Published in final edited form as:

Ann Neurol. 2016 January ; 79(1): 159–161. doi:10.1002/ana.24527.

Is the *MC1R* variant p.R160W associated with Parkinson's?

Steven J Lubbe, PhD¹, Valentina Escott-Price, PhD², Alexis Brice, MD, PhD³, Thomas Gasser, MD, PhD⁴, John Hardy, PhD^{5,6}, Peter Heutink, PhD⁷, Manu Sharma, PhD⁵, Nicholas W Wood, PhD, FRCP, FMedSci^{3,8}, Mike Nalls, PhD⁹, Andrew B Singleton, PhD⁹, Nigel M Williams, PhD², and Huw R Morris, PhD, FRCP¹ for International Parkinson's Disease Genomics Consortium¹⁰

¹Department of Clinical Neuroscience, Institute of Neurology, University College London, London, UK

²Institute of Psychological Medicine and Clinical Neurosciences, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, Cardiff University School of Medicine, Cardiff, UK

³Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, F-75013, Paris, France

⁴Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany; and Genome Biology for Neurodegenerative Diseases, German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

⁵Department of Molecular Neuroscience, Institute of Neurology, University College London, London, UK

⁶Reta Lila Weston Institute, University College London Institute of Neurology, Queen Square, London, UK

⁷Genome Biology for Neurodegenerative Diseases, German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

⁸UCL Genetics Institute, University College London, London, UK

⁹Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland, USA

MC1R variants are known to be involved with pigmentation phenotypes and malignant melanoma (MM), with p.R160W associated with red hair and fair skin, as well as increased MM risk¹. Tell-Marti *et al.* recently reported in the *Annals of Neurology*, that p.R160W conferred an increased risk for Parkinson's (PD)². However, a meta-analysis including

¹⁰See Supplementary Text

AUTHOR CONTRIBUTIONS:

SJL and HRM: conception and design of the study. SJL, VEP, NMW and HRM: data analysis and editing. JMB, AB, TG, JH, PH, NWW, ABS and HRM: sample and/or data collection.

POTENTIAL CONFLICTS OF INTEREST:

Dr. Morris reports grants from Medical Research Council UK, grants from Wellcome Trust, grants from Parkinson's UK, grants from Ipsen Fund, during the conduct of the study; grants from Motor Neuron Disease Association, grants from Welsh Assembly Government, personal fees from Teva, personal fees from Abbvie, personal fees from Teva, personal fees from UCB, personal fees from Boehringer-Ingelheim, personal fees from GSK, outside the submitted work.

International Parkinson's Disease Genomics Consortium (IPDGC) data previously failed to observe any association³. We therefore re-investigated p.R160W in an additional large cohort collected through the IPDGC, using high-quality genotype data obtained from the NeuroX chip.

Based on Tell-Marti's observed control minor allele frequency (MAF), our cohort of 5,944 PD cases and 4,642 controls had 99.3% power to detect a 2.1-fold increased risk (compared to their 32.6% power). Our analysis, using logistic regression (correcting for gender and population structure), did not identify a significant association between p.R160W and PD (OR=1.01, 0.90–1.13) (Table 1). Overall *MC1R* variants can vary greatly between European populations, with higher variant frequencies in fairer Northern European Caucasian populations. Conversely, Mediterranean populations have lower variant frequencies⁴. Different proportions of Mediterranean Caucasian ancestry could contribute to allelic heterogeneity. No evidence of allelic heterogeneity between the different subsets existed in our data ($I^2=0\%$, $P_{het}=0.545$). The MAF for p.R160W in the Greek and French subsets were comparable to Tell-Marti's report and other Mediterranean Caucasian populations^{4,5}. No association with PD was seen in these southern European subsets (Greek, OR=1.34, 0.92–1.95; French, OR=1.00, 0.61–1.66), nor within any other subset (Table 1).

A potential limitation of Tell-Marti's study is their selection of controls which were predominantly collected from the wider Spanish population with cases selected from Barcelona. Although the Spanish population is largely homogenous, patterns of genetic microstructure distinguish people from different regions within Spain. This genetic substructure could therefore be a potential source of bias⁶. Additionally, excluding dermatology and oncology patients as controls could have inadvertently lowered p.R160W incidence and may have inflated their effect size.

A shared genetic background between PD and MM has been suggested, but based on our analysis of >11,000 individuals from various different population groups and that reported by Dong *et al.*³, we can conclude that the p.R160W variant and other common variants are not associated with PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank all of the subjects who donated their time and biological samples to be a part of this study.

This work was supported in part by the Intramural Research Programs of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), and the National Institute of Environmental Health Sciences both part of the National Institutes of Health, Department of Health and Human Services; project numbers Z01-AG000949-02 and Z01-ES101986. In addition this work was supported by the Department of Defence (award W81XWH-09-2-0128), and The Michael J Fox Foundation for Parkinson's Research. This work was supported by National Institutes of Health grants R01NS037167, R01CA141668, P50NS071674, American Parkinson Disease Association (APDA); Barnes Jewish Hospital Foundation; Greater St Louis Chapter of the APDA; Hersenstichting Nederland; Neuroscience Campus Amsterdam; and the section of medical genomics, the Prinses Beatrix Fonds. The KORA (Cooperative Research in the Region of Augsburg) research platform was started and financed by the Forschungszentrum für Umwelt und Gesundheit, which is funded by the German Federal Ministry of Education, Science, Research, and Technology and by the State of Bavaria. This study was also

funded by the German National Genome Network (NGFNplus number 01GS08134, German Ministry for Education and Research); by the German Federal Ministry of Education and Research (NGFN 01GR0468, PopGen); and 01EW0908 in the frame of ERA-NET NEURON and Helmholtz Alliance Mental Health in an Ageing Society (HA-215), which was funded by the Initiative and Networking Fund of the Helmholtz Association. The French GWAS work was supported by the French National Agency of Research (ANR-08-MNP-012). This study was also funded by France-Parkinson Association, the French program “Investissements d’avenir” funding (ANR-10-IAIHU-06) and a grant from Assistance Publique-Hôpitaux de Paris (PHRC, AOR-08010) for the French clinical data. This study was also sponsored by the Landspítali University Hospital Research Fund (grant to SSV); Icelandic Research Council (grant to SSV); and European Community Framework Programme 7, People Programme, and IAPP on novel genetic and phenotypic markers of Parkinson’s disease and Essential Tremor (MarkMD), contract number PIAP-GA-2008-230596 MarkMD (to HP and JHu). This study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (<http://biowulf.nih.gov>), and DNA panels, samples, and clinical data from the National Institute of Neurological Disorders and Stroke Human Genetics Resource Center DNA and Cell Line Repository. People who contributed samples are acknowledged in descriptions of every panel on the repository website. We thank the French Parkinson’s Disease Genetics Study Group and the Drug Interaction with genes (DIGPD) study group: Y Agid, M Anheim, A-M Bonnet, M Borg, A Brice, E Broussolle, J-C Corvol, P Damier, A Destée, A Dürr, F Durif, A Elbaz, D Grabil, S Klebe, P Krack, E Lohmann, L. Lacomblez, M Martinez, V Mesnage, P Pollak, O Rascol, F Tison, C Tranchant, M Vêrin, F Viallet, and M Vidailhet. We also thank the members of the French 3C Consortium: A Alperovitch, C Berr, C Tzourio, and P Amouyel for allowing us to use part of the 3C cohort, and D Zelenika for support in generating the genome-wide molecular data. We thank P Tienari (Molecular Neurology Programme, Biomedicum, University of Helsinki), T Peuralinna (Department of Neurology, Helsinki University Central Hospital), L Myllykangas (Folkhalsan Institute of Genetics and Department of Pathology, University of Helsinki), and R Sulkava (Department of Public Health and General Practice Division of Geriatrics, University of Eastern Finland) for the Finnish controls (Vantaa85+ GWAS data). We used genome-wide association data generated by the Wellcome Trust Case-Control Consortium 2 (WTCCC2) from UK patients with Parkinson’s disease and UK control individuals from the 1958 Birth Cohort and National Blood Service. Genotyping of UK replication cases on ImmunoChip was part of the WTCCC2 project, which was funded by the Wellcome Trust (083948/Z/07/Z). UK population control data was made available through WTCCC1. This study was supported by the Medical Research Council and Wellcome Trust disease centre (grant WT089698/Z/09/Z to NW, JHa, and AS). As with previous IPDGC efforts, this study makes use of data generated by the Wellcome Trust Case-Control Consortium. A full list of the investigators who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the project was provided by the Wellcome Trust under award 076113, 085475 and 090355. This study was also supported by Parkinson’s UK (grants 8047 and J-0804) and the Medical Research Council (G0700943). We thank Jeffrey Barrett for assistance with the design of the ImmunoChip. DNA extraction work that was done in the UK was undertaken at University College London Hospitals, University College London, who received a proportion of funding from the Department of Health’s National Institute for Health Research Biomedical Research Centres funding. This study was supported in part by the Wellcome Trust/Medical Research Council Joint Call in Neurodegeneration award (WT089698) to the Parkinson’s Disease Consortium (UKPDC), whose members are from the UCL Institute of Neurology, University of Sheffield, and the Medical Research Council Protein Phosphorylation Unit at the University of Dundee.

References

1. Raimondi S, Sera F, Gandini S, et al. MC1R variants, melanoma and red hair color phenotype: a meta-analysis. [Internet]. *Int J Cancer*. 2008; 122(12):2753–60. [cited 2015 Mar 18] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18366057>. [PubMed: 18366057]
2. Tell-Marti G, Puig-Butille JA, Potrony M, et al. The MC1R melanoma risk variant p.R160W is associated with Parkinson disease. [Internet]. *Ann Neurol*. 2015; 77(5):889–94. [cited 2015 Apr 24] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25631192>. [PubMed: 25631192]
3. Dong J, Gao J, Nalls M, et al. Susceptibility loci for pigmentation and melanoma in relation to Parkinson’s disease. [Internet]. *Neurobiol Aging*. 2014; 35(6):1512e5–10. [cited 2014 Sep 26] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24439955>. [PubMed: 24439955]
4. Gerstenblith MR, Goldstein AM, Fargnoli MC, et al. Comprehensive evaluation of allele frequency differences of MC1R variants across populations. [Internet]. *Hum Mutat*. 2007; 28(5):495–505. [cited 2015 Apr 27] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17279550>. [PubMed: 17279550]
5. <http://www.1000genomes.org/>
6. Gayán J, Galan JJ, González-Pérez A, et al. Genetic structure of the Spanish population [Internet]. *BMC Genomics*. 2010; 11:326. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2887418&tool=pmcentrez&rendertype=abstract>. [PubMed: 20500880]

Table 1
No association of the *MC1R* variant p.R160W and Parkinson's in a large heterogeneous cohort.

	OR (95% CI)	P-value	Controls		Cases	
			MAF	N	MAF	N
NeuroX Genotyped samples [#]	1.01 (0.90–1.13)	0.853	0.062	4,642	0.064	5,944
Dutch	0.86 (0.57–1.30)	0.469	0.075	409	0.066	312
French	1.00 (0.61–1.66)	0.989	0.040	451	0.036	508
German	1.10 (0.87–1.41)	0.425	0.068	880	0.075	1,296
Greek	1.34 (0.92–1.95)	0.131	0.026	882	0.034	965
UK	0.95 (0.72–1.24)	0.624	0.080	583	0.073	1,107
US	0.92 (0.76–1.12)	0.385	0.077	1,437	0.074	1,756
Tell-Marti <i>et al.</i> [@]	2.10 (1.18–3.73)	0.009	0.010	736	0.025	870
Dong <i>et al.</i> ⁺	0.98 (0.89–1.07)	0.624	-	13,642	-	6,141

KEY:

[#] logistic regression correcting for gender and population stratification.

[@] logistic regression correcting for gender and age.

⁺ meta-analysis of 5,333 cases and 12,019 controls from the International Parkinson's Disease Genomics Consortium; and 808 cases and 1,623 controls from the Parkinson's Genes and Environment Study.

CI, confidence interval; MAF, minor allele frequency; N, number of samples; OR, odds ratio; UK, United Kingdom; US, United States.