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Genetic analysis of SIRT1 gene promoter in sporadic Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. To date, genetic causes and underlying molecular mechanisms for sporadic PD remain largely unknown. Sirtuis are highly conserved NAD-dependent class III deacetylases. SIRT1, the closest to yeast Sir2, has deacetylase activity and ADP-ribosyltransferase activity. SIRT1 gene has been connected to many cellular processes and implicated in human diseases, such as obesity, type 2 diabetes, cancer and neurodegenerative diseases. Studies in animal model have also associated SIRT1 with aggregation of alpha-synuclein, a critical protein in the PD pathogenesis. We hypothesized that the genetic variants within the regulatory regions of SIRT1 gene that repress its gene expression, rather than mutations in its coding region that abolish SIRT1 function, may contribute to PD as a risk factor. In this study, we genetically analyzed the promoter region of SIRT1 gene in sporadic PD patients and ethic-matched healthy controls. Three novel heterozygous sequence variants, g.69644133C>G, g.69644213G>A and g.69644351G>A, were identified in PD patients, but in none of controls, which may alter the transcriptional activities of SIRT1 gene promoter, resulting in reduced SIRT1 levels. One novel heterozygous variant, g.69644219G>A, linked with single-nucleotide polymorphism – g.69644217A>C (rs932658), was only found in one control, which may have no functional activity. Therefore, our results suggested that genetic variants within the SIRT1 gene promoter may repress SIRT1 gene expression, contributing to PD as a risk factor.

1. Introduction

Parkinson's disease (PD) is one of the common neurodegenerative diseases affecting 1–2% of populations over 65 years old. The clinical features include bradykinesia, resting tremor, rigidity and postural instability. Pathologically, PD is characterized by Lewy body deposition and dopaminergic neuronal loss in the substantia nigra. Alpha-synuclein protein, the major components of Lewy bodies, has been demonstrated to play a central role in the PD pathogenesis [1]. Although more than 16 genetic loci and genes, such as SNCA, PINK1, Parkin, LRRK1, UCHL-1, DJ-1 and GBA genes, have been associated with familiar PD cases [2–4], genetic causes and underlying molecular mechanisms for sporadic PD remain largely unknown.

Sirtuis are highly conserved NAD-dependent deacetylases from yeast to human [5]. In lower organisms, such as yeast, worm and fly, surtuins have been shown to regulate lifespan. In mammals, seven sirtuin family members, SIRT1-SIRT7, have been identified with different cellular locations, enzyme activities, target substrates and tissue-specificity. As one that is the closest to yeast Sir2 (silent information regulator 2), SIRT1 has been extensively studied. Localized in the nucleus and the cytoplasm, SIRT1 has deacetylase activity and ADP-ribosyltransferase activity. SIRT1 has been shown to deacetylate histones, preferentially lysine residue 9 of histone 3 and lysine 16 of histone 4, and transcription factors, as well as diverse non-histone proteins. Accumulating evidence has associated SIRT1 with genomic stability, transcription, metabolism, cell stress response neuronal functions and aging process. SIRT1 gene has been also implicated in inflammation, obesity, type 2

Abbreviations: ATG, autophagy-related genes; CREB, cAMP response element-binding protein; DJ-1, Parkinson's disease gene 7; DRAM, damage-regulated autophagy modulator; FOXO, forkhead box transcription factor; GBA, lysosomal glucocerebrosidase; HIC1, hypermethylated in cancer 1; LC3, microtubule-associated protein 1 light chain 3 alpha; LRRK1, leucine-rich repeat kinase 1; NFκB, nuclear factor κB; PARP-2, poly(ADP-ribose) polymerase-2; PD, Parkinson's disease; PGC1α, peroxisome proliferator-activated γ receptor coactivator 1α; PINK1, PTEN-induced kinase 1; PPARs, peroxisome proliferator-activated receptors; Sir2, silent information regulator 2; SIRT1, surtuin 1; SNCA, alpha-synuclein gene; UCHL-1, ubiquitin carboxy-terminal hydrolase L-1.

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diabetes, cardiovascular diseases, cancer and neurodegenerative diseases [6–8].

Many studies in animal model have associated SIRT1 gene with neurodegeneration. SIRT1 activation protects neuronal axons from degeneration in mice [9]. In mouse models of Alzheimer's disease, overexpression of SIRT1 gene in the brain or activation of SIRT1 gene with genetic and pharmacological approaches prevent amyloid plaque formation and ameliate neurodegeneration [10,11]. In mammalian models of Huntington's disease, SIRT1 provides a neuroprotection from mutant huntingtin [12,13]. Resveratrol, a SIRT1 activator, reduces the toxicity of alpha-synuclein protein in cultured cells [14]. In PD animal models, overexpressed SIRT1 gene reduces the alpha-synuclein aggregation [15]. Therefore, SIRT1 may provide a neuronal protection in PD patients.

Numerous studies have shown that SIRT1-null deleted mice die perinatally with serious developmental defects [16,17]. Considering the disparate function of SIRT1, we hypothesized that genetic variants within its regulatory regions that alter the levels of SIRT1 gene expression, rather than the mutations in its coding regions that abolish SIRT1 function, may contribute to PD as a risk factor. In this study, we genetically analyzed the promoter regions of SIRT1 gene in sporadic PD patients and healthy controls.

2. Materials and methods

2.1. Study subjects

All patients with sporadic PD ($n = 97$, mean age 66.78 years, male 49, female 41) and ethic-matched healthy controls ($n = 127$, mean age 60.31 years, male 66, female 57) were recruited from Division of Neurology, Jining Medical College Affiliated Hospital, Jining Medical College, Jining, Shandong, China. PD patients were diagnosed by two neurologists. Healthy controls were recruited from Health and Physical Examination Center of the same hospital. The PD patients and controls with a family PD history were excluded. This study was approved by the Human Ethic Committee of Jining Medical College Affiliated Hospital. Informed consents were obtained.

2.2. Genetic analysis

Genomic DNAs were extracted from peripheral leukocytes with QIAGEN DNeasy Blood and Tissue Kit (Qiagen, Valencia, CA, USA). Two overlapped DNA fragments, covering the putative promoter region of SIRT1 gene (−841 bp upstream to the transcription start site) were generated by PCR with 100 ng DNA template and PCR supermix (Invitrogen, Carlsbad, CA, USA). The PCR primers were designed based on the genomic sequence of human SIRT1 gene (Genebank access number, NC_000010) and shown in Table 1. The DNA fragments were sequenced on a 3730 DNA Analyzer (Applied Biosystems, Foster city, CA, USA). The sequences were aligned and compared with the promoter region of SIRT1 gene. The distributions of sequence variants were compared between PD patients and controls using SPSS v13.0. $P < 0.05$ was considered statistically significant.

3. Results

The distribution of the sequence variants within the SIRT1 gene promoter were summarized in Table 2. The locations of the variants were depicted in Fig. 1A. Five single-nucleotide polymorphisms (SNPs), g.69643959A>G (rs3740051), g.69644217A>C (rs932658), g.69644240G>T (rs35995735), g.69644335A>G (rs3740053) and g.69644341G>C (rs2394443) were found in PD patients and controls with similar frequencies (P>0.05). Three novel heterozygous variants, g.69644133C>G, g.69644213G>A and g.69644351G>A, were identified in three PD patients, but in none of controls (Fig. 1B). Analysis of SIRT1 gene promoter region with transcription element search system (TESS, University of Pennsylvania) suggested that these novel variants may change the putative transcription factor binding sites and alter the transcriptional activity of SIRT1 gene promoter. One novel heterozygous variant, g.69644219G>A, linked with the SNP g.69644217A>C (rs932658), was found in one control, but in none of PD patients, which may have no functional activity.

4. Discussion

In this study, we found three novel heterozygous sequence variants, g.69644133C>G, g.69644213G>A and g.69644351G>A, in PD patients, but in none of controls. Our results suggested that these variants may alter the putative transcriptional factor binding sites of SIRT1 gene promoter and reduce SIRT1 levels, contributing to the PD onset as a risk factor. Although previous studies indicate that SIRT1 gene SNPs and variants increase the risk of obesity and type 2 diabetes [18–20], genetic analysis of SIRT1 gene has not been reported in PD patients. In this study, we, for the first time, connected the sequence variants within SIRT1 gene promoter with sporadic PD.

Human SIRT1 gene, localized to chromosome region 10q21.3 with 9 exons, is widely expressed in fetal and adult tissues [21]. The promoter region of the human SIRT1 gene has not been characterized in details. At various metabolic states, SIRT1 gene expression is regulated by transcriptional factors, such as CREB (cAMP response element-binding protein), FOXO1 (forkhead box transcription factor 1), HIC1 (hypermethylated in cancer 1), PARP-2 (poly(ADP-ribose) polymerase-2) and PPARs (peroxisome proliferator-activated receptors) [7,22–26]. The sequence variants within the promoter region of SIRT1 gene identified in this study may change the putative transcription factor binding sites and repress SIRT1 gene expression in PD patients. In addition, the levels of SIRT1 gene expression were similar in the human brain samples from PD and related disease and controls [27], which may be limited by the small sample size and genetic heterogeneity of PD.

In eukaryotic cells, there are two main proteolytic pathways, autophagy and proteosome [28,29]. Autophagy is a highly conserved cellular process that delivers its components to lysosomes for degradation. There are three subtypes, macroautophagy, microautophagy and chaperone-mediated autophagy. Autophagy is essential to cell differentiation and proliferation, development, homeostasis, immunity and aging process and has been implicated in infection, cancer, neurodegenerative diseases and cardiomyopathy [30–32]. Increasing

Table 1
The PCR primers for the promoter regions of SIRT1 gene.

PCR primers	Sequences	Location	Position to TSS
SIRT1-F1	5′-AGAGGAAAGTGGAAGGGCTT-3′	69643406	−841
SIRT1-R1	5′-TTTCCCACTCTCCTCACACC-3′	69643926	−321
SIRT1-F2	5′-CCATCTTCCAACTGCCTCTC-3′	69643892	−355
SIRT1-R2	5′-AGGAGCTGTCAGAACGGTGT-3′	69644483	+237

PCR primers were designed based on the genomic DNA sequence of SIRT1 gene (NC_000010), in which transcription start site (TSS) is at the position of 69644427 (+1).

Table 2
Sequence variants within the SIRT1 gene promoter regions in PD patients and controls.

Sequence variants	Genotypes	Location[a]	PD (n = 97)	Controls (n = 127)	P value
g.69643959A>G (rs3740051)	AA	−468 bp	57	77	0.778
	AG		34	45	
	GG		6	5	
g.69644133C>G	CG	−334 bp	1	0	–
g.69644213G>A	GA	−214 bp	1	0	–
g.69644217A>C (rs932658)	AA	−210 bp	64	96	0.055
	AC		30	31	
	CC		3	0	
g.69644219G>A	GA	−208 bp	0	1	–
g.69644240G>T (rs35995735)	GG	−187 bp	95	121	0.246
	GT		2	6	
	TT		0	0	
g.69644335A>G (rs3740053)	AA	−92 bp	54	72	0.973
	AG		37	48	
	GG		6	7	
g.69644341G>C (rs2394443)	GG		64	96	0.055
	GC	−86 bp	30	31	
	CC		3	0	
g.69644351G>A	GA	−76 bp	1	0	–

[a] Locations of variants upstream (−) to the transcription start site at 69644427 of NC_000010.

evidence indicates that α-synuclein protein, the critical protein in the PD pathogenesis, is mainly degraded by macroautophagy and chaperone-mediated autophagy [33,34]. SIRT1 deacetylates critical autophagy-related (ATG) genes, such as ATG5, ATG7 and LC3 (microtubule-associated protein 1 light chain 3 alpha) [35]. The effects of SIRT1 on lifespan prolonging is mediated by autophagy [36]. SIRT1 overexpression and resveratrol activate autophagy in animal models of PD [15,37]. Therefore, reduced SIRT1 activities may be linked to the PD pathogenesis with impaired autophagy activities as a major pathway.

To date, a number of substrates for SIRT1 have also been identified, such as FOXO (Forkhead transcription factor O), NFκB (nuclear factor κB), P53 and PGC1α (peroxisome proliferator-activated γ receptor coactivator 1α), as well as histones and ATGs [7,38]. SIRT1 also functions by forming complex with its co-factors

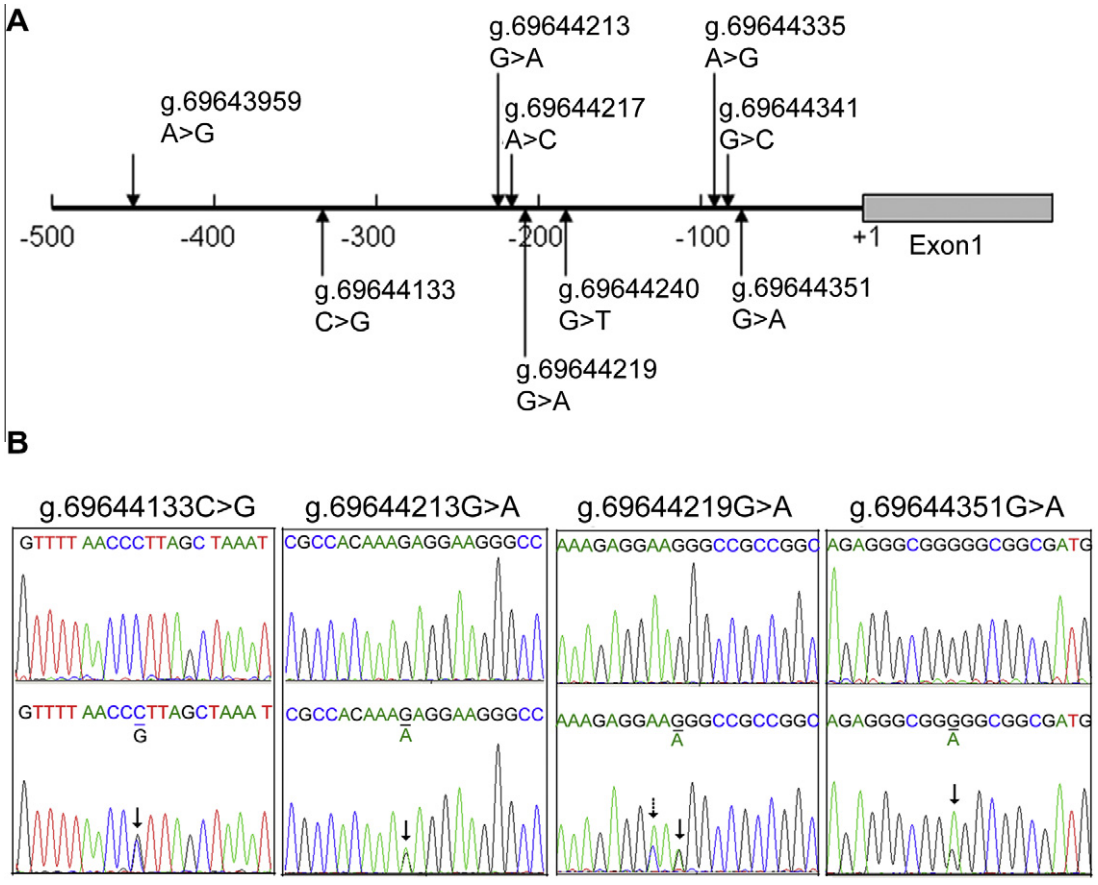

Fig. 1. The sequence variants within the promoter regions of SIRT1 gene in PD patients and controls. (A) Schematic representation of the sequence variants within the SIRT1 gene promoter. The numbers represents the sequence of SIRT1genomic sequences (Genebank accession number NC_000010). All the sequence variants were depicted. The transcription starts at the position of 69644427 of the first exon. (B) Chromatograms of the novel heterozygous sequence variants in forward orientations. Top panel shows wild type and bottom heterozygous. All the variants are marked with solid arrows. The SNP- g.69644217A>C (rs932658), which was linked with the variant g.69644219G>A, was indicated with dashed arrow.

[7]. P53, a tumor repressor, has been shown to regulate autophagy [39,40]. DRAM (Damage-regulated autophagy modulator), a direct target of p53, controls the formation of autophagosomes [41]. In human neuroblastoma SH-SY5Y cells, P53 mediates induction of autophagy [42]. NFκB, a master regulator of inflammation, indirectly regulates autophagy [43–45]. Overexpression of PGC-1a gene in mice protects the dopaminergic neurons from degeneration [46]. Therefore, reduced SIRT1 activity may lead to impaired autophagy, dysfunctional mitochondria and inflammation, contributing to the PD pathogenesis. The molecular mechanisms by which SIRT1 is linked to PD need to be investigated.

In conclusion, we genetically analyzed the promoter regions of SIRT1 gene in sporadic PD patients. Three heterozygous variants identified in sporadic PD patients, but in none of controls, may contribute to the PD onset as a risk factor. As natural compounds have been identified to regulate SIRT1 activities [47], our findings may provide an insight into designing potential personalized therapy for sporadic PD patients.

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