RESEARCH ARTICLE

Identification of Novel Genetic Loci Affecting Age at Onset of Parkinson's Disease: A Genome-wide Association Study

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ABSTRACT: Background: The age at onset (AAO) of Parkinson's disease (PD) varies widely among individuals and significantly influences disease progression and prognosis. However, few genome-wide association studies (GWASs) have investigated genetic variants determining AAO, particularly in East Asian populations.
Objectives: To identify single-nucleotide polymorphisms (SNPs) affecting AAO of PD in Korean patients.
Methods: We conducted a GWAS on AAO of PD in 1048 Korean patients using sex-adjusted linear regression models. Additionally, we conducted downstream analyses of our primary GWAS results.
Results: rs2134545 demonstrated genome-wide significance ($\beta = -2.459$; standard error [SE] $= 0.851$; $P = 1.898 \times 10^{-8}$) and is an intergenic SNP near the *ALCAM* gene associated with an average AAO reduction of 3.47 years. Additionally, rs4366309 (*LYST*; *MIR1537*) demonstrated suggestive significance ($\beta = 2.949$; SE $= 1.072$; $P = 8.68 \times 10^{-8}$) and was associated with an average delay of 3.05 years. The polygenic risk score based on known PD risk loci also affected the AAO for European and Korean PD risk loci, respectively ($\beta = -0.149$; $P < 0.001$ and $\beta = -0.096$; $P = 0.002$). However, the proportion of variance was small ($r^2 = 0.022$ and 0.009, respectively).
Conclusion: We identified a novel SNP associated with the AAO of PD near the *ALCAM* gene, distinct from previously reported PD risk loci. These findings need further functional validation; however, they suggest unique genetic pathways influencing the AAO of PD and highlight the need for further research in diverse populations. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: age at onset; genome-wide association study; Parkinson's disease; polygenic risk score

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Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra of the midbrain,[1-4] and the age at onset (AAO) varies widely among individuals, ranging from 20 to over 90 years, with an average of ~60 years.[5,6] AAO is a crucial clinical marker that influences the progression and prognosis of PD.[7] However, the underlying mechanisms contributing to this heterogeneity are complex and remain largely unexplored.[4,8]

Research on various risk factors for PD has been extensive, including genetic factors for both hereditary and sporadic forms of PD,[1,9] and has identified ~90 common genetic variants associated with PD risk.[10-12] However, although most genome-wide association studies (GWASs) have focused on susceptibility loci for PD occurrence, the genetic determinants of AAO have received less attention.[4,10,13,14] Genetic factors play an important role in the AAO of PD[4,15]; known Mendelian genes such as *PINK1*, *PRKN*, and *PARK7* are associated with earlier onset, whereas *LRRK2* is related to later onset.[4] However, investigations focusing on common genetic variants that affect AAO remain limited, particularly in non-European populations.[16-19] In East Asia, only one study was conducted, which revealed a novel locus around *NDN/PWRN4*.[4] However, this study only involved the Chinese population. This indicates a significant research gap within this demographic. The AAO of PD varies widely among patients, substantially impacting their lives by determining the proportion of life spent with the disease and correlating with different phenotypes and prognoses.[7,20]

Identifying genetic modifiers for the AAO enhances our understanding of the disease mechanisms and opens avenues for developing therapeutic strategies to delay the onset and progression of PD.[21] Although a few PD risk loci have been established to be associated with AAO,[4] many have not. This suggests that distinct genes and variants contribute to PD occurrence and AAO, respectively.[22] Therefore, we aimed to conduct a GWAS among Korean patients with PD to identify single-nucleotide polymorphisms (SNPs) associated with AAO, addressing the research gap in non-European populations.

Methods

Patients

This study initially recruited 1070 ethnically Korean patients with sporadic PD from Asan Medical Center, Seoul, South Korea, from January 2011 to April 2016. Diagnosed with PD by movement disorder specialists based on the United Kingdom Parkinson's Disease Brain Bank Criteria,[3] these patients were initially recruited for our previous Korean-specific PD GWAS.[23] The AAO and sex were assessed for the appropriate analysis. AAO was defined as the age at which one of the cardinal motor symptoms (bradykinesia, rigidity, resting tremor, or postural instability) occurred, and was noted by the patients or their caregivers.

Exclusion criteria included patients with unverifiable AAO, genetically confirmed hereditary parkinsonism because of mutations in known Mendelian genes including *SNCA*, *PRKN*, *PINK1*, *DJ1*, *LRRK2*, *ATP13A2*, and those exhibiting possible symptoms and signs of atypical parkinsonism (definite cerebellar symptoms, early frequent falling, poor responsiveness to levodopa, supranuclear gaze palsy, early severe autonomic dysfunction, early severe cognitive impairment, praxis, and pyramidal signs).

Peripheral blood samples were collected from all patients for DNA extraction. Informed consent was obtained from all participants, and the study protocol was approved by the institutional review board of Asan Medical Center.

Genotyping

Genomic DNA (200 ng) was extracted from the peripheral blood samples. Genotyping used the Korean Chip obtained from the Korean Chip Consortium, designed by the Center for Genome Science, Korea National Institute of Health,[24] developed to establish a standard for the genotypic platform optimal for the Korean population. All samples were assayed using the Affymetrix Axiom *KORV1.1-96* Array, according to the manufacturer's protocol (Supplementary Data S1). Imputation was performed using IMPUTE5 with the 1000 Genomes Project Phase 3 reference panel after phasing with SHAPEIT4.[25] Imputed SNPs with info score <0.8 were removed from the analysis.

Quality Control

This study implemented several quality control (QC) measures to eliminate low-quality samples and SNPs. Sample QC involved excluding samples with a low call rate (<97%), sex discrepancy, extremely high or low heterozygosity rates (deviating by more than ±2 standard deviations), and cryptic relatedness. SNP QC, conducted after the statistical analysis of GWAS, involved excluding markers with a low call rate (<95%), SNPs with minor allele frequency <1%, and those deviating from the Hardy–Weinberg equilibrium ($P < 10^{-4}$). These QC steps were performed using PLINK software v.1.90 and the SNPolisher package in R software (v.3.1.2, Free Software Foundation, Boston, MA) for sample and SNP QC, respectively.

Genome-wide Association Analyses

Before the GWAS, a principal component analysis was conducted to rule out significant population structure differences and reduce biases from the population

substructure. A linear regression model adjusted for sex (AAO ~ SNP + SEX) was used in the GWAS for AAO of PD. β coefficients, standard errors (SEs), and *P*-values were calculated for each variant. We applied a genome-wide significance threshold of $P < 5E{-}08$ and a suggestive threshold of $P < 1E{-}06$ to identify genetic variants that, although not genome-wide significant, merit further investigation. This suggestive threshold is commonly used to balance the detection of true associations and control false positives.[4,17,26,27] The GWAS was conducted using PLINK software (v.1.90). Quantile–quantile (Q–Q) and Manhattan plots were generated in R software (v.3.5.2, R Core Team [2018], R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org). Regional association plots were obtained using the LocusZoom software (v.0.4.8) for all SNPs with $P < 1E{-}04$. We also performed fine-mapping methods to identify potential causal SNPs accounting for linkage disequilibrium (LD). The analysis used summary statistics from our Korean PD AAO GWAS and an LD matrix calculated from the Korean genotype data of our subjects. Fine-mapping was performed using the susieR package and the posterior inclusion probability (PIP) plot from the sum of single effects (SuSiE) results was generated using the ggplot function of the R package (v.4.3.3). Further detailed fine-mapping methods are provided in Supplementary Data S2.

We also conducted a multi-ethnic random effect meta-analysis of the AAO GWAS across Korean and European PD populations. We used the summary statistics from our Korean and previous European PD AAO GWAS datasets.[18] The meta-analysis was performed using PLINK software (v.1.90), and more detailed methods are provided in Supplementary Data S3.

Gene-Based Analysis Using Multi-Marker Analysis of Genomic Annotation

We performed a gene-based analysis using SNP *P*-values with the mean SNP-wise association model in multi-marker analysis of genomic annotation (MAGMA) (v.1.10), mapping GWAS variants to genes to assess their association with AAO of PD. This approach uses the distribution of SNP *P*-values to calculate gene-trait significance. For the Korean PD AAO GWAS, we used Korean genotype data as the LD reference. In the meta-GWAS, we combined our Korean data with the 1000 Genomes Phase 3[25] European reference data to adjust for LD differences between populations using PLINK 1.90. Significance was defined as $P < 0.05$/number of genes (Bonferroni correction).

Quantitative Trait Loci and Colocalization Analyses

The quantitative trait loci (QTL) and colocalization (Coloc) analyses were conducted using the COLOC R package (Bayesian colocalization method).[28] We used the expression QTL (eQTL) data of the Japanese population in Tokyo (JPT), referred to as JPT eQTL data[29] and our Korean PD AAO GWAS data, with LD calculated using the 1000 Genomes Phase 3[25] East Asian reference data for the JPT dataset and our genotype data for the Korean PD AAO GWAS. A detailed protocol is provided in Supplementary Data S4.

Additional Analyses: Correlation between AAO, Identified SNPs, and Polygenic Risk Scores for PD Risk

Survival analyses were performed using Kaplan–Meier curves according to the genotypes of identified SNPs in our PD AAO GWAS. We calculated the polygenic risk scores (PRSs) for each patient using data from previous GWASs for PD susceptibility and estimated the correlation between the PRSs and AAO using a linear regression model. Clinical characteristics were statistically analyzed using SPSS v.21.0 (SPSS, Chicago, IL). PRSs were calculated separately based on European and Korean risk variants for PD, resulting in two distinct PRSs: one derived from the largest European GWAS[10] and the other from our previous Korean-specific GWAS.[23] SNPs with $P < 5E{-}08$ in the GWASs were included in the calculation. We used the sum method on risk allele dosages scaled per SNP using β coefficients. PRSice-2 (v.2.3.3) was used in this process,[30] and the detailed PRS calculating protocol is provided in Supplementary Data S5.

Results

Demographics

The samples from 1050 of the initially recruited 1070 patients passed the sample QC steps. Two patients were additionally excluded because of inaccurate AAO reporting, resulting in a final sample number of 1048 patients (553 females) (Supplementary Table S1). The mean AAO of PD was 58.73 ± 10.17 years (28–87), and the distribution is shown in Supplementary Figure S1. Significant differences were not observed in the AAO between sexes.

Genome-wide Association Analyses

A total of 7,508,513 SNPs passed the marker QC and were analyzed. The Q–Q plot suggested minimal bias from population stratification, and the principal component analysis did not reveal a descent outlier (Supplementary Fig. S2). Figure 1 presents the Manhattan plot of the GWAS. Genomic variants associated with the AAO of PD above genome-wide significant or suggestive significant levels are listed in Supplementary Table S2, and all variants with $P < 1E{-}04$ are documented in Supplementary Data S6.

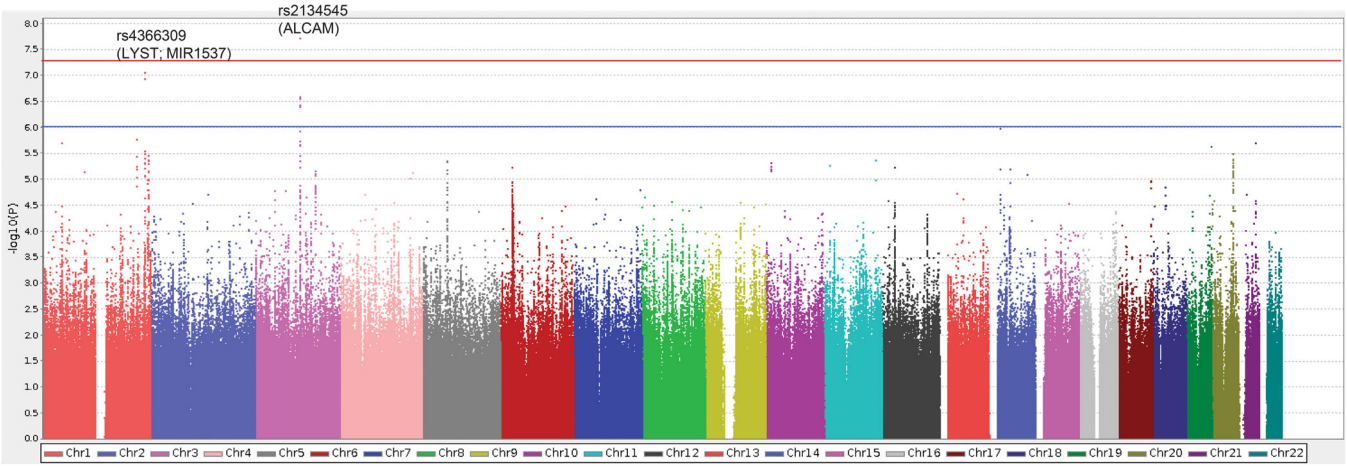

FIG. 1. Manhattan plot of genome-wide association study for age at onset of Parkinson's disease. Locus rs2134545 near *ALCAM* reached genome-wide significance ($P < 5E{-}08$), and locus rs4366309 in *LYST* and *MIR1537* reached suggestive significance ($P < 1E{-}06$). Area above blue line: single-nucleotide polymorphisms (SNPs) with suggestive significance level ($P < 1E{-}06$). Area above red line: SNPs with genome-wide significance level ($P < 5E{-}08$). [Color figure can be viewed at wileyonlinelibrary.com]

We identified the SNP rs2134545, which reached genome-wide significance ($\beta = -2.459$; $SE = 0.851$; $P = 1.898 \times 10^{-8}$) and was located intergenically[31] on chromosome 3. The regional analysis highlighted rs2134545 as a key SNP in LD with rs2062782 (full LD) and other SNPs of suggestive significance ($r^2 > 0.8$) (Supplementary Fig. S3A). SNP rs4366309, located in the LYST gene and near MIR1537, also reached suggestive significance ($\beta = 2.949$; $SE = 1.072$; $P = 8.68 \times 10^{-8}$) and is in LD with other significant SNPs ($r^2 > 0.8$) (Supplementary Fig. S3B). The SNP rs2134545 is near *ALCAM* (chr3:15366909–105576900), ~200 kb away (Supplementary Fig. S4). Fine-mapping using SuSiE identified rs2134545 as the most likely causal variant (PIP = 0.3957) in its locus, with rs2062782 in high LD (Fig. 2, Supplementary Data S7, locus 1). Similarly, for rs4366309, fine-mapping revealed it as the probable causal variant (PIP = 0.1983), along with other notable SNPs such as rs4659610 and rs12048124 (Fig. 2, Supplementary Data S7, locus 2). These findings suggest that rs2134545 and rs4366309 are likely functional variants that influence AAO in PD.

We summarized our GWAS results of previously reported PD loci associated with AAO from PD AAO GWAS studies of other ethnic groups or earlier reports, including loci in the *SNCA*, *TMEM175*, *BST1*, *PWRN4*, *GBA1*, and *LRRK2* genes,[4,18,32,33] as shown in Supplementary Table S3. None of these variants reached the significance threshold. Additionally, none of the common variants within the aforementioned genes, as well as the Mendelian genes *PINK1*, *PRKN*, and *PARK7*,[4,15] which are associated with AAO, were included among the variants that met the threshold of $P < 1E{-}04$ in our GWAS (documented in Supplementary Data S6).

In the meta-analysis combining Korean and European datasets, SNPs rs356203, rs356220, rs356219, rs983361, and rs2245801, located in the *SNCA* gene region, were identified as genome-wide significant loci (Fig. 3). Variants within *TMEM175* and *ALCAM* did not reach statistical significance. However, a variant in TMEM175 reached the borderline of the suggestive significant level ($P = 1.04E{-}06$). All variants with $P < 1E{-}04$ in the meta-analysis are documented in Supplementary Data S8.

MAGMA Analyses

In the MAGMA analysis of the Korean GWAS (Supplementary Fig. S5A), several genes on chromosome 6 emerged as potential associations, including *GPX6* ($P = 3.75E{-}05$), *GPX5* ($P = 4.06E{-}05$), *ZNF184* ($P = 5.77E{-}05$), *RNF39* ($P = 9.85E{-}05$), and *ZNF391* ($P = 1.06E{-}04$). In the multi-ethnic meta-analysis (Supplementary Fig. S5B), *SNCA* ($P = 5.67E{-}06$) was notably associated, followed by *APOE* ($P = 2.68E{-}05$). However, none achieved Bonferroni corrected significance (0.05/~18,000 genes = 2.76E−06). MAGMA analysis results are detailed in Supplementary Data S9.

QTL and Coloc Analyses

In our QTL and Coloc analyses using East Asian reference data from JPT eQTL data,[29] none of the variants within regions spanning ±1 Mb around two loci (rs2134545 and rs4366309) reached significant posterior probability (PP). H4 abf value (>0.8), indicating a shared causal variant between the age at onset (AAO) of Parkinson's disease (PD) and gene expression level of *ALCAM* and *LYST*. Therefore, based on the Coloc analyses, we did not identify genes associated with traits such as the AAO of PD. The results of the QTL

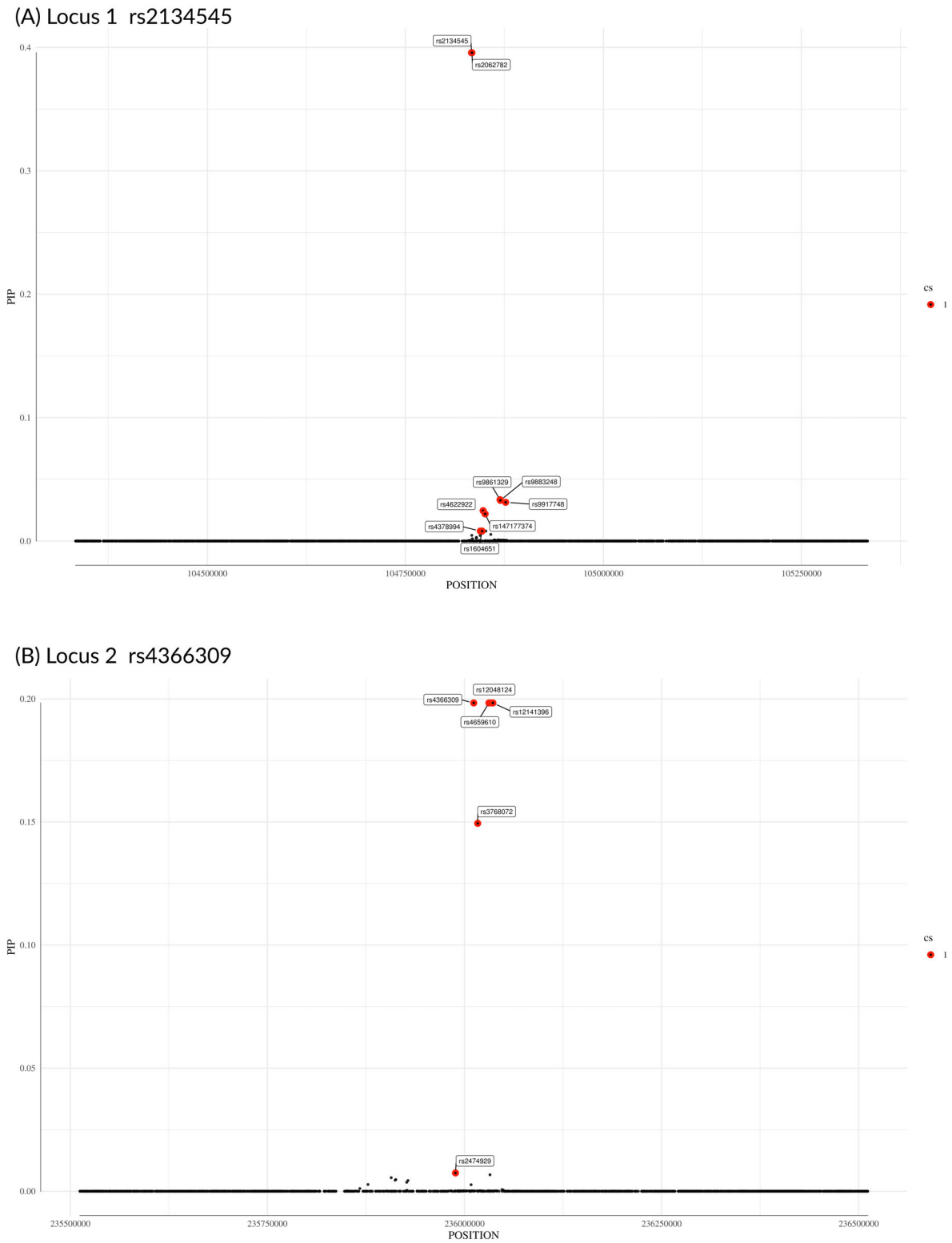

FIG. 2. Posterior inclusion probability (PIP) plots of fine-mapping analyses on locus 1 rs2134545 (**A**) and locus 2 rs4366309 (**B**). In locus 1(**A**), rs2134545 shows highest posterior inclusion probability, found in high linkage disequilibrium with other single-nucleotide polymorphisms (SNPs), such as rs2062782. In locus 2 (**B**), rs4366309 displayed highest PIP (0.1983). Other SNPs, including rs4659610 and rs12048124, also showed notable PIP values but were secondary to rs4366309. [Color figure can be viewed at wileyonlinelibrary.com]

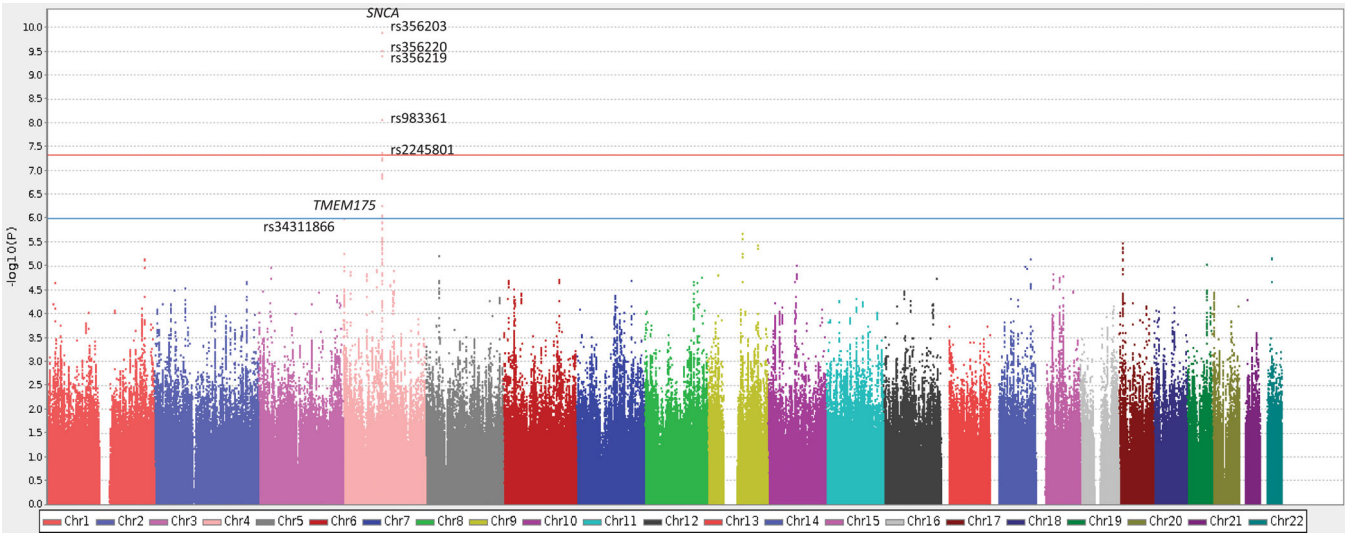

FIG. 3. Manhattan plot of meta-analysis of European and Korean genome-wide association study. Locus rs356203 in *SNCA* reached genome-wide significance ($P < 5E{-}08$) as a leading single-nucleotide polymorphisms (SNPs), and locus rs3431866 in *TMEM175* reached borderline suggestive significance ($P < 1E{-}06$). Area above blue line: SNPs with suggestive significance level ($P < 1E{-}06$). Area above red line: SNPs with genome-wide significance level ($P < 5E{-}08$). [Color figure can be viewed at wileyonlinelibrary.com]

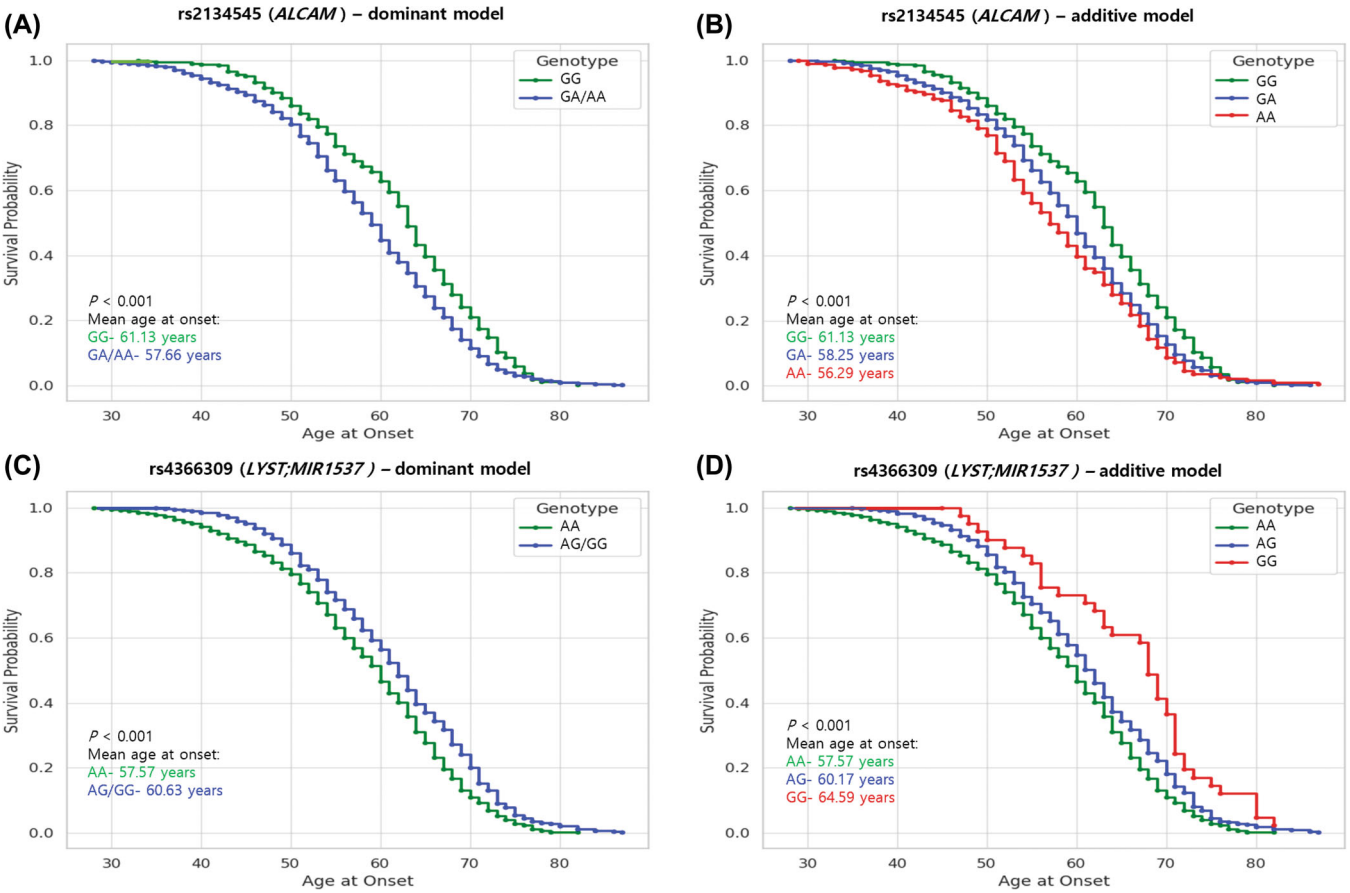

FIG. 4. Effect of risk loci on age at onset (AAO) of Parkinson's disease (PD). Kaplan–Meier survival curves of AAO of PD for (**A**) rs2134545 in dominant model, (**B**) rs2134545 in additive model, (**C**) rs4366309 in dominant model, and (**D**) rs4366309 in additive model. In each dominant model, variant in rs2134545 reduced average AAO by 3.47 years, and variant in rs4366309 delayed average AAO by 3.05 years ($P < 0.001$ for both). [Color figure can be viewed at wileyonlinelibrary.com]

and Coloc analyses are provided in Supplementary Data S10.

Correlation between AAO, Identified SNPs, and PRS for PD Risk

Variants in rs2134545 were linked to a significant reduction in average AAO by 3.47 years ($P < 0.001$) under a dominant model (Fig. 4A). Homozygous rs2134545 variants reduced AAO by 4.84 years compared to non-variant carriers ($P < 0.001$) (Fig. 4B, additive model). SNP rs4366309 was associated with an average AAO delay of 3.05 years for variant carriers ($P < 0.001$) (Fig. 4C, dominant model). Homozygous rs4366309 variants delayed AAO by 7.02 years compared to non-variant carriers ($P < 0.001$) (Fig. 4D, additive model). Comparing AAO effects of variants between sexes revealed no significant differences for either SNP.

We found inverse associations between AAO and PRSs from both European ($\beta = -0.149$; $P < 0.001$) and Korean ($\beta = -0.096$; $P = 0.002$) populations (Supplementary Fig. S4). The variance explained by the PRS from the European and Korean GWASs was $r^2 = 0.022$ and 0.009, respectively. Interaction analysis (Supplementary Table S4) showed significant associations of rs2134545 ($\beta = -0.240$, $P < 0.001$) and rs4366309 ($\beta = 0.287$, $P < 0.001$) with the AAO for the European PRS and similarly for the Korean PRS (rs2134545: $\beta = -0.242$, $P < 0.001$; rs4366309: $\beta = 0.300$, $P < 0.001$). In summary, the PRSs also negatively influenced the AAO in both populations. However, the PRS effect size on the AAO, as indicated by the absolute value of β, was smaller than that of the AAO-specific SNPs identified in our GWAS.

We also analyzed the association between AAO and PRS by sex. For the European PRS (Supplementary Fig. S7A,B), there was a significant negative correlation in males ($\beta = -0.169$; $P < 0.001$; $r^2 = 0.026$) and females ($\beta = -0.132$; $P = 0.001$; $r^2 = 0.019$). For the Korean PRS (Supplementary Fig. 7SC,D), the negative correlation was significant in females ($\beta = -0.107$; $P = 0.008$; $r^2 = 0.013$), but not in males ($\beta = -0.184$; $P = 0.077$; $r^2 = 0.006$).

Discussion

This study identified new genetic loci: intergenic SNP rs2134545 on chromosome 3, near the *ALCAM* gene, and rs4366309 within the *LYST* gene next to *MIR1537*, associated with AAO of PD in Koreans. These findings suggest unique genetic pathways affecting AAO in PD, distinct from known susceptibility loci, indicating different genetic modifiers across populations.

The SNP rs2134545, the most significantly associated variant, is intergenic and located in a gene-poor region. Many disease-associated SNPs are found in such regions, complicating their role in disease phenotypes.[31] The nearest gene, *ALCAM*, encodes a cell surface glycoprotein (cluster of differentiation, CD166: ALCAM) involved in axon guidance and synaptogenesis.[34,35] ALCAM acts as an extracellular substrate to promote the growth of midbrain dopamine neuron axons through a trans-heterophilic interaction with midbrain dopamine neuron-bound adhesion molecules.[35] This is particularly relevant because the midbrain dopaminergic neurons are the primary pathological region affected in PD. Additionally, serum ALCAM protein levels are downregulated in patients with PD and correlate with disease severity, suggesting a link between ALCAM and worse PD prognosis.[36] Although the intergenic location of rs2134545 limits direct insights, existing evidence supports the potential role of *ALCAM* in PD AAO.

The SNP rs4366309 and other variants with suggestive significance for AAO of PD are located in the *LYST* and *MIR1537* gene loci. The LYST gene, associated with Chediak–Higashi Syndrome, a condition with parkinsonism responsive to levodopa[37] and wearing-off phenomenon,[38] may be relevant to the dopaminergic deficits seen in PD, although its exact neuronal role is unclear. No evidence currently links MIR1537, a microRNA gene involved in gene expression,[39] to PD, warranting further research. Although rs4366309 reached only the suggestive significance threshold used previously,[4,17,26,27] it has not reached a genome-wide significance level, so caution is needed when interpreting its association with PD.

A previous GWAS on AAO in European populations identified variants in the *TMEM175* and *SNCA* genes,[18] whereas a Chinese study reported associations with variants around the *NDN* and *PWRN* genes, in addition to *SNCA*.[4] However, these variants and other previously reported variants in *BST1* and *LRRK2*, also associated with AAO,[17,33] did not show any significant associations in our results. These differences underscore the genetic diversity across populations and the need for region-specific studies to fully capture the global genetic diversity underlying PD,[40] emphasizing the importance of tailored genetic research.

However, the lack of *SNCA* variants affecting AAO in our study may be attributed to the small sample size and sex-specific genetic characteristics observed in a previous Korean-specific PD GWAS,[23] in which *SNCA* variants were associated with PD in females, but not in males.[41] Our small sample size, half male, might explain the non-significant results for *SNCA* variants. Similarly, we found a significant correlation between PRS (based on Korean-specific GWAS on PD susceptibility) and AAO in females, but not males. Considering that *SNCA* gene variants were crucial in determining the PRS in our previous Korean GWAS,[23] the lesser effect of PRS on the AAO of PD in male patients may

relate to these Korean-specific genetic characteristics. This may also explain why *SNCA* variants were not significant modifiers of AAO in our present GWAS. However, in a meta-analysis combining our and previous European data, the only *SNCA* variants were shared significant AAO modifiers, suggesting potential shared genetic mechanisms. Therefore, it cannot be conclusively stated that the AAO in Korean patients with PD is unaffected by variants in *SNCA*. Further research, including larger-scale or replication studies, is necessary to determine the impact of *SNCA* on the AAO of PD in the Korean population.

In our MAGMA analysis, no genes met the significant threshold; however, several novel genes within chromosome 6 showed potential associations. The *ZNF184* gene is a zinc-finger protein-encoding gene, with a largely uncharacterized biological function and a notable variant identified in the 2017 European PD GWAS meta-analysis.[42] *GPX6*, *GPX5*, *RNF39*, and *ZNF391* have not been identified as key genes associated with PD. *GPX6* and *GPX5* belong to the glutathione peroxidase family, which encodes antioxidant enzymes,[43] and *RNF39* is involved in immune regulation.[44] Oxidative stress and immune response are major pathological mechanisms in PD,[45] therefore, these genes may indirectly influence the disease. However, there is still insufficient evidence to confirm a direct association.

Unfortunately, our Coloc analysis did not identify genes or causal variants associated with AAO through expression levels in the regions surrounding the SNPs we discovered,[28] that is, the SNPs we identified, such as rs2134545, did not directly influence the *ALCAM* gene expression. Several possibilities should be considered when interpreting these results. First, the identified SNP might be a "proxy" SNP linked to the true causal SNP through LD.[46] In this case, eQTL or colocalization analyses may not detect a direct association. Second, the identified SNP may not directly affect gene expression, but could be a functional variant related to protein-coding or splicing.[47] eQTL analysis may fail to capture this relationship. Conversely, our survival analysis revealed a significant difference in AAO according to the genotype of the identified SNPs. This supports the possibility that these SNPs could influence AAO. Therefore, the effects of the SNPs we identified on AAO may involve mechanisms other than the expression of *ALCAM* or *LYST* genes. Further research is needed to explore these alternative mechanisms.

Despite previous evidence of sex-specific genetic differences in AAO,[4,18,48,49] newly identified SNPs in our PD AAO GWAS did not show different effects on the AAO between sexes, aligning with some European findings, but contrasting with Chinese results.[4,18] As previously mentioned, the PRS based on the Korean GWAS for PD susceptibility significantly impacted the AAO in females, but it was minimal in males. Additionally, the effect of *SNCA* on PD susceptibility showed a gender difference in our population. Generally, the risk of developing PD is ~1.5 times higher in men than in women.[50] However, in Korea, because of an as-yet-unidentified population-specific etiology, the incidence and prevalence of PD are higher in female individuals.[51] This trend was reflected in our study, where more female patients were recruited despite the absence of sex-based selection criteria, which was also observed in another previous domestic study on PD.[52] This observation might also relate to sex in our study. However, the exact mechanisms underlying the observed sex-specific characteristics in our population remain unknown, leaving much to be explored.

Additionally, PRS exhibited an inverse relationship with AAO, indicating that a high PRS is associated with an earlier AAO, consistent with previous reports.[4,53-55] Importantly, the low explanatory power ($r^2 = 0.022$ using SNPs from the European GWAS and $r^2 = 0.009$ using SNPs from the Korean GWAS) suggests that although PRS and AAO are negatively correlated, the explanatory capacity is limited. Our regression model indicated that AAO-associated SNPs had a more significant impact than PRS, emphasizing the importance of ethnicity-specific genetic modifiers.

This study has several limitations. First, it involved a small sample size and lacked replication on independent samples to confirm true-positive associated SNPs. Functional validation of these SNPs was limited, as we did not confirm their biological roles through experimental methods like Clustered Regularly Interspaced Short Palindromic Repeats or in vitro assays. Additionally, the intergenic nature of rs2134545 complicates identifying functional mechanisms without detailed molecular studies. We have not fully investigated the responsible driver gene, although the nearby ALCAM gene may be a potential candidate. The possibility of an unknown gene regulator nearby cannot be ruled out. Therefore, the pathogenic mechanism of this intergenic SNP requires clarification using data on 3D chromatin structure or nuclear architecture.[56,57]

In conclusion, our study identified the associations of loci in *ALCAM* and *LYST* genes with the AAO of PD, distinct from previously reported genetic loci associated with PD susceptibility or AAO in other populations. These findings underscore the importance of genetic research across diverse populations to uncover universal and population-specific risk factors. Future studies in other ethnic populations and functional validations are warranted to translate these genetic insights into therapeutic strategies.

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Ethical Compliance Statement

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (protocol number: 2012-0033). All procedures in the research were performed with informed consent from all patients and conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Availability Statement

Summary statistics of PD risk and AAO loci based on European patients were downloaded from the International Parkinson's Disease Genomics Consortium (https://pdgenetics.org/resources). Participants from 23andMe. were excluded. Summary statistics of PD risk loci based on Korean patients were obtained with permission from the authors of the original publication. The summary data of Korean GWAS and multi-ethnic meta-GWAS-analysis for the AAO of PD from this study are available from the corresponding author on reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.