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Featured Article

A genetic signature including apolipoprotein Eε4 potentiates the risk of herpes simplex–associated Alzheimer's disease

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Abstract

Introduction: Herpes simplex virus type 1 (HSV1) in combination with genetic susceptibility has previously been implicated in Alzheimer's disease (AD) pathogenesis.
Methods: Plasma from 360 AD cases, obtained on average 9.6 years before diagnosis, and their age- and sex-matched controls, were analyzed for anti–HSV1 immunoglobulin (Ig) G with enzyme-linked immunosorbent assays (ELISAs). *APOE* genotype and nine other selected risk genes for AD were extracted from a genome-wide association study analysis by deCODE genetics, Reykjavik, Iceland.
Results: The interaction between *APOEε*4 heterozygosity (*APOEε*2/*ε*4 or *ε*3/*ε*4) and anti–HSV1 IgG carriage increased the risk of AD (OR 4.55, $P = .02$). A genetic risk score based on the nine AD risk genes also interacted with anti–HSV1 IgG for the risk of developing AD (OR 2.35, $P = .01$).
Discussion: The present findings suggest that the *APOEε*4 allele and other AD genetic risk factors might potentiate the risk of HSV1-associated AD.

Keywords: Herpes simplex; HSV; Apolipoprotein E4; *APOEε*4; Alzheimer's disease; Dementia; Nested case-control study

1. Background

The pathogenesis of Alzheimer's disease (AD), the leading cause of major neurocognitive disorders, is still not fully understood. Sporadic AD is considered a multifactorial disease, triggered by environmental factors, in addition to genetic predisposition [1,2]. The genetic component in AD is complex, involving multiple susceptibility genes [3]; however, the ε4 allele of the apolipoprotein E gene (*APOE*) is the strongest genetic risk factor for AD. The *APOE* gene has three predominant allelic variants: *APOEε*2, *ε*3 and *ε*4. Possession of the *APOEε*4 allele increases the risk of AD with an odds ratio (OR) of 15 for homozygous carriers (*APOEε*4/*ε*4) and threefold for heterozygous carriers (*APOEε*2/*ε*4 or *ε*3/*ε*4) [4]. Although *APOEε*4 confers an increased risk of AD, it is not the single cause of the disease.

Large-scale genome-wide association studies (GWASs) have identified additional susceptibility genes for AD, including ATP-binding cassette subfamily A member 7

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(*ABCA7*), bridging integrator 1 (*BIN1*), sialic acid binding Ig-like lectin 3 (*CD33*), Clusterin (*CLU*), complement receptor 1 (*CR1*), ephrin A1 (*EPHA1*), membrane-spanning 4-domain, subfamily A, member 4E (*MS4A4E*), nectin cell adhesion molecule 2 (*NECTIN2*), and phosphatidylinositol-binding clathrin assembly protein (*PICALM*). One emerging pattern is that many of these susceptibility genes associate with the complement system or immune mechanisms related to viral infections [5–7].

Infectious agents have been proposed as important environmental factors for AD development, and herpes simplex virus type 1 (HSV1) is the pathogen most strongly associated with AD [8–10]. Carriage of HSV1 is highly prevalent, reaching 80% in the adult population [11]. HSV1 DNA has been detected in the brains of patients with AD patients and colocalized with amyloid plaques in particular [12–15]. More recently, transcriptomic studies also showed an increased abundance of HSV1 in the brains of patients with AD [16]. In epidemiological studies, both carriage of and reactivated HSV1 infection doubled the risk of developing AD [9,10,17]. Moreover, AD risk appears to decrease after treatment with antiherpetic medications in HSV1-infected patients [18]. The concept of HSV1-associated AD is further supported by the discovery that cultured cells and murine models infected with HSV1 display similar changes to AD pathology [19–23]. These observations are consistent with the finding that amyloid β has antimicrobial activity [22–24]. There are other suggested AD-associated pathogens, among which cytomegalovirus (CMV) [25,26], human herpes virus 6 (HHV6) [27], and *Chlamydophila pneumoniae* (*C. pneumoniae*) [28,29] are highlighted here because they have the common ability to establish latent or chronic infections within the central nervous system (CNS).

It has been hypothesized that concomitant carriage of several AD-related genes and their subsequent synergistic interactions might result in a genetic signature, which predisposes a person to HSV1-associated AD [7,30]. In post-mortem studies, the combination of having *APOEε*4 and HSV1 in the brain was more highly associated with AD than having only one of these factors [15,31]. Previous research has connected the *APOEε*4 allele with HSV1 outcomes [31–34], but no prospective epidemiological survey of AD has specifically investigated the HSV1-*APOEε*4 interaction. There are no studies that have examined the potential interaction between HSV1 and other AD-related genes. The aim of this study was to investigate interactions between HSV1, HSV2, CMV and *C. pneumoniae*; the *APOEε*4 allele; and nine additional AD risk genes, for the risk of subsequent AD development.

2. Methods

2.1. Participants and procedure

The nested case-control study was approved by the Regional Ethical Review Board in Umeå, Sweden (09-190M and 2017/17-31) and is based on the data from the Medical Biobank in Umeå (Northern Sweden Health and Disease Study [35]). The biobank contains plasma samples, previously donated during, for example, regular health checkups. From the biobank, samples from 360 individuals later diagnosed with AD and 360 matched controls were identified using a computerized procedure. Their plasma samples, obtained on average 9.6 years before diagnosis, were extracted for analysis. Controls were closely matched based on sampling date and age and exactly matched based on sex and cohort in the Medical Biobank.

2.2. AD diagnosis

Patients with AD were diagnosed at the Memory Clinic of the University Hospital of Northern Sweden in Umeå. The AD diagnoses were based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [36] and at least one brain imaging technique. The clinical diagnoses were also compatible with the NINCDS-ADRDA criteria [37]. Before final inclusion, an experienced specialist in psychogeriatric medicine verified the diagnoses. The controls were confirmed free of major neurocognitive disorder and alive at the time of diagnosis for their corresponding case. This procedure has been described extensively in a previous publication [10].

2.3. Plasma analyses

Plasma was analyzed for presence of anti–HSV IgG, anti–HSV1 and anti–HSV2 IgG, anti–CMV IgG, and anti–*C. pneumoniae* IgG with enzyme-linked immunosorbent assays (ELISAs). An in-house ELISA was used for the analyses of anti–HSV IgG and anti–CMV IgG as described in a previous publication [38]. Commercial ELISA kits were used to analyze anti–HSV1, anti–HSV2 (HerpeSelect 1, HerpeSelect 2, FOCUS Diagnostics), and anti–*C. pneumoniae* IgG (SeropCp™ Quant IgG).

To determine carriage of anti-HSV1, anti-HSV2, or anti-HSV1+anti-HSV2 IgG, each sample positive for anti–HSV IgG was further analyzed for anti–HSV2 IgG. If the sample is positive for anti–HSV2 IgG, additional analysis was performed for anti–HSV1 IgG, to separate individuals positive for anti–HSV1 IgG, anti–HSV2 IgG, or both.

2.4. Genotyping

Genotyping was performed at deCODE genetics (Reykjavik, Iceland) with Illumina genome-wide arrays (HumanOmniExpress-24). Variants with genotype yield <96 %, MAF <0.5 %, or failed Hardy-Weinberg test were excluded.

2.5. Statistical analyses

2.5.1. APOE *genotype, infections, and the risk of AD*

APOE genotype was classified $\varepsilon2/\varepsilon2$, $\varepsilon2/\varepsilon3$, $\varepsilon2/\varepsilon4$, $\varepsilon3/\varepsilon3$, $\varepsilon3/\varepsilon4$, and $\varepsilon4/\varepsilon4$ based on single nucleotide polymorphisms (SNPs) rs429358 and rs7412. The impact of *APOE* genotype on AD risk was evaluated using conditional logistic regression with *APOE*$\varepsilon3/\varepsilon3$ as reference. Owing to the small number (n = 3) of individuals with *APOE*$\varepsilon2/\varepsilon2$, these three individuals were included in the group with *APOE*$\varepsilon2/\varepsilon3$. To examine possible interactions between anti–HSV1, anti–HSV2, anti–CMV, and anti–*C. pneumoniae* IgG positivity, separately, and *APOE* genotype, conditional logistic regression for AD was repeated including the IgG positivity variables and interaction terms. For the analyses with interaction terms, *APOE* genotype was classified using variables for *APOE*$\varepsilon4$ homozygosity (*APOE*$\varepsilon4/\varepsilon4$), *APOE*$\varepsilon4$ heterozygosity (*APOE*$\varepsilon2/\varepsilon4$ or $\varepsilon3/\varepsilon4$), and *APOE*$\varepsilon2$ carriage. Interactions with each of these three *APOE* genotype variables were analyzed separately, and significant interactions were included in the final models.

2.5.2. *Selection of additional AD risk genes for a genetic risk score*

Nine different genes (*ABCA7*, *BIN1*, *CD33*, *CLU*, *CR1*, *EPHA1*, *MS4A4E*, *NECTIN2*, and *PICALM*) were selected after reviewing previous research [1,6,7,39]. All available SNPs from the selected genes were extracted from the genome-wide association study data files, resulting in a total of 126 SNPs (Fig. 1). Each individual SNP had 2 sets of alleles, "AA, AG, GG" or "AA, AC and CC." The frequency of SNP variants was compared between AD cases and controls. The variants with a higher frequency among cases were given a value of 1 ("risk variant for AD"), and the variants with a lower frequency were subsequently given a value of 0 ("protective variant for AD"). Thus, every individual obtained a value of either 1 or 0 for each specific SNP. The resulting SNPs with a value of 1 or 0 were then analyzed for frequency and missing values in groups of cases and controls separately. Conditional logistic regression for each individual SNP was performed, with the outcome of AD.

The first selection of SNPs was made based on the following criteria: the rarest variant had to have a frequency >5% among cases, missing values should not exceed 10% among cases or controls, and finally, Pearson's correlation between two SNPs from the same gene should be <0.5 because of the risk of multicollinearity. If 2 SNPs originating from the same gene had a Pearson's correlation ≥0.5, the one with the highest OR for AD was selected. The SNPs which fulfilled the criteria for the first selection were included in a gene-specific multivariable conditional logistic regression for AD with backward elimination (likelihood ratio), that is separate models were made for each specific gene. The backward elimination (likelihood ratio) algorithm resulted in 1 to 3 SNPs per gene (Supplementary Table 1 in the Supplementary Appendix).

The final 17 SNPs identified by the gene-specific models were then integrated into the same non-gene-specific multivariable conditional logistic regression for AD and contributed to the genetic risk score (GRS). To achieve a weighted value for each individual SNP with regard to AD risk, carriers were assigned the value of the adjusted OR for AD derived from the non–gene-specific multivariable regression and value 1 for non-carriers. The GRS was calculated by the weighted value of each SNP being multiplied and then normalized. A squared normalized version of the GRS was also calculated to account for potential gene-gene interactions between different SNPs.

2.5.3. *GRS of additional AD risk genes, infections and the risk of AD*

Separate conditional logistic regression models were used to test the GRS and the squared GRS for the risk of AD. Analyses were then carried out to examine infection-gene interactions by including IgG positivity variables and interaction terms of GRS and squared GRS, respectively, with anti–HSV1 IgG, anti–HSV2 IgG, anti–CMV IgG, and anti–*C. pneumoniae* IgG positivity in separate conditional logistic models. The interaction between GRS and anti–*C. pneumoniae* IgG positivity for AD was tested with conditional logistic regression using GRS divided by its standard deviation instead of normalized deviation, to investigate the intercept for anti–*C. pneumoniae* IgG positivity at the lowest possible GRS.

To test if the interactions were independent of each other, we further specified a model including *APOE* genotype, GRS and anti–HSV1 IgG positivity as the main effects and two interaction terms: *APOE*$\varepsilon4$ heterozygosity (*APOE*$\varepsilon2/\varepsilon4$ or $\varepsilon3/\varepsilon4$) x anti–HSV1 IgG and GRS x anti–HSV1 IgG. The same model was repeated including the squared GRS instead of the GRS.

SPSS Statistics, version 24 (IBM Corporation, Armonk, NY), was used. A two-sided P value <.05 was regarded as significant.

3. Results

Our study showed that individuals with the *APOE* genotypes $\varepsilon2/\varepsilon3$, $\varepsilon3/\varepsilon4$, and $\varepsilon4/\varepsilon4$ had ORs of 0.38 ($P = .02$), 3.22 ($P < .001$), and 19.15 ($P < .001$), respectively, for developing AD compared with those with *APOE*$\varepsilon3/\varepsilon3$ (Table 1). Carrying *APOE*$\varepsilon2/\varepsilon4$ did not significantly alter the risk of developing AD compared with carrying *APOE*$\varepsilon3/\varepsilon3$ (OR 1.01, $P = .99$; Table 1).

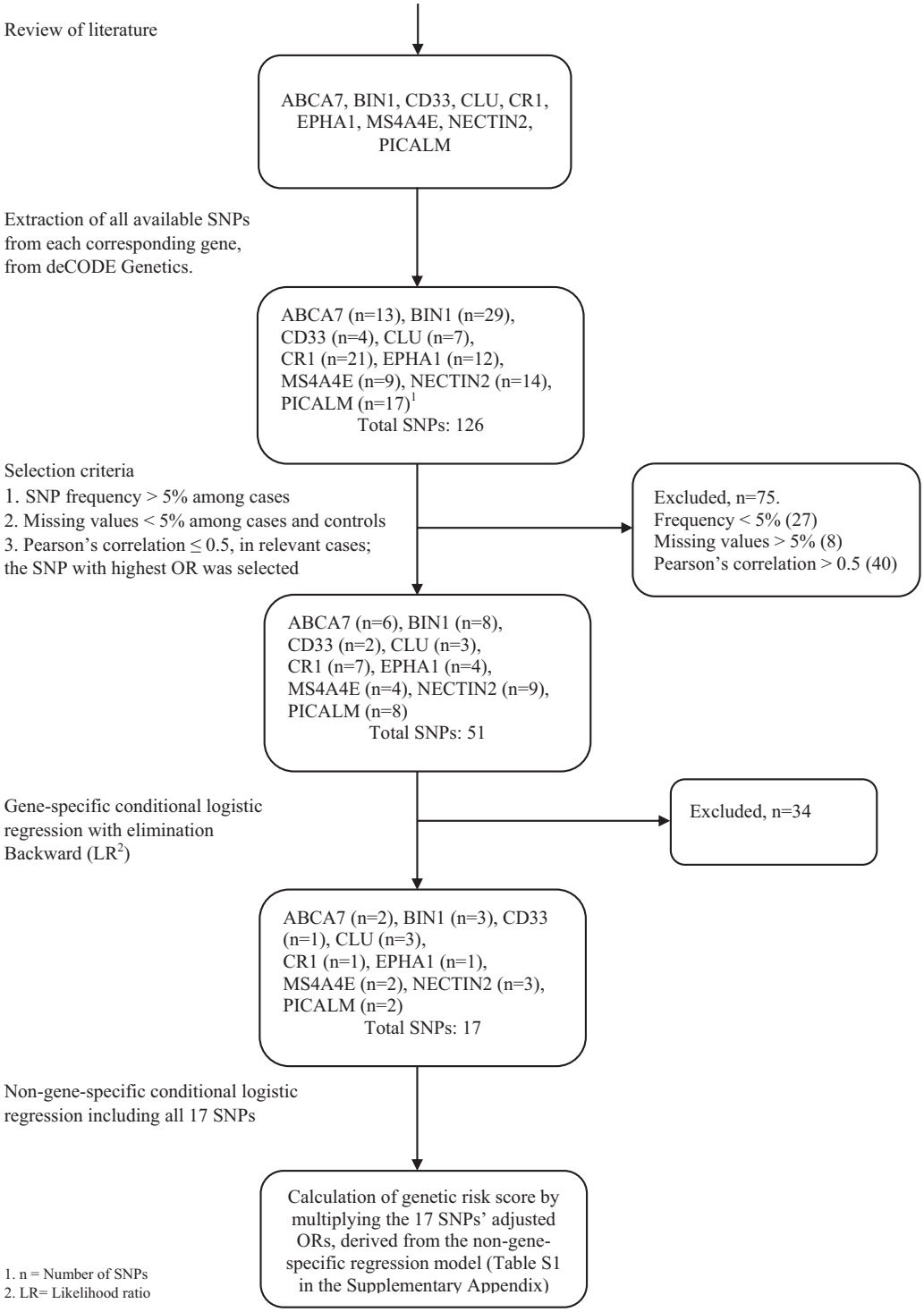

Fig. 1. Flow chart of gene selection and their corresponding single nucleotide polymorphisms.

The interaction between *APOEε4* heterozygosity (*APOEε2/ε4* or *ε3/ε4*) and anti–HSV1 IgG carriage was associated with increased risk of developing AD (OR 4.55, $P = .02$; Table 2), whereas the presence of only one factor was not (OR 0.83, $P = .76$ and OR 0.88 $P = .73$, respectively; Table 2). In the same model, the presence of the *APOEε2* allele decreased the risk of AD (OR 0.36, $P = .001$; Table 2), and *APOEε4* homozygosity (*APOEε4/ε4*) increased the risk (OR 20.48, $P < .001$; Table 2). There were no significant interactions between *APOEε2* carriage and *APOEε4* homozygosity (*APOEε4/ε4*) and anti–HSV1 IgG positivity (data not shown). There were no significant

Table 1
Basic characteristics

Group	Alzheimer's disease cases, n = 360	Controls, n = 360	Odds ratio for AD* (*P* value)
Age at plasma sampling, years mean ± SD	61.2 ± 5.6	61.2 ± 5.6	
Age at diagnosis, years mean ± SD	70.8 ± 6.4		
Sex, female n (%)	271 (75.3)	271 (75.3)	
CT brain scans, n (%)	309 (85.8)		
MRIs of the brain, n (%)	32 (8.9)		
^{99m}Tc SPECT/^{18}F FDG-PET brain scans, n (%)	172 (47.8)		
Neuropsychological examinations, n (%)	125 (34.7)		
Analyses of biomarkers in cerebrospinal fluid, n (%)	34 (9.4)		
MMSE at diagnosis, mean ± SD	21.9 ± 5.0		
APOE genotype			
ε2/ε3†, n (%)	12 (3.3)	51 (14.2)	.38 (.02)
ε2/ε4, n (%)	9 (2.5)	13 (3.6)	1.01 (.99)
ε3/ε3, n (%)	116 (32.2)	185 (51.4)	Ref
ε3/ε4, n (%)	148 (41.1)	74 (20.6)	3.22 (<.001)
ε4/ε4, n (%)	67 (18.6)	6 (1.7)	19.15 (<.001)
HSV1 IgG +, n (%)	329 (91.4)	317 (88.1)	1.44 (.14)
HSV2 IgG +, n (%)	52 (14.4)	46 (12.8)	1.15 (.53)
CMV IgG +, n (%)	312 (86.7)	318 (88.3)	.857 (.50)
C. pneumoniae IgG +, n (%)	222 (61.7)	220 (61.1)	1.03 (.87)

Abbreviations: SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging; ^{99m}Tc SPECT/FDG-PET, technetium (^{99m}Tc) exametazime single-photon emission computed tomography/fludeoxyglucose (^{18}F) positron emission tomography; MMSE, Mini-Mental State Examination; *APOE*, apolipoprotein E; HSV, herpes simplex virus; Ig, Immunoglobulin; CMV, cytomegalovirus; *C. pneumoniae, Chlamydophila pneumoniae*.

*Simple conditional logistic regression. For *APOE* genotypes: with genotype *APOEε3/ε3* as reference category.

†APOE*ε2/ε2* was not analyzed separately because of the small numbers of individuals carrying this specific genotype (n = 3), and those individuals were included in the group *APOEε2/ε3*.

associations of anti–HSV2 IgG, anti–CMV IgG, or anti–*C. pneumoniae* positivity in the *APOE* models and no significant interactions with *APOE* variables (data not shown).

17 different SNPs were identified (Fig. 1) and contributed to the GRSs (Supplementary Table 1 in the Supplementary Appendix). Missing values from the final SNPs ranged from 2.2 to 4.4% for cases and from 2.5 to 3.1% for controls and were excluded from the analyses. Thus, GRSs were calculated for 334 of the 360 AD cases and for 346 of the controls.

The GRS increased the risk of AD (OR 2.64 per standard deviation, $P < .001$), as did squared GRS (OR 5.61, $P < .001$). There was a significant interaction between the GRS and anti–HSV1 IgG positivity for the risk of developing AD (OR 2.35, $P = .01$; Table 2). In this model, GRS on its own did not significantly increase the risk (OR 1.42, $P = .21$; Table 2). The interaction between the squared GRS and anti–HSV1 IgG positivity with an outcome of AD was significant (OR 8.20, $P = .005$). There was also an interaction between both the GRS and squared GRS with anti–*C. pneumoniae* IgG for AD risk (OR 0.53, $P = .04$ and OR 0.13, $P = .02$). When using GRS divided by its standard deviation in the interaction model, anti–*C. pneumoniae* IgG was significantly associated with AD risk

Table 2
Conditional logistic regression of the interaction between *APOEε4* heterozygosity/genetic risk score and herpes simplex virus type 1 carriage in the risk of Alzheimer's disease development

	Model 1, HSV1, and *APOE* variables			Model 2, HSV1, and genetic risk score			Model 3, HSV1, *APOE* variables, and genetic risk score		
Independent variables	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Anti–HSV1 IgG+	0.88	0.43–1.85	.73	1.91	1.09–3.37	.03	1.31	0.56–3.03	.53
APOEε2 carriage	0.36	0.19–0.67	.001				0.35	17–0.75	.007
APOEε4 homozygosity (*APOEε4/ε4*)	20.48	7.14–58.77	<.001				20.80	5.98–72.40	<.001
APOEε4 heterozygosity (*APOEε2/ε4* or *ε3/ε4*)	0.83	0.26–2.70	.76				0.97	0.27–3.46	.96
APOEε4 heterozygosity x anti–HSV1 IgG+	4.55	1.29–16.06	.02				3.75	0.95–14.82	.06
Genetic risk score				1.42	0.82–2.44	.21	1.26	0.55–2.84	.59
Genetic risk score x anti–HSV1 IgG+				2.35	1.21–4.56	.01	2.21	0.87–5.63	.10

Abbreviations: *APOE*, apolipoprotein E; HSV, herpes simplex virus; Ig, immunoglobulin.

(OR 1.95 $P = .04$). There were no significant interactions between the GRS or the squared GRS and anti–HSV2 IgG and anti–CMV IgG positivity for AD risk (data not shown).

In the combined model with interaction terms of both *APOEε4* heterozygosity (*APOEε2/ε4* or *ε3/ε4*) with anti–HSV1 IgG positivity and GRS with anti–HSV1 IgG positivity, the effect sizes of the interactions were nearly the same as models that included only one interaction term, although not significant (OR 3.75, $P = .06$ and OR 2.21, $P = .10$ respectively; Table 2). The effect sizes of the interactions between *APOEε4* heterozygosity (*APOEε2/ε4* or *ε3/ε4*) and anti–HSV1 IgG positivity, and the squared GRS and anti–HSV1 IgG positivity, were also nearly the same but not significant in the combined model that included both interactions of *APOEε4* heterozygosity (*APOEε2/ε4* or *ε3/ε4*) and squared GRS with anti–HSV1 IgG positivity (OR 3.85, $P = .05$ and OR 5.72, $P = .08$, respectively; Table 2).

4. Discussion

In this large nested case-control study, the *APOEε4* allele and a GRS based on nine other AD-risk genes interacted with HSV1 for increased risk of developing AD. For the first time, the host genetic background can here be shown to interact with HSV1 carriage to increase the risk for developing AD in a prospective epidemiological material. The primary strengths of this study include a large number of cases with closely matched controls from the same population, combined with thorough clinical AD diagnosis.

The present results are in accordance with the recent findings of an interaction between *APOEε4* and HSV for episodic memory decline [40]. Thus, an interaction between *APOEε4* and HSV in AD development has been demonstrated in two large independent prospective epidemiological studies. The findings show that genetic background is important for the development of HSV1-associated AD. This corresponds with AD as a multifactorial disease, caused by genetic susceptibility in combination with environmental factors [1,2,7,16,30]. One plausible explanation could be that AD development with amyloid deposition is fueled by persistent and low-grade infection in the CNS over long periods of time. Host genetics might contribute to loss of immunological control over persistent infections, allowing the CNS entry and/or a shift from a protective (innate) immune response to neuropathological processes [16,23]. The squared GRS was associated with increased risk of AD, with a higher estimated risk effect than the non-squared GRS. This might indicate that there are gene-gene interactions between different risk genes, where concomitant carriage of many risk variants results in a genetic pattern which further increases the risk of HSV1-associated AD by multiplicative effects [7,30].

Interestingly, the GRS also interacted with anti–*C. pneumoniae* IgG in regard to the risk of developing AD, although the correlation had the opposite direction compared with HSV1, meaning that with a low GRS, *C. pneumoniae* carriage was associated with increased AD risk. This might indicate that *C. pneumoniae* could be contributing to AD risk in those individuals with the lowest genetic risk of HSV1-associated AD. This may also imply heterogeneity in AD pathogenesis and that the disease is multifactorial. In contrast, anti–HSV2 IgG or anti–CMV IgG did not interact with the *APOEε4* allele, nor the GRS for AD risk.

For the present study, we selected nine genes consistently linked to the risk of AD from several studies for the calculation of the GRS [1,6,7,39]. This enabled investigation of their combined effect on AD. Nonetheless, this makes the contributing effects of individual genes indistinguishable from each other. This strategy was chosen because of the limited statistical power of the material. However, many other AD significant genes could also be worth investigating for their potential interactions with HSV1. The lack of desirable statistical power was also apparent when including the two interaction terms of *APOEε4* heterozygosity (*APOEε2/ε4* or *ε3/ε4*) with HSV1 carriage and GRS with HSV1 carriage simultaneously in the models. While not significant, the ORs of the interactions were almost unaffected when included in the same model. Still, this could indicate that the effects of *APOEε4* and other risk genes are independent of each other.

In conclusion, the interaction between *APOEε4* heterozygosity (*APOEε2/ε4* or *ε3/ε4*) and HSV1 carriage increased the risk of AD by approximately fivefold, whereas the presence of only one factor did not. A calculated GRS, based on nine additional risk genes, also interacted with anti–HSV1 IgG for increased risk of subsequent AD. The present findings suggest that the *APOEε4* allele and other AD genetic risk factors might potentiate the risk of developing HSV1-associated AD. This could provide new insights into the possible mechanisms involved in the development of AD.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2019.09.014.

RESEARCH IN CONTEXT

1. Systematic review: PubMed was used to search for previously published work. Alzheimer's disease (AD) is considered a multifactorial disease, triggered by genetic and environmental factors. A growing body of evidence indicates a potential role of herpes simplex virus type 1 (HSV1) in AD pathogenesis. Previous research has connected HSV1 outcomes with apolipoprotein Eε4 (*APOEε*4). However, no prospective epidemiological study has investigated the HSV1-*APOEε*4 interaction for AD risk.
2. Interpretation: Our findings show that host genetic background interacts with HSV1 carriage to increase the risk of subsequent AD, consistent with our earlier findings concerning HSV and *APOEε*4 in episodic memory decline.
3. Future directions: Interventional studies with antiviral agents are needed to prove the causal effect of herpes viruses in AD. Our results provide a foundation for future trials to target individuals carrying HSV1 in combination with certain genetic traits, thereby promoting a more individualized approach for treatment or prevention of AD.

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