HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Neurobiol Aging. 2021 August ; 104: 111.e1–111.e4. doi:10.1016/j.neurobiolaging.2021.03.006.

Assessment of *ANG* variants in Parkinson's disease

Francis P. Grenn[1], **Anni Moore**[1], **Sara Bandres-Ciga**[1], **Lynne Krohn**[2,3], **Cornelis Blauwendraat**[1] **International Parkinson's Disease Genomics Consortium (IPDGC)**

[1)]Molecular Genetics Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA

[2)]Department of Human Genetics, McGill University, Montreal, Quebec, Canada

[3)]Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

Abstract

Genetic risk factors are occasionally shared between different neurodegenerative diseases. Previous studies have linked *ANG*, a gene encoding angiogenin, to both Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Functional studies suggest *ANG* plays a neuroprotective role in both PD and ALS by reducing cell death. We further explored the genetic association between *ANG* and PD by analyzing genotype data from the International Parkinson's Disease Genomics Consortium (IPDGC) (14,671 cases and 17,667 controls) and whole genome sequencing (WGS) data from the Accelerating Medicines Partnership - Parkinson's disease initiative (AMP-PD, https://amp-pd.org/) (1,647 cases and 1,050 controls). Our analysis did not replicate the findings of previous studies and identified no significant association between *ANG* variants and PD risk.

Keywords

Parkinson's disease; risk factor; ANG

Corresponding Author: Cornelis Blauwendraat, cornelis.blauwendraat@nih.gov. Porter Neuroscience Center, 35 Convent Drive, Bethesda, MD 20892, USA.

Francis P. Grenn: Conceptualization, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization

Anni Moore: Resources, Writing – Original Draft, Writing – Review & Editing

Lynne Krohn: Conceptualization, Writing – Original Draft

Sara Bandres-Ciga: Conceptualization, Resources, Writing – Original Draft

Cornelis Blauwendraat: Conceptualization, Resources, Writing – Original Draft, Writing – Review & Editing, Supervision, Project Administration

Conflicts of Interest:
The authors declare that they have no conflict of interest.

Introduction:

Parkinson's disease (PD) is a neurodegenerative disease characterized by loss of dopaminergic neurons in the substantia nigra leading to symptoms of tremor, rigidity and slowed movement, and is the second most common neurodegenerative disease in the world. Both sporadic and familial forms of PD exist, and much work has been done to identify the environmental and genetic risk factors behind this disease. Over 20 genes have been associated with PD or parkinsonism in recent years, and the largest genome wide association studies for PD risk have identified 92 PD risk variants across 80 loci, explaining 16–36% of the heritable risk of PD (Blauwendraat, Nalls, and Singleton 2020; Nalls et al. 2019; Foo et al. 2020).

It is not uncommon to find genetic variations associated with multiple neurodegenerative disorders, suggesting shared pathways between diseases (Tan et al. 2019). For example, common variations in *MAPT* have been associated with PD (Zabetian et al. 2007), amyotrophic lateral sclerosis (ALS) (Karch et al. 2018) and Alzheimer's disease (AD) (Ferrari et al. 2017), and variations in *GBA* have been associated with PD (Sidransky et al. 2009) and Gaucher disease (Riboldi and Di Fonzo 2019). Therefore, the interrogation of genes common to multiple neurodegenerative disorders is a logical next step in the identification of novel PD risk variants.

One such candidate is *ANG*, a relatively small protein coding gene on chromosome 14 with a 444 base pair coding region on two exons. This gene is thought to confer a large risk for both ALS and PD (Rayaprolu et al. 2012; van Es et al. 2011). However, studies in Asian populations have suggested there is no link between *ANG* variants and PD (Chen et al. 2014; Liu et al. 2013). *ANG* encodes angiogenin, a small protein that plays a role in the angiogenesis pathway, which forms new blood vessels. Angiogenin and its related pathway are thought to play a role in cancer and placental development (Amankwah, Sellers, and Park 2012; Pavlov et al. 2014). An in vitro study has shown that angiogenin has a neuroprotective effect on motor neurons (Subramanian, Crabtree, and Acharya 2008). ALS associated *ANG* variants are suggested to potentiate neuronal death through inhibition of the PI3K-Akt pathway (Kieran et al. 2008). A PD mouse model has also shown this gene has a neuroprotective effect on dopaminergic neurons (Steidinger, Standaert, and Yacoubian 2011). This neuroprotective effect is suggested to be lost when *ANG* is mutated, decreasing the viability of motor neurons (Wu et al. 2007). These findings are of relevance because PD is characterized by the loss of dopaminergic neurons and ALS is characterized by the loss of motor neurons. Angiogenin may play a larger role in areas such as the basal ganglia, a brain structure often associated with PD. This is supported by a study that identified elevated blood serum angiogenin levels in ALS patients, but not in PD patients (van Es et al. 2014). Structural work has shown ten *ANG* coding variants are associated with a decrease in angiogenin activity, and one coding variant, p.Arg145Cys, is associated with an increase in activity (Bradshaw et al. 2017).

Case control studies focusing on *ANG* have reported associations between *ANG* variants and PD. A study including 6,471 ALS cases, 3,146 PD cases and 7,668 controls from American and European populations has reported associations between *ANG* variants and

both PD and ALS (van Es et al. 2011). A separate study including 630 PD cases and 676 controls from American populations has also reported association between *ANG* variants and PD (Rayaprolu et al. 2012). However, to date *ANG* variants have not been associated with either ALS or PD through genome wide association studies (GWAS) (Nicolas et al. 2018; Nalls et al. 2019). Here we scrutinize *ANG* variants in two large PD datasets to assess whether *ANG* variants contribute to PD risk in individuals of European ancestry.

Methods:

Whole-Genome Sequencing and Genotype Data:

We mined whole-genome sequencing (WGS) data from the Accelerating Medicines Partnership - Parkinson's disease initiative (AMP-PD, https://amp-pd.org/) which included 1,647 cases and 1,050 healthy controls from cohorts of European ancestry. The cohorts included were the Fox Investigation for New Discovery of Biomarkers (BioFIND), the Parkinson's Progression Markers Initiative (PPMI), the Harvard Biomarker Study (HBS), and the Parkinson's Disease Biomarkers Program (PDBP). We also looked at *ANG* variants in genotype data from the International Parkinson's Disease Genomics Consortium (IPDGC) which included 14,671 cases and 17,667 healthy controls. IPDGC variants were converted from hg19 to hg38 positions to match AMP-PD variant hg38 positions. Variants from both datasets were annotated using ANNOVAR (Wang, Li, and Hakonarson 2010). Variant frequencies in non-Finnish European populations were obtained from the hg38 gnomAD v3.0 dataset (Karczewski et al. 2020).

Variants identified by amino acid change from previous studies including Van Es et al. and Rayaprolu et al. did not initially match any variants identified in AMP-PD data due to differences in amino acid numbering. To resolve this we mapped each variant amino acid change to the angiogenin protein sequence. This sequence was obtained from Ensembl using the ANG-201 ENST00000336811.10 hg38 transcript (Yates et al. 2020). We learned that the reported amino acid changes from Van Es et al. and Rayaprolu et al. were offset by 25 or 24 amino acids due to numbering differences used for the signal peptide sequence that is cleaved from the mature angiogenin protein. This was accounted for in our analysis.

Statistical Analyses:

PLINK 1.9 was used to perform Fisher's exact test to identify significant variants (Purcell et al. 2007). Rare variant burden tests and single variant score tests were performed using RVTESTS (Zhan et al. 2016). We further analyzed existing summary statistics including the latest GWAS meta-analyses for PD risk and age of onset (Blauwendraat et al. 2019; Nalls et al. 2019) and additionally assessed public summary statistics from the most recent ALS GWAS (Nicolas et al. 2018).

We used the Genetic Association Study Power Calculator to calculate the statistical power of our study (Johnson and Abecasis, n.d.).

Principal component analysis was performed on AMP-PD samples to check for population stratification. Data from the International HapMap Project was merged with AMP-PD data

for comparison (Supplementary Figure 3) (Consortium, the International Hapmap and The International HapMap Consortium 2003).

Code:

The code we used for analysis is available on the IPDGC github (https://github.com/ipdgc/IPDGC-Trainees/blob/master/ANG.md).

Expression Quantitative Trait Loci:

We obtained expression quantitative trait loci (eQTL) data for *ANG* variants found in AMP-PD and IPDGC datasets. Both cis and trans eQTLs were obtained from the eQTLGen Consortium (Võsa 2018). The Genotype-Tissue Expression portal was accessed on November 18, 2020 to obtain additional eQTL data.

Results:

We identified a total of 168 *ANG* variants in the AMP-PD WGS data, with nine of these identified as coding. We compared the nine identified *ANG* coding variants to variants from two other studies (van Es et al. 2011; Rayaprolu et al. 2012) (Supplementary Table 2). Of the coding variants, two were synonymous and the other seven were nonsynonymous. All nonsynonymous variants were rare (MAF<0.01), and allele frequencies did not differ significantly from gnomAD non-Finnish European allele frequencies although most variants were too rare to reliably test individually. The top variant after performing Fisher's exact test (p=0.017) and single variant score test (p=0.016) was not significant after Bonferroni correction for multiple tests (p=0.05/168=2.97E-4) (Supplementary Table 1). Burden tests with a minor allele frequency less than 0.03 reported no significant results when using all variants (N variants=72; CMC p=0.493, Fp p=0.509, MB p=0.880, Skat p=0.454, SkatO p=0.523, Zeggini p=0.395). Likewise, there were no significant results when performing the same test on only coding variants (N variants=9; CMC p=0.866, Fp p=0.510, MB p=0.820, Skat p=0.436, SkatO p=0.556, Zeggini p=0.868).

After excluding the only two synonymous variants, rs11701 (p.G110=) and rs2228653 (p.T121=), from these nine, we observed an average frequency of 0.39% in PD cases and 0.48% in controls. Van Es et al. also removed two common variants, rs121909536 (K41I) and rs121909541 (p.I70V), from their analysis. After removing these same two variants from our data the average frequencies were 0.15% in PD cases and 0.19% in controls. This is in contrast with the 0.45% average frequency in PD cases and 0.05% in controls previously reported (van Es et al. 2011).

Twenty-six *ANG* variants were identified using the IPDGC imputed genotype data, all of which were non-coding (Supplementary Table 1). All variants were high quality imputed (r^2>0.8) or were directly genotyped. No significant association between *ANG* variants and PD risk (Figure 1A) or onset (Supplementary Figure 1) was identified in data from the latest PD risk GWAS or in the PD age of onset GWAS (Nalls et al. 2019; Blauwendraat et al. 2019). No variants had a minor allele frequency less than 0.03, so the threshold was increased to 0.05 for burden tests. Only two variants were included at this threshold, which also reported no significant results (N=2; CMC p=0.893, Fp p=0.960, MB p=0.948, Skat

p=0.980, SkatO p=1, Zeggini p=0.842). Additionally, no GWAS signal of interest is identified in the most recent ALS GWAS (Figure 1B) (Nicolas et al. 2018).

Discussion:

Rare coding variants in *ANG* have been reported to be associated with PD (van Es et al. 2011). Our goal was to further explore the role of *ANG* in PD by analyzing additional datasets from IPDGC and AMP-PD. Our study shows no significant enrichment of *ANG* single variants in PD cases or controls in either of these datasets. Rare variant burden tests also reported no significant results for *ANG*. Our analysis provides no evidence to support the hypothesis that genetic variation of *ANG* plays a role in PD risk or age at onset.

The nine coding *ANG* variants we identified were from AMP-PD WGS data. This dataset included fewer samples (1,647 PD; 1,050 controls) than the Van Es et al. study (6,471 ALS;3,146 PD;7,668 non-ALS controls;5,361 non-PD controls) which identified a total of 29 unique *ANG* coding variants. However, the frequency of *ANG* coding variants detected in AMP-PD data is 0.15% in PD cases and 0.19% in controls which is different from the previously reported 0.45% in PD cases (14 variants in 3,146 PD cases) and 0.05% in controls (3 variants in 5,361 non-PD controls) (van Es et al. 2011).

We queried eQTL datasets from eQTLGen and GTEx for *ANG* eQTLs to identify variants that affect gene expression levels (Võsa 2018). Between both eQTLGen and GTEx data we identified a total of 725 unique *ANG* eQTLs (Supplementary Table 3). Twenty six of these 725 were trans eQTLs and the other 699 were cis eQTLs. Out of the 170 genetic variants identified in AMP-PD and IPDGC data, 74 were eQTLs for *ANG* or the nearby gene, *RNASE4*, ten of these eQTLs were located in the 5' untranslated region of *ANG*, one was exonic, and the other sixty-three were intronic. However, given that the genetic variants were not determined to be significant, it is likely that eQTLs also do not contribute to disease.

We used the Genetic Association Study Power Calculator to determine if our study was sufficiently powered to replicate the findings of previous studies (Johnson and Abecasis, n.d.). We used 1,647 cases and 1,050 controls as inputs, with a significance level of 0.05, and a disease prevalence of 0.01. We calculated the average allele frequency in AMP-PD data to be 0.0017 and included it along with a genotype relative risk of 6.7 which was taken from previous studies to allow for comparison with our study (van Es et al. 2011). We calculated a statistical power of 0.997, suggesting we are sufficiently powered to detect significant rare *ANG* variants in PD cases and controls (Supplementary Figure 2). Additionally, AMP-PD samples used in our study were age matched which is in line with previous studies (Supplementary Table 4). However, the cumulative frequency of *ANG* variants identified in AMP-PD data was not significantly different as previously reported. A larger sample size may be needed to identify the missing coding variants so the role of *ANG* in PD can be assessed on an even larger scale. Overall, despite some potentially interesting functional experiments supporting the neuroprotective effect of angiogenin, we cannot replicate the genetic association between *ANG* coding variants and PD. Therefore, we cannot conclude that *ANG* variants play a role in PD in European populations, which is in line with previous studies done in Asian populations (Chen et al. 2014; Liu et al. 2013).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We would like to thank all of the subjects who donated their time and biological samples to be a part of this study. We also would like to thank all members of the International Parkinson's Disease Genomics Consortium (IPDGC). For a complete overview of members, acknowledgements and funding, please see http://pdgenetics.org/partners. This work was supported in part by the Intramural Research Programs of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), and the National Institute of Environmental Health Sciences (NIEHS), all part of the National Institutes of Health, Department of Health and Human Services; project numbers 1ZIA-NS003154, Z01-AG000949-02 and Z01-ES101986. In addition, this work was supported by the Department of Defense (award W81XWH-09-2-0128), and The Michael J Fox Foundation for Parkinson's Research. Data used in the preparation of this article were obtained from the AMP PD Knowledge Platform. For up-to-date information on the study, visit https://www.amp-pd.org. AMP PD - a public-private partnership – is managed by the FNIH and funded by Celgene, GSK, the Michael J. Fox Foundation for Parkinson's Research, the National Institute of Neurological Disorders and Stroke, Pfizer, and Verily. We would like to thank AMP-PD for the publicly available whole-genome sequencing data, including cohorts from the Fox Investigation for New Discovery of Biomarkers (BioFIND), the Parkinson's Progression Markers Initiative (PPMI), and the Parkinson's Disease Biomarkers Program (PDBP). The Parkinson's Disease Biomarker Program (PDBP) consortium is supported by the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health. A full list of PDBP investigators can be found at https://pdbp.ninds.nih.gov/policy. Harvard Biomarker Study (HBS) is a collaboration of HBS investigators (full list of HBS investigators found at https://www.bwhparkinsoncenter.org/biobank) and funded through philanthropy and NIH and Non-NIH funding sources. The HBS Investigators have not participated in reviewing the data analysis or content of the manuscript. This work utilized the computational resources of the NIH HPC Biowulf cluster (http://hpc.nih.gov).

References:

Amankwah Ernest K., Sellers Thomas A., and Park Jong Y.. 2012. "Gene Variants in the Angiogenesis Pathway and Prostate Cancer." Carcinogenesis 33 (7): 1259–69. [PubMed: 22523086]

Blauwendraat Cornelis, Heilbron Karl, Vallerga Costanza L., Bandres-Ciga Sara, von Coelln Rainer, Pihlstrøm Lasse, Simón-Sánchez Javier, et al. 2019. "Parkinson's Disease Age at Onset Genome-Wide Association Study: Defining Heritability, Genetic Loci, and α-Synuclein Mechanisms." Movement Disorders: Official Journal of the Movement Disorder Society 34 (6): 866–75. [PubMed: 30957308]

Blauwendraat Cornelis, Nalls Mike A., and Singleton Andrew B.. 2020. "The Genetic Architecture of Parkinson's Disease." Lancet Neurology 19 (2): 170–78. [PubMed: 31521533]

Bradshaw William J., Rehman Saima, Pham Tram T. K., Thiyagarajan Nethaji, Lee Rebecca L., Subramanian Vasanta, and Ravi Acharya K. 2017. "Structural Insights into Human Angiogenin Variants Implicated in Parkinson's Disease and Amyotrophic Lateral Sclerosis." Scientific Reports. 10.1038/srep41996.

Chen Meng-Ling, Wu Ruey-Meei, Tai Chun-Hwei, and Lin Chin-Hsien. 2014. "Mutational Analysis of Angiogenin Gene in Parkinson's Disease." PloS One 9 (11): e112661. [PubMed: 25386690]

Consortium, the International Hapmap, and The International HapMap Consortium. 2003. "The International HapMap Project." Nature. 10.1038/nature02168.

van Es Michael A., Schelhaas Helenius J., van Vught Paul W. J., Ticozzi Nicola, Andersen Peter M., Groen Ewout J. N., Schulte Claudia, et al. 2011. "Angiogenin Variants in Parkinson Disease and Amyotrophic Lateral Sclerosis." Annals of Neurology 70 (6): 964–73. [PubMed: 22190368]

van Es Michael A., Veldink Jan H., Schelhaas Helenius J., Bloem Bastiaan R., Sodaar Peter, van Nuenen Bart F. L., Verbeek Marcel, van de Warrenburg Bart P., and van den Berg Leonard H.. 2014. "Serum Angiogenin Levels Are Elevated in ALS, but Not Parkinson's Disease: Table 1." Journal of Neurology, Neurosurgery & Psychiatry. 10.1136/jnnp-2013-307168.

Ferrari Raffaele, Wang Yunpeng, Vandrovcova Jana, Guelfi Sebastian, Witeolar Aree, Karch Celeste M., Schork Andrew J., et al. 2017. "Genetic Architecture of Sporadic Frontotemporal Dementia and Overlap with Alzheimer's and Parkinson's Diseases." Journal of Neurology, Neurosurgery, and Psychiatry 88 (2): 152–64.

Foo Jia Nee, Chew Elaine Guo Yan, Chung Sun Ju, Peng Rong, Blauwendraat Cornelis, Nalls Mike A., Mok Kin Y., et al. 2020. “Identification of Risk Loci for Parkinson Disease in Asians and Comparison of Risk Between Asians and Europeans: A Genome-Wide Association Study.” JAMA Neurology, 4. 10.1001/jamaneurol.2020.0428.

Johnson Jennifer Li, and Abecasis Gonçalo R.. n.d. “GAS Power Calculator: Web-Based Power Calculator for Genetic Association Studies.” 10.1101/164343.

Karch Celeste M., Wen Natalie, Fan Chun C., Yokoyama Jennifer S., Kouri Naomi, Ross Owen A., Gunter Höglinger, et al. 2018. “Selective Genetic Overlap Between Amyotrophic Lateral Sclerosis and Diseases of the Frontotemporal Dementia Spectrum.” JAMA Neurology 75 (7): 860–75. [PubMed: 29630712]

Karczewski Konrad J., Francioli Laurent C., Tiao Grace, Cummings Beryl B., Jessica Alföldi Qingbo Wang, Collins Ryan L., et al. 2020. “The Mutational Constraint Spectrum Quantified from Variation in 141,456 Humans.” Nature 581 (7809): 434–43. [PubMed: 32461654]

Kieran Dairín, Sebastia Jordi, Greenway Matthew J., King Matthew A., Connaughton Dervla, Concannon Caoimhin G., Fenner Beau, Hardiman Orla, and Prehn Jochen H. M.. 2008. “Control of Motoneuron Survival by Angiogenin.” The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 28 (52): 14056–61. [PubMed: 19109488]

Liu Bin, Zhang Yu, Wang Ying, Xiao Qin, Yang Qiong, Wang Gang, Ma Jianfang, et al. 2013. “Angiogenin Variants Are Not Associated with Parkinson’s Disease in the Ethnic Chinese Population.” Parkinsonism & Related Disorders. 10.1016/j.parkreldis.2012.11.016.

Nalls Mike A., Blauwendraat Cornelis, Vallerga Costanza L., Heilbron Karl, Bandres-Ciga Sara, Chang Diana, Tan Manuela, et al. 2019. “Identification of Novel Risk Loci, Causal Insights, and Heritable Risk for Parkinson’s Disease: A Meta-Analysis of Genome-Wide Association Studies.” Lancet Neurology 18 (12): 1091–1102. [PubMed: 31701892]

Nicolas Aude, Kenna Kevin P., Renton Alan E., Ticozzi Nicola, Faghri Faraz, Chia Ruth, Dominov Janice A., et al. 2018. “Genome-Wide Analyses Identify KIF5A as a Novel ALS Gene.” Neuron 97 (6): 1268–83.e6. [PubMed: 29566793]

Pavlov Nadine, Frendo Jean-Louis, Guibourdenche Jean, Degrelle Séverine A., Evain-Brion Danièle, and Badet Josette. 2014. “Angiogenin Expression during Early Human Placental Development; Association with Blood Vessel Formation.” BioMed Research International 2014 (July): 781632. [PubMed: 25093183]

Pruim Randall J., Welch Ryan P., Sanna Serena, Teslovich Tanya M., Chines Peter S., Gliedt Terry P., Boehnke Michael, Abecasis Gonçalo R., and Willer Cristen J.. 2010. “LocusZoom: Regional Visualization of Genome-Wide Association Scan Results.” Bioinformatics 26 (18): 2336–37. [PubMed: 20634204]

Purcell Shaun, Neale Benjamin, Kathe Todd-Brown Lori Thomas, Ferreira Manuel A. R., Bender David, Maller Julian, et al. 2007. “PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses.” The American Journal of Human Genetics. 10.1086/519795.

Rayaprolu Sruti, Soto-Ortolaza Alexandra, Rademakers Rosa, Uitti Ryan J., Wszolek Zbigniew K., and Ross Owen A.. 2012. “Angiogenin Variation and Parkinson Disease.” Annals of Neurology.

Riboldi Giulietta M., and Di Fonzo Alessio B.. 2019. “GBA, Gaucher Disease, and Parkinson’s Disease: From Genetic to Clinic to New Therapeutic Approaches.” Cells. 10.3390/cells8040364.

Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, et al. 2009. “Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson’s Disease.” The New England Journal of Medicine 361 (17): 1651–61. [PubMed: 19846850]

Steidinger Trent U., Standaert David G., and Yacoubian Talene A.. 2011. “A Neuroprotective Role for Angiogenin in Models of Parkinson’s Disease.” Journal of Neurochemistry. 10.1111/j.1471-4159.2010.07112.x.

Subramanian Vasanta, Crabtree Benedict, and Ravi Acharya K. 2008. “Human Angiogenin Is a Neuroprotective Factor and Amyotrophic Lateral Sclerosis Associated Angiogenin Variants Affect Neurite Extension/pathfinding and Survival of Motor Neurons.” Human Molecular Genetics 17 (1): 130–49. [PubMed: 17916583]

Tan Sean Hong, Karri Venkatanaidu, Rong Tay Nicole Wuen, Chang Kuan Hui, Ah Hui Yen, Ng Phui Qi, Ho Hui San, Keh Hsiao Wai, and Candasamy Mayuren. 2019. “Emerging Pathways to Neurodegeneration: Dissecting the Critical Molecular Mechanisms in Alzheimer’s Disease, Parkinson’s Disease.” Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 111 (March): 765–77. [PubMed: 30612001]

Võsa Urmo. 2018. “Unraveling the Polygenic Architecture of Complex Traits Using Blood eQTL Meta-Analysis.” bioRxiv, 10. 10.1101/447367.

Wang Kai, Li Mingyao, and Hakonarson Hakon. 2010. “ANNOVAR: Functional Annotation of Genetic Variants from High-Throughput Sequencing Data.” Nucleic Acids Research 38 (16): e164. [PubMed: 20601685]

Wu David, Yu Wenhao, Kishikawa Hiroko, Folkerth Rebecca D., Iafrate A. John, Shen Yiping, Xin Winnie, Sims Katherine, and Hu Guo-Fu. 2007. “Angiogenin Loss-of-Function Mutations in Amyotrophic Lateral Sclerosis.” Annals of Neurology 62 (6): 609–17. [PubMed: 17886298]

Yates Andrew D., Achuthan Premanand, Akanni Wasiu, Allen James, Allen Jamie, Alvarez-Jarreta Jorge, Ridwan Amode M, et al. 2020. “Ensembl 2020.” Nucleic Acids Research 48 (D1): D682–88. [PubMed: 31691826]

Zabetian CP, Hutter CM, Factor SA, Nutt JG, Higgins DS, Griffith A, Roberts JW, et al. 2007. “Association Analysis of MAPT H1 Haplotype and Subhaplotypes in Parkinson’s Disease.” Annals of Neurology 62 (2). 10.1002/ana.21157.

Zhan Xiaowei, Hu Youna, Li Bingshan, Abecasis Goncalo R., and Liu Dajiang J.. 2016. “RVTESTS: An Efficient and Comprehensive Tool for Rare Variant Association Analysis Using Sequence Data.” Bioinformatics 32 (9): 1423–26. [PubMed: 27153000]

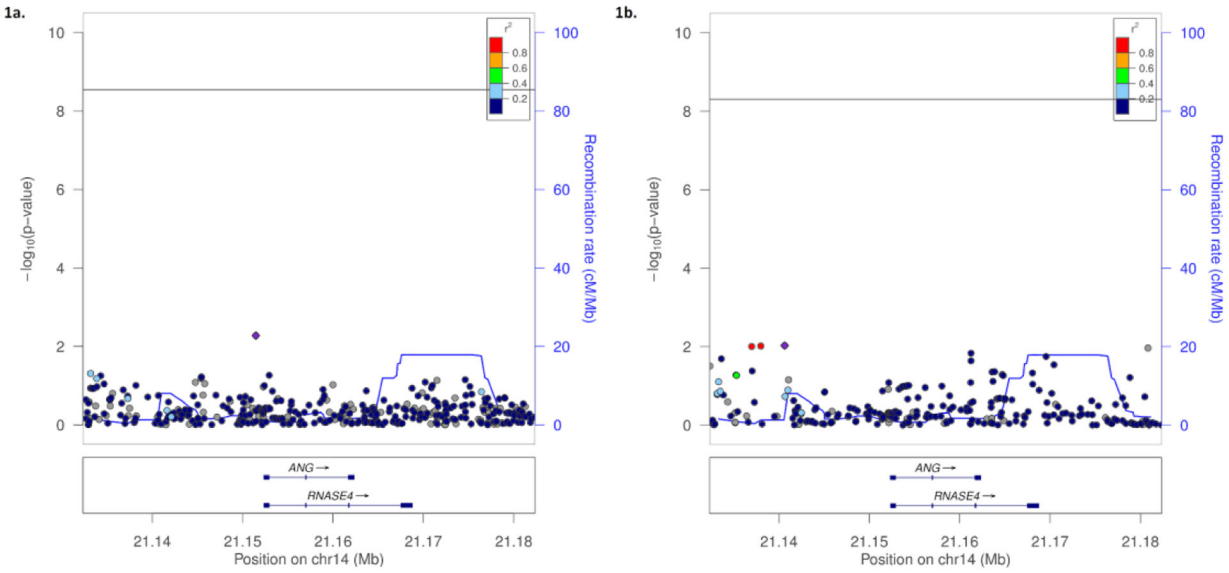

Figure 1. Locus zoom plots for *ANG* and PD risk and ALS risk.

The $-\log_{10}$(p-value) of variants on or near *ANG* are shown on the y-axis, and base-pair position of each variant is on the x-axis. P-values are taken from the PD risk GWAS (Figure 1A) and the ALS risk GWAS (Figure 1B). Variants are colored by their R^2 linkage disequilibrium value which is relative to the variant with the lowest p-value on these plots (colored purple). The genome-wide significance cutoff line for multiple test correction is included in black. Recombination rates are included in blue (Pruim et al. 2010).