# Integrative genomic analyses of the histamine H1 receptor and its role in cancer prediction

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**Abstract.** The human histamine receptor H1 (HRH1) gene is located on chromosome 3p25 and encodes for a 487 amino acid G protein-coupled receptor (GPCR) with a long third intracellular loop (IL3). The HRH1 predominantly couples to $G\alpha_{q/11}$ proteins, leading to the activation of phospholipase C (PLC) and subsequent release of the second messengers inositol trisphosphate ($IP_3$) and diacylglycerol (DAG) followed by the activation of PKC and the release of $[Ca^{2+}]_i$. In the present study, we identified HRH1 genes from 14 vertebrate genomes and found that HRH1 exists in all types of vertebrates including fish, amphibians, birds and mammals. We identified 88 SNPs including 4 available alleles disrupting an existing exonic splicing enhancer and 84 SNPs causing missense mutation, which may impact the effect of histamine on the HRH1 protein. We found that the human HRH1 gene was expressed in many tissues or organs, and predominant expression of HRH1 was shown in the bone marrow, whole blood, lymph node, thymus, brain, cerebellum, retina, spinal cord, heart, smooth muscle, skeletal muscle, small intestine, colon, adipocytes, kidney, liver, lung, pancreas, thyroid salivary gland, skin, ovary, uterus, placenta, prostate and testis. When searched in the PrognoScan database, human HRH1 was also found to be expressed in bladder cancer, blood cancer, brain cancer, breast cancer, colorectal cancer, eye cancer, head and neck cancer, lung cancer, ovarian cancer, skin cancer and soft tissue cancer tissues. The relationship between the expression of HRH1 and prognosis was found to vary in different types of cancers, even in the same cancer from different databases. This implies that the function of HRH1 in these tumors may be multidimensional. GR, STAT5A and c-Myb regulatory transcription factor binding sites were identified in the HRH1 gene upstream (promoter) region, which may be involved in the effect of HRH1 in tumors.

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## Introduction

Histamine is a ubiquitous messenger molecule released from mast cells, enterochromaffin-like cells and neurons. Its various actions are mediated by histamine receptors H1, H2, H3 and H4 (1). The bovine histamine H1 receptor (HRH1) was the first HRH1 gene to be cloned, soon to be followed by other species, including human HRH1. The human HRH1 gene is located on chromosome 3p25 and encodes for a 487 amino acid G protein-coupled receptor (GPCR) with a long third intracellular loop (IL3) (1). The HRH1 predominantly couples to $G\alpha_{q/11}$ proteins, leading to the activation of phospholipase C (PLC) and subsequent release of the second messengers inositol trisphosphate ($IP_3$) and diacylglycerol (DAG) followed by the activation of protein kinase C (PKC) and the release of $[Ca^{2+}]_i$ (1). HRH1 is expressed in a wide variety of tissues including the gastrointestinal tract, the central nervous system, the immunological system, and the cardiovascular and genitourinary systems (2-5).

HRH1 is involved in a wide array of processes including thermal regulation, memory and learning, and control of the sleep-wake cycle, food intake, and emotional and aggressive behaviors. HRH1 is also involved in the pathological process of allergy, including allergic rhinitis, atopic dermatitis, anaphylaxis and asthma, and also has a role in autoimmune diseases and malignancy (2-7). Histamine is involved in cell proliferation, and key events in tumor development and progression have been extensively investigated (8,9). It has been found that H1R stimulates proliferation of breast carcinoma, melanoma and astrocytoma tumor cells (10-12). In this context, the investigation of H1R and its antagonists support a clear rationale for future supportive anticancer therapies. However, a comprehensive investigation of whether HRH1 is involved in the formation of various tumors has not yet been carried out.

In the present study, we identified HRH1 genes from the human, chimpanzee, macaque, orangutan, dog, cow, horse, mouse, rat, opossum, chicken, *Xenopus tropicalis*, zebrafish and fugu by comparative genomic analyses. A search for conserved transcription factor-binding sites within the promoter regions of the human HRH1 gene was then carried out. The expression data, functional relevant single nucleotide polymorphisms (SNPs) and comparative proteomic analyses were conducted. Furthermore, meta-analysis of the prognostic value of HRH1 genes in various types of cancers was also performed.

## Materials and methods

*Identification of novel HRH1 genes in vertebrate genomes and integrative genomic analyses*. A search for HRH1 genes was carried out in the genome sequences of the human *(Homo sapiens)*, chimpanzee *(Pan troglodytes)*, macaque *(Macaca mulatta)*, orangutan *(Pongo pygmaeus)*, dog *(Canis familiaris)*, cow *(Bos taurus)*, horse *(Equus caballus)*, mouse *(Mus musculus)*, rat *(Rattus norvegicus)*, opossum *(Monodelphis domestica)*, chicken *(Gallus gallus)*, *Xenopus tropicalis*, zebrafish *(Danio rerio)* and fugu *(Takifugu rubripes)* by the method described before using the human HRH1 gene (CAA84380) as a query. The assemblies used were human NCBI36, chimpanzee CHIMP2.1, macaque MMUL 1.0, orangutan PPYG2, dog CanFam 2.0, cow Btau_4.0, horse Equ Cab 2, mouse NCBI m37, rat RGSC 3.4, opossum monDom5, chicken WASHUC2, *X. tropicalis* JGI 4.1, zebrafish Zv8 and fugu FUGU 4.0. The identified putative HRH1 genes were BLASTed against the nr database of GenBank to confirm that the best hits were HRH1 genes (13-15). Conserved transcription factor-binding sites within the promoter region of the human HRH1 gene were obtained from SABiosciences' proprietary database which combines Text Mining Application and data from the UCSC Genome Browser.

*Comparative proteomic analyses of HRH1 proteins*. The amino acid sequences of HRH1 were deduced from the identified HRH1 genes and aligned using Clustal X 1.8 software (16). The phylogenetic tree of HRH1 was obtained by using ML (maximum likelihood) (PHYML v2.4.4) (17) and NJ (neighbor-joining) (MEGA 3.0) (18) methods, and the reliability of the tree was evaluated by the bootstrap method with 1,000 replications. The program Codeml implemented in the PAML 3.14 b software package was used to investigate whether HRH1 proteins are under positive selection (19). Six models of codon substitution, M0 (one-ratio), M1a (NearlyNeutral), M2a (PositiveSelection), M3 (discrete), M7 (β), and M8 (β and ω) were used in the analysis (20).

*Functional relevant SNP evaluation of the human HRH1 gene*. Functional relevant SNPs (single nucleotide polymorphisms) of the human HRH1 gene were identified as previously described (13-15,21). The SNPs were extracted from Ensembl (http://www.ensembl.org) and NCBI's SNPdb (http://www.ncbi.nlm.nih.gov). The SNPs that could disrupt ESE/ESS (exonic splicing enhancer/exonic splicing silencer) motifs and cause missence mutation were also identified.

*In silico expression analyses of the human HRH1 gene*. Expressed sequence tags (ESTs) derived from the human HRH1 gene were searched for using the BLAST programs as previously described (22-25). Human HRH1 gene (NM_003118) was used as query sequences for the BLAST programs. The expression profiles for normal human tissues were obtained from GeneAnnot (26) and ArrayExpress (27). Northern analysis of NCBI's uniGene dataset was also extracted (21). Moreover, protein expression of HRH1 was obtained from SPIRE (28) and MOPED (29).

*Meta-analysis of the prognostic value of the HRH1 gene in cancer*. A database named 'PrognoScan' has been developed (30). This is i) a large collection of publicly available cancer microarray datasets with clinical annotation, as well as ii) a tool for assessing the biological relationship between gene expression and prognosis. PrognoScan employs the minimum P-value approach for grouping patients for survival analysis. PrognoScan provides a powerful platform for evaluating potential tumor markers and therapeutic targets and is publicly accessible at http://gibk21.bio.kyutech.ac.jp/PrognoScan/index.html. The human HRH1 gene was inputted as a query and the data were collected for analysis.

## Results

*Comparative proteomics of HRH1 proteins identified in vertebrate genomes*. HRH1 genes were identified in the genome sequences of the human, chimpanzee, macaque, orangutan, dog, cow, horse, mouse, rat, opossum, chicken, *Xenopus tropicalis*, zebrafish and fugu. Refined phylogentic trees using the identified HRH1 protein amino acid sequences by maximum likelihood (ML) and neighbor-joining (NJ) methods were almost identical (Fig. 1). We were unable to identify any site under positive selection with any of the six models in HRH1 proteins. Instead, the HRH1 proteins were under purifying selection (data not shown).

*Expression profile of the human HRH1 gene*. By EST sequence searching, the human HRH1 gene was found to be expressed in stomach, liver, heart, brain, placenta, embryonic tissue, kidney, vascular, intestine, esophagus, lung, adrenal gland, mouth, connective tissue, cervix, ovary, trachea, testis, uterus and skin. The investigation of available microarray experiments and 'virtual northern blot' showed a predominant expression of HRH1 in the bone marrow, whole blood, lymph node, thymus, brain, cerebellum, retina, spinal cord, heart, smooth muscle, skeletal muscle, small intestine, colon, adipocyte, kidney, liver, lung, pancreas, thyroid salivary gland, skin, ovary, uterus, placenta, prostate and testis. When searched in PrognoScan database, human HRH1 was also found to be expressed in bladder cancer, blood cancer, brain cancer, breast cancer, colorectal cancer, eye cancer, head and neck cancer, lung cancer, ovarian cancer, skin cancer and soft tissue cancer tissues. Among the protein expression databases SPIRE and MOPED, HRH1 protein was found to be only highly expressed in blood plasma.

*Comparative genomics on the human HRH1 gene*. Glucocorticoid receptor (GR), germ cell nuclear factor

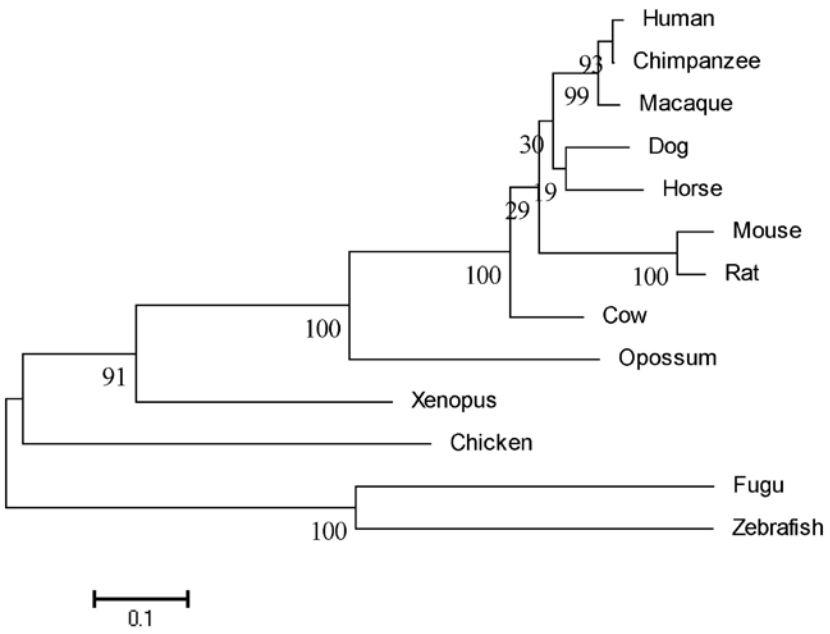


Figure 1. Phylogentic analysis of HRH1. HRH1 genes were identified in the genome sequences of the human, chimpanzee, macaque, orangutan, dog, cow, horse, mouse, rat, opossum, chicken, *Xenopus tropicalis*, zebrafish and fugu. The phylogenetic tree of HRH1 gene was obtained by using maximum likelihood (ML) and neighbor-joining (NJ) methods. Primate HRH1 was clustered into one group, different from the other HRH1 genes.

(GCNF), signal transducer and activator of transcription 5A (STAT5A), mini Zinc finger 1 (MIF-1), heat shock transcription factor 2 (HSF2) and c-Myb regulatory transcription factor binding sites were identified in the HRH1 gene upstream (promoter) region.

*Functional relevant SNP evaluation of the human HRH1 gene*. Available SNPs (2,455) were identified in the human HRH1 gene. Among these, 88 SNPs were functionally relevant; including 4 available alleles disrupting an existing exonic splicing enhancer and 84 SNPs causing missense mutation (Table I).

*Meta-analysis of the prognostic value of the human HRH1 gene in cancer.* When given the gene, PrognoScan displays a summary in table format of tests for the gene with columns for dataset, cancer type, subtype, endpoint, cohort, contributor, array type, probe ID, number of patients, optimal cut-point, Pmin and Pcor. Among the databases which detected the expression of the HRH1 gene, 23 out of 153 tests showed an association between microarray expression in the HRH1 gene and cancer prognosis (bladder cancer 2/4, blood cancer 2/18, brain cancer 1/9, breast cancer 6/50, colorectal cancer 1/18, eye cancer 1/2, head and neck cancer 0/2, lung cancer 6/29, ovarian cancer 2/18, prostate cancer 0/1, skin cancer 0/2 and soft tissue cancer 2/2) with a 5% level of significance (Table II). Among the 6 breast cancer cases, low expression of the HRH1 gene was related to poor survival in 3 cases (GSE12276, GSE9893 and GSE1456-GPL96). However, high expression of the HRH1 gene was related to poor survival in another 3 cases of breast cancer (GSE6532-GPL570 and GSE3494-GPL96). As for the lung cancer cases, we found that high expression of the HRH1 gene was associated with poor survival in all 6 lung cancer cases including 5 adenocarcinoma cases and 1 non-small cell lung cancer case (GSE8894). Among the 2 blood cancer cases, high expression of the HRH1 gene was related to poor survival in the B-cell lymphoma case (GSE4475). However, in 1 multiple myeloma case (GSE2658), low expression of the HRH1 gene was related to poor survival. We found that high expression of the HRH1 gene was associated with poor survival in 2 cases of soft tissue cancer and in 1 case of brain cancer and colorectal cancer. In the other cancer cases, low expression of the HRH1 gene was associated with poor survival in 2 cases of bladder cancer and ovarian cancer and 1 case of eye cancer.

## Discussion

A large number of molecules involved in cell proliferation and key events in tumor development and progression have been extensively investigated including histamine (31-33). Histamine exerts its functions through binding to G protein-associated histamine H1, H2, H3, and H4 receptors (HRH1, HRH2, HRH3 and HRH4), resulting in the activation of different signal transduction pathways (31-33). In addition to the human HRH1, in the present study, we identified other HRH1 genes from other 13 vertebrate genomes and found that HRH1 exists in all types of vertebrates including the fish, amphibians, birds and mammals. All the identified HRH1 genes were encoding for a GPCR protein with a long third intracellular loop (IL3). The phylogenetic tree showed that HRH1 is separated for the order: fish, amphibians, birds and mammals. Primate HRH1s are almost the same and are clustered together. From the alignment and phylogenetic tree, mammalian HRH1s are conserved among the vertebrate genomes, suggesting that the function of HRH1 may have played an important physiological role for all vertebrates in the long process of evolution. Moreover, this process was under purifying selection, in accordance with the fact that multiple biological functions have been ascribed to this protein, including its function in central and peripheral tissues.

Table I. Functional relevant SNP evaluation of the human HRH1 gene.

| SNP ID | Chr 3 position | Sequence | Type | AA change | SNP ID | Chr 3 position | Sequence | Type | AA change |
|---|---|---|---|---|---|---|---|---|---|
| rs79314450 | 11300765(+) | AAGATG/ATGTGA | Missense | /I /M | rs199522994 | 11301463(+) | GGGGGA/TTGCCA | Missense | D V |
| rs2067466 | 11300780(+) | AACAAG/CACCAC | Missense | /N /K | rs199528452 | 11301826(+) | CACAGA/GGACAG | Missense | E G |
| rs61738990 | 11300881(+) | CGTACG/AGAGTG | Missense | /Q /R | rs200787735 | 11301096(+) | TTGATA/CGCTAC | Missense | S R |
| rs189376051 | 11300922(+) | ACATCA/GTCAGC | Missense | I V | rs199720564 | 11301138(+) | AGTATC/TGTACC | Missense | R C |
| rs200571067 | 11300958(+) | GTGCCA/GTCGTC | Missense | I V | rs138669404 | 11300787(+) | CCACTA/GTGGCC | Missense | MV |
| rs139664451 | 11301013(+) | GGGCCG/ATCCTC | Missense | /H /R | rs111632894 | 11301870(+) | ACACAG/TGCCTG | Missense | GC |
| rs146441347 | 11301075(+) | TCAGTG/ATCTTC | Missense | /I /V | rs148511138 | 11300908(+) | TGTGGG/AGAACC | Missense | /E /G |
| rs181783018 | 11301151(+) | GACCCA/GAGCCT | Missense | Q R | rs200335907 | 11301073(+) | TTTCAA/GTGTCT | Missense | N S |
| rs201947424 | 11301246(+) | CGGTGC/TGCCGA | Missense | R C | rs201417298 | 11301732(+) | AGCAGA/GGCCTG | Missense | S G |
| rs138120998 | 11301309(+) | CTGCCA/GTCATC | Missense | I V | rs201480303 | 11301124(+) | CCTCAG/TGTACC | Missense | R M |
| rs201575633 | 11301362(+) | AAGATC/GTACAA | Missense | I M | rs199843421 | 11300782(+) | CAAGAC/GCACTA | Missense | T S |
| rs145938098 | 11301394(+) | GCACCG/AGGAGC | Missense | /Q /R | rs201469326 | 11301462(+) | AGGGGA/GATGCC | Missense | ND |
| rs7651620 | 11301532(+) | TGGTGG/AATCTG | Missense | /E /G | rs201939588 | 11301699(+) | TCAACC/TGGAGC | Missense | RW |
| rs201210547 | 11301661(+) | GGCTGC/TGGCAG | Missense | A V | rs200553830 | 11301854(+) | TTGAGC/GAGTGG | Missense | S R |
| rs149683927 | 11301678(+) | GTAGCA/GGGGAC | Missense | R G | rs199720564 | 11301138(+) | AGTATC/TGTACC | Missense | R C |
| rs147652731 | 11301693(+) | TAGCCG/ATCAAC | Missense | /I /V | rs138669404 | 11300787(+) | CCACTA/GTGGCC | Missense | M V |
| rs74840800 | 11301700(+) | CAACCG/AGAGCC | Missense | /Q /R | rs111632894 | 11301870(+) | ACACAG/TGCCTG | Missense | G C |
| rs189287776 | 11301768(+) | CAGAGC/GATCAG | Missense | H D | rs200695584 | 11300808(+) | TGATGC/TCCCTG | Missense | P S |
| rs2067467 | 11301770(+) | GAGGAT/GCAGAT | Missense | /E /D | rs148511138 | 11300908(+) | TGTGGG/AGAACC | Missense | /E /G |
| rs141914966 | 11301810(+) | CGGACT/CCAGAT | Missense | /P /S | rs201417298 | 11301732(+) | AGCAGA/GGCCTG | Missense | S G |
| rs180831997 | 11301858(+) | GGAGTA/GGGTCT | Missense | R G | rs201480303 | 11301124(+) | CCTCAG/TGTACC | Missense | R M |
| rs199875751 | 11301988(+) | CATGGC/TAGCCT | Missense | A V | rs199843421 | 11300782(+) | CAAGAC/GCACTA | Missense | T S |
| rs2067470 | 11302069(+) | ACATTT/CGCACA | Missense | /S /L | rs201469326 | 11301462(+) | AGGGGA/GATGCC | Missense | N D |
| rs76689102 | 11302092(+) | GGCTGG/TGCTAC | Missense | G C | rs201939588 | 11301699(+) | TCAACC/TGGAGC | Missense | R W |
| rs202025055 | 11301685(+) | GGACTA/GTGTAG | Missense | Y C | rs200553830 | 11301854(+) | TTGAGC/GAGTGG | Missense | S R |
| rs149582378 | 11301513(+) | GGAAGC/GCAAAA | Missense | P A | rs200606524 | 11300890(+) | TGAGCA/GGAAGC | Missense | Q R |
| rs201052869 | 11301024(+) | TCTGCC/GTCTTT | Missense | L V | rs199954618 | 11301561(+) | AAACCC/GCCAAG | Missense | P A |
| rs201175841 | 11301184(+) | GTTTCC/TCTCTT | Missense | P L | rs202064669 | 11302032(+) | TCATGG/TTCATT | Missense | V F |
| rs201785749 | 11301523(+) | AGATGA/CTGGTG | Missense | D A | rs200903220 | 11301886(+) | CATCAA/GGTTTA | Missense | K R |
| rs201217782 | 11300932(+) | CCTCTC/TGGTGG | Missense | S L | rs202100549 | 11302102(+) | CATCAA/GCTCCA | Missense | N S |
| rs200086906 | 11301876(+) | GCCTGA/GATTAC | Missense | N D | rs200892765 | 11302020(+) | ATTTCA/GTCTTC | Missense | I V |

Table I. Continued.

| SNP ID | Chr 3 position | Sequence | Type | AA change | SNP ID | Chr 3 position | Sequence | Type | AA change |
|---|---|---|---|---|---|---|---|---|---|
| rs199638082 | 11301796(+) | ATCCTC/TCTCTC | Missense | S F | rs201450416 | 11301389(+) | TGCCAG/TCACCG | Missense | Q H |
| rs201053001 | 11301951(+) | ACCGCA/GAAAGG | Missense | K E | rs201101191 | 11301348(+) | TCTGGC/TTCTAT | Missense | L F |
| rs201586667 | 11301627(+) | TCTACA/TGCTTT | Missense | S C | rs201720863 | 11300901(+) | TCCACA/GCTGTG | Missense | T A |
| rs199822532 | 11300889(+) | GTGAGC/TGGAAG | Missense | R W | rs138501310 | 11301910(+) | CCGCTC/TGCATT | Missense | S L |
| rs201386658 | 11301550(+) | GTCACC/TATCCC | Missense | P L | rs199645631 | 11300863(+) | CCTGCG/TGGTGC | Missense | R L |
| rs143882995 | 11300977(+) | GAACAT/CCCTCT | Missense | /T /I | rs200066638 | 11301247(+) | GGTGCA/GCCGAG | Missense | H R |
| rs200817909 | 11301139(+) | GTATCA/GTACCA | Missense | H R | rs201661278 | 11301150(+) | AGACCC/GGAGCC | Missense | R G |
| rs201903123 | 11301907(+) | GCTCCA/GCTCGC | Missense | H R | rs113526786 | 11300934(+) | TCTCGG/ATGGCG | Missense | /M /V |
| rs17855034 | 11301646(+) | TATTGA/TGCACA | Missense | E V | rs200526115 | 11302035(+) | TGGTCA/GTTGCC | Missense | I V |
| rs199824154 | 11301171(+) | TTCTGC/GGGGCC | Missense | R G | rs200897870 | 11301538(+) | ATCTGC/TCTTGA | Missense | A V |
| rs200547768 | 11301776(+) | CAGATG/TTAGG | Missense | M I | | | | | |

Available SNPs (2,455) were identified in the human HRH1 gene. Here, we show the 84 SNPs causing a missense mutation. AA change, amino acid change (slashes '/' indicate uncoded amino acids).

Histamine is an endogenous biogenic amine widely distributed throughout the organism and is long known to be a pleiotropic mediator in different (patho)-physiological conditions (1). Accordingly, by EST sequence search, one of its receptors, the HRH1 gene is also expressed in various tissues and cells including stomach, liver, heart, brain, placenta, embryonic tissue, kidney, vascular, intestine, esophagus, lung, adrenal gland, mouth, connective tissue, cervix, ovary, trachea, testis, uterus and skin. The same results were confirmed by the investigation of available microarray experiments and 'virtual northern blot', which showed a predominant expression of HRH1 in the bone marrow, whole blood, lymph node, thymus, brain, cerebellum, retina, spinal cord, heart, smooth muscle, skeletal muscle, small intestine, colon, adipocyte, kidney, liver, lung, pancreas, thyroid salivary gland, skin, ovary, uterus, placenta, prostate and testis. Available SNPs (2,455) were identified in the human HRH1 gene. We identified 88 SNPs including 4 available alleles disrupting an existing exonic splicing enhancer and 84 SNPs causing a missense mutation, which may impact the effect of histamine on the HRH1 protein. However, the effects of these SNPs on the physiological and pathological functions of HRH1 warrant further investigation.

Notably, most malignant cell lines and experimental tumors contain a high concentration of endogenous histamine, which can be released to the extracellular media via a paracrine or autocrine pathway. Moreover, histamine itself may be a crucial mediator in cancer development and progression by regulating diverse biological responses related to tumor growth including angiogenesis, cell invasion, migration, differentiation, apoptosis and modulation of the immune response (31-33). As one receptor of histamine, HRH1 expression in normal tissues vs. cancer samples has not been well studied. Following a search in the PrognoScan database, human HRH1 was also found to be expressed in bladder cancer, blood cancer, brain cancer, breast cancer, colorectal cancer, eye cancer, head and neck cancer, lung cancer, ovarian cancer, skin cancer and soft tissue cancer tissues. The expression of HRH1 in these tumors may explain the effects of histamine on cancer behaviors. Out of 153, 23 tests showed an association between microarray expression in the HRH1 gene and cancer prognosis (bladder cancer 2/4, blood cancer 2/18, brain cancer 1/9, breast cancer 6/50, colorectal cancer 1/18, eye cancer 1/2, head and neck cancer 0/2, lung cancer 6/29, ovarian cancer 2/18, prostate cancer 0/1, skin cancer 0/2 and soft tissue cancer 2/2) with a 5% level of significance. This suggests that the expression of HRH1 is related to the prognosis of many types of cancers including hematological and solid cancers. The mechanism of HRH1 involved in the process of these tumors warrants further investigation. It is important to note that the relationship between the expression of HRH1 and prognosis varied in different cancers, even in the same cancer from different databases. This implies that the function of HRH1 in these tumors may be multidimensional, not just as a tumor suppressor or oncogene.

The GR, GCNF, STAT5A, MIF-1, HSF2 and c-Myb regulatory transcription factor binding sites were identified in the HRH1 gene upstream (promoter) region. GRs are nuclear hormone receptors of the NR3C class, which also includes mineralocorticoid, progesterone and androgen receptors. GRs are ubiquitously expressed and mediate a vast array of physiological functions. Glucocorticoids are widely

Table II. Dataset content from PrognoScan indicated an association between microarray expression of HRH1 and cancer prognosis.

| Database | Case type | Subtype | No. of patients | Endpoint | Cutpoint | P-value | Prognosis | Refs. |
|---|---|---|---|---|---|---|---|---|
| GSE13507 | Bladder cancer | | 165 | Overall survival | 0.25 | 0.012 | 1 | (41,42) |
| GSE13507 | Bladder cancer | Transitional cell carcinoma | 165 | Disease-specific survival | 0.28 | 0.009 | 1 | (41,42) |
| GSE4475 | Blood cancer | B-cell lymphoma | 158 | Overall survival | 0.76 | 0.027 | 2 | (43) |
| GSE2658 | Blood cancer | Multiple myeloma | 559 | Disease-specific survival | 0.67 | 0.002 | 1 | (44) |
| GSE4271-GPL96 | Brain cancer | Astrocytoma | 77 | Overall survival | 0.39 | 0.04 | 2 | (45) |
| GSE12276 | Breast cancer | | 204 | Relapse-free survival | 0.88 | 0.047 | 1 | (46) |
| GSE6532-GPL570 | Breast cancer | | 87 | Distant metastasis-free survival | 0.86 | 0.01 | 2 | (47) |
| GSE6532-GPL570 | Breast cancer | | 87 | Relapse-free survival | 0.86 | 0.01 | 2 | (47) |
| GSE9893 | Breast cancer | | 155 | Overall survival | 0.29 | 0.012 | 1 | (48) |
| GSE1456-GPL96 | Breast cancer | | 159 | Relapse-free survival | 0.11 | 0.007 | 1 | (49) |
| GSE3494-GPL96 | Breast cancer | | 249 | Relapse-free survival | 0.8 | 0.0014 | 2 | (50) |
| GSE17536 | Colorectal cancer | | 145 | Relapse-free survival | 0.9 | 0.043 | 2 | (51) |
| GSE22138 | Eye cancer | Uveal melanoma | 63 | Relapse-free survival | 0.22 | 0.017 | 1 | (52) |
| jacob-00182-CANDF | Lung cancer | Adenocarcinoma | 82 | Relapse-free survival | 0.77 | 0.047 | 2 | (53) |
| GSE13213 | Lung cancer | Adenocarcinoma | 117 | Relapse-free survival | 0.55 | 0.046 | 2 | (54) |
| GSE31210 | Lung cancer | Adenocarcinoma | 204 | Relapse-free survival | 0.68 | 0.03 | 2 | (55) |
| GSE31210 | Lung cancer | Adenocarcinoma | 204 | Relapse-free survival | 0.85 | 0.018 | 2 | (55) |
| jacob-00182-UM | Lung cancer | Adenocarcinoma | 178 | Relapse-free survival | 0.68 | 0.02 | 2 | (53) |
| GSE8894 | Lung cancer | Non-small cell lung cancer | 138 | Relapse-free survival | 0.78 | 0.036 | 2 | (56) |
| GSE17260 | Ovarian cancer | | 110 | Relapse-free survival | 0.88 | 0.048 | 1 | (57) |
| GSE14764 | Ovarian cancer | | 80 | Relapse-free survival | 0.12 | 0.01 | 1 | (57) |
| GSE30929 | Soft tissue cancer | Liposarcoma | 140 | Relapse-free survival | 0.86 | 0.001 | 2 | (58) |
| GSE30929 | Soft tissue cancer | Liposarcoma | 140 | Relapse-free survival | 0.88 | 0.03 | 2 | (58) |

Out of 153 tests, 23 showed an association between microarray expression of HRH1 gene and cancer prognosis (bladder cancer 2/4, blood cancer 2/18, brain cancer 1/9, breast cancer 6/50, colorectal cancer 1/18, eye cancer 1/2, head and neck cancer 0/2, lung cancer 6/29, ovarian cancer 2/18, prostate cancer 0/1, skin cancer 0/2 and soft tissue cancer 2/2) with a 5% significance level.

used for the treatment of lymphoid malignancy due to their marked effects on cell cycle progression and apoptosis (34). Glucocorticoids are able to alter signaling in key survival pathways and this can result in reversible growth arrest or cell death in certain cell types (34-36). STAT5A is a member of the STAT family of transcription factors. It is activated by, and mediates the responses of many cell ligands, such as IL2, IL3, IL7, GM-CSF, erythropoietin, thrombopoietin and different growth hormones. Activation of this protein in many types of cancers has been shown to be essential for tumorigenesis (37,38). C-Myb encodes a transcription factor that regulates the expression of numerous genes during cell cycle progression. c-Myb is a cellular proto-oncogene, which has the ability to regulate the expression of cell cycle genes and is involved in cell proliferation and carcinogenesis (39,40). These tumor-related transcriptional factors may be involved in the effect of HRH1 in tumors.

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