academicJournals

Vol. 12(26), pp. 4187-4193, 26 June, 2013
DOI: 10.5897/AJB12.434
ISSN 1684-5315 ©2013 Academic Journals
http://www.academicjournals.org/AJB

African Journal of Biotechnology

Full Length Research Paper

Bioinformatics and phylogenetic analysis of human *Tp73* gene

Naureen Aslam Khattak[1], Arslan Sehgal[2] and Asif Mir[2]*

[1]Department of Biochemistry, PMAS-Arid University, Rawalpindi
[2]Bioinformatics and Biotechnology, DES, FBAS International Islamic University, Islamabad, Pakistan.

Accepted 26 April, 2013

The *Tp73* gene encoding p73 protein belongs to the *Tp53* gene family and it functions in the initiation of cell-cycle arrest or apoptosis and also involves in regulating a series of pathways including breast cancer, neuroblastoma and cholorectal cancer. New discoveries about the control and function of p73 are still in progress and it is hoped to develop better diagnostics and therapeutics by exploiting this system. Evolutionary studies are of principal importance in the field of biological research since for a very long time as provided the basis for comparative genomics. The sequence of *Homo sapiens* Tp73, transcript variant-7 mRNA sequence was retrieved from the NCBI in FASTA format and was studied for its relationships and percent similarity within human and others species. Genetic variation among Tp73 found in human beings and other organisms were studied in detail. Phylogenetic analysis and multiple sequence alignment of the human Tp73, transcript variant-7 mRNA sequence through unweighted pair group method with arithmetic mean (UPGMA) was performed which showed its pattern of variations and relationship among different organisms especially with rat, mouse and chimpanzee. This current study will help in modern research strategies through the manipulation and exploitation of p73, as its pathways are promising and one can predict its extensive clinical and biological use in the near future for the human benefit worldwide.

Key words: Tp73, Bioinformatics, phylogenetics analysis, cancer, Tp53.

INTRODUCTION

p73 and p63 are two functional and structural homologs of tumor suppressing transcripting factor p53. The *Tp73* gene encodes p73 protein. The tumor proteins p73 (*Tp73* gene), p63 (Tp63 gene) and p53 (*Tp53* gene) belongs to p53 family. The outcome of sequence identity and sharing of domain architecture similarity with p53, p63 and p73 can form oligomers, responsive genes of transactive p53, DNA binding and mediate apoptosis and cell cycle arrest in response the damage of DNA. It also has been involved in regulating a series of pathways including cancer (Jost et al., 1997; De- Laurenzi et al., 1998; Melino et al., 2004; Keyes et al., 2005; Yu et al., 2011).

p73 (Jost et al., 1997) gene maps to the position of the chromosome at 1p36.1 and this region frequently in numerous tumors including breast cancer, cholorectal cancer and neuroblastoma (Kaghad et al., 1997, reviewed by Ikawa et al., 1999). It is also suggested that gene p73 is a tumor suppresser. p73 is absolutely necessary for neural differentiation and olfactory development, immune system and central nervous system. p73 deficient mice have severe truncations of limb, absence of mammary, lachrymal, skin, slivary glands and teeth (Mills et al., 1999) and complicated defects in the development of central nervous system (Yang and Bielawski, 2000; Pozniak et al., 2000). The pro-survival role of gene p73 during the development of nervous system has been assigned with pre dominant expression of anti apoptotic, ΔNp73 isoforms involved in normal brain development

*Corresponding author. E- mail: asif.mir@iiu.edu.pk.

and sympathetic ganglia. Kaghad et al. (1997) proposed that p73 gene is an imprinted gene and expressed by one gene only. If that gene loss that functional allele then, the cell cannot perform its sufficient functions and cause cancer. Further recent studies show that mono allelic expression of p73 is rare (Nomoto et al., 1998; Yokozaki et al., 1999; Yokomizo et al., 1999; Zaika et al., 1999). Due to splicing, variation occurs which are then translated into many different types of proteins. Mostly, splicing occur at 3' end and form proteins that have different C-terminals. The p73 and p63 genes encode numerous different isoforms protein formed by alternative splicing at C-terminal end of that protein and give rise to six different p73 terminal variants. (ά to ζ) and three p63 variants (ά to γ) expressed in both normal and cancer cells (Kaghad et al., 1997; De-Laurenzi et al., 1998,1999; Ueda et al., 1999). In the field of biological research, phylogenetic study provides the basic information for comparative genomics (Pryer et al., 2002; Doyle and Lucknow, 2003). Many molecular and computational biologists are using and analyzing phylogenetic trees to guide the sampling of taxa for comparative research (Soltis and Soltis, 2003). The current study focused to explore the distribution pattern of genetic variation in p73 gene found in different organisms, including *Homo sapiens*. The study also explores the phylogenetic analysis and comparison of *p73* gene in human, rat, mouse and chimpanzee.

MATERIALS AND METHODS

Sequence retrieval

The sequence of *H. sapiens* (Human) tumor protein p73 (Tp73), transcript variant 7 mRNA was retrieved from the biological database NCBI (http://www.ncbi.nlm.nih.gov) in FASTA format.

Local sequence alignment

BLAST (Altschul et al., 1990) was performed for the human Tp73, transcript variant-7 mRNA sequence retrieved from NCBI to identify its relatives in different organisms including man using the online Geneious 5.5.2 software (http://www.geneious.com). This software takes the data and produces the BLAST table.

Phylogenetic analysis

Phylogenetic analysis of *H. sapiens* tumor protein p73 (Tp73), transcript variant-7 mRNA sequence through unweighted pair group method with arithmetic mean (UPGMA) was carried out using Geneious software. Phylogenetic tree was constructed by the software showing the ancestral relationship among the sequences. The tree gives different clusters showing their relationship with each other. The sequences which lie in the same cluster are closely related.

Phylogenetic analysis of human, rat and chimpanzee was also performed by Geneious software. Multiple sequence alignment (MSA) and similar domain comparison of all these organisms were performed by Geneious, ClustalW, BLAST and Emboss suit comparison tools.

RESULTS

H. sapiens tumor protein p73 (Tp73), transcript variant-7 mRNA was retrieved from the NCBI in FASTA format, with accession number NM-001204191. *H. sapiens* tumor protein p73 (Tp73), transcript variant-7 mRNA sequence was studied for its similarity patterns and BLAST was therefore performed by feeding the data of sequence into the online Geneious 5.5.2 software. After performing BLAST, the software produced BLAST table showing the accession numbers, percent similarity, e-value, etc (Table 1). The sequences having lowest e-value were more closely related while the difference in e-value shows the dissimilarity among them.

It is clear from the results that *H. sapiens* tumor protein p73 (Tp73), transcript variant 12, mRNA (NM_001204188), *H. sapiens* tumor protein p73 (Tp73), transcript variant 8, mRNA (NM_001204184), *H. sapiens* tumor protein p73 (Tp73), transcript variant 10, mRNA (NM_001204186), *H. sapiens* tumor protein p73 (Tp73), transcript variant 3, mRNA (NM_001126241), and *H. sapiens* cDNA FLJ50534 complete cds, were highly similar to Tumor protein p73 (AK295669), *H. sapiens* p73 (Tp73) gene, exon 14, and complete cds (AF079094) and *Homo sapiens* tumor protein p73 (Tp73), RefSeqGene on chromosome 1 (NG_017035) were 100% identical with *H. sapiens* tumor protein p73 (Tp73), transcript variant 7(NM_001204191), *H. sapiens* tumor protein p73 (Tp73), transcript variant 2,4,5,6,9,11, mRNA are also 100% identical with *H. sapiens* tumor protein p73 (Tp73), transcript variant 7(NM_001204191), while PREDICTED: *Anolis carolinensis* tumor protein p73 (Tp73), mRNA (XM_003229773) were the most dissimilar sequences with 82.6% identity (Table 1).

p73 and p63 were closely related and distantly related. p73, p53 and p63 had common domains that is, oligomerization domain (OD), DNA binding domain (DBD). p73 and p63 had Sterile Alpha Module domain (SAM). Phylogenetic analysis of *Tp73* gene of human, rat, mouse and chimpanzee were also performed by Geneious software by UPGMA. Phylogenetic tree shows the more similarity between human and chimpanzee, while mouse sequence was distantly related (Figure 1). Tp73 genes of human, mouse, rat and chimpanzee encoded appropriate proteins. The phylogenetic analysis of these proteins is also performed and showed in Figure 2. During the study, our finding showed that, all the four organisms studied had conserved protein domains. Protein and nucleotide comparison of *Tp73* with *Tp63* and *Tp53* genes and p73 with p63 and p53 was done by ClustalW, Emboss and Geneious. Emboss software showed 51.5% (366/710) identity, 65.4% (464/710) similarity and 14.6% (104/710) gaps in between human full length protein P73 and P63

Table 1. BLAST table of Human p73.

S/N	AN	E_value	Organism	Description	Sequence length	% pairwise Identity
1	NM_001204191	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 7, mRNA	4843	100
2	NM_001204188	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 12, mRNA	4571	100
3	NM_001204184	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 8, mRNA	3468	100
4	NM_001204186	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 10, mRNA	3466	100
5	NM_001126241	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 3, mRNA	3468	100
6	AC196698	0	Rhesus Macaque	Rhesus Macaque BAC CH250-329E22 () complete sequence	1757	90
7	AK305292	0	Pan troglodytes	Pan troglodytes mRNA for tumor protein p73, complete cds, clone: PtsC-58-5_H08	1253	98.5
8	AK302118	0	*Homo sapiens*	*Homo sapiens* cDNA FLJ52358 complete cds, highly similar to Tumor protein p73	1011	99.9
9	AK304784	0	*Homo sapiens*	*Homo sapiens* cDNA FLJ52399 complete cds, highly similar to Tumor protein p73	1233	99.9
10	AK139633	0	*Mus musculus*	*Mus musculus* 2 cells egg cDNA, RIKEN full-length enriched library, clone:B020007D18 product:transformation related protein 73, full insert sequence	1743	85.4
11	AK017412	0	*Mus musculus*	*Mus musculus* 6 days neonate head cDNA, RIKEN full-length enriched library, clone:5430439E07 product:transformation related protein 73, full insert sequence	830	86.1
12	AK295669	0	*Homo sapiens*	*Homo sapiens* cDNA FLJ50534 complete cds, highly similar to Tumor protein p73	715	100
13	XM_003434677	0	PREDICTED: *Canis lupus*	PREDICTED: *Canis lupus familiaris* tumor protein p73, transcript variant 2 (TP73), mRNA	1458	89.0
14	XM_003434676	0	PREDICTED: *Canis lupus*	PREDICTED: *Canis lupus familiaris* tumor protein p73, transcript variant 1 (TP73), mRNA	997	90.7
15	XM_002919424	0	PREDICTED: Ailuropoda melanoleuca	PREDICTED: *Ailuropoda melanoleuca* tumor protein p73-like (LOC100480840), mRNA	1029	88.3
16	XM_001915365	0	PREDICTED: Equus caballus	PREDICTED: *Equus caballus* tumor protein p73 (TP73), mRNA	756	90.6
17	XM_593064	0	PREDICTED: Bos taurus	PREDICTED: *Bos taurus* tumor protein p73 (TP73), mRNA	1017	90.3
18	XM_002694119	0	PREDICTED: Bos taurus	PREDICTED: *Bos taurus* tumor protein p73 (TP73), mRNA	1017	90.3
19	XM_001083217	0	PREDICTED: Macaca mulatta	PREDICTED: *Macaca mulatta* tumor protein p73-like, transcript variant 1 (LOC695164), mRNA	1011	95.8
20	XM_002750200	0	PREDICTED: Callithrix jacchus	PREDICTED: *Callithrix jacchus* tumor protein p73-like (LOC100393670), mRNA	551	93.3
21	XM_003471247	0	PREDICTED: Cavia porcellus	PREDICTED: *Cavia porcellus* transformation related protein 73 (Trp73), mRNA	1003	88.9
22	XM_003229773	0	PREDICTED: Anolis carolinensis	PREDICTED*: Anolis carolinensis* tumor protein p73 (tp73), mRNA	1007	82.6
23	XM_002196490	0	PREDICTED: Taeniopygia guttata	PREDICTED: *Taeniopygia guttata* similar to transformation related protein 73, transcript variant 1 (LOC100220605), mRNA	1031	84.1
24	XM_003307781	0	PREDICTED: Pan troglodytes	PREDICTED: Pan troglodytes tumor protein p73-like (LOC100611345), mRNA	875	98.4
25	BC117251	0	*Homo sapiens*	*Homo sapiens* tumor protein p73, mRNA (cDNA clone MGC:150860 IMAGE:40125802), complete cds	1011	99.9
26	BC117253	0	*Homo sapiens*	*Homo sapiens* tumor protein p73, mRNA (cDNA clone MGC:150862 IMAGE:40125804), complete cds	1011	99.9
27	BC066045	0	Mus musculus	*Mus musculus* transformation related protein 73, mRNA (cDNA clone MGC:86129 IMAGE:6812399), complete cds	1134	86.9
28	HQ258345	0	Synthetic construct	Synthetic construct *Homo sapiens* clone IMAGE:100072654 tumor protein p73 (TP73) gene, encodes complete protein	1011	99.9
29	AY040829	0	*Homo sapiens*	*Homo sapiens* DN p73 gamma (TP73) mRNA, complete cds, alternatively spliced	1283	99.9

Table 1. Contd.

30	AY040827	0	*Homo sapiens*	*Homo sapiens* DN p73 alpha (TP73) 31mRNA, complete cds, alternatively spliced	1283	99.9
31	AY040828	0	*Homo sapiens*	*Homo sapiens* DN p73 beta (TP73) mRNA, complete cds, alternatively spliced	1283	99.9
32	AB055066	0	*Homo sapiens*	*Homo sapiens* hDNp73B mRNA for deltaN p73 beta, complete cds	1283	99.9
33	AB221594	0	*Mus musculus*	*Mus musculus* cDNA pooled tissues:(tissue_type=brain,dev_stage=8-12 days neonate,strain=BALB/c),(tissue_type=testis,dev_stage=adult, strain=C57BL/6J), clone:V01X012I01	1021	87.2
34	Y11416	0	H.sapiens mRNA	H.sapiens mRNA for P73	1011	99.9
35	Y19235	0	*Mus musculus*	*Mus musculus* mRNA for P73 delta-N protein (*p73* gene)	1304	85.3
36	Y19234	0	*Mus musculus*	*Mus musculus* mRNA for P73 alpha protein (*p73* gene)	1021	87.2
37	Y11419	0	C.aethiops mRNA	C.aethiops mRNA for P73	1262	91.7
38	AB055065	0	*Homo sapiens*	*Homo sapiens* hDNp73A mRNA for deltaN p73 alpha, complete cds	1283	99.9
39	NM_001204192	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 13, mRNA	3560	100
40	NM_001108696	0	Rattus norvegicus	Rattus norvegicus tumor protein p73 (Tp73), mRNA	1030	87.4
41	NM_001126330	0	*Mus musculus*	*Mus musculus* transformation related protein 73 (Trp73), transcript variant 2, mRNA	439	86.1
42	NM_011642	0	*Mus musculus*	*Mus musculus* transformation related protein 73 (Trp73), transcript variant 1, mRNA	1021	87.2
43	NM_001126331	0	*Mus musculus*	*Mus musculus* transformation related protein 73 (Trp73), transcript variant 3, mRNA	1743	85.5
44	NM_001126240	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 2, mRNA	3560	100
45	NM_001204189	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 5, mRNA	3466	100
46	NM_001126242	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 4, mRNA	3560	100
47	NM_001204185	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 9, mRNA	3560	100
48	NM_001204190	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 6, mRNA	3468	100
49	NM_001204187	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), transcript variant 11, mRNA	3468	100
50	AC196671	0	Rhesus Macaque	Rhesus Macaque BAC CH250-243C8 () complete sequence	1757	90.0
51	AL136528	0	Human DNA	Human DNA sequence from clone RP5-1092A11 on chromosome 1p36.2-36.33 Contains the 5' end of the gene for a novel protein (FLJ32825), a novel gene (KIAA0495), two novel genes, the TP73 gene for tumor protein p73, the 5' end of the *WDR8* gene for WD repeat domain 8 and five CpG islands, complete sequence	3457	100
52	NG_017035	0	*Homo sapiens*	*Homo sapiens* tumor protein p73 (TP73), RefSeqGene on chromosome 1	3457	100
53	AF079094	0	*Homo sapiens*	*Homo sapiens p73* (TP73) gene, exon 14, and complete cds	396	100

while comparison of p73 with p53 with the same software showed 24.6% identity, 33.5% similarity and 47.6% gaps. Geneious and ClustalW also showed the same results.

DISCUSSION

The evolution of p73 was related with the positive selection at the time when the Artiodactyla and Carnivora ancestors diverged from each other. It is identified that viviparity and homoiothermy first appeared among synapsids. These necessary acquirements of evolution have made essential changes in the genetic regulation of ontogeny, and this, in turn, might have caused adaptive evolution in the family of p73. However, the manifestation of the emergence of homoiothermy and the terrestrial animals demanded a high rate of metabolism that most likely acted as carcinogens. (Pintus and Ivanisenko, 2006).

The proteins of p73 family are transcriptional factors that are involved in the cell signaling pathways. The broad spectrum of their functions includes apoptosis and cell cycle arrest in response to the damage of DNA. It also includes series of metabolic pathways (Pintus and Ivanisenko, 2006). Evolution of the Tp73 was studied in different organisms and adaptive changes were in the sequences. Phylogenetic analysis of *H. sapiens* tumor protein p73 (Tp73), transcript

Figure 1. Phylogenetic analysis of protein sequences.

variant-7 mRNA sequence was performed through the Geneious software using Tamura-Nei Algorithm (Tamura and Nei, 1993). The UPGMA rooted tree diagram of *H. sapiens* tumor protein p73 (Tp73), transcript variant-7 mRNA sequence showed different clusters formation. Organism that originated from same ancestors having same e-value and 100% pair wise identity were placed in same clusters whereas those which are distant from each other were placed in separate clusters.

Majority of human p73 sequences are lay in the same clusters. The genes lay in different distinct clusters while PREDICTED: *Anolis carolinensis* tumor protein p73 (Tp73), mRNA (XM_003229773) was the most distinct one with 82.6% pair wise identity with the *H. sapiens* tumor protein p73.

The p53 family members are modular proteins having basic structure and also share very significant homology at protein and genome levels. Each family member of this gene contains three major domains, a TAD, an oligomerization domain (OD) and a DNA binding domain (DBD). Long C-terminal is present in p73 and p63 but absent in p53. The resoluteness of three dimensional solution structure of C-terminus of p73 and p63 has shown that this region contains protein-protein interaction domain that is sterile alpha motif (SAM). The full length proteins of p73 and p63 also contains transcription inhibition domain (TID) (Chi et al., 1999; Serber et al., 2002; Straub et al., 2009). Phylogenetic analysis of *H. sapiens* tumor protein p73 transcript variant 7 mRNA sequence was performed by Geneious software using Tamura-Nei algorithm (Tamura and Nei, 1993). The protein and nucleotide sequence of human, mouse, rat and chimpanzee were used and formed evolutionary tree among themselves by Geneious software. Protein and nucleotide sequences of these four organisms were used for sequence comparison by EMBOSS, ClustalW and Geneious software.

The UPGMA rooted tree diagram of *H. sapiens* tumor protein p73 (Tp73) transcript variant 7 mRNA showed different clusters formation. Three major clusters are shown in Figure 3. Two clusters are of *H. sapien*s and one is of *Mus Musculus*. Monkey is a bit distantly related with *Mus Musculus*. Monkey and chimpanzee are closely related to each other. Phylogenetic tree of Tp 73 show that *Analis Carolinensis* (XM-003229773) and *Taeniopygia Goutatta* (XM-002196490) are evolved from same ancestor and evolution occur between them long time ago. Protein sequences of human and chimpanzee were more closely related. Mouse and rat p73 sequences were closely related to each other but distantly related with human and chimpanzee as shown in our results (Figure 2). Nucleotide sequences of human and chimpanzee are closely related. Mouse Tp73 gene nucleotide sequence is much more distantly related with human, rat and chimpanzee as shown in Figure 1. All of the genetic trees are drawn by software Geneious 5.5.2 through UPGMA.

p73 protein pairwise sequence comparison with p63 and p53 were performed by ClustalW, EMBOSS and Geneious softwares. BLOSSOM 62 was used in

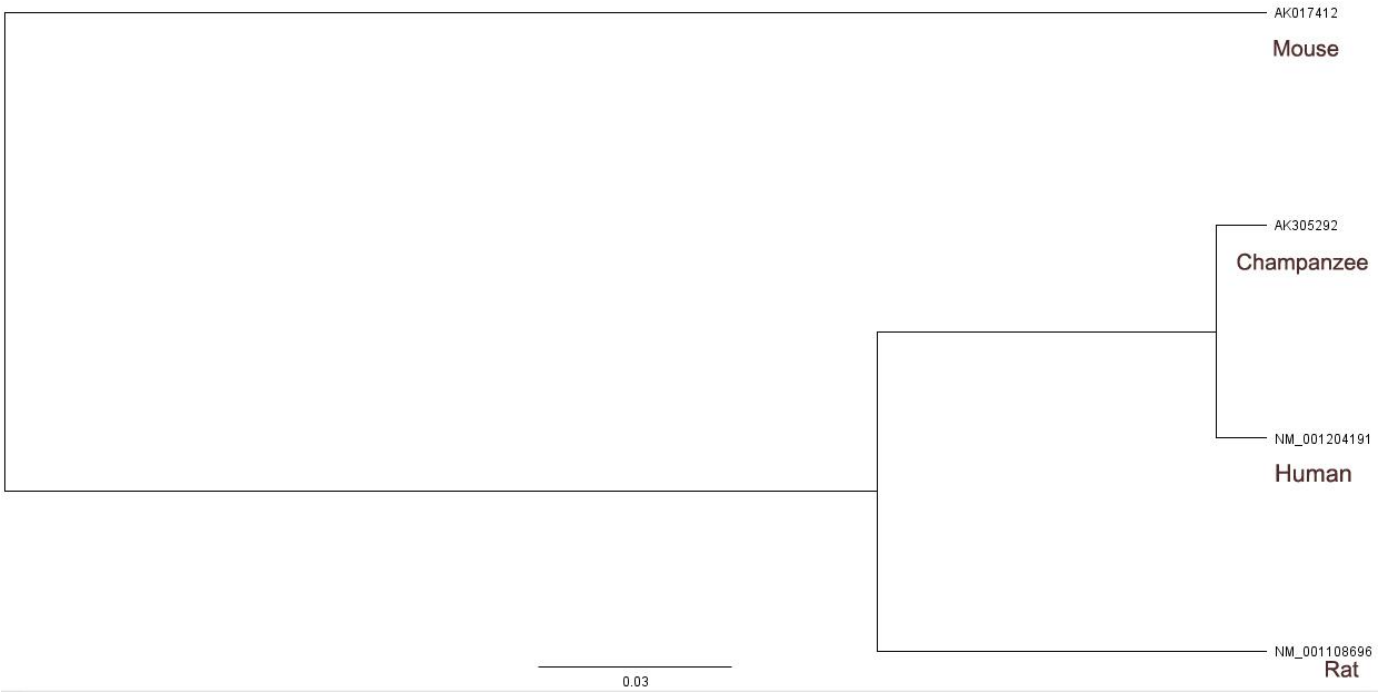

Figure 2. Phylogenetic analysis of nucleotide sequences.

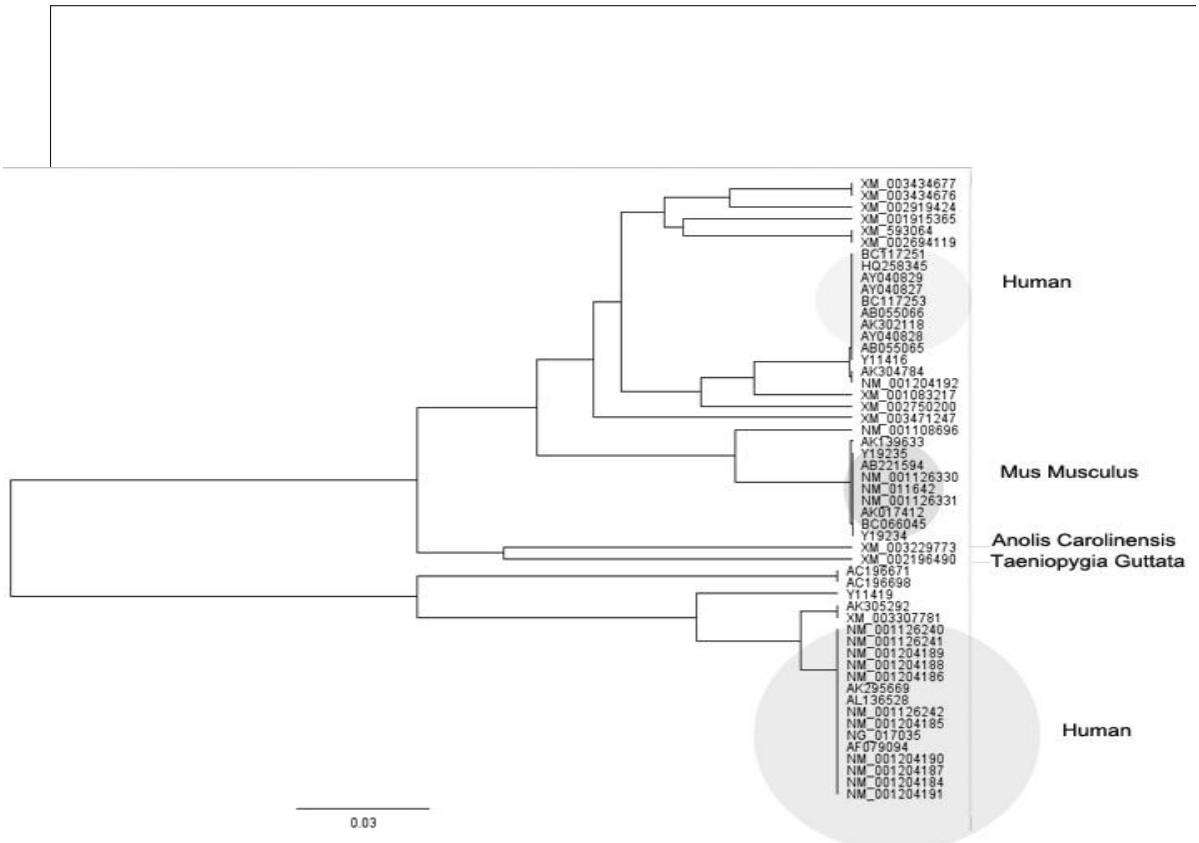

Figure 3. Phylogenetic analysis of Tp73.

ClustalW and EMBOSS as a matrix. *Tp73* gene pairwise sequence comparison with Tp 63 and Tp53 were also performed with same softwares and matrix. ClustalW and EMBOSS software show similarity and identity between protein and nucleotide sequences.

Phylogenetic results and sequence comparison results show that p73 and p63 are closely related. p73 and p53 are distantly related and also considered that p53 is the ancestor of p73 and p63. Tp73 gene was discovered more than one decade before and its many functions are still unknown to us. The published data till now indicate clear participation of p73 in tumorigenesis and TA p73 specially acts as a tumor suppressor. In the era of the last decade, numerous clinical and experimental discoveries were carried out in the field of cancer research. These discoveries lead to the identification of p53 family and *Tp73* genes underlying the diseases. In addition, several crucial and important questions remain unsolved and opened for future work. For example, ΔN p73 in the development and initiation of cancer is still under investigation, both in transgenic and mouse models and tumor samples. Is p73 involved in the senescence of cancer cells? Another question is whether the different C and N-terminals variants of p73 have sole and unique biological functions. The exact function and possible mechanism of mutant p73 remains unresolved and it is very important to understand the poor outcomes in cancer associated with mutant p73. New possible methods of treatment of cancer with mutant p73 make this an important issue for future research and study.

New discoveries about the control and function of p73 are still in progress and it is hoped that better diagnostics and therapeutics be developed by exploiting this system. The current Phylogenetic study of p73 is helpful for researchers and Bioinformaticians for further study and genetic relationship. The current study also supports the modern research for diagnostics and evolutionary history of p73.

REFERENCES

Chi S-W, Ayeda A, Arrowsmith C H (1999). Solution structure of a conserved C-terminal domain of p73 with structural homology to the SAM domain. EMBO J. 18:4438-4445.

De Laurenzi V, Costanzo A, Barcaroli D, Terrinoni A, Falco M, Annicchiarico-Petruzzelli M, Levrero M, Melino G. (1998). Two new p73 splice variants, g and d, with different transcriptional activity. J Exp. Med. 188: 1763-1768.

De Laurenzi VD, Catani MV, Terrinoni A, Corazzari M, Melino G, Costanzo A, Levrero M, Knight RA (1999). Additional complexity in p73: Induction by mitogens in lymphoid cells and identification of two new splicing variants 1´ and z. Cell Death Differ. *6: 389-390.*

Doyle JJ, Luckow MA (2003). The rest of the iceberg. Legume diversity and evolution in a Phylogenetic context. Plant Physiol. 131: 900-910.

Ikawa S, Nakagawara A, Ikawa Y (1999). p53 family genes: structural comparison, expression and mutation. Cell Death Differ. 6:1154-1161.

Jost CA,Marin MC, Kaelin WG Jr (1997). p73 is a simian [correction of human] p53-related protein that can induce apoptosis. Nature 389:191-194.

Kaghad M, Bonnet H, Yang A, Creacier L, Biscan JC, Valent A, Minty A, Chalon P, Lellas JM, Dumont X, Ferrara P, McKeon F, Caput D (1997). Monoallelically expressed gene related to p53 at 1p36, a region frequentely deleted in neuroblastoma and other human cancers. Cell 90:809-819.

Keyes WM, Wu Y, Vogel H, Guo X, Lowe SW, Mills AA (2005). p63 deficiency activates a program of cellular senescence and leads to accelerated aging. Genes Dev. 19:1986-1999.

Melino G, Bernassola F, Ranalli M, Yee K, Zong WX, Corazzari M, Knight RA, Green DR, Thompson C, Vousden KH (2004). p73 Induces apoptosis via PUMA transactivation and Bax mitochondrial translocation. J. Biol. Chem. 279:8076-8083.

Mills AA, Zheng B,Wang XJ, Vogel H, Roop DR, Bradley A (1999). p63 is a p53 homologue required for limb and epidermal morphogenesis. Nature 398:708-713

Nomoto S, Haruki N, Kondo M, Konishi H, Takahashi T, Takahashi T Takahashi T (1998). Search for mutations and examination of allelic expression imbalance of the p73 gene at 1p36. 33 in human lung cancers. Cancer Res. 58:1380-1383.

Pavlopoulos GA, Theodoros GS, Adriano BS, Reinhard S (2010). Areference guide for tree analysis and visualization. BioData Min. 3(1):1.

Pintus SS, Ivanisenko VA (2006) phylogenetic analysisof the p53 AND p63/p73 gene families. Comparative and evolutionary genomics and proteomics

Pozniak CD, Radinovic S, Yang A, McKeon F, Kaplan DR, Miller FD. (2000). An anti-apoptotic role for the p53 familymember, p73, during developmental neuron death. Science 289: 304-306.

Pryer KM, Schneider H, Zimmer EA, Banks JA (2002) Deciding amonggreen plants for whole genome studies. Trends Plant Sci. 7:550-554.

Serber Z, Lai HC, Yang A, Ou HD, Sigal MS, Kelly AE, Darimont BD, Duijf PHG, van Bokhoven H, McKeon F, et al. (2002). AC-terminal inhibitory domain controls the activity of p63 by an intramolecular mechanism. Mol. Cell Biol. 22: 8601-8611.

Soltis DE, Soltis PS (2003). The Role of Phylogenetics in Comparative Genetics. Plant Physiol. 132:1790-1800.

Straub WE, Weber TA, Scha¨fer B, Candi E, Durst F, Ou HD, Rajalingam K, Melino G, Do¨tsch V (2009). The Cterminus of p63 contains multiple regulatory elements with different functions. Cell Death & Disease, in press.

Tamura K, Nei M (1993). Estimation of the number of nucleotidesubstitutions in the control region of mitochondrial DNA in humans and chimpanzees. Mol. Biol. Evol. 10: 512-526.

Ueda Y, Hijikata M, Takagi S, Chiba T, Shimotohno K (1999). New p73 variants with altered C-terminal structures have varied transcriptional activities. Oncogene 18:4993-4998.

Yang A, Walker N, Bronson R, Kaghad M, Oosterwegel M, Bonnin J, Vagner C, Bonnet H, Dikkes P, Sharpe A (2000). P73-deficient mice have neurological, pheromonal and inflammatory defects but lack spontaneous tumours. Nature 404:99-103.

Yang Z, Bielawski JP (2000). Statistical methods for detecting molecular adaptation. Trends Ecol. Evol. 15(12):496-503.

Yokomizo A, Mai M, Tindall DJ, Cheng L, Bostwick DG, Naito S, Smith DI, Liu W (1999). Overexpression of the wild type p73 gene in human bladder cancer. Oncogene 18:1629-1633.

Yokozaki H, Shitara Y, Fujimoto J, Hiyama T, Yasui W, Tahara E (1999). Alterations of p73 preferentially occur in gastric adenocarcinomas with foveolar epithelial phenotype. Int. J. Cancer 83:192-196.

Yu XJ, Fang F, Xie J (2011) Relationship between TP73 polymorphism (G4C14-A4T14) and cancer risk: a meta-analysis based on literatures. Gene 2011 Sep 15. PMID 21672615

Zaika AI, Kovalev S, Marchenko ND, Moll UM (1999). Overexpression of the wild type p73 gene in breast cancer tissues and cell lines. Cancer Res. 59:3257-3263.