Supplementary Table 1. Cold-Heat Pattern Related Studies Based on Clinical Data.

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| Disease | First author, year | Pattern identification method | Discriminative factors between patterns\*  | Disease severity measurement | Patient (*n*) according to pattern | Outcome | Nationality |
| RA | [1] | TCM criteria, specialist | Clinical chemistry measurement, metabolomics, anthropometric evaluation | ACR criteria | Cold (20), heat (19) | Significant biochemical differences between Cold and Heat RA patients, including immune function, CRP, RHF, DHEAS, HPA axis involvement, and muscle breakdown, suggest tailored disease management strategies. | China |
| [2] | TCM criteria, specialist | Clinical chemistry measurement, proteomics | DAS28 | Cold (148), heat (158) | Significant variations were noted in DAS28, ESR, WBC, CRP, PLT, ALB and GLB between the two identified syndromes of RA (*p* < 0.05). | China |
| [3] | TCM criteria | Clinical chemistry measurement, proteomics | ACR criteria, DAS28 | Cold (19), heat (11) | Heat RA showed higher inflammatory and disease activity dependent on IL-33. | China |
| [4] | TCM criteria, specialist | Clinical chemistry measurement, HAQ | ACR criteria, DAS28 | Cold (181), heat (119) | Despite observing no significant differences in the levels of RF and anti-CCP between the cold and heat patterns of RA patients, the levels of CRP (*p* = 0.0019), PLT (*p* = 0.0055), and DAS28-ESR (*p* = 0.0022) were markedly higher in patients with the heat pattern compared to those with the cold pattern. Additionally, the HAQ score was also marginally higher in the heat pattern group. | China |
| [5] | TCM criteria, practitioner | Clinical chemistry measurement, transcriptomics, metabolomics | ACR criteria, symptom questionnaire | Not-defined (33) | Gene network analysis reveals distinct clustering patterns for heat and cold RA patients, with significant upregulation and grouping of apoptosis-related genes observed predominantly in the heat patterns, indicating a more active apoptotic process. Concurrently, metabolomics analysis presents heightened urea production and elevated levels of proline and oxo-proline, both markers for protein and collagen breakdown, in heat RA patients. | China |
| [6] | TCM criteria | Clinical chemistry measurement, transcriptomics, metabolomics, proteomics | ACR criteria | Cold (10), heat (10) | Cold RA patients were related to the TLR signaling pathway, Heat RA patients were related: calcium signaling pathway, cell adhesion molecules, PPAR signaling pathway, fatty acid metabolism. | China |
| [7] | TCM criteria | Transcriptomics, proteomics | Factor loadings | Not-defined (21) | Cold pattern is specifically associated with alanine, aspartate, and tyrosine metabolic processes, while heat pattern is correlated with pathways like TGF-beta signaling, calcium signaling, tumor-associated processes, cell cycling, histidine metabolism, and lysine degradation. | China |
| [8] | TCM criteria | Transcriptomics, proteomics | ACR criteria | Cold (21), heat (12) | Heat RA patients showed an upregulation of genes involved in small G protein signaling pathways, fatty acid metabolism, and T cell proliferation. | China |
| [9] | TCM criteria, practitioner | Transcriptomics, Proteomics | ACR criteria | Cold (21), heat (12) | Cold RA patients are associated EIF4A2, CCNT1, and IL7R, which are related with the promotion of cell proliferation and the Jak-STAT cascade. On the other hand, PRKAA1, HSPA8, and LSM6, implicated in fatty acid metabolism and the I-κB kinase/NF-κB cascade, were discerned as biomarkers of the heat RA patients. | China |
| [10] | TCM criteria | Transcriptomics, proteomics | ACR criteria | Cold (10), heat (10) | Cold pattern was associated with the TLR signaling pathway. In contrast, Heat pattern showed connections with a diverse set of pathways, including the Calcium signaling pathway, Cell adhesion molecules, PPAR signaling pathway, and Fatty acid metabolism. | China |
| [11] | TCM criteria, practitioner | Transcriptomics, proteomics | ACR criteria | Cold (12), heat (21) | TLR activated NF-𝜅B regulated gene transcription and apoptosis pathways appears to be particularly relevant to TCM deficiency patterns observed in RA patients | China |
| Cancer | [12] | TCM criteria, practitioner | Genomics | Cancer staging | NSCLC; cold (175), heat (135) | Cold pattern exhibited a higher likelihood of having *EGFR* gene mutations in cases of NSCLC (*p* = 0.003). | China |
| [13] | Questionnaire for cold sensitivity | Immunomics | Cancer staging | NSCLC IIIB or IV; cold (9), non-cold (11) | No significant difference between the two groups was observed in clinical response to ICIs (*p* = 0.668). PFS seemed to be longer in patients with non-cold pattern than cold pattern (*p* = 0.332). the proportion of effector memory CD8 T-cells was higher in patients with cold pattern than with non-cold pattern (*p* = 0.015), and the proportion of terminal effector CD8 T-cells was lower in patients with cold pattern than with non-cold pattern (*p* = 0.005). | Republic of Korea |
| [14] | Questionnaire for cold-heat & deficiency-excess pattern identification, specialist | BFI, FACT-F | Symptom questionnaire, QoL questionnaire | Cold (82), heat (14) | Moxibustion exhibits greater efficacy in treating the cold pattern compared to the heat pattern. | Republic of Korea |
| Metabolic syndrome | [15] | Questionnaire for cold sensitivity | Anthropometric evaluation | QoL questionnaire | Cold (119), non-cold (56) | Most of the non-Cold pattern group showed high quality of life, BIA and anthropometry. | Republic of Korea |
| [16] | Cold-heat syndrome differentiation questionnaire | Anthropometric evaluation | n.a | Non-defined (1,479) | Cold-Heat score were significantly correlated with weight, BMI, BSA, WHR, FFM, BFM, BCM, ICW, ECW, and BMR; however, the correlation coefficients were mostly low (0.15–0.24). | Republic of Korea |
| [17] | Questionnaire for cold sensitivity, specialist | Anthropometric evaluation, clinical chemistry measurement | n.a | Cold (1,123), heat (1,438) | All components except HDL were higher in the heat pattern group than in the cold pattern group. Metabolic syndrome prevalence showed a significant association between Taeeumin and the heat pattern group (OR = 1.653) but not for non-Taeeumin and the cold pattern group. | Republic of Korea |
| Asthma | [18] | TCM criteria | Anthropometric evaluation, Clinical chemistry measurement | QLQAKA | Cold (35), Heat (5) | the proportion of individuals with the asthma condition remains significantly high in the patient population. But there may be limitations in statistical power. | Republic of Korea |
| Cold-heat syndrome | [19] | Cold-heat syndrome differentiation questionnaire, specialist | Disease history, Anthropometric evaluation | EQ-5D, Degree of Mibyeong | Cold (264), Heat (247) | Cold Syndrome characterizes a cluster of symptoms linked to diminished energy metabolism and metabolic function, posing a higher likelihood of unhealthiness compared to Heat Syndrome (*p* < 0.05). | Republic of Korea |
| Sleep quality | [20] | Questionnaire for cold pattern identification | Anthropometric evaluation, PSQI | PSQI | Cold (1,193), non-cold (805) | Females predominated in cases of poor sleep quality. Non-cold pattern participants demonstrated a higher BMI than the cold pattern. Among the cold pattern individuals, the average quality of sleep was generally poor, and the sleep duration was shorter. | Republic of Korea |

\* Discriminative Factors between Patterns: Each study delineates Cold and Heat patterns based on various factors, including comprehensive analysis platforms (omics), anthropometric evaluations, and clinical chemistry measurements.

ACR = American College of Rheumatology; ALB = Albumin; BCM = Body Cell Mass; BFI = Brief Fatigue Inventory; BFM = Body Fat Mass; BIA = Bioelectrical Impedance Analysis; BMI = Body Mass Index; BMR = Basal Metabolic Rate; BSA = Body Surface Area; CCNT1 = Cyclin T1; CCP = Cyclic Citrullinated Peptide; CRP = C-reactive protein; DAS28 = 28-joint count Disease Activity Score; DHEAS = Dehydroepiandrosterone sulfate; ECW = Extracellular Water; EGFR = Epidermal Growth Receptor; EIF4A2 = Eukaryotic Translation Initiation Factor 4A2; ESR = Erythrocyte Sedimentation Rate; FACT-F = Functional Assessment of Cancer Therapy-Fatigue; FFM = Fat-Free Mass; GLB = Globulin; HAQ = Health Assessment Questionnaire; HDL = High Density Lipoprotein Cholesterol; HPA = Hypothalamic-pituitary-adrenal; HSPA8 = Heat Shock Protein Family A (Hsp70) Member 8; ICI = Immune Checkpoint Inhibitors; ICW = Intracellular Water; IL-33 = Interleukin-33; IL7R = Interleukin 7 Receptor; Jak-STATs = Janus Kinases Signal Transducer and Activator of Transcription proteins; NSCLC = Non-Small Cell Lung Cancer; n.a = not applicable; PFS = Progression-free survival; PLT = Platelet; PPAR = Peroxisome Proliferator-activated Receptors; PRKAA1 = Protein Kinase AMP-Activated Catalytic Subunit Alpha 1; PSQI = Pittsburgh Sleep Quality Index; QLQAKA = Quality of Life Questionnaire for Adult Korean Asthmatics; QoL = Quality of Life; RA = Rheumatoid Arthritis; RF = Rheumatoid Factor; RHF = Rheumatoid factor; TCM = Traditional Chinese Medicine; TGF = Transforming Growth Factor; TLR = Toll-like Receptor; WBC = White Blood Cell; WHR = Waist-Hip Ratio.

Supplementary Table 2. Candidate Genes for Cold-Heat Pattern Identification.

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| Category | Genes | Research articles | Suggested mechanism for cold-heat pattern identification |
| UCP1 | *UCP1* | [21-71] | BAT thermogenesis, activated by cold-induced norepinephrine release and subsequent beta-adrenergic receptor binding, is crucial in maintaining body temperature, primarily through *UCP1*-mediated heat production. |
| [56, 57, 71] | BAT activity may significantly influence non-shivering thermogenesis, glucose homeostasis and lipid metabolism, thus presenting potential therapeutic strategies for obesity, diabetes, and related metabolic disorders. |
| *UCP3* | [41, 72, 73] | Upon cold exposure, there is an elevation in *UCP3* expression in skeletal muscle, leading to the induction of direct thermogenesis. |
| *PGC1-α* | [53-55, 59, 62, 65, 68] | *PGC-1α* plays a crucial role, as it facilitates mitochondrial biogenesis and thermogenic functionality, thereby driving the differentiation and functionality of brown adipose tissue. |
| *PRDM16* | [51, 52, 60, 69] | PRDM16, a transcriptional regulator, has been recognized as a critical determinant in BAT development and function, as it promotes brown adipocyte differentiation and thermogenic gene expression, consequently driving the expansion and activation of brown adipose tissue. |
| *SCD-1* | [58] | Global deletion of *SCD1* in mice impairs the epidermal lipid barrier function, intensifying heat loss and activating thermoregulatory thermogenesis. |
| *CTRP5* | [61] | Lentivirus-mediated overexpression of *CTRP5* in mice curbs adipose tissue browning, resulting in diminished heat production, *UCP1* expression, and browning-related gene expression. |
| *KLF9* | [62] | In human white adipose tissue, *Klf9* expression levels are negatively correlated with adiposity, and its overexpression in primary fat cells enhances Ucp1-dependent cellular thermogenesis. |
| *AIFM2* | [63] | *Aifm2*, a lipid-droplet-associated NADH oxidase specific to brown adipose tissue, facilitates robust glycolysis and thermogenesis by regenerating cytosolic NAD and supporting the electron transport chain through its association with the mitochondrial inner membrane. |
| *FAM195A* | [64] | *FAM195A* knockout mice, characterized by the whitening of BAT and impaired thermoregulation, exhibit down-regulation of enzymes involved in BCAA metabolism in BAT, consequently affecting their response to cold exposure. |
| *ADH5* | [66] | Enhanced Adh5 expression significantly boosts *UCP1*-mediated thermogenesis. |
| *TG2* | [67] | Lacking *TG2* in mice demonstrate diminished cold tolerance, associated with reduced usage of their epididymal adipose tissue and lessened adipose tissue browning. |
| *PEX13* | [68] | *PEX13*, a docking factor involved in protein import into the peroxisome matrix, is significantly upregulated during cold-induced beige adipocyte recruitment in the inguinal WAT of C57BL/6 mice. Notably, thermogenic protein expression, including *UCP1* and *PGC1-α*, is suppressed with siPex13 treatment, demonstrating *PEX13*'s role in cold-induced white adipocyte remodeling. |
| *SOX4* | [69] | *SOX4*, identified as a crucial transcriptional effector of thermogenesis, plays a critical role in maintaining energy expenditure and beige adipocyte formation. Deletion of *SOX4* specifically in adipocytes or *UCP1*+ cells result in significant cold intolerance and decreased thermogenic gene expression, demonstrating its essential role in thermal regulation. |
| *ORMDL3* | [70] | *ORMDL3*, a regulator in the sphingolipid pathway, plays a substantial role in governing BAT thermogenesis, WAT browning, and insulin resistance, implying its potential therapeutic relevance in metabolic disorders. |
| TRP | *TRPM8* | [38, 74-97] | TRPM8 is known as the cold and menthol receptor. It is activated by cool to cold temperatures (8–28°C) and is mainly found in sensory neurons. Its activation can induce cold sensation and cold-induced analgesia. |
| [98, 99] | Cold air stimulation instigates airway inflammation and remodeling via the upregulation of *TRPM8*, and that *TRPM8* knockdown significantly mitigates these responses by inhibiting the mitogen-activated protein kinase and nuclear factor-κB pathways. |
| *TRPA1* | [78, 83-85, 88, 89, 91, 94, 96, 100-107] | TRPA1 is known as the wasabi receptor, it is activated by noxious cold (< 17°C) and various pungent natural compounds like those found in wasabi, garlic, and onions. It is mainly involved in nociception and inflammation. |
| [99, 108] | TRPA1 activation triggers neurogenic inflammation through the TLR4 or CGRP pathways, culminating in the release of artemin and GFRα3 receptor activation, ultimately leading to the sensitization of TRPM8 channels and afferents. |
| *TRPV1* | [76, 78, 88, 89, 91, 100, 102, 109] | TRPV1 is the capsaicin receptor and is sensitive to hot temperatures (> 43°C), capsaicin (the pungent compound in hot chili peppers), and acidic conditions. Its activation results in a sensation of burning pain. *TRPV1* plays a critical role in heat and pain sensation and body temperature regulation. |
| [99] | TRPM8, TRPA1, and TRPV1 channels induced pain and inflammation, which were subsequently alleviated by the application of herbal medicine, demonstrating its therapeutic potential. |
| *TRPV2* | [88, 89, 91] | TRPV2 is activated by extreme heat (> 52°C) and plays a role in high-threshold heat nociception. |
| *TRPV3* | TRPV3 (24–39°C) is expressed in keratinocytes of the skin and plays a role in maintaining skin homeostasis and hair morphogenesis. |
| *TRPV4* | TRPV4 (25–34°C) is found in multiple tissues and is involved in various physiological processes like osmoregulation, mechanosensation, and nociception. |
| *TRPM2* | [89] | TRPM2 plays a critical role in thermal preference, compelling mice to seek cooler temperatures across a wide range from 23°C to over 38°C. On the other hand, there exists a notable co-expression of the newly discovered heat-sensitive mechanism, operative in the range of 34°C to 42°C, with the TRPV1 and TRPM3 channels.The activation of TRPV1, TRPM3, and ANO1 channels imparts a high-temperature, noxious-heat-avoidance signal. |
| *TRPM3* |
| *ANO1* |
| HSP | *HSP70* | [110-114] | HSP70, a heat shock protein, functions as a molecular chaperone, aiding in protein folding, refolding, and degradation. Its upregulation in response to cellular stress (oxidative, thermal stress) and anti-apoptotic properties play a pivotal role in cellular defense mechanisms, making it a noteworthy therapeutic target. |
| CIRBP | *CIRBP* | [115] | The expression of *CIRBP* was confirmed when cold shock, UV irradiation, and oxidative stress were given to the human cell line. |
| [91, 110, 114, 116-118] | CIRBP primarily binds RNA and directs its processing, modulating the expression of specific genes under cold stress. It performs a pivotal function in promoting cell survival in cold environments by stabilizing particular mRNAs and enabling their translation, thereby enhancing the production of proteins vital for cellular cold stress protection. |
| Others | *CYP1A1* | [119] | In an *in vivo* model exposed to a temperature of 4°C for a duration of 5 days, there was a noted increase in the mRNA level of *CYP1A.* |
| *RBM3* | [91, 114, 116] | the induction of RBM3 occurs in response to cold stress, both *in vitro* and *in vivo*. |
| *COMT* | [78] | Gender-specific genetic variations in *TRPA1, COMT*, and *FAAH* play a substantial role in individual variations in sensitivity to short-duration cold pain among a European American cohort. |
| *FAAH* |
| *OPRD1* | There exists a significant correlation between *OPRD1* and heat pain sensitivity based on *in vivo* data. However, *OPRD1* haploblocks do not exhibit a significant association with sensitivity to cold and/or heat pain. |

ADH5 = Alcohol Dehydrogenase 5; ANO1 = Anoctamin 1; Aifm2 = Apoptosis Inducing Factor Mitochondria Associated 2; BAT = Brown Adipose Tissue; BCAA = branched-chain amino acid; CGRP = Calcitonin Gene-Related Peptide; CIRBP = Cold Inducible RNA Binding Protein; COMT = Catechol-O-Methyltransferase; CTRP5 = C1q And Tumor Necrosis Factor Related Protein 5; CYP1A1 = Cytochrome P450 Family 1 Subfamily A Member 1; FAAH = Fatty Acid Amide Hydrolase; FAM195A = Family With Sequence Similarity 195, Member A; HSP70 = Heat Shock Protein Family A (Hsp70) Member 4; KLF9 = KLF Transcription Factor 9; OPRD1 = Opioid Receptor Delta 1; ORMDL3 = ORMDL Sphingolipid Biosynthesis Regulator 3; PEX13 = Peroxisomal Biogenesis Factor 13; PGC1-α = Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha; PRDM16 = PR Domain Zinc Finger Protein 16; RBM3 = RNA Binding Motif Protein 3; SCD1 = Stearoyl-CoA Desaturase 1; SOX4 = SRY-Box Transcription Factor 4; TG2 = Tissue transglutaminase; TLR4 = Toll Like Receptor 4; TRPA1 = Transient Receptor Potential Cation Channel Subfamily A Member 1; TRPM2 = Transient Receptor Potential Cation Channel Subfamily M Member 2; TRPM3 = Transient Receptor Potential Cation Channel Subfamily M Member 3; TRPM8 = Transient Receptor Potential Cation Channel Subfamily M Member 8; TRPV1 = Transient Receptor Potential Cation Channel Subfamily V Member 1; TRPV2 = Transient Receptor Potential Cation Channel Subfamily V Member 2; TRPV3 = Transient Receptor Potential Cation Channel Subfamily V Member 3; TRPV4 = Transient Receptor Potential Cation Channel Subfamily V Member 4; UCP-1 = Uncoupling protein 1; UCP-3 = Uncoupling protein 3; WAT = White Adipose Tissue.

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