

# Genome-wide association study of pain in Parkinson's disease implicates *TRPM8* as a risk factor

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## Letter to the Editor: New Observations

Chronic pain affects 60-85% of people with Parkinson's disease (PD) and has a strong negative effect on quality of life.<sup>1</sup> Genetic factors are significantly associated with a variety of chronic pain conditions.<sup>2</sup> Identifying additional genetic modifiers of pain in people with Parkinson's is of high scientific and clinical interest and could open avenues for novel treatments. Here, we report the results of the first Genome Wide Association Study (GWAS) of pain in PD.

Parkinson's patients were recruited from the UK Parkinson's Pain Study which included patients from the Tracking Parkinson's and the Oxford Parkinson's Disease Centre (OPDC) cohorts. The clinical assessment of pain in these patients has been previously reported.<sup>1</sup> PD patients were stratified into two groups that represented individuals with no/low pain (McGill score < 3 and VAS severity < 2), and high pain (McGill Score  $\geq$  3 and VAS severity  $\geq$  2).

DNA extracted from each sample was genotyped using either the Illumina Human ExomeCore-12 v1.1 array (Tracking Parkinson's) or the InfiniumCoreExome-24 v1.1 (OPDC). Genotype data from both cohorts underwent the same conventional processing, QC and imputation procedures as described elsewhere.<sup>3</sup>

We performed a GWAS of 6,655,232 autosomal SNPs that compared a total of 898 patients with Parkinson's who were classed as suffering high levels of pain to 420 Parkinson's patients who were not experiencing pain. After including covariates for age, gender and ancestry in the association analysis there was no evidence of genomic inflation attributable to population stratification ( $\lambda=1.00$ ).

This analysis identified 2 SNPs (rs11563208 and rs12465950) that were associated with pain in PD at genome wide significance ( $p=1.45E-09$ ; O.R. 1.78 and  $p=9.30E-09$ ; O.R. 1.71 respectively) (Figure 1). The genotypes of these SNPs were strongly correlated ( $r^2=0.85$ ) and are located at the gene encoding the human transient receptor potential cation channel, subfamily M, member 8 (*TRPM8*) on chromosome 2q37.1, with rs11563208 being a synonymous variant located within exon 22 and rs120465950 intronic. SNPs within *TRPM8* are established risk factors for migraine and headaches at genome-wide significance.<sup>4</sup> Using

rs10166942 as a marker for the genetic association with migraine,<sup>4</sup> conditional association analysis of pain in PD confirmed the strong association at rs11563208 (OR=1.81, p=4.2E-08), supporting its independence to the genetic risk for migraine. An assessment of published GWAS data did not identify the lead SNPs at the *TRPM8* locus to be associated with any other pain phenotype.<sup>5</sup>

TRPM8 has several reported functions, most notably as a cold/menthol thermoreceptor and is expressed in dorsal horn neurons.<sup>6</sup> Genetic variants at this locus are also strongly associated with migraine susceptibility,<sup>4</sup> however, we note that our conditional analysis implies that these variants are independent of those associated with pain in PD in our analysis. This suggests the role of TRPM8 in PD pain may be different mechanistically to that of migraine. TRPM8 has been previously linked to chronic pain in animal models and research is ongoing to identify compounds that effectively target TRPM8, with numerous antagonists being patented by pharmaceutical companies.<sup>6</sup> Interestingly, cannabinoid ligands, compounds which have demonstrated efficacy as analgesic agents, have been shown to antagonise the TRPM8 receptor.<sup>7</sup> Indeed some authors have termed TRPM8 and other related TRP channels as ionotropic cannabinoid receptors, suggesting that cannabinoids may be worth pursuing as treatments for PD pain.

In conclusion, we report the first genome-wide significant evidence for association with pain susceptibility in PD, which implicates the gene *TRPM8*. The large body of evidence implicating this gene with migraine and chronic pain has already resulted in this gene being a pharmacologic target, and together with its known relationship with cannabinoids, opens novel therapeutic opportunities for this currently poorly managed symptom.

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2 Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3 Manuscript: A. Writing of the first draft, B. Review and Critique.

## Conflicts of Interest

The authors have no potential conflicts of interest.

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Huw Morris is employed by UCL. In the last 12 months he reports paid consultancy from Biogen, UCB, Abbvie, Denali, Biohaven; lecture fees/honoraria from Biogen, UCB, C4X Discovery, GE-Healthcare, Wellcome Trust, Movement Disorders Society; Research Grants from Parkinson's UK, Cure Parkinson's Trust, PSP Association, CBD Solutions, Drake Foundation, Medical Research Council. Dr Morris is a co-applicant on a patent application related to C9ORF72 - Method for diagnosing a neurodegenerative disease (PCT/GB2012/052140)

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## References

1. Silverdale MA, Kobylecki C, Kass-Iliyya L, et al. A detailed clinical study of pain in 1957 participants with early/moderate Parkinson's disease. *Parkinsonism Relat Disord* 2018;56:27-32.
2. Zorina-Lichtenwalter K, Parisien M, Diatchenko L. Genetic studies of human neuropathic pain conditions: a review. *Pain* 2018;159:583-94.
3. Tan MMX, Malek N, Lawton MA, et al. Genetic analysis of Mendelian mutations in a large UK population-based Parkinson's disease study. *Brain* 2019;142:2828-44.
4. Gormley P, Anttila V, Winsvold BS, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nature genetics* 2016;48:856-66.
5. MacArthur J, Bowler E, Cerezo M, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* 2017;45:D896-D901.
6. Weyer AD, Lehto SG. Development of TRPM8 antagonists to treat chronic pain and migraine. *Pharmaceuticals* 2017;10:1-9.
7. Muller C, Morales P, Reggio PH. Cannabinoid Ligands Targeting TRP Channels. *Frontiers in Molecular Neuroscience* 2019;11:1-15.



## Figure Legend

**Figure 1:** Manhattan plot of  $-\log_{10}$  SNP p-values from a meta-analysis of high pain (n=898) vs low pain (n=420). Red and blue lines represent the thresholds for genome-wide ( $P < 5E-08$ ) and suggestive ( $P < 1E-06$ ) significance respectively.