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(54) Benævnelse: Protein- eller glycoproteinfragment

(57) Sammendrag:

Fragment af et protein eller af et glycoprotein indkodet af en åben læseramme fra RNA-sekvensen fra LAV_{ELI}-virus og svarende til fig. 7A-7J eller af RNA-sekvensen fra LAV_{MAL}-virus og svarende til fig. 8A-8I, hvilket fragment er et immunogent epitopbærende peptid, der genkendes fra antistoffer af LAS-patientsera.

PATENTKRAV

1. Fragment af et protein eller af et glycoprotein indkodet af en åben læseramme fra RNA-sekvensen fra LAV_{ELI}-virus og svarende til fig. 7A-7J eller af RNA-sekvensen fra LAV_{MAL}-virus og svarende til fig. 8A-8I, hvilket fragment er et immunogent epitopbærende peptid, der genkendes fra antistoffer af LAS-patientsera.

2. Fragment af et protein eller af et glycoprotein ifølge krav 1, hvilket fragment er et immunogent peptid med LAV_{MAL}- eller LAV_{ELI}-Env-sekvenser som beskrevet i fig. 3E-3F, i hvilket der er mindst én aminosyresubstitution ved én eller flere af stillingerne 8, 9, 90, 102, 131, 133, 140, 156, 172, 177, 179, 185, 188, 192, 198, 207, 209, 290, 305, 308, 323, 333, 335, 337, 341, 342, 353, 356, 359, 363, 404, 428, 440, 457, 461, 477, 483, 484, 486, 538, 555, 641, 652, 656, 660, 663, 694, 740, 733, 799, 854, 856, 862 og 875, i forhold til Env-sekvenserne fra LAV_{BRU} og LAV_{ARV2}, hvor de immunogene peptider binder til antistoffer fra LAS-patientsera.

3. Fragment af et protein eller af et glycoprotein ifølge krav 2, kendetegnet ved, at peptidet omfatter mindst én af nedenstående konserverede sekvenser: stillinger 37-130, 211-289, 488-830, 490-620, 531-877 og 680-700 fra Env som vist i fig. 3E-3F.

4. Fragment af et protein eller af et glycoprotein ifølge et hvilket som helst af kravene 1-3 med en størrelse, der er mindre end 250 aminosyrerester eller mindre end 150 aminosyrerester.

5. Fragment af et protein eller af et glycoprotein ifølge krav 4 med en størrelse, der ligger på mellem 5 og 150 aminosyrerester.

6. Polypeptid omfattende aminosyresekvensen af et fragment af et protein eller af et glycoprotein ifølge et hvilket som helst af kravene 1-5.

7. Polypeptid ifølge krav 6, hvilket polypeptid er kovalent koblet til et fysiologisk acceptabelt og ikke-toksisk bærermolekyle for at forbedre dets *in vivo*-immunogene karakter.

8. Polypeptid ifølge krav 6, hvilket polypeptid omfatter aminosyresekvensen fra p25-peptidet, mellem resterne 138-385 i *gag*-proteinet fra LAV_{ELI}- eller LAV_{MAL}-viruser, som beskrevet i fig. 3A.

9. Polypeptid ifølge krav 6, hvilket polypeptid omfatter aminosyresekvensen fra p13-peptidet, mellem resterne 385-519 i *gag*-proteinet fra LAV_{ELI}- eller LAV_{MAL}-viruser, som beskrevet i fig. 3A.

10. Polypeptid ifølge krav 6, hvilket polypeptid omfatter en specifik LAV_{ELI}-epitop og bindes til antistoffer fra LAS-patientsera, hvilken LAV_{ELI}-epitop ikke reagerer med antistoffer rettet mod specifikke epitoper af HIV_{BRU}, HIV_{ARV-2} og HIV_{MAL}.

11. Polypeptid ifølge krav 6, hvilket polypeptid omfatter en specifik LAV_{ELI}-epitop og binder til antistoffer fra LAS-patientsera, hvilken LAV_{ELI}-epitop ikke reagerer med antistoffer rettet mod specifikke epitoper af HIV_{BRU} og HIV_{ARV-2}.

12. Polypeptid ifølge krav 6, hvilket polypeptid omfatter en specifik LAV_{MAL}-epitop og binder til antistoffer fra LAS-patientsera, hvilken LAV_{MAL}-epitop ikke reagerer med antistoffer rettet mod specifikke epitoper af HIV_{BRU}, HIV_{ARV-2} og HIV_{ELI}.

13. Polypeptid ifølge krav 6, hvilket polypeptid omfatter en specifik LAV_{MAL}-epitop og binder til antistoffer fra LAS-patientsera, hvilken LAV_{MAL}-epitop ikke reagerer med antistoffer rettet mod specifikke epitoper af HIV_{BRU} og HIV_{ARV-2}.

14. Fragmenter eller polypeptider ifølge et hvilket som helst af kravene 1-13 dannet ved kemisk spaltning.

15. Fragmenter eller polypeptider ifølge et hvilket som helst af kravene 1-13 dannet ved ekspression af en rekombinant DNA.

16. Fragmenter eller polypeptider ifølge et hvilket som helst af kravene 1-13 dannet ved kemisk syntese.

17. Oligomerer af fragmenter eller polypeptider ifølge et hvilket som helst af kravene 1-13, især oligomerer fra 2 til 10 monomerer.

18. Nukleinsyre, der koder for et fragment af et protein eller af et glycoprotein ifølge et hvilket som helst af kravene 1-5.

19. Rekombinant DNA, der indkoder et polypeptid ifølge et hvilket som helst af kravene 6-13.

20. Rekombinant vektor omfattende en nukleinsyre eller en rekombinant DNA ifølge krav 18 eller 19.

21. Mikroorganismer transformeret med en vektor ifølge krav 20.

22. Celler transformeret med en vektor ifølge krav 20, især eukaryote celler.

23. Celler ifølge krav 22, hvilke celler er gærceller eller pattedyrceller, fortrinsvis lymfocytter.

24. Immunogene præparater omfattende mindst ét polypeptid eller fragment ifølge et hvilket som helst af kravene 1-13.

25. Fremgangsmåde til fremstilling af et epitopbærende polypeptid ifølge krav 1-13, hvilken fremgangsmåde omfatter:

- indsættelse af en nukleinsyre, der koder for et epitopbærende polypeptid ifølge et hvilket som helst af kravene 1-13, i en vektor, hvilken nukleinsyre eksprimeres under regulering af en egnet promotor eller replikon;
- transformering af en egnet vært med denne vektor; og
- isolering og rensning af det således vundne epitopbærende polypeptid.

26. Fremgangsmåde ifølge krav 25, hvor det epitopbærende polypeptid isoleres og renses ved elektroforese.

27. Fremgangsmåde til fremstilling af antistoffer, der er specifikke for fragmenter af polypeptider ifølge et hvilket som helst af kravene 1-13, hvilken fremgangsmåde omfatter:

- kondensering af miltceller, der i forvejen er immuniseret med fragmenter eller polypeptider ifølge et hvilket som helst af kravene 1-13, med relevante myelomaceller;
- udvælgelse af de resulterende hybridoma-producerende antistoffer med specificitet for disse fragmenter eller polypeptider; og
- isolering af disse antistoffer, der er specifikke for fragmenter eller polypeptider.

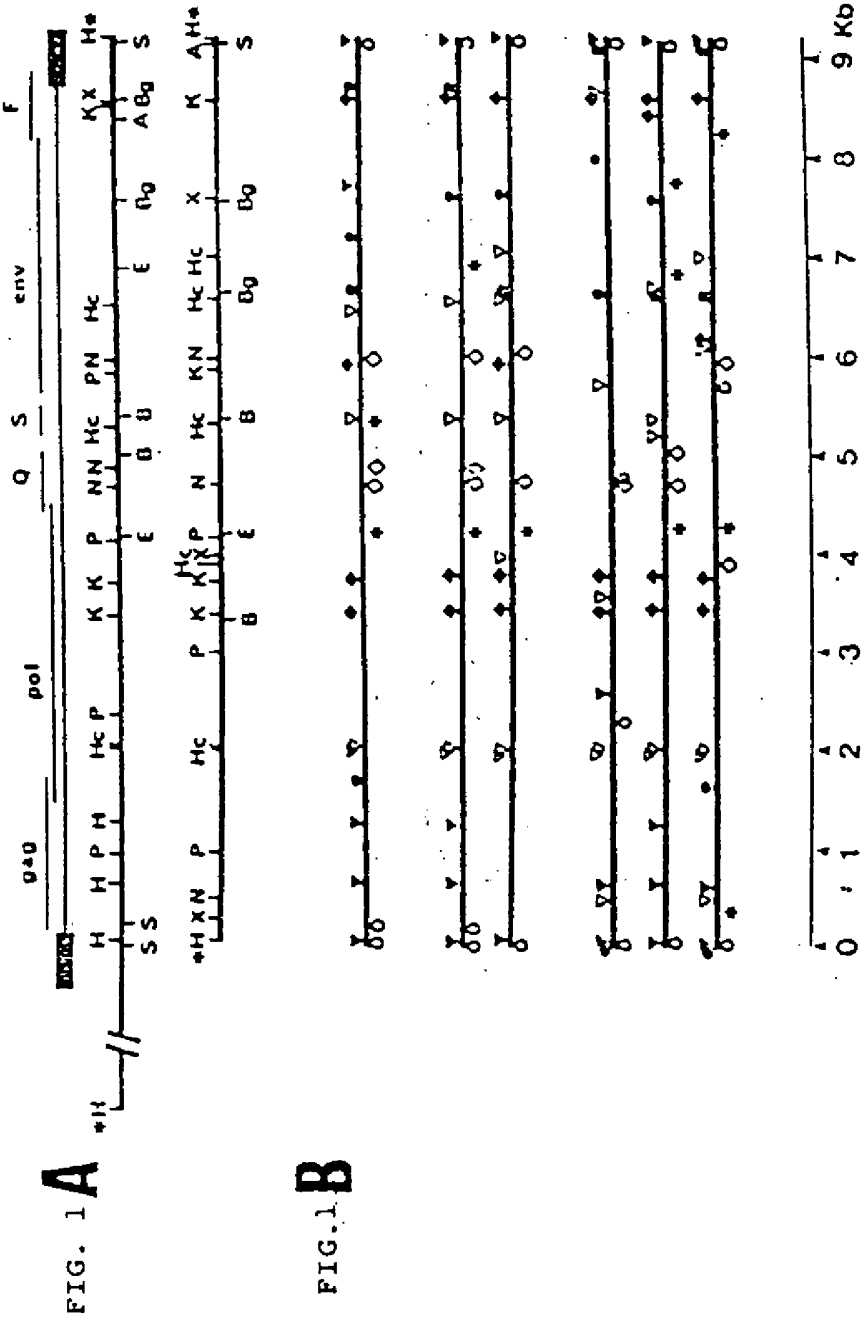
A
gag
pol
env
Q
S
F
LAV eli
LAV mal
B
LAV bru
LAV eli
LAV mal
Z 1
Z 2
Z 3
0
1
2
3
4
5
6
7
8
9 Kb

FIG. 1

FIG. 1

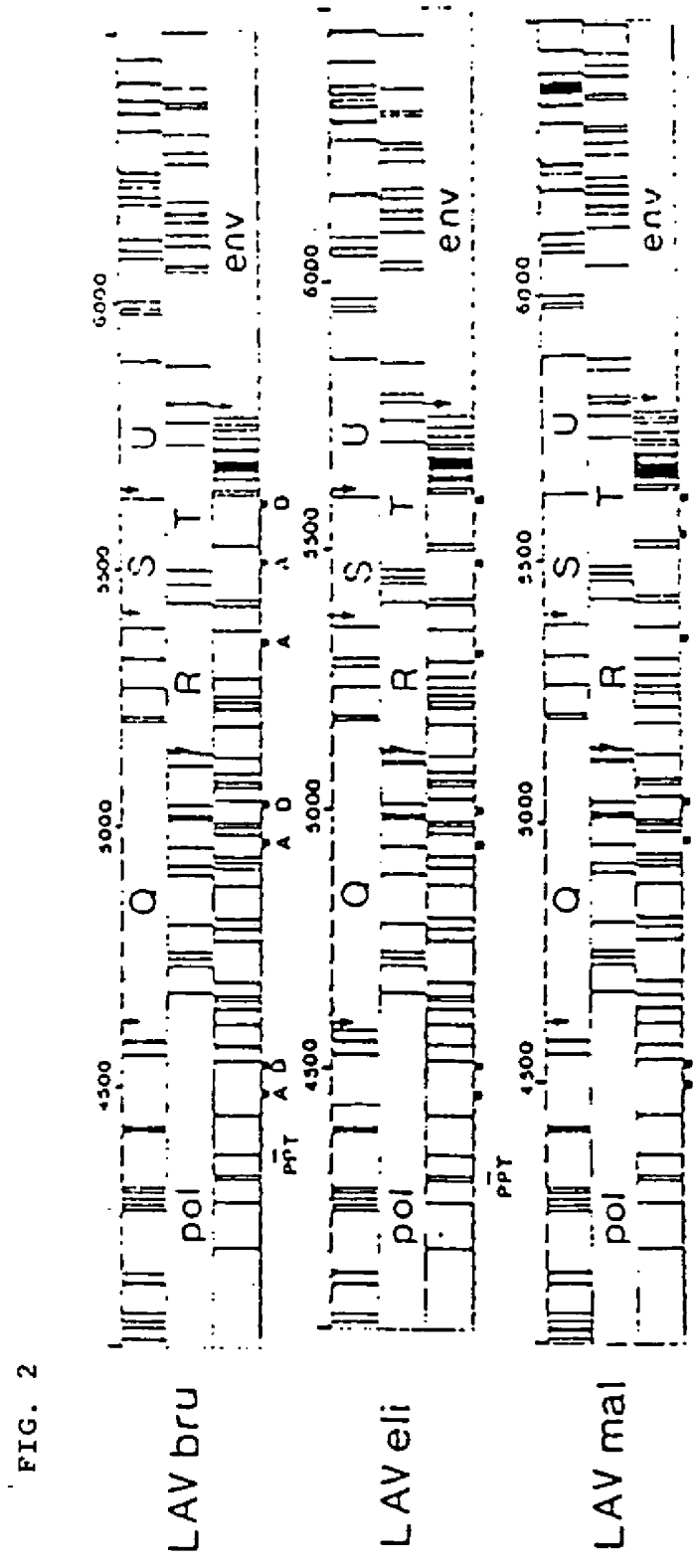

FIG. 2

Cell
66

GAG

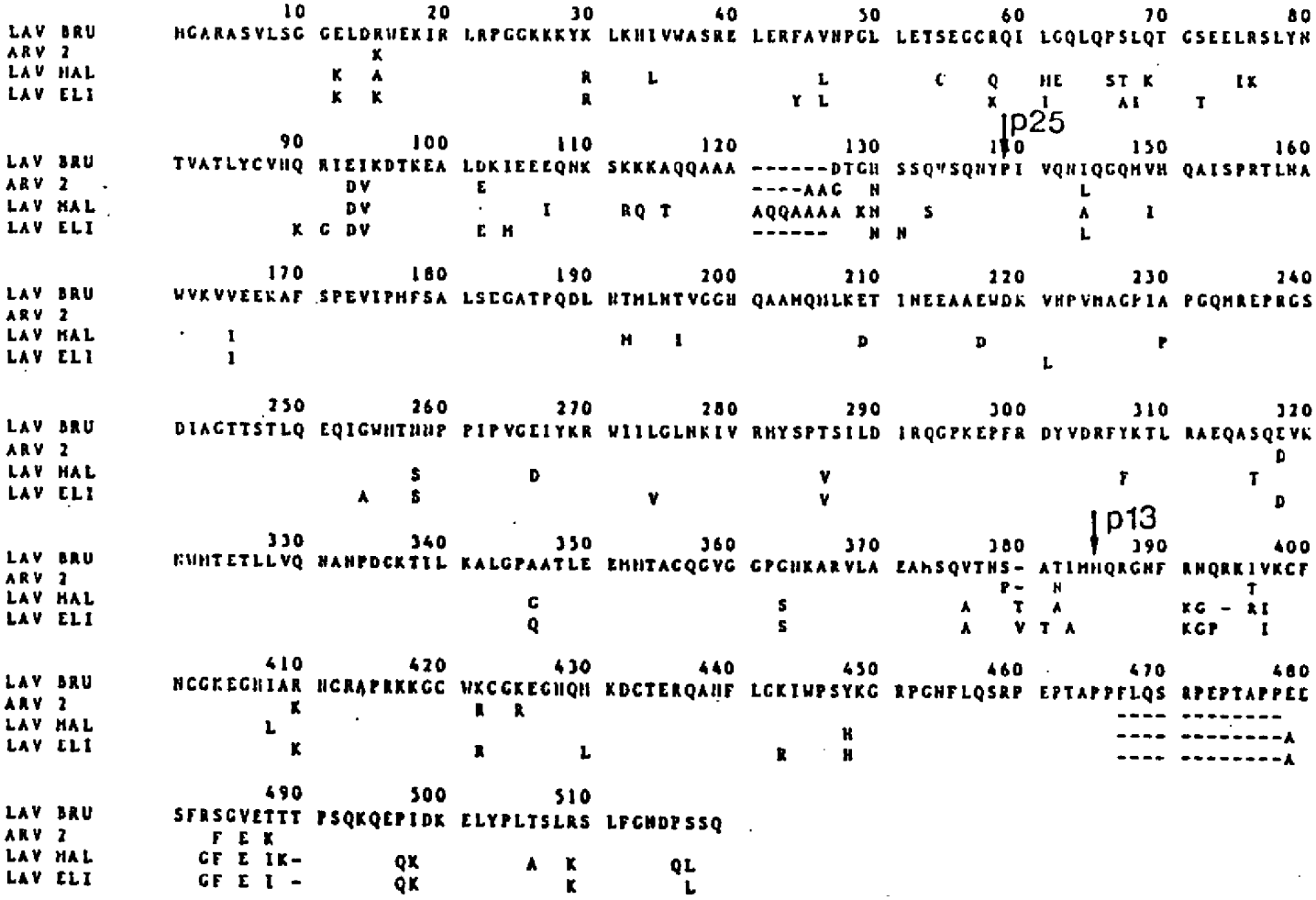

FIG. 3A

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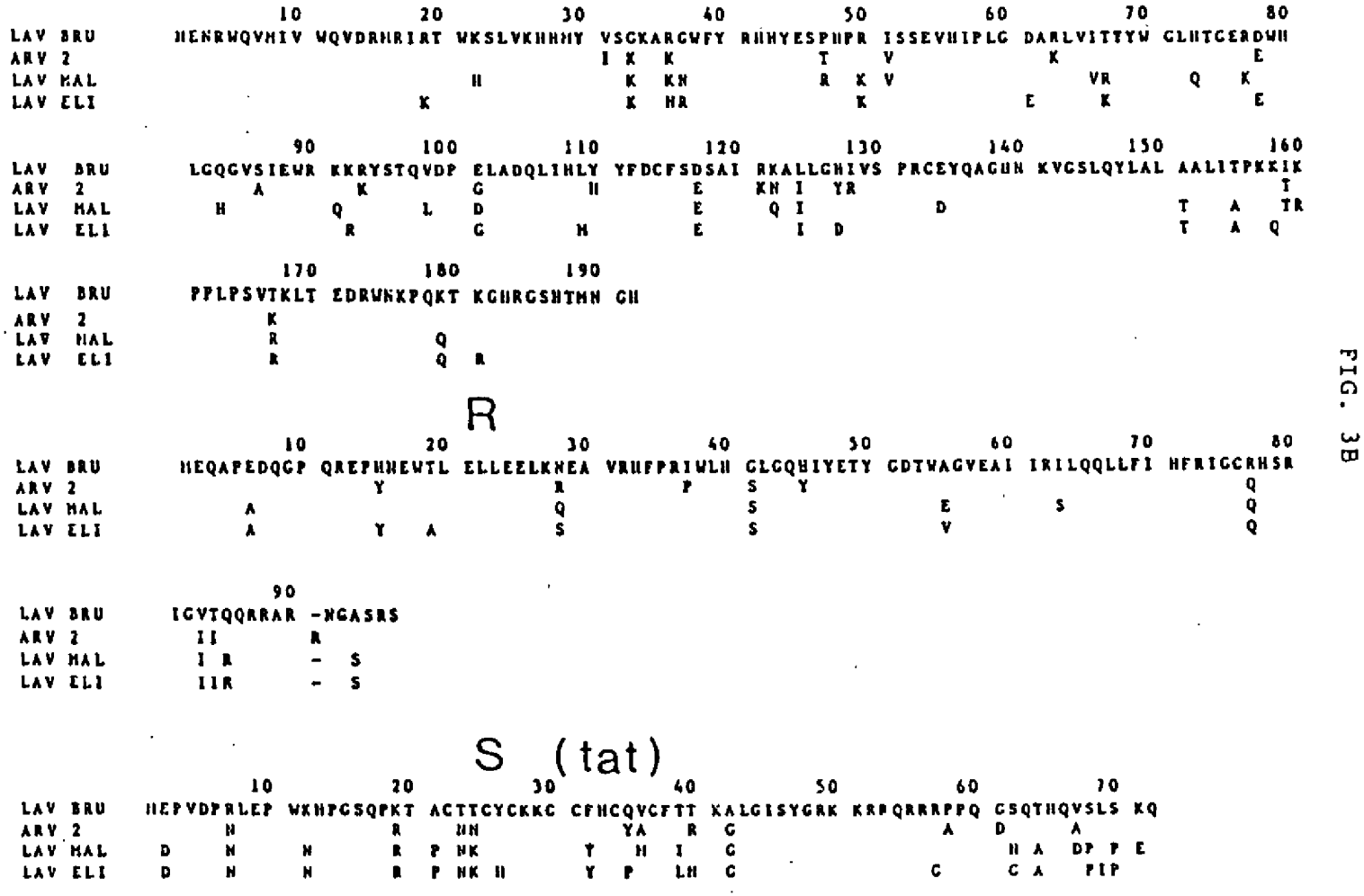


FIG. 3B

2004 01579 L

POL

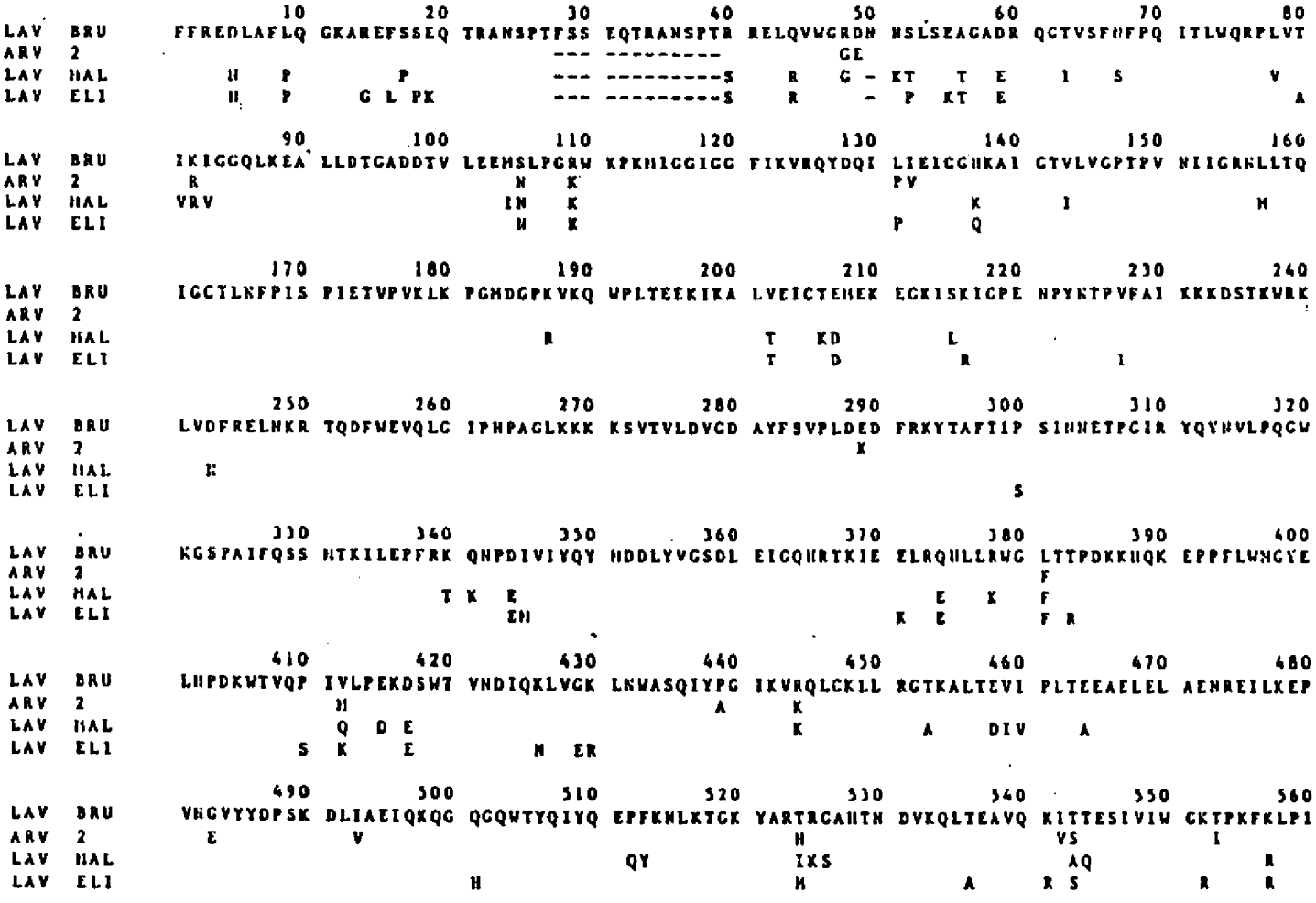


FIG. 3C

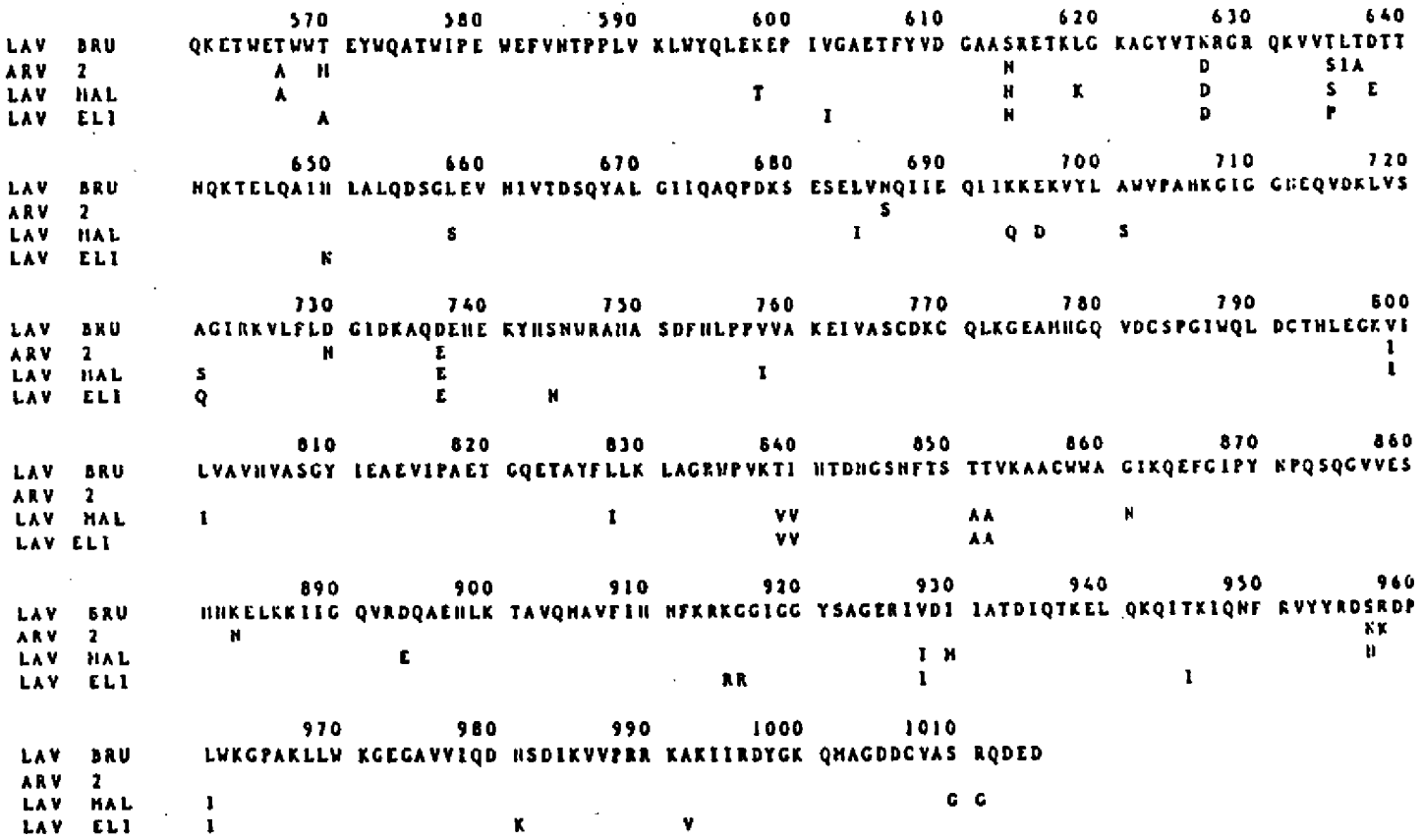


FIG. 3D

FIG. 3E

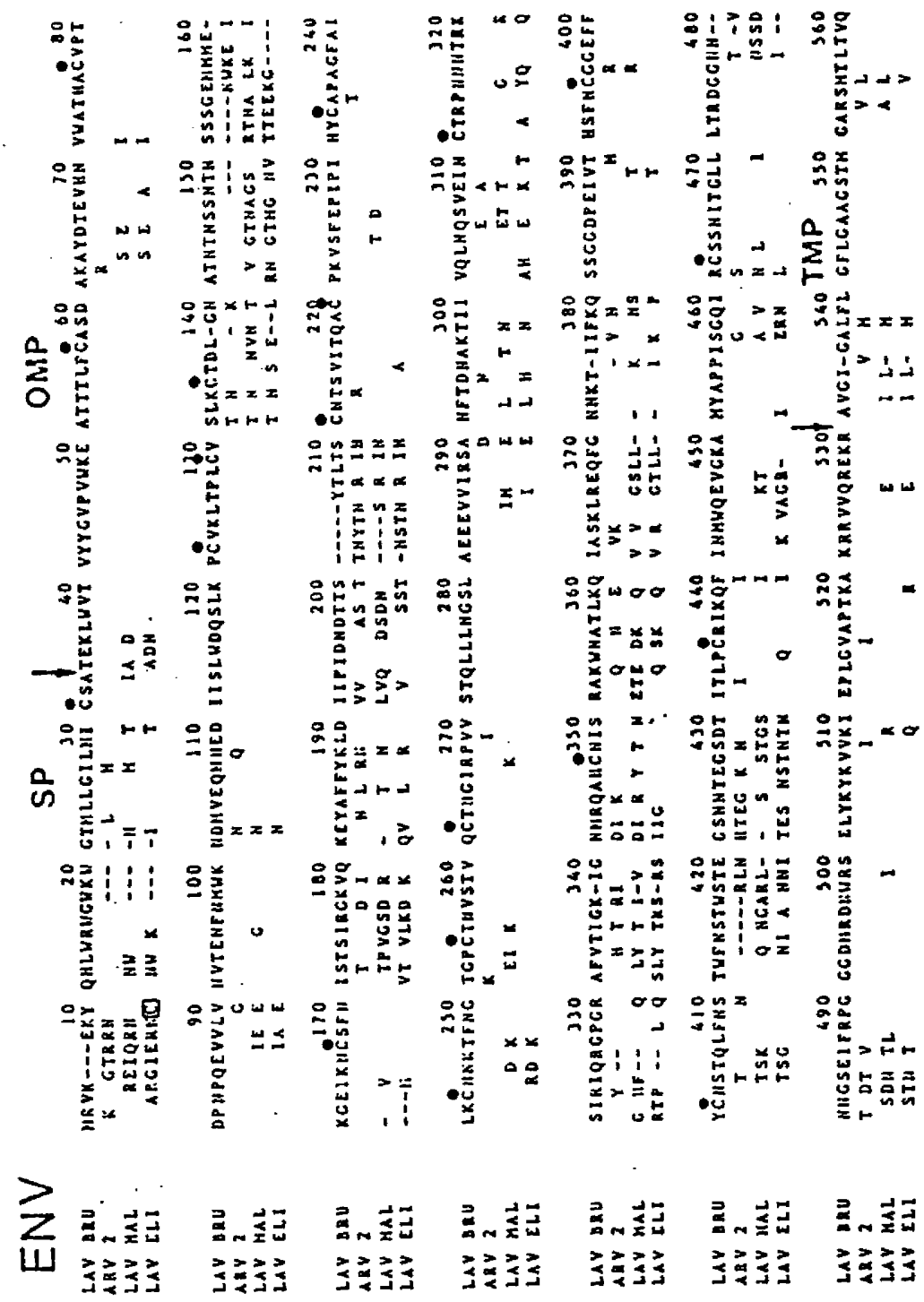


FIG. 3F

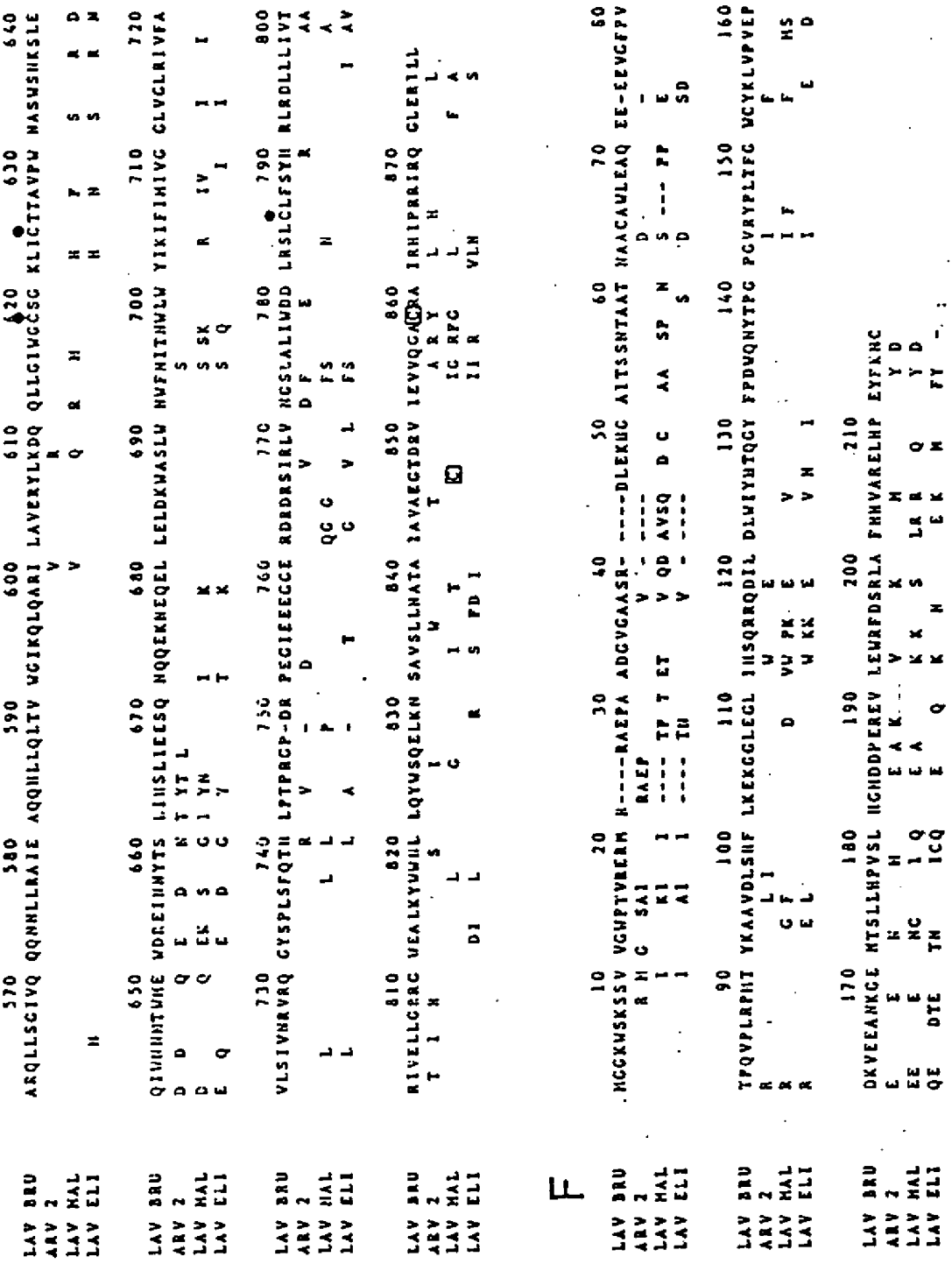


FIG. 4A

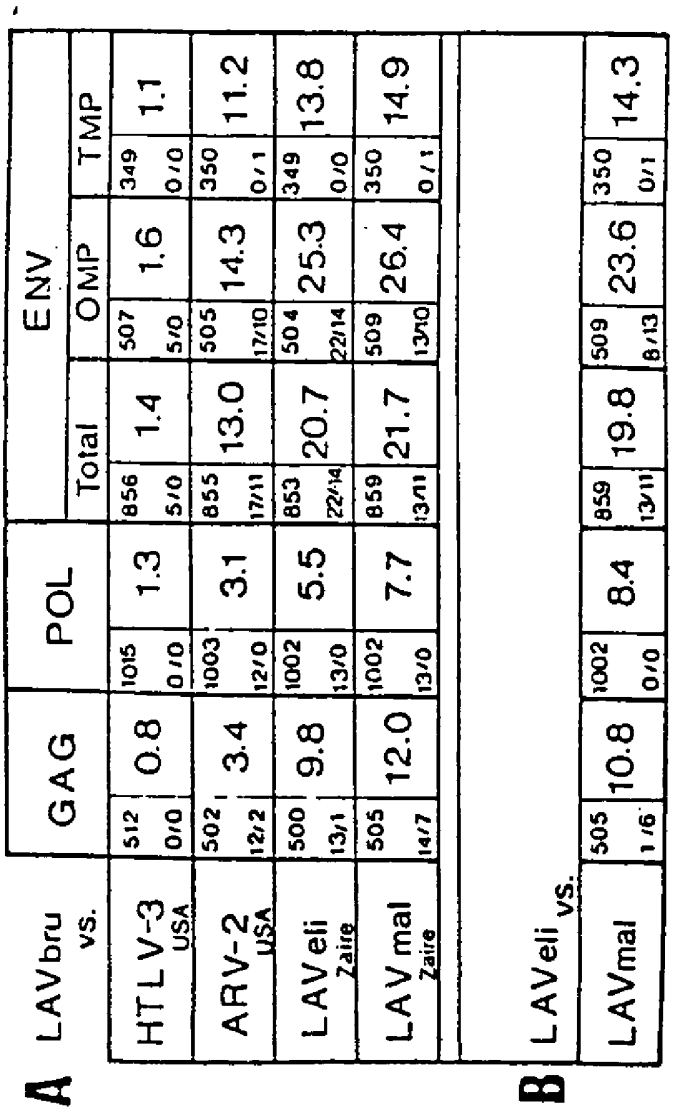
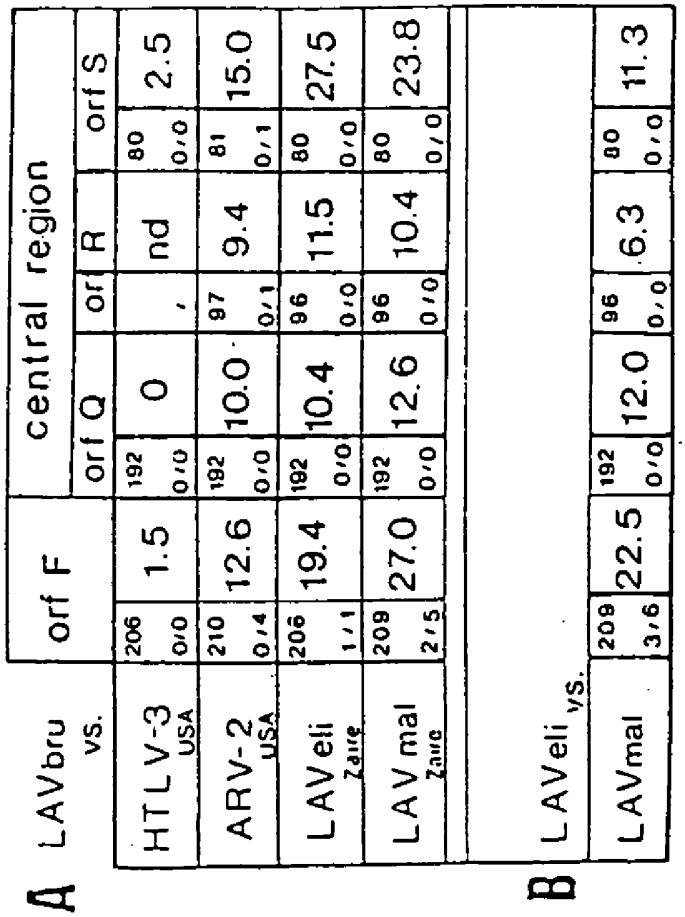

A
LAVbru vs.
GAG
POL
ENV
Total
OMP
TMP
HTLV-3 USA
ARV-2 USA
LAVeli Zaire
LAVmal Zaire
B
LAVeli vs.
LAVmal
512 0/0 0.8
502 12/2 3.4
500 13/1 9.8
505 14/7 12.0
1015 0/0 1.3
1003 12/0 3.1
1002 13/0 5.5
1002 13/0 7.7
856 5/0 1.4
855 17/11 13.0
853 22/14 20.7
859 13/11 21.7
507 5/0 1.6
505 17/10 14.3
504 22/14 25.3
509 13/10 26.4
349 0/0 1.1
350 0/1 11.2
349 0/0 13.8
350 0/1 14.9
505 1/6 10.8
1002 0/0 8.4
859 13/11 19.8
509 8/13 23.6
350 0/1 14.3

FIG. 4B


A
LAVbru vs.
orf F
central region
orf Q
orf
R
orf S
HTLV-3 USA
206 0/0
1.5
192 0/0
0
'
nd
80 0/0
2.5
ARV-2 USA
210 0/4
12.6
192 0/0
10.0
97 0/1
9.4
81 0/1
15.0
LAVeli Zaire
206 1/1
19.4
192 0/0
10.4
96 0/0
11.5
80 0/0
27.5
LAV mal Zaire
209 2/5
27.0
192 0/0
12.6
96 0/0
10.4
80 0/0
23.8
B
LAVeli vs.
LAVmal
209 3/6
22.5
192 0/0
12.0
96 0/0
6.3
80 0/0
11.3

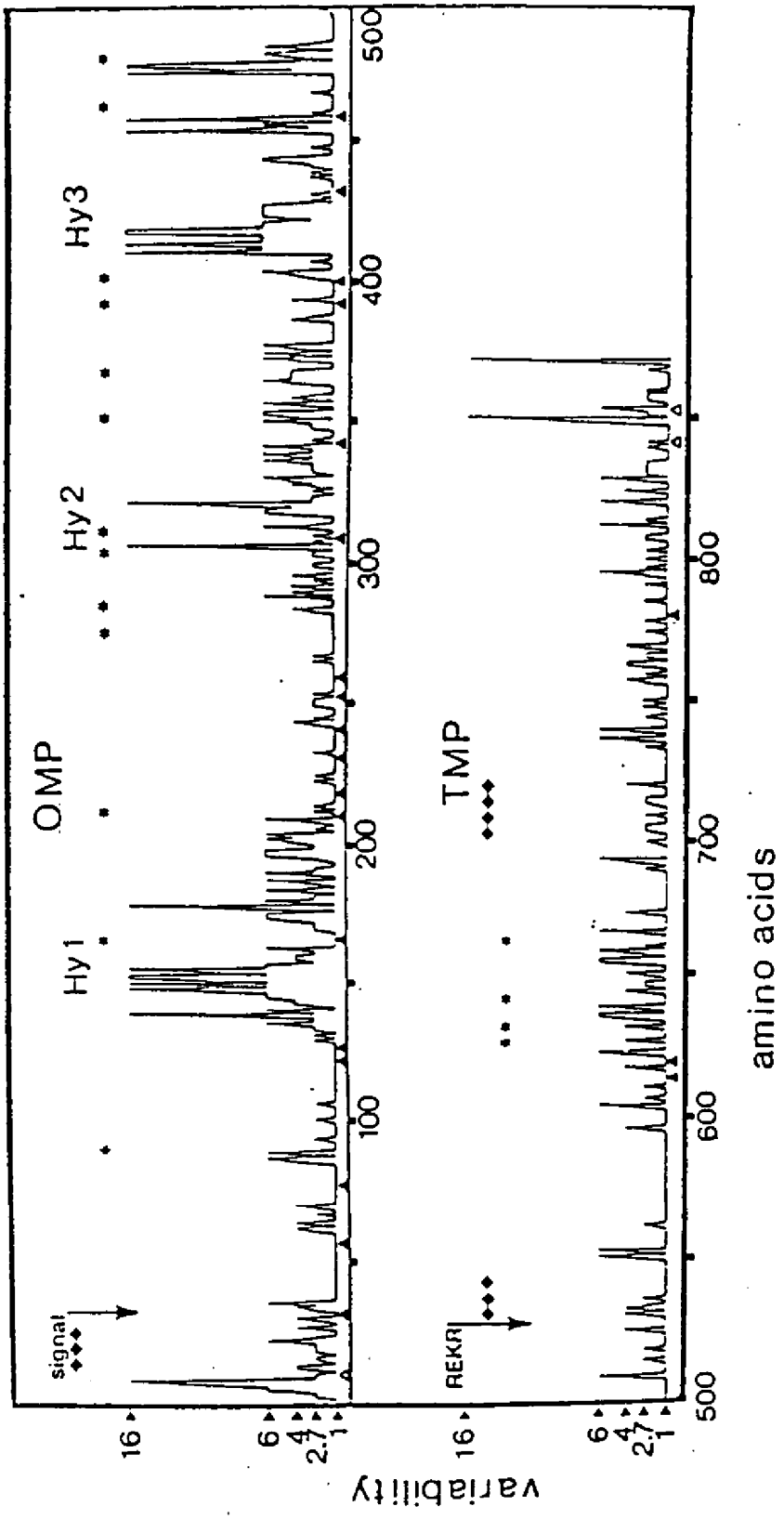

OMP
TMP
Hy1
Hy2
Hy3
signal
REKRI
variability
amino acids
16
6
4
2.7
1
100
200
300
400
500
600
700
800

FIG. 5

FIG. 6A

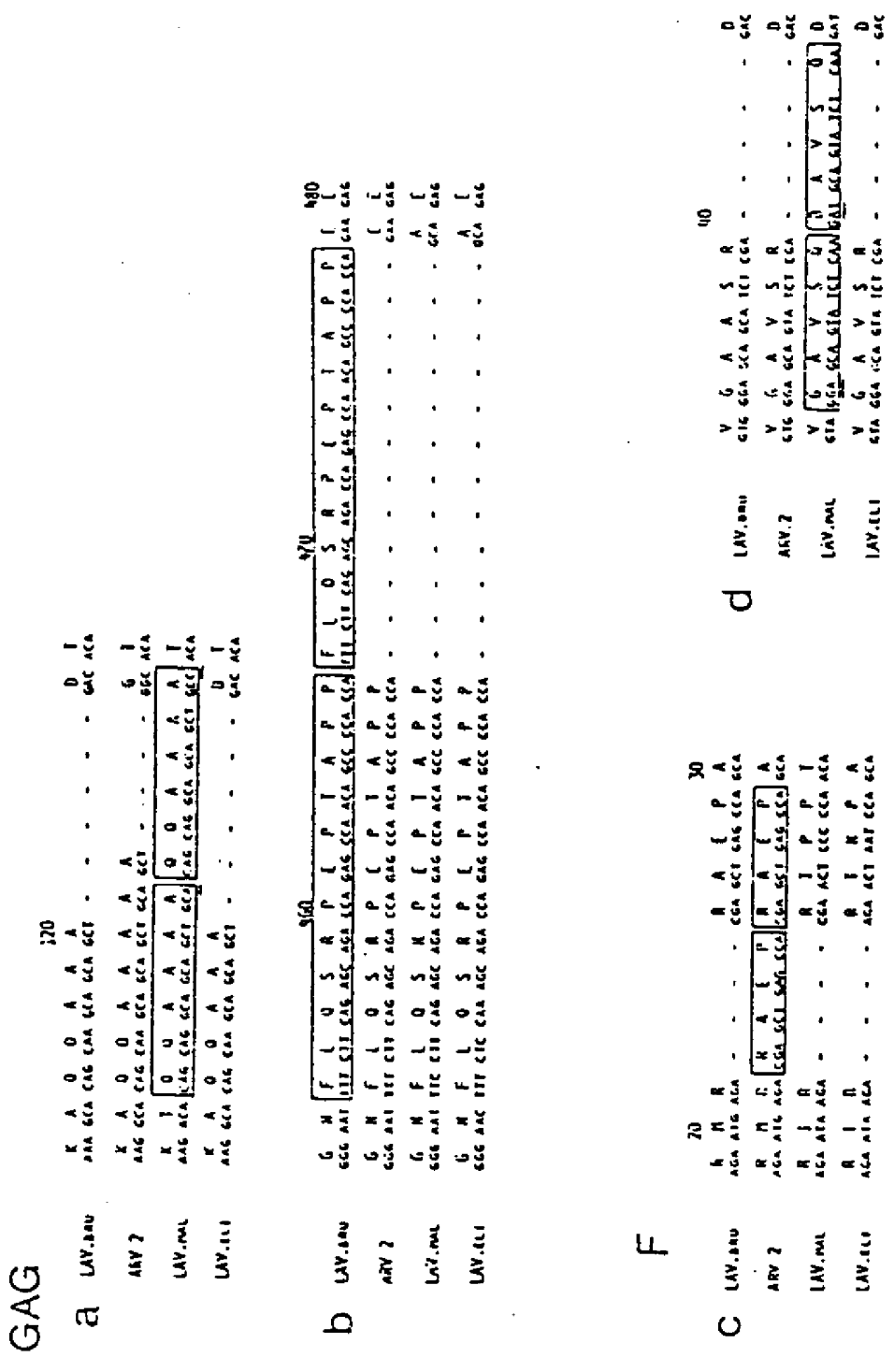
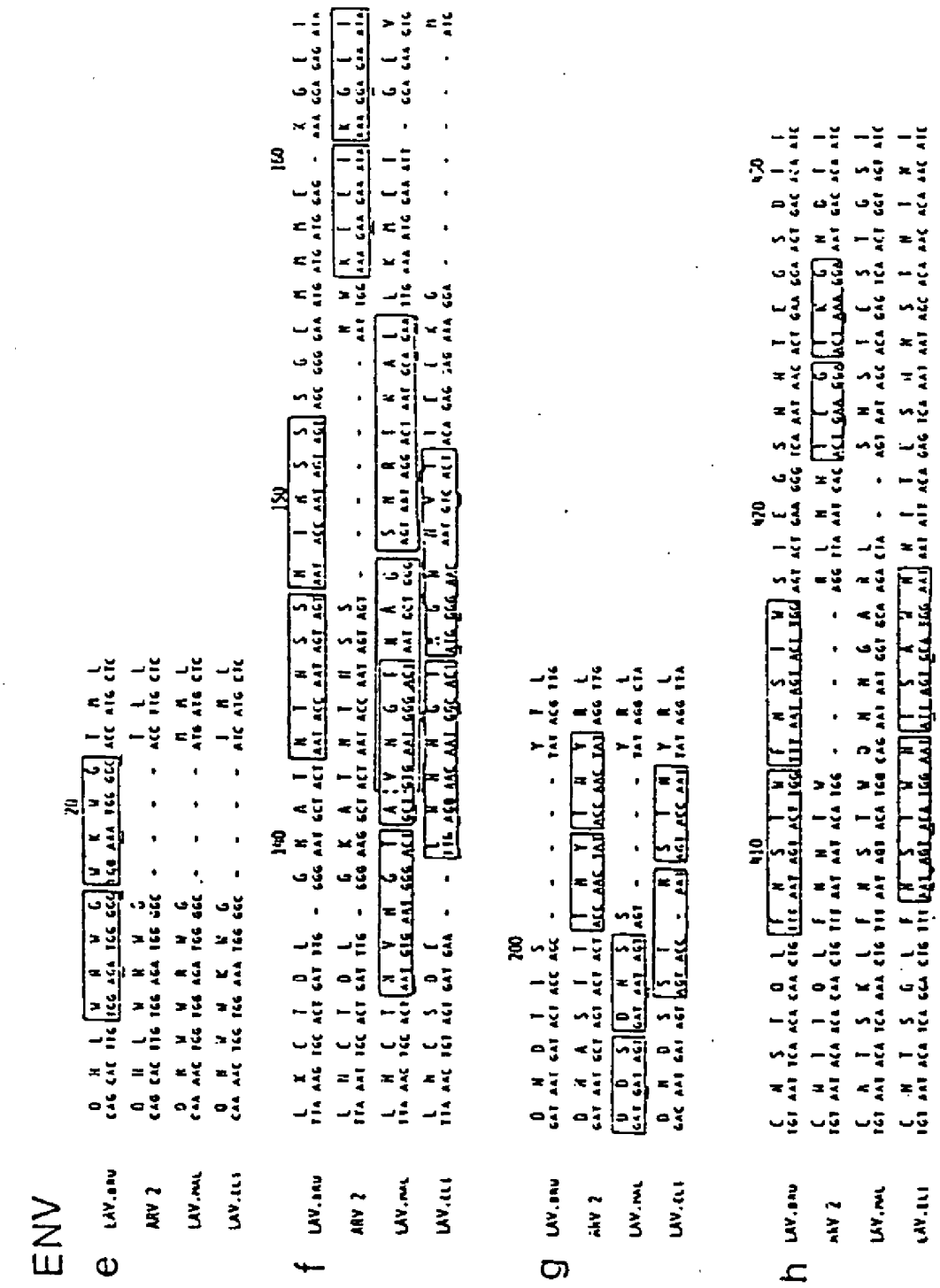


FIG. 6B



LAV.ELI


R
R
U5
U5
GAG
100
200
300
400
500
600
700
800
900
1000
1100
1200
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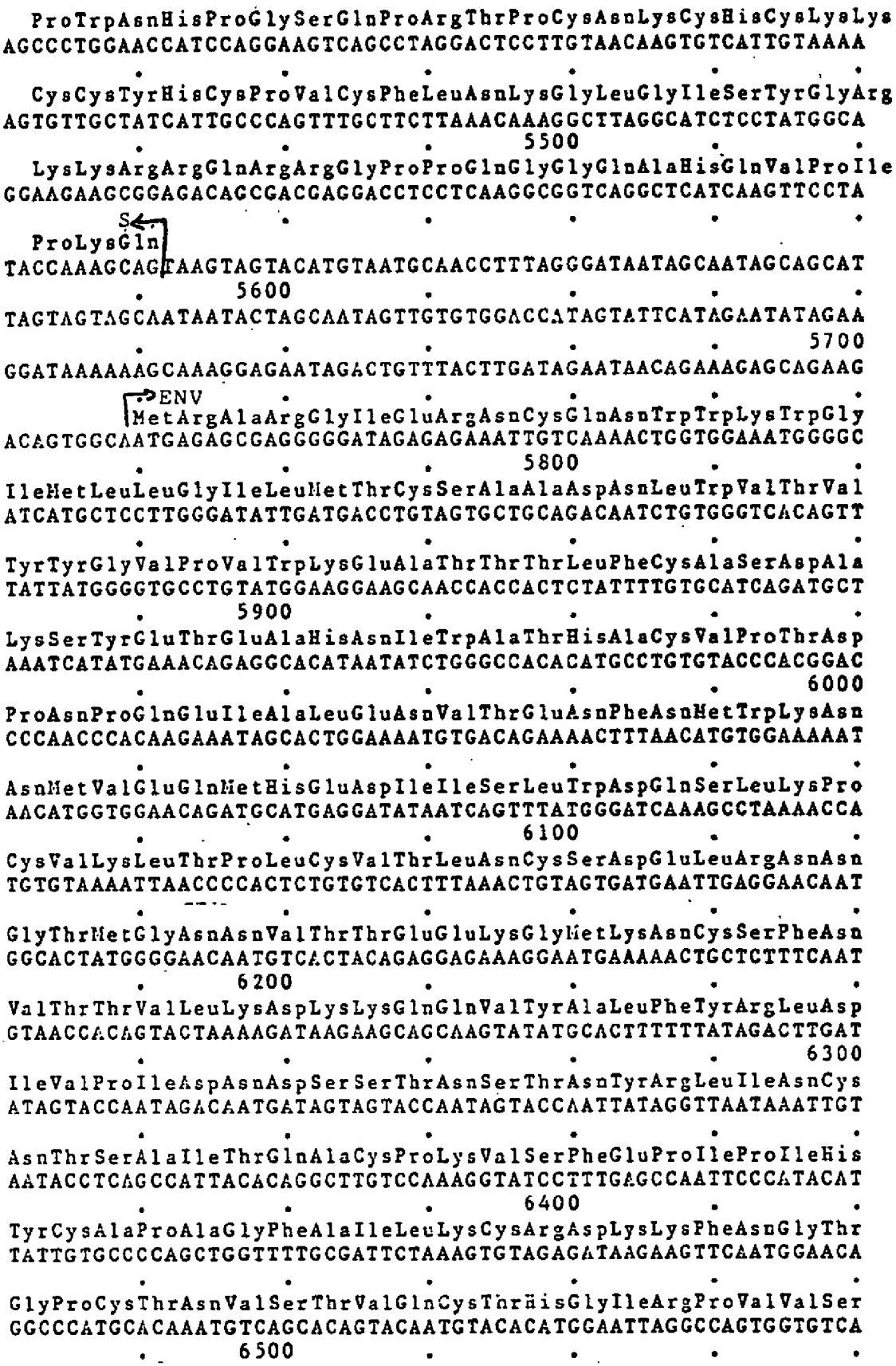
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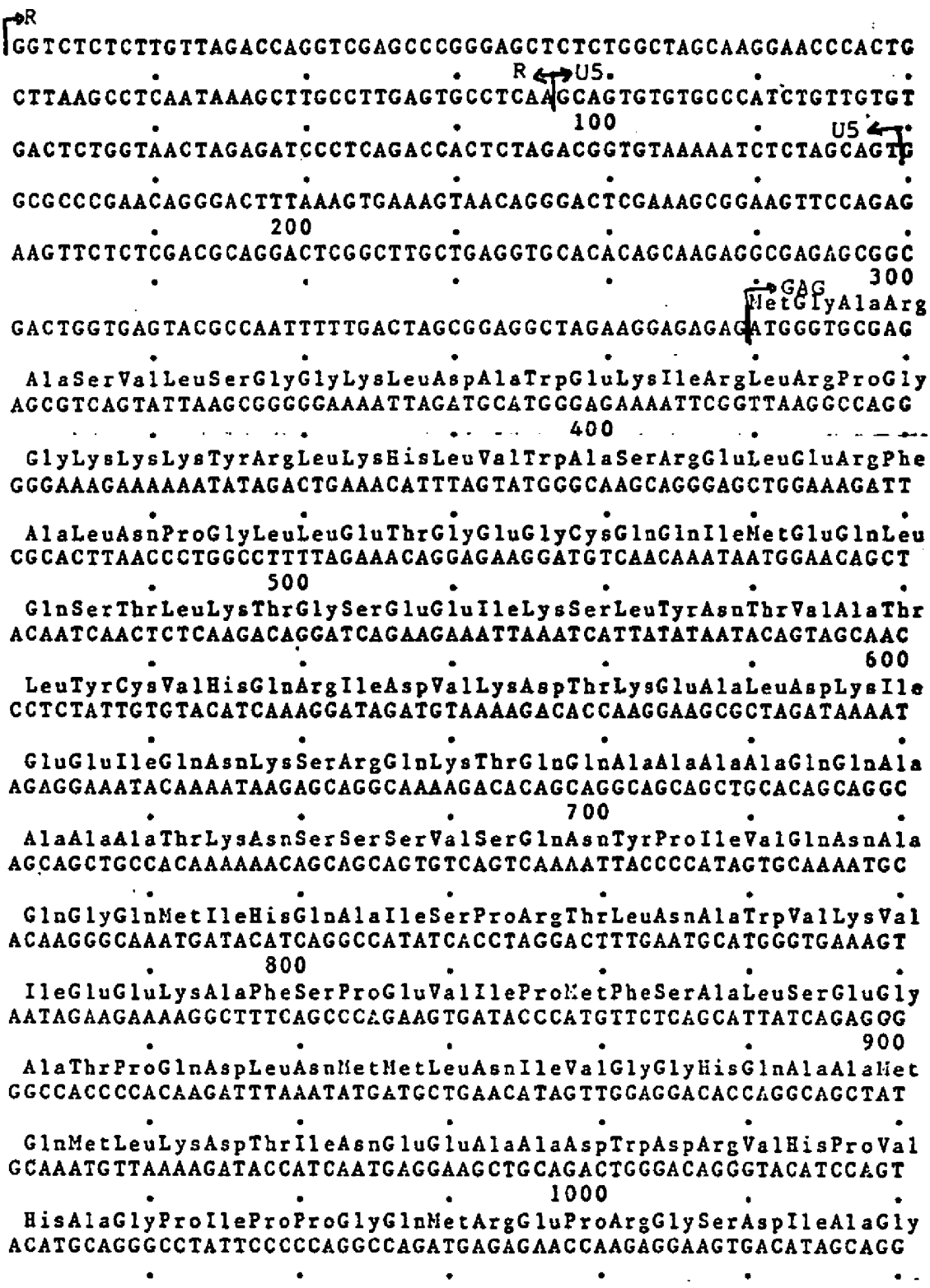
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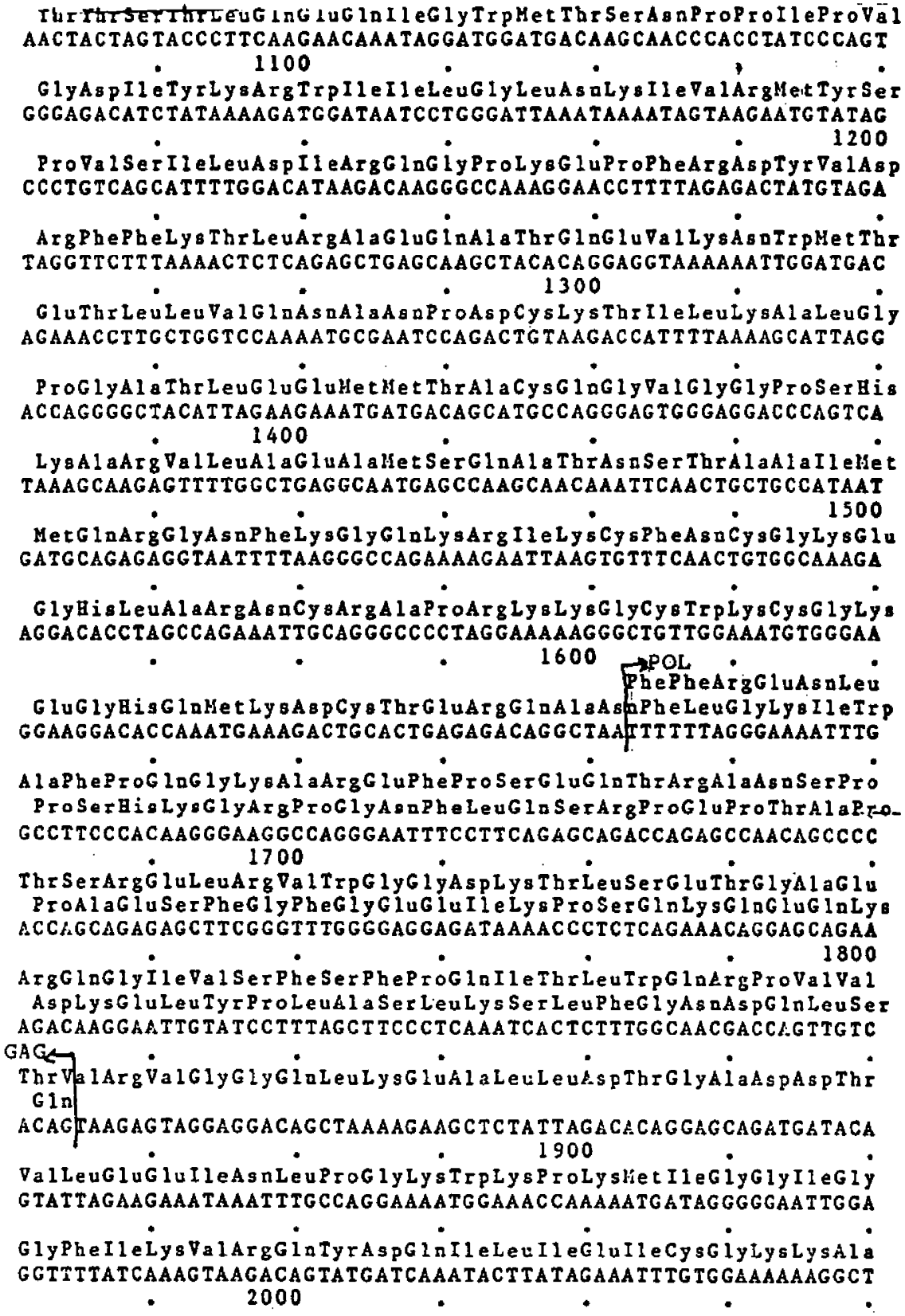
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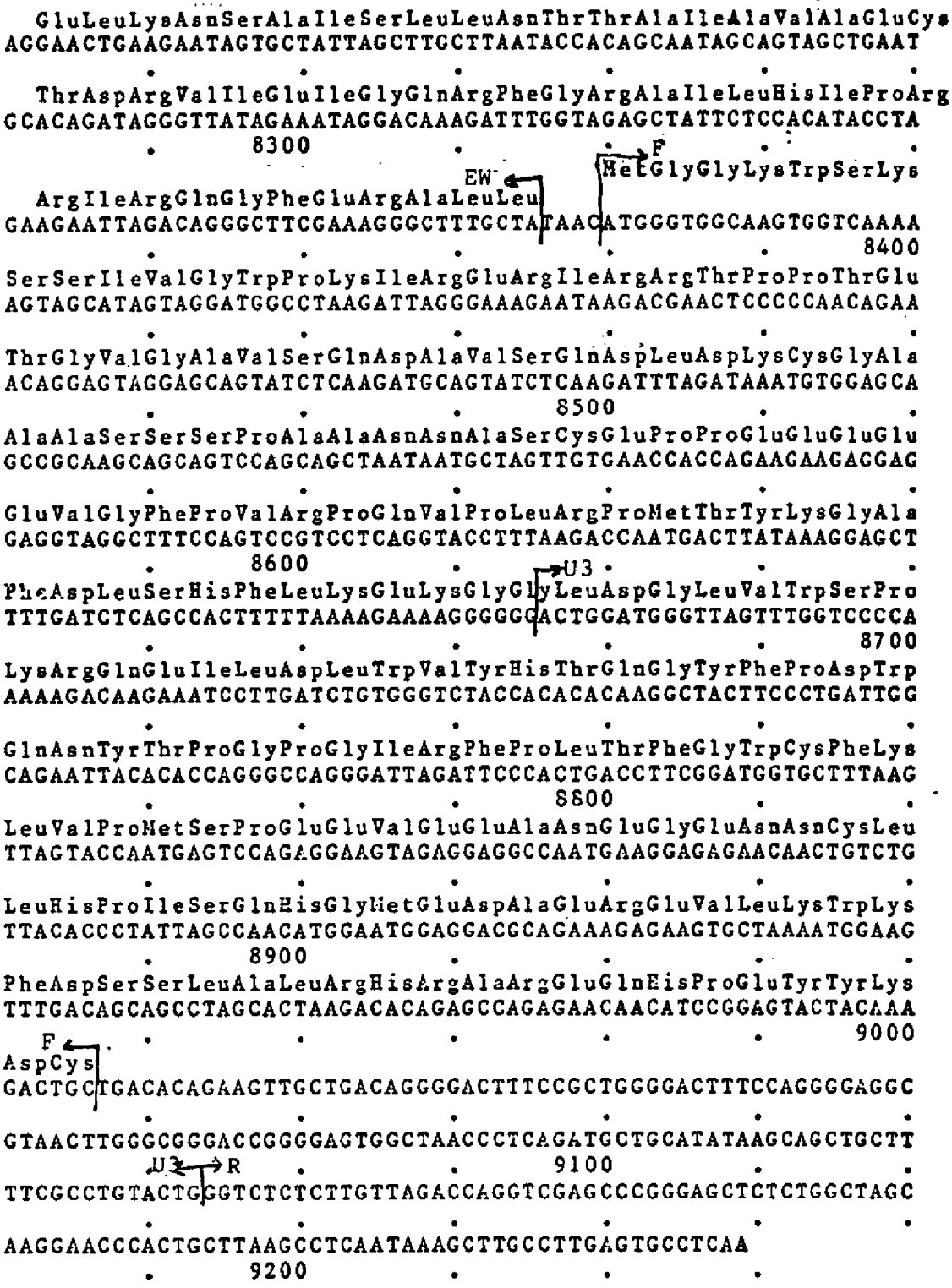
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8600
U3
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8700
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8800
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8900
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9000
F
AspCys
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U3
R
9100
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AAGGAACCCACTGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCCTCAA
9200