BIOCELL
2013, 37(1): 11-16

ISSN 0327 - 9545
PRINTED IN ARGENTINA

Meta-analysis of the cell cycle related *C12orf48*

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Key words: *C12orf48*, cell cycle, co-expression, gene ontology, oncomine

ABSTRACT: The cell cycle is a conserved process from yeast to mammals and focuses on mechanisms that regulate the timing and frequency of DNA replication and cell division. The temporal and spatial expression of the genes is tightly regulated to ensure accurate replication and transmission of DNA to daughter cells during the cycle. Although the genes involved in interphase are well studied, most of the genes which are involved in mitotic events still remain unidentified. Since, the discovery of mitosis related genes is still incomplete, we performed a co-expression and gene ontology analysis for revealing novel mitosis regulated genes. In this study, we showed that *C12orf48* is co-expressed with well-known mitotic genes. Moreover, it is also co-expressed with the genes that have roles in interphase such as DNA replication. Furthermore, our results showed that *C12orf48* is also differentially expressed in various cancers. Therefore, the results presented in this study suggest that C12orf48 may be an important molecule for both interphase and mitosis. Since, the molecules involved in these mechanisms are crucial for proliferation as well as in carcinogenesis, *C12orf48* should be considered as a novel cell cycle and carcinogenesis related gene.

Introduction

The cell cycle is the conserved process from yeast to mammals and focuses on mechanisms that regulate the timing and frequency of DNA replication and cell division. 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. Proper regulation of this process is crucial to the growth and development of all organisms. Therefore, understanding of the regulation of cell cycle is important to gain knowledge of the molecular mechanisms that control DNA replication and accurate segregation of chromosomes to daughter cells which are characteristically aberrant in cancer cells (Ganem *et al.*, 2007).

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Received: September 10, 2012. Revised version received: October 20, 2012. Accepted: October 27, 2012.

The regulation of cell division relies on two major mechanisms which are phosphorylation and transcription (Delcuve *et al.*, 2008). However, transcriptional regulation is poorly studied compared to phosphorylation dependent regulation of cell division (Delcuve *et al.*, 2008). Understanding the transcriptional regulation of cell division requires identification of the novel genes that are involved in this process. Since the inventory of division related genes is still incomplete, we have undertaken a co-expression analysis to reveal novel genes that are involved in these processes. Previously, we have reported that *Fam83d* is a novel mitosis related gene and is differentially expressed in cancer by using *in silico* approaches (Varisli, 2012). In this study, we performed a similar analysis for *C12orf48* and we identified this molecule as a novel division related gene.

C12orf48, encodes a PARP-1 interacting protein (Piao *et al.*, 2011). Although the molecular function of this protein isn't well understood it was shown that it may be involved in recombination process at replication forks and may have proliferation related roles

(Moldovan *et al.*, 2012). In this study, we report that *C12orf48* is co-expressed with mitosis related genes such as *AurkA*, *AurkB*, *Plk-1*, *Plk-4*, *Cdc20*, *Cdk1*, *Nek2*, *Top2A* and CENP family members which are well known genes that have crucial roles not only in different stages of mitosis but also in equal segregation of chromosomes to daughter cells. We also found that, some of the genes that co-expressed with *C12orf48* are involved in other cell cycle related roles such as DNA replication, in concordance with molecular functions of PARP-1. Moreover, our results also show that this gene is differentially expressed in various cancers in concordance with the functions of above-mentioned co-expression partners.

Differentially expressed genes are candidates for diagnosis of cancer and are prognostic markers. Therefore, this article suggests that C12orf48 is a strong candidate for prognostic and diagnostic approaches in cancer and should be further investigated.

Material and Methods

Meta-analysis of C12orf48

To gain insight into the function of C12orf48, co-expression analysis was performed from Oncomine database (http://oncomine.org) as described previously (Varisli, 2012; Wilson, 2008; Wilson and Giguere, 2008) with minor modifications. Threshold was adjusted as p-value <1E-4, fold change; 2 and gene rank; top 1%. 8 different array fulfilled these criteria (Table 1) and the top 200 co-expressed genes were extracted and filtered to give one representative gene per study (removing duplicates and partial ESTs). These filtered gene lists were then compared for repeating co-expressed genes over multiple studies. The frequency cutoff was 4 studies (≥ 50% of 8 studies). This generated a meta-analysis list for *C12orf48*. 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 co-expression data analysis (Huang da *et al.*, 2009). The results were corrected for multiple testing using Benjamini & Hochberg False Discovery Rate (FDR) correction.

TABLE 1.

The arrays that were used for co-expression analysis

	Array Name
1	Lee Brain
2	Zhan myeloma 2
3	Skrzypczak Colorectal
4	Carrasco Myeloma
5	Chapman Myeloma
6	Giordano Adrenal 2
7	DErrico Gastric
8	Wurmbach Liver

C12orf48 and cancer relationship

Oncomine cancer microarray database was used to study gene expression of *C12orf48* in various tumor types and their normal control tissues. The gene transcriptome data only 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 (Rhodes *et al.*, 2004). Student's t test was used for differential expression analysis, and only studies with P value less than 1E-4 and fold change more than two and gene rank 5% were considered, as described previously (Varisli, 2012).

Results

C12orf48 is co-expressed with genes that are involved in mitosis

Using the Oncomine cancer microarray database *C12orf48* was searched for co-expressing genes. After meta-analysis, 133 genes were found co-expressed in four or more studies (Table 2). DAVID was used to perform GO Term Enrichment analysis to obtain characteristics of the set of significant genes from our meta-analyses. This analysis provides a list of gene functions, which are over-represented in a gene set. Analysis of the 133 *C12orf48* co-expressed genes with the DAVID functional annotation tool (GOTERM BP FAT) resulted 186 GO-categories (cut-off p-value < 0.1, count ≥ 2, Fold enrichment > 1.5) (data not shown). To receive a more comprehensive and structured view of the annotation terms a DAVID clustering analysis under high stringency conditions was performed resulting in 20 annotation clusters matching the statistical criteria (p < 0.0001, count ≥ 20, and fold enrichment > 2.0) (Table

TABLE 2.

C12orf48 co-expressed genes.

1	ANLN	**24**	CDCA5	**47**	DSCC1	**70**	HMMR	**93**	NCAPG2	**116**	STIL
2	ATAD2	**25**	CDCA8	**48**	DTL	**71**	KIAA0101	**94**	NCAPH	**117**	TACC3
3	AURKA	**26**	CDK1	**49**	DTYMK	**72**	KIF11	**95**	NDC80	**118**	TCF19
4	AURKB	**27**	CDKN3	**50**	E2F7	**73**	KIF14	**96**	NEK2	**119**	TIMELESS
5	BARD1	**28**	CDT1	**51**	E2F8	**74**	KIF15	**97**	NUF2	**120**	TK1
6	BIRC5	**29**	CENPA	**52**	ECT2	**75**	KIF18A	**98**	NUSAP1	**121**	TMEM194A
7	BRCA1	**30**	CENPE	**53**	ERCC6L	**76**	KIF18B	**99**	OIP5	**122**	TOP2A
8	BUB1	**31**	CENPF	**54**	ESPL1	**77**	KIF20A	**100**	PBK	**123**	TPX2
9	BUB1B	**32**	CENPH	**55**	EXO1	**78**	KIF23	**101**	PHF19	**124**	TRIP13
10	C11ORF82	**33**	CENPI	**56**	EZH2	**79**	KIF2C	**102**	PLK1	**125**	TTK
11	C1ORF112	**34**	CENPK	**57**	FAM54A	**80**	KIF4A	**103**	PLK4	**126**	TYMS
12	C4ORF46	**35**	CENPM	**58**	FAM83D	**81**	KIFC1	**104**	POLE2	**127**	UBE2C
13	CCDC99	**36**	CENPN	**59**	FANCI	**82**	MAD2L1	**105**	PRC1	**128**	UBE2S
14	CCNA2	**37**	CEP55	**60**	FBXO5	**83**	MCM10	**106**	PTTG1	**129**	UBE2T
15	CCNB1	**38**	CHEK1	**61**	FEN1	**84**	MCM4	**107**	RACGAP1	**130**	UHRF1
16	CCNB2	**39**	CHML	**62**	FOXM1	**85**	MCM6	**108**	RFC4	**131**	WEE1
17	CDC20	**40**	CKAP2L	**63**	GINS1	**86**	MCM7	**109**	RRM2	**132**	ZWILCH
18	CDC25A	**41**	CKS1B	**64**	GINS2	**87**	MELK	**110**	SGOL2	**133**	ZWINT
19	CDC25C	**42**	DEPDC1	**65**	GINS4	**88**	MKI67	**111**	SHCBP1		
20	CDC45	**43**	DEPDC1B	**66**	GPSM2	**89**	MND1	**112**	SKA1		
21	CDC6	**44**	DHFR	**67**	GTSE1	**90**	MYBL2	**113**	SMC4		
22	CDCA2	**45**	DIAPH3	**68**	HELLS	**91**	NCAPD2	**114**	SPC24		
23	CDCA3	**46**	DLGAP5	**69**	HJURP	**92**	NCAPG	**115**	SPC25		

3). Subsequently, the aforementioned DAVID annotation tool was used for identification of putative KEGG pathways associated with *C12orf48* co-expressed genes. Consequently, four pathways which associated with cell cycle and related signaling pathways were significantly enriched with *C12orf48* co-expressed genes ($p < 0.0001$, count ≥ 5 and fold enrichment > 1.5) (Table 4). In addition, DAVID was also used for prediction of putative diseases that are linked with *C12orf48* co-expressed genes using Genetic Association Database. The results revealed that breast and colorectal cancers showed significant enrichment of these genes ($p<0.05$, fold enrichment > 1.5) (Table 5).

C12orf48 is differentially expressed in various cancers

We investigated the expression of *C12orf48* in cancer using publicly available gene expression data using Oncomine (Table 6). *C12orf48* has been found up-regulated in various tumors including breast cancer compared to normal breast (Richardson *et al.*, 2006), in colorectal cancer compared to normal colon or rectum in two independent studies (Sabates-Bellver *et al.*, 2007; Skrzypczak *et al.*, 2010), in hepatocellular carcinoma compared to normal liver (Wurmbach *et al.*, 2007), in lung cancer compared to normal lung (Hou *et al.*, 2010), in nasopharyngeal carcinoma compared to normal nasopharynx (Sengupta *et al.*, 2006), in vulvar intraepithelial neoplasia compared to normal vulva (Santegoets *et al.*, 2007) and in various sarcomas compared to their control normal tissues (Detwiller *et al.*, 2005).

Discussion

The cell division is a complicated cellular process involving extensive functional and structural organiza-

TABLE 3.

Functional enrichment of *C12orf48* co-expressed genes.

Term	Count	%	P-Value	Fold	FDR
cell cycle	86	64.7	1.20E-77	12.2	8.38E-75
M phase	67	50.4	2.68E-75	22.4	9.32E-73
cell cycle phase	69	51.9	1.58E-71	18.3	3.67E-69
Mitosis	58	43.6	5.67E-71	29	9.87E-69
nuclear division	58	43.6	5.67E-71	29	9.87E-69
M phase of mitotic cell cycle	58	43.6	1.82E-70	28.5	2.53E-68
organelle fission	58	43.6	7.53E-70	27.9	8.73E-68
cell cycle process	74	55.6	1.14E-69	14.4	1.13E-67
mitotic cell cycle	64	48.1	1.32E-66	19	1.15E-64
cell division	54	40.6	2.60E-56	20.1	2.01E-54
chromosome segregation	28	21.1	4.42E-36	38	3.08E-34
regulation of cell cycle	32	24.1	3.08E-23	10.6	1.95E-21
microtubule-based process	28	21.1	9.38E-22	12.2	5.44E-20
DNA replication	24	18	7.47E-20	13.9	4.00E-18
regulation of mitotic cell cycle	22	16.5	2.11E-19	15.9	1.05E-17
DNA metabolic process	32	24.1	7.87E-18	6.96	3.65E-16
microtubule cytoskeleton org.	20	15	4.46E-17	15	1.94E-15
chromosome organization	28	21.1	1.70E-14	6.35	6.95E-13
cytoskeleton organization	23	17.3	4.32E-11	5.8	1.67E-09
cell proliferation	22	16.5	2.98E-10	5.55	1.09E-08

Count, Gene counts involved in that cellular process; **%**, % ratio of the genes involved in that process; **Fold**, fold enhancement; **FDR**, false discovery ratio

TABLE 4.

Pathway based enrichment of *C12orf48* co-expressed genes.

Term	Count	%	P-Value	Fold	FDR
Cell cycle	21	15.8	6.30E-23	21.4	1.40E-21
Oocyte meiosis	12	9	3.00E-10	13.9	3.30E-09
Progesterone-mediated oocyte maturation	9	6.8	1.90E-07	13.3	1.40E-06
DNA replication	6	4.5	6.50E-06	21.2	3.50E-05

Count, Gene counts involved in that pathway; **%**, % ratio of the genes involved in that pathway; **Fold**, fold enhancement; **FDR**, false discovery ratio

tions in a sequence of highly orchestrated events. The temporal and spatial expression of the genes is tightly regulated to ensure accurate replication and transmission of DNA to daughter cells during cell cycle. Therefore, the expression of many regulator genes changes during different phases of the cell cycle. Although the genes involved in the interphase are well studied, most of the genes which are involved in mitotic events are still unidentified. Therefore, various experimental or *in silico* approaches have been used to identify the novel mitosis related genes. Recently, we reported *Fam83d* as a novel mitosis related gene (Varisli, 2012) when we performed a co-expression and gene ontology analysis to find unidentified mitotic genes.

C12orf48, encodes a PARP-1 interacting protein (Piao *et al.*, 2011). PARP-1 is a multifunctional protein that is involved in DNA repair, maintenance of genomic stability, replication, transcription, telomere dynamics and apoptosis (Hassa and Hottiger, 2008). This molecule is normally distributed in whole chromatin in the nucleus (Rouleau *et al.*, 2004). Furthermore, it was shown that PARP-1 also associates with mammalian centrosomes in a cell-cycle dependent manner and interacts with the CENP family members and other mitotic spindle checkpoint proteins (Perdoni *et al.*, 2009; Saxena *et al.*, 2002), thus suggesting that PARP- 1 might regulate their function in controlling chromosome segregation and mitosis. The activity of PARP-1 is primarily dependent on its poly(ADP-ribosyl)ation activity. Therefore, the molecules involved in regulation of this activity are probably also involved in all PARP-1 mediated processes. In concordance with this hypothesis we suggested that C12orf48 is probably involved in all PARP-1 dependent mechanisms as this molecule positively regulates the poly(ADP-ribosyl)ation activity of PARP-1 (Piao *et al.*, 2011). In co-expression analysis we have seen that *C12orf48* is co-expressed with cell cycle and replication related genes, in concordance with the cellular functions of PARP-1. Moreover, our results have shown that *C12orf48* is also co-expressed with important mitotic genes, of which many are found in association with centrosome. Since most of the cell cycle and mitosis related genes are also involved in carcinogenesis, we searched expressional changes of *C12orf48* in cancers. In concordance with this hypothesis our results revealed that *C12orf48* is differentially expressed in various cancers which have a direct link with centrosome and mitotic abnormalities such as breast (Lingle *et al.*, 1998), lung (Jung *et al.*, 2007) and colon (Nakajima *et al.*, 2004) cancers. Breast cancer is a good model to study the relationship between cancer and mitotic abnormalities since aneuploidy is common.

TABLE 5.

Disease based enrichment of *C12orf48* co-expressed genes.

Term	Count	%	P-Value	Fold	FDR
breast cancer	12	9	2.13E-06	5.3	1.70E-04
colorectal cancer	6	4.5	1.50E-02	3.8	4.63E-01

Count. Gene counts involved in that disease; **%**. % ratio of the genes involved in that disease; **Fold**. fold enhancement; **FDR**. false discovery ratio

TABLE 6.

Over-expression of *C12orf48* in various cancer types compared to their normal counterparts.

Type	Ref	Fold	P-Value
Breast Ca.	Richardson *et al.*. 2006	2.9	6.27E-10
Colorectal Ca.	Skrzypczak *et al.*. 2010	2.4	6.05E-13
	Sabates-Bellver *et al.*. 2007	2.5	2.28E-8
Liver Ca.	Wurmbach *et al.*. 2007	2.1	6.34E-8
Lung Ca.	Hou *et al.*. 2010	2.9	1.75E-6
Nasopharyngeal Ca.	Sengupta *et al.*. 2006	2.6	1.25E-11
Vulva intra. Neop.	Santegoets *et al.*. 2007	2.3	6.7E-5
Fibrosarcoma	Detwiller *et al.*. 2005	7.9	4.61E-7
Leimyosarcoma	Detwiller *et al.*. 2005	4.3	8.99E-5
Fibrous Histiocytoma	Detwiller *et al.*. 2005	8.5	3.24E-7

Bièche et al., reported that the expression of 49 known mitotic genes was deregulated in breast tumors compared to normal breast tissues (Bieche *et al.*, 2011). Interestingly, our results revealed that most of these genes are co-expressed with *C12orf48*. Therefore, we suggest that C12orf48 may be involved in equal segregation of chromosomes during cell division and may have cell cycle dependent roles like its co-expression partners.

Taken together, we performed a meta-analysis for *C12orf48* using *in silico* approaches. Our results have revealed that this molecule may be important for cell cycle and mitotic events and also in carcinogenesis. Therefore, further investigation of the results presented in this study by experimental approaches may increase our understanding of cell cycle, mitosis and carcinogenesis.

Acknowledgment

The author wish to thank Dr. Syed Muhammad Hamid (Izmir Institute of Technology, Turkey) for the language editing of the manuscript.

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