MAP3K3 gene

Mitogen activated protein kinase 3 is an enzyme that in humans is encoded by the MAP3K3 gene, which is located on the long arm of chromosome 17 (17q23.3).

This gene product is a 626-amino acid polypeptide that is 96.5% identical to mouse MEKK3. Its catalytic domain is closely related to those of several other kinases, including mouse MEKK2, tobacco NPK, and yeast STE11. Northern blot analysis revealed a 4.6-kb transcript that appears to be ubiquitously expressed.

MAP3Ks are involved in regulating cell fate in response to external stimuli.

MAP3K3 directly regulates the stress-activated protein kinase (SAPK) and extracellular signal-regulated protein kinase (ERK) pathways by activating SEK and MEK1/2 respectively. In cotransfection assays, it enhanced transcription from a nuclear factor kappa-B (NFKB)-dependent reporter gene, consistent with a role in the SAPK pathway. Alternatively spliced transcript variants encoding distinct isoforms have been observed.[6] MEKK3 regulates the p38, JNK and ERK1/2 pathways.

Cerebral Cavernous Malformation CCMs arise due to loss of function in one of the genes that encode the CCM complex, a negative regulator of MEKK3-KLF2/4 signaling in vascular endothelial cells. Gain-of-function mutations in PIK3CA (encoding the enzymatic subunit of the PI3K (phosphoinositide 3-kinase) pathway associated with cell growth) synergize with CCM gene loss-of-function to generate rapidly growing lesions [1].

Ren et al. analyzed 290 surgical specimens from symptomatic CCM patients, utilizing whole-exome sequencing, droplet digital PCR, and targeted panel sequencing, alongside immunohistology to examine genotypic and phenotypic differences. Among 290 cases, 201 had somatic MAP3K3, PIK3CA, or germline CCM mutations, each associated with distinct clinical parameters: hemorrhage risk ($P < 0.001$), lesion size ($P = 0.019$), non-hemorrhagic epilepsy ($P < 0.001$), Zabramski classifications ($P < 0.001$), developmental venous anomaly presence ($P < 0.001$), and MRI-detected edema ($P < 0.001$). PIK3CA mutations showed a higher hemorrhage risk than MAP3K3 and combined MAP3K3 & PIK3CA mutations ($P < 0.001$). Within PIK3CA mutations, the p.H1047R variant correlated with higher bleeding risk than p.E545K ($P = 0.007$). For non-hemorrhagic epilepsy, patients with single MAP3K3 mutations or combined MAP3K3 & PIK3CA mutations were at greater risk than those with PIK3CA mutations alone. Histopathologically, lesions with PIK3CA mutations displayed cyst walls, pS6-positive dilated capillaries, and fresh blood cells, while MAP3K3 and double mutation lesions exhibited classic CCM pathology with SMA-positive and KLF4-positive vessels, collagen, and calcification. PIK3CA lesions had fewer KLF4-positive cells than double mutations lesions ($P < 0.001$), and EndMT (SMA-positive) cells compared to double mutation lesions ($P < 0.05$) and MAP3K3 mutations ($P < 0.001$), with more pS6 compared to MAP3K3 mutations ($P < 0.05$). This study underscores the diverse clinical, genomic, and histopathological characteristics in CCMs, suggesting potential predictive markers based on mutation subtypes and MRI features [2].

Ren et al. present a compelling study linking genotypic variations in cerebral cavernous

malformations to clinical, histopathological, and imaging features. The study provides valuable predictive markers for hemorrhage risk and epilepsy but would benefit from functional validation and broader cohort inclusion. Future studies should investigate the therapeutic potential of targeting the PI3K and MAP3K3 pathways in CCMs, integrating longitudinal patient data to refine risk assessment and treatment strategies.

1)
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