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Associations of rs823128, rs1572931, and rs823156 polymorphisms with reduced Parkinson's disease risks

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The *PARK16* locus is considered to play a protective role in Parkinson's disease (PD). However, the epidemiological evidence on the relationships between *PARK16* single-nucleotide polymorphisms (rs823128, rs1572931, and rs823156) and PD is inconsistent. Therefore, we carried out a meta-analysis to validate the relationships and performed a bioinformatic analysis to explore putative regulation mechanisms of the single-nucleotide polymorphisms in PD. Through meta-analysis, we confirmed that minor variants of rs823128A > G, rs1572931C > T, and rs823156A > G played protective roles in PD. Through bioinformatic analysis, we predicted that rs823128, rs1572931, and rs823156 as noncoding variants of *NUCKS1*, *RAB29*, and *SLC41A1*, respectively, might affect PD risk by altering the transcription factor-binding capability of the genes. These findings suggest new clues for PD research and potential targets for PD prevention and treatment. *NeuroReport* **28:936–941 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Parkinson's disease (PD) is a common and complex neurodegenerative disorder, which is believed to be caused by the interaction of multiple genes and environmental factors. The disease affects about 1% individuals over 60 years old and the quality of life of patients with this disease is severely affected [1]. However, because of the limited knowledge of the molecular mechanism in PD, effective preventive or curative strategies for the disease are still absent to date.

The etiology of most PD cases is still vague, but increasing evidence shows an important role of genetic susceptibility in PD. Therefore, studies of the relationship between genetic polymorphisms and PD susceptibility may help to elucidate the pathogenesis of the disease.

The *PARK16* locus is the genetic region spanning five genes on chromosome 1. The genes are solute carrier family 45 member 3 (*SLC45A3*), nuclear casein kinase and cyclin-dependent kinase substrate 1 (*NUCKS1*), Ras-related protein Rab29 (*RAB29*), solute carrier family 41 member 1 (*SLC41A1*), and peptidase M20 domain containing 1 (*PM20D1*). In recent years, the *PARK16* has been identified to play a protective role in PD [2,3]. Rs823128, rs1572931, and rs823156 were believed to be among the most PD-associated single-nucleotide polymorphisms (SNPs) in this locus. These SNPs were identified in *NUCKS1*, *RAB29*, and *SLC41A1*, respectively [3]. The association between rs823128 SNP and PD was identified in the White population [2], but showed no relationship in some studies in the East Asian population [4,5]. Rs1572931 SNP was indicated to be associated with PD in the East Asian [6] and the Mediterranean population [7], but not in the White population [2]. As for rs823156, the SNP located in *SLC41A1* was considered to be associated with PD in the White population [2], but not in the Hispanic population [8]. Considering the inconsistent conclusions of studies in association between these SNPs and PD, we decided to carry out a comprehensive review and meta-analysis here to further validate the association of the SNPs with PD risk. Besides these, the findings of our study might provide new insights into the pathogenesis of PD.

Methods

Publication search

Relevant literatures were searched in PubMed, Embase, the Cochrane Library, the Chinese National Knowledge Infrastructure, the China Science and Technology Journal Database (VIP), and the Wanfang database up to

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Table 1 Characteristics of the studies included in the meta-analysis

Polymorphism sites	Number of studies	Sample size (case/control)	References
rs823128	14	11 484/17 859	Chang *et al.* [10], Chang *et al.* [11], Gopalai *et al.* [12], Miyaka *et al.* [13], Pihlstrom *et al.* [2], Yan *et al.* [14], Zhao *et al.* [4], Zhou *et al.* [5], Ramirez *et al.* [15], Satake *et al.* [3], Simon-Sanchez *et al.* [16], Spencer *et al.* [17], Tan *et al.* [18], Vilariño-Güell *et al.* [19]
rs1572931	5	3809/3328	Gan-Or *et al.* [7], Goudarzian *et al.* [20], Pihlstrom *et al.* [2,] Guo *et al.* [6], Liu *et al.* [21]
rs823156	12	12 016/14 609	Chang *et al.* [10], Chang *et al.* [11], Chung *et al.* [22], Gopalai *et al.* [12], Miyaka *et al.* [13], Pihlstrom *et al.* [2], Guo *et al.* [23], Satake *et al.* [3], Mata *et al.* [8], Simon-Sanchez *et al.* [16], Tan *et al.* [18], Yan *et al.* [14]

4 February 2017. Inclusion and exclusion criteria were then used to screen appropriate studies for analysis. The inclusion criteria were as follows: (a) case–control studies only; (b) included an association evaluation between SNPs rs823128, rs823156 or rs1572931, and PD susceptibility; and (c) included allele or genotype frequencies for the calculation of odds ratios (ORs) and 95% confidence intervals. Articles were excluded if (a) they were case reports, reviews, or meta-analyses, and (b) they lacked the data necessary for a meta-analysis.

Statistical analysis

ORs with 95% confidence intervals were calculated to evaluate the associations between SNPs and PD susceptibility under additive models and recessive models; a P value of less than 0.05 was considered statistically significant. Heterogeneity between articles was examined by the I^2 index, a quantity that indicated the consistency of data from trials [9]. Fixed-effects models were used when heterogeneity across studies was low ($I^2 < 50\%$ in meta-analysis); otherwise, random-effects models were applied. Agreement or disagreement of genotype frequencies with Hardy–Weinberg equilibrium in each study was analyzed. Publication bias was evaluated using Egger's test and Begg's test, with a P value of more than 0.10 considered evidence for no potential publication bias. Meta-analysis was carried out using Review Manager 5.3 and publication bias was evaluated using Stata 14 software (Stata Corporation, College Station, Texas, USA).

In silico analysis for the putative transcription factor-binding sites affected by single-nucleotide polymorphisms

Online software Gene-Regulation (*http://www.gene-regulation.com*) was performed to predict the possible effects of the SNPs on putative alteration of transcription factor-binding sites in the relevant genes. Parameters used for the predictions were human matrices only, with a threshold score of 75.0 points (a maximum 100.0).

Results

Study characteristics

A total of 20 eligible studies were included in this meta-analysis. The characteristics of the studies are summarized in Table 1. Among these articles, 14 articles referred to SNP rs823128, 5 referred to rs1572931, and 12 articles referred to rs823156.

Quantitative synthesis

ORs of rs823128, rs1572931, and rs823156 in PD were evaluated; the results are shown in Table 2 and Supplementary Fig. 1 (Supplemental digital content 1, *http://links.lww.com/WNR/A428*). In the overall pooled analysis, PD patients showed significantly lower frequencies of the G allele and the GG genotype than control participants in SNP rs823128. The frequencies of the rs1572931T allele and the TT genotype tended to be lower in PD patients and PD patients showed rarer frequencies in the rs823156 G allele and the GG genotype compared with the controls.

Taking the ethnic variety of association between these SNPs and PD into consideration, we carried out a subgroup analysis determined by sample ethnicity. The results indicated that, for rs823128, PD patients presented lower frequencies of the G allele in the White, East Asian, and Hispanic populations. For rs1572931, PD patients showed a significantly lower frequency of the T allele than the controls in the East Asian population, and showed the same trend of the presence of the rs1572931 T allele and the TT genotype in the Mediterranean population. However, the relationship was not identified between rs1572931 and PD risk in White patients. As for rs823156 SNP, PD patients tended to have lower G allele frequency than control participants in the White population and to have lower frequencies of the G allele and the GG genotype in the East Asian population, but it showed no link between rs823156 SNP and PD risk in the Hispanic population.

In addition, genotype frequencies of rs823128 in controls disagreed with Hardy–Weinberg equilibrium in the overall pooled analysis; thus, the result of this polymorphism should be interpreted with caution.

Publication bias

Additive models were used as representatives to be performed. As shown in Table 3 and Supplementary Fig. 2 (Supplemental digital content 2, *http://links.lww.com/WNR/A429*), there was no publication bias in this study.

Table 2 Associations of rs823128, rs1572931, and rs823156 single-nucleotide polymorphisms with Parkinson's disease risk in meta-analysis

			Additive models		Recessive models		
Single-nucleotide polymorphisms	*N*	Sample size (case/control)	Odds ratio (95% confidence interval)	*P*	Odds ratio (95% confidence interval)	*P*	Hardy–Weinberg equilibrium
rs823128A > G			G/A		GG/AG + AA		
Overall	14	11 484/17 859	0.82 (0.74–0.91)[a]	0.002	0.72 (0.54–0.96)[a]	0.030	No
White	3	6411/10 973	0.80 (0.69–0.93)[a]	0.004	0.63 (0.22–1.81)	0.390	Yes
East Asian	10	4908/6692	0.84 (0.74–0.96)[a]	0.010	0.74 (0.54–1.02)	0.060	Yes
Hispanic	1	165/194	0.52 (0.33–0.83)[a]	0.006	0.51 (0.15–1.69)	0.270	Yes
rs1572931C > T			T/C		TT/CT + CC		
Overall	5	3809/3328	0.75 (0.66–0.86)[a]	< 0.001	0.47 (0.28–0.81)[a]	0.007	Yes
White	2	1835/1715	0.82 (0.64–1.05)	0.120	0.51 (0.15–1.67)	0.260	Yes
East Asian	2	1254/971	0.73 (0.64–0.83)[a]	< 0.001	0.60 (0.34–1.05)	0.070	Yes
Mediterranean	1	720/642	0.64 (0.51–0.81)[a]	< 0.001	0.14 (0.04–0.47)[a]	0.001	Yes
rs823156A > G			G/A		GG/AG + AA		
Overall	12	12 016/14 609	0.84 (0.81–0.88)[a]	< 0.001	0.75 (0.65–0.87)[a]	< 0.001	Yes
White	3	4706/5798	0.88 (0.82–0.95)[a]	< 0.001	0.81 (0.64–1.02)	0.070	Yes
East Asian	8	5865/7650	0.80 (0.75–0.85)[a]	< 0.001	0.69 (0.56–0.84)[a]	< 0.001	Yes
Hispanic	1	1445/1161	0.93 (0.80–1.08)	0.340	0.90 (0.56–1.45)	0.660	Yes

[a]Data were statistically significant in analysis.

Table 3 Results of Egger's and Begg's tests for publication bias (additive models)

			Begg's test		Egger's test	
Single-nucleotide polymorphisms	Model	Number of studies	*Z*	*P*	95% confidence interval	*P*
rs823128A > G	G vs. A allele	14	0.88	0.381	−1.05–4.25	0.213
rs1572931C > T	T vs. C allele	5	−0.24	1.000	−14.00–5.55	0.263
rs823156A > G	G vs. A allele	12	−1.58	0.115	−2.93–0.61	0.175

In-silico analysis

Through bioinformatic analysis using online software Gene-Regulation, we predicted the modified transcription factor-binding sites caused by rs823128, rs1572931, and rs823156. As shown in Fig. 1, in silico analysis, change at rs823128 was predicted to add a binding site for HOXA3 transcription factor (score, 87.5) and eliminated the sites for TSC2 (score, 100.0) and TOPORS (score, 100.0). Change at rs1572931, the transcription factor-binding sites for CTCF (score, 100.0), and estrogen receptor-β (score, 100.0) were predicted to be added and the site for PGR (score, 100.0) was predicted to be eliminated. As for change at rs823156, the SNP was identified to add putative the transcription factor-binding sites for NP-4 (score, 100.0) and RARA (score, 100.0) transcription factors and to eliminate the binding site for the NFASC (score, 100.0) transcription factor.

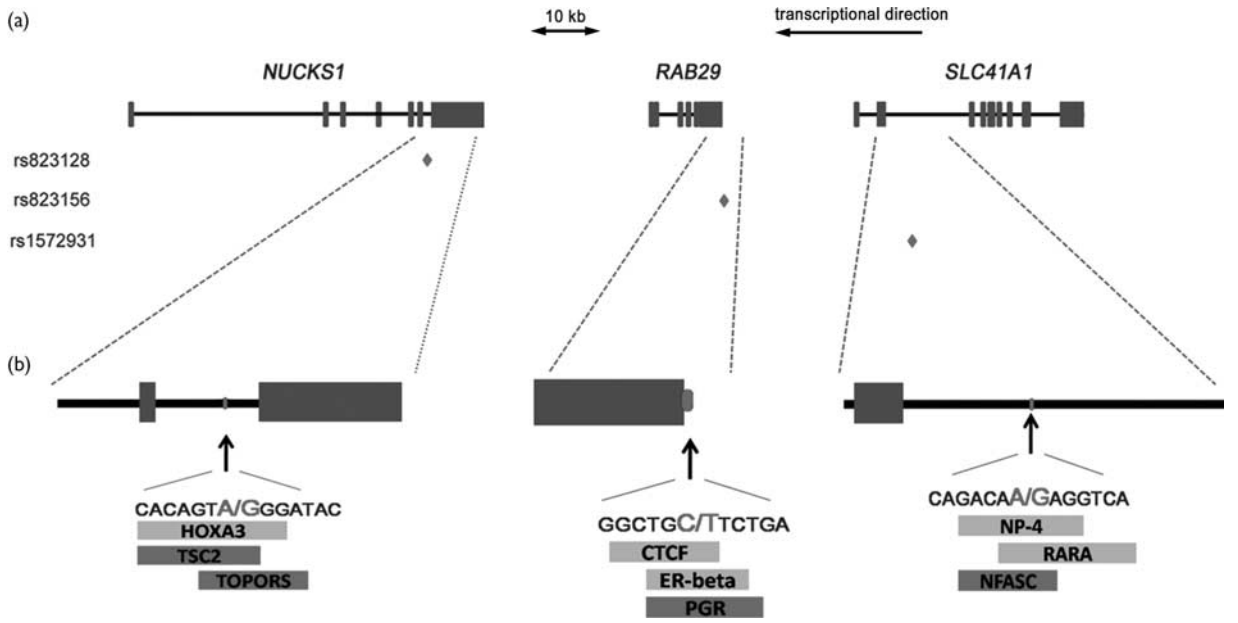
Discussion

In this meta-analysis, the results of overall pooled analysis showed that rs823128, rs1572931, and rs823156 SNPs within *PARK16* were associated with PD susceptibility. The minor alleles of rs823128A > G, rs1572931C > T and rs823156A > G were associated with a reduced PD risk and polymorphisms of these three SNPs showed ethnicity-specific effects on PD, which were consistent with a previous report [24]. The ethnic differences in the relationships between SNPs and PD risk were widely considered to be influenced by environmental factors, such as lifestyles of patients and the extent of pollution in the surroundings [24]. However, the detailed mechanisms of these ethnic differences still need to be confirmed by further investigation.

SNPs rs823128, rs1572931, and rs823156 were identified to be located in *NUCKS1*, *RAB29*, and *SLC41A1*, respectively. Therefore, these genes were implicated to play protective roles in PD.

NUCKS1, the gene rs823128 SNP locates in, is a housekeeping gene expressed in various types of cells. It is a vertebrate-specific gene. Its coding protein, NUCKS1, is a chromatin-associated protein with a role in DNA damage response and homologous recombination [25]. It is responsible for repairing DNA and maintaining chromosome stability, and dysfunction of the protein may lead to increasing cellular sensitivity to the harmful substance, such as reactive oxygen species (ROS) [26]. Although accumulating evidence provided suggestive support that SNP rs1572931 in *NUCKS1* was associated with PD risk, its molecular mechanism is still obscure to date. However, the interaction between ROS-damaged DNA and impairment of DNA repair capability in neurons was found to be an important causative factor of PD, suggesting that capability of DNA repair regulated by NUCKS1 played a critical function in PD prevention [27].

Fig. 1



The putative effects of rs823128, rs1572931, and rs823156 on transcription factor-binding sites. (a) Scheme of the N*UCKS1/RAB29/SLC41A1* (between 205 712 819 and 205 813 759 according to genome assembly GCRh37) showing the structure of *NUCKS1*, *RAB29,* and *SLC41A1* genes (exons are in blue rectangles). The three diamonds represent the locations of the three SNPs analyzed in this study. (b) Enlargement of the partial regions of *NUCKS1*, *RAB29*, and *SLC41A1* the SNPs is located, is conducted. Below, the positions and sequences of rs823128, rs1572931, and rs823156 are presented. The rectangles represent the length of the transcription factor-binding sites. The predicted changes associated with the different alleles are highlighted: additional transcription factor-binding sites are in green and eliminated transcription factor-binding sites are in red. NUCKS1, nuclear casein kinase and cyclin-dependent kinase substrate 1; RAB29, Ras-related protein Rab29; SLC41A1, solute carrier family 41 member 1; SNP, single-nucleotide polymorphism.

RAB29, where rs1572931 locates, is considered to exert protective effects on PD. Its coding protein, as a member of the Ras-related GTP-binding protein subfamily, is ubiquitously expressed in human tissues. The protein has been identified to cooperate with leucine-rich repeat kinase 2 (LKKR2) to reduce human PD risk [28]. LKKR2, a confirmed PD-related protein, was identified to possess GTPase activity [29]. It could activate the Ras signaling pathway and autophagy in neurons when formed as a protein complex with RAB29. The RAB29-LRRK2 complex, as an activator of the Ras signaling pathway, could promote the clearance of a series of PD-causing factors (such as α-synuclein and ROS) in neurons, thus preventing the development of PD [30,31]. In addition, the RAB29-LRRK2 complex was also found to be able to regulate axonal elongation in neurons, contributing toward improving the function of learning and memory in PD patients [29].

SLC41A1, the gene rs823156 SNP locates in, plays a vital role in physiological function. SLC41A1 protein, as a Na^{+}/Mg^{2+} exchanger in eukaryotes, is responsible for balancing magnesium homeostasis, promoting normal metabolism, and maintaining physiological function in the body [32]. SLC41A1 is expressed in numerous tissues, including the kidney and the brain. The SLC41A1 protein in renal epithelial cells of distal convolution plays a crucial role in transcellular Mg2+ reabsorption in the distal convoluted tubule, contributing to magnesium homeostasis in cells, tissues, serum and cerebrospinal fluid. Decreased SLC41A1 expression/activity might decrease the SLC41A1-dependent magnesium recycle of cells, thus causing hypomagnesemia, and decreasing the free intracellular Mg^{2+} in cells [33]. Experimental evidence based on the PD-like dopaminergic cell line PC12 showed that free intracellular Mg^{2+} protected cells from damage of oxidant stress, and expression deficiency of magnesium transporter protein could significantly attenuate the oxidation resistance, thus increasing the susceptibility of neurodegenerative diseases including PD [34]. In all, Mg^{2+} homeostasis regulated by SLC41A1 may play an important role in PD prevention and treatment.

Taken together, this analysis suggests that, *NUCKS1*, *RAB29*, and *SLC41A1*, the gene of the *PARK16* locus, might exert preventive effects on PD; minor variants of these SNPs (rs823128A > G in *NUCKS1*, rs1572931C > T in *RAB29*, and rs823156A > G in *SLC41A1*) were associated with reduced PD risk. Interestingly, all of these SNPs were variants in noncoding regions. To date, there are two known means for noncoding variants to alter the function of relevant genes: (a) to cause the alterative splicing of gene [35] and (b) to alter the binding of transcription factors with

genes [36]. To our knowledge, there are no data showing alterative splicing in *NUCKS1*, *SLC41A1*, or *RAB29* caused by SNPs or noncoding variants. Thus, here, our study focused on the putative alteration of transcription factor-binding sites in these genes. Through bioinformatic analysis, we predicted that the up-regulated relevant DNA-binding capability of transcription factors HOXA3, CTCF, estrogen receptor-β, NP-4 and RARA might play protective roles in PD through regulating gene transcription, and the capability block of transcription factors TSC2, TOPORS, PGR and NFASC might have the same effects. However, the exact effects of these transcription factors on the function of the relevant genes and on the pathophysiology of PD are still obscure and need further investigation.

In summary, this study indicated that SNPs of *NUCKS1*, *RAB29*, and *SLC41A1*, located in *PARK16*, were associated with reduced PD risk. It suggested the potential roles of genes *NUCKS1*, *RAB29*, and SLC41A1 in PD, and might reveal any potential targets for PD prevention and treatment. Besides these, the findings indicated ethnicity-specific effects of rs823128, rs1572931, and rs823156 SNPs on PD, which might be useful in future genetic counseling, to assess PD susceptibility for carriers with different ethnicities. For these ethnicity-specific effects of *PARK16*, although the detailed mechanisms are still unclear, they showed potential population differences in PD susceptibility and PD predisposing factors across ethnicities. However, future well-designed studies, including studies with more clinical and more experimental evidence, are needed to shed more light on these findings. In addition, ethnicity-specific effects of the SNPs on PD susceptibility, even located in the same gene, are still unclear, which should be further explored as well.

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Conflicts of interest

There are no conflicts of interest.

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