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(54) **AMINO ACID TRANSPORTERS AND USES**

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(57) **ABSTRACT**

The present invention relates to novel mammalian amino acid transporter proteins and the genes that encode such proteins. The invention is directed toward the isolation, characterization and pharmacological use of the human amino acid transporter proteins EAAT1, EAAT2, EAAT3 and ASCT1. The invention specifically provides isolated complementary DNA copies of mRNA corresponding to each of these transporter genes. Also provided are recombinant expression constructs capable of expressing each of the amino acid transporter genes of the invention in cultures of transformed prokaryotic and eukaryotic cells, as well as such cultures of transformed cells that synthesize the human amino acid transporter proteins encoded therein. The invention also provides methods for screening in vitro compounds having transport-modulating properties using preparations of transporter proteins from such cultures of cells transformed with recombinant expression constructs.

FIG. 1A

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CACCTCTAGC  TCGGAGCGGC  GTGTAGCGCC  ATG GAG AAG AGC AAC GAG ACC AAC      54
                                    Met Glu Lys Ser Asn Glu Thr Asn
                                     1                5
GGC TAC CTT GAC AGC GCT CAG GCG GGG CCT GCG GCC GGG CCC GGA GCT      102
Gly Tyr Leu Asp Ser Ala Gln Ala Gly Pro Ala Ala Gly Pro Gly Ala
        10                  15                  20
CCG GGG ACC GCG GCG GGA CGC GCA CGG CGT TGC GCG CGC TTC CTG CGG      150
Pro Gly Thr Ala Ala Gly Arg Ala Arg Arg Cys Ala Arg Phe Leu Arg
 25             30                  35                  40
CGC CAA GCG CTG GTG CTG CTC ACC GTG TCC GGG GTG CTG GCG GGC GCG      198
Arg Gln Ala Leu Val Leu Leu Thr Val Ser Gly Val Leu Ala Gly Ala
                45                  50                  55
GGC CTG GGC GCG GCG TTG CGC GGG CTC AGC CTG AGC CGC ACG CAG GTC      246
Gly Leu Gly Ala Ala Leu Arg Gly Leu Ser Leu Ser Arg Thr Gln Val
        60                  65                  70
ACC TAC CTG GCC TTC CCC GGC GAG ATG CTG CTC CGC ATG CTG CGC ATG      294
Thr Tyr Leu Ala Phe Pro Gly Glu Met Leu Leu Arg Met Leu Arg Met
     75                  80                  85
ATC ATC CTG CCG CTG GTG GTC TGC AGC CTG GTG TCG GGC GCC GCC TCG      342
Ile Ile Leu Pro Leu Val Val Cys Ser Leu Val Ser Gly Ala Ala Ser
 90                  95                  100
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FIG. 1B

CTC Leu 105	GAT Asp	GCC Ala	AGC Ser	TGC Cys	CTC Leu 110	GGG Gly	CGT Arg	CTG Leu	GGC Gly	GGC Gly 115	ATC Ile	CGT Arg	GTC Val	GCC Ala	TAC Tyr 120	390
TTT Phe	GGC Gly	CTC Leu	ACC Thr	ACA Thr 125	CTG Leu	AGT Ser	GCC Ala	TCG Ser	GCG Ala 130	CTC Leu	GCC Ala	GTG Val	GCC Ala	TTG Leu 135	GCG Ala	438
TTC Phe	ATC Ile	ATC Ile	AAG Lys 140	CCA Pro	GGA Gly	TCC Ser	GGT Gly	GCG Ala 145	CAG Gln	ACC Thr	CTT Leu	CAG Gln	TCC Ser 150	AGC Ser	GAC Asp	486
CTG Leu	GGG Gly	CTG Leu 155	GAG Glu	GAC Asp	TCG Ser	GGG Gly	CCT Pro 160	CCT Pro	CCT Pro	GTC Val	CCC Pro	AAA Lys 165	GAG Glu	ACG Thr	GTG Val	534
GAC Asp	TCT Ser 170	TTC Phe	CTC Leu	GAC Asp	CTG Leu	GCC Ala 175	AGA Arg	AAC Asn	CTG Leu	TTT Phe	CCC Pro 180	TCC Ser	AAT Asn	CTT Leu	GTG Val	582
GTT Val 185	GCA Ala	GCT Ala	TTC Phe	CGT Arg	ACG Thr 190	TAT Tyr	GCA Ala	ACC Thr	GAT Asp	TAT Tyr 195	AAA Lys	GTC Val	GTG Val	ACC Thr	CAG Gln 200	630
AAC Asn	AGC Ser	AGC Ser	TCT Ser	GGA Gly 205	AAT Asn	GTA Val	ACC Thr	CAT His	GAA Glu 210	AAG Lys	ATC Ile	CCC Pro	ATA Ile	GGC Gly 215	ACT Thr	678

FIG. 1C

GAG Glu	ATA Ile	GAA Glu	GGG Gly 220	ATG Met	AAC Asn	ATT Ile	TTA Leu	GGA Gly 225	TTG Leu	GTC Val	CTG Leu	TTT Phe	GCT Ala 230	CTG Leu	GTG Val	726
TTA Leu	CGA Gly	GTG Val 235	GCC Ala	TTA Leu	AAG Lys	AAA Lys	CTA Leu 240	GGC Gly	TCC Ser	GAA Glu	GGA Gly	GAA Glu 245	GAC Asp	CTC Leu	ATC Ile	774
CGT Arg	TTC Phe 250	TTC Phe	AAT Asn	TCC Ser	CTC Leu	AAC Asn 255	GAG Glu	GCG Ala	ACG Thr	ATG Met	GTG Val 260	CTG Leu	GTG Val	TCC Ser	TGG Trp	822
ATT Ile 265	ATG Met	TGG Trp	TAC Tyr	GTA Val	CCT Pro 270	GTG Val	GGC Gly	ATC Ile	ATG Met	TTC Phe 275	CCT Leu	GTT Val	GGA Gly	AGC Ser	AAG Lys 280	870
ATC Ile	GTG Val	GAA Glu	ATG Met	AAA Lys 285	GAC Asp	ATC Ile	ATC Ile	GTG Val	CTG Leu 290	GTG Val	ACC Thr	AGC Ser	CTG Leu	GGG Gly 295	AAA Lys	918
TAC Tyr	ATC Ile	TTC Phe	GCA Ala 300	TCT Ser	ATA Ile	TTG Leu	GGC Gly	CAT His 305	GTT Val	ATT Ile	CAT His	GGA Gly	GGA Gly 310	ATT Ile	GTT Val	966
CTG Leu	CCA Pro	CTT Leu 315	ATT Ile	TAT Tyr	TTT Phe	GTT Val	TTC Phe 320	ACA Thr	CGA Arg	AAA Lys	AAC Asn	CCA Pro 325	TTC Phe	AGA Arg	TTC Phe	1014

FIG. 1D

CTC Leu	CTG Leu 330	GGC Gly	CTC Leu	CTC Leu	GCC Ala	CCA Pro 335	TTT Phe	GCG Ala	ACA Thr	GCA Ala	TTT Phe 340	GCT Ala	ACC Thr	TGC Cys	TCC Ser	1062
AGC Ser 345	TCA Ser	GCG Ala	ACC Thr	CTT Leu	CCC Pro 350	TCT Ser	ATG Met	ATG Met	AAG Lys	TGC Cys 355	ATT Ile	GAA Glu	GAG Glu	AAC Asn	AAT Asn 360	1110
GGT Gly	GTG Val	GAC Asp	AAG Lys	AGG Arg 365	ATC Ile	AGC Ser	AGG Arg	TTT Phe	ATT Ile 370	CTC Leu	CCC Pro	ATC Ile	GGG Gly	GCC Ala 375	ACC Thr	1158
GTG Val	AAC Asn	ATG Met	GAC Asp 380	GGA Gly	GCA Ala	GCC Ala	ATC Ile	TTC Phe 385	CAG Gln	TGT Cys	GTG Val	GCC Ala	CCG Ala 390	GTG Val	TTC Phe	1206
ATT Ile	GCG Ala	CAA Gln 395	CTC Leu	AAC Asn	AAC Asn	ATA Ile	GAG Glu 400	CTC Leu	AAC Asn	GCA Ala	GGA Gly	CAG Gln 405	ATT Ile	TTC Phe	ACC Thr	1254
ATT Ile	CTA Leu 410	GTG Val	ACT Thr	GCC Ala	ACA Thr	GCG Ala 415	TCC Ser	AGT Ser	GTT Val	GGA Gly	GCA Ala 420	GCA Ala	GGC Gly	GTG Val	CCA Pro	1302
GCT Ala 425	GGA Gly	GGG Gly	GTC Val	CTC Leu	ACC Thr 430	ATT Ile	GCC Ala	ATT Ile	ATC Ile	CTG Leu 435	GAG Glu	GCC Ala	ATT Ile	GGG Gly	CTG Leu 440	1350

FIG. 1E

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CCT ACT CAT GAC CTG CCT CTG ATC CTG GCT GTG GAC TGG ATT GTG GAC          1398
Pro Thr His Asp Leu Pro Leu Ile Leu Ala Val Asp Trp Ile Val Asp
                445                 450             455

CGG ACC ACC ACG GTG GTG AAT GTG GAG GGG GAT GCC CTG GGT GCA GGC          1446
Arg Thr Thr Thr Val Val Asn Val Glu Gly Asp Ala Leu Gly Ala Gly
            460                 465             470

ATT CTC CAC CAC CTG AAT CAG AAG GCA ACA AAG AAA GGC GAG CAG GAA          1494
Ile Leu His His Leu Asn Gln Lys Ala Thr Lys Lys Gly Glu Gln Glu
        475                 480                 485

CTT GCT GAG GTG AAA GTG GAA GCC ATC CCC AAC TGC AAG TCT GAG GAG          1542
Leu Ala Glu Val Lys Val Glu Ala Ile Pro Asn Cys Lys Ser Glu Glu
    490                 495                 500

GAG ACA TCG CCC CTG GTG ACA CAC CAG AAC CCC GCT GGC CCC GTG GCC          1590
Glu Thr Ser Pro Leu Val Thr His Gln Asn Pro Ala Gly Pro Val Ala
505                 510                 515                 520

AGT GCC CCA GAA CTG GAA TCC AAG GAG TCG GTT CTG TGATGGGGCT              1636
Ser Ala Pro Glu Leu Glu Ser Lys Glu Ser Val Leu
                525                 530

GGGCTTTGGG CTTGCCTGCC AGCAGTGATG TCCCACCCTG TTCA                         1680
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FIG. 2A

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AAAGAAGAGA  CCCTCCTAGA  AAAGTAAAAT  ATG ACT AAA AGC AAT GGA GAA GAG          54
                                    Met Thr Lys Ser Asn Gly Glu Glu
                                        1                   5

CCC AAG ATG GGG GGC AGG ATG GAG AGA TTC CAG CAG GGA GTC CTG AAA          102
Pro Lys Met Gly Gly Arg Met Glu Arg Phe Gln Gln Gly Val Arg Lys
    10                  15                  20

CGC ACA CTT TTG GCC AGG AAG AAA GTG CAG AAC ATT ACA AAG GAG GTT          150
Arg Thr Leu Leu Ala Lys Lys Lys Val Gln Asn Ile Thr Lys Glu Val
25                  30                  35                  40

GTT AAA AGT TAC CTG TTT CGG AAT GCT TTT GTG CTG CTC ACA GTC ACC          198
Val Lys Ser Tyr Leu Phe Arg Asn Ala Phe Val Leu Leu Thr Val Thr
                45                  50                  55

GCT GTC ATT GTG GGT ACA ATC CTT GGA TTT ACC CTC CGA CCA TAC AGA          246
Ala Val Ile Val Gly Thr Ile Leu Gly Phe Thr Leu Arg Pro Tyr Arg
            60                  65                  70

ATG AGC TAC CGG GAA GTC AAG TAC TTC TCC TTT CCT GGG GAA CTT CTG          294
Met Ser Tyr Arg Glu Val Lys Tyr Phe Ser Phe Pro Gly Glu Leu Leu
        75                  80                  85

ATG AGG ATG TTA CAG ATG CTG GTC TTA CCA CTT ATC ATC TCC AGT CTT          342
Met Arg Met Leu Gln Met Leu Val Leu Pro Leu Ile Ile Ser Ser Leu
    90                  95                  100
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FIG. 2B

GTC Val 105	ACA Thr	GGA Gly	ATG Met	GCG Ala	GCG Ala 110	CTA Leu	GAT Asp	AGT Ser	AAG Lys	GCA Ala 115	TCA Ser	GGG Gly	AAG Lys	TGG Trp	GAA Glu 120	390
TGC Cys	GGA Gly	GCT Ala	GTA Val	GTC Val 125	TAT Tyr	TAT Tyr	ATG Met	ACT Thr	ACC Thr 130	ACC Thr	ATC Ile	ATT Ile	GCT Ala	GTG Val 135	GTG Val	438
ATT Ile	GGC Gly	ATA Ile	ATC Ile 140	ATT Ile	GTC Val	ATC Ile	ATC Ile	ATC Ile 145	CAT His	CCT Pro	GGG Gly	AAG Lys	GGC Gly 150	ACA Thr	AAG Lys	486
GAA Glu	AAC Asn	ATG Met 155	CAC His	AGA Arg	GAA Glu	GGC Gly	AAA Lys 160	ATT Ile	GTA Val	CGA Arg	GTG Val	ACA Thr 165	GCT Ala	GCA Ala	GAT Asp	534
GCC Ala	TTC Phe 170	CTG Leu	GAC Asp	TTG Leu	ATC Ile	AGG Arg 175	AAC Asn	ATG Met	TTA Leu	AAT Asn	CCA Pro 180	AAT Asn	CTG Leu	GTA Val	GAA Glu	582
GCC Ala 185	TGC Cys	TTT Phe	AAA Lys	GAG Gln	TTT Phe 190	AAA Lys	ACC Thr	AAC Asn	TAT Tyr	GAG Glu 195	AAG Lys	AGA Arg	AGC Ser	TTT Phe	AAA Lys 200	630
GTG Val	CCC Pro	ATC Ile	GAG Gln	GCC Ala 205	AAC Asn	GAA Glu	ACG Thr	CCT Leu	GTG Val 210	GGT Gly	GCT Ala	GTG Val	ATA Ile	AAC Asn 215	AAT Asn	678

FIG. 2C

GTG Val	TCT Ser	GAG Glu	GCC Ala 220	ATG Met	GAG Glu	ACT Thr	CTT Leu	ACC Thr 225	CGA Arg	ATC Ile	ACA Thr	GAG Glu	GAG Glu 230	CTG Leu	GTC Val	726
CCA Pro	GTT Val	CCA Pro 235	GGA Gly	TCT Ser	GTG Val	AAT Asn	GGA Gly 240	GTC Val	AAT Asn	GCC Ala	CTG Leu	GGT Gly 245	CTA Leu	GTT Val	GTC Val	774
TTC Phe	TCC Ser 250	ATG Met	TGC Cys	TTC Phe	GGT Gly	TTT Phe 255	GTG Val	ATT Ile	GGA Gly	AAC Asn	ATG Met 260	AAG Lys	GAA Glu	CAG Gln	GGG Gly	822
GAG Gln 265	GCC Ala	CTG Leu	AGA Arg	GAG Glu	TTC Phe 270	TTT Phe	GAT Asp	TCT Ser	CTT Leu	AAC Asn 275	GAA Glu	GCC Ala	ATC Ile	ATG Met	AGA Arg 280	870
CTG Leu	GTA Val	GCA Ala	GTA Val	ATA Ile 285	ATG Met	TGG Trp	TAT Tyr	GCC Ala	CCC Pro 290	GTG Val	GGT Gly	ATT Ile	CTC Leu	TTC Phe 295	CTG Leu	918
ATT Ile	GCT Ala	GGG Gly	AAG Lys 300	ATT Ile	GTG Val	GAG Glu	ATG Met	GAA Glu 305	GAC Asp	ATG Met	GGT Gly	GTG Val	ATT Ile 310	GGG Gly	GGG Gly	966
CAG Gln	CTT Leu	GCC Ala 315	ATG Met	TAC Tyr	ACC Thr	GTG Val	ACT Thr 320	GTC Val	ATT Ile	GTT Val	GGC Gly	TTA Leu 325	CTC Leu	ATT Ile	CAC His	1014

FIG. 2D

GCA Ala	GTC Val 330	ATC Ile	GTC Val	TTG Leu	CCA Pro	CTC Leu 335	CTC Leu	TAC Tyr	TTC Phe	TTG Leu	GTA Val 340	ACA Thr	CGG Arg	AAA Lys	AAC Asn	1062
CCT Pro 345	TGG Trp	GTT Val	TTT Phe	ATT Ile	GGA Gly 350	GGG Gly	TTG Leu	CTG Leu	CAA Gln	GCA Ala 355	CTC Leu	ATC Ile	ACC Thr	GCT Ala	CTG Leu 360	1110
GGG Gly	ACC Thr	TCT Ser	TCA Ser	AGT Ser 365	TCT Ser	GCC Ala	ACC Thr	CTA Leu	CCC Pro 370	ATC Ile	ACC Thr	TTC Phe	AAG Lys	TGC Cys 375	CTG Leu	1158
GAA Glu	GAG Glu	AAC Asn	AAT Asn 380	GGC Gly	GTG Val	GAC Asp	AAG Lys	CGC Arg 385	GTC Val	ACC Thr	AGA Arg	TTC Phe	GTG Val 390	CTC Leu	CCC Pro	1206
GTA Val	GGA Gly	GCC Ala 395	ACC Thr	ATT Ile	AAC Asn	ATG Met	GAT Asp 400	GGG Gly	ACT Thr	GCC Ala	CTC Leu	TAT Tyr 405	GAG Glu	GCT Ala	TTG Leu	1254
GCT Ala	GCC Ala 410	ATT Ile	TTC Phe	ATT Ile	GCT Ala	CAA Gln 415	GTT Val	AAC Asn	AAC Asn	TTT Phe	GAA Glu 420	CTG Leu	AAC Asn	TTC Phe	GGA Gly	1302
CAA Gln 425	ATT Ile	ATT Ile	ACA Thr	ATC Ile	AGC Ser 430	ATC Ile	ACA Thr	GCC Ala	ACA Thr	GCT Ala 435	GCC Ala	AGT Ser	ATT Ile	GGG Gly	GCA Ala 440	1350

FIG. 2E

GCT Ala	GGA Gly	ATT Ile	CCT Pro	CAG Gln 445	GCG Ala	GGC Gly	CTG Leu	GTC Val	ACT Thr 450	ATG Met	GTC Val	ATT Ile	GTG Val	CTG Leu 455	ACA Thr	1398
TCT Ser	GTC Val	GGC Gly	CTG Leu 460	CCC Pro	ACT Thr	GAC Asp	GAC Asp	ATC Ile 465	ACG Thr	CTC Leu	ATC Ile	ATC Ile	GCG Ala 470	GTG Val	GAC Asp	1446
TGG Trp	TTC Phe	TTG Leu 475	GAT Asp	CGC Arg	CTC Leu	CGG Arg	ACC Thr 480	ACC Thr	ACC Thr	ACC Asn	GTA Val	CTG Leu 485	GGA Gly	GAC Asp	TCC Ser	1494
CTG Leu	GGA Gly 490	GCT Ala	GGG Gly	ATT Ile	GTG Val	GAG Glu 495	CAC His	TTG Leu	TCA Ser	CGA Arg	CAT His 500	GAA Glu	CTG Leu	AAG Lys	AAC Asn	1542
AGA Arg 505	GAT Asp	GTT Val	GAA Glu	ATG Met	GGT Gly 510	AAC Asn	TCA Ser	GTG Val	ATT Ile	GAA Glu 515	GAG Glu	ATT Asn	GAA Glu	ATG Met	AAG Lys 520	1590
AAA Lys	CCA Pro	TAT Tyr	CAA Gln	CTG Leu 525	ATT Ile	GCA Ala	CAG Gln	GAC Asp	AAT Asn 530	GAA Glu	ACT Thr	GAG Glu	AAA Lys	CCC Pro 535	ATC Ile	1638
GAC Asp	AGT Ser	GAA Glu	ACC Thr 540	AAG Lys	ATG Met	TAGACTAACA			TAAAGAAACA			CTTT				1680

FIG. 3A

```
GATAGTGCTG AAGAGGAGGG    GCGTTCCCAG      ACC ATG GCA TCT ACG GAA GGT GCC          54
                                             Met Ala Ser Thr Glu Gly Ala
                                              1                5

AAC AAT ATG CCC AAG CAG GTG GAA GTG CGA ATG CCA GAC AGT CAT CTT                  102
Asn Asn Met Pro Lys Gln Val Glu Val Arg Met Pro Asp Ser His Leu
        10                  15                  20

GGC TCA GAG GAA CCC AAG CAC CGG CAC CTG GGC CTG CGC CTG TGT GAC                  150
Gly Ser Glu Glu Pro Lys His Arg His Leu Gly Leu Arg Leu Cys Asp
    25                  30                  35

AAG CTG GGG AAG AAT CTG CTG CTC ACC CTG ACG GTG TTT GGT GTC ATC                  198
Lys Leu Gly Lys Asn Leu Leu Leu Thr Leu Thr Val Phe Gly Val Ile
40                  45                  50                  55

CTG GGA GCA GTG TGT GGA GGG CTT CTT CGC TTG GCA TCT CCC ATC CAC                  246
Leu Gly Ala Val Cys Gly Gly Leu Leu Arg Leu Ala Ser Pro Ile His
                60                  65                  70

CCT GAT GTG GTT ATG TTA ATA GCC TTC CCA GGG GAT ATA CTC ATG AGG                  294
Pro Asp Val Val Met Leu Ile Ala Phe Pro Gly Asp Ile Leu Met Arg
            75                  80                  85

ATG CTA AAA ATG CTC ATT CTG GGT CTA ATC ATC TCC AGC TTA ATC ACA                  342
Met Leu Lys Met Leu Ile Leu Gly Leu Ile Ile Ser Ser Leu Ile Thr
        90                  95                  100
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FIG. 3B

GGG Gly	TTG Leu 105	TCA Ser	GGC Gly	CTG Leu	GAT Asp	GCT Ala 110	AAG Lys	GCT Ala	AGT Ser	GGC Gly	CGC Arg 115	TTG Leu	GGC Gly	ACG Thr	AGA Arg	390
GCC Ala 120	ATG Met	GTG Val	TAT Tyr	TAC Tyr	ATG Met 125	TCC Ser	ACG Thr	ACC Thr	ATC Ile	ATT Ile 130	GCT Ala	GCA Ala	GTA Val	CTG Leu	GGG Gly 135	438
GTC Val	ATT Ile	CTG Leu	GTC Val	TTG Leu 140	GCT Ala	ATC Ile	CAT His	CCA Pro	GGC Gly 145	AAT Asn	CCC Pro	AAG Lys	CTC Leu	AAG Lys 150	AAG Lys	486
CAG Gln	CTG Leu	GGG Gly	CCT Pro 155	GGG Gly	AAG Lys	AAG Lys	AAT Asn	GAT Asp 160	GAA Glu	GTG Val	TCC Ser	AGC Ser	CTG Leu 165	GAT Asp	GCC Ala	534
TTC Phe	CTG Leu	GAC Asp 170	CTT Leu	ATT Ile	CGA Arg	AAT Asn	CTC Leu 175	TTC Phe	CCT Pro	GAA Glu	AAC Asn	CTT Leu 180	GTC Val	CAA Gln	GCC Ala	582
TGC Cys	TTT Phe 185	CAA Gln	CAG Gln	ATT Ile	CAA Gln	ACA Thr 190	GTG Val	ACG Thr	AAG Lys	AAA Lys	GTC Val 195	CTG Leu	GTT Val	GCA Ala	CCA Pro	630
CCG Pro 200	CCA Pro	GAC Asp	GAG Glu	GAG Glu	GCC Ala 205	AAC Asn	GCA Ala	ACC Thr	AGC Ser	GCT Ala 210	GAA Glu	GTC Val	TCT Ser	CTG Leu	TTG Leu 215	678

FIG. 3C

AAC Asn	GAG Glu	ACT Thr	GTG Val	ACT Thr 220	GAG Glu	GTG Val	CCG Pro	GAG Glu	GAG Glu 225	ACT Thr	AAG Lys	ATG Met	GTT Val	ATC Ile 230	AAG Lys	726
AAG Lys	GGC Gly	CTG Leu	GAG Glu 235	TTC Phe	AAG Lys	GAT Asp	GGG Gly	ATG Met 240	AAC Asn	GTC Val	TTA Leu	GGT Gly	CTG Leu 245	ATA Ile	GGG Gly	774
TTT Phe	TTC Phe	ATT Ile 250	GCT Ala	TTT Phe	GGC Gly	ATC Ile	GCT Ala 255	ATG Met	GGG Gly	AAG Lys	ATG Met	GGA Gly 260	GAT Asp	CAG Gln	GCC Ala	822
AAG Lys	CTG Leu 265	ATG Met	GTG Val	GAT Asp	TTC Phe	TTC Phe 270	AAC Asn	ATT Ile	TTG Leu	AAT Asn	GAG Glu 275	ATT Ile	GTA Val	ATG Met	AAG Lys	870
TTA Leu 280	GTG Val	ATC Ile	ATG Met	ATC Ile	ATG Met 285	TGG Trp	TAC Tyr	TCT Ser	CCC Pro	CTG Leu 290	GGT Gly	ATC Ile	GCC Ala	TGC Cys	CTG Leu 295	918
ATC Ile	TGT Cys	GGA Gly	AAG Lys	ATC Ile 300	ATT Ile	GCA Ala	ATC Ile	AAG Lys	GAC Asp 305	TTA Leu	GAA Glu	GTG Val	GTT Val	GCT Ala 310	AGG Arg	966
CAA Gln	CTG Leu	GGG Gly	ATG Met 315	TAC Tyr	ATG Met	GTA Val	ACA Thr	GTG Val 320	ATC Ile	ATA Ile	GGC Gly	CTC Leu	ATC Ile 325	ATC Ile	CAC His	1014

FIG. 3D

GGG Gly	GGC Gly	ATC Ile 330	TTT Phe	CTC Leu	CCC Pro	TTG Leu	ATT Ile 335	TAC Tyr	TTT Phe	GTA Val	GTG Val	ACC Thr 340	AGG Arg	AAA Lys	AAC Asn	1062
CCC Pro	TTC Phe 345	TCC Ser	CTT Leu	TTT Phe	GCT Ala	GGC Gly 350	ATT Ile	TTC Phe	CAA Gln	GCT Ala	TGG Trp 355	ATC Ile	ACT Thr	GCC Ala	CTG Leu	1110
GGC Gly 360	ACC Thr	GCT Ala	TCC Ser	AGT Ser	GCT Ala 365	GGA Gly	ACT Thr	TTG Leu	CCT Pro	GTC Val 370	ACC Thr	TTT Phe	CGT Arg	TGC Cys	CTG Leu 375	1158
GAA Glu	GAA Glu	AAT Asn	CTG Leu	GGG Gly 380	ATT Ile	GAT Asp	AAG Lys	CGT Arg	GTG Val 385	ACT Thr	AGA Arg	TTC Phe	GTC Val	CTT Leu 390	CCT Pro	1206
GTT Val	GGA Gly	GCA Ala	ACC Thr 395	ATT Ile	AAC Asn	ATG Met	GAT Asp	GGT Gly 400	ACA Thr	GCC Ala	CTT Leu	TAT Tyr	GAA Glu 405	GCG Ala	GTG Val	1254
GCC Ala	GCC Ala	ATC Ile 410	TTT Phe	ATA Ile	GCC Ala	CAA Gln	ATG Met 415	AAT Asn	GGT Gly	GTT Val	GTC Val	CTG Leu 420	GAT Asp	GGA Gly	GGA Gly	1302
CAG Gln	ATT Ile 425	GTG Val	ACT Thr	GTA Val	AGC Ser	CTC Leu 430	ACA Thr	GCC Ala	ACC Thr	CTG Leu	GCA Ala 435	AGC Ser	GTC Val	GGC Gly	GCG Ala	1350

FIG. 3E

GCC Ala 440	AGT Ser	ATC Ile	CCC Pro	AGT Ser	GCC Ala 445	GGG Gly	CTG Leu	GTC Val	ACC Thr	ATG Met 450	CTC Leu	CTC Leu	ATT Ile	CTG Leu	ACA Thr 455	1398
GCC Ala	GTG Val	GGC Gly	CTG Leu	CCA Pro 460	ACA Thr	GAG Glu	GAC Asp	ATC Ile	AGC Ser 465	TTG Leu	CTG Leu	GTG Val	GCT Ala	GTG Val 470	GAC Asp	1446
TGG Trp	CTG Leu	CTG Leu	GAC Asp 475	AGG Arg	ATG Met	AGA Arg	ACT Thr	TCA Ser 480	GTC Val	AAT Asn	GTT Val	GTG Val	GGT Gly 485	GAC Asp	TCT Ser	1494
TTT Phe	GGG Gly	GCT Ala 490	GGG Gly	ATA Ile	GTC Val	TAT Tyr	CAC His 495	CTC Leu	TCC Ser	AAG Lys	TCT Ser	GAG Glu 500	CTG Leu	GAT Asp	ACC Thr	1542
ATT Ile	GAC Asp 505	TCC Ser	GAG Gln	CAT His	CGA Arg	GTG Val 510	CAT His	GAA Glu	GAT Asp	ATT Ile	GAA Glu 515	ATG Met	ACC Thr	AAG Lys	ACT Thr	1590
CAA Gln 520	TCC Ser	ATT Ile	TAT Tyr	GAT Asp	GAC Asp 525	ATG Met	AAG Lys	AAC Asn	CAC His	AGG Arg 530	GAA Glu	AGC Ser	AAC Asn	TCT Ser	ATT Asn 535	1638
CAA Gln	TGT Cys	GTC Val	TAT Tyr	GCT Ala 540	GCA Ala	CAC His	AAC Asn	TCT Ser	GTC Val 545	ATA Ile	GTA Val	GAT Asp	GAA Glu	TGC Cys 550	AAG Lys	1686

FIG. 3F

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GTA ACT CTG GCA GCC AAT GGA AAG TCA GCC GAC TGC AGT GTT GAG GAA          1734
Val Thr Leu Ala Ala Asn Gly Lys Ser Ala Asp Cys Ser Val Glu Glu
                555                 560                 565

GAA CCT TGG AAA CGT GAG AAA TAAGGATATG     AGTCTCAGCA     AATTCTTGAA      1785
Glu Pro Trp Lys Arg Glu Lys
        570

TAAACTCCCC AGCGT                                                        1800
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FIG. 4A

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ATAGCGGCGA CAGCC    ATG GGG AAA CCG GCG AGG AAA GGA TGC CCG AGT TGG          51
                    Met Gly Lys Pro Ala Arg Lys Gly Cys Pro Ser Trp
                     1                   5                  10

AAG CGC TTC CTG AAG AAT AAC TGG GTG TTG CTG TCC ACC GTG GCC GCG          99
Lys Arg Phe Leu Lys Asn Asn Trp Val Leu Leu Ser Thr Val Ala Ala
               15                  20                  25

GTG GTG CTA GGC ATT ACC ACA GGA GTC TTG GTT CGA GAA CAC AGC AAC         147
Val Val Leu Gly Ile Thr Thr Gly Val Leu Val Arg Glu His Ser Asn
          30                  35                  40

CTC TCA ACT CTA GAG AAA TTC TAC TTT GCT TTT CCT GGA GAA ATT CTA         195
Leu Ser Thr Leu Glu Lys Phe Tyr Phe Ala Phe Pro Gly Glu Ile Leu
 45                  50                  55                  60

ATG GGG ATG CTG AAA CTC ATC ATT TTG CCA TTA ATT ATA TCC AGC ATG         243
Met Gly Met Leu Lys Leu Ile Ile Leu Pro Leu Ile Ile Ser Ser Met
                    65                  70                  75

ATT ACA GGT GTT GCT GCA CTG GAT TCC AAC GTA TCC GGA AAA ATT GGT         291
Ile Thr Gly Val Ala Ala Leu Asp Ser Asn Val Ser Gly Lys Ile Gly
               80                  85                  90

CTG CGC GCT GTC GTG TAT TAT TTC TGT ACC ACT CTC ATT GCT GTT ATT         339
Leu Arg Ala Val Val Tyr Tyr Phe Cys Thr Thr Leu Ile Ala Val Ile
          95                 100                 105
```

FIG. 4B

CTA Leu	GGT Gly 110	ATT Ile	GTG Val	CTG Leu	GTG Val	GTG Val 115	AGC Ser	ATC Ile	AAG Lys	CCT Pro	GGT Gly 120	GTC Val	ACC Thr	CAG Gln	AAA Lys	387
GTG Val 125	GGT Gly	GAA Glu	ATT Ile	GCG Ala	AGG Arg 130	ACA Thr	GGC Gly	AGC Ser	ACC Thr	CCT Pro 135	GAA Glu	GTC Val	AGT Ser	ACG Thr	GTG Val 140	435
GAT Asp	GCC Ala	ATG Met	TTA Leu	GAT Asp 145	CTC Leu	ATC Ile	AGG Arg	AAT Asn	ATG Met 150	TTC Phe	CCT Pro	GAG Glu	AAT Asn	CTT Leu 155	GTC Val	483
CAG Gln	GCC Ala	TGT Cys	TTT Phe 160	CAG Gln	CAG Gln	TAC Tyr	AAA Lys	ACT Thr 165	AAG Lys	CGT Arg	GAA Glu	GAA Glu	GTG Val 170	AAG Lys	CCT Pro	531
CCC Pro	AGC Ser	GAT Asp 175	CCA Pro	GAG Glu	ATG Met	AAC Asn	ATG Met 180	ACA Thr	GAA Glu	GAG Glu	TCC Ser	TTC Phe 185	ACA Thr	GCT Ala	GTC Val	579
ATG Met	ACA Thr 190	ACT Thr	GCA Ala	ATT Ile	TCC Ser	AAG Lys 195	AAC Asn	AAA Lys	ACA Thr	AAG Lys	GAA Glu 200	TAC Tyr	AAA Lys	ATT Ile	GTT Val	627
GGC Gly 205	ATG Met	TAT Tyr	TCA Ser	GAT Asp	GGC Gly 210	ATA Ile	AAC Asn	GTC Val	CTG Leu	GGC Gly 215	TTG Leu	ATT Ile	GTC Val	TTT Phe	TGC Cys 220	675
CTT Leu	GTC Val	TTT Phe	GGA Gly	CTT Leu 225	GTC Val	ATT Ile	GGA Gly	AAA Lys	ATG Met 230	GGA Gly	GAA Glu	AAG Lys	GGA Gly	CAA Gln 235	ATT Ile	723

FIG. 4C

CTG Leu	GTG Val	GAT Asp	TTC Phe 240	TTC Phe	AAT Asn	GCT Ala	TTG Leu	AGT Ser 245	GAT Asp	GCA Ala	ACC Thr	ATG Met	AAA Lys 250	ATC Ile	GTT Val	771
CAG Gln	ATC Ile	ATC Ile 255	ATG Met	TGT Cys	TAT Tyr	ATG Met	CCA Pro 260	CTA Leu	GGT Gly	ATT Ile	TTG Leu	TTC Phe 265	CTG Leu	ATT Ile	GCT Ala	819
GGG Gly	AAG Lys 270	ATC Ile	ATA Ile	GAA Glu	GTT Val	GAA Glu 275	GAC Asp	TGG Trp	GAA Glu	ATA Ile	TTC Phe	CGC Arg 280	AAG Lys	CTG Leu	GGC Gly	867
CTT Leu 285	TAC Tyr	ATG Met	GCC Ala	ACA Thr	GTC Val 290	CTG Leu	ACT Thr	GGG Gly	CTT Leu	GCA Ala 295	ATC Ile	CAC His	TCC Ser	ATT Ile	GTA Val 300	915
ATT Ile	CTC Leu	CCG Pro	CTG Leu	ATA Ile 305	TAT Tyr	TTC Phe	ATA Ile	GTC Val	GTA Val 310	CGA Arg	AAG Lys	AAC Asn	CCT Pro	TTC Phe 315	CGA Arg	963
TTT Phe	GCC Ala	ATG Met	GGA Gly 320	ATG Met	GCC Ala	CAG Gln	GCT Ala	CTC Leu 325	CTC Leu	ACA Thr	GCT Ala	CTC Leu	ATG Met 330	ATC Ile	TCT Ser	1011
TCC Ser	AGT Ser	TCA Ser 335	GCA Ala	ACA Thr	CTG Leu	CCT Pro	GTC Val 340	ACC Thr	TTC Phe	CGC Arg	TGT Cys	GCT Ala 345	GAA Glu	GAA Glu	AAT Asn	1059

FIG. 4D

AAC Asn	CAG Gln 350	GTG Val	GAC Asp	AAG Lys	AGG Arg	ATC Ile 355	ACT Thr	CGA Arg	TTC Phe	CTG Val	TTA Leu 360	CCC Pro	GTT Val	GGT Gly	GCA Ala	1107
ACA Thr 365	ATC Ile	AAC Asn	ATG Met	GAT Asp	GGG Gly 370	ACC Thr	GCG Ala	CTC Leu	TAT Tyr	GAA Glu 375	GCA Ala	GTG Val	GCA Ala	GCG Ala	GTG Val 380	1155
TTT Phe	ATT Ile	GCA Ala	CAG Gln	TTG Leu 385	AAT Asn	GAC Asp	CTG Leu	GAC Asp	TTG Leu 390	GGC Gly	ATT Ile	GGG Gly	CAG Gln	ATC Ile 395	ATC Ile	1203
ACC Thr	ATC Ile	AGT Ser	ATC Ile 400	ACG Thr	GCC Ala	ACA Thr	TCT Ser	GCC Ala 405	AGC Ser	ATC Ile	GGA Gly	GCT Ala	GCT Ala 410	GGC Gly	GTG Val	1251
CCC Pro	CAG Gln	GCT Ala 415	GGC Gly	CTG Leu	GTG Val	ACC Thr	ATG Met 420	GTG Val	ATT Ile	GTG Val	CTG Leu	AGT Ser 425	GCC Ala	GTG Val	GGC Gly	1299
CTG Leu	CCC Pro 430	GCC Ala	GAG Glu	GAT Asp	GTC Val	ACC Thr 435	CTG Leu	ATC Ile	ATT Ile	GCT Ala	GTC Val 440	GAC Asp	TGG Trp	CTC Leu	CTG Leu	1347
GAC Asp 445	CGG Arg	TTC Phe	AGG Arg	ACC Thr	ATG Met 450	GTC Val	AAC Asn	GTC Val	CTT Leu	GGT Gly 455	GAT Asp	GCT Ala	TTT Phe	GGG Gly	ACT Thr 460	1395

FIG. 4E

GGC Gly	ATT Ile	GTG Val	GAA Glu	AAG Lys 465	CTC Leu	TCC Ser	AAG Lys	AAG Lys	GAG Glu 470	CTG Leu	GAG Glu	GAG Gln	ATG Met	GAT Asp 475	GTT Val	1443
TCA Ser	TCT Ser	GAA Glu	GTC Val 480	AAC Asn	ATT Ile	GTG Val	AAT Asn	CCC Pro 485	TTT Phe	GCC Ala	TTG Leu	GAA Glu	TCC Ser 490	ACA Thr	ATC Ile	1491
CTT Leu	GAC Asp	AAC Asn 495	GAA Glu	GAC Asp	TCA Ser	GAC Asp	ACC Thr 500	AAG Lys	AAG Lys	TCT Ser	TAT Thr	GTC Val 505	AAT Asn	GGA Gly	GGC Gly	1539
TTT Phe	GCA Ala 510	GTA Val	GAC Asp	AAG Lys	TCT Ser	GAC Asp 515	ACC Thr	ATC Ile	TCA Ser	TTC Phe	ACC Thr 520	GAG Gln	ACC Thr	TCA Ser	CAG Gln	1587
TTC Phe 525	TAGGGCCCCT GGCTGCAGAT GACTGGAAAC AAGGAAGGAC ATTTCGTGAG															1640
AGTCATCTCA AACACGGCTT AAGGAAAAGA GAAA																1674

FIG. 5A

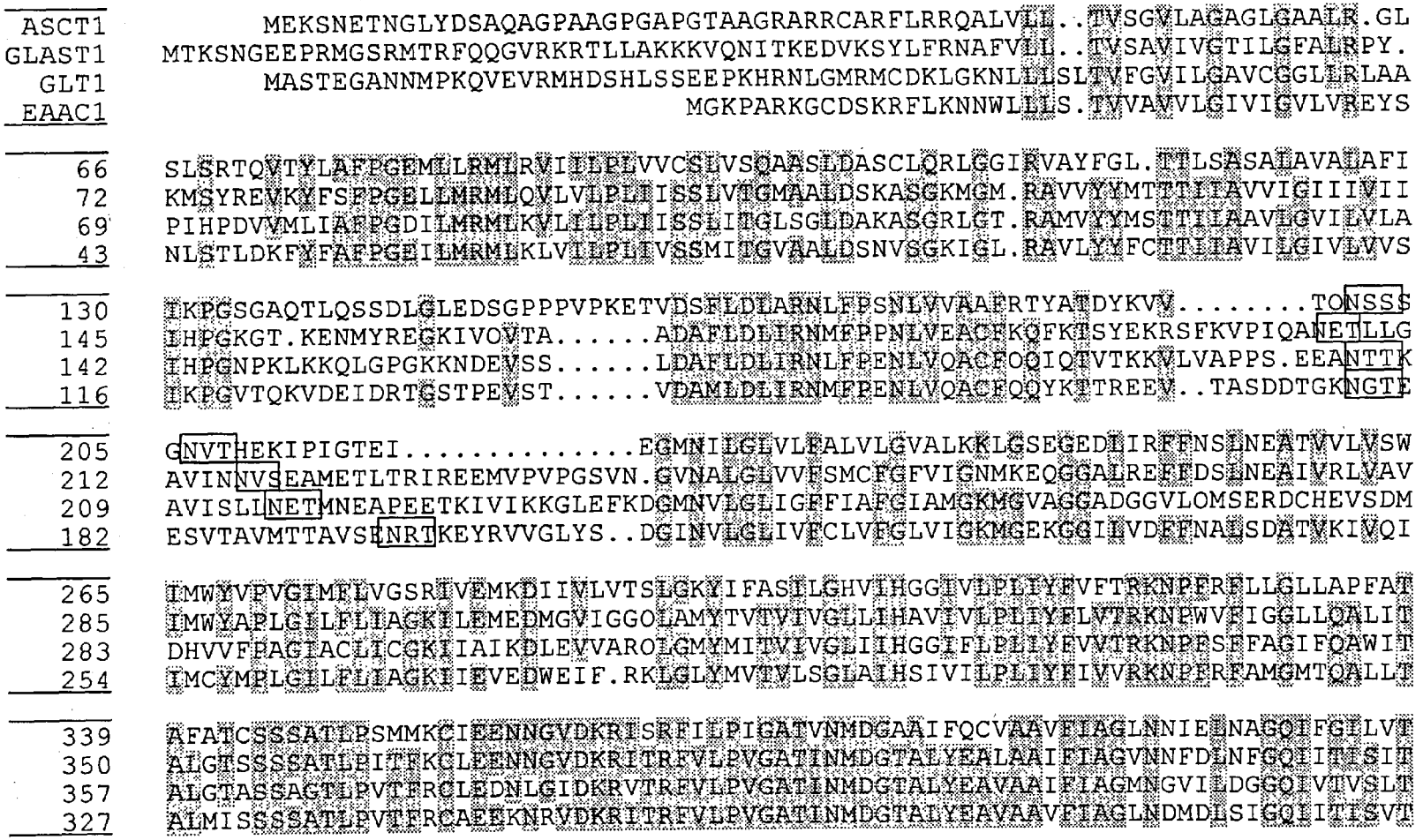

ASCT1
GLAST1
GLT1
EAAC1
66
72
69
43
130
145
142
116
205
212
209
182
265
285
283
254
339
350
357
327

FIG. 5B

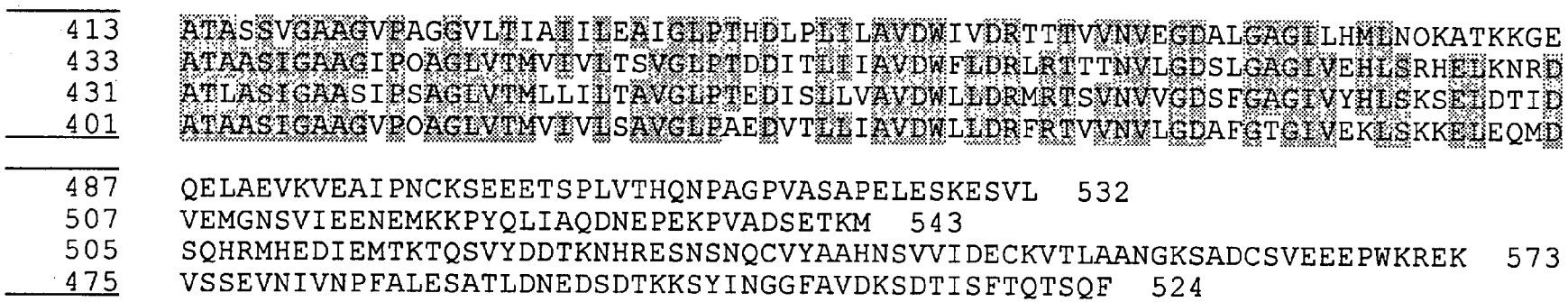

413 ATASSVGAAGVPAGGVLTIATILEAIGLPTHDLPLILAVDWIVDRTTTVVNVEGDALGAGILHMLNQKATKKGE
433 ATAASIGAAGIPQAGLVTMVIVLTSVGLPTDDITLIIAVDWFLDRLRTTTNVLGDSLGAGIVEHLSRHELKNRD
431 ATLASIGAASIPSAGLVTMLLILTAVGLPTEDISLLVAVDWLLDRMRTSVNVVGDSFGAGIVYHLSKSELDTID
401 ATAASIGAAGVPQAGLVTMVIVLSAVGLPAEDVTLLIAVDWLLDRFRTVVNVLGDAFGTGIVEKLSKKELEQMD
487 QELAEVKVEAIPNCKSEEETSPLVTHQNPAGPVASAPELESKESVL 532
507 VEMGNSVIEENEMKKPYQLIAQDNEPEKPVADSETKM 543
505 SQHRMHEDIEMTKTQSVYDDTKNHRESNSNQCVYAAHNSVVIDECKVTLAANGKSADCSVEEEPWKREK 573
475 VSSEVNIVNPFALESATLDNEDSDTKKSYINGGFAVDKSDTISFTQTSQF 524

FIG. 6A

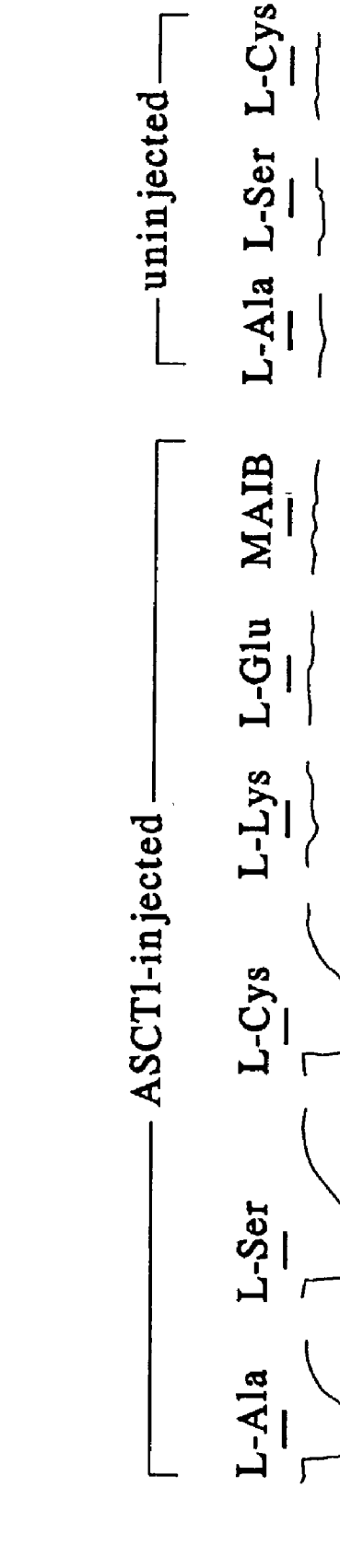

ASCT1-injected
uninjected
L-Ala
L-Ser
L-Cys
L-Lys
L-Glu
MAIB
L-Ala
L-Ser
L-Cys
L-Ala (Na-free)
5nA
1 min

FIG. 6B

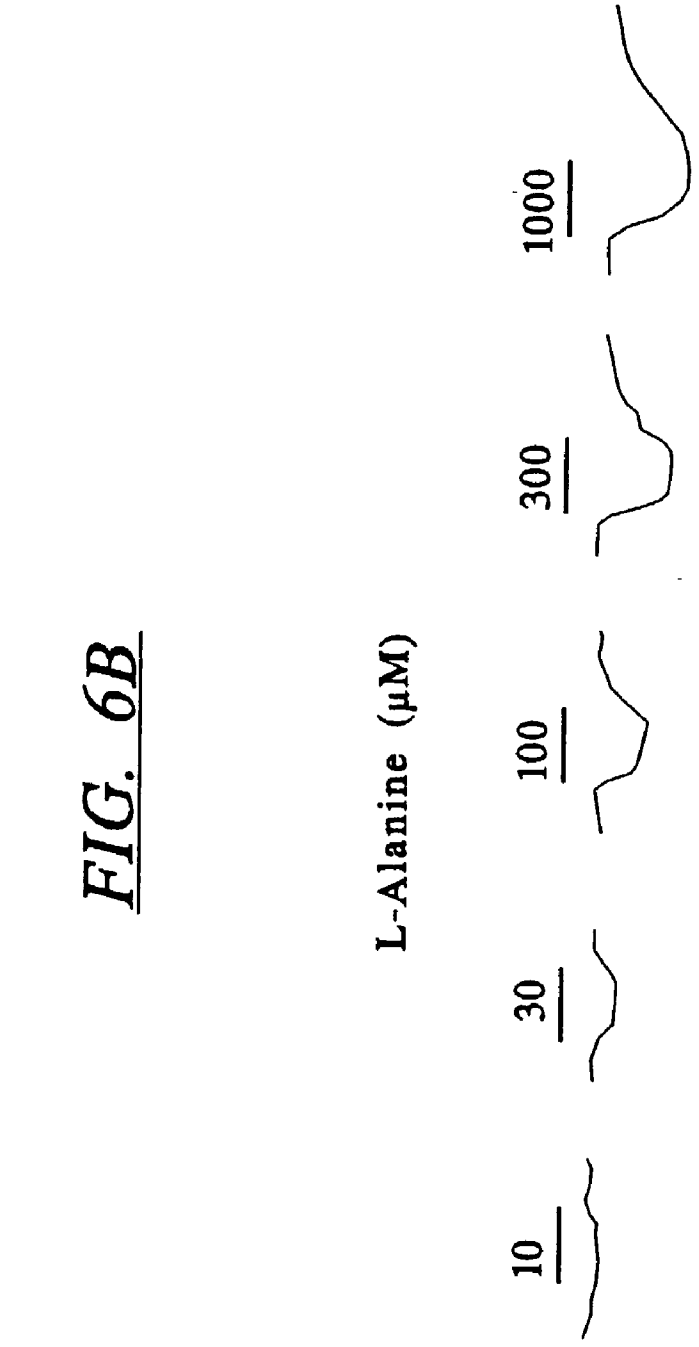


FIG. 6C

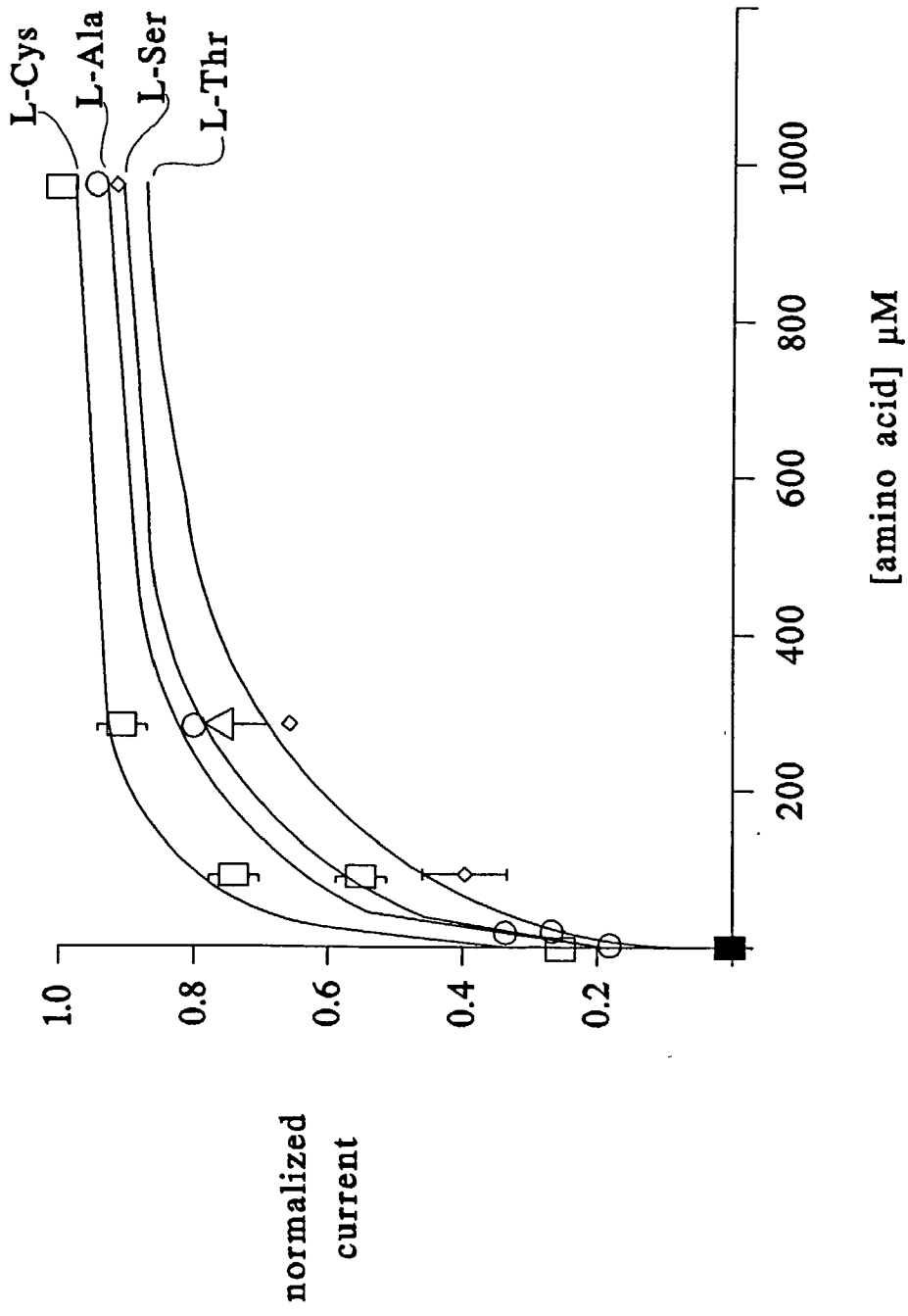

L-Cys
L-Ala
L-Ser
L-Thr
normalized current
1.0
0.8
0.6
0.4
0.2
200
400
600
800
1000
[amino acid] µM

FIG. 7A

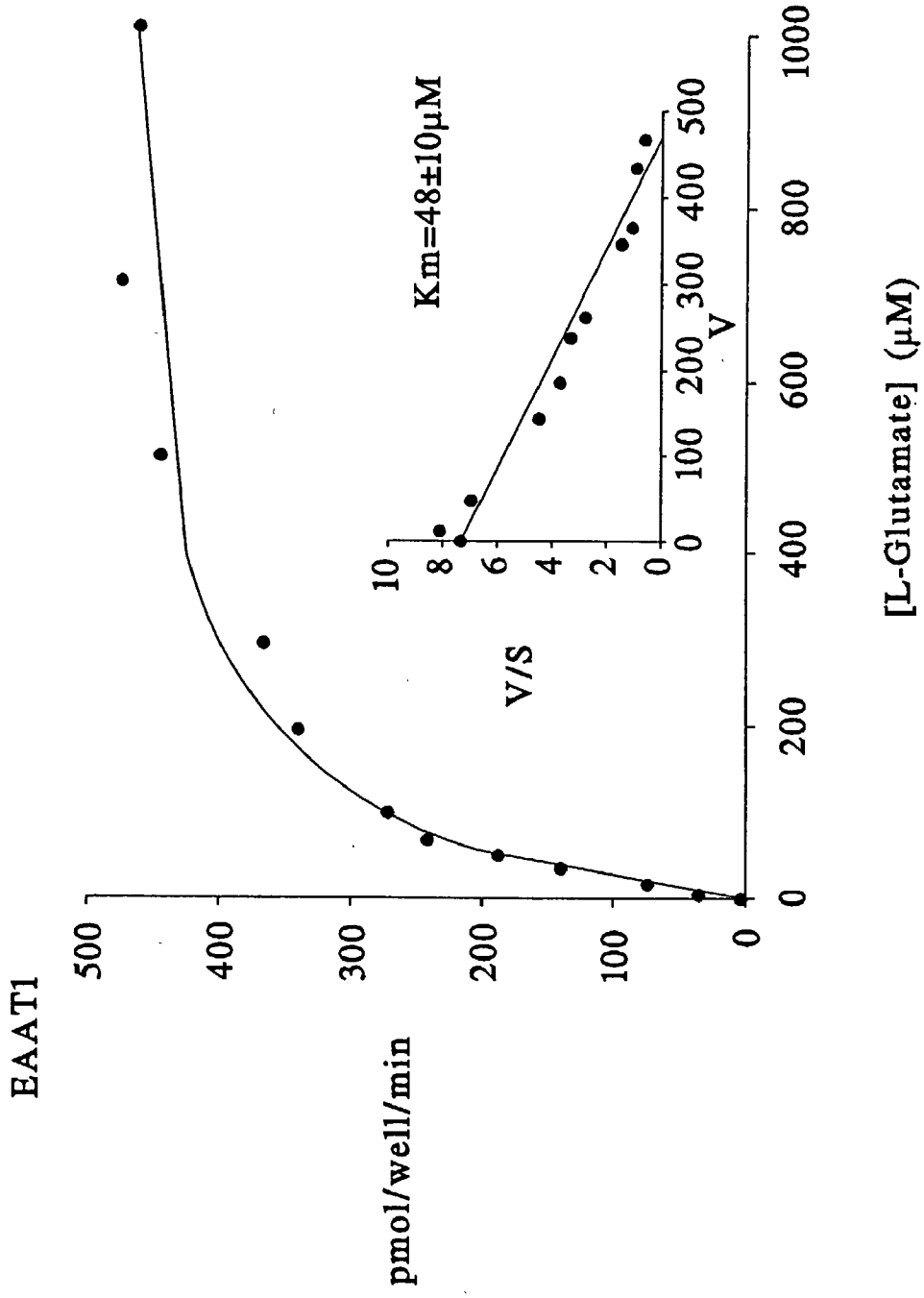

EAAT1
pmol/well/min
0
100
200
300
400
500
0
200
400
600
800
1000
[L-Glutamate] (μM)
Km=48±10μM
V/S
V
0
2
4
6
8
10
0
100
200
300
400
500

FIG. 7B

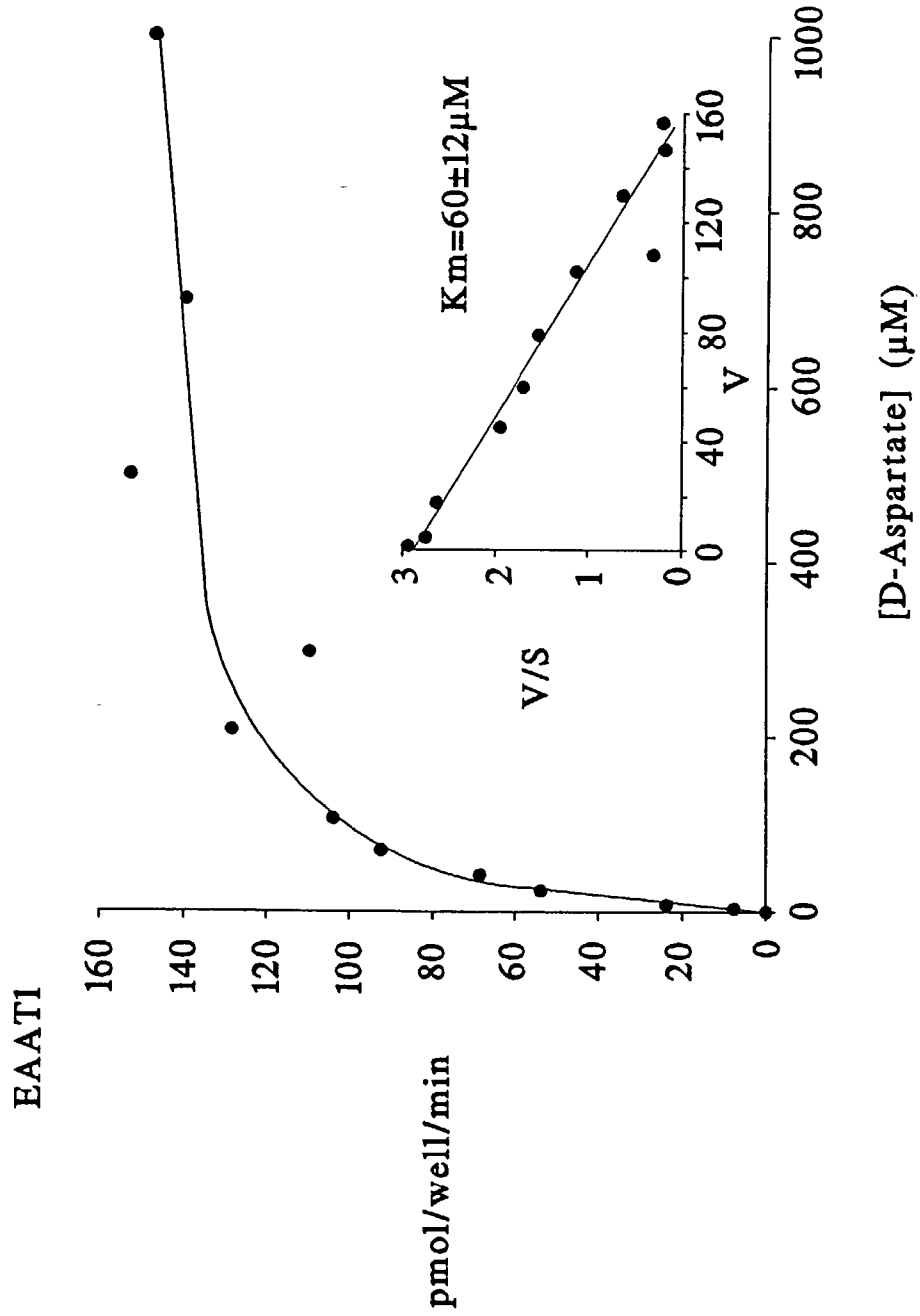

EAAT1
pmol/well/min
160
140
120
100
80
60
40
20
0
0
200
400
600
800
1000
[D-Aspartate] (μM)
Km=60±12μM
V/S
3
2
1
0
0
40
80
120
160
V

FIG. 7C

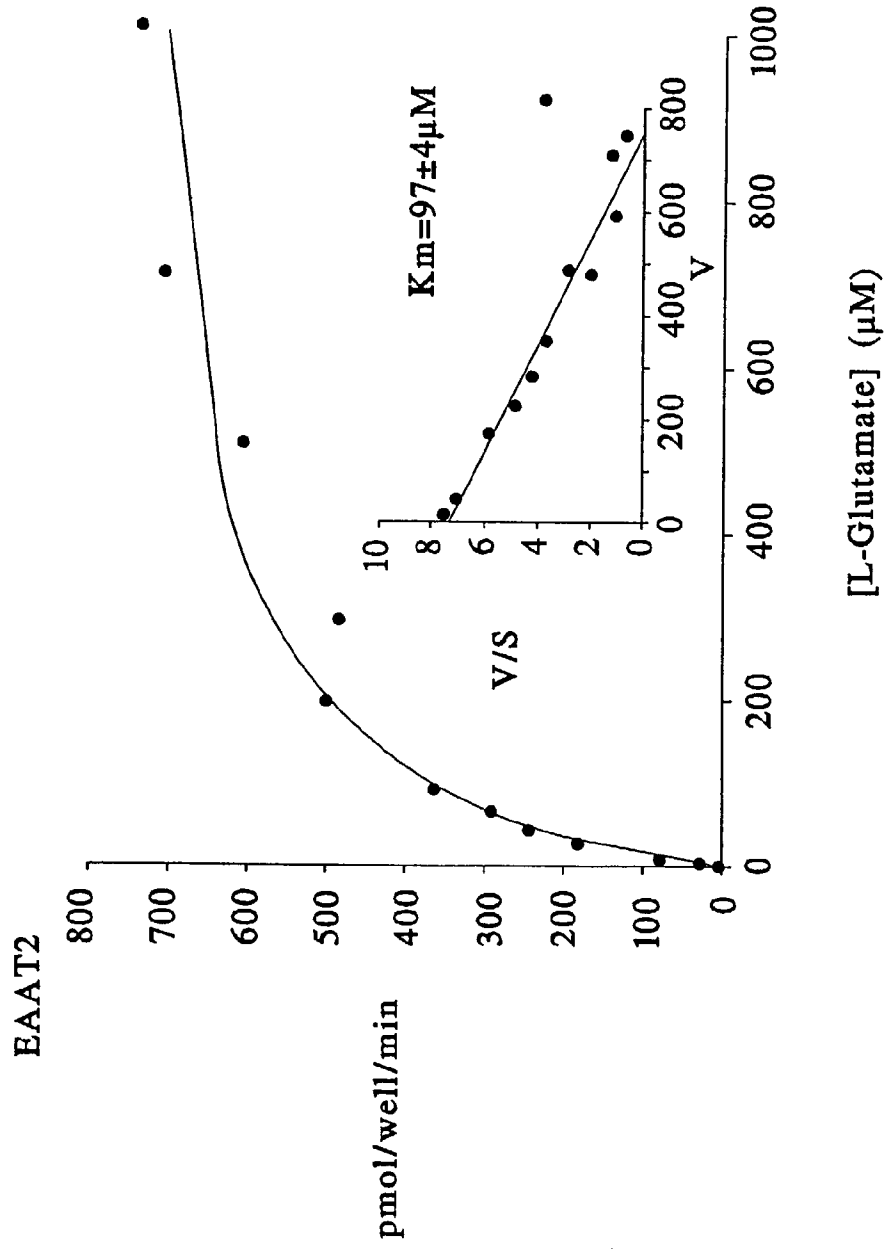

EAAT2
pmol/well/min
800
700
600
500
400
300
200
100
0
0
200
400
600
800
1000
[L-Glutamate] (μM)
Km=97±4μM
V/S
10
8
6
4
2
0
0
200
400
600
800
V

FIG. 7D

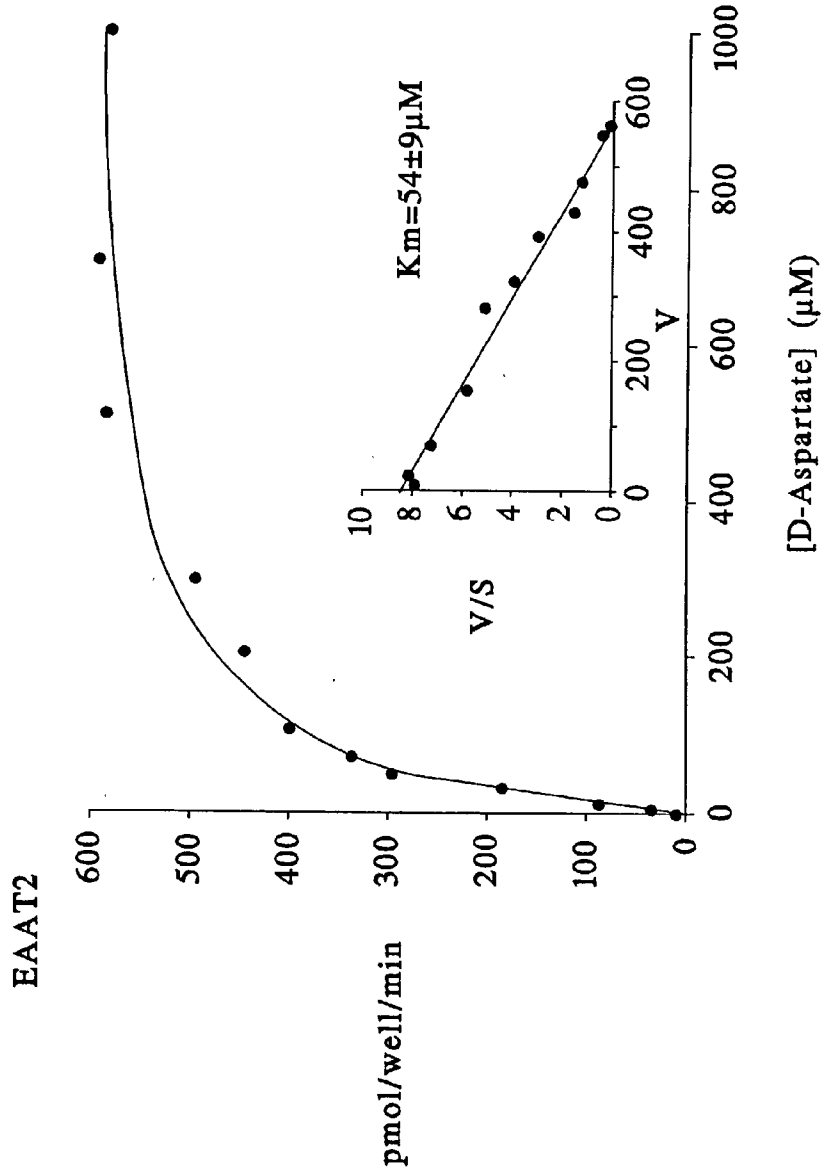

EAAT2
pmol/well/min
600
500
400
300
200
100
0
0
200
400
600
800
1000
[D-Aspartate] (μM)
Km=54±9μM
V/S
V
10
8
6
4
2
0
0
200
400
600

FIG. 7E

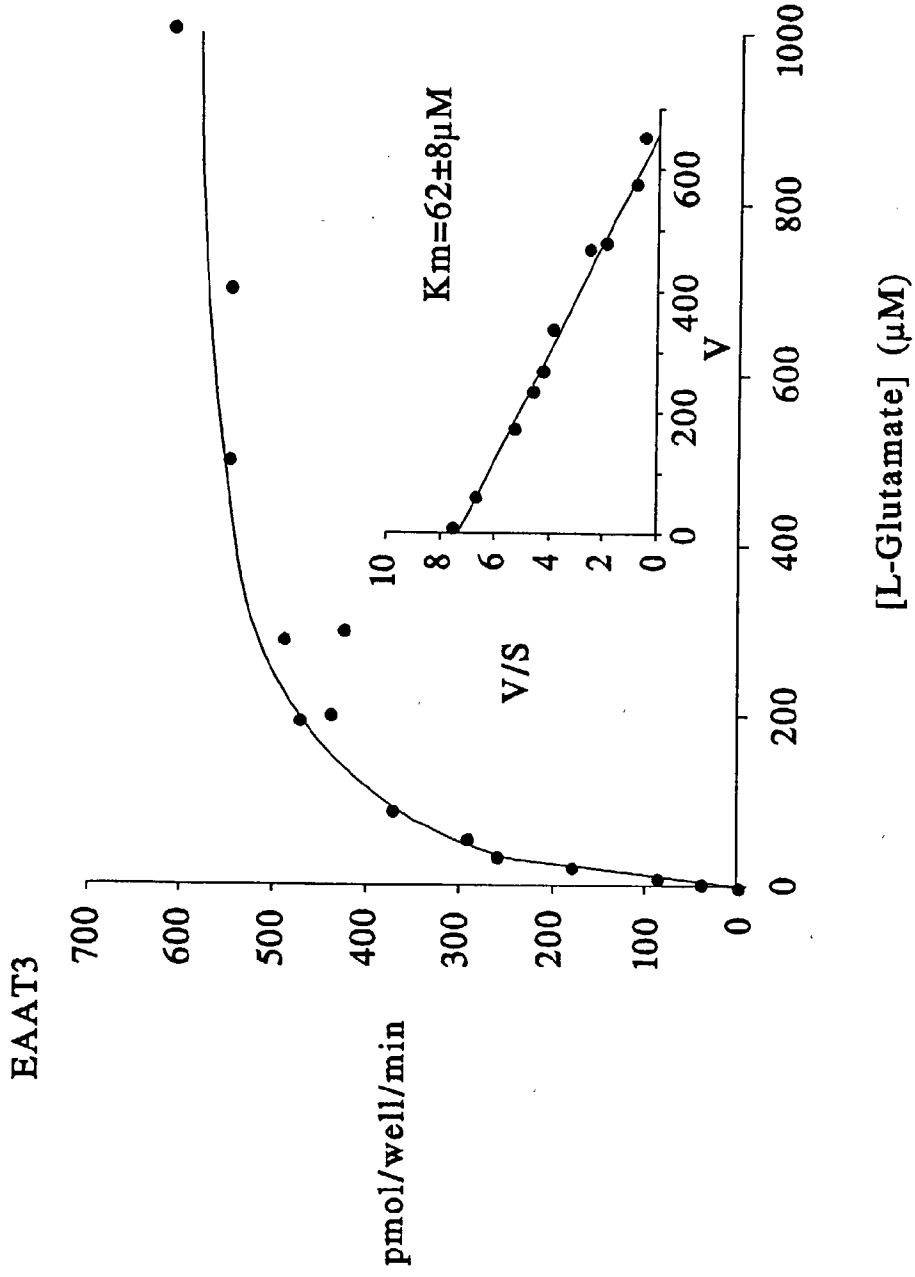

EAAT3
pmol/well/min
700
600
500
400
300
200
100
0
0
200
400
600
800
1000
[L-Glutamate] (μM)
Km=62±8μM
V/S
V
10
8
6
4
2
0
0
200
400
600

FIG. 7F

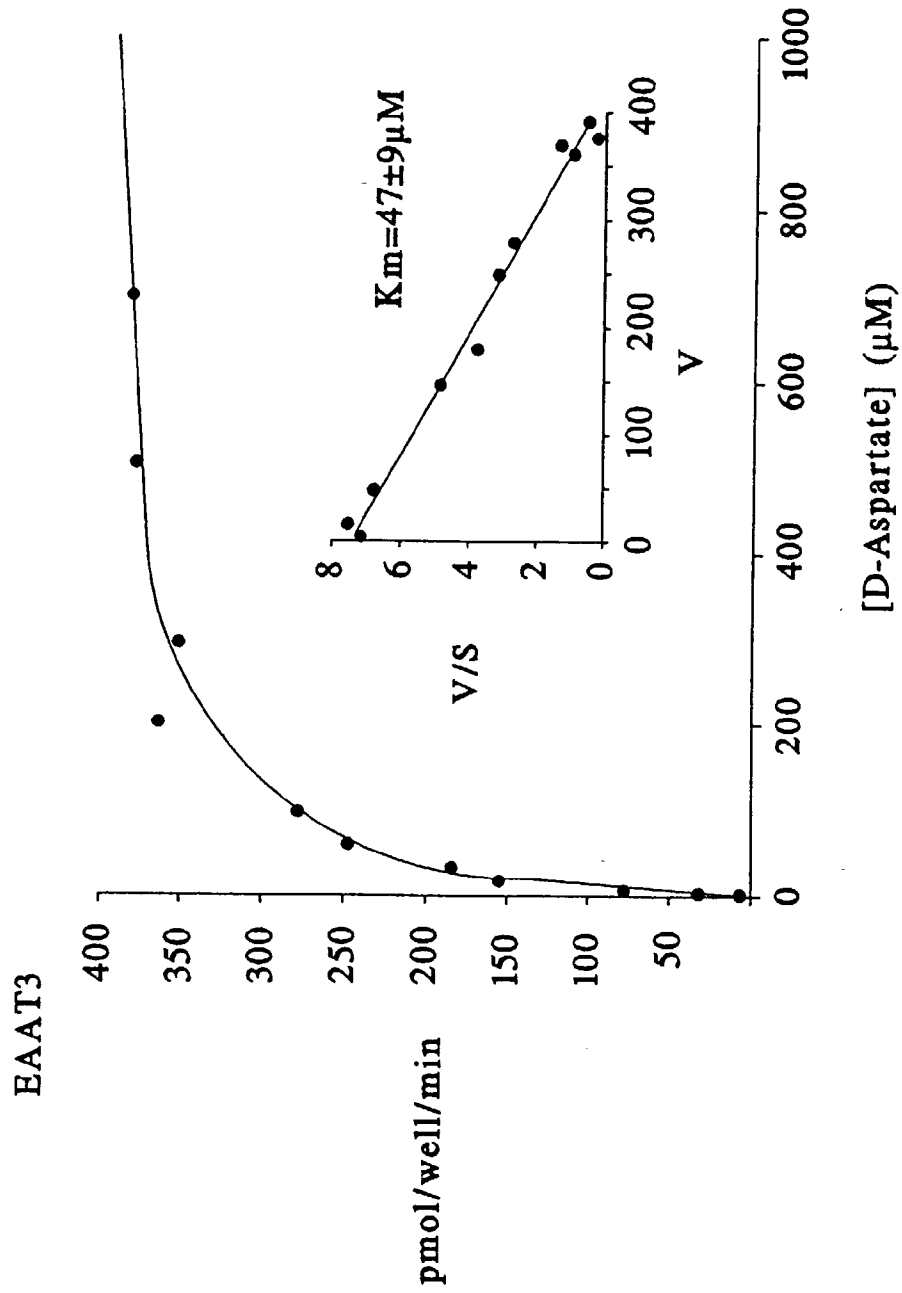

EAAT3
pmol/well/min
400
350
300
250
200
150
100
50
0
200
400
600
800
1000
[D-Aspartate] (μM)
Km=47±9μM
V/S
V
8
6
4
2
0
0
100
200
300
400

FIG. 8A

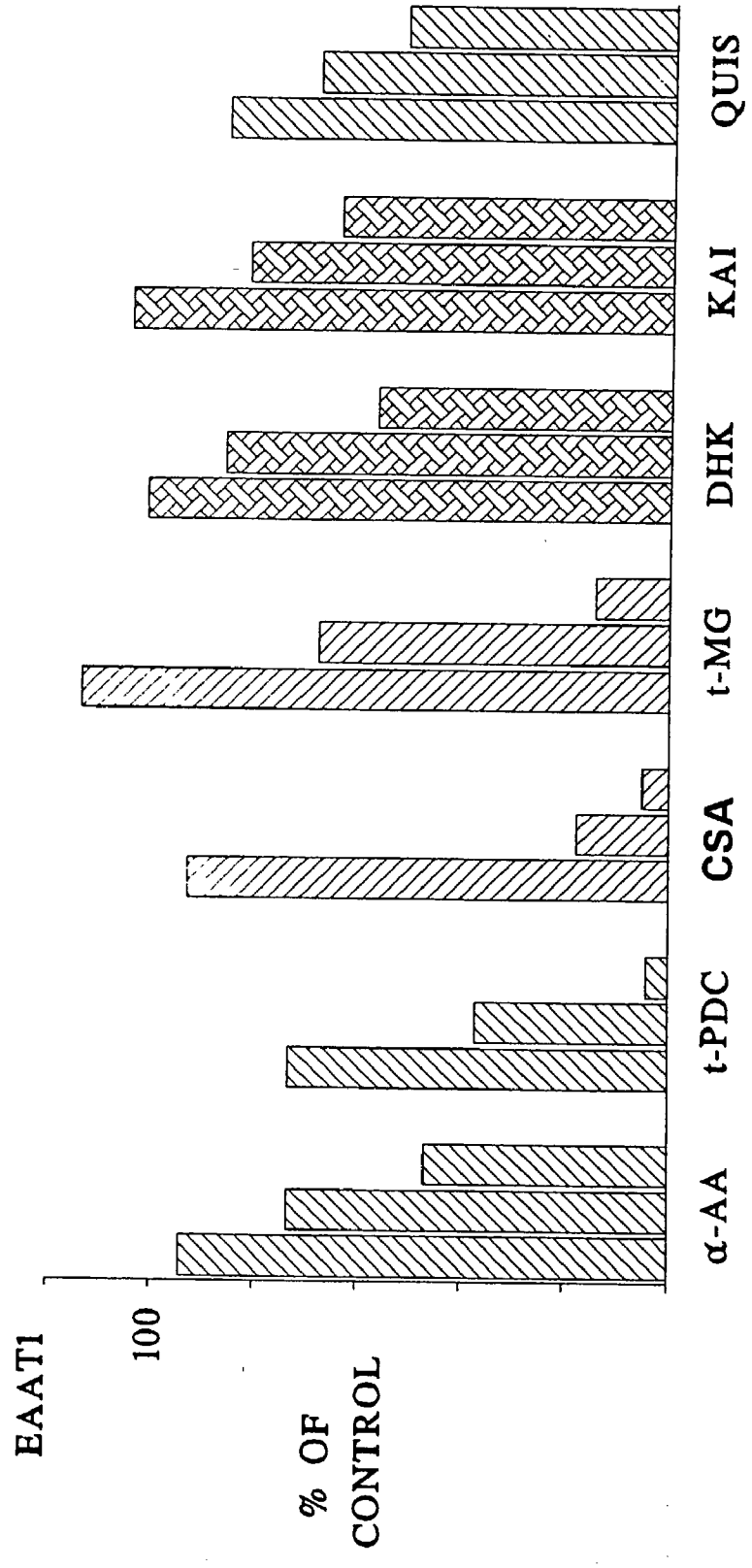


FIG. 8B

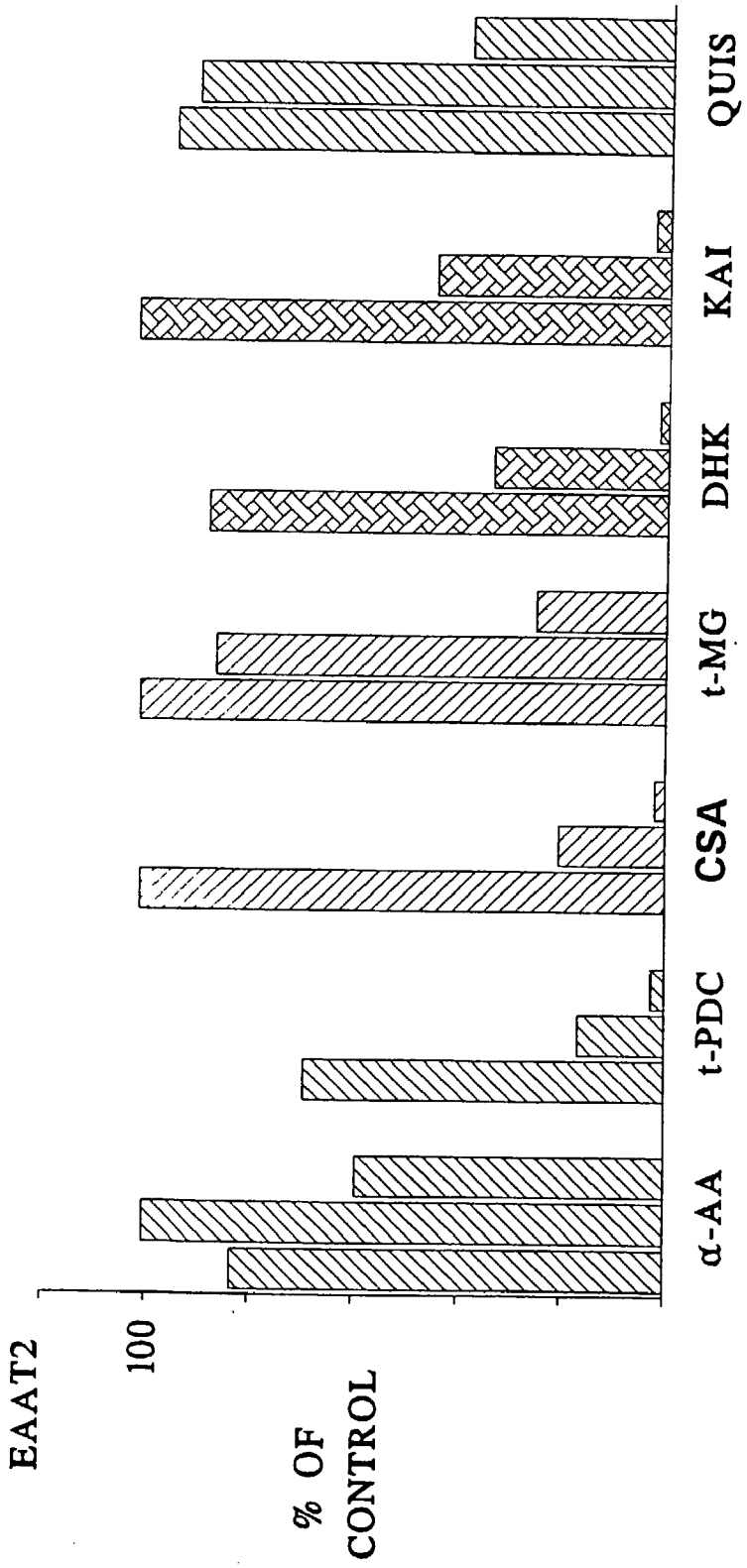
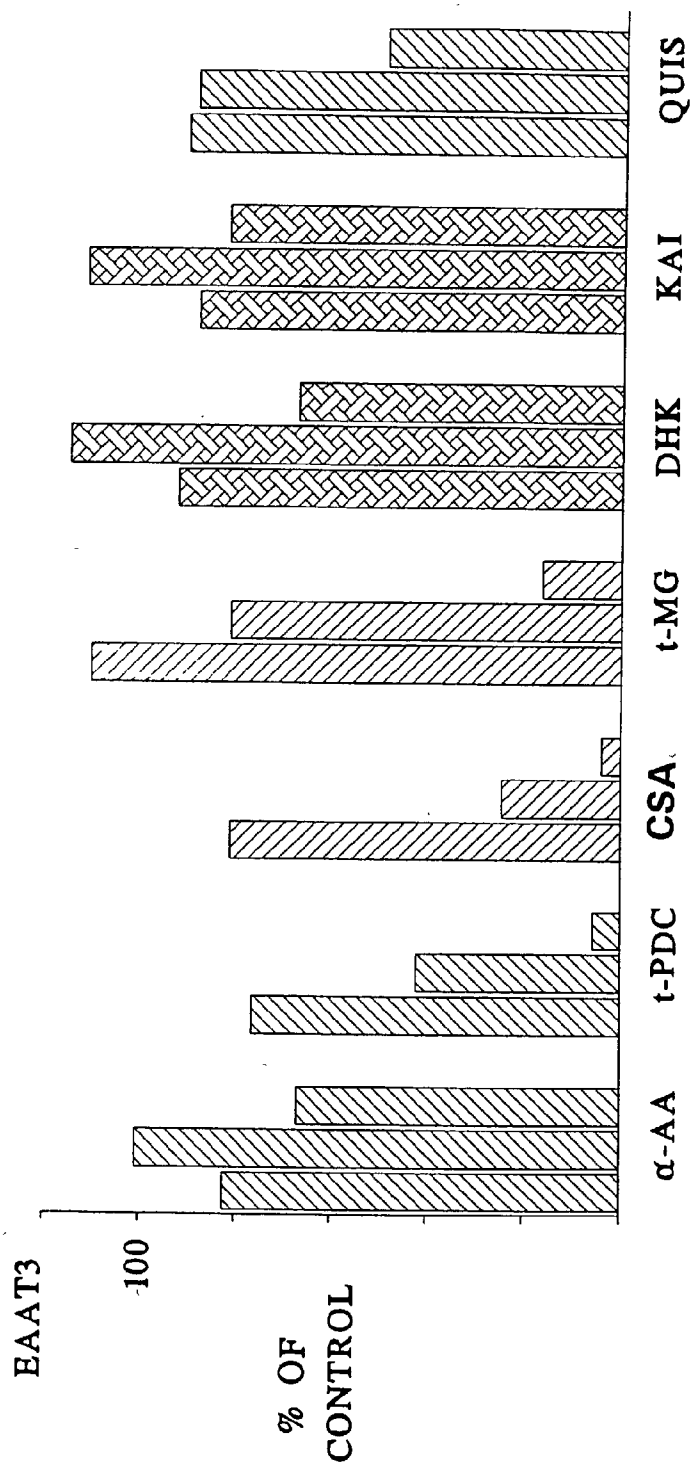


FIG. 8C



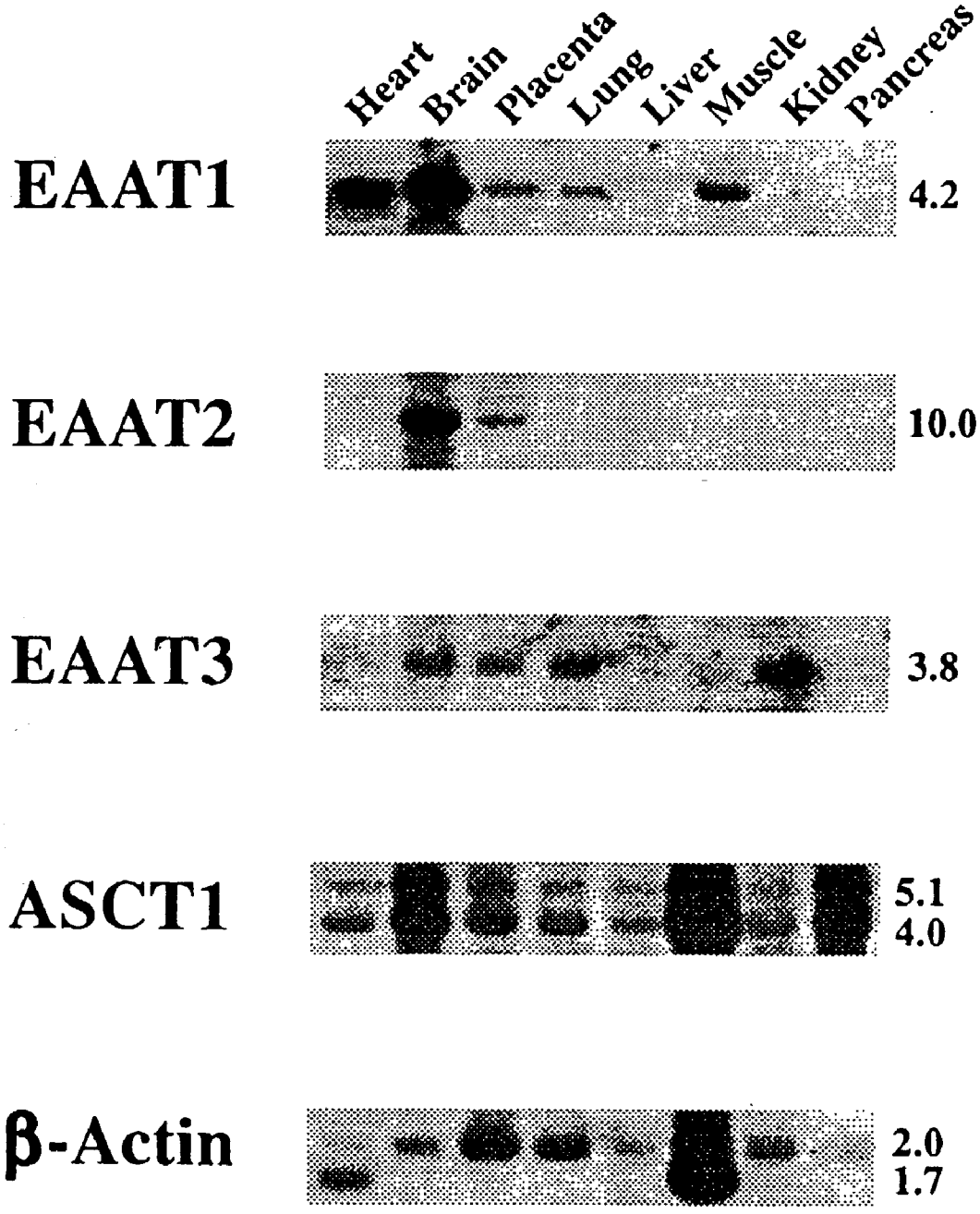

Heart
Brain
Placenta
Lung
Liver
Muscle
Kidney
Pancreas
EAAT1
4.2
EAAT2
10.0
EAAT3
3.8
ASCT1
5.1
4.0
β-Actin
2.0
1.7

Figure 9

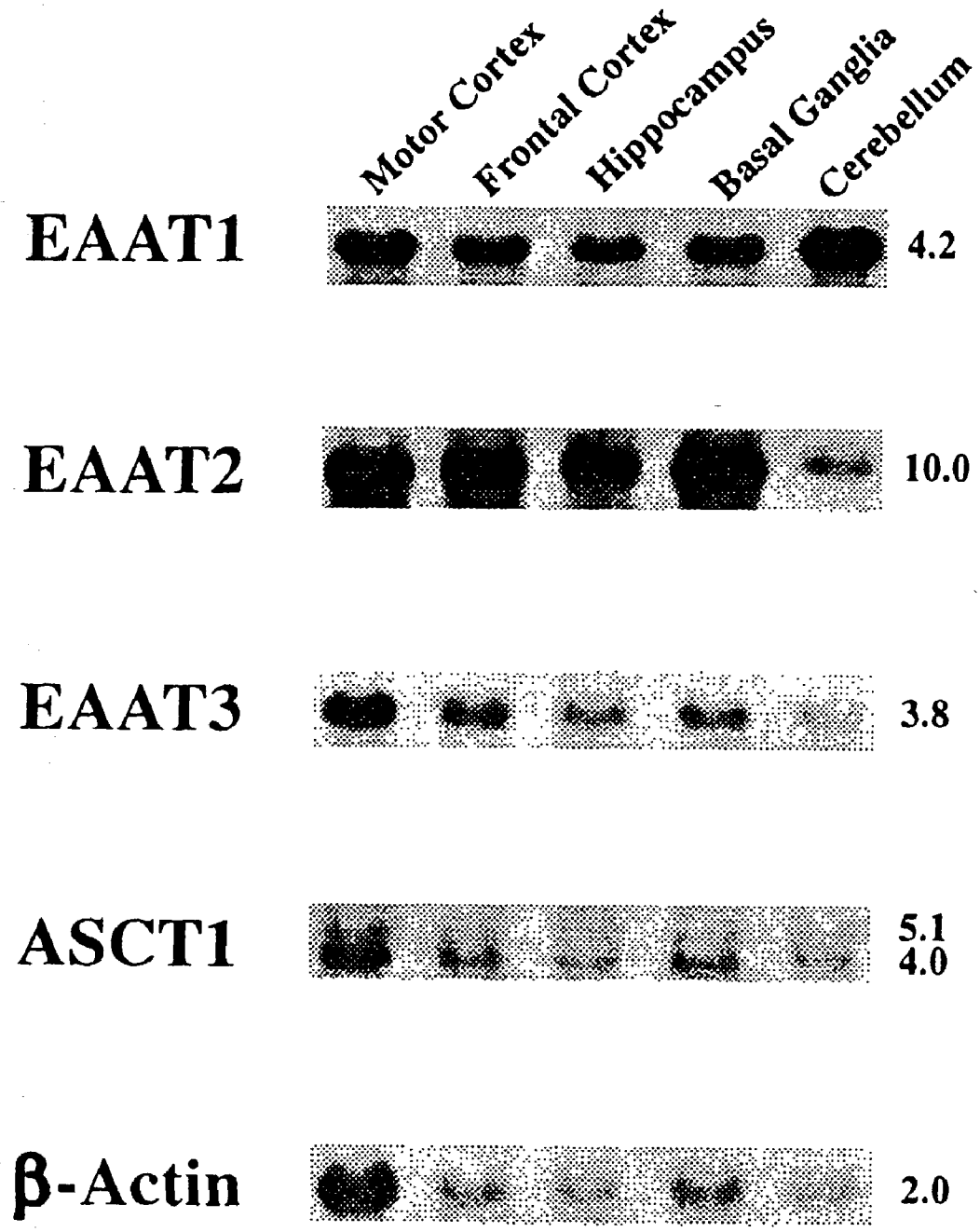

Motor Cortex
Frontal Cortex
Hippocampus
Basal Ganglia
Cerebellum
EAAT1
4.2
EAAT2
10.0
EAAT3
3.8
ASCT1
5.1
4.0
β-Actin
2.0

Figure 10

FIG. 11

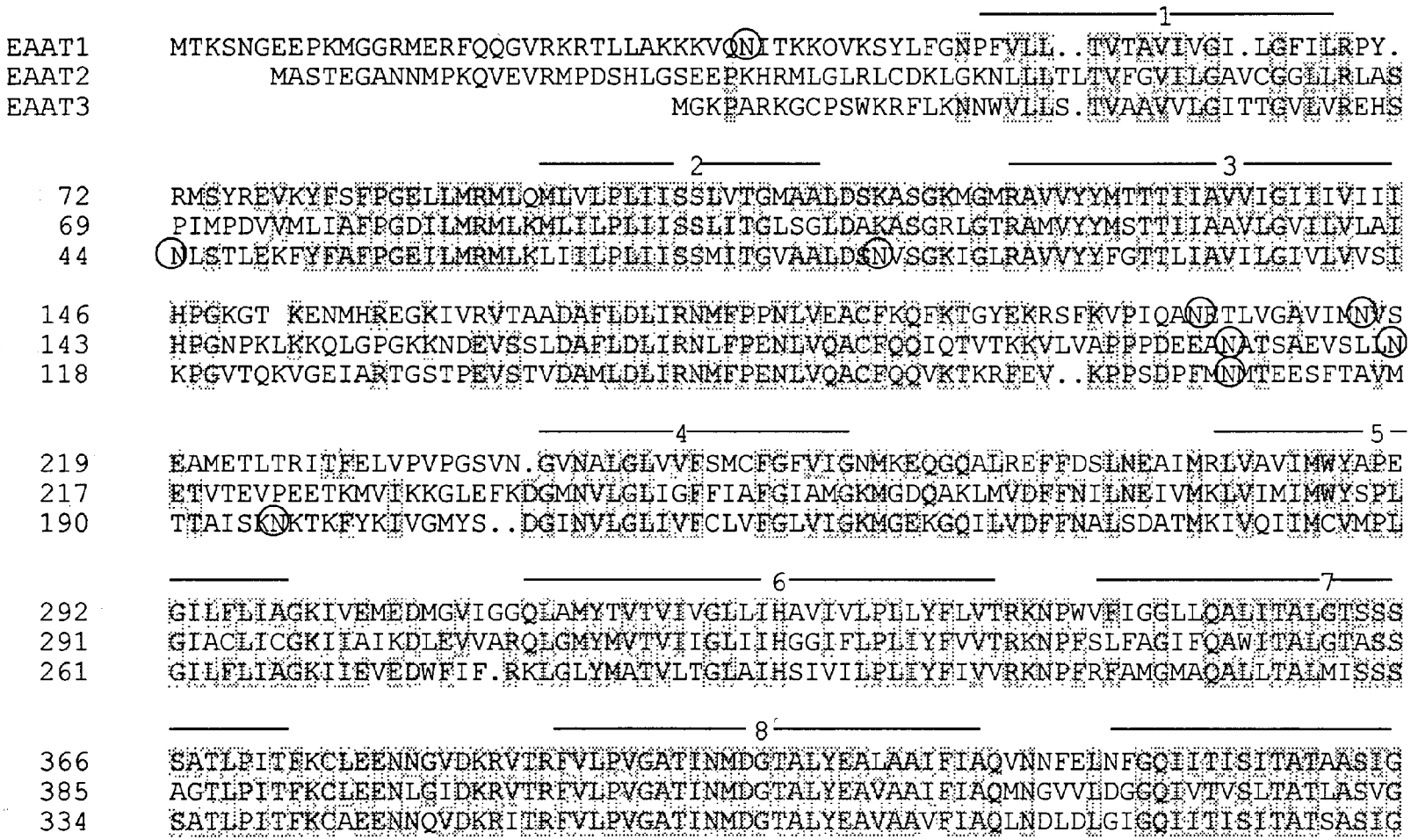

1
EAAT1 MTKSNGEEPKMGGRMERFQQGVRKRTLLAKKKVQNITKKQVKSYLFGNPFVLL..IVTAVIVGI.LGFILRPY.
EAAT2 MASTEGANNMPKQVEVRMPDSHLGSEEPKHRMLGLRLCDKLGKNLLLTLTVFGVILGAVCGGLLRLAS
EAAT3 MGKPARKGCPSWKRFLKNNWVLLS.IVAAVVLGITTGVLVREHS
2
3
72 RMSYREVKYFSFPGELLMRMLQMLVLPLIISSLVTGMAALDSKASGKMGMRAVVYYMTTTIIAVVIGIIIVIII
69 PIMPDVVMLIAFPGDILMRMLKMLILPLIISSLITGLSGLDAKASGRLGTRAMVYYMSTTIIAAVLGVILVLAI
44 NLSTLEKFYFAFPGEILMRMLKLIILPLIISSMITGVAALDSNVSGKIGLRAVVYYFGTTLIAVILGIVLVVSI
146 HPGKGT KENMHREGKIVRVTAADAFLDLIRNMFPPNLVEACFKQFKTGYEKRSFKVPIQANETLVGAVIMNVS
143 HPGNPKLKKQLGPGKKNDEVSSLDAFLDLIRNLFPENLVQACFQQIQTVTKKVLVAPPPDEEANATSAEVSLLN
118 KPGVTQKVGEIARTGSTPEVSTVDAMLDLIRNMFPENLVQACFQQVKTKRFEV..KPPSDPFMNMTEESFTAVM
4
5
219 EAMETLTRITFELVPVPGSVN.GVNALGLVVFSMCFGFVIGNMKEQGQALREFFDSLNEAIMRLVAVIMWYAPE
217 ETVTEVPEETKMVIKKGLEFKDGMNVLGLIGFFIAFGIAMGKMGDQAKLMVDFFNILNEIVMKLVIMIMWYSPL
190 TTAISKNKTKFYKIVGMYS..DGINVLGLIVFCLVFGLVIGKMGEKGQILVDFFNALSDATMKIVQIIMCVMPL
6
7
292 GILFLIAGKIVEMEDMGVIGGQLAMYTVTVIVGLLIHAVIVLPLLYFLVTRKNPWVFIGGLLQALITALGTSSS
291 GIACLICGKIIAIKDLEVVARQLGMYMVTVIIGLIIHGGIFLPLIYFVVTRKNPFSLFAGIFQAWITALGTASS
261 GILFLIAGKIIEVEDWFIF.RKLGLYMATVLTGLAIHSIVILPLIYFIVVRKNPFRFAMGMAQALLTALMISSS
8
366 SATLPITFKCLEENNGVDKRVTRFVLPVGATINMDGTALYEALAAIFIAQVNNFELNFGQIITISITATAASIG
385 AGTLPITFKCLEENLGIDKRVTRFVLPVGATINMDGTALYEAVAAIFIAQMNGVVLDGGQIVTVSLTATLASVG
334 SATLPITFKCAEENNQVDKRITRFVLPVGATINMDGTALYEAVAAVFIAQLNDLDLGIGQIITISITATSASIG

FIG. 11A

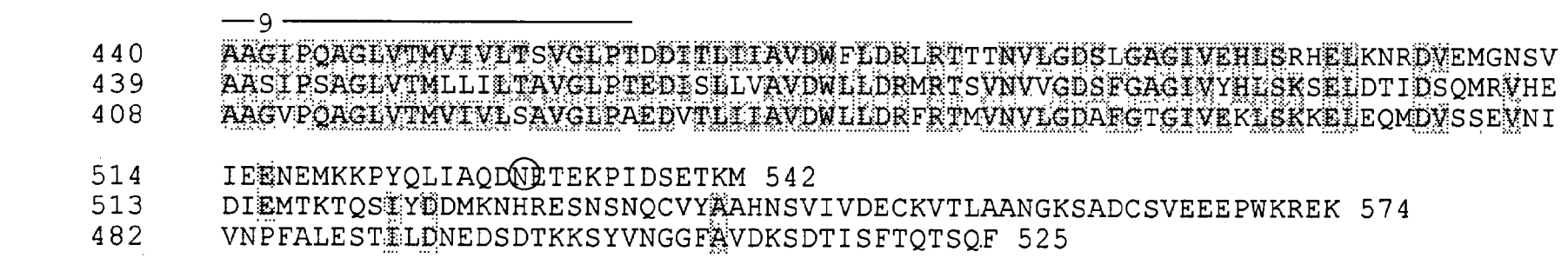

9
440 AAGIPQAGLVTMVIVLTSVGLPTDDITLIIAVDWFLDRLRTTTNVLGDSLGAGIVEHLSRHELKNRDVEMGNSV
439 AASIPSAGLVTMLLILTAVGLPTEDISLLVAVDWLLDRMRTSVNVVGDSFGAGIVYHLSKSELDTIDSQMRVHE
408 AAGVPQAGLVTMVIVLSAVGLPAEDVTLIIAVDWLLDRFRTMVNVLGDAFGTGIVEKLSKKELEQMDVSSEVNI
514 IEENEMKKPYQLIAQDNETEKPIDSETKM 542
513 DIEMTKTQSIYDDMKNHRESNSNQCVYAAHNSVIVDECKVTLAANGKSADCSVEEEPWKREK 574
482 VNPFALESTILDNEDSDTKKSYVNGGFAVDKSDTISFTQTSQF 525

FIG. 12A

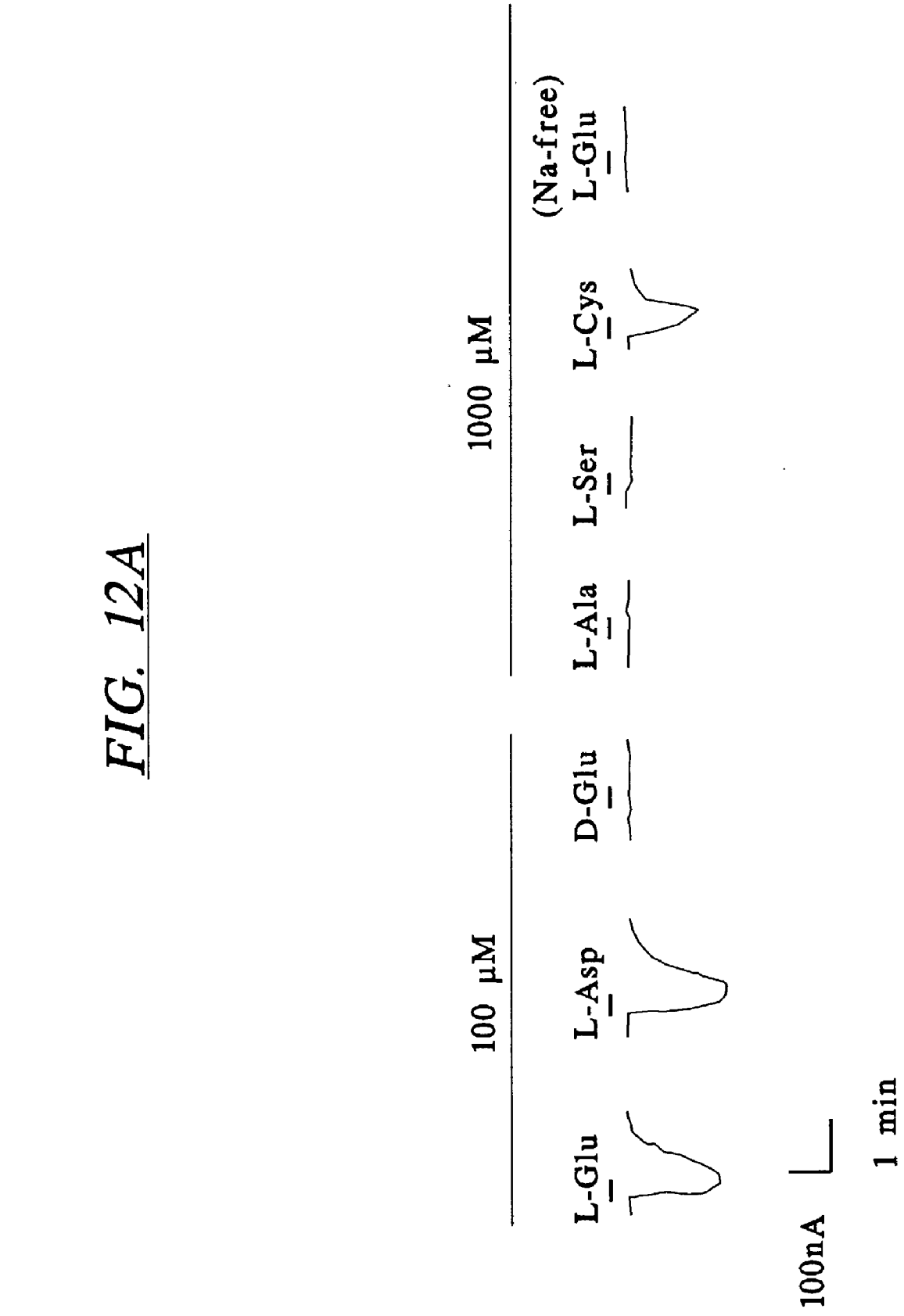

100 μM
1000 μM
(Na-free)
L-Glu
L-Asp
D-Glu
L-Ala
L-Ser
L-Cys
L-Glu
100nA
1 min

FIG. 12B

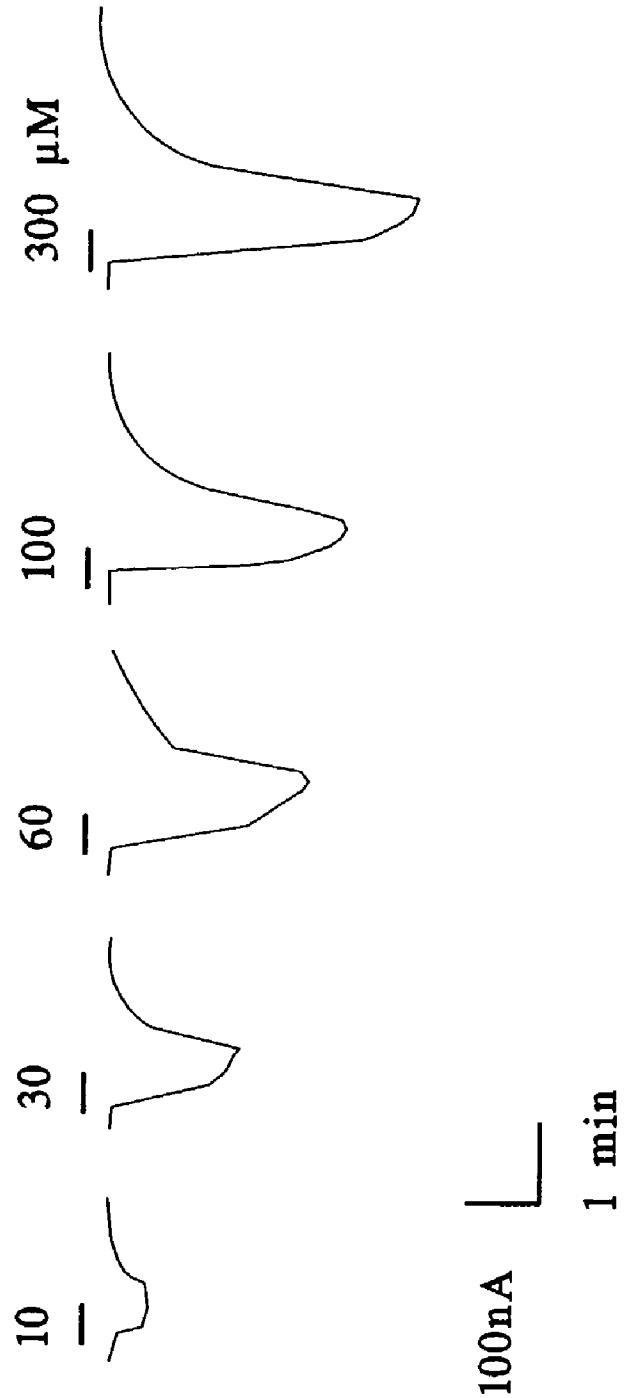
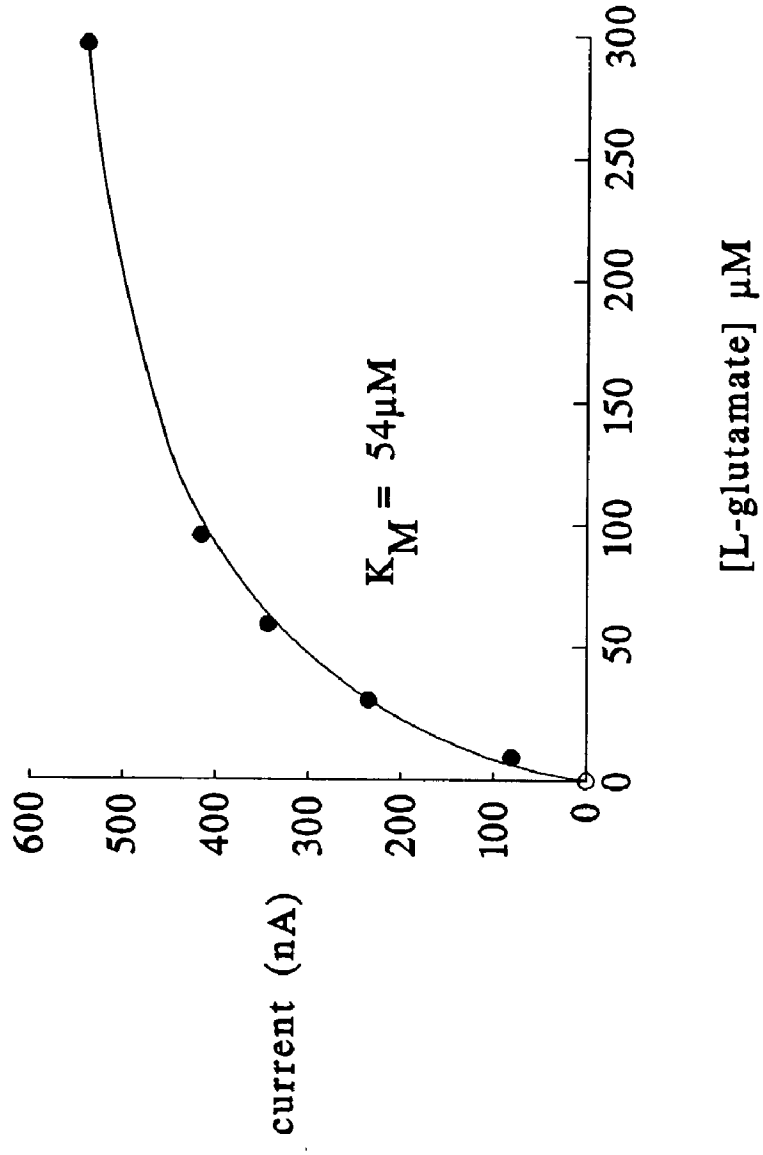


FIG. 12C


600
500
400
300
200
100
0
current (nA)
0
50
100
150
200
250
300
[L-glutamate] μM
K_M = 54μM

AMINO ACID TRANSPORTERS AND USES

[0001] This invention was made with government support under National Institute of Health grants DA07595 and DA03160. The government has certain rights to this invention.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention relates to amino acid transporters from mammalian species and the genes corresponding to such transporters. Specifically, the invention relates to the isolation, cloning and sequencing of complementary DNA (cDNA) copies of messenger RNA (mRNA) encoding each of four novel human amino acid transporter genes. The invention also relates to the construction of recombinant expression constructs comprising such cDNAs from each of the four novel himan amino acid transporter genes of the invention, said recombinant expression constructs being capable of expressing amino acid transporter proteins in cultures of transformed prokaryotic and eukaryotic cells. Production of the transporter proteins in such cultures is also provided. The invention relates to the use of such cultures of such transformed cells to produce homogeneous compositions of each transporter protein. The invention also provides cultures of such cells producing transporter proteins for the characterization of novel and useful drugs. Antibodies against and epitopes of these transporter proteins are also provided by the invention.

[0004] 2. Background of the Invention

[0005] The approximately 20 naturally-occurring amino acids are the basic building blocks for protein biosynthesis. Certain amino acids, such as glutamate and glycine, as well as amino acid derivatives such as γ-aminobutyric acid (GABA), epinephrine and norepinephrine, and histamine, are also used as signaling molecules in higher organisms such as man. For these reasons, specialized trans-membrane transporter proteins have evolved in all organisms to recover or scavenge extracellular amino acids (see Christensen, 1990, Physiol. Rev. 70: 43-77 for review).

[0006] These transporter proteins play a particularly important role in uptake of extracellular amino acids in the vertebrate brain (see Nicholls & Attwell, 1990, TiPS 11: 462-468). Amino acids that function as neurotransmitters must be scavenged from the synaptic cleft between neurons to enable continuous repetitive synaptic transmission. More importantly, it has been found that high extracellular concentrations of certain amino acids (including glutamate and cysteine) can cause neuronal cell death. High extracellular amino acid concentrations are associated with a number of pathological conditions, including ischemia, anoxia and hypoglycemia, as well as chronic illnesses such as Huntington's disease, Parkinson's disease, Alzheimer's disease, epilepsy and amyotrophic lateral sclerosis (ALS; see Pines et al., 1992, Nature **360: 464-467**).

[0007] Glutamate is one example of such an amino acid. Glutamate is an excitatory neurotransmitter (i.e., excitatory neurons use glutamate as a neurotransmitter). When present in excess (>about 300 μM; Bouvier et al., 1992, Nature 360: 471-474; Nicholls & Attwell, ibid.; >5 μM for 5 min.; Choi et al., 1987, J. Neurosci. 7: 357-358), extracellular glutamate causes neuronal cell death. Glutamate transporters play a pivotal role in maintaining non-toxic extracellular concentrations of glutamate in the brain. During anoxic conditions (such as occur during ischemia), the amount of extracellular glutamate in the brain rises dramatically. This is in part due to the fact that, under anoxic conditions, glutamate transporters work in reverse, thereby increasing rather than decreasing the amount of extracellular glutamate found in the brain. The resultingly high extracellular concentration of glutamate causes neuron death, with extremely deleterious consequences for motor and other brain functions, resulting in stroke, anoxia and other instances of organic brain dysfunction.

[0008] This important role for amino acid transporters in maintaining brain homeostasis of extracellular amino acid concentrations has provided the impetus for the search for and development of compounds to modulate and control transporter function. However, conventional screening methods require the use of animal brain slices in binding assays as a first step. This is suboptimal for a number of reasons, including interference in the binding assay by non-specific binding of heterologous (i.e., non-transporter) cell surface proteins expressed by brain cells in such slices; differential binding by cells other than neuronal cells present in the brain slice, such as glial cells or blood cells; and the possibility that putative drug binding behavior in animal brain cells will differ from the binding behavior in human brain cells in subtle but critical ways. The ability to synthesize human transporter molecules in vitro would provide an efficient and economical means for rational drug design and rapid screening of potentially useful compounds.

[0009] Amino acid transporters are known in the art, and some of these proteins have been isolated biochemically and their corresponding genes have been recently cloned using genetic engineering means.

[0010] Christensen et al., 1967, J. Biol. Chem. 242: 5237-5246 report the discovery of a neutral amino acid transporter (termed the ACS transporter) in Erlich ascites tumor cells.

[0011] Makowske & Christensen, 1982, J. Biol. Chem. 257: 14635-14638 provide a biochemical characterization of hepatic amino acid transport.

[0012] Kanner & Schuldiner, 1987, CRC Crit. Rev. Biochem. 22: 1-38 provide a review of the biochemistry of neurotransmitters.

[0013] Olney et al., 1990, Science 248: 596-599 disclose that the amino acid cysteine is a neurotoxin when present in excess extracellularly.

[0014] Wallace et al., 1990, J. Bacteriol. 172: 3214-3220 report the cloning and sequencing of a glutamate/aspartate transporter gene termed gltP from *Escherichia coli* strain K12.

[0015] Kim et al., 1991, Nature 352: 725-728 report the discovery that a cationic amino acid transporter is the cell surface target for infection by ecotropic retroviruses in mice.

[0016] Wang et al., 1991, Nature 352: 729-731 report the discovery that a cationic amino acid transporter is the cell surface target for infection by ecotropic retroviruses in mice.

[0017] Maenz et al., 1992, J. Biol. Chem. 267: 1510-1516 provide a biochemical characterization of amino acid transport in rabbit jejunal brush border membranes.

[0018] Bussolati et al., 1992, J. Biol. Chem. 267: 8330-8335 report that the ASC transporter acts in an electrochemically neutral manner so that sodium ion co-transport occurs without disrupting the normal membrane potential of the cells expressing the transporter.

[0019] Engelke et al., 1992, J. Bacteriol. 171: 5551-5560 report the cloning of a dicarboxylate carrier from *Rhizobium meliloti.*

[0020] Guastella et al., 1992, Proc. Natl. Acad. Sci. USA 89: 7189-7193 disclose the cloning of a sodium ion and chloride ion-dependent glycine transporter from a glioma cell line that is expressed in the rat forebrain and cerebellum.

[0021] Kavanaugh et al., 1992, J. Biol. Chem. 267:22007-22009 report that biochemical characterization of a rat brain GABA transporter expressed in vitro in *Xenopus laevis* oocytes.

[0022] Storck et al., 1992, Proc. Natl. Acad. Sci. USA 89: 10955-10959 disclose the cloning and sequencing of a sodium ion-dependent glutamate/aspartate transporter from rat brain termed GLAST1.

[0023] Bouvier et al., ibid., disclose the biochemical characterization of a glial cell-derived glutamate transporter.

[0024] Pines et al., ibid., report the cloning and sequencing of a glial cell glutamate transporter from rat brain termed GLT-1.

[0025] Kanai & Hediger, 1992, Nature 360: 467-471 disclose the cloning and sequencing of a sodium ion-dependent, high affinity glutamate transporter from rabbit small intestine termed EAAC1.

[0026] Kong et al., 1993, J. Biol. Chem. 268: 1509-1512 report the cloning and sequencing of a sodium-ion dependent neutral amino acid transporter of the A type that is homologous to a sodium-ion dependent glucose transporter.

[0027] Nicholls & Attwell, ibid., review the role of amino acids and amino acid transporters in normal and pathological brain functions.

SUMMARY OF THE INVENTION

[0028] The present invention relates to the cloning, expression and functional characterization of mammalian amino acid transporter genes. The invention comprises nucleic acids, each nucleic acid having a nucleotide sequence of a novel amino acid transporter gene. The nucleic acids provided by the invention each comprise a complementary DNA (cDNA) copy of the corresponding mRNA transcribed in vivo from each of the amino acid transporter genes of the invention. Also provided are the deduced amino acid sequences of each the cognate proteins of the cDNAs provided by the invention.

[0029] This invention provides nucleic acids, nucleic acid hybridization probes, recombinant eukaryotic expression constructs capable of expressing the amino acid transporters of the invention in cultures of transformed cells, such cultures of transformed eukaryotic cells that synthesize the amino acid transporters of the invention, homogeneous compositions of each of the amino acid transporter proteins, and antibodies against and epitopes of each of the amino acid transporter proteins of the invention. Methods for characterizing these transporter proteins and methods for using these proteins in the development of agents having pharmacological uses related to these transporter proteins are also provided by the invention.

[0030] In a first aspect, the invention provides a nucleic acid having a nucleotide sequence encoding a human neutral amino acid transporter that is the ASCT1 transporter (SEQ ID No:2). In this embodiment of the invention, the nucleotide sequence includes 1680 nucleotides of the human ASCT1 cDNA comprising 1596 nucleotides of coding sequence, 30 nucleotides of 5' untranslated sequence and 54 nucleotides of 3' untranslated sequence. In this embodiment of the invention, the nucleotide sequence of the ASCT1 transporter consists essentially of the nucleotide sequence depicted in **FIG. 1** (SEQ ID No:2). The use of the term "consisting essentially of" herein is meant to encompass the disclosed sequence and includes allelic variations of this nucleotide sequence, either naturally occurring or the product of in vitro chemical or genetic modification. Each such variant will be understood to have essentially the same nucleotide sequence as the nucleotide sequence of the corresponding ASCT1 disclosed herein.

[0031] The corresponding ASCT1 protein molecule, having the deduced amino acid sequence consisting essentially of the sequence shown in **FIG. 1** (SEQ ID No.:3), is also claimed as an aspect of the invention. The use of the term "consisting essentially of" herein is as described above. Similarly, the corresponding ASCT1 protein molecule, having the deduced amino acid sequence consisting essentially of the sequence shown in **FIG. 1** (SEQ ID No.:3), is also claimed as an aspect of the invention. ASCT1 protein molecules provided by the invention are understood to have substantially the same biological properties as the ASCT1 protein molecule encoded by the nucleotide sequence described herein.

[0032] In another aspect, the invention comprises a homogeneous composition of the 55.9 kD mammalian ASCT1 transporter or derivative thereof, said size being understood to be the size of the protein before any post-translational modifications thereof. The amino acid sequence of the ASCT1 transporter or derivative thereof preferably consists essentially of the amino acid sequence of the human ASCT1 transporter protein shown in **FIG. 1** (SEQ ID No:3).

[0033] In a second aspect, the invention provides a nucleic acid having a nucleotide sequence encoding a human excitatory amino acid transporter that is the EAAT1 transporter (SEQ ID No:4). In this embodiment of the invention, the nucleotide sequence includes 1680 nucleotides of the human EAAT1 cDNA comprising 1626 nucleotides of coding sequence, 30 nucleotides of 5' untranslated sequence and 24 nucleotides of 3' untranslated sequence. In this embodiment of the invention, the nucleotide sequence of the EAAT1 transporter consists essentially of the nucleotide sequence depicted in **FIG. 2** (SEQ ID No:4). The use of the term "consisting essentially of" herein is as described above.

[0034] In another aspect, the invention comprises a homogeneous composition of the 59.5 kilodalton (kD) mammalian EAAT1 transporter or derivative thereof, said size being understood to be the size of the protein before any post-translational modifications thereof. The amino acid sequence of the EAAT1 transporter or derivative thereof preferably consists essentially of the amino acid sequence of the human EAAT1 transporter protein shown in **FIG. 2**

(SEQ ID No:5). EAAT1 protein molecules provided by the invention are understood to have substantially the same biological properties as the EAAT1 protein molecule encoded by the nucleotide sequence described herein.

[0035] In a third aspect, the invention provides a nucleic acid having a nucleotide sequence encoding a human excitatory amino acid transporter that is the EAAT2 transporter (SEQ ID No:6). In this embodiment of the invention, the nucleotide sequence includes 1800 nucleotides of the human EAAT2 cDNA comprising 1722 nucleotides of coding sequence, 33 nucleotides of 5' untranslated sequence and 45 nucleotides of 3' untranslated sequence. In this embodiment of the invention, the nucleotide sequence of the EAAT2 transporter consists essentially of the nucleotide sequence depicted in **FIG. 3** (SEQ ID No:6). The use of the term "consisting essentially of" herein is as described above.

[0036] The corresponding EAAT2 protein molecule, having the deduced amino acid sequence consisting essentially of the sequence shown in **FIG. 3** (SEQ ID No.:7), is also claimed as an aspect of the invention. EAAT2 protein molecules provided by the invention are understood to have substantially the same biological properties as the EAAT2 protein molecule encoded by the nucleotide sequence described herein.

[0037] In another aspect, the invention comprises a homogeneous composition of the 62.1 kD mammalian EAAT2 transporter or derivative thereof, said size being understood to be the size of the protein before any post-translational modifications thereof. The amino acid sequence of the EAAT2 transporter or derivative thereof preferably consists essentially of the amino acid sequence of the human EAAT2 transporter protein shown in **FIG. 3** (SEQ ID No:7).

[0038] In yet another aspect, the invention provides a nucleic acid having a nucleotide sequence encoding a human excitatory amino acid transporter that is the EAAT3 transporter (SEQ ID No:8). In this embodiment of the invention, the nucleotide sequence includes 1674 nucleotides of the human EAAT3 cDNA comprising 1575 nucleotides of coding sequence, 15 nucleotides of 5' untranslated sequence and 84 nucleotides of 3' untranslated sequence. In this embodiment of the invention, the nucleotide sequence of the EAAT3 transporter consists essentially of the nucleotide sequence depicted in **FIG. 4** (SEQ ID No:8). The use of the term "consisting essentially of" herein is as described above.

[0039] The corresponding EAAT3 protein molecule, having the deduced amino acid sequence consisting essentially of the sequence shown in **FIG. 4** (SEQ ID No.:9), is also claimed as an aspect of the invention. EAAT3 protein molecules provided by the invention are understood to have substantially the same biological properties as the EAAT3 protein molecule encoded by the nucleotide sequence described herein.

[0040] In another aspect, the invention comprises a homogeneous composition of the 57.2 kD mammalian EAAT3 transporter or derivative thereof, said size being understood to be the size of the protein before any post-translational modifications thereof. The amino acid sequence of the EAAT3 transporter or derivative thereof preferably consists essentially of the amino acid sequence of the human EAAT3 transporter protein shown in **FIG. 4** (SEQ ID No:9).

[0041] This invention provides both nucleotide and amino acid probes derived from the sequences herein provided. The invention includes probes isolated from either cDNA or genomic DNA, as well as probes made synthetically with the sequence information derived therefrom. The invention specifically includes but is not limited to oligonucleotide, nick-translated, random primed, or in vitro amplified probes made using cDNA or genomic clone embodying the invention, and oligonucleotide and other synthetic probes synthesized chemically using the nucleotide sequence information of cDNA or genomic clone embodiments of the invention.

[0042] It is a further object of this invention to provide such nucleic acid hybridization probes to determine the pattern, amount and extent of expression of these transporter genes in various tissues of mammals, including humans. It is also an object of the present invention to provide nucleic acid hybridization probes derived from the sequences of the amino acid transporter genes of the invention to be used for the detection and diagnosis of genetic diseases. It is an object of this invention to provide nucleic acid hybridization probes derived from the DNA sequences of the amino acid transporter genes herein disclosed to be used for the detection of novel related receptor genes.

[0043] The present invention also includes synthetic peptides made using the nucleotide sequence information comprising the cDNA embodiments of the invention. The invention includes either naturally occurring or synthetic peptides which may be used as antigens for the production of amino acid transporter-specific antibodies, or used for competitors of amino acid transporter molecules for amino acid, agonist, antagonist or drug binding, or to be used for the production of inhibitors of the binding of agonists or antagonists or analogues thereof to such amino acid transporter molecules.

[0044] The present invention also provides antibodies against and epitopes of the mammalian amino acid transporter molecules of the invention. It is an object of the present invention to provide antibodies that are immunologically reactive to the amino acid transporters of the invention. It is a particular object to provide monoclonal antibodies against these amino acid transporters, must preferably the human excitatory and neutral amino acid transporters as herein disclosed. Hybridoma cell lines producing such antibodies are also objects of the invention. It is envisioned at such hybridoma cell lines may be produced as the result of fusion between a non-immunoglobulin producing mouse myeloma cell line and spleen cells derived from a mouse immunized with a cell line which expresses antigens or epitopes of an amino acid transporter of the invention. The present invention also provides hybridoma cell lines that produces such antibodies, and can be injected into a living mouse to provide an ascites fluid from the mouse that is comprised of such antibodies. It is a further object of the invention to provide immunologically-active epitopes of the amino acid transporters of the invention. Chimeric antibodies immunologically reactive against the amino acid transporter proteins of the invention are also within the scope of this invention.

[0045] The present invention provides recombinant expression constructs comprising a nucleic acid encoding an amino acid transporter of the invention wherein the construct is capable of expressing the encoded amino acid transporter in cultures of cells transformed with the construct. Preferred embodiments of such constructs comprise the human EAAT1 cDNA (SEQ ID No.:4), the human

EAAT2 cDNA (SEQ ID No.:6), the human EAAT3 cDNA (SEQ ID No.:8), and human ASCT1 cDNA (SEQ ID No.:2), each construct being capable of expressing the amino acid transporter encoded therein in cells transformed with the construct.

[0046] The invention also provides cultures cells transformed with the recombinant expression constructs of the invention, each such cultures being capable of and in fact expressing the amino acid transporter encoded in the transforming construct.

[0047] The present invention also includes within its scope protein preparations of prokaryotic and eukaryotic cell membranes containing at least one of the amino acid transporter proteins of the invention, derived from cultures of prokaryotic or eukaryotic cells, respectively, transformed with the recombinant expression constructs of the invention. In a preferred embodiment, each preparation of such cell membranes comprises one species of the amino acid transporter proteins of the invention.

[0048] The invention also provides methods for screening compounds for their ability to inhibit, facilitate or modulate the biochemical activity of the amino acid transporter molecules of the invention, for use in the in vitro screening of novel agonist and antagonist compounds. In preferred embodiments, cells transformed with a recombinant expression construct of the invention are contacted with such a compound, and the effect of the compound on the transport of the appropriate amino acid is assayed. Additional preferred embodiments comprise quantitative analyses of such effects.

[0049] The present invention is also useful for the detection of analogues, agonists or antagonists, known or unknown, of the amino acid transporters of the invention, either naturally occurring or embodied as a drug. In preferred embodiments, such analogues, agonists or antagonists may be detected in blood, saliva, semen, cerebrospinal fluid, plasma, lymph, or any other bodily fluid.

[0050] Specific preferred embodiments of the present invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

DESCRIPTION OF THE DRAWINGS

[0051] **FIG. 1** illustrates the nucleotide (SEQ ID No.:2) and amino acid (SEQ ID No.:3) sequences of the human ASCT1 neutral amino acid transporter.

[0052] **FIG. 2** illustrates the nucleotide (SEQ ID No.:4) and amino acid (SEQ ID No.:5) sequences of the human EAAT1 excitatory amino acid transporter.

[0053] **FIG. 3** illustrates the nucleotide (SEQ ID No.:6) and amino acid (SEQ ID No.:7) sequences of the human EAAT2 excitatory amino acid transporter.

[0054] **FIG. 4** illustrates the nucleotide (SEQ ID No.:8) and amino acid (SEQ ID No.:9) sequences of the human EAAT3 excitatory amino acid transporter.

[0055] **FIG. 5** presents an amino acid sequence comparison between human ASCT1, GLAST1, GLT1 and EAAC1.

[0056] **FIG. 6** illustrates transmembrane electrochemical currents in Xenopus laevis oocytes microinjected with RNA encoding ASCT1 and contacted with the indicated amino acids (Panel A); the amino acid concentration dependence of such electrochemical currents (Panel B); and a plot of normalized current vs. amino acid concentration illustrating the kinetic parameters of amino acid transport (Panel C).

[0057] **FIG. 7** presents glutamate transporter kinetics of EAAT1 (Panel A), EAAT2 (Panel B) and EAAT3 (Panel C).

[0058] **FIG. 8** represents the pharmacological responsiveness of glutamate transport by the human excitatory amino acid transporters EAAT1, EAAT2 and EAAT3 when contacted with the indicated competitors/inhibitors at the indicated concentrations.

[0059] **FIG. 9** shows the pattern of expression of EAAT1, EAAT2, EAAT3 and ASCT1 in human tissues; β-actin is shown as a control for amount of RNA in each lane.

[0060] **FIG. 10** shows the pattern of expression of EAAT1, EAAT2, EAAT3 and ASCT1 in human brain tissue; β-actin is shown as a control for the amount of RNA in each lane.

[0061] **FIG. 11** illustrates the degree of predicted amino acid sequence homology between the novel human glutamate transporters EAAT1, EAAT2 and EAAT3; overbars indicate nine regions of hydrophobicity determined using the algorithm of Eisenberg et al., and potential sites of N-linked glycosylation are shown by the circled asparagine (N) residues.

[0062] **FIG. 12** illustrate electrogenic uptake of various amino acids (Panel A) and the concentration dependence of such uptake of L-glutamate (Panel B) in Xenopus laevis oocytes expressing the EAAT1 amino acid transporter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0063] The term "human amino acid transporter EAAT1" as used herein refers to proteins consisting essentially of, and having substantially the same biological activity as, the protein encoded by the nucleic acid depicted in **FIG. 2** (SEQ ID No.:4). This definition is intended to encompass natural allelic variations in the EAAT1 sequence. Cloned nucleic acid provided by the present invention may encode EAAT1 protein of any species of origin, including, for example, mouse, rat, rabbit, cat, and human, but preferably the nucleic acid provided by the invention encodes EAAT1 receptors of mammalian, most preferably human, origin.

[0064] The term "human amino acid transporter EAAT2" as used herein refers to proteins consisting essentially of, and having substantially the same biological activity as, the protein encoded by the nucleic acid depicted in **FIG. 3** (SEQ ID No.:6). This definition is intended to encompass natural allelic variations in the EAAT2 sequence. Cloned nucleic acid provided by the present invention may encode EAAT2 protein of any species of origin, including, for example, mouse, rat, rabbit, cat, and human, but preferably the nucleic acid provided by the invention encodes EAAT2 receptors of mammalian, most preferably human, origin.

[0065] The term "human amino acid transporter EAAT3" as used herein refers to proteins consisting essentially of, and having substantially the same biological activity as, the protein encoded by the nucleic acid depicted in **FIG. 4** (SEQ ID No.:8). This definition is intended to encompass natural

allelic variations in the EAAT3 sequence. Cloned nucleic acid provided by the present invention may encode EAAT3 protein of any species of origin, including, for example, mouse, rat, rabbit, cat, and human, but preferably the nucleic acid provided by the invention encodes EAAT3 receptors of mammalian, most preferably human, origin.

[0066] The term "human amino acid transporter ASCT1" as used herein refers to proteins consisting essentially of, and having substantially the same biological activity as, the protein encoded by the nucleic acid depicted in **FIG. 1** (SEQ ID No.:2). This definition is intended to encompass natural allelic variations in the ASCT1 sequence. Cloned nucleic acid provided by the present invention may encode ASCT1 protein of any species of origin, including, for example, mouse, rat, rabbit, cat, and human, but preferably the nucleic acid provided by the invention encodes ASCT1 receptors of mammalian, most preferably human, origin.

[0067] Each of the nucleic acid hybridization probes provided by the invention comprise DNA or RNA consisting essentially of the nucleotide sequence of one of the amino acid transporters, depicted in FIGS. **14** (SEQ ID Nos.:2, 4, 6, 8), or any portion thereof effective in nucleic acid hybridization. Mixtures of such nucleic acid hybridization probes are also within the scope of this embodiment of the invention. Nucleic acid probes as provided herein are useful for detecting amino acid transporter gene expression in cells and tissues using techniques well-known in the art, including but not limited to Northern blot hybridization, in situ hybridization and Southern hybridization to reverse transcriptase—polymerase chain reaction product DNAs. The probes provided by the present invention, including oligonucleotides probes derived therefrom, are useful are also useful for Southern hybridization of mammalian, preferably human, genomic DNA for screening for restriction fragment length polymorphism (RFLP) associated with certain genetic disorders.

[0068] The production of proteins such as these amino acid transporter molecules from cloned genes by genetic engineering means is well known in this art. The discussion which follows is accordingly intended as an overview of this field, and is not intended to reflect the full state of the art.

[0069] DNA encoding an amino acid transporter may be obtained, in view of the instant disclosure, by chemical synthesis, by screening reverse transcripts of mRNA from appropriate cells or cell line cultures, by screening genomic libraries from appropriate cells, or by combinations of these procedures, as illustrated below. Screening of mRNA or genomic DNA may be carried out with oligonucleotide probes generated from the nucleic acid sequence information from each of the amino acid transporters disclosed herein. Probes may be labeled with a detectable group such as a fluorescent group, a radioactive atom or a chemiluminescent group in accordance with know procedures and used in conventional hybridization assays, as described in greater detail in the Examples below. In the alternative, amino acid transporter-derived nucleic acid sequences may be obtained by use of the polymerase chain reaction (PCR) procedure, using PCR oligonucleotide primers corresponding to nucleic acid sequence information derived from an amino acid transporter as provided herein. See U.S. Pat. Nos. 4,683,195 to Mullis et al. and 4,683,202 to Mullis.

[0070] Each of the amino acid transporter proteins may be synthesized in host cells transformed with a recombinant expression construct comprising a nucleic acid encoding the particular amino acid transporter cDNA. Such recombinant expression constructs can also be comprised of a vector that is a replicable DNA construct. Vectors are used herein either to amplify DNA encoding an amino acid transporter and/or to express DNA encoding an amino acid transporter gene. For the purposes of this invention, a recombinant expression construct is a replicable DNA construct in which a nucleic acid encoding an amino acid transporter is operably linked to suitable control sequences capable of effecting the expression of the amino acid transporter in a suitable host.

[0071] The need for such control sequences will vary depending upon the host selected and the transformation method chosen. Generally, control sequences include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences which control the termination of transcription and translation. Amplification vectors do not require expression control domains. All that is needed is the ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants. See, Sambrook et al., 1990, *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Press: New York).

[0072] Vectors useful for practicing the present invention include plasmids, viruses (including phage), retroviruses, and integratable DNA fragments (i.e., fragments integratable into the host genome by homologous recombination). The vector replicates and functions independently of the host genome, or may, in some instances, integrate into the genome itself. Suitable vectors will contain replicon and control sequences which are derived from species compatible with the intended expression host. A preferred vector is pCMV5 (Andersson et al., 1989, J. Biol. Chem. 264: 8222-8229). Transformed host cells are cells which have been transformed or transfected with recombinant expression constructs made using recombinant DNA techniques and comprising nucleic acid encoding an amino acid transporter protein. Preferred host cells are COS-7 cells (Gluzman, 1981, Cell 23: 175-182). Transformed host cells may express the amino acid transporter protein, but host cells transformed for purposes of cloning or amplifying nucleic acid hybridization probe DNA need not express the transporter. When expressed, each of the amino acid transporters of the invention will typically be located in the host cell membrane. See, Sambrook et al., ibid.

[0073] Cultures of cells derived from multicellular organisms are a desirable host for recombinant amino acid transporter protein synthesis. In principal, any higher eukaryotic cell culture is useful, whether from vertebrate or invertebrate culture. However, mammalian cells are preferred, as illustrated in the Examples. Propagation of such cells in cell culture has become a routine procedure. See *Tissue Culture,* Academic Press, Kruse & Patterson, editors (1973). Examples of useful host cell lines are human 293 cells, VERO and HeLa cells, Chinese hamster ovary (CHO) cell lines, and WI138, BHK, COS-7, CV, and MDCK cell lines. COS-7 cells are preferred.

[0074] The invention provides homogeneous compositions of each of the human EAAT1, EAAT2, EAAT3 and ASCT1 amino acid transporter proteins produced by transformed eukaryotic cells as provided herein. Each such

homogeneous composition is intended to be comprised of the corresponding amino acid transporter protein that comprises at least 90% of the protein in such a homogenous composition. The invention also provides membrane preparation from cells expressing each of the amino acid transporter proteins as the result of transformation with a recombinant expression construct, as described herein.

[0075] Amino acid transporter proteins made from cloned genes in accordance with the present invention may be used for screening amino acid analogues, or agonist or antagonists of amino acid transport, or for determining the amount of such agonists or antagonists in a solution of interest (e.g., blood plasma or serum). For example, host cells may be transformed with a recombinant expression construct of the present invention, an amino acid transporter expressed in those host cells, and the cells or membranes thereof used to screen compounds for their effect on amino acid transport activity. By selection of host cells that do not ordinarily express a particular amino acid transporter, pure preparations of membranes containing the transporter can be obtained.

[0076] The recombinant expression constructs of the present invention are useful in molecular biology to transform cells which do not ordinarily express a particular amino acid transporter to thereafter express this receptor. Such cells are useful as intermediates for making cell membrane preparations useful for transporter activity assays, which are in turn useful for drug screening. The recombinant expression constructs of the present invention may also be useful in gene therapy. Cloned genes of the present invention, or fragments thereof, may also be used in gene therapy carried out homologous recombination or site-directed mutagenesis. See generally Thomas & Capecchi, 1987, Cell 51: 503-512; Bertling, 1987, Bioscience Reports 7: 107-112; Smithies et al., 1985, Nature 317: 230-234.

[0077] Oligonucleotides of the present invention are useful as diagnostic tools for probing amino acid transporter gene expression in tissues of humans and other animals. For example, tissues are probed in situ with oligonucleotide probes carrying detectable groups by conventional autoradiographic techniques, to investigate native expression of this receptor or pathological conditions relating thereto. Further, chromosomes can be probed to investigate the presence or absence of the corresponding amino acid transporter gene, and potential pathological conditions related thereto.

[0078] The invention also provides antibodies that are immunologically reactive to the amino acid transporter proteins or epitopes thereof provided by the invention. The antibodies provided by the invention may be raised, using methods well known in the art, in animals by inoculation with cells that express an amino acid transporter or epitopes thereof, cell membranes from such cells, whether crude membrane preparations or membranes purified using methods well known in the art, or purified preparations of proteins, including fusion proteins, particularly fusion proteins comprising epitopes of the amino acid transporter proteins of the invention fused to heterologous proteins and expressed using genetic engineering means in bacterial, yeast or eukaryotic cells, said proteins being isolated from such cells to varying degrees of homogeneity using conventional biochemical means. Synthetic peptides made using established synthetic means in vitro and optionally conjugated with heterologous sequences of amino acids, are also encompassed in these methods to produce the antibodies of the invention. Animals that are used for such inoculations include individuals from species comprising cows, sheep, pigs, mice, rats, rabbits, hamsters, goats and primates. Preferred animals for inoculation are rodents (including mice, rats, hamsters) and rabbits. The most preferred animal is the mouse.

[0079] Cells that can be used for such inoculations, or for any of the other means used in the invention, include any cell line which naturally expresses one of the amino acid transporters provided by the invention, or any cell or cell line that expresses one of the amino acid transporters of the invention, or any epitope thereof, as a result of molecular or genetic engineering, or that has been treated to increase the expression of an endogenous or heterologous amino acid transporter protein by physical, biochemical or genetic means. Preferred cells are *E. coli* and insect SF9 cells, most preferably *E. coli* cells, that have been transformed with a recombinant expression construct of the invention encoding an amino acid transporter protein, and that express the transporter therefrom.

[0080] The present invention also provides monoclonal antibodies that are immunologically reactive with an epitope derived from an amino acid transporter of the invention, or fragment thereof, present on the surface of such cells, preferably *E. coli* cells. Such antibodies are made using methods and techniques well known to those of skill in the art. Monoclonal antibodies provided by the present invention are produced by hybridoma cell lines, that are also provided by the invention and that are made by methods well known in the art.

[0081] Hybridoma cell lines are made by fusing individual cells of a myeloma cell line with spleen cells derived from animals immunized with cells expressing an amino acid transporter of the invention, as described above. The myeloma cell lines used in the invention include lines derived from myelomas of mice, rats, hamsters, primates and humans. Preferred myeloma cell lines are from mouse, and the most preferred mouse myeloma cell line is P3X63-Ag8.653. The animals from whom spleens are obtained after immunization are rats, mice and hamsters, preferably mice, most preferably Balb/c mice. Spleen cells and myeloma cells are fused using a number of methods well known in the art, including but not limited to incubation with inactivated Sendai virus and incubation in the presence of polyethylene glycol (PEG). The most preferred method for cell fusion is incubation in the presence of a solution of 45% (w/v) PEG-1450. Monoclonal antibodies produced by hybridoma cell lines can be harvested from cell culture supernatant fluids from in vitro cell growth; alternatively, hybridoma cells can be injected subcutaneously and/or into the peritoneal cavity of an animal, most preferably a mouse, and the monoclonal antibodies obtained from blood and/or ascites fluid.

[0082] Monoclonal antibodies provided by the present invention are also produced by recombinant genetic methods well known to those of skill in the art, and the present invention encompasses antibodies made by such methods that are immunologically reactive with an epitope of an

amino acid transporter of the invention. The present invention also encompasses fragments, including but not limited to F(ab) and F(ab)'$_2$ fragments, of such antibody. Fragments are produced by any number of methods, including but not limited to proteolytic cleavage, chemical synthesis or preparation of such fragments by means of genetic engineering technology. The present invention also encompasses single-chain antibodies that are immunologically reactive with an epitope of an amino acid transporter, made by methods known to those of skill in the art.

[**0083**] The present invention also encompasses an epitope of an amino acid transporter of the invention, comprised of sequences and/or a conformation of sequences present in the transporter molecule. This epitope may be naturally occurring, or may be the result of proteolytic cleavage of a transporter molecule and isolation of an epitope-containing peptide or may be obtained by synthesis of an epitope-containing peptide using methods well known to those skilled in the art. The present invention also encompasses epitope peptides produced as a result of genetic engineering technology and synthesized by genetically engineered prokaryotic or eukaryotic cells.

[**0084**] The invention also includes chimeric antibodies, comprised of light chain and heavy chain peptides immunologically reactive to an amino acid transporter-derived epitope. The chimeric antibodies embodied in the present invention include those that are derived from naturally occurring antibodies as well as chimeric antibodies made by means of genetic engineering technology well known to those of skill in the art.

[**0085**] The Examples which follow are illustrative of specific embodiments of the invention, and various uses thereof. They set forth for explanatory purposes only, and are not to be taken as limiting the invention.

EXAMPLE 1

Isolation of a Human Neutral Amino Acid Transporter cDNA

[**0086**] In order to clone a novel human neutral amino acid transporter, a cDNA library was prepared from human motor cortex mRNA using standard techniques [see Sambrook et al., 1990, *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Press: New York)]. Briefly, total RNA was isolated using the method of Chomczynski & Sacchi (1987, Anal. Biochem. **162: 156-159**), wherein the tissue is disrupted and solubilized in a solution containing guanidinium isothiocyanate and the RNA purified by phenol/chloroform extractions. Total cellular RNA thus isolated was then enriched for poly (A^+) mRNA by oligo (dT) chromatography. A mixture of oligo (dT)-primed and random-primed mRNA was converted to cDNA using the Superscript Choice System (Bethesda Research Labs, Gaithersburg, Md.). cDNA was ligated into the cloning vector λZAPII (Strategene, La Jolla, Calif.), packaged into phage heads using commercially-available packaging extracts (Strategene) and used to infect *E. coli.* Lawns of infected bacterial cells were used to make plaque lifts for hybridization using standard conditions (see Sambrook, et al., ibid.).

[**0087**] This cDNA library was hybridized with a ^{32}P-labeled oligonucleotide having the following sequence:

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 17

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

CTGRGCRATG AARATGGCAG CCAGGGCYTC ATACAGGGCT GTGCCRTCCA TGTTRATGGT 60

RGC 63

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1680 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

-continued

(A) NAME/KEY: 5'UTR
(B) LOCATION: 1..30

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 31..1626

(ix) FEATURE:
(A) NAME/KEY: 3'UTR
(B) LOCATION: 1626..1680

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

```
CACCTCTAGC TCGGAGCGGC GTGTAGCGCC ATG GAG AAG AGC AAC GAG ACC AAC      54
                                 Met Glu Lys Ser Asn Glu Thr Asn
                                   1               5

GGC TAC CTT GAC AGC GCT CAG GCG GGG CCT GCG GCC GGG CCC GGA GCT      102
Gly Tyr Leu Asp Ser Ala Gln Ala Gly Pro Ala Ala Gly Pro Gly Ala
     10                  15                  20

CCG GGG ACC GCG GCG GGA CGC GCA CGG CGT TGC GCG CGC TTC CTG CGG      150
Pro Gly Thr Ala Ala Gly Arg Ala Arg Arg Cys Ala Arg Phe Leu Arg
 25                  30                  35                  40

CGC CAA GCG CTG GTG CTG CTC ACC GTG TCC GGG GTG CTG GCG GGC GCG      198
Arg Gln Ala Leu Val Leu Leu Thr Val Ser Gly Val Leu Ala Gly Ala
                 45                  50                  55

GGC CTG GGC GCG GCG TTG CGC GGG CTC AGC CTG AGC CGC ACG CAG GTC      246
Gly Leu Gly Ala Ala Leu Arg Gly Leu Ser Leu Ser Arg Thr Gln Val
             60                  65                  70

ACC TAC CTG GCC TTC CCC GGC GAG ATG CTG CTC CGC ATG CTG CGC ATG      294
Thr Tyr Leu Ala Phe Pro Gly Glu Met Leu Leu Arg Met Leu Arg Met
         75                  80                  85

ATC ATC CTG CCG CTG GTG GTC TGC AGC CTG GTG TCG GGC GCC GCC TCG      342
Ile Ile Leu Pro Leu Val Val Cys Ser Leu Val Ser Gly Ala Ala Ser
     90                  95                  100

CTC GAT GCC AGC TGC CTC GGG CGT CTG GGC GGC ATC CGT GTC GCC TAC      390
Leu Asp Ala Ser Cys Leu Gly Arg Leu Gly Gly Ile Arg Val Ala Tyr
105                 110                 115                 120

TTT GGC CTC ACC ACA CTG AGT GCC TCG GCG CTC GCC GTG GCC TTG GCG      438
Phe Gly Leu Thr Thr Leu Ser Ala Ser Ala Leu Ala Val Ala Leu Ala
                125                 130                 135

TTC ATC ATC AAG CCA GGA TCC GGT GCG CAG ACC CTT CAG TCC AGC GAC      486
Phe Ile Ile Lys Pro Gly Ser Gly Ala Gln Thr Leu Gln Ser Ser Asp
            140                 145                 150

CTG GGG CTG GAG GAC TCG GGG CCT CCT CCT GTC CCC AAA GAG ACG GTG      534
Leu Gly Leu Glu Asp Ser Gly Pro Pro Pro Val Pro Lys Glu Thr Val
        155                 160                 165

GAC TCT TTC CTC GAC CTG GCC AGA AAC CTG TTT CCC TCC AAT CTT GTG      582
Asp Ser Phe Leu Asp Leu Ala Arg Asn Leu Phe Pro Ser Asn Leu Val
    170                 175                 180

GTT GCA GCT TTC CGT ACG TAT GCA ACC GAT TAT AAA GTC GTG ACC CAG      630
Val Ala Ala Phe Arg Thr Tyr Ala Thr Asp Tyr Lys Val Val Thr Gln
185                 190                 195                 200

AAC AGC AGC TCT GGA AAT GTA ACC CAT GAA AAG ATC CCC ATA GGC ACT      678
Asn Ser Ser Ser Gly Asn Val Thr His Glu Lys Ile Pro Ile Gly Thr
                205                 210                 215

GAG ATA GAA GGG ATG AAC ATT TTA GGA TTG GTC CTG TTT GCT CTG GTG      726
Glu Ile Glu Gly Met Asn Ile Leu Gly Leu Val Leu Phe Ala Leu Val
            220                 225                 230

TTA GGA GTG GCC TTA AAG AAA CTA GGC TCC GAA GGA GAA GAC CTC ATC      774
Leu Gly Val Ala Leu Lys Lys Leu Gly Ser Glu Gly Glu Asp Leu Ile
        235                 240                 245
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CGT TTC TTC AAT TCC CTC AAC GAG GCG ACG ATG GTG CTG GTG TCC TGG      822
Arg Phe Phe Asn Ser Leu Asn Glu Ala Thr Met Val Leu Val Ser Trp
    250                 255                 260

ATT ATG TGG TAC GTA CCT GTG GGC ATC ATG TTC CTT GTT GGA AGC AAG      870
Ile Met Trp Tyr Val Pro Val Gly Ile Met Phe Leu Val Gly Ser Lys
265                 270                 275                 280

ATC GTG GAA ATG AAA GAC ATC ATC GTG CTG GTG ACC AGC CTG GGG AAA      918
Ile Val Glu Met Lys Asp Ile Ile Val Leu Val Thr Ser Leu Gly Lys
                285                 290                 295

TAC ATC TTC GCA TCT ATA TTG GGC CAT GTT ATT CAT GGA GGA ATT GTT      966
Tyr Ile Phe Ala Ser Ile Leu Gly His Val Ile His Gly Gly Ile Val
            300                 305                 310

CTG CCA CTT ATT TAT TTT GTT TTC ACA CGA AAA AAC CCA TTC AGA TTC     1014
Leu Pro Leu Ile Tyr Phe Val Phe Thr Arg Lys Asn Pro Phe Arg Phe
        315                 320                 325

CTC CTG GGC CTC CTC GCC CCA TTT GCG ACA GCA TTT GCT ACC TGC TCC     1062
Leu Leu Gly Leu Leu Ala Pro Phe Ala Thr Ala Phe Ala Thr Cys Ser
    330                 335                 340

AGC TCA GCG ACC CTT CCC TCT ATG ATG AAG TGC ATT GAA GAG AAC AAT     1110
Ser Ser Ala Thr Leu Pro Ser Met Met Lys Cys Ile Glu Glu Asn Asn
345                 350                 355                 360

GGT GTG GAC AAG AGG ATC AGC AGG TTT ATT CTC CCC ATC GGG GCC ACC     1158
Gly Val Asp Lys Arg Ile Ser Arg Phe Ile Leu Pro Ile Gly Ala Thr
                365                 370                 375

GTG AAC ATG GAC GGA GCA GCC ATC TTC CAG TGT GTG GCC GCG GTG TTC     1206
Val Asn Met Asp Gly Ala Ala Ile Phe Gln Cys Val Ala Ala Val Phe
            380                 385                 390

ATT GCG CAA CTC AAC AAC ATA GAG CTC AAC GCA GGA CAG ATT TTC ACC     1254
Ile Ala Gln Leu Asn Asn Ile Glu Leu Asn Ala Gly Gln Ile Phe Thr
        395                 400                 405

ATT CTA GTG ACT GCC ACA GCG TCC AGT GTT GGA GCA GCA GGC GTG CCA     1302
Ile Leu Val Thr Ala Thr Ala Ser Ser Val Gly Ala Ala Gly Val Pro
    410                 415                 420

GCT GGA GGG GTC CTC ACC ATT GCC ATT ATC CTG GAG GCC ATT GGG CTG     1350
Ala Gly Gly Val Leu Thr Ile Ala Ile Ile Leu Glu Ala Ile Gly Leu
425                 430                 435                 440

CCT ACT CAT GAC CTG CCT CTG ATC CTG GCT GTG GAC TGG ATT GTG GAC     1398
Pro Thr His Asp Leu Pro Leu Ile Leu Ala Val Asp Trp Ile Val Asp
                445                 450                 455

CGG ACC ACC ACG GTG GTG AAT GTG GAG GGG GAT GCC CTG GGT GCA GGC     1446
Arg Thr Thr Thr Val Val Asn Val Glu Gly Asp Ala Leu Gly Ala Gly
            460                 465                 470

ATT CTC CAC CAC CTG AAT CAG AAG GCA ACA AAG AAA GGC GAG CAG GAA     1494
Ile Leu His His Leu Asn Gln Lys Ala Thr Lys Lys Gly Glu Gln Glu
        475                 480                 485

CTT GCT GAG GTG AAA GTG GAA GCC ATC CCC AAC TGC AAG TCT GAG GAG     1542
Leu Ala Glu Val Lys Val Glu Ala Ile Pro Asn Cys Lys Ser Glu Glu
    490                 495                 500

GAG ACA TCG CCC CTG GTG ACA CAC CAG AAC CCC GCT GGC CCC GTG GCC     1590
Glu Thr Ser Pro Leu Val Thr His Gln Asn Pro Ala Gly Pro Val Ala
505                 510                 515                 520

AGT GCC CCA GAA CTG GAA TCC AAG GAG TCG GTT CTG TGATGGGGCT          1636
Ser Ala Pro Glu Leu Glu Ser Lys Glu Ser Val Leu
                525                 530

GGGCTTTGGG CTTGCCTGCC AGCAGTGATG TCCCACCCTG TTCA                    1680
```

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(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 532 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
Met Glu Lys Ser Asn Glu Thr Asn Gly Tyr Leu Asp Ser Ala Gln Ala
  1               5                  10                  15

Gly Pro Ala Ala Gly Pro Gly Ala Pro Gly Thr Ala Ala Gly Arg Ala
             20                  25                  30

Arg Arg Cys Ala Arg Phe Leu Arg Arg Gln Ala Leu Val Leu Leu Thr
         35                  40                  45

Val Ser Gly Val Leu Ala Gly Ala Gly Leu Gly Ala Ala Leu Arg Gly
     50                  55                  60

Leu Ser Leu Ser Arg Thr Gln Val Thr Tyr Leu Ala Phe Pro Gly Glu
 65                  70                  75                  80

Met Leu Leu Arg Met Leu Arg Met Ile Ile Leu Pro Leu Val Val Cys
                 85                  90                  95

Ser Leu Val Ser Gly Ala Ala Ser Leu Asp Ala Ser Cys Leu Gly Arg
            100                 105                 110

Leu Gly Gly Ile Arg Val Ala Tyr Phe Gly Leu Thr Thr Leu Ser Ala
        115                 120                 125

Ser Ala Leu Ala Val Ala Leu Ala Phe Ile Ile Lys Pro Gly Ser Gly
    130                 135                 140

Ala Gln Thr Leu Gln Ser Ser Asp Leu Gly Leu Glu Asp Ser Gly Pro
145                 150                 155                 160

Pro Pro Val Pro Lys Glu Thr Val Asp Ser Phe Leu Asp Leu Ala Arg
                165                 170                 175

Asn Leu Phe Pro Ser Asn Leu Val Val Ala Ala Phe Arg Thr Tyr Ala
            180                 185                 190

Thr Asp Tyr Lys Val Val Thr Gln Asn Ser Ser Ser Gly Asn Val Thr
        195                 200                 205

His Glu Lys Ile Pro Ile Gly Thr Glu Ile Glu Gly Met Asn Ile Leu
    210                 215                 220

Gly Leu Val Leu Phe Ala Leu Val Leu Gly Val Ala Leu Lys Lys Leu
225                 230                 235                 240

Gly Ser Glu Gly Glu Asp Leu Ile Arg Phe Phe Asn Ser Leu Asn Glu
                245                 250                 255

Ala Thr Met Val Leu Val Ser Trp Ile Met Trp Tyr Val Pro Val Gly
            260                 265                 270

Ile Met Phe Leu Val Gly Ser Lys Ile Val Glu Met Lys Asp Ile Ile
        275                 280                 285

Val Leu Val Thr Ser Leu Gly Lys Tyr Ile Phe Ala Ser Ile Leu Gly
    290                 295                 300

His Val Ile His Gly Gly Ile Val Leu Pro Leu Ile Tyr Phe Val Phe
305                 310                 315                 320

Thr Arg Lys Asn Pro Phe Arg Phe Leu Leu Gly Leu Leu Ala Pro Phe
                325                 330                 335

Ala Thr Ala Phe Ala Thr Cys Ser Ser Ser Ala Thr Leu Pro Ser Met
            340                 345                 350
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```
Met Lys Cys Ile Glu Glu Asn Asn Gly Val Asp Lys Arg Ile Ser Arg
        355                 360                 365

Phe Ile Leu Pro Ile Gly Ala Thr Val Asn Met Asp Gly Ala Ala Ile
    370                 375                 380

Phe Gln Cys Val Ala Ala Val Phe Ile Ala Gln Leu Asn Asn Ile Glu
385                 390                 395                 400

Leu Asn Ala Gly Gln Ile Phe Thr Ile Leu Val Thr Ala Thr Ala Ser
                405                 410                 415

Ser Val Gly Ala Ala Gly Val Pro Ala Gly Gly Val Leu Thr Ile Ala
            420                 425                 430

Ile Ile Leu Glu Ala Ile Gly Leu Pro Thr His Asp Leu Pro Leu Ile
        435                 440                 445

Leu Ala Val Asp Trp Ile Val Asp Arg Thr Thr Thr Val Val Asn Val
    450                 455                 460

Glu Gly Asp Ala Leu Gly Ala Gly Ile Leu His His Leu Asn Gln Lys
465                 470                 475                 480

Ala Thr Lys Lys Gly Glu Gln Glu Leu Ala Glu Val Lys Val Glu Ala
                485                 490                 495

Ile Pro Asn Cys Lys Ser Glu Glu Glu Thr Ser Pro Leu Val Thr His
            500                 505                 510

Gln Asn Pro Ala Gly Pro Val Ala Ser Ala Pro Glu Leu Glu Ser Lys
        515                 520                 525

Glu Ser Val Leu
    530
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1680 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: 5'UTR
(B) LOCATION: 1..30

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 31..1656

(ix) FEATURE:
(A) NAME/KEY: 3'UTR
(B) LOCATION: 1657..1680

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
AAAGAAGAGA CCCTCCTAGA AAAGTAAAAT ATG ACT AAA AGC AAT GGA GAA GAG      54
                                 Met Thr Lys Ser Asn Gly Glu Glu
                                   1               5

CCC AAG ATG GGG GGC AGG ATG GAG AGA TTC CAG CAG GGA GTC CGT AAA      102
Pro Lys Met Gly Gly Arg Met Glu Arg Phe Gln Gln Gly Val Arg Lys
 10                  15                  20

CGC ACA CTT TTG GCC AAG AAG AAA GTG CAG AAC ATT ACA AAG GAG GTT      150
Arg Thr Leu Leu Ala Lys Lys Lys Val Gln Asn Ile Thr Lys Glu Val
 25                  30                  35                  40

GTT AAA AGT TAC CTG TTT CGG AAT GCT TTT GTG CTG CTC ACA GTC ACC      198
Val Lys Ser Tyr Leu Phe Arg Asn Ala Phe Val Leu Leu Thr Val Thr
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                45                  50                  55

GCT GTC ATT GTG GGT ACA ATC CTT GGA TTT ACC CTC CGA CCA TAC AGA      246
Ala Val Ile Val Gly Thr Ile Leu Gly Phe Thr Leu Arg Pro Tyr Arg
            60                  65                  70

ATG AGC TAC CGG GAA GTC AAG TAC TTC TCC TTT CCT GGG GAA CTT CTG      294
Met Ser Tyr Arg Glu Val Lys Tyr Phe Ser Phe Pro Gly Glu Leu Leu
         75                  80                  85

ATG AGG ATG TTA CAG ATG CTG GTC TTA CCA CTT ATC ATC TCC AGT CTT      342
Met Arg Met Leu Gln Met Leu Val Leu Pro Leu Ile Ile Ser Ser Leu
     90                  95                  100

GTC ACA GGA ATG GCG GCG CTA GAT AGT AAG GCA TCA GGG AAG TGG GAA      390
Val Thr Gly Met Ala Ala Leu Asp Ser Lys Ala Ser Gly Lys Trp Glu
105                 110                 115                 120

TGC GGA GCT GTA GTC TAT TAT ATG ACT ACC ACC ATC ATT GCT GTG GTG      438
Cys Gly Ala Val Val Tyr Tyr Met Thr Thr Thr Ile Ile Ala Val Val
                125                 130                 135

ATT GGC ATA ATC ATT GTC ATC ATC ATC CAT CCT GGG AAG GGC ACA AAG      486
Ile Gly Ile Ile Ile Val Ile Ile Ile His Pro Gly Lys Gly Thr Lys
            140                 145                 150

GAA AAC ATG CAC AGA GAA GGC AAA ATT GTA CGA GTG ACA GCT GCA GAT      534
Glu Asn Met His Arg Glu Gly Lys Ile Val Arg Val Thr Ala Ala Asp
        155                 160                 165

GCC TTC CTG GAC TTG ATC AGG AAC ATG TTA AAT CCA AAT CTG GTA GAA      582
Ala Phe Leu Asp Leu Ile Arg Asn Met Leu Asn Pro Asn Leu Val Glu
    170                 175                 180

GCC TGC TTT AAA CAG TTT AAA ACC AAC TAT GAG AAG AGA AGC TTT AAA      630
Ala Cys Phe Lys Gln Phe Lys Thr Asn Tyr Glu Lys Arg Ser Phe Lys
185                 190                 195                 200

GTG CCC ATC CAG GCC AAC GAA ACG CTT GTG GGT GCT GTG ATA AAC AAT      678
Val Pro Ile Gln Ala Asn Glu Thr Leu Val Gly Ala Val Ile Asn Asn
                205                 210                 215

GTG TCT GAG GCC ATG GAG ACT CTT ACC CGA ATC ACA GAG GAG CTG GTC      726
Val Ser Glu Ala Met Glu Thr Leu Thr Arg Ile Thr Glu Glu Leu Val
            220                 225                 230

CCA GTT CCA GGA TCT GTG AAT GGA GTC AAT GCC CTG GGT CTA GTT GTC      774
Pro Val Pro Gly Ser Val Asn Gly Val Asn Ala Leu Gly Leu Val Val
        235                 240                 245

TTC TCC ATG TGC TTC GGT TTT GTG ATT GGA AAC ATG AAG GAA CAG GGG      822
Phe Ser Met Cys Phe Gly Phe Val Ile Gly Asn Met Lys Glu Gln Gly
    250                 255                 260

CAG GCC CTG AGA GAG TTC TTT GAT TCT CTT AAC GAA GCC ATC ATG AGA      870
Gln Ala Leu Arg Glu Phe Phe Asp Ser Leu Asn Glu Ala Ile Met Arg
265                 270                 275                 280

CTG GTA GCA GTA ATA ATG TGG TAT GCC CCC GTG GGT ATT CTC TTC CTG      918
Leu Val Ala Val Ile Met Trp Tyr Ala Pro Val Gly Ile Leu Phe Leu
                285                 290                 295

ATT GCT GGG AAG ATT GTG GAG ATG GAA GAC ATG GGT GTG ATT GGG GGG      966
Ile Ala Gly Lys Ile Val Glu Met Glu Asp Met Gly Val Ile Gly Gly
            300                 305                 310

CAG CTT GCC ATG TAC ACC GTG ACT GTC ATT GTT GGC TTA CTC ATT CAC     1014
Gln Leu Ala Met Tyr Thr Val Thr Val Ile Val Gly Leu Leu Ile His
        315                 320                 325

GCA GTC ATC GTC TTG CCA CTC CTC TAC TTC TTG GTA ACA CGG AAA AAC     1062
Ala Val Ile Val Leu Pro Leu Leu Tyr Phe Leu Val Thr Arg Lys Asn
    330                 335                 340

CCT TGG GTT TTT ATT GGA GGG TTG CTG CAA GCA CTC ATC ACC GCT CTG     1110
Pro Trp Val Phe Ile Gly Gly Leu Leu Gln Ala Leu Ile Thr Ala Leu
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345                 350                 355                 360

GGG ACC TCT TCA AGT TCT GCC ACC CTA CCC ATC ACC TTC AAG TGC CTG     1158
Gly Thr Ser Ser Ser Ser Ala Thr Leu Pro Ile Thr Phe Lys Cys Leu
                365                 370                 375

GAA GAG AAC AAT GGC GTG GAC AAG CGC GTC ACC AGA TTC GTG CTC CCC     1206
Glu Glu Asn Asn Gly Val Asp Lys Arg Val Thr Arg Phe Val Leu Pro
            380                 385                 390

GTA GGA GCC ACC ATT AAC ATG GAT GGG ACT GCC CTC TAT GAG GCT TTG     1254
Val Gly Ala Thr Ile Asn Met Asp Gly Thr Ala Leu Tyr Glu Ala Leu
        395                 400                 405

GCT GCC ATT TTC ATT GCT CAA GTT AAC AAC TTT GAA CTG AAC TTC GGA     1302
Ala Ala Ile Phe Ile Ala Gln Val Asn Asn Phe Glu Leu Asn Phe Gly
    410                 415                 420

CAA ATT ATT ACA ATC AGC ATC ACA GCC ACA GCT GCC AGT ATT GGG GCA     1350
Gln Ile Ile Thr Ile Ser Ile Thr Ala Thr Ala Ala Ser Ile Gly Ala
425                 430                 435                 440

GCT GGA ATT CCT CAG GCG GGC CTG GTC ACT ATG GTC ATT GTG CTG ACA     1398
Ala Gly Ile Pro Gln Ala Gly Leu Val Thr Met Val Ile Val Leu Thr
                445                 450                 455

TCT GTC GGC CTG CCC ACT GAC GAC ATC ACG CTC ATC ATC GCG GTG GAC     1446
Ser Val Gly Leu Pro Thr Asp Asp Ile Thr Leu Ile Ile Ala Val Asp
            460                 465                 470

TGG TTC TTG GAT CGC CTC CGG ACC ACC ACC AAC GTA CTG GGA GAC TCC     1494
Trp Phe Leu Asp Arg Leu Arg Thr Thr Thr Asn Val Leu Gly Asp Ser
        475                 480                 485

CTG GGA GCT GGG ATT GTG GAG CAC TTG TCA CGA CAT GAA CTG AAG AAC     1542
Leu Gly Ala Gly Ile Val Glu His Leu Ser Arg His Glu Leu Lys Asn
    490                 495                 500

AGA GAT GTT GAA ATG GGT AAC TCA GTG ATT GAA GAG AAT GAA ATG AAG     1590
Arg Asp Val Glu Met Gly Asn Ser Val Ile Glu Glu Asn Glu Met Lys
505                 510                 515                 520

AAA CCA TAT CAA CTG ATT GCA CAG GAC AAT GAA ACT GAG AAA CCC ATC     1638
Lys Pro Tyr Gln Leu Ile Ala Gln Asp Asn Glu Thr Glu Lys Pro Ile
                525                 530                 535

GAC AGT GAA ACC AAG ATG TAGACTAACA TAAAGAAACA CTTT                  1680
Asp Ser Glu Thr Lys Met
            540
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 542 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
Met Thr Lys Ser Asn Gly Glu Glu Pro Lys Met Gly Gly Arg Met Glu
  1               5                  10                  15

Arg Phe Gln Gln Gly Val Arg Lys Arg Thr Leu Leu Ala Lys Lys Lys
             20                  25                  30

Val Gln Asn Ile Thr Lys Glu Val Val Lys Ser Tyr Leu Phe Arg Asn
         35                  40                  45

Ala Phe Val Leu Leu Thr Val Thr Ala Val Ile Val Gly Thr Ile Leu
     50                  55                  60

Gly Phe Thr Leu Arg Pro Tyr Arg Met Ser Tyr Arg Glu Val Lys Tyr
 65                  70                  75                  80
```

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```
Phe Ser Phe Pro Gly Glu Leu Leu Met Arg Met Leu Gln Met Leu Val
                 85                  90                  95

Leu Pro Leu Ile Ile Ser Ser Leu Val Thr Gly Met Ala Ala Leu Asp
            100                 105                 110

Ser Lys Ala Ser Gly Lys Trp Glu Cys Gly Ala Val Val Tyr Tyr Met
        115                 120                 125

Thr Thr Thr Ile Ile Ala Val Val Ile Gly Ile Ile Ile Val Ile Ile
    130                 135                 140

Ile His Pro Gly Lys Gly Thr Lys Glu Asn Met His Arg Glu Gly Lys
145                 150                 155                 160

Ile Val Arg Val Thr Ala Ala Asp Ala Phe Leu Asp Leu Ile Arg Asn
                165                 170                 175

Met Leu Asn Pro Asn Leu Val Glu Ala Cys Phe Lys Gln Phe Lys Thr
            180                 185                 190

Asn Tyr Glu Lys Arg Ser Phe Lys Val Pro Ile Gln Ala Asn Glu Thr
        195                 200                 205

Leu Val Gly Ala Val Ile Asn Asn Val Ser Glu Ala Met Glu Thr Leu
    210                 215                 220

Thr Arg Ile Thr Glu Glu Leu Val Pro Val Pro Gly Ser Val Asn Gly
225                 230                 235                 240

Val Asn Ala Leu Gly Leu Val Val Phe Ser Met Cys Phe Gly Phe Val
                245                 250                 255

Ile Gly Asn Met Lys Glu Gln Gly Gln Ala Leu Arg Glu Phe Phe Asp
            260                 265                 270

Ser Leu Asn Glu Ala Ile Met Arg Leu Val Ala Val Ile Met Trp Tyr
        275                 280                 285

Ala Pro Val Gly Ile Leu Phe Leu Ile Ala Gly Lys Ile Val Glu Met
    290                 295                 300

Glu Asp Met Gly Val Ile Gly Gly Gln Leu Ala Met Tyr Thr Val Thr
305                 310                 315                 320

Val Ile Val Gly Leu Leu Ile His Ala Val Ile Val Leu Pro Leu Leu
                325                 330                 335

Tyr Phe Leu Val Thr Arg Lys Asn Pro Trp Val Phe Ile Gly Gly Leu
            340                 345                 350

Leu Gln Ala Leu Ile Thr Ala Leu Gly Thr Ser Ser Ser Ser Ala Thr
        355                 360                 365

Leu Pro Ile Thr Phe Lys Cys Leu Glu Glu Asn Asn Gly Val Asp Lys
    370                 375                 380

Arg Val Thr Arg Phe Val Leu Pro Val Gly Ala Thr Ile Asn Met Asp
385                 390                 395                 400

Gly Thr Ala Leu Tyr Glu Ala Leu Ala Ala Ile Phe Ile Ala Gln Val
                405                 410                 415

Asn Asn Phe Glu Leu Asn Phe Gly Gln Ile Ile Thr Ile Ser Ile Thr
            420                 425                 430

Ala Thr Ala Ala Ser Ile Gly Ala Ala Gly Ile Pro Gln Ala Gly Leu
        435                 440                 445

Val Thr Met Val Ile Val Leu Thr Ser Val Gly Leu Pro Thr Asp Asp
    450                 455                 460

Ile Thr Leu Ile Ile Ala Val Asp Trp Phe Leu Asp Arg Leu Arg Thr
465                 470                 475                 480
```

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```
Thr Thr Asn Val Leu Gly Asp Ser Leu Gly Ala Gly Ile Val Glu His
                485                 490                 495

Leu Ser Arg His Glu Leu Lys Asn Arg Asp Val Glu Met Gly Asn Ser
            500                 505                 510

Val Ile Glu Glu Asn Glu Met Lys Lys Pro Tyr Gln Leu Ile Ala Gln
        515                 520                 525

Asp Asn Glu Thr Glu Lys Pro Ile Asp Ser Glu Thr Lys Met
    530                 535                 540
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1800 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: 5'UTR
(B) LOCATION: 1..33

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 34..1755

(ix) FEATURE:
(A) NAME/KEY: 3'UTR
(B) LOCATION: 1756..1800

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

```
GATAGTGCTG AAGAGGAGGG GCGTTCCCAG ACC ATG GCA TCT ACG GAA GGT GCC      54
                                      Met Ala Ser Thr Glu Gly Ala
                                        1               5

AAC AAT ATG CCC AAG CAG GTG GAA GTG CGA ATG CCA GAC AGT CAT CTT      102
Asn Asn Met Pro Lys Gln Val Glu Val Arg Met Pro Asp Ser His Leu
         10                  15                  20

GGC TCA GAG GAA CCC AAG CAC CGG CAC CTG GGC CTG CGC CTG TGT GAC      150
Gly Ser Glu Glu Pro Lys His Arg His Leu Gly Leu Arg Leu Cys Asp
     25                  30                  35

AAG CTG GGG AAG AAT CTG CTG CTC ACC CTG ACG GTG TTT GGT GTC ATC      198
Lys Leu Gly Lys Asn Leu Leu Leu Thr Leu Thr Val Phe Gly Val Ile
 40                  45                  50                  55

CTG GGA GCA GTG TGT GGA GGG CTT CTT CGC TTG GCA TCT CCC ATC CAC      246
Leu Gly Ala Val Cys Gly Gly Leu Leu Arg Leu Ala Ser Pro Ile His
                 60                  65                  70

CCT GAT GTG GTT ATG TTA ATA GCC TTC CCA GGG GAT ATA CTC ATG AGG      294
Pro Asp Val Val Met Leu Ile Ala Phe Pro Gly Asp Ile Leu Met Arg
             75                  80                  85

ATG CTA AAA ATG CTC ATT CTG GGT CTA ATC ATC TCC AGC TTA ATC ACA      342
Met Leu Lys Met Leu Ile Leu Gly Leu Ile Ile Ser Ser Leu Ile Thr
         90                  95                  100

GGG TTG TCA GGC CTG GAT GCT AAG GCT AGT GGC CGC TTG GGC ACG AGA      390
Gly Leu Ser Gly Leu Asp Ala Lys Ala Ser Gly Arg Leu Gly Thr Arg
    105                 110                 115

GCC ATG GTG TAT TAC ATG TCC ACG ACC ATC ATT GCT GCA GTA CTG GGG      438
Ala Met Val Tyr Tyr Met Ser Thr Thr Ile Ile Ala Ala Val Leu Gly
120                 125                 130                 135

GTC ATT CTG GTC TTG GCT ATC CAT CCA GGC AAT CCC AAG CTC AAG AAG      486
Val Ile Leu Val Leu Ala Ile His Pro Gly Asn Pro Lys Leu Lys Lys
                140                 145                 150
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CAG CTG GGG CCT GGG AAG AAG AAT GAT GAA GTG TCC AGC CTG GAT GCC      534
Gln Leu Gly Pro Gly Lys Lys Asn Asp Glu Val Ser Ser Leu Asp Ala
            155                 160                 165

TTC CTG GAC CTT ATT CGA AAT CTC TTC CCT GAA AAC CTT GTC CAA GCC      582
Phe Leu Asp Leu Ile Arg Asn Leu Phe Pro Glu Asn Leu Val Gln Ala
        170                 175                 180

TGC TTT CAA CAG ATT CAA ACA GTG ACG AAG AAA GTC CTG GTT GCA CCA      630
Cys Phe Gln Gln Ile Gln Thr Val Thr Lys Lys Val Leu Val Ala Pro
    185                 190                 195

CCG CCA GAC GAG GAG GCC AAC GCA ACC AGC GCT GAA GTC TCT CTG TTG      678
Pro Pro Asp Glu Glu Ala Asn Ala Thr Ser Ala Glu Val Ser Leu Leu
200                 205                 210                 215

AAC GAG ACT GTG ACT GAG GTG CCG GAG GAG ACT AAG ATG GTT ATC AAG      726
Asn Glu Thr Val Thr Glu Val Pro Glu Glu Thr Lys Met Val Ile Lys
                220                 225                 230

AAG GGC CTG GAG TTC AAG GAT GGG ATG AAC GTC TTA GGT CTG ATA GGG      774
Lys Gly Leu Glu Phe Lys Asp Gly Met Asn Val Leu Gly Leu Ile Gly
            235                 240                 245

TTT TTC ATT GCT TTT GGC ATC GCT ATG GGG AAG ATG GGA GAT CAG GCC      822
Phe Phe Ile Ala Phe Gly Ile Ala Met Gly Lys Met Gly Asp Gln Ala
        250                 255                 260

AAG CTG ATG GTG GAT TTC TTC AAC ATT TTG AAT GAG ATT GTA ATG AAG      870
Lys Leu Met Val Asp Phe Phe Asn Ile Leu Asn Glu Ile Val Met Lys
    265                 270                 275

TTA GTG ATC ATG ATC ATG TGG TAC TCT CCC CTG GGT ATC GCC TGC CTG      918
Leu Val Ile Met Ile Met Trp Tyr Ser Pro Leu Gly Ile Ala Cys Leu
280                 285                 290                 295

ATC TGT GGA AAG ATC ATT GCA ATC AAG GAC TTA GAA GTG GTT GCT AGG      966
Ile Cys Gly Lys Ile Ile Ala Ile Lys Asp Leu Glu Val Val Ala Arg
                300                 305                 310

CAA CTG GGG ATG TAC ATG GTA ACA GTG ATC ATA GGC CTC ATC ATC CAC     1014
Gln Leu Gly Met Tyr Met Val Thr Val Ile Ile Gly Leu Ile Ile His
            315                 320                 325

GGG GGC ATC TTT CTC CCC TTG ATT TAC TTT GTA GTG ACC AGG AAA AAC     1062
Gly Gly Ile Phe Leu Pro Leu Ile Tyr Phe Val Val Thr Arg Lys Asn
        330                 335                 340

CCC TTC TCC CTT TTT GCT GGC ATT TTC CAA GCT TGG ATC ACT GCC CTG     1110
Pro Phe Ser Leu Phe Ala Gly Ile Phe Gln Ala Trp Ile Thr Ala Leu
    345                 350                 355

GGC ACC GCT TCC AGT GCT GGA ACT TTG CCT GTC ACC TTT CGT TGC CTG     1158
Gly Thr Ala Ser Ser Ala Gly Thr Leu Pro Val Thr Phe Arg Cys Leu
360                 365                 370                 375

GAA GAA AAT CTG GGG ATT GAT AAG CGT GTG ACT AGA TTC GTC CTT CCT     1206
Glu Glu Asn Leu Gly Ile Asp Lys Arg Val Thr Arg Phe Val Leu Pro
                380                 385                 390

GTT GGA GCA ACC ATT AAC ATG GAT GGT ACA GCC CTT TAT GAA GCG GTG     1254
Val Gly Ala Thr Ile Asn Met Asp Gly Thr Ala Leu Tyr Glu Ala Val
            395                 400                 405

GCC GCC ATC TTT ATA GCC CAA ATG AAT GGT GTT GTC CTG GAT GGA GGA     1302
Ala Ala Ile Phe Ile Ala Gln Met Asn Gly Val Val Leu Asp Gly Gly
        410                 415                 420

CAG ATT GTG ACT GTA AGC CTC ACA GCC ACC CTG GCA AGC GTC GGC GCG     1350
Gln Ile Val Thr Val Ser Leu Thr Ala Thr Leu Ala Ser Val Gly Ala
    425                 430                 435

GCC AGT ATC CCC AGT GCC GGG CTG GTC ACC ATG CTC CTC ATT CTG ACA     1398
Ala Ser Ile Pro Ser Ala Gly Leu Val Thr Met Leu Leu Ile Leu Thr
440                 445                 450                 455
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GCC GTG GGC CTG CCA ACA GAG GAC ATC AGC TTG CTG GTG GCT GTG GAC     1446
Ala Val Gly Leu Pro Thr Glu Asp Ile Ser Leu Leu Val Ala Val Asp
                460                 465                 470

TGG CTG CTG GAC AGG ATG AGA ACT TCA GTC AAT GTT GTG GGT GAC TCT     1494
Trp Leu Leu Asp Arg Met Arg Thr Ser Val Asn Val Val Gly Asp Ser
            475                 480                 485

TTT GGG GCT GGG ATA GTC TAT CAC CTC TCC AAG TCT GAG CTG GAT ACC     1542
Phe Gly Ala Gly Ile Val Tyr His Leu Ser Lys Ser Glu Leu Asp Thr
        490                 495                 500

ATT GAC TCC CAG CAT CGA GTG CAT GAA GAT ATT GAA ATG ACC AAG ACT     1590
Ile Asp Ser Gln His Arg Val His Glu Asp Ile Glu Met Thr Lys Thr
    505                 510                 515

CAA TCC ATT TAT GAT GAC ATG AAG AAC CAC AGG GAA AGC AAC TCT AAT     1638
Gln Ser Ile Tyr Asp Asp Met Lys Asn His Arg Glu Ser Asn Ser Asn
520                 525                 530                 535

CAA TGT GTC TAT GCT GCA CAC AAC TCT GTC ATA GTA GAT GAA TGC AAG     1686
Gln Cys Val Tyr Ala Ala His Asn Ser Val Ile Val Asp Glu Cys Lys
                540                 545                 550

GTA ACT CTG GCA GCC AAT GGA AAG TCA GCC GAC TGC AGT GTT GAG GAA     1734
Val Thr Leu Ala Ala Asn Gly Lys Ser Ala Asp Cys Ser Val Glu Glu
            555                 560                 565

GAA CCT TGG AAA CGT GAG AAA TAAGGATATG AGTCTCAGCA AATTCTTGAA        1785
Glu Pro Trp Lys Arg Glu Lys
        570

TAAACTCCCC AGCGT                                                   1800
```

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 574 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```
Met Ala Ser Thr Glu Gly Ala Asn Asn Met Pro Lys Gln Val Glu Val
  1               5                  10                  15

Arg Met Pro Asp Ser His Leu Gly Ser Glu Glu Pro Lys His Arg His
             20                  25                  30

Leu Gly Leu Arg Leu Cys Asp Lys Leu Gly Lys Asn Leu Leu Leu Thr
         35                  40                  45

Leu Thr Val Phe Gly Val Ile Leu Gly Ala Val Cys Gly Gly Leu Leu
     50                  55                  60

Arg Leu Ala Ser Pro Ile His Pro Asp Val Val Met Leu Ile Ala Phe
 65                  70                  75                  80

Pro Gly Asp Ile Leu Met Arg Met Leu Lys Met Leu Ile Leu Gly Leu
                 85                  90                  95

Ile Ile Ser Ser Leu Ile Thr Gly Leu Ser Gly Leu Asp Ala Lys Ala
            100                 105                 110

Ser Gly Arg Leu Gly Thr Arg Ala Met Val Tyr Tyr Met Ser Thr Thr
        115                 120                 125

Ile Ile Ala Ala Val Leu Gly Val Ile Leu Val Leu Ala Ile His Pro
    130                 135                 140

Gly Asn Pro Lys Leu Lys Lys Gln Leu Gly Pro Gly Lys Lys Asn Asp
145                 150                 155                 160
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Glu Val Ser Ser Leu Asp Ala Phe Leu Asp Leu Ile Arg Asn Leu Phe
                165                 170                 175

Pro Glu Asn Leu Val Gln Ala Cys Phe Gln Gln Ile Gln Thr Val Thr
            180                 185                 190

Lys Lys Val Leu Val Ala Pro Pro Pro Asp Glu Glu Ala Asn Ala Thr
        195                 200                 205

Ser Ala Glu Val Ser Leu Leu Asn Glu Thr Val Thr Glu Val Pro Glu
    210                 215                 220

Glu Thr Lys Met Val Ile Lys Lys Gly Leu Glu Phe Lys Asp Gly Met
225                 230                 235                 240

Asn Val Leu Gly Leu Ile Gly Phe Phe Ile Ala Phe Gly Ile Ala Met
                245                 250                 255

Gly Lys Met Gly Asp Gln Ala Lys Leu Met Val Asp Phe Phe Asn Ile
            260                 265                 270

Leu Asn Glu Ile Val Met Lys Leu Val Ile Met Ile Met Trp Tyr Ser
        275                 280                 285

Pro Leu Gly Ile Ala Cys Leu Ile Cys Gly Lys Ile Ile Ala Ile Lys
    290                 295                 300

Asp Leu Glu Val Val Ala Arg Gln Leu Gly Met Tyr Met Val Thr Val
305                 310                 315                 320

Ile Ile Gly Leu Ile Ile His Gly Gly Ile Phe Leu Pro Leu Ile Tyr
                325                 330                 335

Phe Val Val Thr Arg Lys Asn Pro Phe Ser Leu Phe Ala Gly Ile Phe
            340                 345                 350

Gln Ala Trp Ile Thr Ala Leu Gly Thr Ala Ser Ser Ala Gly Thr Leu
        355                 360                 365

Pro Val Thr Phe Arg Cys Leu Glu Glu Asn Leu Gly Ile Asp Lys Arg
    370                 375                 380

Val Thr Arg Phe Val Leu Pro Val Gly Ala Thr Ile Asn Met Asp Gly
385                 390                 395                 400

Thr Ala Leu Tyr Glu Ala Val Ala Ala Ile Phe Ile Ala Gln Met Asn
                405                 410                 415

Gly Val Val Leu Asp Gly Gly Gln Ile Val Thr Val Ser Leu Thr Ala
            420                 425                 430

Thr Leu Ala Ser Val Gly Ala Ala Ser Ile Pro Ser Ala Gly Leu Val
        435                 440                 445

Thr Met Leu Leu Ile Leu Thr Ala Val Gly Leu Pro Thr Glu Asp Ile
    450                 455                 460

Ser Leu Leu Val Ala Val Asp Trp Leu Leu Asp Arg Met Arg Thr Ser
465                 470                 475                 480

Val Asn Val Val Gly Asp Ser Phe Gly Ala Gly Ile Val Tyr His Leu
                485                 490                 495

Ser Lys Ser Glu Leu Asp Thr Ile Asp Ser Gln His Arg Val His Glu
            500                 505                 510

Asp Ile Glu Met Thr Lys Thr Gln Ser Ile Tyr Asp Asp Met Lys Asn
        515                 520                 525

His Arg Glu Ser Asn Ser Asn Gln Cys Val Tyr Ala Ala His Asn Ser
    530                 535                 540

Val Ile Val Asp Glu Cys Lys Val Thr Leu Ala Ala Asn Gly Lys Ser
545                 550                 555                 560
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```
Ala Asp Cys Ser Val Glu Glu Glu Pro Trp Lys Arg Glu Lys
               565                 570


(2) INFORMATION FOR SEQ ID NO: 8:

     (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 1674 base pairs
          (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: cDNA

    (ix) FEATURE:
          (A) NAME/KEY: 5'UTR
          (B) LOCATION: 1..15

    (ix) FEATURE:
          (A) NAME/KEY: CDS
          (B) LOCATION: 16..1590

    (ix) FEATURE:
          (A) NAME/KEY: 3'UTR
          (B) LOCATION: 1591..1674

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

ATAGCGGCGA CAGCC ATG GGG AAA CCG GCG AGG AAA GGA TGC CCG AGT TGG      51
                 Met Gly Lys Pro Ala Arg Lys Gly Cys Pro Ser Trp
                   1               5                  10

AAG CGC TTC CTG AAG AAT AAC TGG GTG TTG CTG TCC ACC GTG GCC GCG       99
Lys Arg Phe Leu Lys Asn Asn Trp Val Leu Leu Ser Thr Val Ala Ala
         15                  20                  25

GTG GTG CTA GGC ATT ACC ACA GGA GTC TTG GTT CGA GAA CAC AGC AAC      147
Val Val Leu Gly Ile Thr Thr Gly Val Leu Val Arg Glu His Ser Asn
     30                  35                  40

CTC TCA ACT CTA GAG AAA TTC TAC TTT GCT TTT CCT GGA GAA ATT CTA      195
Leu Ser Thr Leu Glu Lys Phe Tyr Phe Ala Phe Pro Gly Glu Ile Leu
 45                  50                  55                  60

ATG CGG ATG CTG AAA CTC ATC ATT TTG CCA TTA ATT ATA TCC AGC ATG      243
Met Arg Met Leu Lys Leu Ile Ile Leu Pro Leu Ile Ile Ser Ser Met
                 65                  70                  75

ATT ACA GGT GTT GCT GCA CTG GAT TCC AAC GTA TCC GGA AAA ATT GGT      291
Ile Thr Gly Val Ala Ala Leu Asp Ser Asn Val Ser Gly Lys Ile Gly
             80                  85                  90

CTG CGC GCT GTC GTG TAT TAT TTC TGT ACC ACT CTC ATT GCT GTT ATT      339
Leu Arg Ala Val Val Tyr Tyr Phe Cys Thr Thr Leu Ile Ala Val Ile
         95                  100                 105

CTA GGT ATT GTG CTG GTG GTG AGC ATC AAG CCT GGT GTC ACC CAG AAA      387
Leu Gly Ile Val Leu Val Val Ser Ile Lys Pro Gly Val Thr Gln Lys
    110                 115                 120

GTG GGT GAA ATT GCG AGG ACA GGC AGC ACC CCT GAA GTC AGT ACG GTG      435
Val Gly Glu Ile Ala Arg Thr Gly Ser Thr Pro Glu Val Ser Thr Val
125                 130                 135                 140

GAT GCC ATG TTA GAT CTC ATC AGG AAT ATG TTC CCT GAG AAT CTT GTC      483
Asp Ala Met Leu Asp Leu Ile Arg Asn Met Phe Pro Glu Asn Leu Val
                145                 150                 155

CAG GCC TGT TTT CAG CAG TAC AAA ACT AAG CGT GAA GAA GTG AAG CCT      531
Gln Ala Cys Phe Gln Gln Tyr Lys Thr Lys Arg Glu Glu Val Lys Pro
            160                 165                 170

CCC AGC GAT CCA GAG ATG AAC ATG ACA GAA GAG TCC TTC ACA GCT GTC      579
Pro Ser Asp Pro Glu Met Asn Met Thr Glu Glu Ser Phe Thr Ala Val
        175                 180                 185
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ATG ACA ACT GCA ATT TCC AAG AAC AAA ACA AAG GAA TAC AAA ATT GTT      627
Met Thr Thr Ala Ile Ser Lys Asn Lys Thr Lys Glu Tyr Lys Ile Val
    190                 195                 200

GGC ATG TAT TCA GAT GGC ATA AAC GTC CTG GGC TTG ATT GTC TTT TGC      675
Gly Met Tyr Ser Asp Gly Ile Asn Val Leu Gly Leu Ile Val Phe Cys
205                 210                 215                 220

CTT GTC TTT GGA CTT GTC ATT GGA AAA ATG GGA GAA AAG GGA CAA ATT      723
Leu Val Phe Gly Leu Val Ile Gly Lys Met Gly Glu Lys Gly Gln Ile
                225                 230                 235

CTG GTG GAT TTC TTC AAT GCT TTG AGT GAT GCA ACC ATG AAA ATC GTT      771
Leu Val Asp Phe Phe Asn Ala Leu Ser Asp Ala Thr Met Lys Ile Val
            240                 245                 250

CAG ATC ATC ATG TGT TAT ATG CCA CTA GGT ATT TTG TTC CTG ATT GCT      819
Gln Ile Ile Met Cys Tyr Met Pro Leu Gly Ile Leu Phe Leu Ile Ala
        255                 260                 265

GGG AAG ATC ATA GAA GTT GAA GAC TGG GAA ATA TTC CGC AAG CTG GGC      867
Gly Lys Ile Ile Glu Val Glu Asp Trp Glu Ile Phe Arg Lys Leu Gly
    270                 275                 280

CTT TAC ATG GCC ACA GTC CTG ACT GGG CTT GCA ATC CAC TCC ATT GTA      915
Leu Tyr Met Ala Thr Val Leu Thr Gly Leu Ala Ile His Ser Ile Val
285                 290                 295                 300

ATT CTC CCG CTG ATA TAT TTC ATA GTC GTA CGA AAG AAC CCT TTC CGA      963
Ile Leu Pro Leu Ile Tyr Phe Ile Val Val Arg Lys Asn Pro Phe Arg
                305                 310                 315

TTT GCC ATG GGA ATG GCC CAG GCT CTC CTG ACA GCT CTC ATG ATC TCT     1011
Phe Ala Met Gly Met Ala Gln Ala Leu Leu Thr Ala Leu Met Ile Ser
            320                 325                 330

TCC AGT TCA GCA ACA CTG CCT GTC ACC TTC CGC TGT GCT GAA GAA AAT     1059
Ser Ser Ser Ala Thr Leu Pro Val Thr Phe Arg Cys Ala Glu Glu Asn
        335                 340                 345

AAC CAG GTG GAC AAG AGG ATC ACT CGA TTC GTG TTA CCC GTT GGT GCA     1107
Asn Gln Val Asp Lys Arg Ile Thr Arg Phe Val Leu Pro Val Gly Ala
    350                 355                 360

ACA ATC AAC ATG GAT GGG ACC GCG CTC TAT GAA GCA GTG GCA GCG GTG     1155
Thr Ile Asn Met Asp Gly Thr Ala Leu Tyr Glu Ala Val Ala Ala Val
365                 370                 375                 380

TTT ATT GCA CAG TTG AAT GAC CTG GAC TTG GGC ATT GGG CAG ATC ATC     1203
Phe Ile Ala Gln Leu Asn Asp Leu Asp Leu Gly Ile Gly Gln Ile Ile
                385                 390                 395

ACC ATC AGT ATC ACG GCC ACA TCT GCC AGC ATC GGA GCT GCT GGC GTG     1251
Thr Ile Ser Ile Thr Ala Thr Ser Ala Ser Ile Gly Ala Ala Gly Val
            400                 405                 410

CCC CAG GCT GGC CTG GTG ACC ATG GTG ATT GTG CTG AGT GCC GTG GGC     1299
Pro Gln Ala Gly Leu Val Thr Met Val Ile Val Leu Ser Ala Val Gly
        415                 420                 425

CTG CCC GCC GAG GAT GTC ACC CTG ATC ATT GCT GTC GAC TGG CTC CTG     1347
Leu Pro Ala Glu Asp Val Thr Leu Ile Ile Ala Val Asp Trp Leu Leu
    430                 435                 440

GAC CGG TTC AGG ACC ATG GTC AAC GTC CTT GGT GAT GCT TTT GGG ACG     1395
Asp Arg Phe Arg Thr Met Val Asn Val Leu Gly Asp Ala Phe Gly Thr
445                 450                 455                 460

GGC ATT GTG GAA AAG CTC TCC AAG AAG GAG CTG GAG CAG ATG GAT GTT     1443
Gly Ile Val Glu Lys Leu Ser Lys Lys Glu Leu Glu Gln Met Asp Val
                465                 470                 475

TCA TCT GAA GTC AAC ATT GTG AAT CCC TTT GCC TTG GAA TCC ACA ATC     1491
Ser Ser Glu Val Asn Ile Val Asn Pro Phe Ala Leu Glu Ser Thr Ile
            480                 485                 490
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CTT GAC AAC GAA GAC TCA GAC ACC AAG AAG TCT TAT GTC AAT GGA GGC     1539
Leu Asp Asn Glu Asp Ser Asp Thr Lys Lys Ser Tyr Val Asn Gly Gly
        495                 500                 505

TTT GCA GTA GAC AAG TCT GAC ACC ATC TCA TTC ACC CAG ACC TCA CAG     1587
Phe Ala Val Asp Lys Ser Asp Thr Ile Ser Phe Thr Gln Thr Ser Gln
    510                 515                 520

TTC TAGGGCCCCT GGCTGCAGAT GACTGGAAAC AAGGAAGGAC ATTTCGTGAG          1640
Phe
525

AGTCATCTCA AACACGGCTT AAGGAAAAGA GAAA                               1674
```

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 525 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

```
Met Gly Lys Pro Ala Arg Lys Gly Cys Pro Ser Trp Lys Arg Phe Leu
  1               5                  10                  15

Lys Asn Asn Trp Val Leu Leu Ser Thr Val Ala Ala Val Val Leu Gly
             20                  25                  30

Ile Thr Thr Gly Val Leu Val Arg Glu His Ser Asn Leu Ser Thr Leu
         35                  40                  45

Glu Lys Phe Tyr Phe Ala Phe Pro Gly Glu Ile Leu Met Arg Met Leu
     50                  55                  60

Lys Leu Ile Ile Leu Pro Leu Ile Ile Ser Ser Met Ile Thr Gly Val
 65                  70                  75                  80

Ala Ala Leu Asp Ser Asn Val Ser Gly Lys Ile Gly Leu Arg Ala Val
                 85                  90                  95

Val Tyr Tyr Phe Cys Thr Thr Leu Ile Ala Val Ile Leu Gly Ile Val
            100                 105                 110

Leu Val Val Ser Ile Lys Pro Gly Val Thr Gln Lys Val Gly Glu Ile
        115                 120                 125

Ala Arg Thr Gly Ser Thr Pro Glu Val Ser Thr Val Asp Ala Met Leu
    130                 135                 140

Asp Leu Ile Arg Asn Met Phe Pro Glu Asn Leu Val Gln Ala Cys Phe
145                 150                 155                 160

Gln Gln Tyr Lys Thr Lys Arg Glu Glu Val Lys Pro Pro Ser Asp Pro
                165                 170                 175

Glu Met Asn Met Thr Glu Glu Ser Phe Thr Ala Val Met Thr Thr Ala
            180                 185                 190

Ile Ser Lys Asn Lys Thr Lys Glu Tyr Lys Ile Val Gly Met Tyr Ser
        195                 200                 205

Asp Gly Ile Asn Val Leu Gly Leu Ile Val Phe Cys Leu Val Phe Gly
    210                 215                 220

Leu Val Ile Gly Lys Met Gly Glu Lys Gly Gln Ile Leu Val Asp Phe
225                 230                 235                 240

Phe Asn Ala Leu Ser Asp Ala Thr Met Lys Ile Val Gln Ile Ile Met
                245                 250                 255

Cys Tyr Met Pro Leu Gly Ile Leu Phe Leu Ile Ala Gly Lys Ile Ile
            260                 265                 270
```

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```
Glu Val Glu Asp Trp Glu Ile Phe Arg Lys Leu Gly Leu Tyr Met Ala
        275                 280                 285

Thr Val Leu Thr Gly Leu Ala Ile His Ser Ile Val Ile Leu Pro Leu
    290                 295                 300

Ile Tyr Phe Ile Val Val Arg Lys Asn Pro Phe Arg Phe Ala Met Gly
305                 310                 315                 320

Met Ala Gln Ala Leu Leu Thr Ala Leu Met Ile Ser Ser Ser Ser Ala
                325                 330                 335

Thr Leu Pro Val Thr Phe Arg Cys Ala Glu Glu Asn Asn Gln Val Asp
            340                 345                 350

Lys Arg Ile Thr Arg Phe Val Leu Pro Val Gly Ala Thr Ile Asn Met
        355                 360                 365

Asp Gly Thr Ala Leu Tyr Glu Ala Val Ala Ala Val Phe Ile Ala Gln
    370                 375                 380

Leu Asn Asp Leu Asp Leu Gly Ile Gly Gln Ile Ile Thr Ile Ser Ile
385                 390                 395                 400

Thr Ala Thr Ser Ala Ser Ile Gly Ala Ala Gly Val Pro Gln Ala Gly
                405                 410                 415

Leu Val Thr Met Val Ile Val Leu Ser Ala Val Gly Leu Pro Ala Glu
            420                 425                 430

Asp Val Thr Leu Ile Ile Ala Val Asp Trp Leu Leu Asp Arg Phe Arg
        435                 440                 445

Thr Met Val Asn Val Leu Gly Asp Ala Phe Gly Thr Gly Ile Val Glu
    450                 455                 460

Lys Leu Ser Lys Lys Glu Leu Glu Gln Met Asp Val Ser Ser Glu Val
465                 470                 475                 480

Asn Ile Val Asn Pro Phe Ala Leu Glu Ser Thr Ile Leu Asp Asn Glu
                485                 490                 495

Asp Ser Asp Thr Lys Lys Ser Tyr Val Asn Gly Gly Phe Ala Val Asp
            500                 505                 510

Lys Ser Asp Thr Ile Ser Phe Thr Gln Thr Ser Gln Phe
        515                 520                 525
```

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

```
CGCGGGTACC GCCATGGAGA AGAGCAAC                                    28
```

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

-continued

CGCGTCTAGA TCACAGAACC GACTCCTTG 29

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

CGCGGGTACC AATATGACTA AAAGCAATG 29

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

CGCGTCTAGA CTACATCTTG GTTTCACTG 29

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

CGCGGGTACC ACCATGGCAT CTACGGAAG 29

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

CGCGTCTAGA TTATTTCTCA CGTTTCCAAG 30

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

-continued

CGCGGGTACC GCCATGGGGA AACCGGCG 28

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

CGCGGGATCC CTAGAACTGT GAGGTCTG 28

What is claimed is:

1. An isolated nucleic acid encoding a human excitatory amino acid transporter that hybridizes to a nucleic acid probe identified by Seq. I.D. No. 4 at a temperature of 42° C. in a solution of 5×SSPE, 50% formamide, 7.5% Denhardt's solution, 2% SDS, and 100 Fg/mL denatured salmon sperm DNA.

2. An isolated nucleic acid according to claim 1 wherein hybridization is detected after washing in a solution of 2×SSPE/0.1% SDS at room temperature and in a solution of 0.1×SSPE/0.1% SDS at 50° C.

* * * * *