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# Racial differences may influence the role of cholecystokinin polymorphisms in Parkinson's Disease hallucinations

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## Keywords

Parkinson's Disease; hallucinations; psychosis; genetic polymorphisms; cholecystokinin

Psychosis is a frequently troublesome complication in Parkinson's disease (PD)1. Various genetic polymorphisms affecting dopamine have been reported as risk factors for PD-related complications such as dyskinesias and hallucinations2, 3. Cholecystokinin (CCK) has been implicated in psychiatric disorders including schizophrenia and panic disorder, and CCK and receptor (CCKAR and CCKBR) gene polymorphisms have been investigated in PD hallucinations4–6. CCK-dopamine interactions may contribute to the neurobiology of psychiatric disorders as CCK co-localizes with dopamine in mesolimbic neurons, including those in the nucleus accumbens and amygdala, and modulates dopaminergic release. In Asian PD patients, an increased hallucination risk was associated with CCK and CCKAR gene polymorphisms4, 5. Since genetic polymorphisms vary across racial groups, we aimed to replicate these findings in white PD patients with chronic hallucinations compared to those who never hallucinated.

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2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
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Mr. Marr has nothing to disclose.
Dr. Zhou has nothing to disclose.
Dr. Ouyang has nothing to disclose.

We conducted a case-control study at the Rush University Movement Disorders clinic, examining 88 pairs of white PD patients with and without chronic hallucinations, matched for age within 3 years, disease duration within 5 years, and dopaminergic medications (levodopa, agonist, or both). Cases hallucinated at least 3 times weekly for the past 2 months and had not experienced hallucinations before dopaminergic treatment, while controls had never hallucinated. Only controls with at least one year of continual clinical follow-up were included. Mini-Mental State Examination (MMSE), Unified Parkinson Disease Rating Scale (UPDRS) motor section, and Hoehn and Yahr staging were also administered. Only white, non-Hispanic or non-Latino, patients participated. The Rush University Institutional Review Board approved this research.

Genomic DNA from coded samples was analyzed for CCK −45C/T, CCKAR 779T/C, and CCKBR 1550G/A polymorphisms by polymerase chain reaction6. We specifically examined polymorphisms identified in the Asian studies, including the promoter region CCK −45C/T polymorphism, which may influence CCK gene transcription based on its Sp1 cis-binding element location. Based on prior studies, our sample size of 88 pairs afforded >90% power to detect a difference of 22% between cases and controls, assuming a CCK-T allele frequency of 14% in white PD controls4¯7. Genotypic and allelic frequencies were compared using Mantel-Haenszel and Chi-square tests. Combined CCK-T and CCKAR-C alleles were analyzed by Mantel-Haenszel tests for synergistically increased hallucinatory risk.

There were no significant differences between PD hallucinators and non-hallucinators in age, gender, disease duration, or levodopa equivalent doses (Supplemental material). PD hallucinators had worse MMSE scores and motor function. Mean clinical follow-up for non-hallucinating controls was 3.79 (SD 3.22) years, maximum 15 years.

CCK, CCKAR, and CCKBR genotype frequencies were in Hardy-Weinberg equilibrium. For CCK, CCKAR, and CCKBR, there were no significant differences in genotype distributions or allele frequencies between hallucinators or non-hallucinators (Table 1). In fact, the CCK-T allele was modestly represented in both groups (16%, hallucinators; 14%, non-hallucinators; p=0.55). We also did not detect increased hallucinatory risk with combined CCK-T and CCKAR-C alleles.

Our matched case-control study did not replicate the association between CCK or CCKAR polymorphisms and increased hallucination risk previously found in Japanese and Chinese PD patients. In both Asian studies, the CCK-T allele frequency in PD hallucinators was about 40%, a finding detected in smaller hallucinator samples (n=23, n=45, respectively)4, 5. In contrast, the overall CCK-T allele frequency was 15% in our white PD cohort, without significant differences between hallucinators and non-hallucinators. Our CCK-T allele frequency, however, was similar to American white studies (14%), but lower than frequencies reported in Asian populations (32%, Japanese; 33%, Chinese)7. Our study was powered to detect a contribution of the CCK-T allele to hallucination status that would account for a similar magnitude of risk as proposed in the Asian studies, despite the lower population CCK-T allele frequency in whites. Thus, the CCK-related polymorphisms studied appear to differentially affect hallucination risk in PD across different racial groups. Genetic polymorphisms as risk factors for disease-related complications such as hallucinations should be interpreted within the context of racial and ethnic diversity.

Our methodological strengths include a well-matched study population, diagnoses by Movement Disorder specialists, and follow-up of non-hallucinating patients to ensure group classification. Limitations include the tertiary care referral pattern, study of only gene

polymorphisms showing prior associations, and that even with rigorous follow-up of non-hallucinators, we cannot confirm that they will never hallucinate.

Although particular CCK and CCK receptor gene polymorphisms may increase hallucination risk in Asian PD patients, the lack of differences in allele frequencies in our cohort suggests that these polymorphisms are not substantial contributors to psychosis risk in white PD patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Goetz has received research support from NIH, Michael J. Fox Foundation, Parkinson's Disease Foundation and received honoraria for consultancy or advisory board membership from Asubio, Campbell Alliance, CNS Therapeutics, Curry Rocherfeller Groupo, Health Advances, Impax Pahrma, Ingenix, Juvantia Pharma, Neurim Pharma, Novartis Pharma, Ono Pharma, Oxford Biomedica, Santhera, Solvay Phara, United Biosource Corp, UCB.

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**Table 1**

*CCK* and *CCK* Receptor Genotype and Allelic Frequencies

| Genotype frequencies | | | |
|---|---|---|---|
| | **Hallucinators, n (%)** | **Non-hallucinators, n (%)** | **P value** |
| **CCK -45C/T** | | | |
| CC | 61 (69.3) | 67 (76.1) | 0.29 |
| CT | 26 (29.5) | 18 (20.5) | |
| TT | 1 (1.13) | 3 (3.4) | |
| **CCKAR 779T/C** | | | |
| CC | 2 (2.3) | 2 (2.3) | 0.98 |
| CT | 24 (27.3) | 23 (26.1) | |
| TT | 62 (70.5) | 63 (71.6) | |
| **CCKBR 1550G/A** | | | |
| AA | 0 (0) | 0 (0) | 1.0 |
| AG | 12 (13.6) | 12 (13.6) | |
| GG | 75 (86.2) | 75 (86.2) | |

| Allelic frequencies | | | | P value | |
|---|---|---|---|---|---|
| | **Hallucinators, n (%)** | **Non-hallucinators, n (%)** | **Total, n (%)** | **Allele Frequency** | **No. of alleles** |
| **CCK -45C/T** | | | | | |
| C | 148 (84) | 152 (86) | 300 (85) | 0.55 | 0.55 |
| T | 28 (16) | 24 (14) | 52 (15) | | |
| **CCKAR 779T/C** | | | | | |
| C | 28 (16) | 27 (15) | 55 (16) | 0.88 | 0.88 |
| T | 148 (84) | 149 (85) | 297 (84) | | |
| **CCKBR 1550G/A** | | | | | |
| A | 12 (7) | 12 (7) | 24 (7) | 1.0 | 1.0 |
| G | 160 (93) | 160 (93) | 320 (93) | | |