Published in final edited form as:

Neurobiol Aging. 2021 November ; 107: 174–177. doi:10.1016/j.neurobiolaging.2021.05.019.

Common and rare variants in HFE are not associated with Parkinson's disease in Europeans

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Abstract

A recent study suggested that the p.H63D variant in *HFE*, a gene involved in iron homeostasis, may modify α-synuclein pathology, the pathological hallmark of Parkinson's disease (PD). If indeed this gene and specific variant are involved in PD, we expect to find differential distribution of *HFE* variants when comparing PD patients and controls. We analyzed genome-wide association study (GWAS) data from 14,671 PD patients and 17,667 controls and full sequencing data from additional 1,647 PD patients and 1,050 controls, using logistic regression models, and burden and Kernel tests. The *HFE* p.H63D variant was not associated with PD, nor did all the other common variants in the *HFE* locus. We did not find association of rare *HFE* variants with PD as well in all types of burden and Kernel tests. Our results do not support a role for *HFE* in PD risk.

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CREDIT author statement

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Ronald B. Postuma – Supervision, Writing- Reviewing and Editing
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Conflict of interests

ZGO has received consulting fees from Lysosomal Therapeutics Inc., Idorsia, Prevail Therapeutics, Denali, Ono Therapeutics, Neuron23, Handl Therapeutics, Deerfield and Inception Sciences (now Ventus). None of these companies were involved in any parts of preparing, drafting and publishing this study. Other authors have no additional disclosures to report.

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder, caused in most cases by multiple genetic and environmental factors, and the normal process of aging. Previous studies have suggested that iron homeostasis may have a role in PD; pathological and imaging studies showed that iron accumulation in the substantia nigra may contribute to PD pathogenesis (Ward et al., 2014). Multiple genes are involved in iron homeostasis, one of the most important of them being *HFE*, encoding the homeostatic iron regulator protein (also called hereditary hemochromatosis protein). This protein is a membrane protein thought to regulate iron absorption, and bi-allelic *HFE* mutations may lead to hereditary haemochromatosis, an iron storage disorder.

Although several genetic studies reported lack of association of the *HFE* p.H63D variant with PD (Biasiotto et al., 2008; Duan et al., 2016; Guerreiro et al., 2006; Rhodes et al., 2014; Xia et al., 2015), a recent study suggested that this variant may be protective in Parkinson's disease pathogenesis by modifying α-synuclein pathology in cell models (Kim et al., 2020). The same group has previously suggested, using a mouse model with the homolog of the same variant (H67D), that *HFE* is a disease modifier in PD (Nixon et al., 2018). In order to examine whether this and other *HFE* variants are associated with PD, we performed a comprehensive analysis of common and rare *HFE* variants in large case-control cohorts of PD patients and controls of European origin.

Methods

Two cohorts were included in the current study: 1) a total of 14,671 PD patients and 17,667 controls collected through collaborators from the International PD Genomics Consortium (IPDGC), and 2) 1,647 PD patients and 1,050 controls from AMP-PD (https://amp-pd.org/). Demographic details on these cohorts can be found in Supplementary Table S1A and S1B. We performed standard genome-wide association study (GWAS) quality control (QC) on the individual and variant level data as previously described (Iwaki et al., 2019). We performed a similar QC process for the AMP-PD whole genome sequencing data, as detailed in the AMP-PD portal (https://amp-pd.org/whole-genome-data). This QC process also excluded, based on genetic relatedness, any relatives up to third degree of relatedness. Genotype data was extracted from both datasets for all variants within 100kb upstream and downstream of *HFE*, and was annotated using ANNOVAR (Wang et al., 2010). To examine whether common variants (allele frequency >0.01) in *HFE* are associated with PD, we performed logistic regression adjusted for age, sex, 10 principal components and sites of cohorts. To determine whether rare *HFE* variants (allele frequency <0.01) are associated with PD, we performed a set of burden and Kernel association tests included in the RVtests R package, including age and sex as covariates when possible (Zhan et al., 2016). Bonferroni correction for multiple comparisons was applied, and all code used in the current study is available at the IPDGC GitHub at https://github.com/ipdgc/IPDGC-Trainees/blob/master/.

Results

None of the common variants in the *HFE* region were associated with risk of PD (Figure 1). The specific *HFE* variant recently reported to be associated with decreased aggregation of α-synuclein, p.H63D, had similar allele frequencies in patients and controls (0.17 and 0.16, respectively), and was not associated with risk of PD (OR=1.02, 95%CI=0.97–1.07, p=0.53). Another *HFE* variant previously reported to be associated with PD, p.C282Y, had similar frequencies in patients and controls as well (0.052 and 0.059, respectively) and was not associated with PD (OR=0.98, 95%CI=0.91–1.07, p=0.69). Similarly, none of the burden and Kernel association tests we used to examine the association of rare *HFE* variants with PD yielded statistically significant results (Table 1). These analyses included all rare variants in *HFE*, and all nonsynonymous variants in *HFE*. No loss-of-function variants were identified, and only one *HFE* variant had a Combined Annotation Dependent Depletion (CADD) score of >20, therefore no additional analyses were performed on these categories of variants. The list of all common and rare variants found in *HFE* is available in Supplementary Table S2 and S3, respectively.

Discussion

In the current study we performed a thorough genetic analysis of *HFE* in large case-control cohorts of PD patients and controls. Our results do not support a role for common or rare *HFE* variants in risk of PD. Previous smaller genetic association studies focusing on *HFE* reported contradicting results, as some studies reported associations of different *HFE* variants with PD, while other studies reported lack of association (Biasiotto et al., 2008; Borie et al., 2002; Buchanan et al., 2002; Duan et al., 2016; Guerreiro et al., 2006; Halling et al., 2008; Rhodes et al., 2014; Xia et al., 2015). Specifically for p.H63D, all the previous studies, including two meta-analyses (Duan et al., 2016; Xia et al., 2015), reported lack of association. Our study, which is a larger-scale analysis combining both GWAS data, as well as full sequencing data on *HFE*, analyzed through the same pipeline and including burden analyses of rare variants, also provides no support for the involvement of *HFE* p.H63D in risk of PD. Furthermore, there is no convincing evidence to suggest an association between other *HFE* variants and risk of PD. We cannot rule out that a very small effect does exist, or that there is an effect on disease progression but not on risk, but since it was not detected by the recent GWAS with over 50,000 PD patients and proxy-cases (Iwaki et al., 2019), it is likely to be too small to be clinically meaningful, if at all.

Clinical and epidemiological studies do suggest a role for iron homeostasis in PD. Neuropathological studies of the substantia nigra pars compacta demonstrated a correlation between increased iron concentrations and increased severity of PD. Transcranial sonography of the substantia nigra shows hyperechogenicity due to iron accumulation in about 90% of PD patients. In the periphery, increased iron levels are associated with reduced risk of PD. A role for iron in PD is further supported by additional histological, biochemical and pathological data (Ward et al., 2014). While genetic data does not support a role for *HFE* in risk of PD, other iron-regulating genes should be further studied.

The main limitation of the current study is that it includes only participants of European descent, therefore multi-ethnic studies are further required to study the role of *HFE* in PD in other populations. In a recent GWAS of Asian population, however, no GWAS-significant association has been reported for *HFE* (Foo et al., 2020).

Despite the lack of association with PD risk in the current study, the role of iron and iron homeostasis in PD should be further studied, whether by genetic studies or by biochemical, functional, clinical and pathological studies. We recommend that genetic data from the IPDGC and other available studies should be consulted before studying specific genetic variants in different models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the participants for contributing to the study. We would like to also thank all members of the International Parkinson Disease Genomics Consortium (IPDGC). For a complete overview of members, acknowledgements and funding, please see http://pdgenetics.org/partners. This research was supported in part by the Intramural Research Program of the NIH, National institute on Aging. This work was also supported in part by grants from the Michael J. Fox Foundation, the Canadian Consortium on Neurodegeneration in Aging (CCNA), and the Canada First Research Excellence Fund (CFREF), awarded to McGill University for the Healthy Brains for Healthy Lives initiative (HBHL). ZGO is supported by the Fonds de recherche du Québec – Santé (FRQS) Chercheurs-boursiers award, in collaboration with Parkinson Quebec, by the Young Investigator Award by Parkinson Canada, and is a William Dawson Scholar.

References

Biasiotto G, Goldwurm S, Finazzi D, Tunesi S, Zecchinelli A, Sironi F, Pezzoli G, Arosio P, 2008. HFE gene mutations in a population of Italian Parkinson's disease patients. Parkinsonism Relat Disord 14(5), 426–430. [PubMed: 18325820]

Borie C, Gasparini F, Verpillat P, Bonnet AM, Agid Y, Hetet G, Brice A, Durr A, Grandchamp B, French Parkinson's disease genetic study, g., 2002. Association study between iron-related genes polymorphisms and Parkinson's disease. J Neurol 249(7), 801–804. [PubMed: 12140659]

Buchanan DD, Silburn PA, Chalk JB, Le Couteur DG, Mellick GD, 2002. The Cys282Tyr polymorphism in the HFE gene in Australian Parkinson's disease patients. Neurosci Lett 327(2), 91–94. [PubMed: 12098643]

Duan C, Wang M, Zhang Y, Wei X, Huang Y, Zhang H, Cheng L, Gai Z, 2016. C282Y and H63D Polymorphisms in Hemochromatosis Gene and Risk of Parkinson's Disease: A Meta-Analysis. Am J Alzheimers Dis Other Demen 31(3), 201–207. [PubMed: 26340960]

Foo JN, Chew EGY, Chung SJ, Peng R, Blauwendraat C, Nalls MA, Mok KY, Satake W, Toda T, Chao Y, Tan LCS, Tandiono M, Lian MM, Ng EY, Prakash KM, Au WL, Meah WY, Mok SQ, Annuar AA, Chan AYY, Chen L, Chen Y, Jeon BS, Jiang L, Lim JL, Lin JJ, Liu C, Mao C, Mok V, Pei Z, Shang HF, Shi CH, Song K, Tan AH, Wu YR, Xu YM, Xu R, Yan Y, Yang J, Zhang B, Koh WP, Lim SY, Khor CC, Liu J, Tan EK, 2020. Identification of Risk Loci for Parkinson Disease in Asians and Comparison of Risk Between Asians and Europeans: A Genome-Wide Association Study. JAMA Neurol 77(6), 746–754. [PubMed: 32310270]

Guerreiro RJ, Bras JM, Santana I, Januario C, Santiago B, Morgadinho AS, Ribeiro MH, Hardy J, Singleton A, Oliveira C, 2006. Association of HFE common mutations with Parkinson's disease, Alzheimer's disease and mild cognitive impairment in a Portuguese cohort. BMC Neurol 6, 24. [PubMed: 16824219]

Halling J, Petersen MS, Grandjean P, Weihe P, Brosen K, 2008. Genetic predisposition to Parkinson's disease: CYP2D6 and HFE in the Faroe Islands. Pharmacogenet Genomics 18(3), 209–212. [PubMed: 18300942]

Iwaki H, Blauwendraat C, Leonard HL, Liu G, Maple-Grodem J, Corvol JC, Pihlstrom L, van Nimwegen M, Hutten SJ, Nguyen KH, Rick J, Eberly S, Faghri F, Auinger P, Scott KM, Wijeyekoon R, Van Deerlin VM, Hernandez DG, Day-Williams AG, Brice A, Alves G, Noyce AJ, Tysnes OB, Evans JR, Breen DP, Estrada K, Wegel CE, Danjou F, Simon DK, Ravina B, Toft M, Heutink P, Bloem BR, Weintraub D, Barker RA, Williams-Gray CH, van de Warrenburg BP, Van Hilten JJ, Scherzer CR, Singleton AB, Nalls MA, 2019. Genetic risk of Parkinson disease and progression:: An analysis of 13 longitudinal cohorts. Neurol Genet 5(4), e348. [PubMed: 31404238]

Kim Y, Stahl MC, Huang X, Connor JR, 2020. H63D variant of the homeostatic iron regulator (HFE) gene alters alpha-synuclein expression, aggregation, and toxicity. J Neurochem.

Nixon AM, Meadowcroft MD, Neely EB, Snyder AM, Purnell CJ, Wright J, Lamendella R, Nandar W, Huang X, Connor JR, 2018. HFE Genotype Restricts the Response to Paraquat in a Mouse Model of Neurotoxicity. J Neurochem 145(4), 299–311. [PubMed: 29315562]

Rhodes SL, Buchanan DD, Ahmed I, Taylor KD, Loriot MA, Sinsheimer JS, Bronstein JM, Elbaz A, Mellick GD, Rotter JI, Ritz B, 2014. Pooled analysis of iron-related genes in Parkinson's disease: association with transferrin. Neurobiol Dis 62, 172–178. [PubMed: 24121126]

Wang K, Li M, Hakonarson H, 2010. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res 38(16), e164. [PubMed: 20601685]

Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L, 2014. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol 13(10), 1045–1060. [PubMed: 25231526]

Xia J, Xu H, Jiang H, Xie J, 2015. The association between the C282Y and H63D polymorphisms of HFE gene and the risk of Parkinson's disease: A meta-analysis. Neurosci Lett 595, 99–103. [PubMed: 25863172]

Zhan X, Hu Y, Li B, Abecasis GR, Liu DJ, 2016. RVTESTS: an efficient and comprehensive tool for rare variant association analysis using sequence data. Bioinformatics 32(9), 1423–1426. [PubMed: 27153000]

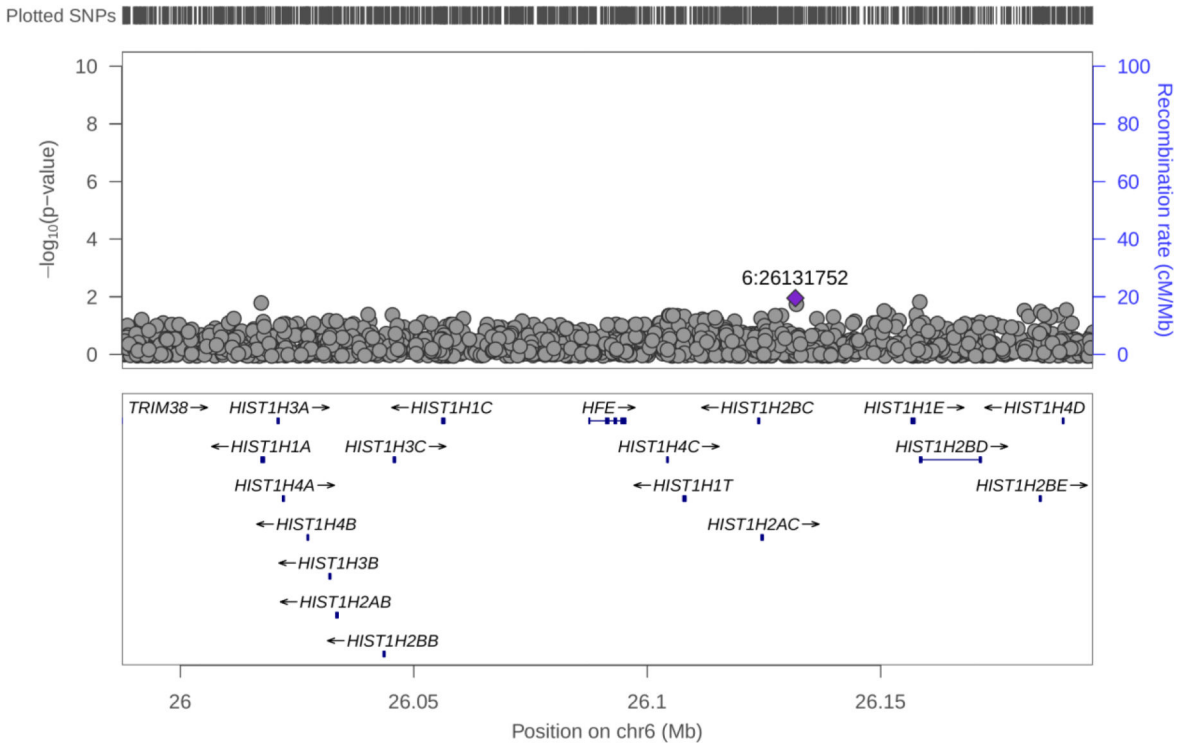

Figure 1.
HFE versus PD risk

Table 1.

Burden tests for *HFE* in the AMP-PD cohorts

Cohort	Burden test	All variants			Missense variants		
		Number of Variants	Number of Analyzed Variants	P-value	Number of Missense Variants	Number of Analyzed Variants	P-value
AMP-PD (PD n=1,647, Controls n=1,050)	Zeggini	54	47	0.5167	10	9	0.3644
	Fp	54	47	0.4510	10	9	0.1134
	CMC	54	47	0.2539	10	9	0.3644
	Madson-Browning	54	47	0.2940	10	9	0.2959
	SKAT	54	47	0.8299	10	9	0.8266
	SKAT-O	54	47	0.6310	10	9	0.3425

Abbreviations: SKAT: Sequence kernel association test, SKAT-O: Sequence kernel association test optimized, CMC: combined multivariate and collapsing