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Molecular Cloning of Testis-Abundant Finger Protein/Ring Finger Protein 23 (RNF23), a Novel RING-B Box-Coiled Coil-B30.2 Protein on the Class I Region of the Human MHC

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We have identified a genomic DNA fragment, using the PCR method with degenerate oligonucleotide primers which contain the conserved sequence of the RING finger domain. Using the DNA fragment as a probe, a novel cDNA was cloned from human and mouse testis. The cDNA had a domain structure of the typical RING-B box-coiled coil (RBCC)-B30.2 domain and therefore was named testis-abundant finger protein (tfp). Indeed, the transcript was highly expressed in the testis, although it was also found ubiquitously in various organs by Northern blot analysis. The tfp gene was mapped at the class I region of the human MHC (major histocompatibility complex), within which some known RBCC-B30.2 proteins such as RFP, RFB30/HERF1, AFP, and HZF had been localized. These findings demonstrate that several RBCC-B30.2 proteins including tfp, which are non-HLA proteins, are clustered within the class I region of the human MHC.

Key Words: **testis-abundant finger protein (tfp); RBCC (RING-B box-coiled coil)-B30.2 protein; class I region of human MHC.**

A large number of RING finger proteins play crucial roles in a variety of biological phenomena such as differentiation, development, oncogenesis, and apoptosis (1, 2). Recently, it is reported that some RING finger proteins are also involved in proteolysis (3, 4). The RING finger domain is likely to be a zinc-binding domain conserved among several kinds of protein species from virus to humans, but it is different from known zinc finger domains in terms of sequence homology and three dimensional structure (5–7). Although the function of the RING finger domain is still unclear, participation in protein–protein interaction is supported by several studies (6, 7). We have attempted to obtain novel RING finger proteins using PCR method with degenerate primers. Using a number of fragments obtained, we already succeeded in identifying a few RING finger proteins such as brain finger protein (bfp)/ZNF179 mapped within the critical region of Smith-Magenis syndrome (8, 9), the testis-ring finger protein (terf)/RNF16 (10, 11) and interferon-responsive finger protein 1 (ifp1)/RNF21 (12).

In this study, novel full-length cDNAs, designated testis-abundant finger protein (tfp), were isolated from human and mouse testis cDNA libraries using a DNA fragment of the PCR product with a novel RING finger domain. Tfp belonged to a family of proteins characterized by the presence of the RING-B box-coiled coil (RBCC)-B30.2 domain and its distribution and the chromosome localization were determined.

MATERIALS AND METHODS

PCR method with degenerate primers and DNA sequence analysis. We synthesized two degenerate primers: PRIMER1, 5′-TCNTG(CT)-TCN(GA)TNTG-(CT)CT-3′; and PRIMER2, 5′-CA(GA)AA(GA) (TGC)

The tfp nucleotide sequences in human and mouse are deposited in GenBank with Accession Nos. AB046381 and AB046382, respectively.

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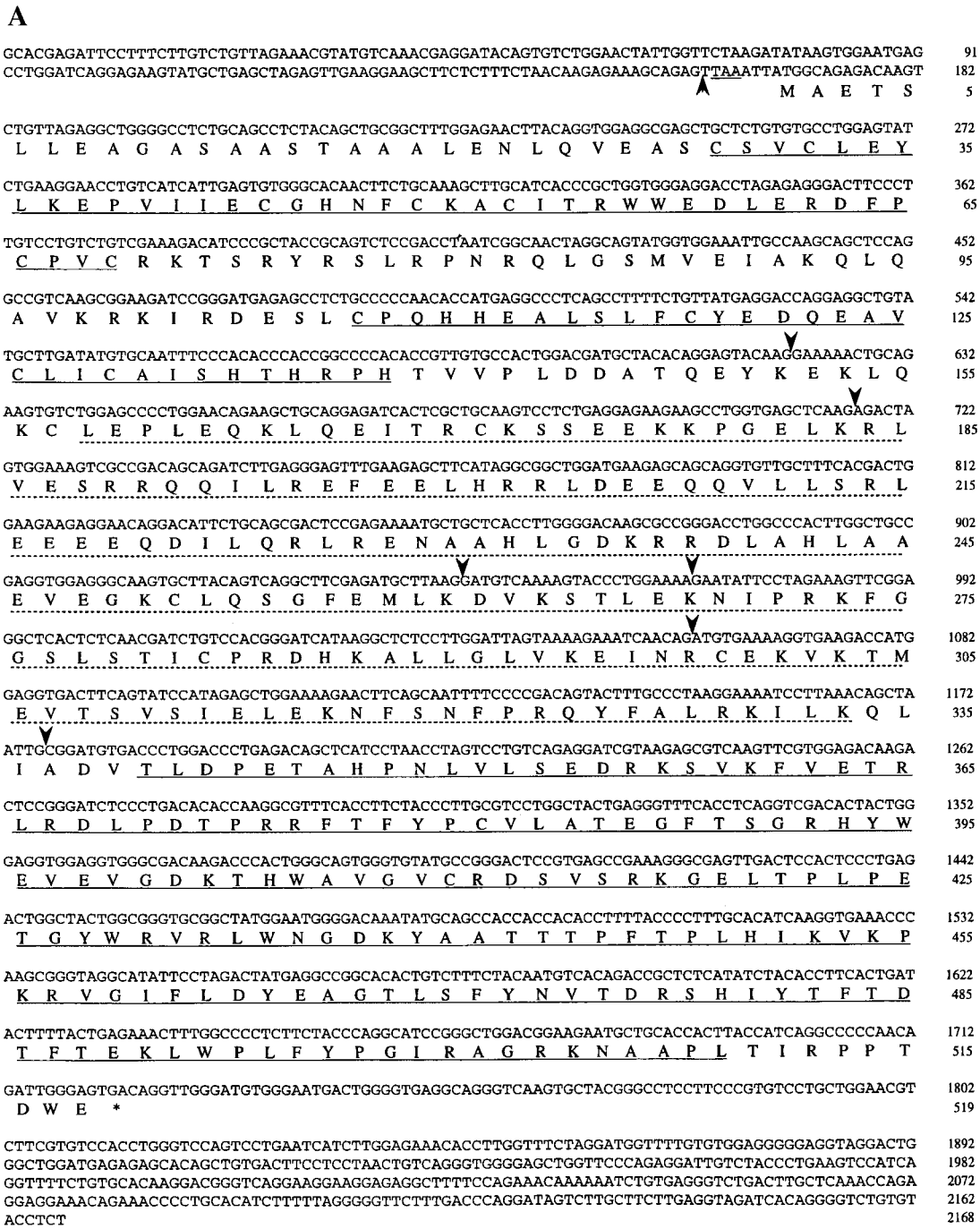

FIG. 1. Nucleotide and predicted amino acid sequences of the human tfp cDNA. (A) The predicted amino acid sequence is shown by amino acids below their respective codons. The RING finger domain (amino acids 29–69) and B box domain (amino acids 107–138) are underlined. The potential coiled-coil domain (amino acids 158–333) is indicated by a dotted line and the B30.2 domain (amino acids 340–509) is also underlined. The TGA stop codon (*) is shown at amino acid 519 and the inframe stop codon (TAA) upstream the N-terminus is underlined (nucleotides 162–164). In addition, exon–intron junctions are indicated by closed arrows. (B) Comparison with the human tfp protein and the mouse homologue. The RING finger domain (amino acids 29–69) and B box domain (amino acids 107–138) are underlined as described in Fig. 1A. Conserved residues including cysteines/histidine, in the RING finger domain and B box domain are denoted by the bold type. The potential coiled-coil domain (amino acids 158–333) is indicated by a dotted line and the B30.2 domain (amino acids 340–509) is underlined. The conserved amino acids with mouse are shown by dots. The 30 amino acids (amino acids 269–298), novel sequence from splicing variant, are indicated by open bold letters in the human tfp protein. (C) Alignment of the conserved amino acid sequence of several RING finger domains among the RBCC-B30.2 proteins. The conserved cysteines/histidine residues are shown in boldface. Gaps to improve sequence alignment are indicated by dashes.

B

RING finger domain

```
htfp MAETSLLEAGASAASTAAALENLQVEASCSVCLEYLKEPVIIECGHNFCKACITRWWEDLERDFPCPVCRKTSRYRSLRPNRQLGSNVEI  90
mtfp ..........................................................................................  90
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B box domain

```
htfp AKQLQAVKRKIRDESLCPQHHEALSLFCYEDQEAVCLICAISHTHRPHTVVPLDDATQEYKEKLQKCLEPLEQKLQEITRCKSSEEKKPG 180
mtfp .....T..........S....P.............................M.........................C..A.......  180
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coiled-coil domain

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htfp ELKRLVESRRQQILREFEELHRRLDEEQQVLLSRLEEEEQDILQRLRENAAHLGDKRRDLAHLAAEVEGKCLQSGFEMLKDVKSTLEKNI 270
mtfp ..............K..............T.........................R..............................--  268

htfp PRKPGGSLSTICPRDHKALLGLVKEINRCEKVKTMEVTSVSIELEKNFSNFPRQYFALRKILKQLIADVTLDPETAHPNLVLSEDRKSVK 360
mtfp ------------------------------.............................................................  330
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B30.2 domain

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htfp FVETRLRDLPDTPRRFTFYPCVLATEGFTSGRHYWEVEVGDKTHWAVGVCRDSVSRKGELTPLPETGYWRVRLWNGDKYAATTTPETPLH 450
mtfp ............Q.............................................................................  420

htfp IKVKPKRVGIFLDYEAGTLSFYNVTDRSHIYTFTDTFTEKLWPLFYPGIRAGRKNAAPLTIRPPTDWE*  519
mtfp ..............................................................*  489
```

C

hTFP	EASCSVCLEYLKEPVIIE	CGHNFCKACITRWWEDLERDFP	CPVC
mTFP	EASCSVCLEYLKEPVIIE	CGHNFCKACITRWWEDLERDFP	CPVC
RFP	ETTCPVCLQYFAEPMMLD	CGHNICCACLARCWGTAETNVS	CPQC
SSA/Ro	EVTCPICLDPFVEPVSIE	CGHSFCQECISQVGKGGGSV	CAVC
TERF	EATCSICLDYFTDPVMTT	CGHNFCRACIQLSWEKAR-----KGSFP	CPEC
XNF-7	ELTCPLCVELFKDPVMVA	CGHNFCRSCIDKAWEGNSSFA	CPEC
RFB30/HERF1	EVNCPICQGTLREPVTID	CGHNFCRACLTRYCEIPGPD LEESPT	CPLC
AFP	EVTCSICLDYLRDPVTID	CGHVFCRSCTTDVRPISGS------ PRV	CPLC
HZF	LATCPLCGGSFEDPVLLA	CEHSFCRACLARRWGTPP-------- PTA	CPCC

FIG. 1—*Continued*

(TA) (GA)TGNCC(GA)CA-3′. Using these primers, mouse genomic DNA from the embryo was reacted using PCR as described previously (8, 10, 12). PCR products were subcloned into pCRII vector (Invitrogen) and then they were sequenced by an automated sequencer (Shimazu, Japan). Subsequently, the nucleotide sequence was searched by the ProDom protein domain database and BLAST database, and the obtained 66 bp DNA fragment (5′-AGCTGTTCTGTATGCCTAGAGTATCTGAAGGAGCCAGTTATTATTGAATGTGGGCA-CAACTTCTGC-3′) which contained a novel sequence corresponding to putative RING finger domain was used as a probe for screening of a mouse genomic library.

Screening of a mouse genomic library and of human and mouse testis cDNA libraries. First, several clones from an identical origin were obtained from a mouse genomic library (Stratagene) by hybridization with the ^{32}P-labeled 66 bp DNA. Subsequently, we have extracted a genomic DNA from the clone and isolated a 346 bp DNA fragment which contained a novel sequence with both the RING finger and B box domains. Subsequently, using the 346 bp DNA, the full length of cDNA was isolated from λZAPII cDNA libraries (Stratagene) of human and mouse testis.

Northern blot analysis. Human multiple tissue Northern blot containing 2 μg poly (A)+RNAs per tissue were purchased from Clontech. The membranes were hybridized with the ^{32}P-labeled 2.1 kb *Eco*RI fragment of the human tfp cDNA. Northern blot analysis was performed as described previously (9). Autoradiography was carried out at −80°C with an intensifying screen for 3 days.

Fluorescence in situ hybridization (FISH) mapping of the human tfp gene. The preparation of human lymphocytes was carried out as described (13). The identical cDNA fragment used in Northern blot analysis was biotinylated with dATP using the BRL BioNick labeling kit. The procedure for FISH analysis was performed according to a previous report (13). FISH signals and DAPI banding pattern were recorded separately, and the assignment of the FISH mapping data with chromosomal bands was achieved by superimposing FISH signals with DAPI banded chromosomes.

RESULTS AND DISCUSSION

Isolation of the Human Tfp and the Mouse Homologue

We have attempted to obtain novel RING finger proteins using PCR method with degenerate primers. First, we have isolated mouse genomic clones from an identical origin using one fragment of PCR products as a probe, which coded for a novel RING finger domain (see Materials and Methods). Subsequently, using the portion of the genomic DNA as a probe, the full length cDNAs were then isolated from λZAPII cDNA libraries of human and mouse testis. The nucleotide sequences of the cDNAs in human and mouse were found to have

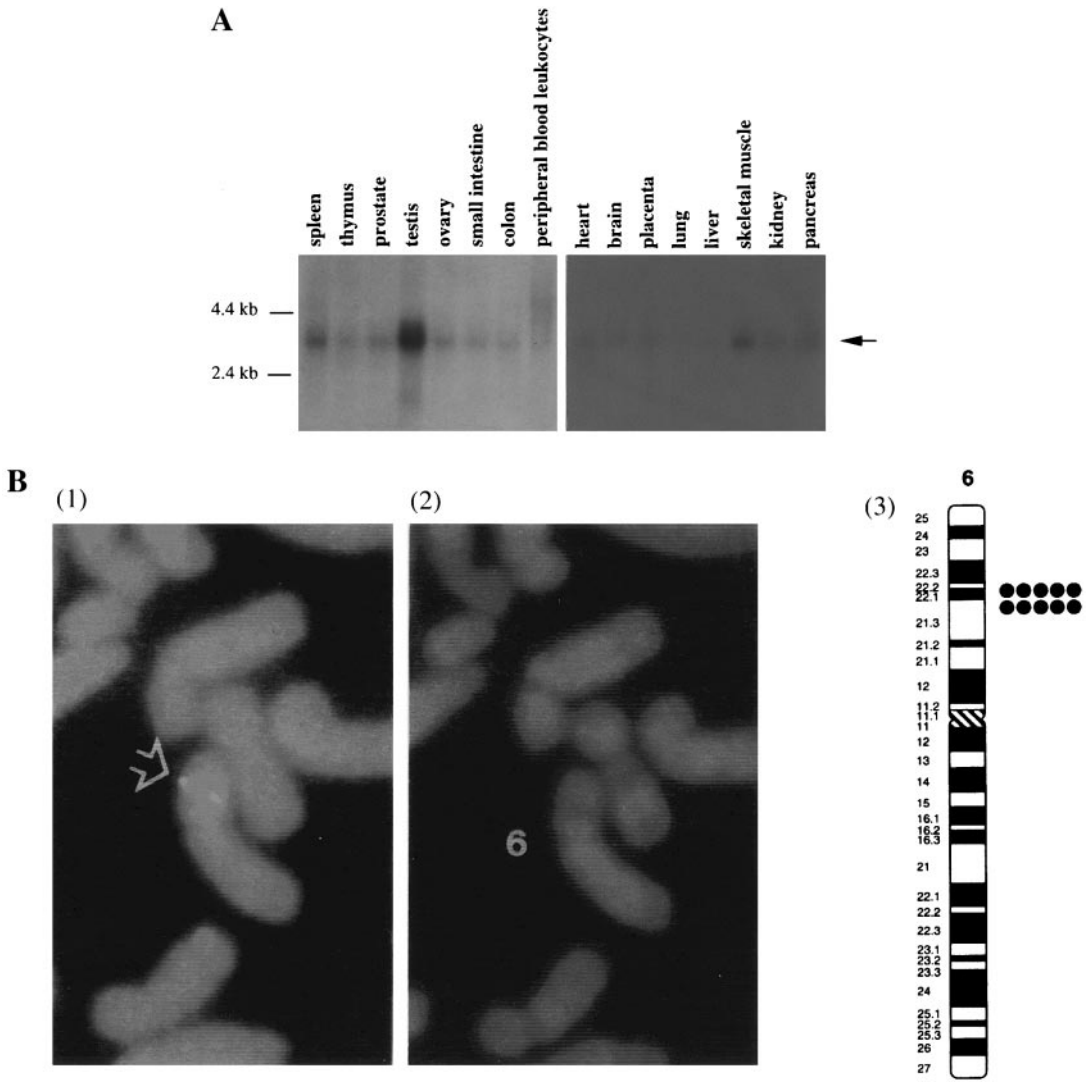

FIG. 2. Tissue expression of the human tfp mRNA and the chromosome localization of the human tfp gene. (A) Tissue distribution of the human tfp mRNA. Human multiple tissue Northern blot membrane (Clontech) containing 2 μg poly. $^{+}$RNAs per tissue was hybridized with the ^{32}P-labeled 2.1 kb fragment of the human tfp cDNA. The arrow indicates the specific band of tfp transcript. (B) Chromosome mapping of the human tfp gene. (1) FISH analysis of the human tfp gene. The procedure for FISH analysis was described in a previous report (13). The arrow indicates a pair of signals on the chromosome. (2) The same mitotic figure stained with DAPI. The left panel which showed the FISH signals on chromosome was stained with DAPI. (3) Diagram of FISH mapping. Each dot indicates the double FISH signals detected on human chromosome 6p21.3-p22.1.

open reading frames each representing 519 and 489 amino acids, respectively, both of which encoded the RING-B box-coiled coil (RBCC)-B30.2 domains (Figs. 1A and 1B). Respective domains are schematically shown in Figs. 1A and 1B. The isolation of complete coding region of the cDNA was possibly supported by the presence of in frame stop codon upstream the N-terminus (Fig. 1A). These findings indicate that the clone, named testis-abundant finger protein (tfp), is really a member of the RBCC-B30.2 protein family (14–16). In Fig. 1B, the alignment between the human tfp protein and the mouse homologue showed 98% identity as a whole. However, the mouse tfp protein lacked 30 amino acids (amino acids 269–298), indicated by open bold letters in the human tfp, due to an alternative splicing (Fig. 1B), because the amino acids were encoded as single exon between two exon–intron junctions (Fig. 1A).

Comparison with Other Members of the RBCC-B30.2 Proteins

The amino acid sequence of the human tfp was compared with other RBCC-B30.2 proteins. It exhibited considerable homology; i.e., 39% identity with SSA/Ro, 38% identity with Rfp, 35% identity with

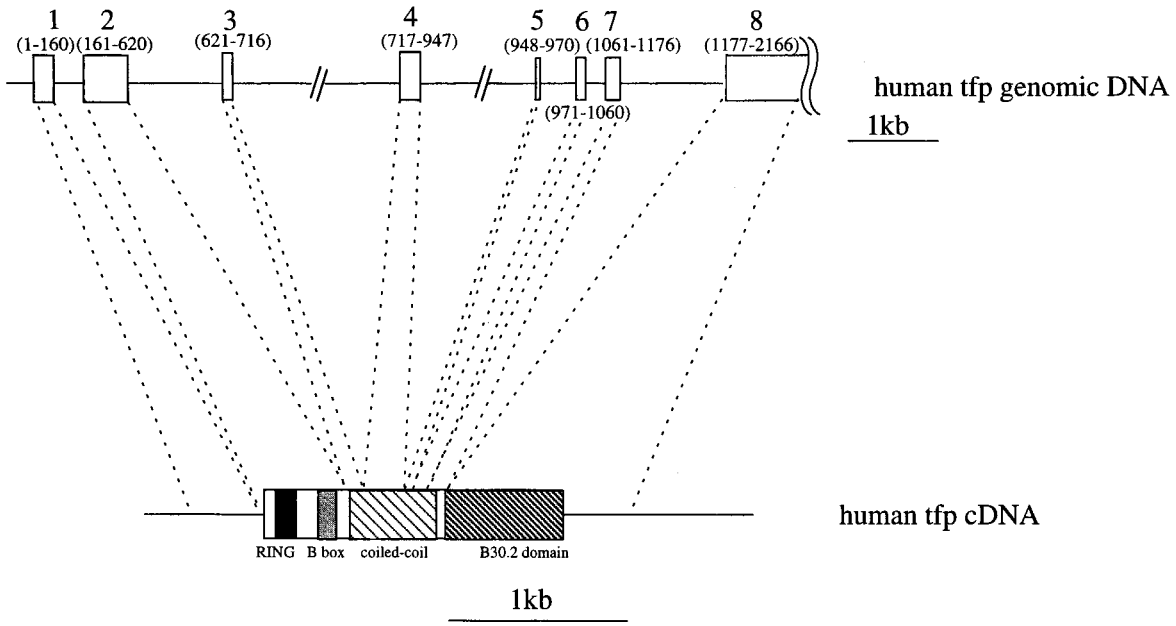

FIG. 3. Genomic structure of the human tfp. (Top) Schematic representation of the human tfp gene, which spans 7 introns and 8 exons. The exons are indicated by open box and the positions of cDNA nucleotide are shown in parentheses. (Bottom) Schematic structure of the human tfp cDNA. Respective conserved domains are indicated by distinct designs. Correlation of each exon to the cDNA is indicated by dashed lines.

terf, and 33% identity with XNF-7 in the GenBank DNA database as determined by BLAST database. The amino acid sequence of the RING finger domain with conserved residues of seven cysteines and a histidine among these proteins was aligned in Fig. 1C. The amino acid sequence of the RING finger domain between the human and mouse tfp was completely conserved, whereas other members of the RBCC-B30.2 proteins appear to be quite less conserved except for the cysteines and histidine residues. Rfp (17) is an oncogenic protein fused to ret proto-oncogene in transformed NIH3T3 cells, and the mice into which the RFP/RET transgene was expressed showed expanded late pro-B cell population prone to malignant transformation (18). The human 52 kD SSA/Ro (19, 20) is the antigen related to autoimmune response found in the patient with SLE and Sjögren syndrome, and it shows a significant response to interferon (IFN) (21). Terf is an abundant gene in the testis which was mapped on the human chromosome 1q42 (10, 11). XNF-7 which is maternally expressed, exhibits phosphorylation-dependent changes in subcellular localization during early Xenopus development (22). RFB30/HERF1 is a regulatory protein involved in the terminal differentiation of erythroid cells (23, 24). AFP (25) and HZF (26) are non-HLA proteins isolated by positional cloning within the classical class I region of the major histocompatibility complex (MHC).

Tissue Distribution of the Human Tfp mRNA

Next, we determined the distribution of the tfp mRNA in different human tissues. Northern blot anal-

TABLE 1

The Exon-Intron Boundaries of the Human TFP Gene

155	GCAGAG/**GT**AAGAGA	Intron 1	269 bp	CTCCCA**AG**/TTAAAT	166
615	TACAAG/**GT**GGGGAA	Intron 2	1010 bp	CCCCTC**AG**/GAAAAA	626
711	CTCAAG/**GT**AAAGGC	Intron 3	4874 bp	CTTCTC**AG**/AGACTA	722
942	CTTAAG/**GT**TCGACC	Intron 4	3932 bp	CCTTCT**AG**/GATGTC	953
965	GGAAAA/**GT**AAGTGA	Intron 5	341 bp	AAATAC**AG**/GAATAT	976
1055	CAACAG/**GT**GAGCTT	Intron 6	143 bp	CCTCCT**AG**/ATGTGA	1066
1171	TAATTG/**GT**GAGTTG	Intron 7	1091 bp	CCCGCC**AG**/CGGATG	1182

Note. The numbers indicate the positions of the 5′ and 3′ nucleotides within the human tfp cDNA. Intron number and size are shown, and splice acceptor and donor sites are shown in boldface type.

ysis showed a strong band at around 3.4 kb in the testis, although it seemed to be present rather ubiquitously in various organs (Fig. 2A). In this context, it is noteworthy that Rfp (17) and terf (10), which are other members of the RBCC-B30.2 genes, are also highly expressed in the testis. The cell types and expression patterns of tfp in testicular cells is now under study.

Chromosome Localization of the Human Tfp Gene

Next, FISH analysis was performed to human chromosome metaphase spreads (Figs. 2B-1 and 2B-3). Under the conditions used, the hybridization efficiency indicated approximately 71% among 100-checked mitotic figures. The DAPI banding (Fig. 2B-2) was used to identify the specific chromosome. The assignment from double signals of the human tfp gene was made at the chromosome 6p21.3-p22.1 (Fig. 2B-3). Hence, it is supposed that at least five RBCC-30.2 genes including RFP, RFB30/HERF1, AFP, HZF, and tfp are clustered in the classical class I region of the MHC within chromosome 6p21.3-p22.1.

It would be interesting to examine the significance of the RBCC-30.2 proteins present in the MHC locus in terms of inflammation, antigen presentation and processing, and immune response, etc. The identical chromosome location among some RBCC-30.2 proteins leads us to suspect their common role as members of the family, although the low homology of the tfp protein less than 40% compared with other members might also imply a distinct function of tfp.

Genomic Structure of the Human Tfp Gene

The human tfp gene sequence was searched from complete sequence of the human MHC (http://www.sanger.ac.uk/HGP/Chr6/MHC_990719.fasta) (27) using the full length of the human tfp cDNA. A schematic view of the human tfp gene structure is shown in Fig. 3. The human tfp gene contains at least 8 exons and 7 introns. The entire RING-B box and the B30.2 domains are encoded by each single exon, exon 2 and 8, respectively. A summary of the exon/intron boundaries is listed in Table 1. All splice donor sites match the 5′-GT rule and all splice acceptor sites also follow the 3′-AG rule. Moreover, these exon/intron junctions were completely conserved in the mouse tfp gene (manuscript in preparation), supporting strongly that the mouse gene is really the orthologue of the human tfp.

It is recapitulated here that there are several RBCC-B30.2 proteins including tfp clustered in the classical class I region of the MHC within chromosome 6p21.3-p22.1, suggesting that the proteins are likely to be originated from an ancestral gene by gene duplication.

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