Journal of Alzheimer's Disease 23 (2011) 1–21
IOS Press

Supplementary Data

A Novel Blood Test for the Early Detection of Alzheimer's Disease

Phil. D. Rye[a,1,2], Birgitte Boonstra Booij[a,1,3], Gisle Grave[a], Torbjørn Lindahl[a], Lena Kristiansen[a], Hilde-Marie Andersen[a], Peter O. Horndalsveen[b], Harald A. Nygaard[c,d], Mala Naik[d,e], Dagne Hoprekstad[f], Peter Wetterberg[g], Christer Nilsson[h], Dag Aarsland[i], Praveen Sharma[a] and Anders Lönneborg[a,*]
[a]*DiaGenic ASA, Oslo, Norway*
[b]*Memory Clinic, Sanderud Hospital, Ottestad, Norway*
[c]*NKS Olaviken Hospital for Old Age Psychiatry, Erdal, Norway*
[d]*Section for Geriatric Medicine, Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway*
[e]*Geriatric Section, Haraldsplass Deaconess Hospital, Bergen, Norway*
[f]*Geriatric Clinic, Stavanger University Hospital, Stavanger, Norway*
[g]*Memory Clinic, Department of Geriatrics, Medical Division, Ullevål University Hospital, Oslo, Norway*
[h]*Department of Clinical Sciences, Lund University Hospital, Lund, Sweden*
[i]*Stavanger University Hospital, and Akershus University Hospital, Department of Psychiatry, Division of Mental Health Services, and Institute of Clinical Medicine, University of Oslo, Lørenskog, Norway*

Accepted 8 September 2010

SUPPLEMENTARY METHODS

Data pre-processing

The raw data generated from the real-time PCR analysis was processed prior to statistical analysis to calculate accurate quantification cycle (C_q) values and quality check the data to eliminate failed measurements/missing values. The SDS files generated from the 7900HT Fast Real-Time PCR System were loaded into the Sequence Detection Systems software distributed by Applied Biosystems. Clipped and Results files are exported for each SDS file. The Clipped-file contains the baseline-corrected normalized reporter signal (ΔRn) values and the Results file contains the threshold and the C_q values automatically assigned by the software.

The threshold is adjusted to a value above the background and significantly below the plateau of an amplification plot. It must be placed within the linear region of the amplification curve, which represents the detectable log-linear range of the PCR. One threshold value is set for each assay, as described below.

1. Log_2 is calculated for all available ΔRn values.
2. Any $Log_2(\Delta Rn)$ values found to be below -6, are set to NA (not available).

[1] Authors contributed equally to the manuscript.

[2] Present address: Phil. D. Rye, GE Healthcare Medical Diagnostics, Nycoveien 2, P.O. Box 4220, Nydalen, 0401 Oslo, Norway.

[3] Present address: Birgitte Boonstra Booij, Clavis Pharma, Parkveien 53 B, 0256 Oslo, Norway.

*Correspondence to: Dr. A. Lönneborg, DiaGenic ASA, Grenseveien 92, 0663 Oslo, Norway. E-mail: anders.lonneborg@diagenic.com.

ISSN 1387-2877/11/$27.50

3. If there are three or more ΔRn points available from the amplification curve, a linear model, $Y = aX + b$, are fitted to three and three of the available $Log_2(\Delta Rn)$ points, beginning with the lowest three points and moving up one point at a time.
4. All linear models are checked whether their slopes and residuals are within pre-defined limits. If so, the corresponding $Log_2(\Delta Rn)$ points involved in models which pass the quality control (QC) criteria, are saved in a register.
5. An upper limit value is set. This value is the highest possible threshold value ($Log_2(\Delta Rn)$) found in the register for this particular assay and sample combination. A lower limit is set in the same manner choosing the lowest possible threshold value ($Log_2(\Delta Rn)$).

The following step is done for each assay across all samples:

6. A suggested threshold value is calculated: the mean of all upper limits is calculated and two standard deviations (SD) are subtracted. The mean of all lower limits is calculated and two standard deviations are added. A threshold value is suggested to be set at upper 15% of the distance between these two values. Suggested threshold = $\text{mean}_{\text{lower}} + 2\,\text{SD}_{\text{lower}} + ((\text{mean}_{\text{upper}} - 2\,\text{SD}_{\text{upper}}) - (\text{mean}_{\text{lower}} + 2\,\text{SD}_{\text{lower}})) \times (1-15\%)$.
7. All upper and lower limits are plotted along with the suggested threshold.

All sample-assay pairs in the data are subjected to the following procedure to set the C_q values.

1. The intersection point between the given threshold and the $Log_2(\Delta Rn)$ curve is found.
2. A linear model, $Y = aX + b$, is fitted to the closest $Log_2(\Delta Rn)$ point below the intersection, along with two of the closest points above.
3. Another linear model is fitted to the closest $Log_2(\Delta Rn)$ point above the intersection, along with two of the closest points below.
4. A QC test is performed on both models to see whether the model's slope is above a predefined value and the residual is below a predefined value.
5. If either one of the models passes the QC test criteria, the intersection point is set as the C_q value.
6. The results are saved to a postscript file.
7. Each C_q value along with the corresponding assay and sample name is stored for further statistical data analysis.

Component selection and decision boundary calculation

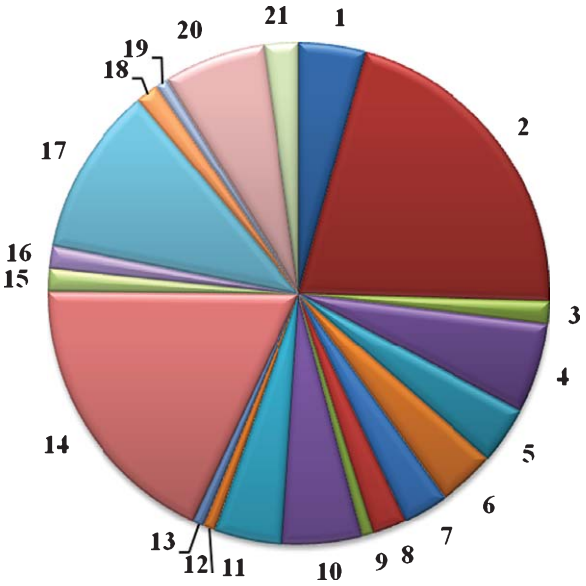
PLSR and LOOCV were used for model building and to estimate classification accuracy of the calibration set. Two components were finally selected as giving the optimum LOOCV efficacy (data not shown), with the β-coefficients for the final PLS model used for classification in the range from -3.46 to $+3.32$. From this LOOCV plot the results are skewed towards higher specificity than sensitivity, which could be compensated by changing the decision boundary (cut-off) from the default value of 0. The ROC for the final PLS model is shown in Fig. 2. From the LOOCV classifications observed using the calibration samples, a possible decision boundary could be -0.077, which would provide an accuracy of 72.6%. However, from the LOOCV classifications, any value between -0.077 and -0.029 would give both sensitivity and specificity above 70%. Therefore after calculation of the midpoints, a plateau value of -0.04155 was chosen as the decision boundary in the final model. Classification values above -0.04155 are thus classified as AD, while values below -0.04155 are classified as cognitively healthy.

Diagnostic accuracy calculation and simulation model

The estimation of accuracy in the calibration and validation analyses were performed using clinical diagnosis as the 'gold standard', which has been assumed to be 100% correct. However, this assumption is overestimated, given that an accurate diagnosis in Alzheimer's disease (AD) may vary from 60% at GP clinics to over 90% at some specialized clinics [1–3]. Using the clinical diagnosis as reference will therefore underestimate the sensitivity and specificity of the test under evaluation. Therefore, a simulation model was prepared to determine the expected accuracy based on the approach proposed by Albert [4] that focuses on joint modeling of multiple tests, but also includes the test-specific estimators. From the article:

$$P(Y_{ij}, T_i) = \sum P(Y_{ij}|T_i, d_i = l)P(T_i|d_i = l)P(d_i = l) \quad (1)$$

where i is the index for subject and j the index for the test, while $P(T_i\,|d_i)$ is estimated from a previous study.



Supplementary Figure 1. Biological processes represented by the products of the genes on the array. 1) Apoptosis, 2) Biological process unclassified, 3) Carbohydrate metabolism, 4) Cell cycle, 5) Cell proliferation and differentiation, 6) Cell structure and mobility, 7) Developmental processes, 8) Electron transport, 9) Homeostasis, 10) Immunity and defense, 11) Intracellular protein traffic, 12) Lipid, fatty acid and steroid metabolism, 13) Miscellaneous, 14) Nucleoside, nucleotide and nucleic acid metabolism, 15) Oncogenesis, 16) Other metabolism, 17) Protein metabolism and modification, 18) Protein targeting and localization, 19) Sensory perception, 20) Signal transduction, 21) Transport.

In both the joint modeling and test-specific modeling, this approach simplifies when $P(\mathbf{Y}_i \,|T_i,d_i) = P(\mathbf{Y}_i \,|d_i)$. According to Albert the sensitivity and specificity for the *j*'th test can be estimated by maximizing the log-likelihood of (1) separately for each test.

In our study there is only one reference test, the clinical diagnosis. Thus for our analysis the 96-gene assay test is Y, the clinical diagnosis is T and *d* is the prevalence. If we assume that Y and T are independent, the equations can be written as:

$$P(Y_i, T_i) = \sum_{l=0}^{1} P(Y_i|d_i = l)P(T_i|d_i = l)P(d_i = l) \qquad (2)$$

From previous studies we have an estimate of $P(Y_i,T_i)$ (the overall accuracy) and have made some assumptions regarding the clinically accuracy. If we assume the sensitivity and specificity are the same in the clinical setting, then $P(T_i|d_i = l)$ will have the same value for both *l*'s in the above equation. If the assumed sensitivity and specificity are the same, the prevalence, $P(d_i = l)$, for this population will be 50%.

With an overall accuracy of 0.726, the assumed sensitivity and specificity of clinical diagnosis of 0.80 and a prevalence of 0.50, then equation (2) can be solved for $P(Y_i|d_i = 1)$ and $P(Y_i|d_i = 0)$. As these are the only functions of the equation, the maximum likelihood is calculated as normal. The sum of these must equal 1.815, giving possible combinations ranging from 0.82 to 1.0 for each of the two probabilities. However, the overall accuracy will be the same for all these combinations, 0.91.

In order to have an overview of the possible impact of an imperfect gold standard some data simulations have been performed. The following method/algorithm was used:

1. One hundred samples were set to have true AD and 100 as true healthy.
2. Each of these 200 samples was diagnosed as AD or healthy, with a probability of 80% being according to true diagnosis (simulation of the clinical diagnosis).
3. Each of the original 200 samples was diagnosed as AD or healthy, with different probabilities (from 60 to 100%) of being in agreement with the true diagnosis (simulation of the 96-gene assay or similar test).
4. The results from 3 were then evaluated using 2 as the gold standard, and the sensitivity according to clinical diagnosis was calculated.
5. Step 1–4 was repeated 100,000 times for each probability used in 3.

The results from the simulations, at an assumed clinical accuracy of 80% are shown below:

	Assumed Clinical Accuracy							
	60%	70%	75%	80%	85%	90%	95%	100%
Min	0.340	0.398	0.446	0.480	0.514	0.564	0.604	0.655
Mean	0.560	0.621	0.651	0.681	0.711	0.741	0.771	0.801
Median	0.560	0.621	0.650	0.680	0.711	0.740	0.771	0.800
Max	0.771	0.813	0.844	0.868	0.888	0.912	0.924	0.943

From this table it can be seen that the mean value and the medians are very similar, and therefore it can be concluded that the underlying distributions are symmetric. Minimum and maximum values should be interpreted in light of 100,000 simulations for each level of accuracy and are therefore expected to be either very low or very high.

Considering the mean values, a true accuracy of 85% would be expected to give an observed accuracy of 71% when compared with the clinical diagnosis, while 100% accuracy would be expected give an observed accuracy of 80%. In the calibration and validation stud-

Supplementary Table 1
Genes of known function represented by the probes included in the model. Probes present in the AlzGene list or are associated with AD, other neurological diseases, neurone or brain functions are indicated in gray shade. AD associated features are indicated with numbers; 1) Amyloid-β, 2) Tau or microtubules, 3) Mitochondrial function, 4) Oxidative stress, 5) Calcium regulation or 6) Inflammation

Gene Symbol	Gene Name	Molecular Function	AlzGene	AD	Other Neur. Dis.	Neurons/Brain	AD Assoc. Feature	References
AARS	alanyl-tRNA synthetase	Nucleic Acid Binding						
ACTB	actin, beta	Cytoskeletal Protein						
ANKRD58	ankyrin repeat domain 58	Cytoskeletal Protein					5	[5]
ATPBD1C	ATP binding domain 1 family, member C	Miscellaneous Function						
BIRC6	baculoviral IAP repeat-containing 6 (apollon)	Regulatory Molecule						
BXDC5	brix domain containing 5	Nucleic Acid Binding						
CALM3	calmodulin 3	Calcium Binding					2, 5	[6-8]
CCDC106	coiled-coil domain containing 106	Miscellaneous Function						
CIRBP	cold inducible RNA binding protein	Nucleic Acid Binding						
CNOT4	CCR4-NOT transcription complex, subunit 4	Transcription Factor						
COX6B1	cytochrome c oxidase subunit Vib polypeptide 1	Oxidoreductase					3	[9]
CRYZL1	crystallin, zeta (quinone reductase)-like 1	Oxidoreductase						[10]
CYBA	cytochrome b-245, alpha polypeptide	Oxidoreductase					4	[11]
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Oxidoreductase						
DDX23	DEAD (Asp-Glu-Ala-Asp) box polypeptide 23	Nucleic Acid Binding						
DENND2D	DENN/MADD domain containing 2D	Signaling					6	[12]
DNAJC13	DnaJ (Hsp40) homolog, subfamily C, member 13	Chaperone						
DNAJC7	DnaJ (Hsp40) homolog, subfamily C, member 7	Chaperone						

Supplementary Table 1
(*continued*)

Gene Symbol	Gene Name	Molecular Function	AlzGene	AD	Other Neur. Dis.	Neurons/Brain	AD Assoc. Feature	References
DNHD1	dynein heavy chain domain 1	Cytoskeletal Protein					2	[13]
EIF1AX	eukaryotic translation initiation factor 1A, X-linked	Not Known						
FAM103A1	family with sequence similarity 103, member A1	Not Known						
FAM38A	family with sequence similarity 38, member A	Not Known						
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	Oxidoreductase						
GFOD1	glucose-fructose oxidoreductase domain containing 1	Oxidoreductase						
GOLGA8A	golgin subfamily a, 8B	Membrane Traffic Protein						
GRB2	growth factor receptor-bound protein 2	Miscellaneous Function					1	[14-16]
GSPT1	G1 to S phase transition 1	Regulatory Molecule						
GUSB	glucuronidase, beta	Hydrolase						
GZMA	granzyme A	Protease						
HDAC1	histone deacetylase 1	Hydrolase					3	[17]
HPS4	Hermansky-Pudlak syndrome 4	Not Known						
IGFBP7	insulin-like growth factor binding protein 7	Miscellaneous Function						
IL2RB	interleukin 2 receptor, beta	Receptor						[18]
JARID1C	jumonji, AT rich interactive domain 1C	Transcription Factor						
JMJD1A	jumonji domain containing 1A	Transcription Factor					4	[19]
KIF13B	kinesin family member 13B	Cytoskeletal Protein					2	[20]

Supplementary Table 1
(*continued*)

Gene Symbol	Gene Name	Molecular Function	AlzGene	AD	Other Neur. Dis.	Neurons/Brain	AD Assoc. Feature	References
LOC552891	hypothetical protein LOC552891	Regulatory Molecule						
LXN	Latexin	Regulatory Molecule						
LYSMD3	LysM, domain containing 3	Not Known						
MAP1S	microtubule-associated protein 1S	Cytoskeletal Protein					2,3	[21]
MARCH1	membrane-associated ring finger (C3HC4) 1	Ligase						
NGDN	neuroguidin (Ngd), EIF4E binding protein	Translation Factor					2	[22]
NXF1	nuclear RNA export factor 1	Nucleic Acid Binding						[23]
PATZ1	POZ (BTB) and AT hook containing zinc finger 1	Transcription Factor						
PDE4A	phosphodiesterase 4A, cAMP-specific	Hydrolase						[24]
PEBP1	phosphatidylethanolamine binding protein 1	Regulatory Molecule					1, 4	[25-26]
PEPD	peptidase D	Protease						
PFDN5	prefoldin subunit 5	Chaperone						
PLEC1	plectin 1, intermediate filament binding protein	Cytoskeletal Protein					2, 3	[27]
PPHLN1	periphilin 1, gastric cancer antigen Ga50	Cytoskeletal Protein						
PTP4A2	protein tyrosine phosphatase type IVA, member 2	Phosphatase						
RAD17	RAD17 homolog	Nucleic Acid Binding						
RBM19	RNA binding motif protein 19	Not Known						
RBM39	RNA binding motif protein 39	Nucleic Acid Binding						

Supplementary Table 1
(*continued*)

Gene Symbol	Gene Name	Molecular Function	AlzGene	AD	Other NeurDis.	Neurons/Brain	AD Assoc. Feature	References
RNF166	ring finger protein 166	Transcription Factor						
RNF31	ring finger protein 31	Not Known						
RPSA	ribosomal protein SA	Nucleic Acid Binding						
S100A6	S100 calcium binding protein A6	Signaling					1	[28-29]
SCNM1	sodium channel modifier 1	Transcription Factor						
SCRIB	scribbled homolog	Cell Adhesion Molecule						
SELM	selenoprotein M	Not Known					1, 2	[30-31]
SFRS5	splicing factor, arginine/serine-rich 5	Transcription Factor						
SH3BGRL	SH3 domain binding glutamic acid-rich protein like	Oxidoreductase						
SH3BGRL3	SH3 domain binding glutamic acid-rich protein like 3	Oxidoreductase					6	[32]
SIDT2	SID1 transmembrane family, member 2	Not Known						
SKAP2	src kinase associated phosphoprotein 2	Signaling						[33]
SMARCA2	SWI/SNF rel.matrix assoc.actin dep.reg.of chromatin,	Transcription Factor						[34]
SSNA1	Sjogren syndrome nuclear autoantigen 1	Not Known						
SUB1	SUB1 homolog	Transcription Factor						
SYTL3	synaptotagmin-like 3	Vesicular Traffiking					5, 6	[35]
TACC1	transforming, acidic coiled-coil containing protein 1	Miscellaneous Function						
TARDBP	TAR DNA binding protein	Transcription Factor						[15, 36-38]

Supplementary Table 1
(*continued*)

Gene Symbol	Gene Name	Molecular Function	AlzGene	AD	Other NeuDis.	Neurons/Brain	AD Assoc. Feature	References
TCEB3	transcription elongation factor B (SIII), polypeptide 3	Transcription Factor						
TCF12	transcription factor 12	Transcription Factor						[15,39]
TCOF1	Treacher Collins-Franceschetti syndrome 1	Transfer/Carrier Protein						[40-41]
TMEM106B	transmembrane protein 106B	Not Known						[42]
TMEM127	transmembrane protein 127	Membrane Traffic Protein						
TNF	tumor necrosis factor, member 2	Signaling					6	[42-46]
TNKS2	tankyrase	Transferase						
TTC14	tetratricopeptide repeat domain 14	Transferase						
UBE3A	ubiquitin protein ligase E3A	Ligase						[47-48]
UBE4B	ubiquitination factor E4B	Miscellaneous Function						[49]
UBL3	ubiquitin-like 3	Miscellaneous Function						[50]
XPO5	exportin 5	Receptor						

ies an accuracy of 72.6% was observed when compared with the clinical diagnosis. According to the simulations this would correspond to accuracy slightly larger than 85%. It should also be noted that the mean values are all smaller than the assumed test accuracy, which means that the observed accuracy, when comparing with the clinical diagnosis, is most likely underestimated.

Therefore, comparing the results of the 96-gene assay test with an imperfect gold standard will most likely underestimate the accuracy. Assuming an accuracy of 80% for the clinical diagnosis compared with the truth, the above calculations and simulations suggest that the accuracy of the 96-gene assay test is in the range 85%–90% when compared with the underlying truth.

Supplementary Table 2
Patient data for calibration cohort

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
1	F	79	26	AD	AD
2	F	79	25	AD	AD
3	F	79	16	AD	AD
4	M	69	12	AD	AD
5	M	81	19	AD	AD
6	M	73	23	AD	AD
7	F	78	16	AD	AD
8	F	76	21	AD	AD
9	F	71	23	AD	AD
10	M	79	26	AD+VaD	AD
11	F	75	17	AD	AD
12	F	76	27	AD	AD
13	F	79	24	AD	AD
14	F	74	15	AD	AD
15	F	74	27	AD+VaD	AD
16	F	76	21	AD	AD
17	F	72	16	AD	AD
18	M	79	13	AD	AD
19	F	74	16	AD	AD
20	F	70	22	AD	AD
21	F	79	25	AD	AD
22	F	78	27	AD	AD
23	F	75	23	AD	AD
24	F	73	24	AD	AD
25	M	68	22	AD	AD
26	F	80	23	AD	AD
27	F	81	19	AD	AD
28	F	75	17	AD	AD
29	F	82	17	AD	AD
30	F	80	25	AD	AD
31	M	80	19	AD	AD
32	M	83	20	AD	AD
33	F	73	24	AD	AD
34	M	75	20	AD	AD
35	F	82	24	AD	AD
36	M	74	26	AD	AD
37	F	77	20	AD	AD
38	F	73	20	AD	AD
39	M	66	26	AD	AD
40	M	85	22	AD	AD
41	F	84	22	AD	AD
42	M	81	27	AD	AD
43	M	82	20	AD	AD
44	F	63	24	AD	AD
45	F	86	25	AD	AD

Supplementary Table 2
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
46	M	60	18	AD	AD
47	M	84	19	AD	AD
48	M	71	14	AD	AD
49	M	76	23	AD	AD
50	M	82	20	AD	AD
51	M	74	19	AD+VaD	AD+VaD
52	F	77	19	AD	AD
53	M	78	19	AD	AD
54	F	67	21	AD	AD
55	M	77	21	VaD	AD
56	F	77	21	AD	AD
57	F	73	17	AD	AD
58	M	78	22	AD + VaD	AD
59	F	78	20	VaD	AD
60	M	81	21	VaD	AD
61	F	86	22	AD	AD
62	F	77	15	AD	AD
63	F	71	15	AD	AD
64	F	74	15	AD	AD
65	F	71	18	AD	AD
66	F	79	21	AD	AD
67	F	75	15	AD	AD
68	M	78	24	AD	AD
69	F	79	23	AD	AD
70	M	80	17	AD	AD
71	M	76	18	AD+VaD	AD
72	F	75	23	AD	AD
73	M	78	17	AD	AD
74	F	76	20	AD	AD
75	F	73	24	AD	AD
76	F	77	17	AD	AD
77	M	75	20	AD	AD
78	F	84	21	AD	AD
79	F	76	22	AD	AD
80	F	84	18	AD+VaD	AD
81	F	75	15	AD	AD
82	F	73	21	VaD	AD
83	M	84	20	AD	AD
84	M	87	20	AD	AD
85	M	81	14	AD	AD
86	F	85	21	AD	AD
87	F	84	20	AD	AD
88	F	81	20	AD	AD
89	M	79	14	AD	AD
90	M	78	23	VaD	AD+VaD

Supplementary Table 2
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
91	F	80	24	AD	AD
92	M	78	19	AD	AD+VaD
93	M	61	20	AD	AD+VaD
94	M	80	26	AD+VaD	AD+VaD
95	F	71	26	AD	NA*
96	F	83	22	AD	NA*
97	M	72	20	AD	NA*
98	F	84	24	AD	NA*
99	M	78	22	AD	NA*
100	M	72	20	AD	NA*
101	F	80	26	AD	NA*
102	F	72	18	AD	NA*
103	F	81	18	AD	NA*
104	F	78	23	AD	NA*
105	F	67	22	AD	NA*
106	F	75	22	AD	NA*
107	M	75	22	AD	NA*
108	F	68	21	AD	NA*
109	F	74	18	AD	NA*
110	F	79	19	AD	NA*
111	F	77	20	AD	NA*
112	F	70	21	AD	NA*
113	F	80	19	AD	NA*
114	F	68	24	AD	NA*
115	F	77	26	AD	NA*
116	M	70	13	AD	NA*
117	F	71	20	AD	NA*
118	F	88	27	AD	NA*
119	F	74	23	AD	NA*
120	M	79	26	AD	NA*
121	F	84	20	AD	NA*
122	F	76	16	AD	NA*
123	F	57	15	AD	NA*
124	M	79	25	AD	NA*
125	M	81	26	AD	NA*
126	M	71	16	AD	NA*
127	M	81	29	Cognitively healthy	Cognitively healthy
128	F	69	30	Cognitively healthy	Cognitively healthy
129	F	71	30	Cognitively healthy	Cognitively healthy
130	F	72	29	Cognitively healthy	Cognitively healthy
131	F	75	29	Cognitively healthy	Cognitively healthy
132	F	78	30	Cognitively healthy	Cognitively healthy
133	F	72	30	Cognitively healthy	Cognitively healthy
134	F	74	30	Cognitively healthy	Cognitively healthy
135	F	69	30	Cognitively healthy	Cognitively healthy

Supplementary Table 2
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
136	F	66	30	Cognitively healthy	Cognitively healthy
137	F	68	29	Cognitively healthy	Cognitively healthy
138	F	77	29	Cognitively healthy	Cognitively healthy
139	F	70	30	Cognitively healthy	Cognitively healthy
140	M	73	30	Cognitively healthy	Cognitively healthy
141	F	70	30	Cognitively healthy	Cognitively healthy
142	M	76	30	Cognitively healthy	Cognitively healthy
143	F	70	30	Cognitively healthy	Cognitively healthy
144	M	76	30	Cognitively healthy	Cognitively healthy
145	M	72	29	Cognitively healthy	Cognitively healthy
146	F	72	30	Cognitively healthy	Cognitively healthy
147	F	68	30	Cognitively healthy	Cognitively healthy
148	F	77	30	Cognitively healthy	Cognitively healthy
149	F	78	28	Cognitively healthy	Cognitively healthy
150	F	65	29	Cognitively healthy	Cognitively healthy
151	F	73	30	Cognitively healthy	Cognitively healthy
152	F	69	30	Cognitively healthy	Cognitively healthy
153	F	75	29	Cognitively healthy	Cognitively healthy
154	F	67	29	Cognitively healthy	Cognitively healthy
155	F	67	30	Cognitively healthy	Cognitively healthy
156	F	66	30	Cognitively healthy	Cognitively healthy
157	F	68	30	Cognitively healthy	Cognitively healthy
158	F	68	30	Cognitively healthy	Cognitively healthy
159	M	78	30	Cognitively healthy	Cognitively healthy
160	M	66	30	Cognitively healthy	Cognitively healthy
161	F	76	30	Cognitively healthy	Cognitively healthy
162	F	67	30	Cognitively healthy	Cognitively healthy
163	M	73	30	Cognitively healthy	Cognitively healthy
164	M	79	30	Cognitively healthy	Cognitively healthy
165	F	73	30	Cognitively healthy	Cognitively healthy
166	F	74	30	Cognitively healthy	Cognitively healthy
167	M	76	30	Cognitively healthy	Cognitively healthy
168	F	73	30	Cognitively healthy	Cognitively healthy
169	M	76	30	Cognitively healthy	Cognitively healthy
170	F	73	30	Cognitively healthy	Cognitively healthy
171	F	67	29	Cognitively healthy	Cognitively healthy
172	F	68	30	Cognitively healthy	Cognitively healthy
173	F	76	29	Cognitively healthy	Cognitively healthy
174	F	84	29	Cognitively healthy	Cognitively healthy
175	F	68	30	Cognitively healthy	Cognitively healthy
176	F	68	30	Cognitively healthy	Cognitively healthy
177	F	66	30	Cognitively healthy	Cognitively healthy
178	F	70	30	Cognitively healthy	Cognitively healthy
179	M	72	30	Cognitively healthy	Cognitively healthy
180	F	73	30	Cognitively healthy	Cognitively healthy

Supplementary Table 2
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
181	F	69	30	Cognitively healthy	Cognitively healthy
182	F	69	29	Cognitively healthy	Cognitively healthy
183	M	61	30	Cognitively healthy	Cognitively healthy
184	F	71	30	Cognitively healthy	Cognitively healthy
185	M	72	30	Cognitively healthy	Cognitively healthy
186	M	67	30	Cognitively healthy	Cognitively healthy
187	F	63	30	Cognitively healthy	Cognitively healthy
188	M	65	30	Cognitively healthy	Cognitively healthy
189	F	63	30	Cognitively healthy	Cognitively healthy
190	F	71	30	Cognitively healthy	Cognitively healthy
191	M	78	30	Cognitively healthy	Cognitively healthy
192	F	69	28	Cognitively healthy	Cognitively healthy
193	F	69	30	Cognitively healthy	Cognitively healthy
194	F	76	29	Cognitively healthy	Cognitively healthy
195	F	76	30	Cognitively healthy	Cognitively healthy
196	F	59	30	Cognitively healthy	Cognitively healthy
197	M	73	29	Cognitively healthy	Cognitively healthy
198	M	78	30	Cognitively healthy	Cognitively healthy
199	F	63	30	Cognitively healthy	Cognitively healthy
200	F	78	29	Cognitively healthy	Cognitively healthy
201	F	75	29	Cognitively healthy	Cognitively healthy
202	F	68	30	Cognitively healthy	Cognitively healthy
203	F	71	29	Cognitively healthy	Cognitively healthy
204	F	81	30	Cognitively healthy	Cognitively healthy
205	F	78	29	Cognitively healthy	Cognitively healthy
206	F	72	30	Cognitively healthy	Cognitively healthy
207	F	78	30	Cognitively healthy	Cognitively healthy
208	F	66	29	Cognitively healthy	Cognitively healthy
209	F	78	30	Cognitively healthy	Cognitively healthy
210	F	68	30	Cognitively healthy	Cognitively healthy
211	F	69	29	Cognitively healthy	Cognitively healthy
212	F	77	30	Cognitively healthy	Cognitively healthy
213	F	70	29	Cognitively healthy	Cognitively healthy
214	F	72	30	Cognitively healthy	Cognitively healthy
215	F	72	30	Cognitively healthy	Cognitively healthy
216	F	73	30	Cognitively healthy	Cognitively healthy
217	M	74	29	Cognitively healthy	Cognitively healthy
218	F	70	29	Cognitively healthy	Cognitively healthy
219	F	76	29	Cognitively healthy	Cognitively healthy
220	F	78	29	Cognitively healthy	Cognitively healthy
221	M	74	30	Cognitively healthy	Cognitively healthy
222	F	69	30	Cognitively healthy	NA*
223	F	69	30	Cognitively healthy	NA*
224	M	68	30	Cognitively healthy	NA*
225	F	60	30	Cognitively healthy	NA*

Supplementary Table 2
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
226	F	68	29	Cognitively healthy	NA*
227	F	68	30	Cognitively healthy	NA*
228	F	64	30	Cognitively healthy	NA*
229	F	67	29	Cognitively healthy	NA*
230	M	77	30	Cognitively healthy	NA*
231	F	60	30	Cognitively healthy	NA*
232	F	63	30	Cognitively healthy	NA*
233	M	72	30	Cognitively healthy	NA*
234	F	70	30	Cognitively healthy	NA*
235	F	70	30	Cognitively healthy	NA*
236	M	73	30	Cognitively healthy	NA*
237	F	71	30	Cognitively healthy	NA*
238	F	71	30	Cognitively healthy	NA*
239	F	74	30	Cognitively healthy	NA*
240	M	67	30	Cognitively healthy	NA*
241	F	61	30	Cognitively healthy	Cognitively healthy
242	F	78	30	Cognitively healthy	Cognitively healthy
243	F	71	30	Cognitively healthy	Cognitively healthy
244	M	64	30	Cognitively healthy	Cognitively healthy
245	F	55	30	Cognitively healthy	Cognitively healthy
246	M	76	30	Cognitively healthy	NA*
247	M	62	30	Cognitively healthy	NA*
248	M	82	30	Cognitively healthy	Cognitively healthy
249	M	70	30	Cognitively healthy	Cognitively healthy
250	M	74	30	Cognitively healthy	Cognitively healthy
251	F	67	30	Cognitively healthy	Cognitively healthy
252	F	64	30	Cognitively healthy	Cognitively healthy

*) NA: Insufficient data for the consensus group to make a consensus read.

Supplementary Table 3
Patient data for initial validation cohort

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
1	F	72	21	AD	AD
3	F	78	19	AD+VaD	AD
4	M	77	25	AD+VaD	AD
5	F	69	22	AD	AD
6	F	66	17	AD	AD
7	M	72	24	AD	AD
8	M	76	20	AD	AD
9	M	58	21	AD	AD
10	F	64	24	AD	AD
11	M	66	26	AD	AD
12	M	61	23	AD	AD
13	F	72	22	AD	AD
14	F	78	16	AD	AD
15	F	77	26	AD	AD
16	M	73	18	AD+VaD	AD+VaD
30	M	78	23	AD+VaD	AD
31	F	68	22	AD	AD
32	F	67	21	AD	AD
33	M	67	10	AD	AD
34	F	57	21	AD	AD
35	F	78	17	AD	AD
36	M	78	24	AD	AD
38	F	75	21	AD+VaD	AD
39	F	66	14	AD	AD
40	F	76	18	AD+VaD	AD+VaD
42	F	77	19	AD	AD
43	F	62	27	MCI	AD
44	M	73	25	AD	AD
45	M	62	27	AD	AD
47	F	59	27	AD	AD
50	F	77	24	AD	AD
52	F	71	26	VaD	AD+VaD
53	F	79	27	AD+VaD	AD+VaD
54	M	70	27	AD+VaD	AD+VaD
76	M	61	30	Cognitively healthy	Cognitively healthy
77	M	73	29	Cognitively healthy	Cognitively healthy
78	M	56	30	Cognitively healthy	Cognitively healthy
79	M	68	30	Cognitively healthy	Cognitively healthy
80	M	60	30	Cognitively healthy	Cognitively healthy
81	F	61	30	Cognitively healthy	Cognitively healthy
82	F	54	30	Cognitively healthy	Cognitively healthy
83	F	51	30	Cognitively healthy	Cognitively healthy
84	M	74	28	Cognitively healthy	Cognitively healthy
85	F	67	30	Cognitively healthy	Cognitively healthy
86	F	72	30	Cognitively healthy	Cognitively healthy

Supplementary Table 3
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
88	F	78	30	Cognitively healthy	Cognitively healthy
89	F	72	29	Cognitively healthy	Cognitively healthy
90	F	62	30	Cognitively healthy	Cognitively healthy
92	F	57	30	Cognitively healthy	Cognitively healthy
94	M	74	30	Cognitively healthy	Cognitively healthy
95	F	76	30	Cognitively healthy	Cognitively healthy
97	F	78	30	Cognitively healthy	Cognitively healthy
98	M	73	30	Cognitively healthy	Cognitively healthy
99	M	69	30	Cognitively healthy	Cognitively healthy
100	F	72	30	Cognitively healthy	Cognitively healthy
101	F	71	30	Cognitively healthy	Cognitively healthy
103	F	73	30	Cognitively healthy	Cognitively healthy
107	F	73	29	Cognitively healthy	Cognitively healthy
108	F	69	30	Cognitively healthy	Cognitively healthy
109	M	73	29	Cognitively healthy	Cognitively healthy
110	F	72	30	Cognitively healthy	Cognitively healthy
111	M	76	29	Cognitively healthy	Cognitively healthy
113	F	73	29	Cognitively healthy	Cognitively healthy
114	F	67	29	Cognitively healthy	Cognitively healthy
118	F	74	29	Cognitively healthy	Cognitively healthy
120	F	73	30	Cognitively healthy	Cognitively healthy
121	M	76	30	Cognitively healthy	Cognitively healthy
122	F	76	30	Cognitively healthy	Cognitively healthy
124	M	77	29	Cognitively healthy	Cognitively healthy
127	F	71	30	Cognitively healthy	Cognitively healthy
128	F	78	29	Cognitively healthy	Cognitively healthy
129	F	77	29	Cognitively healthy	Cognitively healthy
130	F	75	30	Cognitively healthy	Cognitively healthy
133	M	74	28	Cognitively healthy	Cognitively healthy
134	M	77	30	Cognitively healthy	Cognitively healthy
135	M	74	30	Cognitively healthy	Cognitively healthy

Supplementary Table 4
Patient data for extended validation cohort

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
1	F	59	23	AD	AD
2	F	49	10	AD	AD
3	M	76	29	AD	AD
4	F	71	24	AD	AD
5	F	73	19	AD	AD
6	M	78	24	AD	AD
7	F	61	20	AD	AD
8	F	79	22	AD	AD
9	F	76	22	AD	AD
10	F	72	25	AD	AD
11	M	75	25	AD	AD
12	F	58	22	AD	AD
13	F	78	19	AD	AD
14	F	62	23	AD	AD
15	F	74	27	AD	AD
16	F	76	23	AD	AD
17	F	74	11	AD	AD
18	F	72	21	AD	AD
19	F	75	24	AD	AD
20	F	69	27	AD	AD
21	F	69	25	AD	AD
22	F	72	23	AD	AD
23	M	69	20	AD	AD
24	M	72	24	AD	AD
25	M	72	23	AD	AD
26	F	65	21	AD	AD
27	F	73	27	AD	AD
28	F	69	18	AD	AD
29	F	74	23	AD	AD
30	F	75	16	AD	AD
31	M	75	23	AD	AD
32	F	66	10	AD	AD
33	M	78	14	AD	AD
34	M	69	11	AD	AD
35	F	74	20	AD	AD
36	M	78	18	AD	AD
37	M	77	26	AD	AD
38	F	67	25	AD	AD
39	M	79	24	AD	AD
40	F	70	19	AD	AD
41	M	79	17	AD	AD
42	M	66	25	AD	AD
43	M	76	25	AD	AD
44	F	78	14	AD	AD
45	M	62	28	AD	AD

Supplementary Table 4
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
46	M	76	21	AD	AD
47	F	64	7	AD	AD
48	M	79	28	AD	AD
49	M	74	18	AD	AD
50	F	78	17	AD	AD
51	F	78	24	AD	AD
52	M	77	18	AD	AD
53	F	64	28	AD	AD
54	F	67	17	AD	AD
55	F	71	22	AD	AD
56	M	74	25	AD	AD
57	M	69	25	AD	AD
58	F	79	25	AD	AD
59	F	78	23	AD	AD
60	F	78	23	AD	AD
61	F	75	25	AD	AD
62	F	76	12	AD	AD
63	F	76	25	AD	AD
64	M	59	27	AD	AD
65	F	54	19	AD	AD
66	F	68	13	AD	AD
67	F	74	26	AD	AD
68	F	74	25	AD	AD
69	F	74	29	Cognitively healthy	Cognitively healthy
70	F	79	29	Cognitively healthy	Cognitively healthy
71	F	63	29	Cognitively healthy	Cognitively healthy
72	F	68	30	Cognitively healthy	Cognitively healthy
73	F	75	29	Cognitively healthy	Cognitively healthy
74	F	70	28	Cognitively healthy	Cognitively healthy
75	F	73	30	Cognitively healthy	Cognitively healthy
76	F	69	29	Cognitively healthy	Cognitively healthy
77	F	78	30	Cognitively healthy	Cognitively healthy
78	M	52	29	Cognitively healthy	Cognitively healthy
79	F	47	30	Cognitively healthy	Cognitively healthy
80	F	77	28	Cognitively healthy	Cognitively healthy
81	F	71	30	Cognitively healthy	Cognitively healthy
82	F	68	30	Cognitively healthy	Cognitively healthy
83	M	62	28	Cognitively healthy	Cognitively healthy
84	F	75	30	Cognitively healthy	Cognitively healthy
85	F	71	30	Cognitively healthy	Cognitively healthy
86	M	79	29	Cognitively healthy	Cognitively healthy
87	F	79	30	Cognitively healthy	Cognitively healthy
88	F	68	29	Cognitively healthy	Cognitively healthy
89	F	71	30	Cognitively healthy	Cognitively healthy
90	M	65	30	Cognitively healthy	Cognitively healthy

Supplementary Table 4
(*continued*)

	Gender	Age	MMSE score	Site's Dementia Diagnosis ICD-10	Consensus: Dementia Diagnosis ICD-10
91	F	76	30	Cognitively healthy	Cognitively healthy
92	F	54	29	Cognitively healthy	Cognitively healthy
93	F	75	30	Cognitively healthy	Cognitively healthy
94	M	58	30	Cognitively healthy	Cognitively healthy
95	F	66	30	Cognitively healthy	Cognitively healthy
96	F	69	30	Cognitively healthy	Cognitively healthy
97	F	50	29	Cognitively healthy	Cognitively healthy
98	F	69	30	Cognitively healthy	Cognitively healthy
99	F	74	30	Cognitively healthy	Cognitively healthy
100	F	73	30	Cognitively healthy	Cognitively healthy
101	F	72	29	Cognitively healthy	Cognitively healthy
102	F	67	30	Cognitively healthy	Cognitively healthy
103	F	69	30	Cognitively healthy	Cognitively healthy
104	F	79	30	Cognitively healthy	Cognitively healthy
105	F	72	30	Cognitively healthy	Cognitively healthy
106	M	64	30	Cognitively healthy	Cognitively healthy
107	M	70	28	Cognitively healthy	Cognitively healthy
108	M	74	30	Cognitively healthy	Cognitively healthy
109	F	79	29	Cognitively healthy	Cognitively healthy
110	F	61	29	Cognitively healthy	Cognitively healthy
111	M	75	29	Cognitively healthy	Cognitively healthy
112	F	68	29	Cognitively healthy	Cognitively healthy
113	M	67	30	Cognitively healthy	Cognitively healthy
114	M	78	30	Cognitively healthy	Cognitively healthy
115	F	65	28	Cognitively healthy	Cognitively healthy
116	M	79	29	Cognitively healthy	Cognitively healthy
117	F	71	30	Cognitively healthy	Cognitively healthy
118	M	53	30	Cognitively healthy	Cognitively healthy
119	F	76	30	Cognitively healthy	Cognitively healthy
120	F	73	30	Cognitively healthy	Cognitively healthy
121	M	67	30	Cognitively healthy	Cognitively healthy
122	F	53	29	Cognitively healthy	Cognitively healthy
123	F	79	30	Cognitively healthy	Cognitively healthy
124	F	77	29	Cognitively healthy	Cognitively healthy
125	F	63	30	Cognitively healthy	Cognitively healthy
126	F	76	30	Cognitively healthy	Cognitively healthy
127	F	78	29	Cognitively healthy	Cognitively healthy
128	M	71	30	Cognitively healthy	Cognitively healthy
129	M	65	29	Cognitively healthy	Cognitively healthy
130	F	43	30	Cognitively healthy	Cognitively healthy

REFERENCES

[1] Li Y, Rinne JO, Mosconi L, Pirraglia E, Rusinek H, DeSanti S, Kemppainen N, Nagren K, Kim BC, Tsui W, de Leon MJ (2008) Regional analysis of FDG and PIB-PET images in normal aging, mild cognitive impairment, and Alzheimer's disease. *Eur J Nucl Med Mol Imaging* **35**, 2169-2181.

[2] Mok W, Chow TW, Zheng L, Mack WJ, Miller C (2004) Clinicopathological concordance of dementia diagnoses by community versus tertiary care clinicians. *Am J Alzheimers Dis Other Demen* **19**, 161-165.

[3] Zekry D, Duyckaerts C, Belmin J, Geoffre C, Moulias R, Hauw JJ (2002) Alzheimer's disease and brain infarcts in the elderly. Agreement with neuropathology. *J Neurol* **249**, 1529-1534.

[4] Albert PS (2009) Estimating diagnostic accuracy of multiple binary tests with an imperfect reference standard. *Stat Med* **28**, 780-797.

[5] Yamamoto S, Wajima T, Hara Y, Nishida M, Mori Y (2007) Transient receptor potential channels in Alzheimer's disease. *Biochim Biophys Acta* **1772**, 958-967.

[6] Solomon B, Koppel R, Jossiphov J (2001) Immunostaining of calmodulin and aluminium in Alzheimer's disease-affected brains. *Brain Res Bull* **55**, 253-256.

[7] Krauthammer M, Kaufmann CA, Gilliam TC, Rzhetsky A (2004) Molecular triangulation: bridging linkage and molecular-network information for identifying candidate genes in Alzheimer's disease. *Proc Natl Acad Sci U S A* **101**, 15148-15153.

[8] O'Day DH, Myre MA (2004) Calmodulin-binding domains in Alzheimer's disease proteins: Extending the calcium hypothesis. *Biochem Biophys Res Commun* **320**, 1051-1054.

[9] Taanman JW, Schrage C, Ponne NJ, Das AT, Bolhuis PA, de Vries H, Agsteribbe E (1990) Isolation of cDNAs encoding subunit VIb of cytochrome c oxidase and steady-state levels of coxVIb mRNA in different tissues. *Gene* **93**, 285-291.

[10] Fernandez MR, Porte S, Crosas E, Barbera N, Farres J, Biosca JA, Pares X (2007) Human and yeast zeta-crystallins bind AU-rich elements in RNA. *Cell Mol Life Sci* **64**, 1419-1427.

[11] Marshall C, Mamary AJ, Verhoeven AJ, Marshall BE (1996) Pulmonary artery NADPH-oxidase is activated in hypoxic pulmonary vasoconstriction. *Am J Respir Cell Mol Biol* **15**, 633-644.

[12] Del Villar K, Miller CA (2004) Down-regulation of DENN/MADD, a TNF receptor binding protein, correlates with neuronal cell death in Alzheimer's disease brain and hippocampal neurons. *Proc Natl Acad Sci U S A* **101**, 4210-4215.

[13] Vallee RB, Seale GE, Tsai JW (2009) Emerging roles for myosin II and cytoplasmic dynein in migrating neurons and growth cones. *Trends Cell Biol* **19**, 347-355.

[14] Russo C, Venezia V, Repetto E, Nizzari M, Violani E, Carlo P, Schettini G (2005) The amyloid precursor protein and its network of interacting proteins: physiological and pathological implications. *Brain Res Brain Res Rev* **48**, 257-264.

[15] Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007) Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet* **39**, 17-23.

[16] Nizzari M, Venezia V, Repetto E, Caorsi V, Magrassi R, Gagliani MC, Carlo P, Florio T, Schettini G, Tacchetti C, Russo T, Diaspro A, Russo C (2007) Amyloid precursor protein and Presenilin1 interact with the adaptor GRB2 and modulate ERK 1,2 signaling. *J Biol Chem* **282**, 13833-13844.

[17] Kim JY, Shen S, Dietz K, He Y, Howell O, Reynolds R, Casaccia P (2010) HDAC1 nuclear export induced by pathological conditions is essential for the onset of axonal damage. *Nat Neurosci* **13**, 180-189.

[18] Bonotis K, Krikki E, Holeva V, Aggouridaki C, Costa V, Baloyannis S (2008) Systemic immune aberrations in Alzheimer's disease patients. *J Neuroimmunol* **193**, 183-187.

[19] Wellmann S, Bettkober M, Zelmer A, Seeger K, Faigle M, Eltzschig HK, Buhrer C (2008) Hypoxia upregulates the histone demethylase JMJD1A via HIF-1. *Biochem Biophys Res Commun* **372**, 892-897.

[20] Yoshimura Y, Terabayashi T, Miki H (2010) Par1b/MARK2 phosphorylates kinesin-like motor protein GAKIN/KIF13B to regulate axon formation. *Mol Cell Biol* **30**, 2206-2219.

[21] Orban-Nemeth Z, Simader H, Badurek S, Trancikova A, Propst F (2005) Microtubule-associated protein 1S, a short and ubiquitously expressed member of the microtubule-associated protein 1 family. *J Biol Chem* **280**, 2257-2265.

[22] Jung MY, Lorenz L, Richter JD (2006) Translational control by neuroguidin, a eukaryotic initiation factor 4E and CPEB binding protein. *Mol Cell Biol* **26**, 4277-4287.

[23] Saito K, Fujiwara T, Katahira J, Inoue K, Sakamoto H (2004) TAP/NXF1, the primary mRNA export receptor, specifically interacts with a neuronal RNA-binding protein HuD. *Biochem Biophys Res Commun* **321**, 291-297.

[24] Mackenzie KF, Topping EC, Bugaj-Gaweda B, Deng C, Cheung YF, Olsen AE, Stockard CR, High Mitchell L, Baillie GS, Grizzle WE, De Vivo M, Houslay MD, Wang D, Bolger GB (2008) Human PDE4A8, a novel brain-expressed PDE4 cAMP-specific phosphodiesterase that has undergone rapid evolutionary change. *Biochem J* **411**, 361-369.

[25] Chen Q, Wang S, Thompson SN, Hall ED, Guttmann RP (2006) Identification and characterization of PEBP as a calpain substrate. *J Neurochem* **99**, 1133-1141.

[26] George AJ, Holsinger RM, McLean CA, Tan SS, Scott HS, Cardamone T, Cappai R, Masters CL, Li QX (2006) Decreased phosphatidylethanolamine binding protein expression correlates with Abeta accumulation in the Tg2576 mouse model of Alzheimer's disease. *Neurobiol Aging* **27**, 614-623.

[27] Winter L, Abrahamsberg C, Wiche G (2008) Plectin isoform 1b mediates mitochondrion-intermediate filament network linkage and controls organelle shape. *J Cell Biol* **181**, 903-911.

[28] Boom A, Pochet R, Authelet M, Pradier L, Borghgraef P, van Leuven F, Heizmann CW, Brion JP (2004) Astrocytic calcium/zinc binding protein S100A6 over expression in Alzheimer's disease and in PS1/APP transgenic mice models. *Biochim Biophys Acta* **1742**, 161-168.

[29] Zimmer DB, Chaplin J, Baldwin A, Rast M (2005) S100-mediated signal transduction in the nervous system and neurological diseases. *Cell Mol Biol (Noisy-le-grand)* **51**, 201-214.

[30] Hwang DY, Cho JS, Oh JH, Shim SB, Jee SW, Lee SH, Seo SJ, Lee SK, Lee SH, Kim YK (2005) Differentially expressed genes in transgenic mice carrying human mutant presenilin-2 (N141I): sorrelation of selenoprotein M with Alzheimer's disease. *Neurochem Res* **30**, 1009-1019.

[31] Bellinger FP, He QP, Bellinger MT, Lin Y, Raman AV, White LR, Berry MJ (2008) Association of selenoprotein p with Alzheimer's pathology in human cortex. *J Alzheimers Dis* **15**, 465-472.

[32] Berleth ES, Masso-Welch PA, Kazim LA, Ip MM, Mihich E, Ehrke MJ (2001) Expression, tissue distribution, and cellular localization of the antiapoptotic TIP-B1 protein. *J Leukoc Biol* **69**, 995-1005.

[33] Takahashi T, Yamashita H, Nagano Y, Nakamura T, Ohmori H, Avraham H, Avraham S, Yasuda M, Matsumoto M (2003) Identification and characterization of a novel Pyk2/related adhesion focal tyrosine kinase-associated protein that inhibits alpha-synuclein phosphorylation. *J Biol Chem* **278**, 42225-42233.

[34] Koga M, Ishiguro H, Yazaki S, Horiuchi Y, Arai M, Niizato K, Iritani S, Itokawa M, Inada T, Iwata N, Ozaki N, Ujike H, Kunugi H, Sasaki T, Takahashi M, Watanabe Y, Someya T, Kakita A, Takahashi H, Nawa H, Muchardt C, Yaniv M, Arinami T (2009) Involvement of SMARCA2/BRM in the SWI/SNF chromatin-remodeling complex in schizophrenia. *Hum Mol Genet* **18**, 2483-2494.

[35] Gustavsson N, Han W (2009) Calcium-sensing beyond neurotransmitters: functions of synaptotagmins in neuroendocrine and endocrine secretion. *Biosci Rep* **29**, 245-259.

[36] Kabashi E, Valdmanis PN, Dion P, Spiegelman D, McConkey BJ, Vande Velde C, Bouchard JP, Lacomblez L, Pochigaeva K, Salachas F, Pradat PF, Camu W, Meininger V, Dupre N, Rouleau GA (2008) TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. *Nat Genet* **40**, 572-574.

[37] Liscic RM, Grinberg LT, Zidar J, Gitcho MA, Cairns NJ (2008) ALS and FTLD: two faces of TDP-43 proteinopathy. *Eur J Neurol* **15**, 772-780.

[38] Del Bo R, Ghezzi S, Corti S, Pandolfo M, Ranieri M, Santoro D, Ghione I, Prelle A, Orsetti V, Mancuso M, Soraru G, Briani C, Angelini C, Siciliano G, Bresolin N, Comi GP (2009) TARDBP (TDP-43) sequence analysis in patients with familial and sporadic ALS: identification of two novel mutations. *Eur J Neurol* **16**, 727-732.

[39] Uittenbogaard M, Chiaramello A (2002) Expression of the bHLH transcription factor Tcf12 (ME1) gene is linked to the expansion of precursor cell populations during neurogenesis. *Brain Res Gene Expr Patterns* **1**, 115-121.

[40] Dixon J, Jones NC, Sandell LL, Jayasinghe SM, Crane J, Rey JP, Dixon MJ, Trainor PA (2006) Tcof1/Treacle is required for neural crest cell formation and proliferation deficiencies that cause craniofacial abnormalities. *Proc Natl Acad Sci U S A* **103**, 13403-13408.

[41] Sakai D, Trainor PA (2009) Treacher Collins syndrome: unmasking the role of Tcof1/treacle. *Int J Biochem Cell Biol* **41**, 1229-1232.

[42] Wood HB (2010) TMEM106B is a susceptibility locus for Ftld. *Nat Rev Neurol* **6**, 184.

[43] Jimenez S, Baglietto-Vargas D, Caballero C, Moreno-Gonzalez I, Torres M, Sanchez-Varo R, Ruano D, Vizuete M, Gutierrez A, Vitorica J (2008) Inflammatory response in the hippocampus of PS1M146L/APP751SL mouse model of Alzheimer's disease: age-dependent switch in the microglial phenotype from alternative to classic. *J Neurosci* **28**, 11650-11661.

[44] Yang L, Lu R, Jiang L, Liu Z, Peng Y (2009) Expression and genetic analysis of tumor necrosis factor-alpha (TNF-alpha) G-308A polymorphism in sporadic Alzheimer's disease in a Southern China population. *Brain Res* **1247**, 178-181.

[45] Kassner SS, Bonaterra GA, Kaiser E, Hildebrandt W, Metz J, Schroder J, Kinscherf R (2008) Novel systemic markers for patients with Alzheimer disease? – a pilot study. *Curr Alzheimer Res* **5**, 358-366.

[46] Baranowska-Bik A, Bik W, Wolinska-Witort E, Martynska L, Chmielowska M, Barcikowska M, Baranowska B (2008) Plasma beta amyloid and cytokine profile in women with Alzheimer's disease. *Neuro Endocrinol Lett* **29**, 75-79.

[47] Vu TH, Hoffman AR (1997) Imprinting of the Angelman syndrome gene, UBE3A, is restricted to brain. *Nat Genet* **17**, 12-13.

[48] Yamasaki K, Joh K, Ohta T, Masuzaki H, Ishimaru T, Mukai T, Niikawa N, Ogawa M, Wagstaff J, Kishino T (2003) Neurons but not glial cells show reciprocal imprinting of sense and antisense transcripts of Ube3a. *Hum Mol Genet* **12**, 837-847.

[49] Wishart TM, Paterson JM, Short DM, Meredith S, Robertson KA, Sutherland C, Cousin MA, Dutia MB, Gillingwater TH (2007) Differential proteomics analysis of synaptic proteins identifies potential cellular targets and protein mediators of synaptic neuroprotection conferred by the slow Wallerian degeneration (Wlds) gene. *Mol Cell Proteomics* **6**, 1318-1330.

[50] Hochstrasser M (2009) Origin and function of ubiquitin-like proteins. *Nature* **458**, 422-429.