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*Review Article*

# Neuroimaging Measures as Endophenotypes in Alzheimer's Disease

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Late onset Alzheimer's disease (AD) is moderately to highly heritable. Apolipoprotein E allele ε4 (*APOE4*) has been replicated consistently as an AD risk factor over many studies, and recently confirmed variants in other genes such as *CLU, CR1*, and *PICALM* each increase the lifetime risk of AD. However, much of the heritability of AD remains unexplained. AD is a complex disease that is diagnosed largely through neuropsychological testing, though neuroimaging measures may be more sensitive for detecting the incipient disease stages. Difficulties in early diagnosis and variable environmental contributions to the disease can obscure genetic relationships in traditional case-control genetic studies. Neuroimaging measures may be used as endophenotypes for AD, offering a reliable, objective tool to search for possible genetic risk factors. Imaging measures might also clarify the specific mechanisms by which proposed risk factors influence the brain.

## 1. Introduction

Alzheimer's disease (AD) is thought to be at least 58–74% heritable [1–3]. However, much of that heritability has yet to be explained by variants in specific risk genes. Mutations in the amyloid precursor protein (*APP*) [4], presenilin 1 (*PSEN1*) [5], and presenilin 2 (*PSEN2*) [6, 7] genes are known to lead to early onset, familial AD. In familial AD, the disease typically follows an autosomal dominant, usually highly penetrant mode of inheritance. However, for many years only the ε4 allele of apolipoprotein E (*APOE*4) [8] was identified as a reliable genetic risk factor for late-onset AD. On average, 24% of control subjects carry at least one copy of *APOE*4 [9], and each risk allele carries more than threefold odds of developing AD [9], although these numbers vary across studies; this is a relatively large odds ratio for a highly prevalent risk gene. Recently, large sample genome-wide association (GWA) studies have successfully identified and replicated associations between several single nucleotide polymorphisms (SNPs) and AD [10] (Table 1), namely, in the *CLU* [11, 12], *PICALM* [11–13], and *CR1* [13] genes and near the *BIN1* and *EXOC3L2* genes [12]. Numerous other genetic polymorphisms also have been associated with a diagnosis of AD, but with less statistical evidence, and replication results are frequently inconsistent [14] (http://www.alzgene.org/). Much work yet remains in discovering the sources of AD heritability. As we note below, large-scale neuroimaging studies provide an approach to discover, replicate, and study new genetic risk factors.

AD is a complex disease whose onset and trajectory are influenced by (1) environmental factors and (2) many genetic polymorphisms having small effects and/or rare polymorphisms having larger effects. Because contributing genes have large effects in aggregate but small effects individually, association studies typically require large samples to reliably identify the individual contribution of any one polymorphism, especially since stringent corrections for multiple comparisons are required by GWA studies. Additionally, genes involved in either neurodevelopment or degeneration or both may contribute to AD risk. The onset of AD is

Table 1: Top AD risk genes.

| | Gene | Protein | Population | Polymorphism |
|---|---|---|---|---|
| 1 | APOE_e2/3/4 | apolipoprotein E | all | APOE_e2/3/4* |
| 2 | CLU | clusterin | all | rs11136000* |
| 3 | EXOC3L2 | exocyst complex component 3-like 2 | all | rs597668 |
| 4 | BIN1 | bridging integrator 1 | all | rs744373 |
| 5 | PICALM | phosphatidylinositol binding clathrin assembly protein | all | rs541458* |
| 6 | SORL1 | sortilin-related receptor | Asian | rs2282649* |
| 7 | GWA_14q32.13 | unknown | all | rs11622883 |
| 8 | TNK1 | tyrosine kinase non-receptor, 1 | all | rs1554948 |
| 9 | ACE | angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 | Caucasian | rs1800764 |
| 10 | IL8 | interleukin 8 | all | rs4073 |
| 11 | LDLR | low density lipoprotein receptor | all | rs5930 |
| 12 | CST3 | cystatin C | Caucasian | rs1064039* |
| 13 | CR1 | complement component (3b/4b) receptor 1 (Knops blood group) | all | rs6656401 |
| 14 | hCG2039140 | unknown | all | rs1903908 |
| 15 | CHRNB2 | cholinergic receptor, nicotinic, beta polypeptide 2 (neuronal) | all | rs4845378 |
| 16 | SORCS1 | sortilin-related VPS10 domain containing receptor 1 | all | rs600879 |
| 17 | TNF | tumor necrosis factor alpha | Asian | rs4647198 |
| 18 | CCR2 | chemokine (C-C motif) receptor 2 | Caucasian | rs1799864 |

Genes listed represent those most highly associated with AD per alzgene.org [9] as of August 22, 2010. Only those with high or moderate epidemiological evidence are included above. Grading was based on HuGENet (Human Genome Epidemiology Network) interim criteria for the assessment of cumulative evidence of genetic associations [132].

*At least one neuroimaging study has investigated the effects of this polymorphism in the brain.

clinically detectable only when the pathological hallmarks of the disease such as amyloid plaques, neurofibrillary tangles, and neuronal loss have advanced to the point where memory impairment and other behavioral changes become evident. Therefore, symptoms may be manifest when abundant pathology overwhelms an otherwise healthy brain, or limited pathology occurs in a brain whose health and resilience is compromised by cortical thinning, reduced white matter integrity, or restricted blood flow.

It is difficult for case-control studies to identify genetic risk factors for AD based on clinical diagnosis alone. This is because AD diagnosis relies on evidence of cognitive deficits identified using standard cognitive tests. Performance on cognitive tests may be influenced by factors unrelated to disease, such as fatigue, anxiety, general test-taking ability, and practice effects. As such, well-educated people suffering from cognitive decline can appear normal in a clinical setting, while cognitively normal worriers may appear to be impaired. Other late-life dementias also may be clinically misdiagnosed as AD. Using brain endophenotypes that are objective and highly reproducible over time may make it easier to identify AD genetic risk factors and to understand their impact on the brain.

In recent multisite efforts, researchers have performed brain scans on and genotyped large numbers of cognitively intact and impaired older adults. These studies have improved the ability of researchers to identify AD-related genes. In this article, we review the results of neuroimaging studies that evaluate the effects on the brain of top AD-related candidate genes other than *APOE* as well as genetic contributions to brain vulnerability. We discuss the findings from GWA studies that have used neuroimaging measures as endophenotypes for AD, and we offer suggestions for future studies. Finally, we discuss multigene and more advanced genetic models as means to identify specific genetic contributions to AD. The main findings of the studies discussed here are summarized in Table 2 by imaging phenotype.

## 2. Candidate Gene Approach

There are two main ways to investigate effects of AD-relevant genes using brain imaging—the first is to study candidate genes already associated with AD, and the second is to use genome-wide scanning to perform an unbiased search of up to a million genetic polymorphisms. Both types of approach have been applied in neuroimaging studies of AD. The earliest studies have focused on the most widely studied candidate gene, *APOE*.

Although not without conflicting results, many studies have linked *APOE4* to neuroimaging measures such as regional hypometabolism assessed using fluorodeoxyglucose positron emission tomography (FDG-PET) (which measures brain glucose metabolism) [15–17], functional magnetic resonance imaging (fMRI) activity (which measures variations in regional levels of blood oxygenation and is thought to reflect both blood flow and neuronal activity) during memory tasks and at rest [18–26], regional brain volume

Table 2: SNPs with AD-relevant effects detected by neuroimaging measures.

| Neuroimaging measure | SNP | Gene | Location[c] | Neuroimaging association |
|---|---|---|---|---|
| Hippocampal volume or gray matter density | rs429358/rs7412 ($\varepsilon$2/3/4)[b] | *APOE* | 19q13.32 | CG [47], GWA [104] |
| | rs10501927 | *CNTN5* | 11q22.1 | CG [47] |
| | rs3851179[b] | *PICALM* | 11q14.2 | CG [47] |
| | rs4646994[b] | *ACE* | 17q23.3 | CG [68] |
| | rs2075650[b] | *TOMM40* | 19q13.32 | GWA [104] |
| | rs4692256 | *LOC391642* | 4p15.1 | GWA [104] |
| | rs10074258[b] | *EFNA5* | 5q21.3 | GWA [108] |
| | rs12654281[b] | *EFNA5* | 5q21.3 | GWA [108] |
| | rs10781380 | *PRUNE2* | 9q21.2 | GWA [108] |
| | rs1888414 | *FDPSP* | 21q21.1 | GWA [108] |
| ERC thickness | rs429358/rs7412 ($\varepsilon$2/3/4)[b] | *APOE* | 19q13.32 | CG [47] |
| | rs3851179[b] | *PICALM* | 11q14.2 | CG [47] |
| | rs10501927 | *CNTN5* | 11q22.1 | CG [47] |
| | rs1408077[b] | *CR1* | 1q32.2 | CG [47] |
| | rs7561528[b] | *BIN1* | 2q14.3 | CG [47] |
| PHG cortical thickness | rs429358/rs7412 ($\varepsilon$2/3/4)[b] | *APOE* | 19q13.32 | CG [47] |
| | rs10501927 | *CNTN5* | 11q22.1 | CG [47] |
| Amygdala volume | rs429358/rs7412 ($\varepsilon$2/3/4)[b] | *APOE* | 19q13.32 | CG [47], GWA [104] |
| | rs2075650[b] | *TOMM40* | 19q13.32 | GWA [104] |
| | rs4646994[b] | *ACE* | 17q23.3 | CG [68] |
| MTL volume | rs4935775[b] | *SORL1* | 11q24.1 | CG [58] |
| Temporal pole cortical thickness | rs429358/rs7412 ($\varepsilon$2/3/4)[b] | *APOE* | 19q13.32 | CG [47] |
| | rs10501927 | *CNTN5* | 11q22.1 | CG [47] |
| | rs7561528[b] | *BIN1* | 2q14.3 | CG [47] |
| Temporal lobe volume | rs429368/rs7412 ($\varepsilon$2/3/4)[b] | *APOE* | 19q13.32 | GWA [81] |
| | rs10845840 | *GRIN2B* | 12p13.1 | GWA [81] |
| | rs2456930 | chromosome 15 intergenic region | 15q22.2 | GWA [81] |
| Frontal lobe volume | rs3751812 | *FTO* | 16q12.2 | CG[76] |
| GM density-precuneus | rs10932886 | *EPHA4* | 2q36.1 | GWA [104] |
| GM density-frontal cortex | rs10932886 | *EPHA4* | 2q36.1 | GWA [104] |
| | rs6463843 | *NXPH1* | 7p21.3 | GWA [104] |
| Regional brain tissue volume in temporal lobe | rs2429582 | *CADPS2* | 7q31.32 | vGWA [113] |
| Regional brain tissue volume in parietal lobe | rs476463 | *CSMD2* | 1p35.1 | vGWA [113] |
| Whole brain volume | rs1468063[b] | *FAS* | 10q23.31 | CG [71] |
| Ventricular volume | rs1468063[b] | *FAS* | 10q23.31 | CG [71] |

Table 2: Continued.

| Neuroimaging measure | SNP | Gene | Location[c] | Neuroimaging association |
|---|---|---|---|---|
| WM lesion volume[a] | rs10501927 | *CNTN5* | 11q22.1 | CG [47] |
| | rs560573[b] | *SORL1* | 11q24.1 | CG [58] |
| | rs668387[b] | *SORL1* | 11q24.1 | CG [58] |
| | rs689021[b] | *SORL1* | 11q24.1 | CG [58] |
| | rs641120[b] | *SORL1* | 11q24.1 | CG [58] |
| | rs2276346[b] | *SORL1* | 11q24.1 | CG [58] |
| | rs4646994[b] | *ACE* | 17q23 | CG [65] |
| WM integrity[a] | rs11136000[b] | *CLU* | 8p21.1 | CG [54] |

This table summarizes the most promising single SNPs relevant to AD research and identified from associations with neuroimaging characteristics. These characteristics show correlations with the SNP alleles either specifically in AD-related regions (in healthy adults) or anywhere in the brain (in normal adults and those with AD and/or MCI).
Key: GM: gray matter; WM: white matter; MTL: medial temporal lobe; PHG: parahippocampal gyrus; ERC: entorhinal cortex; CG: candidate gene approach; GWA: genome-wide association scan approach; vGWA: voxelwise genome-wide association scan approach.
[a]White matter lesion volume is calculated from a structural MRI scan (usually a T2-weighted scan), while white matter integrity is measured using diffusion tensor imaging and reflects water diffusion directionality.
[b]Previously identified as an AD risk allele [9].
[c]Locations were determined using http://genome.ucsc.edu/ [133], using values from dbSNP build 131.

or cortical thickness (measures of structural gray matter integrity) [27–31], white matter integrity [32–35], cerebral blood flow [36–39], and AD-related pathology such as amyloid and neurofibrillary tangle load [40–44]. Results from such *APOE* neuroimaging studies have been reviewed previously [14, 45, 46].

Neuroimaging differences associated with the *APOE* genotype may result from incipient AD, or they may relate instead to differences specific to the genotype independent of AD pathology (e.g., developmental differences). If other AD risk genes were to resemble *APOE* in their effects on the brain, it would support the notion that those brain differences are related to the pathological processes of AD. Additionally, determining the effects on the brain of other AD risk gene variants would help to characterize the mechanisms of those risk alleles, enabling more targeted therapeutic treatments to be developed. Thus far, relatively few neuroimaging studies have examined the effect of AD candidate risk genes other than *APOE* on the brain (Table 1).

The most recent and comprehensive candidate gene study to date was performed by Biffi and colleagues (2010), who evaluated the effects of top AD risk polymorphisms on six measures shown to predict AD risk and measure disease progression [47]. The authors measured hippocampus, amygdala, and white matter lesion volumes and thickness of the entorhinal cortex, parahippocampal gyrus, and temporal pole cortex in AD patients, mild cognitively impaired (MCI) patients, and normal controls. People with MCI have some degree of demonstrable cognitive impairment not severe enough to warrant a diagnosis of dementia. Approximately 10–15% of those with amnestic MCI convert to probable AD each year compared with an estimated 1-2% of similarly aged cognitively intact individuals [48]. MCI therefore can be used as an indicator of early AD-related changes in the brain. The authors focused on confirmed risk polymorphisms and other potential risk variants identified in recent GWA studies. Among these were *APOE*, *CLU*, *PICALM*, *CR1*, *CNTN5,* and *BIN1*. *APOE,* which encodes apolipoprotein E—an apolipoprotein that interacts with $\beta$-amyloid [49]—was correlated with all brain measures except for white matter lesion volumes. *CNTN5,* which codes for contactin 5—a protein that may play a role in regional axonal development [50]—is not currently listed as a top AD risk gene [9]. However, it was associated with all measures except for amygdala volume. All the genetic variants except for *CLU* were statistically correlated with entorhinal cortex thickness. The *CLU* gene encodes clusterin (also known as apolipoprotein J)—another apolipoprotein that interacts with $\beta$-amyloid [51]. Additionally, a variant in the *PICALM* gene, which codes for phosphatidylinositol binding clathrin assembly protein—a protein involved in regulating the fusion of synaptic vesicles [52]—was correlated with hippocampal volume. Finally, *BIN1,* which encodes bridging integrator 1—a protein involved in neurite growth [53]—was correlated with temporal pole cortical thickness [47]. The authors suggested that although sample sizes affect the power to detect gene effects, the specificity of relationships with particular polymorphisms may reflect the function and expression patterns of the resulting proteins, possibly elucidating mechanisms that contribute to AD risk [47].

The *CLU* risk variant rs11136000 was not associated with any of the measures here, but our research group recently found that in young healthy adults, the risk allele of that SNP was associated with reduced integrity of broad white matter regions, observed with diffusion tensor imaging [54]. The lipid transport and membrane recycling performed by the clusterin protein [55] may be important to myelin development but not to medial temporal lobe gray matter. Choosing measures that reflect the purported protein function associated with risk genes in question might help to focus the search for gene effects in the brain.

Another AD gene with structural effects on the brain is *SORL1,* which encodes the sortilin-related receptor. The gene product is a low-density lipoprotein receptor that may be involved in processing the amyloid precursor protein [56]. *SORL1* may also play a role in cardiovascular health [57]. Cuenco and colleagues (2008) evaluated how 30 different polymorphisms in the *SORL1* gene related to general cerebral atrophy, hippocampal atrophy, white matter hyperintensities and cerebrovascular disease, which they measured semiquantitatively [58]. Among the variants tested in African-American and white AD-control sibships was rs2282649—a top AD genetic risk factor [9]. In whites, this variant was associated with cerebral and hippocampal atrophy as part of a 3 SNP haplotype [58]. SNPs within *SORL1* also were associated with white matter hyperintensities in two studies [58, 59]. The strongest relationship between rs2282649 and AD is in Asian populations (as determined in a large meta-analysis) [9]. Future comparisons of SNP effects on the brain in Asians versus Caucasians may clarify how this polymorphism relates to AD.

Babiloni and colleagues (2006) used electroencephalography (EEG) to examine how another AD risk gene, *CST3,* affects resting cortical rhythmicity (the frequency of repetitive spiking of neuronal activity) in subjects with AD and MCI. One haplotype evaluated contained an AD top risk SNP (rs1064039) [60]. *CST3* codes for cystatin C, a protein that colocalizes with $\beta$-amyloid [61] and may be involved in the proliferation of neural stem cells [62]. The amplitude decrease of alpha 1 sources (parietal, occipital, and temporal areas) was more pronounced in AD and MCI patients with the *CST3* risk haplotype, possibly indicating greater amyloid load or neuronal death [60]. Follow-up studies of this polymorphism that evaluate brain atrophy using MRI or amyloid load using PET imaging may be valuable.

Some additional neuroimaging studies of major AD risk genes examined the *ACE* gene, which codes for angiotensin converting enzyme—a protein that modulates the cardiovascular system by helping to regulate extracellular volume. *ACE* also affects the central nervous system by influencing neurons in the hippocampus and amygdala and helping to maintain the blood brain barrier [63, 64]. All these studies evaluated the commonly evaluated *ACE* insertion/deletion (I/D). The *ACE* D/D polymorphism was associated with increased severity of white matter hyperintensities or cerebral infarction in some [65, 66] but not all [67, 68] studies. One study found that the I/I genotype was associated with increased AD risk, and smaller hippocampi and amygdalae [68]. Another found that D carriers with MCI showed differences in resting state fMRI brain activity compared with I homozygotes [63]. The I/D variant examined in these studies is not one of the two currently listed by a large meta-analysis (http://www.alzgene.org/) [9] as being significantly associated with Alzheimer's disease overall, although some evidence links it with AD risk or unspecified cognitive decline [69, 70]. Regardless, since this variant in the *ACE* gene appears to modulate brain structure and function, it would be valuable to investigate the effects of other *ACE* polymorphisms having stronger relationships to AD: namely rs1800764 and rs4291 [9].

Recently, Erten-Lyons and colleagues (2010) evaluated the effects of a less studied AD risk gene, *FAS*, on the brain in 242 older adults who were cognitively intact or had MCI or AD [71]. *FAS* codes for the Fas (TNF receptor superfamily, member 6) protein, which may be involved in apoptosis in AD [72]. The authors evaluated 97 SNPs in or near the *FAS* gene that had been previously associated with AD. After adjustment for multiple testing, they found that rs1468063 was associated with faster AD progression. Carriers of the T allele of that SNP had greater ventricular volumes and smaller brain volumes in a subgroup of 56 subjects [71].

The candidate gene approach also may be used to evaluate the effects of genes predisposing subjects to characteristics (such as hypertension, obesity, high cholesterol, and diabetes) that increase the risk of AD [73–75] without necessarily being directly involved in the development of classic AD pathology such as amyloid plaques or neurofibrillary tangles. Examining the effects of these variants in healthy adults and focusing on brain areas susceptible to earliest AD processes may be productive in isolating polymorphisms that create a vulnerability that AD-related pathology later exploits. Recent work has already demonstrated that some such genes have an effect in the brain. For instance, Ho et al. (2010) recently demonstrated in 206 cognitively intact older adults from the ADNI study that risk allele carriers for rs3751812 in the fat mass and obesity associated gene (*FTO*) had smaller average brain volumes in frontal and occipital lobes relative to noncarriers (Figure 1) [76]. Those of European descent carrying two copies of the common adverse variant of *FTO* have increased risk for obesity, relative to those carrying no copies [77]. The connection between *FTO* and brain atrophy is important, as it suggests one mechanism whereby cardiovascular risk factors (including risk genes) may make the brain more vulnerable to the later effects of AD. The *FTO* gene may cause brain atrophy by promoting a craving for greater caloric intake resulting in higher body mass index (which is also associated with brain atrophy; [78, 79]). It is also possible that *FTO* affects the brain by direct gene action to promote tissue atrophy or insufficiency. Even so, a variety of lifestyle factors, including education, diet, and exercise, are associated with reduced brain atrophy. This underscores the value of controlling preventable risk factors for brain atrophy [80].

Other studies have focused on variants associated with genes important for blood pressure regulation and cholesterol levels such as the previously mentioned *ACE* [65, 66] and *SORL1* variant studies [58, 59]. Studies focusing on regions affected early in AD such as the hippocampus,

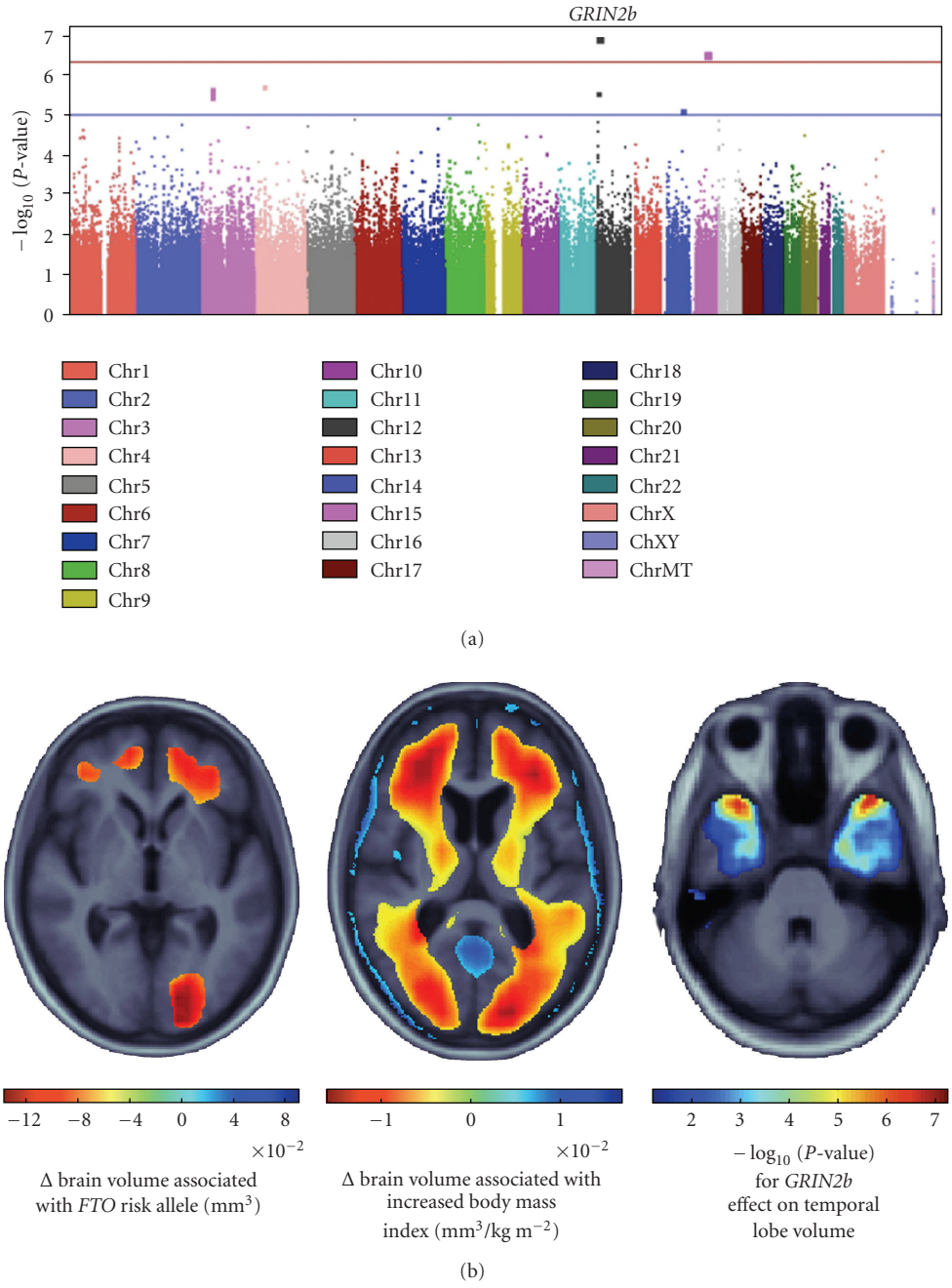


Figure 1: Common genetic variants (single nucleotide polymorphisms) associated with temporal lobe volume in a GWA study are shown in (a) along with an image showing the effects of the top hit, *GRIN2b*, on brain volume [81].The figure is adapted from Stein et al. (2010) with kind permission from the authors and publishers. (b) shows the effect (regression coefficients) of the candidate obesity gene, *FTO*, on brain atrophy in a cognitively normal adults and those with MCI and AD [76]. The figure is adapted from Ho et al. (2010) with kind permission from the authors and publishers.

entorhinal cortex [82], and posterior cingulate cortex [15] may be helpful in further elucidating the links between AD and cardiovascular health.

## 3. Genome-Wide Association Studies

Recently, a small number of studies have used genome-wide association (GWA) to search for novel genetic variants associated with AD endophenotypes. Discovering new risk genes would be extremely beneficial to the study of AD. Clinical trials could then selectively enroll, or perform sub-analyses on risk allele carriers, who are more likely to decline than noncarriers. Those at heightened genetic risk might also benefit the most from early treatment. Additionally, using AD risk genes as covariates would boost power in AD-related studies since modeling the identified genetic risk

factors reduces otherwise unexplained variance in the disease trajectory, making other influential factors easier to detect.

Several initiatives, such as Alzheimer's Disease Neuroimaging Initiative (ADNI) (www.loni.ucla.edu/ADNI), are now searching for new gene risk variants using neuroimaging traits that are highly heritable, easily measured in a reliable way, and associated with AD [83]. This may be a valuable way to overcome some of the obstacles inherent in diagnosis-based searches for risk polymorphisms. For instance, one might use as an endophenotype the baseline regional neuroimaging measures known to predict longitudinal cognitive decline in amnestic MCI or early AD. Such measures make specific diagnoses unnecessary because they focus on symptoms, namely the confluence of longitudinally decreased cognitive ability with specific functional or structural brain deficits that predict that decrease. Also, as continuous measures that vary across the continuum of normalcy from MCI to AD, neuroimaging measures may offer greater statistical power for genetic analysis than binary diagnostic categories. Suggested criteria for endophenotypes are that the measures are associated with illness, are heritable, are apparent in an individual regardless of whether the illness is active, and that they co-segregate with illness within families [84]. Some neuroimaging measures, such as hippocampal and ventricular volume largely meet these criteria as endophenotypes for AD. Both increased ventricular volume [85–88] and decreased volume of medial temporal lobe structures, especially the hippocampus [87–92] predict cognitive decline, are moderately to highly heritable [93–95], and are associated with AD and genetic risk for AD (Table 2). Other measures that show promise in predicting cognitive decline are brain amyloid burden as measured using Pittsburgh Compound B [96] and white matter integrity (in general and perhaps more specifically in the parietal lobe) as measured with diffusion tensor imaging [97] both of which are also highly heritable [98, 99]. Some neuroimaging measures may not yet be considered endophenotypes. For instance, glucose metabolism as measured with FDG-PET [100–102], and cerebral perfusion as measured with arterial spin labeling [103] also may predict cognitive decline, but large-scale heritability studies of these measures in healthy older adults are needed to ascertain their potential for identifying genetic influences. These guidelines may be useful when evaluating the utility of a measure as an endophenotype.

One recent GWA study by Shen and associates (2010) evaluated genetic associations with brain structure using a large number of nonspecific phenotypes. They studied 733 AD and MCI patients and normal controls from the ADNI cohort and controlled for age, sex, education, handedness, and baseline intracranial volume [104]. The authors examined 142 regions of interest and found that the well-known variants in *APOE* (rs429358/rs7412 a.k.a. $\varepsilon$2/3/4) and in a more newly identified gene, *TOMM40* (rs2075650), were strongly associated with bilateral hippocampus and amygdala volumes. Four additional SNPs were associated at the $P < 10^{-7}$ level with regional gray matter density. In the *EPHA4* gene, rs10932886 was correlated with gray matter density in the left precuneus and bilateral frontal regions—regions in which atrophy occurs in late AD [105]. *EPHA4* codes for the EPH receptor A4—a receptor tyrosine kinase that regulates dendritic spine morphology in pyramidal cells of the adult hippocampus. *EPHA4* also helps to control glial glutamate transport resulting in regulation of hippocampal function [106]. Its association with hippocampal structure and function makes this gene an intriguing target for future study. Likewise, rs6463843 in the *NXPH1* gene was associated with gray matter density in the left middle orbital frontal gyrus. *NXPH1* encodes the neurexophilin 1 protein, which is a physical ligand for $\alpha$-neurexins—proteins that may participate in synaptic function [107]. Finally, rs4692256 (LOC391642) was associated with gray matter density in the right hippocampus, but the function of the genetic material containing that SNP is unknown. The authors also reported a number of other associations at the more liberal $P < 10^{-6}$ level [104].

Two other recent ADNI-based GWA studies focused their searches on temporal lobe structures; temporal lobe volume is highly heritable and is also a relatively good predictor of developing AD. Potkin et al. (2009) used a genome-wide search for polymorphisms affecting hippocampal gray matter density, and identified novel AD susceptibility genes in 381 subjects who had AD or were normal controls [108]. AD cases differed in genotype from controls at rs429358 (one of the two SNPs comprising the *APOE* 2/3/4 genotype), and at rs2075650 in the *TOMM40* gene. Using a significance threshold of $P < 10^{-7}$ and covarying for age, sex, and the number of *APOE*4 alleles, four SNPs were associated with right or left hippocampal gray matter density [108]. Two of these, rs10074258 and rs12654281, were in or near the *EFNA5* gene [108], which encodes the ephrin-A5 protein implicated in nervous system development including in the hippocampus [109]. The gene function and association with hippocampal structure across multiple SNPs makes it an alluring target for future study. Two other SNPs associated with hippocampal gray matter density at the $P < 10^{-7}$ level were rs10781380 in the *PRUNE2* gene and rs1888414 near the *FDPSP* gene [108]. These two SNPs have a less clear tie to AD-related symptoms compared with those in *EFNA5*. At the $P < 10^{-6}$ level, the authors also identified correlations of right or left hippocampal gray matter density with genotypes at an additional 11 SNPs.

In a larger study also using the ADNI dataset, Stein and colleagues (2010) used MRI and GWA to identify SNPs associated with temporal lobe and hippocampal volumes in 742 AD and MCI patients and healthy elderly adults, controlling for age and sex (Figure 1) [81]. The authors also evaluated the relationship between temporal lobe volume and the *APOE2/3/4* genotype, which was not part of the Illumina gene chip used in the GWA. As expected, *APOE*4 was associated with lower temporal lobe volume. Additionally, at a significance level of $P < 5 \times 10^{-7}$, the authors identified two SNPs that were associated with bilateral temporal lobe volume across diagnoses: rs10845840 in the *GRIN2B* gene (independent of an *APOE*4 effect), and rs2456930, located in an intergenic region of chromosome 15 [81]. The *GRIN2B* gene codes for a regulatory subunit 2B (NR2B) of the NMDA (N-methyl D-aspartate) glutamate receptor. NR2B is implicated in learning, memory, and

structural plasticity, and cognitive deficits in Alzheimer's disease [110, 111]. The same glutamate receptor is also the target of memantine [112], a drug designed to slow the progression of AD. This makes *GRIN2B* an attractive target for future AD investigations generally, and also specifically with respect to how it may modulate memantine drug effects.

Finally, in the first voxelwise GWA (vGWA) study, Stein and colleagues (2010) examined the effects of genetic variation on brain structure as determined using tensor-based morphometry, while controlling for age and sex [113]. Rather than testing for genetic associations with one or a small number of structural measures, associations were tested at each of hundreds of thousands of voxels in the image—leading to a whole-brain, whole-genome search. The authors evaluated 740 subjects from the ADNI study who had AD or MCI, or were normal controls, and identified only the most significant SNP association at each voxel. Top SNPs identified within known genes in this GWA search were rs476463 in the *CSMD2* gene and rs2429582 in the *CADPS2* gene [113]. *CSMD2* (CUB and Sushi multiple domains 2) maps to a chromosomal region that may contain a suppressor of oligodendrogliomas [114], although little is yet known about the protein function. *CADPS2* codes for $Ca^{++}$-dependent secretion activator 2, a protein that regulates synaptic vesicle and large dense core vesicle priming in neurons, and promotes monoamine uptake and storage in neurons [115]. Although no SNP survived a false discovery rate correction at $P < .05$ [113], this method remains promising when larger sample sizes become available. Stringent corrections are needed when searching an entire image for genomic effects, but the size of the search space can be greatly reduced by carrying forward promising voxels to later analyses. Because of this, the sample sizes needed to replicate a GWA finding, when searching an entire image, are typically much smaller than the discovery sample size (as low as 300-400 rather than 700 subjects [113]) as the voxels with no effects can be discarded in the replication analyses.

The sample size needed to detect statistical relationships between genetic risk factors and specific brain measures depends upon the measure being studied. Beckett and colleagues (2010) recently compared the ability of various MRI- and PET-derived attributes to track the progression of MCI and AD [116]. Regions of interest derived from specific brain voxels showing significant relationships to cognitive impairment in previous studies gave greater power to detect a slowing of the disease than measures related to whole structures such as the hippocampus. The increased power of statistical voxel selection was later reinforced by studies using both MRI [117] and FDG-PET [118]. Such statistically predefined regions of interest may be promising targets of genetic studies in which gene effects can be mapped using statistical mapping approaches. By focusing on regions with greatest statistical effects, the power to detect or replicate genetic effects in follow-up studies is vastly increased [119]. In that regard, imaging studies can avoid a general problem in large-scale genetics; by focusing on promising voxels, replication samples may in fact be smaller than the discovery samples, if the effects of the genes in the brain are somewhat localized. The selection of sets of voxels showing significant genetic associations is helpful to boost power, above and beyond focusing solely on regions that are clinically important to the disease of interest (which is also important). Such an approach has been advocated by Chen et al. (2010) and Wu et al. (2010) [118, 120]. There are at least three advantages in focusing on specific voxels over predefined anatomical regions of interest. First, although a given gene variant may affect a region that shows dramatic effects in a given disease, that whole region may not be equally affected. Using a voxelwise approach may help to identify subregions that would provide a more concentrated focus for future replication efforts. An example is a recent study of the brain derived neurotrophic factor (*BDNF*) genes, in which common variants were associated with brain fiber integrity on DTI, in 455 subjects [119]. When the sample was split into two, the same regions of the white matter showed associations in each subsample, but there would have been no *a priori* reason to select those regions as implicated. Limiting a search to significant voxels in follow-up studies boosts power by avoiding image wide corrections for statistical tests at voxels less likely to show an effect. Secondly, although the focus of a study may be AD, pathways altered by a specific gene variant may be relevant to multiple complex diseases and disorders. Data collection and analysis are costly in genetic neuroimaging studies. Therefore, reporting all significant results can provide information that may not otherwise be easily obtained but may be useful to researchers at large. Thirdly, image based tests for replication, such as conjunction tests, can be devised that allow specific sets of brain regions, not just specific genes, to be replicated as showing associations (see, e.g., Ho et al. 2010 [76]).

In GWA studies, it is conventional to enforce a significance cut-off of $P < 10^{-7}$ or $10^{-8}$. This represents a Bonferroni-type correction for the false positives that could occur when 500,000 SNPs are searched for statistical effects. As adjacent SNPs are somewhat correlated (due to linkage disequilibrium effects), the effective number of tests is slightly fewer than the number of SNPs tested, but even SNPs falling below $P < 10^{-7}$ are considered to show "genome-wide evidence" requiring replication in subsequent studies or in meta-analyses of multiple independent datasets. So far, there is no universal agreement as to what statistical threshold for GWA studies is the best. The above ROI-based GWA studies reviewed here all used a threshold of at least $10^{-7}$ to report their top findings [81, 104, 108], which controls for multiple comparisons in the tests performed. Dudbridge and Gusnanto (2008) suggested that a genome-wide significance threshold should not account only for markers that have been tested in a study, but also for all possible genomic variation. This leads to a more conservative threshold of $P < 7.2 \times 10^{-8}$ [121]. Because of the required time and cost of collecting and analyzing neuroimaging data, the sample sizes here, although large for imaging studies, remain small for genetic studies. These smaller sample sizes may produce false positives unless independent replication is performed. Still, functionally promising SNPs have been identified in these studies, highlighting numerous replication targets for future work.

All four of the above GWA studies were performed using scans from the ADNI dataset with a high degree

of overlap of subjects. Even so, the top SNPs were not replicated across studies. This may be due to a number of methodological factors. First, the sample sizes needed to detect a genetic association depend on the minor allele frequency and effect size, and are typically between a few hundred and several thousand subjects. With this limitation, measures that show association in one study may be missing in another. Even different software used to measure the same structure do not give perfectly correlated measures. Also, many associations will be missed due to imprecision in the measures—single gene effects are typically only detectable for measures with the highest precision and reproducibility. Additionally, across studies, the initial genetic searches did not adjust for the same covariates in addition to age and sex. For instance, Potkin and colleagues covaried for *APOE* genotype [108], but Shen and colleagues covaried for education, handedness, and baseline intracranial volume [104], and the Stein et al. studies did not use additional covariates [81, 113]. Finally, the choices of ROI and methods of delineating those regions varied across studies. The ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) project (http://enigma.loni.ucla.edu/) [122] is one of several multicenter initiatives to standardize genetic and imaging methods. Its goal is to empower future replication efforts and make it easier to perform meta-analyses. Because different SNP sets are genotyped in different studies, imputation methods are employed to allow the same set of genomic variations to be queried across every dataset.

Using GWA to evaluate how genetic variance affects AD endophenotypes in cognitively intact younger and older adults may also aid in identifying AD genetic risk factors. Genetic variants associated with brain measures in young cognitively normal adults are less likely to be associated with molecular pathology. More likely, they support early vulnerabilities in the brain that AD pathology later exploits. The polymorphisms may, for instance, relate to health factors that increase the risk of AD, such as obesity and diabetes, or may relate to neural development in regions affected in early AD, such as the hippocampus and entorhinal cortex. Variants identified in cognitively intact older adults may relate to both AD molecular processes and vulnerabilities in the brain. Using amyloid imaging measures in these subjects may be helpful in identifying genetic risk factors for earliest AD changes.

An imaging measure may be associated with a particular polymorphism during development but may also be related to other gene polymorphisms with respect to degeneration later in life. Therefore, it is not the measurement, but rather its context and other demographic factors that determine whether gene effects relate to neurodevelopment or degeneration. This should be borne in mind when replicating gene effects across cohorts. For instance, in Stein et al. (2011), caudate volume was associated with commonly carried variants in dopamine-related genes, and the effects were found in an large elderly cohort scanned in North America, and replicated in a young adult cohort scanned in Australia [123]. Such replications of SNPs may indicate gene effects that persist throughout life. The use of two very different samples is likely to identify genes of enduring relevance across the lifespan, but may miss or fail to replicate effects that exist or are more dominant only in late or early life. Naturally, there is a greater preponderance of apoptotic events in an elderly sample and more developmental or synaptogenic processes in the younger samples. For this reason, genome-wide meta-analyses must not regard failure to replicate as a sign that gene is not influential in a given part of the lifespan, or in a given cohort or continent.

In a study of normal brain aging, Seshadri and colleagues (2007) investigated genetic associations with measures of total cerebral brain volume, lobar, ventricular and white matter hyperintensity volumes, and scores on six cognitive tests. They identified three SNPs (located in *ERBB4*, *PDLIM5*, and *RFX4*) that were associated both with measures of frontal or parietal brain volumes and with tests of executive function and abstract reasoning. These results did not survive testing for multiple comparisons, but they may be used to generate future hypotheses or to offer support to findings in future GWA studies [124]. As this study was one of brain aging rather than of AD, cognitively normal adults were studied and not all measures examined were specific to AD risk. Therefore, some of the SNPs generated may relate more to brain aging or normal development than to AD risk.

Two GWA studies that we know of have examined endophenotypes in healthy young adults—a GWA study of caudate volume in 1198 young and old adults [123] and the first voxelwise GWA study of diffusion tensor images [125]. Further studies that focus on brain measurements specific to AD would be useful additions to the field. Since the brain differences that are likely to occur in normal adults are subtle compared to those in studies of a brain disease, very large numbers of subjects are needed to perform GWA in healthy young adults and to show that the results are reliable and reproducible across independent samples. The ENIGMA network brings together researchers in imaging and genetics, and current analyses are probing structural and functional neuroimaging and GWA data from over 10,000 subjects. This type of effort will prove invaluable in replication studies. ENIGMA also allows for the identification of "slow climbers"—genetic variants that may not be significant in all studies or in any one study alone, but may become highly significant when data is aggregated across studies.

GWA and vGWA involve huge numbers of comparisons, which may result in false positives if not properly controlled. It is therefore incumbent upon readers of such studies to critically evaluate the significance levels of the studies before basing potentially costly experiments upon their results. However, such exploratory studies may provide information that would not otherwise be easily obtained and can be extremely useful in focusing future work. For instance, one might not collect thousands of MRI scans to test the effect of one SNP previously found to be marginally significant. However, it may make sense to test the effects of that SNP in conjunction with other more established ones when GWA data has already been collected and the MRI scans have been physically analyzed. In this way, it is possible to build easily on previous results until they are strong enough to warrant independent exploration.

In addition, the large number of statistical tests involved in a genome-wide and/or image wide search requires special methods to boost power, including gene-based tests [126], ridge regression models [127], multilocus modeling, and meta-analysis. In the first voxelwise GWA studies of MRI and DTI [113, 125], no single SNP passed the conventional threshold for genome-wide significance; even so, the top SNPs can be prioritized when screening new imaging datasets for replications of these hits. Efforts such as the ENIGMA consortium have found that some SNPs identified by GWA are robustly associated with hippocampal volume and total brain volume. Although no single contributing site was able to find results that were genome-wide significant, the effects of several SNPs were robustly replicated when meta-analyzed across imaging datasets of more than 6400 subjects from 16 imaging sites [128].

## 4. Multiple Genetic Risk Factors

A statistical test of association between a set of SNPs and a disease can offer far greater power and success in determining genetic risk than tests of single SNPs [129]. This is in part because the risk conferred by different SNPs may depend on the context and on several demographic and environmental factors—the age of the cohort, their educational level, and even their socioeconomic status [130]. Because of this, more complex models of gene action in AD are likely to include not only multiple SNPs, but also environmental and other risk factors that affect whether those variants are relevant or innocuous.

Multilocus genetic modeling refers to a large class of methods that assesses the effects of sets of SNPs—within the same or different genes—in predicting clinical diagnosis, prognosis, or disease risk. Looking at the additive or epistatic (interactive) effects of multiple risk gene variants may be useful, especially when the genes in question have similar effects. For instance, Szolnoki and colleagues (2003) found in 961 subjects that carriers of *APOE*2 or *APOE4* had increased risk of white matter hyperintensities in their brains only if they also carried risk variants in the *ACE* or *MTHFR* (methylenetetrahydrofolate reductase (NAD(P)H)) genes [131]. All three are listed as top AD risk genes [9] and also affect the cardiovascular system, so it makes sense to examine their additive effects on the brain. Multilocus genetic models can assess the combined effects of multiple gene sets acting together.

Because adjacent SNPs in a genome-wide association study may be highly correlated due to linkage disequilibrium, it is not possible to use standard statistical methods, such as multiple regression, to identify which SNPs exert an influence on a trait. Machine learning methods that can cope with high-dimensional sets of predictors include such techniques as penalized regression, adaptive boosting, and the "Bayesian lasso". All of these methods have been used widely in quantitative genetics, and show substantial promise for analyzing brain imaging phenotypes.

Multilocus models are conceptually attractive as they allow the testing of the aggregate effect of several SNPs in the same gene, which individually may have effects too weak to detect on their own. In one study [126], we applied a novel method, multivariate principal components regression (PCReg) to test whole genes for associations with imaging data, not just single SNPs within them. When multiple partial-*F* tests were used to test the joint effect of all SNPs in a gene on regional brain volume differences, we identified several genes associated with brain-related disorders that are highly relevant to brain structure. GRB-associated binding protein 2 gene, *GAB2*—the most significantly associated gene in our analysis—has previously been linked to late-onset AD, and *GAB2* associations showed a symmetric signal in the white matter superior to the lateral ventricles. As a caveat, other methods that include multiple SNPs can sacrifice power as increasingly stringent corrections are applied to guard against finding spurious associations using high-dimensional regression models with many parameters. Even so, efficient gene-based association tests across the whole brain can drastically reduce the number of independent tests performed, detecting known genes highly relevant to brain structure that may be missed by univariate methods alone.

## 5. Conclusion

In summary, using neuroimaging endophenotypes to identify AD risk factors is a new and promising enterprise. Future studies of the combined effects of multiple candidate risk factors, and an expansion of genome-wide studies to a wide variety of imaging modalities may help generate new endophenotypes that predict AD. Additionally, a focus on particular contributions to AD risk, such as deposition of AD-related pathology, or developmental vulnerabilities might prove productive in unraveling disease complexity. For instance, searching for gene variants of an AD endophenotype in a large sample of healthy young adults would be most likely to uncover genes affecting developmental vulnerabilities to the disease. In contrast, examining a given endophenotype in AD and MCI patients while controlling for gene variants known to affect that measure in younger adults would boost the power to identify polymorphisms related to AD processes and cumulative environmental risk factors, while excluding some developmental effects. Careful selection of endophenotype, data pooling across studies and analysis of multiple different aspects of AD pathology and vulnerabilities may prove invaluable in the quest to explain the genetic risk for AD.

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