Comparative integromics on FAT1, FAT2, FAT3 and FAT4

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Abstract. WNT5A, WNT5B, WNT11, FZD3, FZD6, VANGL1, VANGL2, DVL1, DVL2, DVL3, PRICKLE1, PRICKLE2, ANKRD6, NKD1, NKD2, DAAM1, DAAM2, CELSR1, CELSR2, CELSR3, ROR1 and ROR2 are planar cell polarity (PCP) signaling molecules implicated in the regulation of cellular polarity, convergent extension, and invasion. FAT1, FAT2, FAT3 and FAT4 are Cadherin superfamily members homologous to *Drosophila* Fat, functioning as a positive regulator of PCP in the *Drosophila* wing. Complete coding sequence (CDS) for human FAT1 (NM_005245.3) and FAT2 (NM_001447.1) are available, while artificial CDS for human FAT3 (XM_926199 and XM_936538) and partial CDS for FAT4 (NM_024582.2). Here, complete CDS of human FAT3 and FAT4 were determined by using bioinformatics and human intelligence (Humint). *FAT3* gene, consisting of 26 exons, encoded a 4557-aa protein with extracellular 33 Cadherin repeats, one Laminin G (LamG) domain and two EGF domains. *FAT4* gene encoded a 4924-aa protein with extracellular 34 Cadherin repeats, two LamG domains and three EGF domains. Cytoplasmic VCSVxPxLP and SDYxS motifs were identified as novel motifs conserved among FAT1, FAT2 and FAT3 orthologs. Domain architecture comparison and phylogenetic analysis revealed that FAT1, FAT2 and FAR3 were divergent from FAT4. *FAT1-MTNR1A* locus at 4q35.2 and *FAT3-MTNR1B* locus at 11q14.3-q21 were paralogous regions within the human genome. *FAT1* mRNA was expressed in embryonic stem (ES) cells, neural tissues, gastric cancer, pancreatic cancer, colorectal cancer, breast cancer, lung cancer and brain tumors. *FAT2* mRNA was expressed in infant brain, cerebellum, gastric cancer, pancreatic cancer, ovarian cancer, esophageal cancer, skin squamous cell carcinoma, head and neck cancer. *FAT3* mRNA was expressed in ES cells, primitive neuroectoderm, fetal brain, infant brain, adult neural tissues and prostate. *FAT4* mRNA was expressed in fetal brain, infant brain, brain tumor and colorectal cancer. FAT family members were revealed to be targets of systems medicine in the fields of oncology and neurology.

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Introduction

Drosophila Frizzled, Dishevelled, Diego, Starry night (Flamingo), Van Gogh (Strabismus) and Prickle are core planar cell polarity (PCP) signaling molecules (1-7). Asymmetrical localization of Frizzled - Dishevelled - Diego - Starry night complex and Van Gogh - Prickle complex induces PCP in the *Drosophila* wing. Human WNT5A, WNT5B, WNT11, FZD3, FZD6, VANGL1, VANGL2, DVL1, DVL2, DVL3, PRICKLE1, PRICKLE2, ANKRD6, NKD1, NKD2, DAAM1, DAAM2, CELSR1, CELSR2, CELSR3, ROR1 and ROR2 are PCP signaling molecules implicated in the regulation of cellular polarity, convergent extension, and invasion (7-26). Activation of PCP signaling pathway controls tissue polarity and cell movement through the activation of RHOA, c-Jun N-terminal kinase (JNK), and nemo-like kinase (NLK) signaling cascades.

Fat, Four-jointed and Dachsous are additional PCP signaling molecules in the *Drosophila* wing (27-29). *Drosophila* Fat, functioning as a positive regulator of PCP in the *Drosophila* wing, is a member of the Cadherin superfamily. *Drosophila* Fat-like, implicated in the morphogenesis of tubular structures of ectodermal origin, is the homolog of Fat (30). Fat1, Fat2, Fat3 and Fat4 are rodent homologs of *Drosophila* Fat and Fat-like (31-33). Complete coding sequence (CDS) for human FAT1 (NM_005245.3) and FAT2 (NM_001447.1) are available in the public database, while artificial CDS for human FAT3 (XM_926199 and XM_936538) and partial CDS for FAT4 (NM_024582.2). Here, complete CDS of human FAT3 and FAT4 were determined by using bioinformatics and human intelligence (Humint). Comparative genomics analyses, proteomics analyses and expression profile analyses on the FAT family members were then performed.

Materials and methods

Determination of complete CDS for FAT3 and FAT4. Human cDNAs, expressed sequence tags (ESTs) and genome sequences, derived from *FAT3* and *FAT4* transcripts, were searched for with BLAST programs as described previously (34-36). Complete CDS of human FAT3 and FAT4 were determined by assembling exonic regions.

Comparative genomics analyses. Intra-species comparative genomics analyses were performed as described previously (37-39). Genome sequences corresponding to human *FAT1*, *FAT2*, *FAT3* and *FAT4* genes were searched for with BLAST programs (http://www.ncbi.nlm.nih.gov). TCF/LEF-binding sites within the 5'-flanking promoter region of above genes were searched for based on bioinformatics and manual inspection as described previously (40-42).

Comparative proteomics analyses. Domain architecture analyses of FAT family members were performed by using RPS-BLAST and PSORT II programs. Phylogenetic analysis on FAT family proteins was performed by using the CLUSTALW program. Human FAT1, FAT2, FAT3, rat Fat1, Fat2 and Fat3 were then aligned by using Genetyx program and manual curation as described previously (43-45).

In silico expression analyses. Expressed sequence tags (ESTs) derived from human *FAT1*, *FAT2*, *FAT3* and *FAT4* genes were searched for by using the BLAST programs as described previously (46-48). The sources of human ESTs derived from *FAT* family genes were listed up for *in silico* expression analyses.

Results

Complete CDS of human FAT3. BLAST programs using rat Fat3 RefSeq (NM_138544.1) revealed that human *FAT3* gene was located within AP000722.5, AP000805.4, AP002514.5, AP003718.3, AC067807.10 and AP003171.2 genome sequences. Because the first exon corresponding to the 5'-UTR of human *FAT3* mRNA was not detected based on the BLAST programs, we searched for human EST spanning the 5'-UTR to identify BF953408.1 EST. By using the nucleotide sequence of BF953408.1 EST as a query sequence for the BLAST programs, the first exon of human *FAT3* gene was identified within AP003124.3 genome sequence.

Exon-intron boundaries of human *FAT3* gene were determined based on the consensus sequence of exon-intron junctions. Exon 1 was located within AP003124.3 genome sequence as mentioned above, exons 2 within AP000722.5, exon 3 within AP000805.4, exon 4 within AP002514.5, exons 5-17 within AP003718.3, exons 5-22 within AC067807.10, and exons 22-26 within AP003171.2. Exons 2, 10 and 26 were larger than 3 kb in length. Human *FAT3* gene was found consisting of 26 exons (Fig. 1A).

Because XM_926199 and XM_936538 were human FAT3 predicted sequences with the artificial first exon, complete CDS of human FAT3 was determined by assembling exonic regions (Fig. 1B). Genetyx program revealed that nucleotide position 67-13740 was the coding region. Human *FAT3* gene was found to encode a 4557-amino-acid FAT3 protein (Fig. 1B).

Complete CDS of human FAT4. Preliminary alignment of FAT family members revealed that human FAT4 RefSeq (NM_024582.2) was a partial CDS, lacking N-terminal one thirds of the coding region. BLAST programs using mouse Fat4 RefSeq (NM_183221.2) revealed that human *FAT4* gene was located within AC079835.5, AC098865.2 and AC092629.2 genome sequences. The 5'-UTR of FAT family transcripts were interrupted by the first intron; however, putative first exon corresponding to the 5'-UTR of *FAT4* gene was not identified in this study due to the absence of EST or cDNA. Complete CDS of human FAT4 was determine by assembling AC079835.5 genome sequence (nucleotide position 102306-107480) and NM_024582.2 RefSeq (nucleotide position 70-9669) (Fig. 2A). Genetyx program revealed that nucleotide position 1-14775 was the coding region. *FAT4* gene was found to encode a 4924-aa FAT4 protein.

Complete CDS of human FAT2. Although human FAT2 RefSeq (NM_001447.1) spanned the entire coding region, its 5'-end did not extend to the first exon corresponding to 5'-UTR. BLAST programs revealed that DA102144.1 EST spanned to the missing first exon. Therefore, full-length complete CDS of human FAT2 was determined by assembling DA102144.1 EST and NM_001447.1 RefSeq (Fig. 2A).

Comparative genomics analyses on FAT family. *FAT1* gene at human chromosome 4q35.2 was linked to the *MTNR1A* gene, while *FAT3* gene at human chromosome 11q14.3-q21 was linked to the *MTNR1B* gene (Fig. 2B). Third *MTNR1* family gene linked *FAT2* or *FAT4* gene was not identified by using the BLAST programs. Based on these facts, it was concluded *FAT1-MTNR1A* and *FAT3-MTNR1B* loci were paralogous regions within the human genome (Fig. 2B).

Full-length complete CDS of human FAT1, FAT2 and FAT3 (Fig. 2A) were used as query sequences for the BLAST programs to identify genome clones corresponding to *FAT* family genes. The 5'-flanking promoter regions of human *FAT1*, *FAT2* and *FAT3* genes were identified within AC107050.3, AC011374.6 and AP003124.3 genome sequences, respectively. Repetitive sequence was located within the 5'-promoter region of *FAT3* gene. TCF/LEF-binding sites within the 5'-promoter region of *FAT1*, *FAT2* and *FAT3* genes were then searched for based on manual inspection. One TCF/LEF-binding site was located about 1100 bp upstream of the transcription start site of *FAT1* gene, and also about 800 bp upstream of the transcription start site of the *FAT2* gene.

Comparative proteomics analyses on the FAT family. FAT1, FAT2, FAT3 and FAT4 are type I transmembrane proteins. Extracellular region of FAT1 and FAT3 consisted of 33 Cadherin repeats, one Laminin G (LamG) domain and two EGF domains. Extracellular region of FAT2 consisted of 32 Cadherin repeats, one LamG domain and two EGF domains. Extracellular region of FAT4 consisted of 34 Cadherin repeats, two LamG domains and three EGF domains. Phylogenetic analyses revealed that FAT1, FAT2 and FAR3 were divergent from FAT4 (Fig. 2C).

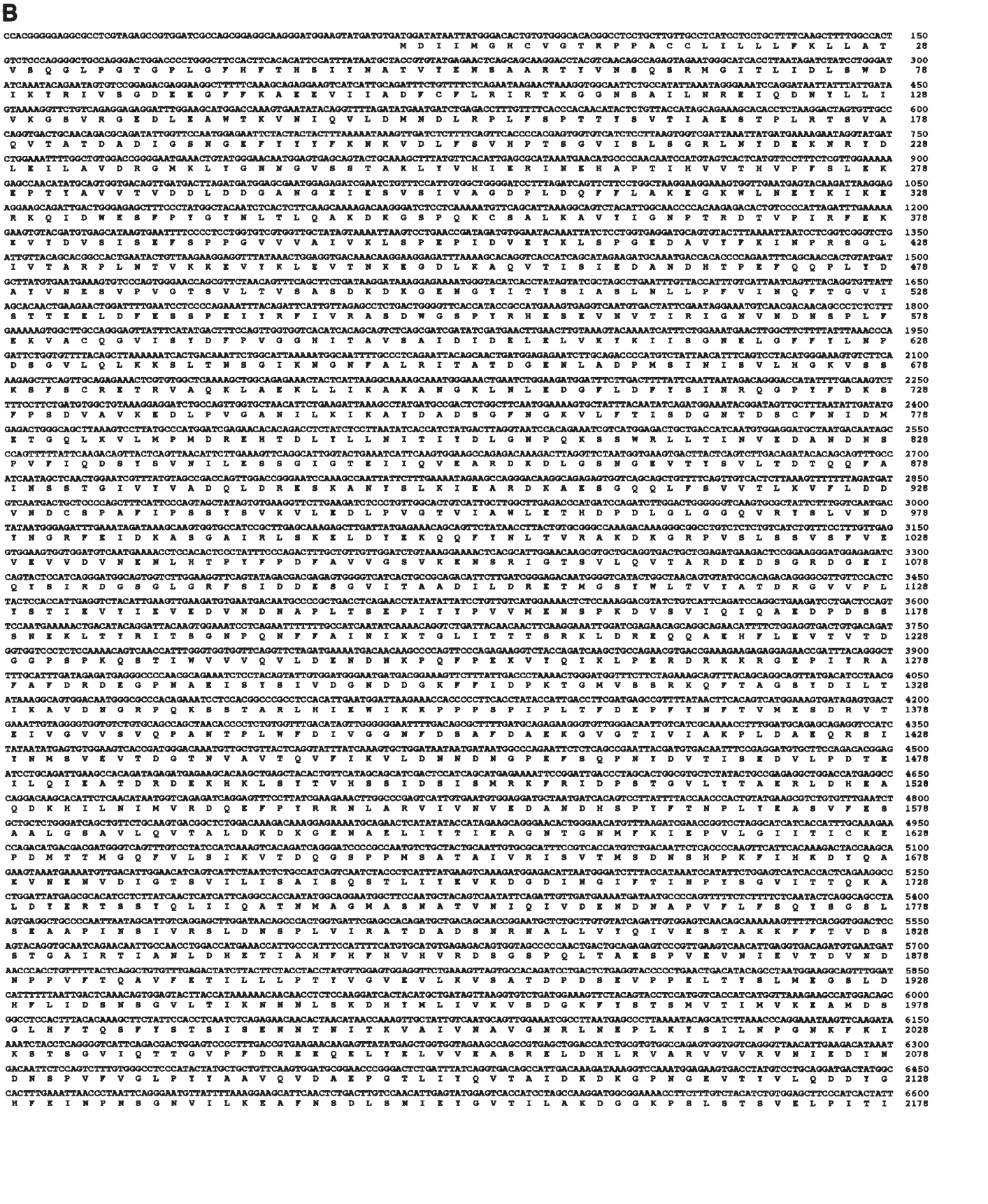
Although extracellular region was relatively well conserved among FAT family members, cytoplasmic region was divergent. Based on the alignment of C-terminal part of FAT family members, cytoplasmic VCSVxPxLP and SDYxS motifs were identified as novel motifs conserved among FAT1, FAT2 and FAT3 orthologs (Fig. 2D).

Expression profile of human FAT family members. *In silico* expression analyses were performed to investigate the

A

Exon No	Nucleotide sequence of human *FAT3* gene around exon - intron boundaries			Exon No	Nucleotide sequence of human *FAT3* gene around exon - intron boundaries		
01		CCACGG------GCAAGG	gtgcgt	14	ccacag	GCATCA------AGACAG	gtgggt
02	ctccag	GATGGA------AGAGTG	gtaagt	15	tcaaag	GGGGTA------ATTTTG	gtaggt
03	tctcag	GGGTCA------AAACAG	gtaagg	16	atgaag	CTAATA------GAACGG	gtaagc
04	acacag	GTCTGA------CTGGAG	gtaagc	17	tggcag	GTGTCT------ATTCAG	gtgaga
05	tttcag	GTGACT------CTAACG	gtaaga	18	atgcag	GAAAAT------GTCCAG	gtatgg
06	gagtag	ATAAAG------TAGTTG	gtaagt	19	ttttag	GCAAAG------GCAATG	gtgagt
07	catcag	GGGGGA------ACTCAG	gtgaga	20	tcacag	GAGGAC------GCTCAG	gtgcag
08	ctacag	GTATTT------ATAATG	gtagga	21	tttcag	GGCACA------CTGAAG	gtaatt
09	ctaaag	GTCAGA------AAGCAG	gtgaga	22	acgcag	ATTGTG------CGGGGG	gtgagt
10	ttttag	GGAACA------TTACAG	gtgagt	23	ccccag	GCTATC------AGTCAC	gtaagt
11	ctgcag	GAGGAA------GATCAG	gtgaga	24	ccgcag	GTGTGA------CTGAGA	gtgagt
12	gtccag	GTTGCA------AAAGTG	gtaagc	25	atgaag	ACAAAG------ACAATG	gtaaga
13	tcacag	GCGAGT------ACATTG	gtaagt	26	ttgcag	CCTATC------TTTTCT	

B



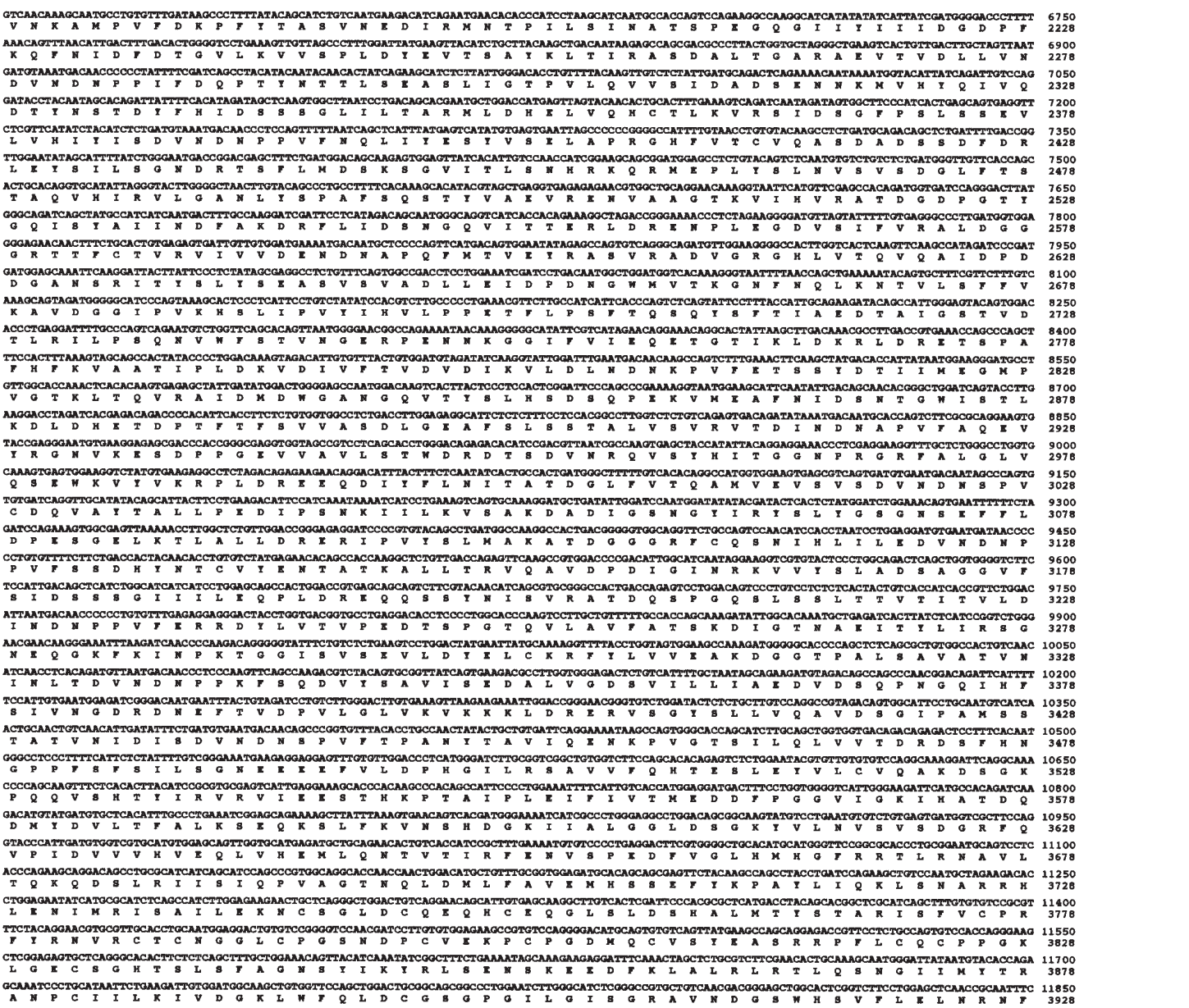


Figure 1. Human FAT3. (A), Exon-intron structure of human *FAT3* gene. (B), Nucleotide and amino-acid sequences of human FAT3 complete CDS. Nucleotides and amino-acid residues are numbered on the right.

expression profile of human *FAT1*, *FAT2*, *FAT3* and *FAT4* mRNAs. *FAT1* mRNA was expressed in embryonic stem (ES) cells, neural tissues, and also in a variety of tumors, such as gastric cancer, pancreatic cancer, colorectal cancer, breast cancer, lung cancer and brain tumors. *FAT2* mRNA was expressed in infant brain, cerebellum, and also in a variety of tumors, such as pancreatic cancer, diffuse type gastric cancer, ovarian cancer, esophageal cancer, skin squamous cell

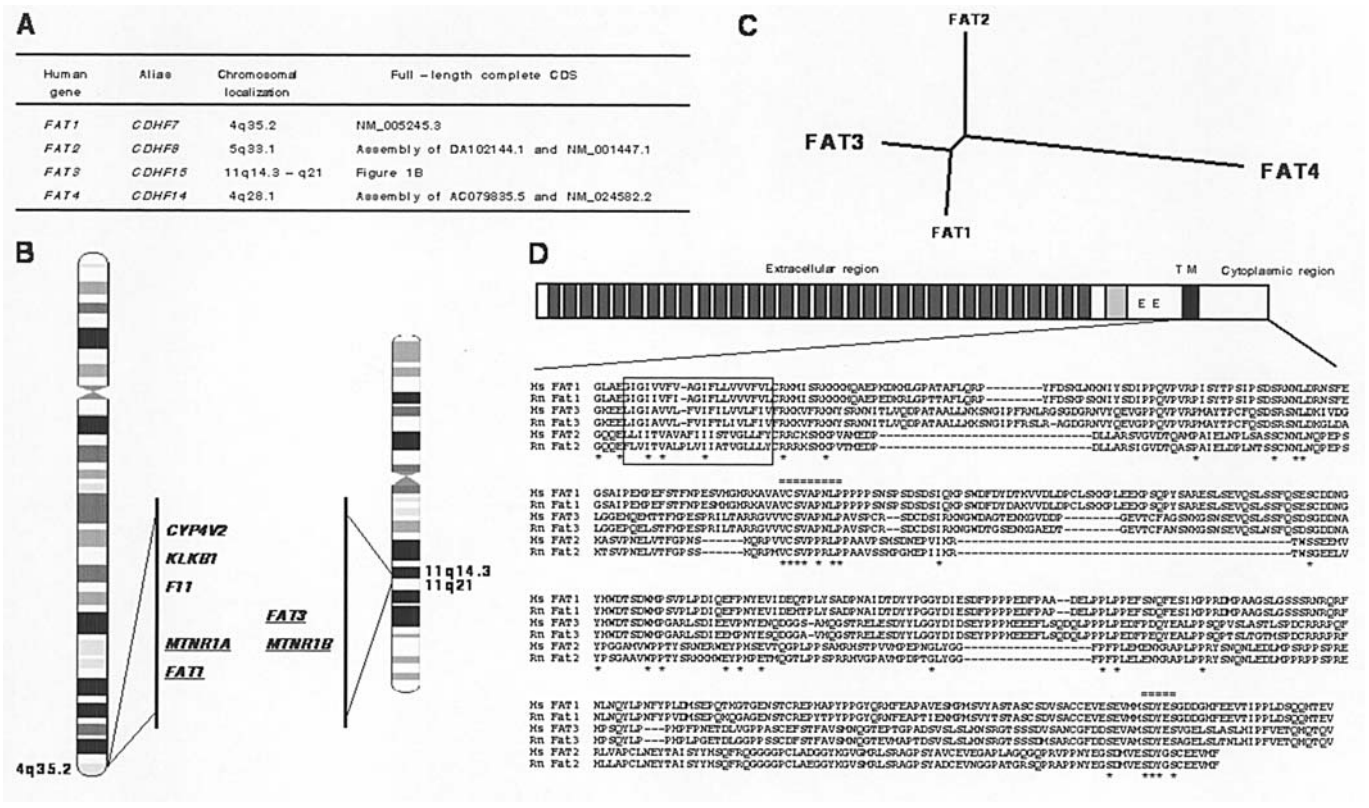


Figure 2. Comparative integromics on FAT family. (A), Human *FAT* gene family. Gene symbol, alias, chromosomal localization and full-length complete coding sequence of *FAT* family genes are listed. (B), Intra-species comparative genomics on *FAT1* and *FAT3* loci. *FAT1-MTNR1A* locus at 4q35.2 and *FAT3-MTNR1B* locus at 11q14.3-q21 are paralogous regions within the human genome. (C), Phylogenetic analysis on human FAT family members. FAT1, FAT2 and FAT3 are divergent from FAT4. (D), Schematic representation of FAT3 and partial alignment of FAT1, FAT2 and FAT3 orthologs. Extracellular region, consisting of Cadherin repeats (dark gray box), Laminin G domain (light gray box) and EGF repeat (E), is well conserved among FAT family members; however cytoplasmic region is divergent. The regions around transmembrane domain and cytoplasmic region of FAT1, FAT2 and FAT3 orthologs are aligned. Hs, human; Rn, rat. Conserved amino-acid residues are shown by asterisks. Two novel cytoplasmic motifs VCSVxPxLP and SDYxS are shown by double overlines.

carcinoma, head and neck cancer. *FAT3* mRNA was expressed in ES cells, primitive neuroectoderm, fetal brain, infant brain, adult neural tissues and prostate. *FAT4* mRNA was expressed in fetal brain, infant brain, brain tumor and colorectal cancer.

Discussion

Complete CDS of human FAT3 and FAT4 were determined for the comparative integromic analyses on FAT family members in this study. *FAT3* gene, consisting of 26 exons, was found to encode a 4557-aa protein with extracellular 33 Cadherin repeats, one LamG domain and two EGF domains (Fig. 1). *FAT4* gene was found to encode a 4924-aa protein with extracellular 34 Cadherin repeats, two LamG domains and three EGF domains. Extracellular region of FAT family members with Cadherin repeats, LamG domain and EGF domains was relatively well conserved; however, cytoplasmic region was divergent. Cytoplasmic VCSVxPxLP and SDYxS motifs were identified as novel motifs conserved among FAT1, FAT2 and FAT3 orthologs (Fig. 2D). Domain architecture comparison and phylogenetic analysis revealed that FAT1, FAT2 and FAR3 were divergent from FAT4.

Intra-species comparative genomics revealed that *FAT1-MTNR1A* locus at 4q35.2 and *FAT3-MTNR1B* locus at 11q14.3-q21 were paralogous regions within the human genome (Fig. 2B). Comparative proteomics analyses revealed that C-terminal PDZ-binding motif was conserved among FAT1 and FAT3 orthologs. Together, these facts indicate that FAT1 and FAT3 are paralogs.

FAT1 mRNA was expressed in ES cells, neural tissues, and a variety of tumors. *FAT2* mRNA was expressed in infant brain, cerebellum, and a variety of tumors. *FAT3* mRNA was expressed in ES cells, primitive neuroectoderm, fetal brain, infant brain, adult neural tissues, and prostate. *FAT4* mRNA was expressed in fetal brain, infant brain, brain tumor and colorectal cancer. FAT family members are implicated in the early embryogenesis and neurogenesis.

The canonical WNT signaling pathway cross-talks with FGF, Notch, Hedgehog and BMP signaling pathways during embryogenesis, chronic persistent inflammation and carcinogenesis (49-56). Because canonical WNT signaling activation leads to transcriptional activation of target genes through the TCF/LEF, ß-catenin, Legless and Pygo complex, TCF/LEF-binding site within the promoter region of human *FAT* family genes were investigated. A single TCF/LEF-binding site was identified within *FAT1* and *FAT2* promoters; however, the relationship between the canonical WNT signaling activation and the expression of *FAT1* or *FAT2* in a variety of human tumors remains to be elucidated.

Drosophila Fat functions as a tumor suppressor (27). Tumor suppressor gene is inactivated due to epigenetic change (CpG hypermethylation) and genetic alterations (mutation or deletion) during multi-stage carcinogenesis (57,58). Epigenetic changes and genetic alterations of *FAT* family genes in a

variety of human tumors should be investigated in the future. FAT family members were revealed to be targets of systems medicine in the fields of oncology and neurology.

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