

Table S1. 31 pain-related genes

Name	Effect (s)	Reference (s)
<i>SCN9A</i>	Conditional KO (cKO) of Scn9a in specific cell populations were shown to decrease sensitivity to various pain stimuli	[1]
<i>SCN10A</i>	The Possum mutant mice bearing a dominant hypermorphic mutation in Scn10a revealed higher sensitivity to noxious stimuli.	[1]
<i>PRDM12</i>	A key transcription factor in nociceptor neurogenesis.	[2]
<i>ANO1</i>	Are critical for sensory signal transduction	[3]
<i>CCK</i>	Pain modulation	[4]
<i>MAPK1</i>	A crucial role in the transduction of pain signal and contributes to pain hypersensitivity	[5]
<i>MAPK3</i>	The phosphorylation of MARK in the dorsal root ganglion (DRG) and dorsal horn neurons occurs in response to noxious stimulation of the peripheral tissue or electrical stimulation to the peripheral nerve	[6]
<i>RUNX1</i>	Runx1 plays essential roles during the development of sensory neurons involved in circuits mediating pain, itch, thermal sensation and sense of relative position	[7]
<i>NGF</i>	Mediating pain transmission and perception during adulthood	[8]
<i>NTRK1</i>	Autophosphorylates in response to NGF, thereby activating various pathways of intracellular pain signaling	[9]
<i>CACNA1G</i>	Cacna1g-null mice show attenuated neuropathic pain	[10]
<i>TRPV1</i>	Heat hyperalgesia, can be induced when TRPV1 is absent	[11]
<i>TRPV4</i>	As molecular sensors of chemical, thermal, and mechanical noxious stimuli to evoke the pain	[12]
<i>P2RX3</i>	P2X3 receptor involvement in pain states	[13]
<i>P2RX4</i>	P2X4R is dependent on ATP ligand-gated ion channel receptor, which can be activated by ATP and plays an important role in the information transmission of nerve system and the formation of pain	[14]
<i>ASIC1</i>	Activation of ASICs (Acid-sensing Ion Channels) leads physiologically to pain perception	[15]
<i>ASIC3</i>	The ASIC1 and ASIC3 isoforms are particularly important in sensory neurons	[16]
<i>ASIC4</i>	Acid-sensing ion channel (ASIC) 4 promotes the	[17]

degradation of *ASIC1* or inhibits its expression.

<i>CA8</i>	Impact on thermal antinociception	[18]
<i>GRK2</i>	Balancing GRK2 and EPAC1 levels prevents and relieves chronic pain	[19]
<i>ARRB2</i>	Association of polymorphisms in ARRB2 and clinical response to methadone for pain in advanced cancer	[20]
<i>KCNA1</i>	KCNA1 mutation in an Italian proband presenting with myokymia aggravated by painful contractures	[21]
<i>KCNA2</i>	KCNA2 can ameliorates neuropathic pain	[22]
<i>TRAAK</i>	TRAAK channels control pain produced by mechanical stimulation and both heat and cold pain perception in mice.	[23]
<i>KCNIP3</i>	Global gene knockout of <i>Kcnip3</i> enhances pain sensitivity	[24]
<i>KCNJ10</i>	Possible contributors to development of trigeminal neuralgia	[25]
<i>ANO3</i>	Painful-diabetic neuropathy patients show potentially pathogenic variants in <i>ANO3</i>	[26]
<i>OPRM1</i>	Association with morphine pain relief	[27]
<i>OPRL1</i>	Opioid-related nociceptin receptor gene	[28]
<i>OPRK1</i>	Associated with opioid effects	[29]
<i>OPRD1</i>	Impact on Morphine Analgesia	[30]

Table S2. Information of genes sequences in this study

Classification	Species name	Accession number							
		SCN9A	SCN10A	PRDM12	ANO1	CCK	MAPK1	MAPK3	RUNX1
Cetartiodactyla	<i>Tursiops truncatus</i>	XM_019923191.2	XM_033864702.1	XM_033859290.1	XM_033861348.1	XM_019946658.2	XM_033837357.1	XM_033840604.1	XM_033856037.1
	<i>Lagenorhynchus obliquidens</i>	XM_027129270.1	XM_027097140.1	XM_027105972.1	XM_027090101.1	XM_027097155.1	XM_027088826.1	XM_027126453.1	XM_027100709.1
	<i>Globicephala melas</i>	XM_030852545.1	XM_030846194.1	XM_030838114.1	XM_030833236.1	XM_030846213.1	XM_030836288.1	XM_030871686.1	XM_030880838.1
	<i>Orcinus orca</i>	XM_004267254.3	XM_033401954.1	XM_004269370.1	XM_033402485.1	XM_004277868.2	XM_012535310.2	BLAST	XM_004264541.3
	<i>Neophocaena asiaorientalis</i>	XM_024735947.1	XM_024768938.1	XM_024762220.1	XM_024749273.1	XM_024754161.1	XM_024763815.1	XM_024744495.1	XM_024758385.1
	<i>Phocoena sinus</i>	XM_032637962.1	XM_032648888.1	XM_032636300.1	XM_032638810.1	XM_032649894.1	XM_032602827.1	XM_032606377.1	XM_032630113.1
	<i>Delphinapterus leucas</i>	XM_022569944.1	XM_022563630.1	XM_022577993.1	XM_022591144.1	XM_022563667.1	XM_022551403.1	XM_022588367.2	XM_022552943.1
	<i>Monodon monoceros</i>	XM_029225298.1	XM_029244012.1	XM_029203485.1	XM_029208737.1	XM_029244108.1	XM_029234034.1	XM_029221610.1	XM_029214051.1
	<i>Lipotes vexillifer</i>	XM_007450046.1	XM_007468152.1	XM_007453140.1	XM_007466015.1	XM_007463234.1	XM_007451015.1	XM_007452780.1	XM_007446482.
	<i>Physeter catodon</i>	XM_024122208.2	XM_007110498.2	XM_024126094.1	XM_024133135.2	XM_007111562.2	XM_024120474.2	XM_024123717.1	XM_007127982.3
	<i>Balaenoptera bonaerensis</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Balaenoptera acutorostrata</i>	XM_007183216.1	XM_007191455.1	XM_007194777.1	XM_007171269.1	XM_007193434.2	XM_007196295.2	XM_007186363.2	XM_007183740.2
	<i>Balaenoptera musculus</i>	XM_036859011.1	XM_036868976.1	XM_036856755.1	XM_036862640.1	XM_036869704.1	XM_036874241.1	XM_036824427.1	XM_036850892.1
	<i>Balaenoptera physalus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Megaptera novaeangliae</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Eschrichtius robustus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Balaena mysticetus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Bos taurus</i>	XM_005202453.4	XM_015459489.2	NM_001206295.1	XM_024987196.1	XM_024983047.1	NM_175793.2	XM_005224919.4	XM_015473952.2
	<i>Ovis aries</i>	XM_027964893.1	XM_015102254.2	XM_027968320.1	XM_027959872.1	XM_027958055.1	XM_027956867.1	XM_015104158.2	XM_027961500.1
	<i>Sus scrofa</i>	XM_021076176.1	XM_021071677.1	XM_003122237.3	XM_021082670.1	NM_214237.2	NM_001198922.1	XM_021088019.1	XM_021068411.1
Perissodactyla	<i>Vicugna pacos</i>	BLAST	XM_015236214.2	XM_031677214.1	XM_031691026.1	XM_015236328.1	XM_006213306.3	XM_006201256.2	XM_031688324.1
	<i>Equus caballus</i>	XM_023623076.1	XM_014731551.2	XM_023629583.1	XM_023654624.1	XM_001501653.4	XM_023646801.1	XM_023616039.1	XM_023630093.1
	<i>Ceratotherium simum</i>	XM_004428233.2	XM_014790672.1	XM_025888525.1	XM_014795811.1	XM_004419556.2	XM_014796714.1	XM_004439522.1	XM_014786827.1

	<i>Callorhinus ursinus</i>	BLAST	XM_025870888.1	XM_025888525.1	XM_025879019.1	XM_025870768.1	XM_025857341.1	BLAST	XM_025871737.1
	<i>Zalophus californianus</i>	XM_027590855.1	XM_027584950.1	XM_027616997.1	XM_027580751.1	XM_027585374.1	NA	XM_027613193.2	XM_027583260.1
	<i>Odobenus rosmarus</i>	XM_004396924.2	XM_004412301.1	XM_004392631.1	XM_004393795.1	XM_004414020.2	XM_004400515.2	XM_004397172.1	XM_012565636.1
Carnivora	<i>Neomonachus schauinslandi</i>	XM_021703139.1	XM_021705864.1	XM_021691557.1	XM_021685595.1	XM_021678857.1	XM_021687870.1	XM_021700441.1	XM_021678047.1
	<i>Enhydra lutris kenyoni</i>	XM_022514231.1	XM_022521407.1	XM_022500350.1	XM_022507499.1	XM_022521534.1	XM_022496056.1	XM_022526505.1	XM_022516231.1
	<i>Ursu maritimus</i>	XM_008687054.1	XM_008710144.1	XM_008698873.1	XM_008699709.1	XM_008709882.1	XM_008697611.1	XM_008685240.1	XM_008701953.1
	<i>Canis lupus familiaris</i>	XM_022414839.1	NM_001003203.1	XM_025475499.2	XM_849396.5	XM_846822.5	NM_001110800.1	NM_001252035.1	XM_022413373.1
	<i>Felis catus</i>	XM_019838208.2	XM_023260720.1	XM_023242854.1	XM_023238951.1	XM_003992210.5	XM_003994973.4	XM_023247125.1	XM_023238765.1
	<i>Eptesicus fuscus</i>	XM_028140516.1	XM_028131986.1	XM_028127132.1	XM_028153731.1	XM_008154648.2	XM_008142643.2	XM_008152868.1	XM_028151671.1
Chiroptera	<i>Myotis brandtii</i>	XM_014546972.1	XM_014534926.1	BLAST	BLAST	XM_005860435.1	XM_014547095.1	XM_005881979.2	XM_014535203.1
	<i>Rhinolophus ferrumequinum</i>	XM_033112803.1	XM_033133226.1	XM_033123475.1	XM_033121009.1	XM_033132670.1	XM_033097341.1	NA	XM_033127961.1
	<i>Pan troglodytes</i>	XM_016949458.2	XM_009445190.2	XM_528445.5	XM_016921437.2	XM_009445273.3	XM_003317123.5	XM_016928783.2	XM_016938506.2
Primates	<i>Homo sapiens</i>	NM_001365536.1	NM_006514.3	NM_021619.3	NM_018043.6	NM_000729.6	NM_002745.5	NM_002746.3	NM_001754.5
	<i>Macaca mulatta</i>	XM_015110280.2	XM_015131314.2	XM_015116553.2	NM_178642.6	XM_002802837.3	XM_015149801.2	XM_028840860.1	NM_001265962.1
Scandentia	<i>Tupaia chinensis</i>	BLAST	XM_009445190.2	XM_006164353.1	XM_014585285.2	XM_006155393.2	XM_014586841.2	XM_027771739.1	BLAST
	<i>Rattus norvegicus</i>	NM_133289.1	NM_017247.1	XM_002726082.5	NM_001107564.1	NM_012829.2	NM_053842.2	NM_017347.2	XM_017598053.1
Rodentia	<i>Mus musculus</i>	NM_001290674.1	NM_001205321.1	NM_001123362.1	XM_015113459.2	NM_001284508.2	NM_011949.3	NM_011952.2	NM_001111023.2
	<i>Heterocephalus glaber</i>	XM_021238552.1	XM_021259819.1	XM_004849106.2	XM_013074944.2	XM_004835106.3	XM_004843322.2	XM_004856274.2	XM_021256212.1
Sirenia	<i>Trichechus manatus</i>	NA	XM_023732211.1	XM_004375840.1	XM_012557644.1	XM_004368424.1	XM_023740543.1	XM_004386624.3	XM_023741332.1
Proboscidea	<i>Loxodonta africana</i>	XM_010602854.2	XM_023554824.1	XM_003407564.1	XM_023541837.1	XM_003409718.1	XM_010598893.2	XM_010598495.2	XM_023548425.1
Classification	Species name	Accession number							
		NGF	NTRK1	CACNA1G	TRPV1	TRPV4	P2RX3	P2RX4	ASIC1
	<i>Tursiops truncatus</i>	XM_004318079.3	XM_033857030.1	XM_033847346.1	XM_019926881.1	XM_033837066.1	XM_033860719.1	XM_004330179.3	XM_033866740.1
	<i>Lagenorhynchus obliquidens</i>	XM_027090969.1	XM_027095266.1	XM_027094399.1	XM_027130680.1	XM_027124505.1	XM_027114691.1	XM_027124824.1	XM_027106231.1
Cetartiodactyla	<i>Globicephala melas</i>	XM_030869133.1	XM_030842062.1	XM_030839818.1	XM_030861763.1	XM_030860606.1	XM_030864399.1	XM_030860287.1	XM_030835108.1
	<i>Orcinus orca</i>	XM_004263233.2	XM_004284532.2	XM_004282573.2	XM_004267034.2	XM_033408605.1	XM_004264119.3	XM_004276721.3	XM_004274347.2
	<i>Neophocaena asiaeorientalis</i>	XM_024764943.1	XM_024748205.1	XM_024743746.1	XM_024736548.1	XM_024741485.1	XM_024749217.1	XM_024758552.1	XM_024736891.1

	<i>Phocoena sinus</i>	XM_032633146.1	XM_032637667.1	XM_032615915.1	XM_032616759.1	XM_032602893.1	XM_032640910.1	XM_032653862.1	XM_032645742.1
	<i>Delphinapterus leucas</i>	XM_030760001.1	XM_022559547.2	XM_022557857.2	XM_022595823.2	XM_030764334.1	XM_022591980.1	XM_022597833.1	XM_022572201.2
	<i>Monodon monoceros</i>	XM_029230947.1	XM_029230923.1	XM_029211329.1	XM_029211930.1	XM_029228313.1	XM_029208585.1	XM_029216388.1	XM_029205422.1
	<i>Lipotes vexillifer</i>	XM_007454787.1	XM_007457870.1	XM_007465006.1	XM_007454184.1	XM_007448216.1	XM_007455714.1	XM_007448718.1	XM_007452281.1
	<i>Physeter catodon</i>	XM_007103024.2	XM_024748205.1	XM_024130076.1	XM_007125466.3	XM_028480246.1	XM_007115874.2	XM_007123245.3	Orthemam
	<i>Balaenoptera bonaerensis</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Balaenoptera acutorostrata</i>	XM_007169341.1	XM_007172018.1	XM_007176453.1	XM_022595823.2	XM_007180110.1	XM_007196450.1	XM_007189529.1	XM_007179337.1
	<i>Balaenoptera musculus</i>	XM_036840585.1	XM_036836292.1	XM_036837223.1	XM_036838427.1	BLAST	XM_036861777.1	XM_036875009.1	XM_036864743.1
	<i>Balaenoptera physalus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Megaptera novaeangliae</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Eschrichtius robustus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Balaena mysticetus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
Perissodactyla	<i>Bos taurus</i>	NM_001099362.1	XM_002685966.6	NM_001193140.3	XM_015458647.2	NM_001192385.3	XM_024975926.1	NM_001034049.1	NM_001192933.1
	<i>Ovis aries</i>	XM_004002369.4	XM_027976575.1	XM_027974720.1	XM_027975474.1	XM_027956636.1	XM_015101165.2	XM_004017580.4	XM_004006368.4
	<i>Sus scrofa</i>	XM_021089997.1	XM_001929525.5	XM_021067168.1	XM_013981216.2	NM_001130729.1	XM_003353865.5	XM_021073038.1	XM_021091639.1
	<i>Vicugna pacos</i>	XM_006213697.3	XM_015248158.2	XM_031676276.1	XM_006213341.2	XM_031669982.1	XM_006214057.2	XM_015239748.2	XM_006202956.2
	<i>Equus caballus</i>	XM_001496187.5	XM_023640974.1	XM_023652720.1	XM_014727972.2	XM_023648063.1	XM_001504914.5	XM_023647186.1	XM_023643524.1
	<i>Ceratotherium simum</i>	XM_004420625.2	XM_004436243.2	XM_004434702.2	XM_004433273.2	XM_004429881.2	XM_004437362.2	XM_004429997.2	XM_004429001.2
	<i>Callorhinus ursinus</i>	XM_025872630.1	XM_027774484.1	XM_025859233.1	XM_025851492.1	XM_025889376.1	XM_025879400.1	XM_025889775.1	XM_004429001.2
	<i>Zalophus californianus</i>	XM_027618984.1	XM_027612047.2	XM_027625233.2	XM_027567722.2	XM_027577421.1	XM_027579308.2	XM_027576877.2	XM_027592606.1
	<i>Odobenus rosmarus</i>	XM_004401273.2	XM_004402890.1	XM_004395166.1	XM_004412121.2	XM_004416178.2	XM_004409265.2	XM_004395865.1	XM_004400839.1
	<i>Neomonachus schauinslandi</i>	XM_021690213.1	XM_021681954.1	XM_021703916.1	XM_021704294.1	XM_021703490.1	XM_021684842.1	XM_021698605.1	XM_021704848.1
Carnivora	<i>Enhydra lutris kenyonii</i>	BLAST	XM_022490805.1	XM_022509041.1	XM_022521029.1	XM_022517275.1	XM_022507296.1	XM_022517426.1	XM_022519560.1
	<i>Ursu maritimus</i>	XM_008697772.1	BLAST	XM_008688551.1	XM_018064037.1	XM_008707622.1	XM_008694134.1	XM_008688985.1	XM_008704561.1
	<i>Canis lupus familiaris</i>	NM_001194950.1	XM_022421240.1	XM_022423104.1	NM_001003970.1	NM_001127315.1	XM_038424307.1	XM_038436608.1	XM_022411216.1
Chiroptera	<i>Felis catus</i>	XM_004001117.4	XM_023247543.1	XM_023244164.1	XM_023244720.1	XM_023241517.1	XM_019812424.1	XM_023241408.1	XM_019834899.2
	<i>Eptesicus fuscus</i>	XM_028154129.1	XM_008155630.1	XM_028128553.1	XM_008156768.2	XM_008158970.2	XM_008159313.2	BLAST	XM_028144343.1
	<i>Myotis brandtii</i>	XM_005859963.2	BLAST	XM_005868217.2	XM_005869032.2	XM_014537663.1	XM_005885097.2	XM_014547038.1	XM_005877303.2

[illegible]

	<i>Balaena mysticetus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
Perissodactyla	<i>Bos taurus</i>	NM_001191251.3	NM_001011678.2	NM_001083690.2	NM_174710.2	NM_001205277.2	XM_005207204.4	XM_005204159.4	XM_024987649.1
	<i>Ovis aries</i>	XM_027969009.1	XM_015093345.2	XM_027972975.1	XM_027959352.1	XM_027975066.1	XM_012176138.2	XM_004002309.3	XM_027959629.1
	<i>Sus scrofa</i>	XM_021078870.1	XM_005671981.3	XM_021089339.1	XM_021078541.1	XM_021067791.1	XM_021092437.1	XM_021088699.1	XM_013994155.2
	<i>Vicugna pacos</i>	XM_031673805.1	XM_031678320.1	XM_015239558.2	XM_006210695.3	XM_006217562.2	XM_015244955.2	XM_015244353.2	XM_031691105.1
	<i>Equus caballus</i>	NM_001195636.1	XM_023622057.1	XM_001496473.6	XM_023654544.1	XM_023653377.1	NM_001256931.1	XM_023641436.1	XM_001489646.6
	<i>Ceratotherium simum</i>	XM_004430614.1	XM_004426661.2	XM_004435728.2	XM_004437694.2	XM_014789607.1	XM_004438743.2	XM_014780045.1	XM_004437551.2
	<i>Callorhinus ursinus</i>	XM_025862183.1	XM_025849627.1	XM_025870626.1	XM_025879353.1	XM_025864300.1	XM_025851967.1	XM_025872383.1	XM_025878368.1
	<i>Zalophus californianus</i>	XM_027574214.1	XM_027588598.1	XM_027619374.1	XM_027580423.2	XM_027625051.1	XM_027594581.1	XM_027621322.1	XM_027579850.1
Carnivora	<i>Odobenus rosmarus</i>	XM_012565386.1	XM_004403725.2	XM_004398774.2	XM_004393851.2	XM_004398561.1	XM_004413371.2	XM_004407154.2	XM_004393996.1
	<i>Neomonachus schauinslandi</i>	XM_021693043.1	XM_021703373.1	XM_021688351.1	XM_021685101.1	XM_021694560.1	XM_021690657.1	XM_021690143.1	XM_021684991.1
	<i>Enhydra lutris kenyonii</i>	XM_022513853.1	XM_022495499.1	XM_022515585.1	XM_022506534.1	XM_022524703.1	XM_022522394.1	XM_022496961.1	XM_022507299.1
	<i>Ursu maritimus</i>	BLAST	XM_008687171.1	XM_008706724.1	XM_008709169.1	XM_008688069.1	BLAST	XM_008704045.1	XM_008709114.1
	<i>Canis lupus familiaris</i>	XM_022403869.1	XM_038447161.1	XM_544094.6	XM_846992.4	XM_022418470.1	NM_001313824.1	NM_001003329.1	XM_005631548.3
Chiroptera	<i>Felis catus</i>	XM_019826020.1	XM_003990893.5	XM_023248778.1	XM_023240104.1	XM_023243688.1	XM_019834392.2	XM_019837595.2	XM_019812622.2
	<i>Eptesicus fuscus</i>	XM_028135579.1	XM_028140905.1	XM_008143311.2	XM_008146878.2	XM_028132982.1	XM_008143755.2	XM_028154036.1	XM_028135921.1
	<i>Myotis brandtii</i>	XM_005880096.2	XM_005857611.2	XM_005871667.2	XM_014538223.1	XM_005882584.1	XM_005877017.2	XM_014534613.1	XM_014538011.1
	<i>Rhinolophus ferrumequinum</i>	XM_033099212.1	XM_033111983.1	XM_033126672.1	XM_033120706.1	XM_033089486.1	XM_033117984.1	XM_033092490.1	XM_033119725.1
Primates	<i>Pan troglodytes</i>	XM_028846475.1	XM_001145876.5	XM_024345179.1	XM_508589.6	XM_016931274.1	XM_003313436.4	NM_001265976.1	NA
	<i>Homo sapiens</i>	NM_020321.3	NM_006164.5	NM_004056.6	NM_001619.5	NM_001257328.2	NM_000217.3	NM_004974.4	NM_033310.3
	<i>Macaca mulatta</i>	XM_009454575.3	NM_001257607.1	NM_001261295.1	XM_028833177.1	XM_015118329.1	XM_001102114.4	XM_001162925.3	XM_016921158.2
Scandentia	<i>Tupaia chinensis</i>	XM_006150218.2	XM_027773121.1	NA	XM_027769428.1	XM_006151854.3	XM_006172022.3	XM_027772296.1	XM_006149842.3
Rodentia	<i>Rattus norvegicus</i>	NM_173135.1	NM_031789.2	NM_001009662.1	NM_012776.1	NM_012911.1	NM_173095.3	NM_012970.3	XM_008760056.2
	<i>Mus musculus</i>	NM_183000.2	NM_010902.4	NM_007592.3	NM_130863.2	NM_001271358.1	NM_010595.3	NM_008417.5	XM_006526720.3
	<i>Heterocephalus glaber</i>	XM_013078018.2	XM_004857736.2	XM_004842145.2	XM_004852257.3	XM_004857272.3	XM_004869373.3	XM_004853692.2	XM_021264669.1
Sirenia	<i>Trichechus manatus</i>	XM_004372736.1	XM_023730537.1	XM_023727774.1	XM_023738164.1	XM_023731114.1	XM_004381168.2	XM_004390417.2	XM_004383782.2
Proboscidea	<i>Loxodonta africana</i>	XM_023548044.1	XM_003406202	XM_003408321.3	XM_023559549.1	XM_023556361.1	XM_003410634.3	XM_023547452.1	XM_003419447.3
Classification	Species name	Accession number							

		KCNIP3	KCNJ10	ANO3	OPRM1	OPRL1	OPRK1	OPRD1
	<i>Tursiops truncatus</i>	XM_033838401.1	XM_033856559.1	XM_019948278.2	XM_019951587.2	XM_033839461.1	XM_019925440.1	XM_033855246.1
	<i>Lagenorhynchus obliquidens</i>	XM_027128984.1	XM_027095083.1	XM_027115153.1	XM_027083030.1	XM_027086652.1	XM_027127872.1	XM_027109413.1
	<i>Globicephala melas</i>	XM_030838967.1	XM_030841942.1	XM_030864848.1	XM_030853121.1	XM_030841458.1	XM_030859828.1	XM_030865523.1
	<i>Orcinus orca</i>	XM_004277795.2	XM_004284454.1	XM_004263929.2	XM_012536769.1	XM_004282377.2	XM_004275020.2	XM_004266575.2
	<i>Neophocaena asiaeorientalis</i>	XM_024744018.1	XM_024750476.1	XM_024764654.1	XM_024748046.1	XM_024750256.1	XM_024742594.1	XM_024766814.1
	<i>Phocoena sinus</i>	XM_032653620.1	XM_032648098.1	XM_032640382.1	XM_032650842.1	XM_032604328.1	XM_032610055.1	XM_032642157.1
	<i>Delphinapterus leucas</i>	XM_022599027.1	XM_022559754.1	XM_022583740.2	XM_022559871.1	XM_022597651.2	XM_022556842.1	XM_022552068.2
	<i>Monodon monoceros</i>	XM_029232659.1	XM_029228840.1	XM_029209693.1	XM_029224170.1	XM_029222037.1	XM_029222825.1	XM_029229318.1
	<i>Lipotes vexillifer</i>	XM_007470197.1	XM_007461279.1	XM_007462608.1	XM_007458731.1	XM_007462220.1	XM_007464020.1	XM_007461817.1
	<i>Physeter catodon</i>	XM_007118470.1	XM_007129619.3	XM_024119081.1	XM_007129176.2	XM_024128409.1	XM_024127031.1	XM_024125424.1
Cetartiodactyla	<i>Balaenoptera bonaerensis</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Balaenoptera acutorostrata</i>	XM_007197357.2	XM_007171784.2	XM_007180984.2	XM_007186136.1	XM_007185174.1	XM_007168611.1	XM_007170618.2
	<i>Balaenoptera musculus</i>	XM_036874091.1	XM_036852607.1	XM_036861881.1	XM_036872213.1	XM_036825787.1	XM_036830487.1	XM_036867319.1
	<i>Balaenoptera physalus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Megaptera novaeangliae</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Eschrichtius robustus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Balaena mysticetus</i>	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST	BLAST
	<i>Bos taurus</i>	NM_001075612.2	NM_001081601.1	NM_001191315.2	NM_174408.2	XM_015474110.2	NM_001318764.1	NM_001191148.1
	<i>Ovis aries</i>	XM_027967108.1	XM_004002660.4	XM_027979573.1	XM_004011420.3	XM_027976897.1	XM_004011957.4	XM_027965410.1
	<i>Sus scrofa</i>	XM_021087059.1	XM_005663208.3	XM_013987284.2	NM_001001538.1	NM_214176.1	XM_003355059.5	XM_003356260.5
	<i>Vicugna pacos</i>	XM_031692051.1	XM_006215640.3	XM_031681078.1	XM_006197712.2	XM_015243904.2	XM_006204664.3	XM_006196882.2:
Perissodactyla	<i>Equus caballus</i>	XM_023618686.1	XM_001491211.5	XM_014741888.2	XM_014738201.2	XM_001495485.5	XM_023648620.1	XM_023634919.1
	<i>Ceratotherium simum</i>	XM_004435806.2	XM_004442773.2	XM_014783643.1	XM_014795480.1	XM_004430168.2	XM_004435697.2	XM_004425847.1
	<i>Callorhinus ursinus</i>	XM_025867613.1	XM_025860752.1	XM_025879336.1	XM_025866359.1	XM_025865055.1	XM_025871427.1	XM_025856040.1
Carnivora	<i>Zalophus californianus</i>	XM_027623931.2	XM_027613702.2	XM_027580367.1	XM_027601049.2	XM_027623227.1	XM_027599696.1	XM_027618330.2
	<i>Odobenus rosmarus</i>	XM_004399843.2	XM_004407858.2	XM_0044416870.1	XM_012566802.1	XM_004410095.1	XM_004416041.2	XM_004394640.1
	<i>Neomonachus schauinslandi</i>	XM_021697498.1	XM_021681916.1	XM_021685869.1	XM_021693699.1	XM_021677749.1	XM_021688277.1	XM_021683630.1

	<i>Enhydra lutris kenyoni</i>	XM_022520465.1	XM_022490971.1	XM_022506952.1	XM_022520971.1	XM_022494199.1	XM_022515599.1	XM_022496667.1
	<i>Ursu maritimus</i>	XM_008700533.1	XM_008700702.1	XM_008686892.1	XM_008688566.1	XM_008688143.1	XM_008706685.1	XM_008694831.1
	<i>Canis lupus familiaris</i>	XM_003639596.4	XM_005640901.3	XM_534094.6	NM_001314122.1	XM_014107305.2	XM_544080.6	XM_544455.6
	<i>Felis catus</i>	XM_003984274.5	XM_019822326.2	XM_023239658.1	XM_019831412.1	XM_019826183.1	XM_023248439.1	XM_003989776.4
	<i>Eptesicus fuscus</i>	XM_008160573.2	XM_008154256.2	XM_028156716.1	XM_008154677.2	XM_008157153.2	XM_028147996.1	XM_008147978.2
Chiroptera	<i>Myotis brandtii</i>	XM_005860465.2	XM_005857772.2	XM_014545226.1	XM_014545053.1	XM_005885520.2	XM_005857314.2	XM_005875244.2
	<i>Rhinolophus ferrumequinum</i>	XM_033100946.1	XM_033093604.1	XM_033120577.1	XM_033094713.1	XM_033094198.1	XM_033125705.1	XM_033115868.1
	<i>Pan troglodytes</i>	XM_016948932.2	XM_009435435.2	XM_001134720.6	NM_001033915.1	XM_016938297.2	XM_009455386.3	XM_513259.6
Primates	<i>Homo sapiens</i>	NM_013434.5	NM_002241.5	NM_001313726.1	XM_017010903.2	NM_001318853.2	NM_001318497.2	NM_000911.4
	<i>Macaca mulatta</i>	NM_001257864.1	XM_015110279.2	NM_001265904.1	NM_001032824.1	NM_001320615.1	NM_001321098.2	XM_001113252.4
Scandentia	<i>Tupaia chinensis</i>	NA	XM_006168841.3	XM_027775367.1	XM_006139989.3	XM_006167092.1	XM_006140344.2	BLAST
	<i>Rattus norvegicus</i>	NM_032462.2	XM_008769737.2	XM_017602571.1	XM_008758731.2	NM_001318947.1	XM_017593203.1	NM_012617.1
Rodentia	<i>Mus musculus</i>	NM_019789.4	XM_006496677.5	NM_001128103.2	XM_006512437.5	NM_001318919.1	NM_001318735.1	NM_013622.3
	<i>Heterocephalus glaber</i>	XM_004844345.3	XM_021239684.1	XM_004851573.3	NM_001267590.1	NM_001310286.1	NM_001310230.1	XM_004850778.2
Sirenia	<i>Trichechus manatus</i>	XM_004369351.1	XM_004390204.2	XM_023737820.1	XM_004368814.2	XM_004370148.1	XM_004375606.1	XM_004377022.1
Proboscidea	<i>Loxodonta africana</i>	XM_023541135.1	XM_003415179.3	XM_023550773.1	XM_010588919.2	XM_003421774.3	XM_003408315.3	XM_003415273.3

BLAST: obtained from the local database blast; NA: Not available

Table S3. Information of genome with Blast

Species	Genome
<i>Tursiops truncatus</i>	GCF_011762595.1_mTurTru1.mat.Y
<i>Lagenorhynchus obliquidens</i>	GCF_003676395.1_ASM367639v1
<i>Globicephala melas</i>	GCF_006547405.1_ASM654740v1
<i>Orcinus orca</i>	GCF_000331955.2_Oorc_1.1
<i>Neophocaena asiaeorientalis</i>	GCF_003031525.1_Neophocaena_asiaeorientalis_V1
<i>Phocoena sinus</i>	GCF_008692025.1_mPhoSin1.pri
<i>Delphinapterus leucas</i>	GCF_002288925.2_
<i>Monodon monoceros</i>	GCF_005190385.1_NGI_Narwhal_1
<i>Lipotes vexillifer</i>	GCF_000442215.1_Lipotes_vexillifer_v1
<i>Physeter catodon</i>	GCF_002837175.2_ASM283717v2
<i>Balaenoptera bonaerensis</i>	GCA_000978805.1_ASM97880v1
<i>Balaenoptera acutorostrata scammoni</i>	GCF_000493695.1_BalAcu1.0
<i>Balaenoptera musculus</i>	GCF_009873245.2_mBalMus1.pri.v3
<i>Balaenoptera physalus</i>	GCA_023338255.1_SBiKF_Bphy_ph2
<i>Megaptera novaeangliae</i>	https://dataverse.harvard.edu/file.xhtml?persistentId=doi:10.7910/DVN/ADHX1O/0J3CYS&version=1.0
<i>Eschrichtius robustus</i>	GCA_002189225.1_ASM218922v1
<i>Balaena mysticetus</i>	http://www.bowhead-whale.org/annotations/
<i>Bos taurus</i>	GCF_002263795.1_GCA_002263795.2
<i>Ovis aries</i>	GCF_002742125.1_Oar_rambouillet_v1.0
<i>Sus scrofa</i>	GCF_000003025.6_Sscrofa11.1
<i>Vicugna pacos</i>	GCF_000164845.3_VicPac3.1
<i>Equus caballus</i>	GCF_002863925.1_EquCab3.0
<i>Ceratotherium simum</i>	GCF_000283155.1_CerSimSim1.0
<i>Callorhinus ursinus</i>	GCF_003265705.1_ASM326570v1
<i>Zalophus californianus</i>	GCF_900631625.1_mZalCal1.pri.v2
<i>Odobenus rosmarus</i>	GCF_000321225.1_Oros_1.0
<i>Neomonachus schauinslandi</i>	GCF_002201575.1_ASM220157v1
<i>Enhydra lutris kenyoni</i>	GCF_002288905.1_ASM228890v2
<i>Ursu maritimus</i>	GCF_000687225.1_UrsMar_1.0
<i>Canis lupus familiaris</i>	GCF_005444595.1_UMICH_Zoey_3.1
<i>Felis catus</i>	GCF_000181335.3_Felis_catus_9.0
<i>Eptesicus fuscus</i>	GCF_000308155.1_EptFus1.0

<i>Myotis brandtii</i>	GCA_000412655.1_ASM41265v1
<i>Rhinolophus ferrumequinum</i>	GCF_004115265.1_mRhiFer1_v1
<i>Pan troglodytes</i>	GCF_002880755.1_Clint_PTRv2
<i>Homo sapiens</i>	GCF_000001405.39_GRCh38.p13
<i>Macaca mulatta</i>	GCF_000002255.3_Mmul_051212
<i>Tupaia chinensis</i>	GCF_000334495.1_TupChi_1.0
<i>Rattus norvegicus</i>	GCF_000002265.2_Rn_Celera
<i>Mus musculus</i>	GCF_000001635.27_GRCm39
<i>Heterocephalus glaber</i>	GCF_000247695.1_HetGla_female_1.0
<i>Trichechus manatus</i>	GCF_000243295.1_TriManLat1.0
<i>Loxodonta africana</i>	GCF_000001905.1_Loxafr3.0

Table S4. Primer sequence information

Primer name	Sequence (5'-3')	Annealing temperature (°C)	Length of product (bp)
<i>N. asiaeorientalis</i> -F	TCTTCCCGTTTGCCCTGAGTT	61.94	548
<i>N. asiaeorientalis</i> -R	TCAGATTGGCCAGGTGGAAGA	61.12	548
<i>L. vexillifer</i> - F	TTCCCGTTTGCCCTGAGTTT	60.11	547
<i>L. vexillifer</i> - R	GTCAGATTGGCCAGGTGGAA	59.96	547

Table S5. Branch detected positive selection for pain-related genes by the branch model

Gene	Branch	ω value	$2\Delta\ln L$	p^{adjust} value
<i>ASIC3</i>	<i>E. robustus</i>	1.299	8.209316	$p<0.05$
<i>TRPV4</i>	<i>M. novaeanglise</i>	1.054	15.56283	$p<0.05$
<i>CA8</i>	LCA of <i>B. mysticetus</i> & <i>B. bonaerensis</i>	1.262	12.820818	$p<0.05$

LAC: last common ancestor

Table S6. Branch detected positive selection for pain-related genes by the branch site model

Gene	Branch	ω value (ω_0 ω_1 ω_2)	2 Δ lnL	p^{adjust} value	Positively selected sites (PP > 0.8)
SCN9A	LAC of <i>Ovis aries</i> & <i>T. truncatus</i>	0.041 1.000 130.796	7.792844	$p < 0.05$	127 L 0.941
	<i>M. brandtii</i>	0.040 1.000 12.300	9.616722	$p < 0.05$	564 G 0.998**; 1140 A 0.998**; 1493 Q 0.995**
SCN10A	<i>B. taurus</i>	0.059 1.000 11.250	8.231646	$p < 0.05$	1866 L 0.981*
	<i>H. glaber</i>	0.040 1.000 12.300	9.540488	$p < 0.05$	1347 A 0.902
ANO1	LAC of <i>B. bonaerensis</i> & <i>B. acutorostrata</i>	0.027 1.000 142.571	9.665078	$p < 0.05$	36 T 0.979*
	<i>R. norvegicus</i>	0.027 1.000 138.433	16.22956	$p < 0.05$	473 K 0.996**
CCK	<i>P. catodon</i>	0.109 1.000 132.637	10.509472	$p < 0.05$	37 E 0.997**; 98 M 0.942; 112 E 0.996**
TRPV1	<i>H. glaber</i>	0.059 1.000 58.050	9.540488	$p < 0.05$	1347 A 0.902
ASIC3	<i>B. physalus</i>	0.075 1.000 349.853	16.91663	$p < 0.05$	468 D 0.998**
	<i>M. mulatta</i>	0.072 1.000 28.035	21.05658	$p < 0.05$	357 I 0.964*; 399 L 0.946
ARRB2	<i>B. physalus</i>	0.011 1.000 181.298	7.824406	$p < 0.05$	124 G 0.984*
KCNK4	<i>E. robustus</i>	0.070 1.000 109.557	6.498806	$p < 0.05$	47 L 0.930; 103 T 0.932; 104 I 0.999**
OPRL1	LAC of <i>Cetacea</i>	0.037 1.000 3.741	8.14323	$p < 0.05$	11 E 0.957*; 19 Q 0.982*; 195 D 1.000**; 196 E 0.801; 225 I 0.999**
OPRM1	<i>S. scrofa</i>	0.032 1.000 55.104	11.033892	$p < 0.05$	47 I 0.993**

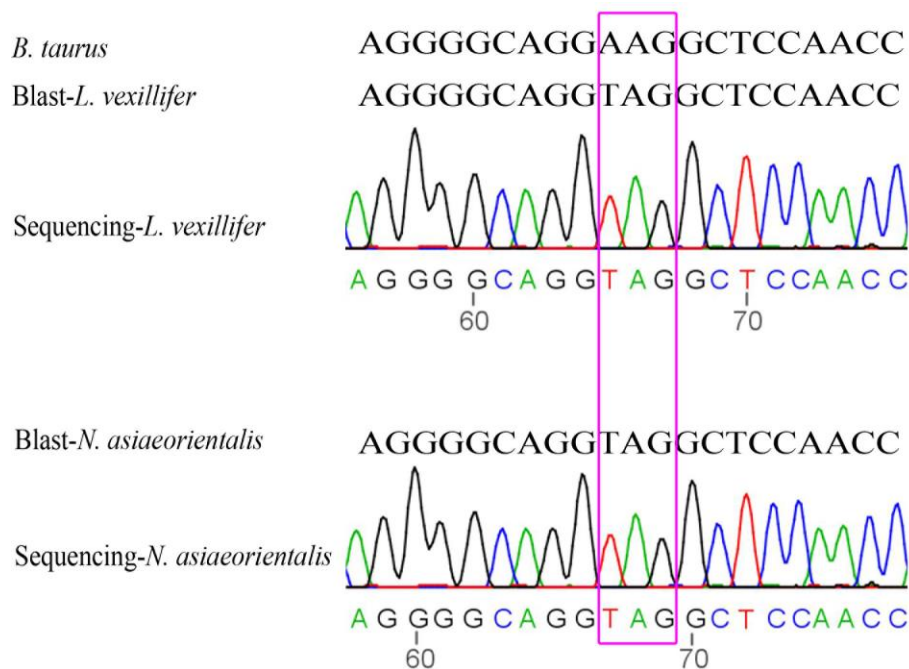
LAC: last common ancestor

Table S7. Predicted deleterious score by PROVEAN and PolyPhen2

Variant	Predicted deleterious score	
	PROVEAN	PolyPhen2
ASIC3(F56L)	-0.540	0.256
ASIC3(D163A)	-1.471	0.987
TRVP1(D471G)	-2.668	0.010
NGF(T202A)	-3.866	0.015
GRK2(E88G)	-1.924	0.992
OPRD1(F159L)	-3.467	0.069
KCNIP3(A127S)	-0.172	0.016
KCNJ10(G350R)	0.450	0.885
ANO3(V635L)	-1.106	0.498

Purplish red labeled values are scores for cetacean-specific amino acid substitutions predicted to affect protein function.

Figure S1



Identification of *ASIC4* gene of *L.vexillifer* and *N. asiaeorientalis*. The purplish red box indicates the stop codon.

References

1. Xue Y, Chidiac C, Herault Y, Gaveriaux-Ruff C: **Pain behavior in SCN9A (Nav1.7) and SCN10A (Nav1.8) mutant rodent models.** *Neuroscience Letters* 2021, **753**:135844.

2. Landy MA, Goyal M, Casey KM, Liu C, Lai HC: **Loss of Prdm12 during development, but not in mature nociceptors, causes defects in pain sensation.** *Cell Rep* 2021, **34**(13):108913-108913.
3. Liu Y, Liu Z, Wang K: **The Ca(2+)-activated chloride channel ANO1/TMEM16A: An emerging therapeutic target for epithelium-originated diseases?** *Acta Pharm Sin B* 2021, **11**(6):1412-1433.
4. McRoberts JW: **Cholecystokinin and pain: a review.** *Anesth Prog* 1986, **33**(2):87-90.
5. Yu L-N, Sun L-H, Wang M, Yan M: **Research progress of the role and mechanism of extracellular signal-regulated protein kinase 5 (ERK5) pathway in pathological pain.** *J Zhejiang Univ Sci B* 2016, **17**(10):733-741.
6. Obata K, Noguchi K: **MAPK activation in nociceptive neurons and pain hypersensitivity.** *Life Sciences* 2004, **74**(21):2643-2653.
7. Wang JW, Stifani S: **Roles of Runx Genes in Nervous System Development.** In: *RUNX Proteins in Development and Cancer*. Edited by Groner Y, Ito Y, Liu P, Neil JC, Speck NA, van Wijnen A. Singapore: Springer Singapore; 2017: 103-116.
8. Testa G, Cattaneo A, Capsoni S: **Understanding pain perception through genetic painlessness diseases: The role of NGF and proNGF.** *Pharmacological Research* 2021, **169**:105662.
9. Indo Y: **Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV.** *Clinical Autonomic Research* 2002, **12**(1):I20-I32.
10. Coutelier M, Blesneac I, Monteil A, Monin M-L, Ando K, Mundwiller E, Brusco A, Le Ber I, Anheim M, Castrioto A *et al*: **A Recurrent Mutation in CACNA1G Alters Cav3.1 T-Type Calcium-Channel Conduction and Causes Autosomal-Dominant Cerebellar Ataxia.** *The American Journal of Human Genetics* 2015, **97**(5):726-737.
11. Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P, Harries MH, Latcham J, Clapham C, Atkinson K *et al*: **Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia.** *Nature* 2000, **405**(6783):183-187.
12. Moore C, Gupta R, Jordt S-E, Chen Y, Liedtke WB: **Regulation of Pain and Itch by TRP Channels.** *Neurosci Bull* 2018, **34**(1):120-142.
13. Wirkner K, Sperlagh B, Illes P: **P2X3 Receptor Involvement in Pain States.** *Molecular Neurobiology* 2007, **36**(2):165-183.
14. Zhang W-j, Luo H-l, Zhu Z-m: **The role of P2X4 receptors in chronic pain: A potential pharmacological target.** *Biomedicine & Pharmacotherapy* 2020, **129**:110447.

15. Chauhan SA, Sahoo CG, Dikhit RM, Das P: **Acid-Sensing Ion Channels Structural Aspects, Pathophysiological Importance and Experimental Mutational Data Available Across Various Species to Target Human ASIC1.** *Current Drug Targets* 2019, **20**(1):111-121.
16. Wemmie JA, Taugher RJ, Kreple CJ: **Acid-sensing ion channels in pain and disease.** *Nature Reviews Neuroscience* 2013, **14**(7):461-471.
17. Donier E, Rugiero F, Jacob C, Wood JN: **Regulation of ASIC activity by ASIC4 - New insights into ASIC channel function revealed by a yeast two-hybrid assay.** *European Journal of Neuroscience* 2008, **28**(1):74-86.
18. Fu ES, Erasso DM, Zhuang GZ, Upadhyay U, Ozdemir M, Wiltshire T, Sarantopoulos KD, Smith SB, Maixner W, Martin ER *et al*: **Impact of human CA8 on thermal antinociception in relation to morphine equivalence in mice.** *Neuroreport* 2017, **28**(18):1215-1220.
19. Wang H, Heijnen CJ, van Velthoven CTJ, Willems HLDM, Ishikawa Y, Zhang X, Sood AK, Vroon A, Eijkelkamp N, Kavelaars A: **Balancing GRK2 and EPAC1 levels prevents and relieves chronic pain.** *J Clin Invest* 2013, **123**(12):5023-5034.
20. Ozberk D, Haywood A, Sutherland HG, Yu C, Albury CL, Zunk M, George R, Good P, Griffiths LR, Hardy J *et al*: **Association of polymorphisms in ARRB2 and clinical response to methadone for pain in advanced cancer.** *Pharmacogenomics* 2022, **23**(5):281-289.
21. Imbrici P, Altamura C, Gualandi F, Mangiatordi GF, Neri M, De Maria G, Ferlini A, Padovani A, D'Adamo MC, Nicolotti O *et al*: **A novel KCNA1 mutation in a patient with paroxysmal ataxia, myokymia, painful contractures and metabolic dysfunctions.** *Molecular and Cellular Neuroscience* 2017, **83**:6-12.
22. Peng Y, Zhang Q, Cheng H, Yan G, Xing C: **Upregulation of ubiquitin conjugating enzyme E2B (Ube2b) ameliorates neuropathic pain by regulating Kcna2 (potassium voltage-gated channel subfamily A member 2) in primary afferent neurons.** *Bioengineered* 2021, **12**(1):7470-7480.
23. Noël J, Zimmermann K, Busserolles J, Deval E, Alloui A, Diochot S, Guy N, Borsotto M, Reeh P, Eschalier A *et al*: **The mechano-activated K⁺ channels TRAAK and TREK-1 control both warm and cold perception.** *The EMBO Journal* 2009, **28**(9):1308-1318.
24. Guo Y-P, Zhi Y-R, Liu T-T, Wang Y, Zhang Y: **Global Gene Knockout of Kcnip3 Enhances Pain Sensitivity and Exacerbates Negative Emotions in Rats.** *Frontiers in Molecular Neuroscience* 2019, **12**.
25. Mannerak MA, Lashkarivand A, Eide PK: **Trigeminal neuralgia and genetics: A systematic review.** *Molecular Pain* 2021, **17**:17448069211016139.
26. Ślęczkowska M, Almomani R, Marchi M, de Greef BTA, Sopacua M, Hoeijmakers JGJ,

- Lindsey P, Salvi E, Bönhof GJ, Ziegler D *et al*: **Peripheral Ion Channel Gene Screening in Painful- and Painless-Diabetic Neuropathy**. *Int J Mol Sci* 2022, **23**(13).
27. Campa D, Gioia A, Tomei A, Poli P, Barale R: **Association of ABCB1/MDR1 and OPRM1 Gene Polymorphisms With Morphine Pain Relief**. *Clinical Pharmacology & Therapeutics* 2008, **83**(4):559-566.
28. Seo E-J, Efferth T, Panossian A: **Curcumin downregulates expression of opioid-related nociceptin receptor gene (OPRL1) in isolated neuroglia cells**. *Phytomedicine* 2018, **50**:285-299.
29. Ho KWD, Wallace MR, Staud R, Fillingim RB: **OPRM1, OPRK1, and COMT genetic polymorphisms associated with opioid effects on experimental pain: a randomized, double-blind, placebo-controlled study**. *The Pharmacogenomics Journal* 2020, **20**(3):471-481.
30. Nielsen LM, Christrup LL, Sato H, Drewes AM, Olesen AE: **Genetic Influences of OPRM1, OPRD1 and COMT on Morphine Analgesia in a Multi-Modal, Multi-Tissue Human Experimental Pain Model**. *Basic & Clinical Pharmacology & Toxicology* 2017, **121**(1):6-12.