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(54) Title: A DIAGNOSTIC METHOD FOR DEMENTIAS

(57) Abstract: The invention relates to a method of determining whether a subject has or is at risk of developing a dementia, such as Alzheimer's disease (AD), a mild cognitive impairment (MCI), fronto-temporal dementia (FTD), or dementia with Lewy bodies (DLB), which method comprises detecting the presence of a mutation, deletion or insertion of one or several nucleotides in the CTGF gene locus in a biological sample of said subject.



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A diagnostic method for dementias

FIELD OF THE INVENTION

5 The present invention relates generally to the fields of genetics and medicine. The present invention discloses in particular the identification of a dementia susceptibility gene, which can be used for the diagnosis or prognosis of a dementia or for the detection of predisposition to a dementia.

10 BACKGROUND OF THE INVENTION

Diagnosing a dementia can often be difficult, especially in the early stages, because many of the symptoms of the disease mirror the natural signs of aging. In some situations, a definitive diagnosis may not be possible until the patient has died and an autopsy can be performed.

15

There are also several forms of dementia, many of which involve a loss and/or cognitive dysfunction. Alzheimer's disease (AD), Mild cognitive impairment (MCI), fronto-temporal dementia (FTD), and dementia with Lewis bodies (DLB), are typical examples of such disorders.

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Alzheimer's disease (AD) is a neurodegenerative disease of the central nervous system associated with progressive memory loss resulting in dementia. The prevalence of AD is expected to reach 8.64 million by the year 2047. AD is characterized by extracellular plaques and intracellular tangles in the hippocampus, cerebral cortex, and other areas of the brain
25 essential for cognitive function. Plaques are formed mostly from the deposition of amyloid beta ("A β "), a peptide derived from amyloid precursor protein ("APP"). Filamentous tangles are formed from paired helical filaments composed of neurofilament and hyperphosphorylated tau protein, a microtubule-associated protein. It is not clear, however, whether these two pathological changes are only associated with the disease or truly involved in the degenerative
30 process.

Two main forms of the disease coexist. First of all, the early onset form (<65 years old) mainly characterized by a strong familial clustering and Mendelian disease transmission.

Early onset familial AD accounts for only 5% of all AD cases. Secondly, a late onset form (>65 years old) showing no obvious familial aggregation.

Genetic studies have identified three genes that cause autosomal dominant, early onset AD, amyloid precursor protein ("APP"), presenilin 1 ("PS1"), and presenilin 2 ("PS2"). A fourth
5 gene, apolipoprotein E ("ApoE"), is the strongest and most common genetic risk factor for AD, but does not necessarily cause it. All mutations associated with APP and PS proteins can lead to an increase in the production of A β peptides, specifically the more amyloidogenic form, A β 42. In addition to genetic influences on amyloid plaque and intracellular tangle formation, environmental factors (e.g., cytokines, neurotoxins, etc.) may also play important
10 roles in the development and progression of AD.

The main clinical feature of AD is a progressive cognitive decline leading to memory loss. Language impairments are a prominent part of AD. Non-cognitive or behavioural symptoms are also common in AD. Personality changes are commonly reported and range from
15 progressive passivity to marked agitation. Patients may exhibit changes such as decreased expressions of affection. Depressive symptoms are present in up to 40%. A similar rate for anxiety has also been recognized. Psychosis occurs in 25%.

Currently, the primary method of diagnosing AD in living patients involves taking detailed
20 patient histories, administering memory and psychological tests, and ruling out other explanations for memory loss, including temporary (e.g., depression or vitamin B12 deficiency) or permanent (e.g., stroke) conditions. These clinical diagnostic methods, however, are not foolproof.

25 Given the magnitude of the public health problem posed by AD, considerable research efforts have been undertaken to elucidate the etiology of AD as well as to identify biomarkers (secreted proteins or metabolites) that can be used to diagnose and/or predict whether a person is likely to develop AD. With regards to biomarkers, the proteins A β and tau are probably the most well characterized.

30

A number of U.S. patents and applications have been published relating to methods for diagnosing AD. For example, US 4,728,605 shows that AD can be diagnosed by testing of

peripheral blood immunocytes (especially T cells), US 5,874,312 describes a method for measuring a cytokine production level of peripheral mononuclear cells to diagnose and determine the disease stage of AD, US 6,027,896 discloses an AD diagnostic method detecting the presence or absence of an apolipoprotein E type 4 in a subject. Additionally, a number of reports in the scientific literature relate to certain biochemical markers and their correlation/association with AD, including Brain Derived Neurotrophic Factor (BDNF) (Fahnestock et al., 2002, J. Neural. Transm. Suppl. 2002(62):241-52); Platelet-Derived Growth Factor (PDGF) (Masliah et al., 1995, Neurobiol. Aging 16(4):549-56); leptin, which could play a role in AD-associated weight loss (Power et al., 2001, Dement. Geriatr. Cogn. Disord. 12(2):167-70).

Mild cognitive impairment (MCI) is a general term most commonly defined as subtle but measurable memory disorder. As MCI is a very early sign of dementia, subjects with MCI are becoming the focus of many prediction studies and early intervention trials. Hence, MCI has emerged as the most convenient avenue to identify AD as early as possible, since most MCI patients will progress to AD (Chételat and al, 2003, Brain, 2003 (126): 1955-1967).

Fronto-temporal dementia (FTD) is one of the most common early onset dementia after AD. FTD is a clinical syndrome caused by degeneration of the frontal lobe of the brain and may extend back to the temporal lobe. Pick's disease is the most known FTD. As AD, FTD is associated with a tau pathology. Symptoms can be classified into two groups which underlie the functions of the frontal lobe: behavioral and cognitive like planning and organizing skills.

Dementia with Lewy bodies (DLB) is an illness that presents with progressive dementia or psychosis. Parkinsonian signs, which may be absent or mild at the onset, eventually become common and rigidity is usually severe. Lewy bodies are found profusely in the brainstem, basal forebrain, hypothalamic nuclei and neocortex. DLB is characterized by the relative absence of tangles and hyperphosphorylated tau in the brain. Parkinson's disease is a type of Lewy Body diseases occurring in the middle or late life, with very gradual progression and a prolonged course.

The genetic component of such dementias remains largely unknown. Exhaustive knowledge of the diseases' genetic determinants will lead to the development of tools to aid early diagnosis.

As CTGF gene strongly promotes extracellular matrix gene expression, it was hypothesized that CTGF gene would be involved in postlesional restructuring of central nervous system tissue, especially in glial scar formation (Hertel and al., Eur J Neurosci. 2000 Jan ;12(1) :376-80). CTGF gene was then shown to be highly expressed in neurons associated with plaques and in neuritic components of plaques in AD's patients (Ueberham and al., Neuroscience 116 (2003) 1-6). Zhong Zhao and al (The FASEB Journal, 19(14):2081-2, September 26, 2005) further disclosed an increased CTGF expression in the brain possibly correlated to the clinical progression of AD.

However, using CTGF as a gene marker in the diagnosis or prognosis of dementia or for the detection of predisposition to dementia, has never been suggested.

15

SUMMARY OF THE INVENTION

The purpose of the present invention is to provide a new genetic approach for dementia diagnostic. The present invention now discloses the identification of a human dementia susceptibility gene locus, the CTGF gene locus (CCN2), which can be used for detecting predisposition to, for diagnosis and prognosis of a dementia, especially dementia with memory and/or cognitive dysfunction, such as MCI, AD, FTD and DLB. The invention resides, in particular, in a method which comprises detecting in a sample from the subject the presence of a mutation, an insertion or a deletion of one or more bases in the CTGF gene locus (CCN2), the presence of said mutation, insertion or deletion being indicative of the presence or predisposition to a dementia.

A particular object of this invention resides in an in vitro method of detecting predisposition to or diagnosis and/or prognosis of a dementia occurring in a subject, the method comprising detecting the presence of a mutation, an insertion or a deletion of one or more bases in the CTGF gene locus in a sample from the subject, the presence of said mutation, insertion or deletion being indicative of the presence of a dementia or the predisposition to a dementia.

In a preferred embodiment, said dementia is a dementia with memory and/or cognitive dysfunction.

- 5 In another preferred embodiment, said dementia is a senile dementia. Preferably it affects humans over 60 or 65 years old.

The method of the invention allows for detection and prognosis of a dementia, especially a dementia with memory and/or cognitive dysfunction selected from mild cognitive impairment,

- 10 Alzheimer's disease, fronto-temporal dementia and dementia with Lewis bodies.

In a preferred embodiment, said mutation, insertion or deletion is located within 20 kb, upstream the start codon of the CTGF gene and 20 kb, downstream the 3'UTR of the CTGF gene. Preferably, the mutation, insertion or deletion lies in the surrounding sequences of 15 kb
15 region, upstream the starting codon of the CTGF gene and 15 kb region, downstream the untranslated region (3'UTR). More preferably, the mutation, insertion or deletion lies in the surrounding sequences of 10 kb region, upstream the starting codon of the CTGF gene and 10 kb region, downstream the untranslated region (3'UTR). Even more preferably, the mutation, insertion or deletion lies in the surrounding sequences of 5 kb region, upstream the starting
20 codon of the CTGF gene and 5 kb region, downstream the untranslated region (3'UTR).

In another preferred embodiment, said mutation, insertion or deletion is one or several single nucleotide polymorphism(s) SNP(s) or a haplotype of SNPs associated with a dementia, especially a dementia with memory and/or cognitive dysfunction.

25

In a more preferred embodiment, said single nucleotide polymorphisms are SNPs flanking CTGF gene, which are allelic variants lying close to the CTGF gene.

Preferably, the alteration in the CTGF gene locus is determined by performing a selective
30 hybridization assay, a sequencing assay, a microsequencing assay, and/or an allele-specific amplification assay.

In another aspect of the invention, said alteration in the CTGF gene is determined by restriction enzyme digestion, the detection of at least one said SNP being an indication of a dementia, especially a dementia with memory and/or cognitive dysfunction.

DETAILED DESCRIPTION OF THE INVENTION

5

This invention provides valuable genetic markers to detect a predisposition or to predict a diagnosis or a prognosis of a dementia, especially a dementia with memory and/or cognitive dysfunction, such as mild cognitive impairment, Alzheimer's disease, fronto-temporal dementia and dementia with Lewy bodies.

10

Early detection of a dementia and regular monitoring of a dementia, would allow for initiation of therapies capable of halting and even reversing the dementia process. This early detection would prevent progression of dementia diseases, especially of mild cognitive impairment, Alzheimer's disease, fronto-temporal dementia and Lewy body dementia, and the important
15 symptoms these conditions entail. The development of these various techniques for early detection of a dementia bodes well for the future care of patients with loss of cognitive functions.

The inventors have now identified a major gene associated with human dementia. They have
20 shown that AD and MCI in Caucasian cohorts, are markedly dependent on allelic variants lying in the CTGF gene locus.

Various nucleic acid samples from individuals with AD or MCI were submitted to a particular analysis process. Three hundred and eighty AD patients were recruited at the Saint Marguerite
25 Hospital, Marseille, France. The clinical diagnosis of AD was established using NINCDS-ADRDA criteria for AD (McKhann et al., Neurology, 1984, 34:939). Four hundred and twenty six MCI patients were also recruited at the Saint Marguerite Hospital, Marseille, France. All MCI patients met criteria for an amnesic form of MCI (Peterson et al., Arch Neurol, 1999, 56:303) as all has memory complaint (usually verified by an informant),
30 performed poorly on neuropsychological tests of verbal memory, and had normal general cognitive function. Finally 90 DLB and 99 FTD patients were included.

Healthy controls (N=376), without any neurological pathology, were recruited at the Blood Bank Center. Some local volunteer were also enrolled

This analysis process led to the identification of particular single nucleotide polymorphism(s)
5 (SNP(s)) in said populations.

The present invention is not limited to the particular SNPs that were found significantly correlated with dementias in all tested populations. Indeed, several reasons could account for the failure in identifying other significant SNPs in some populations, including an insufficient
10 cohort, the incomplete assessment of confounding variables, a lower frequency of the SNPs in said populations, etc.

Definitions

Within the context of this invention, “**Dementia with memory and/or cognitive dysfunction**” refers to a progressive and abnormally accelerated deterioration of mental
15 faculties and emotional stability. It designates any disease resulting in a general loss of cognitive abilities, including impairment of memory as well as one or more of the following: aphasia, apraxia, agnosia, or disturbed planning, organizing, and abstract thinking abilities. It generally affects older persons, usually over the age of 65.

20 Within the context of this invention, “**Alzheimer's patient**” and “**AD patient**” refer to an individual who has been diagnosed with AD or has been given a probable diagnosis of AD.

Within the context of this invention, “**Mild cognitive impairment's patient**” and “**MCI patient**” refer to an individual who has been diagnosed with MCI or has given a probable
25 diagnosis of MCI.

Within the context of this invention, “**Fronto-temporal dementia's patient**” and “**FTD patient**” refer to an individual who has been diagnosed with FTD or has given a probable diagnosis of FTD.

Within the context of this invention, “**Dementia with Lewy bodies’ patient**” and “**DLB patient**” refer to an individual who has been diagnosed with DLB or has given a probable diagnosis of DLB.

- 5 Within the context of this invention, “**the CTGF gene locus**” (Connection Tissue Growth Factor), also called CCN2 gene locus, designates all sequences or products in a cell or organism, including CTGF coding sequences, CTGF non-coding sequences (e.g., introns), CTGF regulatory sequences controlling transcription and/or translation (e.g., promoter, enhancer, terminator, etc.), all corresponding expression products, such as CTGF RNAs (e.g.,
10 mRNAs) and CTGF polypeptides (e.g., a pre-protein and a mature protein); as well as surrounding sequences of 20 kb region, preferably 15 kb region, more preferably 10 kb region and even more preferably 5 kb region upstream the starting codon of the CTGF gene and 20 kb region, preferably 15 kb region, more preferably 10 kb region and even more preferably 5 kb region downstream the untranslated region (3’UTR).
- 15 For example, the CTGF locus comprises surrounding sequences comprising the SNPs of Table 1A (such as rs9399005, rs4897554 and rs6918698) identified by sequencing. For instance, SNP rs6918698 is located into the CTGF promoter whereas rs9399005 and rs4897554 are in the 3’ region.
- 20 Within the context of the present invention, the term “**prognosis**” includes the detection, monitoring, dosing, comparison, etc., at various stages, including early, pre-symptomatic stages, and late stages, in human. Prognosis typically includes the assessment (prediction) of the progression of a dementia, especially a dementia with memory and/or cognitive dysfunction, and the characterization of a subject to define most appropriate treatment
25 (pharmaco-genetics), etc. The present invention provides prognostic methods to determine the speed of the progression of a dementia, especially a dementia with memory and/or cognitive dysfunction, resulting from a mutation or a polymorphism in the CTGF gene locus.

Mutation, deletion or insertion

- 30 The mutation, deletion or insertion may be determined at the level of the CTGF DNA, RNA or polypeptide. Optionally, the detection is performed by sequencing all or part of the CTGF gene locus or by selective hybridization or amplification of all or part of the CTGF gene

locus. More preferably a CTGF gene locus specific amplification is carried out before the mutation, deletion or insertion identification step. The mutation, deletion or insertion may be in the coding and/or non-coding region of the locus, alone or in various combination(s). Mutations more specifically include point mutations. Deletions may encompass any region of

5 two or more residues in a coding or non-coding portion of the gene locus, such as from two residues up to the entire gene or locus. Typical deletions affect smaller regions, such as domains (introns) or repeated sequences or fragments of less than about 50 consecutive base pairs, although larger deletions may occur as well. Insertions may encompass the addition of one or several residues in a coding or non-coding portion of the gene locus. Insertions may

10 typically comprise an addition of between 1 and 50 base pairs in the gene locus. The CTGF gene locus mutation, deletion or insertion may result in the creation of stop codons, frameshift mutations, amino acid substitutions, particular RNA splicing or processing, product instability, truncated polypeptide production, etc. The mutation, deletion or insertion may result in the production of a CTGF polypeptide with altered function, stability, targeting or

15 structure. The mutation, deletion or insertion may also cause a reduction in protein expression or, alternatively, an increase in said production.

A particular object of this invention is a method of detecting predisposition to and/or prognosis of a dementia, especially a dementia with memory and/or cognitive dysfunction, the

20 method comprising detecting the presence of one or several mutation, deletion or insertion or SNPs selected from the SNPs listed Table 1A, Table 1B, or Table 1C.

Table 1A: Dementia - associated mutation(s), deletion(s) or insertion(s) in the CTGF gene locus

Nucleotide position in genomic sequence of chromosome	SNP reference	Polymorphism	Genotype correlated with dementia	Sequence reference
132273257	rs6918698	C/G	GC or GG	SEQ ID NO: 1
132268964	rs9399005	C/T	CC and CT	SEQ ID NO: 2
132304684	rs4897554	A/G	GG	SEQ ID NO: 3

	rs1029122	C/T	TT and CC	SEQ ID NO: 67
	rs11154653	G/T	TG and TT	SEQ ID NO: 68
	rs10293697 (or rs7645481)	C/T		SEQ ID NO: 69
	rs1931001	A/C	AA or CC	SEQ ID NO: 70
	rs9321315	A/T	TT or TA	SEQ ID NO: 71
	rs9483364	A/G	GG or GA	SEQ ID NO: 72

Association with dementia was shown, by comparing the distribution of genotypes between the affected patients and the control groups.

In particular, the presence of at least one allele C at position rs9399005 (which means that the subject is homozygote CC or heterozygote CT) and/or two alleles G at position rs4897554 (which means that the subject is homozygote GG) were shown to be deleterious, i.e. strongly correlated with a dementia, especially a dementia with memory and/or cognitive dysfunction as AD and MCI.

The results show that SNP rs9399005 is more particularly associated with mild cognitive impairment (MCI) and Alzheimer's disease, which means that it correlates with the development of a dementia.

Preferably, the invention thus provides a method of determining whether a subject has or is at risk of developing an early form of dementia such as a mild cognitive impairment (MCI), which method comprises detecting the presence of a SNP at position rs9399005 or rs4897554 in the CTGF gene locus in a biological sample of said subject.

Preferably, the invention further provides a method of determining whether a subject has or is at risk of developing an advanced form of dementia such as Alzheimer's disease (AD) which method comprises detecting the presence of a SNP at position rs9399005 in the CTGF gene locus in a biological sample of said subject.

Linkage Disequilibrium

Once a first SNP has been identified in a genomic region of interest, more particularly in CTGF gene locus, other additional SNPs in linkage disequilibrium with this first SNP can be

identified. Indeed, any SNP in linkage disequilibrium with a first SNP associated with a dementia, especially a dementia with memory and/or cognitive dysfunction will be associated with this trait. Therefore, once the association has been demonstrated between a given SNP and a dementia, especially a dementia with memory and/or cognitive dysfunction, the discovery of additional SNPs associated with this trait can be of great interest in order to increase the density of SNPs in this particular region. Identification of additional SNPs in linkage disequilibrium with a given SNP involves: (a) amplifying a fragment from the genomic region comprising or surrounding a first SNP from a plurality of individuals; (b) identifying of second SNP in the genomic region harboring or surrounding said first SNP; (c) conducting a linkage disequilibrium analysis between said first SNP and second SNP; and (d) selecting said second SNP as being in linkage disequilibrium with said first marker. Sub-combinations comprising steps (b) and (c) are also contemplated. These SNPs in linkage disequilibrium can also be used in the diagnostic methods according to the present invention.

The inventors have already identified several markers in linkage disequilibrium (LD) with rs9399005 or rs4897554. These additional markers are listed in Table 1B. Any of these SNPs may be used in addition or in lieu of rs9399005 or rs4897554.

Table 1B: Markers in linkage disequilibrium (LD)

20

#	SNP reference	Position	LD with rs4897554	LD with rs9399005	Position from start codon of the gene	Position from the end of the gene	Sequence reference
14	rs9493142	132286336	yes		27875	24676	SEQ ID NO: 4
16	rs6929832	132286364	yes	yes	27847	24648	SEQ ID NO: 5
25	rs6914218	132292595	yes	yes	21616	18417	SEQ ID NO: 6
27	rs12194675	132293721	yes	yes	20490	17291	SEQ ID NO: 7
32	rs13211178	132295966	yes	yes	18245	15046	SEQ ID NO: 8
33	rs12200211	132296478	yes	yes	17733	14534	SEQ ID NO: 9
35	rs12214123	132297011	yes	yes	17200	14001	SEQ ID NO: 10
36	rs12192391	132297943	yes	yes	16268	13069	SEQ ID NO: 11
42	rs1931004	132304007	yes	yes	10204	7005	SEQ ID NO: 12
45	rs12526196	132305169	yes	yes	9042	5843	SEQ ID NO: 13
48	rs6917644	132307358	yes	yes	6853	3654	SEQ ID NO: 14

49	rs9399005	132310657	yes	yes	3554	355	SEQ ID NO: 15
50	rs6918698	132314950	yes	yes	-739	-3938	SEQ ID NO: 16
51	rs9493150	132315684	yes		-1473	-4672	SEQ ID NO: 17
53	rs928501	132317130	yes		-2919	-6118	SEQ ID NO: 18
54	rs7748518	132318911	yes		-4700	-7899	SEQ ID NO: 19
57	rs9388949	132319155	yes	yes	-4944	-8143	SEQ ID NO: 20
62	rs10872387	132324004	yes		-9793	-12992	SEQ ID NO: 21
64	rs12192108	132325558	yes		-11347	-14546	SEQ ID NO: 22
65	rs7747551	132325860	yes		-11649	-14848	SEQ ID NO: 23
67	rs12663962	132329042	yes		-14831	-18030	SEQ ID NO: 24
69	rs9402376	132329677	yes		-15466	-18665	SEQ ID NO: 25
72	rs9493157	132330850	yes		-16639	-19838	SEQ ID NO: 26
76	rs11154654	132333478	yes		-19267	-22466	SEQ ID NO: 27
79	rs1930994	132333962	yes		-19751	-22950	SEQ ID NO: 28
81	rs1930995	132334269	yes		-20058	-23257	SEQ ID NO: 29
82	rs7767139	132334474	yes		-20263	-23462	SEQ ID NO: 30
83	rs7767582	132334584	yes		-20373	-23572	SEQ ID NO: 31
85	rs12055428	132335258	yes		-21047	-24246	SEQ ID NO: 32
86	rs9483365	132335602	yes		-21391	-24590	SEQ ID NO: 33
87	rs9402377	132336015	yes		-21804	-25003	SEQ ID NO: 34
93	rs975445	132337814	yes		-23603	-26802	SEQ ID NO: 35
95	rs9493160	132338560	yes		-24349	-27548	SEQ ID NO: 36
96	rs2027034	132338658	yes		-24447	-27646	SEQ ID NO: 37
97	rs9388953	132339202	yes		-24991	-28190	SEQ ID NO: 38
98	rs928505	132339834	yes	yes	-25623	-28822	SEQ ID NO: 39
99	rs928504	132339928	yes		-25717	-28916	SEQ ID NO: 40
101	rs4452668	132341441	yes		-27230	-30429	SEQ ID NO: 41
105	rs9375854	132343988	yes		-29777	-32976	SEQ ID NO: 42
52	rs2151532	132316423		yes	-2212	-5411	SEQ ID NO: 43
55	rs7768619	132319026		yes	-4815	-8014	SEQ ID NO: 44
58	rs1931002	132320175		yes	-5964	-9163	SEQ ID NO: 45

59	rs7763896	132321497		yes	-7286	-10485	SEQ ID NO: 46
60	rs12527379	132321533		yes	-7322	-10521	SEQ ID NO: 47
63	rs2095252	132325281		yes	-11070	-14269	SEQ ID NO: 48
71	rs4897555	132330159		yes	-15948	-19147	SEQ ID NO: 49
73	rs1931000	132331117		yes	-16906	-20105	SEQ ID NO: 50

The experiments of the Example section, shows 25 SNPs associated with Alzheimer's disease (AD), Mild cognitive impairment (MCI), fronto-temporal dementia (FTD), or dementia with Lewis bodies (DLB), These SNPs are listed in Table 1C:

5

Table 1C: Markers associated with dementias

AD	MCI	DLB	FTD
		rs1029122	
			rs11154653
rs12192108			
	rs1931001		
rs2095252	rs2095252		
rs10872387			
	rs12192391		
	rs12194675		
	rs12200211		
	rs12214123		
rs12527379	rs12527379		
	rs13211178		
rs12663962			
rs1931000	rs1931000		rs1931000
rs1931001			
rs4897554	rs4897554	rs4897554	rs4897554
rs6918698	rs6918698		
rs7747551			
			rs9321315
	rs7768619		
rs9388949		rs9388949	
rs9399005	rs9399005		rs9399005
rs9483364			
rs9493150	rs9493150		
rs9493157			

A particular object of this invention is a method of determining whether a subject has or is at risk of developing a dementia, which method comprises detecting the presence of a SNP or combination of SNPs as listed in Table 1C, i.e. selected from the group consisting of

rs12192108, rs2095252, rs10872387, rs12527379, rs12663962, rs1931000, rs1931001,
5 rs4897554, rs6918698, rs7747551, rs9388949, rs9399005, rs9483364, rs9493150, rs9493157,
rs1931001, rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, rs7768619,
rs1029122, rs11154653, and rs9321315, especially wherein said SNP is preferably selected
from the group consisting of rs4897554, rs9399005, rs1931001, rs1931000, rs9388949,
rs13211178, rs1029122, rs9321315, and rs11154653.

10

More particularly, it is provided a method of determining whether a subject has or is at risk of developing AD, which method comprises detecting the presence of a SNP or combination of SNPs, selected from the group consisting of rs12192108, rs2095252, rs10872387, rs12527379, rs12663962, rs1931000, rs1931001, rs4897554, rs6918698, rs7747551,
15 rs9388949, rs9399005, rs9483364, rs9493150 and rs9493157, preferably rs7747551, rs1931001, rs12663962, rs10872387, and/or rs12192108.

It is provided a method of determining whether a subject has or is at risk of developing MCI, which method comprises detecting the presence of a SNP or combination of SNPs, selected
20 from the group consisting of rs1931001, rs2095252, rs12192391, rs12194675, rs12200211, rs12214123, rs12527379, rs13211178, rs1931000, rs4897554, rs6918698, rs7768619, rs9399005, rs9493150, preferably rs1931001, rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, and/or rs7768619.

25 It is also provided a method of determining whether a subject has or is at risk of developing DLB, which method comprises detecting the presence of a SNP or combination of SNPs, selected from the group consisting of rs1029122, rs4897554, rs9388949, preferably rs1029122.

30 It is also provided a method of determining whether a subject has or is at risk of developing FTD, which method comprises detecting the presence of a SNP or combination of SNPs,

selected from the group consisting of rs11154653, rs1931000 , rs4897554, rs9321315, rs9399005, preferably rs11154653 and/or rs9321315.

In a particular aspect of the invention, the presence of one of the following genotypes, alone
5 or in combinations, in a subject is indicative of a development of, or a risk of developing, Alzheimer's disease :

genotype CC or TC with respect to rs9399005

genotype GG with respect to rs4897554

genotype GG or GC with respect to rs9493150

10 genotype GG or GA with respect to rs9483364

genotype AA with respect to rs10872387

genotype GG with respect to rs12527379

genotype GG or GC with respect to rs6918698

genotype CC with respect to rs1931001

15 genotype TT with respect to rs12192108

genotype GG with respect to rs12663962

genotype AA or AG with respect to rs1931000

genotype AA or AG with respect to rs2095252

genotype AA with respect to rs7747551

20 genotype TT or TC with respect to rs9388949; and/or

genotype CC or TC with respect to rs9493157.

More particularly the presence of a combination of risk alleles, in a subject is indicative of a development of, or a risk of developing, Alzheimer's disease, wherein said risk alleles are :

25 genotype GG with respect to rs4897554,

genotype CC or TC with respect to rs9399005,

genotype CC with respect to rs1931001,

genotype AA or AG with respect to rs1931000, and

genotype TT or TC with respect to rs9388949.

In another particular aspect of the invention, the presence of one of the following genotypes, alone or in combinations, in a subject is indicative of a development of, or a risk of developing, mild cognitive impairment:

genotype CC or TC with respect to rs9399005

5 genotype GG with respect to rs4897554

genotype GG or GC with respect to rs9493150

genotype AA or AG with respect to rs12527379

genotype GG or GC with respect to rs6918698:

genotype CC with respect to rs1931001

10 genotype AA with respect to rs12192391

genotype AA with respect to rs12194675

genotype AA with respect to rs12200211

genotype GG with respect to rs12214123

genotype GG with respect to rs13211178

15 genotype AA or AG with respect to rs1931000

genotype AA or AG with respect to rs2095252, and/or

genotype TT with respect to rs7768619.

More particularly the presence of a combination of risk alleles, in a subject is indicative of a
20 development of, or a risk of developing, mild cognitive impairment, wherein said risk alleles are

genotype GG with respect to rs4897554

genotype CC or TC with respect to rs9399005

genotype CC with respect to rs1931001, and

25 genotype GG with respect to rs13211178.

In still another particular aspect of the invention, the presence of one of the following genotypes, alone or in combinations, in a subject is indicative of a development of, or a risk of developing, dementia with Lewis bodies:

30 genotype GG with respect to rs4897554

genotype CT with respect to rs1029122, and/or

genotype TC with respect to rs9388949.

More particularly the presence of a combination of risk alleles, in a subject is indicative of a development of, or a risk of developing, dementia with Lewis bodies, wherein said risk alleles are

- 5 genotype GG with respect to rs4897554 and
genotype CT with respect to rs1029122.

In a further particular aspect of the invention, the presence of one of the following genotypes, alone or in combinations, in a subject is indicative of a development of, or a risk of
10 developing, fronto-temporal dementia:

- genotype CC or TC with respect to rs9399005
genotype GG with respect to rs4897554
genotype TG with respect to rs11154653
genotype AA with respect to rs9321315, and/or
15 genotype AA or AG with respect to rs1931000.

More particularly, the presence of a combination of risk alleles, in a subject is indicative of a development of, or a risk of developing, fronto-temporal dementia, wherein said risk alleles are

- 20 genotype GG with respect to rs4897554
genotype AA with respect to rs9321315, and
genotype TG with respect to rs11154653.

Causal Mutation

- Mutations in the CTGF gene locus which are responsible for a dementia, especially a
25 dementia with memory and/or cognitive dysfunction may be identified by comparing the
sequences of the CTGF gene locus from patients presenting a dementia, especially a dementia
with memory and/or cognitive dysfunction and control individuals. Based on the identified
association of SNPs of CTGF, the identified locus can be scanned for mutations. In a
preferred embodiment, functional regions such as exons and splice sites, promoters and other
30 regulatory regions of the CTGF gene locus are scanned for mutations. Preferably, patients
presenting a dementia, especially a dementia with memory and/or cognitive dysfunction carry
the mutation shown to be associated with a dementia, especially a dementia with memory

and/or cognitive dysfunction and control individuals do not carry the mutation or allele associated with a dementia, especially a dementia with memory and/or cognitive dysfunction. It might also be possible that patients presenting a dementia, especially a dementia with memory and/or cognitive dysfunction carry the mutation shown to be associated with a dementia, especially a dementia with memory and/or cognitive dysfunction with a higher frequency than control individuals. The method used to detect such mutations generally comprises the following steps: amplification of a region of the CTGF gene locus comprising a SNP or a group of SNPs associated with a dementia, especially a dementia with memory and/or cognitive dysfunction from DNA samples of the CTGF gene locus from patients presenting a dementia, especially a dementia with memory and/or cognitive dysfunction and control individuals; sequencing of the amplified region; comparison of DNA sequences of the CTGF gene from patients presenting a dementia, especially a dementia with memory and/or cognitive dysfunction and control individuals; determination of mutations specific to patients presenting a dementia, especially a dementia with memory and/or cognitive dysfunction.

15

Sequencing

Sequencing can be carried out using techniques well known in the art, using automatic sequencers. The sequencing may be performed on the complete CTGF gene locus or, more preferably, on specific domains thereof, typically those known or suspected to carry deleterious mutations or other alterations.

20

Amplification

Amplification is based on the formation of specific hybrids between complementary nucleic acid sequences that serve to initiate nucleic acid reproduction. Amplification may be performed according to various techniques known in the art, such as by polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA) and nucleic acid sequence based amplification (NASBA). These techniques can be performed using commercially available reagents and protocols. Preferred techniques use allele-specific PCR or PCR-SSCP. Amplification usually requires the use of specific nucleic acid primers, to initiate the reaction. Nucleic acid primers useful for amplifying sequences from the CTGF gene locus are able to specifically hybridize with a portion of the CTGF gene locus that flank a target region of said locus, said target region being altered in certain subjects having

30

dementia especially a dementia with memory and/or cognitive dysfunction. Examples of such target regions are provided in Table 2. Another particular object of this invention resides in a nucleic acid primer useful for amplifying sequences from the CTGF gene or locus including surrounding regions. Such primers are preferably complementary to, and hybridize specifically to nucleic acid sequences in the CTGF gene locus. Particular primers are able to specifically hybridize with a portion of the CTGF gene locus that flank a target region of said locus, said target region being altered in certain subjects having a dementia, especially a dementia with memory and/or cognitive dysfunction. Primers that can be used to amplify CTGF target region comprising SNPs as identified in Table 2 may be designed based on their sequence or on the genomic sequence of CTGF.

Selective hybridization

Hybridization detection methods are based on the formation of specific hybrids between complementary nucleic acid sequences that serve to detect nucleic acid sequence mutation(s), deletion(s) or insertion(s). A particular detection technique involves the use of a nucleic acid probe specific for wild-type or altered CTGF gene or RNA, followed by the detection of the presence of a hybrid. The probe may be in suspension or immobilized on a substrate or support (as in nucleic acid array or chips technologies). The probe is typically labeled to facilitate detection of hybrids. In this regard, a particular embodiment of this invention comprises contacting the sample from the subject with a nucleic acid probe specific for an altered CTGF gene locus, and assessing the formation of a hybrid. In a particular preferred embodiment, the method comprises contacting simultaneously the sample with a set of probes that are specific, respectively, for wild type CTGF gene locus and for various altered forms thereof. In this embodiment, it is possible to detect directly the presence of mutation(s), deletion(s) or insertion(s) in the CTGF gene locus in the sample. Also, various samples from various subjects may be treated in parallel.

Within the context of this invention, a probe refers to a polynucleotide sequence which is complementary to and capable of specific hybridization with a (target portion of a) CTGF gene or RNA, and which is suitable for detecting polynucleotide polymorphisms associated with CTGF alleles which predispose to or are associated with a dementia, especially a dementia with memory and/or cognitive dysfunction. Probes are preferably perfectly complementary to the CTGF gene, RNA, or target portion thereof. Probes typically comprise

single-stranded nucleic acids of between 8 to 1000 nucleotides in length, for instance of between 10 and 800, more preferably of between 15 and 700, typically of between 20 and 500. It should be understood that longer probes may be used as well. A preferred probe of this invention is a single stranded nucleic acid molecule of between 8 to 500 nucleotides in length,
5 which can specifically hybridize to a region of a CTGF gene locus or RNA that carries a mutation, a deletion, or an insertion.

The method of the invention employs a nucleic acid probe specific for an altered (e.g., a mutated) CTGF gene or RNA, i.e., a nucleic acid probe that specifically hybridizes to said altered CTGF gene or RNA and essentially does not hybridize to a CTGF gene or RNA
10 lacking said mutation, deletion or insertion. Specificity indicates that hybridization to the target sequence generates a specific signal which can be distinguished from the signal generated through non-specific hybridization. Perfectly complementary sequences are preferred to design probes according to this invention. It should be understood, however, that certain mismatch may be tolerated, as long as the specific signal may be distinguished from
15 non-specific hybridization.

Particular examples of such probes are nucleic acid sequences complementary to a target portion of the genomic region including the CTGF gene locus or RNA carrying a point mutation as listed in Table 1A or 1B above. More particularly, the probes can comprise a sequence selected from the group consisting of SEQ ID NO 1 to 52 or a fragment thereof
20 comprising the SNP or a complementary sequence thereof.

The sequence of the probes can be derived from the sequences of the CTGF gene and RNA as provided in the present application. Nucleotide substitutions may be performed, as well as chemical modifications of the probe. Such chemical modifications may be accomplished to increase the stability of hybrids (e.g., intercalating groups) or to label the probe. Typical
25 examples of labels include, without limitation, radioactivity, fluorescence, luminescence, enzymatic labeling, etc. The invention also concerns the use of a nucleic acid probe as described above in a method of detecting the presence of or predisposition to a dementia, especially a dementia with memory and/or cognitive dysfunction in a subject or in a method of assessing the response of a subject to a treatment of a dementia, especially a dementia with
30 memory and/or cognitive dysfunction.

Further aspects and advantages of the present invention will be disclosed in the following experimental section, which should be regarded as illustrative and not limiting the scope of the present application.

5 MATERIALS AND METHODS

Subjects

Three groups of subjects were recruited.

AD patients (N=380) were recruited at the Saint Marguerite Hospital, Marseille, France. The patients were Caucasians originating from South-East of France. The clinical diagnosis of AD was established using NINCDS-ADRDA criteria for AD (McKhann and al., 1984). This AD group includes 36.2% of male patients and 63.8% of female patients. The age mean is 80 +/- 8.0 years for this group, 78.3 +/- 8.1 years for males and 81.4 +/- 8.0 years for females.

MCI patients (N=426) were recruited at the Saint Marguerite Hospital, Marseille, France. All MCI patients met criteria for an amnesic form of MCI (Peterson and al., 1999) as all had memory complaint (usually verified by an informant), performed poorly on neuropsychological tests of verbal memory, and had normal general cognitive function. This MCI group includes 39.8% males and 60.2% females. The age mean is 70.5 +/- 12.3 years for this group, 70.0 +/- 12.8 years for males and 71 +/- 11.8 years for females.

The gender and age distribution is not significantly different between these two patient groups (respectively $p=0.39$ and $p=0.67$).

DLB (N=90) AND FTD patients (N=99) were recruited at the Saint Marguerite Hospital, Marseille, France.

Healthy controls (N=376), without any neurological pathology, were recruited at the Blood Bank Center (volunteer blood donors). This control group includes 68.0% males and 32.0% females. The median age is 41.8 +/- 10.6 years for this group, 42.8 +/- 9.6 years for males and 40.2 +/- 11.9 years for females.

Statistical analysis

Univariate and multivariate logistic regressions were used to analyse the relationship between the probability of an individual to develop a dementia. Univariate analyses were performed to compare genotype frequencies between cases and controls. Multivariate analyses were

performed on cases and controls including all the genotyped Tag SNPs as covariates. The statistical SPSS software (version 10.0) was used for these analyses.

DNA extraction

Aliquots of 3 to 5 ml of blood were collected on sodium citrate and kept at -20°C. DNA was
5 extracted using the standard salting out method. Some subjects refused blood collection. In this case, mouth cell samples were collected using foam-tipped applicators and applied to indicating FTA1 cards following the protocol described by Whatman (<http://www.whatman.co.uk/>).

10 TagSNPs

TagSNPs were selected according to HapMap Data on the Caucasian reference population. This selection was done on a region covering the CTGF gene $\pm$ 10 kb. This selection was performed on markers characterized by a MAF>15% and the r^2 cut off value was fixed to 0.8. Eight Tag SNPs were selected: rs10872387, rs9483364, rs12527379, rs1931002, rs9493150,
15 rs6918698, rs9399005 and rs4897554. Six SNPs (rs10872387, rs9483364, rs12527379, rs1931002, rs9493150, rs6918698) were located into the CTGF promoter whereas the others (rs9399005 and rs4897554) were located in the 3' region.

DNA amplification

20 Based on the CTGF gene reference sequence (Ensembl reference population ENSG00000118523), the sets of primers used to amplify the human CTGF gene were designed with primer3 software. Polymerase chain reactions were carried out on a robocycler gradient 96 (Stratagene, La Jolla, USA) in 30 ml reactions containing 1mM of each primer, 100ng DNA, 10mM Tris-HCl pH=9, 0,1% Triton X-100, 50mM KCl, 0.2mg/ml BSA, 1.5mM
25 MgCl₂, 1mM of dNTP and 1.5U Taq polymerase. Following the initial denaturation step at 94°C for 5 min, the samples were subjected to 35 cycles consisting of 94°C for 1 min, annealing temperature for 45 sec and 72°C for 45 sec.

Sequencing

30 Purified PCR products were sequenced using ABI Prism BigDye Terminator cycle sequencing system (PE Applied Biosystems, Foster City, U.S.A.) on ABI Prism automatic sequencer.

Sequencing reactions were performed on both strands Sequencing by GATC biotech (GATC, Marseille France).

Polymorphism genotyping by PCR and restriction enzyme digestion

5 Polymorphisms (rs10872387, rs9483364, rs12527379, rs1931002, rs9493150, rs6918698, rs9399005 and rs4897554) were genotyped by restriction enzyme analysis under standard conditions described by the enzyme manufacturers (New England Biolabs, Beverly, USA). Polymerase chain reaction (PCR) amplifications were carried out on a robocycler gradient 96 (Stratagene, La Jolla, U.S.A.) according to standard protocol. Each digestion was resolved on
10 a 12% acrylamide gel, stained with ethidium bromide (1mg/ml) and visualized by UV. Primers are described in Table 2. In order to facilitate detection of the mutation by restriction enzyme digestion: a T has been changed to G (underlined base) in SEQ ID NO: 51, AC has been changed to TG (underlined base) in SEQ ID NO: 60 and AA has been changed to CT (underlined base) in SEQ ID NO: 66.

15

Polymorphism genotyping by PCR with specific TaqMan probes

Half of the DNA samples were genotyped a second time in a double-blind protocol by using TaqMan system (Applied Biosystems, Courtaboeuf, France. Each reaction contained 12.5 ng of genomic DNA, TaqMan Universal PCR Master Mix (Applied Biosystems, Courtaboeuf,
20 France), 900 nM of each primer and 200 nM of each fluorescently-labelled hybridisation probe in a total volume of 5 µl. PCR was conducted in an ABI Prism Sequence Detection System 7900 (Applied Biosystems, Courtaboeuf, France) using the following conditions: 50°C for 2 min, 95°C for 10 min and 40 cycles of amplification (95°C denaturation for 15 s, 60°C annealing/extension for 1 min).

25

Additional markers were genotyped by another technology.

The genotyping was done with the Illumina's GoldenGate Assay (standard used during the International HapMap Project). Custom GoldenGate Genotyping Kits for VeraCode make it possible to simultaneously genotype 384 loci in a single well of a standard 96-well microplate.
30 This technology involves using the holographically inscribed VeraCode beads and two-color detection instrument that identifies individual bead types and detects their assay hybridization signals. First of all, the DNA sample used in this assay is activated for binding to

paramagnetic particles. Then, assay oligonucleotides are hybridized to the activated DNA. Three oligonucleotides are designed to identify the allele at each SNP locus in the experiment. Two oligonucleotides are specific to each allele of the tested SNP site. Each of them, contains a region of genomic complementarity but has a different nucleotide at the 3' end, which
5 corresponds to the complement of each possible allele in the genomic DNA. Moreover each oligonucleotide also contains a unique universal PCR primer sequence. A third oligonucleotide hybridizes several bases downstream from the SNP site. This oligonucleotide also contains a region of genomic complementarity and a universal PCR primer site. This primer is characterized by an additional unique address sequence that targets a particular bead
10 type for assay readout later in the procedure. During the primer hybridization process, the assay oligonucleotides hybridize to the activated genomic DNA sample bound to paramagnetic particles. Following hybridization, several wash steps are performed, reducing noise by removing excess and non-specifically hybridized oligonucleotides. During the next step, a genomic DNA amplification, allele specific, is performed using a DNA polymerase.
15 The generated products provide a template for PCR using universal PCR primers Cy3 and Cy5 labeled. Finally, the dye-labeled single-stranded DNA is hybridized to complementary VeraCode bead types. It allows for the separation of the assay products in solution onto a solid surface for individual SNP genotype readout. After hybridization, the BeadXpress Reader analyzes Cy3 and Cy5 fluorescence signals on each bead in addition to the inscribed
20 holographic element of each bead that identifies the locus of interest. The data were then analyzed with BeadStudio Data Analysis Software for automated genotype calling. This approach is an unmatched combination of sensitivity, high call rates, reproducibility, and accuracy.

The markers identified through this analysis were rs1029122, rs11154653, rs10293697,
25 rs1931001 and rs9321315

Markers in LD with rs4897554 and rs9399005 were genotyped with the Illumina's GoldenGate Assay;

The genotyping was done with the Illumina's GoldenGate Assay for the SNPs in Linkage
30 disequilibrium with rs4897554. These markers are rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, rs6914218, rs6929832, rs12526196, rs6917644, rs6918698, rs7748518, rs928501, rs9399005, rs9493150, rs9388949, rs11154654, rs12055428,

rs1930994, rs9402377, rs10872387, rs12192108, rs2027034, rs7747551, rs975445, rs12663962, rs9375854, rs4452668, rs9402376, rs1931004, rs928505, rs9388953, rs9493157, rs7767139, rs928504, rs1930995, rs7767582, rs9483365, rs9493160, rs9493142. Same approach was done for the markers in LD with rs9399005. These markers are rs7768619, 5 rs12192391, rs12194675, rs12200211, rs12214123, rs12526196, rs13211178, rs4897554, rs6914218, rs6917644, rs6929832, rs6918698, rs1931004, rs9388949, rs12527379, rs2095252, rs1931000, rs928505, rs2151532, rs1931002, rs7763896, rs4897555.

Table 2: Primers for genotyping by restriction enzyme analysis.

Polymorphism	Primer sequences(forward and reverse)	PCR product size	Restriction Enzyme	Expected profiles
rs10872387	GACCTAATATTATAACAC <u>G</u> GAC (SEQ ID NO: 51) AAAGCTGACCAATTATCTGCAA (SEQ ID NO: 52)	190 bp	aVaII	A/A genotype: 190 bp C/C genotype: 19+171 bp
rs19483364	TGTCATCAAATTGCCACAGG (SEQ ID NO: 53) TTTCTCCCTTCTCCTACAGCA (SEQ ID NO: 54)	304 bp	SfaNI	A/A genotype: 304 bp G/G genotype: 120+184 bp
rs12527379	CCATCAGCACTGAAGCAATG (SEQ ID NO: 55) CACACACATGTGCAGGTCAA (SEQ ID NO: 56)	331 bp	Tsp509I	A/A genotype: 30+66+235 bp G/G genotype: 30+301 bp A/G genotype: 19+66+235+301 bp
rs1931002	TGATTCCCATAGGCATGGTT (SEQ ID NO: 57) TTCTTGGAACCAAGGTGGTA (SEQ ID NO: 58)	264 bp	TaqI	A/A genotype: 264 bp G/G genotype: 70+194 bp

rs9493150	TGTTAATACCTCCAGTTCCCATT (SEQ ID NO: 59) TAAAGCCGATCTTTGCTGCA (SEQ ID NO: 60)	186 bp	PstI	C/C genotype: 16+170 bp G/G genotype: 186 bp
rs6918698	CGGTTTTGGGACAAGAAAGA (SEQ ID NO: 61) CTCCTAGGTGAACCCCCTTT (SEQ ID NO: 62)	262 bp	MnII	C/C genotype: 262 bp G/G genotype: 122+139 bp
rs9399005	AAGTTCAGAAACAGACCTAGAGCA (SEQ ID NO: 63) CTTGCAGGCATACACACCAC (SEQ ID NO: 64)	271 bp	MscI	C/C genotype: 271 bp T/T genotype:113+158 bp
rs4897554	TGCAAATTTTCCCTCACAAA (SEQ ID NO: 65) CATCCATCCAAAACTGCTAG (SEQ ID NO: 66)	182 bp	NheI	A/A genotype: 182 bp G/G genotype: 21+161 bp

EXAMPLES

EXAMPLE 1

- 5 Association between SNPs rs9399005, rs4897554, rs9493150 rs9483364, rs10872387, 12527379 and rs6918698 in the CTGF locus with Alzheimer disease in univariate analysis.

The inventors have genotyped SNPs either by performing restriction analysis or by using the TaqMan system according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the AD group and on the control subjects are described in Table 3.

10

Table 3. Genotype distributions of the CTGF SNPs in the various study groups.

Polymorphism	Genotype	Alzheimer	MCI	DLB	FTD	Control
rs10872387	AA	239 (62.9%)	257 (60.5%)	53 (58.9%)	63 (63.6%)	205 (55.3%)
	AC	121 (31.8%)	146 (34.4%)	34 (37.8%)	33	144 (38.8%)

					(33.3%)	
	CC	20 (5.3%)	22 (5.2%)	3 (3.3%)	3 (3.0%)	22 (5.9%)
rs9483364	GG	191 (50.4%)	211 (49.9%)	50 (55.6%)	47 (47.5%)	179 (48.9%)
	AG	169 (44.6%)	173 (40.9%)	29 (32.2%)	42 (42.4%)	144 (39.3%)
	AA	19 (5.0%)	39 (9.2%)	11 (12.2%)	10 (10.1%)	43 (11.7%)
rs12527379	GG	103 (27.1%)	141 (33.1%)	32 (35.6%)	30 (30.3%)	151 (40.5%)
	AG	200 (52.6%)	204 (47.9%)	40 (44.4%)	47 (47.5%)	162 (43.4%)
	AA	77 (20.3%)	81 (19.0%)	18 (20.0%)	22 (22.2%)	60 (16.1%)
rs1931002	GG	313 (82.4%)	357 (84.0%)	79 (87.8%)	79 (79.8%)	305 (82.2%)
	AG	64 (16.8%)	64 (15.1%)	11 (12.2%)	20 (20.2%)	64 (17.3%)
	AA	3 (0.8%)	4 (0.9%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
rs4897554	AA	119 (32.3%)	151 (35.5%)	33 (36.7%)	36 (36.7%)	57 (21.8%)
	AG	186 (50.5%)	195 (45.9%)	44 (48.9%)	45 (45.9%)	191 (73.2%)
	GG	63 (17.1%)	79 (18.6%)	13 (14.4%)	17 (17.3%)	13 (5.0%)
rs6918698	GG	103 (27.5%)	112 (27.1%)	18 (20.9%)	29 (30.9%)	96 (25.9%)
	GC	198 (52.8%)	216 (52.3%)	47 (54.7%)	46 (48.9%)	169 (45.6%)
	CC	74 (19.7%)	85 (20.6%)	21 (24.4%)	19 (20.2%)	106 (28.6%)
rs9399005	CC	196 (51.7%)	221 (52.2%)	48 (53.3%)	57 (57.6%)	183 (49.5%)
	TC	162 (42.7%)	185 (43.7%)	36 (40.0%)	39 (39.4%)	144 (38.9%)
	TT	21 (5.5%)	17 (4.0%)	6 (6.7%)	3 (3.0%)	43 (11.6%)
rs9493150	GG	191 (50.5%)	202 (48.3%)	38 (43.2%)	45 (46.9%)	178 (48.0%)
	GC	157 (41.5%)	180 (43.1%)	42 (47.7%)	41 (42.7%)	143 (38.5%)
	CC	30 (7.9%)	36 (8.6%)	8 (9.1%)	10 (10.4%)	50 (13.5%)

A difference in CTGF genotype distribution between AD patients and controls was observed for seven polymorphisms (rs9399005, rs4897554, rs9493150, rs9483364, rs10872387, rs12527379 and rs6918698).

In the AD subjects group, 358 (94.5%) subjects carry either the rs9399005 C/C or rs9399005C/T genotypes whereas 327 (88.4%) of the controls carry the same genotypes. This difference is significant ($p=0.004$; OR=0.668; 95% CI: 0.509-0.876).

For the rs4897554 polymorphism, 305 (82.9%) AD subjects carry the genotypes rs4897554A/A or rs4897554A/G versus 248 (95%) for the control. This difference is significant ($p=1.510^{-5}$; OR=1.985; 95% CI: 1.456-2.707).

Similarly, 30 (7.9%) AD patients carry the rs9493150C/C genotype whereas up to 50 (13.5%) of the controls carry this genotype. This difference is significant ($p=0.015$; OR=0.744; 95% CI: 0.586-0.944).

Similarly, 19 (5.0%) AD patients carry the rs9483364A/A genotype whereas up to 43 (11.7%) of the controls carry this genotype. This difference is significant ($p=0.001$ OR=0.630; 95% CI: 0.476-0.833).

Similarly, 239 (62.9%) AD patients carry the rs10872387A/A genotype whereas up to 205 (55.3%) of the controls carry this genotype. This difference is significant ($p=0.033$; OR=1.172; 95% CI: 1.012-1.356).

Similarly, in AD patients, 103 (27.1%) carry the rs12527379G/G genotype, 200 (52.6%) carry the rs12527379A/G genotype and 77 (20.3%) carry the rs12527379A/A genotype whereas into the controls group 151 (40.5%) carry the rs12527379G/G genotype, 162 (43.4%) carry the rs12527379A/G genotype and 60 (16.1%) carry the rs12527379A/A genotype. This difference is significant ($p=0.001$; OR=1.431; 95% CI: 1.164-1.759).

Similarly, 301 (80.3%) AD patients carry the rs6918698G/G or rs6918698G/C genotypes whereas up to 265 (71.5%) of the controls carry these two genotypes. This difference is significant ($p=0.005$; OR=0.784; 95% CI: 0.662-0.929). See Table 4.

Table 4. Association between TAG SNPs in the CTGF locus with AD in univariate analysis.

Univariate Analysis : Alzheimer vs Control		
rs10872387	AA vs AC vs CC	$p=0.059$; OR=1.260; 95% CI: 0.992-1.601 (NS)
	AA vs AC + CC	$p=0.033$; OR=1.172; 95% CI: 1.012-1.356 (NS)
	AA + CC vs AC	$p=0.046$; OR=0.858; 95% CI: 0.739-0.997 (S)
	AA + AC vs CC	$p=0.691$; OR=0.939; 95% CI: 0.687-1.282 (NS)
rs9483364	AA vs AG vs GG	$p=0.080$; OR=0.817; 95% CI: 0.652-1.024 (NS)
	AA vs AG + GG	$p=0.001$ OR=0.630; 95% CI: 0.476-0.833 (S)
	AA + GG vs AG	$p=0.147$; OR=1.114; 95% CI: 0.963-1.289 (NS)
	AA + AG vs GG	$p=0.685$; OR=1.030; 95% CI: 0.892-1.189 (NS)
rs12527379	AA vs AG vs GG	$p=0.001$; OR=1.431; 95% CI: 1.164-1.759 (S)

	AA vs AG + GG	p=0.138; OR=1.151; 95% CI: 0.956-1.387 (NS)
	AA + GG vs AG	p=0.012; OR=1.203; 95% CI: 1.042-1.389(S)
	AA + AG vs GG	p=1.2 10 ⁻⁴ ; OR=0.739; 95% CI: 0.634-0.862 (S)
rs1931002	AA vs AG vs GG	p=0.975; OR=1.006; 95% CI: 0.706-1.433 (NS)
	AA vs AG + GG	p=0.675; OR=1.212; 95% CI: 0.494-2.973 (NS)
	AA + GG vs AG	p=0.882; OR=0.986; 95% CI: 0.815-1.192 (NS)
	AA + AG vs GG	p=0.955; OR=1.005; 95% CI: 0.834-1.213 (NS)
rs4897554	AA vs AG vs GG	p=0.741; OR=0.957; 95% CI: 0.739-1.240 (NS)
	AA vs AG + GG	p=0.004; OR=1.308; 95% CI: 1.089-1.570 (S)
	AA + GG vs AG	p=1.710 ⁻⁸ ; OR=0.612; 95% CI: 0.516-0.726 (S)
	AA + AG vs GG	p=1.510 ⁻⁵ ; OR=1.985; 95% CI: 1.456-2.707 (S)
rs6918698	CC vs CG vs GG	p=0.046; OR=0.814; 95% CI: 0.664-0.996 (NS)
	CC vs CG + GG	p=0.005; OR=0.784; 95% CI: 0.662-0.929 (S)
	CC + GG vs CG	p=0.048; OR=1.156; 95% CI: 1.001-1.335 (NS)
	CC + CG vs GG	p=0.623; OR=1.042; 95% CI: 0.885-1.225 (NS)
rs9399005	TT vs TC vs CC	p=0.077; OR=0.817; 95% CI: 0.654-1.022 (NS)
	TT vs TC + CC	p=0.004; OR=0.668; 95% CI: 0.509-0.876 (S)
	TT + CC vs TC	p=0.287; OR=1.082; 95% CI: 0.936-1.252 (NS)
	TT + TC vs CC	p=0.537; OR=1.046; 95% CI: 0.907-1.207 (NS)
rs9493150	CC vs CG vs GG	p=0.100; OR=0.835; 95% CI: 0.674-1.035 (NS)
	CC vs CG + GG	p=0.015; OR=0.744; 95% CI: 0.586-0.944 (S)
	CC + GG vs CG	p=0.404; OR=1.064; 95% CI: 0.919-1.232 (NS)
	CC + CG vs GG	p=0.485; OR=1.052; 95% CI: 0.912-1.215 (NS)

(S) significant ; (NS) non significant

EXAMPLE 2

Association between SNPs rs9399005, rs4897554 in the CTGF locus with Alzheimer disease

5 in a multivariate analysis.

The inventors have performed a multivariate analysis (linear regression, stepwise procedure) to confirm the associations found previously in univariate analysis (polymorphism were analyzed one by one). Similarly to the univariate analysis, the genotypes were considered as binary variables. In this analysis, we included rs9399005, rs4897554, rs9493150 rs9483364, 10 rs10872387, 12527379 and rs6918698 as covariates. In this analysis polymorphisms rs4897554 and rs9399005 were still significantly associated to AD (p=5.8 10⁻⁵; OR=1.897; 95% CI: 1.389-2.591 and p=0.044; OR=0.739; 95% CI: 0.551-0.992 respectively) whereas the other covariates were excluded from the analysis. See Table 5.

15 **Table 5.** Association between TAG SNPs in the CTGF locus with AD in multivariate analysis.

Multivariate Analysis : Alzheimer vs Control

rs4897554	AA + AG vs GG	p=5.8 10 ⁻⁵ ; OR=1.897; 95% CI: 1.389-2.591
rs9399005	TT vs TC + CC	p=0.044; OR=0.739; 95% CI: 0.551-0.992
rs9483364	AA vs AG vs GG	excluded
rs9493150	CC vs CG + GG	excluded
rs10872387	AA vs AC + CC	excluded
rs12527379	AA vs AG vs GG	excluded
rs6918698	CC vs CG + GG	excluded

EXAMPLE 3

Among the additional markers in the CTGF locus, rs1931001 is associated with Alzheimer disease in a univariate analysis.

The inventors have genotyped additional SNPs by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the AD group and on the control subjects are described in Table 6. One marker detects significant difference between cases and controls.

in AD patients, 229 (60.3%) carry the rs1931001C/C or rs1931001A/A genotypes, whereas into the controls group 183 (49.2%) carry these genotypes. This difference is significant (p=0.002; OR=0.799; 95% CI: 0.692-0.923). See Table 7.

Table 7. Association between additional markers in the CTGF locus with AD in univariate analysis.

Univariate Analysis : Alzheimer vs Control

rs1029122	TT vs TC vs CC	p=0.459; OR=1.081; 95% CI: 0.880-1.329 (NS)
	TT vs TC + CC	p=0.878; OR=0.988; 95% CI: 0.848-1.151(NS)
	TT + CC vs TC	p=0.188; OR=1.101; 95% CI: 0.954-1.271 (NS)
	TT + TC vs CC	p=0.125; OR=0.863; 95% CI: 0.715-1.042 (NS)
rs11154653	TT vs TG vs GG	p=0.158; OR=1.392; 95% CI: 0.879-2.205 (NS)
	TT vs TG + GG	p=0.560; OR=0.700; 95% CI: 0.210-2.328 (NS)
	TT + GG vs TG	p=0.076; OR=1.254; 95% CI: 0.977-1.609 (NS)
	TT + TG vs GG	p=0.105; OR=0.817; 95% CI: 0.640-1.043 (NS)
rs10293697	TT vs TC vs CC	p=0.737; OR=0.959; 95% CI: 0.753-1.223 (NS)
	TT vs TC + CC	p=0.645; OR=1.035; 95% CI: 0.894-1.198(NS)
	TT + CC vs TC	p=0.173; OR=0.900; 95% CI: 0.774-1.047 (NS)
	TT + TC vs CC	p=0.057; OR=1.395; 95% CI: 0.990-1.965 (NS)
rs1931001	AA vs AC vs CC	p=0.023; OR=0.775; 95% CI: 0.623-0.965 (S)

	AA vs AC + CC	p=0.985; OR=1.002; 95% CI: 0.794-1.265 (NS)
	AA + CC vs AC	p=0.002; OR=0.799; 95% CI: 0.692-0.923 (S)
	AA + AC vs CC	p=0.002; OR=1.252; 95% CI: 1.083-1.447 (S)
rs9321315	TT vs TA vs AA	p=0.455; OR=0.889; 95% CI: 0.653 - 1.210 (NS)
	TT vs TA + AA	p=0.511; OR=0.808; 95% CI: 0.427 - 1.527 (NS)
	TT + AA vs TA	p=0.641; OR=0.960; 95% CI: 0.809 - 1.139 (NS)
	TT + TA vs AA	p=0.526; OR=1.056; 95% CI: 0.893 - 1.248 (NS)

(S) significant ; (NS) non significant

EXAMPLE 4

Among the markers in LD with rs4897554 or rs9399005, the polymorphisms rs12192108, rs12663962, rs1931000, rs2095252, rs7747551, rs9388949 and rs9493157 are associated with Alzheimer disease in a univariate analysis.

The inventors have genotyped SNPs in LD with rs4897554 or rs9399005 by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the AD group and on the control subjects are described in Table 8.

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Table 8. Genotype distributions of CTGF SNPs that are in linkage disequilibrium either with rs9399005 or rs4897554 in the various study groups.

Polymorphism	Genotype	Alzheimer	MCI	DLB	FTD	Control
rs11154654	TT	237 (62.4%)	256 (60.1%)	52 (57.8%)	63 (63.6%)	208 (55.6%)
	TC	123 (32.4%)	148 (34.7%)	35 (38.9%)	33 (33.3%)	145 (38.8%)
	CC	20 (5.3%)	22 (5.2%)	3 (3.3%)	3 (3.0%)	21 (5.6%)
rs12192108	TT	239 (63.1%)	253 (60.2%)	52 (57.8%)	62 (63.3%)	208 (55.8%)
	TC	120 (31.7%)	145 (34.5%)	35 (38.9%)	33 (33.7%)	143 (38.3%)
	CC	20 (5.3%)	22 (5.2%)	3 (3.3%)	3 (3.1%)	22 (5.9%)
rs12192391	AA	284 (75.1%)	321 (78.5%)	61 (70.1%)	63 (65.6%)	264 (70.8%)
	AG	86 (22.8%)	74 (18.1%)	26 (29.9%)	29 (30.2%)	100 (26.8%)
	GG	8 (2.1%)	14 (3.4%)	0 (0.0%)	4 (4.2%)	9 (2.4%)
rs12194675	AA	291 (76.6%)	337 (79.1%)	63 (70.0%)	69 (69.7%)	265 (71.4%)
	AG	80 (21.1%)	75 (17.6%)	27 (30.0%)	27 (27.3%)	97 (26.1%)

	GG	9 (2.4%)	14 (3.3%)	0 (0.0%)	3 (3.0%)	9 (2.4%)
rs12200211	AA	284 (74.9%)	331 (77.9%)	63 (70.0%)	65 (65.7%)	261 (70.0%)
	AG	86 (22.7%)	80 (18.8%)	27 (30.0%)	30 (30.3%)	101 (27.1%)
	GG	9 (2.4%)	14 (3.3%)	0 (0.0%)	4 (4.0%)	11 (2.9%)
rs12214123	GG	283 (74.9%)	332 (78.1%)	62 (69.7%)	66 (66.7%)	261 (70.2%)
	AG	86 (22.8%)	79 (18.6%)	27 (30.3%)	29 (29.3%)	101 (27.2%)
	AA	9 (2.4%)	14 (3.3%)	0 (0.0%)	4 (4.0%)	10 (2.7%)
rs12526196	TT	305 (80.3%)	321 (75.5%)	71 (78.9%)	73 (73.7%)	302 (81.2%)
	TC	73 (19.2%)	102 (24.0%)	17 (18.9%)	25 (25.3%)	69 (18.5%)
	CC	2 (0.5%)	2 (0.5%)	2 (2.2%)	1 (1.0%)	1 (0.3%)
rs12663962	GG	242 (63.9%)	261 (61.3%)	53 (58.9%)	63 (63.6%)	210 (56.0%)
	TG	119 (31.4%)	145 (34.0%)	34 (37.8%)	34 (34.3%)	143 (38.1%)
	TT	18 (4.7%)	20 (4.7%)	3 (3.3%)	2 (2.0%)	22 (5.9%)
rs13211178	GG	284 (74.7%)	331 (78.3%)	63 (70.0%)	66 (66.7%)	262 (70.4%)
	AG	88 (23.2%)	78 (18.4%)	27 (30.0%)	29 (29.3%)	101 (27.2%)
	AA	8 (2.1%)	14 (3.3%)	0 (0.0%)	4 (4.0%)	9 (2.4%)
rs1930994	AA	237 (62.4%)	256 (60.1%)	52 (57.8%)	63 (63.6%)	205 (55.3%)
	AT	123 (32.4%)	148 (34.7%)	35 (38.9%)	33 (33.3%)	145 (39.1%)
	TT	20 (5.3%)	22 (5.2%)	3 (3.3%)	3 (3.0%)	21 (5.7%)
rs1931000	GG	99 (26.1%)	133 (31.2%)	30 (33.3%)	28 (28.3%)	148 (39.6%)
	AG	198 (52.1%)	207 (48.6%)	41 (45.6%)	47 (47.5%)	161 (43.0%)
	AA	83 (21.8%)	86 (20.2%)	19 (21.1%)	24 (24.2%)	65 (17.4%)

rs1931004	CC	249 (68.2%)	290 (69.5%)	60 (69.8%)	62 (64.6%)	228 (65.3%)
	TC	106 (29.0%)	117 (28.1%)	23 (26.7%)	34 (35.4%)	107 (30.7%)
	TT	10 (2.7%)	10 (2.4%)	3 (3.5%)	0 (0.0%)	14 (4.0%)
rs2095252	GG	102 (26.8%)	137 (32.2%)	32 (36.0%)	30 (30.3%)	149 (39.8%)
	AG	198 (52.1%)	205 (48.2%)	39 (43.8%)	47 (47.5%)	163 (43.6%)
	AA	80 (21.1%)	83 (19.5%)	18 (20.2%)	22 (22.2%)	62 (16.6%)
rs2151532	TT	310 (81.6%)	351 (82.8%)	78 (87.6%)	79 (79.8%)	301 (81.4%)
	TC	67 (17.6%)	69 (16.3%)	11 (12.4%)	20 (20.2%)	67 (18.1%)
	CC	3 (0.8%)	4 (0.9%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
rs6917644	AA	291 (77.2%)	325 (76.3%)	66 (74.2%)	69 (69.7%)	287 (78.0%)
	AG	77 (20.4%)	97 (22.8%)	22 (24.7%)	27 (27.3%)	74 (20.1%)
	GG	9 (2.4%)	4 (0.9%)	1 (1.1%)	3 (3.0%)	7 (1.9%)
rs7747551	AA	235 (61.8%)	250 (59.0%)	52 (57.8%)	60 (60.6%)	202 (54.4%)
	TA	124 (32.6%)	150 (35.4%)	32 (35.6%)	36 (36.4%)	145 (39.1%)
	TT	21 (5.5%)	24 (5.7%)	6 (6.7%)	3 (3.0%)	24 (6.5%)
rs7748518	GG	249 (65.5%)	288 (67.6%)	59 (65.6%)	66 (66.7%)	233 (62.6%)
	AG	120 (31.6%)	126 (29.6%)	31 (34.4%)	33 (33.3%)	122 (32.8%)
	AA	11 (2.9%)	12 (2.8%)	0 (0.0%)	0 (0.0%)	17 (4.6%)
rs7768619	TT	245 (65.3%)	284 (68.9%)	59 (65.6%)	64 (65.3%)	236 (64.1%)
	TC	123 (32.8%)	128 (31.1%)	31 (34.4%)	34 (34.7%)	123 (33.4%)
	CC	7 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (2.4%)
rs928501	CC	218 (57.5%)	220 (51.8%)	39 (43.3%)	51 (52.0%)	199 (53.8%)
	AC	137 (36.1%)	176 (41.4%)	41 (45.6%)	37 (37.8%)	133 (35.9%)
	AA	24 (6.3%)	29 (6.8%)	10 (11.1%)	10	38 (10.3%)

					(10.2%)	
rs9388949	TT	117 (30.9%)	124 (29.3%)	19 (21.1%)	28 (28.6%)	101 (27.0%)
	TC	189 (49.9%)	210 (49.6%)	53 (58.9%)	46 (46.9%)	173 (46.3%)
	CC	73 (19.3%)	89 (21.0%)	18 (20.0%)	24 (24.5%)	100 (26.7%)
rs9402376	TT	235 (62.3%)	252 (59.7%)	53 (58.9%)	61 (61.6%)	208 (55.5%)
	TC	122 (32.4%)	147 (34.8%)	32 (35.6%)	35 (35.4%)	144 (38.4%)
	CC	20 (5.3%)	23 (5.5%)	5 (5.6%)	3 (3.0%)	23 (6.1%)
rs9493157	CC	232 (61.1%)	247 (58.0%)	52 (57.8%)	60 (60.6%)	215 (57.2%)
	TC	131 (34.5%)	149 (35.0%)	32 (35.6%)	33 (33.3%)	122 (32.4%)
	TT	17 (4.5%)	30 (7.0%)	6 (6.7%)	6 (6.1%)	34 (9.0%)

In AD patients, 239 (63.1%) carry the rs12192108T/T genotype, whereas into the controls group 208 (55.8%) carry this genotype. This difference is significant ($p=0.042$; OR=1.164; 95% CI: 1.006-1.347).

- 5 In AD patients, 242 (63.9%) carry the rs12663962G/G genotype, whereas into the controls group 210 (56.0%) carry this genotype. This difference is significant ($p=0.028$; OR=1.178; 95% CI: 1.018-1.364).

In AD patients, 99 (26.1%) carry the rs1931000G/G genotype, whereas into the controls group 148 (39.6%) carry this genotype. This difference is significant ($p=8.3 \cdot 10^{-5}$; OR=0.733; 95% CI: 0.629-0.856).

In AD patients, 102 (26.8%) carry the rs2095252G/G genotype, whereas into the controls group 149 (39.8%) carry this genotype. This difference is significant ($p=1.6 \cdot 10^{-4}$; OR=0.744; 95% CI: 0.638 - 0.868).

- 15 In AD patients, 235 (61.8%) carry the rs7747551A/A genotype, whereas into the controls group 202 (54.4%) carry this genotype. This difference is significant ($p=0.040$; OR=1.164; 95% CI: 1.007 - 1.347).

In AD patients, 73 (19.3%) carry the rs9388949C/C genotype, whereas into the controls group 100 (26.7%) carry this genotype. This difference is significant ($p=0.015$; OR=0.808; 95% CI: 0.681 - 0.960).

In AD patients, 17 (4.5%) carry the rs9493157T/T genotype, whereas into the controls group 34 (9.0%) carry this genotype. This difference is significant ($p=0.012$; OR=0.681; 95% CI: 0.505 - 0.920). All the statistical analyses are described into Table 9.

5 **Table 9.** Association between markers, in LD with rs4897554 and rs9399005, in the CTGF locus with AD disease in univariate analysis.

Univariate Analysis : Alzheimer vs Control		
rs11154654 ¹	TT vs TC vs CC	$p=0.103$; OR=1.221; 95% CI: 0.960-1.551 (NS)
	TT vs TC + CC	$p=0.060$; OR=1.150; 95% CI: 0.994-1.330 (NS)
	TT + CC vs TC	$p=0.067$; OR=0.869; 95% CI: 0.749-1.010 (NS)
	TT + TC vs CC	$p=0.831$; OR=0.966; 95% CI: 0.705-1.324 (NS)
rs12192108 ¹	TT vs TC vs CC	$p=0.071$; OR=1.247; 95% CI: 0.981-1.584 (NS)
	TT vs TC + CC	$p=0.042$; OR=1.164; 95% CI: 1.006-1.347 (S)
	TT + CC vs TC	$p=0.055$; OR=0.863; 95% CI: 0.743-1.003 (NS)
	TT + TC vs CC	$p=0.711$; OR=0.943; 95% CI: 0.690-1.287 (NS)
rs12192391 ^{1,2}	AA vs AG vs GG	$p=0.205$; OR=1.203; 95% CI: 0.904-1.601 (NS)
	AA vs AG + GG	$p=0.179$; OR=1.117; 95% CI: 0.950-1.312 (NS)
	AA + GG vs AG	$p=0.198$; OR=0.897; 95% CI: 0.759-1.059 (NS)
	AA + AG vs GG	$p=0.785$; OR=0.935; 95% CI: 0.578-1.514 (NS)
rs12194675 ^{1,2}	AA vs AG vs GG	$p=0.155$; OR=1.231; 95% CI: 0.924-1.640 (NS)
	AA vs AG + GG	$p=0.108$; OR=1.144; 95% CI: 0.971-1.347 (NS)
	AA + GG vs AG	$p=0.101$; OR=0.868; 95% CI: 0.733-1.028 (NS)
	AA + AG vs GG	$p=0.959$; OR=0.988; 95% CI: 0.619-1.577 (NS)
rs12200211 ^{1,2}	AA vs AG vs GG	$p=0.140$; OR=1.234; 95% CI: 0.933-1.633 (NS)
	AA vs AG + GG	$p=0.128$; OR=1.133; 95% CI: 0.965-1.330 (NS)
	AA + GG vs AG	$p=0.165$; OR=0.889; 95% CI: 0.753-1.049 (NS)
	AA + AG vs GG	$p=0.625$; OR=0.895; 95% CI: 0.573-1.398 (NS)
rs12214123 ^{1,2}	AA vs AG vs GG	$p=0.179$; OR=0.825; 95% CI: 0.622-1.093 (NS)
	AA vs AG + GG	$p=0.789$; OR=0.940; 95% CI: 0.596-1.483 (NS)
	AA + GG vs AG	$p=0.164$; OR=0.889; 95% CI: 0.753-1.049 (NS)
	AA + AG vs GG	$p=0.149$; OR=1.126; 95% CI: 0.958-1.322 (NS)
rs12526196 ^{1,2}	TT vs TC vs CC	$p=0.692$; OR=0.932; 95% CI: 0.656-1.323 (NS)
	TT vs TC + CC	$p=0.749$; OR=0.971; 95% CI: 0.810-1.164 (NS)
	TT + CC vs TC	$p=0.817$; OR=1.022; 95% CI: 0.851-1.227 (NS)
	TT + TC vs CC	$p=0.583$; OR=1.401; 95% CI: 0.421-4.663 (NS)
rs12663962 ¹	TT vs TG vs GG	$p=0.039$; OR=0.775; 95% CI: 0.609-0.987 (S)
	TT vs TG + GG	$p=0.494$; OR=0.894; 95% CI: 0.650-1.232 (NS)
	TT + GG vs TG	$p=0.052$; OR=0.862; 95% CI: 0.741-1.002 (NS)
	TT + TG vs GG	$p=0.028$; OR=1.178; 95% CI: 1.018-1.364 (S)
rs13211178 ^{1,2}	AA vs AG vs GG	$p=0.209$; OR=0.833; 95% CI: 0.627-1.108 (NS)
	AA vs AG + GG	$p=0.772$; OR=0.931; 95% CI: 0.575-1.508 (NS)
	AA + GG vs AG	$p=0.207$; OR=0.899; 95% CI: 0.762-1.061 (NS)
	AA + AG vs GG	$p=0.186$; OR=1.114; 95% CI: 0.949-1.309 (NS)

rs1930994 ¹	TT vs TA vs AA	p=0.086; OR=0.810; 95% CI: 0.637-1.030 (NS)
	TT vs TA + AA	p=0.811; OR=0.962; 95% CI: 0.702-1.318 (NS)
	TT + AA vs TA	p=0.055; OR=0.864; 95% CI: 0.744-1.003 (NS)
	TT + TA vs AA	p=0.048; OR=1.158; 95% CI: 1.001-1.340(NS)
rs1931000 ²	AA vs AG vs GG	p=0.001; OR=1.432; 95% CI: 1.168-1.755 (NS)
	AA vs AG + GG	p=0.124; OR=1.153; 95% CI: 0.962-1.381 (NS)
	AA + GG vs AG	p=0.013; OR=1.200; 95% CI: 1.039-1.385 (NS)
	AA + AG vs GG	p=8.3 10 ⁻⁵ ; OR=0.733; 95% CI: 0.629-0.856 (NS)
rs1931004 ^{1,2}	TT vs TC vs CC	p=0.310; OR=0.870; 95% CI: 0.665 - 1.138 (NS)
	TT vs TC + CC	p=0.349; OR=0.821; 95% CI: 0.543 - 1.240 (NS)
	TT + CC vs TC	p=0.637; OR=0.962; 95% CI: 0.820 - 1.129 (NS)
	TT + TC vs CC	p=0.413; OR=1.067; 95% CI: 0.913 - 1.247 (NS)
rs2095252 ²	AA vs AG vs GG	p=0.001; OR=1.423; 95% CI: 1.159 - 1.747 (S)
	AA vs AG + GG	p=0.117; OR=1.158; 95% CI: 0.964 - 1.392 (NS)
	AA + GG vs AG	p=0.019; OR=1.187; 95% CI: 1.028 - 1.370 (S)
	AA + AG vs GG	p=1.6 10 ⁻⁴ ; OR=0.744; 95% CI: 0.638 - 0.868 (S)
rs2151532 ²	TT vs TC vs CC	p=0.994; OR=0.999; 95% CI: 0.705 - 1.416 (NS)
	TT vs TC + CC	p=0.936; OR=1.008; 95% CI: 0.838 - 1.211 (NS)
	TT + CC vs TC	p=0.865; OR=0.984; 95% CI: 0.816 - 1.186 (NS)
	TT + TC vs CC	p=0.677; OR=1.210; 95% CI: 0.493 - 2.969 (NS)
rs6917644 ^{1,2}	AA vs AG vs GG	p=0.713; OR=0.945; 95% CI: 0.700 - 1.277 (NS)
	AA vs AG + GG	p=0.793; OR=0.977; 95% CI: 0.823 - 1.161 (NS)
	AA + GG vs AG	p=0.915; OR=1.010; 95% CI: 0.845 - 1.207 (NS)
	AA + AG vs GG	p=0.649; OR=1.123; 95% CI: 0.682 - 1.850 (NS)
rs7747551 ¹	TT vs TA vs AA	p=0.061; OR=0.797; 95% CI: 0.629 - 1.010 (NS)
	TT vs TA + AA	p=0.587; OR=0.920; 95% CI: 0.680 - 1.244 (NS)
	TT + AA vs TA	p=0.066; OR=0.869; 95% CI: 0.748 - 1.009 (NS)
	TT + TA vs AA	p=0.040; OR=1.164; 95% CI: 1.007 - 1.347 (S)
rs7748518 ¹	AA vs AG vs GG	p=0.264; OR=0.864; 95% CI: 0.669 - 1.116 (NS)
	AA vs AG + GG	p=0.229; OR=0.789; 95% CI: 0.536 - 1.161 (NS)
	AA + GG vs AG	p=0.721; OR=0.973; 95% CI: 0.835 - 1.133 (NS)
	AA + AG vs GG	p=0.409; OR=1.065; 95% CI: 0.917 - 1.236 (NS)
rs7768619 ²	TT vs TC vs CC	p=0.645; OR=1.066; 95% CI: 0.811 - 1.401 (NS)
	TT vs TC + CC	p=0.732; OR=1.027; 95% CI: 0.883 - 1.193 (NS)
	TT + CC vs TC	p=0.857; OR=0.986; 95% CI: 0.846 - 1.149 (NS)
	TT + TC vs CC	p=0.588; OR=0.871; 95% CI: 0.529 - 1.435 (NS)
rs928501 ¹	AA vs AC vs CC	p=0.104; OR=0.831; 95% CI: 0.664 - 1.039 (NS)
	AA vs AC + CC	p=0.053; OR=0.769; 95% CI: 0.589 - 1.003 (NS)
	AA + CC vs AC	p=0.954; OR=1.004; 95% CI: 0.865 - 1.166 (NS)
	AA + AC vs CC	p=0.304; OR=1.079; 95% CI: 0.934 - 1.246 (NS)
rs9388949 ^{1,2}	TT vs TC vs CC	p=0.031; OR=1.247; 95% CI: 1.021 - 1.523 (NS)
	TT vs TC + CC	p=0.243; OR=1.099; 95% CI: 0.938 - 1.286 (NS)
	TT + CC vs TC	p=0.321; OR=1.075; 95% CI: 0.932 - 1.240 (NS)
	TT + TC vs CC	p=0.015; OR=0.808; 95% CI: 0.681 - 0.960 (S)
rs9402376 ¹	TT vs TC vs CC	p=0.081; OR=1.237; 95% CI: 0.974 - 1.570 (NS)
	TT vs TC + CC	p=0.056; OR=1.153; 95% CI: 0.996 - 1.333 (NS)

	TT + CC vs TC	p=0.084; OR=0.876; 95% CI: 0.754 - 1.018 (NS)
	TT + TC vs CC	p=0.625; OR=0.926; 95% CI: 0.680 - 1.261 (NS)
rs9493157 ¹	TT vs TC vs CC	p=0.086; OR=0.816; 95% CI: 0.648 - 1.029 (NS)
	TT vs TC + CC	p=0.012; OR=0.681; 95% CI: 0.505 - 0.920 (S)
	TT + CC vs TC	p=0.645; OR=1.036; 95% CI: 0.891 - 1.206 (NS)
	TT + TC vs CC	p=0.387; OR=1.066; 95% CI: 0.922 - 1.234 (NS)

(S) significant ; (NS) non significant

¹Markers in LD with rs4897554

²Markers in LD with rs9399005

5 EXAMPLE 5

A multivariate analysis, performed on all the markers associated in univariate analysis, reveals that three main SNPs are associated with an increased risk of developing Alzheimer disease.

The inventors have performed a multivariate analysis (linear regression, stepwise procedure) to confirm the associations found previously in univariate analysis (polymorphism were

10 analyzed one by one). Similarly to the univariate analysis, the genotypes were considered as binary variables. In this analysis, we included 10 polymorphisms: rs9399005, rs4897554, rs1931001, rs12192108, rs12663962, rs1931000, rs2095252, rs7747551, rs9388949 and rs9493157. In this analysis, five polymorphisms were still significantly associated to AD (rs4897554 ($p=2.4 \cdot 10^{-4}$; OR=1.811; 95% CI: 1.319-2.485), rs9399005 ($p=0.033$; OR=0.694; 15 95% CI: 0.496-0.971), rs1931001 ($p=0.006$; OR=0.791; 95% CI: 0.670-0.934), rs1931000 ($p=0.005$; OR=0.732; 95% CI: 0.590-0.908), rs9388949 ($p=0.047$; OR=1.315; 95% CI: 1.004-1.724)) whereas the other covariates were excluded from the analysis. See Table 10.

Table 10. Multivariate analysis between SNPs in the CTGF locus with Alzheimer disease.

20 Multivariate Analysis : Alzheimer vs Control

rs4897554	AA + AG vs GG	$p=2.4 \cdot 10^{-4}$; OR=1.811; 95% CI: 1.319-2.485
rs9399005	TT vs TC + CC	$p=0.033$; OR=0.694; 95% CI: 0.496-0.971
rs1931001	AA+ CC vs AC	$p=0.006$; OR=0.791; 95% CI: 0.670-0.934
rs1931000	AA +AG vs GG	$p=0.005$; OR=0.732; 95% CI: 0.590-0.908
rs9388949	TT + TC vs CC	$p=0.047$; OR=1.315; 95% CI: 1.004-1.724
rs12192108	TT vs TC + CC	excluded
rs12663962	TT + TG vs GG	excluded
rs2095252	AA + AG vs GG	excluded

rs7747551	TT + TA vs AA	excluded
rs9493157	TT vs TC + CC	excluded

EXAMPLE 6

Association between SNPs rs9399005, rs4897554, rs9493150, 12527379 and rs6918698 in the CTGF locus with MCI disease in univariate analysis.

The inventors have investigated whether patients with MCI are also affected by CTGF allelic variants. The TAG polymorphisms were also genotyped on 426 subjects with Mild cognitive impairment disease. The genotype distribution is indicated in Table 3.

In the MCI subjects group, 406 (96.0%) subjects carry either the rs9399005 C/C or rs9399005C/T genotypes whereas 327 (88.4%) of the controls carry the same genotypes. This difference is significant ($p=1.1 \cdot 10^{-4}$; OR=0.564; 95% CI: 0.422-0.754).

In the MCI subjects group, 346 (81.4%) carry the genotypes rs4897554A/A or rs4897554A/G versus 248 (95%) for the control. This difference is significant ($p=2.2 \cdot 10^{-6}$; OR=2.087; 95% CI: 1.539-2.830)

Similarly, 36 (8.6%) MCI patients carry the rs9493150C/C genotype whereas up to 50 (13.5%) of the controls carry this genotype. This difference is significant ($p=0.030$; OR=0.778; 95% CI: 0.620-0.976).

Similarly, in MCI patients, 141 (33.1%) carry the rs12527379G/G genotype, 204 (47.9%) carry the rs12527379A/G genotype and 81 (19.0%) carry the rs12527379A/A genotype whereas into the controls group 151 (40.5%) carry the rs12527379G/G genotype, 162 (43.4%) carry the rs12527379A/G genotype and 60 (16.1%) carry the rs12527379A/A genotype. This difference is significant ($p=0.041$; OR=1.227; 95% CI: 1.008-1.494).

Similarly, 328 (79.4%) MCI patients carry the rs6918698G/G or rs6918698G/C genotypes whereas up to 265 (71.5%) of the controls carry these two genotypes. This difference is significant ($p=0.010$; OR=0.805; 95% CI: 0.683 – 0.948). See Table 11.

Table 11. Association between TAG SNPs in the CTGF locus with MCI disease in univariate analysis.

Univariate Analysis : MCI vs Control		
rs10872387	AA vs AC vs CC	$p=0.162$; OR=1.180; 95% CI: 0.936-1.489 (NS)
	AA vs AC + CC	$p=0.137$; OR=1.113; 95% CI: 0.966-1.282 (NS)

	AA + CC vs AC	p=0.192; OR=0.908; 95% CI: 0.786-1.050 (NS)
	AA + AC vs CC	p=0.643; OR=0.931; 95% CI: 0.687-1.261 (NS)
rs9483364	AA vs AG vs GG	p=0.462; OR=0.924; 95% CI: 0.750-1.140 (NS)
	AA vs AG + GG	p=0.247; OR=0.873; 95% CI: 0.695-1.098 (NS)
	AA + GG vs AG	p=0.657; OR=1.033; 95% CI: 0.895-1.191 (NS)
	AA + AG vs GG	p=0.785; OR=1.020; 95% CI: 0.887-1.173 (NS)
rs12527379	AA vs AG vs GG	p=0.041; OR=1.227; 95% CI: 1.008-1.494 (S)
	AA vs AG + GG	p=0.279; OR=1.107; 95% CI: 0.921-1.330 (NS)
	AA + GG vs AG	p=0.207; OR=1.094; 95% CI: 0.951-1.258 (NS)
	AA + AG vs GG	p=0.031; OR=0.853; 95% CI: 0.738-0.985 (NS)
rs1931002	AA vs AG vs GG	p=0.625; OR=0.917; 95% CI: 0.648-1.298 (NS)
	AA vs AG + GG	p=0.518; OR=1.324; 95% CI: 0.565-3.103 (NS)
	AA + GG vs AG	p=0.401; OR=0.922; 95% CI: 0.763-1.114 (NS)
	AA + AG vs GG	p=0.501; OR=1.066; 95% CI: 0.885-1.283 (NS)
rs4897554	AA vs AG vs GG	p=0.987; OR=1.002; 95% CI: 0.787-1.275 (NS)
	AA vs AG + GG	p=1.7 10 ⁻⁴ ; OR=1.404; 95% CI: 1.176-1.677 (S)
	AA + GG vs AG	p=6.7 10 ⁻¹² ; OR=0.557; 95% CI: 0.472-0.659 (S)
	AA + AG vs GG	p=2.2 10 ⁻⁶ ; OR=2.087; 95% CI: 1.539-2.830 (S)
rs6918698	CC vs CG vs GG	p=0.071; OR=0.834; 95% CI: 0.684 – 1.015 (NS)
	CC vs CG + GG	p=0.010; OR=0.805; 95% CI: 0.683 – 0.948 (S)
	CC + GG vs CG	p=0.059; OR=1.145; 95% CI: 0.995 – 1.318 (NS)
	CC + CG vs GG	p=0.694; OR=1.032; 95% CI: 0.881 – 1.210 (NS)
rs9399005	TT vs TC vs CC	p=0.021; OR=0.769; 95% CI: 0.616-0.961 (NS)
	TT vs TC + CC	p=1.1 10 ⁻⁴ ; OR=0.564; 95% CI: 0.422-0.754 (S)
	TT + CC vs TC	p=0.170; OR=1.105; 95% CI: 0.958-1.263 (NS)
	TT + TC vs CC	p=0.434; OR=1.057; 95% CI: 0.920-1.216 (NS)
rs9493150	CC vs CG vs GG	p=0.277; OR=0.891; 95% CI: 0.724-1.097 (NS)
	CC vs CG + GG	p=0.030; OR=0.778; 95% CI: 0.620-0.976 (S)
	CC + GG vs CG	p=0.198; OR=1.098; 95% CI: 0.952-1.266 (NS)
	CC + CG vs GG	p=0.922; OR=1.007; 95% CI: 0.876-1.158 (NS)

(S) significant ; (NS) non significant

EXAMPLE 7

Association between SNPs rs9399005 and rs4897554 in the CTGF locus with MCI disease in
5 multivariate analysis.

The inventors have performed a multivariate analysis (linear regression, stepwise procedure) to confirm the associations found previously in univariate analysis. In this analysis, the inventors have included the rs9399005, rs4897554, rs9493150, 12527379 and rs6918698 polymorphisms as covariates. In this analysis rs9399005 and rs4897554 are still significantly
10 associated to MCI disease whereas the other polymorphisms were excluded by the software (for rs9399005 polymorphism: p=0.046; OR=0.741; 95% CI: 0.552-0.995 and for rs4897554 polymorphism: p=5.4 10⁻⁵; OR=1.901; 95% CI: 1.392-2.597). See Table 12.

Table 12. Association between TAG SNPs in the CTGF locus with MCI disease in multivariate analysis.

Multivariate Analysis : MCI vs Control		
rs4897554	AA + AG vs GG	p=5.4 10 ⁻⁵ ; OR=1.901; 95% CI: 1.392-2.597
rs9399005	TT vs TC + CC	p=0.046; OR=0.741; 95% CI: 0.552-0.995
rs9493150	CC vs CG + GG	excluded
rs12527379	AA vs AG vs GG	excluded
rs6918698	CC vs CG + GG	excluded

5 EXAMPLE 8

Among the additional markers in the CTGF locus, rs1931001 is associated with MCI disease in a univariate analysis.

The inventors have genotyped additional SNPs by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the MCI group and on the control subjects are described in Table 6. Among these SNPs, only one marker detects significant difference between cases and controls.

In MCI patients, 195 (45.9%) carry the rs1931001C/C genotype, whereas into the controls group 144 (38.7%) carry this genotype. This difference is significant (p=0.041; OR=1.159; 95% CI: 1.006-1.335). See Table 13.

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Table 13. Association between additional markers in the CTGF locus with MCI disease in univariate analysis.

Univariate Analysis : MCI vs Control		
rs1029122	TT vs TC vs CC	p=0.932; OR=0.992; 95% CI: 0.817-1.203 (NS)
	TT vs TC + CC	p=0.899; OR=1.010; 95% CI: 0.871-1.170 (NS)
	TT + CC vs TC	p=0.716; OR=0.974; 95% CI: 0.847-1.120 (NS)
	TT + TC vs CC	p=0.763; OR=1.027; 95% CI: 0.864-1.221(NS)
rs11154653	TT vs TG vs GG	p=0.428; OR=1.199; 95% CI: 0.766-1.876(NS)
	TT vs TG + GG	p=0.763; OR=1.148; 95% CI: 0.468-2.816 (NS)
	TT + GG vs TG	p=0.464; OR=1.100; 95% CI: 0.853-1.419 (NS)
	TT + TG vs GG	p=0.428; OR=0.905; 95% CI: 0.707-1.158(NS)
rs10293697	TT vs TC vs CC	p=0.067; OR=0.803; 95% CI: 0.636-1.015 (NS)
	TT vs TC + CC	p=0.250; OR=0.921; 95% CI: 0.799-1.060(NS)
	TT + CC vs TC	p=0.942; OR=1.005; 95% CI: 0.870-1.161 (NS)
	TT + TC vs CC	p=0.022; OR=1.472; 95% CI: 1.057-2.051 (NS)

rs1931001	AA vs AC vs CC	p=0.050; OR=0.804; 95% CI: 0.647-1.000 (NS)
	AA vs AC + CC	p=0.394; OR=0.902; 95% CI: 0.712-1.143 (NS)
	AA + CC vs AC	p=0.128; OR=0.897; 95% CI: 0.781-1.032 (NS)
	AA + AC vs CC	p=0.041; OR=1.159; 95% CI: 1.006-1.335 (S)
rs9321315	TT vs TA vs AA	p=0.459; OR=0.894; 95% CI: 0.666 - 1.202 (NS)
	TT vs TA + AA	p=0.962; OR=1.013; 95% CI: 0.585 - 1.756 (NS)
	TT + AA vs TA	p=0.384; OR=0.928; 95% CI: 0.785 - 1.098 (NS)
	TT + TA vs AA	p=0.403; OR=1.072; 95% CI: 0.910 - 1.263 (NS)

(S) significant ; (NS) non significant

EXAMPLE 9

Among the markers in LD with rs4897554 or rs9399005, the polymorphisms rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, rs1931000, rs2095252 and rs7768619 are associated with MCI disease in a univariate analysis.

The inventors have genotyped SNPs in LD with rs4897554 or rs9399005 by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the **MCI** group and on the control subjects are described in Table 8.

In MCI patients, 321 (78.5%) carry the rs12192391A/A genotype, whereas 264 (70.8%) within the control group carry this genotype. This difference is significant (p=0.013; OR=1.227; 95% CI: 1.043-1.444).

In MCI patients, 291 (76.6%) carry the rs12194675A/A genotype, whereas into the controls group 265 (71.4%) carry this genotype. This difference is significant (p=0.012; OR=1.231; 95% CI: 1.046-1.447).

In MCI patients, 331 (77.9%) carry the rs12200211A/A genotype, whereas into the controls group 261 (70.2%) carry this genotype. This difference is significant (p=0.011; OR=1.229; 95% CI: 1.048-1.442).

In MCI patients, 332 (78.1%) carry the rs12214123G/G genotype, whereas into the controls group 261 (70.0%) carry this genotype. This difference is significant (p=0.010; OR=1.232; 95% CI: 1.050-1.446).

In MCI patients, 331 (78.3%) carry the rs13211178G/G genotype, whereas into the controls group 262 (70.4%) carry this genotype. This difference is significant (p=0.012; OR=1.229; 95% CI: 1.047-1.443).

In MCI patients, 133 (31.2%) carry the rs1931000G/G genotype, whereas into the controls group 148 (39.6%) carry this genotype. This difference is significant (p=0.014; OR=0.833; 95% CI: 0.720-0.963).

In MCI patients, 137 (32.2%) carry the rs2095252G/G genotype, whereas into the controls group 149 (39.8%) carry this genotype. This difference is significant ($p=0.025$; OR=0.848; 95% CI: 0.733 - 0.980).

In MCI patients, 284 (68.9%) carry the rs7768619T/T genotype, 128 (31.1%) carry the rs7768619T/C genotype, none carries the rs7768619C/C genotype whereas into the controls group 236 (64.1%) carry the rs7768619T/T genotype, 123 (33.4%) carry the rs7768619T/C genotype and 9 (2.4%) carry the rs7768619C/C genotype. This difference is significant ($p=0.043$; OR=1.338; 95% CI: 1.009 - 1.775). All the statistical analyses are described into Table 14.

10

Table 14. Association between markers, in LD with rs4897554 and rs9399005, in the CTGF locus with MCI disease in univariate analysis.

Univariate Analysis : MCI vs Control

rs11154654 ¹	TT vs TC vs CC	$p=0.245$; OR=1.148; 95% CI: 0.910-1.449 (NS)
	TT vs TC + CC	$p=0.200$; OR=1.096; 95% CI: 0.952-1.262 (NS)
	TT + CC vs TC	$p=0.238$; OR=0.917; 95% CI: 0.794-1.059 (NS)
	TT + TC vs CC	$p=0.778$; OR=0.957; 95% CI: 0.704-1.301 (NS)
rs12192108 ¹	TT vs TC vs CC	$p=0.230$; OR=1.153; 95% CI: 0.914-1.455 (NS)
	TT vs TC + CC	$p=0.203$; OR=1.096; 95% CI: 0.952-1.263 (NS)
	TT + CC vs TC	$p=0.265$; OR=0.921; 95% CI: 0.797-1.065 (NS)
	TT + TC vs CC	$p=0.685$; OR=0.939; 95% CI: 0.693-1.273 (NS)
rs12192391 ^{1,2}	AA vs AG vs GG	$p=0.068$; OR=1.293; 95% CI: 0.981-1.704 (NS)
	AA vs AG + GG	$p=0.013$; OR=1.227; 95% CI: 1.043-1.444 (S)
	AA + GG vs AG	$p=0.004$; OR=0.777; 95% CI: 0.655-0.921 (S)
	AA + AG vs GG	$p=0.406$; OR=1.197; 95% CI: 0.783-1.831 (NS)
rs12194675 ^{1,2}	AA vs AG vs GG	$p=0.059$; OR=1.305; 95% CI: 0.990-1.719 (NS)
	AA vs AG + GG	$p=0.012$; OR=1.231; 95% CI: 1.046-1.447 (S)
	AA + GG vs AG	$p=0.004$; OR=0.777; 95% CI: 0.655-0.921 (S)
	AA + AG vs GG	$p=0.471$; OR=1.169; 95% CI: 0.765-1.788 (NS)
rs12200211 ^{1,2}	AA vs AG vs GG	$p=0.040$; OR=1.326; 95% CI: 1.012-1.736 (S)
	AA vs AG + GG	$p=0.011$; OR=1.229; 95% CI: 1.048-1.442 (S)
	AA + GG vs AG	$p=0.006$; OR=0.790; 95% CI: 0.669-0.934 (S)
	AA + AG vs GG	$p=0.780$; OR=1.059; 95% CI: 0.709-1.581 (NS)
rs12214123 ^{1,2}	AA vs AG vs GG	$p=0.045$; OR=0.757; 95% CI: 0.577-0.994 (S)
	AA vs AG + GG	$p=0.618$; OR=1.110; 95% CI: 0.736-1.676 (NS)
	AA + GG vs AG	$p=0.004$; OR=0.783; 95% CI: 0.662-0.925 (S)
	AA + AG vs GG	$p=0.010$; OR=1.232; 95% CI: 1.050-1.446 (S)
rs12526196 ^{1,2}	TT vs TC vs CC	$p=0.053$; OR=0.720; 95% CI: 0.516-1.004 (NS)
	TT vs TC + CC	$p=0.054$; OR=0.846; 95% CI: 0.713-1.003 (NS)
	TT + CC vs TC	$p=0.062$; OR=1.178; 95% CI: 0.992-1.398 (NS)
	TT + TC vs CC	$p=0.647$; OR=1.324; 95% CI: 0.398-4.407 (NS)

rs12663962 ¹	TT vs TG vs GG	p=0.127; OR=0.834; 95% CI: 0.660-1.053 (NS)
	TT vs TG + GG	p=0.459; OR=0.889; 95% CI: 0.651-1.213 (NS)
	TT + GG vs TG	p=0.228; OR=0.915; 95% CI: 0.792-1.057 (NS)
	TT + TG vs GG	p=0.131; OR=1.115; 95% CI: 0.968-1.284 (NS)
rs13211178 ^{1,2}	AA vs AG vs GG	p=0.057; OR=0.767; 95% CI: 0.583-1.008 (NS)
	AA vs AG + GG	p=0.457; OR=1.175; 95% CI: 0.768-1.797 (NS)
	AA + GG vs AG	p=0.004; OR=0.779; 95% CI: 0.659-0.921 (S)
	AA + AG vs GG	p=0.012; OR=1.229; 95% CI: 1.047-1.443 (S)
rs1930994 ¹	TT vs TA vs AA	p=0.209; OR=0.861; 95% CI: 0.682-1.087 (NS)
	TT vs TA + AA	p=0.757; OR=0.953; 95% CI: 0.701-1.296 (NS)
	TT + AA vs TA	p=0.205; OR=0.911; 95% CI: 0.789-1.052 (NS)
	TT + TA vs AA	p=0.168; OR=1.104; 95% CI: 0.959-1.271 (NS)
rs1931000 ²	AA vs AG vs GG	p=0.028; OR=1.244; 95% CI: 1.023-1.512 (S)
	AA vs AG + GG	p=0.312; OR=1.097; 95% CI: 0.917-1.311 (NS)
	AA + GG vs AG	p=0.117; OR=1.118; 95% CI: 0.973-1.286 (NS)
	AA + AG vs GG	p=0.014; OR=0.833; 95% CI: 0.720-0.963 (S)
rs1931004 ^{1,2}	TT vs TC vs CC	p=0.138; OR=0.819; 95% CI: 0.630 - 1.066 (NS)
	TT vs TC + CC	p=0.207; OR=0.767; 95% CI: 0.508 - 1.158 (NS)
	TT + CC vs TC	p=0.431; OR=0.939; 95% CI: 0.803 - 1.098 (NS)
	TT + TC vs CC	p=0.215; OR=1.101; 95% CI: 0.946 - 1.281 (NS)
rs2095252 ²	AA vs AG vs GG	p=0.037; OR=1.232; 95% CI: 1.013 - 1.499 (S)
	AA vs AG + GG	p=0.280; OR=1.105; 95% CI: 0.922 - 1.325 (NS)
	AA + GG vs AG	p=0.188; OR=1.098; 95% CI: 0.955 - 1.263 (NS)
	AA + AG vs GG	p=0.025; OR=0.848; 95% CI: 0.733 - 0.980 (S)
rs2151532 ²	TT vs TC vs CC	p=0.723; OR=1.064; 95% CI: 0.756 - 1.496 (NS)
	TT vs TC + CC	p=0.600; OR=1.050; 95% CI: 0.875 - 1.259 (NS)
	TT + CC vs TC	p=0.494; OR=0.938; 95% CI: 0.779 - 1.128 (NS)
	TT + TC vs CC	p=0.519; OR=1.324; 95% CI: 0.565 - 3.102 (NS)
rs6917644 ^{1,2}	AA vs AG vs GG	p=0.822; OR=0.966; 95% CI: 0.713 - 1.308 (NS)
	AA vs AG + GG	p=0.570; OR=0.953; 95% CI: 0.807 - 1.125 (NS)
	AA + GG vs AG	p=0.363; OR=1.082; 95% CI: 0.913 - 1.283 (NS)
	AA + AG vs GG	p=0.257; OR=0.699; 95% CI: 0.377 - 1.297 (NS)
rs7747551 ¹	TT vs TA vs AA	p=0.219; OR=0.866; 95% CI: 0.689 - 1.089 (NS)
	TT vs TA + AA	p=0.633; OR=0.931; 95% CI: 0.696 - 1.247 (NS)
	TT + AA vs TA	p=0.281; OR=0.924; 95% CI: 0.800 - 1.067 (NS)
	TT + TA vs AA	p=0.200; OR=1.096; 95% CI: 0.952 - 1.262 (NS)
rs7748518 ¹	AA vs AG vs GG	p=0.089; OR=0.805; 95% CI: 0.626 - 1.034 (NS)
	AA vs AG + GG	p=0.191; OR=0.778; 95% CI: 0.534 - 1.133 (NS)
	AA + GG vs AG	p=0.327; OR=0.928; 95% CI: 0.798 - 1.078 (NS)
	AA + AG vs GG	p=0.141; OR=1.116; 95% CI: 0.964 - 1.291 (NS)
rs7768619 ²	TT vs TC vs CC	p=0.043; OR=1.338; 95% CI: 1.009 - 1.775 (S)
	TT vs TC + CC	p=0.156; OR=1.114; 95% CI: 0.960 - 1.293 (NS)
	TT + CC vs TC	p=0.482; OR=0.947; 95% CI: 0.815 - 1.101 (NS)
	TT + TC vs CC	p=0.999; OR=0.000; 95% CI: 0.000 - (NS)
rs928501 ¹	AA vs AC vs CC	p=0.755; OR=0.966; 95% CI: 0.778 - 1.199 (NS)

	AA vs AC + CC	p=0.083; OR=0.800; 95% CI: 0.621 - 1.030 (NS)
	AA + CC vs AC	p=0.115; OR=1.122; 95% CI: 0.972 - 1.295 (NS)
	AA + AC vs CC	p=0.570; OR=0.960; 95% CI: 0.835 - 1.104 (NS)
rs9388949 ^{1,2}	TT vs TC vs CC	p=0.117; OR=1.168; 95% CI: 0.962 - 1.418 (NS)
	TT vs TC + CC	p=0.470; OR=1.059; 95% CI: 0.907 - 1.236 (NS)
	TT + CC vs TC	p=0.339; OR=1.070; 95% CI: 0.931 - 1.230 (NS)
	TT + TC vs CC	p=0.060; OR=0.854; 95% CI: 0.725 - 1.006 (NS)
rs9402376 ¹	TT vs TC vs CC	p=0.250; OR=1.145; 95% CI: 0.909 - 1.441 (NS)
	TT vs TC + CC	p=0.226; OR=1.091; 95% CI: 0.948 - 1.256 (NS)
	TT + CC vs TC	p=0.297; OR=0.926; 95% CI: 0.802 - 1.070 (NS)
	TT + TC vs CC	p=0.680; OR=0.939; 95% CI: 0.697 - 1.265 (NS)
rs9493157 ¹	TT vs TC vs CC	p=0.636; OR=0.949; 95% CI: 0.764 - 1.179 (NS)
	TT vs TC + CC	p=0.273; OR=0.867; 95% CI: 0.671 - 1.119 (NS)
	TT + CC vs TC	p=0.534; OR=1.048; 95% CI: 0.904 - 1.214 (NS)
	TT + TC vs CC	p=0.993; OR=1.001; 95% CI: 0.869 - 1.152 (NS)

(S) significant ; (NS) non significant

¹Markers in LD with rs4897554

EXAMPLE 10

5 A multivariate analysis, performed on all the markers associated in univariate analysis, reveals that four main SNPs are associated with an increased risk of developing MCI.

The inventors have performed a multivariate analysis (linear regression, stepwise procedure) to confirm the associations found previously in univariate analysis (polymorphism were analyzed one by one). Similarly to the univariate analysis, the genotypes were considered as

10 binary variables. In this analysis, we included 11 polymorphisms: rs9399005, rs4897554, rs1931001, rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, rs1931000, rs2095252 and rs7768619. In this analysis, four polymorphisms were still significantly associated to MCI (rs4897554 ($p=1.3 \cdot 10^{-4}$; OR=1.841; 95% CI: 1.347-2.512), rs9399005 ($p=2.7 \cdot 10^{-4}$; OR=0.493; 95% CI: 0.337-0.722), rs1931001 ($p=0.042$; OR=1.191; 95% CI: 1.006-1.409), rs13211178 ($p=0.021$; OR=1.248; 95% CI: 1.034-1.505) whereas the other

15 covariates were excluded from the analysis. See Table 15.

Table 15. Multivariate analysis between SNPs in the CTGF locus with MCI disease.

Multivariate Analysis : MCI vs Control

rs4897554	AA + AG vs GG	$p=1.3 \cdot 10^{-4}$; OR=1.841; 95% CI: 1.347-2.512
rs9399005	TT vs TC + CC	$p=2.7 \cdot 10^{-4}$; OR=0.493; 95% CI: 0.337-0.722
rs1931001	AA+ CC vs AC	$p=0.042$; OR=1.191; 95% CI: 1.006-1.409

rs13211178	AA +AG vs GG	p=0.021; OR=1.248; 95% CI: 1.034-1.505
rs12192391	AA vs AG + GG	excluded
rs12200211	AA vs AG + GG	excluded
rs12214123	AA + AG vs GG	excluded
rs1931000	AA + AG vs GG	excluded
rs12194675	AA vs AG + GG	excluded
rs2095252	AA + AG vs GG	excluded
rs7768619	TT + TC vs CC	excluded

EXAMPLE 11

Association between SNPs rs4897554 in the CTGF locus with DLB disease.

- 5 The TAG polymorphisms were also genotyped on 90 subjects with DLB disease. The genotype distribution is indicated in Table 3.

in DLB patients, 33 (36.7%) carry the rs4897554A/A genotype, 44 (48.9%) carry the rs4897554A/G genotype and 13 (14.4%) carry the rs4897554G/G genotype whereas into the controls group 57 (21.8%) carry the rs4897554A/A genotype, 191 (73.2%) carry the
 10 rs4897554A/G genotype and 13 (5.0%) carry the rs4897554G/G. This difference is significant. AA vs AG + GG (p=0.006; OR=1.439; 95% CI: 1.110-1.867), AA + GG vs AG (p=3.4 10⁻⁵; OR=0.592; 95% CI: 0.462-0.759), AA + AG vs GG (p=0.005; OR=1.795; 95% CI: 1.197-2.691). See Table 16.

Table 16. Association between TAG SNPs in the CTGF locus with DLB disease in univariate
 15 analysis.

Univariate Analysis : DLB vs Control

rs10872387	AA vs AC vs CC	p=0.376; OR=1.196; 95% CI: 0.805-1.776 (NS)
	AA vs AC + CC	p=0.534; OR=1.077; 95% CI: 0.853-1.360 (NS)
	AA + CC vs AC	p=0.856; OR=0.978; 95% CI: 0.772-1.240 (NS)
	AA + AC vs CC	p=0.336; OR=0.740; 95% CI: 0.400-1.367 (NS)
rs9483364	AA vs AG vs GG	p=0.446; OR=0.875; 95% CI: 0.622-1.233 (NS)
	AA vs AG + GG	p=0.901; OR=1.023; 95% CI: 0.718-1.456 (NS)
	AA + GG vs AG	p=0.213; OR=0.856; 95% CI: 0.670-1.093 (NS)
	AA + AG vs GG	p=0.259; OR=1.143; 95% CI: 0.906-1.441 (NS)
rs12527379	AA vs AG vs GG	p=0.294; OR=1.186; 95% CI: 0.863-1.631 (NS)
	AA vs AG + GG	p=0.374; OR=1.142; 95% CI: 0.852-1.531 (NS)
	AA + GG vs AG	p=0.862; OR=1.021; 95% CI: 0.810-1.287 (NS)
	AA + AG vs GG	p=0.391; OR=0.901; 95% CI: 0.709-1.144 (NS)

rs1931002	AA vs AG vs GG	p=0.184; OR=0.635; 95% CI: 0.325-1.241(NS)
	AA vs AG + GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
	AA + GG vs AG	p=0.249; OR=0.817; 95% CI: 0.580-1.152(NS)
	AA + AG vs GG	p=0.207; OR=1.247; 95% CI: 0.885-1.755 (NS)
rs4897554	AA vs AG vs GG	p=0.421; OR=1.198; 95% CI: 0.772-1.859 (NS)
	AA vs AG + GG	p=0.006; OR=1.439; 95% CI: 1.110-1.867 (S)
	AA + GG vs AG	p=3.4 10 ⁻⁵ ; OR=0.592; 95% CI: 0.462-0.759 (S)
	AA + AG vs GG	p=0.005; OR=1.795; 95% CI: 1.197-2.691 (S)
rs6918698	CC vs CG vs GG	p=0.927; OR=1.015; 95% CI: 0.735-1.403 (NS)
	CC vs CG + GG	p=0.439; OR=0.899; 95% CI: 0.686-1.178 (NS)
	CC + GG vs CG	p=0.129; OR=1.200; 95% CI: 0.948-1.519 (NS)
	CC + CG vs GG	p=0.341; OR=0.871; 95% CI: 0.655-1.127 (NS)
rs9399005	TT vs TC vs CC	p=0.265; OR=0.818; 95% CI: 0.574-1.165 (NS)
	TT vs TC + CC	p=0.178; OR=0.737; 95% CI: 0.473-1.148 (NS)
	TT + CC vs TC	p=0.851; OR=1.023; 95% CI: 0.808-1.294 (NS)
	TT + TC vs CC	p=0.510; OR=1.081; 95% CI: 0.858-1.361 (NS)
rs9493150	CC vs CG vs GG	p=0.960; OR=1.009; 95% CI: 0.721 – 1.411 (NS)
	CC vs CG + GG	p=0.269; OR=0.801; 95% CI: 0.541-1.187 (NS)
	CC + GG vs CG	p=0.116; OR=1.207; 95% CI: 0.955 – 1.524 (NS)
	CC + CG vs GG	p=0.418; OR=0.908; 95% CI: 0.718-1.147 (NS)

(S) significant ; (NS) non significant

EXAMPLE 12

Among the additional markers in the CTGF locus, rs1029122 is associated with DLB disease.

- 5 The inventors have genotyped additional SNPs by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the DLB group and on the control subjects are described in Table 6. Among these SNPs, only one marker detects significant difference between cases and controls.
- 10 In DLB patients, 36 (40.4%) carry the rs1029122T/T or rs1029122C/C genotypes, whereas into the controls group 197 (53.0%) carry these genotypes. This difference is significant (p=0.035; OR=1.287; 95% CI: 1.018-1.628). See Table 17.

Table 17. Association between additional markers in the CTGF locus with DLB disease in univariate analysis.

Univariate Analysis : DLB vs Control

rs1029122	TT vs TC vs CC	p=0.970; OR=1.006; 95% CI: 0.723-1.402 (NS)
	TT vs TC + CC	p=0.269; OR=0.865; 95% CI: 0.668-1.119 (NS)
	TT + CC vs TC	p=0.035; OR=1.287; 95% CI: 1.018-1.628 (S)
	TT + TC vs CC	p=0.166; OR=0.792; 95% CI: 0.570-1.102 (NS)

rs11154653	TT vs TG vs GG	p=0.481; OR=1.291; 95% CI: 0.635-2.625 (NS)
	TT vs TG + GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
	TT + GG vs TG	p=0.270; OR=1.239; 95% CI: 0.847-1.814 (NS)
	TT + TG vs GG	p=0.358; OR=0.838; 95% CI: 0.574-1.222 (NS)
rs10293697	TT vs TC vs CC	p=0.165; OR=0.760; 95% CI: 0.515-1.120 (NS)
	TT vs TC + CC	p=0.282; OR=0.881; 95% CI: 0.699-1.110(NS)
	TT + CC vs TC	p=0.589; OR=1.067; 95% CI: 0.843-1.351 (NS)
	TT + TC vs CC	p=0.183; OR=1.403; 95% CI: 0.852-2.308 (NS)
rs1931001	AA vs AC vs CC	p=0.502; OR=0.884; 95% CI: 0.617-1.267 (NS)
	AA vs AC + CC	p=0.862; OR=1.033; 95% CI: 0.715-1.493 (NS)
	AA + CC vs AC	p=0.279; OR=0.880; 95% CI: 0.698-1.109 (NS)
	AA + AC vs CC	p=0.319; OR=1.125; 95% CI: 0.892-1.420 (NS)
rs9321315	TT vs TA vs AA	p=0.869; OR=0.960; 95% CI: 0.587-1.567 (NS)
	TT vs TA + AA	p=0.732; OR=0.830; 95% CI: 0.286-2.408 (NS)
	TT + AA vs TA	p=0.989; OR=1.002; 95% CI: 0.763-1.315 (NS)
	TT + TA vs AA	p=0.934; OR=1.011; 95% CI: 0.774-1.322 (NS)

(S) significant ; (NS) non significant

EXAMPLE 13

Among the markers in LD with rs4897554 or rs9399005, polymorphism rs9388949 is associated with DLB disease.

The inventors have genotyped SNPs in LD with rs4897554 or rs9399005 by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the **DLB** group and on the control subjects are described in Table 8.

In DLB patients, 37 (41.1%) carry the rs9388949T/T or rs9388949C/C genotypes, whereas into the controls group 201 (53.7%) carry these genotypes. This difference is significant (p=0.032; OR=1.290; 95% CI: 1.022-1.629). See Table 18.

Table 18. Association between markers, in LD with rs4897554 and rs9399005, in the CTGF locus with DLB disease in univariate analysis.

15 Univariate Analysis : DLB vs Control

rs11154654 ¹	TT vs TC vs CC	p=0.525; OR=1.137; 95% CI: 0.766-1.687 (NS)
	TT vs TC + CC	p=0.711; OR=1.045; 95% CI: 0.828-1.319 (NS)
	TT + CC vs TC	p=0.983; OR=1.003; 95% CI: 0.792-1.269 (NS)
	TT + TC vs CC	p=0.386; OR=0.761; 95% CI: 0.411-1.410 (NS)
rs12192108 ¹	TT vs TC vs CC	p=0.515; OR=1.139; 95% CI: 0.769-1.687 (NS)
	TT vs TC + CC	p=0.730; OR=1.042; 95% CI: 0.826-1.315 (NS)
	TT + CC vs TC	p=0.923; OR=1.012; 95% CI: 0.799-1.281 (NS)
	TT + TC vs CC	p=0.341; OR=0.742; 95% CI: 0.401-1.371 (NS)
rs12192391 ^{1,2}	AA vs AG vs GG	p=0.771; OR=1.072; 95% CI: 0.671-1.715 (NS)

	AA vs AG + GG	p=0.903; OR=0.984; 95% CI: 0.763-1.270 (NS)
	AA + GG vs AG	p=0.563; OR=1.079; 95% CI: 0.835-1.394 (NS)
	AA + AG vs GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
rs12194675 ^{1,2}	AA vs AG vs GG	p=0.866; OR=1.041; 95% CI: 0.655-1.652 (NS)
	AA vs AG + GG	p=0.788; OR=0.966; 95% CI: 0.751-1.243 (NS)
	AA + GG vs AG	p=0.460; OR=1.100; 95% CI: 0.854-1.418 (NS)
	AA + AG vs GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
rs12200211 ^{1,2}	AA vs AG vs GG	p=0.624; OR=1.121; 95% CI: 0.710-1.770 (NS)
	AA vs AG + GG	p=0.996; OR=1.001; 95% CI: 0.778-1.286 (NS)
	AA + GG vs AG	p=0.578; OR=1.074; 95% CI: 0.834-1.383 (NS)
	AA + AG vs GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
rs12214123 ^{1,2}	AA vs AG vs GG	p=0.717; OR=0.918; 95% CI: 0.580-1.455 (NS)
	AA vs AG + GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
	AA + GG vs AG	p=0.547; OR=1.081; 95% CI: 0.839-1.392 (NS)
	AA + AG vs GG	p=0.927; OR=0.988; 95% CI: 0.768-1.271 (NS)
rs12526196 ^{1,2}	TT vs TC vs CC	p=0.385; OR=0.791; 95% CI: 0.466-1.342 (NS)
	TT vs TC + CC	p=0.621; OR=0.931; 95% CI: 0.700-1.237 (NS)
	TT + CC vs TC	p=0.941; OR=1.011; 95% CI: 0.753-1.358 (NS)
	TT + TC vs CC	p=0.083; OR=2.904; 95% CI: 0.870-9.697 (NS)
rs12663962 ¹	TT vs TG vs GG	p=0.440; OR=0.856; 95% CI: 0.577-1.270 (NS)
	TT vs TG + GG	p=0.345; OR=0.744; 95% CI: 0.402-1.375 (NS)
	TT + GG vs TG	p=0.950; OR=0.992; 95% CI: 0.783-1.258 (NS)
	TT + TG vs GG	p=0.620; OR=1.061; 95% CI: 0.840-1.340 (NS)
rs13211178 ^{1,2}	AA vs AG vs GG	p=0.737; OR=0.924; 95% CI: 0.581-1.468 (NS)
	AA vs AG + GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
	AA + GG vs AG	p=0.588; OR=1.072; 95% CI: 0.833-1.381 (NS)
	AA + AG vs GG	p=0.936; OR=0.990; 95% CI: 0.770-1.273 (NS)
rs1930994 ¹	TT vs TA vs AA	p=0.488; OR=0.870; 95% CI: 0.586-1.291 (NS)
	TT vs TA + AA	p=0.378; OR=0.758; 95% CI: 0.409-1.404 (NS)
	TT + AA vs TA	p=0.973; OR=0.996; 95% CI: 0.786-1.261 (NS)
	TT + TA vs AA	p=0.666; OR=1.053; 95% CI: 0.834-1.329 (NS)
rs1931000 ²	AA vs AG vs GG	p=0.241; OR=1.207; 95% CI: 0.881-1.655 (NS)
	AA vs AG + GG	p=0.410; OR=1.128; 95% CI: 0.847-1.502 (NS)
	AA + GG vs AG	p=0.667; OR=1.052; 95% CI: 0.835-1.326 (NS)
	AA + AG vs GG	p=0.275; OR=0.874; 95% CI: 0.686-1.113 (NS)
rs1931004 ^{1,2}	TT vs TC vs CC	p=0.462; OR=0.849; 95% CI: 0.548-1.314 (NS)
	TT vs TC + CC	p=0.823; OR=0.930; 95% CI: 0.493-1.755 (NS)
	TT + CC vs TC	p=0.478; OR=0.909; 95% CI: 0.698-1.184 (NS)
	TT + TC vs CC	p=0.436; OR=1.107; 95% CI: 0.857-1.428 (NS)
rs2095252 ²	AA vs AG vs GG	p=0.375; OR=1.156; 95% CI: 0.840-1.590 (NS)
	AA vs AG + GG	p=0.414; OR=1.130; 95% CI: 0.843-1.513 (NS)
	AA + GG vs AG	p=0.968; OR=1.005; 95% CI: 0.796-1.268 (NS)
	AA + AG vs GG	p=0.500; OR=0.921; 95% CI: 0.724- 1.170 (NS)
rs2151532 ²	TT vs TC vs CC	p=0.146; OR=1.644; 95% CI: 0.841-3.211 (NS)
	TT vs TC + CC	p=0.163; OR=1.275; 95% CI: 0.906-1.794 (NS)
	TT + CC vs TC	p=0.198; OR=0.799; 95% CI: 0.567-1.125 (NS)

	TT + TC vs CC	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
rs6917644 ^{1,2}	AA vs AG vs GG	p=0.582; OR=0.874; 95% CI: 0.542-1.411 (NS)
	AA vs AG + GG	p=0.440; OR=0.900; 95% CI: 0.689-1.176 (NS)
	AA + GG vs AG	p=0.339; OR=1.142; 95% CI: 0.870-1.500 (NS)
	AA + AG vs GG	p=0.619; OR=0.766; 95% CI: 0.267-2.197 (NS)
rs7747551 ¹	TT vs TA vs AA	p=0.665; OR=0.920; 95% CI: 0.630-1.343 (NS)
	TT vs TA + AA	p=0.946; OR=1.016; 95% CI: 0.640-1.614 (NS)
	TT + AA vs TA	p=0.537; OR=0.927; 95% CI: 0.730-1.178 (NS)
	TT + TA vs AA	p=0.569; OR=1.070; 95% CI: 0.848-1.350 (NS)
rs7748518 ¹	AA vs AG vs GG	p=0.257; OR=0.779; 95% CI: 0.5056-1.199 (NS)
	AA vs AG + GG	p=0.998; OR=0.000; 95% CI: 0.000- (NS)
	AA + GG vs AG	p=0.766; OR=1.038; 95% CI: 0.814-1.323 (NS)
	AA + AG vs GG	p=0.606; OR=1.066; 95% CI: 0.837-1.357 (NS)
rs7768619 ²	TT vs TC vs CC	p=0.530; OR=1.156; 95% CI: 0.736-1.813 (NS)
	TT vs TC + CC	p=0.800; OR=1.032; 95% CI: 0.810-1.314 (NS)
	TT + CC vs TC	p=0.854; OR=1.023; 95% CI: 0.802-1.304 (NS)
	TT + TC vs CC	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
rs928501 ¹	AA vs AC vs CC	p=0.154; OR=1.275; 95% CI: 0.913-1.780 (NS)
	AA vs AC + CC	p=0.815; OR=1.045; 95% CI: 0.723-1.512 (NS)
	AA + CC vs AC	p=0.093; OR=1.221; 95% CI: 0.967- 1.541(NS)
	AA + AC vs CC	p=0.076; OR=0.811; 95% CI: 0.643-1.022 (NS)
rs9388949 ^{1,2}	TT vs TC vs CC	p=0.920; OR=1.017; 95% CI: 0.737-1.402 (NS)
	TT vs TC + CC	p=0.253; OR=0.850; 95% CI: 0.644-1.123 (NS)
	TT + CC vs TC	p=0.032; OR=1.290; 95% CI: 1.022-1.629 (S)
	TT + TC vs CC	p=0.189; OR=0.828; 95% CI: 0.624-1.098 (NS)
rs9402376 ¹	TT vs TC vs CC	p=0.576; OR=1.116; 95% CI: 0.760-1.640 (NS)
	TT vs TC + CC	p=0.557; OR=1.072; 95% CI: 0.849-1.354 (NS)
	TT + CC vs TC	p=0.617; OR=0.941; 95% CI: 0.740-1.195 (NS)
	TT + TC vs CC	p=0.836; OR=0.949; 95% CI: 0.577-1.561 (NS)
rs9493157 ¹	TT vs TC vs CC	p=0.761; OR=0.946; 95% CI: 0.662-1.353 (NS)
	TT vs TC + CC	p=0.452; OR=0.841; 95% CI: 0.536-1.320 (NS)
	TT + CC vs TC	p=0.630; OR=1.061; 95% CI: 0.834-1.351 (NS)
	TT + TC vs CC	p=0.976; OR=0.996; 95% CI: 0.789-1.258 (NS)

(S) significant ; (NS) non significant

¹Markers in LD with rs4897554

²Markers in LD with rs9399005

5 EXAMPLE 14

A multivariate analysis, performed on all the markers associated in univariate analysis, reveals that two main SNPs are associated to an increase risk to develop DLB disease.

The inventors have performed a multivariate analysis (linear regression, stepwise procedure) to confirm the associations found previously in univariate analysis (polymorphism were

analyzed one by one). Similarly to the univariate analysis, the genotypes were considered as binary variables. In this analysis, we included 3 polymorphisms: rs4897554, rs1029122, and rs9388949. In this analysis, two polymorphisms were still significantly associated to DLB disease rs4897554 ($p=0.003$; OR=1.872; 95% CI: 1.240-2.825), rs1029122 ($p=0.057$; OR=1.274; 95% CI: 0.992-1.637) whereas the other covariates were excluded from the analysis. See Table 19.

Table 19. Multivariate analysis between SNPs in the CTGF locus with DLB disease.

Multivariate Analysis : DLB vs Control

rs4897554	AA + AG vs GG	$p=0.003$; OR=1.872; 95% CI: 1.240-2.825
rs1029122	TT + CC vs TC	$p=0.057$; OR=1.274; 95% CI: 0.992-1.637
rs9388949	TT + CC vs TC	excluded

10

EXAMPLE 15

Association between SNPs rs9399005, rs4897554 in the CTGF locus with FTD disease in an univariate analysis.

The TAG polymorphisms were also genotyped on 90 subjects with FTD disease. The genotype distribution is indicated in Table 3.

In the FTD subjects group, 96 (97.0%) subjects carry either the rs9399005 C/C or rs9399005C/T genotypes whereas 327 (88.4%) of the controls carry the same genotypes. This difference is significant ($p=0.018$; OR=0.487; 95% CI: 0.269-0.885).

In FTD patients, 36 (36.7%) carry the rs4897554A/A genotype, 45 (45.9%) carry the rs4897554A/G genotype and 17 (17.3%) carry the rs4897554G/G genotype whereas into the controls group 57 (21.8%) carry the rs4897554A/A genotype, 191 (73.2%) carry the rs4897554A/G genotype and 13 (5.0%) carry the rs4897554G/G. This difference is significant. AA vs AG + GG ($p=0.005$; OR=1.442; 95% CI: 1.120-1.856), AA + GG vs AG ($p=2.1 \cdot 10^{-6}$; OR=0.558; 95% CI: 0.438-0.710), AA + AG vs GG ($p=3.7 \cdot 10^{-4}$; OR=2.001; 95% CI: 1.365-2.932) See Table 20.

Table 20. Association between TAG SNPs in the CTGF locus with FTD disease in univariate analysis.

Univariate Analysis : FTD vs Control

rs10872387	AA vs AC vs CC	$p=0.096$; OR=1.396; 95% CI: 0.942-2.071 (NS)
	AA vs AC + CC	$p=0.136$; OR=1.190; 95% CI: 0.947-1.497 (NS)
	AA + CC vs AC	$p=0.318$; OR=0.888; 95% CI: 0.703-1.121 (NS)

	AA + AC vs CC	p=0.262; OR=0.704; 95% CI: 0.381-1.301 (NS)
rs9483364	AA vs AG vs GG	p=0.978; OR=0.995; 95% CI: 0.718-1.380 (NS)
	AA vs AG + GG	p=0.648; OR=0.919; 95% CI: 0.639-1.321 (NS)
	AA + GG vs AG	p=0.579; OR=1.066; 95% CI: 0.851-1.335 (NS)
	AA + AG vs GG	p=0.800; OR=0.972; 95% CI: 0.778-1.214 (NS)
rs12527379	AA vs AG vs GG	p=0.045; OR=1.369; 95% CI: 1.007-1.860 (NS)
	AA vs AG + GG	p=0.154; OR=1.221; 95% CI: 0.928-1.606 (NS)
	AA + GG vs AG	p=0.472; OR=1.085; 95% CI: 0.869-1.355 (NS)
	AA + AG vs GG	p=0.065; OR=0.800; 95% CI: 0.630-1.014 (NS)
rs1931002	AA vs AG vs GG	p=0.680; OR=1.121; 95% CI: 0.653-1.924 (NS)
	AA vs AG + GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
	AA + GG vs AG	p=0.496; OR=1.102; 95% CI: 0.833-1.458 (NS)
	AA + AG vs GG	p=0.582; OR=0.925; 95% CI: 0.699-1.222 (NS)
rs4897554	AA vs AG vs GG	p=0.702; OR=1.085; 95% CI: 0.715-1.644 (NS)
	AA vs AG + GG	p=0.005; OR=1.442; 95% CI: 1.120-1.856 (S)
	AA + GG vs AG	p=2.1 10 ⁻⁶ ; OR=0.558; 95% CI: 0.438-0.710 (S)
	AA + AG vs GG	p=3.7 10 ⁻⁴ ; OR=2.001; 95% CI: 1.365-2.932 (S)
rs6918698	CC vs CG vs GG	p=0.116; OR=0.779; 95% CI: 0.571-1.064 (NS)
	CC vs CG + GG	p=0.105; OR=0.796; 95% CI: 0.604-1.049 (NS)
	CC + GG vs CG	p=0.557; OR=1.070; 95% CI: 0.853-1.342 (NS)
	CC + CG vs GG	p=0.332; OR=1.131; 95% CI: 0.882-1.448 (NS)
rs9399005	TT vs TC vs CC	p=0.027; OR=0.666; 95% CI: 0.464-0.954 (NS)
	TT vs TC + CC	p=0.018; OR=0.487; 95% CI: 0.269-0.885 (S)
	TT + CC vs TC	p=0.931; OR=1.010; 95% CI: 0.805-1.267 (NS)
	TT + TC vs CC	p=0.152; OR=1.178; 95% CI: 0.941-1.473 (NS)
rs9493150	CC vs CG vs GG	p=0.806; OR=0.960; 95% CI: 0.694-1.328 (NS)
	CC vs CG + GG	p=0.426; OR=0.864; 95% CI: 0.603-1.238 (NS)
	CC + GG vs CG	p=0.457; OR=1.090; 95% CI: 0.868-1.369 (NS)
	CC + CG vs GG	p=0.847; OR=0.978; 95% CI: 0.781-1.225 (NS)

(S) significant ; (NS) non significant

EXAMPLE 16

Association between SNPs rs9399005, rs4897554 in the CTGF locus with FTD disease in a
5 multivariate analysis.

The inventors have performed a multivariate analysis (linear regression, stepwise procedure) to confirm the associations found previously in univariate analysis. In this analysis, the inventors have included the rs9399005 and rs4897554, polymorphisms as covariates. In this analysis rs9399005 and rs4897554 were still significantly associated to FTD disease (for
10 rs9399005 polymorphism: p=0.043; OR=0.534; 95% CI: 0.291-0.981 and for rs4897554 polymorphism: p=0.001; OR=1.899; 95% CI: 1.294-2.786). See Table 21.

Table 21. Association between TAG SNPs in the CTGF locus with FTD disease in multivariate analysis.

Multivariate Analysis : FTD vs Control

rs4897554	AA + AG vs GG	p=0.001; OR=1.899; 95% CI: 1.294-2.786
rs9399005	TT vs TC + CC	p=0.043; OR=0.534; 95% CI: 0.291-0.981

5

EXAMPLE 17

Among the additional markers in the CTGF locus, rs11154653 and rs9321315 are associated with FTD disease.

The inventors have genotyped additional SNPs by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the MCI group and on the control subjects are described in Table 6. Among these SNPs, only one marker detects significant difference between cases and controls.

In FTD patients, 84 (84.8%) carry the rs11154653G/G genotype, whereas into the controls group 342 (91.9%) carry this genotype. This difference is significant (p=0.036; OR=0.701; 95% CI: 0.503-0.977).

In FTD patients, 87 (87.9%) carry the rs9321315A/A genotype, whereas into the controls group 281 (75.1%) carry this genotype. This difference is significant (p=0.008; OR=1.549; 95% CI: 1.121-2.141). See Table 22.

Table 22. Association between additional markers in the CTGF locus with FTD disease in univariate analysis.

Univariate Analysis : FTD vs Control

rs1029122	TT vs TC vs CC	p=0.381; OR=1.151; 95% CI: 0.840-1.578 (NS)
	TT vs TC + CC	p=0.668; OR=1.052; 95% CI: 0.834-1.328 (NS)
	TT + CC vs TC	p=0.664; OR=1.050; 95% CI: 0.841-1.311 (NS)
	TT + TC vs CC	p=0.286; OR=0.848; 95% CI: 0.626-1.148 (NS)
rs11154653	TT vs TG vs GG	p=0.069; OR=1.786; 95% CI: 0.955-3.339 (NS)
	TT vs TG + GG	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
	TT + GG vs TG	p=0.022; OR=1.481; 95% CI: 1.059-2.072 (S)
	TT + TG vs GG	p=0.036; OR=0.701; 95% CI: 0.503-0.977 (S)
rs10293697	TT vs TC vs CC	p=0.470; OR=1.162; 95% CI: 0.773-1.747 (NS)
	TT vs TC + CC	p=0.581; OR=1.066; 95% CI: 0.849-1.340 (NS)
	TT + CC vs TC	p=0.773; OR=0.966; 95% CI: 0.767-1.218 (NS)
	TT + TC vs CC	p=0.461; OR=0.754; 95% CI: 0.355-1.600 (NS)
rs1931001	AA vs AC vs CC	p=0.127; OR=0.759; 95% CI: 0.533-1.081 (NS)

	AA vs AC + CC	p=0.684; OR=0.924; 95% CI: 0.632-1.352 (NS)
	AA + CC vs AC	p=0.139; OR=0.845; 95% CI: 0.675-1.056 (NS)
	AA + AC vs CC	p=0.080; OR=1.221; 95% CI: 0.977-1.526 (NS)
rs9321315	TT vs TA vs AA	p=0.012; OR=0.461; 95% CI: 0.252-0.842 (S)
	TT vs TA + AA	p=0.666; OR=0.791; 95% CI: 0.273-2.293 (NS)
	TT + AA vs TA	p=0.010; OR=0.642; 95% CI: 0.459-0.898 (S)
	TT + TA vs AA	p=0.008; OR=1.549; 95% CI: 1.121-2.141 (S)

(S) significant ; (NS) non significant

EXAMPLE 18

Among the markers in LD with rs4897554 or rs9399005, polymorphism rs1931000 is associated with FTD disease.

The inventors have genotyped SNPs in LD with rs4897554 or rs9399005 by the Illumina's GoldenGate Assay according to the manufacturer's instructions. The genotype frequencies of each polymorphism on the **FTD** group and on the control subjects are described in Table 8.

In FTD patients, 28 (28.3%) carry the rs1931000G/G genotype, whereas into the controls group 148 (39.6%) carry this genotype. This difference is significant (p=0.040; OR=0.776; 95% CI: 0.609-0.988). See Table 23.

Table 23. Association between markers, in LD with rs4897554 and rs9399005, in the CTGF locus with FTD disease in univariate analysis.

Univariate Analysis : FTD vs Control

rs11154654 ¹	TT vs TC vs CC	p=0.115; OR=1.374; 95% CI: 0.926-2.040 (NS)
	TT vs TC + CC	p=0.152; OR=1.182; 95% CI: 0.940-1.486 (NS)
	TT + CC vs TC	p=0.321; OR=0.889; 95% CI: 0.704-1.122 (NS)
	TT + TC vs CC	p=0.305; OR=0.725; 95% CI: 0.392-1.341 (NS)
rs12192108 ¹	TT vs TC vs CC	p=0.128; OR=1.357; 95% CI: 0.916-2.012 (NS)
	TT vs TC + CC	p=0.182; OR=1.169; 95% CI: 0.929-1.470 (NS)
	TT + CC vs TC	p=0.396; OR=0.904; 95% CI: 0.715-1.142 (NS)
	TT + TC vs CC	p=0.274; OR=0.710; 95% CI: 0.384-1.311 (NS)
rs12192391 ^{1,2}	AA vs AG vs GG	p=0.252; OR=0.787; 95% CI: 0.523-1.186 (NS)
	AA vs AG + GG	p=0.328; OR=0.888; 95% CI: 0.700-1.127 (NS)
	AA + GG vs AG	p=0.506; OR=1.087; 95% CI: 0.850-1.390 (NS)
	AA + AG vs GG	p=0.357; OR=1.326; 95% CI: 0.728-2.416 (NS)
rs12194675 ^{1,2}	AA vs AG vs GG	p=0.689; OR=0.918; 95% CI: 0.601-1.400 (NS)
	AA vs AG + GG	p=0.736; OR=0.959; 95% CI: 0.753-1.222 (NS)
	AA + GG vs AG	p=0.821; OR=1.029; 95% CI: 0.802-1.321 (NS)
	AA + AG vs GG	p=0.735; OR=1.121; 95% CI: 0.578-2.176 (NS)
rs12200211 ^{1,2}	AA vs AG vs GG	p=0.374; OR=0.834; 95% CI: 0.559-1.244 (NS)
	AA vs AG + GG	p=0.409; OR=0.906; 95% CI: 0.716-1.146 (NS)
	AA + GG vs AG	p=0.524; OR=1.082; 95% CI: 0.849-1.380 (NS)
	AA + AG vs GG	p=0.584; OR=1.177; 95% CI: 0.657-2.109 (NS)

rs12214123 ^{1,2}	AA vs AG vs GG	p=0.420; OR=1.181; 95% CI: 0.788-1.771 (NS)
	AA vs AG + GG	p=0.484; OR=1.235; 95% CI: 0.684-1.229 (NS)
	AA + GG vs AG	p=0.672; OR=1.054; 95% CI: 0.825-1.347 (NS)
	AA + AG vs GG	p=0.503; OR=0.922; 95% CI: 0.728-1.168 (NS)
rs12526196 ^{1,2}	TT vs TC vs CC	p=0.084; OR=0.645; 95% CI: 0.392-1.061 (NS)
	TT vs TC + CC	p=0.104; OR=0.807; 95% CI: 0.623-1.045 (NS)
	TT + CC vs TC	p=0.140; OR=1.218; 95% CI: 0.938-1.582 (NS)
	TT + TC vs CC	p=0.348; OR=1.946; 95% CI: 0.484-7.815 (NS)
rs12663962 ¹	TT vs TG vs GG	p=0.087; OR=0.707; 95% CI: 0.475-1.052 (NS)
	TT vs TG + GG	p=0.139; OR=0.575; 95% CI: 0.277-1.196 (NS)
	TT + GG vs TG	p=0.488; OR=0.921; 95% CI: 0.730-1.162 (NS)
	TT + TG vs GG	p=0.172; OR=1.173; 95% CI: 0.933-1.474 (NS)
rs13211178 ^{1,2}	AA vs AG vs GG	p=0.366; OR=1.207; 95% CI: 0.803-1.815 (NS)
	AA vs AG + GG	p=0.387; OR=1.303; 95% CI: 0.715-2.374 (NS)
	AA + GG vs AG	p=0.672; OR=1.054; 95% CI: 0.825-1.347 (NS)
	AA + AG vs GG	p=0.470; OR=0.916; 95% CI: 0.723-1.161 (NS)
rs1930994 ¹	TT vs TA vs AA	p=0.102; OR=0.719; 95% CI: 0.484-1.068 (NS)
	TT vs TA + AA	p=0.299; OR=0.722; 95% CI: 0.390-1.335 (NS)
	TT + AA vs TA	p=0.295; OR=0.883; 95% CI: 0.699-1.115 (NS)
	TT + TA vs AA	p=0.136; OR=1.190; 95% CI: 0.947-1.497 (NS)
rs1931000 ²	AA vs AG vs GG	p=0.028; OR=1.407; 95% CI: 1.038-1.906 (S)
	AA vs AG + GG	p=0.122; OR=1.233; 95% CI: 0.945-1.609 (NS)
	AA + GG vs AG	p=0.430; OR=1.094; 95% CI: 0.876-1.366 (NS)
	AA + AG vs GG	p=0.040; OR=0.776; 95% CI: 0.609-0.988 (S)
rs1931004 ^{1,2}	TT vs TC vs CC	p=0.604; OR=0.894; 95% CI: 0.587-1.364 (NS)
	TT vs TC + CC	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
	TT + CC vs TC	p=0.375; OR=1.114; 95% CI: 0.878-1.413 (NS)
	TT + TC vs CC	p=0.892; OR=0.984; 95% CI: 0.777-1.246 (NS)
rs2095252 ²	AA vs AG vs GG	p=0.062; OR=1.338; 95% CI: 0.985-1.817 (NS)
	AA vs AG + GG	p=0.193; OR=1.199; 95% CI: 0.912-1.576 (NS)
	AA + GG vs AG	p=0.489; OR=1.082; 95% CI: 0.866-1.351 (NS)
	AA + AG vs GG	p=0.083; OR=0.810; 95% CI: 0.639-1.028 (NS)
rs2151532 ²	TT vs TC vs CC	p=0.826; OR=0.941; 95% CI: 0.549-1.614 (NS)
	TT vs TC + CC	p=0.726; OR=0.952; 95% CI: 0.721-1.257 (NS)
	TT + CC vs TC	p=0.634; OR=1.070; 95% CI: 0.810-1.414 (NS)
	TT + TC vs CC	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
rs6917644 ^{1,2}	AA vs AG vs GG	p=0.088; OR=0.689; 95% CI: 0.449-1.057 (NS)
	AA vs AG + GG	p=0.087; OR=0.806; 95% CI: 0.629-1.032 (NS)
	AA + GG vs AG	p=0.126; OR=1.221; 95% CI: 0.946-1.576 (NS)
	AA + AG vs GG	p=0.495; OR=1.269; 95% CI: 0.640-2.520 (NS)
rs7747551 ¹	TT vs TA vs AA	p=0.161; OR=0.760; 95% CI: 0.518-1.116 (NS)
	TT vs TA + AA	p=0.202; OR=0.672; 95% CI: 0.365-1.238 (NS)
	TT + AA vs TA	p=0.621; OR=0.944; 95% CI: 0.750-1.188 (NS)
	TT + TA vs AA	p=0.274; OR=1.135; 95% CI: 0.905-1.422 (NS)
rs7748518 ¹	AA vs AG vs GG	p=0.175; OR=0.748; 95% CI: 0.492-1.138 (NS)

	AA vs AG + GG	p=0.998; OR=0.000; 95% CI: 0.000- (NS)
	AA + GG vs AG	p=0.919; OR=1.012; 95% CI: 0.800- 1.281(NS)
	AA + AG vs GG	p=0.459; OR=1.092; 95% CI: 0.865-1.380 (NS)
rs7768619 ²	TT vs TC vs CC	p=0.542; OR=1.145; 95% CI: 0.741-1.749 (NS)
	TT vs TC + CC	p=0.829; OR=1.026; 95% CI: 0.812-1.296 (NS)
	TT + CC vs TC	p=0.813; OR=1.029; 95% CI: 0.814-1.301 (NS)
	TT + TC vs CC	p=0.999; OR=0.000; 95% CI: 0.000- (NS)
rs928501 ¹	AA vs AC vs CC	p=0.826; OR=1.038; 95% CI: 0.746-1.443 (NS)
	AA vs AC + CC	p=0.985; OR=0.996; 95% CI: 0.690-1.439 (NS)
	AA + CC vs AC	p=0.741; OR=1.040; 95% CI: 0.826-1.309 (NS)
	AA + AC vs CC	p=0.758; OR=0.966; 95% CI: 0.773- 1.207 (NS)
rs9388949 ^{1,2}	TT vs TC vs CC	p=0.646; OR=1.074; 95% CI: 0.792-1.455 (NS)
	TT vs TC + CC	p=0.757; OR=1.040; 95% CI: 0.812-1.331 (NS)
	TT + CC vs TC	p=0.904; OR=1.014; 95% CI: 0.811-1.267 (NS)
	TT + TC vs CC	p=0.653; OR=0.943; 95% CI: 0.729-1.219 (NS)
rs9402376 ¹	TT vs TC vs CC	p=0.173; OR=1.308; 95% CI: 0.889-1.925 (NS)
	TT vs TC + CC	p=0.273; OR=1.135; 95% CI: 0.905-1.424 (NS)
	TT + CC vs TC	p=0.578; OR=0.937; 95% CI: 0.744-1.180 (NS)
	TT + TC vs CC	p=0.238; OR=0.692; 95% CI: 0.375-1.275 (NS)
rs9493157 ¹	TT vs TC vs CC	p=0.433; OR=0.869; 95% CI: 0.611-1.235 (NS)
	TT vs TC + CC	p=0.329; OR=0.800; 95% CI: 0.510- 1.253(NS)
	TT + CC vs TC	p=0.933; OR=1.010; 95% CI: 0.798-1.278 (NS)
	TT + TC vs CC	p=0.634; OR=1.057; 95% CI: 0.842-1.325 (NS)

(S) significant ; (NS) non significant

¹Markers in LD with rs4897554

²Markers in LD with rs9399005

5 EXAMPLE 19

A multivariate analysis, performed on all the markers associated in univariate analysis, reveals that three main SNPs are associated to an increase risk to develop FTD disease.

The inventors have performed a multivariate analysis (linear regression, stepwise procedure) to confirm the associations found previously in univariate analysis (polymorphism were analyzed one by one). Similarly to the univariate analysis, the genotypes were considered as binary variables. In this analysis, we included 5 polymorphisms: rs4897554, rs9399005, rs11154653 and rs9321315 and rs1931000. In this analysis, three polymorphisms were still significantly associated to FTD disease rs4897554 ($p=4.6 \cdot 10^{-4}$; OR=2.007; 95% CI: 1.359-2.965), rs9321315 ($p=0.013$; OR=1.538; 95% CI: 1.096-2.159) rs11154653 ($p=0.017$; OR=0.637; 95% CI: 0.440-0.923) whereas the other covariates were excluded from the analysis. See Table 24.

Table 24. Multivariate analysis between SNPs in the CTGF locus with FTD disease.

Multivariate Analysis : FTD vs Control

rs4897554	AA + AG vs GG	p=4.6 10 ⁻⁴ ; OR=2.007; 95% CI: 1.359-2.965
rs9321315	TT + TA vs AA	p=0.013; OR=1.538; 95% CI: 1.096-2.159
rs11154653	TT + TG vs GG	p=0.017; OR=0.637; 95% CI: 0.440-0.923
rs9399005	TT vs TC + CC	excluded
rs1931000	AA + AG vs GG	excluded

CONCLUSION

5

Significant association was shown between several polymorphisms and dementias.

SNPs rs9399005, rs4897554, rs9493150, rs9483364, rs10872387, rs12527379, rs6918698, rs1931001, rs12192108, rs12663962, rs1931000, rs2095252, rs7747551, rs9388949 and rs9493157, in the CTGF locus, are associated with an increased risk of developing **Alzheimer**

10 **disease.**

rs9399005: susceptibility genotypes CC or TC relative risk: 1.50

rs4897554: susceptibility genotype GG relative risk: 1.99

rs9493150: susceptibility genotypes GG or GC relative risk: 1.34

rs9483364: susceptibility genotypes GG or GA relative risk: 1.59

15 rs10872387: susceptibility genotype AA relative risk: 1.17

rs12527379: susceptibility genotype GG relative risk: 1.35

rs6918698: susceptibility genotypes GG or GC relative risk: 1.28

rs1931001: susceptibility genotype CC relative risk: 1.25

rs12192108: susceptibility genotype TT relative risk: 1.16

20 rs12663962: susceptibility genotype GG relative risk: 1.18

rs1931000: susceptibility genotypes AA or AG relative risk: 1.36

rs2095252: susceptibility genotypes AA or AG relative risk: 1.34

rs7747551: susceptibility genotype AA relative risk: 1.16

rs9388949: susceptibility genotypes TT or TC relative risk: 1.24

25 rs9493157: susceptibility genotype CC or TC relative risk: 1.47

These susceptibility genotypes may be combined. For example, subjects carrying the rs12192108TT genotype have an Alzheimer disease risk multiplied by 1.16. Subjects carrying the rs12663962GG genotype have an Alzheimer disease risk multiplied by 1.18. Subjects carrying the rs12192108TT genotype AND the rs12663962GG genotype have an Alzheimer disease risk of 1.37 (1.16x1.18). These combinations may be made with any susceptibility markers.

The preferred set of markers associated with an increased risk of developing **Alzheimer disease** includes rs4897554, rs9399005, rs1931001, rs1931000, rs9388949. The relative risks in this set are: 1.81 (rs4897554), 1.44 (rs9399005), 1.26 (rs1931001), 1.37 (rs1931000), 1.32 (rs9388949).

SNPs rs9399005, rs4897554, rs9493150, rs12527379, rs6918698, rs1931001, rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, rs1931000, rs2095252 and rs7768619 in the CTGF locus, are associated with an increased risk of developing with **MCI disease**.

rs9399005: susceptibility genotypes CC or TC relative risk: 1.77

rs4897554: susceptibility genotype GG relative risk: 2.09

rs9493150: susceptibility genotypes GG or GC relative risk: 1.29

rs12527379: susceptibility genotype AA or AG relative risk: 1.17

rs6918698: susceptibility genotypes GG or GC relative risk: 1.24

rs1931001: susceptibility genotype CC relative risk: 1.16

rs12192391: susceptibility genotype AA relative risk: 1.23

rs12194675: susceptibility genotype AA relative risk: 1.23

rs12200211: susceptibility genotype AA relative risk: 1.23

rs12214123: susceptibility genotype GG relative risk: 1.23

rs13211178: susceptibility genotype GG relative risk: 1.23

rs1931000: susceptibility genotypes AA or AG relative risk: 1.20

rs2095252: susceptibility genotypes AA or AG relative risk: 1.18

rs7768619: susceptibility genotype TT relative risk: 1.11

The preferred set of markers associated with an increased risk of developing **MCI disease** is includes rs4897554, rs9399005, rs1931001, rs13211178. The relative risks in this set are: 1.84 (rs4897554), 2.01 (rs9399005), 1.19 (rs1931001), 1.25(rs13211178).

SNPs rs4897554, rs1029122, rs9388949 in the CTGF locus are associated with an increased risk of developing **DLB disease**.

rs4897554: susceptibility genotype GG relative risk: 1.80

5 rs1029122: susceptibility genotype CT relative risk: 1.29

rs9388949: susceptibility genotypes TC relative risk: 1.29

The preferred set of markers associated with an increased risk of developing **DLB disease** is includes rs4897554, rs1029122. The relative risks in this set are: 1.87 (rs4897554), 1.27
10 (rs1029122).

SNPs rs9399005, rs4897554, rs11154653, rs9321315 rs1931000 in the CTGF locus are associated with an increased risk of developing **FTD disease**.

rs9399005: susceptibility genotypes CC or TC relative risk: 2.05

15 rs4897554: susceptibility genotype GG relative risk: 2.00

rs11154653: susceptibility genotype TG relative risk: 1.48

rs9321315: susceptibility genotype AA relative risk: 1.55

rs1931000: susceptibility genotypes AA or AG relative risk: 1.29

20 The preferred set of markers associated with an increased risk of developing **FTD disease** includes rs4897554, rs9321315, rs11154653. The relative risks in this set are: 2.01 (rs4897554), 1.54 (rs9321315), 1.57 (rs11154653).

CLAIMS

- 5 1. A method of determining whether a subject has or is at risk of developing a dementia, which method comprises detecting the presence of a mutation, deletion or insertion of one or several nucleotides in the CTGF gene locus in a biological sample of said subject.
2. The method of claim 1, wherein said dementia is a dementia with memory and/or cognitive
10 dysfunction.
3. The method of claim 1 or 2, wherein said dementia is a senile dementia, preferably occurring in humans over 65 years old.
- 15 4. The method of anyone of the preceding claims, wherein said dementia is selected from the group consisting of mild cognitive impairment, Alzheimer's disease, fronto-temporal dementia and dementia with Lewis bodies.
5. The method of anyone of the preceding claims, wherein said mutation, deletion or insertion
20 of one or several nucleotides is located from within 20 kb, preferably within 15 kb, more preferably within 10 kb and even more preferably within 5 kb upstream the start codon of the CTGF gene to 20 kb, preferably within 15 kb, more preferably within 10 kb and even more preferably within 5 kb downstream the 3'UTR of the CTGF gene.
- 25 6. The method of any of the preceding claims, wherein said mutation, deletion or insertion of one or several nucleotides is one or several single nucleotide polymorphism(s) (SNPs).
7. The method of claim 6, wherein said SNP is selected from the SNPs listed in Table 1A or Table 1B.
- 30 8. The method of claim 7, comprising detecting the presence of a SNP or a combination of SNPs selected from the group consisting of rs12192108, rs2095252, rs10872387,

rs12527379, rs12663962, rs1931000, rs1931001, rs4897554, rs6918698, rs7747551, rs9388949, rs9399005, rs9483364, rs9493150, rs9493157, rs1931001, rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, rs7768619, rs1029122, rs11154653, and rs9321315., preferably rs4897554, rs9399005, rs1931001, rs1931000, rs9388949, 5 rs13211178, rs1029122, rs9321315, and/or rs11154653.

9. The method of claim 8, comprising detecting the presence of SNP rs9399005 wherein the presence of at least one allele C is indicative of a risk of developing a dementia or of the development of a dementia.

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10. The method of claim 8, comprising detecting the presence of SNP rs4897554 wherein the presence of two alleles G is indicative of a risk of developing a dementia or of the development of a dementia.

15 11. The method of claim 7, for determining whether a subject has or is at risk of developing Alzheimer's disease, which method comprises detecting the presence of a SNP or combination of SNPs, selected from the group consisting of rs12192108, rs2095252, rs10872387, rs12527379, rs12663962, rs1931000, rs1931001, rs4897554, rs6918698, rs7747551, rs9388949, rs9399005, rs9483364, rs9493150 and rs9493157, preferably 20 rs7747551, rs1931001, rs12663962, rs10872387, and/or rs12192108.

12. The method of claim 11, wherein the presence of one of the following genotypes, alone or in combinations, in a subject is indicative of a development of, or a risk of developing, Alzheimer's disease :

25 genotype CC or TC with respect to rs9399005

genotype GG with respect to rs4897554

genotype GG or GC with respect to rs9493150

genotype GG or GA with respect to rs9483364

genotype AA with respect to rs10872387

30 genotype GG with respect to rs12527379

genotype GG or GC with respect to rs6918698

genotype CC with respect to rs1931001

genotype TT with respect to rs12192108

genotype GG with respect to rs12663962

genotype AA or AG with respect to rs1931000

genotype AA or AG with respect to rs2095252

5 genotype AA with respect to rs7747551

genotype TT or TC with respect to rs9388949; and/or

genotype CC or TC with respect to rs9493157.

13. The method of claim 12, wherein the presence of a combination of risk alleles, in a subject
10 is indicative of a development of, or a risk of developing, Alzheimer's disease, wherein said risk alleles are :

genotype GG with respect to rs4897554,

genotype CC or TC with respect to rs9399005,

genotype CC with respect to rs1931001,

15 genotype AA or AG with respect to rs1931000, and

genotype TT or TC with respect to rs9388949.

14. The method of claim 7, for determining whether a subject has or is at risk of developing mild cognitive impairment, which method comprises detecting the presence of a SNP or
20 combination of SNPs, selected from the group consisting of rs1931001, rs2095252, rs12192391, rs12194675, rs12200211, rs12214123, rs12527379, rs13211178, rs1931000, rs4897554, rs6918698, rs7768619, rs9399005, rs9493150, preferably rs1931001, rs12192391, rs12194675, rs12200211, rs12214123, rs13211178, and/or rs7768619.

25 15. The method of claim 14, wherein the presence of one of the following genotypes, alone or in combinations, in a subject is indicative of a development of, or a risk of developing, mild cognitive impairment:

genotype CC or TC with respect to rs9399005

genotype GG with respect to rs4897554

30 genotype GG or GC with respect to rs9493150

genotype AA or AG with respect to rs12527379

genotype GG or GC with respect to rs6918698:

genotype CC with respect to rs1931001

genotype AA with respect to rs12192391

genotype AA with respect to rs12194675

genotype AA with respect to rs12200211

genotype GG with respect to rs12214123

5 genotype GG with respect to rs13211178

genotype AA or AG with respect to rs1931000

genotype AA or AG with respect to rs2095252, and/or

genotype TT with respect to rs7768619.

10 16. The method of claim 15, wherein the presence of a combination of risk alleles, in a subject is indicative of a development of, or a risk of developing, mild cognitive impairment, wherein said risk alleles are

genotype GG with respect to rs4897554

genotype CC or TC with respect to rs9399005

15 genotype CC with respect to rs1931001, and

genotype GG with respect to rs13211178.

17. The method of claim 7, for determining whether a subject has or is at risk of developing Dementia with Lewis bodies, which method comprises detecting the presence of a SNP or
20 combination of SNPs, selected from the group consisting of rs1029122, rs4897554, rs9388949, preferably rs1029122.

18. The method of claim 17, wherein the presence of one of the following genotypes, alone or in combinations, in a subject is indicative of a development of, or a risk of developing,
25 dementia with Lewis bodies:

genotype GG with respect to rs4897554

genotype CT with respect to rs1029122, and/or

genotype TC with respect to rs9388949.

30 19. The method of claim 18, wherein the presence of a combination of risk alleles, in a subject is indicative of a development of, or a risk of developing, dementia with Lewis bodies, wherein said risk alleles are

genotype GG with respect to rs4897554 and
genotype CT with respect to rs1029122.

20. The method of claim 7, for determining whether a subject has or is at risk of developing
5 Frontotemporal Dementia, which method comprises detecting the presence of a SNP or
combination of SNPs, selected from the group consisting of rs11154653, rs1931000 ,
rs4897554, rs9321315, rs9399005, preferably rs11154653 and/or rs9321315.

21. The method of claim 20, wherein the presence of one of the following genotypes, alone or
10 in combinations, in a subject is indicative of a development of, or a risk of developing, fronto-
temporal dementia:

genotype CC or TC with respect to rs9399005

genotype GG with respect to rs4897554

genotype TG with respect to rs11154653

15 genotype AA with respect to rs9321315, and/or

genotype AA or AG with respect to rs1931000.

22. The method of claim 21, wherein the presence of a combination of risk alleles, in a subject
is indicative of a development of, or a risk of developing, fronto-temporal dementia, wherein
20 said risk alleles are

genotype GG with respect to rs4897554

genotype AA with respect to rs9321315, and

genotype TG with respect to rs11154653.

25 23. The method of claim 1, which method comprises detecting the presence of a SNP at
position rs9399005 or rs4897554 in the CTGF gene locus in a biological sample of said
subject, which is indicative of a subject having or being at risk of developing an early form of
dementia such as a mild cognitive impairment (MCI).

30 24. The method of claim 1, which method comprises detecting the presence of a SNP at
position rs9399005 in the CTGF gene locus in a biological sample of said subject, which is

indicative of a subject having or being at risk of developing an advanced form of dementia such as Alzheimer's disease (AD).

25. The method of any one of the preceding claims, wherein the presence of an alteration in
5 the CTGF gene locus is detected by sequencing, selective hybridization and/or selective amplification.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/073814A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/037481 A1 (UNIV MANCHESTER [GB]; PICKERING-BROWN STUART [GB]) 26 March 2009 (2009-03-26) claims 23-27, 34, 36; examples 1,2,4 ----- -/--	1-7,25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/073814

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHONG ZHAO ET AL: "Connective tissue growth factor (CTGF) expression in the brain is a downstream effector of insulin resistance associated promotion of Alzheimer s disease α-amyloid neuropathology", INTERNET CITATION, [Online] 26 September 2005 (2005-09-26), pages 1-25, XP009127353, ISSN: 0892-6638 Retrieved from the Internet: URL:http://www.fasebj.org/cgi/reprint/05-4359fjev1.pdf [retrieved on 2009-12-16] cited in the application the whole document	1-25
A	UEBERHAM U ET AL: "Connective tissue growth factor in Alzheimer's disease", NEUROSCIENCE, NEW YORK, NY, US, vol. 116, no. 1, 15 January 2003 (2003-01-15), pages 1-6, XP004631754, ISSN: 0306-4522, DOI: 10.1016/S0306-4522(02)00670-X cited in the application the whole document	1-25
A	WO 2010/028651 A2 (LUNDBECK & CO AS H [DK]; WILLNOW THOMAS [DE]) 18 March 2010 (2010-03-18) the whole document	1-25
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/073814

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