Mutations of preproparathyroid hormone gene in primary hypoparathyroidism

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Summary

Peptide hormones such as parathyroid hormone (PTH) are processed after translation through steps that are critical for their proper folding, secretion and activity. This mini-review will briefly summarize the known mutations of the preproparathyroid hormone gene that are known to interfere with proper processing of PTH and are a cause of primary hypoparathyroidism.

KEY WORDS: PTH, hypoparathyroidism.

Parathyroid hormone (PTH), one of the major regulators of calcium and phosphate homeostasis, is synthesized by the parathyroid glands as a larger precursor, pre-proparathyroid hormone (preproPTH) (1). The preproPTH is first cleaved to proPTH and then to PTH. The preproPTH has 25-residue "pre" or signal sequence and a 6-residue "pro" sequence. The signal sequence, along with the short "pro" sequence, has the function to direct the protein into the secretory pathway. During transit across the membrane of the endoplasmic reticulum, the signal sequence is cleaved off and rapidly degraded. Like most other signal sequences found at the beginning of precursors of secreted proteins, the signal sequence of preproPTH contains an interrupted stretch of hydrophobic and non-polar amino acids. The importance of the signal sequence for normal secretion of PTH is illustrated by the hypoparathyroidism inherited in families carrying mutations in the signal sequence of preproPTH (see below). Conversely, the role of the short "pro" sequence is not completely understood; however, experimental evidence strongly suggest that the prohormonal hexapeptide sequence of preproPTH functions to optimize the efficiency and accuracy of signal-sequence cleavage (2). After cleavage of the "pro" sequence, the mature PTH 1-84 is accumulated and stored into secretory granules.

Idiopathic hypoparathyroidism is a heterogenous group of metabolic disorders characterized by hypocalcaemia and hypophosphatemia 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 to FIH was a study by Ahn and colleagues in which in 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 last family (5). A single point mutation (T to C transition) in exon2 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 G to C 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

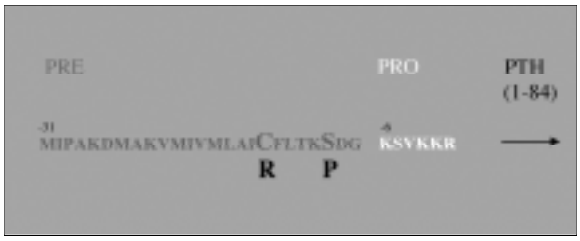

Figure 1 - Human signal sequence and “pro” sequence of human preproPTH.Missense mutations identified inFIH are shown.

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).

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