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Restriction Site Finder: A Tool for Finding Restriction Sites in Genome Using Perl

Bhartesh Kumar[1*], Vijay Laxmi Saxena[1], Ashok Kumar Saxena[2*], Shrasti Gupta [2,] P.P.Mathur[3]

[1*]*(Bioinformatics Infrastructure Facility Centre of D.B.T. D.G.(P.G.),College, Kanpur India.)*
[1]*Head of Department of Zoology, Bioinformatics Infrastructure Facility Centre of D.B.T. D.G.(P.G.),College, Kanpur India.)*
[2*]*(Department of Zoology, D.A.V. College Kanpur, Uttar Pradesh, Pincode-208001, India.)*
[2]*(Bioinformatics Infrastructure Facility Centre of D.B.T. D.G.(P.G.),College, Kanpur India.)*
[3]*(The Dean, School of Life Sciences and Professor of Biochemistry & Molecular Biology&.Vice Chancellor, KIIT University, Bhubaneswar India.)*

ABSTRACT : *Restriction enzymes are the enzymes basicallyused by bacteria for theirdefensemechanism. after the discovery of thèse enzymes their utility in the biotechnology and molecularcloningis of wide perspective, now a daysthis enzyme iswidelyused as molecularscissors in recombinant DNAtechnology. Restriction enzyme cuts double strandedDNAatspecific sites. thispropertycanbeused to generate fragment of Desiredgene as well as Restriction map of genome of an organismthistoolRerstriction site finderis a noveltoolbased on PERLwhichcancomputationallycalculate the positions of DNAwhere a particular Restriction enzyme cuts and Whole restriction map of the DNAsequenceprovided as input . Input must begiven in FASTA format. This isanoveltool to prepare restriction map of a wholegenome and to previouslyfind the restriction sites for it.*

KEYWORDS -*restriction enzyme, DNA, molecule DNA sequence, PERL*

1. INTRODUCTION

A restriction enzyme (or restriction endonuclease) is an enzyme that cuts double-stranded DNA. The enzyme makes two incisions, one through each of the phosphate backbones of the double helix without damaging the bases. The chemical bonds that the enzymes cleave can be reformed by other enzymes known as ligasesr, so that restriction fragments carved from different chromosomes or genes can be spliced together, provided their ends are complementary. Many of the procedures of molecular biology and genetic engineering rely on restriction enzymes. The term restriction comes from the fact that these enzymes were discovered in E. coli strains that appeared to be restricting the infection by certain bacteriophages. Restriction enzymes therefore are believed to be a mechanism evolved by bacteria to resist viral attack and to help in the removal of viral sequences Restriction enzymes are DNA-cutting enzymes found in bacteria (and harvested from them for use). Because they cut within the molecule, they are often called restriction endonucleases. A restriction enzyme recognizes and cuts DNA only at a particular sequence of nucleotides. For example: The bacterium Hemophilusaegypticus produces an enzyme named HaeIII that cuts DNA wherever it encounters the sequence
5'GGCC3'
3'CCGG5'

The cut is made between the adjacent G and C. This particular sequence occurs at 11 places in the circular DNA molecule of the virus phiX174. Thus treatment of this DNA with the enzyme produces 11 fragments, each with a precise length and nucleotide sequence. These fragments can be separated from one another and the sequence of each determined HaeIII and AluI cut straight across the double helix producing "blunt" ends. However, many restriction enzymes cut in an offset fashion. The ends of the cut have an overhanging piece of single-stranded DNA. These are called "sticky ends" because they are able to form base pairs with any DNA molecule that contains the complementary sticky end. Any other source of DNA treated with the same enzyme will produce such molecules. Mixed together, these molecules can join with each other by the base pairing between their sticky ends. The union can be made permanent by another enzyme, DNA ligase, which forms covalent bonds along the backbone of each strand (FIG NO 1). The result is a molecule of recombinant DNA (rDNA). The ability to produce recombinant DNA molecules has not only revolutionized the study of genetics, but has laid the foundation for much of the biotechnology industry.

1.1 MECHANISM OF ACTION OF RESTRICTION ENZYMES

The action of restriction enzymes is in many respects as varied as the enzymes themselves. In general, however, the process is one of recognition of the binding site, binding of the enzyme dimer to the DNA,

cleavage of the DNA, and enzyme release.. To begin, all restriction endonucleases will bind DNA specifically and, with much less strength, non-specifically. This is a characteristic of many proteins that interact with DNA. It is probable that even non-specific DNA binding will induce a conformational change in the restriction enzyme dimer that will result in the protein adapting to the surface of the DNA strands (Vaidiu and Aggarwal, 2000). These changes are not the same as those that occur when the dimmer binds to the recognition site though. As the dimer slides along the DNA strands, it searches for recognition elements and, when these are encountered, an interaction between the protein and the DNA ensues in which the non-specific complex is converted into a specific complex. In general, intimate contact is held by 15 – 20 hydrogen bonds that form between the protein and the DNA bases in the recognition site. These bonds are shown to be mediated through specific amino acids, primarily ASP and GLU, held in a proper threedimensional configuration. (FIG NO :2) Simplified scheme of the mechanism of Type II restriction enzyme digestion. The homodimer will either bind directly to the recognition site (Specific Binding) or nearby (non-specific Binding). The case of non-specific binding, if the recognition site is not too far away the enzyme will move along the DNA strand until it hits the recognition site. Once the enzyme locates the recognition site it will couple and then hydrolyze the sugar phosphate bonds of the DNA. Finally, the enzyme will release leaving the cleaved DNA molecule behind.

1.2 RESTRICTION ENZYME - ACTION OF ECORI

The enzymes Dra I (TTTAAA), Ssp I (AATATT), and Pac I (TTAATTAA) are but three of these "AT-cutters." Further, most restriction enzymes will cleave the DNA inside the recognition site but there are several that do not. The enzyme Mnl I recognizes the non-palindromic sequence CCTC but cleaves the DNA seven bases downstream (i.e., CCTC 7/7). Other examples include Bbv I (GCAGC 8/12) and Hga I (GACGC 5/10). The enzyme Acc I recognizes the sequences GTATAC and GTCGAC. (Fig: 3)

The standard nucleotide coding system is:

A, C, G, T, U
R (G or A) Purine
Y (T or C) Pryimidine
K (G or T) Keto
M (A or C) Amino
S (G or C) Strong
W (A or T) Weak
B (G, T, C) (not A)
D (G, A, T) (not C)
H (A, C, T) (not G)
V (G, C, A) (not T or U)
N (all).
Table:1 and Table No. 2

II. PROPOSED METHOD

Requirment: Perl 5.0 and Restriction Enzyme DatabaseRestriction Enzyme Data.The RE data is available in a variety of formats, as a visit to the REBASE web site at(hhh://www.neb.com/rebase/rebase.html). User can decide to get the information from the bionet file. REBASE version 604 bionet.604REBASE, The Restriction Enzyme Database http://rebase.neb.com Notepad and Microsoft word is usable, but always save as text or ASCII only.

2.1.2 Working of Program:

To run perl program depending on your operating system. Window is closely coupled with Intel 32 bit chip; these are often called wintel or win 32 binaries. Eeample: Perl \usr\local\bin\ Perl re.pl

2.1.3 Windows

On window system, it is usual to associate the file name extension .pl with Perl program. this isdone as a part of the Perl installation process, which modify the registry setting to include this file association. You can launch allergen program by typing perl allergen.pl. Window has a path variable specifying folders in which system looks for program, and this is modified by the Perl installation process to include the path to the folder for the Perl association ,

C:\ If you are trying to run a Perl program that is not installed in a folder known to the path variable , you can type the complete path name of program, for instance . Perl C:\window\desktop\ Perl re.pl.

Input file:

Nucleotide sequence for any gene or whole genome in fasta format.

Eg.: NM_000660. Reports Homo sapiens tran...[gi:63025221]

>gi|63025221|ref|NM_000660.3| Homo sapiens transforming growth factor, beta 1 (Camurati-Engelmann disease) (TGFB1), Mrna

CCTTCGCGCCCTGGGCCATCTCCCTCCCACCTCCCTCCGCGGAGCAGCCAGACAGCGAGGGCC
CCGGCCGGGGGCAGGGGGGACGCCCCGTCCGGGGCACCCCCCCGGCTCTGAGCCGCCCGCGG
GGCCGGCCTCGGCCCGGAGCGGAGGAAGGAGTCGCCGAGGAGCAGCCTGAGGCCCCAGAGTC
TGAGACGAGCCGCCGCCGCCCCCGCCACTGCGGGGAGGAGGGGGAGGAGGAGCGGGAGGAG
GGACGAGCTGGTCGGGAGAAGAGGAAAAAAACTTTTGAGACTTTTCCGTTGCCGCTGGGAGC
CGGAGGCGCGGGGACCTCTTGGCGCGACGCTGCCCCGCGAGGAGGCAGGACTTGGGGACCCC
AGACCGCCTCCCTTTGCCGCCGGGGACGCTTGCTCCCTCCCTGCCCCCTACACGGCGTCCCTCA
GGCGCCCCCATTCCGGACCAGCCCTCGGGAGTCGCCGACCCGGCCTCCCGCAAAGACTTTTCC
CCAGACCTCGGGCGCACCCCCTGCACGCCGCCTTCATCCCCGGCCTGTCTCCTGAGCCCCCGC
GCATCCTAGACCCTTTCTCCTCCAGGAGACGGATCTCTCTCCGACCTGCCACAGATCCCCTATT
CAAGACCACCCACCTTCTGGTACCAGATCGCGCCCATCTAGGTTATTTCCGTGGGATACTGAG
ACACCCCCGGTCCAAGCCTCCCCTCCACCACTGCGCCCTTCTCCCTGAGGACCTCAGCTTTCCC
TCGAGGCCCTCCTACCTTTTGCCGGGAGACCCCCAGCCCCTGCAGGGGCGGGGCCTCCCCACC
ACACCAGCCCTGTTCGCGCTCTCGGCAGTGCCGGGGGGCGCCGCCTCCCCATGCCGCCCTCCG
GGCTGCGGCTGCTGCCGCTGCTGCTACCGCTGCTGTGGCTACTGGTGCTGACGCCTGGCCGGC
CGGCCGCGGGACTATCCACCTGCAAGACTATCGACATGGAGCTGGTGAAGCGGAAGCGCATC
GAGGCCATCCGCGGCCAGATCCTGTCCAAGCTGCGGCTCGCCAGCCCCCCGAGCCAGGGGGA
GGTGCCGCCCGGCCCGCTGCCCGAGGCCGTGCTCGCCCTGTACAACAGCACCCGCGACCGGGT
GGCCGGGGAGAGTGCAGAACCGGAGCCCGAGCCTGAGGCCGACTACTACGCCAAGGAGGTCA
CCCGCGTGCTAATGGTGGAAACCCACAACGAAATCTATGACAAGTTCAAGCAGAGTACACAC
AGCATATATATGTTCTTCAACACATCAGAGCTCCGAGAAGCGGTACCTGAACCCGTGTTGCTC
TCCCGGGCAGAGCTGCGTCTGCTGAGGCTCAAGTTAAAAGTGGAGCAGCACGTGGAGCTGTAC
CAGAAATACAGCAACAATTCCTGGCGATACCTCAGCAACCGGCTGCTGGCACCCAGCGACTCG
CCAGAGTGGTTATCTTTTGATGTCACCGGAGTTGTGCGGCAGTGGTTGAGCCGTGGAGGGGAA
ATTGAGGGCTTTCGCCTTAGCGCCCACTGCTCCTGTGACAGCAGGGATAACACACTGCAAGTG
GACATCAACGGGTTCACTACCGGCCGCCGAGGTGACCTGGCCACCATTCATGGCATGAACCGG
CCTTTCCTGCTTCTCATGGCCACCCCGCTGGAGAGGGCCCAGCATCTGCAAAGCTCCCGGCAC
CGCCGAGCCCTGGACACCAACTATTGCTTCAGCTCCACGGAGAAGAACTGCTGCGTGCGGCAG
CTGTACATTGACTTCCGCAAGGACCTCGGCTGGAAGTGGATCCACGAGCCCAAGGGCTACCAT
GCCAACTTCTGCCTCGGGCCCTGCCCCTACATTTGGAGCCTGGACACGCAGTACAGCAAGGTC
CTGGCCCTGTACAACCAGCATAACCCGGGCGCCTCGGCGGCGCCGTGCTGCGTGCCGCAGGCG
CTGGAGCCGCTGCCCATCGTGTACTACGTGGGCCGCAAGCCCAAGGTGGAGCAGCTGTCCAAC
ATGATCGTGCGCTCCTGCAAGCAGCTGAGGTCCCGCCCCGCCCCGCCCCGCCCCGGCAGGCCC
GGCCCCACCCCGCCCCGCCCCCGTGCCTTGCCCATGGGGGCTGTATTTAAGGACACCCGTGCC
CCAAGCCCACCTGGGGCCCCATTAAAGATGGAGAGAGGACTGCGGATCTCTGTGTCATTGGGC
GCCTGCCTGGGGTCTCCATCCCTGACGTTCCCCACTCCCACTCCCTCTCTCTCCCTCTCTGCCTC
CTCCTGCCTGTCTGCACTATTCCTTTGCCCGGCATCAAGGCACAGGGGACCAGTGGGGAACAC
TACTGTAGTTAGATC

III. EXPERIMENTALRESULTS

3.1: The Restriction Enzyme that cuts the Given Sequence.

The name file is human.txt.(given the >gi|63025221|ref|NM_000660.3| Homo sapiens transforming growth factor, beta 1).Fig No. 4-6

Restriction Enzyme that not cut the sequence:

AvaIII, Ava458I, AviI, AviII, AvrI, AvrII, AvrBII, BacI, Bac465I, BadI, BaeI, BaeI, BaeI,BaeI, BalI, BamFI, BamGI, BamHI, BamKI, BamNI, BanI, BanIII, BauI, BauI, BavI, BavAI, BavBI, BavCI,BazI, BbeI, BbeAI, BbfI, BbiI, BbiII, BbiIII, Bbi24I, BbrI, Bbr7I, Uba1211I, Uba1212I, Uba1213I, Uba1215I, Uba1216I, Uba1217I, Uba1219I, Uba1220I, Uba1221I, Uba1222I, Uba1224I, Uba1225I, Uba1226I, Uba1227I, Uba1229I, Uba1232I, XmaIII, XmaCI, XmaJI, XmiI, XmlI, XmlAI, XniI, XorI, XorII, XpaI, XphI, YenI,YenAIYenBI, YenCI, YenDI, YenEI, ZhoI, ZraI, ZrmI, Zsp2I And More than……

3.2 : Result of Bioedit Software : -

The result is obtained from bioedit software are given below

AflII 453, 561
AflIII 1326
ApoI 955, 1068
BanII 187

BbsI 896
BbvI 111, 621
BglII 16, 1011
BplI 1011, 104
Cac8I 11, 50, 144, 911
CjeI 392, 424, 467
CjeI 351, 426, 465
CjePI 427
CjePI 467
DraI 1052, 1217
DrdII 469, 931
EarI 535, 658, 941
HaeII 10, 727
HaeIV 524
HgaI 45
HgiEII 446
Hin4I 50, 524, 1030
Hpy178III 13, 95, 573, 841, 985, 1010
MboII 9, 172, 529, 544, 550, 652, 679
MnlI 183, 334, 505, 532, 535,
BplI 1011, 1049
BpmI 115, 611, 734
BsaJI 61, 420, 588
BsaWI 983
BsaXI 49
BsbI 811, 1190
BseMII 178, 1355
BseRI 556, 559
BsiHKAI 275
BslI 62, 156, 595, 1240
BsmAI 1037, 1310
Bsp24I 428
Bsp24I 466
Bsp1286I 187, 275
BspEI 983
BspGI 1167
BsrDI 353
BsrGI 402
EciI 121
Eco47III 8
Eco57I 2, 734
EcoO109I 194, 874
EcoRV 1104
FauI 35
FokI 331, 562, 679, 999
SfaNI 513
SfcI 884
SmlI 453, 561
Sse8647I 874
Sth132I 36, 160
StyI 420
TatI 402
Tth111II 926, 1138, 1225
BspLU1 1I 1326
BstYI 16, 1011
Bsu36I 190
538 584, 655, 697, 991, 1017
MslI 178, 488, 1302
MwoI 45, 763

NgoGV 47, 196, 608
NlaIV 47, 196, 608
NruI 13
NspI 1330
PflMI 156
PleI 534, 787
PmeI 1052
PsiI 1122
Psp5II 874
TspRI 386, 452, 485, 734, 1027
XcmI 1237
BsrI 273, 386, 442, 475, 724
BtsI 1022

3.3 :ENZYMES THAT DO NOT CUT:

AarI, AatII, AccI, AceIII, AclI, AhdI, AloI, AlwI, AlwNI, ApaI, ApaLI, AscI, AvaIAvrII, BaeI, BaeI, BamHI, BanI, BbvCI, Bce83I, BcefI, BcgI, BcgI, BciVI, BclI,BglI, BmgI, BmrI, Bpu10I, Bpu1102I, BsaI, BsaAI, BsaBI, BsaHI, BseSI, BsgI, BsiEI ,BsmI, BsmBI, BsmFI, BspMI, BsrBI, BsrFI, BssHII, BssSI, BstAPI, BstDSI, BstEII,BstXI, BstZ17I, BtrI, ClaI, DraIII, DrdI, EaeI, EagI, EcoNI, EcoRI, FseI, FspI,GdiII, HaeI, HincII, HindIII, HpaI, HphI, KpnI, MluI, MmeI, MscI, MspA1I, MunI,NarI, NcoI, NdeI, NgoAIV, NheI, NotI, NsiI, NspV, PacI, Pfl1108I, PinAI, PmlI,PpiI, PshAI, PstI, PvuI, PvuII, RcaI, RleAI, RsrII, SacI, SacII, SalI, SanDI, SapI,SbfI, ScaI, SexAI, SfiI, SgfI, SgrAI, SmaI, SnaBI, SpeI, SphI, SrfI, SspI, StuI,SunI, SwaI, TaqII, TaqII, Tth111I, VspI, XbaI, XhoI

1-To demostrate the using of restriction site finder, input file Homo sapiens transforming growth factor was used the output file gave data for position which restriction could be foundaswellas those restriction enzyme for which no site werwfound .
2-On further validation with bio edit when the result were comparable (please see output input File).
3-The restriction finder computes the sites of DNA sequence which are recognized by Restriction enzymes.

IV. FIGURES AND TABLES

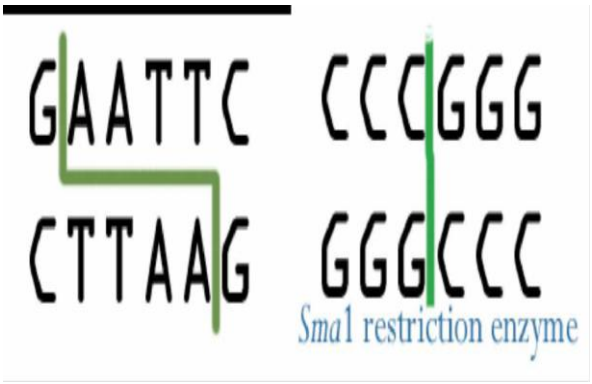

Fig. 1- Buln end and sticky end

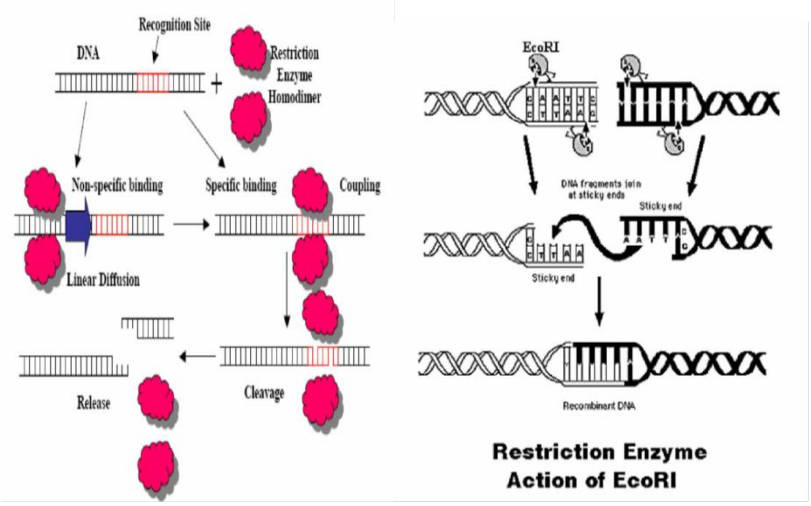

Fig. 2&3- Mechanism of R.E.action

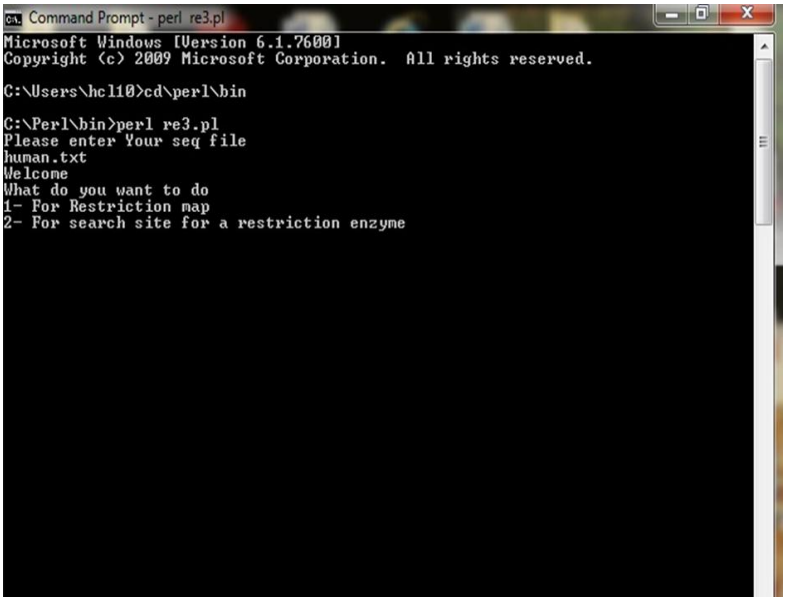

Fig. 4- Choose The Oppition 1 or 2.

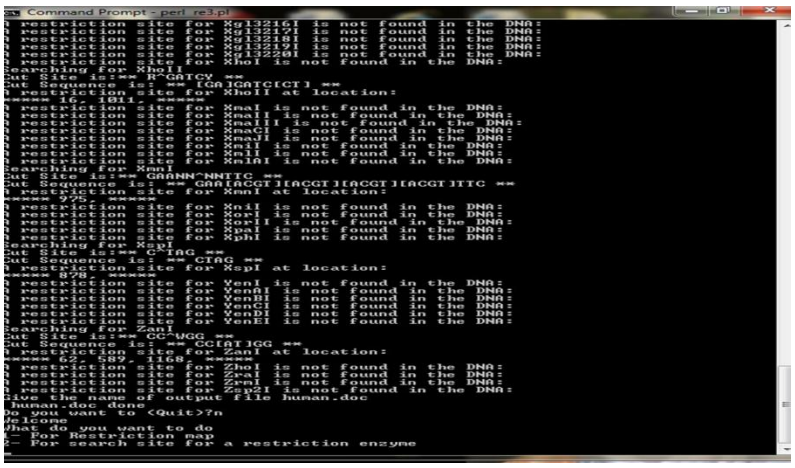

Fig 5: Choose The Options 1 result given.

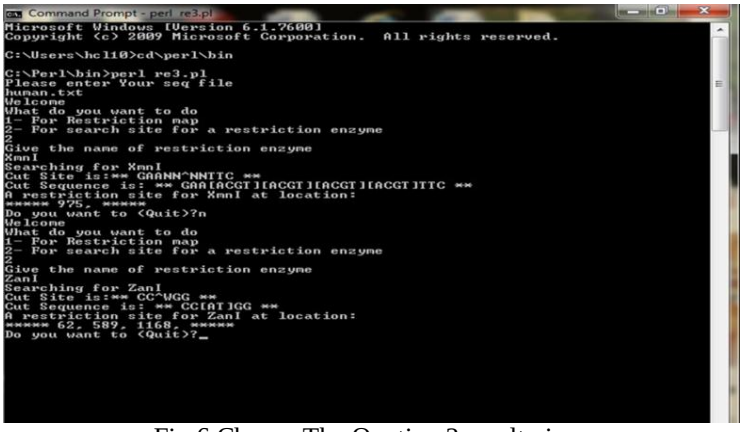

Fig.6:Choose The Opption 2 result given

TABLE 1:Different name of Microorganism and Restriction Enzymes.

Table 1

Examples of Restriction Enzymes

Enzyme	Microorganism	Recognition Sequence	Isoschizomers
Alu I	*Arthrobacter luteus*	AG|CT	
Apa I	*Acetobacter pasteurianus*	GGGCC|C	*Bsp120 I, PspOM I*
Bam HI	*Bacillus amiloliquifaciens*	G|GATCC	
Bgl II	*Bacillus globigii*	A|GATCT	
Cla I	*Caryophanon latum L*	AT|CGAT	*Bsp DI, Bsc I, BspX I*
Dde I	*Desulfovibrio desulfuricans*	C|TNAG	*BstDE I*
Dra I	*Deinococcus radiophilus*	TTT|AAA	
Eco RI	*Escherichia coli RY13*	G|AATTC	
Eco RV	*Escherichia coli J62*	GAT|ATC	*Eco32 I*
Fnu4H I	*Fusobacterium nucleatum 4H*	GC|NGC	*Fsp4H I, Ita I*
Hae III	*Haemophilus aegyptius*	GG|CC	*Bsh I, BsuR I, Pal I*
Hind II	*Haemophilus influenzae Rd*	A|AGCTT	
Hinf I	*Haemophilus influenzae Rf*	G|ANTC	
Kpn I	*Klebsiella pnumoniae OK8*	GGTAC|C	*Acc65 I, Asp718 I*
Mbo I	*Moraxella bovis*	|GATC	*Dpn II, Nde II, Sau3A I*
Msp I	*Moraxella sp.*	C|CGG	*BsiS I, Hap II, Hpa II*
Nde I	*Neisseria dentrificans*	CA|TATG	*FauND I*
Not I	*Nocardia otitidis-caviarum*	GC|GGCCGC	*CciN I*
Pst I	*Providencia stuartii 164*	CTGCA|G	
Pvu II	*Proteus vulgaris*	CAG|CTG	
Rsa I	*Rhodopseudomonas sphaeroides*	GT|AC	
Sma I	*Serratio marcescens S*	CCC|GGG	*Cfr9 I, Psp A I, Xma I*
Taq I	*Thermus aquaticus YT1*	T|CGA	*TtaHB8 I*
Xba I	*Xanthomonas badrii*	T|CTAGA	
Xho I	*Xanthomonas holcicola*	C|TCGAG	*PaeR7 I, Sfr274 I, Tli I*

TABLE 2**:**It is the represented the some enzymes of recognition sequence and cut

Enzyme	**Source**	**Recognition Sequence**	**Cut**
EcoRI	*Escherichia coli*	5'GAATTC 3'CTTAAG	5'---G AATTC---3' 3'---CTTAA G---5'
BamHI	*Bacillus amyloliquefaciens*	5'GGATCC 3'CCTAGG	5'---G GATCC---3' 3'---CCTAG G---5'
HindIII	*Haemophilusinfluenzae*	5'AAGCTT	5'---A AGCTT---3'

		3'TTCGAA	3'---TTCGA A---5'
MstII	*Microcoleus*species	5'CCTNAGG 3'GGANTCC	
TaqI	*Thermusaquaticus*	5'TCGA 3'AGCT	5'---T CGA---3' 3'---AGC T---5'
NotI	*Nocardiaotitidis*	5'GCGGCCGC 3'CGCCGGCG	
HinfI	Haemophilusinfluenzae	5'GANTC 3'CTNAG	
AluI*	*Arthrobacterluteus*	5'AGCT 3'TCGA	5'---AG CT---3' 3'---TC GA---5'

CONCLUSION

Using Perl language a program restriction finder was developed. Which can run on Linux, UNIX and windows platform? Perl is a marvellous language for bioinformatics. Validation of restriction site finder program was performed by comparing output/input file with data with bio edit observed upon analysis of Homo sapiens transforming growth factor obtained 99%accuracy.

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