Effect of Alzheimer's Disease Risk Variant rs3824968 at SORL1 on Regional Gray Matter Volume and Age-Related Interaction in Adult Lifespan

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Sortilin receptor 1 (SORL1) is involved in cellular trafficking of amyloid precursor protein and plays an essential role in amyloid-beta peptide generation in Alzheimer disease (AD). The major A allele in a SORL1 single nucleotide polymorphism (SNP), rs3824968, is associated with an increased AD risk. However, the role of SORL1 rs3824968 in the normal ageing process has rarely been examined in relation to brain structural morphology. This study investigated the association between SORL1 rs3824968 and grey matter (GM) volume in a nondemented Chinese population of 318 adults within a wide age range (21–92 years). Through voxel-based morphometry, we found that participants carrying SORL1 allele A exhibited significantly smaller GM volumes in the right posterior cingulate, left middle occipital, medial frontal, and superior temporal gyri. Considerable interaction between age and SORL1 suggested a detrimental and accelerated ageing effect of allele A on putamen. These findings provide evidence that SORL1 rs3824968 modulates regional GM volume and is associated with brain trajectory during the adult lifespan.

The sortilin-related receptor gene (SORL1) encodes a mosaic protein belonging to at least two families: the vacuolar protein sorting 10 domain-containing receptor family and the low density lipoprotein receptor family. The encoded protein acts as an apolipoprotein E (APOE) binder and sorting receptor that regulates the intracellular transport and processing of the amyloid precursor protein (APP) in neurons1. In addition to the ε4 allele of APOE, the major genetic risk factor for late-onset Alzheimer disease (AD)2, SORL1 is genetically associated with late-onset and sporadic AD3. SORL1 regulates and traps APP in the Golgi apparatus and reduces the production of the amyloid-beta peptide (Aβ3), the main component of senile plaques in AD4. Cell biology experiments have indicated that SORL1 underexpression leads to overproduction of Aβ3, whereas SORL1 overexpression considerably reduces cellular APP and extracellular Aβ3. Although the underlying mechanisms of SORL1 in AD and neurodegenerative processes remain unclear, a recent comprehensive review on multiple functional domains of SORL1 suggested that SORL1 can assume various characters in AD pathogenesis6.

Among single nucleotide polymorphisms (SNPs) in SORL1, Rogaeva et al.3 observed a substantial association between a synonymous SNP in exon 34 (rs3824968) and AD in a northern European case–control cohort and implied that the SNP alters the physiological role of SORL1 in the processing of APP holoprotein. The association between SORL1 rs3824968, neurodegenerative disease, and ageing process has recently been reported6–11. Lower
Main Effect of Age and SORL1 rs3824968 on Regional GM Volume. Regarding the main effect of age, DARTEL-based T1 VBM analyses showed widespread age-related GM volume differences in the study participants (Fig. 1), in accordance with previous studies. Regarding the main effect of the gene obtained from F tests (Table 2, Fig. 2A), on comparing the participants carrying the SORL1 TT, AT, and AA genotypes, the
post hoc analyses revealed positive dosage effect of the T allele on GM volume of the left middle occipital gyrus (Fig. 2B). In addition, participants carrying AA showed lower GM volume in the right cerebellar tonsil than did those carrying AT (Fig. 2C). Moreover, participants carrying AA had lower GM volumes in the left medial frontal and right posterior cingulate gyri than did those carrying the T allele (Fig. 2D,E). The participants carrying the A allele showed significantly lower GM volume in the left superior temporal gyrus than did those carrying TT (Fig. 2F). After controlling APOE genotype as additional nuisance variable, the findings remain consistent with current findings (Supplementary Table 1).

**Table 2. Regional GM volume differences among the three SORL1 rs3824968 genotypic groups.** Z-scores are for the peak statistical significant voxel of each regional cluster with corrected $P_{\text{alpha}}$ of <0.05 (corrected for multiple comparisons by using Monte Carlo simulation) after controlling for age, sex, and education level. Abbreviations: BA, Brodmann area; GM, grey matter; MNI, Montreal Neurological Institute; SE, standard error.

**Figure 1. Age effect: GM differences in a nondemented elderly participants.** Regions of significant GM differences from 318 normal participants superimposed on surface space. T-score maps show clusters at a voxel threshold with $P$ of <0.005 as well as extended voxel sizes of 298, all of the clusters remained significant and survived from the criteria of corrected $P_{\text{alpha}}$ of <0.05 by Monte Carlo simulation.

**Age and SORL1 Interaction Effect on Regional GM Volume.** Regarding the voxelwise covariate interaction analysis, we observed considerable interaction effect between age and the three SORL1 genotypes in the right putamen region (Fig. 3), and the downward slope was steeper in the participants carrying AA and AT than in those carrying TT. To verify whether this accelerated reduction in the putaminal volume was related to cognitive performance, we applied partial correlation for each genotypic group (results are presented in Section 3.4).
Correlation Analysis Between Regional GM Volume and Cognitive Function. In the partial correlation analysis between regional GM volume and cognitive performance levels in all participants, none of the regional GM volume changes for the effect of SORL1 showed correlation with MMSE, digit span forward (DSF), or digit span backward (DSB) scores. For the correlation between the cluster of voxelwise interaction and cognitive tests, although the results failed to survive the criteria of Bonferroni correction, a positive trend between DSB score and putaminal volume was observed in the participants carrying AA ($r = 0.189, P = 0.034$).

Figure 2. Regional GM volume differences among the three SORL1 rs3824968 genotypic groups. T-score map shows significant smaller GM volume in SORL1 A allele carriers compared with those carrying TT (A). The clusters were set at a voxel threshold with $P < 0.005$ as well as extended voxel sizes of 298, all of the clusters remained significant and survived from the criteria of corrected $P_{\text{alpha}}$ of $< 0.05$ by Monte Carlo simulation. Bottom bar graph shows the GM volume difference between the SORL1 genotypes and the regions with significant gene main effect in the left middle occipital gyrus (B), right cerebellum tonsil (C), left medial frontal gyrus (D), right posterior cingulate gyrus (E), and left superior temporal gyrus (F). *Bonferroni-corrected $P < 0.05$ (post hoc tests in analysis of covariance).

Figure 3. Interaction between the SORL1 genotype and age on right putamen GM volume. The scatter plot demonstrates the interaction between the SORL1 genotype and age on right putamen GM volume using voxelwise covariate analysis with the SORL1 genotypes as the condition and age as the covariate, while controlling for sex and education level as nuisance variables (corrected $P_{\text{alpha}}$ of $< 0.05$ by Monte Carlo simulation)).
Discussion
We performed VBM analysis to examine the effect of SORL1 rs3824968 on regional GM volume and age-related changes in the brain GM volume of nondemented participants within a wide age range. The findings of this study showed that the SORL1 rs3824968 A allele carriers had lower GM volume in the left superior temporal, left medial frontal, right posterior cingulate, and left middle occipital gyrus than did those carrying TT. A considerable interaction between age and the SORL1 genotypes was observed, showing an accelerated (downward) slope of GM volume differences in the right putamen of the participants carrying the AD-risk (A) allele compared with those carrying TT. Thus, our findings support the hypothesis that SORL1 rs3824968 is associated with regional GM volume differences in early adulthood and can influence age-related GM morphological changes during the nondemented adult lifespan.

The SORL1 rs3824968 A carriers showed significantly decreased GM volume in the left superior temporal, left medial frontal, right posterior cingulate, and left middle occipital gyrus, suggesting detrimental effects of the A allele on brain GM volume. A trend towards gene dosage effect of the A allele was also observed in the left middle occipital, medial frontal, and right posterior cingulate gyrus. SORL1 SNPs have been found to be associated with an increased risk of neurodegenerative disease in Swedish and African American population through meta-analysis. Nonetheless, association studies have further identified that haplotype SNPs including rs3824968 are associated with lower Aβ levels in CSF and higher AD risk in Asian population. Therefore, the SORL1 risk variants may alter the Aβ expression levels in either healthy adults or patients with neurodegenerative disease, thus suggesting that SORL1 rs3824968 variants may influence amyloid pathology during ageing. Greater amyloid burden has been shown to be positively associated with regional GM atrophy, particularly in the superior temporal, medial frontal, and cingulate gyrus in both structural and functional MRI studies. In addition to the hypothesis of amyloid pathology, a proposition was proposed another viewpoint that SORL1 increases dementia risk through effects on cerebrovascular abnormalities; SORL1 rs3824968 and its haplotypes were found to be associated with brain volume and WM hyperintensities in their study. This biological and neuroimaging evidence may suggest that SORL1 rs3824968 is associated with brain morphology in terms of A allele-related volumetric reduction caused by high Aβ load, cardiovascular disease, or both. However, additional studies are necessary to explore the potential mechanisms of SORL1 rs3824968 on the cellular and molecular determinants of brain structural differences in both demented and nondemented individuals.

Here, we revealed the first evidence of the influence of SORL1 on age-related changes in the brain cortical morphology of nondemented participants over a wide age range. The right putamen of the participants carrying AA and AT showed a considerable effect of interaction between age and the SORL1 genotype with a steeper downward slope of age-related GM volume reduction compared with that of those carrying TT. This finding supports the hypothesis that SORL1 polymorphism plays a role in the ageing process of the human brain with a partially detrimental effect on age-related differences of regional GM volume, particularly in the putamen of the participants with the A allele variant. A previous study reported that participants with presenilin-1, presenilin-2, and APP mutations showed higher amyloid load and greater GM atrophy in the putamen. In other words, if the SORL1 variants contribute to the risk of AD neuropathogenesis through the amyloidogenic pathway, putaminal volume could be a vulnerable subcortical area in the brain ageing process with regard to the SORL1 effect. In addition, such an accelerated regional GM volume reduction effect in the putamen further links to cognitive decline in participants carrying the A allele. A trend of positive correlation between putamen volume and DSB scores was observed in the participants carrying AA. Studies have shown that the basal ganglia play a vital role in working memory and executive function, particularly in the putaminal region. Moreover, increased activity in the putamen during a card sorting test was observed to be related to working memory function, as evident on functional MRI. In the current study, imaging indicated an association between SORL1 rs3824968 and putaminal volume and a trend of neural correlation of working memory (DSB), which may be a marker of accelerated cognitive impairment at preclinical stage.

We observed no age-by-SNP interaction effect in the significant clusters that detected the main effect of genotype: the left superior temporal gyrus, left middle occipital gyrus, right cerebellar tonsil, and right posterior cingulate gyrus. In addition to a previous study, which proposed a pathway by which SORL1 variants could mediated neural risk of AD beginning from teenage years, current data support two pathways of SORL1 rs3824968 effect on GM volume during the ageing process: (1) differences of regional cortical volume between the three genotypes occur from early adult life and preferentially stay stable during adulthood and (2) in contrast to the first pathway, variants of SORL1 rs3824968 do not modulate putaminal volume directly but interact with age during the adult lifespan. Further research is necessary to explore underlying mechanisms for various SORL1 genetic effects along brain ageing trajectory.

The necessity for statistically sufficient sample sizes in imaging studies of genetic variation is increasingly being recognised. The relatively large and (by international standards) homogeneous cohort of participants with a wide age range recruited in this study increased the credibility of our findings, based on previously proposed recommendations regarding cohort sizes. However, the characteristic cross-sectional design of this study may be a limitation. We did not measure Aβ load levels in our participants; the genotypic effect of the SORL1 SNP on GM volume might be affected through Aβ deposition or other mechanisms such as inflammatory signalling modulation. Therefore, the associations between SORL1 variants, biochemical data, and brain morphometry should be investigated simultaneously in future studies to explain the effect of SORL1 on GM volume reduction. In addition, rather than having a direct effect on regional GM volume, SORL1 rs3824968 may be in linkage disequilibrium with truly associated variants; in addition, it may be an intermediate phenotype. Since such a linkage could vary among different populations and the association between rs3824968 and AD was not replicated in studies of other populations, these may confound the generalisability of our findings, which were based on a homogenous Chinese cohort. In addition, no significant correlation was found between general cognitive function (MMSE, DSF, and DSB) and regional GM volume differences of the SORL1 effect. Although MMSE is a widely used tool
for detecting dementia, it may lack sensitivity to and specificity for early signs of subtle cognitive changes. Despite the current samples being from nondemented participants, the ceiling effect of using MMSE, DSF, and DSB for cognition assessment may also have yielded false negative results. Specific cognitive assessments regarding short- and long-term memory should be examined in future to associate cognitive decline with genetic effect and brain structural changes.

The AD-risk SORL1 rs3824968 A allele was associated with decreased GM volume and exhibited a trend towards gene dosage effect in several brain regions during the adult lifespan. Considerable interaction between age and SORL1 suggested a detrimental and accelerated ageing effect of the AD-risk allele on putaminal volume. Although the underlying molecular mechanisms remain unclear, our findings support the hypothesis that SORL1-related genetic factors play a vital role in the process of normal ageing. The regional GM volume alterations associated with the effect of SORL1 rs3824968 might be a potential neuroimaging biomarker for accelerated brain ageing during the adult lifespan.

Methods
Participants and Instruments. This study initially recruited 330 nondemented ethnic Chinese participants from Northern Taiwan (mean age: 55.9 ± 22.1 years; range: 21–92 years; 57.5% males) through an advertisement in local communities and universities. Each participant was administered a diagnostic structured Mini-International Neuropsychiatric Interview (MINI) 51, Mini-Mental State Examination (MMSE) Chinese version 52, and Clinical Dementia Rating (CDR) scale 53. Participants with any of the following conditions were excluded: (1) a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) axis I diagnosis such as mood disorder or psychotic disorder; (2) a neurobiological disorder, such as dementia, head injury, stroke, or Parkinson disease; (3) illiteracy; (4) an MMSE score of ≤24; or (5) ≥65 years of age with a CDR of >0.5 [exclusion criteria (4) and (5) applied to prevent possible inclusion of dementia patients].

The cognitive functioning of the participants was evaluated using the MMSE for general cognitive status and the Wechsler Digit Span subtest for verbal working memory abilities. All participants exhibited sufficient visual and auditory acuity to undergo cognitive testing. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Taipei Veterans General Hospital. Written informed consent was obtained from all participants after they were adequately apprised of the study.

Genotyping. Genomic DNA was extracted from peripheral blood with a commercial kit (Qiagen, Gentra Puregene Blood Kit). SORL1 rs3824968 genotyping was performed using high-throughput matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry. PCR and single-base extension primers were designed using DNA mass arrays (Sequenom, San Diego). The genotyping analysis was performed using an iPLEX Gold Reagent Kit according to the manufacturer's instructions. The purified extension products were spotted onto a 384 SpectroCHIP II array by using a MassArray Nanodispenser RS1000, followed by an analysis on a MassARRAY Compact Analyzer. The resulting spectra were processed, and the alleles were called using a SpectroTYPER. The APOE genotype was determined using the PCR-restriction fragment length polymorphism method, as described by Hong et al. 54.

MRI Acquisition. All MRI scans were performed at National Yang-Ming University, Taipei, Taiwan, on a 3.0-T Siemens MRI scanner with a 12-channel head coil (Siemens Magnetom Tim Trio, Erlangen, Germany). High-resolution structural MR images were acquired through sagittal 3D magnetisation-prepared rapid gradient-echo sequencing (TR = 2530 ms, TE = 3.5 ms, TI = 1100 ms, FOV = 256 mm, flip angle = 7°, matrix size = 256 × 256, 192 sagittal slices, voxel size = 1.0 × 1.0 × 1.0 mm, no gap). All images were acquired parallel to the anterior commissure–posterior commissure line. To minimise motion artefacts generated during image acquisition, each participant's head was immobilised using cushions inside the coil. An experienced radiologist carefully checked each image to ensure the absence of scanner artefacts, motion problems, or gross anatomical abnormalities.

Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra-Based T1 VBM Analysis. Individual T1-weighted volumetric images were processed using Gaser's VBM8 toolbox (http://dbm.neuro.uni-jena.de) within Statistical Parametric Mapping (SPM8; Wellcome Institute of Neurology, University College London, UK). VBM processing was performed using the following procedures: (1) The anterior commissure was set as the origin of each T1-weighted image. (2) A segmentation approach in the VBM8 toolbox was applied in the initial native space. (3) To achieve a higher registration accuracy and account for different brain size among subjects, the native space segments of the GM, WM, and cerebrospinal fluid (CSF) were initially affine registered to the tissue probability maps in the Montreal Neurological Institute (MNI) standard space. (4) All affine registered GM and WM tissue segments were used to generate group-specific templates through nonlinear warping by using the Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) algebra toolbox 55 implemented in SPM8. (5) Nonlinear deformation parameters were obtained in the previous step were used to modulate the GM, WM, and CSF tissue maps of the participants' brains to compare actual volumetric differences among groups. (6) Modulated tissue segments were converted into an isotropic voxel resolution of 1.5 × 1.5 × 1.5 mm. All normalised, segmented, and modulated MNI standard space images were then smoothed with an 8-mm Gaussian kernel before voxelwise group comparisons. Segmented tissue volumes (i.e., GM, WM, and CSF) were estimated in cubic millimetres by counting the voxels representing the native space of the GM, WM, and CSF. Total intracranial volume was calculated as the sum of the GM, WM, and CSF volumes.
Statistical Analysis. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software package (SPSS 20 for Windows, Chicago, IL, USA). Analysis of variance and chi-squared test were respectively applied to compare the continuous and categorical variables of the demographic data among the three groups (participants with the AA, AT, and TT genotypes). Smoothed and modulated GM segments were analysed with SPM8 by using the framework of a general linear model. Analysis of covariance was used by covarying age, sex, and educational levels to reveal the random effect of SORL1 rs3824968 on GM volumes. To prevent possible partial volume effects around the margin between the GM and WM, all voxels with a GM probability value of <0.2 (range: 0–1) were eliminated. In this study, to further investigate the main effects of age-by-SNP interaction on regional GM volumes, voxelwise covariate interaction analysis was used with the SORL1 genotype as a condition and age as a covariate, controlling for sex and education level as nuisance variables. In each model, the main effect and interaction were explored using F tests. Post hoc t tests were subsequentially performed to examine the relationships between genotypic groups for any significant main effects and interaction clusters using Bonferroni corrections for multiple comparisons. The problem of multiple comparisons was corrected using a Monte Carlo simulation created in AlphaSim and implemented in the Analysis of Functional NeuroImages software (http://afni.nimh.nih.gov/afni/). Based on the simulation, the statistical threshold of F tests and post hoc tests were set at corrected $P_{\text{cor}}$ of <0.05, with a minimum cluster size of 298 voxels (AlphaSim with the following parameters: single voxel $P$ value of 0.005, 5000 simulations, $FWHM_{x/y/z}$ = 7.5/8.7/8.1 mm with a GM mask) for multiple comparisons. The coordinates of each significant cluster were transformed from MNI coordinates into Talairach coordinates by using the GingerALE toolbox (BrainMap Development Team; http://brainmap.org/ale/index.html). The anatomical structures of the coordinates representing significant clusters were identified using the Talairach and Tournoux atlas. The volume of each significant cluster was extracted from modulated GM index.html. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet 39, 168–177, doi: 10.1038/ng1943 (2007).

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The volume of each significant cluster was extracted from modulated GM segments in MNI space for each participant and further corrected for the cognitive assessments in the entire study group. Partial correlation analyses between regional GM volume (crucial results of genetic effect/age-by-SNP interaction) and cognitive performance were controlled for nuisance variables (age, sex, and educational levels) and corrected for multiple testing with Bonferroni correction. Since APOE is the major risk factor for AD, additional statistical analyses were performed using age, sex, educational level, and APOE genotype (c2/c2, c2/c3, c3/c3, c2/c4, and c3/c4) as nuisance variable to account for potential effect by APOE status.

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C.C. H., S.J.T. and C.P.L. conceived the experiment, C.C.H., M.E.L., Y.H.W. and T.R.C. conducted the experiment. C.C.H. and K.H.C. analysed the results. C.C.H. wrote the main manuscript, and H.W.K. and M.E.L. edited the manuscript. A.C.Y. gave technical support and conceptual advice. All authors discussed the results and implications and commented on the manuscript at all stages.

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Author Contributions

C.C.H., S.J.T. and C.P.L. conceived the experiment, C.C.H., M.E.L., Y.H.W. and T.R.C. conducted the experiment. C.C.H. and K.H.C. analysed the results. C.C.H. wrote the main manuscript, and H.W.K. and M.E.L. edited the manuscript. A.C.Y. gave technical support and conceptual advice. All authors discussed the results and implications and commented on the manuscript at all stages.

Additional Information

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