**rs11563204 GA   17865678 AG CFS**

# rs11562975 pain inflammation cold and menthol bronchial asma

# rs10166942 migraine TT

<https://www.ncbi.nlm.nih.gov/pubmed/27789940>

# TRPM8 genetic variations associated with COPD risk in the Chinese Han population.

[Xiong M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Xiong%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27789940)1, [Wang J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20J%5BAuthor%5D&cauthor=true&cauthor_uid=27789940)1, [Guo M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Guo%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27789940)1, [Zhou Q](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhou%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=27789940)1, [Lu W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lu%20W%5BAuthor%5D&cauthor=true&cauthor_uid=27789940)1.

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### Abstract

*TRPM8* plays a key role in COPD. The development of pulmonary hypertension (PH) in COPD adversely affects survival and exercise capacity. In the rs9789398 polymorphism, the T/C genotype was associated with an increased risk for COPD (*P*=0.005). Under the assumption of models of inheritance, there was an association between the rs9789398 polymorphism and COPD. In the rs9789675 polymorphism, the G/A genotype was associated with an increased risk for COPD (*P*=0.021). Furthermore, by the *χ*2 test, we found that the minor allele "A" of rs9789675 (odds ratio [OR] =0.63, 95% confidence interval [CI], 0.42-0.97, *P*=0.034) and the minor allele "C" of rs9789398 (OR =1.59, 95% CI, 1.03-2.44, *P*=0.034) were associated with a decreased risk of PH in COPD in allele models. In genetic models, the genotypes "GA" and "AA" of rs9789675 were associated with a decreased risk of PH in COPD. The genotypes "TC" and "CC" of rs9789398 were associated with a decreased risk of PH in COPD. Moreover, "CG" of rs1004478 was significantly associated with a decreased risk of PH in COPD. There was a significant association between the five SNPs (rs2362290, rs9789675, rs9789398, rs1003540, and rs104478) in the *TRPM8* gene and the risk of PH in COPD. Our findings indicated that rs9789398 in the *TRPM8* gene was significantly associated with the risk of COPD in the Chinese Han population. Moreover, rs9789675, rs9789398, and rs1004478 were significantly associated with the risk of PH in COPD. This study provides a novel insight into COPD and PH in the development of COPD.

PMID: 27789940

 <https://www.ncbi.nlm.nih.gov/pubmed/27038374>

# TRPM8 Ion Channels as Potential Cancer Biomarker and Target in Pancreatic Cancer.

[Yee NS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yee%20NS%5BAuthor%5D&cauthor=true&cauthor_uid=27038374)1.

### [Author information](https://www.ncbi.nlm.nih.gov/pubmed/27038374)

### Abstract

This article provides a review and discussion of the transient receptor potential melastatin-subfamily member 8 (TRPM8) ion channel as a potential biomarker and target in cancer. TRPM8 is a Ca(2+)-permeable channel that plays a major physiological role in cellular sensation and transduction of cold temperature. TRPM8 is aberrantly expressed in a variety of solid tumors including pancreatic cancer. In pancreatic adenocarcinoma cell lines and tissues, TRPM8 is overexpressed as compared to normal pancreatic ductal epithelia. Analysis of anti-TRPM8 immunoreactivity in pancreatic adenocarcinoma indicates positive correlation of TRPM8 expression with tumor size and stages. The biological roles of TRPM8 in pancreatic cancer cells have been revealed from studies using RNA interference-mediated silencing of TRPM8. The experimental data show that TRPM8 channels are required for sustaining proliferation and cell cycle progression, preventing replicative senescence, and promoting cell invasion. Evidence to date implicates a contributory role of TRPM8 channels in the pathogenesis of pancreatic neoplasms and other tumors. Research focus on the mechanisms that underlie TRPM8-mediated roles in tumor growth and metastasis may help establish a novel link of physicochemical changes with pancreatic carcinogenesis. Translational and clinical investigation to exploit TRPM8 as a molecular biomarker and therapeutic target is expected to make a positive impact on precision medicine in pancreatic cancer and other malignant diseases.

#### KEYWORDS:

Biomarker; Ion channel; Pancreatic cancer; Precision oncology; TRPM7; TRPM8; Target

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<https://www.ncbi.nlm.nih.gov/pubmed/26660531>

Our results provide novel insight into the likely genes and biological mechanisms that underlie both MA and MO, and when combined with previous data, highlight the neuropeptide FF-amide peptide encoding gene (NPFF) as a novel candidate risk gene for both types of migraine.

Notably, two genes linked to the function “chronic inflammatory disorder”: TRPM8 (2q37.1) and UFL1 (6q16.1) have Fisher’s combined gene-based P-values surpassing the genome-wide threshold (3.45×10−6)

Transient receptor potential cation channel, subfamily M, member 8 (TRPM8) is a calcium channel expressed in primary sensory neurons essential for cold sensation. It can also mediate cold-mediated analgesics in chronic pain models ([30](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541777/" \l "R30)), suggesting a modulatory role for TRPM8 in pain sensation. TRPM8 was also identified in the vasculature where it plays a role in setting the vascular tone ([31](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541777/#R31)), another function through which the channel could play a role in migraine. UFM1-specific ligase 1 (UFL1) is a protein located at the ER membrane. GO molecular functions assigned to UFL1 are ligase activity, protein binding and UFM1 transferase activity. The biological roles of UFL1 are largely unknown, but the protein has recently been associated with female hormone signalling pathways ([32](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541777/#R32)), providing a potential link with female preponderance in migraine. Four and a half LIM domains 5 (FHL5) is a transcriptional activator of cAMP-responsive element modulator that activates transcriptional programs during spermatogenesis, however a brain-related role is currently not known. Low density lipoprotein receptor-related protein 1 (LRP1) is an endocytic receptor with many ligands. Many biological functions have been described for LRP1. In the brain, LRP1 associates with and regulates the expression of NMDAR1 and GluR1 at postsynaptic neurons and can thereby regulate neurotransmission ([33](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541777/#R33)), providing an apparent link with migraine pathophysiology.

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| TRPM8 | rs17863838 (MA[e](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541777/table/T4/#TFN15)) | G AG | AA | 1.21 | 3.63 × 10−6 | 1.26 | 9.69 × 10−7 |
| rs10187654 (MO[f](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541777/table/T4/#TFN16)) | CC TC | TT |  |  |  |  |

<https://www.ncbi.nlm.nih.gov/pubmed/25967713>

#### OBJECTIVE:

Metabolic syndrome (MetS) is correlated with increased cardiovascular risk and characterized by several factors, including visceral obesity, hypertension, dyslipidemia, and insulin resistance.

We also observed that the distribution of genotype and allele frequencies of the TRPM8 gene rs12472151 in MetS patients were significantly different from controls (p < 0.0001).

https://www.ncbi.nlm.nih.gov/pubmed/25348565

We analyzed associations of single nucleotide polymorphisms rsl13004520 (R247T), rs11562975 (L250L), rs7593557 (S419N), rs11563208 (I1016I), and rs11563071 (V1058V) of the cold receptor TRPM8 (2q37.1) gene with blood plasma lipids and anthropometric parameters in Russian population (randomly chosen residents of Novosibirsk: 507 women and 459 men, mean age 57 years). The studied polymorphisms are localized in regions encoding NH2-terminal (R247T, L250L, S419N) and COOH-terminal (I1016I, V1058V) cytoplasmic domains of the channel. We showed association of single nucleotide polymorphism V1058V with the levels of total cholesterol and LDL and HDL cholesterol, and association of I1016I polymorphism with triglyceride content. Polymorphisms L250L and S419N correlated with anthropometric parameters (body mass index and waist and hip circumferences).

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2491334/>

<https://www.ncbi.nlm.nih.gov/pubmed/23185472>

For the mutations of TRPM8, responses to menthol were only compromised if also the expression of the glycosylated channel isoform was prevented. In contrast, responses to cold were consistently and significantly attenuated but not completely abolished.

<https://www.ncbi.nlm.nih.gov/pubmed/22072275?dopt=Abstract>

TRPM8 codes for a cold and cold-induced burning pain sensor [[63](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253157/#CR63)] which is primarily expressed in sensory neurons and the dorsal root ganglion [[64](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253157/#CR64)]. TRPM8 is investigated as a target in animal models of neuropathic pain [[65](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253157/#CR65)]. Since migraine and neuropathic pain share some characteristics [[66](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253157/#CR66)], a role for TRPM8 in migraine as well as a link between both pain syndromes is plausible.

<https://www.ncbi.nlm.nih.gov/pubmed/23294458?dopt=Abstract>

Two out of three SNPs that showed genome-wide significant associations in the previous study: rs10166942 (near TRPM8) and rs11172113 (in LRP1) were significantly associated with migraine in the present study.

<https://www.nature.com/articles/ng.856>

* doi:10.1038/ng.856

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| [(C;C)](https://www.snpedia.com/index.php/Rs10166942(C;C)) | 1.3 | 0.7x lower risk for migraines |
| [(C;T)](https://www.snpedia.com/index.php/Rs10166942(C;T)) | 1.1 | 0.85x lower risk for migraines |
| [(T;T)](https://www.snpedia.com/index.php/Rs10166942(T;T)) | 0 | common in complete genomics |

<https://www.ncbi.nlm.nih.gov/pubmed/21542321?dopt=Abstract>

The examination of people belonging to the Russian ethnic group revealed that 20.3% of subjects had heterozygous genotype, containing the C-allele in single nucleotide polymorphism rs11562975, located in exon 7 of the gene encoding the temperature-sensitive ion channel TRPM8. Functional differences, associated with sensitivity to cold and menthol were identified between subjects with different genotypes of the polymorphism rs11562975 (GG and GC). Subjects with heterozygous genotype GC were characterized by increased sensitivity to cold and reduced sensitivity to menthol, agonist of the ion channel TRPM8, compared with subjects with homozygous genotype GG.

PMID:

21542321

<https://www.ncbi.nlm.nih.gov/pubmed/23942779?dopt=Abstract>

behavioral disinhibition: nicotine, alcohol consumption 8.00 [NR] unit increase AA, AG

<https://www.ncbi.nlm.nih.gov/pubmed/26272603>

Cold-induced airway hyperresponsiveness (CAH) is common in bronchial asthma (BA) patients and represents a problem for those living in cold climate. Transient receptor potential melastatin 8 (TRPM8) channel is the main cold temperature sensor in humans that could mediate cold response in asthmatics with CAH. No associations between TRPM8 gene polymorphisms and CAH have been reported.

GC genotype and C allele carriers of the c.750G > C (rs11562975) polymorphism were more frequently observed to exhibit CAH. The estimated odds ratio for the GC genotype was 3.73 95%CI (1.48; 9.37), P = 0.005. Furthermore, GC heterozygotes had a prominent decrease in forced expiratory volume in 1 s after the challenge as compared to GG homozygotes (-12% (-16; -8.1) vs -6.45% (-11; -2.1), P < 0.001). GC carriers also had a marked reduction in other spirometric parameters.

#### CONCLUSIONS:

The GC variant of the TRPM8:c.750G > C (rs11562975) polymorphism is associated with CAH in patients with BA, which suggests a potential role of TRPM8 in CAH development.

<https://www.ncbi.nlm.nih.gov/pubmed/17217067>

Originally cloned as a prostate-specific protein, TRPM8 is now best known as a cold- and menthol-activated channel implicated in thermosensation. In this chapter we provide a brief review of current knowledge concerning the biophysical properties, gating mechanisms, pharmacology and (patho)physiology of this TRP channel.

<https://www.ncbi.nlm.nih.gov/pubmed/14757700?dopt=Abstract>

TRPM8 (CMR1) is a Ca(2+)-permeable channel, which can be activated by low temperatures, menthol, eucalyptol and icilin.

<https://www.ncbi.nlm.nih.gov/pubmed/17517434>

Some proteins of the transient receptor potential (TRP) family form temperature sensitive ion channels. One member of the melastatin (M) group, namely TRPM8 is activated by cold and cooling compounds such as menthol and icilin, and its gene is up-regulated in prostate cancer and other malignancies. Here we characterise the effects of the carboxamides WS-12, CPS-113, CPS-369, the carboxylic acid WS-30 and the phosphine oxide WS-148 by Ca2+ imaging experiments and whole-cell patch-clamp recordings on TRPM8 expressing human embryonic kidney (HEK), lymph node prostate cancer (LNCaP) and dorsal root ganglia (DRG) cells. The carboxamide WS-12 is most potent in activating TRPM8, its efficacy with respect to TRPM8 is similar to the one of icilin. Such compounds may be beneficial for preventing noxious cold perception. They could also be useful in diagnosis and treatment of most common cancers in which the TRPM8 gene is up-regulated in comparison to the corresponding normal tissue.

<https://www.ncbi.nlm.nih.gov/pubmed/18511441>

Neuropathic pain remains one of the most challenging of all neurological diseases and presents a large unmet need for improved therapies. Many mechanistic details are still lacking, but greater knowledge of overlapping mechanisms and disease comorbidities has highlighted key areas for intervention. These include peripheral and central hyperexcitability. Among the molecular drivers are ion channels (Nav1.7, Nav1.8, Nav1.3, Cav2.2, and alpha2-delta subunits) whose expression is changed during neuropathic pain and their block shows therapeutic utility. Block of a number of ligand-gated channels [transient receptor potential (TRP)V1, TRPM8, and neuronal nicotinic receptors (NNRs)], important in neural sensitization, may also prove beneficial. Other approaches, such as the modulation of peripheral excitability via CB1 receptors, reduction of spinal excitability through block of glutamate receptors (metabotropic glutamate receptor 5 and alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionate), block of activated spinal neuroglial (CCR2 and P2X7), or increasing spinal inhibition by enhancing monoaminergic activity, all offer exciting opportunities currently being validated in the clinic. Finally of note is the emergence of biological approaches, for example, antibodies, siRNA, gene therapy, offering powerful therapeutic additions with which to redress the neurological disease imbalances causing neuropathic pain.

Other TRP channels (TRPV3, TRPV4, TRPA1, and TRPM8) that also act as temperature transducers have been suggested to be involved in pain particularly when sensitized by a pathophysiological environment.  like TRPM8, can also be sensitized by inflammatory mediators and nerve injury to produce cold-induced burning pain

There are two major cannabinoid receptors, CB1 and CB2, associated with pain modulation  nerve growth factor Localized administration of exogenous NGF induces thermal and mechanical hyperalgesia in animals and in human

<https://www.ncbi.nlm.nih.gov/pubmed/18684990>

# Cooling skin cancer: menthol inhibits melanoma growth. Focus on "TRPM8 activation suppresses cellular viability in human melanoma".

<https://www.ncbi.nlm.nih.gov/pubmed/18930858>

he selectivity profile of WS-12 (a menthol derivative), its several-fold higher potency and around two-fold increase in efficacy compared to menthol warrants its potential utility for therapy in chronic neuropathic pain states and as a diagnostic probe in prostate cancer

<https://www.ncbi.nlm.nih.gov/pubmed/20482834>

breast cancer

<https://www.ncbi.nlm.nih.gov/pubmed/22555807>

pancreatic cancer

<https://www.ncbi.nlm.nih.gov/pubmed/24037916>

lung cancer

<https://www.ncbi.nlm.nih.gov/pubmed/25065497>

prostate cancer

<http://www.uniprot.org/uniprot/Q7Z2W7>

# Transient receptor potential cation channel subfamily M member 8

Gene

## TRPM8

Receptor-activated non-selective cation channel involved in detection of sensations such as coolness, by being activated by cold temperature below 25 degrees Celsius. Activated by icilin, eucalyptol, menthol, cold and modulation of intracellular pH. Involved in menthol sensation. Permeable for monovalent cations sodium, potassium, and cesium and divalent cation calcium. Temperature sensing is tightly linked to voltage-dependent gating. Activated upon depolarization, changes in temperature resulting in graded shifts of its voltage-dependent activation curves. The chemical agonist menthol functions as a gating modifier, shifting activation curves towards physiological membrane potentials. Temperature sensitivity arises from a tenfold difference in the activation energies associated with voltage-dependent opening and closing. In prostate cancer cells, shows strong inward rectification and high calcium selectivity in contrast to its behavior in normal cells which is characterized by outward rectification and poor cationic selectivity. Plays a role in prostate cancer cell migration (PubMed:[25559186](http://www.uniprot.org/citations/25559186)). Isoform 2 and isoform 3 negatively regulate menthol- and cold-induced channel activity by stabilizing the closed state of the channel.4 Publications

#### Miscellaneous

The sensation of coolness triggered by eucalyptol or menthol may be explained by the fact that menthol and cool temperatures sensations are detected by this protein.

Its expression in most prostate tumors as well as the presence of an immunogenic epitope suggest that it may be suitable for the design of peptide vaccination strategies for prostate cancers.

#### GO - Molecular functioni

* [calcium channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0005262) Source: Reactome
* [protein homodimerization activity](https://www.ebi.ac.uk/QuickGO/term/GO:0042803) Source: Ensembl

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q7Z2W7)

#### GO - Biological processi

* [calcium ion transmembrane transport](https://www.ebi.ac.uk/QuickGO/term/GO:0070588) Source: Reactome
* [cellular calcium ion homeostasis](https://www.ebi.ac.uk/QuickGO/term/GO:0006874) Source: Ensembl
* [detection of temperature stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:0016048) Source: InterPro
* [protein homotetramerization](https://www.ebi.ac.uk/QuickGO/term/GO:0051289) Source: Ensembl
* [protein homotrimerization](https://www.ebi.ac.uk/QuickGO/term/GO:0070207) Source: Ensembl
* [response to cold](https://www.ebi.ac.uk/QuickGO/term/GO:0009409) Source: Ensembl
* [thermoception](https://www.ebi.ac.uk/QuickGO/term/GO:0050955) Source: Ensembl

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| DrugBanki | [DB00825.](https://www.drugbank.ca/drugs/DB00825) Menthol. |