Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2022 November 14.

Published in final edited form as:

Neurobiol Aging. 2021 November ; 107: 178–180. doi:10.1016/j.neurobiolaging.2021.06.005.

Analysis of PTRHD1 common and rare variants in European patients with Parkinson's disease

Yuri L. Sosero[a,b,*], **Sara Bandres-Ciga**[c], **Ziv Gan-Or**[a,b,d], **Lynne Krohn**[a,b] **IPDGC**

[a]Department of Human Genetics, McGill University, Montréal, QC, Canada

[b]Montreal Neurological Institute, McGill University, Montréal, QC, Canada

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

[d]Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada

Abstract

Three studies in Iranian and African families identified three different variants in the peptidyl-tRNA hydrolase domain containing 1 gene (*PTRHD1*) in patients affected by parkinsonism with intellectual impairment. In the current study, our objective was to investigate whether *PTRHD1* variants are associated with Parkinson's disease (PD) risk and age at onset (AAO). To evaluate the association between *PTRHD1* and PD risk, we analyzed whole genome sequencing data of 1647 PD cases and 1050 healthy controls, as well as genome-wide imputed genotyping data on 14,671 PD cases and 17,667 controls, all of European ancestry. Furthermore, we examined the association of *PTRHD1* with PD risk and AAO using summary statistics data from the most recent PD genome-wide association study meta-analyses. Our results show no association between *PTRHD1* and PD risk or AAO. We conclude that *PTRHD1* does not play a major role in PD in the European population. Further large-scale studies including subjects with different ancestry and family trios are required.

Keywords

PTRHD1; Parkinson's disease; Familial parkinsonism; Burden test; SKATO; GWAS

[*]Corresponding author at: 1033 Pine Avenue, West, Ludmer Pavilion, room 308-309, Montreal, QC, H3A 1A1, Tel.: +1-438-979-5052. yuri.sosero@mail.mcgill.ca (Y.L. Sosero).

CRediT authorship contribution statement

Yuri L Sosero: Conceptualization, Methodology, Validation, Formal analysis. Investigation, Data curation. Writing - original draft. Writing - review & editing. Visualization, Project administration. **Sara Bandres-Ciga:** Validation, Formal analysis. Investigation, Data curation. Writing - review & editing. **Ziv Gan-Or:** Conceptualization, Methodology, Validation, Investigation, Writing - original draft. Writing - review & editing. Resources, Funding acquisition. Project administration. **Lynne Krohn:** Conceptualization, Methodology, Validation, Formal analysis. Investigation, Data curation, Writing - original draft. Writing - review & editing. Visualization, Project administration.

Disclosure statement

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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

1. Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder resulting from a variety of genetic and nongenetic risk factors. Three family studies nominated peptidyl-tRNA hydrolase domain containing 1 gene (*PTRHD1*) as a possible disease-causing gene in atypical parkinsonism Jaberi et al., 2016; Khodadadi et al., 2017; Kuipers et al., 2018). In particular, a study on Iranian families identified the homozygous *PTRHD1* variant c.l57C>T (p.His53Tyr) in two siblings with cognitive impairment and successive development of parkinsonism at the third/fourth decade of life (Khodadadi et al., 2017). Likewise, two independent studies found that homozygous carriers of the *PTRHD1* variant c.155G>A (p.Cys52Tyr) in an Iranian family (Jaberi et al., 2016) and of the homozygous deletion (c.l69_196del, p.Ala57Argfs*26) in an African family, showed similar symptoms, including intellectual disability and early onset parkinsonism (onset at the third decade of life for the Iranian family and first/third decade for the African family) (Kuipers et al., 2018).

Despite these findings, no large-scale study has been performed before in the European population to investigate the relationship between *PTRHD1* and PD. To test this potential association, we examined the *PTRHD1* region in Europeans using whole genome sequencing (WGS) from the Accelerating Medicines Partnership - Parkinson's disease initiative (AMP-PD; www.amp-pd.org) and large-scale genome-wide association study (GWAS) data from the International Parkinson's Disease Genomics Consortium (IPDGC).

2. Methods

To investigate the association of *PTHRD1* common and rare variants with PD, we performed Fisher exact test and logistic regression in WGS AMP-PD data including 1647 PD cases and 1050 healthy controls of European descent (Supplementary Table S7). We repeated the analyses on a large European cohort using individual-level GWAS data including 14,671 PD cases and 17,667 controls from IPDGC (Supplementary Table S7). Logistic regression was adjusted for age, sex, and principal components. Summary statistics from the most recent GWAS meta-analysis on PD risk previously described (Nalls et al., 2019) excluding 23andMe data were also examined. In particular, the meta-analysis consisted of 15,056 PD cases, 18,618 UK Biobank proxy-cases (i.e., subjects with a first degree relative with PD) and 449,056 controls, all of European ancestry. As individuals carrying *PTRHD1* variants displayed early onset parkinsonism we also assessed the most recent meta-analysis on PD AAO previously described (Blauwendraat et al., 2020), including 17,996 PD patients of European ancestry. Finally, as the *PTRHD1* variants analyzed in the reported family studies were all rare, we evaluated the enrichment of *PTRHD1* rare variants in WGS data using burden and kernel tests. The analyses on rare variants were first performed on all *PTRHD1* rare variants that passed quality control, and then repeated only on the nonsynonymous rare variants. Bonferroni correction for multiple comparisons was applied as needed. Association analyses were performed using PLINK vl.9 (Chang et al., 2015) and burden analyses using software package RVTESTS v.2.1.0 (Zhan et al., 2016).

WGS data, processing and quality control pipelines can be found atwww.amp-pd.org. Quality control for GWAS data was performed as previously described (Nalls et al.,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2019). For both genotyping and sequencing datasets, *PTRHD1* region was annotated using ANNOVAR. To specifically analyze rare variants from WGS data, we selected variants with a minor allele frequency (MAF) <0.01.

3. Results

After Bonferroni correction, Fisher exact test and logistic regression showed no association between *PTRHD1* variants and PD both using WGS and GWAS individual-level data (Supplementary Tables S1-S4). The analysis of the PD meta-analysis summary statistics confirmed such lack of association of *PTRHD1* with PD risk (Fig. 1) as well as with PD AAO (Fig. 1). Finally, burden and kernel tests in WGS data did not show an enrichment of *PTRHD1* rare variants in PD, compared to controls (Supplementary Table S5). As the previously identified *PTRHD1* variants were all homozygous, we also assessed the number of homozygous/compound heterozygous carriers of at least one *PTRHD1* coding variant, showing similar proportions of such carriers between PD patients and controls (Supplementary Table S6). Of note, the three *PTRHD1* variants reported in the previous studies on Iranian and African families (Jaberi et al., 2016; Khodadadi et al., 2017; Kuipers et al., 2018) were not found in our dataset.

4. Discussion

Herein, we did not find evidence for an association between *PTRHD1* and PD in the European population. There are several reasons that might explain the discrepancy between our results and the previous findings on *PTRHD1* in parkinsonian families (Jaberi et al., 2016; Khodadadi et al., 2017; Kuipers et al., 2018): 1) The findings from the family studies might not replicate on a large scale, suggesting that *PTRHD1* variants might be either extremely rare in PD or not associated at all; 2) *PTRHD1* carriers in the reported family studies manifested atypical parkinsonism with early-onset intellectual impairment, whereas our study was performed on patients with typical PD. Therefore, *PTRHD1* variants might be associated with rare forms of atypical parkinsonism, rather than typical PD; 3) The family studies were performed in Iranian and African subjects, whereas our study was performed in European patients. These ethnic differences might as well explain the discrepancy between our and the three previous family studies on *PTRHD1.*

In conclusion, our results do not provide evidence for an association between *PTRHD1* and PD in the European population. Larger studies on non-European ancestry populations and family trios are required to clarify the role of *PTRHD1* in PD and atypical parkinsonism.

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, and the National Institute of Environmental Health Sciences both 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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). This work utilized the computational resources of the NIH HPC Biowulf cluster (http://hpc.nih.gov). ZGO is supported by the Fonds de recherche du Québec - Santé (FRQS) Chercheurs-boursiers award, in collaboration with Parkinson Quebec, and by the Young Investigator Award by Parkinson Canada.

References

Blauwendraat C, Nalls MA, Singleton AB, 2020. The genetic architecture of Parkinson's disease. Lancet Neurol 19 (2), 170–178. [PubMed: 31521533]

Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ, 2015. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gi-gascience 4, 7.

Jaberi E, Rohani M, Shahidi CA, Nafissi S, Arefian E, Soleimani M, Moghadam A, Arzenani MK, Keramatian F, Klotzle B, Fan JB, Turk C, Steemers F, Elahi E, 2016. Mutation in ADORA1 identified as likely cause of early-onset parkinsonism and cognitive dysfunction. Mov Disord 31 (7), 1004–1011. [PubMed: 27134041]

Khodadadi H, Azcona LJ, Aghamollaii V, Omrani MD, Garshasbi M, Taghavi S, Tafakhori A, Shahidi GA, Jamshidi J, Darvish H, Paisan-Ruiz C, 2017. PTRHD1 (C2orf79) mutations lead to autosomal-recessive intellectual disability and parkinsonism. Mov Disord 32 (2), 287–291. [PubMed: 27753167]

Kuipers DJS, Carr J, Bardien S, Thomas P, Sebate B, Breedveld GJ, van Minkelen R, Brouwer RWW, van Ijcken WFJ, van Slegtenhorst MA, Bonifati V, Quadri M, 2018. PTRHD1 Loss-of-function mutation in an African family with juvenile-onset Parkinsonism and intellectual disability. Mov Disord 33 (11), 1814–1819. [PubMed: 30398675]

Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A, Bras J, Young E, von Coelln R, Simon-Sanchez J, Schulte C, Sharma M, Krohn L, Pihlstrom L, Siitonen A, Iwaki H, Leonard H, Faghri F, Gibbs JR, Hernandez DG, Scholz SW, Botia JA, Martinez M, Corvol JC, Lesage S, Jankovic J, Shulman LM, Sutherland M, Tienari P, Majamaa K, Toft M, Andreassen OA, Bangale T, Brice A, Yang J, Gan-Or Z, Gasser T, Heutink P, Shulman JM, Wood NW, Hinds DA, Hardy JA, Morris HR, Gratten J, Visscher PM, Graham RR, Singleton ABMe Research T, System Genomics of Parkinson's Disease, C., International Parkinson's Disease Genomics, C., 2019. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 18 (12), 1091–1102. [PubMed: 31701892]

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]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

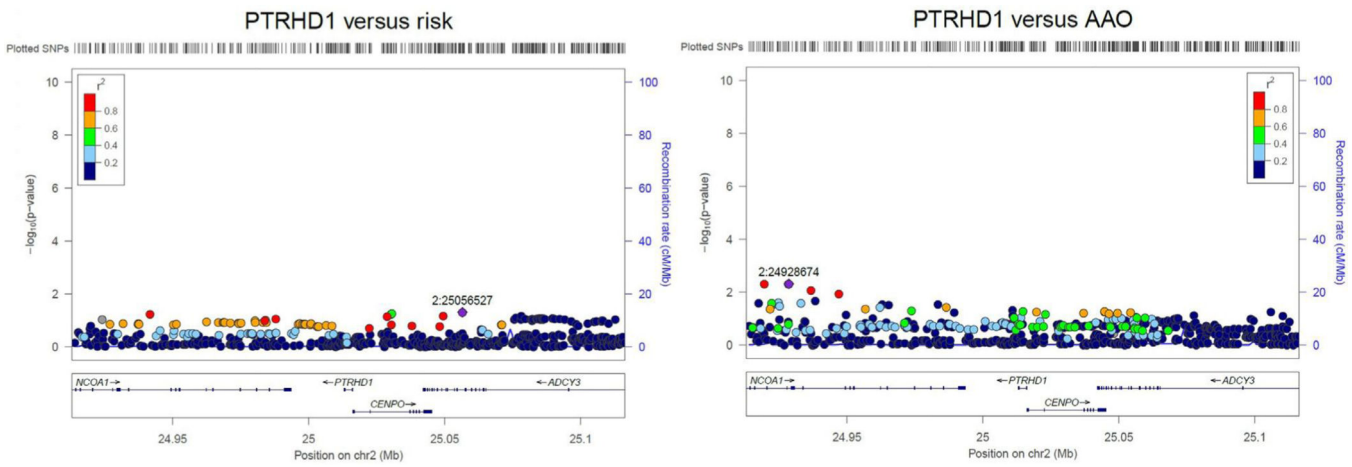

Fig. 1.

(A) Locus zoom plot of *PTRHD1* variants versus PD risk. (B) Locus zoom plot of *PTRHD1* variants versus PD AAO.

The position of the variants on the chromosome 2 (x axis) is plotted against the log10-scaled p-values (left y axis). The most strongly associated SNP is indicated by a purple diamond. Pairwise linkage disequilibrium scores are defined by different colors, explained by the legend on the upper right corner. The right vertical axis indicates the regional recombination rate (cM/Mb).

Abbreviations: chr, chromosome; cM, centimorgan; Mb, Megabase; PD, Parkinson's disease; SNP, single nucleotide polymorphism.