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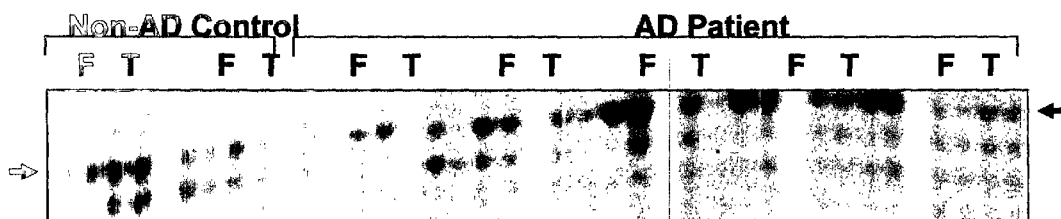
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(54) Title: DIAGNOSTIC AND THERAPEUTIC USE OF A GOLGI PROTEIN FOR NEURODEGENERATIVE DISEASES

Identification of differentially expressed genes in a fluorescence differential display screen



(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.



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DIAGNOSTIC AND THERAPEUTIC USE OF A GOLGI PROTEIN FOR NEURODEGENERATIVE DISEASES

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.

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.

The amyloid- β ($A\beta$) 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 $A\beta$ 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 μ m to 200 μ m and are composed of insoluble fibrillar amyloids, fragments of dead

neurons, of microglia and astrocytes, and other components such as neurotransmitters, apolipoprotein E, glycosaminoglycans, α 1-antichymotrypsin and others. The generation of toxic A β 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).

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).

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.

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 plasmoprotein 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.

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.

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*).

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.

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-ribosylation 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.

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.

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 A β 42, 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.

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.

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.

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, New Jersey, 2000; Mayeux and Christen, *Epidemiology of Alzheimer's Disease: From Gene to Prevention*, Springer Press, Berlin, Heidelberg, New York, 1999; Younkin, Tanzi and Christen, *Presenilins and Alzheimer's Disease*, Springer Press, Berlin, Heidelberg, New York, 1998).

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.

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.

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.

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.

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 variant 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.

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.

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.

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.

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.

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.

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.

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.

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, New York, 2001; Schena M., *Microarray Biochip Technology*, Eaton Publishing, Natick, MA, 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.

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, New York, 1999 and Edwards R, *Immunodiagnosics: 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, MA, 2000).

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.

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:

(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

(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

- 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

- 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.

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.

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 perturbation 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).

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).

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, MA, 1999).

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.

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 DA, *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).

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.

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).

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.

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.

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.

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.

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, New York 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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, New York, 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, NY, 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, New York, 1999 and Edwards R., *Immunodiagnosics: 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.

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 US patent 6150173.

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.

Figure 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).

Figure 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.

Figure 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.

Figure 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).

Figure 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.

Figure 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.

Figure 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.

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

Figure 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.

Figure 10 represents SEQ ID NO. 7, the nucleotide sequence of human golgin-245 splice variant 3 cDNA, comprising 7743 nucleotides.

Figure 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.

Figure 12 represents SEQ ID NO. 9, the nucleotide sequence of human golgin-245 splice variant 4 cDNA, comprising 7761 nucleotides.

Figures 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 (Figure 13b) and samples from the frontal cortex (F) and the hippocampus (H) of AD patients (Figure 14b) was

performed by the LightCycler rapid thermal cycling technique. Likewise, samples of healthy, age-matched control individuals were compared (Figure 13a for frontal cortex and temporal cortex, Figure 14a 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 (Figures 13a and 14a, arrowheads), whereas in Alzheimer's disease (Figures 13b and 14b, 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.

Figures 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 (Figure 15b) and samples from the frontal cortex (F) and the hippocampus (H) of AD patients (Figure 16b) was performed by the LightCycler rapid thermal cycling technique. Likewise, samples of healthy, age-matched control individuals were compared (Figure 15a for frontal cortex and temporal cortex, Figure 16a 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 (Figures 15a and 16a, arrowheads), whereas in Alzheimer's disease (Figures 15b and 16b, 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.

Figure 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) (Figure 17a, low magnification) as perinuclear punctate staining in both neuronal and glial cells, suggesting a localization of golgin-245 on the Golgi stacks (Figure 17b, high magnification). Blue signals indicate nuclei stained with DAPI.

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.

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).

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).

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:

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 Figure 1) and stored at -80°C until RNA extractions were performed.

(ii) Isolation of total mRNA:

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):

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.

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 1x RT buffer (Qiagen), 10 U RNase inhibitor (Qiagen) and 1 µM of either one-base-anchor oligonucleotides HT₁₁A, HT₁₁G or HT₁₁C (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), 1x GeneAmp PCR buffer (Applied Biosystems), 1.5 mM MgCl₂ (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, 60W, 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, overlaid with 200 µl sterile water and kept at -20°C until extraction.

Elution and reamplification of DD products: The differential bands were extracted from the gel by boiling in 200 µl H₂O 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.

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 Figure 2.

(iv) Confirmation of differential expression by quantitative RT-PCR:

Positive corroboration of differential expression of the golgin-245 gene was performed using the LightCycler technology (Roche). This technique features rapid thermal cycling 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).

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'

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'.

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 MgCl₂; 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 MgCl₂. 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.

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'-ACTGAAGCACTACGGGCCTG-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'-GGTCAAATTTACCCTGGCCA-3' and 5'-TTCATCAAGCGTCAGCAGTTC-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'-CGTCATGGGTGTGAACCATG-3' and 5'-GCTAAGCAGTTGGTGGTGACAG-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'-GTCGCTGGTCAGTTCGTGATT-3' and 5'-AGCAGTTGGCTGTTGTACCTCTC-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).

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:

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

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:

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

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

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 Figures 13 and 14, and in Figures 15 and 16, respectively.

(v) Immunohistochemistry:

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 30min, 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 5µM DAPI in PBS for 3min (blue signal). In order to block the autofluorescence 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, distilled water and PBS. The sections were coverslipped by 'Vectrashield mounting medium' (Vector Laboratories, Burlingame, CA) 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)

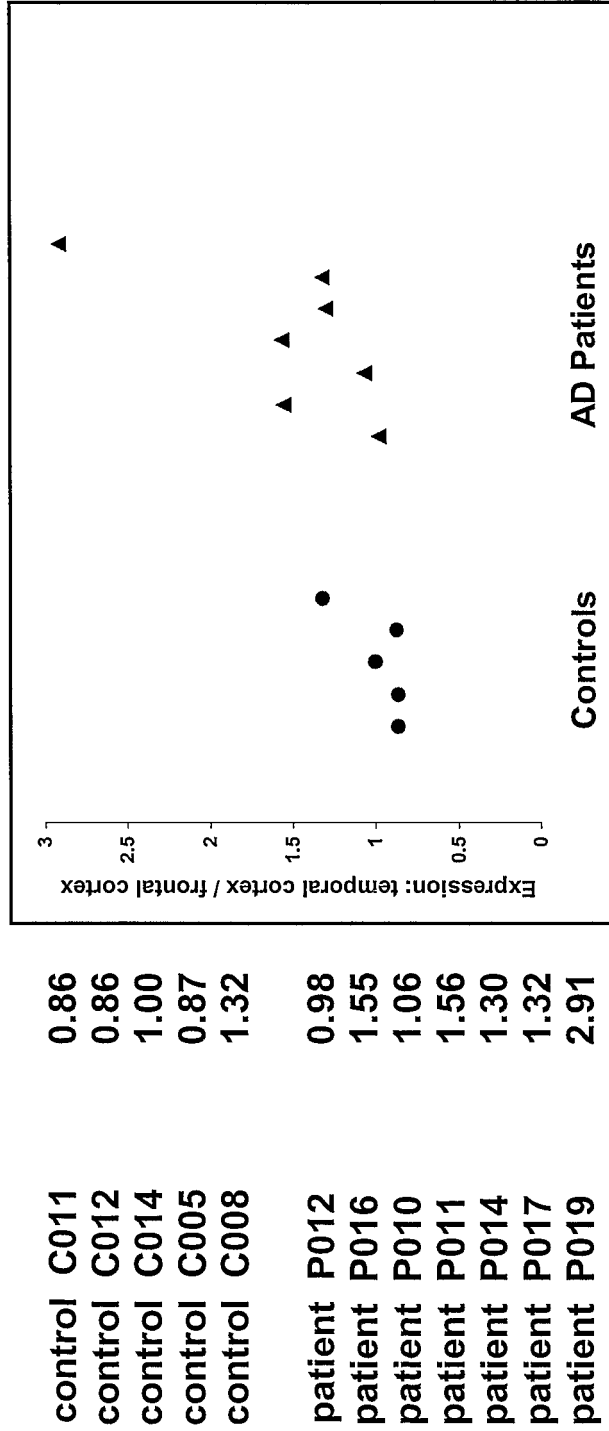
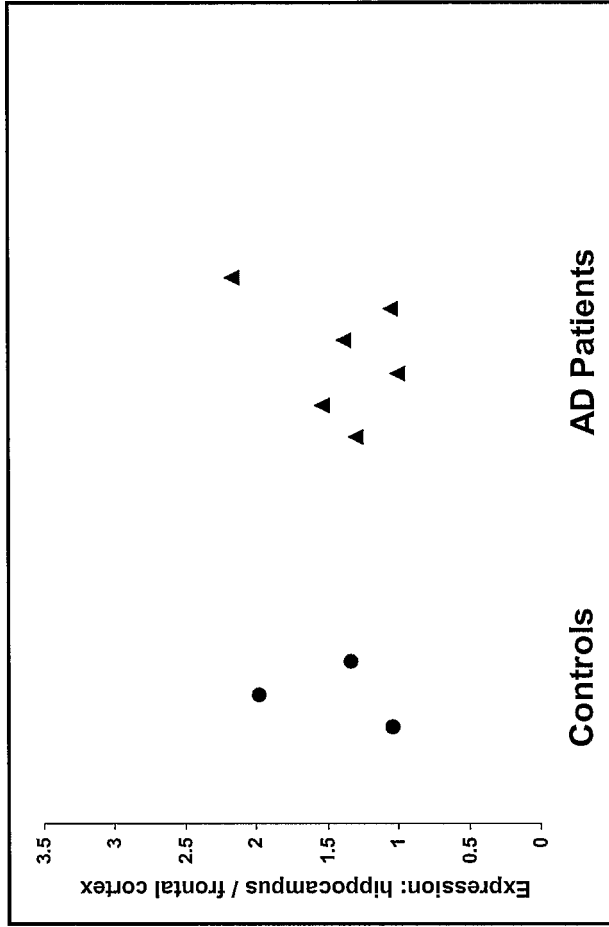


Table 2:

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)

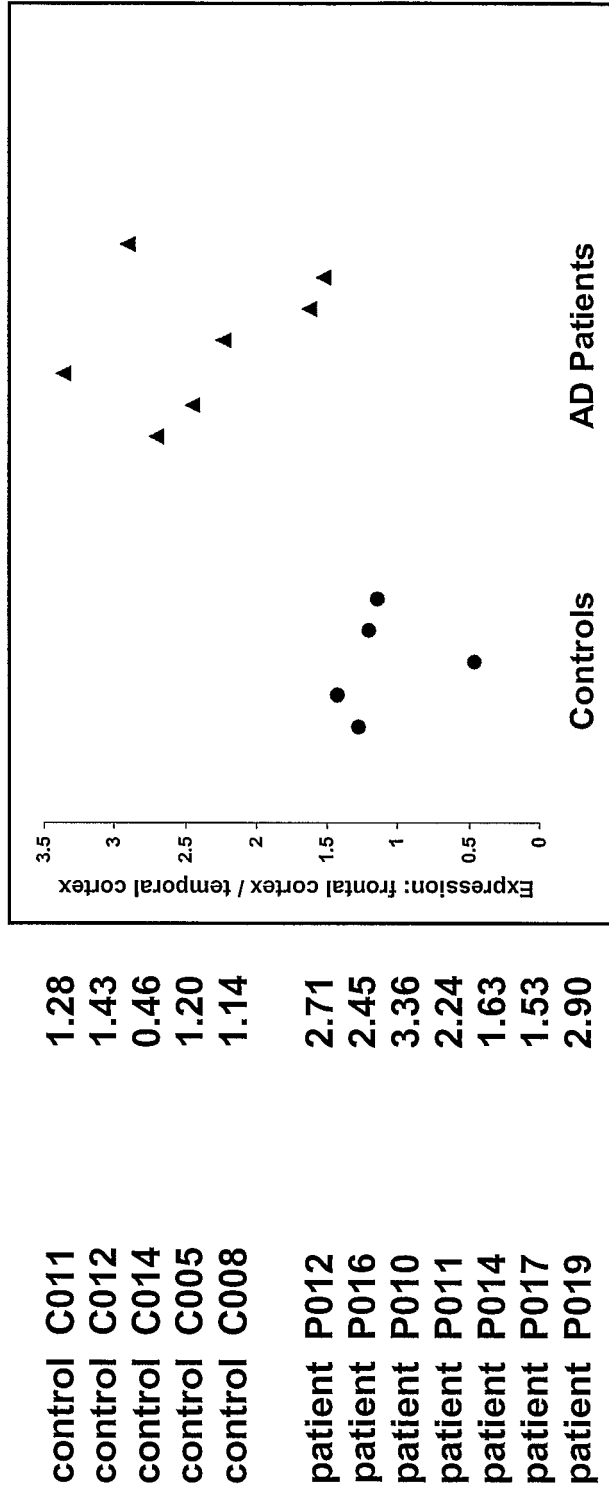
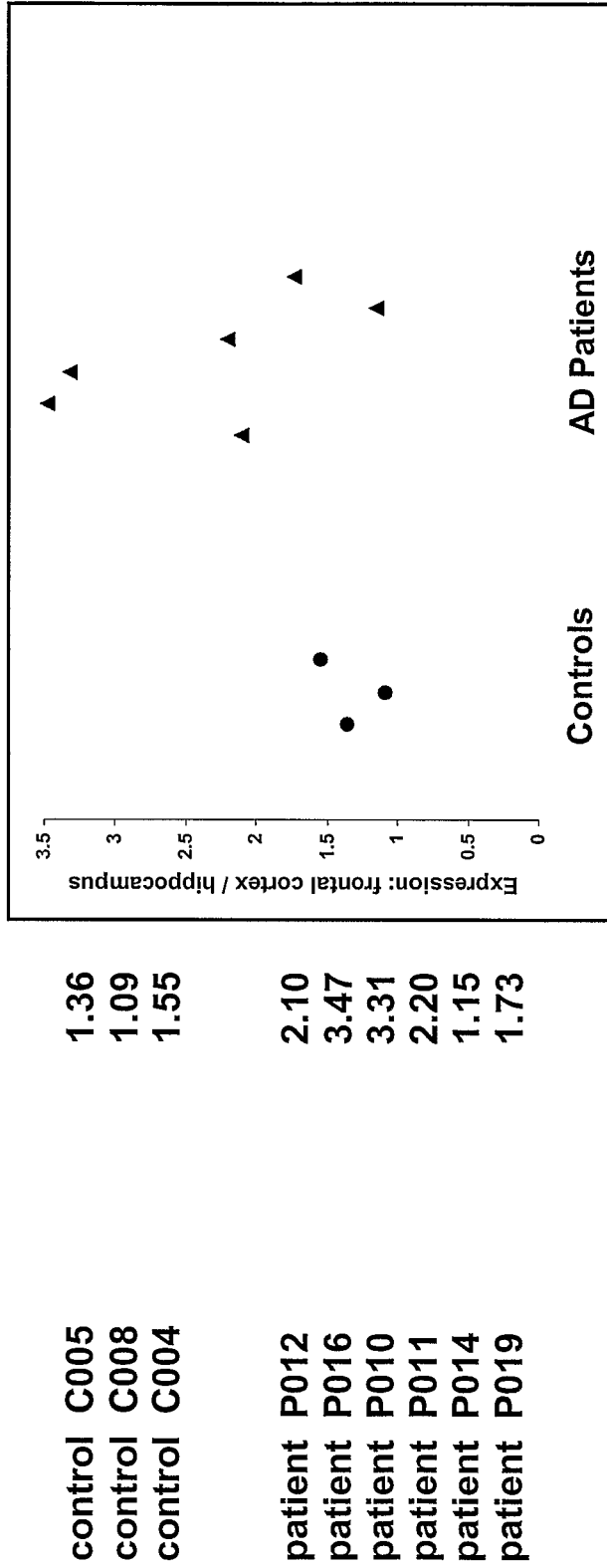


Table 4:

sample Δ (fold)
(frontal cortex / hippocampus)



CLAIMS

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 any of claims 1 to 3 wherein said neurodegenerative disease is Alzheimer's disease.
5. The method according to any of claims 1 to 4 wherein said sample comprises a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.
6. The method according to any of claims 1 to 5 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 any of claims 1 to 6 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 neurodegenerative 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
- (v) 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.

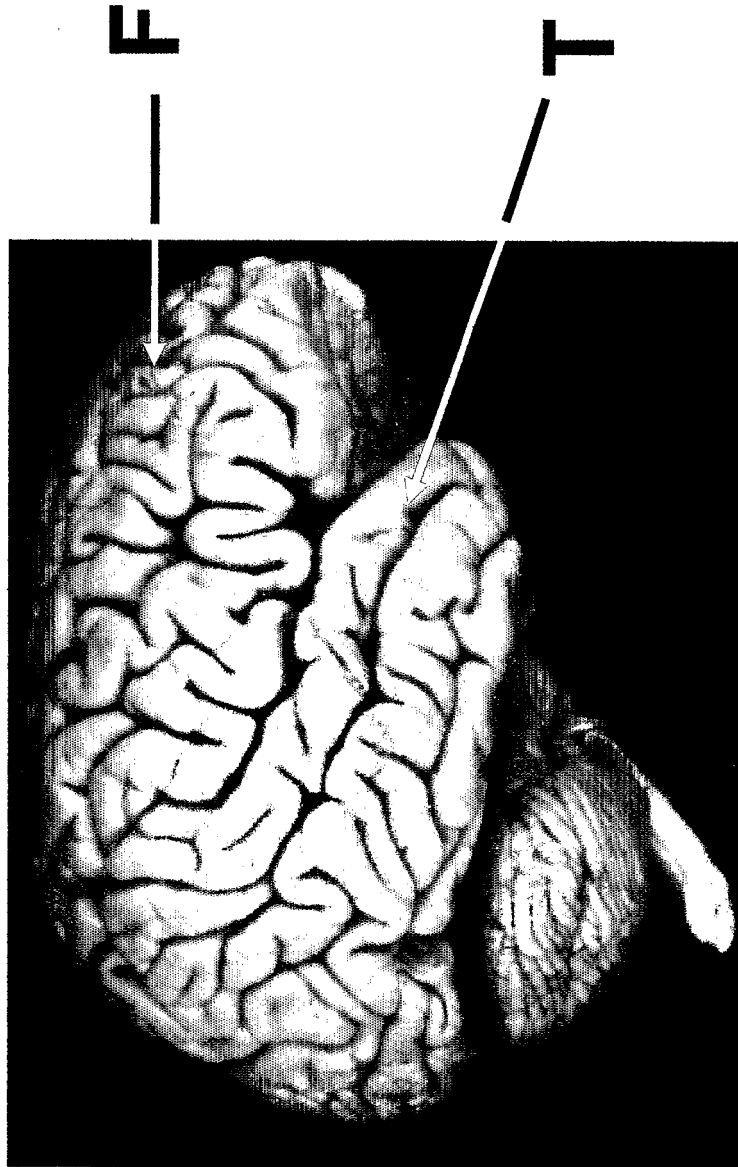
18. A protein molecule, said protein molecule being a translation product of the gene coding for golgin-245, SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, or SEQ ID NO. 8, or a fragment, or derivative, or variant thereof, for use as a diagnostic target for detecting a neurodegenerative disease, preferably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

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



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**Fig. 2: Identification of differentially expressed genes
in a fluorescence differential display screen**



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Figure 3: SEQ ID NO. 1

Length: 36 bp

1 AGTTAAGTTT CTTTGTA AAA CACTGATTTT TTCTCC

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

Length: 2228 aa

1	MFKKLLKQKIS	EEQQQLQQAL	APAQASSNSS	TPTRMRSRTS	SFTEQLDEGT
51	PNRESGDTQS	FAQKLQLRVP	SVESLFRSPI	KESLFRSSSK	ESLVRTSSRE
101	SLNRLDLDS	TASFDPPSDM	DSEAEDLVGN	SDSLNKEQLI	QRLRRMERSL
151	SSYRGKysel	VTAYQMLQRE	KKKLGILSQ	SQDKSLRIA	ELREELQMDQ
201	QAKKHLQEEF	DASLEEKDQY	ISVLQTVVSL	LKQRLRNGPM	NVDVLKPLPQ
251	LEPQAEVFTK	EENPESDGEF	VVEDGTSVKT	LETLQQRVVKR	QENLLKRCCKE
301	TIQSHKEQCT	LLTSEKEALQ	EQLDERLQEL	EKIKDLHMAE	KTKLITQLRD
351	AKNLIEQLEQ	DKGMVIAETK	RQMHEMLEMK	EEETIAQLRSR	IKQMTTQGEE
401	LREQKEKSER	AAFELEKAL	STAQKTEEAR	RKLKAEMDEQ	IKTIEKTSEE
451	ERISLQQELS	RVKQEVVDVM	KKSSEEQIAK	LQKLHEKELA	RKEQELTKKL
501	QTREREFQEQ	MKVALEKSQS	EYLKISQEK	QQESLAEEL	ELOKKAILTE
551	SENKLRDLQ	EAETYRTRIL	ELESSLEKSL	QENKNQSKDL	AVHLEAEKNK
601	HNKEITVMVE	KHKTELESK	HQQDALWTEK	LQVLKQQYQT	EMEKLREKCE
651	QEKETLLKDK	EII FQAHIEE	MNEKTLEKLD	VKQTELESLS	SELSEVLKAR
701	HKLEEEELSVL	KDQTDKMKQE	LEAKMDEQKN	HHQQQVDSII	KEHEVSIQRT
751	EKALKDQINQ	LELLLKERDK	HLKEHQAHVE	NLEADIKRSE	GELQQASAKL
801	DVFQSYQSAT	HEQTKAYEEQ	LAQLQKLLD	LETERILLTK	QVAEVEAQKK
851	DVCTELDAHK	IQVQDLMQQL	EKQNSEMEQK	VKSLTQVYES	KLEDGNKEQE
901	QTKQILVEKE	NMILQMREGQ	KKEIEILTQK	LSAKEDSIHI	LNEEYETKFK
951	NQEKKMEKVK	QKAKEMQETL	KKLLDQEAQ	LKKELENTAL	ELSQKEKQFN
1001	AKMLEMAQAN	SAGISDAVSR	LETNQKEQIE	SLTEVHRRRL	NDVISIWEKK
1051	LNQQAEELQE	IHEIQLQEKE	QEVAEKQKI	LLFGCEKEEM	NKEITWLKEE
1101	GVKQD'TTLNE	LQEQLKQKSA	HVNSLAQDET	KLKAHLEKLE	VDLNLKSLKEN
1151	TFLQEQLEVEL	KMLAEEDKRK	VSELTSLKKT	TDEEFQSLKS	SHEKSNKSLE
1201	DKSLEFKKLS	EELAIQLDIC	CKKTEALLEA	KTNELINISS	SKTNAILSRI
1251	SHCQHRTTKV	KEALLIKTCT	VSELEAQLRQ	LTEEQNTLNI	SFOQATHQLE
1301	EKENQIKSMK	ADIESLVTEK	EALQKEGNQ	QQAASEKESC	ITQLKKELSE
1351	NINAVTLMKE	ELKEKKVEIS	SLSKQLTDLN	VQLQNSISLS	EKEAAISSLR
1401	KQYDEEKCEL	LDQVQDLSFK	VDTLSKEKIS	ALEQVDDWSN	KFSEWKKKAQ
1451	SRFTQHONTV	KELQIQLELK	SKEAYEKDEQ	INLLKEELDQ	QNKRFDCCLKG
1501	EMEDDKSKME	KKESNLETEL	KSQTARIMEL	EDHITQKTIE	IESLNEVLKN
1551	YNQOKDIEHK	ELVQKLQHFQ	ELGEEKDNRV	KEAEEKILTL	ENQVYSMKAE
1601	LETKKKELEH	VNLSVKSKEE	ELKALEDRL	SESAAKLAE	KRKAEQKIAA
1651	IKKQLLSQME	EKEEQYKKG	ESHLSLNTK	LQEREREVHI	LEEKLKSVES
1701	SQSETLIVPR	SAKNVAAYTE	QEEADSQGC	QKTYEEKISV	LQRNLTEKEK
1751	LLQRVGQEK	ETVSSHFEMR	CQYQERLIK	EHAQAKQHED	QSMIGHLQEE
1801	LEEKNKKYSL	IVAQHVEKEG	GKNNIQAKQN	LENVFDVQK	TLQEKELTCQ
1851	ILEQKIKELD	SCLVRQKEVH	RVEMEELTSK	YEKLQALQOM	DGRNKPTTELL
1901	EENTEKSKS	HLVQPKLLSN	MEAQHNDLEF	KLGAEREKQ	KLKKEIVRLQ
1951	KDLRMLRKEH	QQELEILKKE	YDQEREKIK	QELEDLELKH	NSTLQKLMRE
2001	FNTQLAQKEQ	ELEMTIKETI	NKAQVEAE	LESHQEETNQ	LLKKIAEKDD
2051	DLKRTAKRYE	EILDAREEEM	TAKVRDLQTO	LEELQKKYQQ	KLEQEENPGN
2101	DNVTIMELQT	QLAQKTTLIS	DSKLKEQEFR	EQIHNLEDRL	KKYEKNVYAT
2151	TVGTPYKGGN	LYHTDVSLFG	EPTEFEYLRK	VLFYMMGRE	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 GTTGTTCGTCG CCGCCGCGGC TCCCAGGGGCT
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 AACAGAATG AGGAGCAGGA
401 CATCTTCAT TACAGAGCAA CTTGATGAAG GTACACCCAA TAGAGAGTCA
451 GGTGACACAC AGTCTTTTGC ACAGAAGCTC CAGCTCCGGG TGCCCTCCGT
501 GGAGTCTTTG TTTCGAAAGT 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 CTTTCGGAGAA
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 AACAAAGATA GGGAAATGGTA ATCGCAGAGA CAAAACGTCA
1401 GATGCATGAA ACCCTGGAAA TGAAAGAAGA AGAATTGCT CAACTCCGTA
1451 GTCGCATCAA ACAGATGACT ACCCAGGGAG AGGAATTACG GGAACAGAAA
1501 GAAAAGTCCG AAAGAGCTGC TTTTGAGGAA CTTGAAAAAG CTTTGAGTAC
1551 AGCCCAAAA 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 GAATTCAGG AACAAATGAA AGTAGCTCTT GAAAAGAGTC AATCAGAATA
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1901 AGTTAGAGTT GCAGAAAAAA GCAATCCTCA CAGAAAGTGA AAATAAACTT
1951 CGGGACCTTC AGCAAGAAGC AGAGACTTAC AGAACTAGAA TTCTTGAATT
2001 GGAAAGTTCT TTGGAAAAAA GCTTACAAGA AAACAAAAT CAGTCAAAAG
2051 ATTTGGCTGT TCATCTGGAA GCTGAAAAAA ATAAGCACAA TAAGGAGATT
2101 ACAGTCATGG TTGAAAAACA CAAGACAGAA TTGGAAAGCC TTAAGCATCA
2151 GCAGGATGCC CTTTGGACTG AAAAATCCA AGTCTTAAAG CAACAATATC
2201 AGACTGAAAT GGAAAACTT AGGGAAAAGT GTGAACAAGA AAAAGAAACA
2251 TTGTTGAAAG ACAAAGAGAT TATCTTCCAG GCCCACATAG AAGAAATGAA
2301 TGAAAAGACT TTAGAAAAGC TTGATGTGAA GCAAACAGAA CTAGAATCAT
2351 TATCTTCTGA ACTGTCAGAA GTATTAAAAG CCCGTCACAA ACTAGAAGAG
2401 GAACTTCTG 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 TTGTA CTGAG
 2851 TTAGATGCTC ACAAATCCA GGTGCAGGAC TTAATGCAGC AACTTGAAAA
 2901 ACAAATAGT 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 TAAAAACCA AGAAAAAAG
 3151 ATGGAAAAAG TTAAGCAGAA AGCAAAGGAG ATGCAAGAAA CGTTAAAGAA
 3201 AAAATTACTG GATCAGGAAG CCAACTTAA GAAAGAGCTT GAAAATACTG
 3251 CTCTAGAGCT TAGTCAGAAA GAAAAACAGT TTAATGCCAA AATGCTGGAA
 3301 ATGGCACAGG CTAAGTCAGC TGGAAATCAGT GATGCAGTGT CAAGACTGGA
 3351 AACAAACCAA AAAGAACAAA TAGAAAGTCT TACTGAGGTT CATCGACGAG
 3401 AACTCAATGA TGTCATATCA ATCTGGGAAA AGAACTTAA 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 AAATAACT GAAAGCTCAT CTTGAAAAGC
 3701 TAGAGTTGA CTTGAATAAG TCTCTGAAGG AAAATACTTT TCTTCAAGAG
 3751 CAGCTAGTTG AACTGAAGAT GCTGGCAGAA GAAGATAAGC GGAAGGTTTC
 3801 TGAGTTGACT AGCAAGTTGA AAACCACAGA TGAAGAATTC CAGAGTTTGA
 3851 AATCTTACA TGAAAAAGT AACAAAAGCC TAGAGGACAA GAGCTTGGAA
 3901 TTTAAAAAAC TGTCTGAGGA ACTAGCGATT CAGCTAGATA TTTGCTGTAA
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 4051 CGTACAATA AAGTTAAGGA GGCAGTTGTA ATTAAACTT GCACAGTTTC
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 4151 ATATTTCTTT TCAACAGGCT ACTCATCAGT TAGAAGAAA AGAAAATCAA
 4201 ATTAAGAGCA TGAAGGCTGA TATTGAAAGT CTTGTAACAG AAAAAGAAGC
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 4301 CTTGTATAAC ACAGTTGAAG AAAGAGTTAT CTGAAAACAT CAATGCTGTC
 4351 ACATTGATGA AAGAAGAGCT TAAAGAAAA AAAGTTGAGA TTAGCAGTCT
 4401 TAGTAAACAA CTAAGTATT TGAATGTTCA GCTTCAAAT AGCATCAGCC
 4451 TATCCGAAAA AGAAGCAGCC ATTTTCATCAC TAAGAAAGCA GTATGATGAA
 4501 GAAAAATGTG AATTGCTGGA TCAGGTGCAA GATTTATCTT TTAAAGTTGA
 4551 CACTCTGAGT AAAGAGAAAA TTTCTGCTCT TGAGCAGGTA GATGACTGGT
 4601 CCAATAAAT CTGAGAAATG AAGAAGAAAG CACAGTCAAG ATTTACACAG
 4651 CATCAAAACA CTGTTAAAGA ATTCAGATC CAGCTTGAGT TAAAATCAA
 4701 GGAAGCTTAT GAAAAGGATG AGCAGATAAA TTTATTGAAG GAAGAGCTTG
 4751 ATCAGCAAAA TAAAAGATTT GATTGTTTAA AGGGTGAAAT GGAAGACGAC
 4801 AAGAGCAAGA TGGAGAAAA GGAGTCTAAT TTAGAAACAG AGTTAAAGTC
 4851 TCAACAGCA AGAATTATGG AATTAGAGGA CCATATTACC CAGAAAATA
 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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5251 TTATCTCAAA TGGAAGAGAA AGAAGAACAG TATAAAAAAG GTACAGAAAG
 5301 CCATTTGAGT GAGCTAAATA CAAAATTGCA GGAAAGAGAA AGGGAAGTTC
 5351 ACATCTTGGA AGAAAACTT AAGTCAGTGG AAAGTTCACA GTCAGAAACA
 5401 TTAATTGTAC CCAGATCAGC AAAAAATGTG GCAGCATATA CTGAACAAGA
 5451 AGAAGCAGAT TCCCAAGGCT GTGTGCAGAA GACATATGAA GAAAAAATCA
 5501 GTGTTTTACA AAGAACTTA ACTGAAAAAG AAAAGCTATT GCAGAGGGTA
 5551 GGGCAGGAAA AAGAAGAGAC AGTTTCTTCT CATTTTGGAA TGCATGCCA
 5601 ATACCAGGAG CGCTTAATAA AGCTAGAACA TGCTGAGGCA AAGCAACATG
 5651 AAGATCAAAG TATGATAGGT CATCTTCAAG AGGAGCTTGA AGAAAAAAC
 5701 AAGAAATATT CTTGATAGT AGCCCAGCAT GTGGAAAAAG AAGGAGGTAA
 5751 AAATAACATA CAGGCAAAGC AAAACTTGGA AAATGTGTTT GACGACGTCC
 5801 AGAAAACCCCT CCAGGAGAAG GAACCTAACCT GTCAGATTTT GGAGCAAAG
 5851 ATAAAAGAGC TGGATTCTTG CTTAGTAAGA CAGAAAGAAG TACATAGAGT
 5901 TGAAATGGAA GAGTTGACCT CAAAATATGA AAAATTACAG GCTTTTACAAC
 5951 AGATGGATGG AAGAAATAAA CCCACAGAAC TTTTGGAGA AACACTGAA
 6001 GAAAAGTCCA AATCACATTT GGTCCAACCC AAATTGCTTA GTAACATGGA
 6051 AGCCCAGCAC AATGATCTGG AGTTTAAATT AGCCGGGGCA GAACGGGAGA
 6101 AACAGAAACT GGGCAAGGAG ATTGTTAGAT TGCAGAAAGA CCTTCGAATG
 6151 TTGAGAAAGG AGCATCAGCA AGAATGGAA ATACTAAAGA AAGAATATGA
 6201 TCAAGAAAGG GAAGAGAAAA TCAAACAGGA GCAGGAAGAT CTTGAACTGA
 6251 AGCACAATTC CACATTAATA CAGCTGATGA GGGAGTTTAA TACACAGCTG
 6301 GCACAAAAGG AACAAAGACT GGAAATGACC ATAAAAGAAA CTATCAATAA
 6351 GGCCCAGGAG GTGGAGGCTG AACTTTTAGA AAGCCATCAA GAAGAGACAA
 6401 ATCAGTTACT TAAAAAATT GCTGAGAAAG ATGATGATCT AAAACGAACA
 6451 GCCAAAAGAT ATGAAGAAAT CCTTGATGCT CGTGAAGAAG AAATGACTGC
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 6551 AGCAAAAGCT AGAGCAGGAG GAGAACCCTG GCAATGATAA TGTAACAATT
 6601 ATGGAGCTAC AGACACAGCT AGCACAGAAG ACGACTTTAA TCAGTGATTC
 6651 GAAATTGAAA GAGCAAGAGT TCAGAGAACA GATTCACAAT TTAGAAGACC
 6701 GTTTGAAGAA ATATGAAAAG AATGTATATG CAACAACCTGT GGGGACACCT
 6751 TACAAAGGTG GCAATTTGTA CCATACGGAT GTCTCACTCT TTGGAGAACC
 6801 TACCGAATTT GAGTATTTGC GAAAAGTGCT TTTTGAGTAT ATGATGGGTC
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 7251 TCTTTTAAA GAACGGCTTA CCTTTCCTAT TTATTTTATG GGTGATTTTT
 7301 TAAAAAGACT TGTGCAATAC ATTTTGAGGT GAAACTTAGT GGATTTTTTC
 7351 TGATAAATTA GAGCATTTAA TTGACTATTT TATTCAGGTT GATCTGTTGA
 7401 ATATTTGCTA AAGACCAGTT CTTTAAGCTA AGACATGTAA AAAATCCCAA
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 7501 GAAAAACAC TACTGTAAAT TGTGAATAGC CAATACATAA CTGTATTGTA
 7551 TGCAAATCTG TGATTGTTGG CAGTGTATC TCTGAGAAAC AGATAAATAA
 7601 AGTTTATTTA CTATATAACC AAAAAAAAAA AAAAAA

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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  SLNRLDLDS  TASFDPPSDM  DSEAEDLVGN  SDSLNKEQLI  QRLRRMERSL
151  SSYRGKYSEL  VTAYQMLQRE  KKKLQGILSQ  SQDKSLRRIA  ELREELQMDQ
201  QAKKHLQEEF  DASLEEKDQY  ISVLQTVSL  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  SENKLRLDQQ  EAETyrTRIL  ELESSLEKSL  QENKNQSKDL  AVHLEAEKNK
601  HNKEITVMVE  KHKTELESK  HQDALWTEK  LQVLKQQYQT  EMEKLREKCE
651  QEKETLLKDK  EIIFQAHIEE  MNEKTLEKLD  VKQTELESLS  SELSEVLKAR
701  HKLEEEELSVL  KDQTDKMKQE  LEAKMDEQKN  HHQQQVDSII  KEHEVSIQRT
751  EKALKDQINQ  LELLLKERDK  HLKEHQAHVE  NLEADIKRSE  GELQQASAKL
801  DVFQSYQSAT  HEQTKAYEEQ  LAQLQKLLD  LETERILLTK  QVAEVEAQKK
851  DVCTELDAHK  IQVQDLMQQL  EKQNSEMEQK  VKSLTQVYES  KLEDGNKEQE
901  QTKQILVEKE  NMILQMREGQ  KKEIEILTQK  LSAKEDSIHI  LNEEYETKFK
951  NQEKKMEKVK  QKAKEMOETL  KKKLLDQEAk  LKKELENTAL  ELSQKEKQFN
1001  AKMLEMAQAN  SAGISDAVSR  LETNQKEQIE  SLTEVHRREL  NDVISIWEKK
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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
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1601  LETKKKELEH  VNLSVKSKEE  ELKALEDRL  SESAAKLAE  L  KRKAEQKIAA
1651  IKKQLLSQME  EKEEQYKKGt  ESHLSELNTK  LQEREREVHI  LEEKLKSVES
1701  SQSETLIVPR  SAKNVAAYTE  QEEADSQGCv  QKTYEEKISV  LQRLNTEKEK
1751  LLQRVGQEK  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  YDQEREKIK  QEQedLELKH  NSTLQLMRE
2001  FNTQLAQKEQ  ELEMTIKETI  NKAQEVeAEL  LESHQEETNQ  LLKKIAEKDD
2051  DLKRTAKRYE  EILDAREEEM  TAKVRDLQTo  LEELQKKYQQ  KLEQEENPGN
2101  DNVTIMELQT  QLAQKTTLIS  DSKLKEQEFr  EQIHNLEDRL  KKYEKNVYAT
2151  TVGTPYKGGN  LYHTDVSLFG  EPTEFEYLRK  VLFeyMMGRE  TKTMakVITt
2201  VLKFPDDQTQ  KILEREDARL  MFTSPRSgIF

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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 GTTGTCTGTCG CCGCCGCGGC TCCCAGGGCT
51  GGATGGGGGG CCGAGGCCAG CCAGTGGCAC CCGGAAGAAA GAGACGCGGC
101 GGCGGCGACG CCGACACCCT CAGGACGAGT GTCCGGACTT GCCCAGAGCC
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 AACAAAGATG 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 CCACCCCTCTG 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 TGTCTCTCAA 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 TCAGTACAT
1201 AAGGAACAAT GTACACTATT AACTAGTGAA AAAGAAGCTC TGCAAGAACA
1251 ACTGGATGAA AGACTTCAAG AACTAGAAAA GATAAAGGAC CTTCATATGG
1301 CCGAGAAGAC TAAACTTATC ACTCAGTTGC GTGATGCAAA GAACTTAATT
1351 GAACAGCTTG AACAAAGATA GGAATGGTA 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 GTTGTGTGATG TAATGAAAAA
1701 ATCCTCAGAA GAACAAATTG CTAAGCTACA GAAGCTTCAT GAAAAGGAGC
1751 TGGCCAGAAA AGAGCAGGAA CTGACCAAGA AGCTTCAGAC CCGAGAAAGG
1801 GAATTCAGG 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 CAGTCAAAG
2051 ATTTGGCTGT TCATCTGGAA GCTGAAAAAA ATAAGCACAA TAAGGAGATT
2101 ACAGTCATGG TTGAAAAACA CAAGACAGAA TTGGAAAGCC TTAAGCATCA
2151 GCAGGATGCC CTTTGGACTG AAAAATCCA AGTCTTAAAG CAACAATATC
2201 AGACTGAAAT GGAAAACTT AGGGAAAAGT GTGAACAAGA AAAAGAAACA
2251 TTGTTGAAAG ACAAAGAGAT TATCTTCCAG GCCCAGATAG AAGAAATGAA
2301 TGAAAAGACT TTAGAAAAGC TTGATGTGAA GCAAACAGAA CTAGAATCAT
2351 TATCTTCTGA ACTGTCAGAA GTATTTAAAAG CCCGTCACAA ACTAGAAGAG
2401 GAACTTTCTG TTCTGAAAAG TCAAACAGAT AAAATGAAGC AGGAATTAGA
2451 GGCCAAGATG GATGAACAGA AAAATCATCA CCAGCAGCAA GTTGACAGTA

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2501 TCATTAAAGA ACACGAGGTA TCTATCCAGA GGA CTGAGAA 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 ACAAATCCA GGTGCAGGAC TTAATGCAGC AACTTGAAAA
 2901 ACAAATAGT 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 AGAAAAAAG
 3151 ATGGA AAAAG TTAAGCAGAA AGCAAAGGAG ATGCAAGAAA CGTTAAAGAA
 3201 AAAATTACTG GATCAGGAAG CCAA ACTTAA GAAAGAGCTT GAAAATACTG
 3251 CTCTAGAGCT TAGTCAGAAA GAAAAACAGT TTAATGCCAA AATGCTGGAA
 3301 ATGGCACAGG CTA ACTCAGC TGG AATCAGT GATGCAGTGT CAAGACTGGA
 3351 AACAAACCAA AAAGAACAAA TAGAAAGTCT TACTGAGGTT CATCGACGAG
 3401 AACTCAATGA TGT CATATCA 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 AA ACTAACT GAAAGCTCAT CTTGAAAAGC
 3701 TAGAGGTTGA CTTGAATAAG TCTCTGAAGG AAAATACTTT TCTTCAAGAG
 3751 CAGCTAGTTG AACTGAAGAT GCTGGCAGAA GAAGATAAGC GGAAGGTTTC
 3801 TGAGTTGACT AGCAAGTTGA AA ACCACAGA TGAAGAATTC CAGAGTTTGA
 3851 AATCTTCACA TGAAAAAGT AACAAAAGCC TAGAGGACAA GAGCTTGGA
 3901 TTTAAAAAAC TGTCTGAGGA ACTAGCGATT CAGCTAGATA TTTGCTGTAA
 3951 GAAAACCGAA GCCTTATTAG AAGCTAAAAC AAATGAGCTA ATCAACATTA
 4001 GTAGTAGTAA AACTAATGCC ATTTCTTCTA GGATTTCTCA TTGTCAGCAC
 4051 CGTACA ACTA AAGTTAAGGA GGC ACTGTTA ATTAAA ACTT GCACAGTTTC
 4101 TGAATTAGAA GCACA ACTTA GACAGTTGAC AGAGGAGCAA AATACACTAA
 4151 ATATTTCTTT TCAACAGGCT ACTCATCAGT TAGAAGAAA 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 CTA ACTGATT TGAATGTTCA GCTTCAAAT AGCATCAGCC
 4451 TATCCGAAAA AGAAGCAGCC ATTT CATCAC TAAGAAAGCA GTATGATGAA
 4501 GAAAAATGTG AATTGCTGGA TCAGGTGCAA GATTTATCTT TTAAAGTTGA
 4551 CACTCTGAGT AAAGAGAAAA TTTCTGCTCT TGAGCAGGTA GATGACTGGT
 4601 CCAATAAAT CT CAGAATGG AAGAAGAAAG CACAGTCAAG ATTTACACAG
 4651 CATCAAAACA CTGTTAAAGA ATTGCAGATC CAGCTTGAGT TAAAATCAA
 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 GGTT CAGAAA 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
 5251 TTATCTCAA TGGAAGAGAA AGAAGAACAG TATAAAAAAG GTACAGAAAG
 5301 CCATTTGAGT GAGCTAAATA CAAAATTGCA GGAAAGAGAA AGGGAAGTTC
 5351 ACATCTTGGA AGAAAACTT AAGTCAGTGG AAAGTTCACA GTCAGAAACA
 5401 TTAATTGTAC CCAGATCAGC AAAAAATGTG GCAGCATATA CTGAACAAGA
 5451 AGAAGCAGAT TCCCAAGGCT GTGTGCAGAA GACATATGAA GAAAAAATCA
 5501 GTGTTTTACA AAGAACTTA ACTGAAAAAG AAAAGCTATT GCAGAGGGTA
 5551 GGGCAGGAAA AAGAAGAGAC AGTTTCTTCT CATTTTGAAA TGCGATGCCA
 5601 ATACCAGGAG CGCTTAATAA AGCTAGAACA TGCTGAGGCA AAGCAACATG
 5651 AAGATCAAAG TATGATAGGT CATCTTCAAG AGGAGCTTGA AGAAAAAAC
 5701 AAGAAATATT CCTTGATAGT AGCCAGCAT GTGGAAAAAG AAGGAGGTAA
 5751 AAATAACATA CAGGCAAAGC AAAACTTGGA AAATGTGTTT GACGACGTCC
 5801 AGAAAACCCT CCAGGAGAAG GAACTAACCT GTCAGATTTT GGAGCAAAAG
 5851 ATAAAAGAGC TGGATTCTCT CTTAGTAAGA CAGAAAGAAG TACATAGAGT
 5901 TGAAATGGAA GAGTTGACCT CAAAATATGA AAAATTACAG GCTTTACAAC
 5951 AGATGGATGG AAGAAATAAA CCCACAGAAC TTTTGAAGA AAACACTGAA
 6001 GAAAAGTCCA AATCACATTT GGTCCAACCC AAATTGCTTA GTAACATGGA
 6051 AGCCAGCAC AATGATCTGG AGTTTAAAT AGCCGGGCA GAACGGGAGA
 6101 AACAGAACT GGGCAAGGAG ATTGTTAGAT TGCAGAAAGA CCTTCGAATG
 6151 TTGAGAAAGG AGCATCAGCA AGAATTGGAA ATACTAAAGA AAGAATATGA
 6201 TCAAGAAAGG GAAGAGAAAA TCAAACAGGA GCAGGAAGAT CTTGAACTGA
 6251 AGCACAATTC CACATTAATA CAGCTGATGA GGGAGTTTAA TACACAGCTG
 6301 GCACAAAAGG AACAAGAGCT GGAAATGACC ATAAAAGAAA CTATCAATAA
 6351 GGCCAGGAG GTGGAGGCTG AACTTTTAGA AAGCCATCAA GAAGAGACAA
 6401 ATCAGTTACT TAAAAAATTT GCTGAGAAAAG ATGATGATCT AAAACGAACA
 6451 GCCAAAAGAT ATGAAGAAAT CCTTGATGCT CGTGAAGAAG AAATGACTGC
 6501 AAAAGTAAGG GACCTGCAGA CTCAACTTGA GGAGCTGCAG AAGAAATACC
 6551 AGCAAAGCT AGAGCAGGAG GAGAACCCTG GCAATGATAA TGTAACAATT
 6601 ATGGAGCTAC AGACACAGCT AGCACAGAAG ACGACTTTAA TCAGTGATTC
 6651 GAAATTGAAA GAGCAAGAGT TCAGAGAACA GATTCACAAT TTAGAAGACC
 6701 GTTTGAAGAA ATATGAAAAG AATGTATATG CAACAACGTG GGGGACACCT
 6751 TACAAAGGTG GCAATTTGTA CCATACGGAT GTCTCACTCT TTGGAGAACC
 6801 TACCGAATTT GAGTATTTGC GAAAAGTGCT TTTTGAGTAT ATGATGGGTC
 6851 GTGAGACTAA GACCATGGCA AAAGTTATAA CCACCGTACT GAAGTTCCCT
 6901 GATGATCAGA CTCAGAAAAT TTTGGAAAAGA GAAGATGCTC GGCTGATGTT
 6951 TACTTCACCT CGCAGTGATA 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 TTTTAAAAA GACTTGTGCA ATACATTTTG AGGTGAAACT
 7401 TAGTGGATTT TTTCTGATAA ATTAGAGCAT TTAATTGACT ATTTTATTCA
 7451 GGTGATCTG TTGAATATTT GCTAAAGACC AGTTCTTTAA GCTAAGACAT
 7501 GTAAAAAATC CCAAATGGCA GTACCTCATT GTTTACTTAG CTTTGTACT
 7551 TATATTTTTC AGAGGAAAAA ACACTACTGT AAATTGTGAA TAGCCAATAC
 7601 ATAACTGTAT TGTATGCAAA TCTGTGATTG TTGGCAGTGT CATCTCTGAG
 7651 AACAGATAA ATAAAGTTA TTTACTATAA AAAAAAATAA AAAAG

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

Length: 2250 aa

1	MFKKLKQKIS	EEQQQLQQAL	APAQASSNSS	TPTRMRSRTS	SFTEQLDEGT
51	PNRENASTHA	SKSPDSVNGS	EPSIPQSGDT	QSFAQKLQLR	VPSVESLFRS
101	PIKESLFRSS	SKESLVRTSS	RESLNRLDL	SSTASFDPPS	DMDSEAEDLV
151	GNSDSLNEQ	LIQRLRRMER	SLSSYRGKYS	ELVTAYQMLQ	REKKKLQGIL
201	SQSQDKSLRR	IAELREELQM	DQQAKKHLQE	EFDASLEEKD	QYISVLQTQV
251	SLLKQRLRNG	PMNVDVLKPL	PQLEPQAEVF	TKEENPESDG	EPVVEDGTSV
301	KTLETLOQRV	KRQENLLKRC	KETIQSHKEQ	CTLLTSEKEA	LQEQLDERLQ
351	ELEKIKDLHM	AEKTKLITQL	RDANKLIEQL	EQDKGMVIAE	TKRQMHEMLE
401	MKEEEIAQLR	SRIKQMTTQG	EELREQKEKS	ERAAFEELK	ALSTAQKTEE
451	ARRKKAEMD	EQIKTIEKTS	EEERISLQQE	LSRVKQEVVD	VMKKSSEEQI
501	AKLQKLHEKE	LARKEQELTK	KLOTREREFQ	EQMKVALEKS	QSEYLIKISQE
551	KEQQESLAL	ELELQKKAIL	TESENKLRDL	QQEAETYRTR	ILELESSLEK
601	SLQENKNQSK	DLAVHLEAEK	NKHNKEITVM	VEKHKTELES	LKHQQDALWT
651	EKLQVLKQQY	QTEMEKLREK	CEQEKETLLK	DKEIIFQAH	EEMNEKTLEK
701	LDVKQTELES	LSSELSEVLK	ARHKLEEEELS	VLKDQTDKMK	QELEAKMDEQ
751	KNHHQQQVDS	IIKEHEVSIQ	RTEKALKDQI	NQLELLKER	DKHLKEHQAH
801	VENLEADIKR	SEGELQQASA	KLDVFQSYQS	ATHEQTKAYE	EQLAQLQQKL
851	LDLETERILL	TKQVAEVEAQ	KKDVCTELDA	HKIQVQDLMQ	QLEKQNSEME
901	QKVKSLTQVY	ESKLEDGNKE	QEQTQKILVE	KENMILQMR	GQKKEIEILT
951	QKLSAKEDSI	HILNEEYETK	FKNQEKKMEK	VKQKAKEMQE	TLKKKLLDQE
1001	AKLKELENT	ALELSQKEKQ	FNAKMLEMAQ	ANSAGISDAV	SRLETNQKEQ
1051	IESLTEVHRR	ELNDVISIWE	KKLNQQAEE	QEIHEIQLQE	KEQEVAELKQ
1101	KILLFGCEKE	EMNKEITWLK	EEGVKQDTTL	NELQEQLKQK	SAHVNSLAQD
1151	ETKLKAHLEK	LEVDLNKS	ENTFLQEQLV	ELKMLAEDK	RKVSELTSKL
1201	KTTDEEFQSL	KSSHEKS	LEDKSLEFKK	LSEELAIQLD	ICCKKTEALL
1251	EAKTNELINI	SSSKTNAIS	RISHCQHRTT	KVKEALLIKT	CTVSELEAQL
1301	RQLTEEQNTL	NISFQQATHQ	LEEKENQIKS	MKADIESLVT	EKEALQKEGG
1351	NQQQAASEKE	SCITQLKKEL	SENINAVTLM	KEELKEKKVE	ISSLSKQLTD
1401	LNVQLQNSIS	LSEKEAAISS	LRKQYDEEKC	ELLDQVQDLS	FKVDTL
1451	ISALEQVDDW	SNKFSEWKKK	AQSRFTQHQN	TVKELQIQLE	LKSKEAYEKD
1501	EQINLLKEEL	DQQNKRFDCL	KGEMEDDKSK	MEKKESNLET	ELKSQTARIM
1551	ELEDHITQKT	IEIESLNEVL	KNYNQQKDIE	HKELVQKLQH	FQELGEEKDN
1601	RVKEAEEKIL	TLENQVYSMK	ALET	EHVNL	EEELKALED
1651	LESEAAKLA	ELKRKAEQKI	AAIKQLLSQ	MEEKEEQYK	GTESHLSELN
1701	TKLQEREREV	HILEEKLSV	ESSQSETLIV	PRSAKNVAAY	TEQEEADSQG
1751	CVQKTYEKEI	SVLQORNLTEK	EKLLQVRGQE	KEETVSSHFE	MRCQYQERLI
1801	KLEHAAKQH	EDQSMIGHLQ	EEL	SLIVAQHVEK	EGGKNNIQAK
1851	QNLENFDDV	QKTLQEKELT	CQILEQKIKE	LDSC	VHRVEMEELT
1901	SKYEKLQALQ	QMDGRNKPTE	LLEENTEEKS	KSHLVQPKLL	SNMEAQHNDL
1951	EFKLAGAERE	KQKLGKEIVR	LQKDLRMLRK	EHQQE	KEYDQEREEK
2001	IKQEQEDLEL	KHNSTLQML	REFNTQLAQK	EQELEM	TINKAQEVEA
2051	ELLESHQEET	NQLLKKIAEK	DDDLKRTAKR	YEEILDAREE	EMTAKVRDLQ
2101	TQLEELQKKY	QQKLEQEENP	GNDNVTIMEL	QTQLAQKTTL	ISDSKLKEQE
2151	FREQIHNLED	RLKKYEKNVY	ATTVGT	GNLYHTDVSL	FGEPT
2201	RKVLFEYMMG	RETKTMAKVI	TTVLKFPDDQ	TQKIL	REDARLMSWLRSSS

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 GTTGTCTGTCG CCGCCGCGGC TCCCAGGGCT
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 CAAGAACTG
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 CTATTCGGGT CTTCCTCTAA AGAGTCTTTG GTACGAACAT CTTCCAGAGA
651 ATCCCTGAAT CGACTTGACC TGGACAGTTC TACTGCCAGT TTTGATCCAC
701 CCTCTGATAT GGATAGCGAG GCTGAAGACT TGGTAGGGAA TTCAGACAGT
751 CTCAACAAG AACAGTTGAT TCAGCGGTTG CGAAGAATGG AACGAAGCTT
801 AAGTAGCTAC AGGGGAAAAT ATTCTGAGCT TGTTACAGCT TATCAGATGC
851 TTCAGAGAGA GAAGAAAAG 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 GATGGAACCT CTGTAAAAAC ACTGGAACA
1201 CTCCAGCAA GAGTGAAGCG TCAAGAGAAC CTACTTAAGC GTTGTAAAGGA
1251 AACCAATCAG TCACATAAGG AACCAATGTAC ACTATTAACT AGTGAAGAA
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 CAAAAACAG AGGAAGCACG GAGAAAAGTG
1651 AAGGCAGAAA TGGATGAACA AATAAAACT ATCGAAAAA CAAGTGAGGA
1701 GGAACGCATC AGTCTTCAAC AGGAATTAAG TCGGGTGAAA CAGGAGGTTG
1751 TTGATGTAAT GAAAAATCC TCAGAAGAAC AAATTGCTAA GCTACAGAAG
1801 CTTTATGAAA AGGAGCTGGC CAGAAAAGAG CAGGAACTGA CCAAGAAGCT
1851 TCAGACCCGA GAAAGGGAAT TTCAGGAACA AATGAAAGTA GCTCTTGAAA
1901 AGAGTCAATC AGAATATTTG AAGATCAGCC AAGAAAAAGA ACAGCAAGAA
1951 TCTTTGGCCC TAGAAGAGTT AGAGTTGCAG AAAAAAGCAA TCCTCACAGA
2001 AAGTGAAAAT AACTTCGGG ACCTTCAGCA AGAAGCAGAG ACTTACAGAA
2051 CTAGAATTCT TGAATTGGAA AGTTCTTTGG AAAAAAGCTT ACAAGAAAAC
2101 AAAAATCAGT CAAAAGATTT GGCTGTTTCAT CTGGAAGCTG AAAAAATAA
2151 GCACAATAAG GAGATTACAG TCATGGTTGA AAAACACAAG ACAGAATTGG
2201 AAAGCCTTAA GCATCAGCAG GATGCCCTTT GGACTGAAAA ACTCCAAGTC
2251 TTAAAGCAAC AATATCAGAC TGAATGGAA AACTTAGGG AAAAGTGTGA
2301 ACAAGAAAAA GAAACATTGT TGAAGACAA AGAGATTATC TTCCAGGCC
2351 ACATAGAAGA AATGAATGAA AAGACTTTAG AAAAGCTTGA TGTGAAGCAA
2401 ACAGAACTAG AATCATTATC TTCTGAACTG TCAGAAGTAT TAAAAGCCCC
2451 TCACAAACTA GAAGAGGAAC TTTCTGTTCT GAAAGATCAA ACAGATAAAA
2501 TGAAGCAGGA ATTAGAGGCC AAGATGGATG AACAGAAAA 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 ACAAAGCAT
 2801 ATGAGGAACA GTTGGCCCAA TTGCAGCAGA AGTTGTTGGA TTTGGAACA
 2851 GAAAGAATTC TTCTTACCAA ACAGGTTGCT GAAGTTGAAG CACAAAAGAA
 2901 AGATGTTTTGT 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 ATTGTTCAGCC
 3151 AAGGAGGACA GTATTCATAT TTTGAATGAG GAATATGAAA CCAAATTTAA
 3201 AAACCAAGAA AAAAAGATGG AAAAAGTTAA GCAGAAAGCA AAGGAGATGC
 3251 AAGAAACGTT AAAGAAAAAA TTAAGTTGATC AGGAAGCCAA ACTTAAGAAA
 3301 GAGCTTGAAA ATACTGCTCT AGAGCTTAGT CAGAAAGAAA AACAGTTTAA
 3351 TGCCAAAATG CTGGAAATGG CACAGGCTAA CTCAGCTGGA ATCAGTGATG
 3401 CAGTGTCAAG ACTGGAAACA AACCAAAAAG AACAAATAGA AAGTCTTACT
 3451 GAGGTTTCATC 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 GGTGACTTG AATAAGTCTC TGAAGGAAAA
 3801 TACTTTTCTT CAAGAGCAGC TAGTTGAACT GAAGATGCTG GCAGAAGAAG
 3851 ATAAGCGGAA GGTTCCTGAG TTGACTAGCA AGTTGAAAAC CACAGATGAA
 3901 GAATTCAGAA GTTTGAAATC TTCACATGAA AAAAGTAACA AAAGCCTAGA
 3951 GGACAAGAGC TTGGAATTTA AAAAAGTGTG TGAGGAACTA GCGATTGAGC
 4001 TAGATATTTG CTGTAAGAAA ACCGAAGCCT TATTAGAAGC TAAAACAAAT
 4051 GAGCTAATCA ACATTAGTAG TAGTAAACT AATGCCATTC TTTCTAGGAT
 4101 TTCTCATTGT CAGCACCGTA CAACTAAAGT TAAGGAGGCA CTGTTAATTA
 4151 AAACCTGCAC 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
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 4501 CAAAATAGCA TCAGCCTATC CGAAAAAGAA GCAGCCATTT CATCACTAAG
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 4851 TGAAATGGAA GACGACAAGA GCAAGATGGA GAAAAAGGAG TCTAATTTAG
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 5101 GAAGAAAAAA TCTTAACACT TGAAAACCAA GTTTATTCCA TGAAAGCTGA
 5151 ACTTGAAACT AAGAAGAAAG AATTAGAACA TGTGAATTTA AGTGTGAAAA
 5201 GCAAAGAGGA GGAGTTAAAG GCATTGGAAG ATAGGCTTGA GTCAGAAAGT

5251 GCTGCAAAAT TAGCAGAGTT GAAGAGAAAA GCTGAACAAA AAATTGCTGC
 5301 CATTAAGAAG CAGTTGTTAT CTCAAATGGA AGAGAAAGAA GAACAGTATA
 5351 AAAAAGGTAC AGAAAGCCAT TTGAGTGAGC TAAATACAAA ATTGCAGGAA
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 5451 TTCACAGTCA GAAACATTAA TTGTACCCAG ATCAGCAAAA AATGTGGCAG
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 5601 GCTATTGCAG AGGGTAGGGC AGGAAAAAGA AGAGACAGTT TCTTCTCATT
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 5751 GCTTGAAGAA AAAACAAGA AATATTCTTT GATAGTAGCC CAGCATGTGG
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 5901 GATTTTGGAG CAAAAGATAA AAGAGCTGGA TTCCTGCTTA GTAAGACAGA
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 6101 TGCTTAGTAA CATGGAAGCC CAGCACAATG ATCTGGAGTT TAAATTAGCC
 6151 GGGGCAGAAC GGGAGAAACA GAACTGGGC 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 AAGAACTAT 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 TGATTGCGAA TTGAAAGAGC AAGAGTTCAG AGAACAGATT
 6751 CACAATTTAG AAGACCGTTT GAAGAAATAT GAAAAGAATG TATATGCAAC
 6801 AACTGTGGGG ACACCTTACA AAGGTGGCAA TTTGTACCAT ACGGATGTCT
 6851 CACTCTTTGG AGAACCTACC GAATTTGAGT ATTTGCGAAA AGTGCTTTTT
 6901 GAGTATATGA TGGGTCTGTA GACTAAGACC ATGGCAAAAG TTATAACCAC
 6951 CGTACTGAAG TTCCCTGATG ATCAGACTCA GAAAATTTTG GAAAGAGAAG
 7001 ATGCTCGGCT GATGTTTACT TCACCTCGCA GTGGTATCTT CTGAGTAAAC
 7051 CATCAGTCTG TGCTTAGTTA ACATGTGTCA TGGCTCCGAT CTTTCTTTG
 7101 AAGAAGAGTG ACATTGGGTG ACTGCTGCTT GGAAAAGTGT CCACACTTGC
 7151 TACTCTTTGA GAATGAAGTT GTCATTGAGG 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 TATTTTLAGG GTGATTTTTT AAAAAGACTT GTGCAATACA
 7451 TTTTGAGGTG AACTTAGTG GATTTTTTCT GATAAATTAG AGCATTTAAT
 7501 TGAATATTTT ATTCAGGTTG ATCTGTTGAA TATTTGCTAA AGACCAGTTC
 7551 TTTAAGCTAA GACATGTAAA AAATCCCAA TGGCAGTACC TCATTGTTTTA
 7601 CTTAGCTTTT GACTTATAT TTTTCAGAGG AAAAACACT ACTGTAAATT
 7651 GTGAATAGCC AATACATAAC TGTATTGTAT GCAAATCTGT GATTGTTGGC
 7701 AGTGTATCTT 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 EPSIQSGDT QSFAQKLQLR VPSVESLFRS
101 PIKESLFRSS SKESLVRTSS RESLNRLDL D SSTASFDPPS DMDSEAEDLV
151 GNSDSL NKEQ LIQRLRRMER SLSSYRGKYS ELVTAYQMLQ REKKKLQGIL
201 SQSQDKSLRR IAELREELQM DQQA KHLQE EFDASLEEKD QYISVLQTQV
251 SLLKQRLRNG PMNVDVLKPL PQLEPQAEVF TKEENPESDG EPVVEDGTSV
301 KTLETLOQRV KRQENLLKRC KETIQSHKEQ C TLLTSEKEA LQEQLDERLQ
351 ELEKIKDLHM AEKTKLITQL RDAKNLIEQL EQDKGMVIAE TKRQM HETLE
401 MKEEEIAQLR SRIKQMTTQG EELREQKEKS ERAAFEELEK ALSTAQKTEE
451 ARRKLKAEMD EQIKTIEKTS EEERISLQQE LSRVKQEVVD VMKKSSEEQI
501 AKLQKLHEKE LARKEQELTK KLQTREREFQ EQMKVALEKS QSEYLIKISQE
551 KEQQESLAL ELELQKKAIL TESENKLRDL QQEAETYRTR ILELESSLEK
601 SLQENKNQSK DLAVHLEAEK NKHNKEITVM VEKHKTELES LKHQQDALWT
651 EKLQVLKQQY QTEMEKLREK CEQEKETLLK DKEIIFQAH I EEMNEKTLEK
701 LDVKQTELES LSSELSEVLK ARHKLEEEELS VLKDQTDKMK QELEAKMDEQ
751 KNHHQQQVDS I I KEHEVSIQ RTEKALKDQI NQLELLKER DKHLKEHQAH
801 VENLEADIKR SEGELQQASA KLDVFQSYQS ATHEQTKAYE EQLAQLQQKL
851 LDLETERILL TKQVAEVEAQ KKD VCTELDA HKIQVQDLMQ QLEKQNSEME
901 QKVKSLTQVY ESKLEDGNKE QEQTQIILVE KENMILQMR E GQKKEIEILT
951 QKLSAKEDSI HILNEEYETK FKNQEKKMEK VKQKAKEMQE TLKKKLLDQE
1001 AKLKELENT ALELSQKEKQ FNAKMLEMAQ ANSAGISDAV SRLETNQKEQ
1051 IESLTEVHRR ELNDVISIWE KKL NQQA EEL QEIHEIQLOE KEQEVAELKQ
1101 KILLFGCEKE EMNKEITWLK EEGVKQDTTL NELQEQLKQK SAHVNSLAQD
1151 ETKLKAHLEK LEVDLNKSLK ENTFLQEQLV ELKMLAEEDK RKVSELTSKL
1201 KTTDEEFQSL KSSHEKS NKS 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 FKVDTL SKEK
1451 ISALEQVDDW SNKFSEWKKK AQRFTQHQN TVKELQIQLE LKSKEAYEKD
1501 EQINLLKEEL DQQNKRFDCL KGEMEDDKSK MEKKESNLET ELKSQTARIM
1551 ELEDHITQKT IEIESLNEVL KNYNQQKDIE HKELVQKLQH FQELGEEKDN
1601 RVKEAEEKIL TLENQVYSMK AELETKKKEL EHVNL SVKSK EEELKALEDR
1651 LESESAAKLA ELKRKAEQKI AAIKKQLLSQ MEEKEEQYKK GTESHLSELN
1701 TKLQEREREV HILEEKL KSV ESSQSETLIV PRSAKNVAAY TEQEEADSQG
1751 CVQKTYE EKI SVLQORNLTEK EKLLQRVGQE KEETVSSHFE MRCQYQERLI
1801 KLEHAEAKQH EDQSMIGHLQ EELEEK NKKY SLIVAQHVEK EGGKNNIQAK
1851 QNLENFDDV QKTLQEKELT CQILEQKIKE LDSCLVRQKE VHRVEMEELT
1901 SKYEKLQALQ QMDGRNK PTE LLEENTEEKS KSHLVQPKLL SNMEAQHNDL
1951 EFKLAGAERE KQKLGKEIVR LQKDLRMLRK EHQQELEILK KEYDQEREEK
2001 IKQE QEDLEL KHNSTLKQLM REFNTQLA QK EQELEM TIKE TINKAQEVEA
2051 ELLESHQEET NQLLKKIAEK DDDLKRTAKR YEEILDAREE EMTAKVRDLQ
2101 TQLEELQK KY QQKLEQEENP GNDNVTIMEL QTQLAQKTTL ISDSKLKEQE
2151 FREQIHNLED RLKKYEKNVY ATTVGTPYKG GNLYHTDVSL FGEPT EFEYL
2201 RKVLF EYMMG RETKTMAKVI TTVLKF PDDQ TQKILEREDA RLMFTSPRS G
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 GTTGTCTGTCG 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 AAGCAAAGA TCAGCGAGGA GCAGCAGCAG CTCCAGCAGG CGCTGGCTCC
351 TGCTCAGGCG TCCTCCAATT CTTCAACACC AACAGAATG 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 CTATTCGGT CTCTTCTAA 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 GAAGAAAAG 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 ACTGAAACA
1201 CTCCAGCAA GAGTGAAGCG TCAAGAGAAC CTACTTAAGC GTTGTAAAGGA
1251 AACAAATCAG TCACATAAGG ACAATGTAC ACTATTAACT AGTGAAAAG
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1701 GGAACGCATC AGTCTTCAAC AGGAATTAAG TCGGGTGAAC CAGGAGGTTG
1751 TTGATGTAAT GAAAAAATCC TCAGAAGAAC AAATTGCTAA GCTACAGAAG
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2401 ACAGAACTAG AATCATTATC TTCTGAACTG TCAGAAGTAT TAAAAGCCCG
2451 TCACAAACTA GAAGAGGAAC TTTCTGTTCT GAAAGATCAA ACAGATAAAA

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 2551 CAGCAAGTTG ACAGTATCAT TAAAGAACAC GAGGTATCTA TCCAGAGGAC
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 2651 AAAGGGACAA GCATTTGAAA GAGCATCAGG CTCATGTAGA AAATTTAGAG
 2701 GCAGATATTA AAAGGTCTGA AGGGGAACTC CAGCAGGCAT CTGCTAAGCT
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 2901 AGATGTTTGT ACTGAGTTAG ATGCTCACAA AATCCAGGTG CAGGACTTAA
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 5151 ACTTGAAACT AAGAAGAAAG AATTAGAACA TGTGAATTTA AGTGTGAAAA

5201 GCAAAGAGGA GGAGTTAAAG GCATTGGAAG ATAGGCTTGA GTCAGAAAGT
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5301 CATTAAGAAG CAGTTGTTAT CTCAAATGGA AGAGAAAGAA GAACAGTATA
5351 AAAAAGGTAC AGAAAGCCAT TTGAGTGAGC TAAATACAAA ATTGCAGGAA
5401 AGAGAAAGGG AAGTTCACAT CTTGGAAGAA AAACCTAAGT 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 AAAACAAGA AATATTCCCTT GATAGTAGCC CAGCATGTGG
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5851 GTGTTTGACG ACGTCCAGAA AACCCTCCAG GAGAAGGAAC TAACCTGTCA
5901 GATTTTGAG CAAAAGATAA AAGAGCTGGA TTCCTGCTTA GTAAGACAGA
5951 AAGAAGTACA TAGAGTTGAA ATGGAAGAGT TGACCTCAAA ATATGAAAAA
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6301 GAAGATCTTG AACTGAAGCA CAATTCCACA TAAAAACAGC TGATGAGGGA
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6401 AAGAACTAT CAATAAGGCC CAGGAGGTGG AGGCTGAACT TTTAGAAAGC
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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 GGAAAACGTG CCACACTTGC
7151 TACTCTTTGA GAATGAAGTT GTCATTGAGG GCCCCTCATG TAGCCAAAAG
7201 ACCAAGAAAA ATCTGGCCCA CAGATAAGTT GCAGACTGCC TTTAAAATAG
7251 ATTTTATCAG TGGAGAAATG GTGATAGTTT TTTCTTCAGT TTTCTCTTGG
7301 GAAGGAGTTT TATGTTGTTT AAAAGATATT TTGATAACTT AACCTGCTTT
7351 ATGGGCTTAC ATAATATTCC TTTTCATCCAT 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 TGTACTIONATA TTTTTCAGAG GAAAAAACAC TACTGTAAAT
7651 TGTGAATAGC CAATACATAA CTGTATTGTA TGCAAATCTG TGATTGTTGG
7701 CAGTGTATC TCTGAGAAAC AGATAAATAA AGTTTATTTA CTATAAAAAA
7751 AAAAAAAAAA G

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

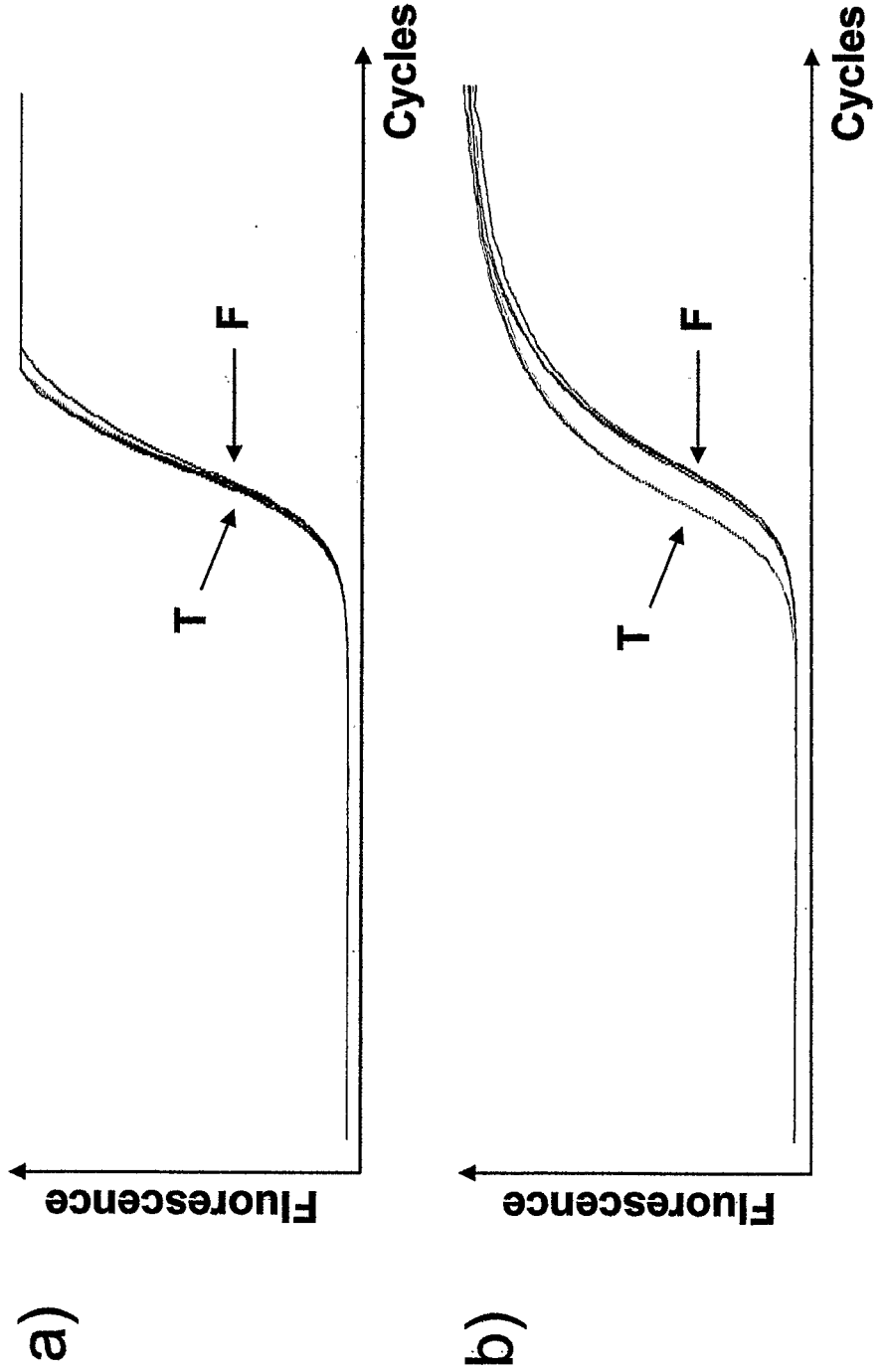


Fig. 14: Verification of differential expression of golgin-245 splice variant 1 and/or 3 by quantitative RT-PCR

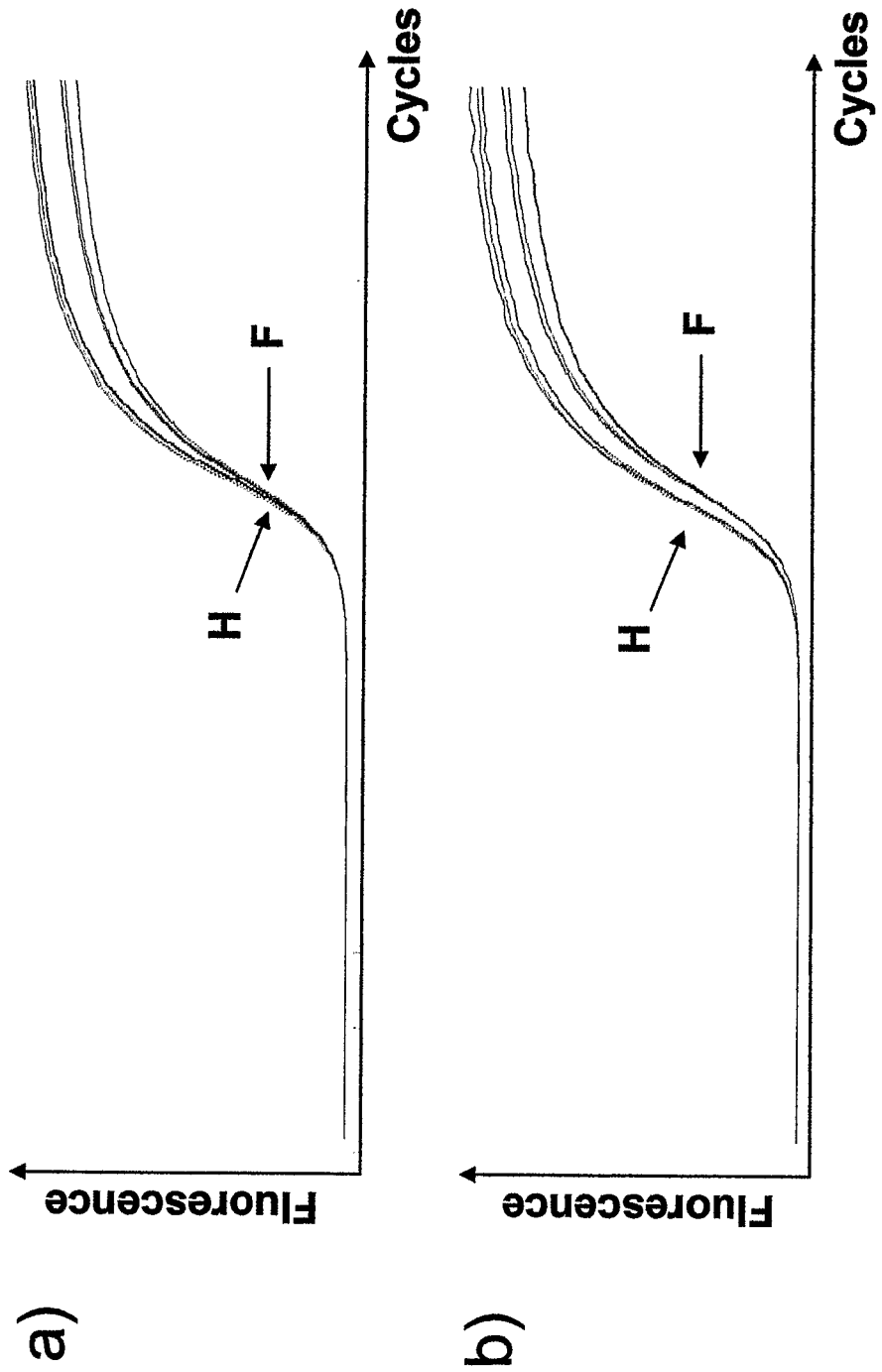


Fig. 15: Verification of differential expression of golgin-245 splice variant 2 and/or 4 by quantitative RT-PCR

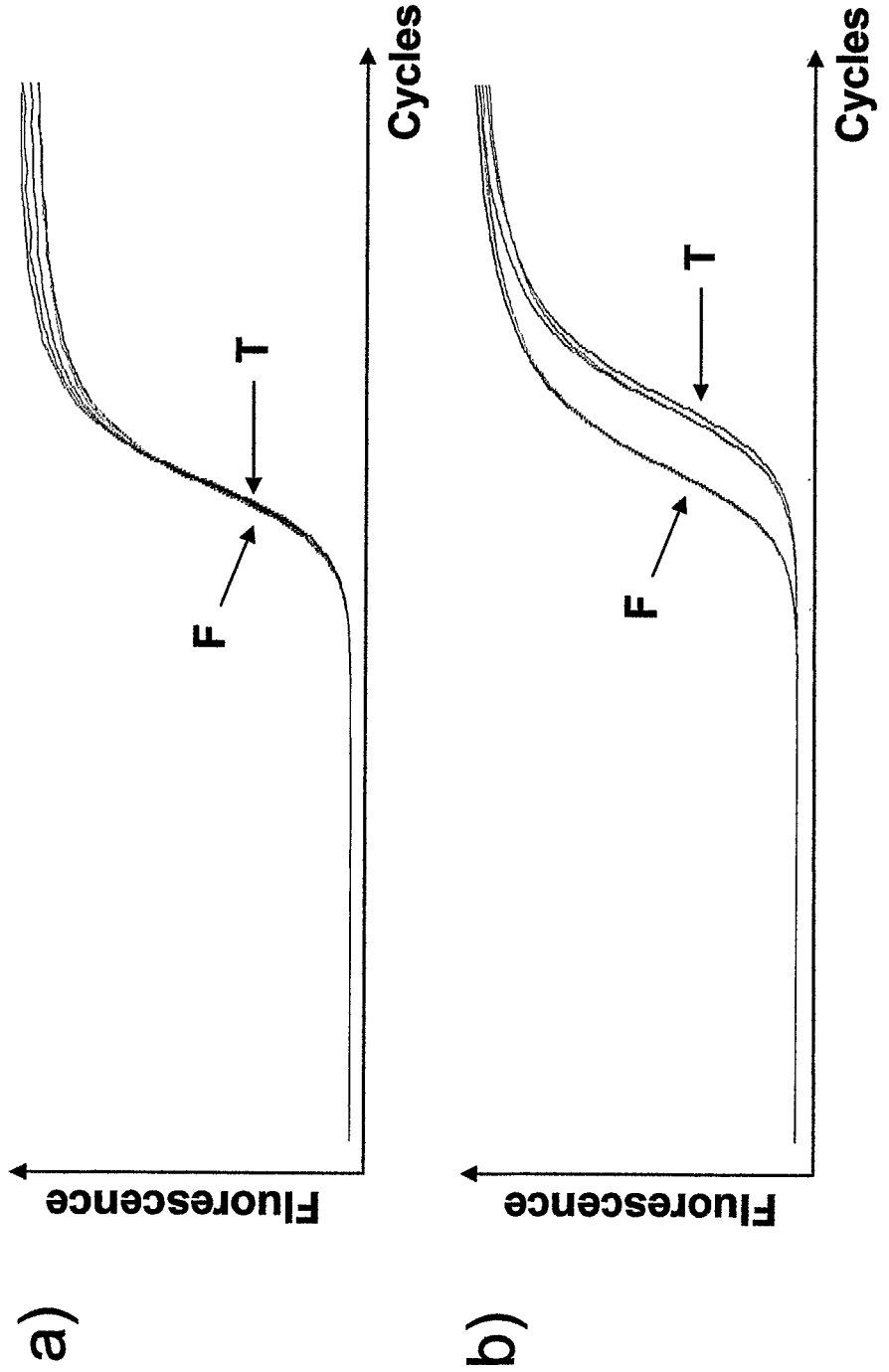


Fig. 16: Verification of differential expression of golgin-245 splice variant 2 and/or 4 by quantitative RT-PCR

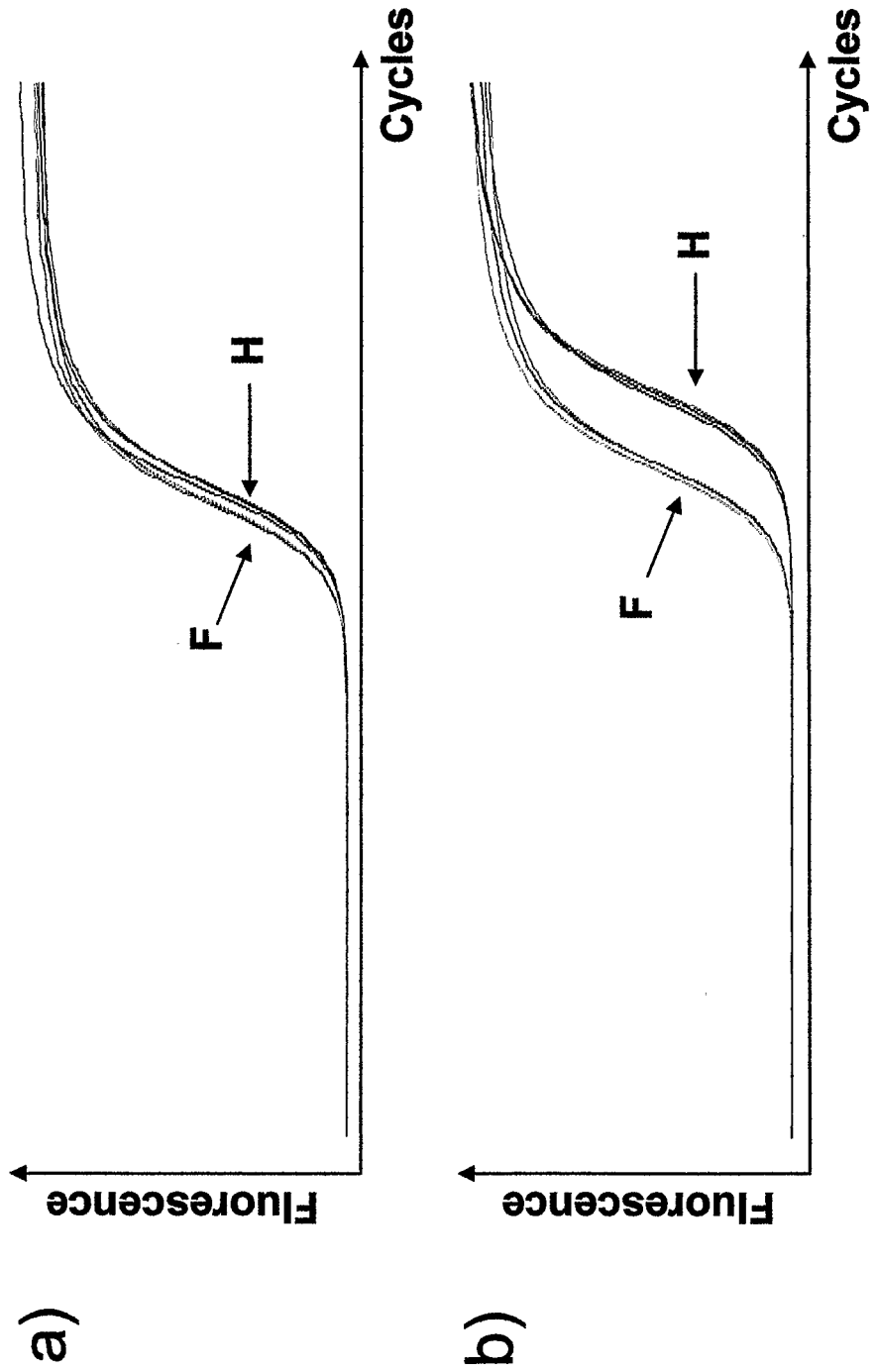
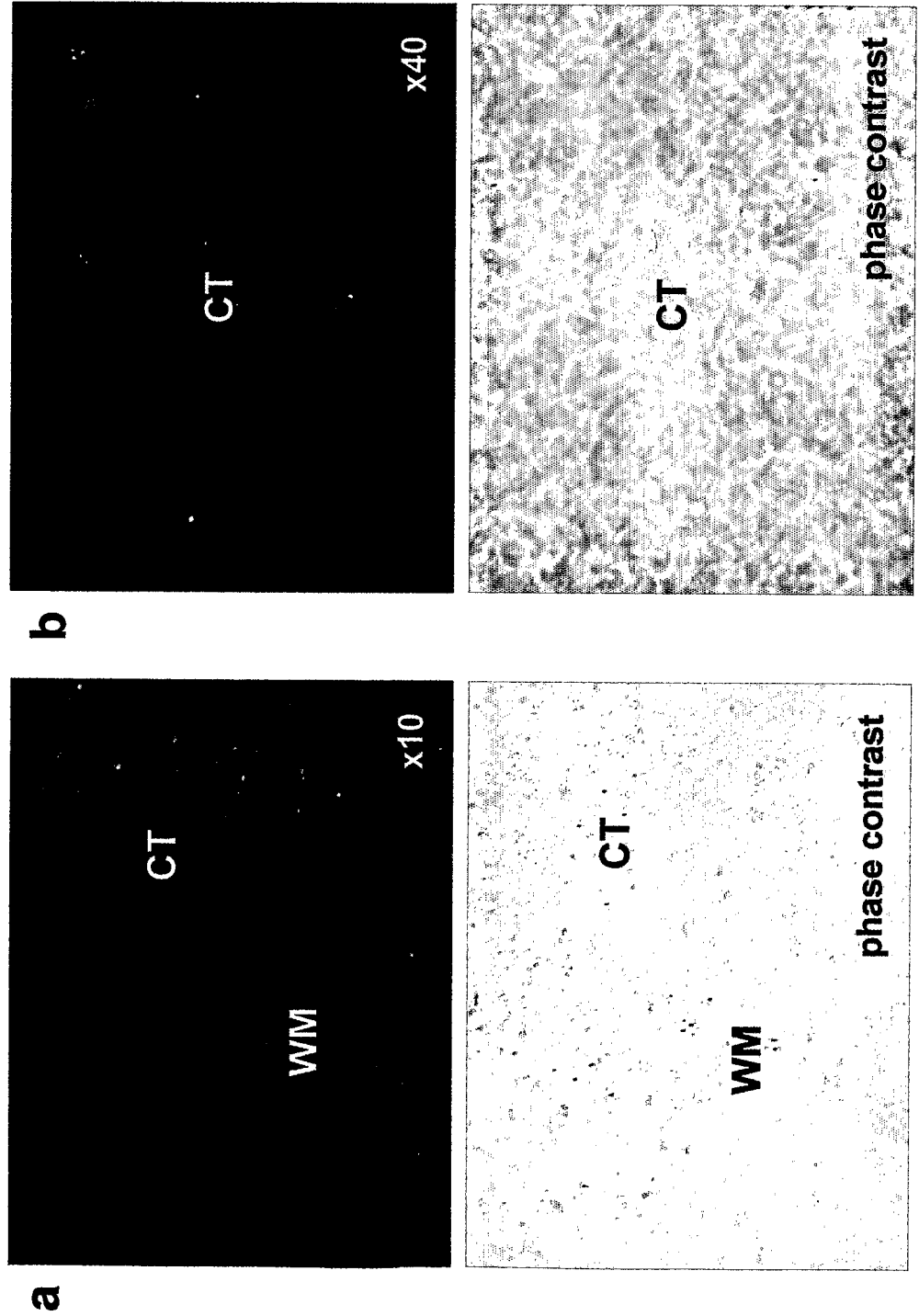


Fig. 17: Images of the human cerebral cortex labeled with anti-golgin-245 monoclonal antibody and with DAPI



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		
公开(公告)号	EP1501946A2	公开(公告)日	2005-02-02
申请号	EP2003720478	申请日	2003-04-16
申请(专利权)人(译)	EVOTEC NEUROSCIENCES GMBH		
当前申请(专利权)人(译)	EVOTEC NEUROSCIENCES GMBH		
[标]发明人	VON DER KAMMER HEINZ POHLNER JOHANNES		
发明人	VON DER KAMMER, HEINZ POHLNER, JOHANNES		
IPC分类号	A01K67/027 A61P25/00 C12Q1/68 G01N33/53		
CPC分类号	A61K38/17 A61P25/00 C12Q1/6883 C12Q2600/158 G01N33/6896 G01N2500/00 G01N2800/2821		
代理机构(译)	VON克莱斯勒SELTING WERNER		
优先权	2002008553 2002-04-16 EP 60/372424 2002-04-16 US		
外部链接	Espacenet		

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。