Smoking and variants related to nicotine enhancement at *CYP1B1, ABCB1* and *MAOB* and the onset of symptoms of Machado-Joseph disease

A. C. Martins 1,2, J. S. Pinheiro2,3, L. Szinwelski2,3, E.R. Cidade2,4, D. Santin2,4, K. C. Santana2,4, L.D. Proença2,5 , B. A. Araújo2,6, M. L. Saraiva-Pereira1,2,7,8, L. B. Jardim1,2,4,7,9

1 Programa de Pós-Graduação em Genética e Biologia Molecular, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

2 Centros de Pesquisa Clínica e Experimental, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

3 Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

4 Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

5 Faculdade de Biologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

6 Curso de Biomedicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

7 Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

8 Departamento de Bioquímica, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

9 Departamento de Medicina Interna, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

**ABSTRACT:**

**Background**: Machado-Joseph disease (SCA3/MJD), caused by an expanded CAG repeat (CAGexp) at ATXN3, presents with a still unexplained variability in the age at onset (AO) of symptoms. Smoking habits might influence this variability, as occurs in other neurodegenerative diseases such as Huntington and Parkinson diseases [1,2]. We aimed to test if smoking alone or in interaction with variants at genes related to nicotine metabolism/signaling *CYP1B1, ABCB1* and *MAOB,* might impact the AO of SCA3/MJD.

**Methods:** a questionnaire on tobacco consumption was applied to adult symptomatic patients and unrelated controls. AO and CAGexp were previously determined. SNPs rs1056836 (*CYP1B1*), rs1045642 (*ABCB1*) and rs1799836 (*MAOB*) were genotyped. AO of subgroups were compared, adjusting the CAGexp to 75 repeats (p<0.05).

**Results:** there were 70/179 and 34/100 smokers among SCA3/MJD subjects and controls (p=0.610). The mean (SD) AO of SCA3/MJD who were and who were not smokers, were of 36.65 (10.78) and 34.52 (10.52) years (p=0.056). The sample necessary for this effect size of 2.13 years to become significant was estimated to be 375 SCA3/MJD symptomatic carriers. The enhancing nicotine alleles in our candidate genes seemed to increase this protectiveness: the AO of SCA3/MJD smokers were of 37.39 (10.08) and 25.43 (10.36) years in carriers and non-carriers of C at rs1056836 (*CYP1B1*), of 36.29 (10.73) and 34.92 (10.93) years in carriers and non-carriers of T at rs1045642 (*ABCB1*), and of 47.67 (6.95) and 36.14 (9.84) years in female carriers and non-carriers of G at  rs1799836 (*MAOB*). However, the number of carriers of the minor alleles were quite small, and nominal significances were not achieved again.

**Discussion:** Although tobacco consumption per se might have a small effect over the SCA3/MJD AO, this effect might be uncovered by the interaction of smoking with variants of genes related to increased effects of nicotine. Since smoking habit and the minor alleles of these genes were all uncommon in our population, we did not achieve power to confirm this hypothesis that should be tested in a larger cohort of this disease.

References:

1. Rose KN, Schwarzschild MA, Gomperts SN. (2024) Clearing the Smoke: What Protects Smokers from Parkinson's Disease? Mov Disord 39(2):267-272
2. Wang M, Liu D, Yang S, Li Y, Lian X. Smoking, alcohol consumption, and age at onset of Huntington's disease: a Mendelian randomization study. Parkinsonism Relat Disord. (2022) Apr;97:34-38.