were cosmid clones. D0832 was kindly provided by S Halford (Institute of Child Health, London, UK). Cos71 was a cosmid clone separated from a microdissected chromosome 22q11 (Kurahashi *et al*, submitted). cHKAD26 and cHKAD9² were provided by the

In a preliminary observation on a small sample, among the 19 pedigrees of inherited disorders, 14 could be maternal in origin and three could be paternal in origin.⁵ More recently, Seaver *et al*⁶ reported four cases of pulmonary atresia associated with maternal 22q11 deletion using the D22S624 dinucleotide repeat polymorphism.

A case of 22q11 deficiency with abnormal face and hypernasal speech, not accompanied by cardiac anomaly, thymic hypoplasia, cleft palate, or hypocalcaemia, has been reported.⁷ Nickel *et al*⁸ reported three patients with meningomyelocele, congenital heart defect, and 22q11 deletion. These recent reports and our observations suggest that the CATCH 22 syndrome has a wider variability of clinical phenotype than previously reported. However, the range of the mild phenotype of this syndrome has not been delineated. Further investigations are needed to identify the clinical spectrum of the CATCH 22 syndrome

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Clinical and laboratory findings in present cases

	Case 1	Case 2
Sex	F	M
Age	18 y	11 y
Hypocalcaemia in 1st year	+	+
PTH level during hypocalcaemia	Not detected	Not detected
Ellsworth-Howard test	Normal*	Normal
Learning disabilities	+†	Attention deficit disorder
Cleft palate	—	—
Congenital heart disease	—	—
T cell impairment	+‡	—
Nasal speech	+	+
Abnormal face	+	+
Psychiatric problem	Symptomatic psychosis	—
Intracranial calcification	+	—

* Normal response to exogenous PTH. This finding is compatible with idiopathic hypoparathyroidism.

† She attends special class for mental retardation.

‡ Low response to concanavalin A and phytohaemagglutinin.

Japanese Cancer Research Resources Bank. The order of the chromosome 22q11 markers is tel-cos71-cHKAD26-D0832-cen (Kurahashi *et al*, submitted). A distal marker, cHKAD9 assigned to 22q13.3, was used as a control probe to identify the chromosome 22 homologues. D0832, cos71, and cHKAD26 were deleted in our patients. These findings are consistent with the presence of a 22q11 deletion.

The acronym CATCH 22 has been proposed to designate the variable expression of Cardiac anomaly, Abnormal face, Thymic hypoplasia, Cleft palate, and Hypocalcaemia, resulting from 22q11 deletion.³ The 22q11 deletion has been widely analysed in patients with conotruncal cardiac defect but not in patients with idiopathic hypoparathyroidism. We used three cosmid probes for the detection of haploinsufficiency of 22q11. All probes we used were deleted in all our patients. These findings suggested that some cases with idiopathic hypoparathyroidism are a part of the CATCH 22 syndrome. Isolated idiopathic hypoparathyroidism (without cardiac defect and thymic defect) occurs in 22q11 haploinsufficiency and one end of the spectrum of the CATCH 22 syndrome.

However, the reason for the clinical heterogeneity in CATCH 22 is not clear. Aetiological DGS can occur because of teratogenic exposure (alcohol, maternal diabetes, retinoids).⁴ Therefore, an environmental factor may also play a role in the heterogeneity of clinical expression of the CATCH 22 syndrome. Also the parental origin of 22q11 deletion may influence the clinical phenotype.

and also to examine the clinical and molecular correlations.

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Prototype sequence clues within the Fanconi anaemia group C gene

Fanconi anaemia (FA) is a genetically heterogeneous disease with variable clinical manifestations that include congenital abnormalities, pancytopenia, and propensity to neoplasia. Recently, FA has received widespread attention as a potential candidate for gene therapy.¹ The complementation group C coding sequence (FAC) has been described² and 15% of FA patients harbour mutations in FAC.^{3,4} However, the function of the predicted FAC protein remains unknown.

As a matter of didactic exercise we have examined the FAC sequence by eye, both at the DNA and protein level. We have found two motifs that might provide clues for the elusive function of the FAC gene. At the DNA level, there is a p53 binding site consensus sequence⁵ near the 3' end of the gene that contains only a single mismatch (table A). Experimental evidence shows that a 3' to 5' orientation of the consensus sequence, such as observed in the FAC gene, is less effective, but does not prevent p53 binding.⁶ The location of a p53 binding site other than within the 5' promoter region is somewhat unusual, but has a precedent in the mdm2 gene.⁷ FA cells show chromosomal instability and a defective cell cycle, both of which could derive from impairment of some p53 mediated function.⁸

At the protein level, there is evidence for two motifs that might function as classical leucine zippers (table B). There are seven instead of six amino acids between one of the leucine repeats, and there are occasional substitutions of leucine by valine, threonine, and isoleucine, but computer modelling predicts a typical alpha helical structure for these

Relative positions of the proposed motifs within the human FAC protein sequence (drawing not to scale).