Experimental Gerontology 107 (2018) 148–160

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Hidden heterogeneity in Alzheimer's disease: Insights from genetic association studies and other analyses

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ARTICLE INFO

Keywords:
Neurodegeneration
Neuroinflammation
Synapse loss
Neuronal death
Pleiotropy
Cancer
Diabetes
Amyloid cascade hypothesis
Response to infection
BBB

ABSTRACT

Despite evident success in clarifying many important features of Alzheimer's disease (AD) the efficient methods of its prevention and treatment are not yet available. The reasons are likely to be the fact that AD is a multifactorial and heterogeneous health disorder with multiple alternative pathways of disease development and progression. The availability of genetic data on individuals participated in longitudinal studies of aging health and longevity, as well as on participants of cross-sectional case-control studies allow for investigating genetic and non-genetic connections with AD and to link the results of these analyses with research findings obtained in clinical, experimental, and molecular biological studies of this health disorder. The objective of this paper is to perform GWAS of AD in several study populations and investigate possible roles of detected genetic factors in developing AD hallmarks and in other health disorders. The data collected in the Framingham Heart Study (FHS), Cardiovascular Health Study (CHS), Health and Retirement Study (HRS) and Late Onset Alzheimer's Disease Family Study (LOADFS) were used in these analyses. The logistic regression and Cox's regression were used as statistical models in GWAS. The results of analyses confirmed strong associations of genetic variants from well-known genes APOE, TOMM40, PVRL2 (NECTIN2), and APOC1 with AD. Possible roles of these genes in pathological mechanisms resulting in development of hallmarks of AD are described. Many genes whose connection with AD was detected in other studies showed nominally significant associations with this health disorder in our study. The evidence on genetic connections between AD and vulnerability to infection, as well as between AD and other health disorders, such as cancer and type 2 diabetes, were investigated. The progress in uncovering hidden heterogeneity in AD would be substantially facilitated if common mechanisms involved in development of AD, its hallmarks, and AD related chronic conditions were investigated in their mutual connection.

1. Introduction

Alzheimer's disease (AD) is a progressive degeneration of the brain, inducing memory decline, learning impairment, language and behavioral disturbances, depressive symptoms, and personality changes, resulting in a marked decline in all mental activities and eventually in death. AD is most prevalent neurological health disorder in developed part of the world today. Recent estimates rank AD as the third cause of death for people older than 75 years. Despite substantial efforts to understand its causes and biological mechanisms the etiology of AD remains largely unknown. There are no medications that can notably influence rate of AD progression when it started. The multifactorial and heterogeneous nature of AD which is manifested in multiple and alternative pathways of its development and progression is likely to be responsible for this situation. This indicates that the improvement in current understanding of AD can be reached by uncovering alternative mechanisms of this health disorder.

The availability of genetic data collected for individuals participated in longitudinal studies of aging, health, and longevity opens a unique opportunity for studying genetic components of hidden heterogeneity using genome wide association studies of AD. Useful insights about the variety of biological mechanisms of AD can also be obtained from findings obtained in clinical, experimental and molecular biological studies of this health disorder. The non-genetic part of heterogeneity in AD can be evaluated from data on aging, health and longevity related traits collected in longitudinal and cross-sectional studies,

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http://dx.doi.org/10.1016/j.exger.2017.10.020
Received 31 May 2017; Received in revised form 20 October 2017; Accepted 22 October 2017
Available online 26 October 2017
0531-5565/

Medicare Service Use files and other datasets. An important feature of aging-related health decline observed in longitudinal data is the dependence among chronic conditions detected in epidemiological studies. For example, AD negatively correlates with cancer. Such connections are likely to be caused by common genetic and non-genetic factors as well as by an increase in susceptibility to these disorders with increasing age.

Most of the information and ideas about potential mechanisms connecting the AD with its various biomarkers and risk factors comes from experimental studies of transgenic animal models and from studies of cell cultures, so it is often difficult to directly translate to humans. Still, such studies generated valuable hypotheses that can be further tested using human data, which may substantially improve current understanding of the mechanisms of AD. The availability of rich genetic, behavioral, environmental and other information collected in longitudinal human studies of aging, health and longevity over recent decades opens a unique opportunity for integrating the knowledge from animal and human studies for better understanding of AD. Particularly useful insights about biological pathways involved in AD can be obtained from integration of the results of genome-wide association studies (GWAS) of AD with research findings from clinical, experimental, epidemiological and population studies of AD and the aging-associated physiological and health decline.

In this paper we present the results of GWAS of AD using data from three longitudinal (CHS, FHS, HRS) and one case-control (LOADFS) human studies. Then we discuss how genes detected in our analyses are involved in mechanisms linking this health disorder with its hallmarks. We emphasize possible involvement of these genes in common biological processes related to health disorders other than AD, such as infectious diseases, cancer, and type 2 diabetes (T2D) - to better understand how exactly the detected genes may contribute to the development of AD, and whether the impact of these genes on AD is a part of their broader pleiotropic influence on organism's vulnerability and resistance to stresses.

2. Data and methods

We used data from the Framingham Heart Study (FHS), Cardiovascular Health Study (CHS), Health and Retirement Study (HRS), and Late Onset Alzheimer Disease Family Study (LOADFS) (Lee et al., 2008), to identify genetic variants associated with AD in genome-wide association study (GWAS). Tables 1.1 and 1.2 provide brief description of these datasets.

More information about the FHS, CHS, HRS, and LOADFS data are given in (Dawber, 1980; Mahmood et al., 2014; D'Agostino et al., 1989; Tucker-Seeley et al., 2011; Lee et al., 2008), respectively. See also dbGaP (https://www.ncbi.nlm.nih.gov/gap).

In the logistic regression model, 'cases' corresponded to study participants with AD, and 'controls' corresponded to study subjects without AD. The Cox regression model was applied to the data where the information on the age at disease onset was available. To take family links in LOADFS into account in the logistic regression model, we used the GLIMMIX program in SAS. The year of birth, gender and race (when available) were used as observed covariates in the analyses.

Table 1.2
The sample sizes in three datasets (by race) before and after quality control (QC) procedure.

By race								
Dataset	Before QC				After QC			
	#White	#Black	#Others		#White	#Black	#Others	
CHS	4434	807	29		4209	781	28	
HRS	7968	1299	374		7960	1297	374	
LOADFS	3894	251	271	145*	3894	251	271	145*

* LOADFS has 145 individuals with missing race values.

To control for possible population stratification we calculated 20 principal components and used them as observed covariate (Price et al., 2006). In the HRS data, the genomic control was used to control for possible population stratification, and to avoid the inflation of association test statistics for both the logistic and Cox regressions (Price et al., 2006).

FHS and CHS CARe data used in this analyses were genotyped on the Illumina IBC chip including ~49 K SNPs in ~2000 candidate genes (for major complex diseases). HRS data were genotyped on the Illumina platform with ~2.5mln SNPs, and LOADFS data – on the Illumina platform with ~600 K SNPs. The quality control (QC) has been performed before running GWAS analyses. Individuals with > 5% missing SNPs we excluded. SNPs are kept only if the genotyping rate is higher than 95% and minor allele frequency (MAF) was higher than 1%. In addition, SNPs failed the Hardy-Weinberg test (p-value < 10^{-7}) were also excluded.

3. Results

3.1. Genetics of AD: results from GWAS of FHS, CHS, HRS, and LOADFS data

Fig. 1 shows the QQ plot and Manhattan plot of the results of GWAS of AD using logistic regression applied to CHS, FHS, HRS, and LOADFS data.

One can see from this figure that in all four analyses the genome wide significant SNPs are located on chromosome 19. Fig. 2 shows the QQ plots and Manhattan plots of the results of GWAS of AD using Cox regression for CHS, FHS and HRS datasets. One can see from Figs. 1 and 2 that in all analyses, SNPs located on chromosome 19 show highly significant associations with AD. Note that CHS and FHS have overall smaller numbers of SNPs with highly significant associations. This is because the genotyping platforms in these datasets contain smaller number of SNPs than those for HRS and LOADFS data (see Data and methods). Tables 2.1 and 2.2 summarize results of these analyses for logistic and Cox regression statistical models, respectively. These tables show that the SNPs on chromosome 19 that demonstrated highly significant associations with AD in more than one dataset (these SNPs are

Table 1.1
The sample sizes (by gender) and the number of SNPs in four datasets before and after quality control (QC) procedure.

By gender								
Dataset	Before QC				After QC			
	#Samples	#Males	#Females	#SNPs	#Samples	#Males	#Females	#SNPs
CHS	5270	2252	3018	49,094	5018	2137	2881	33,328
FHS	3788	1651	2317	49,094	3651	1592	2059	35,259
HRS	9641	4120	5521	2,315,518	9631	4118	5513	1,329,158
LOADFS	4561	1666	2895	590,247	4561	1666	2895	551,330

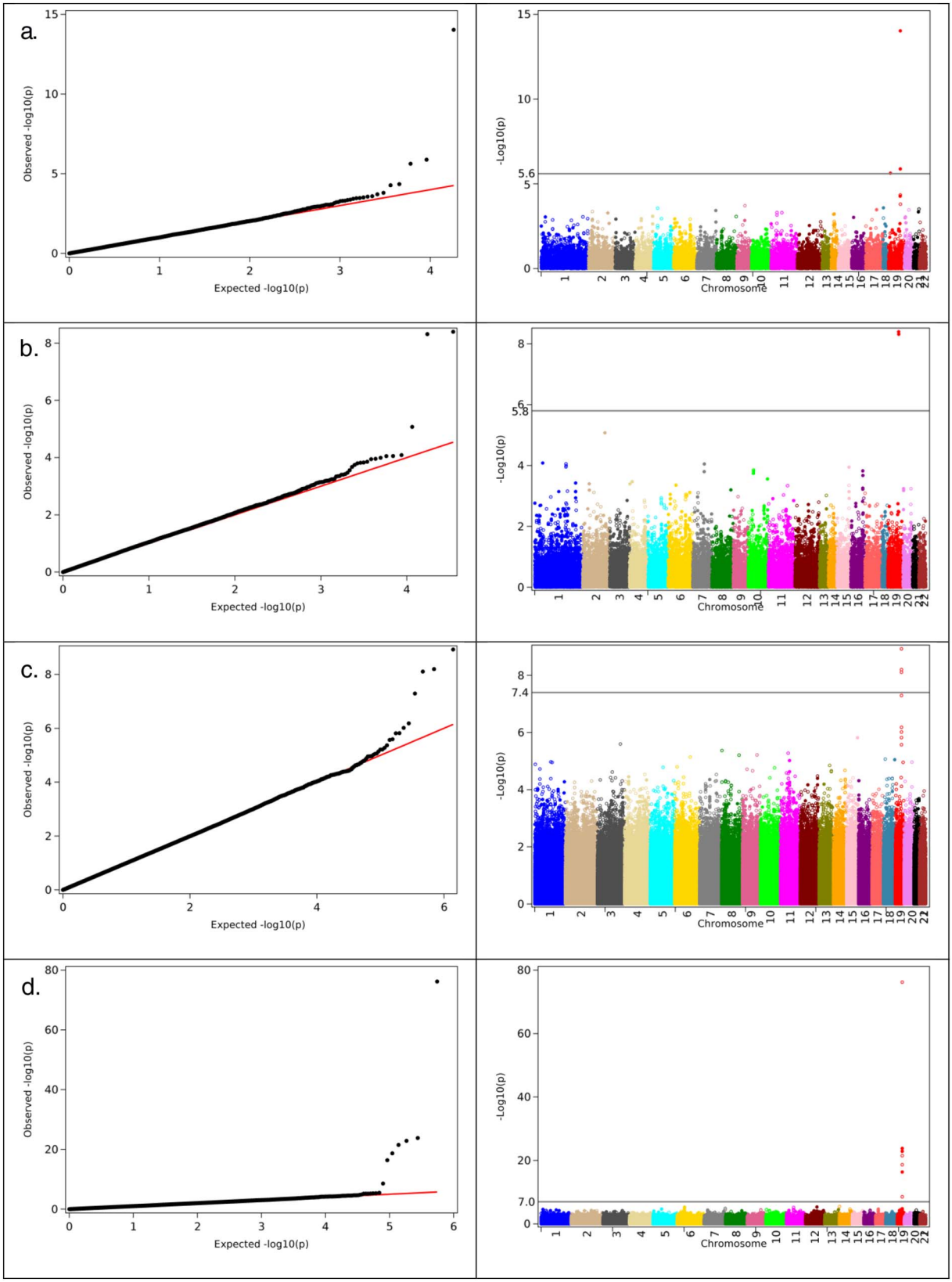

Fig. 1. Left panel. The QQ-plots of the results of GWAS of Alzheimer's disease obtained in the analyses using logistic regression (GLIMMIX in LOADFS) for male and females combined. a). CHS (case: 286; control: 4732); b). FHS (case: 308; control: 3343); c. HRS (case: 656; control: 8768); d). LOADFS (case: 2319; control: 2242). Right panel. Corresponding Manhattan plots for the same analysis as shown on the left panel.

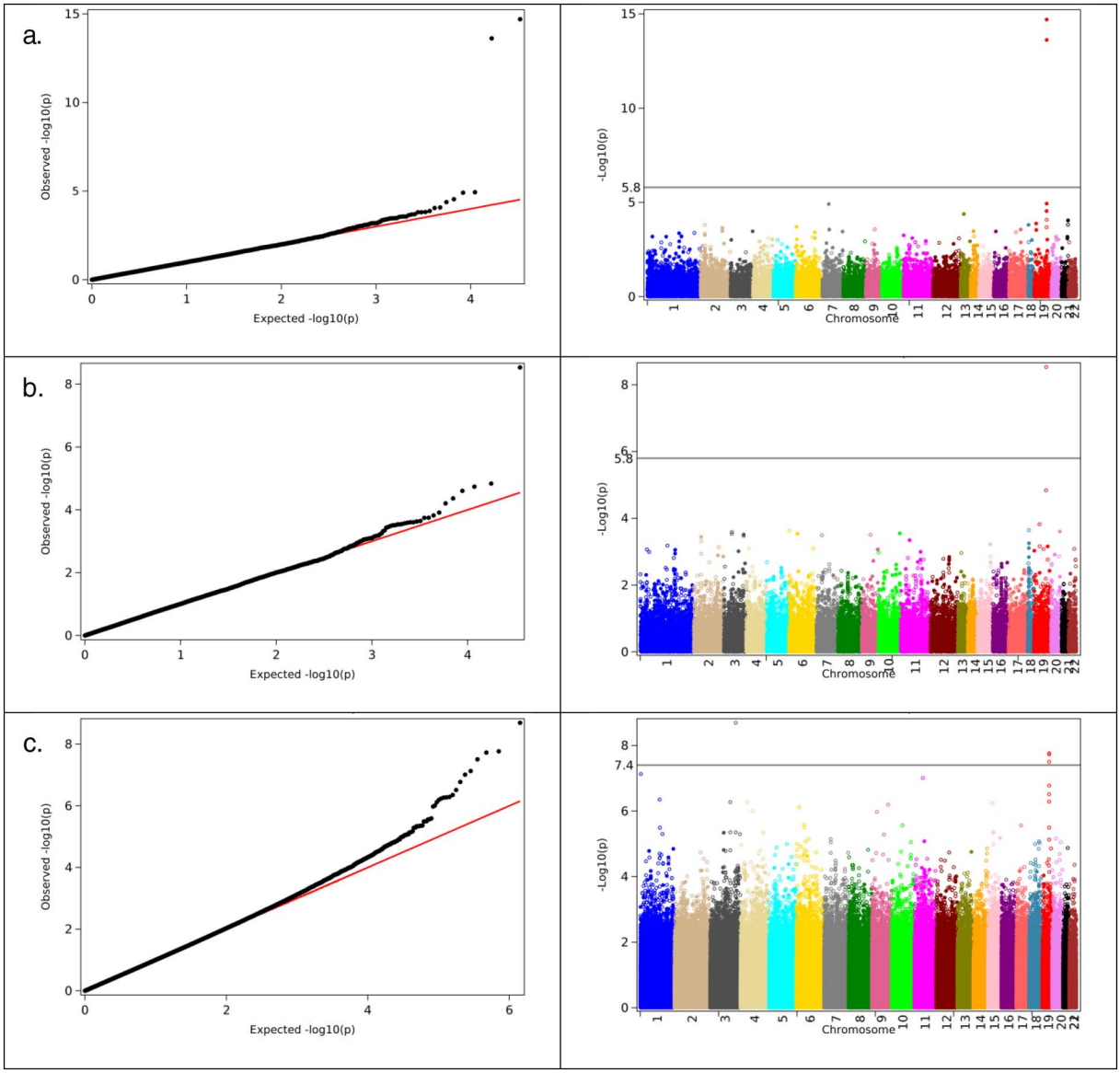

Fig. 2. Left panel. The QQ-plots of the results of GWAS of Alzheimer's disease obtained in the analyses using Cox regression. a). CHS; b). FHS; c). HRS. Right panel. Corresponding Manhattan plots for the same analysis on the left panel.

Table 2.1
SNPs from the TOMM40, APOC1, APOE and PVRL2 (NECTIN2) genes that showed most significant associations in GWAS of Alzheimer's disease in CHS, FHS, HRS and LOADFS, using logistic regression (GLIMMIX in LOADFS).

Dataset	SNP	p-Value	OR	Chr	Minor	Major	MAF case	MAF contr	Gene	Location
CHS	**rs2075650**	9.32E − 15	2.3	19	G	A	0.22	0.12	**TOMM40**	Intron (LD with **rs429358, rs769449** in APOE)
	rs405509	1.31E − 06	1.5	19	T	G	0.53	0.43	**APOE**	Upstream, promoter
	rs8106922	4.54E − 05	0.7	19	G	A	0.3	0.39	**TOMM40**	Intron
	rs6859	5.34E − 05	1.4	19	A	G	0.49	0.4	**PVRL2**	3′-UTR
	rs769450	1.59E − 04	0.7	19	A	G	0.33	0.41	**APOE**	Intron
FHS	**rs2075650**	4.02E − 09	2.3	19	G	A	0.17	0.12	**TOMM40**	Intron (LD with **rs429358, rs769449** in APOE)
	rs12721046	4.87E − 09	2.2	19	A	G	0.18	0.12	**APOC1**	Intron (LD with **rs769449** and **rs429358** in APOE)
HRS	**rs769449**	3.00E − 12	1.9	19	A	G	0.15	0.09	**APOE**	Intron (strong LD with **rs429358** in APOE; moderate LD with **rs12721046** in APOC1, **rs2075650** in TOMM40)
	rs157582	3.32E − 09	1.5	19	T	C	0.31	0.24	**TOMM40**	Intron
	rs283815	1.41E − 08	1.5	19	G	A	0.31	0.25	**PVRL2**	3′-UTR
	rs71352238	7.54E − 08	1.6	19	C	T	0.17	0.12	**TOMM40**	Intron
	rs2075650	1.65E − 07	1.5	19	G	A	0.18	0.13	**TOMM40**	Intron (LD with **rs429358, rs769449** in APOE)

(*continued on next page*)

Table 2.1 (*continued*)

Dataset	SNP	p-Value	OR	Chr	Minor	Major	MAF case	MAF contr	Gene	Location
LOADFS	**rs2075650**	2.86E − 64	3.6	19	G	A	0.34	0.18	**TOMM40**	Intron (LD with **rs429358** in APOE)
	rs8106922	1.14E − 23	0.5	19	G	A	0.26	0.37	**TOMM40**	Intron
	rs157580	1.50E − 23	0.5	19	G	A	0.23	0.33	**TOMM40**	Intron (LD with **rs405509, rs769449** near APOE)
	rs405509	1.50E − 20	1.7	19	T	G	0.59	0.49	**APOE**	Upstream, promoter
	rs6859	1.12E − 18	1.7	19	A	G	0.52	0.42	**PVRL2**	3′-UTR
	rs439401	5.17E − 17	0.6	19	T	C	0.26	0.33	**APOE**, **APOC1**	Between genes

The columns notations: dataset name, SNP name, p-value in logistic regression (GLIMMIX for LOADFS), Odds Ratio (OR) for logistic regression, chromosome (Chr), reference allele (Ref), alternative allele (Alt), minor allele frequencies (MAF) in the case and in control groups, gene's name and location with LD information. (The ORs for LOADFS are from GLIMMIX regression.)

Table 2.2
SNPs from the TOMM40, APOC1, APOE and PVRL2 (NECTIN2) genes that showed most significant associations in GWAS of AD in CHS, FHS and HRS using Cox regression.

Dataset	SNP	p-Value	HR	Chr	Ref	Alt	MAF	Gene	Location
CHS	**rs2075650**	1.99E − 15	2.3	19	A	G	0.12	TOMM40	Intron (LD with **rs429358**, **rs769449** in APOE)
	rs12721046	2.39E − 14	2.2	19	G	A	0.08	APOC1	Intron (LD with **rs769449** and **rs429358** in APOE)
	rs405509	1.16E − 05	1.4	19	T	G	0.47	APOE	Upstream, promoter
	rs6859	2.87E − 05	1.4	19	A	G	0.37	PVRL2	3′-UTR
	rs8106922	8.34E − 05	0.7	19	A	G	0.30	TOMM40	Intron
FHS	**rs12721046**	2.93E − 09	2.0	19	G	A	0.08	APOC1	Intron (LD with **rs769449** and **rs429358** in APOE)
	rs2075650	1.46E − 05	1.7	19	A	G	0.12	TOMM40	Intron (LD with **rs429358**, **rs769449** in APOE)
HRS	rs115881343	2.03E − 09	0.5	19	C	G,T	0.03	TOMM40	Intron
	rs76366838	1.71E − 08	0.4	19	G	A	0.03	TOMM40	Intron
	rs769449	3.12E − 08	1.7	19	G	A	0.06	APOE	Intron (LD with **rs12721046** in APOC1, **rs2075650** in TOMM40, **rs429358** in APOE)
	rs157582	1.68E − 07	0.7	19	C	T	0.29	TOMM40	Intron
	rs283815	3.07E − 07	0.7	19	A	G	0.30	PVRL2	Intron (LD with **rs429358** in APOE)
	rs2075650	5.17E − 07	1.5	19	A	G	0.12	TOMM40	Intron (LD with **rs429358, rs769449** in APOE)
	rs71352238	3.19E − 06	1.5	19	T	C	0.09	TOMM40	Intron

The columns notations: dataset name, SNP name, p-value in Cox regression, Hazard Ratio (HR) for Cox regression, chromosome (Chr), reference allele (Ref), alternative allele (Alt), minor allele frequency (MAF), gene's name and location with LD information.

shown in bold font in "SNP" column), and in both Cox and logistic regression analyses, are located in/near APOE, APOC1, TOMM40, and PVRL2 (NECTIN2) genes. Also shown in bold is rs769449, which is in strong LD (r^2 = 0.82, D' = 1) with rs429358 representing APOE e2/e3/e4 polymorphism.

4. Discussion

The results of GWAS of AD using HRS, CHS, FHS and LOADFS data confirmed strong association of genetic variation in APOE, APOC1, TOMM40, and PVRL2 (NECTIN2) genes with AD. Associations between SNPs in these genes and AD were also detected in earlier studies (Ortega-Rojas et al., 2016; Takei et al., 2009; Seripa et al., 2012; Bagnoli et al., 2013; Roses et al., 2016). Several top significant SNPs in our research showed associations with AD in more than one dataset (CHS, FHS, HRS or LOADFS), using either logistic or Cox model. At least three of these SNPs (rs2075650, rs405509, rs6859) have also been linked to AD in previous research (Harold et al., 2009; Wang et al., 2017; Logue et al., 2011), which supports their true association with AD in present study. These well confirmed associations justify a deeper look into functions of detected SNPs and genes to get insights into potential mechanisms of their connection with AD.

The histopathological manifestation of AD is typically characterized by the two hallmarks: extracellular senile plagues predominantly made up of beta amyloid (Aβ) (a peptide cleaved from the amyloid beta protein precursor (AβPP)), and intracellular neurofibrillary tangles (NFT) made of aggregates of the hyper-phosphorylated tau protein, which plays crucial role in the microtubules assembly and stabilization on neurons. The accumulation of Aβ inside neurons that may contribute to synaptic dysfunction and cognitive impairment, has also been observed in AD (Gouras et al., 2010; Takahashi et al., 2017). Other major features of AD include cerebral cortex atrophy with a loss of neurons and the connections between them, and glucose hypometabolism - reduction of the cerebral metabolic rate for glucose (CMRglc) (Mosconi et al., 2009; Ramos Bernardes da Silva Filho et al., 2017). During 25 + years of studies of AD with main focus on testing the amyloid cascade hypothesis, additional characteristics, biomarkers and risk factors of AD emerged, including mitochondrial dysfunction, oxidative stress, neuro-inflammation, synapse loss, air pollution, viral infection, impaired lipid transport and axonal repair, among others. All these factors may potentially play major roles in AD development or progression in different subsets of AD patients. However, consistent and well replicated in independent datasets, including in present study, findings of AD associated SNPs in/near APOE, APOC1, TOMM40 and PVRL2 (NECTIN2) genes located on chromosome 19 suggest that there may also exist a mechanism of AD, which is linked to biological functions of SNPs in these genes, potentially acting together.

Table 3 shows SNPs that have demonstrated genome-wide significant associations with AD in more than one dataset (CHS, FHS, HRS or LOADFS) using logistic and/or Cox model, that is, were replicated. We also included rs769449 in APOE gene. It was found to be significantly associated with AD in HRS data only (Tables 2.1, 2.2), however, this SNP is in LD with two top replicated SNPs from this study (rs2075650 in TOMM40 and rs12721046 in APOC1), and with rs429358, representing APOE e2/e3/e4 polymorphism.

Table 3
Biological roles of top SNPs (and genes) that showed significant associations with AD in more than one dataset (CHS, FHS, HRS or LOADFS) using logistic and/or Cox model.

SNP	Closest gene (involved in, associated with)	LD with ($0.4 \leq r^2$; $D' > 0.7$)	eQTL (SNP influences expression of)	SNP is in enhancer region in	SNP was previously associated with	References
rs2075650	TOMM40 (protein precursors' import into mitochondria, AD)[a]	**rs429358** and **rs769449** in APOE; SNPs in **PVRL2**	TOMM40, **PVRL2**	12 tissues	Longevity, AD; LDLC	(Harold et al., 2009; Deelen et al., 2011; Holliday et al., 2013; Abe et al., 2015)
rs405509	APOE (lipid transport, AD, stroke, cancer, longevity, hippocampus atrophy, response to viruses (HCV))[b]	SNPs in TOMM40; **PVRL2**	APOE, **PVRL2**	10 tissues	Longevity, AD; cognitive impairment (interacts with APOE e4)	(Wang et al., 2017; Lu et al., 2014; Ryu et al., 2016; Ma et al., 2016)
rs8106922	TOMM40 (protein precursors' import into mitochondria, AD)	SNPs in APOE; **PVRL2**	**PVRL2**	blood	Longevity; TG	(Lin et al., 2016; Salakhov et al., 2014)
rs6859	PVRL2 (adherens junctions, resistance to herpesviruses, cancer prognosis)	SNPs in **PVRL2**	**PVRL2**, TOMM40	7 tissues	AD	(Logue et al., 2011)
rs12721046	APOC1 (AD, cancer, HDL, VLDL, virus (HCV) infectivity)	**rs769449** and **rs429358** in APOE			LDL, HDL	(Kettunen et al., 2012; Musunuru et al., 2012)
rs769449	APOE (lipid transport, AD, stroke, cancer, longevity, response to viruses (HCV))	**rs429358** in APOE, **rs12721046** in APOC1, **rs2075650** in TOMM40; SNPs in **PVRL2**		5 tissues	CSF tau levels, cognitive decline, LDL	(Cruchaga et al., 2013; Zhang and Pierce, 2014; Kettunen et al., 2012)

[a] Biological effects of SNPs were assessed using NCBI resources (PubMed, dbSNP, etc.), NHGRI-EBI Catalog of published GWAS (https://www.ebi.ac.uk/gwas), GRASP (https://grasp.nhlbi.nih.gov), and HaploReg v4.1 (Ward and Kellis, 2016) (http://archive.broadinstitute.org/mammals/haploreg).

[b] LD with other genes column also shows LD with **rs429358**, one of two SNP defining APOE e2/e3/e4 polymorphism, and LD between individual SNPs shown in the table.

4.1. SNP rs2075650 is associated with AD in all datasets

The most consistent association with AD across our datasets, using Cox as well as logistic regression, was observed for the SNP rs2075650 (Tables 2.1 and 2.2). This SNP was previously linked to AD, longevity, cholesterol levels and macular degeneration (e.g., (Deelen et al., 2011; Shadyab et al., 2017; Holliday et al., 2013; Harold et al., 2009). It is located in intron of TOMM40 gene involved in protein precursors' import into mitochondria. It is also in strong ($r^2 \geq 0.92$) LD with several SNPs in PVRL2 (NECTIN2) gene, and in moderate ($r^2 \sim 0.5$) LD with SNPs rs769449 and rs429358 in APOE, representing APOE e2/e3/e4 polymorphism. Notably, the rs2075650 is also eQTL and may influence expression levels of TOMM40 and NECTIN2. Altogether, available information about this SNP (briefly summarized in Table 3) suggests that its phenotypic effects may not necessary be related to functions of TOMM40 itself, but may also be related to the functions of APOE and/or NECTIN2. This means that mechanism connecting rs2075650 and AD may potentially involve biological effects of any or all of these genes; for instance, it could be related to mitochondrial function via TOMM40 and APOE, to lipid transport via APOE, and to resistance to viral infection via APOE and NECTIN2 and their products (De Chiara et al., 2012; Bassendine et al., 2013; Mahley, 2016; Roses et al., 2016; Zeitlow et al., 2017). Comparing potential biological functions of rs2075650 with those of other top SNPs associated with AD in our study may help clarify mechanism connecting these SNPs with AD.

4.2. What do top AD-related SNPs have in common?

AD is a heterogeneous health disorder, which means that the pool of AD patients may contain cases of the different etiology. Some mechanisms, however, may be more prevalent than others and play role in majority of AD cases. If so, then one may expect a certain overlap between the biological effects of SNPs and genes associated with AD. In our study, five SNPs (rs2075650, rs6859, rs405509, rs12721046, and rs8106922) showed top genome-wide significant associations with AD in more than one dataset (CHS, FHS, HRS or LOADFS). Table 3 summarizes biological and health effects of these SNPs, as well as rs769449, based on current literature and results of HaploReg v4.1 (Ward and Kellis, 2016) tool for the analysis of SNPs regulatory effects.

One can see from this table that the selected SNPs and respective genes do share common functional features: Most are involved in lipid metabolism (especially in *LDL cholesterol levels*), *response to viral infection*, *cancer and longevity*. These overlaps in metabolic and health effects indicate that APOE, APOC1, TOMM40 and NECTIN2 might influence AD acting in concert (given that the top AD-associated SNPs in these genes are not in complete LD with each other). Studies of interaction between these genes support a possibility of AD mechanism that involves collective effects of genes on chromosome 19 that have been associated with the disease. For example, mutation in APOC1 in combination with APOE e4 serves as a potential risk factor for developing AD. Individuals carrying both APOE e4 and the APOC1 insertion allele had an approximately 66.49% increased risk of AD (Zhou et al., 2014).

Most SNPs shown in Table 3 (rs2075650, rs6859, rs405509, rs769449, rs8106922) are in LD with SNPs in PVRL2 (emphasized in bold font), and/or influence its expression as eQTLs, as well as located in enhancer regions of genome. This indicates that the SNPs associated with AD may contribute to AD through regulatory effects, by influencing transcription levels and resulting protein concentrations, without changes in protein structure. It is also important to note that while most SNPs from Table 3 are in LD with the SNPs in PVRL2 gene, the rs6859, which is actually located in PVRL2 gene, is not in LD with SNPs in the other genes. This indicates that PVRL2 (NECTIN2) may potentially be main gene functionally related to AD (of the top four AD-associated genes in this study: TOMM40, APOE, APOC1, PVRL2). PVRL2 involvement in AD could be, e.g., through its role in cell adhesion and brain's susceptibility to viral infections, the latter was also suggested for

APOE and APOC1 (Porcellini et al., 2010; De Chiara et al., 2012). This warrants further research into the role of 'brain vulnerability to infection' in AD development, and deserves a deeper look into functions of the detected genes.

PVRL2 (poliovirus receptor-related 2, formerly herpesvirus entry mediator B, HVEB), a.k.a. NECTIN2 (nectin, cell adhesion molecule 2), codes for a human plasma membrane glycoprotein involved in "adherens junction". It also serves as an entry for certain mutant strains of herpes and pseudorabies viruses, and is involved in cell to cell spreading of these viruses. The fact that AD-associated SNPs in TOMM40 and APOE both influence expression of PVRL2 indicates that biological effects of PVRL2 may at least in part explain observed genetic associations with AD. PVRL2 is important for maintaining proper cell junctions and the extra-cellular matrix (ECM) structure. Proper cell junctions are in turn important to control BBB permeability and may protect brain from spreading the viral infection, which was suggested to play role in AD (Urosevic and Martins, 2008; Miklossy, 2011; Itzhaki et al., 2016; Itzhaki, 2016) PVRL2 and respective protein were also implemented in cancer (Oshima et al., 2013; Karabulut et al., 2016). The gene is also responsive to plasma cholesterol acting at endothelial sites of vascular inflammation and could potentially be a new therapeutic target for atherosclerosis prevention. The involvement of PVRL2 in lymphomagenesis has been previously suggested to play a role in the pathogenesis of acute myeloid leukemia (Graf et al., 2005) and in lymphomagenesis (Almire et al., 2007). Furthermore, gene expression profiling performed on hepatocellular carcinomas revealed an up-regulation of PVRL2, which was supposed to participate in the inhibit ion of apoptosis in hepatoma cells (Kurokawa et al., 2006; Logue et al., 2011). In GWAS of the late onset AD in African Americans, SNPs related to APOE, PVRL2, TOMM40 and APOC1 also showed genome-wide significant associations with AD (Logue et al., 2011). Importantly, the association of rs6859 of PVRL2 with AD remained statistically significant after adjusting for the effect of APOE, which supports its independent role in AD. Overall, available evidence suggests that PVRL2 is gene with highly pleiotropic effects on health-related phenotypes. It also has notable overlap in functions with other AD-related genes, which refers to its involvement in brain's susceptibility to viral and bacterial infections.

4.3. Roles of APOE in Aβ clearance and neuro-inflammation

As mentioned, the SNP rs769449 in the APOE gene, found in this study, is in strong LD ($r^2 = 0.82$; $D' = 1$) with rs429358 of APOE e2/e3/e4 polymorphism. The rs769449 is also in moderate LDs ($r^2 \sim 0.5–0.6$) with rs12721046 in APOC1 and rs2075650 in TOMM40, which are of the same strength as LDs between these SNPs and rs429358. This supports the possibility that rs769449 actually represents APOE e2/e3/e4 polymorphism in this study, and the genome-wide significant effect of rs769449 on AD that we observed in HRS data (Table 2.1) is probably related to that effect of APOE e4. The involvement of APOE gene in AD has been confirmed more than two decades ago. The product of this gene interacts with Aβ and that the presence of APOE e4 isoform of this gene in a person's genome increases his/her risks of AD. In the brain apolipoprotein E (apoE) is synthesized predominantly by astrocytes (Koldamova et al., 2010). It is the primary transporter of cholesterol within the blood brain barrier (BBB). ApoE interacts with Aβ during its aggregation and deposition and together they influence risks of AD development. Many studies confirm the presence of such interaction, however, explanations of its nature differ considerably from one study to the next (LaDu et al., 1994; Hashimoto et al., 2012; Manelli et al., 2004; Cerf et al., 2011; Carter, 2005). Recently Verghese et al. (2013) provided evidence that the apoE proteins do not bind to soluble (i.e., monomeric) Aβ. Garai et al. (2014) found that apoE may interact with the Aβ oligomers and fibrils. The researchers emphasized considerable heterogeneity in the size and structures of the Aβ oligomers that are likely to influence such interaction. The presence of APOE e4 variant may also affect Aβ accumulation in brain. Studies of longitudinal cohorts showed that APOE e4 was significantly associated with lower CSF Aβ1–42, suggesting increased Aβ deposition in brain (Resnick et al., 2015). ApoE is involved in complex relationships with Aβ suitable to cross the BBB that may regulate Aβ clearance (Huynh et al., 2017). E.g., apoE4 animals showed reduced Aβ clearance across the BBB compared to apoE3 animals, linked to less efficient regulation by apoE4 isoform of lipoprotein receptor shedding (Bachmeier et al., 2014). Alternative pathways of Aβ clearance could be mediated by microglia (Morgan, 2009). Brains of AD patients carrying the APOE e4 allele were found to have increased density of Aβ deposits, limited capacity to clear Aβ and enhanced neuro-inflammation (Castellano et al., 2011). Despite an association between neurodegenerative disease and APOEe4 many APOEe4 non-carriers develop AD. Analyses of genetic associations of people without APOEe4 allele showed that rs2075650 in TOMM40 is still associated with AD (Bekris et al., 2011; Naj et al., 2014). After adjustment for age, sex, and APOEe4 status the association of rs157580 in TOMM40 with AD also remained statistically significant in Han Chinese cohort (Ma et al., 2013) suggesting APOEe4 independent mechanism of AD involving TOMM40.

4.4. APOC1 encodes a member of the apolipoprotein C1 family

This gene is expressed primarily in the liver and also in the brain. The encoded protein plays a central role in high density lipoprotein (HDL) and very low density lipoprotein (VLDL) metabolism. This protein has also been shown to inhibit cholesteryl ester transfer protein in plasma. Alternative splicing and the use of alternative promoters results in multiple transcript variants. The GWAS of T2D and AD (Gao et al., 2016) identified six SNPs (rs111789331, rs12721046, rs12721051, rs4420638, rs56131196, and rs66626994) related to the APOC1 gene that showed pleiotropic associations with these health disorders. Among them rs12721046, located in the intron area of APOC1 showed genome-wide significant association with AD in our analyses (FHS data in Table 2.1, and CHS and FHS data in Table 2.2). This SNP is in high LD with rs769449, also found in our study, as well as with rs429358 (Table 2.2), which suggests that it's effect might be through APOEe4.

4.5. Connection with human longevity

The genetic variants from the same four genes (and often the same SNPs) were detected in GWAS of human longevity (Ang et al., 2008; Deelen et al., 2011; Nebel et al., 2011; Lu et al., 2014; Garatachea et al., 2014; Garatachea et al., 2015; Deelen et al., 2014; Lin et al., 2016; Nebel et al., 2011; Shadyab et al., 2017). The connection of this set of genes with human longevity suggests that they might play some roles in risks of other diseases or in biological processes that influence such risks. Indeed, a number of studies linked these genes with multiple phenotypes including lipid traits (Teslovich et al., 2010; Chang and Chang, 2017), rate of information processing (Lyall et al., 2014; Smith et al., 2010), cardiovascular risk (Smith et al., 2010), inflammation (Rebeck, 2017), cancer (Slattery et al., 2005; Watson et al., 2003), type 2 diabetes (El-Lebedy et al., 2016). These facts indicate that detected genes are likely to have pleiotropic associations with other health disorders. Such pleiotropy is manifested as dependence among chronic conditions at the population level. The results of epidemiologic studies confirm this conjecture. The dependence between AD and other diseases such as cancer and T2D have been detected and described in a number of studies. It is likely that not only genes detected with high level of statistical significance but also genes whose variants showed less significant associations with AD are involved in development of these health disorders. The existence of connections between AD and other health disorders suggests that better understanding AD can be reached in studies of systemic mechanisms of aging related health decline which involve several pathological conditions.

4.6. TOMM40 and mitochondrial dysfunction

Mutations in TOMM40 have a high potential to result in mitochondria dysfunction – a novel hallmark of AD (Grimm et al., 2016). *TOMM40* encodes the Tom40 a channel-forming subunit of the translocase of the outer mitochondrial membrane (TOM complex), which plays a role in cytoplasmic peptide and protein transport into the mitochondria. Tom40 pores play the central role in the TOM complex that is made of three Tom40 subunits, which are connected to one another by Tom22 subunits. Each Tom40 subunit forms a pore across the membrane through which precursor proteins can pass from the cytosol into the space between the outer and inner mitochondrial membranes. Tom5, Tom6 and Tom7 subunits are located around the periphery of the pores. About 1500 nuclear-encoded mitochondrial proteins are imported from the cytosol to mitochondria through the TOM complex. The results of experimental studies suggest that altered expression of Tom40 may be linked to a spectrum of neurological diseases (Gottschalk et al., 2014). In particular, APP may thwart the TOM40 pore, inhibiting import of proteins needed for normal mitochondrial functioning. Recent study provided arguments that connection between TOMM40 and AD might be a side effect of the evolutionary development of cognitive function in humans (Larsen et al., 2017).

Strong connection between genetic variants from TOMM40 gene and AD has been detected in a number of genetic association studies of this health disorder. The meta-analysis of polymorphisms in TOMM40 gene (Bao et al., 2016) showed that minor allele of rs157580 (TOMM40 intron area) was significantly associated with a reduced risk of AD whereas minor allele of rs2075650 was significantly associated with an increased risk of AD (TOMM40 intron area). The case-control study of AD in Canadian population confirmed the association of rs2075650 with this disorder (Omoumi et al., 2014). The depression is a risk factor for AD. The connection between rs2075650 and depression has been studied in (McFarquhar et al., 2014). It was found that rs2075650 G allele was a significant risk factor for lifetime depression and, in depressed subjects it was a significant predictor of low extraversion. However, the analyses performed by (He et al., 2016) did not show significant association between rs2075650 and AD risk in Chinese population. The genetic analyses of AD using Italian data showed that TOMM40 gene does not have an APOE independent effect on the risk of developing AD.

To explain the role of mitochondria dysregulation in development of AD the mitochondrial cascade hypothesis has been proposed (Swerdlow and Khan, 2009; Swerdlow, 2011; Swerdlow, 2016). This hypothesis states that, in the sporadic AD, mitochondrial dysfunction is the primary event that causes Aβ deposition, synaptic degeneration, NFTs formation, and neuronal death. Indeed, there is a bulk of studies showing that mitochondrial dysfunction is a common event in AD. Although this theory looks plausible, some problems remains. The dysfunction of mitochondria due to relevant TOMM40 SNPs should lead to inadequate ATP (and/or ROS) production, both of which could negatively affect the neuron and glia metabolism in the bearers of relevant SNPs, possibly accelerating death of respective cell types. If the mitochondrial dysfunction decreases ATP output, then it should also negatively affect global rate and bulk of protein phosphorylation, including tau phosphorylation necessary for NFT formation.

4.7. Other mechanism linking AD and genes found in this study: Involvement of genes regulating cellular stress responses

A number of experimental and molecular biological studies provide evidence about strong involvement of genes regulating cellular stress response in the development of AD and other health disorders. Although most of such genes were not detected with the high level of statistical significance in GWAS of AD, many of them showed nominally significant associations ($p < 0.05$). This fact may indicate variability of stressors and other genetic and non-genetic factors affecting cellular stress response outcomes. Cell may have different fate, depending on duration of stress and interactions between pathways promoting specific responses.

4.8. Evidence of connection between AD and T2D

The connection of AD and other dementias with T2D has been widely discussed in the literature (Sun and Alkon, 2006; Bornstein et al., 2014; Alam et al., 2016; Abbatecola et al., 2011; Alam et al., 2016; Barbagallo and Dominguez, 2014; Bosco et al., 2011; Correia et al., 2012; Dai and Kamal, 2014; De Felice et al., 2014). The AD and T2D have comparable pathological features related to the abnormal behavior: of the β-amyloid in the brain in case of AD and of the islet amyloid derived from islet amyloid polypeptide in the pancreas in T2D. Although the biological mechanism that links the progression of T2D and AD is not completely understood the growing evidence supports the concept that AD is a metabolic health disorder that is caused by progressive inability of the brain's to properly respond to insulin and insulin-like growth factor (IGF) stimulation to utilize glucose. The connection between T2D and AD is also manifested in several similarities between the developments of two pathologies (Steen et al., 2005). These include uncontrolled glucose metabolism, glucose toxicity, a direct effect of insulin on amyloid metabolism, oxidative stress, abnormal protein processing, stimulation of inflammatory pathways and inflammation, hypercholesterolemia, dyslipidemia, impaired central nervous response to the adipose tissue-derived hormone leptin, increased oxidative stress and production of advanced glycation end products (Dar et al., 2014).

In addition to similarities between T2D and AD, described above, studies often provide controversial evidence about effects of different factors on disease development. For example, some studies claim that insulin deficiency may cause AD, suggesting that inhibiting the insulin-degrading enzyme (IDE) or the use of other treatments that increase insulin level in the brain could slow down the disease. Other studies provide evidence that hyperinsulinemia causes the disease which implies that treatments increasing insulin level would exacerbate the disease. Further studies are needed to integrate findings linking T2D and AD and provide better understanding of biological mechanisms linking these health disorders.

4.9. AD and cancer

Many recent studies of connection between cancer and AD revealed an inverse association between these disorders (Yashin et al., 2009; Ukraintseva et al., 2010; Akushevich et al., 2013). The quantitative meta-analysis of cohort studies suggested that individuals diagnosed with AD had a decreased risk for incident cancer by 42%, and patients with a history of cancer had a 37% decreased risk of AD. This study demonstrated an inverse association between cancer and AD (Ma et al., 2014). Small inverse associations between cancer and AD were detected in (Schmidt et al., 2017). The authors concluded that these associations might be caused by ascertainment bias due to decreased awareness of non-melanoma skin cancers (NMSC) in persons with undiagnosed early cognitive impairment or by confounding from a more neuroprotective lifestyle among persons with NMSC. The obesity-related mechanism may be involved in trade-off between cancer and AD (Nixon, 2017). The leptin and adiponectin produced by adipose tissues may be responsible for this property. Leptin has cancer-stimulating and AD-inhibiting actions while, in contrast, adiponectin has cancer-inhibiting and AD-stimulating properties. These opposing actions, mediated through p53, Wnt, and other signaling pathways, may account for the inverse cancer/AD relationship.

Recently it was found that the use of androgen-deprivation therapy (ADT) – the preferred first-line treatment for advanced prostate cancer is associated with an increased risk of developing AD (Jhan et al., 2017). Cancer survivors have reduced chances of developing AD and a

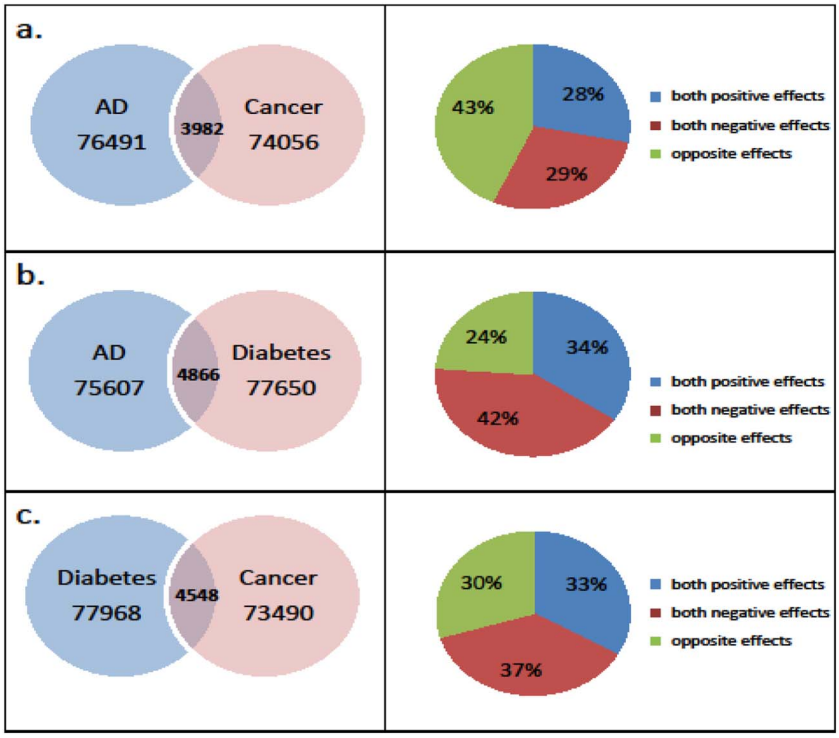

Fig. 3. Left panel. The Venn diagrams of intersection of SNPs obtained from GWAS analyses on HRS white individuals using logistic regression: a). between Alzheimer's/dementia (AD) and cancers (non-skin); b). between Alzheimer's/dementia (AD) and diabetes; c). between cancers (non-skin) and diabetes. Right panel. Distribution of the overlapped SNPs by the effects corresponding to the left panel.

lower burden of neurofibrillary tangle deposition. This conclusion resulted from studying the risks of developing AD among participants with and without a history of cancer at autopsy (Yarchoan et al., 2017). At autopsy, participants with a history of cancer had significantly fewer paired helical filament (PHF) tau tangles ($p < 0.001$) than participants without a history of cancer, but similar levels of Aβ. Comprehensive review of cellular pathways with roles in cancers, cell survival, growth, proliferation, development, aging, and also contributing to AD disease showed the possibility of inverse relationship between AD and cancer (Shafi, 2016). Many factors that are upregulated in any cancer to sustain growth and survival are downregulated in AD contributing to neuro-degeneration. However, cancer did not provide protection from AD in retrospective cohort study using data from the Utah Population Database (Hanson et al., 2017). The authors concluded that taking mortality selection in heterogeneous population into account may explain biased associations.

Note that SNPs from most of genes involved in pleiotropic associations described above did not reach genome wide level of statistical significance in GWAS of AD in our study. Recently the association with AD has been tested in case-control studies for 695 candidate genes (Sun et al., 2014), however, their roles in risks of other health disorders remain unclear.

To test the presence of genetic variants having pleiotropic effects on diseases discussed above we performed GWAS of AD, cancer and T2D using HRS data and identified genetic variants that have pleiotropic effects on these health disorders. In these analyses for each pair of diseases three sets of genetic variants emerged. They include SNPs whose minor alleles have positive, negative and opposite effects on corresponding health disorders. The results of these analyses are shown in Fig. 3.

Table 1S (in Supplementary materials) summarizes the results of these analyses for ten most significant SNPs detected in GWAS for each health disorder and for each intersection with both positive, both negative and the opposite genetic associations with different pairs of selected diseases (AD and cancer, AD and T2D, cancer and T2D). These results show that two SNPs related to detected genes on chromosome 19 have pleiotropic associations with selected health disorders. Specifically, rs34095326 (in the intron of TOMM40) has negative associations with both AD and cancer; rs405697 has negative association with AD and positive association with T2D. SNP rs34095326 SNP is in strong LD ($D' = 1$) with rs15782 in Table 2.1, and rs405697 is in strong LD with rs405509 ($D' = 0.98$), rs769450 ($D' = 0.99$), and rs157580 ($D' = 0.94$) (see Table 2.1). Two more SNPs from chromosome 19 showed pleotropic associations with selected diseases: rs8109796 is positively associated with AD and negatively associated with cancer; rs10411527 is negatively associated with both AD and T2D. However, these SNPs are not related to any specific gene. Note that other SNPs shown in Table 1S showed only nominal levels of statistical significance in GWAS for specific health disorders. Therefore, many of detected connections are likely to be false-positive. More analyses that involve the results of clinical, experimental, and molecular biological studies are needed to separate the true-positive pleiotropic associations with selected diseases from the false-positive ones.

5. Conclusions

The results of GWAS of AD in our study confirm findings from earlier genetic studies of this health disorder. The literature summarizing results of clinical, experimental, and molecular biological studies provides evidence that these genes are highly pleiotropic and participate in signaling and metabolic pathways linked with the origin and progression of AD, as well as several other major health disorders such as cancer, T2D and viral infections. This fact suggests that studying common components of the biological mechanisms may be mutually beneficial for better understanding the etiology of each health disorder.

One hypothesis that converge effects of APOE, APOC1 and PVRL2 (NECTIN2) on AD could be that proper maintenance of cell junctions and ECM structure relevant to functions of PVRL2 may help prevent the spread of viral infection, and such infection could be a common risk factor for AD and all-cause mortality. Proper cell junctions are important to control brain blood barrier (BBB) permeability and protect the brain from infection, especially from viruses, which may play a role in AD (Itzhaki, 2016). Performance of lipid transport particles, such as LDL and HDL, depends on APOE and APOC1, which may be also

involved in host resistance to infection since they can modulate virus life cycle and secretion (Chiba-Falek et al., 2012). Thus, host resistance to infection could potentially contribute to a common mechanism for the involvement of most of the identified genes (APOE, APOC1, PVRL2) in AD.

Some studies also provide evidence about involvement of genes responsible for regulation of cellular stress response in development of AD and other health disorders (Bell et al., 2016; Viana et al., 2012; Shah et al., 2017). Although most of such genes were not detected with high level of statistical significance in GWAS of AD many of them showed nominally significant associations ($p < 0.05$) with this health disorder. These results confirm that AD is likely to be a highly heterogeneous phenotypic trait.

Aging process is likely to be the major factor responsible for the similarity of pathological pathways involved in the development of AD and other diseases of the elderly by increasing organism's vulnerability to different kinds of disturbances (Fulop, 2016). Some of these stresses being transformed to cellular levels induce cellular stress response. The pathological development might be the consequence of the cellular stress response, in which stress is persistent, or damage is not possible to repair or compensate to functional level. The cellular stress response genes are involved in development of cancer and other aging related chronic pathologies (Cunard, 2015; Oakes and Papa, 2015; Alasiri et al., 2017). This means that better understanding AD requires integration of the research results obtained in genetic association studies with findings obtained in clinical, experimental, and molecular biological studies of aging, as well in studies of other health disorders.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2017.10.020.

Acknowledgements

The analyses described in this paper were supported by the National Institutes of Health/National Institute of Aging (NIH/NIA) grants R01AG046860, P01AG043352, P30AG034424. The FHS project is conducted and supported by the National Heart, Lung and Blood Institute (NHLBI) in collaboration with Boston University (N01 HC25195). The FHS data used for the analyses were obtained through the database of Genotypes and Phenotypes (dbGaP). The authors acknowledge the investigators that contributed the phenotype and genotype data for this study. This manuscript was not prepared in collaboration with investigators of the FHS and does not necessarily reflect the opinions or views of the FHS, Boston University or the NHLBI. The CHS project was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant number U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through R01 AG-15928, R01 AG-20098, and AG-027058 from the National Institute on Aging, R01 HL-075366 from the National Heart, Lung and Blood Institute, and the University of Pittsburgh Claude D. Pepper Older Americans Independence Center P30-AG-024827. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. The Health and Retirement Study data is sponsored by the National Institute on Aging (grant number U01AG009740) and is conducted by the University of Michigan. HRS Restricted Data Access #2014-008. The Health and Retirement Study genetic data is sponsored by the National Institute on Aging (grant numbers U01AG009740, RC2AG036495, and RC4AG039029) and was conducted by the University of Michigan. LOADFS: Funding support for the “Genetic Consortium for Late Onset Alzheimer's Disease” was provided through the Division of Neuroscience, NIA. The Genetic Consortium for Late Onset Alzheimer's Disease includes a genome-wide association study funded as part of the Division of Neuroscience, NIA. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by Genetic Consortium for Late Onset Alzheimer's Disease.

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