

Meta-analysis of the expression of the mitosis-related gene Fam83D

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Abstract. The family with sequence similarity 83, member D (Fam83D) encodes a mitotic spindle-associated protein. Its knockdown results in shorter spindles that fail to organize a correct metaphase plate. In this study, we demonstrated that Fam83D is coexpressed with well-known mitotic genes. Pathway analysis results also showed that cell cycle- and mitosis-related pathways are enriched with Fam83D-coexpressed genes. Furthermore, Fam83D is differentially expressed in various types of cancers. The results presented in this study suggest that Fam83D may be an important molecule for mitotic progression and equal segregation of chromosomes. Since the molecules that are involved in these mechanisms are crucial for mitosis as well as carcinogenesis, Fam83D should be considered as a novel regulator of mitosis and a putative carcinogenesis-related gene.

Introduction

The family with sequence similarity 83, member D (Fam83D, also known as CHICA) is located on chromosome 20 of the human genome (1). Fam83D contains an uncharacterized DUF1669 domain in the N terminus. The members of this domain family are found in all eukaryotes and are composed of sequences derived from hypothetical eukaryotic proteins of unknown function. Some members of this domain family are noted as being potential phospholipases, but no evidence from literature or sequence analysis was found to support this (2). Fam83D was identified as a putative mitotic spindle component in a mass spectrometry study (3). Furthermore, another study revealed that although Fam83D is primarily found in the cytoplasm during interphase, during prophase it associates with spindle microtubules, on which it remains throughout metaphase and anaphase (4). The same article also revealed that Fam83D is an interaction partner of chromokinesin KID,

which is required for the generation of polar ejection forces and chromosome congression, and has roles in organizing the metaphase plate (4).

As all the mitotic spindle-associated proteins are involved in the control and regulation of cell proliferation, as well as in carcinogenesis, we further investigated Fam83D using *in silico* tools. Our results revealed that Fam83D is coexpressed with important mitosis-related genes, including Aurora-A, Aurora-B, Plk-1, Plk-4, Cdc20, Cdk1, Nek2, Geminin and CENP family members. All these molecules are well-known genes that have crucial roles in different stages of mitosis, from equal segregation of chromosomes to production of daughter cells. Therefore, we speculate that Fam83D is involved in mitotic processes to regulate cell division. Moreover, our results also demonstrated that this gene is differentially expressed in various cancers in concordance with the previously mentioned coexpression partners.

This is the first study concerning the correlation between Fam83D and cancer. It is well-known that differentially expressed genes in cancers are candidates for diagnostic and prognostic approaches. Therefore, this article suggests that Fam83D is a strong candidate for prognostic and diagnostic approaches and should be investigated further.

Materials and methods

Meta-analysis of Fam83D. To understand the function of Fam83D, coexpression analysis was performed using the Oncomine database (<http://oncomine.org>) as previously described (5,6), but with minor modifications. The threshold was adjusted to P-value <1E-4; fold-change, 2 and gene rank, top 1%. Seventeen different arrays fulfilled these criteria (Table I) and the top 200 coexpressed genes were extracted and filtered to give one representative gene per study (removing duplicates and partial expressed sequence tags). These filtered gene lists were then compared to search for repeatedly coexpressed genes over multiple studies. The frequency cut-off was 6 studies (>30% of 17 studies). This generated a meta-analysis list for Fam83D. The web-based Database for Annotation, Visualization and Integrated Discovery (DAVID; <http://david.abcc.ncifcrf.gov>) was used to assess enriched gene ontology terms within the gene lists produced by the coexpression data analysis (7,8). The results were corrected for multiple testing using the Benjamini and Hochberg false discovery rate (FDR) correction.

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Table I. Arrays used in coexpression analysis.

No.	Array name
1	Lingren Bladder
2	Lee Brain
3	Bittner Breast
4	Richardson Breast 2
5	Meyniel Ovarian
6	Lu Breast
7	HAO Esophagus
8	Anglesio Ovarian
9	Bittner Multicancer
10	Janoueix-Lerosey Brain
11	Lee Brain 2
12	Skrzypczak Colorectal 2
13	Ma Breast2
14	Giordano Adrenal 2
15	Yang Renal
16	Loi Breast 3
17	Bittner Thyroid

Table II. Fam83D-coexpressed genes.

1	ANLN	51	DLGAP5	101	MYBL2
2	APOBEC3B	52	DSCC1	102	NCAPG
3	ATAD2	53	DTL	103	NCAPG2
4	AURKA	54	E2F7	104	NCAPH
5	AURKB	55	E2F8	105	NDC80
6	BIRC5	56	ECT2	106	NEK2
7	BUB1	57	ERCC6L	107	NUF2
8	BUB1B	58	ESPL1	108	NUSAP1
9	C11orf82	59	EXO1	109	IP5
10	C15orf42	60	EZH2	110	PBK
11	C16ORF75	61	FAM54A	111	PHF19
12	CASC5	62	FAM64A	112	PLK1
13	CCNA2	63	FANCI	113	PLK4
14	CCNB1	64	FBXO5	114	POLE2
15	CCNB2	65	FEN1	115	PRC1
16	CDC20	66	FOXM1	116	PTTG1
17	CDC25A	67	GGH	117	RACGAP1
18	CDC25B	68	GIN	118	RAD51
19	CDC25C	69	GINS2 S1	119	RAD54L
20	CDC45	70	GINS4	120	RECQL4
21	CDC6	71	GMNN	121	RFC3
22	CDC7	72	GPSM2	122	RFC4
23	CDCA2	73	GTSE1	123	RNASEH2A
24	CDCA3	74	HELLS	124	RRM2
25	CDCA5	75	HJURP	125	SGOL2
26	CDCA7	76	HMMR	126	SHCBP1
27	CDCA8	77	KIAA0101	127	SLC7A5
28	CDK1	78	KIF11	128	SMC4
29	CDKN3	79	KIF14	129	SPAG5
30	CDT1	80	KIF15	130	SPC24
31	CENPA	81	KIF18B	131	SPC25
32	CENPE	82	KIF20A	132	STIL
33	CENPF	83	KIF23	133	TACC3
34	CENPI	84	KIF2C	134	TFRC
35	CENPJ	85	KIF4A	135	TIMELESS
36	CENPK	86	KIFC1	136	TK1
37	CENPM	87	KPNA2	137	TOP2A
38	CENPN	88	LMNB1	138	TPX2
39	CENPW	89	MAD2L1	139	TRIM59
40	CEP55	90	MASTL	140	TRIP13
41	CHEK1	91	MCM10	141	TROAP
42	CKAP2	92	MCM2	142	TTK
43	CKAP2L	93	MCM4	143	TYMS
44	CKS1B	94	MCM6	144	UBE2C
45	CKS2	95	MCM7	145	UBE2S
46	DBF4	96	MCM8	146	UBE2T
47	DEPDC1	97	MELK	147	UHRF1
48	DEPDC1B	98	MKI67	148	WHSC1
49	DHFR	99	MLF1IP	149	ZNF367
50	DIAPH3	100	MYBL1	150	ZWINT

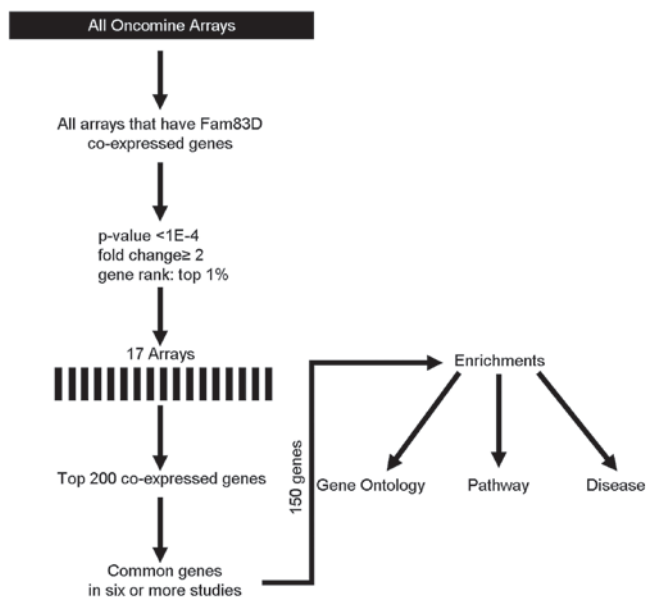


Figure 1. Methodological workflow of Fam83D meta-analysis.

Correlation between Fam83D and cancer. The oncomine cancer microarray database was used to study gene expression of Fam83D in various tumor types and in their normal control tissues. Only the gene transcriptome data from the same study, generated with the same methodology, were used. All gene expression data were log-transformed, median-centered per array, and standard deviation was normalized to one per array (9). Student's t-test was used for differential expression analysis, and only studies with P-value less than 1E-4 and fold-change greater than two were considered.

Table III. Functional enrichment of Fam83D-coexpressed genes.

Term	Count	%	P-value	Fold	FDR
GO:0007049 - Cell cycle	88	59.1	1.90E-74	11.2	1.31E-71
GO:0000279 - M phase	65	43.6	9.23E-68	19.5	3.19E-65
GO:0022403 - Cell cycle phase	69	46.3	3.78E-67	16.5	8.71E-65
GO:0022402 - Cell cycle process	73	49	2.29E-63	12.8	3.96E-61
GO:0000278 - Mitotic cell cycle	62	41.6	1.39E-59	16.5	1.92E-57
GO:0007067 - Mitosis	53	35.6	7.11E-59	23.8	8.19E-57
GO:0000280 - Nuclear division	53	35.6	7.11E-59	23.8	8.19E-57
GO:0000087 - M phase of mitotic cell cycle	53	35.6	2.01E-58	23.4	1.99E-56
GO:0048285 - Organelle fission	53	35.6	7.15E-58	22.9	6.18E-56
GO:0051301 - Cell division	53	35.6	1.10E-51	17.7	8.47E-50
GO:0006260 - DNA replication	31	20.8	8.29E-28	16.1	5.73E-26
GO:0007059 - Chromosome segregation	22	14.8	1.82E-24	26.8	1.14E-22
GO:0006259 - DNA metabolic process	40	26.8	3.13E-24	7.81	1.80E-22
GO:0051726 - Regulation of cell cycle	33	22.1	7.82E-23	9.84	4.16E-21
GO:0007017 - Microtubule-based process	29	19.5	1.31E-21	11.3	6.46E-20
GO:0007051 - Spindle organization	15	10.1	6.83E-18	32.9	3.15E-16
GO:0000070 - Mitotic sister chromatid segregation	14	9.4	1.12E-17	38.4	4.82E-16
GO:0000819 - Sister chromatid segregation	14	9.4	1.71E-17	37.4	6.93E-16
GO:0007346 - Regulation of mitotic cell cycle	21	14.1	3.98E-17	13.6	1.53E-15
GO:0010564 - Regulation of cell cycle process	19	12.8	5.90E-17	16.5	4.00E-15
GO:0000226 - Microtubule cytoskeleton organization	20	13.4	3.60E-16	13.4	1.15E-14
GO:0000075 - Cell cycle checkpoint	15	10.1	3.02E-13	16.3	9.93E-12
GO:0051276 - Chromosome organization	27	18.1	1.98E-12	5.5	6.22E-11
GO:0007126 - Meiosis	13	8.72	2.54E-10	13.1	7.63E-09
GO:0051327 - M phase of meiotic cell cycle	13	8.72	2.54E-10	13.1	7.63E-09
GO:0051321 - Meiotic cell cycle	13	8.72	3.23E-10	12.8	9.29E-09
GO:0007093 - Mitotic cell cycle checkpoint	10	6.71	3.39E-10	23	9.37E-09
GO:0007010 - Cytoskeleton organization	23	15.4	3.87E-10	5.21	1.03E-08
GO:0051329 - Interphase of mitotic cell cycle	13	8.72	4.58E-10	12.5	1.17E-08
GO:0051325 - Interphase	13	8.72	6.43E-10	12.1	1.59E-08
GO:0006974 - Response to DNA damage stimulus	21	14.1	9.27E-10	5.56	2.21E-08
GO:0007088 - Regulation of mitosis	10	6.71	4.08E-09	17.6	9.40E-08
GO:0051783 - Regulation of nuclear division	10	6.71	4.08E-09	17.6	9.40E-08
GO:0006261 - DNA-dependent DNA replication	10	6.71	5.64E-09	17	1.26E-07
GO:0008283 - Cell proliferation	21	14.1	1.34E-08	4.76	2.89E-07
GO:0048015 - Phosphoinositide-mediated signaling	11	7.38	1.75E-08	12.3	3.67E-07
GO:0006323 - DNA packaging	11	7.38	2.71E-07	9.28	5.50E-06
GO:0051640 - Organelle localization	10	6.71	3.45E-07	10.7	6.81E-06
GO:0033554 - Cellular response to stress	21	14.1	9.19E-07	3.66	1.76E-05
GO:0006281 - DNA repair	15	10.1	1.01E-06	5.22	1.88E-05
GO:0007018 - Microtubule-based movement	10	6.71	1.98E-06	8.74	3.61E-05
GO:0033043 - Regulation of organelle organization	11	7.38	6.71E-05	5.01	0.001188

Fold, fold enhancement; FDR, false discovery rate.

Results

Fam83D is coexpressed with genes involved in mitosis. Using the Oncomine cancer microarray database *Fam83D* was searched for coexpressed genes. Fig. 1 indicates the meth-

odological workflow of the meta-analysis and the selected multi-array studies for *Fam83D*. Following meta-analysis, 150 genes were found to be coexpressed in six or more studies (Table II). DAVID was used to perform gene ontology (GO) term enrichment analysis to obtain characteristics of the set

Table IV. Pathway-based enrichment of Fam83D-coexpressed genes.

Term	Count	%	P-value	Fold	FDR
hsa04110: Cell cycle	24	16.1	1.16E-25	20.3	3.24E-24
hsa03030: DNA replication	9	6.04	7.12E-10	26.5	9.97E-09
hsa04114: Oocyte meiosis	12	8.05	2.66E-09	11.6	2.48E-08
hsa04914: Progesterone-mediated oocyte maturation	10	6.71	5.97E-08	12.3	4.18E-07
hsa04115: p53 signaling pathway	6	4.03	3.66E-04	9.35	0.002048

Fold, fold enrichment; FDR, false discovery rate.

Table V. Disease-based enrichment of Fam83D-coexpressed genes.

Term	Count	%	P-value	Fold	FDR
Breast cancer	13	8.7	1.91E-06	4.9	1.39E-04
Colorectal cancer	6	4.0	0.029838	3.2	0.669009

Fold, fold enrichment; FDR, false discovery rate.

of significant genes from our meta-analyses. This analysis provides a list of gene functions, which are overrepresented in a gene set. Analysis of the 150 Fam83D-coexpressed genes with the DAVID functional annotation tool (GOTERM BP FAT) resulted in 181 GO categories (cut-off, $P < 0.05$; count ≥ 2 and fold enrichment > 1.5) (data not shown). To produce a more comprehensive and structured view of the annotation terms, a DAVID clustering analysis under high-stringency conditions was performed, resulting in 42 annotation clusters matching the statistical criteria ($P < 0.0001$, count ≥ 10 and fold enrichment > 1.5) (Table III). Subsequently, the aforementioned DAVID annotation tool was used for identification of putative KEGG pathways associated with Fam83D-coexpressed genes. Consequently, five pathways associated with the cell cycle, mitosis and related signaling pathways were significantly enriched with Fam83D-coexpressed genes ($P < 0.05$ and fold enrichment > 1.5) (Table IV). In addition, DAVID was used for predicting putative diseases that linked with Fam83D-coexpressed genes using the Genetic Association Database. The results revealed that breast and colorectal cancers were significantly enriched with these genes ($P < 0.05$ and fold enrichment > 1.5) (Table V).

Fam83D is differentially expressed in various cancers. We investigated the expression of Fam83D in cancer using publicly available gene expression data from Oncomine (Table VI). Fam83D has been found to be upregulated in various tumors including in breast cancer compared to normal breast (10); in colorectal cancer compared to normal colon or rectum in three independent studies (11-13); in gastric cancer compared to gastric mucosa in two independent studies (14,15); in hepatocellular carcinoma compared to normal liver in two independent studies (16,17); in lung cancer compared to normal lung in two independent studies (18,19) and in vulva intraepithelial neoplasia compared to normal vulva (20).

Table VI. Differential expression of Fam83D in cancer types compared to their normal counterparts, using the Oncomine cancer microarray database.

Type of cancer	Overexpressed	Underexpressed	Ref.
Breast	+		(10)
Cervical	+		(20)
Colorectal	+		(11-13)
Esophageal		+	(22)
Gastric	+		(14,15)
Glioblastoma		+	(21)
Hepatocellular	+		(16,17)
Leukemia		+	(23)
Lung	+		(18,19)

Conversely, downregulation of Fam83D was found in glioblastoma compared to neural stem cells (21); in esophageal cancer compared to normal esophagus (22) and in leukemia compared to peripheral blood mononuclear cells (23).

Discussion

The main function of the cell cycle is to accurately duplicate the entire genome and segregate a copy of each chromosome precisely into two daughter cells. Maintenance of a correct chromosome number is essential for the survival of an organism. Errors in the cell division may lead to loss or gain of chromosomes and consequently to aneuploidy. In mitotically dividing cells, aneuploidy is a hallmark of cancer and many cancer cells are characterized by high rates of chromosomal

instability (CIN). CIN leads to the persistent generation of new chromosomal variations, to tumor progression and to the development of more aggressive phenotypes (24). Centrosomes have important roles in equal segregation of chromosomes through the establishment of bipolar spindle formation during mitosis. Many studies have reported that centrosome-located proteins are involved in the regulation of centrosome organization (25,26). Moreover, it has been demonstrated that deregulation of the centrosome organization machinery is a clear source of centrosome amplification (27). There is a growing line of evidence to suggest that most solid tumors and many hematopoietic malignancies contain cells with centrosome abnormalities (28-30). For example, the centrosomal mitotic kinases Aurora-A, Plk-1, Plk-4 and Nek2 are all Fam83D-coexpressed genes (Table II), involved in multiple mitotic events. These range from centrosome maturation to centrosome separation, spindle formation and cytokinesis, and their deregulation has been linked to centrosome abnormalities and consequently carcinogenesis (31-35). Therefore, all centrosome and bipolar spindle-associated proteins are considered as putative cancer-related molecules. Santamaria *et al* have demonstrated that Fam83D localizes to the mitotic spindle, and Fam83D-depleted cells form shorter spindles and fail to organize a correct metaphase plate (4). In this study, we showed that Fam83D is coexpressed with many centrosome-located and mitosis-related genes, which are involved in normal cell cycle progression as well as in carcinogenesis. Notably, the majority of the coexpressed genes were key molecules for entry into mitosis, mitotic progression and cytokinesis. All these processes are related to centrosome organization and important to the faithful segregation of chromosomes. Therefore, we suggested that Fam83D may be involved in equal segregation of chromosomes during mitosis. In concordance with this hypothesis, our results also revealed that Fam83D is differentially expressed in some cancers that are directly linked to centrosome abnormalities, such as bladder (36), breast (37), lung (38), colorectal (30) or hepatocellular (39) carcinomas and leukemia (40).

In conclusion, we performed a meta-analysis for Fam83D using *in silico* approaches. Our results revealed that this molecule may be important for centrosome organization, mitotic processes and also in carcinogenesis. *In silico* studies support wet-lab approaches to finding new diagnostic, therapeutic and prognostic factors by using various tools, software and large-scale databases. However, the results of *in silico* studies generally need confirmation by lab experiments. Therefore, further investigation of the results presented in this study by experimental approaches may increase our understanding of centrosome organization, mitosis and carcinogenesis.

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