**Atlas of Genetics and Cytogenetics in Oncology and Haematology**

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# Gene Section
**Review**

# MAPK3 (mitogen-activated protein kinase 3)

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## Identity

**Other names:** EC 2.7.11.24; ERK1; ERK-1; ERT2; HS44KDAP; HUMKER1A; MAPK 1; MGC20180; PRKM3; P44ERK1; P44MAPK; p44-ERK1; p44-MAPK

**HGNC (Hugo):** MAPK3

**Location:** 16p11.2

**Local order:** According to NCBI Map Viewer, genes flanking ERK1 (MAPK3) in centromere to telomere direction on 16p11.2 are:

centromere

- Hypothetical LOC100271831, Location: 16p11.2

- YPEL3, yippee-like 3 (Drosophila), Location: 16p11.2

- GDPD3, glycerophosphodiester phosphodiesterase domain containing 3, Location: 16p11.2

- MAPK3, 16p11.2

- CORO1A, coronin, actin binding protein 1A, Location: 16p11.2

- BOLA2B, bolA homolog 2B (E. coli), Location: 16p11.2

- GIYD1, GIY-YIG domain containing 1, Location: 16p11.2

telomere.

## DNA/RNA

### *Description*

According to Entrez Gene MAPK3 gene maps to NC_000016.9 and spans a region of 9.21 kb. According to Spidey mRNA-to-genomic alignment program ERK1 (MAPK3) variant 1 (the most common variant) has 8 exons, the sizes being 170, 183, 190, 117, 115, 132, 110, 123 bps (mRNA coordinates).

### *Transcription*

The promoter analysis of the human MAPK3 has shown that the elements responsible for basal transcriptional activity are located within 200 bp upstream of the initiation codon in the 5' UTR and rich in G/C content (80.5%). The sequence has four SP1 sites and an E box as the most relevant motifs. Site-directed mutagenesis, EMSA, and DNase I footprinting experiments proved that all these elements are required to achieve a significant level of transcription. It has also been reported that the promoter activity is strongly repressed when the cells are grown under growth arrest conditions, such as confluence or serum withdrawal.

### *Pseudogene*

No pseudogenes have been reported for MAPK3.


**Diagram of the ERK1 (MAPK3) gene (isoform 1).** Exons are represented by open boxes (in scale). Exons 1 to 8 are from the 5' to 3' direction.

# Protein

**Note**

ERK1 (MAPK3) is identified by the specific TEY (Thr-Glu-Tyr) sequence in its activation loop. ERK1 (MAPK3) is activated by dual phosphorylation of tyrosine (Tyr204) and threonine (Thr202) residues which is required for complete activation of the protein. Activated ERK1 (MAPK3) migrates into the nucleus and phosphorylates transcription factors.

## Description

ERK1 (MAPK3) is a 43 kDa protein consisting of 379 amino acids. ERK1 (MAPK3) protein is 85% identical to ERK2 (MAPK1) (another MAP kinase family member) and the two proteins have even higher levels of similarity in their substrate binding regions. ERK1 (MAPK3) and ERK2 (MAPK1) both possess 2 DXXD docking sites that provide interaction sites with a Kinase Interaction Motif (KIM), which can be found on activators (MAPKK), inhibitors (PTP-SL (PTPRR) and dual specificity phosphatases) and substrates (ELK-1).

## Expression

Ubiquitously expressed with varying levels in different tissues.

## Localisation

Subcellular location of ERK1 (MAPK3) protein is the cytoplasm, and the nucleus. Upon activation by dual phosphorylation on its Tyr and Thr residues by upstream kinases, ERK1 (MAPK3) is translocated into the nucleus from cytoplasm where it phosphorylates its nuclear targets.

## Function

Being one of the most studied cytoplasmic signaling pathways, the ERK pathway is activated via GTP-loading of RAS at the plasma membrane and sequential activation of a series of protein kinases. Activated RAS recruits the RAF family of kinases such as RAF1 to the plasma membrane which in turn acts as a MAPKKK and activates MAP kinase/ERK kinase 1 and 2 (MEK1 (MAP2K1) and MEK2 (MAP2K2)) by serine phosphorylation. MEK1/2 catalyze the phosphorylation of ERK1 (MAPK3) and ERK2 (MAPK1). Activated ERK1/2 (MAPK3/1) phosphorylates many different substrates involved in various cellular responses from cytoskeletal changes to gene transcription. ERK1 (MAPK3) was initially identified as an insulin-stimulated protein kinase which has an activity towards microtubule-associated protein-2. Today, it is well known that ERK1/2 (MAPK3/1) is especially involved in the control of cell proliferation, cell differentiation and cell survival.

It has been shown that activation of ERK1/2 (MAPK3/1) is crucial for cyclin D1 induction, providing a molecular link between ERK signaling and cell cycle control as cyclin D1 gene is essential for G1 to S-phase progression.

In response to Angiotensin II, ERK1/2 (MAPK3/1) regulates cell proliferation by either one of two signaling pathways which are heterotrimeric G protein/PKC zeta-dependent signaling and SRC/YES1/FYN signaling. ERK1/2 (MAPK3/1) phosphorylates specific transcription factors ELK-1 (leading to c-FOS transcriptional activity) following its translocation into the nucleus due to heterotrimeric G protein/PKC zeta-dependent signaling. Due to its phosphorylation in the cytoplasm by SRC/YES1/FYN signaling, ERK1/2 (MAPK3/1) complexes with RSK2 (RPS6KA), which in turn become activated and translocates into the nucleus to modulate c-FOS transcription and c-FOS protein activity.

The ERK pathway has been found to be responsible for the phosphorylation of BCL2 that contributes to cell survival, the suppression of the apoptotic effect of BAD, the up-regulation of the antiapoptotic protein MCL-1. Moreover, it has been also shown that ERK1/2 (MAPK3/1) is one of the regulators of TP53 protein accumulation and activation during the DNA damage response.

ERK1/2 (MAPK3/1) induces expression of PAI-1 (plasminogen activator type-1 inhibitor) which is closely associated with dynamic changes in cellular morphology and shape-altering physiologic processes.

ERK1/2 (MAPK3/1) has been shown to regulate PPARg1 following EGF stimulation.

CIITA is a critical transcription factor that initiates the expression of MHC class II genes and the subsequent induction of the immune response. Studies have indicated that ERK1/2 (MAPK3/1) negatively regulates CIITA by blocking expression of the CIITA gene and/or by phosphorylating CIITA at residues including serine 288, resulting in the loss of CIITA transactivation potential by enabling it to interact with CRM1 (XPO1) which causes export of CIITA protein from the nucleus.

## Homology

- P. troglodytes, MAPK3, mitogen-activated protein kinase 3
- C. lupus familiaris, MAPK3, mitogen-activated protein kinase 3
- B. taurus, MAPK3, mitogen-activated protein kinase 3
- M. musculus, MAPK3, mitogen-activated protein kinase 3
- R. norvegicus, MAPK3, mitogen activated protein kinase 3
- D. rerio, MAPK3, mitogen-activated protein kinase 3
- S. pombe, spk1, MAP kinase Spk1
- S. cerevisiae, FUS3, Fus3p
- K. lactis, KLLA0E10527g, hypothetical protein
- E. gossypii, AGOS_AFR019W, AFR019Wp
- M. grisea, MGG_09565, mitogen-activated protein kinase

- N. crassa, NCU02393.1, hypothetical protein ((AF348490) MAP kinase [Neurospora crassa OR74A])
- A. thaliana, ATMPK13, ATMPK13; MAP kinase/ kinase

# Implicated in

## *Various diseases*

**Disease**

Although both ERK1 (MAPK3) and ERK2 (MAPK1) have very similar functions, $ERK2^{-/-}$ mice are embryonic lethal while $ERK1^{-/-}$ mice are viable and show normal size and fertility. Thus each isoform may have a unique role, or there may be threshold of total ERK activity for normal viability.
Although viable, $ERK1^{-/-}$ mice have reduced ability for thymocyte maturation and proliferation when T cell receptors are activated. These mice also show an enhancement of long term memory that was shown to be dependent on the striatum. Additionally, the loss of ERK1 results in a loss of adipocity, with the mice having fewer adipocytes than the wild type counterparts.

**Oncogenesis**

Elevated and constitutive activation of ERK1/2 has been detected in a large number of human tumors; including colon, kidney, gastric, prostate, breast, non-small cell lung cancer, bladder, chondrosarcomas and glioblastoma multiforme which show especially high frequencies of kinase activation. The reason for constitutive activation of the ERK pathway in the majority of tumor cells seems to be due to a disorder in RAF, RAS, EGFR or other upstream signaling molecules. In addition, several studies have shown that the ERK-MAPK pathway can directly promote cell motility and the migration of tumor cells.

## *Gastric cancer*

**Note**

Epidermal growth factor (EGF) and urokinase plasminogen activator receptor (uPAR (PLAUR)) are elevated in human gastric cancers and it has been shown that uPAR expression is induced by EGF via ERK1/2 as well as AP-1 (JUN) and NF-kB signaling pathways which in turn, stimulates cell invasiveness in human gastric cancer AGS cells.

## *Breast cancer*

**Note**

In breast cancer patients, ERK1/2 has been found to be heavily phosphorylated on tyrosyl residues and have a 5-10 fold elevated activity compared to benign conditions (fibroadenoma and fibrocystic disease). Localization studies showed that hyperexpressed ERK1/2 mRNA localized to malignant epithelial cells. Furthermore, hyperexpression of ERK1/2 mRNA (5-20 fold) was also observed in metastatic cells within the lymph nodes of breast cancer patients. In addition, in a recent study it was also shown that phosphorylated ERK1/2 levels were significantly high in breast cancer cell lines with high metastatic potential compared to non metastatic breast cancer cell lines. beta-catenin, cyclin D1, and survivin have been shown to be downstream effectors of pERK1/2, while G1/0 proteins, phospholipase C, and protein kinase C serve as upstream activators of pERK1/2 in those cells.

## *Colorectal cancer*

**Note**

Several lines of evidence indicate that overexpression and activation of ERK-MAPK pathway play an important part in progression of colorectal cancer. The constitutive activation of the RAF/MEK/ERK has been shown to be necessary for RAS-induced transformation of HT1080 human colon carcinoma cell line.

## *Non-small-cell lung cancer*

**Note**

It has been found that nuclear and cytoplasmic ERK1/2 activation positively correlates with the stage and lymph node metastases in lung cancer. Therefore ERK1/2 is associated with advanced and aggressive NSCLC tumors.

## *Bladder cancer*

**Note**

ERK1/2 has been shown to mediate TNF-alpha-induced MMP-9 expression by regulating the binding activity of the transcription factors, NF-kB, AP-1 and SP-1, in urinary bladder cancer HT1376 cells.

## *Glioblastoma multiforme*

**Note**

The activation of ERK1/2 has been implicated in different pathobiological processes of GBM which is the most common and malignant brain tumor. The ERK1/2 activation has been linked to EGFR overexpression and hypermethylation of 9p21 locus.

## *Prostate cancer*

**Note**

In prostate tumors, the level of activated MAP kinase were found to be increased with increasing Gleason score and tumor stage while nonneoplastic prostate tissue showed little or no staining with activated MAP kinase antiserum.

## *Kidney cancer*

**Note**

In a high number of human renal cancers ERK1/2 has been found to be constitutively activated.
Moreover, ERK1/2 activation was observed more frequently with high-grade renal cancer cells (RCC) compared to low-grade RCC.

## *Chondrosarcomas*

**Note**

Activation of the JNK (MAPK8) and ERK signal

transduction pathways have been shown to increase the activity and expression levels of their downstream effectors, transcription factors AP-1 and RUNX2. These transcription factors, in turn, stimulate genes that are involved in chondroblast cell biology, ultimately inducing chondroblastic tumorigenesis.

### *Cardiac hypertrophy*

**Note**

It has been implicated that ERK1/2 mediate cardiac hypertrophy, which is a major risk factor for the development of arrhythmias, heart failure and sudden death.

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