Journal of the Neurological Sciences 362 (2016) 47–52

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

PARK16 polymorphisms, interaction with smoking, and sporadic Parkinson's disease in Japan

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ARTICLE INFO

Article history:
Received 8 July 2015
Received in revised form 15 December 2015
Accepted 12 January 2016
Available online 14 January 2016

Keywords:
Case–control study
Gene–environment interaction
Japanese
Parkinson's disease
Smoking
PARK16 polymorphisms

ABSTRACT

Epidemiological evidence on the relationships between *PARK16* single nucleotide polymorphisms (SNPs) and Parkinson's disease (PD) is inconsistent. We examined this issue in Japan. Included were 229 cases within six years of PD onset. Controls were 356 patients without neurodegenerative disease. Compared with subjects with the AA genotype of SNP rs823128, those with the AG genotype, but not the GG genotype, had a significantly reduced risk of sporadic PD. Compared with the AA genotype of SNP rs947211, both the AG genotype and the GG genotype were significantly related to an increased risk of sporadic PD. Using subjects with the AA genotype of SNP rs823156 as a reference group, there were significant inverse relationships under the additive and dominant models. No significant relationships were found between SNPs rs16856139 or rs11240572 and sporadic PD. The CAAAC, the TGAGA, and the CAGAC haplotypes were significantly related to sporadic PD. The additive interaction between SNP rs823128 and smoking affecting sporadic PD was significant, although the multiplicative interaction was not significant. The *PARK16* SNPs rs823128, rs947211, and rs823156 and the CAAAC, TGAGA, and CAGAC haplotypes may be significantly associated with sporadic PD in Japan. New evidence of an additive interaction between SNP rs823156 and smoking is suggested.

1. Introduction

PARK16, located on 1q32, which contains five genes (*SLC45A3*, *NUCKS1*, *RAB7L1*, *SLC41A1*, and *PM20D1*) within 169.6 kb, was identified as a new Parkinson's disease (PD) susceptibility locus in a genome-wide association study (GWAS) in the Japanese population in 2009. The association between PD and each of seven single nucleotide polymorphisms (SNPs) (rs16856139, rs823128, rs823122, rs947211, rs823156, rs708730, and rs11240572) surpassed genome-wide significance [1]. In a GWAS in Caucasians, the relationships between SNPs rs823128, rs823156, or rs11240572 and PD did not reach genome-wide significance: the minor allele frequencies of these SNPs in controls were 0.04, 0.18, and 0.04, respectively, though the association with SNP rs823128 was significant among combined samples from stage I and stage II [2]. Two GWAS conducted in the UK and US found no associations between *PARK16* SNPs and PD [3,4]. *PARK16* was not included in the top 57 candidate SNPs in a GWAS in the Ashkenazi Jewish population [5]. Several genetic association studies [6–19] have investigated the relationships between *PARK16* SNPs and PD, but these studies have produced mixed findings. A 2012 meta-analysis using the PDGene

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http://dx.doi.org/10.1016/j.jns.2016.01.021
0022-510X/

database reported evidence for genome-wide significance, showing that SNP rs947211 was significantly associated with PD in Caucasian populations, while SNP rs823156 was significantly associated with PD in Asian populations [20].

To contribute to the body of available evidence regarding the association between *PARK16* SNPs and the risk of sporadic PD, we examined this issue using data from a multicenter hospital-based case–control study in Japan. In addition, we conducted haplotype analyses and investigated the possibility of interaction between the SNPs and smoking, which is known to be inversely related to PD.

2. Methods

2.1. Study population

PD cases were recruited at three university hospitals and one national hospital in Fukuoka Prefecture, on the island of Kyushu in southern Japan, and at three university hospitals, three national hospitals and one municipal hospital in Osaka, Kyoto, and Wakayama Prefectures, all of which are in the Kinki region, located in the mid-western part of the mainland. Eligible cases were patients who were within six years of the onset of PD and who had been diagnosed by one of the collaborating neurologists at one of the 11 collaborating hospitals according to the United Kingdom PD Society Brain Bank clinical diagnostic criteria [21]. The neurologists in charge asked their eligible PD patients to participate in our case–control study. Of 298 eligible PD cases identified during the period between April 1, 2006 and March 31, 2008, 250 agreed to participate in the study (response rate: 84%).

In the same time period, control subjects were recruited from departments other than neurology (orthopedic surgery, ophthalmology, otorhinolaryngology, plastic surgery, and oral surgery) at three of the 11 collaborating hospitals: one university hospital in Fukuoka Prefecture and one university hospital and one national hospital in the Kinki region. Control subjects were not matched to cases, either individually or in larger groups. Control candidates, who were inpatients or outpatients without neurodegenerative diseases at any of these three hospitals, were approached by an attending doctor or by one of our research nurses to participate in our case–control study. Eventually, 372 control candidates participated in our study whereas 156 refused (response rate: 70%).

Of the 250 cases and 372 control subjects who participated in our study, 240 cases and 371 controls gave informed consent to genotyping. Excluded were 11 cases and 12 controls with a family history of PD, one control with missing data on smoking, one control with missing data on caffeine intake, and one control with missing data on SNPs because genotype identification was impossible. The final analysis thus comprised 229 cases and 356 control subjects. The ethics committees of the 11 collaborating hospitals (Fukuoka University, Utano National Hospital, Osaka City University, Kyushu University, Wakayama Medical University, Kyoto University, Kurume University, Minami-Kyoto National Hospital, Toneyama National Hospital, Kyoto City Hospital, and National Omuta Hospital) approved our case–control study. Written informed consent was obtained from all subjects.

2.2. Questionnaire

Participants filled out a set of two self-administered questionnaires and mailed these materials to the data management center or handed them to research nurses. Our research technicians completed missing answers and/or illogical data by telephone or in-person interview.

Dietary habits during the preceding month were assessed using a self-administered, semi-quantitative, comprehensive diet history questionnaire. Reported intake levels of coffee, black tea, and Japanese and Chinese teas were used to estimate caffeine intake. Energy-adjusted intake was calculated according to the density method. A second questionnaire elicited information on sex, age, smoking habits, and family history of PD. A history of smoking was defined as having smoked at least once per day for at least one year.

2.3. DNA extraction and genotyping

Genomic DNA from buccal specimens collected with BuccalAmp swabs (Epicenter BioTechnologies, Madison, WI, USA) was extracted using a QIAmp DNA mini kit (Qiagen, Inc., Valencia, CA, USA). Five *PARK16* SNPs [rs16856139 (*SLC45A3*), rs823128 (*NUCKS1*), rs947211 (Intergenic), rs823156 (*SLC41A1*), and rs11240572 (*PM20D1*)] were genotyped using TaqMan SNP Genotyping Assays on the StepOnePlus machine (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Of the seven SNPs identified in a 2009 Japanese GWAS [1], SNPs rs708730 and rs823122 were excluded in a case–control study conducted in Singapore because r^2 between rs708730 and rs823156 and r^2 between rs823122 and rs823128 > 0.8 [6]; this finding prompted us to exclude the two SNPs from the present study as well.

2.4. Statistical analysis

Departures from the Hardy–Weinberg equilibrium were assessed among the control subjects using the chi-square test. Linkage disequilibrium was examined using Haploview software version 4.2 (Broad Institute, Cambridge, MA, USA) [22]. Logistic regression analysis was performed to calculate the crude odds ratios (ORs) and 95% confidence intervals (CIs) for sporadic PD relative to the SNPs under study, with the reference category being the homozygote of the major allele among the control subjects. Multiple logistic regression analysis was used to control for sex, age, region of residence, smoking, and caffeine intake. Smoking and caffeine intake were inversely associated with PD in this population [23,24]. The statistical power calculation was performed using QUANTO version 1.2 [25]. Haplotypes and their frequencies were inferred according to the expectation maximization algorithm. For differences in haplotype frequency between the cases and control subjects, crude ORs and 95% CIs were calculated based on the frequency of each haplotype relative to all other haplotypes combined. We examined multiplicative and additive interactions between *PARK16* rs823128 and smoking with regard to the risk of sporadic PD. Multiplicative interaction was estimated by introducing a multiplicative term into a multiple logistic regression model. Three measures for the additive interaction were calculated using the Excel sheet provided by Andersson et al. [26]: 1) relative excess risk due to interaction (RERI), 2) attributable proportion due to interaction (AP), and 3) synergy index (S). RERI is the excess risk due to an interaction relative to the risk without exposure. AP refers to the attributable proportion of disease among individuals exposed to both factors that is due to the factors' interaction. S is the excess risk from both exposures when there is an additive interaction, relative to the risk from both exposures without an interaction. RERI = 0, AP = 0, or S = 1 means no interaction or strict additivity; RERI > 0, AP > 0, or S > 1 means positive interaction or more than additivity; RERI < 0, AP < 0, or S < 1 means negative interaction or less than additivity [27]. If any of the null values (0 in RERI and AP or 1 in S) falls outside the 95% CI of its respective measurement, then the additive interaction is considered statistically significant. Excluding the calculation of linkage disequilibrium and statistical power calculation, all statistical analyses were performed using STATA/SE software version 13.1 (StataCorp, College Station, TX, USA).

3. Results

Compared with control subjects, cases were more likely to be older and non-smokers and to report a low caffeine intake (Table 1). There were no differences between cases and controls with regard to sex or region of residence.