Neurobiology of Aging 74 (2019) 236.e7–236.e8

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

CHCHD2 mutational screening in Brazilian patients with familial Parkinson's disease

Danielle D. Voigt [a,b,1], Caroline M. Nascimento [c,1], Ritiele B. de Souza [a], Pedro H. Cabello Acero [a,b,d], Mário Campos Júnior [d], Camilla P. da Silva [c], João S. Pereira [e], Ana Lucia Rosso [f], Marco A. Araujo Leite [g], Luiz Felipe R. Vasconcellos [h,i], Marcus V. Della Coletta [j], Delson J. da Silva [k,l], Denise H. Nicaretta [m,n], Andressa P. Gonçalves [c], Jussara M. dos Santos [c], Veluma Calassara [c], Cíntia B. Santos-Rebouças [c], Márcia M.G. Pimentel [c,*]

[a] *Laboratory of Genetics, School of Health Science, University of Grande Rio, Rio de Janeiro, Brazil*
[b] *Postgraduate Program in Translational Biomedicine, University of Grande Rio, Rio de Janeiro, Brazil*
[c] *Department of Genetics, Institute of Biology Roberto Alcantara Gomes, State University of Rio de Janeiro, Rio de Janeiro, Brazil*
[d] *Human Genetics Laboratory, Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil*
[e] *Movement Disorders Section, Neurology Service, Pedro Ernesto University Hospital, State University of Rio de Janeiro, Rio de Janeiro, Brazil*
[f] *University Hospital Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil*
[g] *Division of Neurology, Movement Disorders Unit, Hospital Antônio Pedro, Fluminense Federal University, Brazil*
[h] *Institute of Neurology Deolindo Couto, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil*
[i] *Federal Hospital of Servidores do Estado, Rio de Janeiro, Brazil*
[j] *University Hospital Getúlio Vargas, Federal University of Amazonas, Amazonas, Brazil*
[k] *Neuroscience Core, Hospital Clinics, Federal University of Goiás, Brazil*
[l] *Integrated Neurosciences Institute, Goiás, Brazil*
[m] *Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro, Brazil*
[n] *University Hospital Gaffrée and Guinle, Federal University of the State of Rio de Janeiro, Brazil*

ARTICLE INFO

Article history:
Received 21 May 2018
Accepted 21 September 2018
Available online 27 September 2018

Keywords:
Parkinson's disease
CHCHD2
ADPD
Familial PD
Brazilian

ABSTRACT

Robust evidence on the involvement of genetic factors in the etiology of Parkinson's disease (PD) expands our knowledge about monogenic causes that contribute for this important neurodegenerative disorder. Mutations in the *CHCHD2* gene have been linked to autosomal dominant forms of PD, although there is still lack of evidence for *CHCHD2* variants leading to the disease in mixed populations as those from South America. To assess the contribution of *CHCHD2* as a causal factor for familial PD in Brazil, one of the most heterogeneous populations in the world, we conducted the first molecular analysis of the *CHCHD2* gene in a cohort of 122 index cases from Brazilian families with autosomal dominant forms of PD. Genomic DNA was isolated from peripheral blood and the 4 exons of the *CHCHD2* gene, and their intron-exon boundaries were analyzed by bidirectional Sanger sequencing. No pathogenic or risk variants were found, suggesting that genetic variants of *CHCHD2* are not a common cause of familial PD in Brazilian patients.

1. Introduction

Despite the obscure etiology of Parkinson's disease (PD, MIM 168600), the accumulated evidence supports an extensive genetic contribution for this complex disorder, and novel PD-related genes have provided further insights into the pathophysiology of the disease (Deng et al., 2018). The coiled-coil-helix-coiled-coil-helix domain-containing 2 gene (*CHCHD2*), located at 7q11.2, encodes a small mitochondrial protein involved in the biogenesis and regulation of the electron transport chain (Aras et al., 2015). The association between *CHCHD2* gene and PD was first observed in Japanese families (Funayama et al., 2015). Two missense mutations (182C>T, Thr61Ile, and 434G>A, Arg145Gln) and one splice-site mutation (300+5G>A) were found segregating with the disease

* Corresponding author at: Department of Genetics, Institute of Biology Roberto Alcantara Gomes, State University of Rio de Janeiro, Rua São Francisco Xavier 524, PHLC Sala 501F, 20550-013, Rio de Janeiro, Brazil. Tel.: +55 21 23340039; fax: +55 21 23340309.
E-mail address: pimentel@uerj.br (M.M.G. Pimentel).
[1] These authors contributed equally to this work.

0197-4580/$ – see front matter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.neurobiolaging.2018.09.026

in 4 Japanese genealogies with autosomal dominant forms of PD (ADPD). Important in vivo evidence of the pathological effects related to *CHCHD2* mutations came from functional analysis of *CHCHD2* using the transgenic *Drosophila* model (Tio et al., 2017). The researchers demonstrated that the variants Arg145Gln and Thr61Ile are pathogenic and cause protein dysfunction at different levels, promoting the deregulation of mitochondrial metabolism, which affects the survival and neuronal function. Also, was observed that *Drosophila* expressing mutant CHCHD2 proteins displayed characteristics as seen in patients with PD such as locomotor dysfunction.

Through subsequent studies, pathogenic or risk variants in the *CHCHD2* gene were also identified in a few patients with PD, although several analyses have failed to find mutations in the *CHCHD2* gene in probands from different populations (Supplementary Table 4). Nonetheless, there is no report focusing on the association between *CHCHD2* variants and PD in Latin America populations. Here, we performed the molecular analysis of the *CHCHD2* gene in a cohort of Brazilian probands with ADPD, aimed to investigate the contribution of the *CHCHD2* mutations for PD in Brazil.

2. Methods

The screening for mutations in *CHCHD2* was accomplished in 122 unrelated Brazilian patients (**41 women and 81men**; mean age 60.5 ± 11.1 years; mean age at onset 52.1 ± 12.0 years) with familial PD compatible with autosomal dominant inheritance pattern. PD was diagnosed according to clinical criteria of the United Kingdom Parkinson's Disease Society Brain Bank. Mutations in genes *SNCA*, *LRRK2*, *VPS35*, *and GBA* were previously excluded in these patients. The four exons and exon-intron boundaries of the *CHCHD2* gene were amplified through polymerase chain reaction, and purified amplicons were sequenced by the bidirectional Sanger method (Supplementary Tables 1, 2 and 3). The Institutional Ethics Committee approved the research, and informed consent was obtained from each participant.

3. Results

We did not find pathogenic or risk variants in the *CHCHD2* gene in 122 probands from Brazilian families with ADPD (Supplementary Fig. 1).

4. Discussion

The association of *CHCHD2* mutations/risk variants with PD, initially reported by Funayama et al (2015), was replicated in some data sets, but not in others (Supplementary Table 4), and in part, these controversial results may be due to ethnic differences. Overall, *CHCHD2* mutations appear to be rare and restricted to some genealogies, predominantly from Asian origin (Supplementary Table 4).

In the present survey, we analyzed the incidence of mutations in the *CHCHD2* gene in a representative cohort of probands with familial PD from Brazil, and pathogenic or risk variants were not found. To the best of our knowledge, our data represent the first findings in a South American population, whose ethnicity is represented by a complex miscegenation, and they are consistent with results from previous studies that also failed to detect *CHCHD2* mutations in patients with PD from other origins.

In conclusion, the absence of pathogenic or risk variants in the *CHCHD2* gene in our cohort reveals that *CHCHD2* mutations might not be a common cause of familial PD in Brazil, as also observed by us in relation to the *VPS35* gene (Abreu et al., 2016). Although the majority of the genetic component for PD still remains to be discovered, PD-susceptibility genes provide new insights into the etiology of the disease and should be further explored (Deng et al., 2018).

Disclosure statement

The authors declare no conflicts of interest.

Acknowledgements

The authors thank the patients and their families for their cooperation and the PDTIS/FIOCRUZ for DNA sequencing. This work was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq - Brazil)(Finance Code 305239/2017-1) and by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES - Brazil) (Finance Code 001).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.09.026.

References

Abreu, G. de M., Valença, D.C., Campos, M., da Silva, C.P., Pereira, J.S., Araujo Leite, M.A., Rosso, A.L., Nicaretta, D., Vasconcellos, L.F., da Silva, D.J., Della Coletta, M.V., dos Santos, J.M., Gonçalves, A.P., Santos-Rebouças, C.B., Pimentel, M.M.G., 2016. Autosomal dominant Parkinson's disease: incidence of mutations in LRRK2, SNCA, VPS35 and GBA genes in Brazil. Neurosci. Lett. 635, 67–70.

Aras, S., Bai, M., Lee, I., Springett, R., Hüttemann, M., Grossman, L.I., 2015. MNRR1 (formerly CHCHD2) is a bi-organellar regulator of mitochondrial metabolism. Mitochondrion 20, 43–51.

Deng, H., Wang, P., Jankovic, J., 2018. The genetics of Parkinson disease. Ageing Res. Rev. 42, 72–85.

Funayama, M., Ohe, K., Amo, T., Furuya, N., Yamaguchi, J., Saiki, S., Li, Y., Ogaki, K., Ando, M., Yoshino, H., Tomiyama, H., Nishioka, K., Hasegawa, K., Saiki, H., Satake, W., Mogushi, K., Sasaki, R., Kokubo, Y., Kuzuhara, S., Toda, T., Mizuno, Y., Uchiyama, Y., Ohno, K., Hattori, N., 2015. CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. Lancet Neurol. 14, 274–282.

Tio, M., Wen, R., Lim, Y.L., Zukifli, Z.H.B., Xie, S., Ho, P., Zhou, Z., Koh, T.W., Zhao, Y., Tan, E.K., 2017. Varied pathological and therapeutic response effects associated with CHCHD2 mutant and risk variants. Hum. Mutat. 38, 978–987.