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Negative results

Failure to detect synergy between variants in transferrin and hemochromatosis and Alzheimer's disease in large cohort

Elizabeth Vance [a], Josue D. Gonzalez Murcia [a], Justin B. Miller [a], Alzheimer's Disease Genetics Consortium (ADGC), Lyndsay Staley [a], Paul K. Crane [b], Shubhabrata Mukherjee [b], John S.K. Kauwe [a,*]

[a] Department of Biology, Brigham Young University, Provo, UT, USA
[b] Department of Medicine, University of Washington, Seattle, WA, USA

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia and, despite decades of effort, there is no effective treatment. In the last decade, many association studies have identified genetic markers that are associated with AD status. Two of these studies suggest that an epistatic interaction between variants *rs1049296* in the transferrin (*TF*) gene and *rs1800562* in the homeostatic iron regulator (*HFE*) gene, commonly known as hemochromatosis, is in genetic association with AD. *TF* and *HFE* are involved in the transport and regulation of iron in the brain, and disrupting these processes exacerbates AD pathology through increased neurodegeneration and oxidative stress. However, by using a significantly larger data set from the Alzheimer's Disease Genetics Consortium, we fail to detect an association between *TF rs1049296* or *HFE rs1800562* with AD risk (*TF rs1049296* $p = 0.38$ and *HFE rs1800562* $p = 0.40$). In addition, logistic regression with an interaction term and a synergy factor analysis both failed to detect epistasis between *TF rs1049296* and *HFE rs1800562* (SF = 0.94; $p = 0.48$) in AD cases. Each of these analyses had sufficient statistical power (power > 0.99), suggesting that previously reported associations may be the result of more complex epistatic interactions, genetic heterogeneity, or false-positive associations because of limited sample sizes.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and inflicts an estimated 24 to 35 million people worldwide, with incidences predicted to increase dramatically as the population ages (Alzheimer's Association, 2018). Although decades of research have been spent investigating the causes and architecture of this neurodegenerative disease, it still inflicts an estimated 5.7 million people in the United States alone. This number is projected to increase to 13.8 million by mid-century (Alzheimer's Association, 2018). Association studies have accurately identified single-nucleotide polymorphisms (SNPs) associated with AD (Harold et al., 2009; Hollingworth et al., 2011; Lambert et al., 2009, 2013; Seshadri et al., 2010; Shen et al., 2015; Shuai et al., 2015; Yan et al., 2015). However, these genetic loci account for only a fraction of AD heritability (Ridge, Mukherjee, Crane, Kauwe, & Alzheimer's Disease Genetics, 2013), suggesting that much of the unexplained genetics affecting AD etiology may be due to epistasis (Bullock et al., 2013; Combarros et al., 2009; Ebbert et al., 2014; Infante et al., 2004). Epistasis occurs when multiple genes interact to create a single phenotype (Cordell, 2002). These kinds of synergetic relationships play a critical role in the etiology of complex diseases, yet remain vastly understudied in AD pathology (Alzheimer's Association, 2018; Ebbert, Ridge and Kauwe, 2015; Raghavan and Tosto, 2017).

The transferrin (*TF*) gene and the homeostatic iron regulator (*HFE*) gene, commonly known as hemochromatosis, have been reported to show epistasis and play a role in the development of AD (Robson et al., 2004; Tisato et al., 2018). TFs are a group of nonheme iron-binding glycoproteins found in fluids and cells of vertebrates. The main role of *TF* is to maintain iron homeostasis in the body (Gkouvatsos et al., 2012). In the brain, *TF* interacts with the amyloid precursor protein (Belaidi et al., 2018) and tau (Jahshan et al., 2016), 2 of the major protein families implicated in AD pathology. Because iron is essential for oxygen transport, its misregulation in the brain can lead to oxidative stress and neurodegeneration (Dias et al., 2013; Matak et al., 2016; Yarjanli et al., 2017). *HFE* encodes for a transmembrane glycoprotein that binds to a *TF* receptor,

* Corresponding author at: Department of Biology, Brigham Young University, Provo, UT, USA. Tel.: +18014222993; fax: +18014220004.
E-mail address: kauwe@byu.edu (J.S.K. Kauwe).

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subsequently regulating iron in the cell (Bennett et al., 2000; Feder et al., 1996; Lebron et al., 1998). Mutations in *HFE* are associated with neurodegenerative diseases through increasing neuroinflammation and production of free radicals in the brain (Andersen et al., 2014; Lull and Block, 2010). In addition, other studies suggest that *TF* and *HFE* are involved in the transport and regulation of iron in the brain, and disrupting these processes potentially affects AD pathology through increased neurodegeneration and oxidative stress (Ali-Rahmani et al., 2014; Lehmann et al., 2006).

Robson et al. (2004) suggested that epistasis between *TF* variant rs1049296 and *HFE* variant rs1800562 is associated with AD. Although neither SNP alone was a risk factor for AD, the presence of both alleles resulted in a 5 times greater risk of developing AD (Robson et al., 2004). Because the sample size for that study was relatively small (191 cases and 269 controls), a replication of these findings on a slightly larger data set (1161 cases and 1342 controls) was conducted. A logistic regression analysis and a synergy factor analysis (SFA) corroborated a significant association with AD risk among bi-allelic carriers of rs1049296 and rs1800562 (synergy factor= 2.71; $p = 0.0016$) (Kauwe et al., 2010).

Our study expands on these previous studies and attempts to detect statistical epistasis between *TF* rs1049296 and *HFE* rs1800562 with respect to AD risk using 25,666 individuals (12,532 cases and 13,134 controls) from the Alzheimer's Disease Genetic Consortium (ADGC), which is an expansion of the data set used by Kauwe et al. (2010).

2. Materials and methods

2.1. Data set and filtering

Our analysis started with genetic data from all 28,730 individuals in the Alzheimer's Disease Genetics Consortium (ADGC) data set as described by Naj et al. (2011). ADGC is a collection of 30 merged data sets spanning 1984 to 2012, and was established to help identify genetic markers of late onset AD (Boehme et al. 2014) (see Supplementary Table 1 for ADGC demographics). ADGC imputed the 30 data sets to the Haplotype Reference Consortium reference panel, which includes 64,976 haplotypes and 39,235,157 SNPs (Loh et al., 2016; Naj et al., 2017). Genotyped markers with a minor allele frequency less than 1% and a deviation from Hardy-Weinberg equilibrium where $\alpha < 10^{-6}$ were removed. All aspects of the study were approved by institutional review boards, and each applicant signed a written form of consent for their genetic data to be used for research purposes.

We followed the same filtering protocols established by Ridge et al. (2013) by genotyping markers with a minor allele frequency less than 1% and removing markers with a Hardy-Weinberg equilibrium p-value less than 10^{-6}. Principle components were calculated using EIGENSOFT (Patterson et al., 2006; Price et al., 2006) to account for population specific variations in allele distribution. After filtering, 12,532 cases and 13,134 control subjects contained genotypes for *TF* rs1049296 and *HFE* rs1800562.

2.2. Genetic analyses

The main effects of *TF* rs1049296 and *HFE* rs1800562 on AD risk were measured using a multivariate nonparametric logistic regression analysis. Each SNP was first analyzed as a single term and then as an interaction term in a subsequent analysis. Similar to the study by Kauwe et al. (2010), we used the annotations in the ADGC data set to include sex, age of onset, *APOE e4* allele status, cohort, and 10 principle components as covariates. In addition, we performed a χ^2 analysis to determine odds ratios between AD status in each SNP as a single term and as an interaction term, respectively. Finally, we performed a SFA to calculate the size and significance of the interaction between *TF* rs1049296 and *HFE* rs1800562 and AD risk with minor allele noncarriers as the reference group (Cortina-Borja et al., 2009) (see Supplementary Table 3 for detailed SFA calculations). These analyses were performed for each of the 30 cohorts separately and for the entire ADGC data set combined as a single cohort.

Furthermore, we calculated the power of analysis for the ADGC data set using an online power tool available at https://www.dartmouth.edu/~eugened/power-samplesize.php (Demidenko, 2007, 2008). The previous analysis performed by Kauwe et al. (2010) had 0.31 power to detect an effect size of 1.14 at an alpha of 0.05 by using a sample size of 2503. Our logistic regression model has power of >0.99 to detect a similar effect size of 1.14 at an alpha of 0.05 by using a sample size of 25,666 (see Supplemental Fig. 1).

3. Results

The nonparametric logistic regression analysis using ADGC as one cohort demonstrated that when testing the main effects, neither *TF* rs1049296 nor *HFE* rs1800562 was associated with AD risk (*TF* rs1049296 $p = 0.38$; *HFE* rs1800562 $p = 0.40$). The logistic regression analyses including an interaction term for the 2 variants also failed to show significant association ($p = 0.23$). Similarly, the SFA analysis did not find epistasis between *TF* rs1049296 and *HFE* rs1800562 (SF = 0.94; $p = 0.48$).

We performed logistic regression on all 30 individual cohorts (see Supplemental Fig. 2). We detected a significant epistatic association between the interaction term and AD status in the ACT cohort ($p = 0.038$) and a suggested association in the ADC1 cohort ($p = 0.063$). In addition, the individual effect of *HFE* rs1800562 shows a suggested association with AD status in the ADC6 ($p = 0.099$), WHICAP ($p = 0.052$), ADC4 ($p = 0.076$), and ROSMAP ($p = 0.094$) cohorts. Furthermore, logistic regression for the individual effect of *TF* rs1049296 determined a significant association with AD status in the WASHU cohort ($p = 0.016$). However, none of these associations remained significant after a Bonferroni correction for multiple tests.

In addition, χ^2 analyses between terms and AD status demonstrated a nonsignificant likelihood for any single term or interaction. The odds ratio for rs1049269 was 0.97 with a 95% confidence interval (CI) between 0.92 and 1.03, whereas rs1800562 had an odds ratio of 1.06 with a CI of 0.98–1.15, and the interaction term had an odds ratio of 0.99 with a CI of 0.86–1.14. The odds ratios and CIs for main effects and the interaction in each cohort are displayed in Supplemental Fig. 3.

4. Discussion

We failed to detect evidence that epistasis between *TF* rs1049296 and *HFE* rs1800562 increases risk for AD in the ADGC data set. These findings do not support the conclusions drawn in the previous reports by Robson et al. (2004) and Kauwe et al. (2010). The cause for this variability among studies could be a result of genetic heterogeneity, the complex nature of epistasis, or false positives in these previous studies due to limited sample size.

Although recent literature suggests that much of the unidentified genetic makeup of AD is due to epistasis (Bullock et al., 2013; Combarros et al., 2009; Ebbert et al., 2014; Infante et al., 2004; Mez, 2016), the complex nature of these gene-gene interactions makes it difficult to define specific epistatic interactions when multiple genes could be involved (Gilbert-Diamond and Moore, 2011; Kouyos et al., 2007; Urbanowicz et al., 2012). Models for epistatic interactions are challenging to create because the models

require large data sets to analyze combinations of variables simultaneously (Moore and Williams, 2009).

When an insufficient number of samples are used, results have poor statistical power, which leads to frequent false negatives in gene-gene interaction studies. Likewise, the numerous comparisons required to assess epistasis may generate false-positive findings (Mackay and Moore, 2014). Inadequate sample size can also result in false positives and is identified through statistical power analyses (Christley, 2010). The analyses performed by Robson et al. (2004) and Kauwe et al. (2010) used data sets with much fewer individuals than the data set used in this article and consequently have lower statistical power than our analysis. Although it is difficult to assess the proper significance threshold for power calculations, our study has significantly more power than the study by Kauwe et al. (2010) regardless of the alpha value used in the power calculation (see Supplemental Fig. 1). Our analysis attains a power of 0.80 with an alpha value of just 0.003, whereas the study by Kauwe et al. (2010) would need a significance threshold of 0.55 to reach the same level of power. Current research suggests a phenomenon known as the "winner's curse," which occurs when the estimated effect of an association is inflated compared with the true genetic effect and the effects later measured in follow-up studies (Huang et al., 2018; Palmer & Pe'er, 2017). The level of power necessary to accurately detect epistasis is currently unknown, and as such, replication studies are a necessary part of validating epistasis. As our results show, statistical studies should be re-evaluated when larger data sets become available.

Heterogeneity in the genetic causes of AD is certainly present (Mez, 2016) and further erodes power to detect statistical epistasis. Similarly, combining various studies that use different diagnostic techniques could decrease our power to detect an epistatic signal if the classification criteria result in some patients being misclassified (Manchia et al., 2013). However, although the classification criteria for patients with AD might vary depending on the sample, our analysis requires a large sample size to detect any synergetic relationship. Finally, even when statistical evidence for epistasis is detected, it does not necessarily indicate the presence of a physical biological interaction between the implicated proteins (Ebbert et al., 2015). Statistical patterns can be a product of a variety of underlying mechanisms. Therefore, the complexity of biological and statistical epistasis could also account for disparities in replication studies. Increasing sample sizes gives us better statistical power. Likewise, increasing the amount of multidimensional -omics data will help us focus our efforts on specific candidate interactions. For instance, we can use protein interaction networks and expression quantitative trait loci (eQTLs) to identify different loci that have similar effects on gene expression. This will help limit the search space of synergetic interactions. We anticipate that as more multidimensional -omics data become available, our ability to identify and understand the role of epistasis in AD risk will improve and help in the development of novel approaches to prevent and treat the disease.

Disclosure statement

None.

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Authors' contributions: EV contributed to conceptualization, methodology, formal analysis, writing—original draft, writing—review and editing, and visualization. JDGM contributed to methodology and writing—original draft. JBM contributed to writing—original draft, writing—review and editing, and supervision. Alzheimer's Disease Genetic Consortium contributed to data curation. LS contributed to methodology and formal analysis. PKC contributed to validation and data curation. SM contributed to validation and data curation. JSKK contributed to supervision and data curation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.01.013.

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