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Supplementary Data

The Impact of Mitochondrial and Nuclear DNA Variants on Late-Onset Alzheimer's Disease Risk

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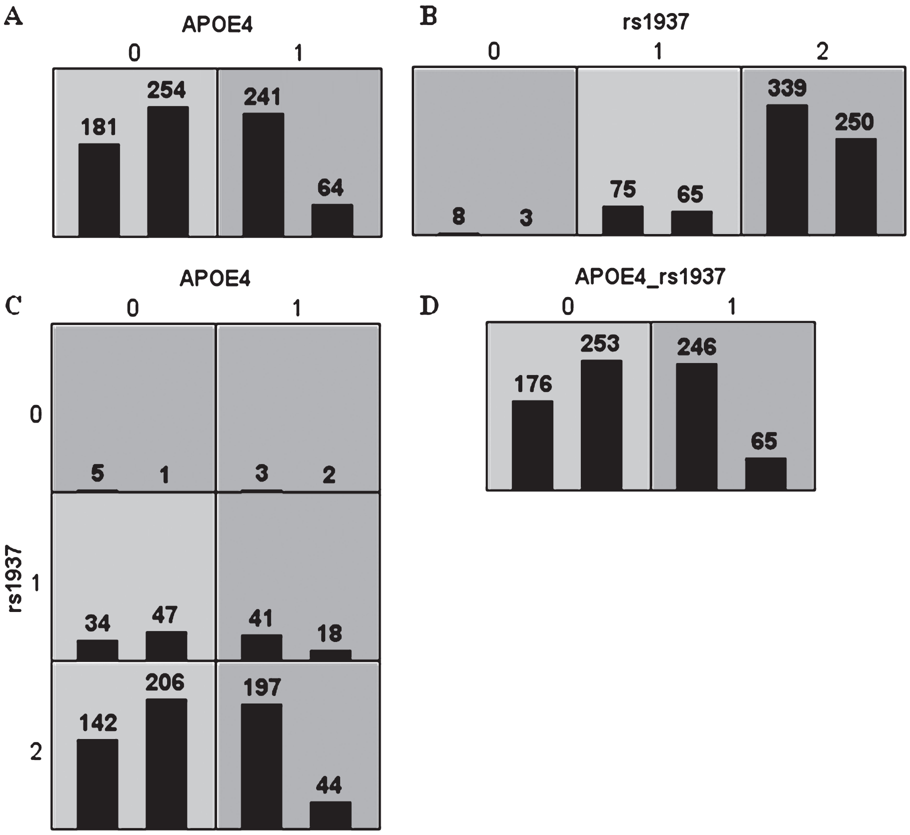

Supplementary Figure 1. Summary of the main effects (A, B) and interaction model of two-factor (*APOE4* status, rs1937) combinations (C) associated with high risk (dark box) or low risk (light box) for LOAD from MDR analysis (described in detail in Table 11). For each genotype combination, the number of cases (left bar in boxes) and control individuals (right bar in boxes) is displayed. *APOE4*+ status is indicated as 1, *APOE4*− as 0; *TFAM* rs1937 GG genotype is indicated as 2, GC as 1 and CC as 0. A) Results of MDR analysis for single locus model - *APOE4* status. *Testing Balanced Accuracy* = 0,685, CVC 10/10, *p* = 0,0014; B) Results of MDR analysis for single locus model – rs1937 (*Search type: forced*), *Testing Balanced Accuracy* = 0.513, *p* = 0.772; D) Results of MDR analysis for two-locus model – *APOE4* status × rs1937 (*Search type: forced; Testing Balanced Accuracy* = 0.689, *p* = 0.0011).

Supplementary Table 1

MtDNA polymorphisms, haplogroups and haplogroup clusters found associated with AD risk

Polymorphism/Haplogroup/ haplogroup cluster	Effect on LOAD risk	Population	LOAD/Control group (N/N)	References
m.4336T>C	↑	European Caucasians (USA)	62/125	[27]
	↑	German	28/100	[28]
	↑	mixed (USA)*	72/296	[29]
	↓	mixed (USA)*	155/105	[30]
m.11467A>G	↑	ADNI**	170/188	[25]
m.10398A>G	↑for males	European Caucasians (USA)	989/328	[31]
m.12308A>G	↓for females	European Caucasians (USA)	989/328	[31]
	↑	ADNI	170/188	[25]
m.12372G>A, m.9698C>T m.16270C>T	↑	ADNI	170/188	[25]
HV	↑	Polish	222/252	[32]
H	↑	Iranian	30/100	[33]

↑symbolizes an increase and↓a decrease in AD risk; * Mixed population means that it comprised Africans, Asians and Europeans; **ADNI - *Alzheimer's Disease Neuroimaging Initiative.*

Supplementary Table 1
(*Continued*)

Polymorphism/Haplogroup/ haplogroup cluster	Effect on LOAD risk	Population	LOAD/Control group (N/N)	References
H5	↑	citizens of Southern and Central Italy	936/776	[26]
J	↑	French Canadians	69/83	[34]
K	neutralizes *APOE4* effect	Italian	213/179	[35]
T	↓	French Canadians	69/83	[34]
U	neutralizes *APOE4* effect	Italian	213/179	[35]
	↑for males, ↓for females	European Caucasians(USA)	989/328	[31]
	↑	Iranian	30/100	[33]
	↑	ADNI	170/188	[25]

↑symbolizes an increase and↓a decrease in AD risk; * Mixed population means that it comprised Africans, Asians and Europeans; **ADNI - *Alzheimer's Disease Neuroimaging Initiative.*

Supplementary Table 2
Haplogroup H subhaplogroups with defining mtDNA coding region polymorphisms. The primers used to amplify the fragment of mtDNA sequence with particular polymorphism are also presented

Subhaplogroup of haplogroup H	mtDNA polymorphism	Primers (5’→3’)		Tm
H1	3010G>A	F	ACTCAATTGATCCAATAACTTGACC	60°C
		R	GTAGATAGAAACCGACCTGGATTAC	
H1-709	709G>A	F	GGCTCACATCACCCCATAAA	56°C
		R	GCTTGATGCTTGTTCCTTTTG	
H2	1438A>G	F	TGGCAAGAAATGGGCTACAT	60°C
		R	GTGTGTACGCGCTTCAGG	
H3	6776T>C	F	GTCACCCTGAAGTTTATATTCTTATCCTAC	60°C
		R	GTGTGTCTACGTCTATTCCTACTGTAAACA	
H4a	4024T>A	F	CCCTTCGCCCTATTCTTCAT	59°C
		R	GGGAGGTTAGAAGTAGGGTCTTG	
H4	5004T>C	F	CCATCATAGCAGGCAGTTGA	58°C
		R	AGGAATGCGGTAGTAGTTAGGA	
H5a	4336T>C	F	AGCATTCCCCCTCAAACCTA	56°C
		R	ATGGGCCCGATAGCTTATTT	
H7	4793A>G	F	CCGGACAATGAACCATAACC	56°C
		R	TGATTGAGATGGGGGCTAGT	
H9	13020T>C	F	CCCACAACAAATAGCCCTTC	56°C
		R	TGGAGTAGGGCTGAGACTGG	
H10	14470T>A	F	CCCCATGCCTCAGGATACTC	56°C
		R	TGATTGTTAGCGGTGTGGTC	
H13	14872C>T	F	CAACATCTCCGCATGATGAA	54°C
		R	ATTGATGAAAAGGCGGTTGA	
H14	7645T>C	F	ACATGCAGCGCAAGTAGGTC	59°C
		R	GGGCATACAGGACTAGGAAGC	
H16	10394C>T	F	CCCTACCATGAGCCCTACAA	56°C
		R	AATGAGGGGCATTTGGTAAA	
H12	3936C>T	F	TCATGACCCTTGGCCATAAT	56°C
H17	3915G>A	R	ATTCGGCTATGAAGAATAGGG	
H23	10211C>T	F	ACCACAACTCAACGGCTACA	56°C
		R	TTGTAGGGCTCATGGTAGGG	
H25	9620C>T	F	GCCTTTTACCACTCCAGCCTA	56°C
		R	TGGTGAGCTCAGGTGATTGA	
H26	11152>C	F	CGCCACTTATCCAGTGAACC	56°C
		R	GGAAGTATGTGCCTGCGTTC	
H33	11447G>C	F	TGACTCCCTAAAGCCCATGT	56°C
		R	TTTTGTCAGGGGGTTGAGAA	
H24	3333C>T	F	CACCCAAGAACAGGGTTTGT	56°C
H35	3342C>T	R	TCGTTCGGTAAGCATTAGGA	
H37	3531G>A	F	TCTTCACCAAAGAGCCCCTA	56°C
		R	GCCTAGGTTGAGGTTGACCA	

F, *forward*, R, *reverse,* Tm, *melting temperature*.

Supplementary Table 3
Distribution of subhaplogroups of mtDNA haplogroups in the LOAD patients and in the control group

Subhaplogroup				Whole group, *n* (%)		Females, *n* (%)		Males, *n* (%)	
				LOAD	Control group	LOAD	Control group	LOAD	Control group
HV	H	H1	H1*	29 (6.87)	17 (5.35)	18 (6.62)	14 (6.09)	11 (7.33)	3 (3.41)
			H1a	2 (0.47)	2 (0.63)	2 (0.73)	0 (0.0)	0 (0.0)	2 (2.27)
			H1a1	3 (0.71)	3 (0.71)	2 (0.73)	3 (1.30)	1 (0.67)	0 (0.0)
			H1a3	0 (0.0)	3 (0.71)	0 (0.0)	2 (0.87)	0 (0.0)	1 (1.14)
			H1b	18 (4.26)	7 (2.20)	9 (3.31)	4 (1.74)	9 (6.0)	3 (3.41)
			H1c	24 (5.69)	14 (4.40)	14 (5.15)	9 (3.91)	10 (6.67)	5 (5.68)
			H1c1	2 (0.47)	1 (0.31)	2 (0.73)	0 (0.0)	0 (0.0)	1 (1.14)
			H1f	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			H1k	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		H2	H2*	4 (0.95)	3 (0.71)	2 (0.73)	1 (0.43)	2 (1.33)	2 (2.27)
			H2a1	7 (1.66)	5 (1.57)	6 (2.21)	4 (1.74)	1 (0.67)	1 (1.14)
			H2a2b1	1 (0.24)	1 (0.31)	1 (0.37)	1 (0.43)	0 (0.0)	0 (0.0)
			H2a3	2 (0.47)	1 (0.31)	1 (0.37)	1 (0.43)	1 (0.67)	0 (0.0)
			H2a5	1 (0.24)	1 (0.31)	1 (0.37)	1 (0.43)	0 (0.0)	0 (0.0)
		H3	H3	11 (2.61)	11 (3.46)	8 (2.94)	9 (3.91)	3 (2.0)	2 (2.27)
		H4	H4a	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
			H4a1a1	1 (0.24)	1 (0.31)	1 (0.37)	0 (0.0)	0 (0.0)	1 (1.14)
			H4a1b	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		H5'36	H5*	3 (0.71)	4 (1.26)	2 (0.73)	1 (0.43)	1 (0.67)	3 (3.41)
			H5a	20 (4.74)	8 (2.52)	13 (4.78)	8 (3.48)	7 (4.67)	0 (0.0)
			H36	1 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.67)	0 (0.0)
		H6	H6	9 (2.13)	8 (2.52)	8 (2.94)	5 (2.17)	1 (0.67)	3 (3.41)
		H7	H7*	3 (0.71)	3 (0.71)	2 (0.73)	2 (0.87)	1 (0.67)	1 (1.14)
			H7a1	1 (0.24)	2 (0.63)	0 (0.0)	2 (0.87)	1 (0.67)	0 (0.0)
			H7c1	1 (0.24)	1 (0.31)	0 (0.0)	1 (0.43)	1 (0.67)	0 (0.0)
		H8		2 (0.47)	0 (0.0)	1 (0.37)	0 (0.0)	1 (0.67)	0 (0.0)
		H9	H9*	1 (0.24)	1 (0.31)	1 (0.37)	1 (0.43)	0 (0.0)	0 (0.0)
		H10	H10*	3 (0.71)	2 (0.63)	3 (1.10)	2 (0.87)	0 (0.0)	0 (0.0)
			H10a	0 (0.0)	2 (0.63)	0 (0.0)	1 (0.43)	0 (0.0)	1 (1.14)
		H11	H11*	3 (0.71)	1 (0.31)	2 (0.73)	1 (0.43)	1 (0.67)	0 (0.0)
			H11a	7 (1.66)	5 (1.57)	4 (1.47)	5 (2.17)	3 (2.0)	0 (0.0)
		H13	H13	1 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
			H13a1	2 (0.47)	2 (0.63)	1 (0.37)	0 (0.0)	0 (0.0)	2 (2.27)
			H13a2	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		H15		1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		H16		6 (1.42)	0 (0.0)	3 (1.10)	0 (0.0)	3 (2.0)	0 (0.0)
		H17		1 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.67)	0 (0.0)
		H18		2 (0.47)	3 (0.94)	1 (0.37)	2 (0.87)	1 (0.67)	1 (1.14)
		H21		1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		H24		2 (0.47)	1 (0.31)	2 (0.73)	1 (0.43)	0 (0.0)	0 (0.0)
		H27		1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		H28		1 (0.24)	1 (0.31)	1 (0.37)	0 (0.0)	0 (0.0)	1 (1.14)
		H31		1 (0.24)	1 (0.31)	1 (0.37)	1 (0.43)	0 (0.0)	0 (0.0)
		H34		0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
		H*		25 (5.92)	15 (4.72)	17 (6.25)	10 (4.35)	8 (5.33)	5 (5.68)
	HV1		HV1a1a1	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
			HV1*	2 (0.47)	1 (0.31)	1 (0.37)	0 (0.0)	1 (0.67)	1 (1.14)
	HV0		HV0*	2 (0.47)	1 (0.31)	2 (0.73)	1 (0.43)	0 (0.0)	0 (0.0)
			HV0b'c	3 (0.71)	1 (0.31)	1 (0.37)	1 (0.43)	2 (1.33)	0 (0.0)
			HV6a	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		V	V*	9 (2.13)	4 (1.26)	5 (1.84)	2 (0.87)	4 (2.67)	2 (2.27)
			V7a	4 (0.95)	4 (1.26)	2 (0.73)	4 (1.74)	2 (1.33)	0 (0.0)
IWX	I	I*		2 (0.47)	2 (0.63)	0 (0.0)	2 (0.87)	2 (1.33)	0 (0.0)
		I1	I1	1 (0.24)	2 (0.63)	1 (0.37)	2 (0.87)	0 (0.0)	0 (0.0)
			I1a	3 (0.71)	2 (0.63)	1 (0.37)	2 (0.87)	2 (1.33)	0 (0.0)
		I3		1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
		I4		1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
	W	W1	W1b	2 (0.24)	0 (0.0)	2 (0.73)	0 (0.0)	0 (0.0)	0 (0.0)
			W1e	2 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.33)	0 (0.0)
		W3	W3'5	6 (1.42)	2 (0.63)	5 (1.84)	1 (0.43)	1 (0.67)	1 (1.14)
		W5	W5a	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.31)	0 (0.0)	0 (0.0)
		W6		3 (0.71)	1 (0.31)	2 (0.73)	1 (0.43)	1 (0.67)	0 (0.0)

Supplementary Table 3
(*Continued*)

Subhaplogroup				Whole group, *n* (%)		Females, *n* (%)		Males, *n* (%)	
				LOAD	Control group	LOAD	Control group	LOAD	Control group
	X	X2	X2*	0 (0.0)	3 (0.94)	0 (0.0)	2 (0.87)	0 (0.0)	1 (1.14)
			X2b	3 (0.71)	0 (0.0)	3 (1.10)	0 (0.0)	0 (0.0)	0 (0.0)
			X2c	0 (0.0)	1 (0.31)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.14)
JT	J	J1	J1*	2 (0.47)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.33)	0 (0.0)
			J1b1a	3 (0.71)	8 (2.52)	2 (0.73)	4 (1.74)	1 (0.67)	4 (4.54)
			J1c	12 (2.84)	10 (3.14)	9 (3.31)	6 (2.61)	3 (2.0)	4 (4.54)
			J1c1	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			J1c1a	2 (0.47)	4 (1.26)	1 (0.37)	2 (0.87)	1 (0.67)	2 (2.27)
			J1c2	3 (0.71)	5 (1.57)	2 (0.73)	2 (0.87)	1 (0.67)	3 (3.41)
			J1c2c1	1 (0.24)	2 (0.63)	1 (0.37)	2 (0.87)	0 (0.0)	0 (0.0)
			J1c6	1 (0.24)	1 (0.31)	1 (0.37)	1 (0.43)	0 (0.0)	0 (0.0)
			J1c7	2 (0.47)	1 (0.31)	1 (0.37)	0 (0.0)	1 (0.67)	1 (1.14)
		J2	J2a	3 (0.71)	0 (0.0)	2 (0.73)	0 (0.0)	1 (0.67)	0 (0.0)
			J2a1	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
			J2b	2 (0.47)	1 (0.31)	0 (0.0)	1 (0.43)	2 (1.33)	0 (0.0)
			J2b1a	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
	T	T*		7 (1.66)	6 (1.89)	2 (0.73)	5 (2.17)	5 (3.33)	1 (1.14)
		T1	T1*	0 (0.0)	2 (0.63)	0 (0.0)	1 (0.43)	0 (0.0)	1 (1.14)
			T1a	7 (1.66)	8 (2.52)	2 (0.73)	7 (3.04)	5 (3.33)	1 (1.14)
		T2	T2*	2 (0.47)	5 (1.57)	1 (0.37)	4 (1.74)	1 (0.67)	1 (1.14)
			T2b	13 (3.08)	15 (4.72)	6 (2.21)	12 (5.22)	7 (4.67)	3 (3.41)
			T2b4	3 (0.71)	0 (0.0)	2 (0.73)	0 (0.0)	1 (0.67)	0 (0.0)
			T2c1b	2 (0.47)	0 (0.0)	1 (0.37)	0 (0.0)	1 (0.67)	0 (0.0)
			T2e	2 (0.47)	0 (0.0)	1 (0.37)	0 (0.0)	1 (0.67)	0 (0.0)
			T2f1	1 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.67)	0 (0.0)
KU	K	K*		1 (0.24)	2 (0.63)	1 (0.37)	2 (0.87)	0 (0.0)	0 (0.0)
		K1	K1a	2 (0.47)	6 (1.89)	2 (0.73)	3 (1.30)	0 (0.0)	3 (3.41)
			K1a1	2 (0.47)	0 (0.0)	1 (0.37)	0 (0.0)	1 (0.67)	0 (0.0)
			K1a1a	0 (0.0)	4 (1.26)	0 (0.0)	2 (0.87)	0 (0.0)	2 (2.27)
			K1a9	0 (0.0)	2 (0.63)	0 (0.0)	2 (0.87)	0 (0.0)	0 (0.0)
			K1a11	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
			K1b1a1	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
			K1c	4 (0.95)	0 (0.0)	3 (1.10)	0 (0.0)	1 (0.67)	0 (0.0)
		K2		1 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.67)	0 (0.0)
	U	U1	U1*	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			U1a1	2 (0.47)	0 (0.0)	1 (0.37)	0 (0.0)	1 (0.67)	0 (0.0)
			U1c	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
		U2	U2*	2 (0.47)	1 (0.31)	2 (0.73)	0 (0.0)	0 (0.0)	1 (1.14)
			U2e	9 (2.13)	1 (0.31)	4 (1.47)	1 (0.43)	5 (3.33)	0 (0.0)
			U2e1	3 (0.71)	1 (0.31)	3 (1.10)	1 (0.43)	1 (0.67)	0 (0.0)
		U3	U3*	5 (1.18)	0 (0.0)	3 (1.10)	0 (0.0)	2 (1.33)	0 (0.0)
			U3a	2 (0.47)	0 (0.0)	2 (0.73)	0 (0.0)	0 (0.0)	0 (0.0)
		U4	U4*	2 (0.47)	5 (1.57)	2 (0.73)	4 (1.74)	0 (0.0)	1 (1.14)
			U4a1	4 (0.95)	3 (0.94)	3 (1.10)	1 (0.43)	1 (0.67)	2 (2.27)
			U4a1c	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			U4a2	4 (0.95)	1 (0.31)	2 (0.73)	0 (0.0)	2 (1.33)	1 (1.14)
			U4a2a	3 (0.71)	3 (0.94)	1 (0.37)	3 (1.30)	2 (1.33)	0 (0.0)
			U4a2b	0 (0.0)	2 (0.63)	0 (0.0)	2 (0.87)	0 (0.0)	0 (0.0)
			U4a3	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			U4b1b	0 (0.0)	1 (0.31)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.14)
			U4c1	3 (0.71)	1 (0.31)	3 (1.10)	1 (0.43)	0 (0.0)	0 (0.0)
		U5	U5a	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			U5a1	12 (2.84)	21 (6.60)	11 (4.04)	16 (6.96)	1 (0.67)	5 (5.68)
			U5a1b1	4 (0.95)	0 (0.0)	2 (0.73)	0 (0.0)	2 (1.33)	0 (0.0)
			U5a2	2 (0.47)	4 (1.26)	1 (0.37)	3 (1.30)	1 (0.67)	1 (1.14)
			U5a2a	6 (1.42)	1 (0.31)	4 (1.47)	0 (0.0)	2 (1.33)	1 (1.14)
			U5b	3 (0.71)	0 (0.0)	3 (1.10)	0 (0.0)	0 (0.0)	0 (0.0)
			U5b1a	0 (0.0)	1 (0.31)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.14)
			U5b1b	5 (1.18)	1 (0.31)	3 (1.10)	1 (0.43)	2 (1.33)	0 (0.0)
			U5b1c	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			U5b2*	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			U5b1b1a	0 (0.0)	4 (1.26)	0 (0.0)	4 (1.74)	0 (0.0)	0 (0.0)

Supplementary Table 3
(*Continued*)

Subhaplogroup				Whole group, *n* (%)		Females, *n* (%)		Males, *n* (%)	
				LOAD	Control group	LOAD	Control group	LOAD	Control group
			U5b2a1	0 (0.0)	4 (0.94)	0 (0.0)	2 (0.87)	0 (0.0)	2 (2.27)
			U5b2a2	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
			U5b2c	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
		U7		0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
		U8	U8a1	2 (0.47)	2 (0.63)	1 (0.37)	1 (0.43)	1 (0.67)	1 (1.14)
			U8b	0 (0.0)	2 (0.63)	0 (0.0)	2 (0.87)	0 (0.0)	0 (0.0)
N	N1		N1a	1 (0.24)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.67)	0 (0.0)
			N1a1	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
			N1b	4 (0.95)	3 (0.94)	3 (1.10)	2 (0.87)	1 (0.67)	1 (1.14)
	Y		Y1b	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
	A		A8	1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
R*	R2		R2*	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
	R0		R0a	0 (0.0)	1 (0.31)	0 (0.0)	1 (0.43)	0 (0.0)	0 (0.0)
M	C	C*		1 (0.24)	0 (0.0)	1 (0.37)	0 (0.0)	0 (0.0)	0 (0.0)
	D	D4/G		1 (0.24)	1 (0.31)	1 (0.37)	1 (0.43)	0 (0.0)	0 (0.0)
	M37	M37a		1 (0.24)	1 (0.31)	1 (0.37)	1 (0.43)	0 (0.0)	0 (0.0)
L2				1 (0.24)	1 (0.31)	0 (0.0)	0 (0.0)	1 (0.67)	0 (0.0)
Unclassified				0 (0.0)	4 (1.26)	0 (0.0)	3 (1.30)	0 (0.0)	0 (0.0)

Supplementary Table 4
Odds ratios of LOAD, when the individuals that do not carry H5 subhaplogroup or APOE4 are the reference group (OR = 1)

H5 subhaplogroup	*APOE4* status	Control group, *n*	LOAD patients, *n*	OR
-	-	243	179	1
+	-	11	2	0.25
-	+	63	220	4.74
+	+	1	21	28.51

Supplementary Table 5
Odds ratios for LOAD with aggregated mitochondrial haplogroups and subhaplogroups harboring variants in *CYTB* and/or *ATP6*. Statistical analysis was performed using χ^2 test or Fisher's exact test

Aggregated mtDNA haplogroups	Whole group			Females			Males		
and subhaplogroups	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
U4 + U5a1 + K	0.58	0.38–0.89	0.013	0.70	0.42–1.15	0.161	0.38	0.17–0.88	0.024
U4 + U5a1 + K + J	0.58	0.41–0.83	0.002	0.72	0.47–1.09	0.124	0.34	0.20–0.69	0.002
U4 + U5a1 + K + J1c	0.59	0.41–0.85	0.005	0.77	0.50–1.20	0.246	0.32	0.16–0.64	0.001
U4 + U5a1 + K + J1c + J2	0.61	0.43–0.88	0.008	0.75	0.49–1.16	0.195	0.39	0.20–0.75	0.005
U4 + U5a1 + K+J1c+J2 + T	0.62	0.45–0.84	0.003	0.58	0.39–0.85	0.005	0.68	0.39–1.19	0.179
U4 + U5a1 + K + J + T	0.58	0.42–0.79	0.0006	0.56	0.38–0.82	0.003	0.62	0.36–1.07	0.087
UKJT	0.69	0.51–0.92	0.012	0.68	0.48–0.97	0.035	0.68	0.40–1.15	0.152

Supplementary Table 6
Nucleotide substitutions in the mtDNA control region of LOAD patients and the control group as compared with revised Cambridge Reference Sequence

Nucleotide position in mtDNA	Nucleotide change	Locus	LOAD patients, *n*	Control individuals, *n*
3	T>C	7S DNA	0	1
55	T>C	7S DNA	1	0
57	T>C	7S DNA, HVSII	1	0
60	T>C	7S DNA, HVSII	0	1
64	C>T	7S DNA, HVSII	3	2
72	T>C	7S DNA, HVSII	16	9
73	A>G	7S DNA, HVSII	199	119
89	T>C	7S DNA, HVSII	0	3
93	A>G	7S DNA, HVSII	14	7
95	A>C	7S DNA, HVSII	1	0

Supplementary Table 6
(*Continued*)

Nucleotide position in mtDNA	Nucleotide change	Locus	LOAD patients, *n*	Control individuals, *n*
114	C>T	7S DNA, OH, HVSII	5	1
119	T>C	7S DNA, OH, HVSII	1	0
143	G>A	7S DNA, OH, HVSII	2	1
146	T>C	7S DNA, OH, HVSII	29	17
150	C>T	7S DNA, OH, HVSII	33	29
151	C>T	7S DNA, OH, HVSII	6	4
152	T>C	7S DNA, OH, HVSII	96	56
153	A>G	7S DNA, OH, HVSII	3	3
185	G>A	7S DNA, OH, HVSII	22	23
186	C>A	7S DNA, OH, HVSII	1	2
188	A>G	7S DNA, OH, HVSII	7	7
189	A>G	7S DNA, OH, HVSII	13	6
193	A>G	7S DNA, OH, HVSII	1	0
194	C>T	7S DNA, OH, HVSII	10	5
195	T>C	7S DNA, OH, HVSII	74	66
196	T>C	7S DNA, OH, HVSII	1	0
198	C>T	7S DNA, OH, HVSII	1	2
199	T>C	7S DNA, OH, HVSII	14	8
200	A>G	7S DNA, OH, HVSII	2	4
203	G>A	7S DNA, OH, HVSII	1	1
204	T>C	7S DNA, OH, HVSII	25	12
207	G>A	OH, HVSII	17	8
210	A>G	OH, HVSII	1	0
211	A>G	OH, HVSII	1	1
214	A>G	OH, CSB1, HVSII	2	0
215	A>G	OH, CSB1, HVSII	3	3
217	T>C	OH, CSB1, HVSII	13	2
222	C>T	OH, CSB1, HVSII	1	2
225	G>A	OH, CSB1, HVSII	3	2
226	T>C	OH, CSB1, HVSII	3	1
227	A>G	OH, CSB1, HVSII	1	1
228	G>A	OH, CSB1, HVSII	18	21
235	A>G	OH, CSB1, HVSII	1	0
236	T>C	OH, HVSII	0	1
239	T>C	OH, TFX, HVSII	13	8
240	A>G	OH, TFX, HVSII	1	0
242	C>T	OH, TFX, HVSII	6	9
247	G>A	OH, TFX, HVSII	1	1
248	A>G	OH, TFX, HVSII	0	1
249	A>G	OH, TFX, HVSII	1	0
250	T>C	OH, TFX, HVSII	8	6
252	T>C	OH, TFX, HVSII	1	0
257	A>G	OH, TFX, HVSII	6	1
259	A>G	OH, TFX, HVSII	1	0
262	C>T	OH, TFX, HVSII	1	1
263	A>G	OH, TFX, HVSII	421	315
279	T>C	OH, TFY, HVSII	2	0
282	T>C	OH, TFY, HVSII	2	2
285	C>T	OH, TFY, HVSII	3	1
288	A>G	OH, TFY, HVSII	1	1
292	T>C	OH, TFY, HVSII	1	0
293	T>C	OH, TFY, HVSII	1	0
295	C>T	OH, TFY, HVSII	33	34
296	C>A	OH, TFY, HVSII	0	1
297	A>G	OH, TFY, HVSII	1	0
310	T>C	OH, TFY, HVSII	10	7
316	G>A	OH, TFY, HVSII	0	0
319	T>C	OH, TFY, HVSII	3	1
326	A>G	OH, TFY, HVSII	0	1

Supplementary Table 6
(*Continued*)

Nucleotide position in mtDNA	Nucleotide change	Locus	LOAD patients, *n*	Control individuals, *n*
338	C>T	OH, TFY, HVSII	1	0
340	C>T	OH, TFY, HVSII	8	3
373	A>G	OH, mt4H, HVSII	1	0
385	A>G	OH, mt3H, HVSII	2	0
430	T>C	OH, PL, HVSII, mtTF1 binding site	2	0
456	C>T	HVSIII	24	13
461	C>T	HVSIII	1	0
462	C>T	HVSIII	26	31
477	T>C	HVSIII	27	15
482	T>C	HVSIII	3	4
489	T>C	HVSIII	35	35
497	C>T	HVSIII	4	14
499	G>A	HVSIII	18	15
507	T>C	HVSIII	1	0
508	A>G	HVSIII	13	3
513	G>A	HVSIII	6	2
515	A>G	HVSIII	0	1
516	C>T	HVSIII	1	1
533	A>G	HVSIII, mtTF1 binding site	1	0
538	A>G	HVSIII, mtTF1 binding site	1	1
560	C>T	HVSIII, PH1	2	0
16051	A>G	HVSI	17	7
16066	A>G	HVSI	0	2
16067	C>T	HVSI	1	2
16069	C>T	HVSI	33	34
16070	A>G	HVSI	1	0
16071	C>T	HVSI	0	1
16075	T>C	HVSI	3	1
16080	A>G	HVSI	5	0
16086	T>C	HVSI	2	1
16092	T>A	HVSI	10	4
16093	T>C	HVSI	22	17
16104	C>T	HVSI	1	0
16108	C>T	7S DNA, HVSI	1	1
16111	C>G	7S DNA, HVSI	1	0
16111	C>T	7S DNA, HVSI	3	1
16113	A>C	7S DNA, HVSI	1	0
16114	C>A	7S DNA, HVSI	1	0
16114	C>G	7S DNA, HVSI	4	3
16124	T>C	7S DNA, HVSI	0	1
16126	T>C	7S DNA, HVSI	71	72
16129	G>A	7S DNA, HVSI	16	13
16129	G>C	7S DNA, HVSI	14	3
16134	C>T	7S DNA, HVSI	4	3
16136	T>C	7S DNA, HVSI	0	1
16140	T>C	7S DNA, HVSI	2	2
16144	T>C	7S DNA, HVSI	0	4
16145	G>A	7S DNA, HVSI	13	14
16146	A>G	7S DNA, HVSI	3	2
16147	C>A	7S DNA, HVSI	2	0
16147	C>T	7S DNA, HVSI	1	1
16148	C>T	7S DNA, HVSI	2	2
16153	G>A	7S DNA, HVSI	10	7
16157	T>C	7S DNA, TAS, HVSI	2	0
16160	A>G	7S DNA, TAS, HVSI	1	0
16162	A>G	7S DNA, TAS, HVSI	2	6
16163	A>G	7S DNA, TAS, HVSI	7	10
16167	C>T	7S DNA, TAS, HVSI	1	1
16168	C>T	7S DNA, TAS, HVSI	0	1
16169	C>T	7S DNA, TAS, HVSI	0	1

Supplementary Table 6
(*Continued*)

Nucleotide position in mtDNA	Nucleotide change	Locus	LOAD patients, *n*	Control individuals, *n*
16172	T>C	7S DNA, TAS, HVSI	13	14
16174	C>T	7S DNA, HVSI	2	0
16176	C>A	7S DNA, HVSI	4	3
16179	C>T	7S DNA, HVSI	4	2
16181	A>G	7S DNA, HVSI	1	0
16182	A>C	7S DNA, HVSI	3	2
16183	A>C	7S DNA, HVSI	24	14
16184	C>T	7S DNA, HVSI	1	0
16185	C>T	7S DNA, HVSI	0	2
16186	C>T	7S DNA, HVSI	7	10
16188	C>G	7S DNA, HVSI	1	1
16188	C>T	7S DNA, HVSI	2	0
16189	T>A	7S DNA, HVSI	0	1
16189	T>C	7S DNA, HVSI	67	55
16192	C>T	7S DNA, HVSI	31	29
16193	C>T	7S DNA, HVSI	4	3
16195	T>C	7S DNA, mt5, HVSI	1	0
16209	T>C	7S DNA, HVSI	8	5
16212	A>G	7S DNA, HVSI	1	0
16214	C>T	7S DNA, HVSI	1	1
16216	A>G	7S DNA, HVSI	2	2
16218	C>T	7S DNA, HVSI	0	2
16221	C>T	7S DNA, HVSI	2	0
16222	C>T	7S DNA, HVSI	5	5
16223	C>T	7S DNA, HVSI	35	22
16224	T>C	7S DNA, HVSI	11	19
16227	A>G	7S DNA, HVSI	1	0
16230	A>G	7S DNA, HVSI	1	0
16231	T>C	7S DNA, HVSI	4	1
16234	C>T	7S DNA, HVSI	5	5
16235	A>G	7S DNA, HVSI	1	1
16239	C>T	7S DNA, HVSI	2	1
16240	A>G	7S DNA, HVSI	0	1
16241	A>T	7S DNA, HVSI	0	1
16245	C>T	7S DNA, HVSI	0	1
16247	A>G	7S DNA, HVSI	1	0
16248	C>T	7S DNA, HVSI	3	1
16249	T>C	7S DNA, HVSI	3	4
16255	G>A	7S DNA, HVSI	0	2
16256	C>T	7S DNA, HVSI	31	28
16257	C>T	7S DNA, HVSI	1	1
16258	A>G	7S DNA, HVSI	1	0
16260	C>T	7S DNA, HVSI	0	3
16261	C>T	7S DNA, HVSI	12	14
16263	T>C	7S DNA, HVSI	2	1
16264	C>T	7S DNA, HVSI	1	1
16265	A>G	7S DNA, HVSI	4	3
16266	C>A	7S DNA, HVSI	1	0
16266	C>T	7S DNA, HVSI	5	1
16270	C>T	7S DNA, HVSI	34	35
16271	T>C	7S DNA, HVSI	0	1
16272	A>G	7S DNA, HVSI	2	2
16274	G>A	7S DNA, HVSI	3	4
16278	C>T	7S DNA, HVSI	14	11
16284	A>G	7S DNA, HVSI	0	1
16286	C>T	7S DNA, HVSI	1	0
16287	C>A	7S DNA, HVSI	1	0
16288	T>C	7S DNA, HVSI	2	0
16289	A>G	7S DNA, HVSI	0	1
16290	C>T	7S DNA, HVSI	1	1

Supplementary Table 6
(*Continued*)

Nucleotide position in mtDNA	Nucleotide change	Locus	LOAD patients, *n*	Control individuals, *n*
16291	C>T	7S DNA, HVSI	9	10
16292	C>T	7S DNA, HVSI	20	8
16293	A>G	7S DNA, HVSI	9	9
16294	C>T	7S DNA, HVSI	48	40
16295	C>A	7S DNA, HVSI	3	0
16296	C>T	7S DNA, HVSI	21	21
16297	T>C	7S DNA, HVSI	0	1
16298	T>C	7S DNA, HVSI	21	11
16299	A>G	7S DNA, HVSI	2	0
16300	A>G	7S DNA, HVSI	0	2
16302	A>G	7S DNA, HVSI	0	1
16304	T>C	7S DNA, HVSI	42	30
16309	A>G	7S DNA, HVSI	1	2
16310	G>A	7S DNA, HVSI	0	2
16311	T>C	7S DNA, HVSI	52	47
16316	A>G	7S DNA, HVSI	1	0
16318	A>T	7S DNA, HVSI	0	1
16319	G>A	7S DNA, HVSI	4	1
16320	C>T	7S DNA, HVSI	5	3
16324	T>C	7S DNA, HVSI	3	2
16325	T>C	7S DNA, HVSI	3	3
16327	C>T	7S DNA, HVSI	2	1
16335	A>G	7S DNA, HVSI	2	0
16342	T>C	7S DNA, HVSI	2	2
16343	A>G	7S DNA, HVSI	9	0
16344	C>T	7S DNA, HVSI	1	0
16354	C>T	7S DNA, HVSI	7	5
16355	C>T	7S DNA, HVSI	4	1
16356	T>C	7S DNA, HVSI	32	23
16357	T>C	7S DNA, HVSI	2	0
16360	C>T	7S DNA, HVSI	3	0
16362	T>C	7S DNA, HVSI	36	24
16366	C>T	7S DNA, HVSI	1	0
16368	T>C	7S DNA, HVSI	2	1
16380	C>T	7S DNA, HVSI	0	1
16390	G>A	7S DNA	10	5
16391	G>A	7S DNA	8	6
16398	G>A	7S DNA	1	1
16399	A>G	7S DNA	17	21
16400	C>T	7S DNA	1	1
16456	G>A	7S DNA	1	2
16465	C>T	7S DNA	1	2
16482	A>G	7S DNA	8	8
16483	G>A	7S DNA	1	0
16497	A>G	7S DNA	1	0
16519	T>C	7S DNA	263	206
16526	G>A	7S DNA	11	9
16527	C>T	7S DNA	1	2

HVSI-III- hypervariable segment I-III; TFX, TFY - mtTF1 binding sites; mtTF1 - mitochondrial transcription factor; OH - H-strand origin; CSB1–3 - Conserved sequence block 1–3; mt3H, mt4H, mt5H – regulatory elements on H-strand; PL – L-strand promoter; TAS – termination associated sequence; PH1 – Major H-strand promoter.

Supplementary Table 7
Distribution of deletions and insertions detected in mtDNA control region of LOAD patients and the control group

	LOAD patients, *n*	Control group, *n*
Deletions		
249D	2	1
307–309D	0	1
498D	5	0
523–524D	43	28
16257D	1	0
Insertions		
42.1G	0	1
309.1C	231	173
309.2C	58	35
309.3C	0	1
310.1T	2	1
315.1C	413	308
455.1T	3	3
523.1C 523.2A	37	33
573*n*C	18	9

Supplementary Table 8
Single nucleotide heteroplasmic substitutions detected in the mitochondrial control region of LOAD patients and in the control group

Heteroplasmic substitution	LOAD patients, *n*	Control group, *n*
m.152T/C	3	0
m.195T/C	0	0
m.204T/C	2	1
m.310C/T	1	1
m.497C/T	0	0
m.499G/A	0	1
m.16093C/T	1	0
m.16129G/A	0	0
m.16183C/A	1	0
m.16189C/T	2	0
m.16192C/T	1	1
m.16193C/T	0	1
m.16291C/T	1	0
m.16294C/T	0	1
m.16301C/T	0	1
m.16519T/C	0	0

Supplementary Table 9
Variants in the mitochondrial control region not described in MITOMAP and Human Mitochondrial Genome database

Variant Variant	LOAD patients, *n*	Control group, *n*	Haplogroup, subhaplogroup	Locus	*APOE*
m.203G>C	1	0	H2	HVSII, OH	33
m.273C>T	1	0	H6	OH, TFY, HVSII	34
m.299D	1	0	H6	CSB2, TFY, HVSII	34
m.16474G>T	1	0	K1c	–	33
m.16290C>G	1	0	A8	HVSI, 7S DNA	33
m.16213G>C	1	0	H1c	HVSI, 7S DNA	44
m.16078A>C	1	0	U3	HVSI	44
m.490.1C	0	1	J1c	HVSIII	33
m.42.1G	0	1	H11	7S DNA	33
m.16179C>G	0	1	J1c	7S DNA, HVSI	24

D- deletion; F- female, M- male; HVSI-III- hypervariable segment I-III; TFY - mtTF1 binding site, OH - H-strand origin; CSB2 - Conserved sequence block 2.

Supplementary Table 10

Odds ratios for LOAD risk associated with the variants m.217T>C, m.242C>T, m.497C>T, m.16126T>C, m.16343A>G, m.16129G>C and m.16224T>C. Statistical analysis was performed using Fisher's exact test and multivariate logistic regression controlling for *APOE4* status, AAO/age and gender

Control region polymorphism	Univariate analysis			Multivariate logistic regression		
	p	OR	95% CI	*p*	OR	95% CI
m.217T>C	0.019	5.02	1.26– 20.03	0.079	4.42	0.84–23.19
m.242C>T	0.036	0.25	0.07–0.92	0.039	0.20	0.04–0.92
m.497C>T	0.003	0.21	0.07–0.61	0.002	0.15	0.05–0.50
m.16126T>C	0.049	0.69	0.48–0.996	0.052	0.66	0.43–1.00
m.16343A>G	0.012	∞	1.80–∞	n.a.	n.a.	n.a.
m.16129G>C	0.012	4.77	1.45–15.64	0.129	2.94	0.73–11.82
m.16224T>C	0.024	0.42	0.20–0.88	0.028	0.38	0.16–0.90

Supplementary Table 11

Testing balanced accuracy and cross validation consistency for the best MDR models for the prediction of LOAD risk with one to four loci

# of loci	Model	Testing Balanced Accuracy	Cross Validation Consistency (CVC)	*p*
1	*APOE4* status	0.6849	10/10	0.0014
2	*APOE4* status × rs1937	0.6857	10/10	0.0013
3	*APOE4* status × rs1937 × rs8192678	0.6692	7/10	0.0036
4	*APOE4* status × rs1937 × rs8192678 × U5b	0.6771	10/10	0.0025

Supplementary Table 12

Multivariate logistic regression for LOAD including *APOE4* status, rs1937, subhaplogroup H5, gender, AAO/age and interactions H5 × *APOE4* status, rs1937 × *APOE4* status and rs1937 × haplogroup H5

Covariates	*p*	OR	95% CI
APOE4 status	0.020	2.37	1.15–4.88
H5 subhaplogroup	0.027	0.05	0.03–0.70
rs1937 genotype	0.133	0.67	0.40–1.13
APOE4 status × H5	0.021	26.09	1.65–412.39
rs1937 × *APOE4* status	0.017	2.75	1.19–6.32
rs1937 × H5	0.152	8.19	0.46–145.85
AAO/age	<0.001	1.15	1.12–1.19
gender	0.143	0.76	0.53–1.10