Figure S1. Hypothetical signal transduction pathway that involves PAR2 and TRPM8 in cold stimulation based on the reported pathway. After TRPM8 is activated by cold stimulation, Ca\(^{2+}\) that has entered the cell via TRPM8 (a) activates PLCδ4 (b). PLC hydrolyzes PIP2 to IP3 and DAG (c). TRPM8 requires PIP2 for its activity (d). During PAR2 activation, the G\(_{αq}\) subunit stimulates PLCβ (e) and causes a decrease in PIP2 levels (c), which could impair TRPM8 channel activity. At the same time, the G\(_{αq}\) subunit which may be activated by PAR2 binds directly to the TRPM8 channel to impair channel activity (f). IP3 mobilizes Ca\(^{2+}\) stores from the endoplasmic reticulum (g) and increases intracellular Ca\(^{2+}\) concentrations. DAG or high Ca\(^{2+}\) levels further activate PKC (h) to inhibit TRPM8 (i). In carriers of the A allele of the rs2243057 SNP of PAR2, PAR2 expression is higher and PIP2 levels would be lower through PLC activation, possibly resulting in the stronger inhibition of TRPM8 activity. C allele carriers of the rs12992084 SNP of TRPM8 may speculatively have low TRPM8 expression. However, further direct evidence is needed to confirm this hypothesis.

Terms enclosed by rectangles: protein. Terms enclosed by circles: molecule. Red arrows: activate. Blue arrows: inhibit. Dotted line arrows: release. Question mark: a speculation. PAR2, protease activated receptor 2; TRPM8, transient receptor potential melastatin 8; GPCR, G protein-coupled receptor; G\(_{αq}\), G-protein αq subunit; PIP2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; PKC, phosphokinase C; ER, endoplasmic reticulum; PM, plasma membrane.