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REVİEW

The Genetics of Parkinson's Disease

Parkinson Hastalığı Genetiği

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ABSTRACT

Parkinson's disease (PD) is one of the most common neurodegenerative diseases worldwide. Approximately 15% of PD patients have a family history of the disease in one or more first-degree relatives, and 5-10% of PD cases exhibit a classical Mendelian inheritance pattern. In 1997, the heritable transmission of PD was first documented. Recent studies have found 90 independent genome-wide signals at 78 loci that may be associated with PD. The identification of genes linked to PD and their functions has uncovered novel biological pathways and treatment options that play a role in the development of PD. In this article, it is aimed to review up-to-date information on the genetics of PD.

Keywords: Parkinson's Disease, Inheritance, Autosomal Dominant, Autosomal Recessive

ÖZ

Parkinson hastalığı (PH), dünya çapında en yaygın nörodejeneratif hastalıklardan biridir. PH hastalarının yaklaşık %15'inde bir veya daha fazla birinci derece akrabada hastalık öyküsü vardır ve PH vakalarının %5-10'u klasik Mendel kalıtım modeli sergiler. 1997'de, PH'nın kalıtsal geçişi ilk kez belgelenmiştir. Son yapılan araştırmalarda, PD ile ilişkili olabilecek 78 lokusta 90 bağımsız genom çapında sinyal bulunmuştur. PH ile bağlantılı genlerin ve bunların işlevlerinin tanımlanması, PH gelişiminde rol oynayan yeni biyolojik yolları ve tedavi seçeneklerini ortaya çıkmasını sağlamıştır. Bu yazıda Parkinson hastalığının genetiği ile ilgili güncel bilgilerin gözden geçirilmesi amaçlanmıştır.

Anahtar Kelimeler: Parkinson Hastalığı, Kalıtım, Otozomal Dominant, Otozomal Resesif

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (1). Its prevalence is estimated at over six million worldwide and is expected to double by 2040 (2). The pathogenesis of PD is based on the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and intraneuronal aggregation of misfolded alpha-synuclein called Lewy bodies (3). The underlying mechanisms leading to the loss of dopaminergic neurons in the SNpc can be listed as pathological alpha-synuclein aggregation, disruption of intracellular protein degradation systems such as the endo-lysosomal autophagy and the ubiquitin-proteasome pathways, mitochondrial dysfunction, oxidative and metabolic stress, excitotoxicity, and inflammation (4). Clinical findings of PD can be divided into two categories: motor symptoms; the cardinal signs of PD, and non-motor symptoms which can even be present in the pre-clinical phase. Motor symptoms can be characterized as tremors, rigidity, bradykinesia/akinesia, and postural instability. Non-motor symptoms may occur years before the diagnosis of the disease and include constipation, hyposmia, sleep-wake cycle disorders, apathy and depression (5).

The etiology of the disease is obscure, and most PD cases are sporadic. Approximately 15% of patients have a family history of PD in one or more first-degree relatives and 5–10% of PD show a classical Mendelian inheritance pattern (6). The first evidence of heritable transmission of PD was reported in 1997. Rare mutations in the alpha-synuclein (SNCA) gene responsible for a monogenic form of PD was defined (7). Shortly after this discovery, many studies identified numerous genes with autosomal recessive (AR) and autosomal dominant (AD) inheritances. Recently, Nalls et al. have conducted the largest study to date for the genetics of PD, analyzing 7.8 million single nucleotide polymorphisms (SNPs) in 37.688 PD cases, 18.618 United Kingdom Biobank (UKB) "proxy cases (individuals who do not have Parkinson's disease but have a first degree relative that has)" and 1.4 million controls. They found 90 independent genome-wide significant signals at 78 loci that are thought to be associated with PD (8).

The acquisition of new genetic technologies is rapidly illuminating both the pathogenesis and clinical and genetic diversity of PD. Therefore, it is very important to understand the genetic factors behind PD. In this review, we summarized the genetic etiologies associated with PD.

Monogenic Forms of PD

Historically, the monogenic forms of PD predominantly were detected through linkage analysis of affected families. On the other hand, few variants were also revealed by genome-wide association studies (GWAS). The loci associated with PD phenotypes were named

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the 'PARK' loci and are indicated by the number representing the chronological order of discovery. For example, the PRKN gene is also referred to as PARK2. However, multiple PARK loci may refer to the same gene, and some PARK loci do not appear to cause disease. Therefore, the current recommendation is to use gene names instead of PARK loci (9). Monogenic forms of PD are summarized in Table 1.

Autosomal dominant forms of PD

These are the genes that are clearly identified as risk factors for PD: SCNA (Synuclein, Alpha), LRRK2 (Leucine-Rich Repeat Kinase 2), and VPS35 (Vacuolar Protein Sequence 35 Retromer Complex Component). More recently, the association with LRP10 (Low Density Lipoprotein Receptor-Related Protein 10) and EIF4G1 (Eukaryotic Translation Initiation Factor 4G) are being studied. Moreover, some pathogenic variations of GBA (Beta-glucosidase) gene, which cause Gaucher's disease in biallelic state, can lead to PD with variable penetrance in monoallelic state (10).

SNCA

The SNCA (PARK1, PARK4; OMIM: 163890) gene is responsible for producing the alpha-synuclein protein. The exact function of alpha-synuclein (a-synuclein) is yet to be determined. However, its role is thought to regulate neurotransmitter release, synaptic vesicles and neuronal differentiation (11).

The SNCA gene was the first gene determined to be linked to PD. In 1997, Polymeropoulos et al. identified a missense variant that substituted the amino-acids alanine with threonine at position 53 (p.A53T) of the SNCA gene in an Italian family (7). The same variant was also found to be associated with the PD in three Greek kindreds. Afterwards, several missense SNCA variants were identified, including p.A30P, p.E46K, p.H50Q and p.G51D (12–15). Missense mutations of SNCA are reported to have a direct impact on a-synuclein conformation and function. Patients with pathogenic missense variations in this gene often tend to develop PD before 50 years of age, and the symptoms worsen rapidly; but respond well to levodopa (L-DOPA). The phenotype also differs between different missense variants of SNCA. For instance, patients with p.G51D show extremely rapid disease progression causing some patients to die within ten years of onset. Atypical findings such as pyramidal signs, cognitive decline, psychiatric disturbances, myoclonus, and seizures can be observed too (15).

Apart from nucleotide substitutions that disrupt the protein function, altered dosage of the protein can also cause protein misexpression. Several studies showed that duplication or triplication of SNCA can lead to an increase in a-synuclein expression, which increases the risk of developing PD (16,17). These studies also reported that patients with duplications or triplications of SNCA tend to experience a faster progression (16,17).

LRRK2

The LRRK2 (PARK8; OMIM: 609007) gene encodes the LRRK2 protein (18). LRKK2, also known as dardarin, is a large protein that is involved in a wide variety of cellular functions including autophagy, cytoskeletal dynamics, intracellular membrane trafficking, synaptic vesicle turnover and inflammation (19,20). Dardarin dysfunction leads to the disruption of a-synuclein degradation in cellular clearance pathways and thus causes the accumulation of misfolded a-synucleins (21).

In 2004, it was discovered that the LRRK2 gene is linked to the development of PD. A Japanese family with AD parkinsonism was found to have the c.6055G>A variant (p.G2019S). This variant is the most prevalent pathogenic mutation worldwide that causes PD (18). Its incidence is particularly high in the Ashkenazi Jewish (26%) and North African Berber (41%) populations (22–24). Other diverse variants of the LRKK2 gene were explored, yet only eight proved to be pathogenic (N1437H, R1441 G/H/C, Y1699C, G2019S, S1761R, G2385R, R1628P and I2020T) (25). These variants result in advanced age-onset PD clinically resembling a sporadic PD (26).

VPS35

The VPS35 (PARK17; OMIM: 601501) gene enables the production of a component of the multimeric retromeric complex. The complex is one of the main conductors in endosomal sorting and trafficking (27,28).

A missense mutation (p.D620N) in the VPS35 gene was detected in Swiss and Australian families in 2011 (29). However, in a study conducted by Nuytemans et al. (30), 213 patients with PD were analyzed through whole-exome sequencing and the results showed no evidence indicating that genetic variations of VPS35 significantly impacted the development of PD. Nevertheless, considering rarity (<%1 of familial PD cases) and lack of functional evidence of VPS35 variants except p.D620N, further studies with larger samples are needed for a clearer deduction (31).

GBA

The GBA (OMIM: 606463) gene encodes for a lysosomal enzyme, beta-glucosidase. Beta-glucosidase catalyzes the breakdown of the glycolipid glucosylceramide into ceramide and glucose (32). Biallelic pathogenic GBA variants can lead to Gaucher disease, a lysosomal storage disorder caused by reduced glucocerebrosidase activity (33). Whereas heterozygous carriers are in an increased risk of developing PD (10).

Various case-control studies showed that signs of PD such as tremor and bradykinesia can be exhibited in Gaucher patients; whereupon PD symptoms were included in the spectrum of the disease (34,35).

The two most prevalent variants are p.N370S and p.L444P globally; p.N370S heterozygosity raises the risk of PD by four times whereas p.L444P increases it by twelve times (36). The clinical findings of GBA-

associated PD are similar to idiopathic PD. However, studies showed earlier age of onset, higher dementia rates, and faster worsening of the symptoms in PD patients with heterozygous pathogenic GBA variants (37–39).

LRP10

The LRP10 (OMIM: 609921) gene enables formation of the LRP10 protein, which contains a class of surface receptors that play an important role in the trafficking and processing of amyloid precursor protein (40). First, a LRP10 missense mutation, c.1807G>A (p.G603R) was detected in an Italian family with hereditary PD (41). Subsequently, Kia et al. investigated the LRP10 gene in a study involving 2835 PD patients and 5343 controls (42). However, they found no significant difference in LRP10 gene variants between controls and PD patients. Currently, the pathogenic role of LRP10 mutations in PD is still unclear.

EIF4G1

The EIF4G1 (PARK18; OMIM: 600495) gene responsible for a member of eukaryotic translation initiation factors that play important roles for the ribosome/mRNA-bridge (43). Initially, the R1205H variant in the EIF4G1 gene were identified in a French family (44). In a cohort study of 4,708 PD patients screened for R1205H, nine patients from seven families from the USA, Canada, Ireland, Italy, and Tunisia were found to carry this variant (45). Subsequently, Huttenlocher et al. (46) studied a cohort of 2,146 European PD patients to evaluate the relationship between EIF4G1 mutations and PD. They identified the R1205H mutation in only one patient. Moreover, a recent study found no association between EIF4G1 and PD (47).

Autosomal recessive forms of PD

There are specific genes that are strongly linked to the autosomal recessive (AR) types of PD, including PRKN (RBR E3 ubiquitin protein ligase), PINK1 (PTEN-derived putative kinase 1) and DJ-1 (Oncogene DJ1). These three genes interplay in a mitochondria proteolysis pathway. Patients with these variants have similar clinical manifestations to sporadic PD, although the age of onset is earlier. ATP13A2 (ATPase 13A2), PLA2G6 (Phospholipase A2, Group VI), FBXO7 (F-Box Only Protein 7), DNAJC6 (DNAJ/HSP40 Homolog, Subfamily C, Member 6), SYNJ1 (Synaptojanin 1) appear as infrequent and complex forms of autosomal recessive PD. Parkinsonism is the primary clinical feature of these patients, but they may also present with atypical manifestations such as supranuclear gaze palsy, mental retardation, or seizures.

PRKN

The PRKN (Parkin; PARK2; OMIM: 602544) gene, is one of the largest genes in humans and is responsible for producing a protein called parkin (48). The parkin protein is involved in the process of ubiquitination, a form of post-translational modification, and is responsible for the breakdown of damaged or excess proteins (49).

Parkin-associated PD includes marked degeneration of dopaminergic neurons in the main pathology of the substantia nigra pars compacta. Lewy bodies, the pathognomonic finding for idiopathic PD, may be absent in these cases (50). The characteristics of PRKN related PD share a remarkable similarity with idiopathic PD signs such as tremors, rigidity and bradykinesia (51). However, the disease usually has an earlier onset; even childhood-onset cases have been reported (51). Additionally, biallelic PRKN mutations are the most common genetic variants in juvenile PD (52). Another study revealed that PRKN mutations occur in 77% of familial cases with an age of onset <30 and in 10-20% of patients with early-onset PD (53).

Although biallelic PRKN variants are an established risk of developing PD, there is much debate on the potential influence of heterozygous PRKN variants on PD. Several small studies have claimed that heterozygous PRKN variants increase the risk of PD (54,55). However, this could not be confirmed in other studies and meta-analyses (56–58). More recently, a study involving 2809 PD patients and 3629 healthy controls has been conducted to investigate the potential link between PD and heterozygous PRKN variants, including single nucleotide variants and copy number variations (CNVs) (59). The findings have indicated that there is no connection between heterozygous PRKN variants and PD (59).

PINK1

The PINK1 (PARK6; OMIM: 608309) gene encodes a mitochondrial serine/threonine kinase (60). Two-thirds of the mutations reported in PINK1 are loss-of-function mutations that affect serine/threonine kinase activity. These findings highlight the importance of mitochondrial proteolysis pathway in the pathogenesis of PD (61–63). PINK1-related PD findings clinically overlap with sporadic PD and present at early-onset. Moreover, in these patients, non-motor findings are observed more commonly (10).

DJ-1

The DJ-1 (PARK7; OMIM: 602533) gene encodes a 189 amino acid-long protein, named DJ-1, that functions in regulation of transcription, oxidative stress, and mitochondrial metabolism (64). The discovery of DJ-1 as a causative gene for PD was brought about by its occurrence in two consanguineous families of Dutch and Italian origin (65). Single nucleotide and structural variations such as Glu163Lys, Leu166Pro, and g.168-185dup have been reported (66,67). DJ-1 gene mutations occur in approximately 1-2% of early-onset PD (68). PD patients with DJ-1 mutations show early-onset Parkinson's symptoms followed by psychiatric disturbances such as psychotic disorder, anxiety, and cognitive decline, and generally respond well to L-DOPA treatment (69–71).

DNAJC6

The DNAJC6 (PARK19; OMIM: 608375) gene encodes auxilin, a neuronal protein that regulates molecular chaperone activity by stimulating ATPase activity

(72). First, a homozygous splice mutation (c.801-2A>G) of the DNAJC6 gene is identified in two Palestinian brothers. The symptoms were rapidly progressive and unresponsive to treatment (73). The DNAJC6 gene variants that cause truncation of the protein lead to juvenile atypical parkinsonism, while non-truncating variants cause early-onset parkinsonism (74).

ATP13A2

The ATP13A2 (PARK9; OMIM: 610513) gene encodes ATP13A2 protein, acts as a critical regulator of lysosomal functions (75). A study identified upregulated ATP1A32 expression in surviving dopaminergic neurons of patients with idiopathic PD, suggesting a neuroprotective role of this protein (76). The ATP13A2 protein deficiency leads to Kufor-Rakeb syndrome (KRS; OMIM: 606693), characterized by juvenile, levodopa-responsive Parkinsonism, pyramidal manifestations, and dementia. The presence of iron accumulation in the basal ganglia in some patients with KRS suggests that it can be considered among neurodegenerative syndromes with brain iron accumulation (NBIAs) (77).

FBXO7

Mutations in the FBXO7 (PARK15; OMIM: 605648) gene, responsible for producing F-box protein 7, can cause a rare autosomal recessive Parkinsonian-pyramidal syndrome (78). The syndrome shows symptoms of early-onset parkinsonism, along with pyramidal system involvement like psychomotor retardation, eyelid apraxia, and chorea (79).

PLA2G6

The PLA2G6 (PARK14; OMIM: 603604) gene encodes a phospholipase A2 enzyme subgroup, and has a key role in inflammation, cell proliferation, apoptosis, and remodeling of membrane phospholipids (80). PLA2G6 mutations are highly heterogeneous and result in a complex group of neurodegenerative diseases. The clinical picture of PLA2G6-related neurodegeneration is classified in three overlapping phenotypes, one of which is 'PLA2G6-related dystonia-parkinsonism' (81). PLA2G6-related dystonia-parkinsonism begins in late adolescence and presents with early-onset PD, gait disturbance, and neuropsychiatric symptoms (81).

SYNJ1

The SYNJ1 (PARK20; OMIM: 604297) gene produces a protein called Synaptojanin 1, which plays a crucial role in regulating vesicle endocytosis and recycling (82,83). In several studies, biallelic mutations of SYNJ1 were associated with two distinct phenotypes: early-onset PD and a severe neurodegenerative disorder with epilepsy and tauopathies (84–86). A recent study has revealed that homozygous missense mutations such as p.R839C and p.Y832C result in typical PD or early-onset atypical parkinsonism (87). On the other hand, it is suggested that p.Y888C homozygous missense mutations could lead to severe progressive neurodegeneration. All of these findings suggest wide clinical and genetic heterogeneity for SYNJ1 variations.

Table 1. Summary of monogenic variants associated with Parkinson's disease.

Gene	PARK locus	Chromosomal Location	İnheritance	Predominantly involved pathway	Predominant phe-notype	Penetrance
SNCA	*PARK1*, *PARK4*,	4q21-22	AD	a-Synuclein aggregation	Typical PD	High
LRRK2	PARK8	12q12	AD	Endosomal/lysoso- mal and mito-chondrial dysfunction	Typical PD	Variable
VPS35	PARK17	16q11.2	AD	Endosomal/lysoso- mal dysfunction	Typical PD	High
GBA		1q21	AD	Endosomal/lysoso- mal dysfunction	More aggressive dis-ease course as PD	Variable
LRP10	-	14q11.2	AD	mRNA translation dysfunction	Typical PD	Unclear Patho-geneity
EIF4G1	-	3q27.1	AD	mRNA translation dysfunction	Typical PD	Unclear Patho-geneity
PRKN	*PARK2*, *PARKIN*	6q25.2-q27	AR	Mitochondrial dysfunction	Early-onset PD	High
PINK1	PARK6	1p35-p36	AR	Mitochondrial dysfunction	Early-onset PD	High
DJ1	PARK7	1p36	AR	Mitochondrial dysfunction	Early-onset PD	High
DNAJC6	PARK19	7q36.3	AR	Endosomal/lysoso- mal dysfunction	Atypical PD	High
ATP13A2	PARK9	1p36	AR	Endosomal/lysoso- mal dysfunction	Atypical PD	High
FBXO7	PARK145	22q12-q13	AR	Mitochondrial impairment and endo-somal/lysoso- mal dysfunction	Early-onset PD	High
PLA2G6	PARK14	22q13.1	AR	Phospholipid remodeling, a-synuclein aggregation	Early-onset PD	High
SYNJ1	PARK20	21q22.11	AR	Endosomal/lysoso- mal dysfunction	Atypical PD	High
TAF1	-	Xq13.1	XLR	Transcription factor II D dysfunction	Atypical PD	High

X-linked forms of PD

TAF1

TAF1 (TATA-binding protein-associated factor-1) (OMIM: 313650) is responsible for the only known X-linked PD: X-linked torsion dystonia-parkinsonism syndrome. TAF1 encodes an essential component of Transcription factor II D which is critical for RNA polymerase II–mediated gene transcription (88). SVA (short interspersed nuclear element, variable number of tandem repeats, and Alu composite) retrotransposon insertion in intron 32 of the TAF1 is a founder variant in Philippines and the only known pathogenic variation to date that causes X-linked torsion dystonia-parkinsonism syndrome (89,90).

Multifactorial Inheritance in PD

Genetic and environmental factors play a role in the development of multifactorial diseases. Most of the adult-onset chronic diseases show multifactorial inheritance pattern, which is usually characterized by familial aggregation of disease (91). Likewise, apart from the PD cases with highly penetrant genetic variants as discussed above, majority of late-onset sporadic PD cases show no sign of Mendelian inheritance. Moreover, the variants of some genes (e.g., SNCA and GBA) show low penetrance indicating additional contribution of other genetic and environmental factors (10).

To reveal genetic factors taking part in complex diseases with multifactorial features like PD, GWAS are powerful assets. There are several GWAS pointing multiple loci with potential significance for the association with PD (92). For instance, GWAS analysis done by Nalls et al. associated seven loci containing LRRK2, GBA, CATSPER3, LAMB2, LOC442028, NFKB2, and SCARB2 genes with PD (8). Additionally, NSF gene which encodes N-ethylmaleimide sensitive fusion protein that have a role in synaptic neurotransmission, also associated with PD in another study (93). However, all variants are not associated positively with PD. An example is MAPT gene H2 haplotype, which was associated with later age at onset (93). Moreover, CRHR1 gene which encodes corticotropin releasing hormone receptor 1, has also been shown to be associated with a reduced risk of PD (94). Despite all these findings, even GWAS cannot reveal a genetic component in majority of PD patients; the broadest study to date has explained only 16%−36% of PD heritability (8).

Where some GWAS are underpowered to find an associated locus, polygenic risk scores (PRS) which utilize multiple loci in the genome including common polymorphisms, can be helpful to reveal the complex relationship between genotype and phenotype of PD cases. In PRS studies, a polygenic score, and a threshold of liability for disease are calculated by analyzing a combination of multiple common genetic variants between genomic datasets of disease and control groups. PRS studies showed to have a potential to predict the liability to some diseases with multifactorial inheritance such as schizophrenia and bipolar disorder (95). Escott-Price et al. designed a polygenic risk score for PD and found significant correlation between higher risk score and PD liability, especially in cases with early age at onset (96). Moreover, Searles Nielsen et al. found an association between age at onset and SNPs in CYP2J2, GSTM5 and SLC11A2 genes (97). These findings are promising for a future PRS that will include a broad spectrum of ethnicities and PD subtypes.

Although both GWAS and PRS studies have shown important results for comprehension of multifactorial nature of PD, it is still preliminary to make a general deduction in this field. Therefore, more population-based studies are necessary to fully illuminate this aspect of PD.

Genetic Testing for PD

Genetic screening is recommended for Parkinson's patients with one or more; early onset of the disease (age at onset <50 years old), positive family history suggesting autosomal dominant or autosomal recessive inheritance, and high-risk ethnicities such as Ashkenazi Jewish or North African Berber (98). The choice of genetic tests should be determined by the patient's unique circumstances. For example, the SNCA, GBA, PRKN, PINK1 and DJ1 genes may be considered in patients with age at onset <50. Disease specific genetic panels containing multiple genes rather than single gene screening are more convenient due to locus heterogeneity, lower cost, and increased efficiency. It is important to note that PD panels can vary greatly between laboratories in terms of the genes they contain.

More comprehensive genetic testing, such as Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS), can also be utilized. However, complexity of bioinformatic pipelines, issues related to variants of unknown significance and reporting of secondary findings may further complicate diagnosis and management of patients. Therefore, multidisciplinary approach is essential for the proper diagnosis, genetic counselling and management of these patients.

Conclusion

PD is a disabling neurodegenerative disorder with increasing prevalence worldwide. In the last three decades, significant strides have been made in understanding the genetics of PD. The identification of genes related to PD and their functions has uncovered novel biological pathways that play a role in the development of PD. These new pathways not only helped us better understand the disease but also shed light on potential treatment options. On the other hand, advancements in genetic information have enabled the optimization of existing treatment options specific to each patient.

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