Gene Section
Review

PDE11A (phosphodiesterase 11A)
Rossella Libé, Jérôme Bertherat

INserm U567, CNRS 8104, Institut Cochin, Service de Maladies Endocriniennes et Metabolique, Hopital Cochin, Paris, France (RL, JB)

Published in Atlas Database: January 2010
Online updated version: http://AtlasGeneticsOncology.org/Genes/PDE11AID44448ch2q31.html
DOI: 10.4267/2042/44886

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Identity
Other names: FLJ23693; MGC133355; MGC133356; PDE11A1; PDE11A2; PDE11A3; PPNA2
HGNC (Hugo): PDE11A
Location: 2q31.2

DNA/RNA
Description
PDE11A is the most recently discovered PDE enzyme family. In this family, only one gene, PDE11A, has been identified. It is a dual phosphodiesterase that hydrolyzes both cAMP and cGMP.

Transcription
Four different isoforms of PDE11A (PDE11A1→A4) have been identified. The longest variant, PDE11A4 is composed of 20 coding exons of varying length, separated by introns, giving the gene a total length of 4441 bps.

Protein
Description
PDE11A4 is a protein of 104 kDa: it contains two N-terminal GAF domains (between exons 3-12) and one C-terminal catalytic domain (between exons 14-22).

Expression
Isoform 1 is present in prostate, pituitary, heart, liver and skeletal muscle. Isoform 2 and 3 are expressed in the testis. Isoform 4 is the only isoform of the enzyme expressed in the adrenal cortex, where it is expressed substantially less than in the prostate.

Localisation
Cytoplasm > cytosol.

Function
PDE11A enzymes catalyze the hydrolysis of both cAMP and cGMP to 5’-AMP and 5’-GMP, respectively. This takes part in the down-regulation of the cAMP and cGMP signaling.
Inactive mutations of the isoform PDE11A4 gene have been identified in patients with adrenal Cushing syndrome due to micronodular adrenocortical hyperplasia. An association of PDE11A4 variants and other neoplasms is suggested since a higher frequency of PDE11A4 missense mutations is observed in patients with macronodular adrenal hyperplasia and testicular tumors than in the controls.

**Homology**

The catalytic domain is conserved among the 4 isoforms of PDE11A. A high sequence similarity of 42-51% is found within the amino acid sequences of the catalytic regions of PDEs containing a Ga f sequence (i.e. PDE2A, PDE5A, PDE6B, PDE6C, PDE10A and PDE11A).

Gene conserved among species: Pan troglodytes: 98.6%; Canis lupus familiaris: 96.4%; Bos taurus: 95.9%; Mus musculus: 94.6%; Rattus norvegicus: 94.5%; Gallus gallus: 90%; Danio rerio: 90%.

**Mutations**

**Germinal**

Non sense.

Three PDE11A nonsense mutations leading to a premature stop codon were identified in 3 kindreds with adrenal Cushing syndrome due to micronodular adrenocortical hyperplasia. Other missense mutations (genetic variants) are described in adrenocortical tumor, as macronodular adrenal hyperplasia (AIMAH), adrenocortical adenoma (ACA), adrenocortical carcinoma (ACC) and testicular tumors.

**Somatic**

Loss of heterozygosity with loss of wild type allele has been reported in adrenocortical tumor (benign and malignant) with PDE11A4 missense mutations.

**Implicated in**

**Adrenal Cushing syndrome due to micronodular adrenocortical hyperplasia**

**Disease**

ACTH-independent chronic oversecretion of cortisol due to bilateral adrenal involvement. Pathological examination demonstrates diffuse micronodular hyperplasia of the cortex of both adrenal. These nodules can be pigmented as observed in primary pigmented nodular adrenocortical disease (PPNAD).

**Prognosis**

Morbidity and mortality of non treated Cushing syndrome is high. However after treatment (bilateral adrenalectomy in most cases) there is a clear improvement and the overall prognosis is good, the main side effect of the treatment being adrenal deficiency.

**Oncogenesis**

In the patients with non-sense mutations a loss of the wild type allele was demonstrated in the adrenal nodes, supporting the hypothesis that PDE11A4 is a tumor suppressor gene.

**ACTH-independent macronodular adrenal hyperplasia (AIMAH)**

**Disease**

AIMAH is a rare form of benign bilateral adrenocortical tumor. It can be associated to an overt Cushing's syndrome (CS). Nowadays, the most frequent clinical presentation is that of bilateral adrenal incidentalomas. The initial endocrine evaluation usually demonstrates subtle abnormalities of cortisol secretion, suggesting a subclinical CS.

**Prognosis**

Morbidity and mortality of non treated Cushing syndrome is high. However after treatment (bilateral adrenalectomy in most cases) there is a clear improvement and the overall prognosis is good, the main side effect of the treatment being adrenal deficiency.

**Cytogenetics**

A higher frequency of missense PDE11A mutations (genetic variants) than in healthy subjects is found.

**Oncogenesis**

The higher frequency of PDE11A missense mutations suggests a role of PDE11A in the genetic predisposition to adrenal tumors.
Non-sense mutations (yellow) and missense mutations (green) described in adrenocortical tumor (PPNAD, AIMAH, ACA and ACC).

Testicular germ cells tumors (TGCT)

Disease
It is the most common malignancy in Caucasian men aged from 15 to 45 years old. A genetic basis for TGCT is supported by familial clustering, younger-than-usual age at diagnosis, and an increased risk of bilateral disease.

Prognosis
More than 90% of patients with newly diagnosed TGCT are cured, and delay in diagnosis correlates with a higher stage at presentation for treatment.

Cytogenetics
Recently, PDE11A missense mutations (genetic variants) have been reported in TGCT. The frequency was significantly higher in patients with TGCT than in healthy subjects.

Oncogenesis
PDE11A variants are involved in the testicular tumorigenesis and may modify the risk of familial and bilateral TGCT.

Adrenocortical carcinoma (ACC)

Disease
ACC is a rare malignant tumor, with an estimated prevalence between 4 and 12 per million in adults.

Prognosis
The overall survival varies according to tumor stage. However the overall survival is poor and below 30% at 5 years in most series.

Cytogenetics
A higher frequency of a polymorphism in exon 6 (E421E) and of three associated polymorphisms located in intron 10-exon 11-intron 11 is found in ACCs than in healthy subjects.

Oncogenesis
The synonymous E421E variant and the intron 10/intron 11 variants could play a role in the predisposition to ACC development.

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Atlas Genet Cytogenet Oncol Haematol. 2010; 14(11)


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