Title
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 APP, TREM2, and 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 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.

Keywords

Alzheimer's disease; Genetics; Genetic Variance

1. Introduction

Alzheimer's disease is the most common form of dementia, affects an estimated 5.3 million people in the United States, and is the only one of the top 10 causes-of-death with no disease-altering treatments (Ridge, et al., 2013a). The majority of affected individuals succumb to disease within seven 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, Alzheimer's disease costs the health care system in the United States more than $200 billion annually (Alzheimer's, 2015). As the population ages, Alzheimer's disease 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, 2015)).

Alzheimer's disease can be classified as either early or late-onset, with the majority (>99%) of cases being late-onset. Early-onset Alzheimer's disease is characterized by autosomal dominant mutations in one of three genes (presenilin 1, presenilin 2, or amyloid precursor protein). The genetic architecture of late-onset Alzheimer's disease (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 (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 manuscript 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 Alzheimer's disease, 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 (ADGC). 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,Howie, et al., 2009) format files to PLINK (Purcell, et al., 2007) allele calls/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 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 non-ambiguous 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 principal components (PC) for the 28,730 unrelated participants using the QC'd, LD-pruned directly observed set of SNPs common to all 32 studies. In summary, individuals

more closely related than third cousins were removed, 10 PCs calculated using EIGENSTRAT (Price, et al., 2006), and SNPs with a minor allele frequency (MAF) less than 0.01 were removed.

The initial dataset contained 28,730 samples. In order 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 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 two 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 above. 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 two different SNPs, rs9271192 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 (GCTA) (Yang, et al., 2011) to estimate phenotypic and genetic variances for different partitions of SNPs as described above. 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 (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%. In order 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 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 four 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 due to 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 has, 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.

4.1 Conclusions

In summary, the results in Table 3 provide a clear assessment of our progress in understanding genetic variance in AD. The majority (69%) of 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.

Supplementary Material

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- The majority of Alzheimer's disease is unexplained by known Alzheimer's disease SNPs
- 41% of the remaining unexplained genetic variance is explained by SNPs located near known SNPs
- Known Alzheimer's disease markers only explain 31% of genetic variance

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.

Table 2

Demographics of the dataset used in this research.

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

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 *	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 **	15.24% (0.0348)	28.63%
SNPs outside regions of known Alzheimer's disease SNPs	21.69% (0.0373)	40.74%

* Known GWAS SNPs refers to SNPs in top part of Table 1

** 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.