

# D130A variant on Parkinson 22-related CHCHD2 is predicted to have decreased protein movement

Hanna J. Jefcoat<sup>1</sup>, Cynthia L. Stenger<sup>2§</sup>, Luke Terwilliger<sup>3</sup>, Michele Morris<sup>4</sup>, Olivia Morris<sup>1</sup>

<sup>1</sup>Biology, University of North Alabama, Florence, Alabama, United States

<sup>2</sup>Mathematics, University of North Alabama, Florence, Alabama, United States

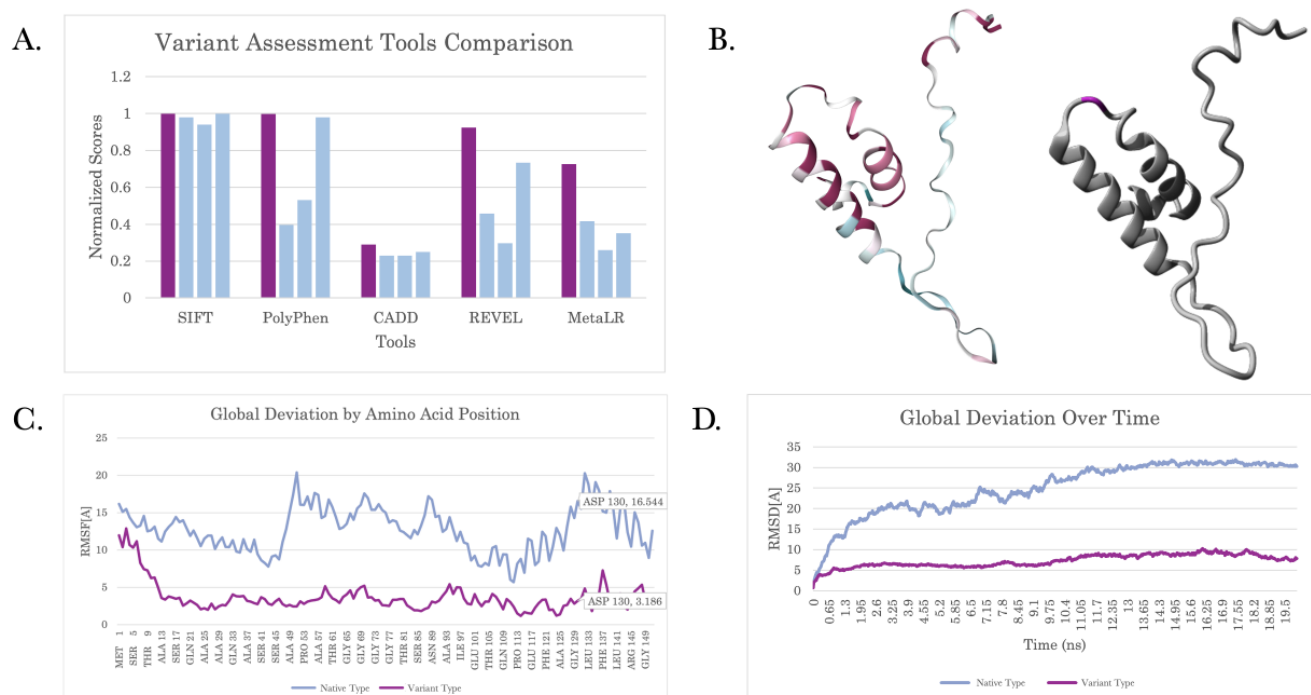
<sup>3</sup>Computer Science, University of North Alabama, Florence, Alabama, United States

<sup>4</sup>HudsonAlpha Institute for Biotechnology, Huntsville, Alabama, United States

§To whom correspondence should be addressed: clstenger@una.edu

## Abstract

Parkinson's disease is the second most common neurodegenerative disease which is caused by a lack of dopamine in the brain. Parkinson 22 is a form of Parkinson's disease caused by variations in the coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2) protein. This study investigates an aspartic acid-to-alanine swap on amino acid position 130 (D130A) of the CHCHD2 protein. We have employed protein modeling, conservation analysis, and molecular dynamics simulations to gain an understanding of the effects of the D130A variant on CHCHD2 protein structure and movement.



**Figure 1. Characterization of D130A:**

**A)** Analyzed pathogenicity using in silico predictors SIFT, PolyPhen-2, CADD Tools, REVEL, and Meta LR. All scores were normalized for comparison. D130A variant (purple) is ranked as more likely pathogenic than the known pathogenic variants (blue) of CHCHD2 (Ng & Henikoff, 2001; Adzhubei et al., 2010; Rentzsch et al., 2021; Ioannidis et al., 2016; Willer et al., 2010). **B)** Amino acid conservation analysis of the 150 species (left). YASARA homology modeling of CHCHD2 protein (right) (Ashkenazy et al, 2016)(Land et al. 2016). **C)** The carbon alpha root-mean-squared fluctuation (RMSF) of each amino acid throughout the 20 ns simulation. **D)** 20 nanoseconds (ns) of molecular dynamic simulation for the CHCHD2 protein shows the root-mean-squared deviation (RMSD) of the average carbon alpha from the initial structure to each time point of the simulation.

## Description

Parkinson 22 is a form of Parkinson's Disease caused by mutations on the *CHCHD2* gene; however, few *CHCHD2* variants are characterized (Kee et al., 2021). *CHCHD2* is a mitochondrial protein with functions expressed all over the body. This gene is strongly expressed in dopaminergic neurons of the brain, including the substantia nigra. *CHCHD2* plays a crucial role in regulating mitochondrial electron flow while also regulating cell migration and differentiation, mitochondrial cristae structure, and apoptosis. Because Parkinson's disease is caused by a lack of dopamine in the substantia nigra, mutations of the *CHCHD2* gene can cause Parkinson 22.

The variant on amino acid position 130 which has a swap from aspartic acid-to-alanine was studied for characterization. All nonpolar amino acid swaps on this gene are classified as pathogenic except for one; D130A is the only polar to nonpolar swap left unclassified (Landrum et al., 2016). This variant was also found in the CHCH domain, which is a functional region (Apweiler et al., 2004).

Amino acid position 130 was conserved in 150/150 species, indicating it is likely to serve an important role in the structure and/or function of the *CHCHD2* protein (Ashkenazy et al, 2016). A study on the effect of the D130A swap in a different gene influencing influenza found that this swap had a pathogenic effect (Staller et al., 2021). The D130A swap on this gene and D130A on *CHCHD2* are both located near the end of an alpha helix.

Additionally, the D130A variant has similar pathogenicity scores to the known pathogenic variants. *D130A* was ranked as more likely pathogenic than all other known pathogenic variants. (Ng & Henikoff, 2001; Adzhubei et al., 2010; Rentzsch et al., 2021; Ioannidis et al., 2016; Willer et al., 2010).

An aspartic acid-to-alanine swap (D212A) in bacteriorhodopsin, a proton-pumping protein used by Archaea, caused the protein to become sensitive to light and stop proton pumping (Mogi et al., 1988). This finding is consistent with the results of the *CHCHD2* D130A molecular dynamics simulations. The molecular dynamics simulations showed that this variant greatly reduced protein movement, indicating the D130A is likely to negatively affect protein function.

According to these findings, the D130A variant of *CHCHD2* has a high likelihood of being pathogenic. D130A is a polar to non-polar swap, which is the same as the known pathogenic variants. Many pathogenicity predictors indicate D130A as being pathogenic, and it is ranked as more pathogenic than the known pathogenic variants as shown in Figure 1. The swap is located in the CHCH functional region and is conserved in 150/150 species. There was a significant decrease in protein movement in the variant type; an RMSD of 13.36Å was measured at D130A with movement across the entire protein. This reveals that D130A potentially has a significant effect on protein function.

## Methods

*CHCHD2* was chosen for study because it is the only gene associated with Parkinson 22 (Landrum et al., 2016). A variant of unknown significance (VUS) from *CHCHD2* was chosen from analyzing different pathogenicity predictors (SIFT, PolyPhen-2, CADD Tools, REVEL, and Meta LR). All scores were normalized for comparison. Slow homology protein models of both the native type and variant type of the protein were constructed from a FASTA file retrieved from Uniprot. These models were used to run molecular dynamics simulation (mds) using YASARA protein modeling to assess how the variant affects protein functionality.

## References

- Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR. 2010. A method and server for predicting damaging missense mutations. *Nat Methods* 7(4): 248-9. PubMed ID: [20354512](#)
- Apweiler R, Bairoch A, Wu CH, Barker WC, Boeckmann B, Ferro S, et al., Yeh LS. 2004. UniProt: the Universal Protein knowledgebase. *Nucleic Acids Res* 32(Database issue): D115-9. PubMed ID: [14681372](#)
- Ashkenazy H, Abadi S, Martz E, Chay O, Mayrose I, Pupko T, Ben-Tal N. 2016. ConSurf 2016: an improved methodology to estimate and visualize evolutionary conservation in macromolecules. *Nucleic Acids Res* 44(W1): W344-50. PubMed ID: [27166375](#)
- Ioannidis NM, Rothstein JH, Pejaver V, Middha S, McDonnell SK, Baheti S, et al., Sieh W. 2016. REVEL: An Ensemble Method for Predicting the Pathogenicity of Rare Missense Variants. *Am J Hum Genet* 99(4): 877-885. PubMed ID: [27666373](#)
- Kee TR, Espinoza Gonzalez P, Wehinger JL, Bukhari MZ, Ermekbaeva A, Sista A, et al., Woo JA. 2021. Mitochondrial *CHCHD2*: Disease-Associated Mutations, Physiological Functions, and Current Animal Models. *Front Aging Neurosci* 13: 660843. PubMed ID: [33967741](#)

Land H, Humble MS. 2018. YASARA: A Tool to Obtain Structural Guidance in Biocatalytic Investigations. *Methods Mol Biol* 1685: 43-67. PubMed ID: [29086303](#)

Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al., Maglott DR. 2018. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res* 46(D1): D1062-D1067. PubMed ID: [29165669](#)

Mogi T, Stern LJ, Marti T, Chao BH, Khorana HG. 1988. Aspartic acid substitutions affect proton translocation by bacteriorhodopsin. *Proc Natl Acad Sci U S A* 85(12): 4148-52. PubMed ID: [3288985](#)

Ng PC, Henikoff S. 2001. Predicting deleterious amino acid substitutions. *Genome Res* 11(5): 863-74. PubMed ID: [11337480](#)

Pérez-Palma E, Gramm M, Nürnberg P, May P, Lal D. 2019. Simple ClinVar: an interactive web server to explore and retrieve gene and disease variants aggregated in ClinVar database. *Nucleic Acids Res* 47(W1): W99-W105. PubMed ID: [31114901](#)

Rentsch P, Schubach M, Shendure J, Kircher M. 2021. CADD-Splice-improving genome-wide variant effect prediction using deep learning-derived splice scores. *Genome Med* 13(1): 31. PubMed ID: [33618777](#)

Staller E, Sheppard CM, Baillon L, Frise R, Peacock TP, Sancho-Shimizu V, Barclay WS. 2021. A natural variant in ANP32B impairs influenza virus replication in human cells. *J Gen Virol* 102(9). PubMed ID: [34524075](#)

Willer CJ, Li Y, Abecasis GR. 2010. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 26(17): 2190-1. PubMed ID: [20616382](#)

**Funding:** This work is supported by the National Science Foundation under Grant Number 2120918. Any opinions, findings, conclusions, or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation

**Author Contributions:** Hanna J. Jefcoat: conceptualization, data curation, formal analysis, investigation, methodology, writing - original draft, writing - review editing. Cynthia L. Stenger: project administration, supervision, writing - review editing. Luke Terwilliger: writing - review editing, data curation. Michele Morris: writing - review editing. Olivia Morris: writing - review editing.

**Reviewed By:** Jenna Ridlen

**History:** Received November 21, 2023 **Revision Received** December 12, 2023 **Accepted** December 15, 2023 **Published Online** December 22, 2023 **Indexed** January 5, 2024

**Copyright:** © 2023 by the authors. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Citation:** Jefcoat, HJ; Stenger, CL; Terwilliger, L; Morris, M; Morris, O (2023). D130A variant on Parkinson 22-related CHCHD2 is predicted to have decreased protein movement. *microPublication Biology*. [10.17912/micropub.biology.001093](#)