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Gene Section
Review

MEN1 multiple endocrine neoplasia I

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Identity

HGNC (Hugo): MEN1

Location: 11q13

Note: Mutiple Endocrine neoplasia type 1: MEN1 (or Wermer syndrome) is an inherited predisposition to parathyroid, endocrine pancreas, pituitary, adrenal and neuroendocrine tumors and segregates as an autosomal dominant disease with high penetrance.

DNA/RNA

Description

The MEN1 gene spans 9 kb of the genome and is characterized by 10 exons; exon 1 and the 3' 832 bp of exon 10 are untranslated. The figure shows the general structure of the gene and some of germline mutations in patients affected by inherited MEN1 disease.

Transcription

A major 2,8 kb transcript is detected in all tissues tested; a large 4,0 kb mRNA has been characterized in the pancreas and in the thymus but the 5' structure of the MEN1 gene and the promoter region remain to date unknown; the 2,8 kb major mRNA could be initiated inside exon 1.

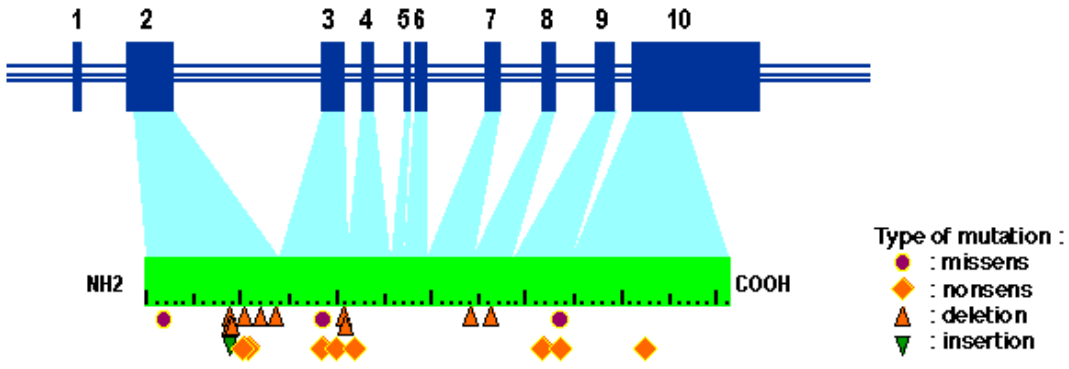
Protein

Description

The MEN1 protein, menin, contains 610 amino-acids (67 kDa); contains two nuclear localization signals (NLS-1 and NLS-2) at the C-terminal end of the protein (exon 10), between amino-acids 479-497 for NLS-1 and 588-608 for NLS-2; this has been shown in vitro by deletion mutants construction with GFP-coexpressing vectors.

Expression

Menin is widely expressed and mainly in testis and central nervous system; murine equivalent to MEN1 has been cloned and most of the expression data have been confirmed in murine tissues, either in adults and during embryogenesis by RNA in situ experiments.



Structure of the MEN1 gene (The European Consortium on MEN1, 1997).

Localisation

Primarily localized in the nucleus and could translate in the cytoplasm during specific steps of the cell cycle.

Function

The MEN1 gene is a growth-suppressor gene, as shown by allelic deletion (LOH) in tumoral DNA from MEN1 patients; menin has been showed to interact with the AP1 transcrition factor through his JunD component; this interaction involves mainly the first 40 amino-acids at the N-terminal end of menin and some specifics amino-acids in the central domain of the protein; Menin interacts specifically with JunD but with none of the other AP1 proteins, such as JunB, c-Jun, c-Fos and Fra1/2; among 11 missense mutations described in MEN1 patients, the authors reported that four of them decreased or abolished binding to JunD suggesting a separate domain between amino-acids residues 139 and 142 could have a critical role in menin-JunD interaction; using mammalian two-hybrid assays, menin has been shown to repress JunD-mediated transcriptionnal activation but most of menin mutatnts with impaired JunD-binding properties lossed this inhibitory activity; strikingly, overexpression of normal or mutant menin in similar experimental assays led to the absence of repressional activity suggesting that unknown factors could be involved in the menin-JunD interaction; new partners binding menin will be probably characterized in a near future and help us to understand the MEN1-related pathways.

Homology

No homology has been found to date either by comparison of primary sequence and secondary/tertiary structure of this protein with all known proteins involved in cellular physiology.

Mutations

Germinal

Germline mutations in the MEN1 gene cause familial and sporadic multiple endocrine neoplasia type 1 (MEN1) and the majority of mutations described predict premature protein truncation either by nonsenses and frameshifts in coding sequences; missense mutations have been identified in » 30% of cases and when characterized in sporadic cases, most of them need analysis of a large (>50) number of control individuals in order to exclude frequent polymorphisms; interestingly, all truncating mutations affect one or both NLS's and no missense mutations were observed inside NLS-1 and NLS-2; mutations are spread over the gene and most of them occur once in a single family; some mutations were observed in more than one family and when a common ancestor was excluded by haplotyping, these recurrent mutations might be accounted for 'hot-spots' in the MEN1 sequence; most recurrent mutations are nonsenses and frameshifts in exons 2 and 10; for example, single base deletion occurs frequently at nucleotide 1650 in exon 10 and has been related to the presence of an highly repetitive motif (CCCCCCCG) in this region inducing replication errors by slipped-strand mispairing; between 10 and 15% of sporadic MEN1 could be explained by de novo mutations, but this must be confirmed by an exhaustive analysis of affected individuals and both parents.

Implicated in

Multiple endocrine neoplasia type 1 or Wermer syndrome

Disease

An inherited autosomal dominant predisposition to endocrine tumors, including parathyroids, endocrine pancreas, pituitary, adrenal glands, and the diffuse neuroendocrine tissues deriving from foregut; non-endocrine tumors have been observed in some MEN1 patients, including ependymoma, meningioma, cutaneous angiofibroma and lipoma, melanoma and rare visceral lesions such as rhabdomyosarcoma and leiomyoma; MEN1 is highly penetrant and more than 90% of gene-carriers will present biological and/or clinical signs of the disease affter the fifth decade; around 5-10% of patients have an agressive disease before age 20

No genotype-phenotype correlation were found to date in MEN1; nevertheless, most families with agressive NET have truncating mutations either in exons 2, 3, 9 or 10 but no studies have been able to find statistical evidence of this putative correlation; recent investigations suggested that some MEN1 families could express only primary hyperparathyroidism, so called familial primary hyperparathyroidism (FIHPT), an allelic variant of MEN1; MEN1-related FIHPT appears as a benign disease but hyperplasia and/or adenoma occur in all parathyroid glands; recent data suggest that this variant could be associated to missense mutations in exons 4 to 7 of the MEN1 sequence; nevertheless, such correlations remain uncertain an do not have clinical implications in medical practice; the identification of germline missense mutations in exons 4 to 7 must lead to an extensive biological and clinical screening of patients in order to exclude the occurrence of pancreatic and pituitary disease, as recently shown in a typical MEN1 family carrying a Leu264Pro in exon 5; approximately 10-15% of MEN1 families do not show any mutation in the known part of MEN1 sequence; clinical profile in these families do not differ from that of families with identified mutations and it is therefore possible that MEN1 mutations occur outside the coding sequence; deletion of part or full MEN1 sequence has been also suggested as a rare mechanism of germline mutation.

Prognosis

It is mainly related to metabolic and organic complications of hormonal hypersecretion by tumoral cells (Zollinger-Ellison syndrome induced by gastrinoma, hyperinsulinism, hyperparathyroidism,

hyeperaldoseronism, Cushing syndrome, hyperprolactinemia, acromegaly; more than 30-50% of digestive neuroendocrine tumors and those localized in thymus and bronchi have a metastatic potential.

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