Neurobiology of Aging xxx (2015) 1–10

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Candidate genes for Alzheimer's disease are associated with individual differences in plasma levels of beta amyloid peptides in adults with Down syndrome

Nicole Schupf[a,b,c,d,*], Annie Lee[a], Naeun Park[a], Lam-Ha Dang[a], Deborah Pang[e], Alexander Yale[f], David Kyung-Taek Oh[f], Sharon J. Krinsky-McHale[e], Edmund C. Jenkins[g], José A. Luchsinger[h], Warren B. Zigman[e], Wayne Silverman[i], Benjamin Tycko[f], Sergey Kisselev[a], Lorraine Clark[a], Joseph H. Lee[a,b,c]

[a] The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA
[b] G.H. Sergievsky Center, New York, NY, USA
[c] Department of Epidemiology, Columbia University Medical Center, New York, NY, USA
[d] Department of Psychiatry, Columbia University Medical Center, New York, NY, USA
[e] Department of Psychology, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA
[f] Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA
[g] Department of Human Genetics, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA
[h] Department of Medicine, Columbia University Medical Center, New York, NY, USA
[i] Kennedy Krieger Institute and Johns Hopkins University School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 1 October 2014
Received in revised form 8 June 2015
Accepted 14 June 2015

Keywords:
Down syndrome
β Amyloid peptides
Genetics
Biomarkers

ABSTRACT

We examined the contribution of candidates genes for Alzheimer's disease (AD) to individual differences in levels of beta amyloid peptides in adults with Down syndrom, a population at high risk for AD. Participants were 254 non-demented adults with Down syndrome, 30–78 years of age. Genomic deoxyribonucleic acid was genotyped using an Illumina GoldenGate custom array. We used linear regression to examine differences in levels of Aβ peptides associated with the number of risk alleles, adjusting for age, sex, level of intellectual disability, race and/or ethnicity, and the presence of the *APOE* ε4 allele. For Aβ42 levels, the strongest gene-wise association was found for a single nucleotide polymorphism (SNP) on *CAHLM1*; for Aβ40 levels, the strongest gene-wise associations were found for SNPs in *IDE* and *SOD1*, while the strongest gene-wise associations with levels of the Aβ42/Aβ40 ratio were found for SNPs in *SORCS1*. Broadly classified, variants in these genes may influence amyloid precursor protein processing (*CALHM1*, *IDE*), vesicular trafficking (*SORCS1*), and response to oxidative stress (*SOD1*).

1. Introduction

Amyloid β (Aβ) plays a critical role in the development of Alzheimer's disease (AD). Aβ peptides Aβ40 and Aβ42 are the 2 major species generated by sequential proteolytic cleavage by β and γ secretases of the amyloid precursor protein (APP) (Selkoe, 2001). Brain levels of Aβ42 increase early in the development of dementia (Cummings and Cotman, 1995; Naslund et al., 2000), and studies of Aβ peptides in cerebrospinal fluid (CSF) have consistently shown that declining or low levels of Aβ42 and Aβ42/Aβ40 ratio and high concentrations of tau in patients with mild cognitive impairment are associated with higher brain Aβ load (Fagan et al., 2006, 2007, 2009) and predict conversion to AD (Blennow and Hampel, 2003; Hansson et al., 2007; Jack et al., 2013). Studies of plasma Aβ have shown less consistent relationships to risk of AD than studies of CSF Aβ and inconsistent correlations between plasma and CSF Aβ peptides (Toledo et al., 2013). Elevated plasma Aβ42 levels have been proposed as a risk factor related to both age and risk for AD. Thus, although deposition of Aβ42 in brain tissue is unlikely to result directly from increased plasma levels, both brain and plasma levels may reflect a general alteration in Aβ processing and individual differences in plasma Aβ42 peptide level may serve as biological markers of risk, sensitive to the development and progression of AD.

Individuals with Down syndrome (DS) have increased risk for AD neuropathology and clinical dementia, which has been

* Corresponding author at: Taub Institute for Research on Alzheimer's Disease and the Aging Brain, P.O. Box 16, 630 West 168th Street, New York, NY 10032, USA. Tel.: +1 212 305 2381; fax: +1 212 305 2426.
E-mail address: ns24@cumc.columbia.edu (N. Schupf).

0197-4580/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2015.06.020

attributed to triplication and overexpression of the gene for *APP* located on chromosome 21 (Head et al., 2012), which leads to elevated levels of Aβ peptides from an early age (Conti et al., 2010; Head et al., 2011; Mehta et al., 1998; Schupf et al., 2001; Teller et al., 1996; Tokuda et al., 1997). In adults with DS, high initial levels of plasma Aβ42 are associated with increased risk for AD (Coppus et al., 2012; Head et al., 2011; Jones et al., 2009; Matsuoka et al., 2009; Schupf et al., 2001, 2007). However, there are large individual differences in initial Aβ peptide levels and a wide range of age at the onset of AD within this population, suggesting a more complex underlying mechanism and a role for additional risk factors.

The factors that influence individual differences in plasma Aβ peptides are not well understood. Genetic and environmental risk factors may influence the development of AD by increasing production of Aβ or by reducing clearance or excess deposition of Aβ. Compared with individuals without DS, adults with DS could also be at increased risk for AD through triplication and overexpression of genes on chromosome 21 other than *APP*, and genes on other chromosomes may modify this risk. Multiple genome-wide association studies (GWAS) have identified potential genetic pathways for AD (Bertram and Tanzi, 2012; Hollingworth et al., 2011; Jun et al., 2010; Lambert et al., 2009a, 2013; Naj et al., 2011) but only a few studies have examined their relation to Aβ levels (Bali et al., 2012; Chouraki et al., 2014; Kim et al., 2011; Miners et al., 2010; Reitz et al., 2011b). Reasoning that individuals with DS may be a population group with increased sensitivity for revealing such pathways, in this study we examined the relation of candidate genes for AD to baseline levels of Aβ peptides, Aβ42, Aβ40, and the Aβ42/Aβ40 ratio in older adults with DS. The aim was to identify genetic factors associated with individual differences in level of Aβ peptides, which might act as biomarkers of risk for AD.

2. Methods

2.1. Study population

The study sample included 254 members of a community-based cohort of adults with confirmed DS, non-demented at their initial examination. Dementia status at baseline was classified using data from all available sources reviewed during a consensus conference. Following recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability (Aylward et al., 1997; Burt and Aylward, 2000), participants were classified into 2 groups: (1) dementia, if there was a history of progressive memory loss, disorientation, and functional decline over a period of at least 1 year and if there were no other medical or psychiatric conditions that might result in or mimic dementia present (e.g., untreated hypothyroidism, stroke) and (2) without dementia, if they were without cognitive or functional decline based on performance on neuropsychological assessments referenced to level of intellectual disability tested in young adulthood, review of medical records, and interviews with informants (Silverman et al., 2004). Among participants who were non-demented at baseline, we analyzed the relation of single nucleotide polymorphisms (SNPs) in candidate genes to Aβ levels using plasma from the baseline visit (Schupf et al., 2010) to identify genetic factors associated with individual difference in levels of Aβ peptides, which might act as biomarkers of risk. All individuals were 31 years of age and older (range 31–78) and resided in New York, Connecticut, New Jersey, or northern Pennsylvania. Participants were recruited with the help of state and voluntary service provider agencies and were eligible for inclusion in the present study if (1) a family member or correspondent provided informed consent, (2) he or she either provided consent or assent indicating willingness to participate, and (3) he or she was willing and able to provide blood samples. 76.4% of the study sample was women. The high frequency of women in the study sample reflects a focus in our research program on the relationship between menopause and risk for dementia among women with Down syndrome. Recruitment, informed consent, and study procedures were approved by the Institutional Review Boards of the New York State Institute for Basic Research in Developmental Disabilities, Columbia University Medical Center, and the Johns Hopkins University School of Medicine.

2.2. Clinical assessment

Assessments included evaluations of cognition and functional abilities, behavioral and/or psychiatric conditions, and health status. Cognitive function was evaluated with a test battery designed for use with individuals varying widely in their initial levels of intellectual functioning, as previously described (Silverman et al., 2004). Structured interviews were conducted with caregivers to collect information on adaptive behavior and medical history. Past and current medical records were reviewed for all participants.

2.3. Plasma Aβ42 and Aβ40

Participants were asked to provide a 10 mL venous non-fasting blood sample (K_2EDTA lavender-top tube) at each assessment cycle. Blood draws were done between 10 AM and 4 PM. Plasma levels of Aβ42 and Aβ40 were measured blind to clinical status using a combination of monoclonal antibody 6E10 (specific to an epitope present on 1–16 amino acid residues of Aβ) and rabbit antisera R165 (vs. Aβ42) and R162 (vs. Aβ40) in a double antibody sandwich enzyme-linked immunosorbent assay as previously described (Mayeux et al., 2003; Mehta et al., 1998; Schupf et al., 2007). The detection limit for these assays was 5 pg/mL for Aβ40 and 10 pg/mL for Aβ42. Aβ40 and Aβ42 levels from each sample were measured twice using separate aliquots. Reliability between measurements was substantial for both peptides ($r = 0.93$ and 0.97 for Aβ40 and Aβ42, respectively, $p < 0.001$), and the mean of the 2 measurements was used in statistical analyses.

2.4. Apolipoprotein E genotypes

Apolipoprotein E (*APOE*) genotyping used standard polymerase chain reaction-restriction fragment length polymorphism methods using *Hha*1 (*Cfo*I) digestion of an *APOE* genomic polymerase chain reaction product spanning the polymorphic (cys/arg) sites at codons 112 and 158. Acrylamide gel electrophoresis was used to assess and document the restriction fragment sizes (Hixson and Vernier, 1990). Participants were classified according to the presence or absence of an *APOE* ε4 allele.

2.4.1. Selection of candidate genes

An initial set of candidate genes included the top candidate genes from the ALZGENE database (http://www.alzgene.org) and additional positional candidate genes from published genome-wide linkage and association studies. We used SNAP (http://www.broadinstitute.org/mpg/snap/ldsearch.php) to identify genes within the candidate regions. This process generated 6 candidate genes on chromosome 21, and 41 genes on other chromosomes. Candidate genes on chromosome 21 included the genes for *APP*, β amyloid converting enzyme-2 (*BACE2*), the Down syndrome critical region-1 (*DSCR1*), runt-related transcription factor 1 (*RUNX1*), the astrocyte-derived neurotrophic factor *S100β*, and Cu/Zn superoxide dismutase (*SOD-1*). Additional candidate

genes were on chromosomes 1, 2, 6–11, 15, 17, 19, 20, and X (see Supplementary Table 1 for the full list of genes). Fig. 1 provides an overview of SNP selection and SNP analysis performed in the two-stage candidate gene study.

2.5. SNP selection

We genotyped each gene with a sufficient number of SNPs to provide dense coverage ($r^2 \sim 0.8$), and the selected SNPs had a relatively high minor allele frequency (MAF > 0.15). To identify tag SNPs in these genes, we applied the TAGGER program (de Bakker, 2009) to a Caucasian population available from the HapMap dataset (http://hapmap.ncbi.nlm.nih.gov/). In addition, we used SNAP (http://www.broadinstitute.org/mpg/snap/ldsearch.php) to check linkage disequilibrium patterns across the genic region to ensure that the coverage was comprehensive. For chromosome 21, 263 SNPs from the 6 genes had a median MAF of 0.30 and a median inter-marker distance of 1914.5 base pairs. For chromosomes other than 21, 1110 SNPs, exclusive of *APOE*, from 41 genes had a median MAF of 0.30 and a median inter-marker distance of 1955 base pairs. We present top strands generated from the Illumina customized platform.

2.6. SNP genotyping: customized SNP array in trisomic samples

Genomic deoxyribonucleic acid was genotyped using an Illumina GoldenGate custom array. Clustering and genotype calling of chromosome 21 SNPs and non-Chr21 SNPs were performed using GenomeStudio genotyping module v1.8, which supports polyploidy loci. For SNPs on chromosome 21, the custom cluster option in GenomeStudio Genotyping Module v1.8 was used to specify 4 clusters and the custom GType was used to display genotype calls for polyploidy loci (AAA, AAB, ABB, or BBB). All genotype calls were inspected manually by viewing SNP graph cluster plots. Fig. 2 shows a typical cluster plot for one of the trisomy SNPs tested (rs2830054). The minor allele was always coded as the risk allele.

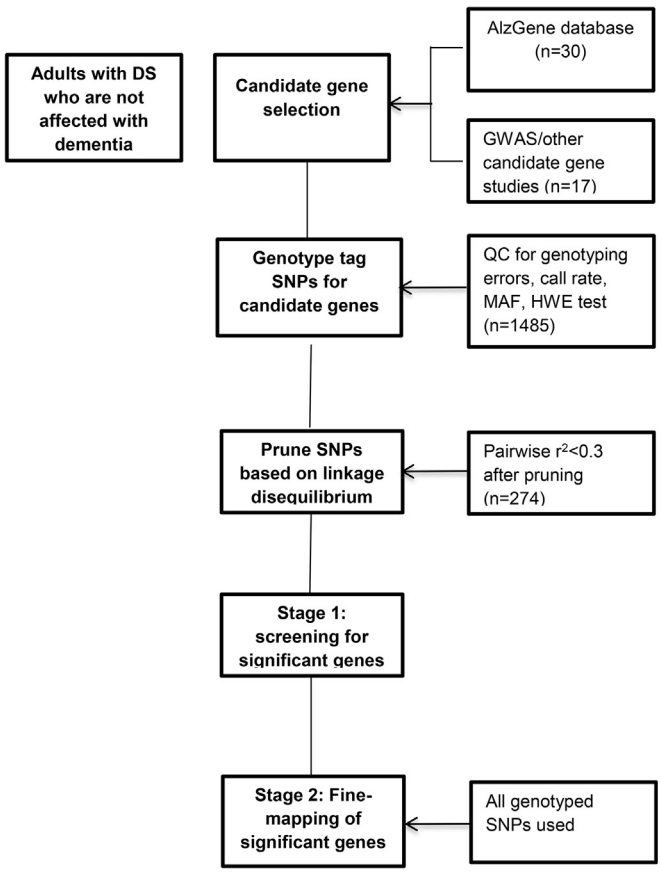

Fig. 1. Flow chart for a two-stage candidate gene study of Aβ42, Aβ40, or Aβ42/40 ratio. Abbreviation: Aβ, amyloid beta.

2.7. Quality control assessment

Before allelic association analysis, we first checked the quality of SNP genotyping. Quality scores were determined from allele cluster definitions for each SNP as determined by the Illumina GenomeStudio Genotyping Module version 3.0 and the combined intensity data from 100% of study samples. Genotype calls with a quality score (Gencall value) of ≥0.25 were considered acceptable. For chromosome 21, the average call rate was 98%. We dropped SNPs with a call rate <90% ($n = 23$) or SNPs that did not produce genotypes ($n = 9$). For chromosomes other than 21, the call rate for SNPs was 99%. A total of 11 SNPs were dropped because they had GenTrain scores below threshold or had a call rate of <98%. After the filtering process, we analyzed 231 SNPs on chromosome 21 and 1099 SNPs on chromosomes other than 21. As a further test of assay reliability, 15 randomly selected samples were genotyped in duplicate. The concordance rates for genotyped SNPs in these samples ranged from 91.8% to 100% for Chr 21 SNPs and from 95.2% to 99.6% for non-Chr 21 SNPs. We then conducted additional quality control assessments using PLINK (Purcell et al., 2007). We excluded SNPs with the following characteristics: missing genotyping rate >5%; minimum allele frequency <1%; Hardy-Weinberg equilibrium test [27] at a p value of <0.000001.

2.8. Population stratification

To adjust for population stratification, we applied the multidimensional scaling method as implemented in PLINK. Using all available SNPs that survived the quality control process, genetic similarity across individuals was estimated by computing identity by state. To anchor and cross-check against individuals with known ethnic background, we also included whites ($n = 165$), Africans ($n = 165$), and Asians ($n = 170$) from the HapMap database (www.hapmap.org). This analysis generated 3 distinct racial and/or ethnic clusters. These clusters were included in the multivariate model to account for ancestry.

2.9. Covariates

Covariates included age, sex, level of intellectual disability, race and/or ethnicity clusters from multidimensional scaling analysis, and the presence or absence of an *APOE* ε4 allele. Level of intellectual disability was classified into 2 groups based on intelligence quotient (IQ) scores obtained before onset of cognitive impairment because of onset of CMI or dementia: mild/moderate (IQ 35–70) and severe/profound (IQ < 35).

2.10. Statistical analyses

Linear regression was used to examine the relationship of potential confounders, including age, sex, race/ethnicity clusters, level of intellectual disability, and the presence of an *APOE* ε4 allele to peptide levels. To minimize penalties for multiple testing, we conducted a two-stage analysis to identify SNPs that are associated with levels of amyloid Aβ42 and Aβ40 (Fig. 1). In stage 1 (screening stage), using PLINK, we pruned SNPs to achieve a variance inflation

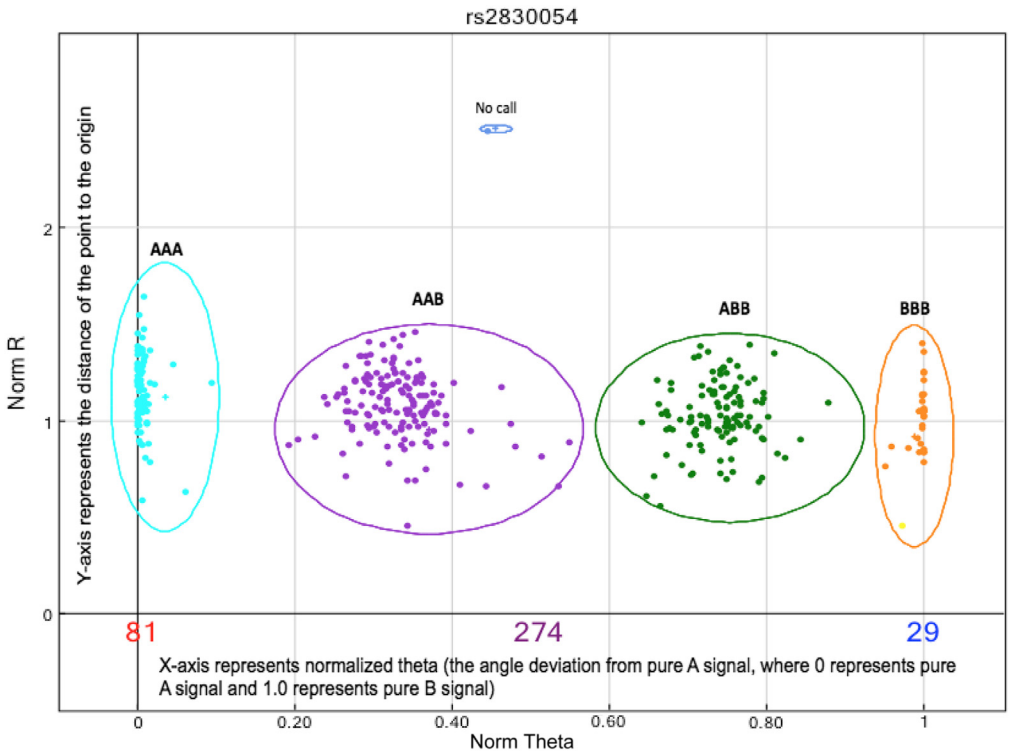

Fig. 2. Cluster plot for an SNP on chromosome 21: rs2830054 as an example. Abbreviation: SNP, single nucleotide polymorphism.

factor of 1.43, which is equivalent to a pairwise $r^2 < 0.3$. Using PLINK, we evaluated the allelic association between a SNP and Aβ42, Aβ40, and Aβ42/Aβ40 levels using a linear regression model after adjusting for confounders. An additive model was used: based on the number of risk alleles. An empirical *p*-value was computed using 10,000 permutations. In stage 2 (fine mapping stage), we focused on candidate genes where at least one SNP met an empirical *p*-value <0.05. To perform the fine mapping analysis, we included all SNPs that were genotyped within that gene. We repeated the linear regression model and, in addition, we computed adjusted *p*-values to correct for multiple testing, as proposed by Benjamini and Hochberg (1995) and Benjamini and Yekutieli (2001). The R statistical package (http://www.r-project.org/) was used to compute adjusted *p*-values. For the 3 most promising genes from the single point analysis (*CALMH1* and Aβ42, *IDE* and Aβ40, *SORCS1* and Aβ42/Aβ40 ratio), we used PLINK to conduct haplotype analysis with a 3-SNP sliding windows approach to identify contiguous regions with significant association.

3. Results

Valid genotypes were obtained for 254 participants for chromosome 21 genes and for 219 participants for non-chromosome 21 genes. The demographic characteristics of the 2 subsets of participants were comparable. For both subsets, mean age was 49.6 years, 76.4% of the study sample was women, 56.7% had a mild or moderate level of intellectual disability whereas the remainder had severe intellectual disability, and 90.6% of the sample was Caucasian. The *APOE* ε4 allele frequency was 11.3% (Table 1). Mean levels of Aβ peptides were also comparable across both sets. Mean Aβ42 level was 28.2 pg/mL (8.0–132.4) for the 254 participants with genotypes on chromosome 21 and 27.3 pg/mL (8.0–110.7) for the 219 participants with genotypes on other chromosomes. Mean Aβ40 level was 156.0 pg/mL (24.3–491.4) and the mean Aβ42/Aβ40 ratio was 0.21 pg/mL (0.047–1.15) for both subsets of participants.

For all participants, level of intellectual disability, sex, race/ethnicity components, and the presence of an *APOE* ε4 allele were not related to baseline levels of Aβ42, Aβ40, or Aβ42/Aβ40 ratio. Aβ40 levels increased with age ($r = 0.135$, $p = 0.031$), whereas levels of Aβ42 and Aβ42/Aβ40 ratio decreased with age ($r = -0.17$, $p = 0.008$ and $r = -0.16$, $p = 0.009$, respectively).

3.1. Aβ42

Stage 1 screening based on tag SNPs identified SNPs in *RUNX1* and *DSCR1* on chromosome 21 genes (Table 2), and identified SNPs in *MTHFR*, *MTHFD1L*, *RELN*, *CALHM1*, *SORCS1*, *SORL1*, *ACAN*, and *PCDH11X* on non-chromosome 21 genes that were associated with Aβ42 levels at an empirical *p*-value of <0.05 (Table 2). In stage 2 fine mapping for genes on chromosome 21, none of the SNPs for Aβ42 level achieved the adjusted gene-wise empirical *p*-values using the Benjamini and Hochberg approach (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001) (Table 2). In stage 2 fine mapping for non-chromosome 21 genes, 2 SNPs (rs177736358 and rs755577) that are ~2.5 kb apart on the calcium homeostasis modulator 1 (*CALHM1*) gene were significant after correcting for multiple testing, and 2 SNPs (rs11814111 and rs8878183) on *SORCS1* had adjusted *p*-values of 0.066, approaching the threshold of 0.05, whereas SNPs on the other non-chromosome 21 genes failed to achieve the adjusted gene-level empirical *p*-values (Table 2).

3.2. Aβ40

Stage 1 screening based on tag SNPs identified SNPs in the *APP*, *SOD1*, *DSCR1*, and *BACE2* chromosome 21 genes (Table 3) and SNPs in the *BIN1*, *RELN*, *DAPK1*, *IDE*, *ACAN*, *LDLR*, and *PCDH11X* non-chromosome 21 genes that were associated with Aβ40 levels at an

Table 1
Demographic characteristics

Characteristic	Participants
Sample size	254
Age (mean ± S.D.)	49.6 ± 6.8
Sex (n, %)	
Male	60 (23.6)
Female	194 (76.4)
Level of intellectual disability (n, %)	
Mild/moderate	144 (56.7)
Severe/profound	110 (43.3)
Ethnicity (n, %)	
White	230 (90.6)
Non-white	24 (9.4)
APOE allele frequency	
E4	0.113
E3	0.806
E2	0.0801
Aβ peptides (pg/mL: mean, range)	
Aβ42	28.2 (8.0–132.4)
Aβ40	156.0 (24.3–491.4)
Aβ42/Aβ40 ratio	0.21 (0.047–1.15)

Key: Aβ, amyloid beta; S.D., standard deviation.

empirical *p*-value of <0.05 (Table 3). In stage 2 fine mapping, 3 SNPs in the *SOD1* gene that were significant at the *p*-value of 0.05 for single point analysis barely missed the threshold $p = 0.05$ for significance ($p = 0.0529$) in the gene-wise analysis correcting for multiple testing, but none of the SNPs in *APP*, *DSCR1*, or *BACE2* chromosome 21 genes achieved significance in the gene-wise analysis (Table 2). Twelve of 13 SNPs in the insulin degrading enzyme (*IDE*) gene, spanning 20 kb, remained significant after adjusting for multiple testing, whereas SNPs in the other non-chromosome 21 genes did not achieve gene-wise empirical *p*-values (Table 3).

3.3. Aβ42/Aβ40 ratio

In stage 1 screening, SNPs in the *APP*, *RUNX1*, and *BACE2* chromosome 21 genes (Table 4) and SNPs in the *DAPK1*, *SORCS1*, *SORL1*, and *LDLR* non-chromosome 21 genes reached the threshold of 0.05 for single point analysis and were associated with variation in the level of the Aβ42/Aβ40 ratio (Table 4). In stage 2 fine mapping, the contiguous 7 SNPs for the sortilin-related VPS10 domain containing receptor 1 (*SORCS1*) gene located on 10q23-q25, which were strongly associated with the Aβ42/Aβ40 ratio in stage 1 screening, remained significant after multiple testing adjustment ($0.0337 < p < 0.0394$), whereas SNPs in the other genes did not achieve statistical significance (Table 4).

3.4. Haplotype analysis

To further characterize candidate regions that may harbor putative variants, we then performed a 3-mer sliding window haplotype analysis for the 3 promising candidate genes with the strongest support for association, *CALHM1* for Aβ42, *IDE* for Aβ40, and *SORCS1* for Aβ42/Aβ40. As shown in Supplementary Tables 2–4, multiple haplotypes anchoring on the SNPs that were significant from the single point gene-wise analysis strengthened the support for association.

4. Discussion

We found significant SNP-wise associations with Aβ peptide levels for SNPs on 17 genes of 47 candidate genes examined, and 3 genes (*CALHM1*, *IDE*, and *SORCS1*) remained significant after correcting for multiple testing. These 47 candidate genes were selected from previous genome-wide linkage, association, and expression studies of AD in the DS and general populations. Our results extend previous findings of a relationship between SNPs in *APP*, *PICALM*, *SORL1*, *BACE1*, *ALDH18A*, and *RUNX1* and risk of AD in adults with DS (Jones et al., 2013; Lee et al., 2007; Margallo-Lana et al., 2004; Patel et al., 2011) to include examination of plasma beta amyloid peptides as a critical risk factor for AD in DS, and using a wider range of SNPs and genes. We found significant gene-wise associations with Aβ peptide levels for SNPs in 3 genes: *CALHM1*, *IDE*, and *SORCS1*. For Aβ42 levels, 2 SNPs (rs755577 and rs17736358) in *CAHLM1* were associated at the gene-wise level. For Aβ40 levels, the strongest gene-wise associations were found for a set of SNPs on *IDE*, located 94,217,038 to 94,335,799 bp. These were represented by a set of contiguous 3-mer haplotypes with empirical *p*-values ranging from 0.00015 to 0.00063 (see Supplementary Table 3). As an external confirmation, the 2-stage meta-analysis of the Alzheimer Disease Genetics Consortium (ADGC) dataset reported that rs2421942 was significantly associated with AD. For levels of the Aβ42/Aβ40 ratio, the strongest gene-wise associations were found for SNPs in *SORCS1*, located in the region encompassing 108,479,649 to 108,647,761 bp. Although the exact same set of SNPs were associated with AD in the Alzheimer Disease Genetics

Table 2
Aβ42 SNPs significant in stage 1[a] and stage 2 analysis

Chr	Gene	SNP[b]	Location (Hg19)	Risk allele	MAF	Beta	SE	Empirical (pointwise)	Genewise BH adjusted empirical *p*
21	*RUNX1*	*rs8134179*	*36,279,713*	*G*	*0.188*	*3.08*	*1.20*	*0.0107*	*0.7169*
21	*DSCR1*	*rs2284599*	*35,952,322*	*T*	*0.315*	*−2.01*	*0.95*	*0.0361*	*0.1487*
21	*DSCR1*	*rs3787720*	*35,904,053*	*T*	*0.352*	*−2.10*	*1.01*	*0.0374*	*0.1487*
1	*MTHFR*	*rs17037425*	*11,870,383*	*A*	*0.131*	*3.58*	*1.81*	*0.0469*	*0.0871*
6	*MTHFD1L*	*rs10457867*	*151,318,079*	*A*	*0.172*	*3.69*	*1.61*	*0.0205*	*0.7708*
7	*RELN*	*rs362710*	*103,177,947*	*G*	*0.267*	*−2.76*	*1.34*	*0.0421*	*0.5810*
7	*RELN*	*rs362642*	*103,249,871*	*A*	*0.486*	*2.71*	*1.16*	*0.0167*	*0.5762*
10	***CALHM1***	**rs755577**	**105,224,066**	**A**	0.302	**3.32**	**1.30**	**0.0088**	**0.0352**
10	***CALHM1***	***rs17736358***	***105,226,538***	***G***	*0.174*	***4.36***	***1.51***	***0.0036***	***0.0288***
10	*SORCS1*	*rs11814111*	*108,355,659*	*A*	*0.251*	*−3.78*	*1.42*	*0.0090*	*0.0665*
10	*SORCS1*	*rs878183*	*108,533,358*	*A*	*0.183*	*4.77*	*1.54*	*0.0022*	*0.0661*
10	*SORCS1*	*rs4918282*	*108,862,741*	*A*	*0.412*	*−2.70*	*1.18*	*0.0241*	*0.1004*
11	*SORL1*	*rs578506*	*121,323,477*	*G*	*0.482*	*2.86*	*1.17*	*0.0143*	*0.8294*
15	*ACAN*	*rs2280468*	*89,381,556*	*A*	*0.299*	*−2.76*	*1.33*	*0.0371*	*0.7580*
X	*PCDH11X*	*rs5984894*	*91,393,737*	*G*	*0.461*	*3.01*	*1.21*	*0.0145*	*0.2973*
X	*PCDH11X*	*rs2573905*	*91,402,220*	*G*	*0.495*	*3.21*	*1.22*	*0.0107*	*0.2973*

Key: BH, Benjamini and Hochberg; Chr, chromosome; MAF, minor allele frequency; SNP, single nucleotide polymorphism.
[a] Positive SNPs from stage 1 are given in italics. Nonitalicized SNPs were added in stage 2.
[b] SNPs with adjusted empirical $p < 0.05$ based on the genewise Benjamini and Hochberg method in stage 2 are in bold.

Table 3
Aβ40 SNPs significant in stage 1[a] and stage 2 analysis

Chr	Gene	SNP[b]	Location (Hg19)	Minor allele	MAF	Beta	SE	Empirical (pointwise)	Genewise BH adjusted empirical *p*
21	*APP*	*rs7283500*	*27,343,288*	*C*	*0.207*	*−11.61*	*5.45*	*0.0326*	*0.7137*
21	*SOD1*	rs1041740	33,040,162	T	0.319	−10.61	4.51	0.0191	0.0529
21	*SOD1*	*rs4817420*	*33,040,371*	*A*	*0.323*	*−9.5*	*4.49*	*0.037*	*0.0529*
21	*SOD1*	rs12626475	33,042,929	G	0.339	−8.73	4.52	0.0529	0.0529
21	*DSCR1*	*rs3787720*	*35,904,053*	*T*	*0.352*	*−10.88*	*4.47*	*0.0149*	*0.1886*
21	*BACE2*	*rs6517653*	*42,534,253*	*A*	*0.169*	*13.05*	*5.45*	*0.0174*	*0.2353*
2	*BIN1*	*rs1866236*	*127,895,655*	*C*	*0.287*	*17.95*	*6.17*	*0.0041*	*0.1148*
7	*RELN*	*rs11981312*	*103,289,857*	*A*	*0.351*	*18.53*	*7.07*	*0.0089*	*0.4071*
7	*RELN*	*rs12705170*	*103,581,271*	*A*	*0.208*	*−18.11*	*7.13*	*0.0118*	*0.4071*
9	*DAPK1*	*rs3128522*	*90,216,821*	*G*	*0.299*	*−14.01*	*6.45*	*0.0290*	*0.6386*
10	***IDE***	**rs11187009**	**94,217,038**	**A**	**0.224**	**23.37**	**6.75**	**0.0005**	**0.0020**
10	***IDE***	**rs7899603**	**94,225,017**	**G**	**0.373**	**20.78**	**5.97**	**0.0003**	**0.0020**
10	***IDE***	**rs4646957**	**94,229,912**	**A**	**0.339**	**18.61**	**6.10**	**0.0022**	**0.0048**
10	***IDE***	**rs11187025**	**94,257,976**	**A**	**0.188**	**24.34**	**7.29**	**0.0009**	**0.0021**
10	***IDE***	**rs17445028**	**94,271,176**	**G**	**0.188**	**24.34**	**7.29**	**0.0009**	**0.0021**
10	***IDE***	**rs7078413**	**94,290,484**	**C**	**0.315**	**24.29**	**6.19**	**0.0001**	**0.0020**
10	***IDE***	**rs1832197**	**94,298,331**	**A**	**0.364**	**20.17**	**5.90**	**0.0007**	**0.0020**
10	***IDE***	**rs11187060**	**94,304,132**	**A**	**0.321**	**20.72**	**6.02**	**0.0005**	**0.0020**
10	***IDE***	**rs17445328**	**94,305,189**	**G**	**0.224**	**23.37**	**6.75**	**0.0005**	**0.0020**
10	***IDE***	**rs11187064**	**94,308,253**	**G**	**0.224**	**23.37**	**6.75**	**0.0005**	**0.0020**
10	***IDE***	**rs7076966**	**94,325,511**	**A**	**0.491**	**−14.29**	**6.37**	**0.0267**	**0.0534**
10	***IDE***	**rs7099761**	**94,335,799**	**A**	**0.480**	**20.54**	**6.20**	**0.0007**	**0.0020**
10	***IDE***	***rs11187076***	***94,336,963***	***G***	***0.423***	***22.57***	***6.46***	***0.0006***	***0.0020***
15	*ACAN*	*rs1983332*	*89,409,603*	*G*	*0.290*	*−12.83*	*6.39*	*0.0456*	*0.3053*
19	*LDLR*	*rs4804570*	*11,256,059*	*G*	*0.224*	*−18.26*	*7.60*	*0.0172*	*0.2408*
X	*PCDH11X*	*rs5942146*	*91,437,953*	*A*	*0.491*	*−14.03*	*6.06*	*0.0181*	*0.2255*
X	*PCDH11X*	*rs3855797*	*91,704,677*	*A*	*0.246*	*−15.70*	*7.68*	*0.0431*	*0.2895*

Key: BH, Benjamini and Hochberg; Chr, chromosome; MAF, minor allele frequency; SE, standard error; SNP, single nucleotide polymorphism.
[a] Positive SNPs from stage 1 are given in italics. Nonitalicized SNPs were added in stage 2.
[b] SNPs with adjusted empirical $p < 0.05$ based on the genewise Benjamini and Hochberg method in stage 2 are in bold.

Consortium meta-analysis, rs12248379 (chr10:108562008) ($p = 0.00534$) overlapped with haplotype A–C–C that was significant in our dataset ($p = 0.00329$). Broadly classified, variants in these genes may influence APP processing (*CALHM1*, *IDE*) and vesicular trafficking (*SORCS1*), neurodevelopmental processes, response to oxidative stress (*SOD1*).

Processing of APP by cleavage by β and γ secretases to generate Aβ peptides is central to the pathogenesis of AD (Vardarajan et al., 2012). Missense mutations in the gene for *APP*, which increase the proteolytic conversion of APP into the fibrillogenic Aβ42 peptide, have been shown to lead to early onset of AD (Goate et al., 1991; Guerreiro et al., 2012; Rogaeva et al., 2007; Scheuner et al., 1996; Younkin, 1997), but less work has been done on the relation of common SNPs in *APP* to age at onset, risk of AD, or individual differences in Aβ peptide levels (Benitez et al., 2013; Chapman et al., 2013; Kimura et al., 2007; Shulman et al., 2013). Several, but not all, studies have found a relationship between high initial levels of Aβ42 and subsequent development of AD, both among adults with Down syndrome (Coppus et al., 2012; Head et al., 2011; Jones et al., 2009; Matsuoka et al., 2009; Schupf et al., 2001, 2007) and in the general population (Blasko et al., 2010; Mayeux et al., 1999, 2003; Pomara et al., 2005; Schupf et al., 2008). However, large GWAS studies of AD have not found an association between SNPs in *APP* and late onset AD (LOAD) (Bertram and Tanzi, 2012; Hollingworth et al., 2011; Lambert

Table 4
Aβ42/Aβ40 SNPs significant in stage 1[a] and stage 2 analysis

Chr	Gene	SNP[b]	Location (Hg19)	Minor allele	MAF	Beta	SE	Empirical (pointwise)	Genewise BH adjusted empirical *p*
21	*APP*	*rs7283500*	*27,343,288*	*C*	*0.207*	*0.03*	*0.01*	*0.049*	*0.3305*
21	*RUNX1*	*rs12627198*	*36,420,786*	*A*	*0.156*	*−0.04*	*0.02*	*0.0163*	*0.3585*
21	*BACE2*	*rs6517653*	*42,534,253*	*A*	*0.169*	*−0.04*	*0.01*	*0.0144*	*0.2496*
21	*BACE2*	*rs8130833*	*42,556,885*	*G*	*0.278*	*−0.03*	*0.01*	*0.0462*	*0.3295*
21	*BACE2*	*rs960230*	*42,622,479*	*T*	*0.171*	*0.05*	*0.02*	*0.0056*	*0.2496*
9	*DAPK1*	*rs2058882*	*90,114,746*	*G*	*0.1878*	*−0.04*	*0.02*	*0.0436*	*0.8611*
9	*DAPK1*	*rs3095747*	*90,218,678*	*C*	*0.3416*	*−0.04*	*0.02*	*0.0152*	*0.8611*
10	*SORCS1*	*rs11814111*	*108,355,659*	*A*	*0.2511*	*−0.05*	*0.02*	*0.0067*	*0.0577*
10	***SORCS1***	**rs10884341**	**108,479,649**	**A**	0.1946	**0.06**	**0.02**	**0.0022**	**0.0337**
10	***SORCS1***	**rs11193042**	**108,531,704**	**C**	0.2081	**0.06**	**0.02**	**0.0021**	**0.0337**
10	***SORCS1***	***rs878183***	***108,533,358***	***A***	*0.1833*	***0.07***	***0.02***	***0.0017***	***0.0337***
10	***SORCS1***	**rs11193046**	**108,536,810**	**A**	0.2104	**0.06**	**0.02**	**0.0021**	**0.0337**
10	***SORCS1***	**rs7091546**	**108,546,957**	**G**	0.2081	**0.06**	**0.02**	**0.0015**	**0.0337**
10	***SORCS1***	**rs10509823**	**108,554,591**	**G**	0.2104	**0.06**	**0.02**	**0.0021**	**0.0337**
10	***SORCS1***	**rs7916892**	**108,647,761**	**C**	0.4072	**0.05**	**0.02**	**0.0030**	**0.0394**
11	*SORL1*	*rs578506*	*121,323,477*	*G*	*0.4819*	*0.03*	*0.02*	*0.0323*	*0.9796*
19	*LDLR*	*rs4804570*	*11,256,059*	*G*	*0.224*	*0.04*	*0.02*	*0.0352*	*0.2464*

Key: Aβ, amyloid beta; BH, Benjamini and Hochberg; Chr, chromosome; MAF, minor allele frequency; SE, standard error; SNP, single nucleotide polymorphism.
[a] Positive SNPs from stage 1 are given in italics. Nonitalicized SNPs were added in stage 2.
[b] SNPs with adjusted empirical $p < 0.05$ based on the genewise Benjamini and Hochberg method in stage 2 are in bold.

et al., 2009b; Naj et al., 2011). A recent GWAS meta-analysis of plasma Aβ peptide concentrations in non-demented elderly also failed to find SNPs on *APP* that were associated with Aβ levels, although several suggestive loci were found on other genes; the gene most strongly associated with Aβ42 was *CTXN3* (cortexin3), involved in Aβ42 secretion (Chouraki et al., 2014). In our cohort of adults with DS, we did find SNPs on *APP* that were significantly associated with Aβ peptides in the single point analysis; however, after correcting for multiple testing at the gene-wise level, those SNPs were no longer significant. This may reflect the very high level of Aβ that is found among all adults with DS (Conti et al., 2010; Head et al., 2011; Mehta et al., 1998; Schupf et al., 2001; Teller et al., 1996; Tokuda et al., 1997): it may be that processing and clearance rather than generation of Aβ are more important factors associated with the individual differences we have examined. It is also possible, given the results of the single point analysis, that studies of SNPs in *APP*, using a much larger sample than we were able to study in this article, will identify SNPs in *APP* associated with individual differences in levels of Aβ peptides.

We found that the A allele in rs755577 and the G allele in rs17736358 on *CALHM1* were associated with individual differences in Aβ42 levels. However, this SNP is located 5.8 and 8.3 kb away from rs2986017 the SNP that has been associated with increased risk and age at onset in some (Boada et al., 2010; Dreses-Werringloer et al., 2008; Lambert et al., 2010), but not all (Beecham et al., 2009; Bertram et al., 2008; Minster et al., 2009) prior studies. *CALHM1* is expressed in the hippocampus and encodes a calcium channel involved in APP processing. The *CALHM1* rs2986017 polymorphism has been proposed to increase Aβ levels by interfering with *CALHM1*-mediated Ca^{2+} permeability (Dreses-Werringloer et al., 2008). Replication in a larger dataset will be required to confirm this finding.

We found SNPs on *IDE* that were associated with individual differences in Aβ40 levels. *IDE* shares insulin and Aβ as substrates (Kurochkin and Goto, 1994). Consistent with our findings, *IDE* is upregulated in amyloid plaques (Bernstein et al., 1999) and lower expression of *IDE* is found in the hippocampus in brains of elders with LOAD who are *APOE* ε4 positive (Cook et al., 2003; Qiu and Folstein, 2006), and in persons with mild cognitive impairment (Zhao et al., 2007), who are at highest risk for LOAD. Lower *IDE* expression has also been found to correlate with higher levels of cellular Aβ42 associated with *PSEN1* mutations in cellular models. Several studies have found an association between a variant on *IDE* and plasma Aβ42 or Aβ40 levels (Carrasquillo et al., 2010; Reitz et al., 2012). However, data on the relation of the *IDE* locus with AD are conflicting. Some studies showed no association between the *IDE* locus and LOAD (Abraham et al., 2001; Boussaha et al., 2002; Nowotny et al., 2005; Ozturk et al., 2006; Sakai et al., 2004), whereas other studies have found an association (Carrasquillo et al., 2010; Vepsalainen et al., 2007; Zuo and Jia, 2009).

SORCS1 is a member of the vacuolar protein sorting 10 (VPS10) domain-containing receptor protein family. VPS10 receptors are involved with APP trafficking and can influence APP processing and Aβ production through linking APP to the endosomal retromer complex and access to secretases that cleave APP (Lane et al., 2010, 2013). SNPs in *SORCS1* have been associated with increased risk for late onset AD (Reitz et al., 2011a; Rogaeva et al., 2007) and also influence Aβ peptide levels where overexpression of *SORCS1* reduces γ-secretase activity and Aβ levels, and *SORCS1* suppression increases γ-secretase processing of APP and Aβ levels (Rogaeva et al., 2007).

An interesting connection between *IDE* and *SORCS1*, the candidate genes with strongest signals in chromosome 10 in our study, is that both may be related to hyperinsulinemia and type 2 diabetes, potential important risk factors for LOAD (Cheng et al., 2011; Luchsinger et al., 2004). Certain *IDE* genotypes are related to a higher risk of diabetes (Fakhrai-Rad et al., 2000; Karamohamed et al., 2003; Kwak et al., 2008; Rudovich et al., 2009), although the contribution of *IDE* to diabetes is controversial (Groves et al., 2003) and other studies have found no relationship (Florez et al., 2006; Qin and Jia, 2008). *SORCS1* may also affect insulin levels and the risk of diabetes (Clee et al., 2006; Goodarzi et al., 2007; Lane et al., 2010). Diabetes and insulin resistance are also more prevalent in persons with Down syndrome (Fonseca et al., 2005). Thus, the connection of *IDE*, *SORCS1*, insulin resistance and diabetes, Aβ and AD in Down syndrome requires further investigation.

Several genes on chromosome 21 are involved in inflammation and are overexpressed in DS, including *APP*, superoxide dismutase (*SOD-1*), Ets-2 transcription factors, Down Syndrome Critical Region 1 (*DSCR1*) stress-inducible factor, beta-site APP cleaving enzyme (*BACE-2*), and *S100β*. In this study, SNPs in *SOD1* were associated with individual differences in levels of Aβ40, but not with Aβ42 or the Aβ42/Aβ40 ratio, and *SOD1* has been implicated in neurodegenerative processes (Lott et al., 2006). Adults with DS overexpress *SOD1* and show increased free radical–mediated oxidative damage (Markesbery and Lovell, 2007; Reynolds and Cutts, 1993). Increased SOD1 expression has been found in degenerating neurons in the brain of adults with DS (Furuta et al., 1995). The rate of production of Aβ from APP may be increased in the presence of this type of oxidative damage (Dickinson and Singh, 1993; Lott and Head, 2001), where membrane damage secondary to lipoperoxidation allows for abnormal cleavage of the protein (Singth and Dickinson, 2006). Zis et al. (2012) observed in a longitudinal study that higher SOD levels were positively associated with memory performance over a period of 4 years in 26 adults with Down syndrome and suggested that these enzymes may have protective, antioxidant effects. Further work will need to be conducted to determine the contribution of SOD levels to onset of dementia in adults with DS.

In sum, recent GWAS and meta-analyses of genes associated with risk for AD have identified SNPs associated with several major pathways, including amyloid production, lipid/cholesterol metabolism, immune response and inflammation, vesicular trafficking/synaptic function, and neurodevelopment. Our study examined the relation of candidate genes for AD to individual differences in Aβ peptide levels among unaffected adults with Down syndrome. We found significant associations with candidate genes in several of these pathways but the strongest associations were related to Aβ processing, neuro-developmental processes, and oxidative damage. These findings support the hypothesis that individual differences in Aβ processing or deposition, distinct from overexpression of *APP*, may act as an initial step in the pathogenesis of AD.

Our study has several limitations. Timing of blood draws was not specifically controlled for. Blood draws were done between 10 AM and 4 PM. We believe that this diurnal variation is unlikely to alter the relation between Aβ levels and SNPs, since timing was randomly distributed and variations would be expected to lead to non-differential bias. However, this is a potential source of increased variability in our Aβ measures.

Not all the genes associated with individual differences in Aβ peptide levels in our cohort of adults with DS have been confirmed in recent large GWAS and meta-analyses as associated with risk for AD in the general population. Our study is limited by a relatively small sample size, but examined the role of these genes in a very high-risk group that is characterized by early onset of AD and by especially high levels of Aβ peptides. These findings may therefore help to clarify pathways that contribute to the development of AD, both in adults with DS and within the broader population.

Disclosure statement

The authors have no conflicts of interest to declare.

Acknowledgements

This research was supported by grants R01AG014673 (Schupf) and P01HD35897 (Silverman) from NIA and NICHD and by NYS through its Office for People with Developmental Disabilities.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2015.06.020.

References

Abraham, R., Myers, A., Wavrant-DeVrieze, F., Hamshere, M.L., Thomas, H.V., Marshall, H., Compton, D., Spurlock, G., Turic, D., Hoogendoorn, B., Kwon, J.M., Petersen, R.C., Tangalos, E., Norton, J., Morris, J.C., Bullock, R., Liolitsa, D., Lovestone, S., Hardy, J., Goate, A., O'Donovan, M., Williams, J., Owen, M.J., Jones, L., 2001. Substantial linkage disequilibrium across the insulin-degrading enzyme locus but no association with late-onset Alzheimer's disease. Hum. Genet. 109, 646–652.

Aylward, E.H., Burt, D.B., Thorpe, L.U., Lai, F., Dalton, A., 1997. Diagnosis of dementia in individuals with intellectual disability. J. Intellect. Disabil. Res. 41 (Pt 2), 152–164.

Bali, J., Gheinani, A.H., Zurbriggen, S., Rajendran, L., 2012. Role of genes linked to sporadic Alzheimer's disease risk in the production of beta-amyloid peptides. Proc. Natl. Acad. Sci. U. S. A. 109, 15307–15311.

Beecham, G.W., Schnetz-Boutaud, N., Haines, J.L., Pericak-Vance, M.A., 2009. CALHM1 polymorphism is not associated with late-onset Alzheimer disease. Ann. Hum. Genet. 73 (Pt 3), 379–381.

Benitez, B.A., Karch, C.M., Cai, Y., Jin, S.C., Cooper, B., Carrell, D., Bertelsen, S., Chibnik, L., Schneider, J.A., Bennett, D.A., Alzheimer's Disease Neuroimaging, IGenetic, environmental risk for Alzheimer's disease consortium, G, Fagan, A.M., Holtzman, D., Morris, J.C., Goate, A.M., Cruchaga, C., 2013. The PSEN1, p.E318G variant increases the risk of Alzheimer's disease in APOE-epsilon4 carriers. PLoS Genet. 9, e1003685.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Statist. Soc. B (Methodological) 57, 289–300.

Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing under dependency. Ann. Stat. 29, 1165–1188.

Bernstein, H.G., Ansorge, S., Riederer, P., Reiser, M., Frolich, L., Bogerts, B., 1999. Insulin-degrading enzyme in the Alzheimer's disease brain: prominent localization in neurons and senile plaques. Neurosci. Lett. 263, 161–164.

Bertram, L., Schjeide, B.M., Hooli, B., Mullin, K., Hiltunen, M., Soininen, H., Ingelsson, M., Lannfelt, L., Blacker, D., Tanzi, R.E., 2008. No association between CALHM1 and Alzheimer's disease risk. Cell 135, 993–994.

Bertram, L., Tanzi, R.E., 2012. The genetics of Alzheimer's disease. Prog. Mol. Biol. Transl. Sci. 107, 79–100.

Blasko, I., Kemmler, G., Jungwirth, S., Wichart, I., Krampla, W., Weissgram, S., Jellinger, K., Tragl, K.H., Fischer, P., 2010. Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer disease. Am. J. Geriatr. Psychiatry 18, 973–982.

Blennow, K., Hampel, H., 2003. CSF markers for incipient Alzheimer's disease. Lancet Neurol. 2, 605–613.

Boada, M., Antunez, C., Lopez-Arrieta, J., Galan, J.J., Moron, F.J., Hernandez, I., Marin, J., Martinez-Lage, P., Alegret, M., Carrasco, J.M., Moreno, C., Real, L.M., Gonzalez-Perez, A., Tarraga, L., Ruiz, A., 2010. CALHM1 P86L polymorphism is associated with late-onset Alzheimer's disease in a recessive model. J. Alzheimers Dis. 20, 247–251.

Boussaha, M., Hannequin, D., Verpillat, P., Brice, A., Frebourg, T., Campion, D., 2002. Polymorphisms of insulin degrading enzyme gene are not associated with Alzheimer's disease. Neurosci. Lett. 329, 121–123.

Burt, D.B., Aylward, E.H., 2000. Test battery for the diagnosis of dementia in individuals with intellectual disability. Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Intellectual Disability. J. Intellect. Disabil. Res. 44 (Pt 2), 175–180.

Carrasquillo, M.M., Belbin, O., Zou, F., Allen, M., Ertekin-Taner, N., Ansari, M., Wilcox, S.L., Kashino, M.R., Ma, L., Younkin, L.H., Younkin, S.G., Younkin, C.S., Dincman, T.A., Howard, M.E., Howell, C.C., Stanton, C.M., Watson, C.M., Crump, M., Vitart, V., Hayward, C., Hastie, N.D., Rudan, I., Campbell, H., Polasek, O., Brown, K., Passmore, P., Craig, D., McGuinness, B., Todd, S., Kehoe, P.G., Mann, D.M., Smith, A.D., Beaumont, H., Warden, D., Holmes, C., Heun, R., Kolsch, H., Kalsheker, N., Pankratz, V.S., Dickson, D.W., Graff-Radford, N.R., Petersen, R.C., Wright, A.F., Younkin, S.G., Morgan, K., 2010. Concordant association of insulin degrading enzyme gene (IDE) variants with IDE mRNA, Abeta, and Alzheimer's disease. PLoS One 5, e8764.

Chapman, J., Rees, E., Harold, D., Ivanov, D., Gerrish, A., Sims, R., Hollingworth, P., Stretton, A., Holmans, P., Owen, M.J., ODonovan, M.C., Williams, J., Kirov, G., Consortium, G, 2013. A genome-wide study shows a limited contribution of rare copy number variants to Alzheimer's disease risk. Hum. Mol. Genet. 22, 816–824.

Cheng, D., Noble, J., Tang, M.X., Schupf, N., Mayeux, R., Luchsinger, .A., 2011. Type 2 diabetes and late-onset Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 31, 424–430.

Chouraki, V., De Bruijn, R.F., Chapuis, J., Bis, J.C., Reitz, C., Schraen, S., Ibrahim-Verbaas, C.A., Grenier-Boley, B., Delay, C., Rogers, R., Demiautte, F., Mounier, A., Fitzpatrick, A.L., Alzheimer's Disease Neuroimaging, I, Berr, C., Dartigues, J.F., Uitterlinden, A.G., Hofman, A., Breteler, M., Becker, J.T., Lathrop, M., Schupf, N., Alperovitch, A., Mayeux, R., van Duijn, C.M., Buee, L., Amouyel, P., Lopez, O.L., Ikram, M.A., Tzourio, C., Lambert, J.C., 2014. A genome-wide association meta-analysis of plasma Aβ peptides concentrations in the elderly. Mol. Psychiatry 19, 1326–1335.

Clee, S.M., Yandell, B.S., Schueler, K.M., Rabaglia, M.E., Richards, O.C., Raines, S.M., Kabara, E.A., Klass, D.M., Mui, E.T., Stapleton, D.S., Gray-Keller, M.P., Young, M.B., Stoehr, J.P., Lan, H., Boronenkov, I., Raess, P.W., Flowers, M.T., Attie, A.D., 2006. Positional cloning of Sorcs1, a type 2 diabetes quantitative trait locus. Nat. Genet. 38, 688–693.

Conti, E., Galimberti, G., Piazza, F., Raggi, M.E., Ferrarese, C., 2010. Increased soluble APPalpha, Abeta 1-42, and anti-Abeta 1-42 antibodies in plasma from down syndrome patients. Alzheimer Dis. Assoc. Disord. 24, 96–100.

Cook, D.G., Leverenz, J.B., McMillan, P.J., Kulstad, J.J., Ericksen, S., Roth, R.A., Schellenberg, G.D., Jin, L.W., Kovacina, K.S., Craft, S., 2003. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-epsilon4 allele. Am. J. Pathol. 162, 313–319.

Coppus, A.M., Schuur, M., Vergeer, J., Janssens, A.C., Oostra, B.A., Verbeek, M.M., van Duijn, C.M., 2012. Plasma beta amyloid and the risk of Alzheimer's disease in Down syndrome. Neurobiol. Aging 33, 1988–1994.

Cummings, B.J., Cotman, C.W., 1995. Image analysis of beta-amyloid load in Alzheimer's disease and relation to dementia severity. Lancet. 346, 1524–1528.

de Bakker, P.I., 2009. Selection and evaluation of Tag-SNPs using Tagger and HapMap. Cold Spring Harb. Protoc. 2009 pdb ip67.

Dickinson, M.J., Singh, I., 1993. Down's syndrome, dementia, and superoxide dismutase. Br. J. Psychiatry 162, 811–817.

Dreses-Werringloer, U., Lambert, J.C., Vingtdeux, V., Zhao, H., Vais, H., Siebert, A., Jain, A., Koppel, J., Rovelet-Lecrux, A., Hannequin, D., Pasquier, F., Galimberti, D., Scarpini, E., Mann, D., Lendon, C., Campion, D., Amouyel, P., Davies, P., Foskett, J.K., Campagne, F., Marambaud, P., 2008. A polymorphism in CALHM1 influences Ca^{2+} homeostasis, Abeta levels, and Alzheimer's disease risk. Cell 133, 1149–1161.

Fagan, A.M., Mintun, M.A., Mach, R.H., Lee, S.Y., Dence, C.S., Shah, A.R., LaRossa, G.N., Spinner, M.L., Klunk, W.E., Mathis, C.A., DeKosky, S.T., Morris, J.C., Holtzman, D.M., 2006. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann. Neurol. 59, 512–519.

Fagan, A.M., Mintun, M.A., Shah, A.R., Aldea, P., Roe, C.M., Mach, R.H., Marcus, D., Morris, J.C., Holtzman, D.M., 2009. Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. EMBO Mol. Med. 1, 371–380.

Fagan, A.M., Roe, C.M., Xiong, C., Mintun, M.A., Morris, J.C., Holtzman, D.M., 2007. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Arch. Neurol. 64, 343–349.

Fakhrai-Rad, H., Nikoshkov, A., Kamel, A., Fernstrom, M., Zierath, J.R., Norgren, S., Luthman, H., Galli, J., 2000. Insulin-degrading enzyme identified as a candidate diabetes susceptibility gene in GK rats. Hum. Mol. Genet. 9, 2149–2158.

Florez, J.C., Wiltshire, S., Agapakis, C.M., Burtt, N.P., de Bakker, P.I., Almgren, P., Bengtsson Bostrom, K., Tuomi, T., Gaudet, D., Daly, M.J., Hirschhorn, J.N., McCarthy, M.I., Altshuler, D., Groop, L., 2006. High-density haplotype structure and association testing of the insulin-degrading enzyme (IDE) gene with type 2 diabetes in 4,206 people. Diabetes 55, 128–135.

Fonseca, C.T., Amaral, D.M., Ribeiro, M.G., Beserra, I.C., Guimaraes, M.M., 2005. Insulin resistance in adolescents with Down syndrome: a cross-sectional study. BMC Endocr. Disord. 5, 6.

Furuta, A., Price, D.L., Pardo, C.A., Troncoso, J.C., Xu, Z.S., Taniguchi, N., Martin, L.J., 1995. Localization of superoxide dismutases in Alzheimer's disease and Down's syndrome neocortex and hippocampus. Am. J. Pathol. 146, 357–367.

Goate, A., Chartier-Harlin, M.C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot, C., Pericak-Cance, M., Roses, A., Williamson, R., Rossor, M., Owen, M., Hardy, J., 1991. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 349, 704–706.

Goodarzi, M.O., Lehman, D.M., Taylor, K.D., Guo, X., Cui, J., Quinones, M.J., Clee, S.M., Yandell, B.S., Blangero, J., Hsueh, W.A., Attie, A.D., Stern, M.P., Rotter, J.I., 2007. SORCS1: a novel human type 2 diabetes susceptibility gene suggested by the mouse. Diabetes 56, 1922–1929.

Groves, C.J., Wiltshire, S., Smedley, D., Owen, K.R., Frayling, T.M., Walker, M., Hitman, G.A., Levy, J.C., O'Rahilly, S., Menzel, S., Hattersley, A.T., McCarthy, M.I., 2003. Association and haplotype analysis of the insulin-degrading enzyme (IDE) gene, a strong positional and biological candidate for type 2 diabetes susceptibility. Diabetes 52, 1300–1305.

Guerreiro, R.J., Gustafson, D.R., Hardy, J., 2012. The genetic architecture of Alzheimer's disease: beyond APP, PSENs and APOE. Neurobiol. Aging. 33, 437–456.

Hansson, O., Zetterberg, H., Buchhave, P., Andreasson, U., Londos, E., Minthon, L., Blennow, K., 2007. Prediction of Alzheimer's disease using the CSF Abeta42/Abeta40 ratio in patients with mild cognitive impairment. Dement. Geriatr. Cogn. Disord. 23, 316–320.

Head, E., Doran, E., Nistor, M., Hill, M., Schmitt, F.A., Haier, R.J., Lott, I.T., 2011. Plasma amyloid-beta as a function of age, level of intellectual disability, and presence of dementia in Down syndrome. J. Alzheimers Dis. 23, 399–409.

Head, E., Silverman, W., Patterson, D., Lott, I.T., 2012. Aging and Down syndrome. Curr. Gerontol. Geriatr. Res. 2012, 412536.

Hixson, J.E., Vernier, D.T., 1990. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with Hhal. J. Lipid Res. 31, 545–548.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J.C., Carrasquillo, M.M., Abraham, R., Hamshere, M.L., Pahwa, J.S., Moskvina, V., Dowzell, K., Jones, N., Stretton, A., Thomas, C., Richards, A., Ivanov, D., Widdowson, C., Chapman, J., Lovestone, S., Powell, J., Proitsi, P., Lupton, M.K., Brayne, C., Rubinsztein, D.C., Gill, M., Lawlor, B., Lynch, A., Brown, K.S., Passmore, P.A., Craig, D., McGuinness, B., Todd, S., Holmes, C., Mann, D., Smith, A.D., Beaumont, H., Warden, D., Wilcock, G., Love, S., Kehoe, P.G., Hooper, N.M., Vardy, E.R., Hardy, J., Mead, S., Fox, N.C., Rossor, M., Collinge, J., Maier, W., Jessen, F., Ruther, E., Schurmann, B., Heun, R., Kolsch, H., van den Bussche, H., Heuser, I., Kornhuber, J., Wiltfang, J., Dichgans, M., Frolich, L., Hampel, H., Gallacher, J., Hull, M., Rujescu, D., Giegling, I., Goate, A.M., Kauwe, J.S., Cruchaga, C., Nowotny, P., Morris, J.C., Mayo, K., Sleegers, K., Bettens, K., Engelborghs, S., De Deyn, P.P., Van Broeckhoven, C., Livingston, G., Bass, N.J., Gurling, H., McQuillin, A., Gwilliam, R., Deloukas, P., Al-Chalabi, A., Shaw, C.E., Tsolaki, M., Singleton, A.B., Guerreiro, R., Muhleisen, T.W., Nothen, M.M., Moebus, S., Jockel, K.H., Klopp, N., Wichmann, H.E., Pankratz, V.S., Sando, S.B., Aasly, J.O., Barcikowska, M., Wszolek, Z.K., Dickson, D.W., Graff-Radford, N.R., Petersen, R.C., Alzheimer's Disease Neuroimaging, I, van Duijn, C.M., Breteler, M.M., Ikram, M.A., DeStefano, A.L., Fitzpatrick, A.L., Lopez, O., Launer, L.J., Seshadri, S., Consortium, C, Berr, C., Campion, D., Epelbaum, J., Dartigues, J.F., Tzourio, C., Alperovitch, A., Lathrop, M., Consortium, E, Feulner, T.M., Friedrich, P., Riehle, C., Krawczak, M., Schreiber, S., Mayhaus, M., Nicolhaus, S., Wagenpfeil, S., Steinberg, S., Stefansson, H., Stefansson, K., Snaedal, J., Bjornsson, S., Jonsson, P.V., Chouraki, V., Genier-Boley, B., Hiltunen, M., Soininen, H., Combarros, O., Zelenika, D., Delepine, M., Bullido, M.J., Pasquier, F., Mateo, I., Frank-Garcia, A., Porcellini, E., Hanon, O., Coto, E., Alvarez, V., Bosco, P., Siciliano, G., Mancuso, M., Panza, F., Solfrizzi, V., Nacmias, B., Sorbi, S., Bossu, P., Piccardi, P., Arosio, B., Annoni, G., Seripa, D., Pilotto, A., Scarpini, E., Galimberti, D., Brice, A., Hannequin, D., Licastro, F., Jones, L., Holmans, P.A., Jonsson, T., Riemenschneider, M., Morgan, K., Younkin, S.G., Owen, M.J., O'Donovan, M., Amouyel, P., Williams, J., 2011. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat. Genet. 43, 429–435.

Jack Jr, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–216.

Jones, E.L., Hanney, M., Francis, P.T., Ballard, C.G., 2009. Amyloid beta concentrations in older people with Down syndrome and dementia. Neurosci. Lett. 451, 162–164.

Jones, E.L., Mok, K., Hanney, M., Harold, D., Sims, R., Williams, J., Ballard, C., 2013. Evidence that PICALM affects age at onset of Alzheimer's dementia in Down syndrome. Neurobiol. Aging 34, 2441.e1–2441.e5.

Jun, G., Naj, A.C., Beecham, G.W., Wang, L.S., Buros, J., Gallins, P.J., Buxbaum, J.D., Ertekin-Taner, N., Fallin, M.D., Friedland, R., Inzelberg, R., Kramer, P., Rogaeva, E., St George-Hyslop, P., Alzheimer's Disease Genetics, C, Cantwell, L.B., Dombroski, B.A., Saykin, A.J., Reiman, E.M., Bennett, D.A., Morris, J.C., Lunetta, K.L., Martin, E.R., Montine, T.J., Goate, A.M., Blacker, D., Tsuang, D.W., Beekly, D., Cupples, L.A., Hakonarson, H., Kukull, W., Foroud, T.M., Haines, J., Mayeux, R., Farrer, L.A., Pericak-Vance, M.A., Schellenberg, G.D., 2010. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. Arch. Neurol. 67, 1473–1484.

Karamohamed, S., Demissie, S., Volcjak, J., Liu, C., Heard-Costa, N., Liu, J., Shoemaker, C.M., Panhuysen, C.I., Meigs, J.B., Wilson, P., Atwood, L.D., Cupples, L.A., Herbert, A., 2003. Polymorphisms in the insulin-degrading enzyme gene are associated with type 2 diabetes in men from the NHLBI Framingham Heart Study. Diabetes 52, 1562–1567.

Kim, S., Swaminathan, S., Shen, L., Risacher, S.L., Nho, K., Foroud, T., Shaw, L.M., Trojanowski, J.Q., Potkin, S.G., Huentelman, M.J., Craig, D.W., DeChairo, B.M., Aisen, P.S., Petersen, R.C., Weiner, M.W., Saykin, A.J., Alzheimer's Disease Neuroimaging, I, 2011. Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. Neurology 76, 69–79.

Kimura, R., Kamino, K., Yamamoto, M., Nuripa, A., Kida, T., Kazui, H., Hashimoto, R., Tanaka, T., Kudo, T., Yamagata, H., Tabara, Y., Miki, T., Akatsu, H., Kosaka, K., Funakoshi, E., Nishitomi, K., Sakaguchi, G., Kato, A., Hattori, H., Uema, T., Takeda, M., 2007. The DYRK1A gene, encoded in chromosome 21 Down syndrome critical region, bridges between beta-amyloid production and tau phosphorylation in Alzheimer disease. Hum. Mol. Genet. 16, 15–23.

Kurochkin, I.V., Goto, S., 1994. Alzheimer's beta-amyloid peptide specifically interacts with and is degraded by insulin degrading enzyme. FEBS Lett. 345, 33–37.

Kwak, S.H., Cho, Y.M., Moon, M.K., Kim, J.H., Park, B.L., Cheong, H.S., Shin, H.D., Jang, H.C., Kim, S.Y., Lee, H.K., Park, K.S., 2008. Association of polymorphisms in the insulin-degrading enzyme gene with type 2 diabetes in the Korean population. Diabetes Res. Clin. Pract. 79, 284–290.

Lambert, J.C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., Combarros, O., Zelenika, D., Bullido, M.J., Tavernier, B., Letenneur, L., Bettens, K., Berr, C., Pasquier, F., Fievet, N., Barberger-Gateau, P., Engelborghs, S., De Deyn, P., Mateo, I., Franck, A., Helisalmi, S., Porcellini, E., Hanon, O., de Pancorbo, M.M., Lendon, C., Dufouil, C., Jaillard, C., Leveillard, T., Alvarez, V., Bosco, P., Mancuso, M., Panza, F., Nacmias, B., Bossu, P., Piccardi, P., Annoni, G., Seripa, D., Galimberti, D., Hannequin, D., Licastro, F., Soininen, H., Ritchie, K., Blanche, H., Dartigues, J.F., Tzourio, C., Gut, I., Van Broeckhoven, C., Alperovitch, A., Lathrop, M., Amouyel, P., 2009a. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat. Genet. 41, 1094–1099.

Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., DeStafano, A.L., Bis, J.C., Beecham, G.W., Grenier-Boley, B., Russo, G., Thorton-Wells, T.A., Jones, N., Smith, A.V., Chouraki, V., Thomas, C., Ikram, M.A., Zelenika, D., Vardarajan, B.N., Kamatani, Y., Lin, C.F., Gerrish, A., Schmidt, H., Kunkle, B., Dunstan, M.L., Ruiz, A., Bihoreau, M.T., Choi, S.H., Reitz, C., Pasquier, F., Cruchaga, C., Craig, D., Amin, N., Berr, C., Lopez, O.L., De Jager, P.L., Deramecourt, V., Johnston, J.A., Evans, D., Lovestone, S., Letenneur, L., Moron, F.J., Rubinsztein, D.C., Eiriksdottir, G., Sleegers, K., Goate, A.M., Fievet, N., Huentelman, M.W., Gill, M., Brown, K., Kamboh, M.I., Keller, L., Barberger-Gateau, P., McGuiness, B., Larson, E.B., Green, R., Myers, A.J., Dufouil, C., Todd, S., Wallon, D., Love, S., Rogaeva, E., Gallacher, J., St George-Hyslop, P., Clarimon, J., Lleo, A., Bayer, A., Tsuang, D.W., Yu, L., Tsolaki, M., Bossu, P., Spalletta, G., Proitsi, P., Collinge, J., Sorbi, S., Sanchez-Garcia, F., Fox, N.C., Hardy, J., Deniz Naranjo, M.C., Bosco, P., Clarke, R., Brayne, C., Galimberti, D., Mancuso, M., Matthews, F., European Alzheimer's Disease, IGenetic, Environmental Risk in Alzheimer's, DAlzheimer's Disease Genetic, CCohorts for, H., Aging Research in Genomic, E, Moebus, S., Mecocci, P., Del Zompo, M., Maier, W., Hampel, H., Pilotto, A., Bullido, M., Panza, F., Caffarra, P., Nacmias, B., Gilbert, J.R., Mayhaus, M., Lannefelt, L., Hakonarson, H., Pichler, S., Carrasquillo, M.M., Ingelsson, M., Beekly, D., Alvarez, V., Zou, F., Valladares, O., Younkin, S.G., Coto, E., Hamilton-Nelson, K.L., Gu, W., Razquin, C., Pastor, P., Mateo, I., Owen, M.J., Faber, K.M., Jonsson, P.V., Combarros, O., O'Donovan, M.C., Cantwell, L.B., Soininen, H., Blacker, D., Mead, S., Mosley Jr., T.H., Bennett, D.A., Harris, T.B., Fratiglioni, L., Holmes, C., de Bruijn, R.F., Passmore, P., Montine, T.J., Bettens, K., Rotter, J.I., Brice, A., Morgan, K., Foroud, T.M., Kukull, W.A., Hannequin, D., Powell, J.F., Nalls, M.A., Ritchie, K., Lunetta, K.L., Kauwe, J.S., Boerwinkle, E., Riemenschneider, M., Boada, M., Hiltuenen, M., Martin, E.R., Schmidt, R., Rujescu, D., Wang, L.S., Dartigues, J.F., Mayeux, R., Tzourio, C., Hofman, A., Nothen, M.M., Graff, C., Psaty, B.M., Jones, L., Haines, J.L., Holmans, P.A., Lathrop, M., Pericak-Vance, M.A., Launer, L.J., Farrer, L.A., van Duijn, C.M., Van Broeckhoven, C., Moskvina, V., Seshadri, S., Williams, J., Schellenberg, G.D., Amouyel, P., 2013. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat. Genet. 45, 1452–1458.

Lambert, J.C., Schraen-Maschke, S., Richard, F., Fievet, N., Rouaud, O., Berr, C., Dartigues, J.F., Tzourio, C., Alperovitch, A., Buee, L., Amouyel, P., 2009b. Association of plasma amyloid beta with risk of dementia: the prospective Three-City Study. Neurology 73, 847–853.

Lambert, J.C., Sleegers, K., Gonzalez-Perez, A., Ingelsson, M., Beecham, G.W., Hiltunen, M., Combarros, O., Bullido, M.J., Brouwers, N., Bettens, K., Berr, C., Pasquier, F., Richard, F., Dekosky, S.T., Hannequin, D., Haines, J.L., Tognoni, G., Fievet, N., Dartigues, J.F., Tzourio, C., Engelborghs, S., Arosio, B., Coto, E., De Deyn, P., Del Zompo, M., Mateo, I., Boada, M., Antunez, C., Lopez-Arrieta, J., Epelbaum, J., Schjeide, B.M., Frank-Garcia, A., Giedraitis, V., Helisalmi, S., Porcellini, E., Pilotto, A., Forti, P., Ferri, R., Delepine, M., Zelenika, D., Lathrop, M., Scarpini, E., Siciliano, G., Solfrizzi, V., Sorbi, S., Spalletta, G., Ravaglia, G., Valdivieso, F., Vepsalainen, S., Alvarez, V., Bosco, P., Mancuso, M., Panza, F., Nacmias, B., Bossu, P., Hanon, O., Piccardi, P., Annoni, G., Mann, D., Marambaud, P., Seripa, D., Galimberti, D., Tanzi, R.E., Bertram, L., Lendon, C., Lannfelt, L., Licastro, F., Campion, D., Pericak-Vance, M.A., Soininen, H., Van Broeckhoven, C., Alperovitch, A., Ruiz, A., Kamboh, M.I., Amouyel, P., 2010. The CALHM1 P86L polymorphism is a genetic modifier of age at onset in Alzheimer's disease: a meta-analysis study. J. Alzheimers Dis. 22, 247–255.

Lane, R.F., Raines, S.M., Steele, J.W., Ehrlich, M.E., Lah, J.A., Small, S.A., Tanzi, R.E., Attie, A.D., Gandy, S., 2010. Diabetes-associated SorCS1 regulates Alzheimer's amyloid-beta metabolism: evidence for involvement of SorL1 and the retromer complex. J. Neurosci. 30, 13110–13115.

Lane, R.F., Steele, J.W., Cai, D., Ehrlich, M.E., Attie, A.D., Gandy, S., 2013. Protein sorting motifs in the cytoplasmic tail of SorCS1 control generation of Alzheimer's amyloid-beta peptide. J. Neurosci. 33, 7099–7107.

Lee, J.H., Chulikavit, M., Pang, D., Zigman, W.B., Silverman, W., Schupf, N., 2007. Association between genetic variants in sortilin-related receptor 1 (SORL1) and Alzheimer's disease in adults with Down syndrome. Neurosci. Lett. 425, 105–109.

Lott, I.T., Head, E., 2001. Down syndrome and Alzheimer's disease: a link between development and aging. Ment. Retard. Dev. Disabil. Res. Rev. 7, 172–178.

Lott, I.T., Head, E., Doran, E., Busciglio, J., 2006. Beta-amyloid, oxidative stress and down syndrome. Curr. Alzheimer Res. 3, 521–528.

Luchsinger, J.A., Tang, M.-X., Shea, S., Mayeux, R., 2004. Hyperinsulinemia and risk of Alzheimer disease. Neurology 63, 1187–1192.

Margallo-Lana, M., Morris, C.M., Gibson, A.M., Tan, A.L., Kay, D.W., Tyrer, S.P., Moore, B.P., Ballard, C.G., 2004. Influence of the amyloid precursor protein locus on dementia in Down syndrome. Neurology 62, 1996–1998.

Markesbery, W.R., Lovell, M.A., 2007. Damage to lipids, proteins, DNA, and RNA in mild cognitive impairment. Arch. Neurol. 64, 954–956.

Matsuoka, Y., Andrews, H.F., Becker, A.G., Gray, A.J., Mehta, P.D., Sano, M.C., Dalton, A.J., Aisen, P.S., 2009. The relationship of plasma Abeta levels to dementia in aging individuals with Down syndrome. Alzheimer Dis. Assoc. Disord. 23, 315–318.

Mayeux, R., Honig, L.S., Tang, M.X., Manly, J., Stern, Y., Schupf, N., Mehta, P.D., 2003. Plasma A[beta]40 and A[beta]42 and Alzheimer's disease: relation to age, mortality, and risk. Neurology 61, 1185–1190.

Mayeux, R., Tang, M.X., Jacobs, D.M., Manly, J., Bell, K., Merchant, C., Small, S.A., Stern, Y., Wisniewski, H.M., Mehta, P.D., 1999. Plasma amyloid beta-peptide 1-42 and incipient Alzheimer's disease. Ann. Neurol. 46, 412–416.

Mehta, P.D., Dalton, A.J., Mehta, S.P., Kim, K.S., Sersen, E.A., Wisniewski, H.M., 1998. Increased plasma amyloid beta protein 1–42 levels in Down syndrome. Neurosci. Lett. 241, 13–16.

Miners, J.S., van Helmond, Z., Raiker, M., Love, S., Kehoe, P.G., 2010. ACE variants and association with brain Abeta levels in Alzheimer's disease. Am. J. Transl. Res. 3, 73–80.

Minster, R.L., Demirci, F.Y., DeKosky, S.T., Kamboh, M.I., 2009. No association between CALHM1 variation and risk of Alzheimer disease. Hum. Mutat. 30, E566–E569.

Naj, A.C., Jun, G., Beecham, G.W., Wang, L.S., Vardarajan, B.N., Buros, J., Gallins, P.J., Buxbaum, J.D., Jarvik, G.P., Crane, P.K., Larson, E.B., Bird, T.D., Boeve, B.F., Graff-Radford, N.R., De Jager, P.L., Evans, D., Schneider, J.A., Carrasquillo, M.M., Ertekin-Taner, N., Younkin, S.G., Cruchaga, C., Kauwe, J.S., Nowotny, P., Kramer, P., Hardy, J., Huentelman, M.J., Myers, A.J., Barmada, M.M., Demirci, F.Y., Baldwin, C.T., Green, R.C., Rogaeva, E., St George-Hyslop, P., Arnold, S.E., Barber, R., Beach, T., Bigio, E.H., Bowen, J.D., Boxer, A., Burke, J.R., Cairns, N.J., Carlson, C.S., Carney, R.M., Carroll, S.L., Chui, H.C., Clark, D.G., Corneveaux, J., Cotman, C.W., Cummings, J.L., DeCarli, C., DeKosky, S.T., Diaz-Arrastia, R., Dick, M., Dickson, D.W., Ellis, W.G., Faber, K.M., Fallon, K.B., Farlow, M.R., Ferris, S., Frosch, M.P., Galasko, D.R., Ganguli, M., Gearing, M., Geschwind, D.H., Ghetti, B., Gilbert, J.R., Gilman, S., Giordani, B., Glass, J.D., Growdon, J.H., Hamilton, R.L., Harrell, L.E., Head, E., Honig, L.S., Hulette, C.M., Hyman, B.T., Jicha, G.A., Jin, L.W., Johnson, N., Karlawish, J., Karydas, A., Kaye, J.A., Kim, R., Koo, E.H., Kowall, N.W., Lah, J.J., Levey, A.I., Lieberman, A.P., Lopez, O.L., Mack, W.J., Marson, D.C., Martiniuk, F., Mash, D.C., Masliah, E., McCormick, W.C., McCurry, S.M., McDavid, A.N., McKee, A.C., Mesulam, M., Miller, B.L., Miller, C.A., Miller, J.W., Parisi, J.E., Perl, D.P., Peskind, E., Petersen, R.C., Poon, W.W., Quinn, J.F., Rajbhandary, R.A., Raskind, M., Reisberg, B., Ringman, J.M., Roberson, E.D., Rosenberg, R.N., Sano, M., Schneider, L.S., Seeley, W., Shelanski, M.L., Slifer, M.A., Smith, C.D., Sonnen, J.A., Spina, S., Stern, R.A., Tanzi, R.E., Trojanowski, J.Q., Troncoso, J.C., Van Deerlin, V.M., Vinters, H.V., Vonsattel, J.P., Weintraub, S., Welsh-Bohmer, K.A., Williamson, J., Woltjer, R.L., Cantwell, L.B., Dombroski, B.A., Beekly, D., Lunetta, K.L., Martin, E.R., Kamboh, M.I., Saykin, A.J., Reiman, E.M., Bennett, D.A., Morris, J.C., Montine, T.J., Goate, A.M., Blacker, D., Tsuang, D.W., Hakonarson, H., Kukull, W.A., Foroud, T.M., Haines, J.L., Mayeux, R., Pericak-Vance, M.A., Farrer, L.A., Schellenberg, G.D., 2011. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat. Genet. 43, 436–441.

Naslund, J., Haroutonian, V., Mohs, R., Davis, K., Davies, P., Greengard, P., Buxbaum, J.D., 2000. Correlation between elevated levels of amyloid β-peptide in the brain and cognitive decline. JAMA 283, 1571–1577.

Nowotny, P., Hinrichs, A.L., Smemo, S., Kauwe, J.S., Maxwell, T., Holmans, P., Hamshere, M., Turic, D., Jehu, L., Hollingworth, P., Moore, P., Bryden, L., Myers, A., Doil, L.M., Tacey, K.M., Gibson, A.M., McKeith, I.G., Perry, R.H., Morris, C.M., Thal, L., Morris, J.C., O'Donovan, M.C., Lovestone, S., Grupe, A., Hardy, J., Owen, M.J., Williams, J., Goate, A., 2005. Association studies between risk for late-onset Alzheimer's disease and variants in insulin degrading enzyme. Am. J. Med. Genet. B Neuropsychiatr. Genet. 136B, 62–68.

Ozturk, A., DeKosky, S.T., Kamboh, M.I., 2006. Lack of association of 5 SNPs in the vicinity of the insulin-degrading enzyme (IDE) gene with late-onset Alzheimer's disease. Neurosci. Lett. 406, 265–269.

Patel, A., Rees, S.D., Kelly, M.A., Bain, S.C., Barnett, A.H., Thalitaya, D., Prasher, V.P., 2011. Association of variants within APOE, SORL1, RUNX1, BACE1 and ALDH18A1 with dementia in Alzheimer's disease in subjects with Down syndrome. Neurosci. Lett. 487, 144–148.

Pomara, N., Willoughby, L.M., Sidtis, J.J., Mehta, P.D., 2005. Selective reductions in plasma Abeta 1–42 in healthy elderly subjects during longitudinal follow-up: a preliminary report. Am. J. Geriatr. Psychiatry 13, 914–917.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81, 559–575.

Qin, W., Jia, J., 2008. Down-regulation of insulin-degrading enzyme by presenilin 1 V97L mutant potentially underlies increased levels of amyloid beta 42. Eur. J. Neurosci. 27, 2425–2432.

Qiu, W.Q., Folstein, M.F., 2006. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. Neurobiol. Aging. 27, 190–198.

Reitz, C., Cheng, R., Rogaeva, E., Lee, J.H., Tokuhiro, S., Zou, F., Bettens, K., Sleegers, K., Tan, E.K., Kimura, R., Shibata, N., Arai, H., Kamboh, M.I., Prince, J.A., Maier, W., Riemenschneider, M., Owen, M., Harold, D., Hollingworth, P., Cellini, E., Sorbi, S., Nacmias, B., Takeda, M., Pericak-Vance, M.A., Haines, J.L., Younkin, S., Williams, J., van Broeckhoven, C., Farrer, L.A., St George-Hyslop, P.H., Mayeux, R., Genetic, Environmental Risk in Alzheimer Disease, C, 2011a. Meta-analysis of the association between variants in SORL1 and Alzheimer disease. Arch. Neurol. 68, 99–106.

Reitz, C., Cheng, R., Schupf, N., Lee, J.H., Mehta, P.D., Rogaeva, E., St George-Hyslop, P., Mayeux, R., 2012. Association between variants in IDE-KIF11-HHEX and plasma amyloid beta levels. Neurobiol. Aging 33, 199.e13–199.e17.

Reitz, C., Tokuhiro, S., Clark, L.N., Conrad, C., Vonsattel, J.P., Hazrati, L.N., Palotas, A., Lantigua, R., Medrano, M., Jiménez Velázquez, I., Vardarajan, B., Simkin, I., Haines, J.L., Pericak-Vance, M.A., Farrer, L.A., Lee, J.H., Rogaeva, E., George-Hyslop, P.S., Mayeux, R., 2011b. SORCS1 alters amyloid precursor protein processing and variants may increase Alzheimer's disease risk. Ann. Neurol. 69, 47–64.

Reynolds, G.P., Cutts, A.J., 1993. Free radical damage in Down's syndrome brain. Biochem. Soc. Trans. 21, 221S.

Rogaeva, E., Meng, Y., Lee, J.H., Gu, Y., Kawarai, T., Zou, F., Katayama, T., Baldwin, C.T., Cheng, R., Hasegawa, H., Chen, F., Shibata, N., Lunetta, K.L., Pardossi-Piquard, R., Bohm, C., Wakutani, Y., Cupples, L.A., Cuenco, K.T., Green, R.C., Pinessi, L., Rainero, I., Sorbi, S., Bruni, A., Duara, R., Friedland, R.P., Inzelberg, R., Hampe, W., Bujo, H., Song, Y.Q., Andersen, O.M., Willnow, T.E., Graff-Radford, N., Petersen, R.C., Dickson, D., Der, S.D., Fraser, P.E., Schmitt-Ulms, G., Younkin, S., Mayeux, R., Farrer, L.A., St George-Hyslop, P., 2007. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat. Genet. 39, 168–177.

Rudovich, N., Pivovarova, O., Fisher, E., Fischer-Rosinsky, A., Spranger, J., Mohlig, M., Schulze, M.B., Boeing, H., Pfeiffer, A.F., 2009. Polymorphisms within insulin-degrading enzyme (IDE) gene determine insulin metabolism and risk of type 2 diabetes. J. Mol. Med. (Berl.). 87, 1145–1151.

Sakai, A., Ujike, H., Nakata, K., Takehisa, Y., Imamura, T., Uchida, N., Kanzaki, A., Yamamoto, M., Fujisawa, Y., Okumura, K., Kuroda, S., 2004. No association between the insulin degrading enzyme gene and Alzheimer's disease in a Japanese population. Am. J. Med. Genet. B Neuropsychiatr. Genet. 125B, 87–91.

Scheuner, D., Eckman, C., Jensen, M., Song, X., Citron, M., Suzuki, N., Bird, T.D., Hardy, J., Hutton, M., Kukull, W., Larson, E., Levy-Lahad, E., Viitanen, M., Peskind, E., Poorkaj, P., Schellenberg, G., Tanzi, R., Wasco, W., Lannfelt, L., Selkoe, D., Younkin, S., 1996. Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. Nat. Med. 2, 864–870.

Schupf, N., Patel, B., Silverman, W., Zigman, W.B., Zhong, N., Tycko, B., Mehta, P.D., Mayeux, R., 2001. Elevated plasma amyloid beta-peptide 1–42 and onset of dementia in adults with Down syndrome. Neurosci. Lett. 301, 199–203.

Schupf, N., Patel, B., Pang, D., Zigman, W.B., Silverman, W., Mehta, P.D., Mayeux, R., 2007. Elevated plasma beta-amyloid peptide Abeta(42) levels, incident dementia, and mortality in Down syndrome. Arch. Neurol. 64, 1007–1013.

Schupf, N., Tang, M.X., Fukuyama, H., Manly, J., Andrews, H., Mehta, P., Ravetch, J., Mayeux, R., 2008. Peripheral Abeta subspecies as risk biomarkers of Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 105, 14052–14057.

Schupf, N., Zigman, W.B., Tang, M.X., Pang, D., Mayeux, R., Mehta, P., Silverman, W., 2010. Change in plasma Aβ peptides and onset of dementia in adults with Down syndrome. Neurology 75, 1639–1644.

Selkoe, D.J., 2001. Alzheimer's disease: genes, proteins, and therapy. Physiol. Rev. 81, 741–766.

Shulman, J.M., Chen, K., Keenan, B.T., Chibnik, L.B., Fleisher, A., Thiyyagura, P., Roontiva, A., McCabe, C., Patsopoulos, N.A., Corneveaux, J.J., Yu, L., Huentelman, M.J., Evans, D.A., Schneider, J.A., Reiman, E.M., De Jager, P.L., Bennett, D.A., 2013. Genetic susceptibility for Alzheimer disease neuritic plaque pathology. JAMA Neurol. 70, 1150–1157.

Silverman, W., Schupf, N., Zigman, W., Devenny, D., Miezejeski, C., Schubert, R., Ryan, R., 2004. Dementia in adults with mental retardation: assessment at a single point in time. Am. J. Ment. Retard. 109, 111–125.

Singth, I., Dickinson, M., 2006. Down syndrome, dementia and superoxide dismutase. In: Prasher, V. (Ed.), Down Syndrome and Alzheimer's Disease: Biological Correlates. Raadcliffe, Oxford, pp. 79–85.

Teller, J.K., Russo, C., DeBusk, L.M., Angelini, G., Zaccheo, D., Dagna-Bricarelli, F., Scartezzini, P., Bertolini, S., Mann, D.M., Tabaton, M., Gambetti, P., 1996. Presence of soluble amyloid beta-peptide precedes amyloid plaque formation in Down's syndrome. Nat. Med. 2, 93–95.

Tokuda, T., Fukushima, T., Ikeda, S., Sekijima, Y., Shoji, S., Yanagisawa, N., Tamaoka, A., 1997. Plasma levels of amyloid beta proteins Abeta1-40 and Abeta1-42(43) are elevated in Down's syndrome. Ann. Neurol. 41, 271–273.

Toledo, J.B., Shaw, L.M., Trojanowski, J.Q., 2013. Plasma amyloid beta measurements—a desired but elusive Alzheimer's disease biomarker. Alzheimers Res. Ther. 5, 8.

Vardarajan, B.N., Bruesegem, S.Y., Harbour, M.E., St George-Hyslop, P., Seaman, M.N., Farrer, L.A., 2012. Identification of Alzheimer disease-associated variants in genes that regulate retromer function. Neurobiol. Aging 33, 2231e15–2231e30.

Vepsalainen, S., Parkinson, M., Helisalmi, S., Mannermaa, A., Soininen, H., Tanzi, R.E., Bertram, L., Hiltunen, M., 2007. Insulin-degrading enzyme is genetically associated with Alzheimer's disease in the Finnish population. J. Med. Genet. 44, 606–608.

Younkin, S.G., 1997. The AAP and PS1/2 mutations linked to early onset familial Alzheimer's disease increase the extracellular concentration and A beta 1-42(43). Rinsho Shinkeigaku. 37, 1099.

Zhao, Z., Xiang, Z., Haroutunian, V., Buxbaum, J.D., Stetka, B., Pasinetti, G.M., 2007. Insulin degrading enzyme activity selectively decreases in the hippocampal formation of cases at high risk to develop Alzheimer's disease. Neurobiol. Aging. 28, 824–830.

Zis, P., Dickinson, M., Shende, S., Walker, Z., Strydom, A., 2012. Oxidative stress and memory decline in adults with Down syndrome: longitudinal study. J. Alzheimers Dis. 31, 277–283.

Zuo, X., Jia, J., 2009. Promoter polymorphisms which modulate insulin degrading enzyme expression may increase susceptibility to Alzheimer's disease. Brain Res. 1249, 1–8.