

ORCA - Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:https://orca.cardiff.ac.uk/id/eprint/130355/

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Williams, Nigel M., Hubbard, Leon, Sandor, Cynthia, Webber, Caleb, Hendry, Hannah, Lawton, Michael, Carroll, Camille, Chaudhuri, K. Ray, Morris, Huw, Hu, Michele T., Grosset, Donald G., Kobylecki, Christopher and Silverdale, Monty 2020. Genome-wide association study of pain in Parkinson's disease implicates TRPM8 as a risk factor. Movement Disorders 35 (4), pp. 705-707. 10.1002/mds.28001

Publishers page: http://dx.doi.org/10.1002/mds.28001

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



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

Nigel M. Williams, BSc, PhD,^{1*} Leon Hubbard, BSc, PhD,^{1*} Cynthia Sandor, BSc, PhD,² Caleb Webber, BSc, PhD,² Hannah Hendry, BSc,¹ Michael Lawton, M.Phil,³ Camille Carroll, MD, PhD,⁴ K Ray Chaudhuri, DSc, FRCP, MD,⁵ Huw Morris, PhD, FRCP,⁶ Michael T. Hu, PhD, FRCP,² Donald G. Grosset, BSc, MD,⁷ Christopher Kobylecki, MBChB, PhD,⁸ and Monty Silverdale, MD, PhD,⁸ on behalf of the UK Parkinson's Pain Study.

¹Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom

²Division of Neurology, Nuffield Department of Clinical Neurosciences, Oxford University, United Kingdom

³Dept. of Population Health Sciences, Bristol Medical School, University of Bristol, United Kingdom

⁴University of Plymouth and University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom.

⁵Dept. Basic and Clinical Neuroscience, The Maurice Wohl Clinical Neuroscience Institute,

King's College and King's College Hospital, London, United Kingdom

⁶Department of Clinical Neuroscience, UCL, Institute of Neurology, United Kingdom

⁷Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, United Kingdom

⁸Department of Neurology, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, United Kingdom

*joint first author

Corresponding author

Dr Monty Silverdale

Department of Neurology.

Salford Royal NHS Foundation Trust

Manchester Academic Health Science Centre

University of Manchester

Manchester. M6 8HD

UK

Tel: +44 (0)161 2062574

Email: monty.silverdale@manchester.ac.uk

Running title: GWAS implicates TRPM8 in PD pain

Word count: 596

Number of characters in title: 94

Number of characters in running title: 32

Key words: Pain; Parkinson's disease; nonmotor; GWAS; TRPM8, cannabinoids

Number of Figures/Tables: 1

Financial Disclosures / conflicts of interest relevant to manuscript: none

Funding sources of the study: This work was funded by Parkinson's UK (grant numbers J1101 and K1301). The funding source had no other involvement in the study.

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. Genetic factors are significantly associated with a variety of chronic pain conditions. 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. 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 >= 3 and VAS severity >= 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.³

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 (λ =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 (r²=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.⁴ Using

rs10166942 as a marker for the genetic association with migraine,⁴ 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.⁵

TRPM8 has several reported functions, most notably as a cold/menthol thermoreceptor and is expressed in dorsal horn neurons.⁶ Genetic variants at this locus are also strongly associated with migraine susceptibility,⁴ 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.⁶ Interestingly, cannabinoid ligands, compounds which have demonstrated efficacy as analgesic agents, have been shown to antagonise the TRPM8 receptor.⁷ 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.

Acknowledgements

The authors would like to acknowledge the help of the UK Parkinson's Pain Study Collaboration

Principal Investigators:

C.Borland, A.Graham, S.Guptha, T.Ward, P.Worth, P.Sarda, W.Dwornik, G.Mamutse, J.Hindle, S.Jones, A.Church, R.Athey, D.Bathgate, N.Archibald, N.Pavese, D.Burn, U.Nath, M.Carson, R.Walker, T.Foltynie, A.Misbahuddin, A.Schrag, S.Sveinbjornsdottir, Y.Adenwala, B.Boothman, J.George, A.O'Callahan, M.O'Neill, J.Raw, M.Steiger, M.Wilson, K.Amar, S.Arianayagam, Z.Hemsley, H.Roberts, J.Stern, T.Andrews, D.Paviour, J.Frost, V.Lyell, T.Harrower, R.Sheridan, P.Critchley, L.Sugathapala, N.Bajaj, J.Sharma, C.Clarke, S.Ellis, K.Nithi, N.Kock, Z.Dhakam, C.Ruffman, P.Tomlinson, T.Quinell, S.Molloy, A.Whone, O.Bandmann, E.Capps, R.Bland.

Research Nurses:

C.Downes, C.Vandor, J.Frost, D.Cooper, K.Dixon, R.Norton, M.Clarke, C.Hall, O.Olanrewaju, V.Hetherington, K.Blachford, S.Guptha, B.Bishop, D.Nesbitt, J.McEntee, F.Frenais, A.Hursey, E.Visentin, C.Edwards, J.Newman, r.james, E.Johnson, K.Ullyart, J.Brooke, I.Bataller, J.Rickett, T.Mahan, L.Craven, K.Powell, R.Humphries, B.Wilson, M.Trimmer, L.Whelan, A.McNichol, T.Fuller, L.Alderton, A.Henderson, P.Brown, V.Visentin, C.Parker, S.Large, H.Vanek, D.Wilson, A.Misbahuddin, F.Foster, S.Dube, E.Gunter, K.Amar, S.Dodds, G.Brown, G.Webster, P.Critchley, L.Foster, L.Dudgeon, K.Holmes, D.Nithi, K.K.Nithi, A.Donaldson, A.Dougherty, M.Misbahuddin, S.Atkinson, G.Carey, L.Catterall, D.Dellafera, C.Sunderland, A.Lyle, C.Sequeira, M.Hare, E.Ekins, K.Maitland, C.O'Reilly, M.Prabhakaran, P.Paterson, J.Connell, A.Pilcher, J.Birt, N.Vernon, T.McElwaine, M.Humphries, A.Lehn, T.Murphy, D.Critchley, M.Rolinsky, N.Temple, C.Brugaletta, S.Cable, D.Mills, S.Levy, E.Templeman, L.Wyatt, I.Massey, R.Innis, C.Ruffman, C.Schofield, E.Oughton, A.Davies, A.Lehn, M.Korley, N.Verstraelen, S.Morgan, W.Dwornik, J.Gilford, P.Aruldoss, A.Foster, C.Chaudhuri, L.Gethin, Y.Croucher, M.Williams, T.Roberts, R.Carson, R.Athey, V.Agarwal, P.Rachman, V.Ludley, T.Talbot, I.Inniss, R.Gentle, C.Hewitt, J.Stickley, E.White, K.Ward, S.Butler, S.Gallahawk, R.Fernandes, P.Zettergren, B.Tobin, K.Huyalt, U.Ullyart, E.Henderson, P.Forbes, M.Heywood, J.O'Brien, R.Rettergra, F.Bowring, S.Large, R.Roopun.

Author Contributions

Nigel Williams. 1A, 1B, 1C, 2A, 2B, 3A

Leon Hubbard. 1C, 2A, 2B, 3B

Cynthia Sandor. 1C, 3B

Caleb Webber. 1C, 3B

Hannah Hendry. 1C, 3B

Michael Lawton. 1C, 3B

Camille Carroll. 1C, 3B

Ray Chaudhuri. 1C, 3B

Huw Morris. 1C, 3B

Michele Hu. 1C, 3B

Donald Grosset. 1C, 3B

Christopher Kobylecki. 1A, 1B, 1C, 2C, 3B

Monty Silverdale: 1A, 1B, 1C, 2A, 2B, 3A.

- 1 Research project: A. Conception, B. Organization, C. Execution;
- 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.

Financial Disclosures for all authors (for the preceding 12 months)

Nigel Williams has no financial disclosures.

Leon Hubbard has no financial disclosures.

Cynthia Sandor has no financial disclosures.

Caleb Webber has no financial disclosures.

Hannah Hendry has no financial disclosures.

Michael Lawton is employed by a Parkinson's UK grant.

Camille Carroll has received meeting and consulting honoraria from UCB, GKC, Bial, Pfizer, Abidetex, EverPharma and Abbvie, as well as conference expenses from Bial.

Ray Chaudhuri has received consultancy honoraria from AbbVie, UCB, Sunovion, Pfizer, Jazz Pharma, GKC, Bial, Cynapsus, Novartis, Lobsor, Stada, Medtronic, Zambon, Profile, Sunovion. Meeting honoraria from AbbVie, Britannia, UCB, Mundipharma, Zambon, Novartis, Boeringer Ingelheim Neuroderm, Sunovion. Grants from Britania Pharmaceuticals, AbbVie, UCB, GKC, Bial, Aacdemic grants: EU, IMI EU, Horizon 2020, Parkinson's UK, NIHR, PDNMG, EU (Horizon 2020), Kirby Laing Foundation, NPF, MRC.

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)

Michele Hu has undertaken consultancies for Biogen and Roche. The Oxford Discovery Cohort was funded by Parkinson's UK and is supported by NIHR and DeNDRoN. Donald Grosset has received honoraria from Bial, UCB and Merz Pharma.

Christopher Kobylecki has received meeting and consulting honoraria from Bial and Abbvie as well as conference expenses from Bial and Merz.

Monty Silverdale has received meeting honoraria from UCB as well as conference expenses from Bial and Abbvie.

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 genomewide 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 -log10 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.