Contrary to traditional clinical practice, dopaminergic medication status did not affect behavioral performance on the Bistable Percept Paradigm (all P values >0.05). In addition, we observed no overall difference in the whole-brain or ROI–ROI analyses when comparing the correct and incorrect perception of single images on the Bistable Percept Paradigm comparing *on* and *off* dopaminergic medication states (all P values >0.05).

Our results augment accumulating evidence suggesting that dopaminergic medication status is unlikely to be the primary factor regulating the complex pathogenesis of VH in PD. Indeed, PD patients with VH will almost certainly demonstrate idiosyncratic patterns and degrees of neurodegeneration and different risk factor profiles and medication combinations. This suggests that the individual effect of dopamine may be mediated by several other factors. The impacts of degeneration across other nondopaminergic neurotransmitter pathways, such as serotonin, noradrenaline, and acetylcholine, and medications that affect these pathways should be considered in future studies. In addition, dynamic functional magnetic resonance imaging studies techniques that can probe the degree of integration and segregation across the whole-brain network[6] and have been shown to be sensitive to neuromodulatory tone[7] may also provide unique viewpoints into this troubling symptom of PD.

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Genome-Wide Association Study of Pain in Parkinson's Disease Implicates *TRPM8* as a Risk Factor

Chronic pain affects 60% to 85% of people with Parkinson's disease (PD) and has a strong negative effect on quality of life.[1] Genetic factors are significantly associated with a variety of chronic pain conditions.[2] Identifying additional genetic modifiers of pain in people with PD 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 of pain in PD.

PD 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 cohorts. The clinical assessment of pain in these patients has been previously reported.[1] PD patients were stratified into 2 groups that represented individuals with no/low pain (McGill score < 3 and Visual Analog Scale severity <2) and high pain (McGill Score ≥ 3 and Visual Analog Scale severity ≥2).

DNA extracted from each sample was genotyped using either the Illumina Human ExomeCore-12 v1.1 array, Illumina, Cambridge, UK (Tracking Parkinson's) or the InfiniumCoreExome-24 v1.1, Illumina, Cambridge, UK (Oxford Parkinson's Disease Centre). Genotype data from both cohorts underwent the same conventional processing, quality control, and imputation procedures as described elsewhere.[3]

We performed a genome-wide association study of 6,655,232 autosomal single nucleotide polymorphisms (SNPs) that compared a total of 898 patients with PD who were classed as suffering high levels of pain to 420 PD 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

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Members of the UK Parkinson's Pain Study are listed in the Appendix.

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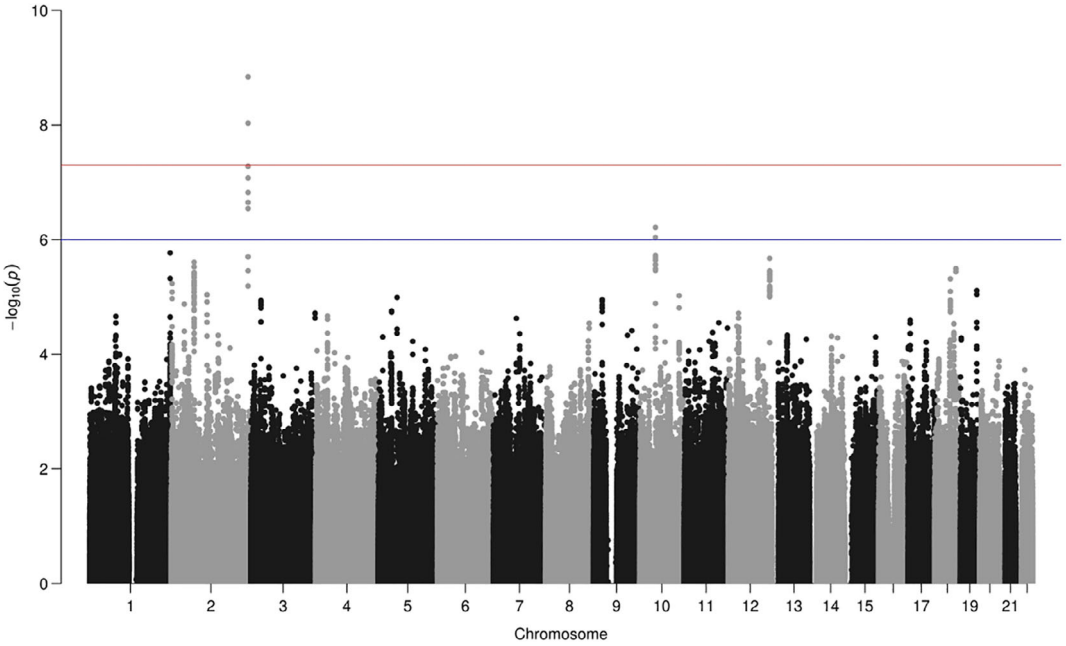

FIG. 1. Manhattan plot of −log10 single nucleotide polymorphism *P* values from a meta-analysis of high pain (n = 898) versus low pain (n = 420). Red and blue lines represent the thresholds for genome-wide (P < 5E-08) and suggestive (P < 1E-06) significance, respectively.

significance (*P* = 1.45E-09, odds ratio [OR] = 1.78, and *P* = 9.30E-09, OR = 1.71, respectively; Fig. 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.[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 genome-wide association study 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 that have demonstrated efficacy as analgesic agents, have been shown to antagonize the TRPM8 receptor.[7] Indeed, some authors have termed TRPM8 and other related Transient Receptor Potential 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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