ONLINE DATA SUPPLEMENT

No Clear Support for a Role for Vitamin D in Parkinson's Disease: A Mendelian Randomization Study

Table of contents

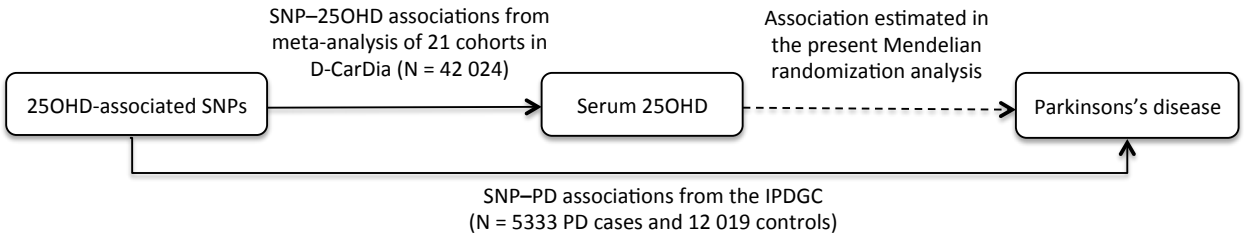
Supplemental Figure 1. Mendelian randomization study framework and data sources used for investigating whether 25OHD concentration is causally associated with Parkinson's disease 2

Supplemental Figure 2. Mendelian randomization study framework and data sources used for investigating whether 25OHD concentration is causally associated with Parkinson's disease..... 3

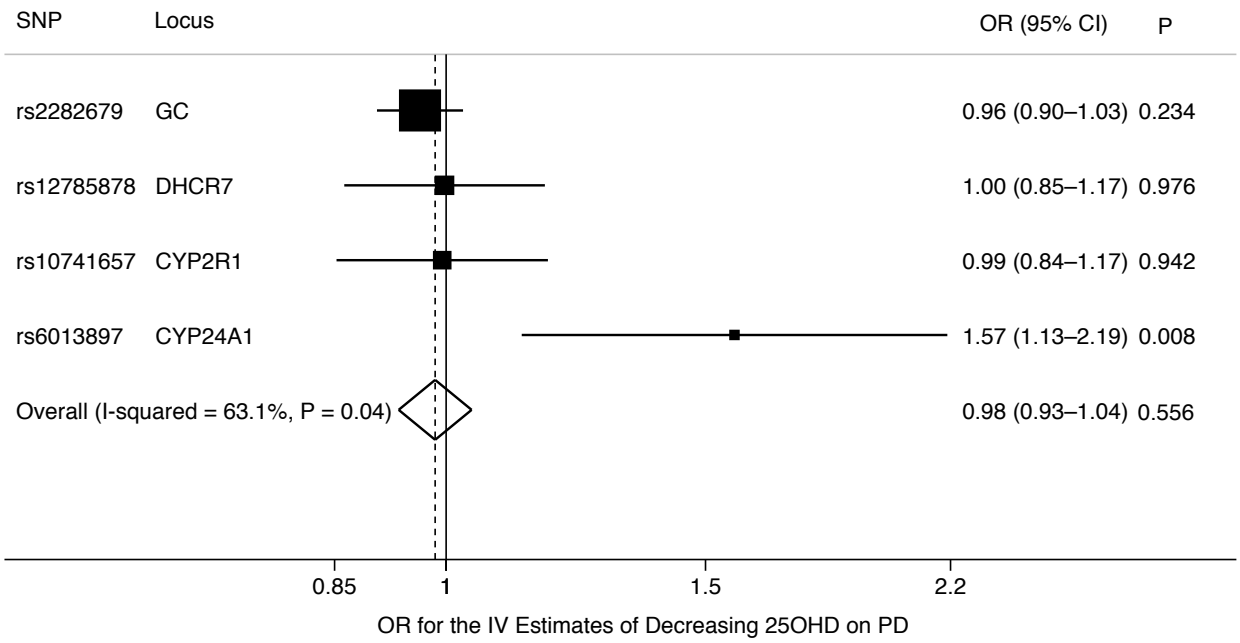
Supplemental Table 1. Associations of the 25-hydroxyvitamin D-associated single nucleotide polymorphisms with other phenotypes 4

IPDGC consortium members and affiliations 5

Acknowledgments 8



Supplemental Figure 1. Mendelian randomization study framework and data sources used for investigating whether 25OHD concentration is causally associated with Parkinson's disease. 25OHD, 25-hydroxyvitamin D; D-CarDia, vitamin D and the risk of cardiovascular disease and related traits collaboration; IPDGC, International Parkinson's Disease Genomics Consortium; PD, Parkinson's disease; SNP, single nucleotide polymorphism.



Supplemental Figure 2. Mendelian randomization estimates of the association between decreased 25OHD concentration and Parkinson's disease. The OR estimates are per 10% decrease in 25OHD concentration. The hollow diamond represents the overall IV estimate with its 95% CI. Weights for each SNP in the meta-analysis are as follows: rs2282679: 71.9%; rs12785878: 13.2%; rs10741657: 11.9%; rs6013897: 2.9%. 25OHD, 25-hydroxyvitamin D; CI, confidence interval; IV, instrumental variable; OR, odds ratio; PD, Parkinson's disease; SNP, single nucleotide polymorphism.

Supplemental Table 1. Associations of the 25OHD-associated single nucleotide polymorphisms with other phenotypes[a]

SNP	Locus	Chr	Phenotype	*P* value	PMID
rs2282679	*GC*	4	Height	0.004	25282103
			log(Proinsulin)	0.006	21873549
			log(Corrected insulin response)	0.029	24699409
			Years of education	0.032	23722424
			Waist-hip-ratio in males >50 years of age	0.040	26426971
			Geographic atrophy	0.045	23455636
rs12785878	*DHCR7*	11	Attention deficit hyperactivity disorder	4.03×10^{-5}	20732625
			Waist-hip-ratio in males ≤50 years of age	0.009	26426971
			Total cholesterol	0.014	24097068
			log(eGFR creatinine)	0.017	26831199
			Years of education in females	0.034	27225129
			Low-density lipoprotein cholesterol	0.042	20686565
			High-density lipoprotein cholesterol	0.046	24097068
rs10741657	*CYP2R1*	11	Hip circumference	0.001	25673412
			Height	0.002	25282103
			Conscientiousness	0.002	21173776
			log(eGFR creatinine)	0.003	26831199
			Body mass index	0.017	25673413
			Birth length	0.017	25281659
			Adiponectin levels	0.022	22479202
			Weight	0.005	23754948
			Schizophrenia	0.038	25056061
rs6013897	*CYP24A1*	20	log(eGFR creatinine)	1.60×10^{-9}	26831199
			Serum creatinine	2.80×10^{-5}	20383146
			Femoral neck bone mineral density	3.04×10^{-5}	22504420
			log(eGFR cystatin C)	0.008	26831199
			log(Urinary albumin creatinine ratio)	0.014	26631737
			Diastolic blood pressure	0.023	21909115
			Neuroticism	0.035	27089181
			Serum urate	0.039	23263486
			Systolic blood pressure	0.045	21909115

[a]Only associations with $P < 0.05$ are shown. 25OHD, 25-hydroxyvitamin D; Chr, chromosome; eGFR, estimated glomerular filtration rate; SNP, single nucleotide polymorphism.

IPDGC consortium members and affiliations

Alastair J Noyce (Department of Molecular Neuroscience, UCL, London, UK), Alexis Brice (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Anamika Giri (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Angelika Oehmig (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Arianna Tucci (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Aude Nicolas (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Claudia Schulte (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research), Mark R Cookson (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA), Cornelis Blauwendraat (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA), Kathrin Brockmann (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Demis Kia (UCL Genetics Institute; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Fabrice Danjou (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Faraz Faghri (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA; Department of Computer Science, University of Illinois at Urbana-Champaign, Urbana, IL, USA), Gavin Charlesworth (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), J Raphael Gibbs (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Huw R Morris (National Hospital for Neurology and Neurosurgery, University College London, London, UK), Helene Plun-Favreau (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Dena G Hernandez (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Peter Holmans (Biostatistics & Bioinformatics Unit, Institute of Psychological Medicine and Clinical Neuroscience, MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff, UK), Huw R Morris (National Hospital for Neurology and Neurosurgery, University College London, London, UK), Iris Jansen (VU University Medical Center, Amsterdam, Netherlands), John Hardy (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Javier Simón-Sánchez (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German

Center for Neurodegenerative Diseases, Tübingen, Germany), Jose M Bras (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Joshua M. Shulman (Baylor College of Medicine, Houston, Texas, USA), John Quinn (Institute of Translational Medicine, University of Liverpool, Liverpool, UK), Juan A. Botía (Universidad de Murcia, Murcia, Spain), Kin Y Mok (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Kimberley Billingsley (Institute of Translational Medicine, University of Liverpool, Liverpool, UK), Lasse Pihlstrom (Department of Neurology, Oslo University Hospital, Oslo, Norway), Lea R'Bibo (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Codrin Lungu (National Institutes of Health Parkinson Clinic, NINDS, National Institutes of Health, Bethesda, MD, USA), Manu Sharma (Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tubingen and Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen Germany), Maria Martinez (INSERM UMR 1220; and Paul Sabatier University, Toulouse, France), Mina Ryten (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Valentina Escott-Price (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK), Niccolo E. Mencacci (Department of Molecular Neuroscience, UCL, London, UK), Mike A. Nalls (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA; Contractor/consultant with Kelly Services, Rockville, MD, USA), Nicholas W Wood (UCL Genetics Institute; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Patrick Lewis (University of Reading, Reading, UK), Paul Denny (University College London, London, UK), Peter Heutink (DZNE, German Center for Neurodegenerative Diseases and Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany), Patrizia Rizzu (DZNE, German Center for Neurodegenerative Diseases), Pille Taba (Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia), Rita Guerreiro (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Ruth Lovering (University College London, London, UK), Raquel Duran Ogalla (University College London, London, UK), Rebecca Foulger (University College London, London, UK), Laurie Robak (Baylor College of Medicine, Houston, Texas, USA), Steven Lubbe (Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA), Steven Finkbeiner (Departments of Neurology and Physiology, University of California, San Francisco; Gladstone Institute of Neurological Disease; Taube/Koret Center for Neurodegenerative Disease Research, San Francisco, CA, USA), Sigurlaug Sveinbjörnsdóttir (Department of Neurology, Landspítali University Hospital, Reykjavík, Iceland; Department of Neurology, MEHT Broomfield Hospital, Chelmsford, Essex, UK; and Queen Mary College, University of London, London, UK), Andrew B Singleton (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Sonja Scholz (Neurodegenerative Diseases Research

Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA), Sulev Koks (Department of Pathophysiology, University of Tartu, Tartu, Estonia), Suzanne Lesage (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Jean-Christophe Corvol (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, Centre d'Investigation Clinique Pitié Neurosciences CIC-1422, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Thomas Foltynie (UCL Institute of Neurology, London, UK), Thomas Gasser (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), T. Ryan Price (University California Irvine, Irvine, CA, USA), Una-Marie Sheerin (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Nigel Williams (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff, UK), Xylena Reed (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA).

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 Defense (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; 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 Landspitali 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 Vérin, F Viallet, and

M Vidailhet. We also thank the members of the French 3C Consortium: A Alpérovitch, 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 ASc). 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 and G1100643). We thank Jeffrey Barrett and Jason Downing for assistance with the design of the ImmunoChip and NeuroX arrays. 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. Mike Nalls' participation is supported by a consulting contract between Kelly Services and the National Institute on Aging, NIH, Bethesda, MD, USA. Faraz Faghri's contribution to this work has been supported in part through the RDA/US Data Share grant from the Alfred P. Sloan Foundation #G-2014-13746 and supported by grant 1U54GM114838 awarded by NIGMS through funds provided by the trans-NIH big data to Knowledge (BD2K) initiative (www.bd2k.nih.gov) and a collaborative award from the National Science Foundation (NSF award numbers CNS-1329686, CNS-1329737, CNS-1330142, and CNS-1330491). This work was supported by the Medical Research Council grant MR/N026004/1.