Alzheimer risk loci and associated neuropathology in a population-based study (Vantaa 85+)

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Abstract

Objective
To test the association of distinct neuropathologic features of Alzheimer disease (AD) with risk loci identified in genome-wide association studies.

Methods
Vantaa 85+ is a population-based study that includes 601 participants aged ≥85 years, of which 256 were neuropathologically examined. We analyzed 29 AD risk loci in addition to APOE e4, which was studied separately and used as a covariate. Genotyping was performed using a single nucleotide polymorphism (SNP) array (341 variants) and imputation (6,038 variants). Participants with Consortium to Establish a Registry for Alzheimer Disease (CERAD) (neuritic Aβ plaques) scores 0 (n = 65) vs score M + F (n = 171) and Braak (neurofibrillary tangle pathology) stages 0–II (n = 74) vs stages IV–VI (n = 119), and with capillary Aβ (CapAβ, n = 77) vs without (n = 179) were compared. Cerebral amyloid angiopathy (CAA) percentage was analyzed as a continuous variable.

Results
Altogether, 24 of the 29 loci were associated (at \(p < 0.05\)) with one or more AD-related neuropathologic features in either SNP array or imputation data. Fifteen loci associated with CERAD score, smallest \(p = 0.0002122\), odds ratio (OR) 2.67 (1.58–4.49) at MEF2C locus. Fifteen loci associated with Braak stage, smallest \(p = 0.004372\), OR 0.31 (0.14–0.69) at GAB2 locus. Twenty loci associated with CAA, smallest \(p = 7.17E-07\), \(β = 14.4\) (8.88–20) at CR1 locus. Fifteen loci associated with CapAβ, smallest \(p = 0.002594\), OR 0.54 (0.37–0.81) at HLA-DRB1 locus. Certain loci associated with specific neuropathologic features. CASS4, CLU, and ZCWPW1 associated only with CAA, while TREM2 and HLA-DRB5 associated only with CapAβ.

Conclusions
AD risk loci differ in their association with neuropathologic features, and we show for the first time distinct risk loci for CAA and CapAβ.

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Glossary

Aβ = amyloid-β; AD = Alzheimer disease; APOE = apolipoprotein E; CAA = cerebral amyloid angiopathy; CapAβ = capillary Aβ; CERAD = Consortium to Establish a Registry for Alzheimer Disease; Chr9 region = chromosome 9 region; CI = confidence interval; GWAS = genome-wide association study; IHC = immunohistochemistry; LOAD = late-onset Alzheimer disease; OR = odds ratio; SNP = single nucleotide polymorphism.

Late-onset Alzheimer disease (LOAD) is neuro-pathologically characterized by cerebral accumulation of amyloid-β (Aβ) peptide containing neuritic plaques and hyperphosphorylated tau-protein, and by cerebral amyloid angiopathy (CAA) and capillary Aβ (CapAβ) deposition. LOAD is known to have a fairly strong hereditary risk, the apolipoprotein E (APOE) e4 being the strongest genetic risk factor. Recently, genome-wide association studies (GWASs) have identified approximately 30 Alzheimer disease (AD)-associated risk loci, which are known to encode proteins involved in immune system and inflammation (CLU, CR1, ABCA7, MS4A, CD33, EPHA1, MEF2C, HLA-DRB1/DRB5, TRIP4, and TREM2), cholesterol metabolism (APP, CLU, ABCA7, and SORL1), synaptic and membrane function (PICALM, BIN1, CD33, CD2AP, EPHA1, INPP5D, PTK2B, SORL1, and SLC2A4), tau pathology (BIN1), and Aβ metabolism (APP, CLU, CR1, ABCA7, INPP5D, and SORL1). Most of the previous GWASs have been based on large clinically diagnosed hospital-based samples, but recently, a few GWASs have been published based on neuropathologically verified data sets. In those studies, ABCA7 and CD2AP as well as a variant near APP (rs2829887) and ABCG1, GALNT7 and an intergenic region on chr 9 (9: 129,280,000–129,380,000) loci have been found to be associated with neuritic plaque pathology. The Consortium to Establish a Registry for Alzheimer disease (CERAD) score and Braak stage have also been associated with ABCA7, BIN1, CASS4, MEF2C, and PICALM, and Braak stage with CLU, SORL1, ZCWPW1, and CERAD score with MS4A6A, and CD33.

Here, we analyzed possible associations of AD risk loci with each neuropathologic feature (neuritic plaque, neurofibrillary tangle and CAA, and CapAβ) in a population-based sample of very elderly Finns (Vantaa 85+ Study).

Methods

Study population

The Vantaa 85+ Study includes 601 individuals, aged at least 85 years, who were living in the city of Vantaa on April 1, 1991. Autopsy and neuropathologic examination were performed on 300 (mean age 92.4 ± SD 3.7 years, range 85–105). The clinical characteristics of the whole genotyped subpopulation (N = 512) and the whole genotyped neuropathologically examined subpopulation (N = 300) are shown in table e-1 (http://links.lww.com/NXG/A16).

Imputation

Imputation was performed using IMPUTE2. 1000 Genomes phase3 data (October 2014 release) supplied by IMPUTE2 were used as the reference panel. Imputation was performed on the same candidate genes as in the SNP array–based analyses and on the 44 previously reported index variants. The whole available Vantaa 85+ data set (n = 512) was imputed. We have whole-genome sequences of a subset of the Vantaa 85+ study (n = 286), and we
compared the imputed genotypes to the whole-genome sequencing-derived genotypes. The median discordance between genotypes was 0.7%, which indicates successful imputation. We performed the same quality control steps and association analyses as we did to the SNP array data, but the genotyping rate threshold was not defined for the 44 index variants.

**Statistical analyses**

In the analyses, participants with moderate or frequent CERAD scores were compared with participants with no neuritic plaques (CERAD 0). Similarly, participants with Braak stages 0–II were compared with the high-stage group (Braak stages IV–VI). All participants without CapAβ were regarded as controls in analyses related to that pathology. The associations between APOE ε4 allele and neuropathologic features were performed using logistic or linear regression analysis with age and sex as covariates on SPSS (version 23) (table 1). Other statistical analyses were performed using PLINK. Case-control association tests were calculated using logistic regression. Quantitative trait associations were calculated using linear regression. Each regression analysis was performed twice with either age and sex or age, sex, and APOE ε4 status as covariates. In this candidate gene analysis of GWAS known AD loci, $p < 0.05$ was considered statistically significant.

**Standard protocol approvals, registrations, and patient consents**

The Vantaa 85+ study was approved by the Ethics Committee of the Health Centre of the City of Vantaa in 1991 and by the Coordinating Ethics Committee of the Helsinki University Central Hospital in 2014. The Finnish Health and Social Ministry has approved the use of the health and social work records and death certificates. Blood samples were collected only after the participants or their relatives provided written informed consent. The National Authority for Medicolegal Affairs (VALVIRA) has approved the collection of the tissue samples at autopsy as well as their use for research. Written informed consent for autopsy was obtained from the nearest relatives.

**Results**

**SNP array and imputation**

After quality control, 341 variants at 26 candidate loci remained in the SNP array data (table e-2, http://links.lww.com/NXG/A16). There were no variants in EXOC3L2, HLA-DRB1, and TREM2 loci. In the imputed data set, 6,038 variants remained in 28 loci after quality control. Imputation was not successful in INPP5D, but it was covered with 26 variants in the SNP array data. Thus, all 29 candidate loci were covered in either the original SNP array or imputed data sets. Imputation of the index variants in ABCG1, APP, and chromosome 9 region (Chr9 region) was not successful because of too small minor allele frequency or low genotyping quality. Associations between the candidate loci and neuropathologic features are summarized in table 2.

Of the 512 samples, 487 passed the quality control criteria. Samples from 3 individuals were excluded because of difference in reported and estimated sex, 4 because of relatedness of participants, and 18 because of excessive missing data rate or heterozygosity.

**Neuropathologic findings**

The characteristics of the whole Vantaa 85+ sample (n = 512) and the neuropathologically and genetically examined subpopulations (n = 256) are shown in table e-1 (http://links.lww.com/NXG/A16). Neuropathologic analysis and data details have been previously reported.19–21 No statistically significant differences were found in age at death or sex between the whole study population and the neuropathologically examined subpopulation, but there were slightly more females in the neuropathologically examined subpopulation.

**APOE**

As expected and already previously published using other types of analyses,28–29 the APOE ε4 allele was strongly associated with all AD-related neuropathologic features (table 1). Further analyses were performed with and without APOE ε4 adjustment.

**Association of the 29 risk loci with distinct neuropathologic features**

Overall distribution of associations between the 26 candidate loci covered by the SNP array and neuropathologic features are shown in table e-3 (http://links.lww.com/NXG/A16). EXOC3L2, HLA-DRB1, and TREM2 could not be analyzed since there were no variants at these loci in the SNP array. Variant details and $p$ values are shown in table e-4. APOE was treated as a covariate and not included in the list of tested loci. Nine of the 26 SNP array loci were not associated with any histopathologic variables in SNP array data.
After imputation of all 29 loci, associations were found with 24 loci. The 5 loci that did not show association with any neuropathologic feature were CD33, CELF1, EPHA1, EXOC3L2, and INPP5D. We found an association at $p < 0.05$ with a neuropathologic feature for 7 of the previously reported 44 index variants, while 9 other variants showed a trend at $0.05 < p < 0.10$ (table e-5). However, the genotyping rate of index variants was <95% for 14 variants.

**CERAD score of neuritic plaques**

In the SNP array data, we identified 8 loci that were associated with the CERAD score when adjusted for age at death and sex.
Table 3  Associations in SNP array data between the CERAD score (CERAD score 0 vs M + F) and previously known AD risk loci (341 variants)

| CERAD   | Rs          | p Valuea | OR (95% CI) | p Valueb | OR (95% CI) |
|---------|-------------|----------|-------------|----------|-------------|
| ABCG1 chr 21 | rs225443    | 0.03456  | 1.67 (1.04–2.67) |          |             |
|         | rs183436    | 0.01556  | 1.78 (1.12–2.84) |          |             |
|         | rs225385    | 0.01347  | 0.56 (0.35–0.89) | 0.02533  | 0.62 (0.41–0.94) |
|         | rs2234718   | 0.01432  | 0.53 (0.31–0.88) | 0.01775  | 0.56 (0.35–0.90) |
|         | rs2234718   | 0.01432  | 0.53 (0.31–0.88) | 0.01775  | 0.56 (0.35–0.90) |
| FERMT2 chr 14 | rs1112777   | 0.01733  | 0.56 (0.35–0.90) |          |             |
| MEF2C chr 5  | rs187270    | 0.003969 | 1.99 (1.25–3.18) | 0.006607 | 1.82 (1.18–2.81) |
|          | rs190436    | 0.003805 | 2.20 (1.29–3.78) | 0.003842 | 2.14 (1.28–3.58) |
|          | rs34318     | 0.004267 | 1.98 (1.24–3.16) | 0.009478 | 1.76 (1.15–2.71) |
|          | rs412458    | 0.0005646| 3.04 (1.62–5.71) | 0.0004791| 3.01 (1.62–5.59) |
|          | rs661311    | 0.0005646| 3.04 (1.62–5.71) | 0.0004791| 3.01 (1.62–5.59) |
|          | rs700591    | 0.02687  | 1.69 (1.06–2.68) | 0.01942  | 1.66 (1.09–2.54) |
|          | rs700588    | 0.0002122| 2.67 (1.59–4.49) | 0.0003895| 2.40 (1.48–3.88) |
|          | rs160034     | 0.0002684| 2.62 (1.56–4.38) | 0.0004573| 2.37 (1.46–3.83) |
|          | rs1004432   | 0.0008274| 3.65 (1.71–7.79) | 0.001522 | 3.27 (1.57–6.8)  |
|          | rs3850653   | 0.0304   | 0.54 (0.31–0.94) | 0.017    | 0.60 (0.40–0.91) |
|          | rs770463    | 0.02303  | 0.59 (0.37–0.93) | 0.017    | 0.60 (0.40–0.91) |
| MS4A chr 11 | rs4939387   | 0.03929  | 0.44 (0.21–0.96) | 0.03674  | 0.38 (0.20–0.73) |
|          | rs6591595   | 0.03037  | 0.47 (0.23–0.93) | 0.00674  | 0.38 (0.20–0.73) |
|          | rs2847212   | 0.04648  | 0.51 (0.27–0.99) | 0.008148 | 0.44 (0.24–0.81) |
|          | rs4939416   | 0.04648  | 0.51 (0.27–0.99) | 0.008148 | 0.44 (0.24–0.81) |
|          | rs474347    | 0.007831 | 0.44 (0.24–0.81) |          |             |
| PICALM chr11 | rs2077815   | 0.04248  | 0.55 (0.31–0.98) |          |             |
|          | rs10501604  | 0.0108   | 2.41 (1.23–4.74) | 0.04079  | 1.98 (1.03–3.80) |
|          | rs713346    | 0.02167  | 1.98 (1.11–3.55) |          |             |
|          | rs475639    | 0.01235  | 1.77 (1.13–2.76) |          |             |
|          | rs680119    | 0.013    | 0.58 (0.38–0.89) |          |             |
|          | rs642949    | 0.04878  | 1.63 (1.00–2.66) |          |             |
|          | rs10501608  | 0.01042  | 2.42 (1.23–4.76) | 0.03225  | 2.05 (1.06–3.94) |
| PTK2 chr 8  | rs2322606   | 0.01452  | 2.34 (1.18–4.61) | 0.0109   | 2.30 (1.21–4.37) |
|          | rs10097861  | 0.01611  | 2.20 (1.16–4.20) | 0.01598  | 2.12 (1.15–3.91) |
|          | rs1879188   | 0.007295 | 2.43 (1.27–4.65) | 0.02249  | 2.01 (1.10–3.65) |
|          | rs1879189   | 0.007295 | 2.43 (1.27–4.65) | 0.02249  | 2.01 (1.10–3.65) |
|          | rs3735759   | 0.01496  | 2.43 (1.19–4.95) | 0.02571  | 2.17 (1.10–4.28) |
|          | rs4733058   | 0.0406   | 0.55 (0.31–0.98) | 0.02569  | 0.55 (0.33–0.93) |

Continued
but not for APOE e4 (Table 3). When APOE e4 was included as a covariate, all these associations remained significant, and an additional association was detected with FERMT2 (rs1112777, \( p = 0.01733 \), odds ratio [OR] 0.5587, 95% confidence interval [CI] 0.35–0.90). The strongest association was found between the CERAD score and the MEF2C locus (rs700588) (when adjusted with age, sex, and APOE e4, \( p = 0.0002122 \), OR 2.67, 95% CI 1.59–4.49 and without APOE e4 \( p = 0.0003895 \), OR 2.40, 95% CI 1.48–3.88).

MEF2C did not associate with any other histopathologic variables (Braak, CAA, and CapAβ).

In the imputed data, we identified 14 loci that were associated with the CERAD score (Table 2, tables e-6 and e-7, http://links.lww.com/NXG/A16). The strongest association found was the same as in the SNP array data: rs700588 at MEF2C.

**Braak stage**

In the SNP array data, 6 loci were associated with a high Braak stage (IV–VI vs 0–II) (APP, GALNT7, PTK2B, SLC24A4, SORL1, and TRIP4), and when adjusted for APOE e4, associations were also found with ABCG1 (Table 4). Overall, the associations with the Braak stage were weaker than those with the CERAD score. The strongest association was found with ABCG1 (rs532345, \( p = 0.02671 \), OR 0.5671, 95% CI 0.33–0.93 with APOE e4 adjustment).

In the imputed data, we identified 15 loci that showed association with the Braak stage (ABCA7, ABCG1, APP, CD2AP,

### Table 3 Associations in SNP array data between the CERAD score (CERAD score 0 vs M + F) and previously known AD risk loci (341 variants) (continued)

| CERAD | Rs         | \( p \) Value | OR (95% CI) | \( p \) Value | OR (95% CI) |
|-------|------------|--------------|-------------|--------------|-------------|
| SLC24A4 chr 14 | rs11623019 | 0.04134 | 0.58 (0.35–0.98) | 0.03965 | 0.61 (0.37–0.97) |
| SORL1 chr 11 | rs2298525  | 0.01498 | 0.37 (0.17–0.82) | 0.02715 | 0.45 (0.22–0.91) |

Abbreviations: APOE = apolipoprotein E; CERAD = Consortium to Establish a Registry for Alzheimer Disease; CI = confidence interval; M = moderate neuritic plaques; F = frequent neuritic plaques (moderate or frequent, \( n = 171 \)) vs CERAD (no neuritic plaques, \( n = 65 \)); OR = odds ratio; SNP = single nucleotide polymorphism.

Binary logistic regression analysis with and without adjustment for APOE e4. Binary logistic regression analysis adjusted for age at death and sex and with and without carrier status of the APOE e4 allele. All variants with \( p < 0.05 \) are shown.

### Table 4 Associations in SNP array data between the Braak stage and previously known AD risk loci (341 variants) comparing participants with Braak stage IV–VI (\( n = 119 \)) vs Braak stage 0–II (\( n = 74 \))

| Braak | Rs         | \( p \) Value | OR (95% CI) | \( p \) Value | OR (95% CI) |
|-------|------------|--------------|-------------|--------------|-------------|
| ABCG1 chr 21 | rs225443 | 0.0267 | 0.57 (0.34–0.94) | 0.04806 | 0.42 (0.18–0.99) |
|        | rs532345  | 0.02671 | 0.56 (0.33–0.93) | 0.04217 | 0.59 (0.35–0.98) |
|        | rs691687  | 0.02671 | 0.56 (0.33–0.93) | 0.04217 | 0.59 (0.35–0.98) |
| APP chr 21 | rs400603 | 0.04174 | 1.93 (1.03–3.62) | 0.02477 | 1.96 (1.09–3.52) |
|        | rs2830104 | 0.04174 | 1.93 (1.03–3.62) | 0.02477 | 1.96 (1.09–3.52) |
| GALNT7 chr 4 | rs7658148 | 0.03616 | 0.63 (0.41–0.97) | 0.03353 | 1.99 (1.06–3.57) |
| PTK2b chr 8 | rs2322606 | 0.04005 | 1.96 (1.03–3.73) | 0.02477 | 1.96 (1.09–3.52) |
|        | rs1009786 | 0.04979 | 1.84 (1.00–3.40) | 0.02477 | 1.96 (1.09–3.52) |
| SLC24A4 chr14 | rs2402130 | 0.02 | 2.24 (1.12–4.46) | 0.03353 | 1.99 (1.06–3.76) |
| SORL1 chr 11 | rs1532763 | 0.048 | 0.59 (0.35–1.00) | 0.0324 | 0.60 (0.37–0.96) |
| TRIP4 chr15 | rs936689  | 0.03045 | 2.24 (1.08–4.66) | 0.03045 | 2.24 (1.08–4.66) |

Abbreviations: AD = Alzheimer disease; APOE = apolipoprotein E; CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism.

Binary logistic regression analysis with and without adjustment for APOE e4. Binary logistic regression analysis adjusted for age at death and sex and with and without carrier status of the APOE e4 allele for 341 variants. All variants with \( p < 0.05 \) are shown.
Chr9 region, CRI, GAB2, GALNT7, MEF2C, MS4A, NME8, PTK2B, SLC24A4, SORL1, and TRIP4) (table 2, tables e-8 and e-9, http://links.lww.com/NXG/A16). All except for MEF2C showed association regardless of APOE ε4 adjustment. Rs2512518 at GAB2 locus had the strongest association (p = 0.004372, OR 0.31, 95% CI 0.14–0.69) when adjusted for age and sex.

**CAA**

In the SNP array data, 7 loci were associated with CAA (ABCA7, CRI, FERMT2, NME8, SLC24A4, SORL1, and ZCWPW1), and when adjusted for APOE ε4, an additional locus (GALNT7) was found (table 5). The strongest association was with CRI (rs65087, p = 0.004934, β 2.52, 95% CI 0.78–4.26 without APOE ε4 adjustment); CRI and ABCA7 were not associated with any other histopathologic variable than CAA.

**CapAβ**

In SNP array data, 4 loci were associated with CapAβ (APP, BIN1, MS4A, and PTK2B), and when adjusted for APOE ε4, age, and sex, 3 additional loci were associated with CapAβ (GALNT7, NME8, and FERMT2, table 6). The strongest association was for rs185310342 at CRI locus (p = 7.17E-07, β 14.4, 95% CI 8.88–20) when adjusted for age and sex.

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**Table 5** Associations in SNP array data between CAA and previously known AD risk loci (341 variants) adjusted for age at death and sex and with and without carrier status of the APOE ε4 allele

| CAA                  | Rs       | p Value<sup>a</sup> | β (95% CI)   | p Value<sup>b</sup> | β (95% CI)   |
|----------------------|----------|---------------------|--------------|---------------------|--------------|
| **ABCA7 chr 19**     |          |                     |              |                     |              |
| rs3752240            | 0.007962 | -1.97 (-3.41 to -0.53) | 0.01813      | -1.86 (-3.38 to -0.33) |
| rs2279796            | 0.04255  | 1.44 (0.06 to 2.82)  |              |                     |              |
| **CRI chr 1**        |          |                     |              |                     |              |
| rs11117959           | 0.03422  | 1.83 (0.15 to 3.52)  | 0.004963     | 2.53 (0.78 to 4.27)  |
| rs650877             | 0.03592  | 1.81 (0.13 to 3.49)  | 0.004934     | 2.52 (0.78 to 4.26)  |
| rs11118131           | 0.03592  | 1.81 (0.13 to 3.49)  | 0.004934     | 2.52 (0.78 to 4.26)  |
| rs677066             |          |                     |              |                     |              |
| rs6691117            |          |                     |              |                     |              |
| rs12734030           |          |                     |              |                     |              |
| **FERMT2 chr 14**    |          |                     |              |                     |              |
| rs8007536            | 0.008585 | 3.29 (0.86 to 5.72)  | 0.04077      | 2.701 (0.13 to 5.28) |
| rs4901318            | 0.009914 | 2.79 (0.69 to 4.89)  | 0.04571      | 2.28 (0.05 to 4.50)  |
| **GALNT7 chr 4**     |          |                     |              |                     |              |
| rs10001613           | 0.04873  | -1.46 (-2.90 to -0.02) |              |                     |              |
| **NME8 chr 7**       |          |                     |              |                     |              |
| rs2722301            | 0.01244  | 2.13 (0.47 to 3.79)  | 0.01564      | 2.18 (0.42 to 3.93)  |
| **SLC24A4 chr 14**   |          |                     |              |                     |              |
| rs4904896            | 0.03997  | -1.51 (-2.95 to -0.08) | 0.01082      |                     |              |
| rs4904903            |          |                     |              |                     |              |
| rs10498633           | 0.04763  | 1.78 (0.03 to 3.53)  | 0.04017      | 1.946 (0.10 to 3.80) |
| **SORL1 chr 11**     |          |                     |              |                     |              |
| rs661057             | 0.02727  | -1.74 (-3.27 to -0.20) |              |                     |              |
| rs676795             | 0.04524  | -1.54 (-3.04 to -0.04) |              |                     |              |
| rs666004             | 0.03078  | -1.62 (-3.08 to -0.16) | 0.01868      | -1.86 (-3.40 to -0.32) |
| rs3781827            | 0.01306  | 1.87 (0.40 to 3.33)  | 0.008359     | 2.09 (0.55 to 3.64)  |
| **ZCWPW1 chr 7**     |          |                     |              |                     |              |
| rs5015756            | 0.009438 | -1.89 (-3.31 to -0.47) | 0.02247      | -1.76 (-3.26 to -0.26) |

Abbreviations: AD = Alzheimer disease; APOE = apolipoprotein E; CAA = cerebral amyloid angiopathy; CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism. The severity of CAA is expressed using the percentage of blood vessels with CAA of all blood vessels visible in the tissue slide. Linear regression analysis adjusted for age at death and sex and with<sup>a</sup> and without<sup>b</sup> carrier status of the APOE ε4 allele for 341 variants (N = 256). All variants with p < 0.05 are shown.
Binary logistic regression analysis adjusted for age at death and sex and with a and without b carrier status of the comparison between participants with CapA polymorphism.

Abbreviations: AD = Alzheimer disease; PTK2b chr 8

In this study, we found strong associations between participants with CapA features (CERAD, Braak, CAA, and CapA AD risk loci with one or more AD-related neuropathologic con

OR 2.01, 95% CI 1.22–3.30

In this study, we focused on previously reported genetic AD risk loci with one or more AD-related neuropathologic features (CERAD, Braak, CAA, and CapA) (table 2).

In addition to APOE, APP, Chr9 region, NME8, PICALM, and SLC24A4 were associated with all neuropathologic variables (CERAD, Braak, CAA, and CapA) (table 2).

On the other hand, certain loci were associated only with specific neuropathologic features. CASS4, CLU, and ZCWPW1 were associated only with CAA. TREM2 and HLA-DRB5 were associated with only CapA, whereas HLA-DRB1 was associated with both CAA and CapA but not with other pathologies (table 2). These are interesting findings suggesting that the risk loci (and mechanisms) for CAA and CapA may be partially distinct. It is of note that there has

Table 6 Associations in SNP array data between CapA and previously known AD risk loci (341 variants)

| CapA | Rs       | p Valuea | OR (95% CI) | p Valueb | OR (95% CI) |
|------|----------|----------|-------------|----------|-------------|
| APP chr 21 | Rs1783016 | 0.005933 | 2.01 (1.22–3.30) | 0.02242 | 1.67 (1.08–2.61) |
|       | Rs214488 | 0.0259 | 0.52 (0.29–0.92) |           |              |
|       | Rs383700 | 0.03333 | 0.34 (0.13–0.92) | 0.0479 | 0.40 (0.16–0.99) |
|       | Rs2014146 | 0.03392 | 0.61 (0.38–0.96) |           |              |
|       | Rs2830000 | 0.02793 | 0.53 (0.30–0.93) |           |              |
|       | Rs466609 |           |               | 0.03013 | 0.40 (0.18–0.92) |
| BIN1 chr 2 | Rs873270 | 0.01358 | 0.43 (0.22–0.84) | 0.01855 | 0.54 (0.31–0.97) |
| FERMT2 chr 14 | Rs1112777 | 0.04187 | 0.62 (0.39–0.98) |           |              |
|       | Rs7494379 | 0.01501 | 1.78 (1.12–2.83) |           |              |
| GALNT7 chr 4 | Rs2332655 | 0.03211 | 0.62 (0.39–0.96) |           |              |
|       | Rs10001613 | 0.01362 | 0.57 (0.36–0.89) |           |              |
|       | Rs12644699 | 0.04208 | 0.56 (0.32–0.98) |           |              |
| MS4A chr 11 | Rs2847212 |           |               | 0.04211 | 0.47 (0.23–0.97) |
|       | Rs4939416 |           |               | 0.04211 | 0.47 (0.23–0.97) |
| NME8 chr 7 | Rs1048617 | 0.04465 | 0.58 (0.34–0.99) |           |              |
| PTK2b chr 8 | Rs6986075 | 0.02349 | 1.67 (1.07–2.59) | 0.027 | 1.60 (1.09–2.34) |

Abbreviations: AD = Alzheimer disease; APOE = apolipoprotein E; CapA = capillary A; CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism.

Comparison between participants with CapA (n = 77) and all other participants (n = 179) using binary logistic regression analysis. Binary logistic regression analysis adjusted for age at death and sex and with and without carrier status of the APOE ε4 allele for 341 variants. All variants with p < 0.05 are shown.

association was found with APP (rs1783016, p = 0.005933, OR 2.01, 95% CI 1.22–3.30 with APOE ε4 adjustment).

In imputed data, we found association for 15 loci (table 2, tables e-12 and e-13, http://links.lww.com/NXG/A16). Of these, 9 were associated regardless of APOE ε4 adjustment (APP, BIN1, FERMT2, GALNT7, HLA-DRB1, MS4A, NME8, PTK2b, and Chr9 region), 3 loci (MEF2C, PICALM, and SORL1) when adjusted for age, sex, and APOE ε4, and 3 loci (CR1, SLC24A4, and TREM2) when adjusted for age and sex. The strongest association was found for rs66962766 at HLA-DRB1 locus (p = 0.002594, OR 0.54, 95% CI 0.37–0.81).

Discussion

In this study, we focused on previously reported genetic AD risk loci identified in GWAS analyses on clinically or neuro-pathologically verified patients with AD and controls. We confirmed the association of 24 of the 29 previously known AD risk loci with one or more AD-related neuropathologic features (CERAD, Braak, CAA, and CapA) (table 2).

In this study, we found strong associations between APOE ε4 and all AD-related neuropathologic features (CERAD, Braak, CAA, and CapA, table 1). This is in line with previous studies. To take into account the strong effect of APOE on the other loci, we performed analyses in 2 ways, testing each neuropathologic feature with and without the adjustment for the APOE ε4 carrier status. Previously, certain loci have been reported to be more likely influenced by APOE ε4 than others; e.g., PICALM and EXOC3L2 have been found to show stronger associations with neuropathologically confirmed AD without APOE ε4 adjustment, whereas adjustment with APOE was reported to have no effect on the association between CR1, CLU, or BIN1 and neuropathologic AD. We found that the APOE adjustment did not remarkably alter the associations between neuropathologic features in most loci (table 2).
been only 1 previous GWAS that investigated the genetic background of CAA, in which the only significant association was found between CAA and the APOE locus. However, in a previous candidate gene analysis, CR1 was associated with CAA pathology burden. The association between CAA and CR1 was confirmed in our study. No previous GWAS has been performed using CapAβ as the phenotype. Here, we reported significant associations between CapAβ and 15 loci (APP, BNI1, Chr9 region, CR1, FERMT2, GALNT7, HLA-DRB1, MEF2C, MS4A, NME8, PICALM, PTK2B, SLC24A4, SORL1, and TREM2). Our results provide information on the partly shared and partly distinct genetic backgrounds of AD-related neuropathologic features.

Author contributions
Mira Mäkelä and Karri Kaivola: acquisition of data, analysis and interpretation of data, and drafting the manuscript. Miko Valori: acquisition of data and analysis and interpretation of data. Anders Paetau and Tuomo Polvikoski: acquisition of data and critical revision of the manuscript for intellectual content. Andrew B. Singleton: acquisition of data and analysis and interpretation of data. Bryan J. Traynor: acquisition of data and critical revision of the manuscript for intellectual content. David J. Stone and Terhi Peuralinna: acquisition of data and analysis and interpretation of data. Pentti J. Tienari: analysis and interpretation of data, study concept and design, and critical revision of the manuscript for intellectual content. Liisa Myllykangas: analysis and interpretation of data, supervision, study concept and design, and critical revision of the manuscript for intellectual content.

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