

## Genomic Analysis and comparative genomics in reference to cystic fibrosis, sickle cell and Alzheimer's diseases.

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**Abstract:** Increasing the activity of defective cystic fibrosis transmembranes conductance regulator (CFTR) protein is a potential treatment for cystic fibrosis. The life expectancy of people with cystic fibrosis (CF), a lethal inherited disease, has been greatly extended by advances in therapy. Currently, there are a number of potential drugs for treatment of CF lung disease in clinical trials. These therapies are targeted at all points in the pathogenesis of lung disease, from gene transfer to drugs that treat mucus, infection and inflammation in the airways. An exciting development is that of modulation of the abnormal protein that causes CF, the cystic fibrosis transmembrane conductance regulator (CFTR), where drugs are targeted at specific defects in CFTR transcription, processing or functioning. A number of antibacterial agents formulated for inhalation are at various stages of study or newly approved, which should improve options for chronic management of airway infection. Cystic fibrosis (CF) is a pleiotropic disease, originating from mutations in the CF transmembrane conductance regulator (CFTR). Both higher adherence to a Mediterranean-type diet and more physical activity have been independently associated with lower Alzheimer disease (AD) risk. Therefore comparative genomics analysis of these diseases is done. In this context Exons and CNS were observed in all three sequences. This paper provides information meant to increase an understanding of the public-health impact of cystic fibrosis, sickle cell and Alzheimer's diseases including incidence and prevalence, mortality, lifetime risks, costs, and impact on family caregivers.

**Keywords:** Fibrosis Transmembrane Conductance Regulator (CFTR) protein, Pleiotropic disease, Alzheimer disease (AD) and Comparative Genomics.

### Introduction:

Genomics is a discipline in genetics concerned with the study of the genomes of organisms. The field includes efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping. The field also includes studies of intra genomic phenomena such as heterosis, epistasis, pleiotropy and other interactions between loci and alleles within the genome. There are two types of genomics-Structural and Functional genomics. Cystic fibrosis is an inherited disease of your secretory glands, including the glands that make mucus and sweat. "Inherited" means that the disease is passed through the genes from parents to children. People who have cystic fibrosis inherit two faulty cystic fibrosis genes—one from each parent. The parents likely don't have the disease themselves. [1] Cystic fibrosis mostly affects the lungs, pancreas, liver, intestines, sinuses, and sex organs. The symptoms of cystic fibrosis vary from person to person and over time. Sometimes you will have few symptoms. CFTR conducts thiocyanate (SCN<sup>-</sup>) ions and it is important because, in several ways, they can limit potentially harmful accumulations of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and hypochlorite (OCI<sup>-</sup>). Oxidation of SCN<sup>-</sup> to hypothiocyanite (OSCN<sup>-</sup>), consumes H<sub>2</sub>O<sub>2</sub>. Second, SCN<sup>-</sup> even at low concentrations competes effectively with Cl<sup>-</sup> for myeloperoxidase (MPO) (which is released by white blood cells), thus limiting OCI<sup>-</sup> production by the enzyme. Third, SCN<sup>-</sup> can rapidly reduce OCI<sup>-</sup> without catalysis. It shows that SCN<sup>-</sup> protect a lung cell line from injuries caused by H<sub>2</sub>O<sub>2</sub>; and that SCN<sup>-</sup> protects from OCI<sup>-</sup> made by MPO. BCL11A serves as a barrier to HbF reactivation by known HbF inducing agents. Inactivation of BCL11A in SCD transgenic mice corrects the hematologic and pathologic defects associated with SCD through high-level pan cellular HbF induction. Thus, interference with HbF silencing by manipulation of a single target protein is sufficient to reverse SCD. [2] Other times, your symptoms may become more severe. Sickle cell disease is an inherited blood disorder that affects nearly 100,000 people in the United States. Red blood cells contain hemoglobin, a protein

that carries oxygen in the blood. Normal red blood cells are round and flexible, which enables them to travel through small blood vessels to deliver oxygen to all parts of the body. <sup>[3]</sup> Alzheimer's disease is an irreversible, progressive brain disease. It is characterized by the development of amyloid plaques and neurofibrillary tangles, the loss of connections between nerve cells, or neurons, in the brain, and the death of these nerve cells. There are two types of Alzheimer's—early-onset and late-onset. Both types have a genetic component. <sup>[4]</sup>

### Methods:

1. Sequence Retrieval from NCBI: Sequence details of the target gene for cystic fibrosis are retrieved from NCBI.
2. Similarity search is performed using BLAST.
3. The sequence of gene is saved in FASTA format for further use in comparison.
4. Genes from other diseases are selected so that it can be compared with gene causing cystic fibrosis using comparative tools. Alzheimer's disease and sickle cell disease are chosen and their sequence details of target gene are retrieved from NCBI.
5. Alzheimer's disease: gene sequence is retrieved from NCBI.
6. Gene sequence is saved in FASTA format for further use.
7. Sickle cell Disease: gene sequence is retrieved from NCBI.
8. Gene sequence is saved in FASTA format.
9. Now, with these sequences in FASTA format, comparison is done using tools.

### Results:

T-COFFEE: Result of T-Coffee tool which is a multiple sequence alignment program which allows us to combine results obtained with several alignment methods, is shown below. First sequence is entered or pasted in any supported format, then it is submitted to get results of comparison.

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### T-Coffee Multiple Sequence Alignment

EBI > Tools > Multiple Sequence Alignment > T-Coffee

#### T-Coffee - Multiple Sequence Alignment

T-Coffee is a multiple sequence alignment program. Its main characteristic is that it will allow you to combine results obtained with several alignment methods.

**Use this tool**

- Unable to read sequence from input file. Please check your input.

**STEP 1 - Enter your input sequences**

Enter or paste a set of sequences in any supported format:

```
>gi|90421312|ref|NM_000492.3| Homo sapiens cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) (CFTR), mRNA
AATTGGAAAGCAAATGACATCACAGCAGGTCAGAGAAAAAGGGTTGAGCGGCAGCCACCCAGAGTAGTAG
G
TCTTTGGCATTAGGAGCTTGAGCCAGACGGCCCTAGCAGGGACCCCAGCGCCGAGAGACCATGCAGAG
G
GTCGCCCTTGGAAGGCGGAGCGTTGTCTCCAAACTTTTTTTCAGCTGGACCAGACC&AATTTTGAGGAA
```

Or upload a file:

**STEP 2 - Set your Parameters**

The default settings will fulfill the needs of most users and, for that reason, are not visible.

(Click here, if you want to view or change the default settings.)

**STEP 3 - Submit your job**

Be notified by email (Tick this box if you want to be notified by email when the results are available)

Result is obtained as follows, where red color of bases shows the sequence similarity

```

T-COFFEE, Version 8.93 (Thu Aug 5 18:09:23 CEST 2010)
Cedric Notredame
CPU TIME: 0 sec.
SCORE=33
*
BAD AVG GOOD
*
gi|166795291|re : 35
gi|28302128|ref : 19
gi|90421312|ref : 35
cons : 33

gi|166795291|re AA---AA---ACTGCCATCACTG-----
gi|28302128|ref ---A-----CA-----
gi|90421312|ref AATTGGAAGCAAATG-ACATCACAGCAGGTCAG
cons          *      **

gi|166795291|re GGGAAAAGAATTT-----A-TTATGCAAAGCT
gi|28302128|ref -----TTT-----
gi|90421312|ref AGAAAAAGGGTTGAGCGGCCAGGCACCCAGAGTA
cons          **

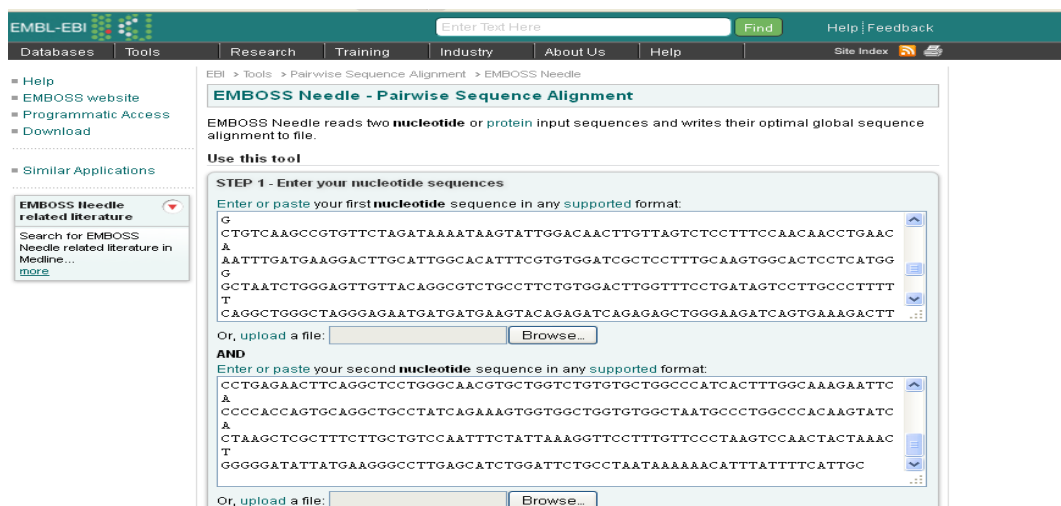
gi|166795291|re -----TCAACGCTATTACAGTT-----TAGA
gi|28302128|ref -----GCTT-----
gi|90421312|ref GTAGGTCCTTTGGCATTAGGAGCTTGAGCCAGA
cons          * *

gi|166795291|re CT---TTGTAGCTATTGAAG-G-CTGA-----
gi|28302128|ref ---CTGA-----
gi|90421312|ref CGGCCCTAGCAGGGACCCAGCGCCGAGAGAC

```

T-Coffee result in colour format is shown below.

PAIRWISE SEQUENCE ALIGNMENT-EMBOSS NEEDLE: It is used to identify regions of similarity that may indicate functional, structural or evolutionary relationships between two biological sequences. Result of EMBOSS Needle are as follows. Sequence is entered and submitted.



Result of EMBOSS Needle of sequence of Alzheimer's disease and Cystic fibrosis.

```
# Score: 911.0
#
#
#-----
NG_007376.1      1  AAAAACTGCCCATCACTGGGAAAAGAATTTTATTATGCAAAGTTCAAC      50
NM_000492.3      1  -----                                                    0
NG_007376.1      51 GCTATTTACAGTTTAGACTTTTGTAGCTATTGAAGGCTGACATTGAGATA      100
NM_000492.3      1  -----AATTG-----                                          5
NG_007376.1     101 AAGAAGTTAAT--CATGTCCTTCTGTCTTGGAGGAGT-----AGAAAAGA      143
NM_000492.3      6  --GAAGCAAATGCATCAC-----AGCAGGTCAGAGAAAAAGG           41
NG_007376.1     144 GATGA---GAATGAATACA-ATTCAGGATCTACTTCTGGTCTTTG--ATG      187
NM_000492.3     42 GTTGAGCGGCAGGCACCAGAGT-AGTA-----GGTCTTTGGCATT        81
NG_007376.1     188 AGGAGTTAG----CACACGGTCTGGGAG-----GAAAAGAC           219
NM_000492.3     82 AGGAGCTTGAGCCAGACGGCCCTAGCAGGGACCCAGCGCCCGAGAGAC      131
NG_007376.1     220 -----AGGT-----TAAGAGGCATGTG-----AAACTCT---      243
NM_000492.3     132 CATGCAGAGGTCGCCCTCTGGAAAAGGCCAGCGTTGTCTCCAAACTTTTTT    181
NG_007376.1     244 -----CAA-----ATAC-GTCACTGCCTCTGC           264
NM_000492.3     182 TCAGCTGGACCAGACCAATTTTGAAGAAAGGATACAG--ACAGCGCTGG      229
NG_007376.1     265 CAACGT---ACATGATACCCAGCAA-----GCTCAC-           292
NM_000492.3     230 AATTGTGACACAT-ATAC---CAAATCCCTTCTGTTGATTCTGCTGACA      274
NG_007376.1     293 ---ATCTTCA---TGGAA--AGCATGG-----              311
NM_000492.3     275 ATCTATCTGAAAAATTGAAAAGAGAATGGGATAGAGAGCTGGCTTCAAAG    324
```

Here, ----- represents gaps and dot will represent the mismatch of the sequences whereas lines between two sequences shows the similarity. In the shown figure number of similar bases are 145. Mentioned figure shows that there are 41 mismatches. Result of EMBOSS Needle for the sequence of Sickle cell disease and Alzheimer's disease.

```

# Score: 571.5
#
#
#=====
NM_000518.4      1 ----- 0
NG_007376.1     1 AAAAACTGCCCATCACTGGGAAAAAGAATTTTATTATGCAAAGCTTCAAC 50
NM_000518.4      1 ----- 0
NG_007376.1     51 GCTATTTACAGTTTACACTTTTGTAGCTATTGAAGGCTGACATTGAGATA 100
NM_000518.4      1 ----- 0
NG_007376.1     101 AAGAAAGTTAATCATGTCTTCTTCTTGGAGGAGGTAGAAAAGAGATGAGA 150
NM_000518.4      1 ----- 0
NG_007376.1     151 ATGAATACAATTGAGGATCTACTTCTGTGCTTTTGTAGGAGGTTAGCACA 200
NM_000518.4      1 ----- 0
NG_007376.1     201 CGGTTCTGGGAGGAAACACAGGTTAAGAGGCATGTGAAACTCTCAAATAC 250
NM_000518.4      1 ---ACATTGCTTCTGACACAACCTGTGTTCA-----CTAGCAACCTCAA 41
NG_007376.1     251 GTCAC---TGCCTCTG---CCAAC---GTACATGATACCAGCAAGCTCAC 292
NM_000518.4      42 A----CA--GACACCATGGT----GCATCTGACTCTGAGGAGAAGTCT 80
NG_007376.1     293 ATCTTCATGGAAGCATGGTAATTCCCAAC--ACTACCG---GAAATCT 336
NM_000518.4      81 GCCGTTACTGCCCTGTGGGGCAAGG-----TCAACCTGGATGA 118
NG_007376.1     337 G-----GAGTGGCTAAGTAATCCATATATTCAACCAGGAAGC 373
NM_000518.4     119 AG-----TTGGTGTGAGGCCCTGGGCAGGCTGCTGCT----- 151
NG_007376.1     374 AGCTAAAGAAATATT---CTAATTACCTAGGAAGTTCTGATTTCAAA 419


```

Here, ---- represents gaps and dots represents the mismatch whereas line between the two sequences represents the similarity between the sequences. In the shown figure there are 89 similar bases. Mentioned figure shows that there are 31 mismatches.

CLUSTALW2: It is a general purpose multiple sequence alignment program for DNA or proteins. To compare the sequences, sequences are first submitted in supportable form as shown below.



After submission of sequences, one link is obtained through which we can access the comparison results.


Your job is currently running...  
please be patient

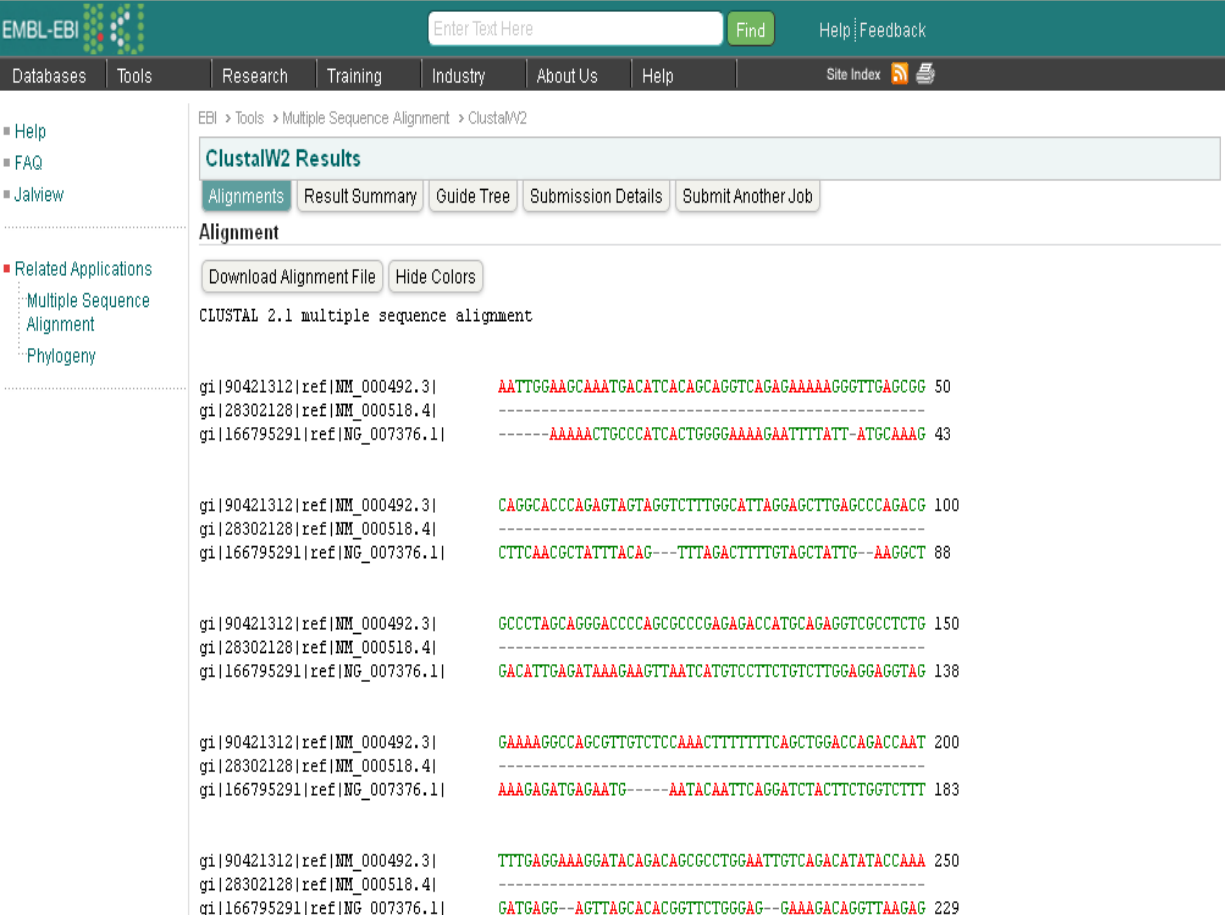
**The result of your job will appear in this browser window**

Your Job output: [toolresult.embl-ebi.org/tool=clustalw2&jobid=clustalw2-I20120302-065139-0015-66526666-oy](http://toolresult.embl-ebi.org/tool=clustalw2&jobid=clustalw2-I20120302-065139-0015-66526666-oy)

**Please note the following**

- You may press Shift+Refresh or Reload on your browser at any time to check if results are ready. Should this window go blank please press the Shift+Refresh or Reload button on your browser.
- You may bookmark this page to view your results later if you wish.
- Results are stored for 7 days.

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EBI > Tools > Multiple Sequence Alignment > ClustalW2

### ClustalW2 Results

Alignments | Result Summary | Guide Tree | Submission Details | Submit Another Job

#### Alignment

Download Alignment File | Hide Colors

CLUSTAL 2.1 multiple sequence alignment

```

gi|90421312|ref|NM_000492.3|      AATGGGAAGCAAATGACATCACAGCAGGTCAGAGAAAAAGGGTTGACGGG 50
gi|28302128|ref|NM_000518.4|      -----
gi|166795291|ref|NG_007376.1|      -----AAAAACTGCCCATCACTGGGGAAAAAATTTTATT-ATGCAAAAG 43

gi|90421312|ref|NM_000492.3|      CAGGCACCCAGAGTACTAGGTTCTTTGGCATTAGGAGCTTGAGCCCAAGC 100
gi|28302128|ref|NM_000518.4|      -----
gi|166795291|ref|NG_007376.1|      CTTCAACGGCTATTTACAG---TTTACTTTTGTAGCTATTG--AAGGCT 88

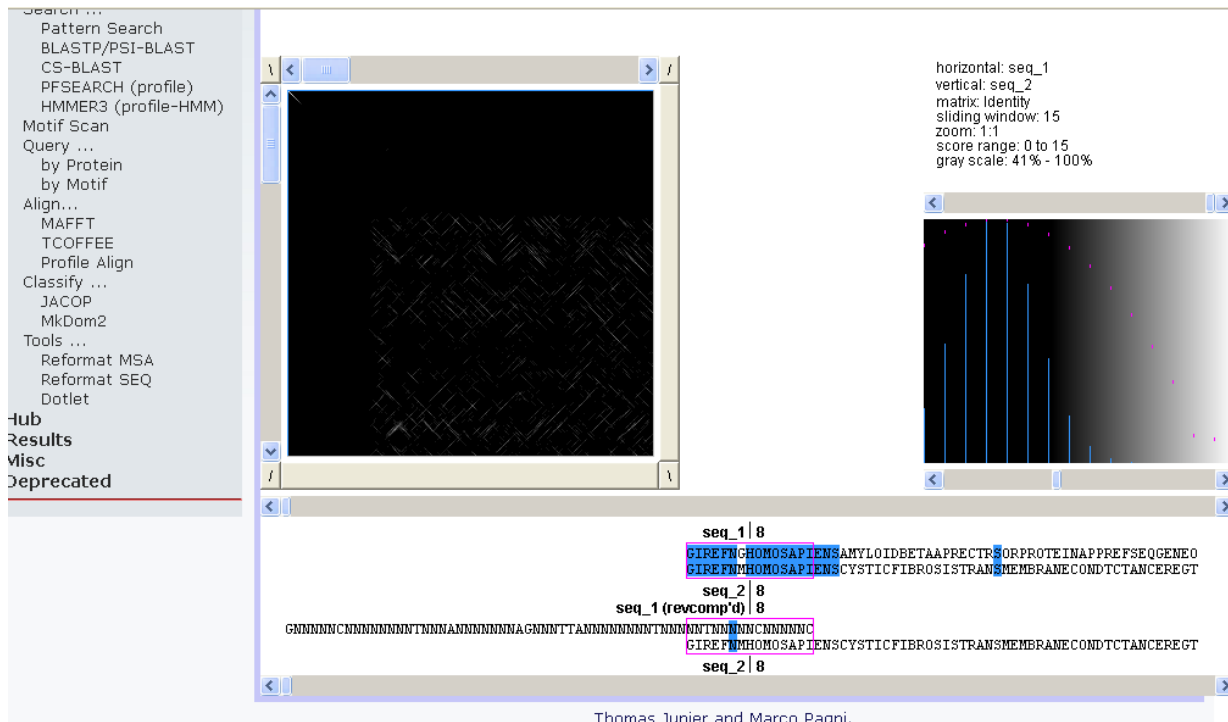
gi|90421312|ref|NM_000492.3|      GCCCTAGCAGGGACCCCAAGCAGCCGAGAGACCATGCAGAGGTGCGCTCTG 150
gi|28302128|ref|NM_000518.4|      -----
gi|166795291|ref|NG_007376.1|      GACATTGAGATAAAGAAGTTAATCATGTCTCTGTCTTGGAGGAGGTAG 138

gi|90421312|ref|NM_000492.3|      GAAAAGGCCAGCGTTGTCTCTCAAACCTTTTTTTCAGCTGGACCAACCAAT 200
gi|28302128|ref|NM_000518.4|      -----
gi|166795291|ref|NG_007376.1|      AAAGAGATCAGAAATG----AATACAATTCAGCATCTACTTCTGGTCTTT 183

gi|90421312|ref|NM_000492.3|      TTTGAGGAAAGGATACAGACAGCGCCTGGAAATTGTCAGACATATACCAAA 250
gi|28302128|ref|NM_000518.4|      -----
gi|166795291|ref|NG_007376.1|      GATGAGG--AGTTAGCACACGGTTCTGGGAG--GAAAGACAGGTTAAGAG 229
    
```

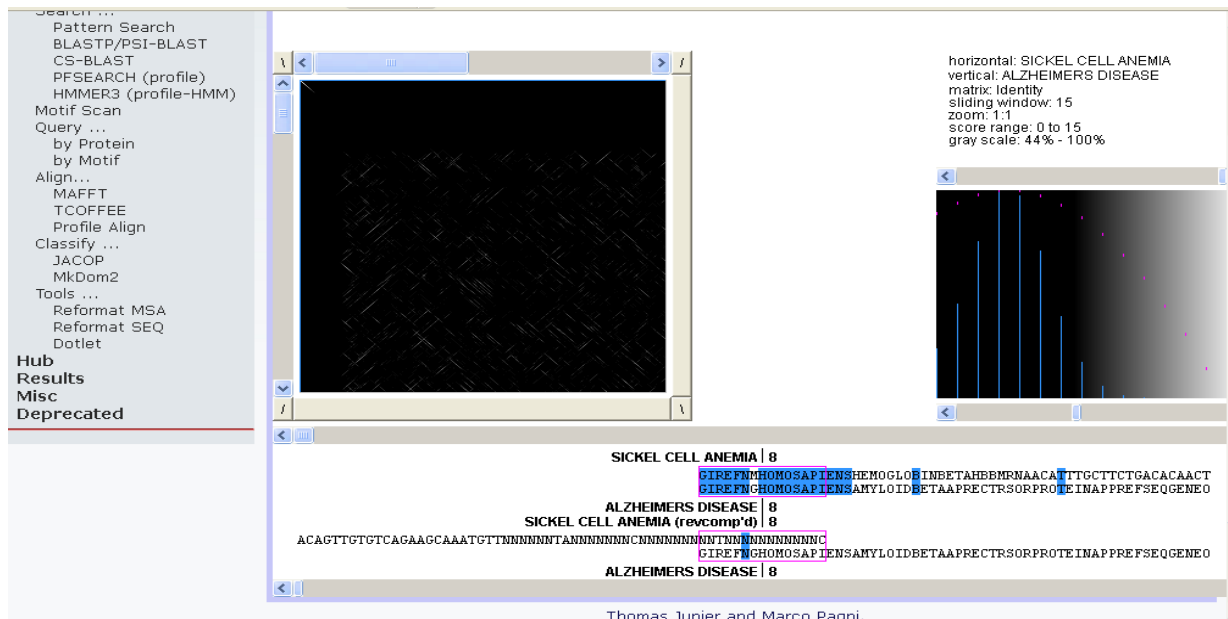
Here, red color of bases shows the similarity of the sequences. There are 30 similar bases in the shown figure. DOTLET: It is a program for comparing sequences by the diagonal plot method. The sequences are entered and then computed to get the results as follows.

Sequence of Alzheimer's disease is compared with Cystic fibrosis



Each pixel represents a score. High score means good match. Pixel's colour depends on how similar the two sequences are. Darker the pixel, lower the score. Histogram window represents the frequency of each score, on linear (blue) and logarithmic (purple). Lowest possible score on the left and the highest on the right. Larger peak represents low score. Here in horizontal column sequence1 is used and second sequence is used in vertical column. 1:1 zoom is used for observing the results. 41 percent grey scale is used out of 100 to view the results. The grey scale can be adjusted accordingly.

Comparison of sequence of Sickle cell disease with Alzheimer's disease



Below the comparison window, sequence similarity can be seen covering few bases at a time. GENOME VISTA: It uses a computational strategy where query sequence contigs are anchored on the base genome by local alignment matches and then globally aligned to candidate regions by AVID program. Here, human march 2006 genome is used as a base genome for comparison of sequences.

**Result of genome VISTA for Cystic fibrosis.**

When sequences are submitted then one link is obtained through which result can be accessed as follows.

**VISTA Tools for Comparative Genomics**

VISTA Home | Custom Alignment | **Browser** | Enhancer DB | Downloads | Publications | Training | Help

mVISTA | rVISTA | GenomeVISTA | wgVISTA | Phylo-VISTA

GenomeVISTA Submit:

Your request has been submitted. The results will be available at:  
<http://pipeline.lbl.gov/cgi-bin/textBrowser2?act=summary&run=u380-NXtnYKqv&base=hg18>

Your Unique Run Identifier is **u380-NXtnYKqv**

Once they are ready, you can retrieve the results by following the link above or by entering the Run Identifier on the GenomeVista page

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When link is opened the result is obtained in vista point format.

Human Mar. 2006 (chr7:117,015,024-117,039,099) View with: Vista Browser | Vista Point | Svrtery | Dot Plot | Help

clade: Vertebrate | genome: Human | release: Mar 2006 | alignment: sequence1 [381] | add alignment: 7 Vertebrates [80]

chr7 | chr7:117,015,024-117,039,099 | length: 24,076 bp

CFTR

sequence1

sequence1 [381] Show alignments longer than 50 bp | Download RefSeq genes

alignment in PDF | get CNSs: Human Mar. 2006 - sequence1 | Page 1 of 1 | Displaying 1 - 2 of 2

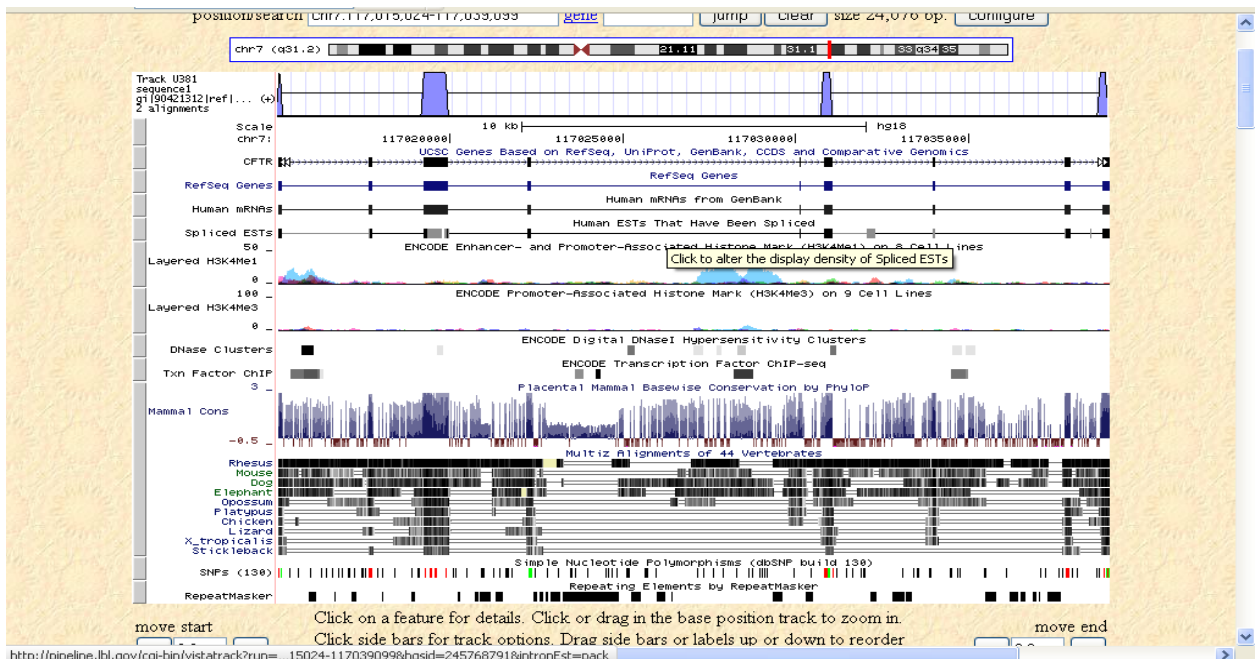
Location on Human Mar. 2006	Tools	Location on sequence1
chr7:117,015,024-117,019,948 (+) Sequence (softmasked) length: 4,925 bp	<a href="#">rankVISTA</a> pairwise alignments: Alignment: <a href="#">Human Mar. 2006 - sequence1</a> MFA: <a href="#">Human Mar. 2006 - sequence1</a> CNS: <a href="#">Human Mar. 2006 - sequence1</a> rVista: <a href="#">Human Mar. 2006 - sequence1</a> PDF: <a href="#">Human Mar. 2006 - sequence1</a>	gi 90421312 ref NM_000492.3 :1,712-2,623 (+) Sequence length: 912 bp <a href="#">Vista Point</a> <a href="#">Vista Browser</a>

Result in VISTA browser format is obtained as follows.





Result in VISTA Track format is shown below.



**Result for Alzheimer's disease.**

Result as VISTA point is shown below.

*Genomic Analysis and comparative genomics in reference to cystic fibrosis, sickle cell and Alzheimer's diseases.*

chr21 chr21:26,468,674-26,470,003 Go -10x -3x -1.5x +1.5x +3x +10x length: 1,330 bp

sequence1

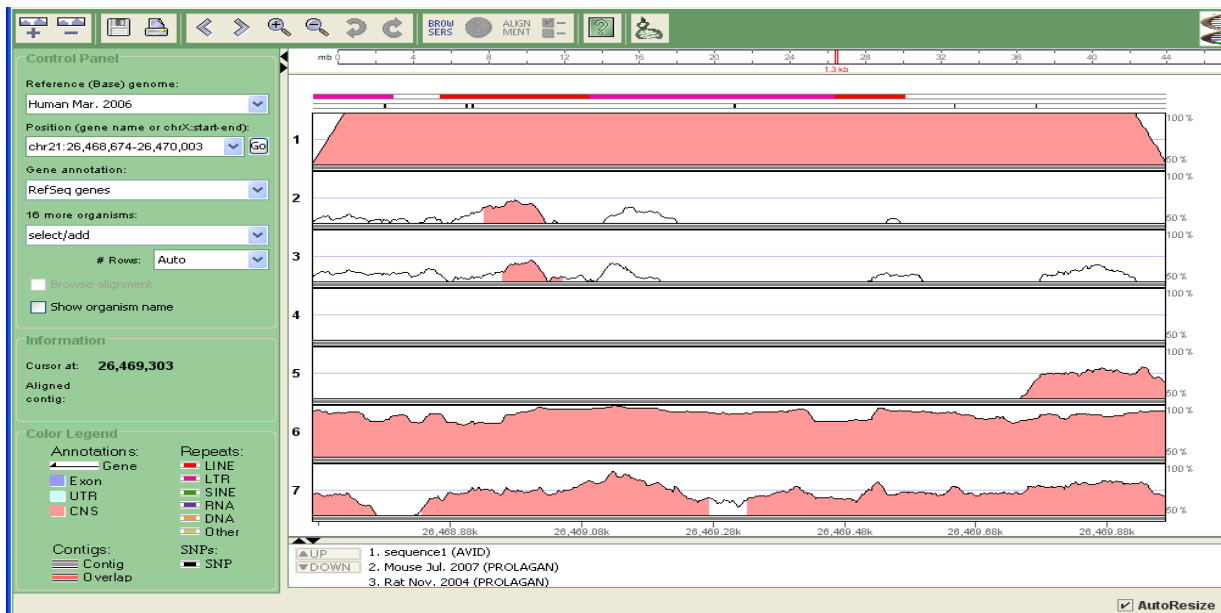
Show alignments longer than 50 bp Download RefSeq genes

sequence1 [428]

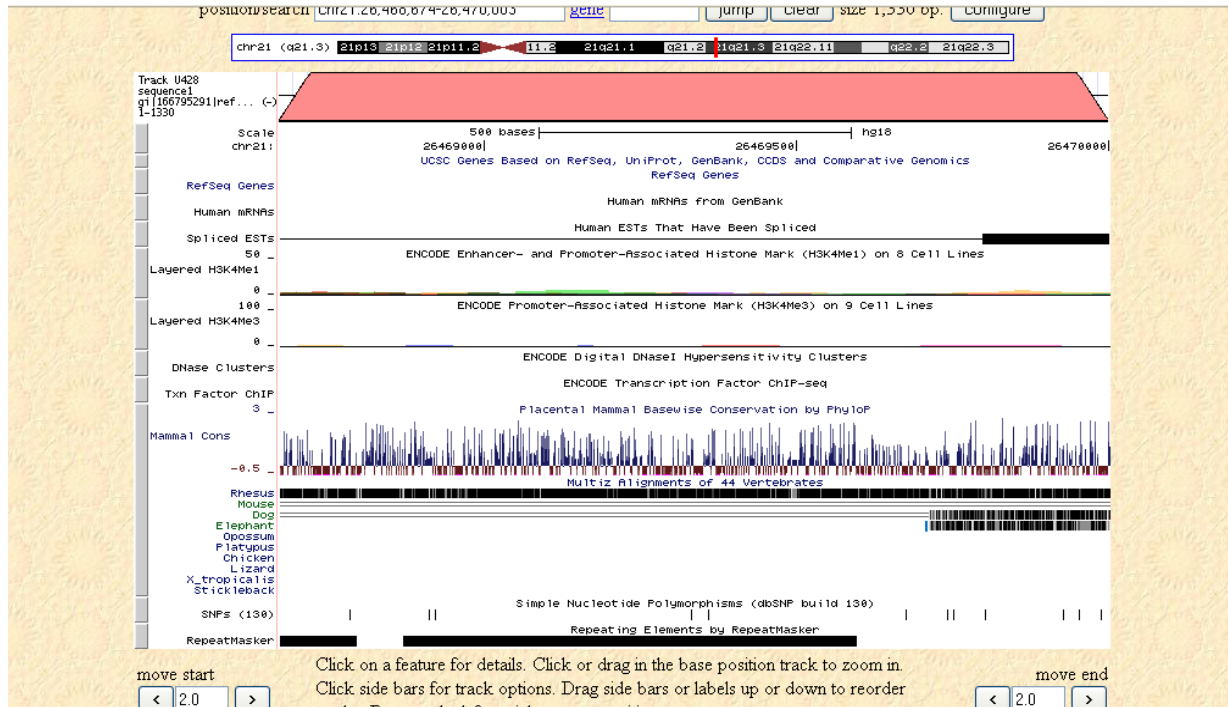
alignment in PDF get CNSs: Human Mar. 2006 - sequence1 Page 1 of 1 Displaying 1 - 1 of 1

Location on Human Mar. 2006 Mar 2006	Tools	Location on sequence1 Unknown
chr21:26,468,674-26,470,003 (+) <a href="#">Sequence (softmasked)</a> length: 1,330 bp	<a href="#">rankVISTA</a>  pairwise alignments: Alignment: <a href="#">Human Mar. 2006 - sequence1</a> MFA: <a href="#">Human Mar. 2006 - sequence1</a> CNS: <a href="#">Human Mar. 2006 - sequence1</a> rVista: <a href="#">Human Mar. 2006 - sequence1</a> PDF: <a href="#">Human Mar. 2006 - sequence1</a>	gil166795291 reflNG_007376.1 1-1,330 (-) <a href="#">Sequence</a> length: 1,330 bp <a href="#">Vista Point</a> <a href="#">Vista Browser</a>

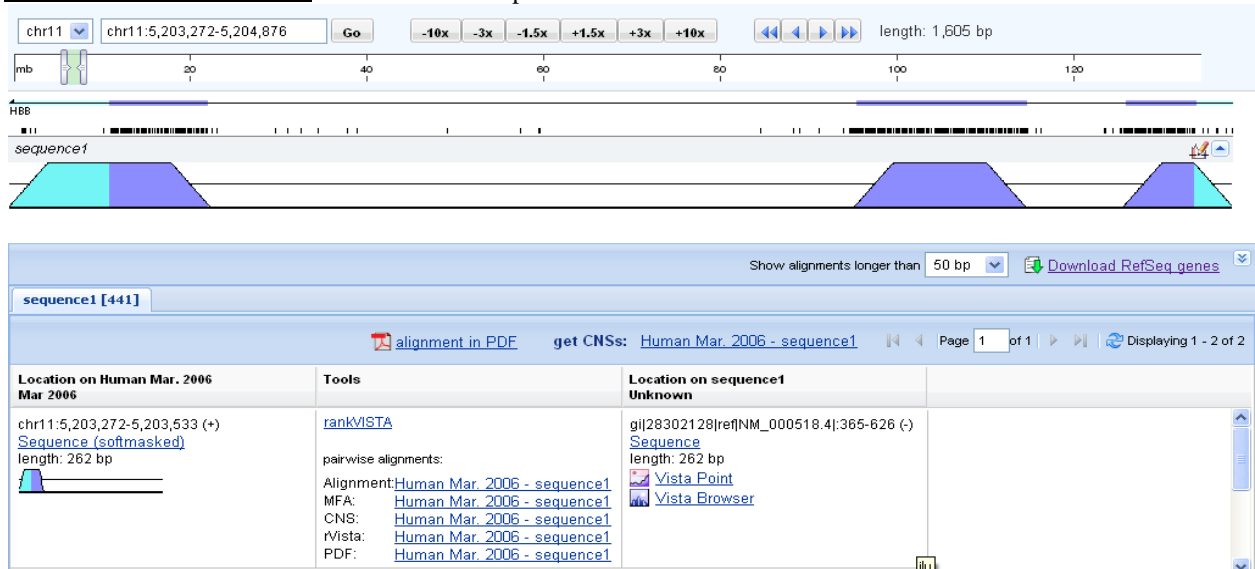
Result in VISTA Browser format is as follows



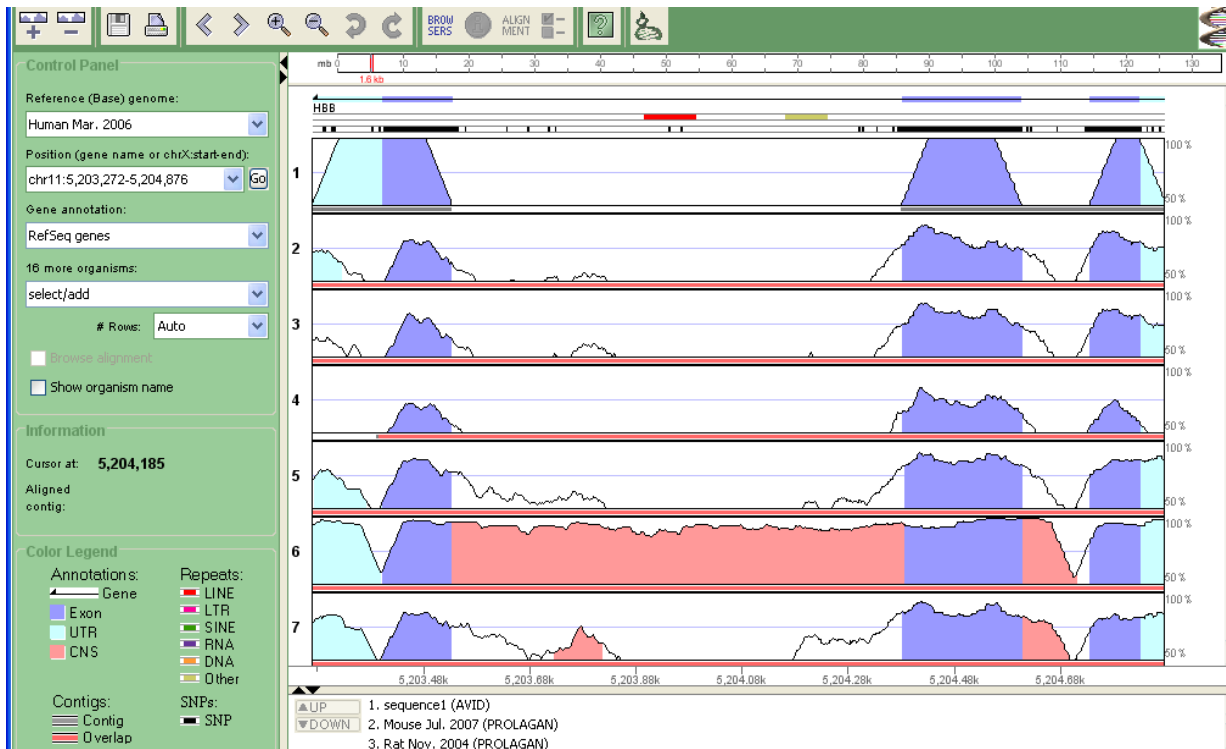
Result in VISTA track format



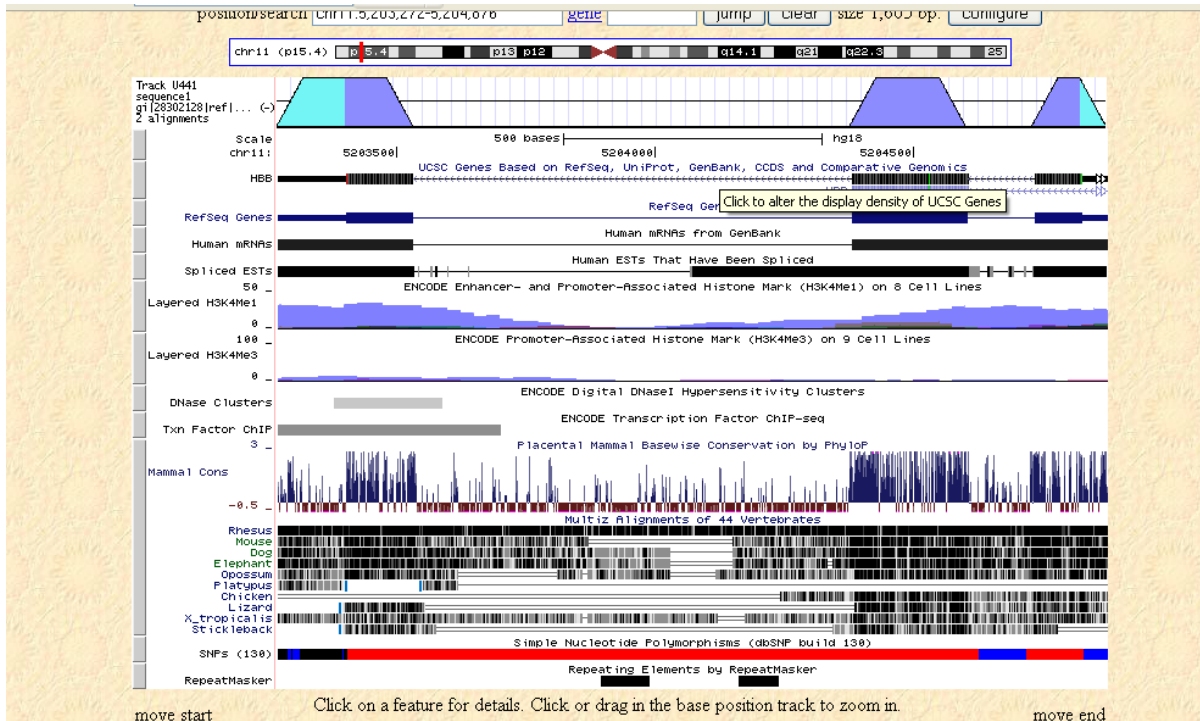
Result for Sickle cell anemia. Result in VISTA point format.



Result in VISTA Browser format.



Result in VISTA track format.



Comparing sequences of the three diseases by using VISTA TOOL, it is clear that untranslated sequence is observed only in Sickle cell disease at position Chromosome11 between 5,203,272 -5,204,876. Exons and CNS is observed in all three sequences. So, by using these tools we analyze gene of our interest and compare it with many other sequences to get the similarity results which is biologically very useful in different aspects of life.

### **Discussion:**

When sequencing is done using different tools, then it is noticeable that two or more sequence varies with respect to each other by very few bases. Knowing these variations and their positions, possible actions can be taken to exploit these sequences or if these causes disease then drugs can be made accordingly. Different tools give results in different format. Like in T coffee and in Clustal-W color variation shows the sequence variation. In pair wise alignment tool ----represents gaps and ... represents mismatch. In Dotlet each pixel represents a score and high score means good match. In genome vista similarity is shown graph wise. Gene similarity results are very useful and can be used for different research work.

### **Conclusion:**

Sequence comparison based on T-Coffee Version 8.9 was having consensus similarity of 33 score in which first sequence was having 35 score, second sequence was having 19 score and third sequence of score 35. When sequence is compared with T-Coffee then multiple sequences can be taken at a time while with the Pair wise Alignment Tool, two sequences is taken at a time. In T-Coffee similarity is Maximum for Adenine but it is not in the case of Pair wise Alignment Tool. In T-Coffee result, score is obtained for the similarity but score is not obtained in Pair wise Alignment TOOL. During the genomic sequence comparison of Cystic Fibrosis with Alzheimer's disease 19 amino acids were found to be similar in one window. While in case of AD with SCD there were 20 amino acids similar. So the maximum genomic similarity is for AD with SCD. When sequence of three diseases is compared by VISTA TOOL, then UTR is observed only in SCD at position of Chromosome 11 between 5,203,272 -5,204,876. Exons and CNS are observed in all three sequences.

### **Acknowledgement:**

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