Integrative genomic analysis of interleukin-36RN and its prognostic value in cancer

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Abstract. Interleukin (IL)-36RN, previously known as IL1-F5 and IL-1δ, shares a 360-kb region of chromosome 2q13 with members of IL-1 systems. IL-36RN encodes an anti-inflammatory cytokine, IL-36 receptor antagonist (IL-36Ra). In spite of IL-36Ra showing the highest homology to IL-1 receptor (IL-1R) antagonist, it differs from the latter in aspects including its binding to IL-lRrp2 but not to IL-1R1. IL-36RN is mainly expressed in epithelial cells and has important roles in inflammatory diseases. In the present study, IL-36RN was identified in the genomes of 27 species, including human, chimpanzee, mouse, horse and dolphin. Human IL-36RN was mainly expressed in the eye, head and neck, fetal heart, lung, testis, cervix and placenta; furthermore, it was highly expressed in bladder and parathyroid tumors. Furthermore, a total of 30 single nucleotide polymorphisms causing missense mutations were determined, which are considered to be the causes of various diseases, such as generalized pustular psoriasis. In addition, the link between IL-36RN and the prognosis of certain cancer types was revealed through meta-analysis. Tumor-associated transcriptional factors c-Fos, activator protein-1, c-Jun and nuclear factor κB were found to bind to the upstream region in the IL-36RN gene. This may indicate that IL-36RN is involved in tumorigenesis and tumor progression through the regulation of tumor-associated transcriptional factors. The present study identified IL-36RN in various species and investigated the associations between IL-36RN and cancer prognosis, which would determine whether IL-36RN drove the evolution of the various species with regard to tumorigenesis.

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Introduction

Interleukin (IL)-36RN was first discovered as an IL-1 family cytokine, also known as IL-1F5, IL-1δ, IL-1Hy1, FIL-1δ, IL-1H3, IL-1RP3 and IL-1L1 (1,2), which is, together with classic IL-1 members, IL-37 and other IL-36 cytokines (IL-36α, IL-36β and IL-36γ) located in a 360-kb region of chromosome 2q13 (3). IL-36RN was identified to encode anti-inflammatory cytokine IL-36Ra, which is 52% homologous to the IL receptor antagonist (IL-1Ra) (4). IL-36Ra binds to IL-1Rrp2 and inhibits IL-36α, IL-36β and IL-36γ in similar manner to IL-1Ra inhibiting IL-1α and IL-1β (5). In spite of its similar functions to those of IL-1Ra, IL-36Ra itself can induce IL-4 expression in glial cells, while IL-4 is indispensable for the anti-inflammatory activities of IL-36Ra in the brain; however, IL-1Ra has not been found to induce any cytokines (6). To facilitate functional investigations, IL-36 cytokines, including IL-36Ra, were re-named in 2010 with the aim to distinguish them from the IL-1 cytokines (2).

With regard the functions of IL-36, the perturbation of the IL-36 signaling balance contributes to the pathogenesis of immunological and inflammatory diseases (7). The balance can be disrupted by aberrant expression of either agonists or antagonists of IL-36 signaling. The IL-36R signaling agonists IL-36α, -β and -γ are highly expressed in several inflammatory diseases, including chronic obstructive pulmonary disease (8), asthma (9), obesity (10), ankylosing spondylitis (11), rheumatoid arthritis (12) and allergic contact dermatitis (13), and have a significant role in these diseases. As an antagonist of IL-36 signaling, IL-36Ra is also implicated in the pathogenesis of immunological and inflammatory conditions. IL-36Ra expression is associated with Kindler syndrome (14), brain micromotion (15) and psoriasis (16). It was recently shown that mutations of IL36RN are closely associated with a serious disease called general pustular psoriasis (GPP) (17-20). Single-nucleotide polymorphisms (SNPs) in the IL-36RN gene can lead to induction of a premature stop-codon, frame-shift mutation or an amino acid substitution, resulting in a misfolded IL-36Ra protein that is less stable and poorly expressed (17,18,20). However, the roles of IL-36Ra in inflammation-associated tumors have not been clearly elucidated, while IL-36 signaling has been implicated

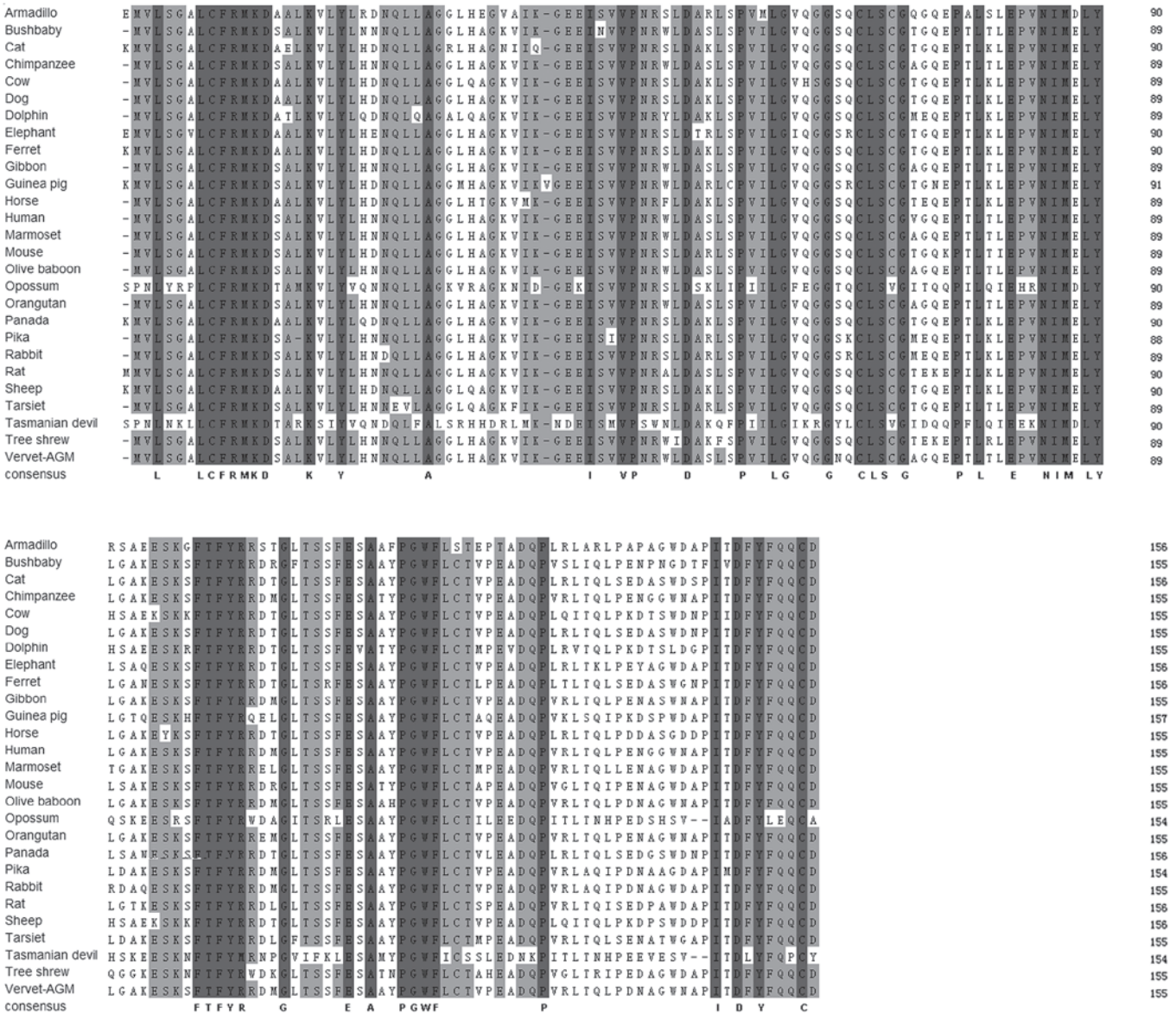

Figure 1. Alignments of amino acid sequence of the identified IL-36RN. The complete IL-36RN genes were identified in 27 mammalian genomes. AGM, African green monkey.

in inflammatory diseases; therefore, an integrative analysis of IL-36RN and its prognostic value in cancer is required.

The present study assessed the IL-36RN gene in a wide range of genomes using integrative genomic analyses. Subsequently, functionally relevant SNP analysis and comparative proteomic analysis of IL-36RN were conducted. The conserved transcription-factor binding sites within the upstream region of IL-36RN as well as the prognostic value of IL-36RN in cancer were investigated.

Materials and methods

Identification of the IL-36RN gene in vertebrate genomes and integrative genomic analyses. The nucleotide and amino acid sequences of IL-36RN were obtained from the Ensembl database (www.ensembl.org), based on orthologous and paralogous relationships. The IL-36RN gene sequences subjected to analysis with the Basic Local Alignment Search Tool (BLAST; http://blast.ncbi.nlm.nih.gov/Blast.cgi) against the GenBank database (http://www.ncbi.nlm.nih.gov/genbank/) to confirm that the best hits were the IL36RN genes for the selected species. Conserved transcription-factor binding sites within promoter regions of the human IL-36RN gene were obtained from the DECipherment Of DNA Elements proprietary database (http://www.sabiosciences.com/chipqpcrsearch.php?app=TFBS) of SABiosciences (Qiagen, Hilden, Germany), which combines text mining with data from the genome browser of the University of California, Santa Cruz (https://genome.ucsc.edu/).

Comparative proteomic analysis of the IL-36RN protein. The ClustalW software implemented in MEGA 5.05 (http://www.megasoftware.net/) was used to align the protein-coding sequences of IL-36RN. A maximum likelihood tree of IL-36RN amino acid sequences was constructed using MEGA 5.05 with the Kimura 2-parameter model (21). For the relative support of the internal node, bootstrap analysis was

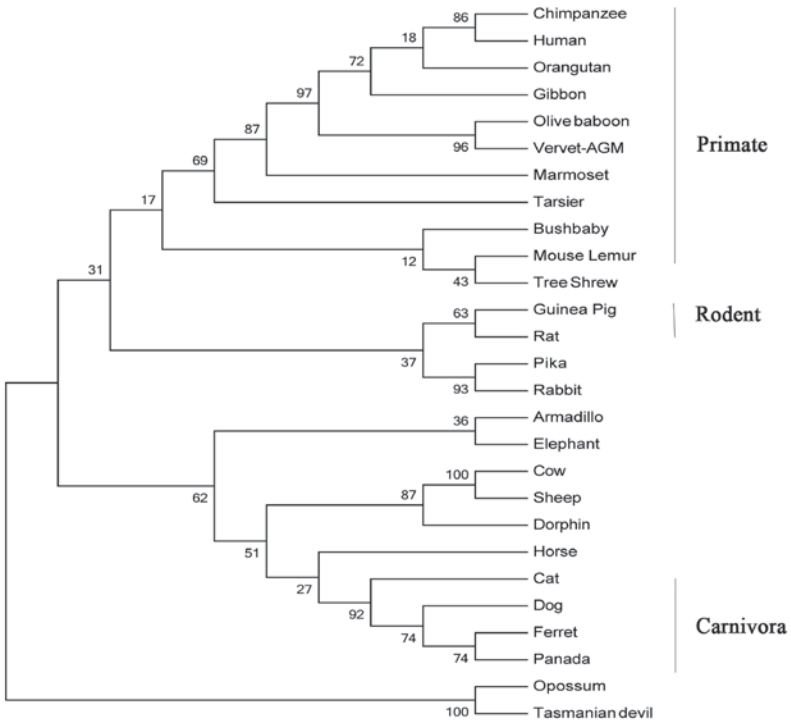

Figure 2. Phylogenetic analysis of IL-36RN. The phylogenetic tree was constructed according to the protein coding sequences using the maximum likelihood and neighbor-joining methods. The IL-36RN gene from primate lineage was clustered into a species-specific group. IL-36RN, interleukin-36RN.

performed with 1,000 replications for ML reconstructions. The positive selection of IL-36RN during evolution (22) was analyzed using the program CodeML implemented in the PAML4.7 software package (http://abacus.gene.ucl.ac.uk/software/paml.html). Codon subsitution models M0 (one ratio), M1a (NearlyNeutral), M2a (PositveSelection), M7 (β) and M8 (β and ω) were used. The site-specific model was generated using likelihood ratio tests to compare the models as previously described (23).

In silico expression analyses of the human IL-36RN gene. The expression profiles of normal human tissues were acquired from GeneAnnot (http://genecards.weizmann.ac.il/geneannot/index.shtml) and ArrayExpress (https://www.ebi.ac.uk/arrayexpress/). Using the human IL-36RN gene (GenBank ID, NC_000002.12) as a query sequence, expressed sequence tags (ESTs) derived from the human IL-36RN gene were identified by BLAST as described previously (24). Virtual northern blot analysis was also performed by searching the uniGene database of the National Center of Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/unigene). In addition, protein expression profiles of IL-36RN were obtained from the Systematic Protein Investigative Research Environment (25) and the Model Organism Protein Expression Database (26).

Evaluation of functionally relevant SNPs of the human IL-36RN gene and identification of somatic mutations in human cancer. Ensembl (http://www.ensembl.org/index.html) and the NCBI's Database of SNPs (http://www.ncbi.nlm.nih.gov/snp/) were used to obtain functionally relevant SNPs of the human IL-36RN gene as previously described (24,27,28). The SNPs that could disrupt exonic splicing enhancer (ESE)/exonic splicing silencer (ESS) motifs or cause a missense mutation were identified. Somatic mutations of the IL-36RN gene were identified in human cancer types from the Catalogue Of Somatic Mutations In Cancer (COSMIC) database (http://cancer.sanger.ac.uk/cosmic/), which mines complete cancer genomes (29).

Meta-analysis of the prognostic value of the IL-36RN gene in cancer. The PrognoScan database (http://www.prognoscan.org/) (30) contains a large collection of publicly available cancer microarray datasets with clinical annotation, enabling it to also be used as an efficient tool for assessing the association between gene expression and cancer prognosis. During gene analysis, PrognoScan employed the minimum P-value approach for grouping patients for survival analysis. Data was collected for further analysis by searching the IL-36RN gene as a query in PrognoScan.

Results

Comparative proteomic analysis of the IL-36RN protein. All the IL-36RN gene and protein sequences were collected from the Ensembl database and then confirmed by BLAST. The complete IL-36RN genes were identified in human, chimpanzee, gibbon, orangutan, olive baboon, vervet-African green monkey, marmoset, bush baby, tarsier, rabbit, pika, rat, mouse, elephant, cat, dog, panda, ferret, horse, cow, dolphin, guinea pig, sheep, opossum, tasmanian devil, armadillo and tree shrew genomes. The sequence and structural alignment of IL-36RN is illustrated in Fig. 1. Refined phylogentic trees generated using the identified IL-36RN protein amino acid sequences by ML and neighbor-joining (NJ) methods were almost identical; therefore, only the results of the ML method are presented (Fig. 2). It appeared that the IL-36RN protein from the primate lineage forms a species-specific cluster. Site-specific analysis for posi-

Table I. Exon and intron lengths of IL-36RN.

	Length (bp)											
Species	Exon 1	Intron 1	Exon 2	Intron 2	Exon 3	Intron 3	Exon 4	Intron 4	Exon 5	Intron 5	Exon 6	Total exons
Armadillo	32	734	86	820	128	756	225	-	-	-	-	471
Bushbaby	29	1343	86	1280	128	199	225	-	-	-	-	468
Cat	32	1334	86	1036	128	202	225	-	-	-	-	471
Chimpanzee	29	1384	86	1187	128	201	225	-	-	-	-	468
Cow	29	1334	86	1014	128	171	225	-	-	-	-	468
Dog	29	1553	86	1058	128	194	225	-	-	-	-	468
Dolphin	29	1518	86	998	128	171	225	-	-	-	-	468
Elephant	32	1510	86	976	128	220	225	-	-	-	-	471
Ferret	32	1539	86	1032	128	175	225	-	-	-	-	471
Gibbon	29	1382	86	1182	128	201	225	-	-	-	-	468
Guinea Pig	32	1650	86	1282	131	203	225	-	-	-	-	474
Horse	29	1369	86	1050	128	197	225	-	-	-	-	468
Human	29	1384	86	1186	128	201	225	-	-		-	468
Marmoset	29	1380	86	1187	128	201	225	-	-	-	-	468
Mouse Lemur	29	1353	86	1264	128	200	225	-	-	-	-	468
Olive baboon	29	1385	86	1197	128	200	222	-	-	-	-	465
Opossum	118	1450	128	348	219	-	-	-	-	-	-	465
Orangutan	29	1384	86	1184	128	201	225	-	-	-	-	468
Panda	32	1579	86	1055	128	201	225	-	-	-	-	471
Pika	29	797	16	3	25	1	42	1449	128	161	225	465
Rabbit	29	1491	86	1141	128	198	225	-	-	-	-	468
Rat	32	2070	86	1069	128	205	225	-	-	-	-	471
Sheep	32	1332	86	974	128	174	225	-	-	-	-	471
Tarsier	29	1348	86	1774	128	218	225	-	-	-	-	468
Tasmanian devil	88	1432	25	765	5	38	128	293	216	-	-	462
Tree Shrew	29	1509	86	1084	128	237	225	-	-	-	-	468
Vervet African green monkey	29	1392	86	1201	128	201	225	-	-	-	-	468

tive selection was performed for primate, rodent, carnivora, mammalian and mammalian excluding primate lineages. By using any of the six models in the IL-36RN proteins, no positive selection site was identified. Instead, purifying selection was observed among the proteins (data not shown). Furthermore, the exon-intron information was collected from the Ensembl database and presented in Table I and Fig. 3. In most of the mammalian genomes, IL-36RN genes had four exons and three introns of similar length. In the primate lineage, IL-36RN genes showed the same exon lengths and numbers with similar exon-intron conservations (Table I). However, IL-36RN genes had six exons and five introns in pikas and only three exons and two introns in opossums. Furthermore, the tasmanian devil was shown to have five exons and four introns in its IL-36RN genes (Table I and Fig. 3).

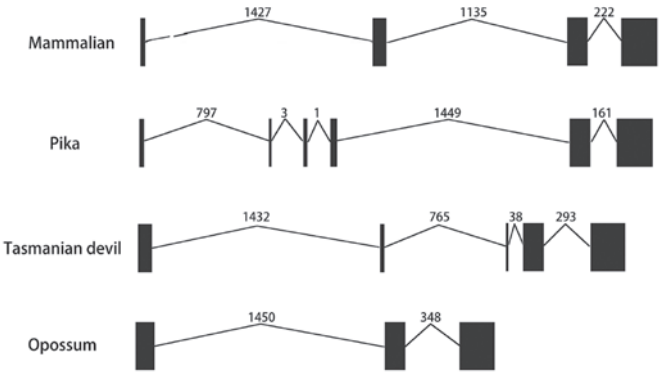

Figure 3. Exon-intron conservation analysis of IL-36RN. In the majority of mammalian genomes, IL-36RN has four exons and three introns of similar length. By contrast, in pikas, IL-36RN has six exons and five introns, while it has five exons and four introns in tasmanian devils, and only three exons and two introns in opossums.

Expression profile of the human IL-36RN gene. A search of the EST sequence database revealed that the human IL-36RN gene was expressed in the placenta, cervix, lung, head and neck, eye, fetal heart and testis, and furthermore, that it was highly expressed in bladder and parathyroid tumors. Examination of microarray analyses and 'virtual northern blot analysis'

Table II. Evaluation of the functionally relevant SNP in the human IL-36RN gene.

SNP ID	Chr 2 position sequence	Sequence	Type	Amino acid change
rs143724424	113820120	GCTTC[A/G]AGTCG	Missense	EK
rs144478519	113820124	CGAGT[C/T]GGCTG	Missense	SL
rs151325121	113819727	CCAAT[C/T]GGTGG	Missense	RW
rs387906914	113818479	GCTTC[C/T]AGCTG	Missense	LP
rs397514629	113820154	GTGCA[C/G]GGTGC	Missense	TR
rs28938777	113819725	CCCCA[A/G]TCGGT	Missense	NS
rs77864207	113819754	CCCCC[A/G]TCATC	Missense	VI
rs139497891	113819812	GGAGC[C/T]GACTC	Missense	PL
rs141341649	113820136	CTACC[C/T]GGGCT	Missense	PL
rs144182857	113820031	GCAGC[C/T]AGTGA	Missense	PL
rs144420774	113820103	CATGG[C/G]GCTCA	Missense	GA
rs145099228	113819721	TGGTC[C/T]CCAAT	Missense	PS
rs147389610	113818487	CTGGA[A/G]GGCTG	Missense	GR
rs147410197	113820087	CCTTC[C/T]ACCGG	Missense	YH
rs187015338	113818503	AGGGA[A/G]GGTCA	Missense	KR
rs199932303	113820090	TCTAC[C/T]GGCGG	Missense	RW
rs202059991	113820222	CCCCC[A/G]TCACA	Missense	IV
rs369259981	113820048	TGGAG[C/T]TCTAT	Missense	LF
rs371819085	113820091	CTACC[A/G]GCGGG	Missense	RQ
rs372880215	113819815	GCCGA[C/T]TCTAA	Missense	TI
rs374900764	113820247	GCAGT[A/G]TGACT	Missense	CY
rs375207169	113820093	ACCGG[C/T]GGGAC	Missense	RW
rs375718709	113819793	TGTCA[C/T]GTGGG	Missense	CR
rs377330697	113820172	CGATC[A/G]GCCTG	Missense	QR
rs537559199	113820044	ATCAT[A/G]GAGCT	Missense	MI
rs542606182	113820094	CCGGC[A/G]GGACA	Missense	RQ
rs545202535	113820237	TCTAC[A/T]TCCAG	Missense	FI
rs545673991	113818451	TGAAG[G/T]TGCTT	Missense	VL
rs397514630	113817043	GCTTC[C/T]GGTGA	Nonsense	R-Ter
rs368461730	113819805	TGGGG[C/T]AGGAG	Nonsense	Q-Ter

Among the 543 available SNPs identified in the human IL-36RN gene, a total of 30 SNPs were functionally relevant, including 28 SNPs causing missense mutations and 2 SNPs causing nonsense mutations. SNP, single nucleotide polymorphism; Chr 2, chromosome 2.

revealed a predominant expression of IL-36RN in cervix, larynx, lung, mouth, muscle, parathyroid, pharynx, placenta and testis. A search of the PrognoScan database revealed that human IL-36RN was also expressed in bladder, blood, brain, breast, colorectal, esophageal, eye, head and neck, lung, ovarian, skin and soft tissue cancer.

Comparative genomics analysis of human IL-36RN. Activator protein 1 (AP-1), c-Fos, c-Jun and nuclear factor (NF)-κB binding sites were identified within the upstream regions of the transcriptional start site of human IL-36RN.

Functionally relevant SNP evaluation of the human IL-36RN gene and identification of somatic mutations in human cancer. A total of 543 SNPs were identified in the human IL-36RN gene through searching the NCBI SNP and Ensembl databases. Among these SNPs, 30 were functionally relevant, causing missense and nonsense mutations (Table II). As presented in Table III, by searching the COSMIC database, 31 somatic mutations of the IL-36RN gene were identified in cancer.

Meta-analysis of the prognostic value of IL-36RN gene in cancer. PrognoScan employs the minimum P-value approach for grouping patients with varied cancer types for survival analysis and produces a data-set of results, including cancer type, subtype, endpoint, cohort, contributor, array type, probe ID, number of patients, optimal cut-off point, Pmin and Pcor. For the IL-36RN gene, 7 out of the 84 cancer cases showed correlations between microarray expression in the IL-36RN gene and cancer prognosis (bladder cancer, 1/2; blood cancer, 0/9; brain cancer, 0/4; breast cancer, 1/30; colorectal cancer, 1/9; esophageal cancer, 0/1; eye cancer, 0/1; head and neck cancer, 0/1; lung cancer, 2/15; ovarian cancer, 2/9; skin cancer, 0/1; soft tissue cancer, 0/1) with a 5% significance level (Table IV). Among the two ovarian cancer cases, poor survival in one case was associated with elevated expression of IL-36RN (DUKE-OC), and the

Table III. Somatic mutations of IL-36RN in tumor tissues.

Position (AA)	Mutation (CDS)	Mutation (amino acid)	Mutation ID (COSM)	Count	Mutation type
3	c.9G>C	p.L3L	COSM3836628	1	Substitution-coding silent
5	c.15G>A	p.G5G	COSM3894558	1	Substitution-coding silent
6	c.17C>T	p.A6V	COSM240220	1	Substitution-missense
10	c.28C>T	p.R10*	COSM126741	1	Substitution-nonsense
14	c.41C>T	p.S14L	COSM714706	1	Substitution-missense
15	c.44C>A	p.A15E	COSM714705	1	Substitution-missense
21	c.63G>T	p.L21L	COSM381474	1	Substitution-coding silent
29	c.85G>A	p.G29R	COSM1690946	1	Substitution-missense
34	c.102G>A	p.G34G	COSM3894559	1	Substitution-coding silent
36	c.108C>A	p.V36V	COSM169172	1	Substitution-coding silent
37	c.110T>C	p.I37T	COSM4084297	1	Substitution-missense
46	c.137C>T	p.P46L	COSM1690947	1	Substitution-missense
48	c.142C>T	p.R48W	COSM441016	1	Substitution-missense
54	c.160C>A	p.L54M	COSM300070	1	Substitution-missense
54	c.160C>T	p.L54L	COSM3565457	1	Substitution-coding silent
55	c.164C>T	p.S55F	COSM1690948	1	Substitution-missense
56	c.168C>A	p.P56P	COSM3565458	1	Substitution-coding silent
71	c.212G>A	p.G71E	COSM3565459	1	Substitution-missense
73	c.218G>C	p.G73A	COSM1527707	1	Substitution-missense
86	c.258G>T	p.M86I	COSM3565460	1	Substitution-missense
92	c.275C>A	p.A92D	COSM4133012	1	Substitution-missense
95	c.284C>T	p.S95F	COSM3565461	1	Substitution-missense
97	c.290G>A	p.S97N	COSM3565462	1	Substitution-missense
106	c.317G>A	p.G106E	COSM3565463	1	Substitution-missense
112	c.334G>A	p.E112K	COSM107437	1	Substitution-missense
117	c.350C>A	p.P117Q	COSM3961011	1	Substitution-missense
126	c.378A>G	p.E126E	COSM4084298	1	Substitution-coding silent
136	c.406C>A	p.L136I	COSM4084299	1	Substitution-missense
137	c.411C>T	p.P137P	COSM3565464	1	Substitution-coding silent
138	c.412G>A	p.E138K	COSM275559	2	Substitution-missense
142	c.425G>T	p.W142L	COSM336664	1	Substitution-missense

IL-36RN, interleukin-36RN; COSM, catalogue of somatic mutations; CDS, coding sequences.

other one was associated with decreased expression of IL-36RN (GSE17260). While one case out of nine cases of colorectal cancer showed poor survival associated with decreased expression of IL-36RN, elevated expression of IL-36RN in one case of bladder cancer, one case of breast cancer and two cases of lung cancer was found to be associated with poor survival.

Discussion

The IL-36RN gene encodes the anti-inflammatory cytokine IL-36Ra, which was previously known as IL-1F5 and later re-defined as a member of the IL-36 cytokine family.

The present study identified IL-36RN from 27 genomes and found that IL-36RN exists in all types of mammals, including primates, rodents and carnivora, as well as elephant, dolphin, sheep, rabbit, horse and armadillo. In the phylogenetic tree, all of the primates were clustered. Furthermore, the exon-intron information indicated that all primates were almost identical with regard to the IL-36RN gene. According to the alignment and phylogenetic tree, IL-36RN was evolutionarily conserved among mammals, indicating a significant biological function of this gene. It is known that IL-36 cytokines are expressed in various tissue types and contribute to inflammatory diseases (7), confirming its biological importance indicated by the present study.

EST sequence analysis revealed that the IL-36RN gene is expressed in the placenta, cervix, lung, head and neck, eye, fetal heart and testis; furthermore, high expression had been detected in bladder and parathyroid tumors. This result implied that IL-36RN is extensively expressed in a large variety of organ and tissue types. A total of 30 SNPs, including 28 SNPs causing missense mutations and 2 SNPs causing nonsense mutations, were analyzed from 543 available SNPs in human IL-36RN genes. Recently, several IL-36RN mutations among the 28 SNPs have been reported as causative genetic defects associated with GPP and related pustular disor-

Table IV. Dataset contents from PrognoScan showing an association between microarray expression of IL-36RN and cancer prognosis.

Database	Cancer type	Patients (n)	Endpoint	Cut-off point	P-value	Prognosis	Reference
GSE13507	Bladder cancer	165	Overall survival	0.87	0.046	2	(32)
GSE12276	Breast cancer	204	Relapse-free survival	0.46	0.042	2	(33)
GSE17536	Colorectal cancer	177	Overall survival	0.21	0.033	1	(34)
GSE31210	Lung cancer[a]	204	Overall survival	0.84	<0.001	2	(35)
GSE31210	Lung cancer[a]	204	Relapse-free survival	0.89	0.002	2	(35)
DUKE-OC	Ovarian cancer	133	Overall survival	0.44	0.031	2	
GSE17260	Ovarian cancer	110	Overall survival	0.12	0.009	1	(36)

[a]Sub-type, Adenocarcinoma. In total, 7 out of the 84 cancer cases showed correlations between microarray expression in the IL-36RN gene and cancer prognosis (bladder cancer, 1/2; blood cancer, 0/9; brain cancer, 0/4; breast cancer, 1/30; colorectal cancer, 1/9; esophageal cancer, 0/1; eye cancer, 0/1; head and neck cancer, 0/1; lung cancer, 2/15; ovarian cancer, 2/9; skin cancer, 0/1; soft tissue, cancer 0/1) with a 5% significance level.

ders (18-20,31), which indicates that changes in IL-36RN SNPs truly contribute to physiological and pathological functions of IL-36Ra. However, another reported IL-36RN mutation in the intron region, rs148755083, which causes GPP (31), was not included in the present study; therefore, further investigation is required to reveal the effects of the other SNPs on the links between IL-36RN and diseases.

In the present study, assessment of the prognostic value of IL-36RN in cancer using the PrognoScan database revealed that IL-36RN is expressed in various cancer types including bladder (32), breast (33), colorectal (34), lung (35) and ovarian cancer (36). In 7 out of 84 cancer cases, IL-36RN was identified as a promising prognostic factor. Furthermore, IL-36RN expression varied among different types of cancer and the prognostic value varied within entries of different databases for the same cancer type. These results suggested that IL-36RN may have multiple roles in cancer development. In addition, 31 somatic mutations of IL-36RN in cancer tissues were identified in the present study. Thus, additional study is required to confirm the preliminary findings of the present study, which indicated that IL-36RN takes part in cancer development, and to assess the underlying mechanisms.

The IL-36RN gene was identified to bind with the AP-1, c-Fos, c-Jun, and NF-κB regulatory transcription factors in the upstream (promoter) region. Transcription factor AP-1 regulates a broad range of genes involved in cell cycle and inflammation. It mediates the anti-apoptotic response to hypoxic conditions and contributes to resistance to chemo- and radiotherapy in colon cancer cells (37), while it influences pivotal regulators of cell proliferation, migration and survival involved in melanoma progression (38) as well as in the carcinogenesis of the respiratory epithelium (39). c-Fos has been found to be associated with lipid- and phospholipid synthesis in several cell types (40) and activates biogenesis in certain types of tumor cell to support tumor growth (41,42). c-Jun is a critical transcription factor involved in major cell-biological activities, including cell proliferation, apoptosis, angiogenesis and invasiveness by specific regulation of epidermal growth factor receptor, keratinocyte growth factor, cyclin D1, p53, proliferin and CD44 (43-46). NF-κB is known to be the key regulator of apoptosis and controlled cell suicide by means of controlling pro-apoptotic and anti-apoptotic genes (47-50). NF-κB exacerbates inflammation-induced cancer types, while it suppresses chemically induced skin and liver cancers (51-53), which suggests that NF-κB has a dual role in cancer. These transcription factors associated with tumorigenesis may represent a link between IL-36RN and tumorigenesis or cancer progression.

In conclusion, the present study investigated IL-36RN in various species and types of cancer at the gene and protein levels, and the results demonstrated that IL-36RN may have an important role in cancer progression through tumor-associated transcription factors and signaling pathways, but this hypothesis requires further investigation.

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