Chapter

The Relationship between Alpha-Synuclein (SNCA) Gene Polymorphisms and Development Risk of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder affecting the motor system and occurring in the central nervous system. One of the symptoms of PD is accumulation of Lewy bodies and Lewy neurites. The alpha-synuclein (SNCA) gene is part of the protein complex called Lewy body. The SNCA gene encoding a presynaptic protein product is thought to play a role in PD-related important pathways. It is suggested that there is a relationship between the risk of PD development and SNCA levels, and it is suggested that SNCA level is an important marker in PD diagnosis. Various polymorphisms have been identified in the 5′ and/or 3′ UTR regions of the SNCA gene, and as a result of these polymorphisms, changes occur in the binding of transcription factors. The identification of the roles of SNCA gene polymorphisms in PD development may enable the development of new methods for the treatment of PD.

Keywords: Parkinson's disease, neurodegenerative disorders, SNCA gene polymorphisms, Lewy bodies, SNCA levels

1. Introduction

The most important feature of age-related neurodegenerative diseases is the slow and irreversible deterioration of brain function. PD affects the motor system and is a neurodegenerative disorder of the central nervous system [1]. The prevalence of PD, which is known to be the second progressive neurodegenerative disease, increases with age. PD, which causes severe morbidity, has motor symptoms such as tremors, bradykinesia, muscle stiffness, and postural instability and non-motor symptoms, i.e., autonomic dysfunction, sensory symptoms, sleep disturbances, and fatigue. These symptoms occur as a result of the progressive neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta, clustering of proteins within the brain, Lewy bodies, and Lewy neurites [2, 3]. As a result of degeneration of dopaminergic neurons, movement disorder occurs, and the cause of this movement disorder is the neurotransmitter dopamine deficiency. Although the basic mechanism of neuronal death in PD is unknown, genetic and environmental factors have been found to be effective in the pathogenesis of the disease [4].

It has been reported that many genes play a role in the pathogenesis of PD, and polymorphisms in these genes may be genetic risk factors for PD development [5]. A large number of different DNA variants have been identified in disease genes associated with familial PD in molecular genetic analyses. These genetic variants include SNCA, Parkin (PARK2), PTEN-induced putative kinase 1 (PINK1), DJ-1 (PARK7), and leucine-rich repeat kinase 2 (LRRK2) variants [6].

The SNCA gene plays a role in important pathways associated with PD. It is suggested that there is a significant relationship between SNCA levels and the risk of PD development, and SNCA levels are thought to be an important marker in the diagnosis of PD. Several studies have been conducted to explain the relationship between genetic polymorphisms in different regions of the SNCA gene and risk of PD [7].

Polymorphisms that occur in different regions of the SNCA gene, an important gene for PD etiology, have been identified in relation to PD [7, 8]. Changes in SNCA expression levels are one of the main mechanisms of SNCA to cause PD [7, 9, 10]. As a result of polymorphisms in the 5′ and 3′ UTR regions of the SNCA gene, the binding of transcription factors and miRNAs can be altered, and promoter activity is affected. Thus, gene expression can be regulated. According to the general results from the studies aimed to investigate the relationship between SNCA gene polymorphisms and the risk of PD development, the SNCA gene and some polymorphisms of this gene have been identified as genetic risk factors in PD development [7].

The purpose of this chapter is, in addition to giving general information about PD, to summarize the studies that investigated on the relationship between SNCA gene polymorphisms and the risk of developing PD.

2. Parkinson's disease

Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's disease, affects approximately 1–2% of individuals over 65 years of age [11, 12]. The incidence of PD usually begins after 50 years of age and increases more after 60 years of age [13]. The prevalence of PD increases approximately 4% in people over 85 years of age [6]. PD is a neurological disorder associated with increased morbidity and reduced survival [14, 15].

PD is characterized by bradykinesia, resting tremor, rigidity, and postural instability. PD is associated with the formation of Lewy bodies [16]. Lewy bodies of postmortem that are determined in brain autopsy specimens are the distinguishing features of PD. These bodies are observed in intense eosinophilic nuclei and cytoplasmic inclusions. The presence of intraneuronal protein inclusions, called Lewy bodies or Lewy neurites, is one of the neuropathological features of PD [17].

In PD, in addition to motor symptoms, non-motor symptoms occur. Motor symptoms in PD are due to the selective loss of dopaminergic neurons in the midbrain and the axon terminals reflected in the dorsal striatum [18]. Motor symptoms occur when neuronal cell loss reaches 80% or more as a result of progressive loss in the dopaminergic neurons of substantia nigra pars compacta [19]. Non-motor symptoms of PD are autonomic dysfunction and cognitive impairment [20]. The motor and non-motor symptoms of PD are caused by the loss of the dopaminergic neurons of the substantia nigra [21–23]. PD is defined as a syndrome because it is a complex disease characterized by motor and non-motor symptoms [20].

The majority of PD cases are sporadic cases; however, it is known that 10–15% are familial cases, and the majority of these cases are hereditary. Environmental and genetic factors play a role together in the pathogenesis of PD, which has a complex etiology [24].

3. Protein encoded by SNCA gene

SNCA protein is the major protein of Lewy bodies. This protein is a presynaptic phosphoprotein that has a specific tendency to aggregation that plays an important role in both hereditary and idiopathic PD [25]. SNCA protein and fibrils constitute Lewy bodies [16]. In Lewy bodies, SNCA protein is predominant and is therefore known to be associated with the etiology of PD. SNCA also has an important function in the pathological process of PD [26, 27]. SNCA, an important component of Lewy bodies, is one of the distinctive features of PD [28–30].

The SNCA protein, which contains 144 amino acids, found as a soluble protein, not naturally folded in the cytoplasm, is encoded by three different SNCA transcripts. The function of the SNCA protein in the brain is still not fully elucidated, but it has been found to play an important role in the neurotransmitter release and vesicle cycle at presynaptic terminals [6]. SNCA plays an important role in the regulation of neurotransmitter release, synaptic function, and plasticity of dopaminergic neurons [31–33].

Dopamine from presynaptic vesicles plays an important role in the normal functioning of a presynaptic complex [34–36]. Function of the SNCA protein, which is highly expressed in the brain; is the vesicle formation required for storage and transport of dopamine. Dopamine transported from the presynaptic neuron to the postsynaptic neuron is important for smooth and coordinated movements of the body. As a result of mutations in the SNCA protein, the vesicle that required for the dopamine transport cannot form, and the aggregates are formed. These aggregates are identified as important distinguishing features in PD pathogenesis. Genetic changes known to be effective in PD pathogenesis disrupt normal function of SNCA protein [37, 38].

4. Gene of SNCA

The SNCA gene is localized on the fourth chromosome in the human genome. It is the first gene associated with PD that contains a pathogenic missense mutation (Ala53Thr) responsible for the disease in a large Italian family [6]. The SNCA gene plays a role in important pathways associated with PD and encodes the presynaptic protein product. Therefore, this gene is one of the genes that are extensively studied among PD susceptibility genes [39].

It is the first causal gene in familial PD, and it encodes SNCA with main component of Lewy bodies. Lewy bodies accumulate in neural cells in familial PD cases. The reason of this accumulation is overproduction of SNCA. Overproduction of normal SNCA also plays an important role in the pathogenesis of sporadic PD [40].

The chromosomal location is presented in **Figure 1**.

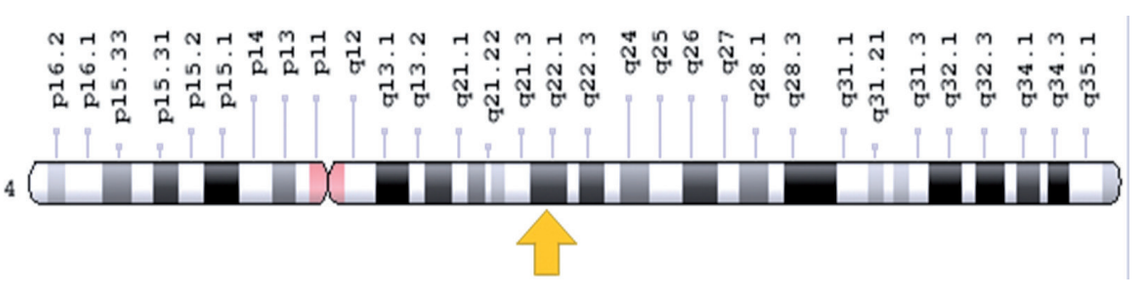

Figure 1.
Chromosomal location of SNCA gene [41].

5. Gene polymorphisms of SNCA

Genetic predisposition plays an important role in the etiology of PD. Multiple linkage and genome-wide association studies (GWAS) were performed to determine genetic polymorphisms in the SNCA gene. Single-nucleotide gene polymorphisms in the SNCA gene were found to be associated with increased PD risk. Single-nucleotide polymorphisms in the SNCA gene can lead to a change in PD susceptibility, resulting in increased or decreased PD risk. Several genes and several polymorphisms of the SNCA gene have been identified in GWAS. It has been determined that some of these gene polymorphisms may be important risk factors especially for sporadic PD [26]. Polymorphisms in different regions of the SNCA gene have been studied in various studies with different populations [7]. Genetic risk factors are very important in the development of PD, and up to now, 16 loci have been identified, which are known to be associated with the development of PD. Very few of the PD, which is mostly sporadic, are familial. The cause of familial PD development is autosomal recessive or dominant mutations. In particular, mutagenic mutations (SNCA, LRRK2, PRKN, DJ-1, and PINK1) occurring in five genes were found to be related to familial PD. Six loci such as MAPT, SNCA, HLA-DRBS, BST1, GAK, and LRRK2, which are associated with sporadic PD, are also defined. In a meta-analysis of various GWAS studies, five new loci identified to be associated with idiopathic PD were identified. ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R loci are found among these loci [20]. SNCA mutations contribute to PD development as a result of amino acid displacements and configuration changes in the encoded protein [41, 42].

Mata et al. found that SNCA gene polymorphisms were important risk factors for PD development risk. In a study conducted by Mata et al., a significant relationship was found between SNCA plasma levels and rs356219 single-nucleotide gene polymorphism [43]. In a study conducted with the Korean population, it was determined that the G allele of rs356219 gene polymorphism was associated with the risk of PD development [44]. In studies conducted with populations of North America, Spain, Russia, and China, rs356219 gene polymorphism was identified as a genetic risk factor for PD development risk [26].

In several families of Greek origin and in families of Asian, Swedish, and Polish origins, p.Ala53Thr polymorphism, one of the rare mutations in the SNCA gene, was detected [6].

In a study that performed to investigate the relationship between rs2301134, rs2301135, rs356221, and rs11931074 gene polymorphisms and PD development risk, the significant relationship was determined between two promoter polymorphisms of the SNCA gene (rs2301134 and rs2301135 gene polymorphisms) and PD development risk. In this study, genotype frequencies in rs11931074 gene polymorphism in 3′ UTR region of SNCA gene were found to be significantly different in patient and control groups. In this study conducted with the Iranian population, SNCA gene polymorphisms were identified as a genetic risk factor in PD development. In another study, the relationships between the rs2301134, rs2301135, rs11931074, and rs356221 gene polymorphisms and the risk of PD development were determined in the SNCA gene. In this study, CC genotype and C allele of rs2301134 gene polymorphism were found to be related to increased PD risk. In addition, CC genotype and C allele of rs2301135 gene polymorphism and GG genotype of rs11931074 gene polymorphism were determined to be associated with decreased PD [6]. In another study conducted with the Han-Chinese population, rs2301135 gene polymorphism was found to be an important risk factor for sporadic PD development. However, rs356221 gene polymorphism was not effective in PD development [45]. Mata et al. also found that SNCA gene polymorphisms

were important risk factors for PD development risk [43]. A meta-analysis study to determine 10 candidate single-nucleotide polymorphisms of the SNCA gene showed a significant relationship between rs11931074 gene polymorphism and PD development risk [28]. In a study conducted in the United States, it was found that some single-nucleotide gene polymorphisms in the SNCA gene were associated with the risk of PD development, but no significant relationship was determined between rs11931074 gene polymorphism and PD development risk [46]. In a study conducted with a South American Brazilian population, the relationship between rs2583988, rs356219, rs2736990, and rs11931074 gene polymorphisms and the risk of PD development was investigated, and the significant relationship was determined between rs356219 gene polymorphism and increased cognitive disorder in PD patients [13]. In studies conducted with European and North American populations, rs2736990 gene polymorphism has been identified as a genetic risk factor in PD development [47]. In another study conducted with a Chinese population, a significant relationship was found between the T allele of the rs11931074 polymorphism of the SNCA gene and the G allele and PD risk of the rs894278 polymorphism. G allele of gene polymorphism of rs11931074 was found associated with decreased progression PD risk [29]. Primer sequences for rs2301134, rs2301135, rs356221, and rs11931074 gene polymorphisms are presented in **Table 1** [7].

In a study conducted by Yu et al. with Han-Chinese population, a significant relationship was found between the risk of PD development and the polymorphism of rs7684318, which is the intronic polymorphism of the SNCA gene [48].

Rep 1, a complex microsatellite repeat of about 10 kilobases in length, is located in the translation start region of the SNCA gene. In some studies, a significant relationship was found between specific SNCA-Rep 1 alleles and the risk of late onset idiopathic PD development. However, there are also studies indicating that Rep 1 risk alleles are not a genetic risk factor for the development of idiopathic PD or that these risk alleles and PD development are inversely related [49]. Rep 1 polymorphic microsatellite repeat is localized in the promoter region (above 10 kb the transcription start site) of the SNCA gene [49]. Rep 1–261 is a microsatellite polymorphic variant associated with an increase in SNCA mRNA levels [47]. There are two common Rep 1 alleles as 251 and 261 bp in length, and functional assays about these alleles were performed. According to these functional analyses, while a significant relationship was found between the risky allele with a length of 261 bp and the upregulation of SNCA gene expression, a significant relationship was found

SNPs	Forward primer (5′-3′)	Reverse primer (5′-3′)
rs2301134	F_1: AAAGGGTCCTGAGGGTGCAA F_0: CTGAAATTTAATCACGGTC ACAGGTTA	R_1: CCTGTGACTCTTCCTTAGTAG TCTCACC R_0: GAAAAGCCTTAGGACCGCTTGT
rs2301135	F: TCCACAAGAGTGCTCGTGAC	R_1:CTGATTTGTCAGCGCTTCTG R_2: CTGATTTGTCAGCGCTTCTC
rs356221	F_1: GTTCATAAGAGAAG CCATCCTACTA F_0: CATGGGTTAGGTTTCATTTTGT	R_1: GTTGATCTGCAACTATAGGT TAAGAA R_0: ATTGGAAGCAGTTAAACCACAT
rs11931074	F_1: AATTGTGAATATGTCTTTGACCGG F_0: ATTCTGTCACTGGGTAGGCAGA	R_1: CAGCCTTCCAAATCATAAT TCCTTA R_0: TCTGTAGAAAGAACCCATTTGGC

PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism.

Table 1.
Primer sequences used in PCR for single-nucleotide polymorphisms (rs2301134, rs2301135, rs356221, and rs11931074).

between protective variant 259 bp length and decreased SNCA gene expression [49]. In addition, variability in the length of the Rep 1 repeat sequence is associated with PD susceptibility. Genotypes containing 263 bp allele of this sequence were associated with increased risk of PD development, and genotypes containing 259 bp allele were associated with decreased risk of PD development [42]. Changes in the promoter region and genetic variations in 30 untranslated SNCA gene regions have been associated with susceptibility to PD [49]. In the SNCA promoter (SNCA-Rep 1), it was determined that the localized Rep 1 and 3′ untranslated region polymorphisms interfered with the transcription binding regions and played an important role in increasing PD susceptibility. Thus, target regions of miRNAs that alter SNCA gene expression are formed or disappear [26]. The significant difference was determined between Rep 1–259 allele and low levels of SNCA mRNA in post-mortem brain tissues of patients with PD. Rep 1 microsatellite repeat and rs2583988, rs2619363, rs2619364 gene polymorphisms were found to be a relationship between. In a study conducted with a population selected from Belgium, Germany, and Serbia, the relationship was found between Rep 1 microsatellite repeat; rs2583988, rs2619363, and rs2619364 gene polymorphisms; and PD. In a study conducted with German and Japanese populations, it was observed that there was a link between intron 4 and 5′ and 3′ untranslated regions (UTRs) in the SNCA gene [6]. In a Russian population study, TT genotype of rs2583988 and rs2619363 gene polymorphisms and the GG genotype of rs2619364 gene polymorphism were found to be associated with higher levels of SNCA mRNA [47]. There are many small-scale studies aimed at investigating this relationship, and also, in a meta-analysis study conducted by Maraganore et al., in a large population selected from 11 different regions, the relationship between the rep 1 gene polymorphism and the risk of PD development has been proven [42].

In an analysis with the Caucasus population to investigate the relationship between 12 single-nucleotide polymorphisms and PD, including the whole SNCA gene region, it was determined that signals were collected in a 24 kb-long region in the middle of intron 4 of the SNCA gene, and it was determined that these signals were confirmed by haplotype analysis showing the presence of a strong protective allele [42].

In addition to these gene polymorphisms, SNCA gene polymorphisms which are known to be associated with PD include rs104893875 (G > A), rs104893877 (G > A), and rs104893878 (G > C) gene polymorphisms. It has been reported that the polymorphism rs104893875 (G > A) has been identified primarily in a multinational Spanish family. The significant relationship was determined between rs104893875 (G > A) gene polymorphism and increased SNCA protein aggregation. In another study conducted with the Swedish population, as a result of rs104893877 (G > A) mutation, PD and encephalopathy with cortical involvement develop. Immunoreactive Lewy neurites were detected in brain stem pigmented nuclei, the hippocampus, and temporal neocortexes of PD patients in whom this gene polymorphism was detected. In a study that is significant relationship between rs104893878 (G > C) gene polymorphism and autosomal dominant PD, hypometabolism was determined in frontal, parietal, and left temporal cortexes of PD patients in whom this polymorphism was detected. As a result of postmortem examination of brain slices of these patients, Lewy bodies and neurodegeneration developed and correspondingly identified. Primer sequences for rs104893875 (G/A), rs104893877 (G > A), and rs104893878 (G > C) gene polymorphisms are presented in **Table 2** [38].

There are three missense mutations, A53T, A30P, and E46K, as the most common pathogenic changes of the SNCA gene. In a study conducted with the Mexican Mestizos population, a significant relationship was determined between the rs1801133 and rs3857059 allelic variations of the SNCA gene and the risk of PD development. In addition, GG genotype of rs3857059 gene polymorphism was found to be

SNPs	Forward primer (5′-3′)	Reverse primer (5′-3′)
rs104893875 (G/A)	GGCCCCGGTGTTATCTCAT (SN-75-CF) TTGTAGGCTCCAAAACCATGG (SN-75-GF)	AATTCAAAGCCCTCATTA TTCTTGG (SN-75-CR) CACCATG CACCACTCCCTT (SN-75-AR)
rs104893877 (G > A)	GGCCCCGGTGTTATCTCAT (SN-75-CF) GGAGTGGTGCATGGTGAGA (SN-77-AF)	AATTCAAAGCCCTCATTATT CTTGG (SN-75-CR) GCACAATGGAGCTTACCTGTAGC (SN-77-GR)
rs104893878 (G > C)	TCCGTGGTTAGGTGGCTAGA (SN-78-CF) ACCAAACAGGGTGTGGCAGAAGCAG (SN-78-GF)	CACACGTTCACATTCACCTACCT (SN-78-CR1) ACCCTCTTTTGT CTTTCCAGC (SN-78-CR2)

PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism.

Table 2.
Primer sequences used in PCR for single-nucleotide polymorphisms [rs104893875 (G/A), rs104893877 (G > A), and rs104893878 (G > C)].

a genetic risk factor for PD development [50]. While A18T and A29S missense mutations in patients with sporadic PD; A53T, A30P, E46K, and H50Q missense mutations in familial PD patients have been described. Dual and triple copies of the SNCA locus known to be associated with PD severity cause familial Parkinsonism [26].

There are studies showing that there are significant relationships between some polymorphisms in the SNCA gene and the risk of sporadic PD development. It is also known that these polymorphisms are associated with increased levels of plasmatic SNCA. Tyrosine hydroxylase activity and dopamine release decrease as a result of SNCA overexpression. In order to investigate the relationship between SNCA gene polymorphisms and the risk of PD development, different results have been obtained in studies performed with different populations [13].

6. Conclusions

It is known that environmental and genetic factors play a role together in PD pathogenesis. Several studies have been carried out to investigate the relationship between gene polymorphisms and PD development risk, which are important among genetic factors, and different results have been obtained in these studies. It is thought that the differences in the results of these studies are due to of PD patient and healthy control groups' different selection criteria and different race and populations. The identification of genetic polymorphisms that play an important role in the development of PD will enable us to have knowledge about the mechanism of PD. In addition, new treatment methods can be improved in order to prevent PD. By increasing the number of PD patients and healthy controls, different results can be obtained in studies with larger populations. As a result, in studies aimed at the relationship between SNCA gene polymorphisms and the risk of PD development, some of the SNCA gene polymorphisms were found to be genetic risk factors for PD development and play an important role in the pathogenesis of the disease.

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Conflict of interest

We declare that there is no conflict of interest with any financial organization regarding the material discussed in the chapter.

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