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Association between mitochondrial DNA variations and Alzheimer's Disease in the ADNI cohort

Anita Lakatos[1,*], **Olga Derbeneva**[2], **Danny Younes**[3], **David Keator**[1], **Trygve Bakken**[4], **Maria Lvova**[2], **Marty Brandon**[2], **Guia Guffanti**[1], **Dora Reglodi**[5], **Andrew Saykin**[6], **Michael Weiner**[7], **Fabio Macciardi**[2], **Nicholas Schork**[4], **Douglas C. Wallace**[2], **Steven G. Potkin**[1], and **the Alzheimer's Disease Neuroimaging Initiative**

[1]Department of Psychiatry and Human Behavior, 5251 California Avenue, Suite 240, University of California, Irvine, CA 92617 USA

[2]Center for Molecular and Mitochondrial Medicine and Genetics, University of California, 2014 Hewitt Building, Irvine, CA 92697 USA

[3]Medical School, University of California, San Francisco, San Francisco, CA 94143 USA

[4]The Scripps Translational Science Institute, Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California, USA

[5]Department of Anatomy, University of Pecs, Pecs, Hungary

[6]Center for Neuroimaging, Department of Radiology, Indiana University School of Medicine, 950 W. Walnut Street, Indianapolis IN, 46206

[7]Department of Radiology, Psychiatry and Neurology, University of California San Francisco, San Francisco, CA 94121

Abstract

Despite the central role of amyloid deposition in the development of Alzheimer's disease (AD), the pathogenesis of AD still remains elusive at the molecular level. Increasing evidence suggests that compromised mitochondrial function contributes to the aging process and thus may increase the risk of AD. Dysfunctional mitochondria contribute to reactive oxygen species (ROS) which can lead to extensive macromolecule oxidative damage and the progression of amyloid pathology. Oxidative stress and amyloid toxicity leave neurons chemically vulnerable. Because the brain relies on aerobic metabolism, it is apparent that mitochondria are critical for the cerebral function. Mitochondrial DNA sequence-changes could shift cell dynamics and facilitate neuronal vulnerability. Therefore we postulated that mitochondrial DNA sequence polymorphisms may increase the risk of AD. We evaluated the role of mitochondrial haplogroups derived from 138 mitochondrial polymorphisms in 358 Caucasian ADNI subjects. Our results indicate that the

[*]To whom correspondence should be addressed Corresponding authors: Anita Lakatos, Department of Psychiatry and Human Behavior, 5251 California Ave, suite 240, Phone: 949-824-4423, Fax: 949-824-3324, alakatos@uci.edu.

[#]**Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging** Initiative (ADNI) database (http://www.loni.ucla.edu\ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at http://www.loni.ucla.edu\ADNI\Collaboration\ADNI Manuscript Citations.pdf

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mitochondrial haplogroup UK may confer genetic susceptibility to AD independently of the APOE4 allele.

Keywords

ADNI; Alzheimer's disease; mitochondrial polymorphism; mitochondrial haplogroups

1. Introduction

Despite the remarkable effort and resources devoted to Alzheimer's disease (AD) this last decade, the pathophysiology of AD has not been well characterized. The current animal models of AD pathogenesis and the human genome-wide association studies (GWAS) have not resulted in a single common origin for the irregular but common incidences of AD, thus implying extensive heterogeneity in the underlying pathophysiology. One clear underlying pathophysiologic feature of AD has been identified and this centered on “the amyloid and tau pathology” that is believed to lead to neuronal loss, decreased synaptic density, brain atrophy, and a subsequent progressive cognitive decline associated with AD (Yankner et al., 2008). Nevertheless, recent research into AD provides compelling evidence for a variety of additional pathological events including oxidative stress and apoptosis (Mamelak, 2007).

It is has been postulated that the accumulation of reactive oxygen species (ROS) over a period time is negatively correlated with mitochondrial function and significantly contributes to the aging process (Wallace and Fan, 2009). As the primary source of ROS, mitochondria play pivotal roles in maintaining cellular energy balance and lie at the nexus of the signaling pathways controlling apoptosis. As such, it is conceivable that mitochondria may mediate the development and clinical outcome of AD. In fact, numerous research findings suggest a link between altered cerebral metabolic rate for glucose (CMR_{glc}) in subjects with mitochondrial mutations (Lindroos et al., 2009). PET imaging studies have demonstrated a detectable decline in cerebral metabolism prior to any brain atrophy or abnormality found by neuropsychiatric testing in subjects who later developed AD (Reiman et al., 2004). Postmortem studies on AD brains have revealed a reduction in the mitochondrial respiratory chain proteins in the posterior cingulate (Liang et al., 2008). The projection neurons of the cerebral cortex which tend to die first in AD, and show increased vulnerability to decreased mitochondrial efficiency (Gotz et al., 2009).

The Down-syndrome (DS) brain, with accelerated amyloid deposition and high propensity for AD, implies a possible synergy between amyloid deposition and ROS production. The structural changes that caused DS harbor APP, a precursor molecule of amyloid β as well as gene SOD1 encoding an enzyme named superoxide dismutase 1. SOD1 marks the first important step in scavenging and neutralizing ROS in cells (Engidawork and Lubec, 2001). The amyloid β, a product of APP processing, has been shown to be transported into the mitochondria through the TOMM complex (Devi et al., 2006) and inhibit the oxidative phosphorylation system (OXPHOS) in line with APOE (Crouch et al., 2005). In addition, DNA sequence variations within both the APOE and TOMM40 genes have been found to be significantly associated with AD in genome-wide association studies (Potkin et al., 2009; Roses et al., 2009; Shen et al., 2010). Mitochondria efficiency may decrease in response to amyloid toxicity and interfering proteins like APOE and Drp1 (Cho et al., 2009) that initiate a “vicious cycle” in ROS production facilitating apoptosis and leading to cell death (Reddy, 2009).

Therefore, it is plausible link AD to the functional status of mitochondria that critically relies on the mitochondrially expressed OXPHOS proteins (Fosslien, 2001). Because the

mitochondria genome differs from the nuclear genome in the rate of accumulation of mutations, it has been proposed that some common mitochondrial DNA (mtDNA) polymorphisms probably alter protein functions and compromise mitochondria efficiency (Tuppen et al., 2009). There is growing evidence that certain mtDNA clusters and polymorphisms as well as the somatically acquired mutations could predispose to psychiatric disorders (Coskun et al., 2004; Jou et al., 2009; McMahon et al., 2000; Zecavati and Spence, 2009).

To further elucidate the relation between mitochondrial DNA sequences polymorphisms and risk of AD, we calculated the association of mitochondrial haplogroups derived from 138 mitochondrial polymorphisms in 358 ADNI subjects. To the best of our knowledge this is the first report considering mitochondrial SNPs in the context of a longitudinal clinical study of AD.

2. Methods

2.1 Ethics

The ADNI data was previously collected across 50 research sites. Study subjects gave written informed consent at the time of enrollment for imaging and genetic sample collection and completed questionnaires approved by each participating sites' Institutional Review Board (IRB).

2.2 The Alzheimer's Disease Neuroimaging Initiative (ADNI)

ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations as a $60 million, 5-year public–private partnership. The primary goal of ADNI is to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians in the development of new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. ADNI participants include approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. Participants are evaluated at baseline, 6, 12, 18 (for MCI only), 24, and 36 months (although AD participants do not have a 36 month evaluation). For additional information see http://www.adni-info.org.

2.3 Identification of 138 mitochondrial SNPs

The genotyping procedure for the mtDNA and APOE variations was executed as described in (Potkin et al., 2009). Genotyping was performed on the Illumina Human610-Quad Infinium HD platform. The Illumina Human610-Quad BeadChip has of 550,000 polymorphic sites (SNP), plus an additional 60,000 genetic markers including 138 mitochondrial DNA sequence polymorphic sites. The 138 mitochondrial SNPs are based on the AF347015.1 mtDNA reference sequences, one of 53 African sequences deposited in Genbank by Ingman et al in 2001 (Ingman and Gyllensten, 2001). As the first step, the 138

mitochondrial AF347015.1 DNA SNPs were mapped to revised Cambridge Reference Sequence (rCRS) and manually annotated. The 138 SNPs consist of 21 noncoding, 91 protein coding, 4 rRNA, 11 tRNA and 1 termination sites. A subset of the 138 SNPs is shown in Table 1.

2.4 Haplotyping and haplogroup assignment

Since variation in the mtDNA genome arose as result of the sequential accumulation of mutations over time (1 mutation/10,000 years), specific combinations of these ancient mutations can cluster as haplotypes, and subsequently define haplogroups. The hierarchical relationship amongst these haplogroups based on mutations can be represented by a phylogenetic tree via available programs (http://www.phylotree.org). The nucleotide changes of the 138 mitochondrial SNPs for each subject were compared to rCRS and used to identify motifs that characterize mitochondrial haplotype (van Oven and Kayser, 2009). Assignment of each individual mtDNA “sequence” to specific haplogroups was performed according to criteria as published (Torroni et al., 1996) (e.g. haplogroup J is define by mutations at locations 11251, 16126, and no mutation at 16294). Based on each subject's available genotyping, all 816 ADNI subjects were haplotyped and assigned to a haplogroup.

2.5 Population and stratification

Population heterogeneity has been cited as one of many difficulties in studying complex diseases (Schork et al., 2001). Although race and ethnicity were available as surrogates to evaluate genetic similarity amongst individuals, race does not always correctly reflect population of origin, particularly in heterogeneous admixed groups - as expected for the ADNI dataset. In order to avoid the confounding effect due to population stratification, we assessed evidence for genetic background heterogeneity and by leveraging publicly available, well-defined populations. Briefly, Phase 2 HapMap dataset (n=270 subjects) were merged with the entire genome-wide scan of 816 ADNI subjects (http://pngu.mgh.harvard.edu/~purcell/plink/res.shtml) (Enoch et al., 2006). For all individuals in the merged dataset, a pair-wise identity-by-state (IBS) distance matrix was created by a linkage agglomerative algorithm implemented in PLINK (Purcell et al., 2007). Subsequently, Multidimensional Distance Scaling (MDS) analysis was carried out on the genome-wide IBS pair-wise-distance matrix of the merged dataset to display the structure of the distance between individuals as a geometrical picture (JMP Genomics 4.00). For the purpose of this study, the ADNI individuals that clustered with CEU founders (Utah resident with ancestry from northern and western Europe), and belonged to the diagnostic AD (n=170) or control (n=188) groups were selected for further statistical analyses. Analysis comparing nuclear DNA genetic background differences among individuals in the different mitochondrial haplogroups did not reveal any obvious associations among European sample of individuals chosen for study.

2.6 Statistical analyses

Student's t-tests were used to evaluate the differences in means between AD and control (CTRL) groups for continuous variables. Statistical significance was assesses on the basis of a 2-sided test with $\alpha=0.05$. Frequency differences for categorical outcomes in AD and CTRL groups were assessed via Chi-square (χ^2) test statistic or Fisher's exact test (Table 2). Mitochondrial haplogroups and allelic frequencies were compared between AD and CTRL using χ^2 test or Fisher's test. Effect size for the association was measured as an odds ratio (OR) with a 95% confidence interval (CI). Cochran-Mantel-Haenszel (CMH) tests were performed to adjust for APOE4 allele genotype (i.e. E4 “dose”). The homogeneity of odds ratios across strata was tested by the Breslow-Day test. Logistic regression was performed to assess the contribution of mtDNA haplogroup, APOE4 allele, and their potential interaction

effects to AD risk. Adaptive permutation tests were employed for accommodating multiple-testing.

2.6.1 Statistical Package—JMP Genomics Version 4.00. (SAS Institute Inc., Cary, NC, 1989-2007); PLINK (Purcell et al., 2007); STATA10 (StataCorp. 2007. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP).

3. Results

3.1 Demographic

All subjects were part of the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal multi-site observational study including. All the participants in this study were confined to group case (AD) or control (CTLR) defined at baseline diagnosis. Following MDS analysis (section 2.7), a total of 170 AD subjects and 188 healthy controls were included in this analysis. The two groups were compared at different variables and summarized in Table 2.

AD and cognitively normal participant (CTRL) groups do not differ in age, gender, smoking and handedness. However, AD subjects had a lower education level ($p \leq 5.4E\text{-}5$) and had a disproportionally higher APOE4 allele frequency ($p \leq 4.77E\text{-}17$) than the CTRL group. The two groups also significantly differed in ADAS-cog ($p \leq 0.00001$) and MMSE scores ($p \leq 0.00001$) reflecting the enrollment criteria for ADNI.

3.2 Association Analysis

3.2.1 Case-control differences in mitochondrial haplogroups—All subjects with Caucasian origin belonged to a major haplogroup N which was rooted approximately 70,000 years before present (YBP). Haplotype N consisted of 358 subjects who were distributed among the 9 designated haplogroups: H, I, J, K, T, U, V, W, and X. These 9 haplogroups were partitioned into 4 encompassing haplogroup clusters 1) HV, 2) JT, 3) UK, and 4) IWX based on their relation to ancestor lineage N (Finnila et al., 2001; Richards et al., 1996; Richards et al., 1998) as detailed in Figure 1.

The frequency of the haplogroups for each of the 4 clusters is demonstrated in Figure 2. The frequency distribution of the clusters is consistent with the reported worldwide mitochondrial haplogroup distribution reported at the MITOMAP database (www.mitomap.org). From the 358 ADNI participants, 86 subjects (24%) belong to haplogroup UK, 67 subjects (19%) belong to haplogroup JT, 183 (51%) to haplogroup HV, and 22 subjects (6%) to haplogroup IWX.

The chi-square (χ^2) test statistics revealed significant association between disease status and mitochondrial haplogroups ($\chi 2=7.99$, df=3, p-value$\leq$0.046). The strongest association among the 4 haplogroups involved in the UK haplogroup with a contrast between CTRL ($\chi^2=2.75$) versus AD ($\chi^2=3.05$) and associated odds ratio of (1.92, 95% CI: 1.13, 3.26; p-value < 0.013). A formal test for homogeneity confirmed that UK haplogroup appeared to have a stronger association with AD than the other haplogroups ($\chi^2=7.97$ df=3 p-value < 0.045). A score test for trend of odds supported this ($\chi^2= 4.76$, p-value < 0.03). The magnitude of association remained significant ($\chi^2=7.63$, df=3,p-value$\leq$0.0057 CI 1.12, 195) after adjusting for APOE4 allele dose.

3.2.2 Case-control differences in mitochondrial single nucleotide polymorphism—An allelic association analysis was conducted for each of the polymorphic mtDNA sites. In the analysis, all the 138 SNPs were calculated for association

regardless of haplogroup specificity or minor allele frequency. Adaptive permutation analysis for each polymorphism was performed to determine an empirical p-value. All the mtSNPs with an empirical p-value < 0.05 were considered statistically significant. The SNP DNA position, minor allele frequency in AD and CTRL, asymptotic p-value, odds ratio, confidence interval, functional consequence and haplogroup specificity are reported in Table 4.

Analysis of individual SNP revealed that risk of AD was increased in subjects who carried minor allele MitoA11467G (OR=2.22; 95% CI, 1.30 3.78; p value≤0.003). The MitoA11467G is a synonymous polymorphism located in gene NADH dehydroenase 4 (ND4). The encoded protein of this gene is a subunit of a large enzyme complex known as complex I. Complex I is responsible for the first step in the oxidative phosphorylation process by transferring electrons from NADH to ubiquinone. The second most significant SNP was MitoA12308G (OR=2.03; 95% CI, 1.23 3.34; p value≤0.006) located in a tRNA which transfers the amino acid leucine for protein synthesis. This polymorphism was found highly significant in an interaction with 10398G (empirical P value = 0.0028) suggesting some women are at increased risk to develop breast cancer (Kinoshita et al., 1996). MitoG12372A (OR=1.996; 95% CI, 1.21 3.27., p value≤0.006) located in gene NADH dehydrogenase 5 (ND5) that encodes a subunit for complex I. MitoC9698T (OR=2.265; 95% CI, 1.16 4.41; p value ≤0.003) is synonymous variant encoding Cytochrome C oxidase III (COIII) enzyme found in complex IV. Defects in mitochondrial COIII gene implicated in Leber hereditary optic neuropathy (LHON) (Brown et al., 1992; Eichhorn-Mulligan and Cestari, 2008) and age-dependent accumulation of mutations in mitochondrial DNA (mtDNA) in cytochrome *c* oxidase has been implicated in the onset of sporadic AD (Davis et al., 1997; Lin and Beal, 2006) MitoC16270T (OR=2.527; 95% CI, 1.16 4.41; p value=≤0.048) is located in the hypervariable segment assumed to represent a mutational hotspot (see summary in Table 4)

Besides age as a major risk for AD, APOE 4 is the most consistently replicated genetic risk factor for late-onset AD. Since there is a significant APOE allele frequency difference in our cohort, a subsequent analysis was performed to assess the potential for an APOE4 cofounding or interactive effect. Logistic regression revealed no evidence for an interaction effect. However, APOE revealed strong association with AD at level of OR=4.11-5.35 independently of mtSNPs.

The location and potential effect on gene function of the significant mutations in relation to mtDNA are depicted in Figure 3.

Thus, based on χ^2 tests and logistic regression analysis, the APOE4 allele, and the mitochondrial haplogroup UK, as well as specific mitochondrial polymorphisms, are significantly associated with AD in the ADNI cohort. Given the functional consequences of the significant mitochondrial polymorphisms, the possession of these polymorphisms may predispose to AD.

4. Discussion

Recent research studies have found links between mitochondrial dysfunction and common diseases of aging, such as Parkinson's (PD) and Alzheimer's disease (AD) (Wang et al., 2009; Wang et al., 2007). A growing body of evidence suggests a reasonable association between amyloid-β toxicity, mitochondrial dysfunction, oxidative stress and neuronal damage in AD pathophysiology (Mancuso et al., 2006) The impact of the dysfunctional mitochondria on the integrity of neuronal cells is not fully understood. Mitochondria are exclusively positioned to play a pivotal role in neuronal cell survival or death by controlling

energy metabolism and apoptotic pathways. Mitochondrial malfunction can alter the delicate bioenergetics balance making neuronal cells vulnerable to challenge (Wallace et al., 2010). Mitochondrial haplogroups and polymorphisms have also received substantial consideration in psychiatric and neurodegenerative diseases (Tuppen et al., 2009). Mitochondrial associations were found between AD and haplogroup J with increased susceptibility, while haplogroup T was found to have protective effect (Chagnon et al., 1999). Increased risk of AD in males with haplogroup U (van der Walt et al., 2004) as well as the mitochondrial tRNA(Glu) 4336 SNP have been reported (Brown et al., 1996; Shoffner et al., 1993). In addition, we report 5 mitochondrial SNPs, 3 of which define haplogroup UK and 2 of them specific to certain UK haplotypes in association exhibit associations with AD in the ADNI cohort.

One potential explanation for the associations is that mtDNA haplogroups correlates with genetic background that are distinctive between geographically separated populations. However, our population stratification analysis did not find significant difference between the major haplogroups and nuclear DNA-based genetic background and hence argues against a population substructure confounding effect. Another potential explanation is that the underlying mechanism for the predisposition for Alzheimer disease is related to energy deficiency. Observations on longevity, neurodegenerative disease susceptibility (van der Walt et al., 2004; Wallace et al., 1998), sperm viability (Montiel-Sosa et al., 2006), and climate adaptation propose association between functional mtDNA variations and ATP production efficiency and correlated ROS and heat generation in different haplogroups (Arning et al., 2010). The mtDNA haplogroup most prone to energy deficiency in Europe are haplogroups U and Uk (Hendrickson et al., 2008). It is conceivable that additional genetic risk factors further compromise the mitochondrial ATP production causing it to fall below the threshold level needed for optimal neuronal functioning. It is important to note that mitochondria genome expresses 37 genes and other approximately 1500-2000 nuclear genes may play critical role in optimal mitochondria function (Wallace, 2008). This interaction between the two genomes may influence brain function (Roubertoux et al., 2003) and may contribute to the complexity of AD pathophysiology.

Despite few contradictory research findings in haplogroup association to AD (Chinnery et al., 2000; Coppede et al., 2007; Elson et al., 2006), the design of ADNI provides the opportunity to follow up our findings with neuroimaging and psychometric examination in addition to a nuclear DNA–based GWAS interrogation. This comprehensive approach has the potential to provide novel insight into the underlying pathomechanisms of Alzheimer's disease and possibly open up a new prospect for novel pharmacological targets and therapeutic strategies (Wallace, 2005).

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The Principle Investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada.

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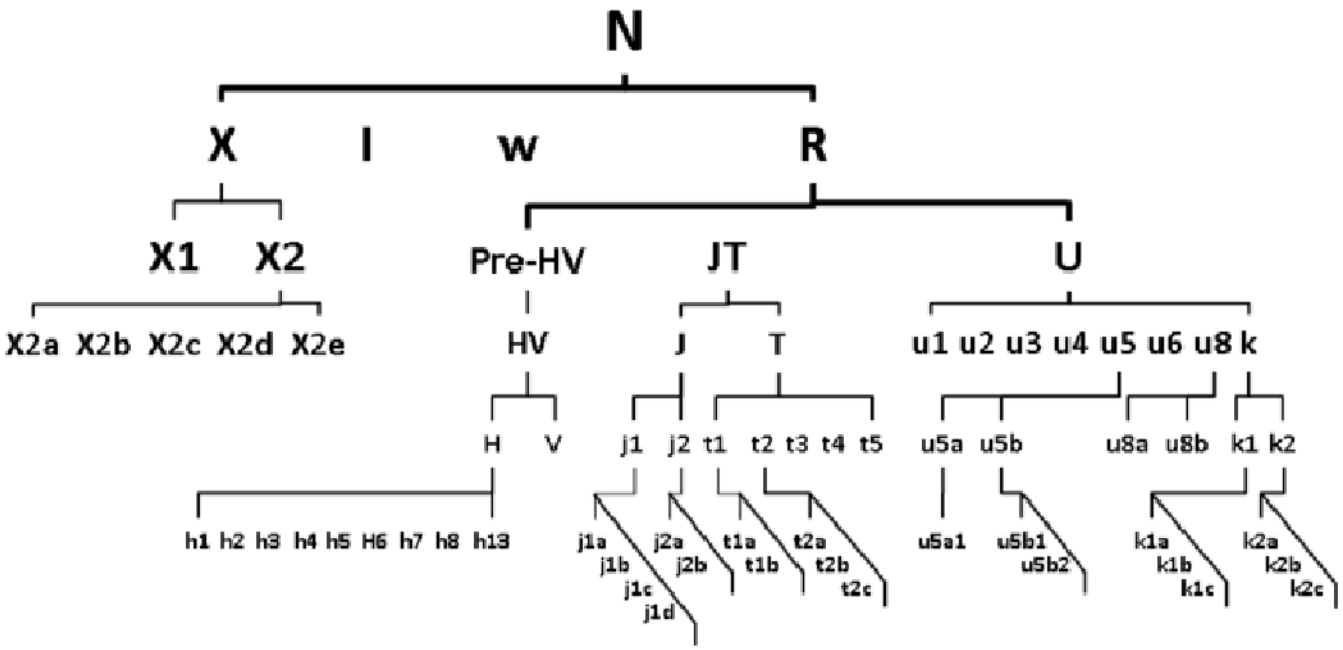

Figure 1.

Schematic phylogeny of the basal European mtDNA haplogroups.

Legend: Simplified mtDNA phylogeny tree demonstrate the Caucasian lineages exclusively originated from haplogroup N approximately 50,000-70,000 YBR. The alphabetical symbols illustrate the descendant lineages of macrograph N and indicate the phylogenic relationship amongst haplogroups as a basis of the haplogroup designation to clusters. The global mtDNA variations are available at http://www.phylotree.org.

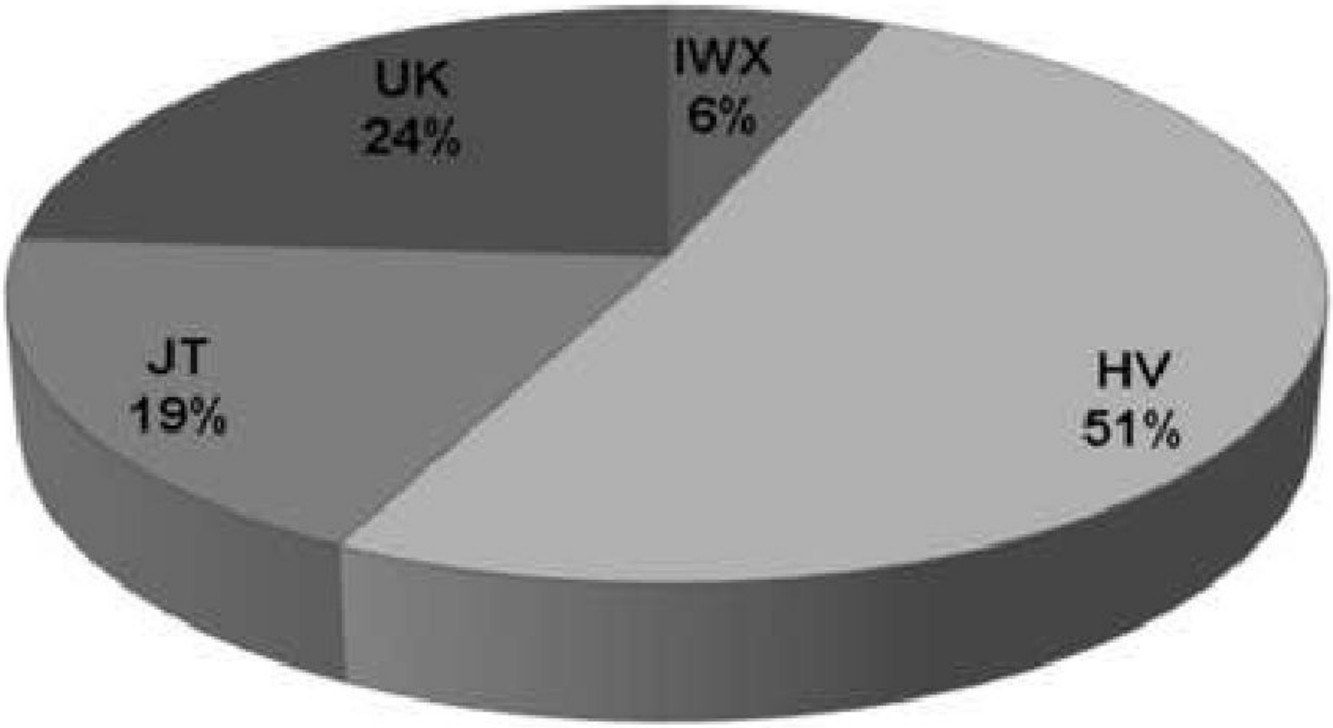

Figure 2.
Overall distribution of mtDNA haplogroups of 358 subjects in the ADNI dataset.
Legend: Labels designate the name of the haplogroup clusters and the relative frequencies of the haplogroup expressed in percentages.

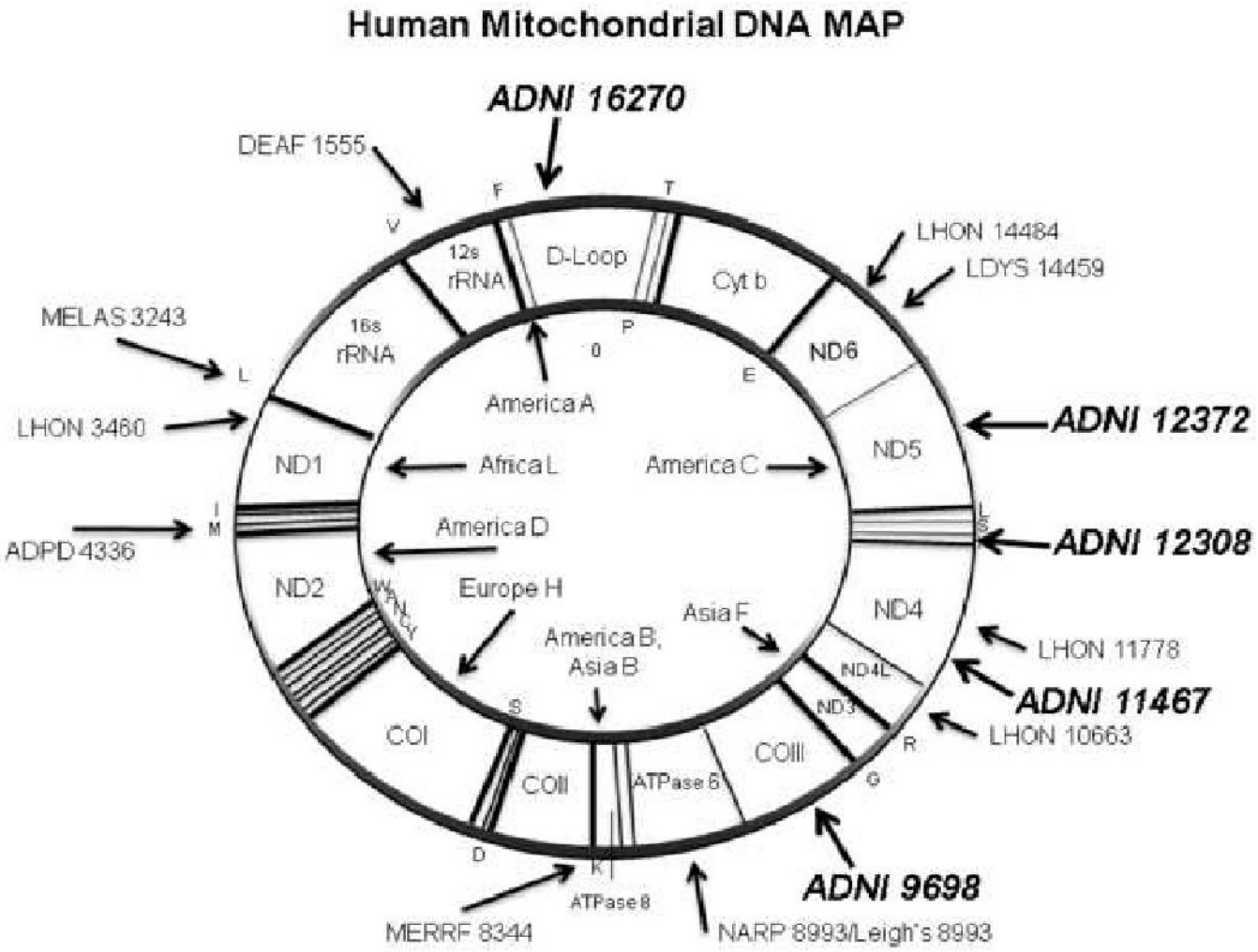

Figure 3.

Semantic illustration of the Human Mitochondrial Genome

Legend: The 5 significant mitochondrial polymorphisms in *italics* (ADNI prefix followed by SNP number) are mapped to mtDNA. The most well-know pathogenic mutations are also outlined. The abbreviations are DEAF=deafness; MELAS=mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; LHON=Leber's hereditary optic neuropathy; ADPD=Alzheimer's and Parkinson's disease; MERRF=myoclonic epilepsy and ragged red fiber disease; NARP=neurogenic muscle weakness, ataxia, retinitis pigmentosum; LDYS=LHON+dystonia modified from (Wallace, 2005).

Table 1

Annotations of a subset of 138 mtDNA polymorphic site interrogated on the Illumina Human610-Quad Infinium HD platform

AF347015.1 mtDNA SNP	Corresponding rCRS SNP	Change	Type	Function	Haplogroup
MitoT9699C	9698	T>C	synonymous	Cytochtome C oxidase III (COIII)	U8
MitoA11252G	11251	A>G	synonymous	NADH dehydrogenase 4 (ND4)	JT
MitoG12373A	12372	G>A	Synonymous	NADH dehydrogenase 5 (ND5)	UK

The table illustrates a random subset of the 138 annotated mtDNA polymorphisms. The first column represents SNPs derived from the AF347015.1 mtDNA sequence. The second column represents the corresponding rCRS mtDNA sequence position. The last four columns describe the corresponding rCRS SNP characteristics.

Table 2
Summary of demographic and clinical data of the 358 participating subjects

	CTRL	AD	Statistical Significance (p-value)
# Subjects	188	170	
Mean Age	75.93±5.01	75.79±7.57	p≥0.83
Gender (Male/Female)	98/90	101/91	p≥0.706
Smoker/non-smoker	69/101	222/135	p≥0.26
Handedness (right/left)	171/17	158/12	p≥0.5
Mean MMSE	29.11±0.93	23.40±2.07	p≤0.00001
Mean ADAS-cog	9.37±4.09	28.65±8.7	p≤0.00001
Mean years of Education	16.18± 2.81	14.9± 3.0	p≤5.4E-5
APOE (ε2/ε3/ε4)	27/297/52	8/189/143	p≤4.7755E-17

Mean ± standard deviation (SD) and the frequency of each category are represented with test statistics.

Table 3

The number of expected and observed observations in each haplogroup

Diagnostic category	Haplogroup frequency	HV	JT	IWX	UK
CTRL	Observed (%)	28.50%	3.35%	11.10%	9.50%
	Expected (%)	26.80%	3.22%	9.80%	12.61%
AD	Observed (%)	22.63%	2.80%	7.60%	14.53%
	Expected (%)	24.27%	2.91%	8.90%	11.40%

The contingency table shows the number of observed and expected subjects for each haplogroup by diagnostic categories.

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Table 4

The results of the allelic association study by significant SNPs

SNP	Position in mtDNA (bp)	Allele frequency		P-value	OR	CI		Function	Haplogroup
		AD	CTRL			L95	U95		
MitoA11467G	11467	0.28	0.14	0.003	2.22	1.3	3.78	NADH dehydroenase (ND4)	U and Uk
MitoA12308G	12308	0.3	0.17	0.006	2.03	1.23	3.34	tRNA for leucine (CUN)	U and Uk
MitoG12372A	12372	0.3	0.18	0.006	1.99	1.21	3.27	NADH dehydroenase (ND5)	U and Uk
MitoC9698T	9698	0.17	0.08	0.021	2.26	1.16	4.41	Cytochrome C oxidase (COIII)	U8 (Uk)
MitoC16270T	16270	0.09	0.03	0.048	2.52	1	6.36	non-coding region	Not specific