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(54) **DIAGNOSTIC AND THERAPEUTIC USE OF A GOLGI PROTEIN FOR NEURODEGENERATIVE DISEASES**

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(57) **ABSTRACT**

The present invention discloses the differential expression of golgin-245 in specific brain regions of Alzheimer's disease patients. Based on this finding, this invention provides a method for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or for determining whether a subject is at increased risk of developing such a disease. Furthermore, this invention provides therapeutic and prophylactic methods for treating or preventing Alzheimer's disease and related neurodegenerative disorders using a gene coding for golgin-245. A method of screening for modulating agents of neurodegenerative diseases is also disclosed.

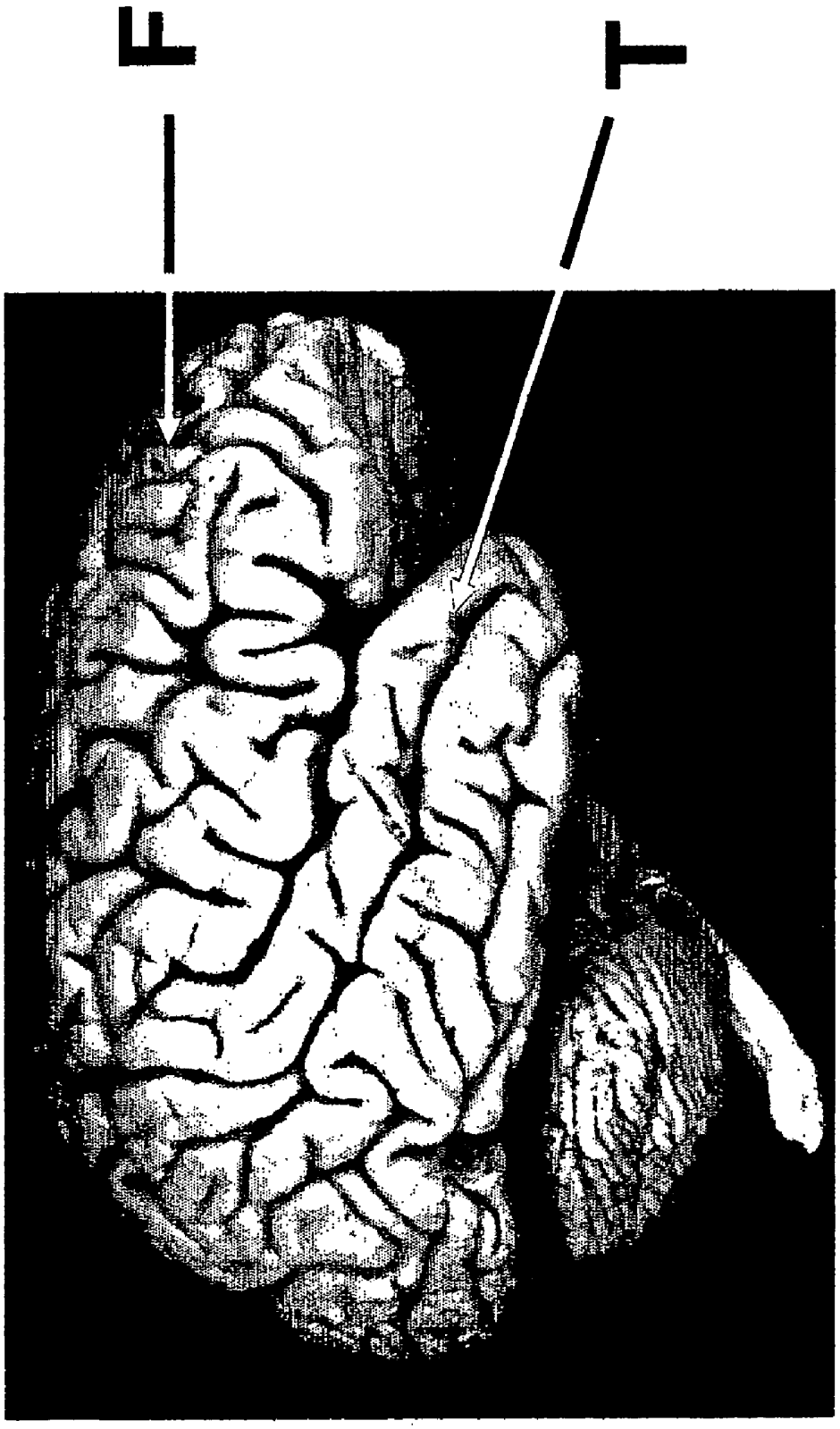

Fig. 1: Identification of Genes Involved in Alzheimer's Disease Pathology

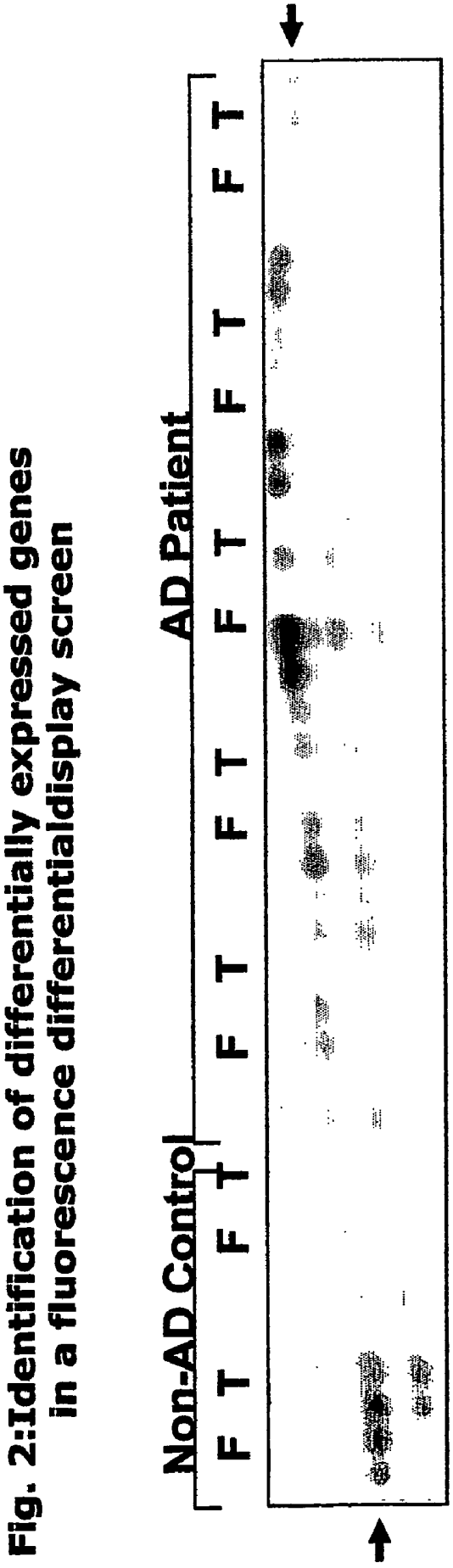

Fig. 2:Identification of differentially expressed genes in a fluorescence differentialdisplay screen

Figure 3: SEQ ID NO. 1

Length: 36 bp

1 AGTTAAGTTT CTTTGTAAAA CACTGATTTT TTCTCC

Fig. 4: Alignment of SEQ ID NO. 1 with human golgin-245 cDNA (GenBank accession number U41740)

Fig. 5: SEQ ID NO. 2: amino acid sequence of human golgin-245, splice variant 1

Length: 2228 aa

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   1  MFKKLKQKIS EEQQQLQQAL APAQASSNSS TPTRMRSRTS SFTEQLDEGT
  51  PNRESGDTQS FAQKLQLRVP SVESLFRSPI KESLFRSSSK ESLVRTSSRE
 101  SLNRLDLDSS TASFDPPSDM DSEAEDLVGN SDSLNKEQLI QRLRRMERSL
 151  SSYRGKYSEL VTAYQMLQRE KKKLQGILSQ SQDKSLRRIA ELREELQMDQ
 201  QAKKHLQEEF DASLEEKDQY ISVLQTQVSL LKQRLRNGPM NVDVLKPLPQ
 251  LEPQAEVFTK EENPESDGEP VVEDGTSVKT LETLQQRVKR QENLLKRCKE
 301  TIQSHKEQCT LLTSEKEALQ EQLDERLQEL EKIKDLHMAE KTKLITQLRD
 351  AKNLIEQLEQ DKGMVIAETK RQMHETLEMK EEEIAQLRSR IKQMTTQGEE
 401  LREQKEKSER AAFEELEKAL STAQKTEEAR RKLKAEMDEQ IKTIEKTSEE
 451  ERISLQQELS RVKQEVVDVM KKSSEEQIAK LQKLHEKELA RKEQELTKKL
 501  QTREREFQEQ MKVALEKSQS EYLKISQEKE QQESLALEEL ELQKKAILTE
 551  SENKLRDLQQ EAETYRTRIL ELESSLEKSL QENKNQSKDL AVHLEAEKNK
 601  HNKEITVMVE KHKTELESLK HQQDALWTEK LQVLKQQYQT EMEKLREKCE
 651  QEKETLLKDK EIIFQAHIEE MNEKTLEKLD VKQTELESLS SELSEVLKAR
 701  HKLEEELSVL KDQTDKMKQE LEAKMDEQKN HHQQQVDSII KEHEVSIQRT
 751  EKALKDQINQ LELLLKERDK HLKEHQAHVE NLEADIKRSE GELQQASAKL
 801  DVFQSYQSAT HEQTKAYEEQ LAQLQQKLLD LETERILLTK QVAEVEAQKK
 851  DVCTELDAHK IQVQDLMQQL EKQNSEMEQK VKSLTQVYES KLEDGNKEQE
 901  QTKQILVEKE NMILQMREGQ KKEIEILTQK LSAKEDSIHI LNEEYETKFK
 951  NQEKKMEKVK QKAKEMQETL KKKLLDQEAK LKKELENTAL ELSQKEKQFN
1001  AKMLEMAQAN SAGISDAVSR LETNQKEQIE SLTEVHRREL NDVISIWEKK
1051  LNQQAEELQE IHEIQLQEKE QEVAELKQKI LLFGCEKEEM NKEITWLKEE
1101  GVKQDTTLNE LQEQLKQKSA HVNSLAQDET KLKAHLEKLE VDLNKSLKEN
1151  TFLQEQLVEL KMLAEEDKRK VSELTSKLKT TDEEFQSLKS SHEKSNKSLE
1201  DKSLEFKKLS EELAIQLDIC CKKTEALLEA KTNELINISS SKTNAILSRI
1251  SHCQHRTTKV KEALLIKTCT VSELEAQLRQ LTEEQNTLNI SFQQATHQLE
1301  EKENQIKSMK ADIESLVTEK EALQKEGGNQ QQAASEKESC ITQLKKELSE
1351  NINAVTLMKE ELKEKKVEIS SLSKQLTDLN VQLQNSISLS EKEAAISSLR
1401  KQYDEEKCEL LDQVQDLSFK VDTLSKEKIS ALEQVDDWSN KFSEWKKKAQ
1451  SRFTQHQNTV KELQIQLELK SKEAYEKDEQ INLLKEELDQ QNKRFDCLKG
1501  EMEDDKSKME KKESNLETEL KSQTARIMEL EDHITQKTIE IESLNEVLKN
1551  YNQQKDIEHK ELVQKLQHFQ ELGEEKDNRV KEAEEKILTL ENQVYSMKAE
1601  LETKKKELEH VNLSVKSKEE ELKALEDRLE SESAAKLAEL KRKAEQKIAA
1651  IKKQLLSQME EKEEQYKKGT ESHLSELNTK LQERErEVHI LEEKLKSVES
1701  SQSETLIVPR SAKNVAAYTE QEEADSQGCV QKTYEEKISV LQRNLTEKEK
1751  LLQRVGQEKE ETVSSHFEMR CQYQERLIKL EHAEAKQHED QSMIGHLQEE
1801  LEEKNKKYSL IVAQHVEKEG GKNNIQAKQN LENVFDDVQK TLQEKELTCQ
1851  ILEQKIKELD SCLVRQKEVH RVEMEELTSK YEKLQALQQM DGRNKPTELL
1901  EENTEEKSKS HLVQPKLLSN MEAQHNDLEF KLAGAEREKQ KLGKEIVRLQ
1951  KDLRMLRKEH QQELEILKKE YDQEREEKIK QEQEDLELKH NSTLKQLMRE
2001  FNTQLAQKEQ ELEMTIKETI NKAQEVEAEL LESHQEETNQ LLKKIAEKDD
2051  DLKRTAKRYE EILDAREEEM TAKVRDLQTQ LEELQKKYQQ KLEQEENPGN
2101  DNVTIMELQT QLAQKTTLIS DSKLKEQEFR EQIHNLEDRL KKYEKNVYAT
2151  TVGTPYKGGN LYHTDVSLFG EPTEFEYLRK VLFEYMMGRE TKTMAKVITT
2201  VLKFPDDQTQ KILEREDARL MSWLRSSS
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Fig. 6: SEQ ID NO. 3: nucleotide sequence of human golgin-245 cDNA, splice variant 1

Length: 7636 bp

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   1  GCAACGAAGG TACCATGGCC GTTGTCGTCG CCGCCGCGGC TCCCGGGGCT
  51  GGATGGGGGG CCGAGGCCAG CCAGTGGCAC CCGGAAGAAA GAGACGCGGC
 101  GGCGGCGACG CCGACACCCT CAGGACGAGT GTCCGGACTT GCCCACAGCC
 151  TCAAGGAGGA GACGGCGAGG CCCGGCCCCC GCTGTCCCTG GTGTAAAGAA
 201  GTCGCCGTAG CCGTCGCGGC CGGGACTCCC CGGGCTCTCG CCCTTCAGGT
 251  TTCGTTGACA CTCAGGACCG TACGTACGCT GCGCCATGTT CAAGAAACTG
 301  AAGCAAAAGA TCAGCGAGGA GCAGCAGCAG CTCCAGCAGG CGCTGGCTCC
 351  TGCTCAGGCG TCCTCCAATT CTTCAACACC AACAAGAATG AGGAGCAGGA
 401  CATCTTCATT TACAGAGCAA CTTGATGAAG GTACACCCAA TAGAGAGTCA
 451  GGTGACACAC AGTCTTTTGC ACAGAAGCTC CAGCTCCGGG TGCCCTCCGT
 501  GGAGTCTTTG TTTCGAAGTC CGATAAAGGA ATCTCTATTC CGGTCTTCTT
 551  CTAAAGAGTC TTTGGTACGA ACATCTTCCA GAGAATCCCT GAATCGACTT
 601  GACCTGGACA GTTCTACTGC CAGTTTTGAT CCACCCTCTG ATATGGATAG
 651  CGAGGCTGAA GACTTGGTAG GGAATTCAGA CAGTCTCAAC AAAGAACAGT
 701  TGATTCAGCG GTTGCGAAGA ATGGAACGAA GCTTAAGTAG CTACAGGGGA
 751  AAATATTCTG AGCTTGTTAC AGCTTATCAG ATGCTTCAGA GAGAGAAGAA
 801  AAAGCTACAA GGTATATTAA GTCAGAGTCA GGATAAATCA CTTCGGAGAA
 851  TAGCAGAATT AAGAGAGGAG CTCCAAATGG ACCAGCAGGC AAAGAAACAT
 901  CTGCAAGAGG AGTTTGATGC ATCTTTAGAG GAGAAAGATC AGTATATCAG
 951  TGTTCTCCAA ACTCAGGTTT CTCTACTGAA ACAACGATTA CGAAATGGCC
1001  CGATGAATGT TGATGTACTG AAACCACTTC CTCAGCTGGA ACCACAGGCT
1051  GAAGTCTTCA CTAAAGAAGA GAATCCAGAA AGTGATGGAG AGCCAGTAGT
1101  GGAAGATGGA ACTTCTGTAA AAACACTGGA AACACTCCAG CAAAGAGTGA
1151  AGCGTCAAGA GAACCTACTT AAGCGTTGTA AGGAAACAAT TCAGTCACAT
1201  AAGGAACAAT GTACACTATT AACTAGTGAA AAAGAAGCTC TGCAAGAACA
1251  ACTGGATGAA AGACTTCAAG AACTAGAAAA GATAAAGGAC CTTCATATGG
1301  CCGAGAAGAC TAAACTTATC ACTCAGTTGC GTGATGCAAA GAACTTAATT
1351  GAACAGCTTG AACAAGATAA GGGAATGGTA ATCGCAGAGA CAAAACGTCA
1401  GATGCATGAA ACCCTGGAAA TGAAAGAAGA AGAAATTGCT CAACTCCGTA
1451  GTCGCATCAA ACAGATGACT ACCCAGGGAG AGGAATTACG GGAACAGAAA
1501  GAAAAGTCCG AAAGAGCTGC TTTTGAGGAA CTTGAAAAAG CTTTGAGTAC
1551  AGCCCAAAAA ACAGAGGAAG CACGGAGAAA ACTGAAGGCA GAAATGGATG
1601  AACAAATAAA AACTATCGAA AAAACAAGTG AGGAGGAACG CATCAGTCTT
1651  CAACAGGAAT TAAGTCGGGT GAAACAGGAG GTTGTTGATG TAATGAAAAA
1701  ATCCTCAGAA GAACAAATTG CTAAGCTACA GAAGCTTCAT GAAAAGGAGC
1751  TGGCCAGAAA AGAGCAGGAA CTGACCAAGA AGCTTCAGAC CCGAGAAAGG
1801  GAATTTCAGG AACAAATGAA AGTAGCTCTT GAAAAGAGTC AATCAGAATA
1851  TTTGAAGATC AGCCAAGAAA AAGAACAGCA AGAATCTTTG GCCCTAGAAG
1901  AGTTAGAGTT GCAGAAAAAA GCAATCCTCA CAGAAAGTGA AAATAAACTT
1951  CGGGACCTTC AGCAAGAAGC AGAGACTTAC AGAACTAGAA TTCTTGAATT
2001  GGAAAGTTCT TTGGAAAAAA GCTTACAAGA AAACAAAAAT CAGTCAAAAG
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2201  AGACTGAAAT GGAAAAACTT AGGGAAAAGT GTGAACAAGA AAAAGAAACA
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2301  TGAAAAGACT TTAGAAAAGC TTGATGTGAA GCAAACAGAA CTAGAATCAT
2351  TATCTTCTGA ACTGTCAGAA GTATTAAAAG CCCGTCACAA ACTAGAAGAG
2401  GAACTTTCTG TTCTGAAAGA TCAAACAGAT AAAATGAAGC AGGAATTAGA
2451  GGCCAAGATG GATGAACAGA AAAATCATCA CCAGCAGCAA GTTGACAGTA
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2601  GAAAGAGCAT CAGGCTCATG TAGAAAATTT AGAGGCAGAT ATTAAAAGGT
2651  CTGAAGGGGA ACTCCAGCAG GCATCTGCTA AGCTGGACGT TTTTCAGTCT
2701  TACCAGAGTG CCACACATGA GCAGACAAAA GCATATGAGG AACAGTTGGC
2751  CCAATTGCAG CAGAAGTTGT TGGATTTGGA AACAGAAAGA ATTCTTCTTA
2801  CCAAACAGGT TGCTGAAGTT GAAGCACAAA AGAAAGATGT TTGTACTGAG
2851  TTAGATGCTC ACAAAATCCA GGTGCAGGAC TTAATGCAGC AACTTGAAAA
2901  ACAAAATAGT GAAATGGAGC AAAAAGTAAA ATCTTTAACC CAAGTCTATG
2951  AGTCCAAACT TGAAGATGGT AACAAAGAAC AGGAACAGAC AAAGCAAATC
3001  TTGGTGGAAA AGGAAAATAT GATTTTACAA ATGAGAGAAG GACAGAAGAA
3051  AGAAATTGAG ATACTCACAC AGAAATTGTC AGCCAAGGAG GACAGTATTC
3101  ATATTTTGAA TGAGGAATAT GAAACCAAAT TTAAAAACCA AGAAAAAAAG
3151  ATGGAAAAAG TTAAGCAGAA AGCAAAGGAG ATGCAAGAAA CGTTAAAGAA
3201  AAAATTACTG GATCAGGAAG CCAAACTTAA GAAAGAGCTT GAAAATACTG
3251  CTCTAGAGCT TAGTCAGAAA GAAAAACAGT TTAATGCCAA AATGCTGGAA
3301  ATGGCACAGG CTAACTCAGC TGGAATCAGT GATGCAGTGT CAAGACTGGA
3351  AACAAACCAA AAAGAACAAA TAGAAAGTCT TACTGAGGTT CATCGACGAG
3401  AACTCAATGA TGTCATATCA ATCTGGGAAA AGAAACTTAA TCAGCAAGCT
3451  GAAGAACTTC AGGAAATACA TGAAATCCAA TTACAGGAAA AAGAACAAGA
3501  GGTAGCAGAA CTGAAACAAA AGATCCTCCT ATTTGGGTGT GAAAAAGAAG
3551  AGATGAACAA GGAAATAACA TGGCTGAAGG AAGAAGGTGT TAAGCAGGAT
3601  ACAACATTAA ATGAATTACA GGAACAGTTA AAGCAGAAGT CTGCCCATGT
3651  GAATTCTCTT GCACAAGATG AAACTAAACT GAAAGCTCAT CTTGAAAAGC
3701  TAGAGGTTGA CTTGAATAAG TCTCTGAAGG AAAATACTTT TCTTCAAGAG
3751  CAGCTAGTTG AACTGAAGAT GCTGGCAGAA GAAGATAAGC GGAAGGTTTC
3801  TGAGTTGACT AGCAAGTTGA AAACCACAGA TGAAGAATTC CAGAGTTTGA
3851  AATCTTCACA TGAAAAAAGT AACAAAAGCC TAGAGGACAA GAGCTTGGAA
3901  TTTAAAAAAC TGTCTGAGGA ACTAGCGATT CAGCTAGATA TTTGCTGTAA
3951  GAAAACCGAA GCCTTATTAG AAGCTAAAAC AAATGAGCTA ATCAACATTA
4001  GTAGTAGTAA AACTAATGCC ATTCTTTCTA GGATTTCTCA TTGTCAGCAC
4051  CGTACAACTA AAGTTAAGGA GGCACTGTTA ATTAAAACTT GCACAGTTTC
4101  TGAATTAGAA GCACAACTTA GACAGTTGAC AGAGGAGCAA AATACACTAA
4151  ATATTTCTTT TCAACAGGCT ACTCATCAGT TAGAAGAAAA AGAAAATCAA
4201  ATTAAGAGCA TGAAGGCTGA TATTGAAAGT CTTGTAACAG AAAAAGAAGC
4251  CTTACAGAAG GAAGGAGGCA ATCAGCAACA GGCTGCTTCT GAAAAGGAGT
4301  CTTGTATAAC ACAGTTGAAG AAAGAGTTAT CTGAAAACAT CAATGCTGTC
4351  ACATTGATGA AAGAAGAGCT TAAAGAAAAA AAAGTTGAGA TTAGCAGTCT
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4751  ATCAGCAAAA TAAAAGATTT GATTGTTTAA AGGGTGAAAT GGAAGACGAC
4801  AAGAGCAAGA TGGAGAAAAA GGAGTCTAAT TTAGAAACAG AGTTAAAGTC
4851  TCAAACAGCA AGAATTATGG AATTAGAGGA CCATATTACC CAGAAAACTA
4901  TTGAAATAGA GTCCTTAAAT GAAGTTCTTA AAAATTACAA TCAACAAAAG
4951  GATATTGAAC ACAAAGAATT GGTTCAGAAA CTTCAACATT TTCAAGAGTT
5001  AGGAGAAGAA AAGGACAACA GGGTTAAAGA AGCTGAAGAA AAAATCTTAA
5051  CACTTGAAAA CCAAGTTTAT TCCATGAAAG CTGAACTTGA AACTAAGAAG
5101  AAAGAATTAG AACATGTGAA TTTAAGTGTG AAAAGCAAAG AGGAGGAGTT
5151  AAAGGCATTG GAAGATAGGC TTGAGTCAGA AAGTGCTGCA AAATTAGCAG
5201  AGTTGAAGAG AAAAGCTGAA CAAAAAATTG CTGCCATTAA GAAGCAGTTG
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5301 CCATTTGAGT GAGCTAAATA CAAAATTGCA GGAAAGAGAA AGGGAAGTTC
5351 ACATCTTGGA AGAAAAACTT AAGTCAGTGG AAAGTTCACA GTCAGAAACA
5401 TTAATTGTAC CCAGATCAGC AAAAAATGTG GCAGCATATA CTGAACAAGA
5451 AGAAGCAGAT TCCCAAGGCT GTGTGCAGAA GACATATGAA GAAAAAATCA
5501 GTGTTTTACA AAGAAACTTA ACTGAAAAAG AAAAGCTATT GCAGAGGGTA
5551 GGGCAGGAAA AAGAAGAGAC AGTTTCTTCT CATTTTGAAA TGCGATGCCA
5601 ATACCAGGAG CGCTTAATAA AGCTAGAACA TGCTGAGGCA AAGCAACATG
5651 AAGATCAAAG TATGATAGGT CATCTTCAAG AGGAGCTTGA AGAAAAAAAC
5701 AAGAAATATT CCTTGATAGT AGCCCAGCAT GTGGAAAAAG AAGGAGGTAA
5751 AAATAACATA CAGGCAAAGC AAAACTTGGA AAATGTGTTT GACGACGTCC
5801 AGAAAACCCT CCAGGAGAAG GAACTAACCT GTCAGATTTT GGAGCAAAAG
5851 ATAAAAGAGC TGGATTCCTG CTTAGTAAGA CAGAAAGAAG TACATAGAGT
5901 TGAAATGGAA GAGTTGACCT CAAAATATGA AAAATTACAG GCTTTACAAC
5951 AGATGGATGG AAGAAATAAA CCCACAGAAC TTTTGGAAGA AAACACTGAA
6001 GAAAAGTCCA AATCACATTT GGTCCAACCC AAATTGCTTA GTAACATGGA
6051 AGCCCAGCAC AATGATCTGG AGTTTAAATT AGCCGGGGCA GAACGGGAGA
6101 AACAGAAACT GGGCAAGGAG ATTGTTAGAT TGCAGAAAGA CCTTCGAATG
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6251 AGCACAATTC CACATTAAAA CAGCTGATGA GGGAGTTTAA TACACAGCTG
6301 GCACAAAAGG AACAAGAGCT GGAAATGACC ATAAAAGAAA CTATCAATAA
6351 GGCCCAGGAG GTGGAGGCTG AACTTTTAGA AAGCCATCAA GAAGAGACAA
6401 ATCAGTTACT TAAAAAAATT GCTGAGAAAG ATGATGATCT AAAACGAACA
6451 GCCAAAAGAT ATGAAGAAAT CCTTGATGCT CGTGAAGAAG AAATGACTGC
6501 AAAAGTAAGG GACCTGCAGA CTCAACTTGA GGAGCTGCAG AAGAAATACC
6551 AGCAAAAGCT AGAGCAGGAG GAGAACCCTG GCAATGATAA TGTAACAATT
6601 ATGGAGCTAC AGACACAGCT AGCACAGAAG ACGACTTTAA TCAGTGATTC
6651 GAAATTGAAA GAGCAAGAGT TCAGAGAACA GATTCACAAT TTAGAAGACC
6701 GTTTGAAGAA ATATGAAAAG AATGTATATG CAACAACTGT GGGGACACCT
6751 TACAAAGGTG GCAATTTGTA CCATACGGAT GTCTCACTCT TTGGAGAACC
6801 TACCGAATTT GAGTATTTGC GAAAAGTGCT TTTTGAGTAT ATGATGGGTC
6851 GTGAGACTAA GACCATGGCA AAAGTTATAA CCACCGTACT GAAGTTCCCT
6901 GATGATCAGA CTCAGAAAAT TTTGGAAAGA GAAGATGCTC GGCTGATGTC
6951 ATGGCTCCGA TCTTCATCTT GAAGAAGAGT GACATTGGGT GACTGCTGCT
7001 TGGAAAACTG TCCACACTTG CTACTCTTTG AGAATGAAGT TGTCATTCAG
7051 GGCCCCTCAT GTAGCCAAAA GACCAAGAAA AATCTGGCCC ACAGATAAGT
7101 TGCAGACTGC CTTTAAAATA GATTTTATCA GTGGAGAAAT GGTGATAGTT
7151 TTTTCTTCAG TTTTCTCTTG GGAAGAGTTT TATGTTGTTT AAAAGATATT
7201 TTGATAACTT AACCTGCTTT ATGGGCTTAC ATAATATTCC TTTCATCCAT
7251 TCTTTTTAAA GAACGGCTTA CCTTTCCTAT TTATTTTTAG GGTGATTTTT
7301 TAAAAAGACT TGTGCAATAC ATTTTGAGGT GAAACTTAGT GGATTTTTTC
7351 TGATAAATTA GAGCATTTAA TTGACTATTT TATTCAGGTT GATCTGTTGA
7401 ATATTTGCTA AAGACCAGTT CTTTAAGCTA AGACATGTAA AAAATCCCAA
7451 ATGGCAGTAC CTCATTGTTT ACTTAGCTTT TGTACTTATA TTTTTCAGAG
7501 GAAAAAACAC TACTGTAAAT TGTGAATAGC CAATACATAA CTGTATTGTA
7551 TGCAAATCTG TGATTGTTGG CAGTGTCATC TCTGAGAAAC AGATAAATAA
7601 AGTTTATTTA CTATATAACC AAAAAAAAAA AAAAAA

Fig. 7: SEQ ID NO. 4: amino acid sequence of human golgin-245, splice variant 2 (GenBank accession number Q13439)

Length: 2230 aa

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   1  MFKKLKQKIS EEQQQLQQAL APAQASSNSS TPTRMRSRTS SFTEQLDEGT
  51  PNRESGDTQS FAQKLQLRVP SVESLFRSPI KESLFRSSSK ESLVRTSSRE
 101  SLNRLDLDSS TASFDPPSDM DSEAEDLVGN SDSLNKEQLI QRLRRMERSL
 151  SSYRGKYSEL VTAYQMLQRE KKKLQGILSQ SQDKSLRRIA ELREELQMDQ
 201  QAKKHLQEEF DASLEEKDQY ISVLQTQVSL LKQRLRNGPM NVDVLKPLPQ
 251  LEPQAEVFTK EENPESDGEP VVEDGTSVKT LETLQQRVKR QENLLKRCKE
 301  TIQSHKEQCT LLTSEKEALQ EQLDERLQEL EKIKDLHMAE KTKLITQLRD
 351  AKNLIEQLEQ DKGMVIAETK RQMHETLEMK EEEIAQLRSR IKQMTTQGEE
 401  LREQKEKSER AAFEELEKAL STAQKTEEAR RKLKAEMDEQ IKTIEKTSEE
 451  ERISLQQELS RVKQEVVDVM KKSSEEQIAK LQKLHEKELA RKEQELTKKL
 501  QTREREFQEQ MKVALEKSQS EYLKISQEKE QQESLALEEL ELQKKAILTE
 551  SENKLRDLQQ EAETYRTRIL ELESSLEKSL QENKNQSKDL AVHLEAEKNK
 601  HNKEITVMVE KHKTELESLK HQQDALWTEK LQVLKQQYQT EMEKLREKCE
 651  QEKETLLKDK EIIFQAHIEE MNEKTLEKLD VKQTELESLS SELSEVLKAR
 701  HKLEEELSVL KDQTDKMKQE LEAKMDEQKN HHQQQVDSII KEHEVSIQRT
 751  EKALKDQINQ LELLLKERDK HLKEHQAHVE NLEADIKRSE GELQQASAKL
 801  DVFQSYQSAT HEQTKAYEEQ LAQLQQKLLD LETERILLTK QVAEVEAQKK
 851  DVCTELDAHK IQVQDLMQQL EKQNSEMEQK VKSLTQVYES KLEDGNKEQE
 901  QTKQILVEKE NMILQMREGQ KKEIEILTQK LSAKEDSIHI LNEEYETKFK
 951  NQEKKMEKVK QKAKEMQETL KKKLLDQEAK LKKELENTAL ELSQKEKQFN
1001  AKMLEMAQAN SAGISDAVSR LETNQKEQIE SLTEVHRREL NDVISIWEKK
1051  LNQQAEELQE IHEIQLQEKE QEVAELKQKI LLFGCEKEEM NKEITWLKEE
1101  GVKQDTTLNE LQEQLKQKSA HVNSLAQDET KLKAHLEKLE VDLNKSLKEN
1151  TFLQEQLVEL KMLAEEDKRK VSELTSKLKT TDEEFQSLKS SHEKSNKSLE
1201  DKSLEFKKLS EELAIQLDIC CKKTEALLEA KTNELINISS SKTNAILSRI
1251  SHCQHRTTKV KEALLIKTCT VSELEAQLRQ LTEEQNTLNI SFQQATHQLE
1301  EKENQIKSMK ADIESLVTEK EALQKEGGNQ QQAASEKESC ITQLKKELSE
1351  NINAVTLMKE ELKEKKVEIS SLSKQLTDLN VQLQNSISLS EKEAAISSLR
1401  KQYDEEKCEL LDQVQDLSFK VDTLSKEKIS ALEQVDDWSN KFSEWKKKAQ
1451  SRFTQHQNTV KELQIQLELK SKEAYEKDEQ INLLKEELDQ QNKRFDCLKG
1501  EMEDDKSKME KKESNLETEL KSQTARIMEL EDHITQKTIE IESLNEVLKN
1551  YNQQKDIEHK ELVQKLQHFQ ELGEEKDNRV KEAEEKILTL ENQVYSMKAE
1601  LETKKKELEH VNLSVKSKEE ELKALEDRLE SESAAKLAEL KRKAEQKIAA
1651  IKKQLLSQME EKEEQYKKGT ESHLSELNTK LQERE REVHI LEEKLKSVES
1701  SQSETLIVPR SAKNVAAYTE QEEADSQGCV QKTYEEKISV LQRNLTEKEK
1751  LLQRVGQEKE ETVSSHFEMR CQYQERLIKL EHAEAKQHED QSMIGHLQEE
1801  LEEKNKKYSL IVAQHVEKEG GKNNIQAKQN LENVFDDVQK TLQEKELTCQ
1851  ILEQKIKELD SCLVRQKEVH RVEMEELTSK YEKLQALQQM DGRNKPTELL
1901  EENTEEKSKS HLVQPKLLSN MEAQHNDLEF KLAGAEREKQ KLGKEIVRLQ
1951  KDLRMLRKEH QQELEILKKE YDQEREEKIK QEQEDLELKH NSTLKQLMRE
2001  FNTQLAQKEQ ELEMTIKETI NKAQEVEAEL LESHQEETNQ LLKKIAEKDD
2051  DLKRTAKRYE EILDAREEEM TAKVRDLQTQ LEELQKKYQQ KLEQEENPGN
2101  DNVTIMELQT QLAQKTTLIS DSKLKEQEFR EQIHNLEDRL KKYEKNVYAT
2151  TVGTPYKGGN LYHTDVSLFG EPTEFEYLRK VLFEYMMGRE TKTMAKVITT
2201  VLKFPDDQTQ KILEREDARL MFTSPRSGIF
```

Fig. 8: SEQ ID NO. 5: nucleotide sequence of human golgin-245 cDNA, splice variant 2 (GenBank accession number U41740)

Length: 7695 bp

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   1  GCAACGAAGG TACCATGGCC GTTGTCGTCG CCGCCGCGGC TCCCGGGGCT
  51  GGATGGGGGG CCGAGGCCAG CCAGTGGCAC CCGGAAGAAA GAGACGCGGC
 101  GGCGGCGACG CCGACACCCT CAGGACGAGT GTCCGGACTT GCCCACAGCC
 151  TCAAGGAGGA GACGGCGAGG CCCGGCCCCC GCTGTCCCTG GTGTAAAGAA
 201  GTCGCCGTAG CCGTCGCGGC CGGGACTCCC CGGGCTCTCG CCCTTCAGGT
 251  TTCGTTGACA CTCAGGACCG TACGTACGCT GCGCCATGTT CAAGAAACTG
 301  AAGCAAAAGA TCAGCGAGGA GCAGCAGCAG CTCCAGCAGG CGCTGGCTCC
 351  TGCTCAGGCG TCCTCCAATT CTTCAACACC AACAAGAATG AGGAGCAGGA
 401  CATCTTCATT TACAGAGCAA CTTGATGAAG GTACACCCAA TAGAGAGTCA
 451  GGTGACACAC AGTCTTTTGC ACAGAAGCTC CAGCTCCGGG TGCCCTCCGT
 501  GGAGTCTTTG TTTCGAAGTC CGATAAAGGA ATCTCTATTC CGGTCTTCTT
 551  CTAAAGAGTC TTTGGTACGA ACATCTTCCA GAGAATCCCT GAATCGACTT
 601  GACCTGGACA GTTCTACTGC CAGTTTTGAT CCACCCTCTG ATATGGATAG
 651  CGAGGCTGAA GACTTGGTAG GGAATTCAGA CAGTCTCAAC AAAGAACAGT
 701  TGATTCAGCG GTTGCGAAGA ATGGAACGAA GCTTAAGTAG CTACAGGGGA
 751  AAATATTCTG AGCTTGTTAC AGCTTATCAG ATGCTTCAGA GAGAGAAGAA
 801  AAAGCTACAA GGTATATTAA GTCAGAGTCA GGATAAATCA CTTCGGAGAA
 851  TAGCAGAATT AAGAGAGGAG CTCCAAATGG ACCAGCAGGC AAAGAAACAT
 901  CTGCAAGAGG AGTTTGATGC ATCTTTAGAG GAGAAAGATC AGTATATCAG
 951  TGTTCTCCAA ACTCAGGTTT CTCTACTGAA ACAACGATTA CGAAATGGCC
1001  CGATGAATGT TGATGTACTG AAACCACTTC CTCAGCTGGA ACCACAGGCT
1051  GAAGTCTTCA CTAAAGAAGA GAATCCAGAA AGTGATGGAG AGCCAGTAGT
1101  GGAAGATGGA ACTTCTGTAA AAACACTGGA AACACTCCAG CAAAGAGTGA
1151  AGCGTCAAGA GAACCTACTT AAGCGTTGTA AGGAAACAAT TCAGTCACAT
1201  AAGGAACAAT GTACACTATT AACTAGTGAA AAAGAAGCTC TGCAAGAACA
1251  ACTGGATGAA AGACTTCAAG AACTAGAAAA GATAAAGGAC CTTCATATGG
1301  CCGAGAAGAC TAAACTTATC ACTCAGTTGC GTGATGCAAA GAACTTAATT
1351  GAACAGCTTG AACAAGATAA GGGAATGGTA ATCGCAGAGA CAAAACGTCA
1401  GATGCATGAA ACCCTGGAAA TGAAAGAAGA AGAAATTGCT CAACTCCGTA
1451  GTCGCATCAA ACAGATGACT ACCCAGGGAG AGGAATTACG GGAACAGAAA
1501  GAAAAGTCCG AAAGAGCTGC TTTTGAGGAA CTTGAAAAAG CTTTGAGTAC
1551  AGCCCAAAAA ACAGAGGAAG CACGGAGAAA ACTGAAGGCA GAAATGGATG
1601  AACAAATAAA AACTATCGAA AAAACAAGTG AGGAGGAACG CATCAGTCTT
1651  CAACAGGAAT TAAGTCGGGT GAAACAGGAG GTTGTTGATG TAATGAAAAA
1701  ATCCTCAGAA GAACAAATTG CTAAGCTACA GAAGCTTCAT GAAAAGGAGC
1751  TGGCCAGAAA AGAGCAGGAA CTGACCAAGA AGCTTCAGAC CCGAGAAAGG
1801  GAATTTCAGG AACAAATGAA AGTAGCTCTT GAAAAGAGTC AATCAGAATA
1851  TTTGAAGATC AGCCAAGAAA AAGAACAGCA AGAATCTTTG GCCCTAGAAG
1901  AGTTAGAGTT GCAGAAAAAA GCAATCCTCA CAGAAAGTGA AAATAAACTT
1951  CGGGACCTTC AGCAAGAAGC AGAGACTTAC AGAACTAGAA TTCTTGAATT
2001  GGAAAGTTCT TTGGAAAAAA GCTTACAAGA AAACAAAAAT CAGTCAAAAG
2051  ATTTGGCTGT TCATCTGGAA GCTGAAAAAA ATAAGCACAA TAAGGAGATT
2101  ACAGTCATGG TTGAAAAACA CAAGACAGAA TTGGAAAGCC TTAAGCATCA
2151  GCAGGATGCC CTTTGGACTG AAAAACTCCA AGTCTTAAAG CAACAATATC
2201  AGACTGAAAT GGAAAAACTT AGGGAAAAGT GTGAACAAGA AAAAGAAACA
2251  TTGTTGAAAG ACAAAGAGAT TATCTTCCAG GCCCACATAG AAGAAATGAA
2301  TGAAAAGACT TTAGAAAAGC TTGATGTGAA GCAAACAGAA CTAGAATCAT
2351  TATCTTCTGA ACTGTCAGAA GTATTAAAAG CCCGTCACAA ACTAGAAGAG
2401  GAACTTTCTG TTCTGAAAGA TCAAACAGAT AAAATGAAGC AGGAATTAGA
2451  GGCCAAGATG GATGAACAGA AAAATCATCA CCAGCAGCAA GTTGACAGTA
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2501  TCATTAAAGA ACACGAGGTA TCTATCCAGA GGACTGAGAA GGCATTAAAA
2551  GATCAAATTA ATCAACTTGA GCTTCTCTTG AAGGAAAGGG ACAAGCATTT
2601  GAAAGAGCAT CAGGCTCATG TAGAAAATTT AGAGGCAGAT ATTAAAAGGT
2651  CTGAAGGGGA ACTCCAGCAG GCATCTGCTA AGCTGGACGT TTTTCAGTCT
2701  TACCAGAGTG CCACACATGA GCAGACAAAA GCATATGAGG AACAGTTGGC
2751  CCAATTGCAG CAGAAGTTGT TGGATTTGGA AACAGAAAGA ATTCTTCTTA
2801  CCAAACAGGT TGCTGAAGTT GAAGCACAAA AGAAAGATGT TTGTACTGAG
2851  TTAGATGCTC ACAAAATCCA GGTGCAGGAC TTAATGCAGC AACTTGAAAA
2901  ACAAAATAGT GAAATGGAGC AAAAAGTAAA ATCTTTAACC CAAGTCTATG
2951  AGTCCAAACT TGAAGATGGT AACAAAGAAC AGGAACAGAC AAAGCAAATC
3001  TTGGTGGAAA AGGAAAATAT GATTTTACAA ATGAGAGAAG GACAGAAGAA
3051  AGAAATTGAG ATACTCACAC AGAAATTGTC AGCCAAGGAG GACAGTATTC
3101  ATATTTTGAA TGAGGAATAT GAAACCAAAT TTAAAAACCA AGAAAAAAAG
3151  ATGGAAAAAG TTAAGCAGAA AGCAAAGGAG ATGCAAGAAA CGTTAAAGAA
3201  AAAATTACTG GATCAGGAAG CCAAACTTAA GAAAGAGCTT GAAAATACTG
3251  CTCTAGAGCT TAGTCAGAAA GAAAAACAGT TTAATGCCAA AATGCTGGAA
3301  ATGGCACAGG CTAACTCAGC TGGAATCAGT GATGCAGTGT CAAGACTGGA
3351  AACAAACCAA AAAGAACAAA TAGAAAGTCT TACTGAGGTT CATCGACGAG
3401  AACTCAATGA TGTCATATCA ATCTGGGAAA AGAAACTTAA TCAGCAAGCT
3451  GAAGAACTTC AGGAAATACA TGAAATCCAA TTACAGGAAA AAGAACAAGA
3501  GGTAGCAGAA CTGAAACAAA AGATCCTCCT ATTTGGGTGT GAAAAAGAAG
3551  AGATGAACAA GGAAATAACA TGGCTGAAGG AAGAAGGTGT TAAGCAGGAT
3601  ACAACATTAA ATGAATTACA GGAACAGTTA AAGCAGAAGT CTGCCCATGT
3651  GAATTCTCTT GCACAAGATG AAACTAAACT GAAAGCTCAT CTTGAAAAGC
3701  TAGAGGTTGA CTTGAATAAG TCTCTGAAGG AAAATACTTT TCTTCAAGAG
3751  CAGCTAGTTG AACTGAAGAT GCTGGCAGAA GAAGATAAGC GGAAGGTTTC
3801  TGAGTTGACT AGCAAGTTGA AAACCACAGA TGAAGAATTC CAGAGTTTGA
3851  AATCTTCACA TGAAAAAAGT AACAAAAGCC TAGAGGACAA GAGCTTGGAA
3901  TTTAAAAAAC TGTCTGAGGA ACTAGCGATT CAGCTAGATA TTTGCTGTAA
3951  GAAAACCGAA GCCTTATTAG AAGCTAAAAC AAATGAGCTA ATCAACATTA
4001  GTAGTAGTAA AACTAATGCC ATTCTTTCTA GGATTTCTCA TTGTCAGCAC
4051  CGTACAACTA AAGTTAAGGA GGCACTGTTA ATTAAAACTT GCACAGTTTC
4101  TGAATTAGAA GCACAACTTA GACAGTTGAC AGAGGAGCAA AATACACTAA
4151  ATATTTCTTT TCAACAGGCT ACTCATCAGT TAGAAGAAAA AGAAAATCAA
4201  ATTAAGAGCA TGAAGGCTGA TATTGAAAGT CTTGTAACAG AAAAAGAAGC
4251  CTTACAGAAG GAAGGAGGCA ATCAGCAACA GGCTGCTTCT GAAAAGGAGT
4301  CTTGTATAAC ACAGTTGAAG AAAGAGTTAT CTGAAAACAT CAATGCTGTC
4351  ACATTGATGA AAGAAGAGCT TAAAGAAAAA AAAGTTGAGA TTAGCAGTCT
4401  TAGTAAACAA CTAACTGATT TGAATGTTCA GCTTCAAAAT AGCATCAGCC
4451  TATCCGAAAA AGAAGCAGCC ATTTCATCAC TAAGAAAGCA GTATGATGAA
4501  GAAAAATGTG AATTGCTGGA TCAGGTGCAA GATTTATCTT TTAAAGTTGA
4551  CACTCTGAGT AAAGAGAAAA TTTCTGCTCT TGAGCAGGTA GATGACTGGT
4601  CCAATAAATT CTCAGAATGG AAGAAGAAAG CACAGTCAAG ATTTACACAG
4651  CATCAAAACA CTGTTAAAGA ATTGCAGATC CAGCTTGAGT TAAAATCAAA
4701  GGAAGCTTAT GAAAAGGATG AGCAGATAAA TTTATTGAAG GAAGAGCTTG
4751  ATCAGCAAAA TAAAAGATTT GATTGTTTAA AGGGTGAAAT GGAAGACGAC
4801  AAGAGCAAGA TGGAGAAAAA GGAGTCTAAT TTAGAAACAG AGTTAAAGTC
4851  TCAAACAGCA AGAATTATGG AATTAGAGGA CCATATTACC CAGAAAACTA
4901  TTGAAATAGA GTCCTTAAAT GAAGTTCTTA AAAATTACAA TCAACAAAAG
4951  GATATTGAAC ACAAAGAATT GGTTCAGAAA CTTCAACATT TTCAAGAGTT
5001  AGGAGAAGAA AAGGACAACA GGGTTAAAGA AGCTGAAGAA AAAATCTTAA
5051  CACTTGAAAA CCAAGTTTAT TCCATGAAAG CTGAACTTGA AACTAAGAAG
5101  AAAGAATTAG AACATGTGAA TTTAAGTGTG AAAAGCAAAG AGGAGGAGTT
5151  AAAGGCATTG GAAGATAGGC TTGAGTCAGA AAGTGCTGCA AAATTAGCAG
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5201 AGTTGAAGAG AAAAGCTGAA CAAAAAATTG CTGCCATTAA GAAGCAGTTG
5251 TTATCTCAAA TGGAAGAGAA AGAAGAACAG TATAAAAAAG GTACAGAAAG
5301 CCATTTGAGT GAGCTAAATA CAAAATTGCA GGAAAGAGAA AGGGAAGTTC
5351 ACATCTTGGA AGAAAAACTT AAGTCAGTGG AAAGTTCACA GTCAGAAACA
5401 TTAATTGTAC CCAGATCAGC AAAAAATGTG GCAGCATATA CTGAACAAGA
5451 AGAAGCAGAT TCCCAAGGCT GTGTGCAGAA GACATATGAA GAAAAAATCA
5501 GTGTTTTACA AAGAAACTTA ACTGAAAAAG AAAAGCTATT GCAGAGGGTA
5551 GGGCAGGAAA AAGAAGAGAC AGTTTCTTCT CATTTTGAAA TGCGATGCCA
5601 ATACCAGGAG CGCTTAATAA AGCTAGAACA TGCTGAGGCA AAGCAACATG
5651 AAGATCAAAG TATGATAGGT CATCTTCAAG AGGAGCTTGA AGAAAAAAAC
5701 AAGAAATATT CCTTGATAGT AGCCCAGCAT GTGGAAAAAG AAGGAGGTAA
5751 AAATAACATA CAGGCAAAGC AAAACTTGGA AAATGTGTTT GACGACGTCC
5801 AGAAAACCCT CCAGGAGAAG GAACTAACCT GTCAGATTTT GGAGCAAAAG
5851 ATAAAAGAGC TGGATTCCTG CTTAGTAAGA CAGAAAGAAG TACATAGAGT
5901 TGAAATGGAA GAGTTGACCT CAAAATATGA AAAATTACAG GCTTTACAAC
5951 AGATGGATGG AAGAAATAAA CCCACAGAAC TTTTGGAAGA AAACACTGAA
6001 GAAAAGTCCA AATCACATTT GGTCCAACCC AAATTGCTTA GTAACATGGA
6051 AGCCCAGCAC AATGATCTGG AGTTTAAATT AGCCGGGGCA GAACGGGAGA
6101 AACAGAAACT GGGCAAGGAG ATTGTTAGAT TGCAGAAAGA CCTTCGAATG
6151 TTGAGAAAGG AGCATCAGCA AGAATTGGAA ATACTAAAGA AAGAATATGA
6201 TCAAGAAAGG GAAGAGAAAA TCAAACAGGA GCAGGAAGAT CTTGAACTGA
6251 AGCACAATTC CACATTAAAA CAGCTGATGA GGGAGTTTAA TACACAGCTG
6301 GCACAAAAGG AACAAGAGCT GGAAATGACC ATAAAAGAAA CTATCAATAA
6351 GGCCCAGGAG GTGGAGGCTG AACTTTTAGA AAGCCATCAA GAAGAGACAA
6401 ATCAGTTACT TAAAAAAATT GCTGAGAAAG ATGATGATCT AAAACGAACA
6451 GCCAAAAGAT ATGAAGAAAT CCTTGATGCT CGTGAAGAAG AAATGACTGC
6501 AAAAGTAAGG GACCTGCAGA CTCAACTTGA GGAGCTGCAG AAGAAATACC
6551 AGCAAAAGCT AGAGCAGGAG GAGAACCCTG GCAATGATAA TGTAACAATT
6601 ATGGAGCTAC AGACACAGCT AGCACAGAAG ACGACTTTAA TCAGTGATTC
6651 GAAATTGAAA GAGCAAGAGT TCAGAGAACA GATTCACAAT TTAGAAGACC
6701 GTTTGAAGAA ATATGAAAAG AATGTATATG CAACAACTGT GGGGACACCT
6751 TACAAAGGTG GCAATTTGTA CCATACGGAT GTCTCACTCT TTGGAGAACC
6801 TACCGAATTT GAGTATTTGC GAAAAGTGCT TTTTGAGTAT ATGATGGGTC
6851 GTGAGACTAA GACCATGGCA AAAGTTATAA CCACCGTACT GAAGTTCCCT
6901 GATGATCAGA CTCAGAAAAT TTTGGAAAGA GAAGATGCTC GGCTGATGTT
6951 TACTTCACCT CGCAGTGGTA TCTTCTGAGT AAACCATCAG TCTGTGCTTA
7001 GTTAACATGT GTCATGGCTC CGATCTTCAT CTTGAAGAAG AGTGACATTG
7051 GGTGACTGCT GCTTGGAAAA CTGTCCACAC TTGCTACTCT TTGAGAATGA
7101 AGTTGTCATT CAGGGCCCCT CATGTAGCCA AAAGACCAAG AAAAATCTGG
7151 CCCACAGATA AGTTGCAGAC TGCCTTTAAA ATAGATTTTA TCAGTGGAGA
7201 AATGGTGATA GTTTTTTCTT CAGTTTTCTC TTGGGAAGGA GTTTTATGTT
7251 GTTTAAAAGA TATTTTGATA ACTTAACCTG CTTTATGGGC TTACATAATA
7301 TTCCTTTCAT CCATTCTTTT TAAAGAACGG CTTACCTTTC CTATTTATTT
7351 TTAGGGTGAT TTTTTAAAAA GACTTGTGCA ATACATTTTG AGGTGAAACT
7401 TAGTGGATTT TTTCTGATAA ATTAGAGCAT TTAATTGACT ATTTTATTCA
7451 GGTTGATCTG TTGAATATTT GCTAAAGACC AGTTCTTTAA GCTAAGACAT
7501 GTAAAAAATC CCAAATGGCA GTACCTCATT GTTTACTTAG CTTTTGTACT
7551 TATATTTTTC AGAGGAAAAA ACACTACTGT AAATTGTGAA TAGCCAATAC
7601 ATAACTGTAT TGTATGCAAA TCTGTGATTG TTGGCAGTGT CATCTCTGAG
7651 AAACAGATAA ATAAAGTTTA TTTACTATAA AAAAAAAAAA AAAAG

Fig. 9: SEQ ID NO. 6:amino acid sequence of human golgin-245, splice variant 3

Length: 2250 aa

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   1  MFKKLKQKIS EEQQQLQQAL APAQASSNSS TPTRMRSRTS SFTEQLDEGT
  51  PNRENASTHA SKSPDSVNGS EPSIPQSGDT QSFAQKLQLR VPSVESLFRS
 101  PIKESLFRSS SKESLVRTSS RESLNRLDLD SSTASFDPPS DMDSEAEDLV
 151  GNSDSLNKEQ LIQRLRRMER SLSSYRGKYS ELVTAYQMLQ REKKKLQGIL
 201  SQSQDKSLRR IAELREELQM DQQAKKHLQE EFDASLEEKD QYISVLQTQV
 251  SLLKQRLRNG PMNVDVLKPL PQLEPQAEVF TKEENPESDG EPVVEDGTSV
 301  KTLETLQQRV KRQENLLKRC KETIQSHKEQ CTLLTSEKEA LQEQLDERLQ
 351  ELEKIKDLHM AEKTKLITQL RDAKNLIEQL EQDKGMVIAE TKRQMHETLE
 401  MKEEEIAQLR SRIKQMTTQG EELREQKEKS ERAAFEELEK ALSTAQKTEE
 451  ARRKLKAEMD EQIKTIEKTS EEERISLQQE LSRVKQEVVD VMKKSSEEQI
 501  AKLQKLHEKE LARKEQELTK KLQTREREFQ EQMKVALEKS QSEYLKISQE
 551  KEQQESLALE ELELQKKAIL TESENKLRDL QQEAETYRTR ILELESSLEK
 601  SLQENKNQSK DLAVHLEAEK NKHNKEITVM VEKHKTELES LKHQQDALWT
 651  EKLQVLKQQY QTEMEKLREK CEQEKETLLK DKEIIFQAHI EEMNEKTLEK
 701  LDVKQTELES LSSELSEVLK ARHKLEEELS VLKDQTDKMK QELEAKMDEQ
 751  KNHHQQQVDS IIKEHEVSIQ RTEKALKDQI NQLELLLKER DKHLKEHQAH
 801  VENLEADIKR SEGELQQASA KLDVFQSYQS ATHEQTKAYE EQLAQLQQKL
 851  LDLETERILL TKQVAEVEAQ KKDVCTELDA HKIQVQDLMQ QLEKQNSEME
 901  QKVKSLTQVY ESKLEDGNKE QEQTKQILVE KENMILQMRE GQKKEIEILT
 951  QKLSAKEDSI HILNEEYETK FKNQEKKMEK VKQKAKEMQE TLKKKLLDQE
1001  AKLKKELENT ALELSQKEKQ FNAKMLEMAQ ANSAGISDAV SRLETNQKEQ
1051  IESLTEVHRR ELNDVISIWE KKLNQQAEEL QEIHEIQLQE KEQEVAELKQ
1101  KILLFGCEKE EMNKEITWLK EEGVKQDTTL NELQEQLKQK SAHVNSLAQD
1151  ETKLKAHLEK LEVDLNKSLK ENTFLQEQLV ELKMLAEEDK RKVSELTSKL
1201  KTTDEEFQSL KSSHEKSNKS LEDKSLEFKK LSEELAIQLD ICCKKTEALL
1251  EAKTNELINI SSSKTNAILS RISHCQHRTT KVKEALLIKT CTVSELEAQL
1301  RQLTEEQNTL NISFQQATHQ LEEKENQIKS MKADIESLVT EKEALQKEGG
1351  NQQQAASEKE SCITQLKKEL SENINAVTLM KEELKEKKVE ISSLSKQLTD
1401  LNVQLQNSIS LSEKEAAISS LRKQYDEEKC ELLDQVQDLS FKVDTLSKEK
1451  ISALEQVDDW SNKFSEWKKK AQSRFTQHQN TVKELQIQLE LKSKEAYEKD
1501  EQINLLKEEL DQQNKRFDCL KGEMEDDKSK MEKKESNLET ELKSQTARIM
1551  ELEDHITQKT IEIESLNEVL KNYNQQKDIE HKELVQKLQH FQELGEEKDN
1601  RVKEAEEKIL TLENQVYSMK AELETKKKEL EHVNLSVKSK EEELKALEDR
1651  LESESAAKLA ELKRKAEQKI AAIKKQLLSQ MEEKEEQYKK GTESHLSELN
1701  TKLQERE REV HILEEKLKSV ESSQSETLIV PRSAKNVAAY TEQEEADSQG
1751  CVQKTYEEKI SVLQRNLTEK EKLLQRVGQE KEETVSSHFE MRCQYQERLI
1801  KLEHAEAKQH EDQSMIGHLQ EELEEKNKKY SLIVAQHVEK EGGKNNIQAK
1851  QNLENVFDDV QKTLQEKELT CQILEQKIKE LDSCLVRQKE VHRVEMEELT
1901  SKYEKLQALQ QMDGRNKPTE LLEENTEEKS KSHLVQPKLL SNMEAQHNDL
1951  EFKLAGAERE KQKLGKEIVR LQKDLRMLRK EHQQELEILK KEYDQEREEK
2001  IKQEQEDLEL KHNSTLKQLM REFNTQLAQK EQELEMTIKE TINKAQEVEA
2051  ELLESHQEET NQLLKKIAEK DDDLKRTAKR YEEILDAREE EMTAKVRDLQ
2101  TQLEELQKKY QQKLEQEENP GNDNVTIMEL QTQLAQKTTL ISDSKLKEQE
2151  FREQIHNLED RLKKYEKNVY ATTVGTPYKG GNLYHTDVSL FGEPTEFEYL
2201  RKVLFEYMMG RETKTMAKVI TTVLKFPDDQ TQKILEREDA RLMSWLRSSS
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Fig. 10: SEQ ID NO. 7: nucleotide sequence of human golgin-245 cDNA, splice variant 3

Length: 7743 bp

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   1  GCAACGAAGG TACCATGGCC GTTGTCGTCG CCGCCGCGGC TCCCGGGGCT
  51  GGATGGGGGG CCGAGGCCAG CCAGTGGCAC CCGGAAGAAA GAGACGCGGC
 101  GGCGGCGACG CCGACACCCT CAGGACGAGT GTCCGGACTT GCCCACAGCC
 151  TCAAGGAGGA GACGGCGAGG CCCGGCCCCC GCTGTCCCTG GTGTAAAGAA
 201  GTCGCCGTAG CCGTCGCGGC CGGGACTCCC CGGGCTCTCG CCCTTCAGGT
 251  TTCGTTGACA CTCAGGACCG TACGTACGCT GCGCCATGTT CAAGAAACTG
 301  AAGCAAAAGA TCAGCGAGGA GCAGCAGCAG CTCCAGCAGG CGCTGGCTCC
 351  TGCTCAGGCG TCCTCCAATT CTTCAACACC AACAAGAATG AGGAGCAGGA
 401  CATCTTCATT TACAGAGCAA CTTGATGAAG GTACACCCAA TAGAGAGAAT
 451  GCATCTACTC ATGCCTCGAA ATCTCCTGAC AGTGTTAATG GAAGTGAACC
 501  AAGCATTCCT CAGTCAGGTG ACACACAGTC TTTTGCACAG AAGCTCCAGC
 551  TCCGGGTGCC CTCCGTGGAG TCTTTGTTTC GAAGTCCGAT AAAGGAATCT
 601  CTATTCCGGT CTTCTTCTAA AGAGTCTTTG GTACGAACAT CTTCCAGAGA
 651  ATCCCTGAAT CGACTTGACC TGGACAGTTC TACTGCCAGT TTTGATCCAC
 701  CCTCTGATAT GGATAGCGAG GCTGAAGACT TGGTAGGGAA TTCAGACAGT
 751  CTCAACAAAG AACAGTTGAT TCAGCGGTTG CGAAGAATGG AACGAAGCTT
 801  AAGTAGCTAC AGGGGAAAAT ATTCTGAGCT TGTTACAGCT TATCAGATGC
 851  TTCAGAGAGA GAAGAAAAAG CTACAAGGTA TATTAAGTCA GAGTCAGGAT
 901  AAATCACTTC GGAGAATAGC AGAATTAAGA GAGGAGCTCC AAATGGACCA
 951  GCAGGCAAAG AAACATCTGC AAGAGGAGTT TGATGCATCT TTAGAGGAGA
1001  AAGATCAGTA TATCAGTGTT CTCCAAACTC AGGTTTCTCT ACTGAAACAA
1051  CGATTACGAA ATGGCCCGAT GAATGTTGAT GTACTGAAAC CACTTCCTCA
1101  GCTGGAACCA CAGGCTGAAG TCTTCACTAA AGAAGAGAAT CCAGAAAGTG
1151  ATGGAGAGCC AGTAGTGGAA GATGGAACTT CTGTAAAAAC ACTGGAAACA
1201  CTCCAGCAAA GAGTGAAGCG TCAAGAGAAC CTACTTAAGC GTTGTAAGGA
1251  AACAATTCAG TCACATAAGG AACAATGTAC ACTATTAACT AGTGAAAAAG
1301  AAGCTCTGCA AGAACAACTG GATGAAAGAC TTCAAGAACT AGAAAAGATA
1351  AAGGACCTTC ATATGGCCGA GAAGACTAAA CTTATCACTC AGTTGCGTGA
1401  TGCAAAGAAC TTAATTGAAC AGCTTGAACA AGATAAGGGA ATGGTAATCG
1451  CAGAGACAAA ACGTCAGATG CATGAAACCC TGGAAATGAA AGAAGAAGAA
1501  ATTGCTCAAC TCCGTAGTCG CATCAAACAG ATGACTACCC AGGGAGAGGA
1551  ATTACGGGAA CAGAAAGAAA AGTCCGAAAG AGCTGCTTTT GAGGAACTTG
1601  AAAAAGCTTT GAGTACAGCC CAAAAAACAG AGGAAGCACG GAGAAAACTG
1651  AAGGCAGAAA TGGATGAACA AATAAAAACT ATCGAAAAAA CAAGTGAGGA
1701  GGAACGCATC AGTCTTCAAC AGGAATTAAG TCGGGTGAAA CAGGAGGTTG
1751  TTGATGTAAT GAAAAAATCC TCAGAAGAAC AAATTGCTAA GCTACAGAAG
1801  CTTCATGAAA AGGAGCTGGC CAGAAAAGAG CAGGAACTGA CCAAGAAGCT
1851  TCAGACCCGA GAAAGGGAAT TTCAGGAACA AATGAAAGTA GCTCTTGAAA
1901  AGAGTCAATC AGAATATTTG AAGATCAGCC AAGAAAAAGA ACAGCAAGAA
1951  TCTTTGGCCC TAGAAGAGTT AGAGTTGCAG AAAAAAGCAA TCCTCACAGA
2001  AAGTGAAAAT AAACTTCGGG ACCTTCAGCA AGAAGCAGAG ACTTACAGAA
2051  CTAGAATTCT TGAATTGGAA AGTTCTTTGG AAAAAAGCTT ACAAGAAAAC
2101  AAAAATCAGT CAAAAGATTT GGCTGTTCAT CTGGAAGCTG AAAAAAATAA
2151  GCACAATAAG GAGATTACAG TCATGGTTGA AAAACACAAG ACAGAATTGG
2201  AAAGCCTTAA GCATCAGCAG GATGCCCTTT GGACTGAAAA ACTCCAAGTC
2251  TTAAAGCAAC AATATCAGAC TGAAATGGAA AAACTTAGGG AAAAGTGTGA
2301  ACAAGAAAAA GAAACATTGT TGAAAGACAA AGAGATTATC TTCCAGGCCC
2351  ACATAGAAGA AATGAATGAA AAGACTTTAG AAAAGCTTGA TGTGAAGCAA
2401  ACAGAACTAG AATCATTATC TTCTGAACTG TCAGAAGTAT TAAAAGCCCG
2451  TCACAAACTA GAAGAGGAAC TTTCTGTTCT GAAAGATCAA ACAGATAAAA
2501  TGAAGCAGGA ATTAGAGGCC AAGATGGATG AACAGAAAAA TCATCACCAG
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2551  CAGCAAGTTG ACAGTATCAT TAAAGAACAC GAGGTATCTA TCCAGAGGAC
2601  TGAGAAGGCA TTAAAAGATC AAATTAATCA ACTTGAGCTT CTCTTGAAGG
2651  AAAGGGACAA GCATTTGAAA GAGCATCAGG CTCATGTAGA AAATTTAGAG
2701  GCAGATATTA AAAGGTCTGA AGGGGAACTC CAGCAGGCAT CTGCTAAGCT
2751  GGACGTTTTT CAGTCTTACC AGAGTGCCAC ACATGAGCAG ACAAAAGCAT
2801  ATGAGGAACA GTTGGCCCAA TTGCAGCAGA AGTTGTTGGA TTTGGAAACA
2851  GAAAGAATTC TTCTTACCAA ACAGGTTGCT GAAGTTGAAG CACAAAAGAA
2901  AGATGTTTGT ACTGAGTTAG ATGCTCACAA AATCCAGGTG CAGGACTTAA
2951  TGCAGCAACT TGAAAAACAA AATAGTGAAA TGGAGCAAAA AGTAAAATCT
3001  TTAACCCAAG TCTATGAGTC CAAACTTGAA GATGGTAACA AAGAACAGGA
3051  ACAGACAAAG CAAATCTTGG TGGAAAAGGA AAATATGATT TTACAAATGA
3101  GAGAAGGACA GAAGAAAGAA ATTGAGATAC TCACACAGAA ATTGTCAGCC
3151  AAGGAGGACA GTATTCATAT TTTGAATGAG GAATATGAAA CCAAATTTAA
3201  AAACCAAGAA AAAAAGATGG AAAAAGTTAA GCAGAAAGCA AAGGAGATGC
3251  AAGAAACGTT AAAGAAAAAA TTACTGGATC AGGAAGCCAA ACTTAAGAAA
3301  GAGCTTGAAA ATACTGCTCT AGAGCTTAGT CAGAAAGAAA AACAGTTTAA
3351  TGCCAAAATG CTGGAAATGG CACAGGCTAA CTCAGCTGGA ATCAGTGATG
3401  CAGTGTCAAG ACTGGAAACA AACCAAAAAG AACAAATAGA AAGTCTTACT
3451  GAGGTTCATC GACGAGAACT CAATGATGTC ATATCAATCT GGGAAAAGAA
3501  ACTTAATCAG CAAGCTGAAG AACTTCAGGA AATACATGAA ATCCAATTAC
3551  AGGAAAAAGA ACAAGAGGTA GCAGAACTGA AACAAAAGAT CCTCCTATTT
3601  GGGTGTGAAA AAGAAGAGAT GAACAAGGAA ATAACATGGC TGAAGGAAGA
3651  AGGTGTTAAG CAGGATACAA CATTAAATGA ATTACAGGAA CAGTTAAAGC
3701  AGAAGTCTGC CCATGTGAAT TCTCTTGCAC AAGATGAAAC TAAACTGAAA
3751  GCTCATCTTG AAAAGCTAGA GGTTGACTTG AATAAGTCTC TGAAGGAAAA
3801  TACTTTTCTT CAAGAGCAGC TAGTTGAACT GAAGATGCTG GCAGAAGAAG
3851  ATAAGCGGAA GGTTTCTGAG TTGACTAGCA AGTTGAAAAC CACAGATGAA
3901  GAATTCCAGA GTTTGAAATC TTCACATGAA AAAAGTAACA AAAGCCTAGA
3951  GGACAAGAGC TTGGAATTTA AAAAACTGTC TGAGGAACTA GCGATTCAGC
4001  TAGATATTTG CTGTAAGAAA ACCGAAGCCT TATTAGAAGC TAAAACAAAT
4051  GAGCTAATCA ACATTAGTAG TAGTAAAACT AATGCCATTC TTTCTAGGAT
4101  TTCTCATTGT CAGCACCGTA CAACTAAAGT TAAGGAGGCA CTGTTAATTA
4151  AAACTTGCAC AGTTTCTGAA TTAGAAGCAC AACTTAGACA GTTGACAGAG
4201  GAGCAAAATA CACTAAATAT TTCTTTTCAA CAGGCTACTC ATCAGTTAGA
4251  AGAAAAAGAA AATCAAATTA AGAGCATGAA GGCTGATATT GAAAGTCTTG
4301  TAACAGAAAA AGAAGCCTTA CAGAAGGAAG GAGGCAATCA GCAACAGGCT
4351  GCTTCTGAAA AGGAGTCTTG TATAACACAG TTGAAGAAAG AGTTATCTGA
4401  AAACATCAAT GCTGTCACAT TGATGAAAGA AGAGCTTAAA GAAAAAAAAG
4451  TTGAGATTAG CAGTCTTAGT AAACAACTAA CTGATTTGAA TGTTCAGCTT
4501  CAAAATAGCA TCAGCCTATC CGAAAAAGAA GCAGCCATTT CATCACTAAG
4551  AAAGCAGTAT GATGAAGAAA AATGTGAATT GCTGGATCAG GTGCAAGATT
4601  TATCTTTTAA AGTTGACACT CTGAGTAAAG AGAAAATTTC TGCTCTTGAG
4651  CAGGTAGATG ACTGGTCCAA TAAATTCTCA GAATGGAAGA AGAAAGCACA
4701  GTCAAGATTT ACACAGCATC AAAACACTGT TAAAGAATTG CAGATCCAGC
4751  TTGAGTTAAA ATCAAAGGAA GCTTATGAAA AGGATGAGCA GATAAATTTA
4801  TTGAAGGAAG AGCTTGATCA GCAAAATAAA AGATTTGATT GTTTAAAGGG
4851  TGAAATGGAA GACGACAAGA GCAAGATGGA GAAAAAGGAG TCTAATTTAG
4901  AAACAGAGTT AAAGTCTCAA ACAGCAAGAA TTATGGAATT AGAGGACCAT
4951  ATTACCCAGA AAACTATTGA AATAGAGTCC TTAAATGAAG TTCTTAAAAA
5001  TTACAATCAA CAAAAGGATA TTGAACACAA AGAATTGGTT CAGAAACTTC
5051  AACATTTTCA AGAGTTAGGA GAAGAAAAGG ACAACAGGGT TAAAGAAGCT
5101  GAAGAAAAAA TCTTAACACT TGAAAACCAA GTTTATTCCA TGAAAGCTGA
5151  ACTTGAAACT AAGAAGAAAG AATTAGAACA TGTGAATTTA AGTGTGAAAA
5201  GCAAAGAGGA GGAGTTAAAG GCATTGGAAG ATAGGCTTGA GTCAGAAAGT
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5251  GCTGCAAAAT TAGCAGAGTT GAAGAGAAAA GCTGAACAAA AAATTGCTGC
5301  CATTAAGAAG CAGTTGTTAT CTCAAATGGA AGAGAAAGAA GAACAGTATA
5351  AAAAAGGTAC AGAAAGCCAT TTGAGTGAGC TAAATACAAA ATTGCAGGAA
5401  AGAGAAAGGG AAGTTCACAT CTTGGAAGAA AAACTTAAGT CAGTGGAAAG
5451  TTCACAGTCA GAAACATTAA TTGTACCCAG ATCAGCAAAA AATGTGGCAG
5501  CATATACTGA ACAAGAAGAA GCAGATTCCC AAGGCTGTGT GCAGAAGACA
5551  TATGAAGAAA AAATCAGTGT TTTACAAAGA AACTTAACTG AAAAAGAAAA
5601  GCTATTGCAG AGGGTAGGGC AGGAAAAAGA AGAGACAGTT TCTTCTCATT
5651  TTGAAATGCG ATGCCAATAC CAGGAGCGCT TAATAAAGCT AGAACATGCT
5701  GAGGCAAAGC AACATGAAGA TCAAAGTATG ATAGGTCATC TTCAAGAGGA
5751  GCTTGAAGAA AAAAACAAGA AATATTCCTT GATAGTAGCC CAGCATGTGG
5801  AAAAAGAAGG AGGTAAAAAT AACATACAGG CAAAGCAAAA CTTGGAAAAT
5851  GTGTTTGACG ACGTCCAGAA AACCCTCCAG GAGAAGGAAC TAACCTGTCA
5901  GATTTTGGAG CAAAAGATAA AAGAGCTGGA TTCCTGCTTA GTAAGACAGA
5951  AAGAAGTACA TAGAGTTGAA ATGGAAGAGT TGACCTCAAA ATATGAAAAA
6001  TTACAGGCTT TACAACAGAT GGATGGAAGA AATAAACCCA CAGAACTTTT
6051  GGAAGAAAAC ACTGAAGAAA AGTCCAAATC ACATTTGGTC CAACCCAAAT
6101  TGCTTAGTAA CATGGAAGCC CAGCACAATG ATCTGGAGTT TAAATTAGCC
6151  GGGGCAGAAC GGGAGAAACA GAAACTGGGC AAGGAGATTG TTAGATTGCA
6201  GAAAGACCTT CGAATGTTGA GAAAGGAGCA TCAGCAAGAA TTGGAAATAC
6251  TAAAGAAAGA ATATGATCAA GAAAGGGAAG AGAAAATCAA ACAGGAGCAG
6301  GAAGATCTTG AACTGAAGCA CAATTCCACA TTAAAACAGC TGATGAGGGA
6351  GTTTAATACA CAGCTGGCAC AAAAGGAACA AGAGCTGGAA ATGACCATAA
6401  AAGAAACTAT CAATAAGGCC CAGGAGGTGG AGGCTGAACT TTTAGAAAGC
6451  CATCAAGAAG AGACAAATCA GTTACTTAAA AAAATTGCTG AGAAAGATGA
6501  TGATCTAAAA CGAACAGCCA AAAGATATGA AGAAATCCTT GATGCTCGTG
6551  AAGAAGAAAT GACTGCAAAA GTAAGGGACC TGCAGACTCA ACTTGAGGAG
6601  CTGCAGAAGA AATACCAGCA AAAGCTAGAG CAGGAGGAGA ACCCTGGCAA
6651  TGATAATGTA ACAATTATGG AGCTACAGAC ACAGCTAGCA CAGAAGACGA
6701  CTTTAATCAG TGATTCGAAA TTGAAAGAGC AAGAGTTCAG AGAACAGATT
6751  CACAATTTAG AAGACCGTTT GAAGAAATAT GAAAAGAATG TATATGCAAC
6801  AACTGTGGGG ACACCTTACA AAGGTGGCAA TTTGTACCAT ACGGATGTCT
6851  CACTCTTTGG AGAACCTACC GAATTTGAGT ATTTGCGAAA AGTGCTTTTT
6901  GAGTATATGA TGGGTCGTGA GACTAAGACC ATGGCAAAAG TTATAACCAC
6951  CGTACTGAAG TTCCCTGATG ATCAGACTCA GAAAATTTTG GAAAGAGAAG
7001  ATGCTCGGCT GATGTTTACT TCACCTCGCA GTGGTATCTT CTGAGTAAAC
7051  CATCAGTCTG TGCTTAGTTA ACATGTGTCA TGGCTCCGAT CTTCATCTTG
7101  AAGAAGAGTG ACATTGGGTG ACTGCTGCTT GGAAAACTGT CCACACTTGC
7151  TACTCTTTGA GAATGAAGTT GTCATTCAGG GCCCCTCATG TAGCCAAAAG
7201  ACCAAGAAAA ATCTGGCCCA CAGATAAGTT GCAGACTGCC TTTAAAATAG
7251  ATTTTATCAG TGGAGAAATG GTGATAGTTT TTTCTTCAGT TTTCTCTTGG
7301  GAAGAGTTTT ATGTTGTTTA AAAGATATTT TGATAACTTA ACCTGCTTTA
7351  TGGGCTTACA TAATATTCCT TTCATCCATT CTTTTTAAAG AACGGCTTAC
7401  CTTTCCTATT TATTTTTAGG GTGATTTTTT AAAAAGACTT GTGCAATACA
7451  TTTTGAGGTG AAACTTAGTG GATTTTTTCT GATAAATTAG AGCATTTAAT
7501  TGACTATTTT ATTCAGGTTG ATCTGTTGAA TATTTGCTAA AGACCAGTTC
7551  TTTAAGCTAA GACATGTAAA AAATCCCAAA TGGCAGTACC TCATTGTTTA
7601  CTTAGCTTTT GTACTTATAT TTTTCAGAGG AAAAAACACT ACTGTAAATT
7651  GTGAATAGCC AATACATAAC TGTATTGTAT GCAAATCTGT GATTGTTGGC
7701  AGTGTCATCT CTGAGAAACA GATAAATAAA GTTTATTTAC TAT
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Fig. 11: SEQ ID NO. 8: amino acid sequence of human golgin-245, splice variant 4

Length: 2252 aa

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   1  MFKKLKQKIS EEQQQLQQAL APAQASSNSS TPTRMRSRTS SFTEQLDEGT
  51  PNRENASTHA SKSPDSVNGS EPSIPQSGDT QSFAQKLQLR VPSVESLFRS
 101  PIKESLFRSS SKESLVRTSS RESLNRLDLD SSTASFDPPS DMDSEAEDLV
 151  GNSDSLNKEQ LIQRLRRMER SLSSYRGKYS ELVTAYQMLQ REKKKLQGIL
 201  SQSQDKSLRR IAELREELQM DQQAKKHLQE EFDASLEEKD QYISVLQTQV
 251  SLLKQRLRNG PMNVDVLKPL PQLEPQAEVF TKEENPESDG EPVVEDGTSV
 301  KTLETLQQRV KRQENLLKRC KETIQSHKEQ CTLLTSEKEA LQEQLDERLQ
 351  ELEKIKDLHM AEKTKLITQL RDAKNLIEQL EQDKGMVIAE TKRQMHETLE
 401  MKEEEIAQLR SRIKQMTTQG EELREQKEKS ERAAFEELEK ALSTAQKTEE
 451  ARRKLKAEMD EQIKTIEKTS EEERISLQQE LSRVKQEVVD VMKKSSEEQI
 501  AKLQKLHEKE LARKEQELTK KLQTREREFQ EQMKVALEKS QSEYLKISQE
 551  KEQQESLALE ELELQKKAIL TESENKLRDL QQEAETYRTR ILELESSLEK
 601  SLQENKNQSK DLAVHLEAEK NKHNKEITVM VEKHKTELES LKHQQDALWT
 651  EKLQVLKQQY QTEMEKLREK CEQEKETLLK DKEIIFQAHI EEMNEKTLEK
 701  LDVKQTELES LSSELSEVLK ARHKLEEELS VLKDQTDKMK QELEAKMDEQ
 751  KNHHQQQVDS IIKEHEVSIQ RTEKALKDQI NQLELLLKER DKHLKEHQAH
 801  VENLEADIKR SEGELQQASA KLDVFQSYQS ATHEQTKAYE EQLAQLQQKL
 851  LDLETERILL TKQVAEVEAQ KKDVCTELDA HKIQVQDLMQ QLEKQNSEME
 901  QKVKSLTQVY ESKLEDGNKE QEQTKQILVE KENMILQMRE GQKKEIEILT
 951  QKLSAKEDSI HILNEEYETK FKNQEKKMEK VKQKAKEMQE TLKKKLLDQE
1001  AKLKKELENT ALELSQKEKQ FNAKMLEMAQ ANSAGISDAV SRLETNQKEQ
1051  IESLTEVHRR ELNDVISIWE KKLNQQAEEL QEIHEIQLQE KEQEVAELKQ
1101  KILLFGCEKE EMNKEITWLK EEGVKQDTTL NELQEQLKQK SAHVNSLAQD
1151  ETKLKAHLEK LEVDLNKSLK ENTFLQEQLV ELKMLAEEDK RKVSELTSKL
1201  KTTDEEFQSL KSSHEKSNKS LEDKSLEFKK LSEELAIQLD ICCKKTEALL
1251  EAKTNELINI SSSKTNAILS RISHCQHRTT KVKEALLIKT CTVSELEAQL
1301  RQLTEEQNTL NISFQQATHQ LEEKENQIKS MKADIESLVT EKEALQKEGG
1351  NQQQAASEKE SCITQLKKEL SENINAVTLM KEELKEKKVE ISSLSKQLTD
1401  LNVQLQNSIS LSEKEAAISS LRKQYDEEKC ELLDQVQDLS FKVDTLSKEK
1451  ISALEQVDDW SNKFSEWKKK AQSRFTQHQN TVKELQIQLE LKSKEAYEKD
1501  EQINLLKEEL DQQNKRFDCL KGEMEDDKSK MEKKESNLET ELKSQTARIM
1551  ELEDHITQKT IEIESLNEVL KNYNQQKDIE HKELVQKLQH FQELGEEKDN
1601  RVKEAEEKIL TLENQVYSMK AELETKKKEL EHVNLSVKSK EEELKALEDR
1651  LESESAAKLA ELKRKAEQKI AAIKKQLLSQ MEEKEEQYKK GTESHLSELN
1701  TKLQERE REV HILEEKLKSV ESSQSETLIV PRSAKNVAAY TEQEEADSQG
1751  CVQKTYEEKI SVLQRNLTEK EKLLQRVGQE KEETVSSHFE MRCQYQERLI
1801  KLEHAEAKQH EDQSMIGHLQ EELEEKNKKY SLIVAQHVEK EGGKNNIQAK
1851  QNLENVFDDV QKTLQEKELT CQILEQKIKE LDSCLVRQKE VHRVEMEELT
1901  SKYEKLQALQ QMDGRNKPTE LLEENTEEKS KSHLVQPKLL SNMEAQHNDL
1951  EFKLAGAERE KQKLGKEIVR LQKDLRMLRK EHQQELEILK KEYDQEREEK
2001  IKQEQEDLEL KHNSTLKQLM REFNTQLAQK EQELEMTIKE TINKAQEVEA
2051  ELLESHQEET NQLLKKIAEK DDDLKRTAKR YEEILDAREE EMTAKVRDLQ
2101  TQLEELQKKY QQKLEQEENP GNDNVTIMEL QTQLAQKTTL ISDSKLKEQE
2151  FREQIHNLED RLKKYEKNVY ATTVGTPYKG GNLYHTDVSL FGEPTEFEYL
2201  RKVLFEYMMG RETKTMAKVI TTVLKFPDDQ TQKILEREDA RLMFTSPRSG
2251  IF
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Fig. 12: SEQ ID NO. 9: nucleotide sequence of human golgin-245 cDNA, splice variant 4

Length: 7761 bp

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   1  GCAACGAAGG TACCATGGCC GTTGTCGTCG CCGCCGCGGC TCCCGGGGCT
  51  GGATGGGGGG CCGAGGCCAG CCAGTGGCAC CCGGAAGAAA GAGACGCGGC
 101  GGCGGCGACG CCGACACCCT CAGGACGAGT GTCCGGACTT GCCCACAGCC
 151  TCAAGGAGGA GACGGCGAGG CCCGGCCCCC GCTGTCCCTG GTGTAAAGAA
 201  GTCGCCGTAG CCGTCGCGGC CGGGACTCCC CGGGCTCTCG CCCTTCAGGT
 251  TTCGTTGACA CTCAGGACCG TACGTACGCT GCGCCATGTT CAAGAAACTG
 301  AAGCAAAAGA TCAGCGAGGA GCAGCAGCAG CTCCAGCAGG CGCTGGCTCC
 351  TGCTCAGGCG TCCTCCAATT CTTCAACACC AACAAGAATG AGGAGCAGGA
 401  CATCTTCATT TACAGAGCAA CTTGATGAAG GTACACCCAA TAGAGAGAAT
 451  GCATCTACTC ATGCCTCGAA ATCTCCTGAC AGTGTTAATG GAAGTGAACC
 501  AAGCATTCCT CAGTCAGGTG ACACACAGTC TTTTGCACAG AAGCTCCAGC
 551  TCCGGGTGCC CTCCGTGGAG TCTTTGTTTC GAAGTCCGAT AAAGGAATCT
 601  CTATTCCGGT CTTCTTCTAA AGAGTCTTTG GTACGAACAT CTTCCAGAGA
 651  ATCCCTGAAT CGACTTGACC TGGACAGTTC TACTGCCAGT TTTGATCCAC
 701  CCTCTGATAT GGATAGCGAG GCTGAAGACT TGGTAGGGAA TTCAGACAGT
 751  CTCAACAAAG AACAGTTGAT TCAGCGGTTG CGAAGAATGG AACGAAGCTT
 801  AAGTAGCTAC AGGGGAAAAT ATTCTGAGCT TGTTACAGCT TATCAGATGC
 851  TTCAGAGAGA GAAGAAAAAG CTACAAGGTA TATTAAGTCA GAGTCAGGAT
 901  AAATCACTTC GGAGAATAGC AGAATTAAGA GAGGAGCTCC AAATGGACCA
 951  GCAGGCAAAG AAACATCTGC AAGAGGAGTT TGATGCATCT TTAGAGGAGA
1001  AAGATCAGTA TATCAGTGTT CTCCAAACTC AGGTTTCTCT ACTGAAACAA
1051  CGATTACGAA ATGGCCCGAT GAATGTTGAT GTACTGAAAC CACTTCCTCA
1101  GCTGGAACCA CAGGCTGAAG TCTTCACTAA AGAAGAGAAT CCAGAAAGTG
1151  ATGGAGAGCC AGTAGTGGAA GATGGAACTT CTGTAAAAAC ACTGGAAACA
1201  CTCCAGCAAA GAGTGAAGCG TCAAGAGAAC CTACTTAAGC GTTGTAAGGA
1251  AACAATTCAG TCACATAAGG AACAATGTAC ACTATTAACT AGTGAAAAAG
1301  AAGCTCTGCA AGAACAACTG GATGAAAGAC TTCAAGAACT AGAAAAGATA
1351  AAGGACCTTC ATATGGCCGA GAAGACTAAA CTTATCACTC AGTTGCGTGA
1401  TGCAAAGAAC TTAATTGAAC AGCTTGAACA AGATAAGGGA ATGGTAATCG
1451  CAGAGACAAA ACGTCAGATG CATGAAACCC TGGAAATGAA AGAAGAAGAA
1501  ATTGCTCAAC TCCGTAGTCG CATCAAACAG ATGACTACCC AGGGAGAGGA
1551  ATTACGGGAA CAGAAAGAAA AGTCCGAAAG AGCTGCTTTT GAGGAACTTG
1601  AAAAAGCTTT GAGTACAGCC CAAAAAACAG AGGAAGCACG GAGAAAACTG
1651  AAGGCAGAAA TGGATGAACA AATAAAAACT ATCGAAAAAA CAAGTGAGGA
1701  GGAACGCATC AGTCTTCAAC AGGAATTAAG TCGGGTGAAA CAGGAGGTTG
1751  TTGATGTAAT GAAAAAATCC TCAGAAGAAC AAATTGCTAA GCTACAGAAG
1801  CTTCATGAAA AGGAGCTGGC CAGAAAAGAG CAGGAACTGA CCAAGAAGCT
1851  TCAGACCCGA GAAAGGGAAT TTCAGGAACA AATGAAAGTA GCTCTTGAAA
1901  AGAGTCAATC AGAATATTTG AAGATCAGCC AAGAAAAAGA ACAGCAAGAA
1951  TCTTTGGCCC TAGAAGAGTT AGAGTTGCAG AAAAAAGCAA TCCTCACAGA
2001  AAGTGAAAAT AAACTTCGGG ACCTTCAGCA AGAAGCAGAG ACTTACAGAA
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2101  AAAAATCAGT CAAAAGATTT GGCTGTTCAT CTGGAAGCTG AAAAAAATAA
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2201  AAAGCCTTAA GCATCAGCAG GATGCCCTTT GGACTGAAAA ACTCCAAGTC
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2301  ACAAGAAAAA GAAACATTGT TGAAAGACAA AGAGATTATC TTCCAGGCCC
2351  ACATAGAAGA AATGAATGAA AAGACTTTAG AAAAGCTTGA TGTGAAGCAA
2401  ACAGAACTAG AATCATTATC TTCTGAACTG TCAGAAGTAT TAAAAGCCCG
2451  TCACAAACTA GAAGAGGAAC TTTCTGTTCT GAAAGATCAA ACAGATAAAA
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2551  CAGCAAGTTG ACAGTATCAT TAAAGAACAC GAGGTATCTA TCCAGAGGAC
2601  TGAGAAGGCA TTAAAAGATC AAATTAATCA ACTTGAGCTT CTCTTGAAGG
2651  AAAGGGACAA GCATTTGAAA GAGCATCAGG CTCATGTAGA AAATTTAGAG
2701  GCAGATATTA AAAGGTCTGA AGGGGAACTC CAGCAGGCAT CTGCTAAGCT
2751  GGACGTTTTT CAGTCTTACC AGAGTGCCAC ACATGAGCAG ACAAAAGCAT
2801  ATGAGGAACA GTTGGCCCAA TTGCAGCAGA AGTTGTTGGA TTTGGAAACA
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4651  CAGGTAGATG ACTGGTCCAA TAAATTCTCA GAATGGAAGA AGAAAGCACA
4701  GTCAAGATTT ACACAGCATC AAAACACTGT TAAAGAATTG CAGATCCAGC
4751  TTGAGTTAAA ATCAAAGGAA GCTTATGAAA AGGATGAGCA GATAAATTTA
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4851  TGAAATGGAA GACGACAAGA GCAAGATGGA GAAAAAGGAG TCTAATTTAG
4901  AAACAGAGTT AAAGTCTCAA ACAGCAAGAA TTATGGAATT AGAGGACCAT
4951  ATTACCCAGA AAACTATTGA AATAGAGTCC TTAAATGAAG TTCTTAAAAA
5001  TTACAATCAA CAAAAGGATA TTGAACACAA AGAATTGGTT CAGAAACTTC
5051  AACATTTTCA AGAGTTAGGA GAAGAAAAGG ACAACAGGGT TAAAGAAGCT
5101  GAAGAAAAAA TCTTAACACT TGAAAACCAA GTTTATTCCA TGAAAGCTGA
5151  ACTTGAAACT AAGAAGAAAG AATTAGAACA TGTGAATTTA AGTGTGAAAA
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5251  GCTGCAAAAT TAGCAGAGTT GAAGAGAAAA GCTGAACAAA AAATTGCTGC
5301  CATTAAGAAG CAGTTGTTAT CTCAAATGGA AGAGAAAGAA GAACAGTATA
5351  AAAAAGGTAC AGAAAGCCAT TTGAGTGAGC TAAATACAAA ATTGCAGGAA
5401  AGAGAAAGGG AAGTTCACAT CTTGGAAGAA AAACTTAAGT CAGTGGAAAG
5451  TTCACAGTCA GAAACATTAA TTGTACCCAG ATCAGCAAAA AATGTGGCAG
5501  CATATACTGA ACAAGAAGAA GCAGATTCCC AAGGCTGTGT GCAGAAGACA
5551  TATGAAGAAA AAATCAGTGT TTTACAAAGA AACTTAACTG AAAAAGAAAA
5601  GCTATTGCAG AGGGTAGGGC AGGAAAAAGA AGAGACAGTT TCTTCTCATT
5651  TTGAAATGCG ATGCCAATAC CAGGAGCGCT TAATAAAGCT AGAACATGCT
5701  GAGGCAAAGC AACATGAAGA TCAAAGTATG ATAGGTCATC TTCAAGAGGA
5751  GCTTGAAGAA AAAAACAAGA AATATTCCTT GATAGTAGCC CAGCATGTGG
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5851  GTGTTTGACG ACGTCCAGAA AACCCTCCAG GAGAAGGAAC TAACCTGTCA
5901  GATTTTGGAG CAAAAGATAA AAGAGCTGGA TTCCTGCTTA GTAAGACAGA
5951  AAGAAGTACA TAGAGTTGAA ATGGAAGAGT TGACCTCAAA ATATGAAAAA
6001  TTACAGGCTT TACAACAGAT GGATGGAAGA AATAAACCCA CAGAACTTTT
6051  GGAAGAAAAC ACTGAAGAAA AGTCCAAATC ACATTTGGTC CAACCCAAAT
6101  TGCTTAGTAA CATGGAAGCC CAGCACAATG ATCTGGAGTT TAAATTAGCC
6151  GGGGCAGAAC GGGAGAAACA GAAACTGGGC AAGGAGATTG TTAGATTGCA
6201  GAAAGACCTT CGAATGTTGA GAAAGGAGCA TCAGCAAGAA TTGGAAATAC
6251  TAAAGAAAGA ATATGATCAA GAAAGGGAAG AGAAAATCAA ACAGGAGCAG
6301  GAAGATCTTG AACTGAAGCA CAATTCCACA TTAAAACAGC TGATGAGGGA
6351  GTTTAATACA CAGCTGGCAC AAAAGGAACA AGAGCTGGAA ATGACCATAA
6401  AAGAAACTAT CAATAAGGCC CAGGAGGTGG AGGCTGAACT TTTAGAAAGC
6451  CATCAAGAAG AGACAAATCA GTTACTTAAA AAAATTGCTG AGAAAGATGA
6501  TGATCTAAAA CGAACAGCCA AAAGATATGA AGAAATCCTT GATGCTCGTG
6551  AAGAAGAAAT GACTGCAAAA GTAAGGGACC TGCAGACTCA ACTTGAGGAG
6601  CTGCAGAAGA AATACCAGCA AAAGCTAGAG CAGGAGGAGA ACCCTGGCAA
6651  TGATAATGTA ACAATTATGG AGCTACAGAC ACAGCTAGCA CAGAAGACGA
6701  CTTTAATCAG TGATTCGAAA TTGAAAGAGC AAGAGTTCAG AGAACAGATT
6751  CACAATTTAG AAGACCGTTT GAAGAAATAT GAAAAGAATG TATATGCAAC
6801  AACTGTGGGG ACACCTTACA AAGGTGGCAA TTTGTACCAT ACGGATGTCT
6851  CACTCTTTGG AGAACCTACC GAATTTGAGT ATTTGCGAAA AGTGCTTTTT
6901  GAGTATATGA TGGGTCGTGA GACTAAGACC ATGGCAAAAG TTATAACCAC
6951  CGTACTGAAG TTCCCTGATG ATCAGACTCA GAAAATTTTG GAAAGAGAAG
7001  ATGCTCGGCT GATGTTTACT TCACCTCGCA GTGGTATCTT CTGAGTAAAC
7051  CATCAGTCTG TGCTTAGTTA ACATGTGTCA TGGCTCCGAT CTTCATCTTG
7101  AAGAAGAGTG ACATTGGGTG ACTGCTGCTT GGAAAACTGT CCACACTTGC
7151  TACTCTTTGA GAATGAAGTT GTCATTCAGG GCCCCTCATG TAGCCAAAAG
7201  ACCAAGAAAA ATCTGGCCCA CAGATAAGTT GCAGACTGCC TTTAAAATAG
7251  ATTTTATCAG TGGAGAAATG GTGATAGTTT TTTCTTCAGT TTTCTCTTGG
7301  GAAGGAGTTT TATGTTGTTT AAAAGATATT TTGATAACTT AACCTGCTTT
7351  ATGGGCTTAC ATAATATTCC TTTCATCCAT TCTTTTTAAA GAACGGCTTA
7401  CCTTTCCTAT TTATTTTTAG GGTGATTTTT TAAAAAGACT TGTGCAATAC
7451  ATTTTGAGGT GAAACTTAGT GGATTTTTTC TGATAAATTA GAGCATTTAA
7501  TTGACTATTT TATTCAGGTT GATCTGTTGA ATATTTGCTA AAGACCAGTT
7551  CTTTAAGCTA AGACATGTAA AAAATCCCAA ATGGCAGTAC CTCATTGTTT
7601  ACTTAGCTTT TGTACTTATA TTTTTCAGAG GAAAAAACAC TACTGTAAAT
7651  TGTGAATAGC CAATACATAA CTGTATTGTA TGCAAATCTG TGATTGTTGG
7701  CAGTGTCATC TCTGAGAAAC AGATAAATAA AGTTTATTTA CTATAAAAAA
7751  AAAAAAAAAA G
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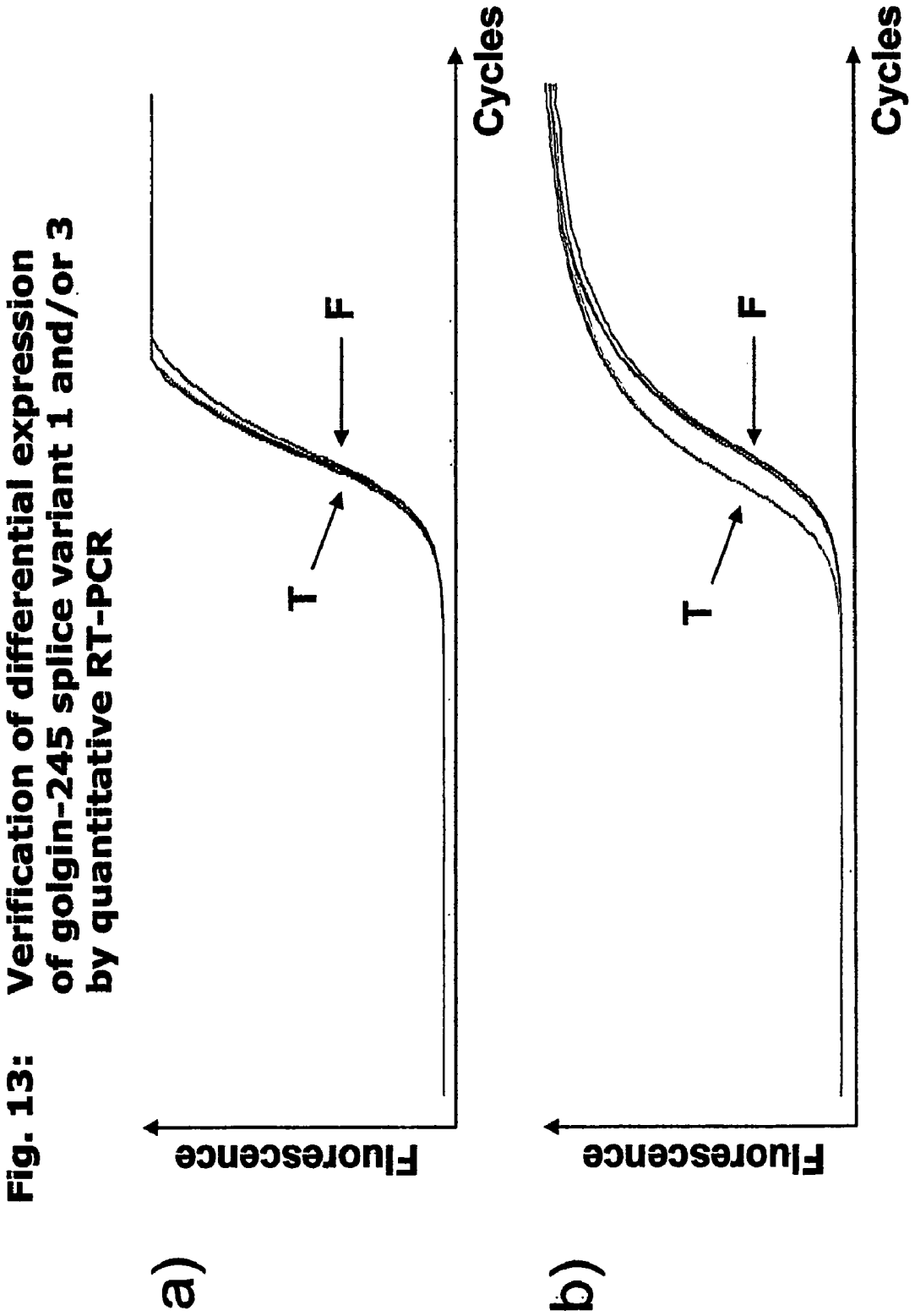


Fig. 13: Verification of differential expression of golgin-245 splice variant 1 and/or 3 by quantitative RT-PCR

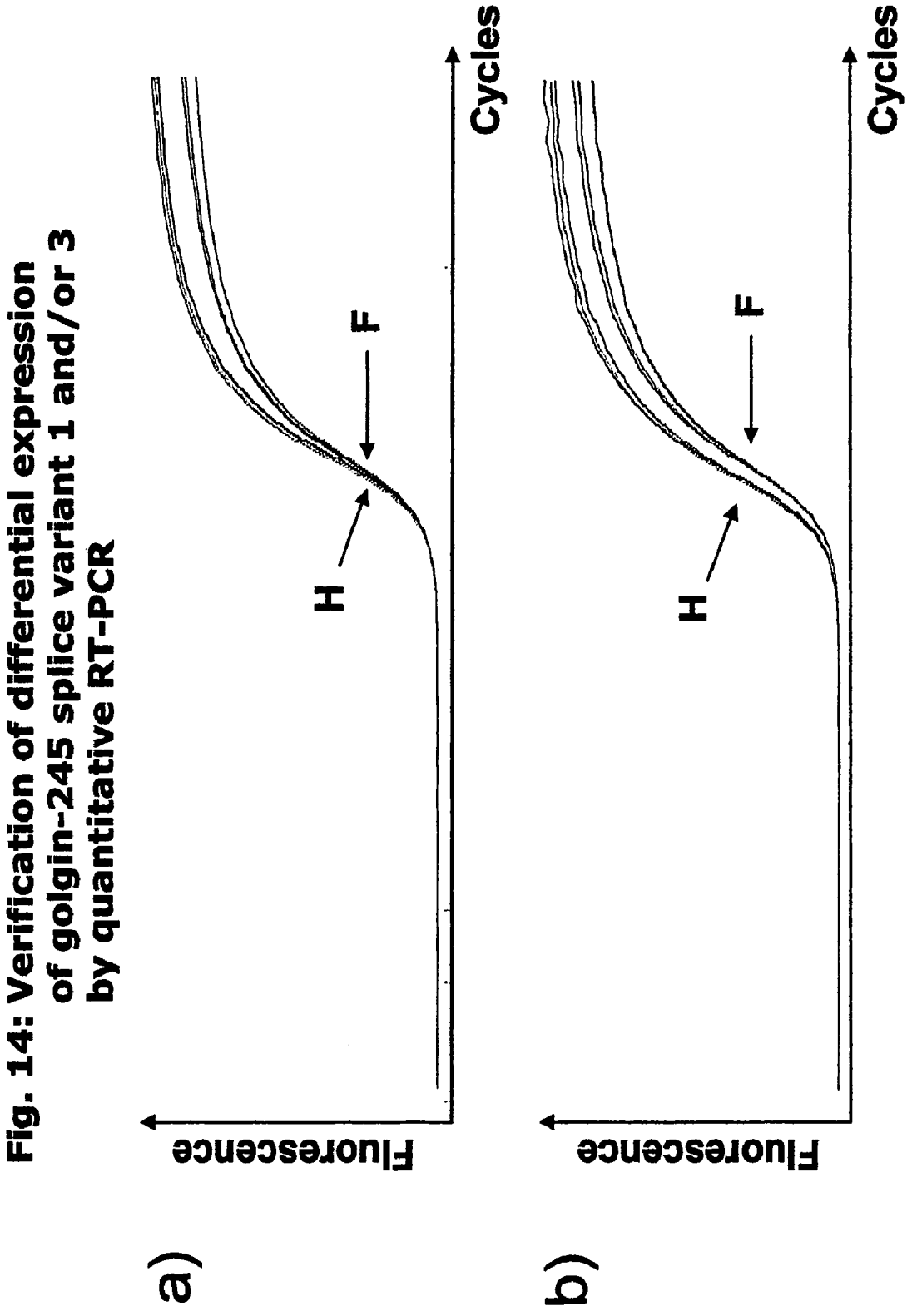


Fig. 14: Verification of differential expression of golgin-245 splice variant 1 and/or 3 by quantitative RT-PCR

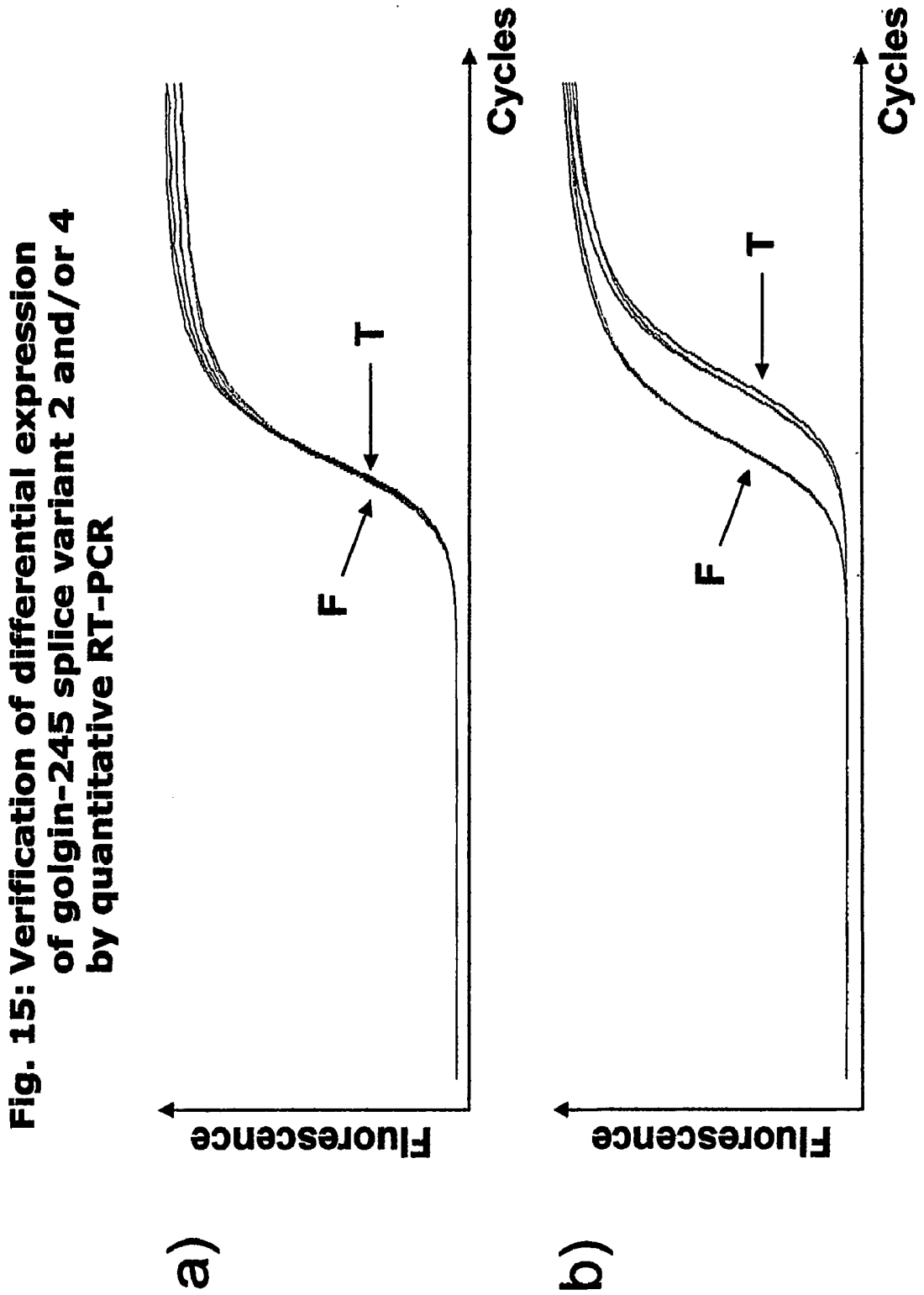


Fig. 15: Verification of differential expression of golgin-245 splice variant 2 and/or 4 by quantitative RT-PCR

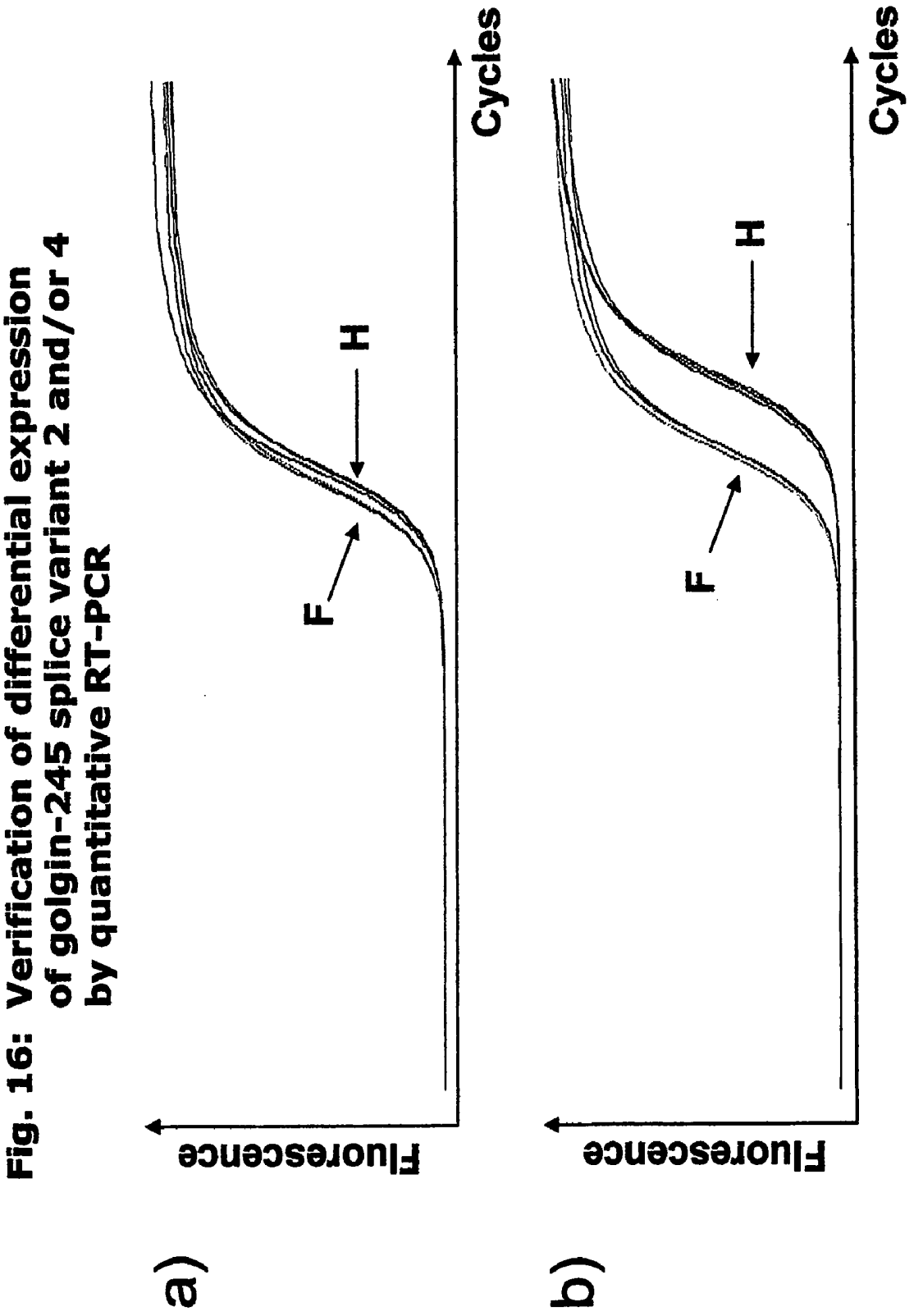
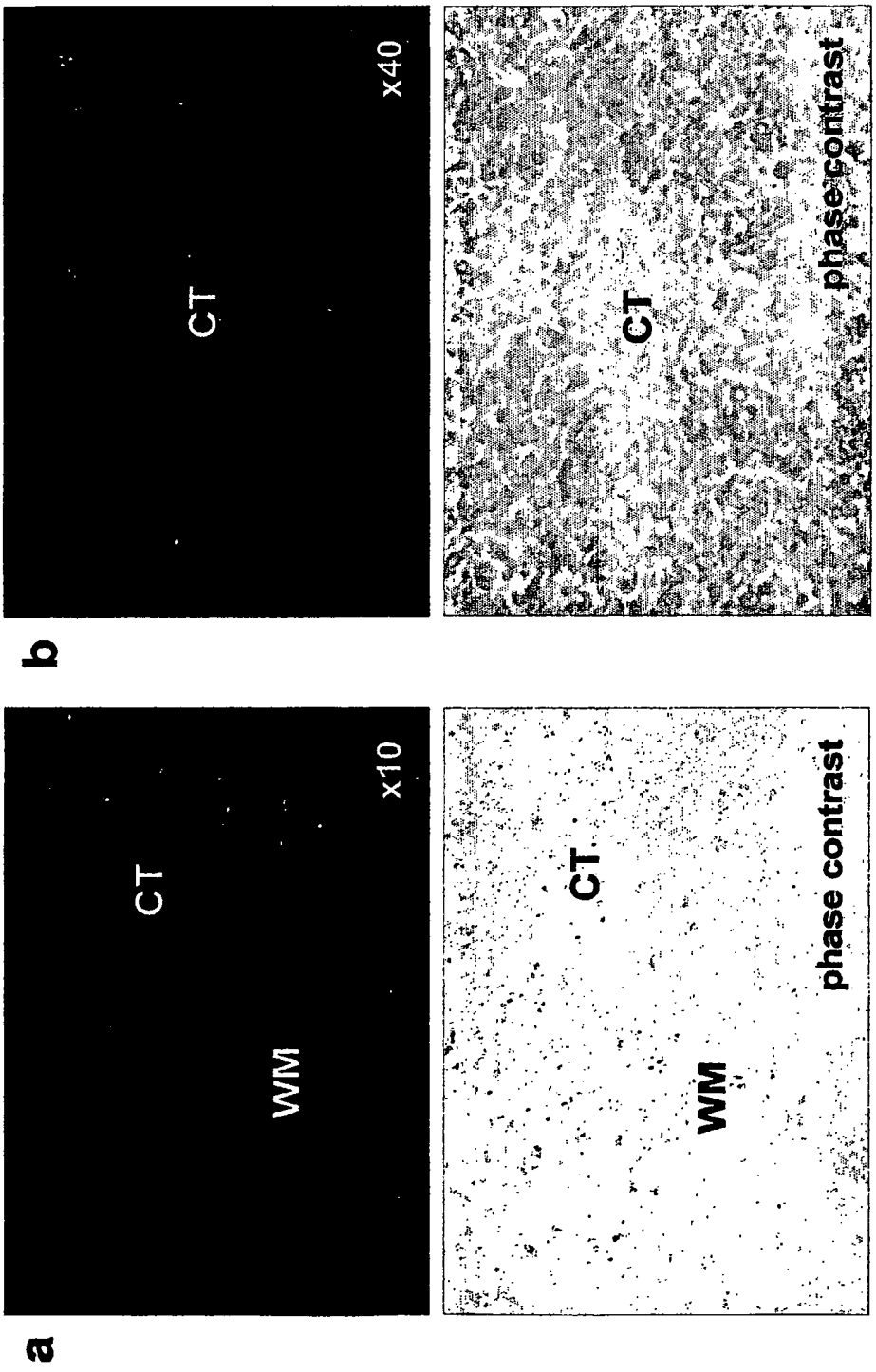


Fig. 16: Verification of differential expression of golgin-245 splice variant 2 and/or 4 by quantitative RT-PCR

Fig. 17: Images of the human cerebral cortex labeled with anti-golgin-245 monoclonal antibody and with DAPI



DIAGNOSTIC AND THERAPEUTIC USE OF A GOLGI PROTEIN FOR NEURODEGENERATIVE DISEASES

[0001] The present invention relates to methods of diagnosing, prognosticating and monitoring the progression of neurodegenerative diseases in a subject. Furthermore, methods of therapy control and screening for modulating agents of neurodegenerative diseases are provided. The invention also discloses pharmaceutical compositions, kits, and recombinant animal models.

[0002] Neurodegenerative diseases, in particular Alzheimer's disease (AD), have a strongly debilitating impact on a patient's life. Furthermore, these diseases constitute an enormous health, social, and economic burden. AD is the most common neurodegenerative disease, accounting for about 70% of all dementia cases, and it is probably the most devastating age-related neurodegenerative condition affecting about 10% of the population over 65 years of age and up to 45% over age 85 (for a recent review see Vickers et al., Progress in Neurobiology 2000, 60: 139-165). Presently, this amounts to an estimated 12 million cases in the US, Europe, and Japan. This situation will inevitably worsen with the demographic increase in the number of old people ("aging of the baby boomers") in developed countries. The neuropathological hallmarks that occur in the brains of individuals with AD are senile plaques, composed of amyloid-β protein, and profound cytoskeletal changes coinciding with the appearance of abnormal filamentous structures and the formation of neurofibrillary tangles.

[0003] The amyloid-β (Aβ) protein evolves from the cleavage of the amyloid precursor protein (APP) by different kinds of proteases. The cleavage by the β/γ-secretase leads to the formation of Aβ peptides of different lengths, typically a short more soluble and slow aggregating peptide consisting of 40 amino acids and a longer 42 amino acid peptide, which rapidly aggregates outside the cells, forming the characteristic amyloid plaques (Selkoe, *Physiological Rev* 2001, 81: 741-66; Greenfield et al., *Frontiers Bioscience* 2000, 5: D72-83). Two types of plaques, diffuse plaques and neuritic plaques, can be detected in the brain of AD patients, the latter ones being the classical, most prevalent type. They are primarily found in the cerebral cortex and hippocampus. The neuritic plaques have a diameter of 50 μm to 200 μm and are composed of insoluble fibrillar amyloids, fragments of dead neurons, of microglia and astrocytes, and other components such as neurotransmitters, apolipoprotein E, glycosaminoglycans, α1-antichymotrypsin and others. The generation of toxic Aβ deposits in the brain starts very early in the course of AD, and it is discussed to be a key player for the subsequent destructive processes leading to AD pathology. The other pathological hallmarks of AD are neurofibrillary tangles (NFTs) and abnormal neurites, described as neuropil threads (Braak and Braak, *Acta Neuropathol* 1991, 82: 239-259). NFTs emerge inside neurons and consist of chemically altered tau, which forms paired helical filaments twisted around each other. Along the formation of NFTs, a loss of neurons can be observed. It is discussed that said neuron loss may be due to a damaged microtubule-associated transport system (Johnson and Jenkins, *J Alzheimers Dis* 1996, 1: 38-58; Johnson and Hartigan, *J Alzheimers Dis* 1999, 1: 329-351). The appearance of neurofibrillary tangles and their increasing number correlates well with the clinical severity of AD (Schmitt et al., *Neurology* 2000, 55: 370-376).

[0004] AD is a progressive disease that is associated with early deficits in memory formation and ultimately leads to the complete erosion of higher cognitive function. The cognitive disturbances include among other things memory impairment, aphasia, agnosia and the loss of executive functioning. A characteristic feature of the pathogenesis of AD is the selective vulnerability of particular brain regions and subpopulations of nerve cells to the degenerative process. Specifically, the temporal lobe region and the hippocampus are affected early and more severely during the progression of the disease. On the other hand, neurons within the frontal cortex, occipital cortex, and the cerebellum remain largely intact and are protected from neurodegeneration (Terry et al., *Annals of Neurology* 1981, 10: 184-92).

[0005] The age of onset of AD may vary within a range of 50 years, with early-onset AD occurring in people younger than 65 years of age, and late-onset of AD occurring in those older than 65 years. About 10% of all AD cases suffer from early-onset AD, with only 1-2% being familial, inherited cases.

[0006] Currently, there is no cure for AD, nor is there an effective treatment to halt the progression of AD or even to diagnose AD ante-mortem with high probability. Several risk factors have been identified that predispose an individual to develop AD, among them most prominently the epsilon 4 allele of the three different existing alleles (epsilon 2, 3, and 4) of the apolipoprotein E gene (ApoE) (Strittmatter et al., *Proc Natl Acad Sci USA* 1993, 90: 1977-81; Roses, *Ann NY Acad Sci* 1998, 855: 738-43). The polymorphic plasmaprotein ApoE plays a role in the intercellular cholesterol and phospholipid transport by binding low-density lipoprotein receptors, and it seems to play a role in neurite growth and regeneration. Efforts to detect further susceptibility genes and disease-linked polymorphisms, lead to the assumption that specific regions and genes on human chromosomes 10 and 12 may be associated with late-onset AD (Myers et al., *Science* 2000, 290: 2304-5; Bertram et al., *Science* 2000, 290: 2303; Scott et al., *Am J Hum Genet* 2000, 66: 922-32). Although there are rare examples of early-onset AD which have been attributed to genetic defects in the genes for amyloid precursor protein (APP) on chromosome 21, presenilin-1 on chromosome 14, and presenilin-2 on chromosome 1, the prevalent form of late-onset sporadic AD is of hitherto unknown etiologic origin. The mutations found to date account for only half of the familial AD cases, which is less than 2% of all AD patients. The late onset and complex pathogenesis of neurodegenerative disorders pose a formidable challenge to the development of therapeutic and diagnostic agents. It is crucial to expand the pool of potential drug targets and diagnostic markers. It is therefore an object of the present invention to provide insight into the pathogenesis of neurological diseases and to provide methods, materials, agents, compositions, and animal models which are suited inter alia for the diagnosis and development of a treatment of these diseases. This object has been solved by the features of the independent claims. The subclaims define preferred embodiments of the present invention.

[0007] The Golgi-complex is an intracellular network which was first described in 1898. It has been shown to

function as an organelle responsible for the processing, transporting and sorting of intracellular and secreted proteins (reviewed in Nilsson and Warren, *Curr. Opin. Cell Biol.* 1994, 6: 517-521). Localized at the perinuclear site of cells, the Golgi-apparatus can be described as stacks of membranous cisternae which form functionally distinct networks. Briefly, membrane proteins are routed via the endoplasmic reticulum in vesicles through the cis-, medial- and trans-Golgi network and are then transported to their intracellular destination. The transport vesicles which mediate the transport bud from donor membranes and are transported to and fused with an acceptor membrane. The control of these events so far is poorly understood although several proteins have been characterized which play important roles in the targeting and transport of the vesicles, among them being coating proteins (COPs), adaptins, GTP-binding proteins, ADP-ribosylation factors (ARFs), and resident proteins. Several auto-antigens that are responsible for autoimmune diseases have been shown to be integral parts of the Golgi-apparatus. Such diseases are Sjögren's disease, rheumatoid arthritis or systemic lupus erythematosus (see review by Chan and Frizler, *Electr. J. Biotechn.* 1998, 1: 1-10). Common to those diseases is the fact that the auto-antigens represent a class of proteins with extended coiled coil domains and non alpha-helical domains at their N- and C-termini. So far, several Golgi auto-antigens are known which are referred to as golgins, such as golgin-95/GM130, golgin-97, golgin-256, golgin-160/GCP170, giantin/macrogolgin/GCP372, and golgin-245/p230. Currently, it is postulated that the golgins form intermolecular complexes that in concert with other proteins serve as docking stations for vesicles and are important for guiding the vesicles through the Golgi-apparatus.

[**0008**] Golgin-245, also referred to as p230, trans-Golgi p230, golga4, or golgi autoantigen, was first identified by antibodies derived from a patient suffering from Sjögren's syndrome (Kooy et al., *J. Biol. Chem* 1992, 267: 20255-20263). Indirect immunofluorescence analysis revealed that the protein is localized at the Golgi-apparatus, and it has been hypothesized that the protein plays an important role in compartmentalization of the Golgi-apparatus or in sorting and transport of proteins. Subsequently, golgin-245 was cloned and molecularly characterised by two independent groups (Fritzler et al., *J. Biol. Chem.* 1995, 270: 31263-31268; Erlich et al., *J. Biol. Chem.* 1996, 271: 8328-8337). The proteins described in these two studies have been shown to be identical except for an additional 145 amino acids at the N-terminus of the longer isoform. It turned out that the longer isoform of the protein is encoded by an open reading frame of 6693 base pairs and is comprised of 2230 amino acids, resulting in a molecular weight of ~261 kDa (GenBank accession number U41740; 7695 bp mRNA). Two alternatively spliced mRNAs of approximately 7.7 kb have been detected which differ by 21-base pair and 63-base pair inserts in the 3'-region of the gene. The gene coding for golgin-245 has been mapped to chromosome 6p12-22 (Erlich et al., ibid). Secondary structure analysis predicts an extraordinary high level of coiled-coil elements, and it has been speculated that these regions might mediate multimerization or the induction of conformational changes as shown for other coiled-coil proteins. The protein is very hydrophilic and shares a 17-20% homology with other coiled-coil proteins such as kinesin related microtubule motor proteins. In addition, homology has been observed with the granin family of proteins which are present in the secretory granules of neuroendocrine cells (Erlich et al., ibid).

[**0009**] Golgin-245 has been shown to be associated with vesicles budding from the trans-Golgi network (Gleeson et al., *J. Cell Sci.* 1996, 109: 2811-2821). The protein faces the intracellular compartment and recycles between cytosol and trans-Golgi derived vesicles. Golgin-245 is found primarily on a defined subset of these vesicles and might play a role in the assembly of said vesicles.

[**0010**] The Golgi-targeting sequence has been narrowed down to a stretch of 42 amino acids located at the C-terminus of golgin-245 (Kjer-Nielssen et al., *J. Cell Sci.* 1999, 112: 1645-1654). This domain is highly homologous within the golgin-family of proteins and is characterized by a conserved tyrosine residue within said stretch (Munro and Nichols, *Curr. Biol.* 1999, 9: 377-380). The GRIP-domain has also been shown to bind to rab6, a member of a class of proteins thought to regulate vesicle docking and membrane-tethering (Barr, *Curr. Biol.* 1999, 9: 381-384). The Golgin-family of proteins has only recently been assigned a role in maintaining the structural scaffold which is responsible for the integrity of the Golgi-apparatus (Seeman et al., *Nature* 2000, 407: 1022-1026). According to that study, the golgins can be separated from Golgi-enzymes and are sufficient for a correct rebuilding of the Golgi-apparatus. Hence it is speculated that they may constitute a network by binding either directly or indirectly to the Golgi membranes, implying that the Golgi apparatus functions as an autonomous organelle rather than representing a temporary membraneous system being in equilibrium between endoplasmic reticulum and secretory vesicles. Golgin-245 has been found to bind to ADP-ribsoylation factor (ARF)-related proteins (ARL) (Van Valkenburgh et al., *J. Biol. Chem.* 2001, 276: 22826-22837). ARL-proteins share a 40-60% identity to ARFs, small GTP-binding proteins. However, ARLs are devoid of enzymatic activities, and it is speculated that they function as binding partners for golgin-245 at the Golgi apparatus.

[**0011**] Golgins are a target for caspases (Mancini et al., *J. Cell Biol.* 2000, 149: 603-612). In a recent report it has been proposed that apoptotic signals may be passed through the Golgi apparatus by the specific cleavage of golgin-160 by caspase-2. Since Golgi autoantigens in patients with systemic auto-immune diseases are frequently cleaved by caspases, and golgin-245 represents the major auto-antigen in Sjögren's disease, it might be speculated that golgin-245 may also play a role in apoptotic signal transduction.

[**0012**] The integrity of intracellular transport processes is a valuable target for the treatment of several disorders, among them neurological and neuro-degenerative disorders. It is a feature of the present invention to modulate the interaction of golgin-245 with its target molecules in order to influence processing, trafficking and sorting of intracellular and/or secreted proteins. Of special interest in this context is the fact that one of the key players of Alzheimer's disease, amyloid precursor protein (APP), matures during the secretory pathway through the Golgi apparatus, and it has been speculated that the proteolytic processing of APP, which yields the highly amyloidogenic Aβ42, takes place in the trans-Golgi compartment (Greenfield et al., *Proc. Natl. Acad. Sci.* 1999, 96: 742-747). To date, there are no drugs on

the market nor in clinical development which specifically and potently target proteins of the golgin family, in particular golgin-245.

[0013] In the present invention, using an unbiased and sensitive differential display approach, a transcription product of the gene coding for golgin-245 is detected in human brain samples. Importantly, the present invention discloses a dysregulation of golgin-245 transcripts in the inferior temporal lobe or in the hippocampus of brain samples taken from AD patients relative to frontal cortex samples. No such dysregulation is observed in corresponding samples from age-matched healthy controls. To date, no experiments have been described that demonstrate a relationship between the dysregulation of golgin-245 gene expression and the pathology of neurodegenerative disorders, in particular AD. Such a link, as disclosed in the present invention, offers new ways, inter alia, for the diagnosis and treatment of said disorders, in particular AD.

[0014] The singular forms "a", "an", and "the" as used herein and in the claims include plural reference unless the context dictates otherwise. For example, "a cell" means as well a plurality of cells, and so forth. The term "and/or" as used in the present specification and in the claims implies that the phrases before and after this term are to be considered either as alternatives or in combination. For instance, the wording "determination of a level and/or an activity" means that either only a level, or only an activity, or both a level and an activity are determined. The term "level" as used herein is meant to comprise a gage of, or a measure of the amount of, or a concentration of a transcription product, for instance an mRNA, or a translation product, for instance a protein or polypeptide. The term "activity" as used herein shall be understood as a measure for the ability of a transcription product or a translation product to produce a biological effect or a measure for a level of biologically active molecules. The term "activity" also refers to enzymatic activity. The terms "level" and/or "activity" as used herein further refer to gene expression levels or gene activity. Gene expression can be defined as the utilization of the information contained in a gene by transcription and translation leading to the production of a gene product. "Dysregulation" shall mean an upregulation or downregulation of gene expression. A gene product comprises either RNA or protein and is the result of expression of a gene. The amount of a gene product can be used to measure how active a gene is. The term "gene" as used in the present specification and in the claims comprises both coding regions (exons) as well as non-coding regions (e.g. non-coding regulatory elements such as promoters or enhancers, introns, leader and trailer sequences). The term "ORF" is an acronym for "open reading frame" and refers to a nucleic acid sequence that does not possess a stop codon in at least one reading frame and therefore can potentially be translated into a sequence of amino acids. "Regulatory elements" shall comprise inducible and non-inducible promoters, enhancers, operators, and other elements that drive and regulate gene expression. The term "fragment" as used herein is meant to comprise e.g. an alternatively spliced, or truncated, or otherwise cleaved transcription product or translation product. The term "derivative" as used herein refers to a mutant, or an RNA-edited, or a chemically modified, or otherwise altered transcription product, or to a mutant, or chemically modified, or otherwise altered translation product. For instance, a "derivative" may be generated by processes such as altered phosphorylation, or glycosylation, or acetylation, or lipidation, or by altered signal peptide cleavage or other types of maturation cleavage. These processes may occur post-translationally. The term "modulator" as used in the present invention and in the claims refers to a molecule capable of changing or altering the level and/or the activity of a gene, or a transcription product of a gene, or a translation product of a gene. Preferably, a "modulator" is capable of changing or altering the biological activity of a transcription product or a translation product of a gene. Said modulation, for instance, may be an increase or a decrease in enzyme activity, a change in binding characteristics, or any other change or alteration in the biological, functional, or immunological properties of said translation product of a gene. The terms "agent", "reagent", or "compound" refer to any substance, chemical, composition or extract that have a positive or negative biological effect on a cell, tissue, body fluid, or within the context of any biological system, or any assay system examined. They can be agonists, antagonists, partial agonists or inverse agonists of a target. Such agents, reagents, or compounds may be nucleic acids, natural or synthetic peptides or protein complexes, or fusion proteins. They may also be antibodies, organic or anorganic molecules or compositions, small molecules, drugs and any combinations of any of said agents above. They may be used for testing, for diagnostic or for therapeutic purposes. The terms "oligonucleotide primer" or "primer" refer to short nucleic acid sequences which can anneal to a given target polynucleotide by hybridization of the complementary base pairs and can be extended by a polymerase. They may be chosen to be specific to a particular sequence or they may be randomly selected, e.g. they will prime all possible sequences in a mix. The length of primers used herein may vary from 10 nucleotides to 80 nucleotides. "Probes" are short nucleic acid sequences of the nucleic acid sequences described and disclosed herein or sequences complementary therewith. They may comprise full length sequences, or fragments, derivatives, isoforms, or variants of a given sequence. The identification of hybridization complexes between a "probe" and an assayed sample allows the detection of the presence of other similar sequences within that sample. As used herein, "homolog or homology" is a term used in the art to describe the relatedness of a nucleotide or peptide sequence to another nucleotide or peptide sequence, which is determined by the degree of identity and/or similarity between said sequences compared. The term "variant" as used herein refers to any polypeptide or protein, in reference to polypeptides and proteins disclosed in the present invention, in which one or more amino acids are added and/or substituted and/or deleted and/or inserted at the N-terminus, and/or the C-terminus, and/or within the native amino acid sequences of the native polypeptides or proteins of the present invention. Furthermore, the term "variant" shall include any shorter or longer version of a polypeptide or protein. "Variants" shall also comprise a sequence that has at least about 80% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity with the amino acid sequences of the golgin-245 protein, of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, and SEQ ID NO. 8. "Variants" of a protein molecule include, for example, proteins with conservative amino acid substitutions in highly conservative regions. "Proteins and polypeptides" of the present invention include variants, fragments and chemical derivatives of

the protein comprising the amino acid sequences of golgin-245, of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, and SEQ ID NO. 8. They can include proteins and polypeptides which can be isolated from nature or be produced by recombinant and/or synthetic means. Native proteins or polypeptides refer to naturally-occurring truncated or secreted forms, naturally occurring variant forms (e.g. splice-variants) and naturally occurring allelic variants. The term "isolated" as used herein is considered to refer to molecules that are removed from their natural environment, i.e. isolated from a cell or from a living organism in which they normally occur, and that are separated or essentially purified from the coexisting components with which they are found to be associated in nature. This notion further means that the sequences encoding such molecules can be linked by the hand of man to polynucleotides, to which they are not linked in their natural state, and that such molecules can be produced by recombinant and/or synthetic means. Even if for said purposes those sequences may be introduced into living or non-living organisms by methods known to those skilled in the art, and even if those sequences are still present in said organisms, they are still considered to be isolated. In the present invention, the terms "risk", "susceptibility", and "predisposition" are tantamount and are used with respect to the probability of developing a neurodegenerative disease, preferably Alzheimer's disease.

[**0015**] The term 'AD' shall mean Alzheimer's disease. "AD-type neuropathology" as used herein refers to neuropathological, neurophysiological, histopathological and clinical hallmarks as described in the instant invention and as commonly known from state-of-the-art literature (see: Iqbal, Swaab, Winblad and Wisniewski, *Alzheimer's Disease and Related Disorders* (Etiology, Pathogenesis and Therapeutics), Wiley & Sons, New York, Weinheim, Toronto, 1999; Scinto and Daffner, *Early Diagnosis of Alzheimer's Disease*, Humana Press, Totowa, N.J., 2000; Mayeux and Christen, *Epidemiology of Alzheimer's Disease: From Gene to Prevention*, Springer Press, Berlin, Heidelberg, N.Y., 1999; Younkin, Tanzi and Christen, *Presenilins and Alzheimer's Disease*, Springer Press, Berlin, Heidelberg, N.Y., 1998).

[**0016**] Neurodegenerative diseases or disorders according to the present invention comprise Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Pick's disease, fronto-temporal dementia, progressive nuclear palsy, corticobasal degeneration, cerebro-vascular dementia, multiple system atrophy, argyrophilic grain dementia and other tauopathies, and mild-cognitive impairment. Further conditions involving neurodegenerative processes are, for instance, age-related macular degeneration, narcolepsy, motor neuron diseases, prion diseases, traumatic nerve injury and repair, and multiple sclerosis.

[**0017**] In one aspect, the invention features a method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease. The method comprises: determining a level, or an activity, or both said level and said activity of (i) a transcription product of a gene coding for golgin-245, and/or of (ii) a translation product of a gene coding for golgin-245, and/or of (iii) a fragment, or derivative, or variant of said transcription or translation product in a sample from said subject and comparing said level, and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

[**0018**] The invention also relates to the construction and the use of primers and probes which are unique to the nucleic acid sequences, or fragments, or variants thereof, as disclosed in the present invention. The oligonucleotide primers and/or probes can be labeled specifically with fluorescent, bioluminescent, magnetic, or radioactive substances. The invention further relates to the detection and the production of said nucleic acid sequences, or fragments and/or variants thereof, using said specific oligonucleotide primers in appropriate combinations. PCR-analysis, a method well known to those skilled in the art, can be performed with said primer combinations to amplify said gene specific nucleic acid sequences from a sample containing nucleic acids. Such sample may be derived either from healthy or diseased subjects. Whether an amplification results in a specific nucleic acid product or not, and whether a fragment of different length can be obtained or not, may be indicative for a neurodegenerative disease, in particular Alzheimer's disease. Thus, the invention provides nucleic acid sequences, oligonucleotide primers, and probes of at least 10 bases in length up to the entire coding and gene sequences, useful for the detection of gene mutations and single nucleotide polymorphisms in a given sample comprising nucleic acid sequences to be examined, which may be associated with neurodegenerative diseases, in particular Alzheimer's disease. This feature has utility for developing rapid DNA-based diagnostic tests, preferably also in the format of a kit.

[**0019**] In a further aspect, the invention features a method of monitoring the progression of a neurodegenerative disease in a subject. A level, or an activity, or both said level and said activity, of (i) a transcription product of a gene coding for golgin-245, and/or of (ii) a translation product of a gene coding for golgin-245, and/or of (iii) a fragment, or derivative, or variant of said transcription or translation product in a sample from said subject is determined. Said level and/or said activity is compared to a reference value representing a known disease or health status. Thereby the progression of said neurodegenerative disease in said subject is monitored . . .

[**0020**] In still a further aspect, the invention features a method of evaluating a treatment for a neurodegenerative disease, comprising determining a level, or an activity, or both said level and said activity of (i) a transcription product of a gene coding for golgin-245, and/or of (ii) a translation product of a gene coding for a golgin-245, and/or of (iii) a fragment, or derivative, or variamt of said transcription or translation product in a sample obtained from a subject being treated for said disease. Said level, or said activity, or both said level and said activity are compared to a reference value representing a known disease or health status, thereby evaluating the treatment for said neurodegenerative disease.

[**0021**] In a preferred embodiment of the herein claimed methods, kits, recombinant animals, molecules, assays, and uses of the instant invention, said gene coding for a golgin protein is the gene coding for the golgin protein golgin-245, also termed p230, trans-Golgi p230, golga4, or golgi autoantigen, herein also referred to as golgin-245 splice variant 2

(SEQ ID NO. 5, GenBank accession number: U41740), and coding for the splice variants golgin-245 splice variant 1 (SEQ ID NO. 3, constructed from GenBank accession numbers U41740 and U31906), golgin-245 splice variant 3 (SEQ ID NO. 7), and golgin-245 splice variant 4 (SEQ ID NO. 9). In the instant invention, the gene coding for said golgin-245 protein is also generally referred to as the golgin-245 gene, or golgin-245.

[0022] In another preferred embodiment of the herein claimed methods, kits, recombinant animals, molecules, assays, and uses of the instant invention, said golgin protein is the golgin protein golgin-245, also termed p230, trans-Golgi p230, golga4, or golgi autoantigen, herein also referred to as golgin-245 splice variant 2 (SEQ ID NO. 4, GenBank accession number: Q13439), the golgin protein golgin-245 splice variant 1 (SEQ ID NO. 2), the golgin protein golgin-245 splice variant 3 (SEQ ID NO. 6), and the golgin protein golgin-245 splice variant 4 (SEQ ID NO. 8). In the instant invention, said golgin protein is also generally referred to as the golgin-245 protein, or golgin-245.

[0023] In a further preferred embodiment of the herein claimed methods, kits, recombinant animals, molecules, assays, and uses of the instant invention, said neurodegenerative disease or disorder is Alzheimer's disease, and said subjects suffer from Alzheimer's disease.

[0024] The present invention discloses the detection and differential expression and regulation of the golgin-245 gene in specific brain regions of AD patients. Consequently, the golgin-245 gene and its corresponding transcription and translation products may have a causative role in the regional selective neuronal degeneration typically observed in AD. Alternatively, golgin-245 may confer a neuroprotective function to the remaining surviving nerve cells. Based on these disclosures, the present invention has utility for the diagnostic evaluation and prognosis as well as for the identification of a predisposition to a neurodegenerative disease, in particular AD. Furthermore, the present invention provides methods for the diagnostic monitoring of patients undergoing treatment for such a disease.

[0025] It is particularly preferred that said sample to be analyzed and determined is selected from the group comprising brain tissue or other tissues or body cells. The sample can also comprise cerebrospinal fluid or other body fluids including saliva, urine, blood, serum plasma, or mucus. Preferably, the methods of diagnosis, prognosis, monitoring the progression or evaluating a treatment for a neurodegenerative disease, according to the instant invention, can be practiced ex corpore, and such methods preferably relate to samples, for instance, body fluids or cells, removed, collected, or isolated from a subject or patient.

[0026] In further preferred embodiments, said reference value is that of a level, or an activity, or both said level and said activity of (i) a transcription product of a gene coding for golgin-245, and/or of (ii) a translation product of a gene coding for golgin-245, and/or of (iii) a fragment, or derivative, or variant of said transcription or translation product in a sample from a subject not suffering from said neurodegenerative disease.

[0027] In preferred embodiments, an alteration in the level and/or activity of a transcription product of the gene coding for golgin-245 and/or of a translation product of the gene coding for golgin-245 and/or of a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of becoming diseased with a neurodegenerative disease, particularly AD.

[0028] In preferred embodiments, measurement of the level of transcription products of a gene coding for golgin-245 is performed in a sample from a subject using a quantitative PCR-analysis with primer combinations to amplify said gene specific sequences from cDNA obtained by reverse transcription of RNA extracted from a sample of a subject. A Northern blot with probes specific for said gene can also be applied. It might further be preferred to measure transcription products by means of chip-based micro-array technologies. These techniques are known to those of ordinary skill in the art (see Sambrook and Russell, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2001; Schena M., *Microarray Biochip Technology*, Eaton Publishing, Natick, Mass., 2000). An example of an immunoassay is the detection and measurement of enzyme activity as disclosed and described in the patent application WO 02/14543.

[0029] Furthermore, a level and/or an activity of a translation product of a gene coding for golgin-245 and/or of a fragment, or derivative, or variant of said translation product, and/or a level of activity of said translation product and/or of a fragment, or derivative, or variant of said translation product, can be detected using an immunoassay, an activity assay, and/or a binding assay. These assays can measure the amount of binding between said protein molecule and an anti-protein antibody by the use of enzymatic, chromodynamic, radioactive, magnetic, or luminescent labels which are attached to either the anti-protein antibody or a secondary antibody which binds the anti-protein antibody. In addition, other high affinity ligands may be used. Immunoassays which can be used include e.g. ELISAs, Western blots and other techniques known to those of ordinary skill in the art (see Harlow and Lane, *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1999 and Edwards R, *Immunodiagnostics: A Practical Approach*, Oxford University Press, Oxford; England, 1999). All these detection techniques may also be employed in the format of microarrays, protein-arrays, antibody microarrays, tissue microarrays, electronic biochip or protein-chip based technologies (see Schena M., *Microarray Biochip Technology*, Eaton Publishing, Natick, Mass., 2000).

[0030] In a preferred embodiment, the level, or the activity, or both said level and said activity of (i) a transcription product of a gene coding for golgin-245, and/or of (ii) a translation product of a gene coding for golgin-245, and/or of (iii) a fragment, or derivative, or variant of said transcription or translation product in a series of samples taken from said subject over a period of time is compared, in order to monitor the progression of said disease. In further preferred embodiments, said subject receives a treatment prior to one or more of said sample gatherings. In yet another preferred embodiment, said level and/or activity is determined before and after said treatment of said subject.

[0031] In another aspect, the invention features a kit for diagnosing or prognosticating neurodegenerative diseases,

in particular AD, in a subject, or determining the propensity or predisposition of a subject to develop a neurodegenerative disease, in particular AD, said kit comprising:

[0032] (a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for golgin-245 (ii) reagents that selectively detect a translation product of a gene coding for golgin-245; and

[0033] (b) instruction for diagnosing, or prognosticating a neurodegenerative disease, in particular AD, or determining the propensity or predisposition of a subject to develop such a disease by

[0034] detecting a level, or an activity, or both said level and said activity, of said transcription product and/or said translation product of a gene coding for golgin-245, in a sample from said subject; and

[0035] diagnosing or prognosticating a neurodegenerative disease, in particular AD, or determining the propensity or predisposition of said subject to develop such a disease,

wherein a varied level, or activity, or both said level and said activity, of said transcription product and/or said translation product compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of said transcription product and/or said translation product similar or equal to a reference value representing a known disease status, indicates a diagnosis or prognosis of a neurodegenerative disease, in particular AD, or an increased propensity or predisposition of developing such a disease. The kit, according to the present invention, may be particularly useful for the identification of individuals that are at risk of developing a neurodegenerative disease, in particular AD. Consequently, the kit, according to the invention, may serve as a means for targeting identified individuals for early preventive measures or therapeutic intervention prior to disease onset, before irreversible damage in the course of the disease has been inflicted. Furthermore, in preferred embodiments, the kit featured in the invention is useful for monitoring a progression of a neurodegenerative disease, in particular AD in a subject, as well as monitoring success or failure of therapeutic treatment for such a disease of said subject.

[0036] In another aspect, the invention features a method of treating or preventing a neurodegenerative disease, in particular AD, in a subject comprising the administration to said subject in a therapeutically or prophylactically effective amount of an agent or agents which directly or indirectly affect a level, or an activity, or both said level and said activity, of (i) a gene coding for golgin-245, and/or (ii) a transcription product of a gene coding for golgin-245, and/or (iii) a translation product of a gene coding for golgin-245, and/or (iv) a fragment, or derivative, or variant of (i) to (iii). Said agent may comprise a small molecule, or it may also comprise a peptide, an oligopeptide, or a polypeptide. Said peptide, oligopeptide, or polypeptide may comprise an amino acid sequence of a translation product of a gene coding for golgin-245, or a fragment, or derivative, or a variant thereof. An agent for treating or preventing a neurodegenerative disease, in particular AD, according to the instant invention, may also consist of a nucleotide, an oligonucleotide, or a polynucleotide. Said oligonucleotide or polynucleotide may comprise a nucleotide sequence of the gene coding for golgin-245, either in sense orientation or in antisense orientation.

[0037] In preferred embodiments, the method comprises the application of per se known methods of gene therapy and/or antisense nucleic acid technology to administer said agent or agents. In general, gene therapy includes several approaches: molecular replacement of a mutated gene, addition of a new gene resulting in the synthesis of a therapeutic protein, and modulation of endogenous cellular gene expression by recombinant expression methods or by drugs. Gene-transfer techniques are described in detail (see e.g. Behr, *Acc Chem Res* 1993, 26: 274-278 and Mulligan, *Science* 1993, 260: 926-931) and include direct gene-transfer techniques such as mechanical microinjection of DNA into a cell as well as indirect techniques employing biological vectors (like recombinant viruses, especially retroviruses) or model liposomes, or techniques based on transfection with DNA coprecipitation with polycations, cell membrane pertubation by chemical (solvents, detergents, polymers, enzymes) or physical means (mechanic, osmotic, thermic, electric shocks). The postnatal gene transfer into the central nervous system has been described in detail (see e.g. Wolff, *Curr Opin Neurobiol* 1993, 3: 743-748).

[0038] In particular, the invention features a method of treating or preventing a neurodegenerative disease by means of antisense nucleic acid therapy, i.e. the down-regulation of an inappropriately expressed or defective gene by the introduction of antisense nucleic acids or derivatives thereof into certain critical cells (see e.g. Gillespie, *DN&P* 1992, 5: 389-395; Agrawal and Akhtar, *Trends Biotechnol* 1995, 13: 197-199; Crooke, *Biotechnology* 1992, 10: 882-6). Apart from hybridization strategies, the application of ribozymes, i.e. RNA molecules that act as enzymes, destroying RNA that carries the message of disease has also been described (see e.g. Barinaga, *Science* 1993, 262: 1512-1514). In preferred embodiments, the subject to be treated is a human, and therapeutic antisense nucleic acids or derivatives thereof are directed against transcripts of a gene coding for golgin-245. It is preferred that cells of the central nervous system, preferably the brain, of a subject are treated in such a way. Cell penetration can be performed by known strategies such as coupling of antisense nucleic acids and derivatives thereof to carrier particles, or the above described techniques. Strategies for administering targeted therapeutic oligo-deoxynucleotides are known to those of skill in the art (see e.g. Wickstrom, *Trends Biotechnol* 1992, 10: 281-287). In some cases, delivery can be performed by mere topical application. Further approaches are directed to intracellular expression of antisense RNA. In this strategy, cells are transformed ex vivo with a recombinant gene that directs the synthesis of an RNA that is complementary to a region of target nucleic acid. Therapeutical use of intracellularly expressed antisense RNA is procedurally similar to gene therapy. A recently developed method of regulating the intracellular expression of genes by the use of double-stranded RNA, known variously as RNA interference (RNAi), can be another effective approach for nucleic acid therapy (Hannon, *Nature* 2002, 418: 244-251).

[0039] In further preferred embodiments, the method comprises grafting donor cells into the central nervous system,

preferably the brain, of said subject, or donor cells preferably treated so as to minimize or reduce graft rejection, wherein said donor cells are genetically modified by insertion of at least one transgene encoding said agent or agents. Said transgene might be carried by a viral vector, in particular a retroviral vector. The transgene can be inserted into the donor cells by a nonviral physical transfection of DNA encoding a transgene, in particular by microinjection. Insertion of the transgene can also be performed by electroporation, chemically mediated transfection, in particular calcium phosphate transfection or liposomal mediated transfection (see Mc Celland and Pardee, *Expression Genetics: Accelerated and High-Throughput Methods*, Eaton Publishing, Natick, Mass., 1999).

[**0040**] In preferred embodiments, said agent for treating and preventing a neurodegenerative disease, in particular AD, is a therapeutic protein which can be administered to said subject, preferably a human, by a process comprising introducing subject cells into said subject, said subject cells having been treated in vitro to insert a DNA segment encoding said therapeutic protein, said subject cells expressing in vivo in said subject a therapeutically effective amount of said therapeutic protein. Said DNA segment can be inserted into said cells in vitro by a viral vector, in particular a retroviral vector.

[**0041**] Methods of treatment, according to the present invention, comprise the application of therapeutic cloning, transplantation, and stem cell therapy using embryonic stem cells or embryonic germ cells and neuronal adult stem cells, combined with any of the previously described cell- and gene therapeutic methods. Stem cells may be totipotent or pluripotent. They may also be organ-specific. Strategies for repairing diseased and/or damaged brain cells or tissue comprise (i) taking donor cells from an adult tissue. Nuclei of those cells are transplanted into unfertilized egg cells from which the genetic material has been removed. Embryonic stem cells are isolated from the blastocyst stage of the cells which underwent somatic cell nuclear transfer. Use of differentiation factors then leads to a directed development of the stem cells to specialized cell types, preferably neuronal cells (Lanza et al., *Nature Medicine* 1999, 9: 975-977), or (ii) purifying adult stem cells, isolated from the central nervous system, or from bone marrow (mesenchymal stem cells), for in vitro expansion and subsequent grafting and transplantation, or (iii) directly inducing endogenous neural stem cells to proliferate, migrate, and differentiate into functional neurons (Peterson D A, *Curr. Opin. Pharmacol.* 2002, 2: 34-42). Adult neural stem cells are of great potential for repairing damaged or diseased brain tissues, as the germinal centers of the adult brain are free of neuronal damage or dysfunction (Colman A, *Drug Discovery World* 2001, 7: 66-71).

[**0042**] In preferred embodiments, the subject for treatment or prevention, according to the present invention, can be a human, an experimental animal, e.g. a mouse or a rat, a domestic animal, or a non-human primate. The experimental animal can be an animal model for a neurodegenerative disorder, e.g. a transgenic mouse and/or a knock-out mouse with an AD-type neuropathology.

[**0043**] In a further aspect, the invention features a modulator of an activity, or a level, or both said activity and said level of at least one substance which is selected from the group consisting of (i) a gene coding for golgin-245, and/or (ii) a transcription product of a gene coding for a golgin-245, and/or (iii) a translation product of a gene coding for golgin-245, and/or (iv) a fragment, or derivative, or variant of (i) to (iii).

[**0044**] In an additional aspect, the invention features a pharmaceutical composition comprising said modulator and preferably a pharmaceutical carrier. Said carrier refers to a diluent, adjuvant, excipient, or vehicle with which the modulator is administered.

[**0045**] In a further aspect, the invention features a modulator of an activity, or a level, or both said activity and said level of at least one substance which is selected from the group consisting of (i) a gene coding for golgin-245, and/or (ii) a transcription product of a gene coding for golgin-245, and/or (iii) a translation product of a gene coding for golgin-245, and/or (iv) a fragment, or derivative, or variant of (i) to (iii) for use in a pharmaceutical composition.

[**0046**] In another aspect, the invention provides for the use of a modulator of an activity, or a level, or both said activity and said level of at least one substance which is selected from the group consisting of (i) a gene coding for golgin-245, and/or (ii) a transcription product of a gene coding for golgin-245 and/or (iii) a translation product of a gene coding for golgin-245, and/or (iv) a fragment, or derivative, or variant of (i) to (iii) for a preparation of a medicament for treating or preventing a neurodegenerative disease, in particular AD.

[**0047**] In one aspect, the present invention also provides a kit comprising one or more containers filled with a therapeutically or prophylactically effective amount of said pharmaceutical composition.

[**0048**] In a further aspect, the invention features a recombinant, non-human animal comprising a non-native gene sequence coding for golgin-245, or a fragment thereof, or a derivative thereof. The generation of said recombinant, non-human animal comprises (I) providing a gene targeting construct containing said gene sequence and a selectable marker sequence, and (ii) introducing said targeting construct into a stem cell of a non-human animal, and (iii) introducing said non-human animal stem cell into a non-human embryo, and (iv) transplanting said embryo into a pseudopregnant non-human animal, and (v) allowing said embryo to develop to term, and (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and (vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said gene is mis-expressed, or under-expressed, or over-expressed, and wherein said disruption or alteration results in said non-human animal exhibiting a predisposition to developing symptoms of neuropathology similar to a neurodegenerative disease, in particular AD. Strategies and techniques for the generation and construction of such an animal are known to those of ordinary skill in the art (see e.g. Capecchi, *Science* 1989, 244: 1288-1292 and Hogan et al., 1994, *Manipulating the Mouse Embryo: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Jackson and Abbott, *Mouse Genetics and Transgenics: A Practical Approach*, Oxford University Press, Oxford, England, 1999). It is preferred to make use of

such a recombinant non-human animal as an animal model for investigating neurodegenerative diseases, in particular Alzheimer's disease. Such an animal may be useful for screening, testing and validating compounds, agents and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

[0049] In another aspect, the invention features an assay for screening for a modulator of neurodegenerative diseases, in particular AD, or related diseases and disorders of one or more substances selected from the group consisting of (i) a gene coding for golgin-245, and/or (ii) a transcription product of a gene coding for golgin-245, and/or (iii) a translation product of a gene coding for golgin-245, and/or (iv) a fragment, or derivative, or variant of (i) to (iii). This screening method comprises (a) contacting a cell with a test compound, and (b) measuring the activity, or the level, or both the activity and the level of one or more substances recited in (i) to (iv), and (c) measuring the activity, or the level, or both the activity and the level of said substances in a control cell not contacted with said test compound, and (d) comparing the levels of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of said substances in the contacted cells indicates that the test compound is a modulator of said diseases and disorders.

[0050] In one further aspect, the invention features a screening assay for a modulator of neurodegenerative diseases, in particular AD, or related diseases and disorders of one or more substances selected from the group consisting of (i) a gene coding for golgin-245, and/or (ii) a transcription product of a gene coding for golgin-245, and/or (iii) a translation product of a gene coding for golgin-245, and/or (iv) a fragment, or derivative, or variant of (i) to (iii), comprising (a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders, and (b) measuring the activity and/or level of one or more substances recited in (i) to (iv), and (c) measuring the activity and/or level of said substances in a matched control animal which is equally predisposed to developing or has already developed symptoms of said diseases and to which animal no such test compound has been administered, and (d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of said diseases and disorders.

[0051] In a preferred embodiment, said test animal and/or said control animal is a recombinant, non-human animal which expresses a gene coding for golgin-245, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional regulatory element which is not the native golgin-245 gene transcriptional control regulatory element.

[0052] In another embodiment, the present invention provides a method for producing a medicament comprising the steps of (i) identifying a modulator of neurodegenerative diseases by a method of the aforementioned screening assays and (ii) admixing the modulator with a pharmaceutical carrier. However, said modulator may also be identifiable by other types of screening assays.

[0053] In another aspect, the present invention provides for an assay for testing a compound, preferably for screening a plurality of compounds, for inhibition of binding between a ligand and golgin-245 protein, or a fragment, or derivative, or variant thereof. Said screening assay comprises the steps of (i) adding a liquid suspension of said golgin-245 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers, and (ii) adding a compound or a plurality of compounds to be screened for said inhibition to said plurality of containers, and (iii) adding a detectable, preferably a fluorescently labelled ligand to said containers, and (iv) incubating said golgin-245 protein, or said fragment, or derivative, or variant thereof, and said compound or plurality of compounds, and said detectable, preferably fluorescently labelled ligand, and (v) measuring the amounts of fluorescence associated with said golgin-245 protein, or with said fragment, or derivative, or variant thereof, and (vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said golgin-245 protein, or said fragment, or derivative, or variant thereof. Instead of utilizing a fluorescently labelled ligand, it might in some aspects be preferred to use any other detectable label known to the person skilled in the art, e.g. radioactive labels, and detect it accordingly. Said method may be useful for the identification of novel compounds as well as for evaluating compounds which have been improved or otherwise optimized in their ability to inhibit the binding of a ligand to a gene product of a gene coding for golgin-245, or a fragment, or derivative, or variant thereof. One example of a fluorescent binding assay, in this case based on the use of carrier particles, is disclosed and described in patent application WO 00/52451. A further example is the competitive assay method as described in patent WO 02/01226. Preferred signal detection methods for screening assays of the instant invention are described in the following patent applications: WO 96/13744, WO 98/16814, WO 98/23942, WO 99/17086, WO 99/34195, WO 00/66985, WO 01/59436, WO 01/59416.

[0054] In one further embodiment, the present invention provides a method for producing a medicament comprising the steps of (i) identifying a compound as an inhibitor of binding between a ligand and a gene product of a gene coding for golgin-245 by the aforementioned inhibitory binding assay and (ii) admixing the compound with a pharmaceutical carrier. However, said compound may also be identifiable by other types of screening assays.

[0055] In another aspect, the invention features an assay for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to golgin-245 protein, or to a fragment, or derivative, or variant thereof. Said screening assay comprises (i) adding a liquid suspension of said golgin-245 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers, and (ii) adding a detectable, preferably a fluorescently labelled compound or a plurality of fluorescently labelled compounds to be screened for said binding to said plurality of containers, and (iii) incubating said golgin-245 protein, or said fragment, or derivative, or variant thereof, and said detectable, preferably fluorescently labelled compound or fluorescently labelled compounds, and (iv) measuring the amounts of fluorescence associated with said golgin-245 protein, or with said fragment, or derivative, or variant thereof, and (v) determining the degree of binding by one or more of said compounds to said golgin-245 protein, or said fragment, or derivative, or variant thereof. In this type of assay it might be preferred to use

a fluorescent label. However, any other type of detectable label might also be employed. Said method may be useful for the identification of novel compounds as well as for evaluating compounds which have been improved or otherwise optimized in their ability to bind to golgin-245, or a fragment, or derivative, or variant thereof.

[0056] In one further embodiment, the present invention provides a method for producing a medicament comprising the steps of (i) identifying a compound as a binder to a gene product of a gene coding for golgin-245 by the aforementioned binding assays and (ii) admixing the compound with a pharmaceutical carrier. However, said compound may also be identifiable by other types of screening assays.

[0057] In another embodiment, the present invention provides for a medicament obtainable by any of the methods according to the herein claimed screening assays. In one further embodiment, the instant invention provides for a medicament obtained by any of the methods according to the herein claimed screening assays.

[0058] The present invention features protein molecules shown in SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, and SEQ ID NO. 8, said protein molecules being translation products of the gene coding for golgin-245, or a fragment, or derivative, or variant thereof, for use as diagnostic targets for detecting a neurodegenerative disease, preferably Alzheimer's disease.

[0059] Furthermore, the present invention features protein molecules shown in SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, and SEQ ID NO. 8, said protein molecules being translation products of the gene coding for golgin-245, or a fragment, or derivative, or variant thereof, for use as screening targets for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

[0060] The present invention features an antibody which is specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for golgin-245, or a fragment, or derivative, or variant thereof. The immunogen may comprise immunogenic or antigenic epitopes or portions of a translation product of said gene, wherein said immunogenic or antigenic portion of a translation product is a polypeptide, and wherein said polypeptide elicits an antibody response in an animal, and wherein said polypeptide is immunospecifically bound by said antibody. Methods for generating antibodies are well known in the art (see Harlow et al., *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1988). The term "antibody", as employed in the present invention, encompasses all forms of antibodies known in the art, such as polyclonal, monoclonal, chimeric, recombinatorial, anti-idiotypic, humanized, or single chain antibodies, as well as fragments thereof (see Dubel and Breitling, *Recombinant Antibodies*, Wiley-Liss, New York, N.Y., 1999). Antibodies of the present invention are useful, for instance, in a variety of diagnostic and therapeutic methods, based on state-in-the-art techniques (see Harlow and Lane, *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1999 and Edwards R., *Immunodiagnostics: A Practical Approach*, Oxford University Press, Oxford, England, 1999) such as enzyme-immuno assays (e.g. enzyme-linked immunosorbent assay, ELISA), radioimmuno assays, chemoluminescence-immuno assays, Western-blot, immunoprecipitation and antibody microarrays. These methods involve the detection of translation products of a gene coding for golgin-245, or fragments, or derivatives, or variants thereof.

[0061] In a preferred embodiment of the present invention, said antibodies can be used for detecting the pathological state of a cell in a sample from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell. Preferably, the pathological state relates to a neurodegenerative disease, in particular to AD. Immunocytochemical staining of a cell can be carried out by a number of different experimental methods well known in the art. It might be preferred, however, to apply an automated method for the detection of antibody binding, wherein the determination of the degree of staining of a cell, or the determination of the cellular or subcellular staining pattern of a cell, or the topological distribution of an antigen on the cell surface or among organelles and other subcellular structures within the cell, are carried out according to the method described in U.S. Pat. No. 6,150,173.

[0062] Other features and advantages of the invention will be apparent from the following description of figures and examples which are illustrative only and not intended to limit the remainder of the disclosure in any way.

[0063] **FIG. 1** depicts the brain regions with selective vulnerability to neuronal loss and degeneration in AD. Primarily, neurons within the inferior temporal lobe, the entorhinal cortex, the hippocampus, and the amygdala are subject to degenerative processes in AD (Terry et al., *Annals of Neurology* 1981, 10:184-192). These brain regions are mostly involved in the processing of learning and memory functions. In contrast, neurons within the frontal cortex, the occipital cortex, and the cerebellum remain largely intact and preserved from neurodegenerative processes in AD. Brain tissues from the frontal cortex (F), the temporal cortex (T), and the hippocampus (H) of AD patients and healthy, age-matched control individuals were used for the herein disclosed examples. For illustrative purposes, the image of a normal healthy brain was taken from a publication by Strange (*Brain Biochemistry and Brain Disorders*, Oxford University Press, Oxford, 1992, p. 4).

[0064] **FIG. 2** discloses the initial identification of the differential expression of the gene coding for golgin-245 in a fluorescence differential display screen. The figure shows a clipping of a large preparative fluorescent differential display gel. PCR products from the frontal cortex (F) and the temporal cortex (T) of two healthy control subjects and six AD patients were loaded in duplicate onto a denaturing polyacrylamide gel (from left to right). PCR products were obtained by amplification of the individual cDNAs with the corresponding one-base-anchor oligonucleotide and the specific Cy3 labelled random primers. The arrow indicates the migration position where significant differences in intensity of the signals for a transcription product of the gene coding for golgin-245 derived from frontal cortex as compared to the signals derived from the temporal cortex of AD patients exist. The differential expression reflects an up-regulation of golgin-245 gene transcription in the temporal cortex compared to the frontal cortex of AD patients. Comparing the

signals derived from temporal cortex and frontal cortex of healthy non-AD control subjects with each other, no difference in signal intensity, i.e. no altered expression level can be detected.

[0065] **FIG. 3** depicts SEQ ID NO. 1, the nucleotide sequence of the 36 bp golgin-245 cDNA fragment, identified and obtained by fluorescence differential display and subsequent cloning.

[0066] **FIG. 4** outlines the sequence alignment of SEQ ID NO. 1, the 36 bp human golgin-245 cDNA fragment, with the nucleotide sequence of the human golgin-245 cDNA, GenBank accession number U41740 (nucleotides 5488 to 5523).

[0067] **FIG. 5** discloses SEQ ID NO. 2, the polypeptide sequence of human golgin-245 splice variant 1 comprising 2228 amino acids. The protein is deduced from a consensus cDNA sequence constructed from the nucleotides 1 to 6946 of GenBank accession number U41740 and the nucleotides 6276 to 6965 of GenBank accession number U31906. Golgin-245 splice variant 1 harbors several distinct functional domains which are situated as follows: amino acid residues 1 to 117 and 239 to 270 form proline-rich domains, amino acid residues 533 to 542 generate the granine signature, and the Golgi-targeting signal spans amino acids 2158-2228 containing the highly conserved tyrosine residue Y2177.

[0068] **FIG. 6** represents SEQ ID NO. 3, the nucleotide sequence of human golgin-245 splice variant 1 cDNA, comprising 7636 nucleotides, constructed from the nucleotides 1 to 6946 of GenBank accession number U41740 and the nucleotides 6276 to 6965 of GenBank accession number U31906.

[0069] **FIG. 7** discloses SEQ ID NO. 4, the polypeptide sequence of human golgin-245 splice variant 2, comprising 2230 amino acids (GenBank accession number Q13439). Golgin-245 splice variant 2 differs from the golgin-245 splice variant 1, SEQ ID NO. 2, in the C-terminal nine amino acids (amino acids 2222 to 2230). The Golgin-245 splice variant 2 harbors several distinct functional domains which are situated as follows: amino acid residues 1 to 117 and 239 to 270 form proline-rich domains, amino acid residues 533 to 542 generate the granine signature, and the Golgi-targeting signal spans amino acids 2158-2221 containing the highly conserved tyrosine residue Y2177.

[0070] **FIG. 8** represents SEQ ID NO. 5, the nucleotide sequence of human golgin-245 splice variant 2 cDNA (GenBank accession number U41740), comprising 7695 nucleotides.

[0071] **FIG. 9** discloses SEQ ID NO. 6, the polypeptide sequence of human golgin-245 splice variant 3, comprising 2250 amino acids. The protein differs from golgin-245 splice variant 1, SEQ ID NO. 2, in that it comprises additional 22 amino acids located at the N-terminus (amino acids 55 to 76). Golgin-245 splice variant 3 harbors several distinct functional domains which are situated as follows: amino acid residues 1 to 139 and 261 to 292 form proline-rich domains, amino acid residues 555 to 564 generate the granine signature, and the Golgi-targeting signal spans amino acids 2180-2250 containing the highly conserved tyrosine residue Y2199.

[0072] **FIG. 10** represents SEQ ID NO. 7, the nucleotide sequence of human golgin-245 splice variant 3 cDNA, comprising 7743 nucleotides.

[0073] **FIG. 11** discloses SEQ ID NO. 8, the polypeptide sequence of human golgin-245 splice variant 4, comprising 2252 amino acids. Golgin-245 splice variant 4 differs from the golgin-245 splice variant 2, SEQ ID NO. 4, in that it comprises additional 22 amino acids located at the N-terminus (amino acids 55 to 76). The Golgin-245 splice variant 4 harbors several distinct functional domains which are situated as follows: amino acid residues 1 to 139 and 261 to 292 form proline-rich domains, amino acid residues 555 to 564 generate the granine signature, and the Golgi-targeting signal spans amino acids 2180-2243 containing the highly conserved tyrosine residue Y2199.

[0074] **FIG. 12** represents SEQ ID NO. 9, the nucleotide sequence of human golgin-245 splice variant 4 cDNA, comprising 7761 nucleotides.

[0075] **FIGS. 13 and 14** illustrate the verification of the differential expression of the human golgin-245 gene, in particular of the golgin-245 splice variant 1 and/or golgin-245 splice variant 3, in AD brain tissues by quantitative RT-PCR analysis. Quantification of RT-PCR products from RNA samples collected from the frontal cortex (F) and the temporal cortex (T) of AD patients (**FIG. 13***b*) and samples from the frontal cortex (F) and the hippocampus (H) of AD patients (**FIG. 14***b*) was performed by the LightCycler rapid thermal cycling technique. Likewise, samples of healthy, age-matched control individuals were compared (**FIG. 13***a* for frontal cortex and temporal cortex, **FIG. 14***a* for frontal cortex and hippocampus). The data were normalized to the combined average values of a set of standard genes which showed no significant differences in their gene expression levels. Said set of standard genes consisted of genes for cyclophilin B, the ribosomal protein S9, the transferrin receptor, GAPDH, and beta-actin. The figures depict the kinetics of amplification by plotting the cycle number against the amount of amplified material as measured by its fluorescence. Note that the amplification kinetics of golgin-245 splice variant 1 and/or golgin-245 splice variant 3 cDNAs from both, the frontal and temporal cortices of a normal control individual, and from the frontal cortex and hippocampus of a normal control individual, respectively, during the exponential phase of the reaction are juxtaposed (**FIGS. 13***a* and **14***a*, arrowheads), whereas in Alzheimer's disease (**FIGS. 13***b* and **14***b*, arrowheads) there is a significant separation of the corresponding curves, indicating a differential expression of the gene coding for golgin-245, in particular of the golgin-245 splice variant 1 and/or golgin-245 splice variant 3, in the respective analyzed brain regions, preferably an up-regulation of a transcription product of the human golgin-245 gene, in particular of the golgin-245 splice variant 1 and/or golgin-245 splice variant 3, in the temporal cortex relative to frontal cortex, and in the hippocampus relative to the frontal cortex, respectively.

[0076] **FIGS. 15 and 16** illustrate the verification of the differential expression of the human golgin-245 gene, in particular of the golgin-245 splice variant 2 and/or golgin-245 splice variant 4, in AD brain tissues by quantitative RT-PCR analysis. Quantification of RT-PCR products from RNA samples collected from the frontal cortex (F) and the temporal cortex (T) of AD patients (**FIG. 15***b*) and samples from the frontal cortex (F) and the hippocampus (H) of AD patients (**FIG. 16***b*) was performed by the LightCycler rapid thermal cycling technique. Likewise, samples of healthy, age-matched control individuals were compared (**FIG. 15***a*

for frontal cortex and temporal cortex, **FIG. 16***a* for frontal cortex and hippocampus). The data were normalized to the combined average values of a set of standard genes which showed no significant differences in their gene expression levels. Said set of standard genes consisted of genes for cyclophilin B, the ribosomal protein S9, the transferrin receptor, GAPDH, and beta-actin. The figures depict the kinetics of amplification by plotting the cycle number against the amount of amplified material as measured by its fluorescence. Note that the amplification kinetics of golgin-245 splice variant 2 and/or golgin-245 splice variant 4 cDNAs from both, the frontal and temporal cortices of a normal control individual, and from the frontal cortex and hippocampus of a normal control individual, respectively, during the exponential phase of the reaction are juxtaposed (**FIGS. 15***a* and **16***a*, arrowheads), whereas in Alzheimer's disease (**FIGS. 15***b* and **16***b*, arrowheads) there is a significant separation of the corresponding curves, indicating a differential expression of the gene coding for golgin-245, in particular of the golgin-245 splice variant 2 and/or golgin-245 splice variant 4, in the respective analyzed brain regions, preferably an up-regulation of a transcription product of the human golgin-245 gene, in particular of the golgin-245 splice variant 2 and/or golgin-245 splice variant 4, in the frontal cortex relative to the temporal cortex, and in the frontal cortex relative to the hippocampus, respectively.

[**0077**] **FIG. 17** depicts human cerebral cortex labeled with anti-golgin-245 mouse monoclonal antibodies (red signals). Immunoreactivity of golgin-245 was detected in both the pre-central cortex (CT) and in the white matter (WM) (**FIG. 17***a*, low magnification) as perinuclear punctate staining in both neuronal and glial cells, suggesting a localization of golgin-245 on the Golgi stacks (**FIG. 17***b*, high magnification). Blue signals indicate nuclei stained with DAPI.

[**0078**] Table 1 lists the gene expression levels in the temporal cortex relative to the frontal cortex for the golgin-245 gene (splice variants 1 and/or 3) in seven AD patients, herein identified by internal reference numbers P010, P011, P012, P014, P016, P017, P019 (0.98 to 2.91 fold) and five healthy, age-matched control individuals, herein identified by internal reference numbers C005, C008, C011, C012, C014 (0.86 to 1.32 fold). The scatter diagram visualizes individual values of the temporal to frontal cortex regulation ratios in control samples (dots) and in AD patient samples (triangles), respectively.

[**0079**] Table 2 lists the gene expression levels in the hippocampus relative to the frontal cortex for the golgin-245 gene (splice variants 1 and/or 3) in six Alzheimer's disease patients, herein identified by internal reference numbers P010, P011, P012, P014, P016, P019 (1.00 to 2.16 fold) and three healthy, age-matched control individuals, herein identified by internal reference numbers C004, C005, C008 (1.04 to 1.98 fold). The scatter diagram visualizes individual values of the hippocampus to frontal cortex regulation ratios in control samples (dots) and in AD patient samples (triangles).

[**0080**] Table 3 lists the gene expression levels in the frontal cortex relative to the temporal cortex for the golgin-245 gene (splice variants 2 and/or 4) in seven AD patients, herein identified by internal reference numbers P010, P011, P012, P014, P016, P017, P019 (1.53 to 3.36 fold) and five healthy, age-matched control individuals, herein identified by internal reference numbers C005, C008, C011, C012, C014 (0.46 to 1.43 fold). The scatter diagram visualizes individual values of the frontal to temporal cortex regulation ratios in control samples (dots) and in AD patient samples (triangles). The values shown are reciprocal values according to the formula described herein (see below).

[**0081**] Table 4 lists the gene expression levels in the frontal cortex relative to the hippocampus for the golgin-245 gene (splice variants 2 and/or 4) in six Alzheimer's disease patients, herein identified by internal reference numbers P010, P011, P012, P014, P016, P019 (1.15 to 3.47 fold) and three healthy, age-matched control individuals, herein identified by internal reference numbers C004, C005, C008 (1.09 to 1.55 fold). The scatter diagram visualizes individual values of the frontal cortex to hippocampus regulation ratios in control samples (dots) and in AD patient samples (triangles). The values shown are reciprocal values according to the formula described herein (see below).

EXAMPLE I

(i) Brain Tissue Dissection from Patients with AD:

[**0082**] Brain tissues from AD patients and age-matched control subjects were collected within 6 hours post-mortem and immediately frozen on dry ice. Sample sections from each tissue were fixed in paraformaldehyde for histopathological confirmation of the diagnosis. Brain areas for differential expression analysis were identified (see **FIG. 1**) and stored at −80° C. until RNA extractions were performed.

(ii) Isolation of Total mRNA:

[**0083**] Total RNA was extracted from post-mortem brain tissue by using the RNeasy kit (Qiagen) according to the manufacturer's protocol. The accurate RNA concentration and the RNA quality were determined with the DNA LabChip system using the Agilent 2100 Bioanalyzer (Agilent Technologies). For additional quality testing of the prepared RNA, i.e. exclusion of partial degradation and testing for DNA contamination, specifically designed intronic GAPDH oligonucleotides and genomic DNA as reference control were utilised to generate a melting curve with the LightCycler technology as described in the supplied protocol by the manufacturer (Roche).

(iii) cDNA Synthesis and Identification of Differentially Expressed Genes by Fluorescence Differential Display (FDD):

[**0084**] In order to identify changes in gene expression in different tissues we employed a modified and improved differential display (DD) screening method. The original DD screening method is known to those skilled in the art (Liang and Pardee, *Science* 1995, 267: 1186-7). This technique compares two populations of RNA and provides clones of genes that are expressed in one population but not in the other. Several samples can be analyzed simultaneously and both up- and down-regulated genes can be identified in the same experiment. By adjusting and refining several steps in the DD method as well as modifying technical parameters, e.g. increasing redundancy, evaluating optimized reagents and conditions for reverse transcription of total RNA, optimizing polymerase chain reactions (PCR) and separation of the products thereof, a technique was' developed which allows for highly reproducible and sensitive results. The

applied and improved DD technique was described in detail by von der Kammer et al. (*Nucleic Acids Research* 1999, 27: 2211-2218). A set of 64 specifically designed random primers was developed (standard set) to achieve a statistically comprehensive analysis of all possible RNA species. Further, the method was modified to generate a preparative DD slab-gel technique, based on the use of fluorescently labelled primers. In the present invention, RNA populations from carefully selected post-mortem brain tissues (frontal and temporal cortex) of AD patients and age-matched control subjects were compared.

[**0085**] As starting material for the DD analysis we used total RNA, extracted as described above (ii). Equal amounts of 0.05 μg RNA each were transcribed into cDNA in 20 μl reactions containing 0.5 mM each dNTP, 1 μl Sensiscript Reverse Transcriptase and 1×RT buffer (Qiagen), 10 U RNase inhibitor (Qiagen) and 1 μM of either one-base-anchor oligonucleotides $HT_{11}A$, $HT_{11}G$ or $HT_{11}C$ (Liang et al., *Nucleic Acids Research* 1994, 22: 5763-5764; Zhao et al., *Biotechniques* 1995, 18: 842-850). Reverse transcription was performed for 60 min at 37° C. with a final denaturation step at 93° C. for 5 min. 2 μl of the obtained cDNA each was subjected to a polymerase chain reaction (PCR) employing the corresponding one-base-anchor oligonucleotide (1 μM) along with either one of the Cy3 labelled random DD primers (1 μM), 1×GeneAmp PCR buffer (Applied Biosystems), 1.5 mM $MgCl_2$ (Applied Biosystems), 2 μM dNTP-Mix (dATP, dGTP, dCTP, dTTP Amersham Pharmacia Biotech), 5% DMSO (Sigma), 1 U AmpliTaq DNA Polymerase (Applied Biosystems) in a 20 μl final volume. PCR conditions were set as follows: one round at 94° C. for 30 sec for denaturing, cooling 1° C./sec down to 40° C., 40° C. for 4 min for low-stringency annealing of primer, heating 1° C./sec up to 72° C., 72° C. for 1 min for extension. This round was followed by 39 high-stringency cycles: 94° C. for 30 sec, cooling 1° C./sec down to 60° C., 60° C. for 2 min, heating 1° C./sec up to 72° C., 72° C. for 1 min. One final step at 72° C. for 5 min was added to the last cycle (PCR cycler: Multi Cycler PTC 200, MJ Research). 8 μl DNA loading buffer were added to the 20 μl PCR product preparation, denatured for 5 min and kept on ice until loading onto a gel. 3.5 μl each were separated on 0.4 mm thick, 6%-polyacrylamide (Long Ranger)/7 M urea sequencing gels in a slab-gel system (Hitachi Genetic Systems) at 2000 V, 60 W, 30 mA, for 1 h 40 min. Following completion of the electrophoresis, gels were scanned with a FMBIO II fluorescence-scanner (Hitachi Genetic Systems), using the appropriate FMBIO II Analysis 8.0 software. A full-scale picture was printed, differentially expressed bands marked, excised from the gel, transferred into 1.5 ml containers, overlayed with 200 μl sterile water and kept at −20° C. until extraction.

[**0086**] Elution and reamplification of DD products: The differential bands were extracted from the gel by boiling in 200 μl H_2O for 10 min, cooling down on ice and precipitation from the supernatant fluids by using ethanol (Merck) and glycogen/sodium acetate (Merck) at −20° C. over night, and subsequent centrifugation at 13.000 rpm for 25 min at 4° C. Pellets were washed twice in ice-cold ethanol (80%), resuspended in 10 mM Tris pH 8.3 (Merck) and dialysed against 10% glycerol (Merck) for 1 h at room temperature on a 0.025 μm VSWP membrane (Millipore). The obtained preparations were used as templates for reamplification by 15 high-stringency cycles in 25-μl PCR mixtures containing the corresponding primer pairs as used for the DD PCR (see above) under identical conditions, with the exception of the initial round at 94° C. for 5 min, followed by 15 cycles of: 94° C. for 45 sec, 60° C. for 45 sec, ramp 1° C./sec to 70° C. for 45 sec, and one final step at 72° C. for 5 min.

[**0087**] Cloning and sequencing of DD products: Re-amplified cDNAs were analyzed with the DNA LabChip system (Agilent 2100 Bioanalyzer, Agilent Technologies) and ligated into the pCR-Blunt II-TOPO vector and transformed into *E. coli* Top10F' cells (Zero Blunt TOPO PCR Cloning Kit, Invitrogen) according to the manufacturer's instructions. Cloned cDNA fragments were sequenced by commercially available sequencing facilities. The result of one such FDD experiment for the golgin-245 gene is shown in **FIG. 2**.

(iv) Confirmation of Differential Expression by Quantitative RT-PCR:

[**0088**] Positive corroboration of differential expression of the golgin-245 gene was performed using the LightCycler technology (Roche). This technique features rapid thermal cyling for the polymerase chain reaction as well as real-time measurement of fluorescent signals during amplification and therefore allows for highly accurate quantification of RT-PCR products by using a kinetic, rather than an endpoint readout. The ratios of golgin-245 cDNA from the temporal cortex and frontal cortex, and from the hippocampus and frontal cortex, respectively, were determined (relative quantification).

[**0089**] First, a standard curve was generated to determine the efficiency of the PCR with specific primers for the golgin-245 splice variant 1 and/or splice variant 3 gene:

```
5'-AGATGCTCGGCTGATGTCATG-3'
and

5'-AAGCAGCAGTCACCCAATGTC-3'
```

[**0090**] and with specific primers for the golgin-245 splice variant 2 and/or splice variant 4 gene, respectively:

```
5'-ACCTCGCAGTGGTATCTTCTGAG-3'
and

5'-TCGGAGCCATGACACATGTT-3'.
```

[**0091**] PCR amplification (95° C. and 1 sec, 56° C. and 5 sec, and 72° C. and 5 sec) was performed in a volume of 20 μl containing LightCycler-FastStart DNA Master SYBR Green I mix (contains FastStart Taq DNA polymerase, reaction buffer, dNTP mix with dUTP instead of dTTP, SYBR Green I dye, and 1 mM $MgCl_2$; Roche), 0.5 μM primers, 2 μl of a cDNA dilution series (final concentration of 40, 20, 10, 5, 1 and 0.5 ng human total brain cDNA; Clontech) and, depending on the primers used, additional 3 mM $MgCl_2$. Melting curve analysis revealed a single peak with no visible primer dimers at approximately 82.5° C. for the golgin-245 splice variant 1 and/or splice variant 3 gene specific primers and at 80° C. for the golgin-245 splice variant 2 and/or splice variant 4 gene specific primers. Quality and size of the PCR product were determined with the DNA LabChip system (Agilent 2100 Bioanalyzer, Agilent Technologies). A single peak at the expected size of 69

bp for the golgin-245 splice variant 1 and/or splice variant 3 gene and at 67 bp for the golgin-245 splice variant 2 and/or splice variant 4 gene was observed in the electropherogram of the sample.

[0092] In an analogous manner, the PCR protocol was applied to determine the PCR efficiency of a set of reference genes which were selected as a reference standard for quantification. In the present invention, the mean value of five such reference genes was determined: (1) cyclophilin B, using the specific primers 5'-ACTGAAGCACTACGGGC-CTG-3' and 5'-AGCCGTTGGTGTCTTTGCC-3' except for $MgCl_2$ (an additional 1 mM was added instead of 3 mM). Melting curve analysis revealed a single peak at approximately 87° C. with no visible primer dimers. Agarose gel analysis of the PCR product showed one single band of the expected size (62 bp). (2) Ribosomal protein S9 (RPS9), using the specific primers 5'-GGTCAAATTTACCCTG-GCCA-3' and 5'-TCTCATCAAGCGTCAGCAGTTC-3' (exception: additional 1 mM $MgCl_2$ was added instead of 3 mM). Melting curve analysis revealed a single peak at approximately 85° C. with no visible primer dimers. Agarose gel analysis of the PCR product showed one single band with the expected size (62 bp). (3) beta-actin, using the specific primers 5'-TGGAACGGTGAAGGTGACA-3' and 5'-GGCAAGGGACTTCCTGTAA-3'. Melting curve analysis revealed a single peak at approximately 87° C. with no visible primer dimers. Agarose gel analysis of the PCR product showed one single band with the expected size (142 bp). (4) GAPDH, using the specific primers 5'-CGT-CATGGGTGTGAACCATG-3' and 5'-GCTAAGCAGTTG-GTGGTGCAG-3'. Melting curve analysis revealed a single peak at approximately 83° C. with no visible primer dimers. Agarose gel analysis of the PCR product showed one single band with the expected size (81 bp). (5) Transferrin receptor TRR, using the specific primers 5'-GTCGCTGGTCAGT-TCGTGATT-3' and 5'-AGCAGTTGGCTGTTGTAC-CTCTC-3'. Melting curve analysis revealed a single peak at approximately 83° C. with no visible primer dimers. Agarose gel analysis of the PCR product showed one single band with the expected size (80 bp).

[0093] For calculation of the values, first the logarithm of the cDNA concentration was plotted against the threshold cycle number C_t for golgin-245, i.e. for the golgin-245 splice variant 1 and/or splice variant 3 and for the golgin-245 splice variant 2 and/or splice variant 4, respectively, and the five reference standard genes. The slopes and the intercepts of the standard curves (i.e. linear regressions) were calculated for all genes. In a second step, cDNAs from temporal cortex and frontal cortex, and from hippocampus and frontal cortex, respectively, were analyzed in parallel and normalized to cyclophilin B. The C_t values were measured and converted to ng total brain cDNA using the corresponding standard curves:

$$10\hat{}((C_t \text{ value} - \text{intercept})/\text{slope})[\text{ng total brain cDNA}]$$

[0094] The values for temporal and frontal cortex and the values for hippocampus and frontal cortex cDNAs of golgin-245 (i.e. of the golgin-245 splice variant 1 and/or splice variant 3 and of the golgin-245 splice variant 2 and/or splice variant 4, respectively) were normalized to cyclophilin B, and the ratios were calculated using the following formula:

$$\text{Ratio} = \frac{\text{golgin-245 temporal [ng]} / \text{cyclophilin } B \text{ temporal [ng]}}{\text{golgin-245 frontal [ng]} / \text{cyclophilin } B \text{ frontal [ng]}}$$

$$\text{Ratio} = \frac{\text{golgin-245 hippocampus [ng]} / \text{cyclophilin } B \text{ hippocampus [ng]}}{\text{golgin-245 frontal [ng]} / \text{cyclophilin } B \text{ frontal [ng]}}$$

[0095] In a third step, the set of reference standard genes was analyzed in parallel to determine the mean average value of the temporal to frontal ratios, and of the hippocampal to frontal ratios, respectively, of expression levels of the reference standard genes for each individual brain sample. As cyclophilin B was analyzed in step 2 and step 3, and the ratio from one gene to another gene remained constant in different runs, it was possible to normalize the values for golgin-245, i.e. for the golgin-245 splice variant 1 and/or splice variant 3 and for the golgin-245 splice variant 2 and/or splice variant 4, respectively, to the mean average value of the set of reference standard genes instead of normalizing to one single gene alone. The calculation was performed by dividing the respective ratio shown above by the deviation of cyclophilin B from the mean value of all housekeeping genes. The results of such quantitative RT-PCR analysis for the golgin-245 gene, for the golgin-245 splice variant 1 and/or splice variant 3 and for the golgin-245 splice variant 2 and/or splice variant 4, are shown in **FIGS. 13 and 14**, and in **FIGS. 15 and 16**, respectively.

(v) Immunohistochemistry:

[0096] For immunofluorescence staining of golgin-245 in human brain, frozen sections were prepared from post-mortem pre-central gyrus of a donor person (Cryostat Leica CM3050S) and fixed in acetone for 10 min. After washing in PBS, the sections were pre-incubated with blocking buffer (10% normal goat serum, 0.2% Triton X-100 in PBS) for 30 min, and then incubated with anti-golgin-245 mouse monoclonal antibodies (1:50 diluted in blocking buffer, BD Biosciences, Heidelberg) overnight at 4° C. After rinsing three times in 0.1% Triton X-100/PBS, the sections were incubated with Cy3-conjugated goat anti-mouse IgG (1:600 diluted in 1% BSA/PBS) for 2 hours at room temperature, and then again washed in PBS. Staining of the nuclei was performed by incubation of the sections with 5 μM DAPI in PBS for 3 min (blue signal). In order to block the autofluoresence of lipofuscin in human brain, the sections were treated with 1% Sudan Black B in 70% ethanol for 2-10 min at room temperature, sequentially dipped in 70% ethanol, destined water and PBS. The sections were coverslipped by 'Vectrashield mounting medium' (Vector Laboratories, Burlingame, Calif.) and observed under an inverted microscope (IX81, Olympus Optical). The digital images were captured with the appropriate software (AnalySiS, Olympus Optical).

Table 1 :

sample	Δ (fold) (temporal / frontal cortex)
control C011	0.86
control C012	0.86
control C014	1.00
control C005	0.87
control C008	1.32
patient P012	0.98
patient P016	1.55
patient P010	1.06
patient P011	1.56
patient P014	1.30
patient P017	1.32
patient P019	2.91

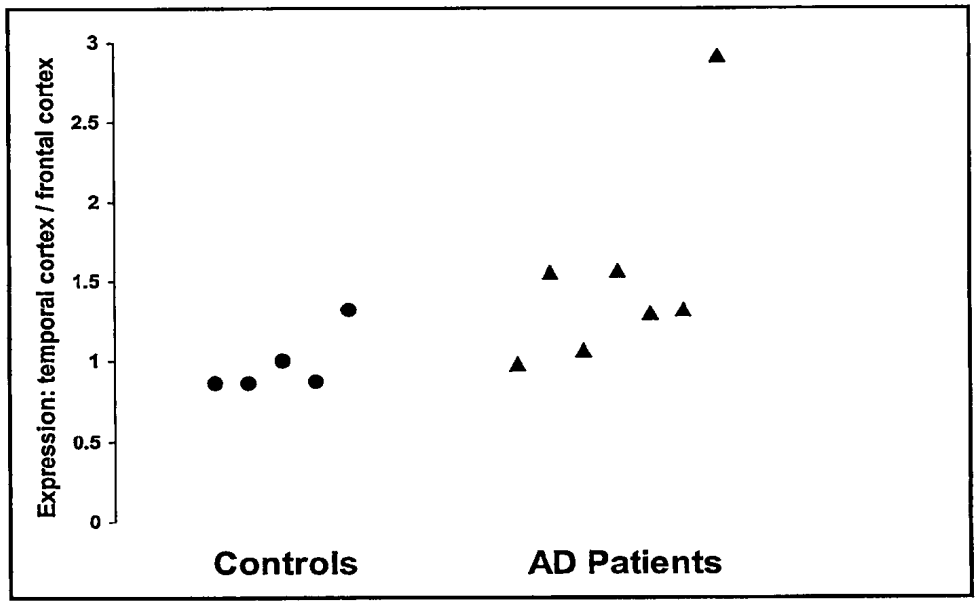


Table 2:

sample	Δ (fold) (hippocampus / frontal cortex)
control C005	1.04
control C008	1.98
control C004	1.34
patient P012	1.30
patient P016	1.53
patient P010	1.00
patient P011	1.38
patient P014	1.05
patient P019	2.16

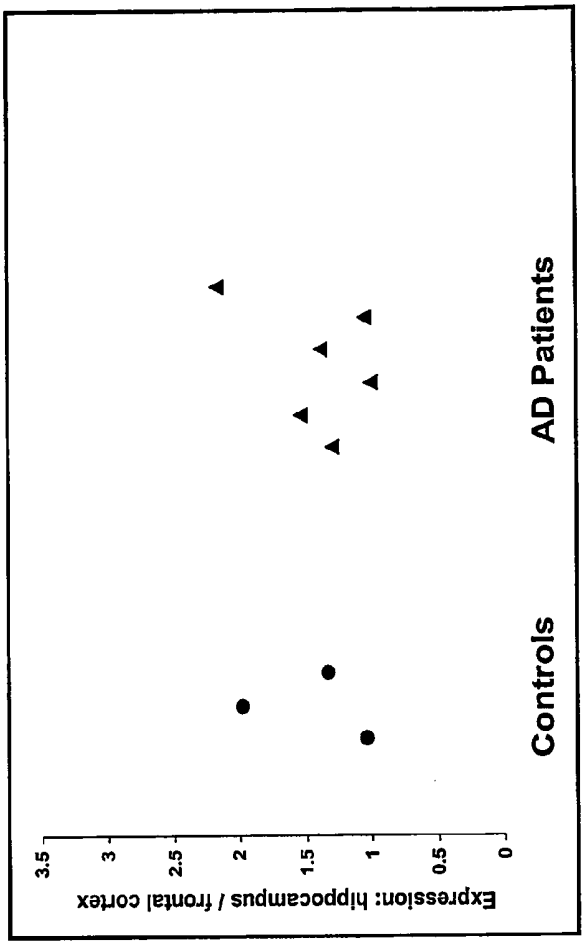


Table 3 :

sample	Δ (fold) (frontal / temporal cortex)
control C011	1.28
control C012	1.43
control C014	0.46
control C005	1.20
control C008	1.14
patient P012	2.71
patient P016	2.45
patient P010	3.36
patient P011	2.24
patient P014	1.63
patient P017	1.53
patient P019	2.90

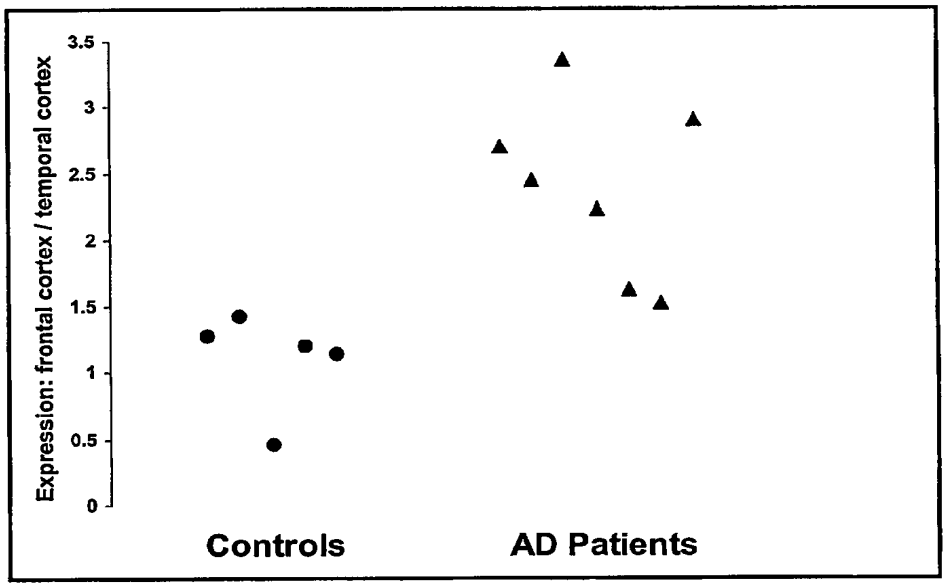
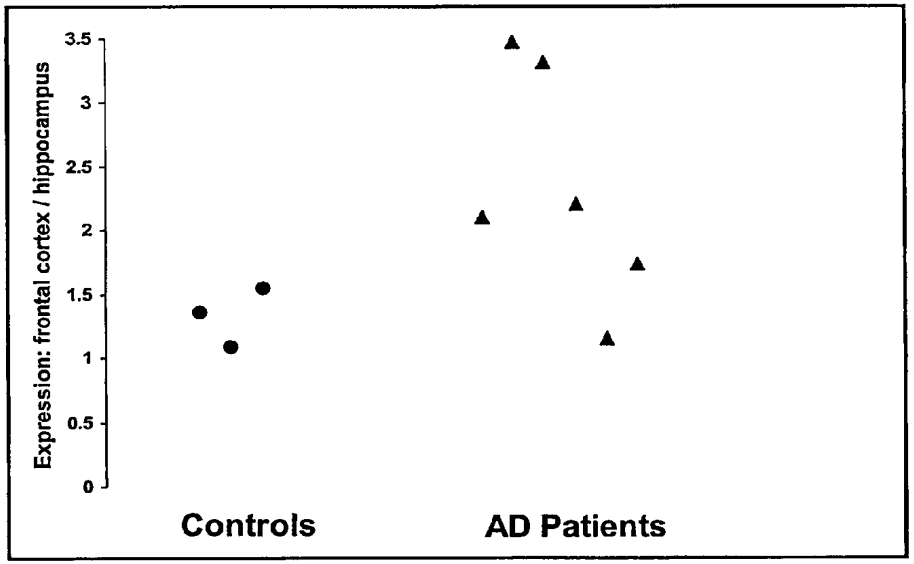


Table 4:

sample	Δ (fold) (frontal cortex / hippocampus)
control C005	1.36
control C008	1.09
control C004	1.55
patient P012	2.10
patient P016	3.47
patient P010	3.31
patient P011	2.20
patient P014	1.15
patient P019	1.73



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35 40 45

Gly Thr Pro Asn Arg Glu Ser Gly Asp Thr Gln Ser Phe Ala Gln Lys
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Leu Gln Leu Arg Val Pro Ser Val Glu Ser Leu Phe Arg Ser Pro Ile
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Ser Ser Arg Glu Ser Leu Asn Arg Leu Asp Leu Asp Ser Ser Thr Ala
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Arg Met Glu Arg Ser Leu Ser Ser Tyr Arg Gly Lys Tyr Ser Glu Leu
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Ile Leu Ser Gln Ser Gln Asp Lys Ser Leu Arg Arg Ile Ala Glu Leu
180 185 190

Arg Glu Glu Leu Gln Met Asp Gln Gln Ala Lys Lys His Leu Gln Glu
195 200 205

Glu Phe Asp Ala Ser Leu Glu Glu Lys Asp Gln Tyr Ile Ser Val Leu
210 215 220

Gln Thr Gln Val Ser Leu Leu Lys Gln Arg Leu Arg Asn Gly Pro Met
225 230 235 240

Asn Val Asp Val Leu Lys Pro Leu Pro Gln Leu Glu Pro Gln Ala Glu
245 250 255

Val Phe Thr Lys Glu Glu Asn Pro Glu Ser Asp Gly Glu Pro Val Val
260 265 270

-continued

```
Glu Asp Gly Thr Ser Val Lys Thr Leu Glu Thr Leu Gln Gln Arg Val
        275                 280                 285

Lys Arg Gln Glu Asn Leu Leu Lys Arg Cys Lys Glu Thr Ile Gln Ser
    290                 295                 300

His Lys Glu Gln Cys Thr Leu Leu Thr Ser Glu Lys Glu Ala Leu Gln
305                 310                 315                 320

Glu Gln Leu Asp Glu Arg Leu Gln Glu Leu Glu Lys Ile Lys Asp Leu
                325                 330                 335

His Met Ala Glu Lys Thr Lys Leu Ile Thr Gln Leu Arg Asp Ala Lys
            340                 345                 350

Asn Leu Ile Glu Gln Leu Glu Gln Asp Lys Gly Met Val Ile Ala Glu
        355                 360                 365

Thr Lys Arg Gln Met His Glu Thr Leu Glu Met Lys Glu Glu Glu Ile
    370                 375                 380

Ala Gln Leu Arg Ser Arg Ile Lys Gln Met Thr Thr Gln Gly Glu Glu
385                 390                 395                 400

Leu Arg Glu Gln Lys Glu Lys Ser Glu Arg Ala Ala Phe Glu Glu Leu
                405                 410                 415

Glu Lys Ala Leu Ser Thr Ala Gln Lys Thr Glu Glu Ala Arg Arg Lys
            420                 425                 430

Leu Lys Ala Glu Met Asp Glu Gln Ile Lys Thr Ile Glu Lys Thr Ser
        435                 440                 445

Glu Glu Glu Arg Ile Ser Leu Gln Gln Glu Leu Ser Arg Val Lys Gln
    450                 455                 460

Glu Val Val Asp Val Met Lys Lys Ser Ser Glu Glu Gln Ile Ala Lys
465                 470                 475                 480

Leu Gln Lys Leu His Glu Lys Glu Leu Ala Arg Lys Glu Gln Glu Leu
                485                 490                 495

Thr Lys Lys Leu Gln Thr Arg Glu Arg Glu Phe Gln Glu Gln Met Lys
            500                 505                 510

Val Ala Leu Glu Lys Ser Gln Ser Glu Tyr Leu Lys Ile Ser Gln Glu
        515                 520                 525

Lys Glu Gln Gln Glu Ser Leu Ala Leu Glu Glu Leu Glu Leu Gln Lys
    530                 535                 540

Lys Ala Ile Leu Thr Glu Ser Glu Asn Lys Leu Arg Asp Leu Gln Gln
545                 550                 555                 560

Glu Ala Glu Thr Tyr Arg Thr Arg Ile Leu Glu Leu Glu Ser Ser Leu
                565                 570                 575

Glu Lys Ser Leu Gln Glu Asn Lys Asn Gln Ser Lys Asp Leu Ala Val
            580                 585                 590

His Leu Glu Ala Glu Lys Asn Lys His Asn Lys Glu Ile Thr Val Met
        595                 600                 605

Val Glu Lys His Lys Thr Glu Leu Glu Ser Leu Lys His Gln Gln Asp
    610                 615                 620

Ala Leu Trp Thr Glu Lys Leu Gln Val Leu Lys Gln Gln Tyr Gln Thr
625                 630                 635                 640

Glu Met Glu Lys Leu Arg Glu Lys Cys Glu Gln Glu Lys Glu Thr Leu
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Glu Lys Thr Leu Glu Lys Leu Asp Val Lys Gln Thr Glu Leu Glu Ser
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Leu Glu Ala Lys Met Asp Glu Gln Lys Asn His His Gln Gln Gln Val
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Asp Ser Ile Ile Lys Glu His Glu Val Ser Ile Gln Arg Thr Glu Lys
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Ala Leu Lys Asp Gln Ile Asn Gln Leu Glu Leu Leu Leu Lys Glu Arg
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Asp Lys His Leu Lys Glu His Gln Ala His Val Glu Asn Leu Glu Ala
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Asp Ile Lys Arg Ser Glu Gly Glu Leu Gln Gln Ala Ser Ala Lys Leu
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Asp Val Phe Gln Ser Tyr Gln Ser Ala Thr His Glu Gln Thr Lys Ala
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Tyr Glu Glu Gln Leu Ala Gln Leu Gln Gln Lys Leu Leu Asp Leu Glu
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Thr Glu Arg Ile Leu Leu Thr Lys Gln Val Ala Glu Val Glu Ala Gln
        835                 840                 845

Lys Lys Asp Val Cys Thr Glu Leu Asp Ala His Lys Ile Gln Val Gln
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Asp Leu Met Gln Gln Leu Glu Lys Gln Asn Ser Glu Met Glu Gln Lys
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Val Lys Ser Leu Thr Gln Val Tyr Glu Ser Lys Leu Glu Asp Gly Asn
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Ile Leu Gln Met Arg Glu Gly Gln Lys Lys Glu Ile Glu Ile Leu Thr
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Gln Lys Leu Ser Ala Lys Glu Asp Ser Ile His Ile Leu Asn Glu Glu
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Tyr Glu Thr Lys Phe Lys Asn Gln Glu Lys Lys Met Glu Lys Val Lys
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Ser Gln Lys Glu Lys Gln Phe Asn Ala Lys Met Leu Glu Met Ala Gln
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Ala Asn Ser Ala Gly Ile Ser Asp Ala Val Ser Arg Leu Glu Thr Asn
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Gln Lys Glu Gln Ile Glu Ser Leu Thr Glu Val His Arg Arg Glu Leu
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Asn Asp Val Ile Ser Ile Trp Glu Lys Lys Leu Asn Gln Gln Ala Glu
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Glu Leu Gln Glu Ile His Glu Ile Gln Leu Gln Glu Lys Glu Gln Glu
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Val Ala Glu Leu Lys Gln Lys Ile Leu Leu Phe Gly Cys Glu Lys Glu
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His Val Asn Ser Leu Ala Gln Asp Glu Thr Lys Leu Lys Ala His Leu
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Glu Lys Leu Glu Val Asp Leu Asn Lys Ser Leu Lys Glu Asn Thr Phe
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Leu Gln Glu Gln Leu Val Glu Leu Lys Met Leu Ala Glu Glu Asp Lys
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Arg Lys Val Ser Glu Leu Thr Ser Lys Leu Lys Thr Thr Asp Glu Glu
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Phe Gln Ser Leu Lys Ser Ser His Glu Lys Ser Asn Lys Ser Leu Glu
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Asp Lys Ser Leu Glu Phe Lys Lys Leu Ser Glu Glu Leu Ala Ile Gln
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Leu Asp Ile Cys Cys Lys Lys Thr Glu Ala Leu Leu Glu Ala Lys Thr
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Asn Glu Leu Ile Asn Ile Ser Ser Ser Lys Thr Asn Ala Ile Leu Ser
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Arg Ile Ser His Cys Gln His Arg Thr Thr Lys Val Lys Glu Ala Leu
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Leu Ile Lys Thr Cys Thr Val Ser Glu Leu Glu Ala Gln Leu Arg Gln
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Leu Thr Glu Glu Gln Asn Thr Leu Asn Ile Ser Phe Gln Gln Ala Thr
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His Gln Leu Glu Glu Lys Glu Asn Gln Ile Lys Ser Met Lys Ala Asp
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Asn Gln Gln Gln Ala Ala Ser Glu Lys Glu Ser Cys Ile Thr Gln Leu
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Lys Lys Glu Leu Ser Glu Asn Ile Asn Ala Val Thr Leu Met Lys Glu
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Glu Leu Lys Glu Lys Lys Val Glu Ile Ser Ser Leu Ser Lys Gln Leu
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Thr Asp Leu Asn Val Gln Leu Gln Asn Ser Ile Ser Leu Ser Glu Lys
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Glu Ala Ala Ile Ser Ser Leu Arg Lys Gln Tyr Asp Glu Glu Lys Cys
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Glu Leu Leu Asp Gln Val Gln Asp Leu Ser Phe Lys Val Asp Thr Leu
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Ser Lys Glu Lys Ile Ser Ala Leu Glu Gln Val Asp Asp Trp Ser Asn
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Lys Phe Ser Glu Trp Lys Lys Lys Ala Gln Ser Arg Phe Thr Gln His
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Gln Asn Thr Val Lys Glu Leu Gln Ile Gln Leu Glu Leu Lys Ser Lys
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Lys Ser Gln Thr Ala Arg Ile Met Glu Leu Glu Asp His Ile Thr Gln
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Lys Thr Ile Glu Ile Glu Ser Leu Asn Glu Val Leu Lys Asn Tyr Asn
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Gln Gln Lys Asp Ile Glu His Lys Glu Leu Val Gln Lys Leu Gln His
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Phe Gln Glu Leu Gly Glu Glu Lys Asp Asn Arg Val Lys Glu Ala Glu
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Glu Lys Ile Leu Thr Leu Glu Asn Gln Val Tyr Ser Met Lys Ala Glu
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Leu Glu Thr Lys Lys Lys Glu Leu Glu His Val Asn Leu Ser Val Lys
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Ser Lys Glu Glu Glu Leu Lys Ala Leu Glu Asp Arg Leu Glu Ser Glu
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Ser Ala Ala Lys Leu Ala Glu Leu Lys Arg Lys Ala Glu Gln Lys Ile
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Ala Ala Ile Lys Lys Gln Leu Leu Ser Gln Met Glu Glu Lys Glu Glu
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Gln Tyr Lys Lys Gly Thr Glu Ser His Leu Ser Glu Leu Asn Thr Lys
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Leu Gln Glu Arg Glu Arg Glu Val His Ile Leu Glu Glu Lys Leu Lys
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Ser Val Glu Ser Ser Gln Ser Glu Thr Leu Ile Val Pro Arg Ser Ala
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Lys Asn Val Ala Ala Tyr Thr Glu Gln Glu Glu Ala Asp Ser Gln Gly
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Cys Val Gln Lys Thr Tyr Glu Glu Lys Ile Ser Val Leu Gln Arg Asn
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Leu Thr Glu Lys Glu Lys Leu Leu Gln Arg Val Gly Gln Glu Lys Glu
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Glu Thr Val Ser Ser His Phe Glu Met Arg Cys Gln Tyr Gln Glu Arg
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Leu Ile Lys Leu Glu His Ala Glu Ala Lys Gln His Glu Asp Gln Ser
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Met Ile Gly His Leu Gln Glu Glu Leu Glu Glu Lys Asn Lys Lys Tyr
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Ser Leu Ile Val Ala Gln His Val Glu Lys Glu Gly Gly Lys Asn Asn
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Ile Gln Ala Lys Gln Asn Leu Glu Asn Val Phe Asp Asp Val Gln Lys
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Thr Leu Gln Glu Lys Glu Leu Thr Cys Gln Ile Leu Glu Gln Lys Ile
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Lys Glu Leu Asp Ser Cys Leu Val Arg Gln Lys Glu Val His Arg Val
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Arg Glu Lys Gln Lys Leu Gly Lys Glu Ile Val Arg Leu Gln Lys Asp
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Leu Arg Met Leu Arg Lys Glu His Gln Gln Glu Leu Glu Ile Leu Lys
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Lys Glu Tyr Asp Gln Glu Arg Glu Glu Lys Ile Lys Gln Glu Gln Glu
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Asp Leu Glu Leu Lys His Asn Ser Thr Leu Lys Gln Leu Met Arg Glu
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Phe Asn Thr Gln Leu Ala Gln Lys Glu Gln Glu Leu Glu Met Thr Ile
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Ser His Gln Glu Glu Thr Asn Gln Leu Leu Lys Lys Ile Ala Glu Lys
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Asp Asp Asp Leu Lys Arg Thr Ala Lys Arg Tyr Glu Glu Ile Leu Asp
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Ala Arg Glu Glu Glu Met Thr Ala Lys Val Arg Asp Leu Gln Thr Gln
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Leu Glu Glu Leu Gln Lys Lys Tyr Gln Gln Lys Leu Glu Gln Glu Glu
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Phe Arg Glu Gln Ile His Asn Leu Glu Asp Arg Leu Lys Lys Tyr Glu
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Lys Asn Val Tyr Ala Thr Thr Val Gly Thr Pro Tyr Lys Gly Gly Asn
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Leu Tyr His Thr Asp Val Ser Leu Phe Gly Glu Pro Thr Glu Phe Glu
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Ser Phe Asp Pro Pro Ser Asp Met Asp Ser Glu Ala Glu Asp Leu Val
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Gly Asn Ser Asp Ser Leu Asn Lys Glu Gln Leu Ile Gln Arg Leu Arg
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Arg Met Glu Arg Ser Leu Ser Ser Tyr Arg Gly Lys Tyr Ser Glu Leu
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Val Thr Ala Tyr Gln Met Leu Gln Arg Glu Lys Lys Lys Leu Gln Gly
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Ile Leu Ser Gln Ser Gln Asp Lys Ser Leu Arg Arg Ile Ala Glu Leu
180 185 190

Arg Glu Glu Leu Gln Met Asp Gln Gln Ala Lys Lys His Leu Gln Glu
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Glu Phe Asp Ala Ser Leu Glu Glu Lys Asp Gln Tyr Ile Ser Val Leu

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Gln Thr Gln Val Ser Leu Leu Lys Gln Arg Leu Arg Asn Gly Pro Met
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Asn Val Asp Val Leu Lys Pro Leu Pro Gln Leu Glu Pro Gln Ala Glu
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Val Phe Thr Lys Glu Glu Asn Pro Glu Ser Asp Gly Glu Pro Val Val
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Glu Asp Gly Thr Ser Val Lys Thr Leu Glu Thr Leu Gln Gln Arg Val
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Lys Arg Gln Glu Asn Leu Leu Lys Arg Cys Lys Glu Thr Ile Gln Ser
    290                 295                 300

His Lys Glu Gln Cys Thr Leu Leu Thr Ser Glu Lys Glu Ala Leu Gln
305                 310                 315                 320

Glu Gln Leu Asp Glu Arg Leu Gln Glu Leu Glu Lys Ile Lys Asp Leu
                325                 330                 335

His Met Ala Glu Lys Thr Lys Leu Ile Thr Gln Leu Arg Asp Ala Lys
            340                 345                 350

Asn Leu Ile Glu Gln Leu Glu Gln Asp Lys Gly Met Val Ile Ala Glu
        355                 360                 365

Thr Lys Arg Gln Met His Glu Thr Leu Glu Met Lys Glu Glu Glu Ile
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Ala Gln Leu Arg Ser Arg Ile Lys Gln Met Thr Thr Gln Gly Glu Glu
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Leu Arg Glu Gln Lys Glu Lys Ser Glu Arg Ala Ala Phe Glu Glu Leu
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Glu Lys Ala Leu Ser Thr Ala Gln Lys Thr Glu Glu Ala Arg Arg Lys
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Leu Lys Ala Glu Met Asp Glu Gln Ile Lys Thr Ile Glu Lys Thr Ser
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Glu Glu Glu Arg Ile Ser Leu Gln Gln Glu Leu Ser Arg Val Lys Gln
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Glu Val Val Asp Val Met Lys Lys Ser Ser Glu Glu Gln Ile Ala Lys
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Leu Gln Lys Leu His Glu Lys Glu Leu Ala Arg Lys Glu Gln Glu Leu
                485                 490                 495

Thr Lys Lys Leu Gln Thr Arg Glu Arg Glu Phe Gln Glu Gln Met Lys
            500                 505                 510

Val Ala Leu Glu Lys Ser Gln Ser Glu Tyr Leu Lys Ile Ser Gln Glu
        515                 520                 525

Lys Glu Gln Gln Glu Ser Leu Ala Leu Glu Glu Leu Glu Leu Gln Lys
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Lys Ala Ile Leu Thr Glu Ser Glu Asn Lys Leu Arg Asp Leu Gln Gln
545                 550                 555                 560

Glu Ala Glu Thr Tyr Arg Thr Arg Ile Leu Glu Leu Glu Ser Ser Leu
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Glu Lys Ser Leu Gln Glu Asn Lys Asn Gln Ser Lys Asp Leu Ala Val
            580                 585                 590

His Leu Glu Ala Glu Lys Asn Lys His Asn Lys Glu Ile Thr Val Met
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Val Glu Lys His Lys Thr Glu Leu Glu Ser Leu Lys His Gln Gln Asp
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Ala Leu Trp Thr Glu Lys Leu Gln Val Leu Lys Gln Gln Tyr Gln Thr
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Glu Met Glu Lys Leu Arg Glu Lys Cys Glu Gln Glu Lys Glu Thr Leu
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Leu Lys Asp Lys Glu Ile Ile Phe Gln Ala His Ile Glu Glu Met Asn
            660                 665                 670

Glu Lys Thr Leu Glu Lys Leu Asp Val Lys Gln Thr Glu Leu Glu Ser
        675                 680                 685

Leu Ser Ser Glu Leu Ser Glu Val Leu Lys Ala Arg His Lys Leu Glu
    690                 695                 700

Glu Glu Leu Ser Val Leu Lys Asp Gln Thr Asp Lys Met Lys Gln Glu
705                 710                 715                 720

Leu Glu Ala Lys Met Asp Glu Gln Lys Asn His His Gln Gln Gln Val
                725                 730                 735

Asp Ser Ile Ile Lys Glu His Glu Val Ser Ile Gln Arg Thr Glu Lys
            740                 745                 750

Ala Leu Lys Asp Gln Ile Asn Gln Leu Glu Leu Leu Leu Lys Glu Arg
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Asp Lys His Leu Lys Glu His Gln Ala His Val Glu Asn Leu Glu Ala
    770                 775                 780

Asp Ile Lys Arg Ser Glu Gly Glu Leu Gln Gln Ala Ser Ala Lys Leu
785                 790                 795                 800

Asp Val Phe Gln Ser Tyr Gln Ser Ala Thr His Glu Gln Thr Lys Ala
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Tyr Glu Glu Gln Leu Ala Gln Leu Gln Gln Lys Leu Leu Asp Leu Glu
            820                 825                 830

Thr Glu Arg Ile Leu Leu Thr Lys Gln Val Ala Glu Val Glu Ala Gln
        835                 840                 845

Lys Lys Asp Val Cys Thr Glu Leu Asp Ala His Lys Ile Gln Val Gln
    850                 855                 860

Asp Leu Met Gln Gln Leu Glu Lys Gln Asn Ser Glu Met Glu Gln Lys
865                 870                 875                 880

Val Lys Ser Leu Thr Gln Val Tyr Glu Ser Lys Leu Glu Asp Gly Asn
                885                 890                 895

Lys Glu Gln Glu Gln Thr Lys Gln Ile Leu Val Glu Lys Glu Asn Met
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Ile Leu Gln Met Arg Glu Gly Gln Lys Lys Glu Ile Glu Ile Leu Thr
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Gln Lys Leu Ser Ala Lys Glu Asp Ser Ile His Ile Leu Asn Glu Glu
    930                 935                 940

Tyr Glu Thr Lys Phe Lys Asn Gln Glu Lys Lys Met Glu Lys Val Lys
945                 950                 955                 960

Gln Lys Ala Lys Glu Met Gln Glu Thr Leu Lys Lys Lys Leu Leu Asp
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Gln Glu Ala Lys Leu Lys Lys Glu Leu Glu Asn Thr Ala Leu Glu Leu
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Ser Gln Lys Glu Lys Gln Phe Asn Ala Lys Met Leu Glu Met Ala Gln
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Ala Asn Ser Ala Gly Ile Ser Asp Ala Val Ser Arg Leu Glu Thr Asn
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Gln Lys Glu Gln Ile Glu Ser Leu Thr Glu Val His Arg Arg Glu Leu
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Asn Asp Val Ile Ser Ile Trp Glu Lys Lys Leu Asn Gln Gln Ala Glu
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Glu Leu Gln Glu Ile His Glu Ile Gln Leu Gln Glu Lys Glu Gln Glu
            1060                1065                1070

Val Ala Glu Leu Lys Gln Lys Ile Leu Leu Phe Gly Cys Glu Lys Glu
        1075                1080                1085

Glu Met Asn Lys Glu Ile Thr Trp Leu Lys Glu Glu Gly Val Lys Gln
    1090                1095                1100

Asp Thr Thr Leu Asn Glu Leu Gln Glu Gln Leu Lys Gln Lys Ser Ala
1105                1110                1115                1120

His Val Asn Ser Leu Ala Gln Asp Glu Thr Lys Leu Lys Ala His Leu
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Glu Lys Leu Glu Val Asp Leu Asn Lys Ser Leu Lys Glu Asn Thr Phe
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Leu Gln Glu Gln Leu Val Glu Leu Lys Met Leu Ala Glu Glu Asp Lys
        1155                1160                1165

Arg Lys Val Ser Glu Leu Thr Ser Lys Leu Lys Thr Thr Asp Glu Glu
    1170                1175                1180

Phe Gln Ser Leu Lys Ser Ser His Glu Lys Ser Asn Lys Ser Leu Glu
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Asp Lys Ser Leu Glu Phe Lys Lys Leu Ser Glu Glu Leu Ala Ile Gln
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Leu Asp Ile Cys Cys Lys Lys Thr Glu Ala Leu Leu Glu Ala Lys Thr
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Asn Glu Leu Ile Asn Ile Ser Ser Ser Lys Thr Asn Ala Ile Leu Ser
        1235                1240                1245

Arg Ile Ser His Cys Gln His Arg Thr Thr Lys Val Lys Glu Ala Leu
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Leu Ile Lys Thr Cys Thr Val Ser Glu Leu Glu Ala Gln Leu Arg Gln
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Leu Thr Glu Glu Gln Asn Thr Leu Asn Ile Ser Phe Gln Gln Ala Thr
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His Gln Leu Glu Glu Lys Glu Asn Gln Ile Lys Ser Met Lys Ala Asp
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Ile Glu Ser Leu Val Thr Glu Lys Glu Ala Leu Gln Lys Glu Gly Gly
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Asn Gln Gln Gln Ala Ala Ser Glu Lys Glu Ser Cys Ile Thr Gln Leu
    1330                1335                1340

Lys Lys Glu Leu Ser Glu Asn Ile Asn Ala Val Thr Leu Met Lys Glu
1345                1350                1355                1360

Glu Leu Lys Glu Lys Lys Val Glu Ile Ser Ser Leu Ser Lys Gln Leu
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Thr Asp Leu Asn Val Gln Leu Gln Asn Ser Ile Ser Leu Ser Glu Lys
            1380                1385                1390

Glu Ala Ala Ile Ser Ser Leu Arg Lys Gln Tyr Asp Glu Glu Lys Cys
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Glu Leu Leu Asp Gln Val Gln Asp Leu Ser Phe Lys Val Asp Thr Leu
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Ser Lys Glu Lys Ile Ser Ala Leu Glu Gln Val Asp Asp Trp Ser Asn
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Lys Phe Ser Glu Trp Lys Lys Lys Ala Gln Ser Arg Phe Thr Gln His
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Gln Asn Thr Val Lys Glu Leu Gln Ile Gln Leu Glu Leu Lys Ser Lys
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Glu Ala Tyr Glu Lys Asp Glu Gln Ile Asn Leu Leu Lys Glu Glu Leu
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Asp Gln Gln Asn Lys Arg Phe Asp Cys Leu Lys Gly Glu Met Glu Asp
    1490                1495                1500

Asp Lys Ser Lys Met Glu Lys Lys Glu Ser Asn Leu Glu Thr Glu Leu
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Lys Ser Gln Thr Ala Arg Ile Met Glu Leu Glu Asp His Ile Thr Gln
                1525                1530                1535

Lys Thr Ile Glu Ile Glu Ser Leu Asn Glu Val Leu Lys Asn Tyr Asn
            1540                1545                1550

Gln Gln Lys Asp Ile Glu His Lys Glu Leu Val Gln Lys Leu Gln His
        1555                1560                1565

Phe Gln Glu Leu Gly Glu Glu Lys Asp Asn Arg Val Lys Glu Ala Glu
    1570                1575                1580

Glu Lys Ile Leu Thr Leu Glu Asn Gln Val Tyr Ser Met Lys Ala Glu
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Leu Glu Thr Lys Lys Lys Glu Leu Glu His Val Asn Leu Ser Val Lys
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Ser Lys Glu Glu Glu Leu Lys Ala Leu Glu Asp Arg Leu Glu Ser Glu
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Ser Ala Ala Lys Leu Ala Glu Leu Lys Arg Lys Ala Glu Gln Lys Ile
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Ala Ala Ile Lys Lys Gln Leu Leu Ser Gln Met Glu Glu Lys Glu Glu
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Gln Tyr Lys Lys Gly Thr Glu Ser His Leu Ser Glu Leu Asn Thr Lys
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Leu Gln Glu Arg Glu Arg Glu Val His Ile Leu Glu Glu Lys Leu Lys
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Ser Val Glu Ser Ser Gln Ser Glu Thr Leu Ile Val Pro Arg Ser Ala
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Lys Asn Val Ala Ala Tyr Thr Glu Gln Glu Glu Ala Asp Ser Gln Gly
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Cys Val Gln Lys Thr Tyr Glu Glu Lys Ile Ser Val Leu Gln Arg Asn
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Leu Thr Glu Lys Glu Lys Leu Leu Gln Arg Val Gly Gln Glu Lys Glu
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Glu Thr Val Ser Ser His Phe Glu Met Arg Cys Gln Tyr Gln Glu Arg
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Leu Ile Lys Leu Glu His Ala Glu Ala Lys Gln His Glu Asp Gln Ser
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Met Ile Gly His Leu Gln Glu Glu Leu Glu Glu Lys Asn Lys Lys Tyr
        1795                1800                1805

Ser Leu Ile Val Ala Gln His Val Glu Lys Glu Gly Gly Lys Asn Asn
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Ile Gln Ala Lys Gln Asn Leu Glu Asn Val Phe Asp Asp Val Gln Lys
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Thr Leu Gln Glu Lys Glu Leu Thr Cys Gln Ile Leu Glu Gln Lys Ile
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Lys Glu Leu Asp Ser Cys Leu Val Arg Gln Lys Glu Val His Arg Val
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Glu Met Glu Glu Leu Thr Ser Lys Tyr Glu Lys Leu Gln Ala Leu Gln
        1875                1880                1885

Gln Met Asp Gly Arg Asn Lys Pro Thr Glu Leu Leu Glu Glu Asn Thr
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Glu Glu Lys Ser Lys Ser His Leu Val Gln Pro Lys Leu Leu Ser Asn
1905                1910                1915                1920

Met Glu Ala Gln His Asn Asp Leu Glu Phe Lys Leu Ala Gly Ala Glu
                1925                1930                1935

Arg Glu Lys Gln Lys Leu Gly Lys Glu Ile Val Arg Leu Gln Lys Asp
            1940                1945                1950

Leu Arg Met Leu Arg Lys Glu His Gln Gln Glu Leu Glu Ile Leu Lys
        1955                1960                1965

Lys Glu Tyr Asp Gln Glu Arg Glu Glu Lys Ile Lys Gln Glu Gln Glu
    1970                1975                1980

Asp Leu Glu Leu Lys His Asn Ser Thr Leu Lys Gln Leu Met Arg Glu
1985                1990                1995                2000

Phe Asn Thr Gln Leu Ala Gln Lys Glu Gln Glu Leu Glu Met Thr Ile
                2005                2010                2015

Lys Glu Thr Ile Asn Lys Ala Gln Glu Val Glu Ala Glu Leu Leu Glu
            2020                2025                2030

Ser His Gln Glu Glu Thr Asn Gln Leu Leu Lys Lys Ile Ala Glu Lys
        2035                2040                2045

Asp Asp Asp Leu Lys Arg Thr Ala Lys Arg Tyr Glu Glu Ile Leu Asp
    2050                2055                2060

Ala Arg Glu Glu Glu Met Thr Ala Lys Val Arg Asp Leu Gln Thr Gln
2065                2070                2075                2080

Leu Glu Glu Leu Gln Lys Lys Tyr Gln Gln Lys Leu Glu Gln Glu Glu
                2085                2090                2095

Asn Pro Gly Asn Asp Asn Val Thr Ile Met Glu Leu Gln Thr Gln Leu
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Ala Gln Lys Thr Thr Leu Ile Ser Asp Ser Lys Leu Lys Glu Gln Glu
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Phe Arg Glu Gln Ile His Asn Leu Glu Asp Arg Leu Lys Lys Tyr Glu
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Lys Asn Val Tyr Ala Thr Thr Val Gly Thr Pro Tyr Lys Gly Gly Asn
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Leu Tyr His Thr Asp Val Ser Leu Phe Gly Glu Pro Thr Glu Phe Glu
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Tyr Leu Arg Lys Val Leu Phe Glu Tyr Met Met Gly Arg Glu Thr Lys
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Thr Met Ala Lys Val Ile Thr Thr Val Leu Lys Phe Pro Asp Asp Gln
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Gly Thr Pro Asn Arg Glu Asn Ala Ser Thr His Ala Ser Lys Ser Pro
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Asp Ser Val Asn Gly Ser Glu Pro Ser Ile Pro Gln Ser Gly Asp Thr
65 70 75 80

Gln Ser Phe Ala Gln Lys Leu Gln Leu Arg Val Pro Ser Val Glu Ser
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Leu Phe Arg Ser Pro Ile Lys Glu Ser Leu Phe Arg Ser Ser Ser Lys
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Glu Ser Leu Val Arg Thr Ser Ser Arg Glu Ser Leu Asn Arg Leu Asp
115 120 125

Leu Asp Ser Ser Thr Ala Ser Phe Asp Pro Pro Ser Asp Met Asp Ser
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Glu Ala Glu Asp Leu Val Gly Asn Ser Asp Ser Leu Asn Lys Glu Gln
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Leu Ile Gln Arg Leu Arg Arg Met Glu Arg Ser Leu Ser Ser Tyr Arg
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Gly Lys Tyr Ser Glu Leu Val Thr Ala Tyr Gln Met Leu Gln Arg Glu
            180                 185                 190

Lys Lys Lys Leu Gln Gly Ile Leu Ser Gln Ser Gln Asp Lys Ser Leu
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Arg Arg Ile Ala Glu Leu Arg Glu Glu Leu Gln Met Asp Gln Gln Ala
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Lys Lys His Leu Gln Glu Glu Phe Asp Ala Ser Leu Glu Glu Lys Asp
225                 230                 235                 240

Gln Tyr Ile Ser Val Leu Gln Thr Gln Val Ser Leu Leu Lys Gln Arg
                245                 250                 255

Leu Arg Asn Gly Pro Met Asn Val Asp Val Leu Lys Pro Leu Pro Gln
            260                 265                 270

Leu Glu Pro Gln Ala Glu Val Phe Thr Lys Glu Glu Asn Pro Glu Ser
        275                 280                 285

Asp Gly Glu Pro Val Val Glu Asp Gly Thr Ser Val Lys Thr Leu Glu
    290                 295                 300

Thr Leu Gln Gln Arg Val Lys Arg Gln Glu Asn Leu Leu Lys Arg Cys
305                 310                 315                 320

Lys Glu Thr Ile Gln Ser His Lys Glu Gln Cys Thr Leu Leu Thr Ser
                325                 330                 335

Glu Lys Glu Ala Leu Gln Glu Gln Leu Asp Glu Arg Leu Gln Glu Leu
            340                 345                 350

Glu Lys Ile Lys Asp Leu His Met Ala Glu Lys Thr Lys Leu Ile Thr
        355                 360                 365

Gln Leu Arg Asp Ala Lys Asn Leu Ile Glu Gln Leu Glu Gln Asp Lys
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Gly Met Val Ile Ala Glu Thr Lys Arg Gln Met His Glu Thr Leu Glu
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Met Lys Glu Glu Glu Ile Ala Gln Leu Arg Ser Arg Ile Lys Gln Met
                405                 410                 415

Thr Thr Gln Gly Glu Glu Leu Arg Glu Gln Lys Glu Lys Ser Glu Arg
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Ala Ala Phe Glu Glu Leu Glu Lys Ala Leu Ser Thr Ala Gln Lys Thr
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Glu Glu Ala Arg Arg Lys Leu Lys Ala Glu Met Asp Glu Gln Ile Lys
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Thr Ile Glu Lys Thr Ser Glu Glu Glu Arg Ile Ser Leu Gln Gln Glu
465                 470                 475                 480

Leu Ser Arg Val Lys Gln Glu Val Val Asp Val Met Lys Lys Ser Ser
                485                 490                 495

Glu Glu Gln Ile Ala Lys Leu Gln Lys Leu His Glu Lys Glu Leu Ala
            500                 505                 510

Arg Lys Glu Gln Glu Leu Thr Lys Lys Leu Gln Thr Arg Glu Arg Glu
        515                 520                 525

Phe Gln Glu Gln Met Lys Val Ala Leu Glu Lys Ser Gln Ser Glu Tyr
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Leu Lys Ile Ser Gln Glu Lys Glu Gln Gln Glu Ser Leu Ala Leu Glu
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Leu Arg Asp Leu Gln Gln Glu Ala Glu Thr Tyr Arg Thr Arg Ile Leu
            580                 585                 590

Glu Leu Glu Ser Ser Leu Glu Lys Ser Leu Gln Glu Asn Lys Asn Gln
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Ser Lys Asp Leu Ala Val His Leu Glu Ala Glu Lys Asn Lys His Asn
    610                 615                 620

Lys Glu Ile Thr Val Met Val Glu Lys His Lys Thr Glu Leu Glu Ser
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Leu Lys His Gln Gln Asp Ala Leu Trp Thr Glu Lys Leu Gln Val Leu
                645                 650                 655

Lys Gln Gln Tyr Gln Thr Glu Met Glu Lys Leu Arg Glu Lys Cys Glu
            660                 665                 670

Gln Glu Lys Glu Thr Leu Leu Lys Asp Lys Glu Ile Ile Phe Gln Ala
        675                 680                 685

His Ile Glu Glu Met Asn Glu Lys Thr Leu Glu Lys Leu Asp Val Lys
    690                 695                 700

Gln Thr Glu Leu Glu Ser Leu Ser Ser Glu Leu Ser Glu Val Leu Lys
705                 710                 715                 720

Ala Arg His Lys Leu Glu Glu Glu Leu Ser Val Leu Lys Asp Gln Thr
                725                 730                 735

Asp Lys Met Lys Gln Glu Leu Glu Ala Lys Met Asp Glu Gln Lys Asn
            740                 745                 750

His His Gln Gln Gln Val Asp Ser Ile Ile Lys Glu His Glu Val Ser
        755                 760                 765

Ile Gln Arg Thr Glu Lys Ala Leu Lys Asp Gln Ile Asn Gln Leu Glu
    770                 775                 780

Leu Leu Leu Lys Glu Arg Asp Lys His Leu Lys Glu His Gln Ala His
785                 790                 795                 800

Val Glu Asn Leu Glu Ala Asp Ile Lys Arg Ser Glu Gly Glu Leu Gln
                805                 810                 815

Gln Ala Ser Ala Lys Leu Asp Val Phe Gln Ser Tyr Gln Ser Ala Thr
            820                 825                 830

His Glu Gln Thr Lys Ala Tyr Glu Glu Gln Leu Ala Gln Leu Gln Gln
        835                 840                 845

Lys Leu Leu Asp Leu Glu Thr Glu Arg Ile Leu Leu Thr Lys Gln Val
    850                 855                 860

Ala Glu Val Glu Ala Gln Lys Lys Asp Val Cys Thr Glu Leu Asp Ala
865                 870                 875                 880

His Lys Ile Gln Val Gln Asp Leu Met Gln Gln Leu Glu Lys Gln Asn
                885                 890                 895

Ser Glu Met Glu Gln Lys Val Lys Ser Leu Thr Gln Val Tyr Glu Ser
            900                 905                 910

Lys Leu Glu Asp Gly Asn Lys Glu Gln Glu Gln Thr Lys Gln Ile Leu
        915                 920                 925

Val Glu Lys Glu Asn Met Ile Leu Gln Met Arg Glu Gly Gln Lys Lys
    930                 935                 940

Glu Ile Glu Ile Leu Thr Gln Lys Leu Ser Ala Lys Glu Asp Ser Ile
945                 950                 955                 960
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His Ile Leu Asn Glu Glu Tyr Glu Thr Lys Phe Lys Asn Gln Glu Lys
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Lys Met Glu Lys Val Lys Gln Lys Ala Lys Glu Met Gln Glu Thr Leu
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Lys Lys Lys Leu Leu Asp Gln Glu Ala Lys Leu Lys Lys Glu Leu Glu
        995                 1000                1005

Asn Thr Ala Leu Glu Leu Ser Gln Lys Glu Lys Gln Phe Asn Ala Lys
    1010                1015                1020

Met Leu Glu Met Ala Gln Ala Asn Ser Ala Gly Ile Ser Asp Ala Val
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Ser Arg Leu Glu Thr Asn Gln Lys Glu Gln Ile Glu Ser Leu Thr Glu
                1045                1050                1055

Val His Arg Arg Glu Leu Asn Asp Val Ile Ser Ile Trp Glu Lys Lys
            1060                1065                1070

Leu Asn Gln Gln Ala Glu Glu Leu Gln Glu Ile His Glu Ile Gln Leu
        1075                1080                1085

Gln Glu Lys Glu Gln Glu Val Ala Glu Leu Lys Gln Lys Ile Leu Leu
    1090                1095                1100

Phe Gly Cys Glu Lys Glu Glu Met Asn Lys Glu Ile Thr Trp Leu Lys
1105                1110                1115                1120

Glu Glu Gly Val Lys Gln Asp Thr Thr Leu Asn Glu Leu Gln Glu Gln
                1125                1130                1135

Leu Lys Gln Lys Ser Ala His Val Asn Ser Leu Ala Gln Asp Glu Thr
            1140                1145                1150

Lys Leu Lys Ala His Leu Glu Lys Leu Glu Val Asp Leu Asn Lys Ser
        1155                1160                1165

Leu Lys Glu Asn Thr Phe Leu Gln Glu Gln Leu Val Glu Leu Lys Met
    1170                1175                1180

Leu Ala Glu Glu Asp Lys Arg Lys Val Ser Glu Leu Thr Ser Lys Leu
1185                1190                1195                1200

Lys Thr Thr Asp Glu Glu Phe Gln Ser Leu Lys Ser Ser His Glu Lys
                1205                1210                1215

Ser Asn Lys Ser Leu Glu Asp Lys Ser Leu Glu Phe Lys Lys Leu Ser
            1220                1225                1230

Glu Glu Leu Ala Ile Gln Leu Asp Ile Cys Cys Lys Lys Thr Glu Ala
        1235                1240                1245

Leu Leu Glu Ala Lys Thr Asn Glu Leu Ile Asn Ile Ser Ser Ser Lys
    1250                1255                1260

Thr Asn Ala Ile Leu Ser Arg Ile Ser His Cys Gln His Arg Thr Thr
1265                1270                1275                1280

Lys Val Lys Glu Ala Leu Leu Ile Lys Thr Cys Thr Val Ser Glu Leu
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Glu Ala Gln Leu Arg Gln Leu Thr Glu Glu Gln Asn Thr Leu Asn Ile
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Ser Phe Gln Gln Ala Thr His Gln Leu Glu Glu Lys Glu Asn Gln Ile
        1315                1320                1325

Lys Ser Met Lys Ala Asp Ile Glu Ser Leu Val Thr Glu Lys Glu Ala
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Leu Gln Lys Glu Gly Gly Asn Gln Gln Gln Ala Ala Ser Glu Lys Glu
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Ser Cys Ile Thr Gln Leu Lys Lys Glu Leu Ser Glu Asn Ile Asn Ala
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Val Thr Leu Met Lys Glu Glu Leu Lys Glu Lys Lys Val Glu Ile Ser
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Ser Leu Ser Lys Gln Leu Thr Asp Leu Asn Val Gln Leu Gln Asn Ser
        1395                1400                1405

Ile Ser Leu Ser Glu Lys Glu Ala Ala Ile Ser Ser Leu Arg Lys Gln
    1410                1415                1420

Tyr Asp Glu Glu Lys Cys Glu Leu Leu Asp Gln Val Gln Asp Leu Ser
1425                1430                1435                1440

Phe Lys Val Asp Thr Leu Ser Lys Glu Lys Ile Ser Ala Leu Glu Gln
                1445                1450                1455

Val Asp Asp Trp Ser Asn Lys Phe Ser Glu Trp Lys Lys Lys Ala Gln
            1460                1465                1470

Ser Arg Phe Thr Gln His Gln Asn Thr Val Lys Glu Leu Gln Ile Gln
        1475                1480                1485

Leu Glu Leu Lys Ser Lys Glu Ala Tyr Glu Lys Asp Glu Gln Ile Asn
    1490                1495                1500

Leu Leu Lys Glu Glu Leu Asp Gln Gln Asn Lys Arg Phe Asp Cys Leu
1505                1510                1515                1520

Lys Gly Glu Met Glu Asp Asp Lys Ser Lys Met Glu Lys Lys Glu Ser
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Asn Leu Glu Thr Glu Leu Lys Ser Gln Thr Ala Arg Ile Met Glu Leu
            1540                1545                1550

Glu Asp His Ile Thr Gln Lys Thr Ile Glu Ile Glu Ser Leu Asn Glu
        1555                1560                1565

Val Leu Lys Asn Tyr Asn Gln Gln Lys Asp Ile Glu His Lys Glu Leu
    1570                1575                1580

Val Gln Lys Leu Gln His Phe Gln Glu Leu Gly Glu Glu Lys Asp Asn
1585                1590                1595                1600

Arg Val Lys Glu Ala Glu Glu Lys Ile Leu Thr Leu Glu Asn Gln Val
                1605                1610                1615

Tyr Ser Met Lys Ala Glu Leu Glu Thr Lys Lys Lys Glu Leu Glu His
            1620                1625                1630

Val Asn Leu Ser Val Lys Ser Lys Glu Glu Glu Leu Lys Ala Leu Glu
        1635                1640                1645

Asp Arg Leu Glu Ser Glu Ser Ala Ala Lys Leu Ala Glu Leu Lys Arg
    1650                1655                1660

Lys Ala Glu Gln Lys Ile Ala Ala Ile Lys Lys Gln Leu Leu Ser Gln
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Met Glu Glu Lys Glu Glu Gln Tyr Lys Lys Gly Thr Glu Ser His Leu
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Ser Glu Leu Asn Thr Lys Leu Gln Glu Arg Glu Arg Glu Val His Ile
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Leu Glu Glu Lys Leu Lys Ser Val Glu Ser Ser Gln Ser Glu Thr Leu
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Ile Val Pro Arg Ser Ala Lys Asn Val Ala Ala Tyr Thr Glu Gln Glu
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Glu Ala Asp Ser Gln Gly Cys Val Gln Lys Thr Tyr Glu Glu Lys Ile
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Ser Val Leu Gln Arg Asn Leu Thr Glu Lys Glu Lys Leu Leu Gln Arg
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Val Gly Gln Glu Lys Glu Glu Thr Val Ser Ser His Phe Glu Met Arg
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Cys Gln Tyr Gln Glu Arg Leu Ile Lys Leu Glu His Ala Glu Ala Lys
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Gln His Glu Asp Gln Ser Met Ile Gly His Leu Gln Glu Glu Leu Glu
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Glu Lys Asn Lys Lys Tyr Ser Leu Ile Val Ala Gln His Val Glu Lys
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Glu Gly Gly Lys Asn Asn Ile Gln Ala Lys Gln Asn Leu Glu Asn Val
                1845                1850                1855

Phe Asp Asp Val Gln Lys Thr Leu Gln Glu Lys Glu Leu Thr Cys Gln
            1860                1865                1870

Ile Leu Glu Gln Lys Ile Lys Glu Leu Asp Ser Cys Leu Val Arg Gln
        1875                1880                1885

Lys Glu Val His Arg Val Glu Met Glu Glu Leu Thr Ser Lys Tyr Glu
    1890                1895                1900

Lys Leu Gln Ala Leu Gln Gln Met Asp Gly Arg Asn Lys Pro Thr Glu
1905                1910                1915                1920

Leu Leu Glu Glu Asn Thr Glu Glu Lys Ser Lys Ser His Leu Val Gln
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Pro Lys Leu Leu Ser Asn Met Glu Ala Gln His Asn Asp Leu Glu Phe
            1940                1945                1950

Lys Leu Ala Gly Ala Glu Arg Glu Lys Gln Lys Leu Gly Lys Glu Ile
        1955                1960                1965

Val Arg Leu Gln Lys Asp Leu Arg Met Leu Arg Lys Glu His Gln Gln
    1970                1975                1980

Glu Leu Glu Ile Leu Lys Lys Glu Tyr Asp Gln Glu Arg Glu Glu Lys
1985                1990                1995                2000

Ile Lys Gln Glu Gln Glu Asp Leu Glu Leu Lys His Asn Ser Thr Leu
                2005                2010                2015

Lys Gln Leu Met Arg Glu Phe Asn Thr Gln Leu Ala Gln Lys Glu Gln
            2020                2025                2030

Glu Leu Glu Met Thr Ile Lys Glu Thr Ile Asn Lys Ala Gln Glu Val
        2035                2040                2045

Glu Ala Glu Leu Leu Glu Ser His Gln Glu Glu Thr Asn Gln Leu Leu
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Lys Lys Ile Ala Glu Lys Asp Asp Asp Leu Lys Arg Thr Ala Lys Arg
2065                2070                2075                2080

Tyr Glu Glu Ile Leu Asp Ala Arg Glu Glu Glu Met Thr Ala Lys Val
                2085                2090                2095

Arg Asp Leu Gln Thr Gln Leu Glu Glu Leu Gln Lys Lys Tyr Gln Gln
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Lys Leu Glu Gln Glu Glu Asn Pro Gly Asn Asp Asn Val Thr Ile Met
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Glu Leu Gln Thr Gln Leu Ala Gln Lys Thr Thr Leu Ile Ser Asp Ser
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Lys Leu Lys Glu Gln Glu Phe Arg Glu Gln Ile His Asn Leu Glu Asp
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Arg Leu Lys Lys Tyr Glu Lys Asn Val Tyr Ala Thr Thr Val Gly Thr
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Thr Arg Met Arg Ser Arg Thr Ser Ser Phe Thr Glu Gln Leu Asp Glu
35 40 45

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Gly Thr Pro Asn Arg Glu Asn Ala Ser Thr His Ala Ser Lys Ser Pro
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Asp Ser Val Asn Gly Ser Glu Pro Ser Ile Pro Gln Ser Gly Asp Thr
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Gln Ser Phe Ala Gln Lys Leu Gln Leu Arg Val Pro Ser Val Glu Ser
                 85                  90                  95

Leu Phe Arg Ser Pro Ile Lys Glu Ser Leu Phe Arg Ser Ser Ser Lys
            100                 105                 110

Glu Ser Leu Val Arg Thr Ser Ser Arg Glu Ser Leu Asn Arg Leu Asp
        115                 120                 125

Leu Asp Ser Ser Thr Ala Ser Phe Asp Pro Pro Ser Asp Met Asp Ser
    130                 135                 140

Glu Ala Glu Asp Leu Val Gly Asn Ser Asp Ser Leu Asn Lys Glu Gln
145                 150                 155                 160

Leu Ile Gln Arg Leu Arg Arg Met Glu Arg Ser Leu Ser Ser Tyr Arg
                165                 170                 175

Gly Lys Tyr Ser Glu Leu Val Thr Ala Tyr Gln Met Leu Gln Arg Glu
            180                 185                 190

Lys Lys Lys Leu Gln Gly Ile Leu Ser Gln Ser Gln Asp Lys Ser Leu
        195                 200                 205

Arg Arg Ile Ala Glu Leu Arg Glu Glu Leu Gln Met Asp Gln Gln Ala
    210                 215                 220

Lys Lys His Leu Gln Glu Glu Phe Asp Ala Ser Leu Glu Glu Lys Asp
225                 230                 235                 240

Gln Tyr Ile Ser Val Leu Gln Thr Gln Val Ser Leu Leu Lys Gln Arg
                245                 250                 255

Leu Arg Asn Gly Pro Met Asn Val Asp Val Leu Lys Pro Leu Pro Gln
            260                 265                 270

Leu Glu Pro Gln Ala Glu Val Phe Thr Lys Glu Glu Asn Pro Glu Ser
        275                 280                 285

Asp Gly Glu Pro Val Val Glu Asp Gly Thr Ser Val Lys Thr Leu Glu
    290                 295                 300

Thr Leu Gln Gln Arg Val Lys Arg Gln Glu Asn Leu Leu Lys Arg Cys
305                 310                 315                 320

Lys Glu Thr Ile Gln Ser His Lys Glu Gln Cys Thr Leu Leu Thr Ser
                325                 330                 335

Glu Lys Glu Ala Leu Gln Glu Gln Leu Asp Glu Arg Leu Gln Glu Leu
            340                 345                 350

Glu Lys Ile Lys Asp Leu His Met Ala Glu Lys Thr Lys Leu Ile Thr
        355                 360                 365

Gln Leu Arg Asp Ala Lys Asn Leu Ile Glu Gln Leu Glu Gln Asp Lys
    370                 375                 380

Gly Met Val Ile Ala Glu Thr Lys Arg Gln Met His Glu Thr Leu Glu
385                 390                 395                 400

Met Lys Glu Glu Glu Ile Ala Gln Leu Arg Ser Arg Ile Lys Gln Met
                405                 410                 415

Thr Thr Gln Gly Glu Glu Leu Arg Glu Gln Lys Glu Lys Ser Glu Arg
            420                 425                 430

Ala Ala Phe Glu Glu Leu Glu Lys Ala Leu Ser Thr Ala Gln Lys Thr
        435                 440                 445

Glu Glu Ala Arg Arg Lys Leu Lys Ala Glu Met Asp Glu Gln Ile Lys
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Thr Ile Glu Lys Thr Ser Glu Glu Glu Arg Ile Ser Leu Gln Gln Glu
465                 470                 475                 480

Leu Ser Arg Val Lys Gln Glu Val Val Asp Val Met Lys Lys Ser Ser
                485                 490                 495

Glu Glu Gln Ile Ala Lys Leu Gln Lys Leu His Glu Lys Glu Leu Ala
            500                 505                 510

Arg Lys Glu Gln Glu Leu Thr Lys Lys Leu Gln Thr Arg Glu Arg Glu
        515                 520                 525

Phe Gln Glu Gln Met Lys Val Ala Leu Glu Lys Ser Gln Ser Glu Tyr
    530                 535                 540

Leu Lys Ile Ser Gln Glu Lys Glu Gln Gln Glu Ser Leu Ala Leu Glu
545                 550                 555                 560

Glu Leu Glu Leu Gln Lys Lys Ala Ile Leu Thr Glu Ser Glu Asn Lys
                565                 570                 575

Leu Arg Asp Leu Gln Gln Glu Ala Glu Thr Tyr Arg Thr Arg Ile Leu
            580                 585                 590

Glu Leu Glu Ser Ser Leu Glu Lys Ser Leu Gln Glu Asn Lys Asn Gln
        595                 600                 605

Ser Lys Asp Leu Ala Val His Leu Glu Ala Glu Lys Asn Lys His Asn
    610                 615                 620

Lys Glu Ile Thr Val Met Val Glu Lys His Lys Thr Glu Leu Glu Ser
625                 630                 635                 640

Leu Lys His Gln Gln Asp Ala Leu Trp Thr Glu Lys Leu Gln Val Leu
                645                 650                 655

Lys Gln Gln Tyr Gln Thr Glu Met Glu Lys Leu Arg Glu Lys Cys Glu
            660                 665                 670

Gln Glu Lys Glu Thr Leu Leu Lys Asp Lys Glu Ile Ile Phe Gln Ala
        675                 680                 685

His Ile Glu Glu Met Asn Glu Lys Thr Leu Glu Lys Leu Asp Val Lys
    690                 695                 700

Gln Thr Glu Leu Glu Ser Leu Ser Ser Glu Leu Ser Glu Val Leu Lys
705                 710                 715                 720

Ala Arg His Lys Leu Glu Glu Glu Leu Ser Val Leu Lys Asp Gln Thr
                725                 730                 735

Asp Lys Met Lys Gln Glu Leu Glu Ala Lys Met Asp Glu Gln Lys Asn
            740                 745                 750

His His Gln Gln Gln Val Asp Ser Ile Ile Lys Glu His Glu Val Ser
        755                 760                 765

Ile Gln Arg Thr Glu Lys Ala Leu Lys Asp Gln Ile Asn Gln Leu Glu
    770                 775                 780

Leu Leu Leu Lys Glu Arg Asp Lys His Leu Lys Glu His Gln Ala His
785                 790                 795                 800

Val Glu Asn Leu Glu Ala Asp Ile Lys Arg Ser Glu Gly Glu Leu Gln
                805                 810                 815

Gln Ala Ser Ala Lys Leu Asp Val Phe Gln Ser Tyr Gln Ser Ala Thr
            820                 825                 830

His Glu Gln Thr Lys Ala Tyr Glu Glu Gln Leu Ala Gln Leu Gln Gln
        835                 840                 845

Lys Leu Leu Asp Leu Glu Thr Glu Arg Ile Leu Leu Thr Lys Gln Val
    850                 855                 860
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Ala Glu Val Glu Ala Gln Lys Lys Asp Val Cys Thr Glu Leu Asp Ala
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His Lys Ile Gln Val Gln Asp Leu Met Gln Gln Leu Glu Lys Gln Asn
                885                 890                 895

Ser Glu Met Glu Gln Lys Val Lys Ser Leu Thr Gln Val Tyr Glu Ser
            900                 905                 910

Lys Leu Glu Asp Gly Asn Lys Glu Gln Glu Gln Thr Lys Gln Ile Leu
        915                 920                 925

Val Glu Lys Glu Asn Met Ile Leu Gln Met Arg Glu Gly Gln Lys Lys
    930                 935                 940

Glu Ile Glu Ile Leu Thr Gln Lys Leu Ser Ala Lys Glu Asp Ser Ile
945                 950                 955                 960

His Ile Leu Asn Glu Glu Tyr Glu Thr Lys Phe Lys Asn Gln Glu Lys
                965                 970                 975

Lys Met Glu Lys Val Lys Gln Lys Ala Lys Glu Met Gln Glu Thr Leu
            980                 985                 990

Lys Lys Lys Leu Leu Asp Gln Glu Ala Lys Leu Lys Lys Glu Leu Glu
        995                 1000                1005

Asn Thr Ala Leu Glu Leu Ser Gln Lys Glu Lys Gln Phe Asn Ala Lys
    1010                1015                1020

Met Leu Glu Met Ala Gln Ala Asn Ser Ala Gly Ile Ser Asp Ala Val
1025                1030                1035                1040

Ser Arg Leu Glu Thr Asn Gln Lys Glu Gln Ile Glu Ser Leu Thr Glu
                1045                1050                1055

Val His Arg Arg Glu Leu Asn Asp Val Ile Ser Ile Trp Glu Lys Lys
            1060                1065                1070

Leu Asn Gln Gln Ala Glu Glu Leu Gln Glu Ile His Glu Ile Gln Leu
        1075                1080                1085

Gln Glu Lys Glu Gln Glu Val Ala Glu Leu Lys Gln Lys Ile Leu Leu
    1090                1095                1100

Phe Gly Cys Glu Lys Glu Glu Met Asn Lys Glu Ile Thr Trp Leu Lys
1105                1110                1115                1120

Glu Glu Gly Val Lys Gln Asp Thr Thr Leu Asn Glu Leu Gln Glu Gln
                1125                1130                1135

Leu Lys Gln Lys Ser Ala His Val Asn Ser Leu Ala Gln Asp Glu Thr
            1140                1145                1150

Lys Leu Lys Ala His Leu Glu Lys Leu Glu Val Asp Leu Asn Lys Ser
        1155                1160                1165

Leu Lys Glu Asn Thr Phe Leu Gln Glu Gln Leu Val Glu Leu Lys Met
    1170                1175                1180

Leu Ala Glu Glu Asp Lys Arg Lys Val Ser Glu Leu Thr Ser Lys Leu
1185                1190                1195                1200

Lys Thr Thr Asp Glu Glu Phe Gln Ser Leu Lys Ser Ser His Glu Lys
                1205                1210                1215

Ser Asn Lys Ser Leu Glu Asp Lys Ser Leu Glu Phe Lys Lys Leu Ser
            1220                1225                1230

Glu Glu Leu Ala Ile Gln Leu Asp Ile Cys Cys Lys Lys Thr Glu Ala
        1235                1240                1245

Leu Leu Glu Ala Lys Thr Asn Glu Leu Ile Asn Ile Ser Ser Ser Lys
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Thr Asn Ala Ile Leu Ser Arg Ile Ser His Cys Gln His Arg Thr Thr
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Lys Val Lys Glu Ala Leu Leu Ile Lys Thr Cys Thr Val Ser Glu Leu
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Glu Ala Gln Leu Arg Gln Leu Thr Glu Glu Gln Asn Thr Leu Asn Ile
            1300                1305                1310

Ser Phe Gln Gln Ala Thr His Gln Leu Glu Glu Lys Glu Asn Gln Ile
        1315                1320                1325

Lys Ser Met Lys Ala Asp Ile Glu Ser Leu Val Thr Glu Lys Glu Ala
    1330                1335                1340

Leu Gln Lys Glu Gly Gly Asn Gln Gln Gln Ala Ala Ser Glu Lys Glu
1345                1350                1355                1360

Ser Cys Ile Thr Gln Leu Lys Lys Glu Leu Ser Glu Asn Ile Asn Ala
                1365                1370                1375

Val Thr Leu Met Lys Glu Glu Leu Lys Glu Lys Lys Val Glu Ile Ser
            1380                1385                1390

Ser Leu Ser Lys Gln Leu Thr Asp Leu Asn Val Gln Leu Gln Asn Ser
        1395                1400                1405

Ile Ser Leu Ser Glu Lys Glu Ala Ala Ile Ser Ser Leu Arg Lys Gln
    1410                1415                1420

Tyr Asp Glu Glu Lys Cys Glu Leu Leu Asp Gln Val Gln Asp Leu Ser
1425                1430                1435                1440

Phe Lys Val Asp Thr Leu Ser Lys Glu Lys Ile Ser Ala Leu Glu Gln
                1445                1450                1455

Val Asp Asp Trp Ser Asn Lys Phe Ser Glu Trp Lys Lys Lys Ala Gln
            1460                1465                1470

Ser Arg Phe Thr Gln His Gln Asn Thr Val Lys Glu Leu Gln Ile Gln
        1475                1480                1485

Leu Glu Leu Lys Ser Lys Glu Ala Tyr Glu Lys Asp Glu Gln Ile Asn
    1490                1495                1500

Leu Leu Lys Glu Glu Leu Asp Gln Gln Asn Lys Arg Phe Asp Cys Leu
1505                1510                1515                1520

Lys Gly Glu Met Glu Asp Asp Lys Ser Lys Met Glu Lys Lys Glu Ser
                1525                1530                1535

Asn Leu Glu Thr Glu Leu Lys Ser Gln Thr Ala Arg Ile Met Glu Leu
            1540                1545                1550

Glu Asp His Ile Thr Gln Lys Thr Ile Glu Ile Glu Ser Leu Asn Glu
        1555                1560                1565

Val Leu Lys Asn Tyr Asn Gln Gln Lys Asp Ile Glu His Lys Glu Leu
    1570                1575                1580

Val Gln Lys Leu Gln His Phe Gln Glu Leu Gly Glu Glu Lys Asp Asn
1585                1590                1595                1600

Arg Val Lys Glu Ala Glu Glu Lys Ile Leu Thr Leu Glu Asn Gln Val
                1605                1610                1615

Tyr Ser Met Lys Ala Glu Leu Glu Thr Lys Lys Lys Glu Leu Glu His
            1620                1625                1630

Val Asn Leu Ser Val Lys Ser Lys Glu Glu Glu Leu Lys Ala Leu Glu
        1635                1640                1645

Asp Arg Leu Glu Ser Glu Ser Ala Ala Lys Leu Ala Glu Leu Lys Arg
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Lys Ala Glu Gln Lys Ile Ala Ala Ile Lys Lys Gln Leu Leu Ser Gln
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Met Glu Glu Lys Glu Glu Gln Tyr Lys Lys Gly Thr Glu Ser His Leu
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Ser Glu Leu Asn Thr Lys Leu Gln Glu Arg Glu Arg Glu Val His Ile
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Leu Glu Glu Lys Leu Lys Ser Val Glu Ser Ser Gln Ser Glu Thr Leu
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Ile Val Pro Arg Ser Ala Lys Asn Val Ala Ala Tyr Thr Glu Gln Glu
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Glu Ala Asp Ser Gln Gly Cys Val Gln Lys Thr Tyr Glu Glu Lys Ile
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Ser Val Leu Gln Arg Asn Leu Thr Glu Lys Glu Lys Leu Leu Gln Arg
                1765                1770                1775

Val Gly Gln Glu Lys Glu Glu Thr Val Ser Ser His Phe Glu Met Arg
            1780                1785                1790

Cys Gln Tyr Gln Glu Arg Leu Ile Lys Leu Glu His Ala Glu Ala Lys
        1795                1800                1805

Gln His Glu Asp Gln Ser Met Ile Gly His Leu Gln Glu Glu Leu Glu
    1810                1815                1820

Glu Lys Asn Lys Lys Tyr Ser Leu Ile Val Ala Gln His Val Glu Lys
1825                1830                1835                1840

Glu Gly Gly Lys Asn Asn Ile Gln Ala Lys Gln Asn Leu Glu Asn Val
                1845                1850                1855

Phe Asp Asp Val Gln Lys Thr Leu Gln Glu Lys Glu Leu Thr Cys Gln
            1860                1865                1870

Ile Leu Glu Gln Lys Ile Lys Glu Leu Asp Ser Cys Leu Val Arg Gln
        1875                1880                1885

Lys Glu Val His Arg Val Glu Met Glu Glu Leu Thr Ser Lys Tyr Glu
    1890                1895                1900

Lys Leu Gln Ala Leu Gln Gln Met Asp Gly Arg Asn Lys Pro Thr Glu
1905                1910                1915                1920

Leu Leu Glu Glu Asn Thr Glu Glu Lys Ser Lys Ser His Leu Val Gln
                1925                1930                1935

Pro Lys Leu Leu Ser Asn Met Glu Ala Gln His Asn Asp Leu Glu Phe
            1940                1945                1950

Lys Leu Ala Gly Ala Glu Arg Glu Lys Gln Lys Leu Gly Lys Glu Ile
        1955                1960                1965

Val Arg Leu Gln Lys Asp Leu Arg Met Leu Arg Lys Glu His Gln Gln
    1970                1975                1980

Glu Leu Glu Ile Leu Lys Lys Glu Tyr Asp Gln Glu Arg Glu Glu Lys
1985                1990                1995                2000

Ile Lys Gln Glu Gln Glu Asp Leu Glu Leu Lys His Asn Ser Thr Leu
                2005                2010                2015

Lys Gln Leu Met Arg Glu Phe Asn Thr Gln Leu Ala Gln Lys Glu Gln
            2020                2025                2030

Glu Leu Glu Met Thr Ile Lys Glu Thr Ile Asn Lys Ala Gln Glu Val
        2035                2040                2045

Glu Ala Glu Leu Leu Glu Ser His Gln Glu Glu Thr Asn Gln Leu Leu
    2050                2055                2060

Lys Lys Ile Ala Glu Lys Asp Asp Asp Leu Lys Arg Thr Ala Lys Arg
2065                2070                2075                2080
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Tyr Glu Glu Ile Leu Asp Ala Arg Glu Glu Glu Met Thr Ala Lys Val
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Arg Asp Leu Gln Thr Gln Leu Glu Glu Leu Gln Lys Lys Tyr Gln Gln
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Lys Leu Glu Gln Glu Glu Asn Pro Gly Asn Asp Asn Val Thr Ile Met
        2115                2120                2125

Glu Leu Gln Thr Gln Leu Ala Gln Lys Thr Thr Leu Ile Ser Asp Ser
    2130                2135                2140

Lys Leu Lys Glu Gln Glu Phe Arg Glu Gln Ile His Asn Leu Glu Asp
2145                2150                2155                2160

Arg Leu Lys Lys Tyr Glu Lys Asn Val Tyr Ala Thr Thr Val Gly Thr
                2165                2170                2175

Pro Tyr Lys Gly Gly Asn Leu Tyr His Thr Asp Val Ser Leu Phe Gly
            2180                2185                2190

Glu Pro Thr Glu Phe Glu Tyr Leu Arg Lys Val Leu Phe Glu Tyr Met
        2195                2200                2205

Met Gly Arg Glu Thr Lys Thr Met Ala Lys Val Ile Thr Thr Val Leu
    2210                2215                2220

Lys Phe Pro Asp Asp Gln Thr Gln Lys Ile Leu Glu Arg Glu Asp Ala
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Arg Leu Met Phe Thr Ser Pro Arg Ser Gly Ile Phe
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1. A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising determining a level and/or an activity of

(i) a transcription product of a gene coding for golgin-245, and/or

(ii) a translation product of a gene coding for golgin-245 and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

2. A method of monitoring the progression of a neurodegenerative disease in a subject, comprising determining a level and/or an activity of

(i) a transcription product of a gene coding for golgin-245, and/or

(ii) a translation product of a gene coding for golgin-245, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby monitoring the progression of said neurodegenerative disease in said subject.

3. A method of evaluating a treatment for a neurodegenerative disease, comprising determining a level and/or an activity of

(i) a transcription product of a gene coding for golgin-245, and/or

(ii) a translation product of a gene coding for golgin-245, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample from a subject being treated for said disease and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby evaluating said treatment for said neurodegenerative disease.

4. The method according to claim 1 wherein said neurodegenerative disease is Alzheimer's disease.

5. The method according to claim 1 wherein said sample comprises a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.

6. The method according to claim 1 wherein said reference value is that of a level and/or an activity of

(i) a transcription product of a gene coding for golgin-245, and/or

(ii) a translation product of a gene coding for golgin-245, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample from a subject not suffering from said neurodegenerative disease.

7. The method according to claim 1 wherein an alteration in the level and/or activity of a transcription product of the gene coding for golgin-245 and/or a translation product of a gene coding for golgin-245 and/or a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of Alzheimer's disease in said subject.

8. A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease, said kit comprising:

(a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for golgin-245 and (ii) reagents that selectively detect a translation product of a gene coding for golgin-245, and

(b) an instruction for diagnosing, or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of a subject to develop such a disease by (i) detecting a level, or an activity, or both said level and said activity, of said transcription product and/or said translation product of a gene coding for golgin-245, in a sample from said subject; and (ii) diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of said subject to develop such a disease, wherein a varied level, or activity, or both said level and said activity, of said transcription product and/or said translation product compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of said transcription product and/or said translation product similar or equal to a reference value representing a known disease status indicates a diagnosis or prognosis of a neurodegenera-

tive disease, in particular Alzheimer's disease, or an increased propensity or predisposition of developing such a disease.

9. A method of treating or preventing a neurodegenerative disease, in particular Alzheimer's disease, in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of

(i) a gene coding for golgin-245, and/or

(ii) a transcription product of a gene coding for golgin-245, and/or

(iii) a translation product of a gene coding for golgin-245, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

10. A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

(i) a gene coding for golgin-245 and/or

(ii) a transcription product of a gene coding for golgin-245 and/or

(iii) a translation product of a gene coding for golgin-245, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

11. A recombinant, non-human animal comprising a non-native gene sequence coding for golgin-245 or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

(i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and

(ii) introducing said targeting construct into a stem cell of a non-human animal, and

(iii) introducing said non-human animal stem cell into a non-human embryo, and

(iv) transplanting said embryo into a pseudopregnant non-human animal, and

(v) allowing said embryo to develop to term, and

(vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and

(vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

12. Use of the recombinant, non-human animal according to claim 11 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

13. An assay for screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) a gene coding for golgin-245, and/or

(ii) a transcription product of a gene coding for golgin-245, and/or

(iii) a translation product of a gene coding for golgin-245, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii), said method comprising:

(a) contacting a cell with a test compound;

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and

(d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

14. A method of screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) a gene coding for golgin-245, and/or

(ii) a transcription product of a gene coding for golgin-245, and/or

(iii) a translation product of a gene coding for golgin-245, and/or

(i) a fragment, or derivative, or variant of (i) to (iii), said method comprising:

(a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) or (iv) in a matched control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which animal no such test compound has been administered;

(d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of said diseases or disorders.

15. The method according to claim 14 wherein said test animal and/or said control animal is a recombinant animal which expresses the gene coding for golgin-245, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native golgin-245 gene transcriptional control element.

16. An assay for testing a compound, preferably for screening a plurality of compounds for inhibition of binding between a ligand and golgin-245 protein, or a fragment, or derivative, or variant thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said golgin-245 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a compound or a plurality of compounds to be screened for said inhibition of binding to said plurality of containers;

(iii) adding a detectable ligand, in particular a fluorescently detectable ligand, to said containers;

(iv) incubating the liquid suspension of said golgin-245 protein, or said fragment, or derivative, or variant thereof, and said compound or compounds, and said ligand;

(v) measuring amounts of detectable ligand or fluorescence associated with said golgin-245 protein, or with said fragment, or derivative, or variant thereof; and

(vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said golgin-245 protein, or said fragment, or derivative, or variant thereof.

17. An assay for testing a compound, preferably for screening a plurality of compounds, to determine the degree of binding of said compound or compounds to golgin-245 protein, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said golgin-245 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a detectable compound, preferably a plurality of detectable compounds, in particular fluorescently detectable compounds, to be screened for said binding to said plurality of containers;

(iii) incubating said liquid suspension of said golgin-245 protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds;

(iv) measuring amounts of detectable compound or fluorescence associated with said golgin-245 protein, or with said fragment, or derivative, or variant thereof; and

(v) determining the degree of binding by one or more of said compounds to said golgin-245 protein, or said fragment, or derivative, or variant thereof.

18. A protein molecule, said protein molecule being a translation product of the gene coding for golgin-245, SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, or SEQ ID NO. 8, or a fragment, or derivative, or variant thereof, for use as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.

19. A protein molecule, said protein molecule being a translation product of the gene coding for golgin-245, SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, or SEQ ID NO. 8, or a fragment, or derivative, or variant thereof, for use as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

20. Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for golgin-245, SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, or SEQ ID NO. 8, or a fragment, or derivative, or variant thereof, for detecting the pathological state of a cell in a sample from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell.

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专利名称(译)	高尔基体蛋白质用于神经退行性疾病的诊断和治疗用途		
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摘要(译)

本发明公开了golgin-245在阿尔茨海默病患者的特定脑区中的差异表达。基于该发现，本发明提供了用于诊断或预测受试者中的神经变性疾病，特别是阿尔茨海默氏病，或用于确定受试者是否具有发展这种疾病的风险增加的方法。此外，本发明提供了使用编码golgin-245的基因治疗或预防阿尔茨海默病和相关神经变性疾病的治疗和预防方法。还公开了筛选神经变性疾病的调节剂的方法。