Supplementary Information

Supplementary Discussion

In the present study, we conducted a simulation based on a permutation test to extract genes that are both diagnostic markers (for discrimination of histological subtypes) and prognostic markers (for overall survival in STS). As shown in Table 2, 25 genes were extracted, and their adjusted p values were statistically significant (adjusted $p < 0.05$). We analyzed studies related to these 25 genes and found many reports suggesting that these 25 genes are effective prognostic/predictive factors or therapeutic targets, as shown in Supplementary Table S7. Among the 25 genes, 8 genes were extracted using Welch's t test to compare UPS and MFS ($q < 0.05$). Four of these genes, *MIF*, *SCD1*, *ENO1/MBP1*, and *P4HA1*, were also extracted in our previous study [1]. Among the 4 genes, *MIF* and *SCD1* are potential prognostic/predictive markers and/or therapeutic targets not only for UPS but also for other cancers [2-26].

MIF expression is induced by HIF-1 under hypoxia [27,28]. Secreted MIF interacts with the cell surface molecule CD74 [29]. CD74 lacks a signal-transducing intracellular domain but interacts with the proteoglycan CD44 and mediates signaling via CD44 to activate Src-family kinase and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), either to stimulate the phosphatidylinositol 3-kinase (PI3K)/Akt pathway or to initiate the p53-dependent inhibition of apoptosis [30]. MIF can also promote invasion and metastasis via G-protein-coupled chemokine receptors (CXCR2, CXCR4, and CXCR7) [22,31,32]. Furthermore, MIF activates *HIF-1α* expression in a p53-dependent manner [33]. MIF promotes not only tumor metastasis [1,12,19,21,22] but also apoptosis [34,35], cell growth [10,18], and angiogenesis [2,3,36]. *SCD1* expression is also induced by hypoxia [37]. *SCD1* and *HIF-2α* are overexpressed in clear cell renal cell

carcinoma under hypoxia; they synergistically inhibit apoptosis and promote cell migration [38]. Hypoxia-induced SCD1 activates the Akt pathway via regulation of the Δ9 monounsaturated fatty acid (MUFA)/saturated fatty acid (SFA) balance in mammalian cells [37,39,40].

The 2 remaining genes, *ENO1/MBP1* and *P4HA1*, also showed statistical significance, not only for UPS vs. MFS but also for UPS vs. SS and for UPS vs. MLS, as shown in Table 4 and Fig. 6. Recent studies have revealed that *ENO1/MBP1* and *P4HA1* are target genes of hypoxia-inducible factor 1 (*HIF-1*) [41,42]. Furthermore, *ENO1/MBP1* is a repressor of *MYC* [43], a prognostic marker for many cancers [44-49] and a therapeutic target in breast cancer (in combination with radiation therapy) [50]. Knockdown of *ENO1/MBP1* inhibits hypoxic cell growth in clear cell ovarian cancer [51]. Hypoxia-induced *P4HA1*, *P4HA2*, and procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (*PLOD2*) promote invasiveness and metastasis by altering the composition, alignment, and mechanical properties of the extracellular matrix (ECM) [41]. *P4HA1* and *P4HA2* encode collagen prolyl hydroxylases that are essential for cancer invasion and metastasis [52]. Among our 25 genes, *P4HA1* showed the strongest association with the histological grade ($\rho = 0.449$, $p = 1.12 \times 10^{-5}$) and with metastasis ($\rho = 0.424$, $p = 3.89 \times 10^{-5}$), as shown in Table 3. These results suggest that the malignancy of UPS depends on the activation of genes downstream of *HIF*s under hypoxic conditions. A study of the relationship between a hypoxia-induced transcription profile and the metastatic potential of STS has been published [53]. In the present study, we enriched the set of potential disease-associated genes by combining knowledge-based filtering with a simulation based on the integration of multiple statistics.

Among the 8 genes selected by Welch's *t* test (comparison of UPS with MFS), 4 genes, that is, *MIF*, *SCD1*, *ENO1*, and *P4HA1*, had been extracted in our previous study [1]. The 4 remaining genes, that is, *PRDX1*, *CD34*, *FAM162A*/*HGTD-P*, and *PTK7*, have not been

extracted by comparison of UPS with MFS in any previous study. CD34 has been used successfully for the differential diagnosis (immunohistochemical analysis) of STS [54]. CD34 is also a marker for progenitor and stem cells [55,56] and vascular endothelial cells [57]. Therefore, CD34 will likely be a useful prognostic marker in some cancers [58-62]. *PRDX1* encodes a member of the peroxiredoxin family of antioxidant enzymes. PRDX1 interacts with the cellular oncogene products c-Abl and c-Myc and inhibits c-Abl kinase activity [63] and Myc-mediated transformation [64], independent of its antioxidant activity. Thus, PRDX1 acts as a tumor suppressor. In addition, PRDX1 promotes nuclear factor kappa B (NF-κB) activity, which induces the expression of HIF-1α via toll-like receptor 4 (TLR4) in prostate cancer [65]. NF-κB directly binds to the *HIF-1α* promoter [66]. Many studies suggest that *PRDX1* is a useful prognostic marker in various cancers [67-71], but there are no data for STS in this regard. In the present study, *PRDX1* showed statistical significance not only for UPS vs. MFS but also for UPS vs. SS and UPS vs. MLS, as shown in Table 4 and Fig. 6.

FAM162A/*HGTD-P* is a HIF-1 target gene and is an indispensable mediator of the mitochondrial apoptotic pathway [72,73]. PTK7 is a regulator of noncanonical WNT/planar cell polarity (PCP) signaling [74]. PTK7 also inhibits canonical Wnt/β-catenin signaling [75,76]. *PTK7* is upregulated in many cancers, and knockdown of *PTK7* in colon carcinoma cells inhibits cell proliferation and induces caspase 10-dependent apoptosis via the mitochondrial pathway [77]. Many studies suggest that *PTK7* is a useful prognostic/predictive marker and/or therapeutic target in various cancers [77-84].

When CINSARC was compared with our 25 genes, 4 common genes, *PTTG1*, *ASPM*, *CDC20*, and *KIF20A*/*MKlp2*, were extracted, as shown in Fig. 4. *PTTG1*, *ASPM*, and *CDC20* are downstream of breast cancer susceptibility gene 1 (*BRCA1*) [85]. Knockdown of *BRCA1* with small interfering RNA (siRNA) downregulates multiple genes implicated in

chromosome segregation (e.g., *PTTG1*), centrosome function (e.g., *ASPM*), and progression into and through mitosis (e.g., *CDC20*) in human prostate (DU-145) and breast (MCF-7) cancer cells [85]. *PTTG1* is a proto-oncogene originally cloned from a rat pituitary tumor [86]. *PTTG1* encodes a protein that interacts with p53, modulates p53-mediated transcriptional activity and apoptosis [87], and prevents the activation of separin, which induces sister chromatid separation in the transition from metaphase to anaphase [88]. Many studies suggest that *PTTG1* is a useful prognostic/predictive marker and/or therapeutic target in various cancers [89-98].

ASPM is the putative human ortholog of the *Drosophila melanogaster* abnormal spindle gene (Asp), which is involved in mitosis [99] and DNA repair [100]. Many studies suggest that *ASPM* is a useful prognostic/predictive marker and/or therapeutic target in various cancers [101-106]. CDC20 is an essential regulator of cell division in humans [107,108]. CDC20 is downregulated by p53 [109], and many studies have suggested that *CDC20* is a useful prognostic/predictive marker and/or therapeutic target in various cancers [110-116].

KIF20A/MKlp2, encodes a member of the kinesin superfamily of motor proteins [117]. KIF20A/MKlp2 is a mitotic inhibitory target of mitotic arrest deficient 2 (MAD2) and is necessary for proper mitotic progression and cytokinesis [118]. Direct interaction between MAD2 and CDC20 is a key event during the checkpoint activation of spindle assembly [119]. Inhibition of *KIF20A*/*MKlp2* induces lysosomal cell death and cell cycle arrest in the G1 phase in breast cancer cells [120] and G2/M arrest in gastric cancer cells [121]. Many studies suggest that *KIF20A*/*MKlp2* is a useful prognostic/predictive marker and/or therapeutic target in different types of cancer [120-123].

These results indicate that the 4 genes common to CINSARC and our analysis are linked to cell cycle checkpoints. This is logical because CINSARC genes were selected for

the prediction of metastasis in STS, and our 25 genes were selected as both diagnostic markers (for histological subtypes) and prognostic markers of overall survival in STS. Among the 25 genes, 13 genes remained after using Welch's *t* test to compare UPS and SS or UPS and MLS ($q < 0.05$): solute carrier family 16, member 1 (*SLC16A1*)/monocarboxylate transporter 1 (*MCT1*); cell adhesion molecule 1 (*CADM1*)/tumor suppressor in non-small cell lung cancer 1 (*TSLC1*); trichorhinophalangeal syndrome 1 (*TRPS1*); protein kinase, DNA-activated, catalytic polypeptide (*PRKDC*)/DNA-dependent protein kinase catalytic subunit (*DNA-PKcs*); cyclin-dependent kinase 1 (*CDK1*)/cell division cycle protein 2 (*CDC2*); transforming, acidic coiled-coil containing protein 3 (*TACC3*); lysosomal protein transmembrane 4 β (*LAPTM4B*); fibronectin 1 (*FN1*); H2A histone family, member Y (*H2AFY*)/histone H2A variant (*H2AX*); *STAT1*; caveolin 1 (*CAV1*); caveolin 2 (*CAV2*); and insulin-like growth factor-binding protein 4 (*IGFBP4*).

SLC16A1/*MCT1* encodes a monocarboxylate transporter that drives the movement of lactate and pyruvate across cell membranes [124]. SLC16A1/MCT1 counteracts p53 activity at the transcriptional level, and the loss of p53 along with SLC16A1/MCT1 overexpression synergistically promotes chromosomal instability and tumorigenicity [125]. Lactate taken up by SLC16A1/MCT1 activates HIF-1 and triggers tumor angiogenesis and tumor growth [126,127]. SLC16A1/MCT1 inhibition has antitumor effects that are associated with the NF-κB pathway [128]. Many studies suggest that *SLC16A1*/*MCT1* is a promising prognostic/predictive marker and/or therapeutic target in various types of cancer [126,128-135].

CADM1/*TSLC1* encodes an immunoglobulin-like cell adhesion molecule with 3 immunoglobulin loops [136]. The ectodomain of CADM1/TSLC1 mediates intercellular adhesion through homophilic or heterophilic *trans*-interactions between neighboring cells [137]. CADM1/TSLC1 is implicated in cell proliferation, invasion, and apoptosis via

regulation of the Akt signaling pathway [138]. Promoter methylation of the *CADM1*/*TSLC1* gene is frequently observed in many cancers [139]. CADM1/TSLC1 is a useful prognostic/predictive marker and/or therapeutic target because it acts as a tumor suppressor in various cancers [138,140-143]. In addition, T-cell lymphoma invasion and metastasis 1 (TIAM1) integrates signals from CADM1/TSLC1 to regulate the actin cytoskeleton through Rac activation, which leads to tissue infiltration by leukemic cells in adult T-cell leukemia/lymphoma (ATL) [136].

TRPS1 encodes a GATA-type zinc-finger protein [144]. TRPS1 is a nuclear protein that binds GATA sequences, and TRPS1 potently and specifically prevents transcriptional activation mediated by other GATA factors [144]. TRPS1 is a crucial regulator of the mesenchymal-to-epithelial cell transition [145,146]; accordingly, *TRPS1* is a prognostic marker in breast cancer [145,146] and colon cancer [147].

PRKDC/*DNA-PKcs* encodes a member of the phosphatidylinositol 3-kinase-like kinase (PIKK) family of protein kinases [148]. Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) protein also belong to the PIKK family, and PRKDC/DNA-PKcs cooperates with these genes to phosphorylate proteins involved in the DNA damage checkpoint [149]. Inhibition of PRKDC/DNA-PKcs activity prevents binding of PRKDC/DNA-PKcs to p53 on the *p21* promoter [150]. Several studies suggest that *PRKDC*/*DNA-PKcs* is a good prognostic/predictive marker and/or therapeutic target in various cancers [151-153].

CDK1/CDC2 is a serine/threonine kinase that interacts with cyclin B1 (CCNB1) to form a complex known as the maturation-promoting factor (MPF), which is essential for cell cycle progression through mitosis [154]. Inhibition of CDK1/CDC2 induces G2/M arrest [155]. Many studies suggest that *CDK1*/*CDC2* is a useful prognostic/predictive marker and/or therapeutic target in various types of cancer [156-160].

TACC3 is necessary for the regulation of mitotic spindle assembly and chromosome segregation [161]. This protein regulates the transcriptional activation of HIF-1 through interaction with aryl hydrocarbon receptor nuclear translocator (ARNT) (also known as HIF-1β) [162]. TACC3 deficiency is associated with a high rate of apoptosis and expression of the p53 target gene *p21* [163]. Several studies suggest that *TACC3* is a useful prognostic/predictive marker and/or therapeutic target in various cancers [164-166].

LAPTM4B, which encodes a protein containing a lysosome localization motif that localizes to the late endosomes and lysosomes [167], was originally identified as a hepatocellular carcinoma-associated gene [167]. LAPTM4B promotes autophagy and tolerance to metabolic stress [168], enhances the multidrug resistance of cancer cells by promoting drug efflux through colocalization and interaction with P glycoprotein (P-gp), and inhibits apoptosis by activating PI3K/AKT signaling [169]. Many studies suggest that *LAPTM4B* is a useful prognostic/predictive marker and/or therapeutic target in various cancers [170-174].

FN1, a HIF-1 target gene in colon carcinoma [175] and a SRY-related HMG-box gene 2 (*SOX2*) target gene in ovarian cancer [176], promotes cell migration and invasion in various cancers [177,178].

H2AFY/*H2AX* encodes a histone protein that consists of a histone H2A-like histone domain and a large, globular C-terminal macrodomain that is not present in other histone proteins [179]. H2AFY/H2AX is required for the repair of DNA double-strand breaks in the ATM signaling pathway [180], and active expression of H2AFY/H2AX (γH2AX) is an indicator of DNA double-strand breaks [181]. H2AFY/H2AX was found to interact with human epidermal growth factor receptor 2 (HER2) in cancer cells that overexpress HER2 [182]. H2AFY/H2AX has also been shown to interact with tumor suppressor p53-binding protein 1 (TP53BP1) [183-185], BRCA1 [186-188], and BRCA1-associated RING domain

protein 1 (BARD1) [186,188]. The absence of H2AFY/H2AX causes proteasome-dependent degradation of p21 under conditions of DNA damage [189]. Many studies have suggested that *H2AFY*/*H2AX* is a promising prognostic marker in various cancers [190-193].

The protein encoded by *STAT1* was the first identified member of a multigene family targeted by both the type I and type II interferon (IFN) pathways [194-197]. STAT1 maintains cellular homeostasis by controlling cell growth, proliferation, apoptosis, and immune reactions. Expression and posttranslational aberrations of STAT1 have been identified in a variety of human pathological conditions, including cancer [198]. STAT1 acetylation depends on the balance between the activity of histone deacetylases (HDACs) and histone acetyltransferases (HATs). STAT1 acetylation is involved in the regulation of NF-κB activity and thus of apoptosis [199]. STAT1 also directly interacts with p53 to enhance DNA damage-induced apoptosis [200]. In addition, *STAT1* is downstream of HIF-1; the latter downregulates the expression of *STAT1* through differentiated embryo-chondrocyte expressed gene 1 (DEC1)/stimulated by retinoic acid 13 (STRA13) in an HDAC1-dependent manner [201]. Many studies have suggested that *STAT1* would be an effective prognostic/predictive marker and/or therapeutic target in various types of cancer [202-207].

CAV1 and CAV2 are integral membrane proteins that are essential components of caveolar membranes. They contribute to the negative regulation of tyrosine and serine/threonine kinase activities by binding to epidermal growth factor receptor (EGFR) [208]. CAV1 and CAV2 modulate downstream signaling, such as RAS/ERK signaling, via a nonreceptor tyrosine kinase (Src/Fyn/Abl) [209-211]. CAV2 interacts with CAV1 [210], and *CAV1* expression induces the downregulation of MAPK, PI3K/AKT, and mTOR signaling as well as the activation of apoptotic pathways [212]. Many studies have suggested that *CAV1* and *CAV2* are useful prognostic markers in various cancers [211-215]. However, these

genes might behave either as tumor suppressors or as oncogenes depending on the cell type and tumor stage/grade [216,217]. In the present study, *CAV1* and *CAV2* expression levels were negatively associated with the histological grade in STS, as shown in Table 3.

IGFBP4 encodes a protein that is a potent inhibitor of IGF activity [218-220]. IGFBP4 inhibits IGF-dependent growth and angiogenic effects in glioblastoma [221] and colorectal cancer [222]. In addition, IGFBP4 expression activates cell growth, metastasis, and Wnt/β-catenin signaling in renal cell carcinoma [223]. The expression of IGFBP4 in lung adenocarcinomas is downregulated by epigenetic silencing in association with tumor differentiation, resulting in the disruption of IGFBP4-mediated growth inhibition [224]. A negative correlation between the Ki-67 labeling index and IGFBP4 expression was reported in lung adenocarcinoma [224]. This result is consistent with our study results, as shown in Table 3.

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