Severe pulmonary and digestive disease in a cystic fibrosis child homozygous for G542X

In southern France, the G542X mutation,\(^1\) in which the glycine (GCA) at amino acid position 542 in exon 11 is mutated to a stop codon (TGA), accounts for 5-6% of the CF chromosomes\(^2\) and represents the second most frequent CF mutation in this population after the deletion ΔF508. In a sample of 150 patients who have been genotyped for CFTR mutations (unpublished results), we identified only one patient with two 542X alleles. In contrast to other reports on homozygous nonsense mutations\(^3,4\) describing mild expression of the disease, the 6 year old girl presented here has been severely affected since infancy.

The patient is the youngest of two sibs born to healthy, unrelated patients originat-

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**LETTERS TO THE EDITOR**

Paternal and maternal transmission of pseudohyoparathyroidism type Ia in a family with Albright hereditary osteodystrophy: no evidence of genomic imprinting

Albright hereditary osteodystrophy (AHO) is a rare autosomal dominant disorder characterised by short stature, obesity, round facies, subcutaneous calcifications, and characteristic skeletal defects.\(^5\) Pseudohyoparathyroidism type Ia (PHP-Ia) is AHO with resistance to parathyroid hormone (PTH) and other hormones acting via cyclic adenosine monophosphate (cAMP), which is encoded by the GNAS1 gene,\(^6\) which stimulates the adenylyl cyclase, has been identified in patients with AHO,\(^7\) whether they were affected by PHP-Ia or PPHP.

After reviewing published reports of 31 AHO kindreds, it has been recently suggested that genomic imprinting may be involved in the differing phenotypic expression: in all families studied so far PHP was solely maternally inherited, whereas PPHP was transmitted by the father.\(^8\)

We recently reported on a family with AHO and reduced GNAS1 activity.\(^9\) The pedigree of this family is shown in the figure. One male infant (IV-3) was affected by PHP-Ia and four family members (II-6, III-2, III-3, and III-5) had PPHP.\(^9\) A female infant (IV-1) was born to a healthy mother (III-1) and a father affected by PHP-Ila (III-2). During the first year of life several subcutaneous nodules (osteoma cutis) developed on the child's back and left arm. So far serum calcium, parathyroid hormone (PTH), free triiodothyronine (FT3), free thyroxine (FT4), and thyrotropin (TSH) are normal, but phosphorus has gradually risen to 9.3 mg/dl (normal 5 to 8 mg/dl). At the age of 14 months a modified Ellsworth-Howard test was performed.\(^9\) Injection of synthetic 1-38 hPTH resulted in a blunted response of plasma cAMP (basal 25-2 nmol/l, after five minutes 29-0 nmol/l, after 10 minutes 21-0 nmol/l; normal >100 nmol/l after five or 10 minutes) and urinary cAMP (basal 3-6 nmol/dl glomerular filtrate, after 90 minutes 3-4 nmol/dl glomerular filtrate; normal >60 nmol/dl glomerular filtrate). The tubular reabsorption of phosphate (TRP) did not decrease after injection of PTH. Injection of thyrotropin releasing hormone (TRH) resulted in an exaggerated response of TSH (basal 30 mU/l, after 30 minutes 28-6 mU/l; normal 3 to 25 mU/l after 30 minutes). Therefore, the diagnosis of normocalcaemic PHP-Ia was made.

A similar pattern of hormone unresponsiveness has been found in the other patient with PHP-Ia (IV-3) at the age of 10 years. In addition, this child also exhibited hypocalcaemia and hyperphosphataemia and serum PTH was increased (230 pg/ml, normal 15 to 55 pg/ml).\(^9\)

All patients with PHP-Ia (III-2, III-3, and III-5) showed a normal increase of cAMP after injection of 1-38 hPTH.\(^9\) The results show that PHP-Ia can be inherited paternally as well as maternally, suggesting that mechanisms other than genomic imprinting are responsible for the full expression of hormone resistance, at least within this family. It has been suggested by others that additional components of the G protein coupled signal transduction (for example, calmodulin, cAMP phosphodiesterase, protein kinase A) may be responsible for the difference between PHP-Ia and PPHP.\(^9\)

Recently, a proximal 15q chromosomal deletion was detected in a female with PHP-Ia as well as in her mother, who also had PHP-Ia.\(^9\) Molecular analyses with 10 different DNA markers in this region did not detect any uniparental disomy or deletion.

Further studies are needed to clarify whether genomic imprinting (especially within the region 20q12-q13.2, which includes the locus for GNAS1) accounts for variable expression of AHO in most affected families.

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