BIOINFORMATION
Discovery at the interface of physical and biological sciences

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Volume 8(4)

Insight into *trichomonas vaginalis* genome evolution through metabolic pathways comparison

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Received February 11, 2012; Accepted February 11, 2012; Published February 28, 2012

Abstract:
Trichomonas vaginalis causes the trichomoniasis, in women and urethritis and prostate cancer in men. Its genome draft published by TIGR in 2007 presents many unusual genomic and biochemical features like, exceptionally large genome size, the presence of hydrogenosome, gene duplication, lateral gene transfer mechanism and the presence of miRNA. To understand some of genomic features we have performed a comparative analysis of metabolic pathways of the *T. vaginalis* with other 22 significant common organisms. Enzymes from the biochemical pathways of *T. vaginalis* and other selected organisms were retrieved from the KEGG metabolic pathway database. The metabolic pathways of *T. vaginalis* common in other selected organisms were identified. Total 101 enzymes present in different metabolic pathways of *T. vaginalis* were found to be orthologous by using BLASTP program against the selected organisms. Except two enzymes all identified orthologous enzymes were also identified as paralogous enzymes. Seventy-five of identified enzymes were also identified as essential for the survival of *T. vaginalis*, while 26 as non-essential. The identified essential enzymes also represent as good candidate for novel drug targets. Interestingly, some of the identified orthologous and paralogous enzymes were found playing significant role in the key metabolic activities while others were found playing active role in the process of pathogenesis. The N-acetylneuraminate lyase was analyzed as the candidate of lateral genes transfer. These findings clearly suggest the active participation of lateral gene transfer and gene duplication during evolution of *T. vaginalis* from the enteric to the pathogenic urogenital environment.

Key words: *T. vaginalis*, metabolic pathway, genome evolution, lateral gene transfer.

Background:
Trichomonas vaginalis was first described by Donne in 1836 **[1].** *T. vaginalis* cause of trichomoniasis with an estimate, number one nonviral and second most sexually transmitted disease (STD) **[2].** According to WHO trichomoniasis results women with 250 million infections in the world each year. *T. vaginalis* transmitted mostly by sexual contact it results in bad pregnancy outcome and also increases the chances of HIV infection **[3, 4]**. Infection is treated and cured with metronidazole or tinidazole, and is prescribed to any sexual partner(s) as well because they may be asymptomatic carriers **[5].** The draft genome sequence of the *Trichomonas vaginalis*, a sexually transmitted human pathogen has been published in 2007 **[6].** Its genome presents many unusual genomic and biochemical feature like, an abnormally large genome size of 160 Mb**.** *T. vaginalis* has been evolved to the pathogenic urogenital environment from the enteric environment. Therefore it is important to get insight into the mechanism of genome evolution that enabled *T. vaginalis* in acquiring the adaptations essential for the pathogenic behavior. Essential enzymes are those which are indispensable for the

survival of an organism, and therefore are considered a foundation of life. Therefore the identified orthologous and paralogous enzymes were also analyzed whether they belongs to essential gene category or not. The N-acetylneuraminate lyase was investigated as the candidate of lateral genes transfer. Here, we present a comparative metabolic pathway analysis 1) To identify metabolic pathways in *T. vaginalis* which are common in selected organisms; 2) To identify orthologous and paralogous enzymes among common identified metabolic pathways; 3) To identify the essential enzymes.

Methodology:

The enzymes and metabolic pathways of *T. vaginalis* and other 22 common selected organisms were retrieved from KEGG pathway database **[7].** Metabolic pathways which were common with *T. vaginalis* were identified. Each *T. vaginalis* enzyme in common metabolic pathways are used for the database search against all 22 selected organisms for the identification of orthologous enzymes. The database search was performed with BLAST program **[8].** Using sequence identity more than 40 %, query coverage more than 80 % and having significantly low e value. Paralogous enzymes were identified from selected orthologous enzymes by performing the database search of selected orthologous enzymes against the *T. vaginalis* proteome. The identified orthologous & paralogous enzymes were again screened against the Database of Essential Genes. BLASTP search for N-acetylneuraminate lyase of *T. vaginalis* (Q27818) was performed to select the related sequences in different organisms. Four other N-acetylneuraminate lyase sequences in *Haemophilus parainfluenzae* (E1W1D4), *Pasteurella dagmatis* (C9PLY8), *Haemophilus influenza* (A4N656) and *Aggregatibacter actinomycetemcomitans* (G4B7P9) were selected. The physicochemical properties were calculated by ProtParam, motif prediction by motif search (www.genome.jp/tools/motif/), secondary structures prediction by GOR IV method, predicting Pfam families and conserved domain by (NCBI CD search tool).

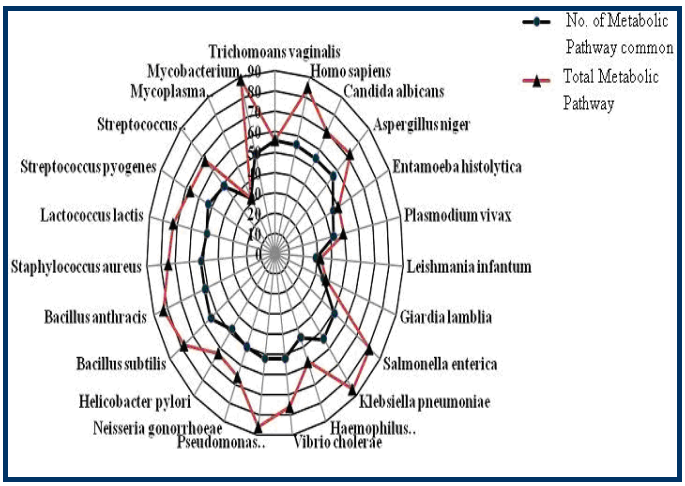

Figure 1: Comparison of metabolic pathway comparison with selected organism

Discussion:

The comparative analysis of *T. vaginalis* metabolic pathways was carried out with the selected 22 common organisms. Most of the selected organisms were having maximum conserved metabolic pathways **(Figure 1)**. We have found that although the selected organisms belong to different kingdoms like Eukaryota, Animalia, Fungi and Bacteria most of the metabolic pathways were common. Some metabolic pathways like Caffeine metabolism, N-Glycan biosynthesis and Glycosaminoglycan degradation were conserved only in few organisms like *Aspergillus niger, Bacillus subtilis, Homo sapiens, Candida albicans, Entamoeba histolytica, Plasmodium vivax, Giardia lamblia* etc, **Table 1 (see supplementary material**). The orthologous and paralogous *T.vaginalis* enzymes which were and found in the selected organism were also identified **Table 2** (**see supplementary material**). In most of the organisms almost all metabolic pathway are conserved, except some organism, like *Entamoeba histolytica, Plasmodium vivax, Salmonella enteric, Haemophilus influenza* and *Helicobacter pylori* where there was difference in the metabolic pathways (Figure 1). Red pattern represents total metabolic pathways present in selected organism while blue pattern represent common metabolic pathway.

T. vaginalis has evolved from enteric environment to the urinary tract environment where it causes the infection. The evolution of a parasitic lifestyle of *T. vaginalis* necessitates adaptations to specialized features essential for pathogenesis **[9].** Examples of common adaptive features include host interaction systems, metabolic pathways that allow the acquisition of nutrients from the host and mechanisms to evade host defenses. Such traits could originate by a process of gradual change, but there are mechanisms that would allow potential parasites to adapt very quickly. One of these mechanisms is lateral gene transfer. Lateral transfer is the process by which genetic information is passed from one genome to an unrelated genome, where it is stably integrated and maintained. There is growing evidence from whole-genome analyses, which concludes this process as an important mechanism in genome evolution **[10].** In the present study we have found total 101 orthologous enzymes **Table 2 (see supplementary material**), present in different organisms. Presence of large number of orthologous proteins across wide range of different organisms indicates the active participation of lateral gene transfer events in the *T. vaginalis* from other genomes. This may have helped *T. vaginalis* in acquiring features required for pathogenicity as lateral transfer could allow a previously harmless organism to rapidly colonize a new environment by acquiring highly specific biochemical functionality by gradual adaptation.

Herein, the important identified orthologous enzymes which are possible of lateral gene transfer and also playing key roles like host interaction systems, metabolic pathways that allow the acquisition of nutrients from the host and mechanisms to evade host defenses, are discussed. TVAG_044970 (N-acetylneuraminate lyase) identified as orthologous enzymes. *N*-acetylneuraminate lyase is an enzyme involved in the metabolism of sialic acids. *N-acetylneuraminate* lyase is an enzyme involved in the metabolism of sialic acids. *N-acetylneuraminate* lyase is the final enzyme in the sialic acid degradative pathway therefore, plays significant role in the sialic acid metabolism. Moreover, this event may represent an important factor in the evolution of parasitism **[11].** The physicochemical properties **Table 3 (see supplementary materials)** and amino acid composition **Table 4 (see supplementary material)** of N-acetylneuraminate lyase in selected organisms was found to be similar with no significant

variations. The percentage of different secondary structures (alpha helix, extended strand & random coil) was also found to be similar (**Figure 2**). Similarly no significant variation was also found in the number of motif, their length and their composition **Table 5 (see supplementary material)**. The Pfam **Table 6 (see supplementary material**) and conserved domain **Table 7 (see supplementary material**) predicted for N-acetylneuraminate lyase in different organisms was also found to be same. From the sequence (physicochemical properties), pattern (motif & conserved domain), Pfam and structural (secondary structures) analysis, it is clear that the N-acetylneuraminate lyase of *T. vaginalis* was very similar with N-acetylneuraminate lyase in other selected organisms (bacteria). It thus supports the role of lateral gene transfer mechanism in the transfer of N-acetylneuraminate lyase from bacterial genome and to the *T. vaginalis* genome **[11].** Similar studies can also be carried out to investigate other identified enzymes as the possible candidate of lateral gene transfer.

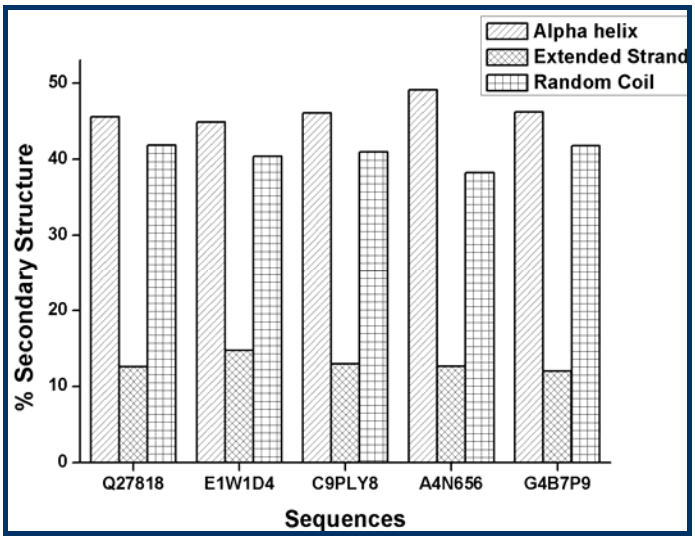

Figure 2: Secondary Structure of N-acetylneuraminate lyase in selected organisms.

TVAG_318670 (AP33), TVAG_318670 (AP33), TVAG_144730 (AP51) and TVAG_183500 (AP51) were identified as orthologous proteins, all are adhesin proteins helping the *T. vaginalis* in adhering the site of infection and colonization of vaginal mucosa. *T. vaginalis* is a mucosal parasite of the urogenital vaginal tract thus it needs pathogenesis of adherence to the cervicovaginal epithelium and get colonization therefore these adhesin proteins are playing key role in host-pathogen interaction. These proteins mediate the interaction of the parasite to the receptor molecules **[12, 13].** Similarly other important enzymes like TVAG_261970 Carbamate kinase and TVAG_387920 cysteine synthase were also identified as orthologous. Carbamate kinase catalyzes the reversible reaction of carbamoyl phosphate, ADP to ATP and ammonium phosphate which is then hydrolyzed to ammonia and carbonate. This enzyme has involved in the different metabolic pathways like purine, arginine, proline, and nitrogen metabolisms of the *T.vaginalis*. These metabolic pathways in trichomonads cause the rapid depletion of arginine in vaginal and seminal fluid with an accompanied production of putrescine. This carbamate kinase pathway has been reported in many prokaryotes and two primitive eukaryotes namely *Giardia lamblia* and *T. vaginalis* **[14].** TVAG_387920 (cysteine synthase) is also identified as orthologous. *T. vaginalis* is an anaerobic protozoan parasite of humans that relies heavily on cysteine, a major redox buffer, as it lacks glutathione. This has been reported that for synthesis of cysteine from sulfide, *T. vaginalis* relies upon cysteine synthase. This parasite enzyme could be an exploitable drug target **[15],** TVAG_474980 (thioredoxin reductase) also identified as orthologous protein. The thioredoxin system is one of the important defense mechanisms in trichomonads as if offers major antioxidant activity in response to environmental changes. Increase in the levels of thioredoxin and thioredoxin peroxidase has been reported. Sequence data indicate that the thioredoxin reductase of trichomonads differs fundamentally in structure from that of its human host and thus may represent as a useful drug target **[16].**

In the present study 75 orthologous enzymes were identified which were found as essential enzymes while 26 enzymes as non-essential **Table 2 (see supplementary material)**. Essential genes constitute a minimal genome, forming a set of functional modules, which play key roles in activities essential for the survival of an organism. Therefore essential gene products also comprise excellent targets for antibacterial drugs. It has been reported that the most recent common ancestor of *T. vaginalis* underwent a population bottleneck during its transition from an enteric environment (the habitat of most trichomonads) to the urogenital tract. During this time, the decreased effectiveness of selection resulted in repeat accumulation and differential gene family expansion. One of the possible mechanisms behind genome expansion is gene duplication. In case of gene duplication, a non functional copy of a gene gets incorporated in the host genome. Many protein families underwent massive duplication **[17].** Pseudogenes are DNA sequences that were derived from a functional copy of a gene but which have acquired mutations that are deleterious to function. This duplicated copy of original functional gene gets incorporated into a new chromosomal location leading to expansion of the existing gene family and hence can lead to genome expansion **[9].** The pseudogenes get expressed in the form of paralogous proteins. In present study we have found that except TVAG_243770 (hypoxanthine phosphoribosyltransferase) and TVAG_248810 (Glutathione peroxidase) all identified orthologous enzymes were also identified as paralogous proteins. In case of *T. vaginalis* it is an interesting finding because the genome draft of *T. vaginalis* reveals exceptionally large genome size of 160 Mb nearly ten times larger than predicted earlier. The genome expansion has been thought to be cause of exceptionally large genome **[17].**

It will be interesting to predict and validate other examples of lateral gene transfer and investigate whether these examples are involved in pathogenesis or not. Due to a lack of supporting data in the literature, about other identified orthologous and paralogous enzymes in *T. vaginalis*, these predicted enzymes reported in this paper are only a "first order guess" for probable candidate of lateral gene transfer mechanism. These enzymes are of particular interest for further characterization to verify the roles and essentiality for *T. vaginalis* survival.

Conclusion:

The comparison of metabolic pathways of *T. vaginalis* with 22 common organism revealed 101 enzymes present in *T. vaginalis* as orthologous while 99 enzymes as paralogous. It is significant

finding as 75 of these enzymes were also identified as essential for the survival of *T. vaginalis*. Identification of orthologous and paralogous enzymes clearly indicates the involvement of lateral gene transfer (indicated by case study of N-acetylneuraminate lyase) and gene duplication events during the genome evolution of *T. vaginalis*. We can conclude that the expansion of genetic material may be due to the adaptations of the *T. vaginalis* during its transition to a urogenital environment from enteric environment (the habitat of most trichomonads).

Acknowledgement:
The authors are grateful to the Sam Higginbottom Institute of Agriculture, Technology and Sciences (Formerly Allahabad Agriculture Institute) (Deemed-to-be-University) Allahabad for providing the facilities and support to complete the present research work.

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Edited by P Kangueane
Citation: Singh *et al*. Bioinformation 8(4): 189-195 (2012)

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Supplementary material:

Table 1: Metabolic pathway common in few organism

S.No.	Organism	Classification	Metabolic pathway
1.	*Trichomonas vaginalis*	Eukaryota	
2.	*Aspergillus niger*	Eukaryota	Caffeine metabolism
3.	*Bacillus subtilis*	Bacteria	
4.	*Homo sapiens*	Animalia	
5.	*Trichomonas vaginalis*	Eukaryota	
6.	*Homo sapiens*	Animalia	
7.	*Candida albicans*	Fungi	
8.	*Aspergillus niger*	Eukaryota	N-Glycan biosynthesis
9.	*Entamoeba histolytica*	Eukaryota	
10.	*Plasmodium vivax*	Eukaryota	
11.	*Giardia lamblia*	Eukaryota	
12.	*Trichomonas vaginalis*	Eukaryota	
13.	*Homo sapiens*	Animalia	Glycosaminoglycan degradation
14.	*Candida albicans*	Fungi	
15.	*Aspergillus niger*	Eukaryota	
16.	*Entamoeba histolytica*	Eukaryota	

Table 2: *T. vaginalis* orthologous genes identified by metabolic pathway comparison

S.No.	Essential Gene with Gene ID	Non-Essential Gene with Gene ID
1.	TVAG_096350	TVAG_193000
2.	TVAG_268050	TVAG_102390
3.	TVAG_113710	TVAG_133030
4.	TVAG_282090	TVAG_292550
5.	TVAG_054830	TVAG_357180
6.	TVAG_043060	TVAG_416300
7.	TVAG_318670	TVAG_038580
8.	TVAG_144730	TVAG_416300
9.	TVAG_183500	TVAG_151830
10.	TVAG_259190	TVAG_135190
11.	TVAG_213710	TVAG_127180
12.	TVAG_061930	TVAG_025910
13.	TVAG_006140	TVAG_109540
14.	TVAG_212020	TVAG_139240
15.	TVAG_272910	TVAG_139240
16.	TVAG_135240	TVAG_151830
17.	TVAG_043060	TVAG_006140
18.	TVAG_413930	TVAG_109540
19.	TVAG_027620	TVAG_348330
20.	TVAG_096350	TVAG_102390
21.	TVAG_213710	TVAG_221830
22.	TVAG_054830	TVAG_318670
23.	TVAG_114530	TVAG_109540
24.	TVAG_479680	TVAG_139240
25.	TVAG_324980	TVAG_151830
26.	TVAG_136250	TVAG_116230
27.	TVAG_243770	
28.	TVAG_293370	
29.	TVAG_373720	
30.	TVAG_261970	
31.	TVAG_430670	
32.	TVAG_379530	
33.	TVAG_591230	
34.	TVAG_591230	
35.	TVAG_125360	
36.	TVAG_050740	
37.	TVAG_020800	
38.	TVAG_134820	
39.	TVAG_011780	
40.	TVAG_478320	
41.	TVAG_099570	
42.	TVAG_387920	
43.	TVAG_252200	
44.	TVAG_210320	
45.	TVAG_405240	
46.	TVAG_147790	

47. TVAG_063510
48. TVAG_368740
49. TVAG_134820
50. TVAG_261970
51. TVAG_020800
52. TVAG_258280
53. TVAG_147790
54. TVAG_474980
55. TVAG_134820
56. TVAG_089600
57. TVAG_248810
58. TVAG_114530
59. TVAG_061930
60. TVAG_389760
61. TVAG_453180
62. TVAG_185930
63. TVAG_044970
64. TVAG_344880
65. TVAG_353000
66. TVAG_187740
67. TVAG_096350
68. TVAG_388650
69. TVAG_009460
70. TVAG_139300
71. TVAG_005950
72. TVAG_239660
73. TVAG_409820
74. TVAG_425810
75. TVAG_224040
76. TVAG_188330

Table 3: Physicochemical properties of N-acetylneuraminate lyase in selected organisms

Physicochemical properties	**Q27818**	**E1W1D4**	**C9PLY8**	**A4N656**	**G4B7P9**
Number of amino acids	318	292	293	293	293
Molecular weight	35083.5	32491.5	32637.6	32637.6	32549.6
Theoretical pI	6.04	5.91	5.47	5.47	5.93
negatively charged	37	36	38	38	38
positively charged	35	33	33	33	35
Extinction coefficients	27975	27850	29340	29340	24995
Estimated half-life	30 hours	30 hours	30 hours	30 hours	30 hours
Instability index	24.48	24.52	29.35	29.35	22.93
Aliphatic index	93.02	97.88	98.87	98.87	97.24
Grand average of hydropathicity	-0.013	-0.080	-0.054	-0.054	-0.071

Table 4: Amino acid composition N-acetylneuraminate lyase in selected organisms.

S. No	Amino Acid	Q27818	E1W1D4	C9PLY8	A4N656	G4B7P9
1.	Ala	10.1	8.2	7.8	7.8	8.5
2.						
3.	Arg	2.8	2.7	2.4	2.4	2.7
4.	Asn	4.7	5.1	4.8	4.8	4.8
5.	Asp	4.4	4.8	4.1	4.1	4.8
6.	Cys	0.9	0.3	0.3	0.3	0.7
7.	Gln	2.5	3.1	2.4	2.4	2.4
8.	Glu	7.2	7.5	8.9	8.9	8.2
9.	Gly	8.2	8.9	8.9	8.9	8.9
10.	His	0.9	1.4	1.0	1.0	1.4
11.	Ile	7.5	7.2	7.5	7.5	7.5
12.	Leu	9.7	11.0	11.	11.3	10.9
13.	Lys	8.2	8.6	8.9	8.9	9.2
14.	Met	3.1	2.7	2.4	2.4	2.7
15.	Phe	5.3	4.8	5.1	5.1	5.1
16.	Pro	2.8	2.7	2.7	2.7	2.4
17.	Ser	5.3	4.1	5.1	5.1	4.1
18.	Thr	5.7	4.8	4.4	4.4	5.1
19.	Trp	0.3	0.3	0.3	0.3	0.3
20.	Tyr	4.7	5.1	5.5	5.5	4.4
21.	Val	5.3	6.5	6.1	6.1	5.8

Table 5: Motifs predicted for N-acetylneuraminate lyase in selected organisms.

Selected Sequences	Motif found	Motif Position	No. of amino acids involved
	GLYVGGSTGENFELSTEE	66..83	17
Q27818	YSIPALTGVSMTADQFGELFENPKIIGVKFT	161..191	30
	IDGLYVGGSTGENFELSTEEKKQIFR	64..89	25
	GLYVGGSTGENFMLSTEE	41..58	17
E1W1D4	YSIPFLTGVNMGIEQFGELYKNPKVLGVKFT	136..166	30
	IDGLYVGGSTGENFMLSTEEKKQIFR	39..64	25
	GLYVGGSTGENFMLSTEE	41..58	17
C9PLY8	YSIPFLTGVNIGVEQFGELYKNPKVLGVKFT	136..166	30
	VDGLYVGGSTGENFMLSTEEKKEIFR	39..64	25
	GLYVGGSTGENFMLSTEE	41..58	17
A4N656	MRDL	1..4	03
	YSIPFLTGVNMGIEQFGELYKNPKVLGVKFT	136..166	30
	VDGLYVGGSTGENFMLSTEEKKEIFR	39..64	25
	GLYVGGSTGENFMLSTEE	41..58	17
G4B7P9	MRDL	1..4	03
	YSIPFLTGVNMGIEQFGELYKNPKVLGVKFT	136..166	30
	VDGLYVGGSTGENFMLSTEEKKQIFR	39..64	25

Table 6: Pfam predicted for N-acetylneuraminate lyase in selected organisms

S.No.	Protein	HMM Accession	HMM name	HMM type	Clan
1.	Q27818	PF00701.17	DHDPS	Domain	1 CL0036
2.	E1W1D4	PF00701.17	DHDPS	Domain	1 CL0036
3.	C9PLY8	PF00701.17	DHDPS	Domain	1 CL0036
4.	A4N656	PF00701.17	DHDPS	Domain	1 CL0036
5.	G4B7P9	PF00701.17	DHDPS	Domain	1 CL0036

Table 7: Conserved domain predicted for N-acetylneuraminate lyase in selected organisms

Query	Hit type	Accession	Short name	Superfamily
Q27818	specific	cd00954	NAL	cl09108
	superfamily	cl09108	TIM_phosphate_binding superfamily	-
	multi-dom	TIGR00683	nanA	-
QE1W1D4	specific	cd00954	NAL	cl09108
	superfamily	cl09108	TIM_phosphate_binding superfamily	-
	multi-dom	TIGR00683	nanA	-
C9PLY8	specific	cd00954	NAL	cl09108
	superfamily	cl09108	TIM_phosphate_binding superfamily	-
	multi-dom	TIGR00683	nanA	-
A4N656	specific	cd00954	NAL	cl09108
	superfamily	cl09108	TIM_phosphate_binding superfamily	-
	multi-dom	TIGR00683	nanA	-
G4B7P9	specific	cd00954	NAL	cl09108
	superfamily	cl09108	TIM_phosphate_binding superfamily	-
	multi-dom	TIGR00683	nanA	-