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Gene Section
Review

PDE11A (phosphodiesterase 11A)

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Identity

Other names: FLJ23693; MGC133355; MGC133356; PDE11A1; PDE11A2; PDE11A3; PPNAD2

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

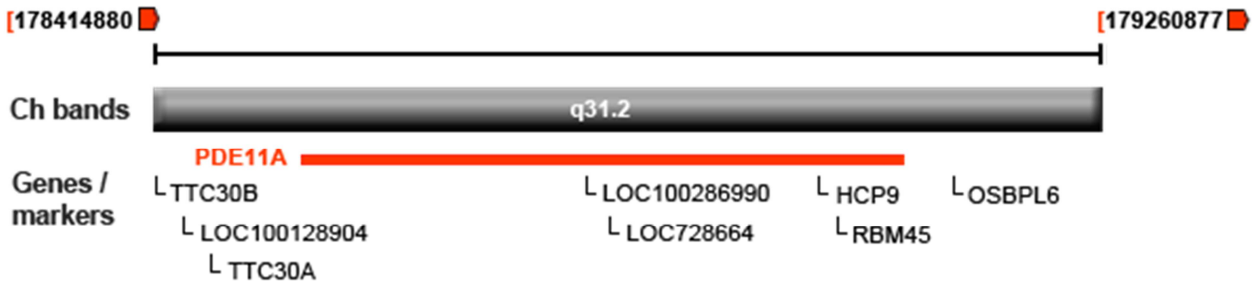
Isoform 1 is present in prostate, pituitary, heart, liver and skeletal muscle. Isoform 2 and 3 are expressed in the testis. Isoform 4 is the only isoform of the enzyme expressed in the adrenal cortex, where it is expressed substantially less than in the prostate.

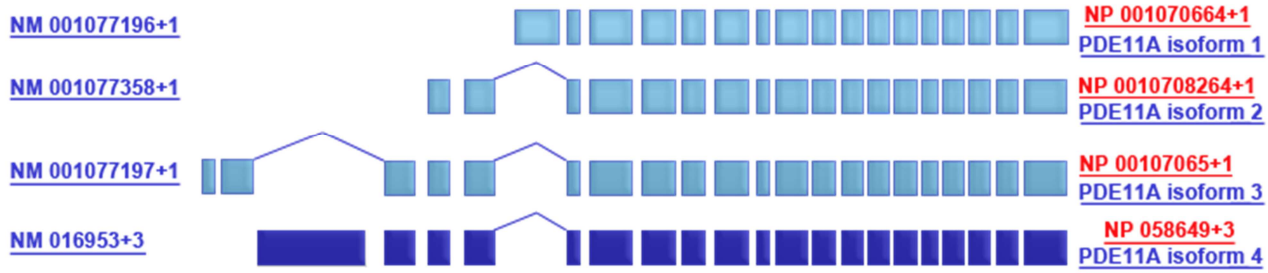
Localisation

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 Gaf 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-independant chronic oversecretion of cortisol due to bilateral adrenal involvement. Pathological examination demonstrates diffuse micronodular hyperaplasia 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.

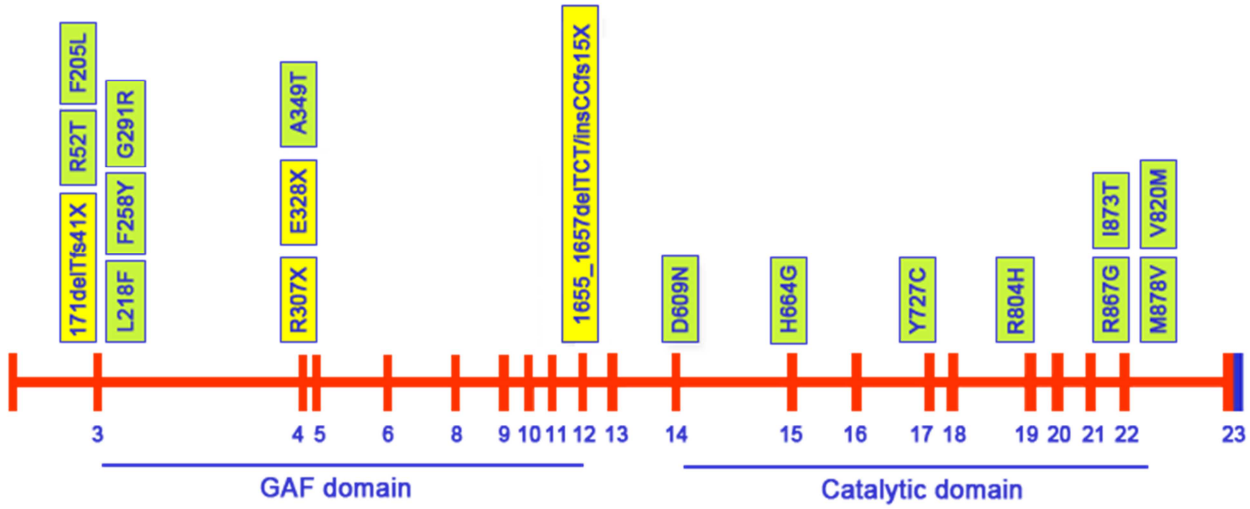
ACTH-independent macronodular adrenal hyperplasia (AIMAH)

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.

References

Fawcett L, Baxendale R, Stacey P, McGrouther C, Harrow I, Soderling S, Hetman J, Beavo JA, Phillips SC. Molecular cloning and characterization of a distinct human phosphodiesterase gene family: PDE11A. Proc Natl Acad Sci U S A. 2000 Mar 28;97(7):3702-7

Hetman JM, Robas N, Baxendale R, Fidock M, Phillips SC, Soderling SH, Beavo JA. Cloning and characterization of two splice variants of human phosphodiesterase 11A. Proc Natl Acad Sci U S A. 2000 Nov 7;97(23):12891-5

Yuasa K, Kotera J, Fujishige K, Michibata H, Sasaki T, Omori K. Isolation and characterization of two novel phosphodiesterase PDE11A variants showing unique structure and tissue-specific expression. J Biol Chem. 2000 Oct 6;275(40):31469-79

Yuasa K, Kanoh Y, Okumura K, Omori K. Genomic organization of the human phosphodiesterase PDE11A gene. Evolutionary relatedness with other PDEs containing GAF domains. Eur J Biochem. 2001 Jan;268(1):168-78

Yuasa K, Ohgaru T, Asahina M, Omori K. Identification of rat cyclic nucleotide phosphodiesterase 11A (PDE11A): comparison of rat and human PDE11A splicing variants. Eur J Biochem. 2001 Aug;268(16):4440-8

Zoraghi R, Kunz S, Gong K, Seebeck T. Characterization of TbPDE2A, a novel cyclic nucleotide-specific phosphodiesterase from the protozoan parasite Trypanosoma brucei. J Biol Chem. 2001 Apr 13;276(15):11559-66

Ahlström M, Pekkinen M, Huttunen M, Lamberg-Allardt C. Dexamethasone down-regulates cAMP-phosphodiesterase in human osteosarcoma cells. Biochem Pharmacol. 2005 Jan 15;69(2):267-75

D'Andrea MR, Qiu Y, Haynes-Johnson D, Bhattacharjee S, Kraft P, Lundeen S. Expression of PDE11A in normal and malignant human tissues. J Histochem Cytochem. 2005 Jul;53(7):895-903

Francis SH. Phosphodiesterase 11 (PDE11): is it a player in human testicular function? Int J Impot Res. 2005 Sep-Oct;17(5):467-8

Loughney K, Taylor J, Florio VA. 3',5'-cyclic nucleotide phosphodiesterase 11A: localization in human tissues. Int J Impot Res. 2005 Jul-Aug;17(4):320-5

Pomara G, Morelli G. Inhibition of phosphodiesterase 11 (PDE11) impacts on sperm quality. Int J Impot Res. 2005 Jul-Aug;17(4):385-6; author reply 387

Seftel AD. 3',5'-Cyclic nucleotide phosphodiesterase 11A: localization in human tissues. J Urol. 2005 Sep;174(3):1044

Seftel AD. Phosphodiesterase 11 (PDE11) regulation of spermatozoa physiology. J Urol. 2005 Sep;174(3):1043-4

Wayman C, Phillips S, Lunny C, Webb T, Fawcett L, Baxendale R, Burgess G. Phosphodiesterase 11 (PDE11) regulation of spermatozoa physiology. Int J Impot Res. 2005 May-Jun;17(3):216-23

Weeks JL, Zoraghi R, Beasley A, Sekhar KR, Francis SH, Corbin JD. High biochemical selectivity of tadalafil, sildenafil and vardenafil for human phosphodiesterase 5A1 (PDE5) over PDE11A4 suggests the absence of PDE11A4 cross-reaction in patients. Int J Impot Res. 2005 Jan-Feb;17(1):5-9

Cazabat L, Ragazzon B, Groussin L, Bertherat J. PRKAR1A mutations in primary pigmented nodular adrenocortical disease. Pituitary. 2006;9(3):211-9

Gross-Langenhoff M, Hofbauer K, Weber J, Schultz A, Schultz JE. cAMP is a ligand for the tandem GAF domain of human phosphodiesterase 10 and cGMP for the tandem GAF domain of phosphodiesterase 11. J Biol Chem. 2006 Feb 3;281(5):2841-6

Horvath A, Boikos S, Giatzakis C, Robinson-White A, Groussin L, Griffin KJ, Stein E, Levine E, Delimpasi G, Hsiao HP, Keil M, Heyerdahl S, Matyakhina L, Libè R, Fratticci A, Kirschner LS, Cramer K, Gaillard RC, Bertagna X, Carney JA, Bertherat J, Bossis I, Stratakis CA. A genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia. Nat Genet. 2006 Jul;38(7):794-800

Horvath A, Giatzakis C, Robinson-White A, Boikos S, Levine E, Griffin K, Stein E, Kamvissi V, Soni P, Bossis I, de Herder W, Carney JA, Bertherat J, Gregersen PK, Remmers EF, Stratakis CA. Adrenal hyperplasia and adenomas are associated with inhibition of phosphodiesterase 11A in carriers of PDE11A sequence variants that are frequent in the population. Cancer Res. 2006 Dec 15;66(24):11571-5

Wong ML, Whelan F, Deloukas P, Whittaker P, Delgado M, Cantor RM, McCann SM, Licinio J. Phosphodiesterase genes are associated with susceptibility to major depression and antidepressant treatment response. Proc Natl Acad Sci U S A. 2006 Oct 10;103(41):15124-9

Horvath A, Stratakis C. Primary pigmented nodular adrenocortical disease and Cushing's syndrome. Arq Bras Endocrinol Metabol. 2007 Nov;51(8):1238-44

Pomara G, Morelli G, Canale D, Turchi P, Caglieresi C, Moschini C, Liguori G, Selli C, Macchia E, Martino E, Francesca F. Alterations in sperm motility after acute oral administration of sildenafil or tadalafil in young, infertile men. Fertil Steril. 2007 Oct;88(4):860-5

Stratakis CA. Adrenocortical tumors, primary pigmented adrenocortical disease (PPNAD)/Carney complex, and other bilateral hyperplasias: the NIH studies. Horm Metab Res. 2007 Jun;39(6):467-73

Teranishi KS, Slager SL, Garriock H, Kraft JB, Peters EJ, Reinalda MS, Jenkins GD, McGrath PJ, Hamilton SP. Variants in PDE11A and PDE1A are not associated with citalopram response. Mol Psychiatry. 2007 Dec;12(12):1061-3

Weeks JL 2nd, Zoraghi R, Francis SH, Corbin JD. N-Terminal domain of phosphodiesterase-11A4 (PDE11A4) decreases affinity of the catalytic site for substrates and tadalafil, and is involved in oligomerization. Biochemistry. 2007 Sep 11;46(36):10353-64

Boikos SA, Horvath A, Heyerdahl S, Stein E, Robinson-White A, Bossis I, Bertherat J, Carney JA, Stratakis CA. Phosphodiesterase 11A expression in the adrenal cortex, primary pigmented nodular adrenocortical disease, and other corticotropin-independent lesions. Horm Metab Res. 2008 May;40(5):347-53

Gross-Langenhoff M, Stenzl A, Altenberend F, Schultz A, Schultz JE. The properties of phosphodiesterase 11A4 GAF domains are regulated by modifications in its N-terminal domain. FEBS J. 2008 Apr;275(8):1643-50

Horvath A, Giatzakis C, Tsang K, Greene E, Osorio P, Boikos S, Libè R, Patronas Y, Robinson-White A, Remmers E, Bertherat J, Nesterova M, Stratakis CA. A cAMP-specific phosphodiesterase (PDE8B) that is mutated in adrenal hyperplasia is expressed widely in human and mouse tissues: a novel PDE8B isoform in human adrenal cortex. Eur J Hum Genet. 2008 Oct;16(10):1245-53

Horvath A, Stratakis CA. Unraveling the molecular basis of micronodular adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes. 2008 Jun;15(3):227-33

Libé R, Fratticci A, Coste J, Tissier F, Horvath A, Ragazzon B, Rene-Corail F, Groussin L, Bertagna X, Raffin-Sanson ML, Stratakis CA, Bertherat J. Phosphodiesterase 11A (PDE11A) and genetic predisposition to adrenocortical tumors. Clin Cancer Res. 2008 Jun 15;14(12):4016-24

Tadjine M, Lampron A, Ouadi L, Horvath A, Stratakis CA, Bourdeau I. Detection of somatic beta-catenin mutations in primary pigmented nodular adrenocortical disease (PPNAD). Clin Endocrinol (Oxf). 2008 Sep;69(3):367-73

Tissier F. [Sporadic adrenocortical tumors: genetics and perspectives for the pathologist]. Ann Pathol. 2008 Oct;28(5):409-16

Waddleton D, Wu W, Feng Y, Thompson C, Wu M, Zhou YP, Howard A, Thornberry N, Li J, Mancini JA. Phosphodiesterase 3 and 4 comprise the major cAMP metabolizing enzymes responsible for insulin secretion in INS-1 (832/13) cells and rat islets. Biochem Pharmacol. 2008 Oct 1;76(7):884-93

Alevizaki M, Stratakis CA. Multiple endocrine neoplasias: advances and challenges for the future. J Intern Med. 2009 Jul;266(1):1-4

Bimpaki EI, Nesterova M, Stratakis CA. Abnormalities of cAMP signaling are present in adrenocortical lesions associated with ACTH-independent Cushing syndrome despite the absence of mutations in known genes. Eur J Endocrinol. 2009 Jul;161(1):153-61

Cabanero M, Laje G, Detera-Wadleigh S, McMahon FJ. Association study of phosphodiesterase genes in the Sequenced Treatment Alternatives to Relieve Depression sample. Pharmacogenet Genomics. 2009 Mar;19(3):235-8

Horvath A, Korde L, Greene MH, Libe R, Osorio P, Faucz FR, Raffin-Sanson ML, Tsang KM, Drori-Herishanu L, Patronas Y, Remmers EF, Nikita ME, Moran J, Greene J, Nesterova M, Merino M, Bertherat J, Stratakis CA. Functional phosphodiesterase 11A mutations may modify the risk of familial and bilateral testicular germ cell tumors. Cancer Res. 2009 Jul 1;69(13):5301-6

Hsiao HP, Kirschner LS, Bourdeau I, Keil MF, Boikos SA, Verma S, Robinson-White AJ, Nesterova M, Lacroix A, Stratakis CA. Clinical and genetic heterogeneity, overlap with other tumor syndromes, and atypical glucocorticoid hormone secretion in adrenocorticotropin-independent macronodular adrenal hyperplasia compared with other adrenocortical tumors. J Clin Endocrinol Metab. 2009 Aug;94(8):2930-7

Kruse LS, Møller M, Tibaek M, Gammeltoft S, Olesen J, Kruuse C. PDE9A, PDE10A, and PDE11A expression in rat trigeminovascular pain signalling system. Brain Res. 2009 Jul 24;1281:25-34

Laje G, Perlis RH, Rush AJ, McMahon FJ. Pharmacogenetics studies in STAR*D: strengths, limitations, and results. Psychiatr Serv. 2009 Nov;60(11):1446-57

Luo HR, Wu GS, Dong C, Arcos-Burgos M, Ribeiro L, Licinio J, Wong ML. Association of PDE11A global haplotype with major depression and antidepressant drug response. Neuropsychiatr Dis Treat. 2009;5:163-70

Matthiesen K, Nielsen J. Binding of cyclic nucleotides to phosphodiesterase 10A and 11A GAF domains does not stimulate catalytic activity. Biochem J. 2009 Oct 12;423(3):401-9

Owen DR, Walker JK, Jon Jacobsen E, Freskos JN, Hughes RO, Brown DL, Bell AS, Brown DG, Phillips C, Mischke BV, Molyneaux JM, Fobian YM, Heasley SE, Moon JB, Stallings WC, Joseph Rogier D, Fox DN, Palmer MJ, Ringer T, Rodriquez-Lens M, Cubbage JW, Blevis-Bal RM, Benson AG, Acker BA, Maddux TM, Tollefson MB, Bond BR, Macinnes A, Yu Y. Identification, synthesis and SAR of amino substituted pyrido[3,2b]pyrazinones as potent and selective PDE5 inhibitors. Bioorg Med Chem Lett. 2009 Aug 1;19(15):4088-91

Peverelli E, Ermetici F, Filopanti M, Elli FM, Ronchi CL, Mantovani G, Ferrero S, Bosari S, Beck-Peccoz P, Lania A,

Spada A. Analysis of genetic variants of phosphodiesterase 11A in acromegalic patients. Eur J Endocrinol. 2009 Nov;161(5):687-94

Stratakis CA. New genes and/or molecular pathways associated with adrenal hyperplasias and related adrenocortical tumors. Mol Cell Endocrinol. 2009 Mar 5;300(1-2):152-7

Weeks JL 2nd, Corbin JD, Francis SH. Interactions between cyclic nucleotide phosphodiesterase 11 catalytic site and substrates or tadalafil and role of a critical Gln-869 hydrogen bond. J Pharmacol Exp Ther. 2009 Oct;331(1):133-41

Louiset E, Gobet F, Libé R, Horvath A, Renouf S, Cariou J, Rothenbuhler A, Bertherat J, Clauser E, Grise P, Stratakis CA, Kuhn JM, Lefebvre H. ACTH-independent Cushing's syndrome with bilateral micronodular adrenal hyperplasia and ectopic adrenocortical adenoma. J Clin Endocrinol Metab. 2010 Jan;95(1):18-24

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