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Assessment of the genetic variance of late-onset Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a complex genetic disorder with no effective treatments. More than 20 common markers have been identified, which are associated with AD. Recently, several rare variants have been identified in Amyloid Precursor Protein (*APP*), Triggering Receptor Expressed On Myeloid Cells 2 (*TREM2*) and Unc-5 Netrin Receptor C (*UNC5C*) that affect risk for AD. Despite the many successes, the genetic architecture of AD remains unsolved. We used Genome-wide Complex Trait Analysis to (1) estimate phenotypic variance explained by genetics; (2) calculate genetic variance explained by known AD single nucleotide polymorphisms (SNPs); and (3) identify the genomic locations of variation that explain the remaining unexplained genetic variance. In total, 53.24% of phenotypic variance is explained by genetics, but known AD SNPs only explain 30.62% of the genetic variance. Of the unexplained genetic variance, approximately 41% is explained by unknown SNPs in regions adjacent to known AD SNPs, and the remaining unexplained genetic variance outside these regions.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, affects an estimated 5.3 million people in the United States and is the only 1 of the top 10 causes-of-death with no disease-altering treatments (Ridge et al., 2013a). Most of the affected individuals succumb to disease within 7 years of diagnosis. As the disease progresses, affected individuals eventually require fulltime care, which exacts a substantial emotional and economic burden on families of affected individuals and society at large. Currently, AD costs the health care system in the United States more than $200 billion annually (Alzheimer's Association, 2015). As the population ages, AD incidence is expected to rapidly increase (projected to be 13.8 million affected individuals in 2050), which will cause tremendous suffering for affected individuals and their families, and health care systems worldwide (costs are expected to exceed $1 trillion annually by 2050 [Alzheimer's Association, 2015]).

AD can be classified as either early- or late-onset, with most of (>99%) cases being late-onset. Early-onset AD is characterized by autosomal dominant mutations in 1 of 3 genes (presenilin 1, presenilin 2, or amyloid precursor protein). The genetic architecture of late-onset AD is more complex. To date, more than 20 distinct genetic loci have been implicated in AD by genome-wide association studies (GWAS) and linkage studies (Lambert et al., 2013), and additional rare variants in several genes have been identified

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(Cruchaga et al., 2014; Guerreiro et al., 2012; Jonsson et al., 2012). Despite these successes, the combined effects of these variants only explain a fraction of the total estimated genetic variance of AD (Ridge et al., 2013b).

Solving the genetic architecture of AD (i.e., identifying the genomic variation that explains the remaining genetic variance of AD) may provide the necessary insights into disease processes to lead to the development of effective therapeutics. We recently analyzed AD datasets to determine how much genetic variance remained to be identified (Ridge et al., 2013b). In this article, we report the results from an expanded analysis that improves our previous study in two ways. First, we used a more densely imputed dataset, and second, we incorporated common variants recently identified by GWAS and rare variants into the study design. We determined that approximately half of the estimated genetic variance of AD is unexplained by variants known to effect risk for AD, and that remaining important variation is located throughout the genome.

2. Methods

2.1. Dataset

In this work, we used a SNP dataset from the Alzheimer's Disease Genetics Consortium. This dataset is the combination of 30 separate studies imputed by Naj et al. (Naj et al., 2011) using the 1000 Genomes Project as reference panel (Genomes Project et al., 2012). We combined and prepared the data by the following: (1) converted IMPUTE2/SNPTEST (Howie et al., 2011, 2009) format files to PLINK (Purcell et al., 2007) allele calls and/or best guess genotype (binary) format (uncertainty cutoff 0.1); (2) filtered SNPs imputed with low information (info $<$ 0.5) from each dataset; (3) used the default PLINK 1.9 (Purcell et al., 2007) uncertainty cutoff of 0.1 (i.e., any imputed call with uncertainty greater than 0.1 was treated as missing); (4) removed duplicate SNPs from each dataset; (5) ensured each SNP had the same strand orientation and genomic coordinates in each dataset; (6) merged the datasets; (7) filtered the datasets using a minor allele frequency of 0.01 to retain common SNPs; and (8) used directly genotyped (not imputed) SNPs for identifying cryptic relatedness and for calculating principal components (PCs) to account for population structure. There were 17,146 directly genotyped SNPs in common across all 30 studies, none of which were symmetrical. We used PLINK to LD-prune these SNPs using the following settings: maf 0.01, geno 0.02, indep-pairwise 1500 150 0.2. These steps resulted in an LD-pruned, directly observed, and nonambiguous dataset with 14,675 SNPs. Finally, we used KING-Robust to identify the 28,730 participants who were no more related than 3rd degree relatives (kinship coefficient 0.0442) and EIGENSTRAT (Price et al., 2006) to calculate the first 10 PCs for the 28,730 unrelated participants using the QC'd, LD-pruned directly observed set of SNPs common to all 30 studies. In summary, individuals more closely related than third cousins were removed, 10 PCs were calculated using EIGENSTRAT (Price et al., 2006), and SNPs with a minor allele frequency less than 0.01 were removed.

The initial dataset contained 28,730 samples. To perform these analyses, we applied additional strict filters, specific to this research, to this dataset. First, we removed any individuals missing case/control status. Next, we removed any individuals missing one or more covariates (age, sex, PCs). Finally, we removed any individuals missing data for any of the 21 known Alzheimer's disease GWAS SNPs (Table 1, Supplementary Tables 1 and 2) or Apolipoprotein E (*APOE*). *APOE* ε2 and ε4 alleles were treated as a special case. The ε2 and ε4 alleles were directly genotyped for most of the individuals in the dataset, whereas others had imputed genotypes, and many had both. For these 2 alleles, if an individual was directly genotyped for these alleles, or if there was disagreement between the *APOE* genotypes by imputation and direct genotyping, we used the genotypes from direct genotyping. However, if only imputed genotypes were available for an individual then we used imputed genotypes. In summary, we removed any individual who was missing case/control status, age, sex, principal components, *APOE* genotype for the ε2 or ε4 allele, or genotype for any of the 21 known AD genes listed in Table 1, which resulted in 19,031 samples being removed. The final filtered dataset consisted of 9,699 individuals and 8,712,879 SNPs (Table 2).

We created several additional datasets using PLINK (Purcell et al., 2007), and covariate files using custom scripts, based on different partitions from the original filtered dataset described previously. First, we created a dataset containing only the two *APOE* SNPs. Second, we created a dataset with only SNPs from genomic regions of known AD SNPs (Table 1). For the purposes of this research, we defined a genomic region as the 50-kilobases upstream and downstream of each gene named in the primary publication reporting the association of different GWAS SNPs. For 2 different SNPs, rs9271192

Table 1
Genes and/or SNPs that affect risk for Alzheimer's disease

Gene	Disease SNP	Effect of minor allele
GWAS SNPs with strongest evidence		
BIN1 (Biffi et al., 2010; Naj et al., 2011)	rs744373	Risk
CLU (Lambert et al., 2009)	rs11136000	Protective
ABCA7 (Hollingworth et al., 2011)	rs3764650	Risk
CR1 (Lambert et al., 2009)	rs3818361	Risk
PICALM (Corneveaux et al., 2010; Naj et al., 2011)	rs3851179	Protective
MS4A6A (Hollingworth et al., 2011; Naj et al., 2011)	rs610932	Protective
CD33 (Hollingworth et al., 2011; Naj et al., 2011)	rs3865444	Protective
MS4A4E (Hollingworth et al., 2011; Naj et al., 2011)	rs670139	Risk
CD2AP (Hollingworth et al., 2011; Naj et al., 2011)	rs9349407	Risk
HLA-DRB5/HLA-DRB1 (Lambert et al., 2013)	rs9271192	Risk
PTK2B (Lambert et al., 2013)	rs28834970	Risk
SORL1 (Lambert et al., 2013)	rs11218343	Protective
SLC24A4/RIN3 (Lambert et al., 2013)	rs10498633	Protective
DSG2 (Lambert et al., 2013)	rs8093731	Protective
INPP5D (Lambert et al., 2013)	rs35349669	Risk
MEF2C (Lambert et al., 2013)	rs190982	Protective
NME8 (Lambert et al., 2013)	rs2718058	Protective
ZCWPW1 (Lambert et al., 2013)	rs1476679	Protective
CELF1 (Lambert et al., 2013)	rs10838725	Risk
FERMT2 (Lambert et al., 2013)	rs17125944	Risk
CASS4 (Lambert et al., 2013)	rs7274581	Protective
Linkage studies (common SNPs only)		
APOE (ε2 and ε4) (Corder et al., 1994; Pericak-Vance et al., 1991; Saunders et al., 1993)	rs7412/rs429358	Protective/Risk
Rare and other SNPs		
APP (Goate et al., 1991; Jonsson et al., 2012)	Multiple	Both
PSEN1 (Sherrington et al., 1995)	Multiple	Risk
PSEN2 (Levy-Lahad et al., 1995)	Multiple	Risk
EPHA1 (Hollingworth et al., 2011; Naj et al., 2011)	rs11771145	Protective
TREM2 (Guerreiro et al., 2012)	rs75932628	Risk
UNC5C (Wetzel-Smith et al., 2014)	rs137875858	Risk

GWAS SNPs in the top section of the table are described as "known GWAS SNPs" in the text. All SNPs in the table were included in analyses of phenotypic variance in regions of known AD SNPs.
Key: AD, Alzheimer's disease; GWAS, genome-wide association studies.

Table 2
Demographics of the dataset used in this research

Category	Mean age	Cases	Controls	Totals
Male	77.79	1605	2358	3963
Female	77.57	2272	3464	5736
Total	77.70	3877	5822	9699

and rs10498633, the original publication named two genes, *HLA-DRB5* and *HLA-DRB1*, and *SLC24A4* and *RIN3*, respectively. For each of these SNPs, we included both named genes. In addition to GWAS SNPs, we included genes that contain rare variants that affect risk for AD, and *APP*, *PSEN1*, and *PSEN2*, which contain functional variants that cause early-onset AD and possibly harbor additional variants that affect risk for late-onset AD (Table 1). Finally, we counted the number of minor alleles of known GWAS SNPs for each individual and included the genotype counts in covariate files to be used when we wanted to control for known GWAS SNPs. So an individual could have a count of 0 (indicating the individual is homozygous for the major allele), 1 (indicating the individual is heterozygous for the minor allele), or 2 (indicating the individual is homozygous for the minor allele).

2.2. Genetic analyses

We used Genome-wide Complex Trait Analysis (Yang et al., 2011) to estimate phenotypic and genetic variances for the different partitions of SNPs as described previously. For each analysis, we controlled for age, gender, and PCs. For some of the analyses, we also controlled for dosage of known AD GWAS SNPs (as described in the Results). For all analyses, we used a population disease prevalence of 0.13 (Alzheimer's Association, 2012).

3. Results

We estimated the proportion of the total phenotypic variance explained by all SNPs in the combined dataset to be 53.24%. To determine the phenotypic variance explained by known GWAS SNPs with the strongest evidence for association with AD and the two *APOE* alleles, we controlled for each of these SNPs, and created an additional dataset with only the *APOE* alleles. Based on these analyses, we estimated the phenotypic variance explained by known GWAS SNPs to be 16%, of which 13% was explained by *APOE*, and almost 3% explained by other genes.

A total of 37% of phenotypic variance is tagged by SNPs in our dataset, but unexplained by known AD SNPs. To determine whether the unexplained phenotypic variance tagged by genetics is located adjacent to known AD SNPs or throughout the genome, we created an additional dataset with all SNPs located in regions of known AD SNPs (Table 1). We defined a region as 50-kilobases upstream and downstream of the named GWAS gene, or the gene harboring a rare variant. We found that 15% and 22% of phenotypic variance tagged by known disease SNPs is located in regions adjacent to SNPs that affect risk for AD and outside these regions, respectively. In summary, of the remaining phenotypic variance that can be explained by unknown SNPs, approximately 41% is located adjacent to known AD SNPs and 59% in other genomic regions. Results are summarized in Table 3.

4. Discussion

Using data from 9,699 individuals and 8,712,879 SNPs, we have carefully assessed the genetic variance for AD and the proportion of that variance that is accounted for by known markers and genes. Our results improve over previous studies in several ways. First, we have more than 4 times as many SNPs as the largest previous study (8.7 million vs. 2 million [Ridge et al., 2013b]). Second, we have been able to incorporate evaluation of additional recently discovered AD risk loci. Third, we have evaluated not just known markers but gene regions associated with known markers to test the hypothesis that additional, possibly rare markers in regions of GWAS identified risk variants also impact risk for disease (Singleton and Hardy, 2011).

We report much higher genetic variance explained than previous reports. This is likely because of the significant increase in markers used in our analysis, including many more rare variants than previous work. Our estimate of the variance explained by *APOE* haplotypes is not significantly different from our previous report ($p = 0.17$; 13.42% and 5.92%, respectively) (Ridge et al., 2013b). However, inclusion of the recently reported markers from the IGAP GWAS (Lambert et al., 2013) and rare variants discovered using other approaches have, as expected, accounted for a significant increase in variance explained by known markers ($p = 0.01$; 16.3% compared to 7.78%) (Ridge et al., 2013b).

By evaluating all SNPs in the regions surrounding known AD variants, we have evaluated the hypothesis of the existence of pleomorphic risk loci proposed by Singleton and Hardy in 2011 (Singleton and Hardy, 2011). Such loci harbor both common and rare variants that alter risk for common disease. Our results clearly demonstrate that variation in the regions surrounding known AD variants but not including known risk variants, accounts for 29% of all genetic variance in AD, and 41% of remaining unexplained genetic variance. This suggests that variants in these known AD risk regions, which are not detectable with the study designs that have been applied to date, contribute significantly to variance in AD risk.

Table 3
Summary of results

SNP set	Proportion of phenotypic variance explained (standard error)	Proportion of genetic variance explained
Variance explained by all SNPs in the dataset	53.24% (0.0448)	100%
Variance explained by known AD SNPs:		
Total variance explained by known AD SNPs[a]	16.30% (0.0448)	30.62%
APOE (ε2 and ε4 alleles)	13.42% (0.0447)	25.21%
All known GWAS SNPs, except *APOE* SNPs	2.88% (0.0448)	5.41%
Variance explained by undiscovered AD SNPs:		
Total variance explained by unknown AD SNPs	36.94% (0.0448)	69.38%
SNPs in regions of known Alzheimer's disease SNPs[b]	15.24% (0.0348)	28.63%
SNPs outside regions of known Alzheimer's disease SNPs	21.69% (0.0373)	40.74%

Key: AD, Alzheimer's disease; GWAS, genome-wide association studies.
[a] Known GWAS SNPs refers to SNPs in top part of Table 1.
[b] Includes regions for all SNPs listed in Table 1. Regions are defined as ±50 kilobases from the gene named in Table 1. Regions estimates were calculated using all SNPs in the region except the known AD SNP.

5. Conclusions

In summary, the results in Table 3 provide a clear assessment of our progress in understanding genetic variance in AD. Most (69%) of the genetic variance remains unexplained by known AD-risk variants. Much of the remaining variance is accounted for by genetic

variation near already identified AD-risk variants, and other important genetic regions remain to be discovered. As we have discussed previously (Ridge et al., 2013b), these are likely to be rare variants of varying effects and may also include gene × gene interactions. Novel approaches to leveraging whole genome and exome sequences in families (Cruchaga et al., 2014; Guerreiro et al., 2012; Kauwe et al., 2013), or careful identification of candidate genes from other diseases (Guerreiro et al., 2012) or biological work (Lu et al., 2014), will also facilitate identification of additional variants. Such work is vital to the development of therapeutics and each gene represents a potential target for development.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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