Idiopathic hypoparathyroidism is a heterogenous group of metabolic disorders characterized by hypocalcaemia and hypophosphataemia due to deficient secretion of PTH, and not secondary to surgery or other acquired disorders (3). Idiopathic hypoparathyroidism can be either familial or sporadic. Sporadic idiopathic hypoparathyroidism is more frequent. Familial idiopathic hypoparathyroidism can be part of a complex autoimmune disorder or occur as an isolated entity. This form of the disorder is called “familial isolated hypoparathyroidism” (FIH) (3). This review will briefly discuss the cases of FIH due to mutations in the preproPTH sequence.

The human PTH gene contains 3 exons that are located on the short arm of chromosome 11 (4). Exon 1 contains the untranslated region. Exon 2 encodes the signal peptide and part of the prohormone sequence. Exon 3 encodes the rest of the prohormone sequence, the 84-aminoacid peptide, and the 3'-untranslated region (4).

The first indication that the preproPTH sequence could be associated with FIH was a study by Ahn and colleagues in which 2 out of 8 families with FIH concordance was identified between the inheritance of hypoparathyroidism and specific PTH alleles in affected members. In particular, in one family, for which inheritance of FIH was consistent with the presence of hypoparathyroidism, evidence for linkage analysis was sufficiently strong (LOD score 1.505) (3). Arnold and colleagues pursued this interesting finding, and they cloned and analyzed the putatively abnormal preproPTH gene and the putative wild-type allele from an affected member of the first family (5). A single point mutation (T to C transition) in exon 2 that resulted in substitution of cysteine with an arginine at position 18 of the signal sequence was identified in the putatively abnormal gene, and not in the normal one (Figure 1). The presence of this single point mutation was confirmed in affected family members and excluded in the others. Detailed and elegant analysis of the biological consequences of this missense mutation by Karaplis and colleagues provided clear evidence that the mutation was associated with deleterious effects on the processing of preproPTH to proPTH (6).

Thakker and colleagues investigated one kindred with autosomal recessive FIH, and identified a C to T substitution in the first nucleotide of intron 2 of the PTH gene, generating a donor splice mutation (7). This study revealed that the patients were homozygous for the mutant alleles, while the unaffected relatives were heterozygous, and unrelated normals were homozygous for the wild type alleles. The mutation resulted in exon skipping with a loss of exon 2, which encodes the initiation codon and the signal peptide, thereby causing PTH deficiency (7).

In 1999, a novel mutation of the signal peptide of the preproPTH gene associated with autosomal recessive FIH was described (8). A replacement of T to C was found in the first nucleotide of position 23 in the 25-amino acid signal peptide (Figure 1). This resulted in the replacement of the normal serine with a proline. Affected family members were homozygous for the mutation, whereas the parents were heterozygous, supporting autosomal recessive inheritance. As this mutation is very close to the cleavage site, it is likely that the preproPTH mutant may not be cleaved by signal peptidase at the normal position, and it might be degraded in rough endoplasmic reticulum.

Taken together, mutations in the PTH gene have been reported in three families with FIH. The first family had mutation in the hydrophobic core of the signal peptide, producing the autosomal dominant form of FIH. The second family had a mutation in the exon2-intron2 junction that skipped the next exon and thereby caused PTH deficiency (7).
produced the autosomal recessive form of FIH. The third family had a new autosomal recessive form of FIH with a point mutation in the signal peptide that leads to the amino acid substitution serine 23 to proline at position.

Further studies are now required to elucidate whether genes coding for other molecules, such as calcium sensing receptor are indeed involved in additional cases of FIH for which the genetic defect has not been yet identified (9).

References