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*Article*

# Single Nucleotide Polymorphisms of Indoleamine 2,3-Dioxygenase 1 Influenced the Age Onset of Parkinson's Disease

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**Abstract:** Earlier studies reported alterations of the kynurenine (KYN) pathway of tryptophan (TRP) metabolism in Parkinson's disease (PD). The first rate-limiting enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan dioxygenase were observed upregulated, resulting elevated KYN/TRP ratios in the serum and cerebrospinal fluid samples of patients with PD. An increasing number of single nucleotide polymorphisms (SNPs) have been identified in a population of PD. However, little is known if genetic variations of the IDO contribute to disturbance of the KYN metabolism in and the pathogenesis of PD. SNP analysis of IDO1 was performed by allelic discrimination assay with fluorescently labelled TaqMan probes and a subgroup analysis was conducted according to the age of PD onset. The frame shifts variant rs34155785, intronic variant rs7820268, and promotor region variant rs9657182 SNPs of 105 PD patients without comorbidity were analyzed and compared to 129 healthy controls. No significant correlation was found in three SNPs between PD patients and healthy controls. However, the subgroup analysis revealed that A alleles of rs7820268 SNP or rs9657182 SNP carriers contribute to later onset of PD than non-carriers. The study suggested that SNPs of IDO1 influenced the age onset of PD and genotyping of SNPs in certain alleles potentially serves as a risk biomarker of PD.

**Keywords:** kynurenines; tryptophan; indoleamine 2,3-dioxygenase; single nucleotide polymorphisms; Parkinson's diseases; neurodegenerative diseases

## 1. Introduction

Parkinson's disease (PD) is the second most prevalent chronic progressive neurodegenerative disease characterized by motor symptoms such as tremor, rigidity, and hypokinesia. Relatively significant symptoms are autonomic dysfunction including arrythmia, blood pressure irregularity, asymmetric sweating, and incontinence and psychobehavioral manifestations including dementia, depression, anxiety, paranoia, and psychosis. The non-motor symptoms may appear in early stages of the disease and even before the appearance of classical motor symptoms [1-3]. The histopathological and clinical hallmarks of PD include the degeneration of dopaminergic neurons in the substantia nigra pars compacta, the presence of Lewy bodies, and the positive response to dopamine (DA) replacement therapy. The disease affects primarily the elderly, imposing a serious

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burden on the aging societies. The prevalence of PD is approximately 0.2% on average in the general population, but it is increasing with age up to 1.9% [4].

The etiology of PD remains poorly understood. Besides genetic disposition, pathological findings are abnormal protein aggregation, elevated oxidative stress, mitochondrial dysfunction, increased glutamate excitotoxicity, alteration of immune response, disturbance of kynurenine pathway (KP) of tryptophan (TRP) metabolism, and among others [5-10]. Altered levels of and ratios of kynurenine (KYN) metabolites have been observed in neurologic and psychiatric diseases [3,11-16]. Earlier studies revealed that the activities of indoleamine 2,3-dioxygenase (IDO) 1/TRP 2,3-dioxygenase (TDO) were upregulated in PD patients compared to controls, which was indicated by elevation of L-KYN/TRP ratios in the serum and in cerebrospinal fluid (CSF) samples of the patients [17]. The cascade of KP produces several neuroactive metabolites such as neurotoxic 3-hydroxykynurenine (3-HK) quinolinic acid (QUIN), 3-hydroxyanthranillic acid (3-HAA) and neuroprotective kynurenic acid (KYNA).

3-HK and 3-HAA generate reactive oxygen species (ROS) [10]. An elevation of 3-HK levels was related to excitotoxic injury and is observed in patients with neurodegenerative diseases [3]. The neurotoxic effects of 3-HK and 3-HAA involve the generation of superoxide anion and hydrogen peroxide, which contribute to the oxidative processes implicated in the pathophysiology of meningitis [18]. QUIN is a free-radical metabolite. Interferon (IFN)-γ activates IDO, formamidase, and kynurenine 3-monooxygenase (KMO) activities in human microglial cells and macrophages, increasing QUIN synthesis [19].

KYNA is a broad-spectrum, competitive antagonist of all three ionotropic excitatory glutamate receptors including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, kainate receptor, and *N*-methyl-D-aspartate (NMDA) receptor [20,21]. However, KYNA exhibited dual actions at AMPA receptors dependent on its concentration: inhibitory at micromolar concentrations, while excitatory at nanomolar concentrations. The micromolar concentrations are inhibitory, while the nanomolar concentrations are facilitatory by allosteric modulation of the AMPA receptor [22.23]. The actions of KYNA at the α-7 nicotinic acetylcholine receptor remain controversial [24]. KYNA has antioxidant properties that scavenges ROS to suppress overshooting inflammation in damaging tissues. Reduced concentrations of KYNA may contribute to tissue damage and inflammatory cell proliferation neurodegenerative diseases [3,10,25,26]. In addition, KYNA was reported to contribute to weight reduction without affecting osteogenesis [27].

The indoleamine 2,3-dioxygenase IDO1 is one of the first rate-limiting enzymes that converts L-TRP to N-formyl KYN in TRP metabolism, which play a crucial role in governing concentrations of downward bioactive KYN metabolites (Figure 1) [10]. Activation of IDO1 and the KYN system promotes immunosuppressive effects by inhibition of Natural Killer cells, inhibition of T cell functions, and activation of the regulatory T cells [28]. Firstly, single nucleotide polymorphisms (SNPs) analysis was performed in three loci of IDO1 in PD patients and healthy controls. The frameshift mutation rs34155785 SNP causes a drastic change in the gene product. Both intronic variant rs7820268 SNP, and promotor region variant rs9657182 SNP affect the immune system. The T allelic variants of the rs7820268 showed impaired $CD8^+$ regulatory T cell function, while the rs9657182 SNP was found more susceptible to IFN-alpha treatment, which induced depressive symptoms [29,30] (Figure 2). Secondly, a subgroup analysis was conducted according to the age of PD onset in search of the genetic link between the IDO1 variants and PD.

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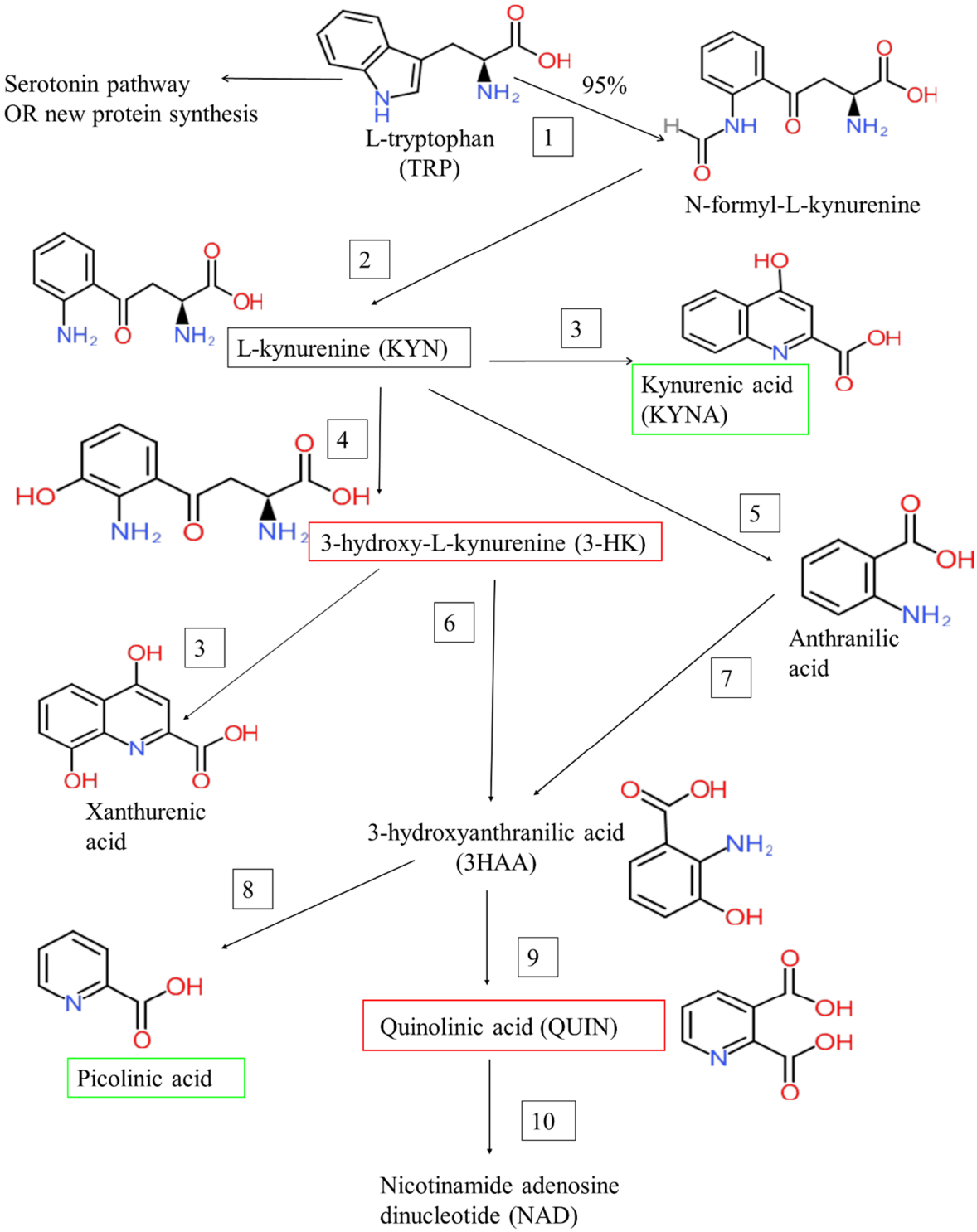


**Figure 1.** The kynurenine pathway (KP) is the degradation route of tryptophan (TRP) metabolism producing an end-product nicotinamide adenine dinucleotide (NAD). The indoleamine 2,3-dioxygenase (IDO) 1, IDO2, and the tryptophan 2,3-dioxygenase (TDO) (1) are the first rate-liming enzymes that convert the L-tryptophan (TRP) to *N*-formyl-L-kynurenine. *N*-formyl-L-kynurenine is converted by formamidase (2) to L-kynurenine (L-KYN) (black bracket). L-KYN is metabolized into various bioactive compounds: the neuroprotective metabolites are kynurenic acid and picolinic acid (green brackets), while the neurotoxic ones are the 3-hydroxy-L-kynurenine (3-HK) and the quinolinic acid (red brackets). The following are main enzymes of the KP: 1: tryptophan dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO), 2: formamidase, 3: kynurenine aminotransferases (KATs), 4: kynurenine 3-monooxygenase (KMO), 5: kynureninase, 6: kynureninase, 7: non-specific hydroxylation, 8: 2-amino-3-carboxymuconate-semialdehyde decarboxylase, 9: 3-hydroxyanthranilic acid oxygenase, 10: quinolinic acid phosphoribosyltransferase

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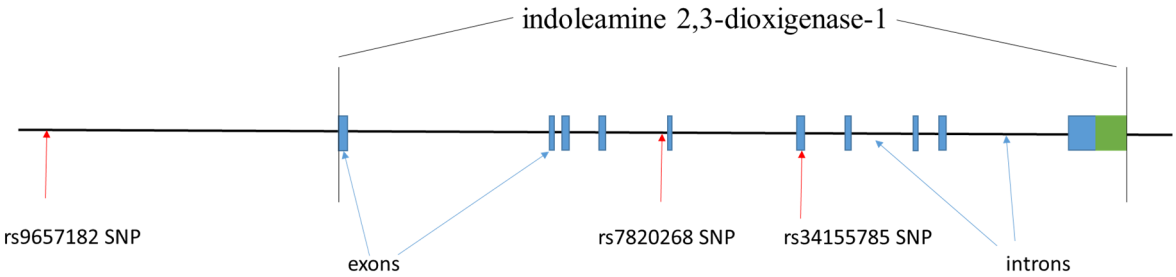


**Figure 2.** Schematic of the indoleamine 2,3-dioxygenase (IDO) 1 gene. The IDO1 gene consist of 10 exons and 9 introns localized in 8p11.21 chromosome region. It has 9 transcript variants. The encoded protein is 403 amino acid long. The rs9657182 SNP is located 5′ upstream from the promoter region of the IDO1 gene. The rs7820268 SNP is localized in the fourth intron and the last rs34155785 SNP, which is a frame shift mutation, is located in the sixth exon.

## 2. Experimental Section

### *2.1. Ethics*

The blood samples of 105 PD patients and 129 healthy controls were examined for the study. All patients gave their informed consent in accordance with the Declaration of Helsinki, and the study was approved by the Medical Research Council Scientific and Research Ethics Committee (47066-3/2013/EKU (556/2013)). The samples were collected at two sites (at the Department of Neurology, Faculty of Medicine, University of Szeged, Hungary, and at the Department of Neurology and Cerebrovascular Diseases, Pándy Kálmán County Hospital, Gyula, Hungary). The patient and the control groups were age- and gender-matched (gender ratio p=0.989; mean age, p=0.310). The onset of the disease could not be established for two patients. The sociodemographic data of the two groups are presented in Table 1.

**Table 1.** the sociodemographic data of PD patients and controls.

| Group | Male | Female | Mean age | Median | Min | Max | Age at onset |
|---|---|---|---|---|---|---|---|
| PD patients (105) | 48 | 57 | 66.42±9.24 | 68 | 34 | 84 | 58.81±10.970 |
| Controls (129) | 58 | 71 | 65.26±8.1 | 63 | 53 | 87 | - |

Min: minimum age in the group, Max: maximum age in the group

### *2.2. Methods*

#### 2.2.1. DNA isolation and polymerase chain reaction

Peripheral whole blood samples (stored at -80°C) were subjected to genomic DNA isolation by the desalting method developed by Miller et al [31]. The purified genomic DNA were stored at -20°C at the biobank of the Department of Neurology, Faculty of Medicine, University of Szeged (biobank license: Regional Human Biomedical Research Ethics Committee: 135/2008).

The IDO1 genotypes were determined by allelic discrimination study with TaqMan probes. Three SNP of the IDO1 gene were investigated. The rs34155785SNP is a frame shift mutation in the human genome (results a Phe (F)>Leu (L) exchange), which localize in the sixth exon of the IDO1 gene. The rs7820268SNP is intronic SNP (G/A change) of the IDO1 gene is localized in the fourth intron. The rs9657182SNP (G/A change) is localized 5′ upstream from the beginning of the IDO1 promoter region.

For the rs34155785 SNP, the following primers were used for the amplification of the DNA forward primer: 5′- CTA AAC TTC TTG CCT TCC TTA TC-3′; reverse primer: 5′- AGA CGT ACT TTG ATT GCA GA-3′. The following probes were applied for allelic discrimination: wild type allele:

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5′-Fam- GAC GTT TTG TTC TCA TTT CGT G-BHQ-1-3′; and C allele: 5′-Hex- GAC GTT TTG TTG CTC ATT TCG TG-BHQ-1-3′.

The rs7820268 SNP, the following primers were applied for the amplification of the G/A at chromosome 8: forward primer: 5′- TAA ATG TAA TGC CTA CTG AAG AA-3′; reverse primer: 5′- CCT TAT GAA AGC AGC CAT G-3′. The following probes were designed for allelic discrimination: G allele: 5′-Fam- GTA GCA TTC AAT CAA ATA GCA ACA AC-1-3′; and A allele: 5′-Hex- GTA GCA TTC AAT TAA ATA GCA ACA AC-1-3′.

The rs9657182 SNP, the following primers were used for the: forward primer: 5′- ATT GTT GTA GGT CAT AAA AGG AG-3′; reverse primer: 5′- TGA AGA CAC AAC ACT TAA GGA-3′. The following probes were applied for the separation of the alleles: G allele: 5′-Fam- CCA TCT TTA ACC ACG GCC A-BHQ-1-3′; A allele: 5′-Hex- CCA TCT TTA ACC ATG GCC A-1-3′.

The parameters for PCR amplifications were as follows: 95°C for 3 min, followed by 44 cycles of 95°C for 10 s, and then 59°C for 50 s (rs34155785 SNP) or 57°C for 50 s (rs7820268 SNP) or 55°C for 50 s (rs9657182 SNP). The genotyping specific master mix from the PCR Biosystem (2x PCRBio Genotyping mix Lo-ROX) was used. The PCR experiments were performed with a BioRad CFX96 C1000 real-time thermal cycler machine, and the data analysis was carried out with BioRad software (BioRad CFX Manager version 1.6).

#### 2.1.3. Statistical methods

SPSS software version 26.0 was utilized for data analysis. We applied the chi-square test for comparing the distributions of the examined genotypes and alleles, and the t-test for comparing the averages in the two groups. The observed genotype frequencies of the PD and the control groups were in accordance with the Hardy-Weinberg equilibrium.

## 3. Results

The genotype distribution of rs34155785 was 105 (100%) homozygous wild-types in the PD patient group, and 129 (100%) in the control group, we did not detect the insertion allele in either group. The allele frequencies were 210 (100%) wild-type alleles in the patient and 258 (100%) in the control group (Table 2). This SNP variant is probably not associated with PD and do not affect the age at disease onset either, as no allelic differences could be observed between the two groups (Table 3)

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167 **Table 2. Genotype and allele distribution of the investigated SNPs.**

| | | Genotype frequency | | | | Allele frequency | | Allele distribution | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | - | | C | |
| | | -/- | -/C | CC | p value | - | C | Carriers | Non-carriers | Carriers | Non-carriers |
| rs34155785 | PD patients | 105 | 0 | 0 | - | 210 (100%) | 0 | 105 | - | - | - |
| | Controls | 129 | 0 | 0 | | 258 (100%) | 0 | 129 | - | - | - |
| p value | | | | | | - | | - | | - | |

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| | | Genotype frequency | | | | Allele frequency | | Allele distribution | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | G | | A | |
| | | GG | AG | AA | p value | G | A | Carriers | Non-carriers | Carriers | Non-carriers |
| rs7820268 | PD patients | 56 | 38 | 11 | p=0.093 | 150 (71.4%) | 60 (28.6%) | 94 | 11 | 49 | 56 |
| | Controls | 59 | 63 | 7 | | 181 (70.2%) | 77 (29.8%) | 122 | 7 | 70 | 59 |
| p value | | | | | | p=0.763 | | p=0.149 | | p=0.248 | |

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| | | Genotype frequency | | | | Allele frequency | | Allele distribution | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | G | | A | |
| | | GG | AG | AA | p value | G | A | Carriers | Non-carriers | Carriers | Non-carriers |
| rs9657182 | PD patients | 29 | 48 | 28 | p=0.186 | 106 (50.5%) | 104 (49.5%) | 77 | 28 | 76 | 29 |
| | Controls | 23 | 70 | 36 | | 116 (45%) | 142 (55%) | 93 | 36 | 106 | 23 |
| p value | | | | | | p=0.235 | | p=0.832 | | p=0.149 | |

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**Table 2. Genotype frequency, allele distribution and age at onset of the PD patients.**

| Genotype frequency rs7820268 | | Age at onset | | |
|---|---|---|---|---|
| | | Early onset | Late onset | p value |
| GG | | 34 (64.2%) | 21 (42%) | p=0.042 |
| AG | | 13 (24.5%) | 24 (48%) | |
| AA | | 6 (11.3%) | 5 (10%) | |
| Allele distribution rs7820268 | | Age at onset | | |
| | | Early onset | Late onset | p value |
| G | Carriers | 47 (50.1%) | 45 (48.9%) | p=0.828 |
| | Non-carriers | 6 (54.5%) | 5 (45.5%) | |
| A | Carriers | 19 (39.6%) | 29 (60.4%) | p=0.024 |
| | Non-carriers | 34 (61.8%) | 21 (38.2%) | |
| Genotype frequency rs9657182 | | Age at onset | | |
| | | Early onset | Late onset | p value |
| GG | | 19 (35.9%) | 9 (18%) | p=0.091 |
| AG | | 23 (43.4%) | 24 (48%) | |
| AA | | 11 (20.8%) | 17 (34%) | |
| Allele distribution rs9657182 | | Age at onset | | |
| | | Early onset | Late onset | p value |
| G | Carriers | 42 (56%) | 33 (44%) | p=0.131 |
| | Non-carriers | 11 (39.3% | 17 (60.7%) | |
| A | Carriers | 34 (45.3%) | 41 (54.7%) | p=0.042 |

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| | | | | |
|---|---|---|---|---|
| | Non-carriers | 19 (67.9%) | 9 (32.1%) | |

Early onset < 60 years; Late onset ≥ 60

The genotype distribution of rs7820268 in the patient cohort was 56 GG, 38 GA and 11 AA, and in the control group was 59 GG, 63 GA and 7 AA. The allele frequencies were very similar, with 71.4% G allele and 28.6% A allele in the PD group and 70.2% G and 29.8% A in the controls (Table 2). This SNP variant is not significantly associated with the PD (genotype: p=0.093, G allele: p=0.149, A allele: p=0.248), but it affects the age at disease onset (genotype: p=0.042, G allele: p=0.828, A allele p=0.024) (Table 3) (Figure 2A).

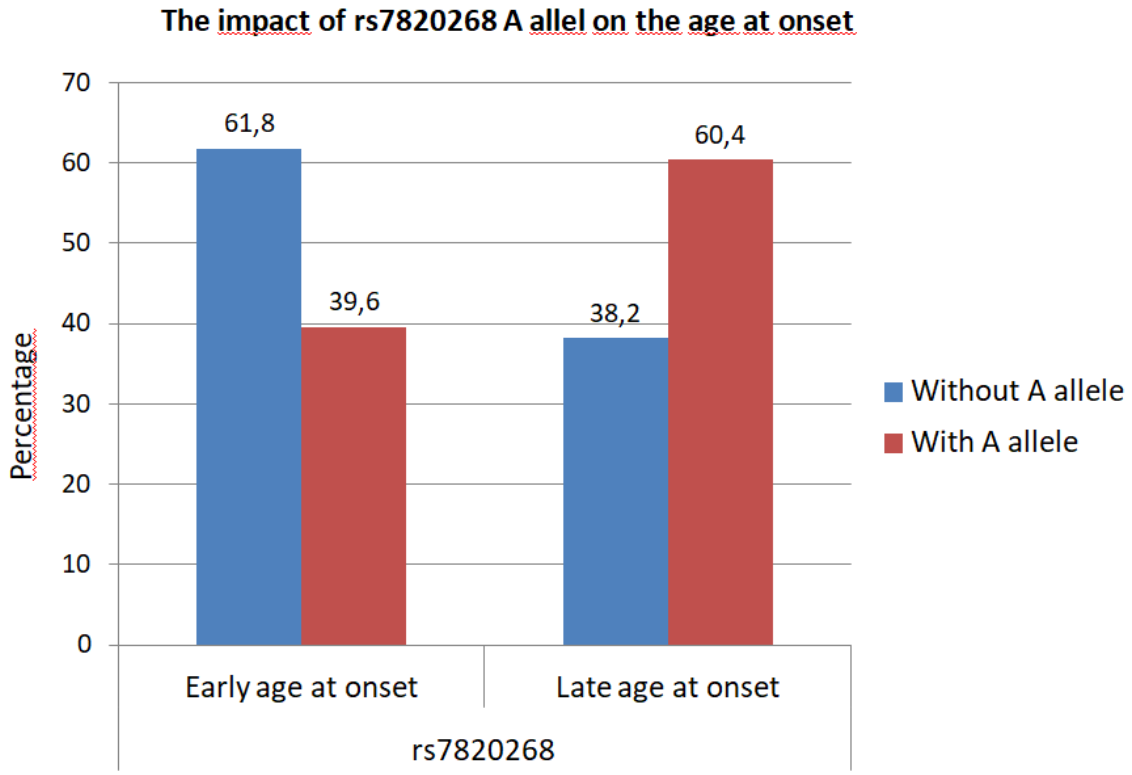


**Figure 2A.** The impact of the A allel of the IDO1 rs7820268SNP on the age at onset of PD.

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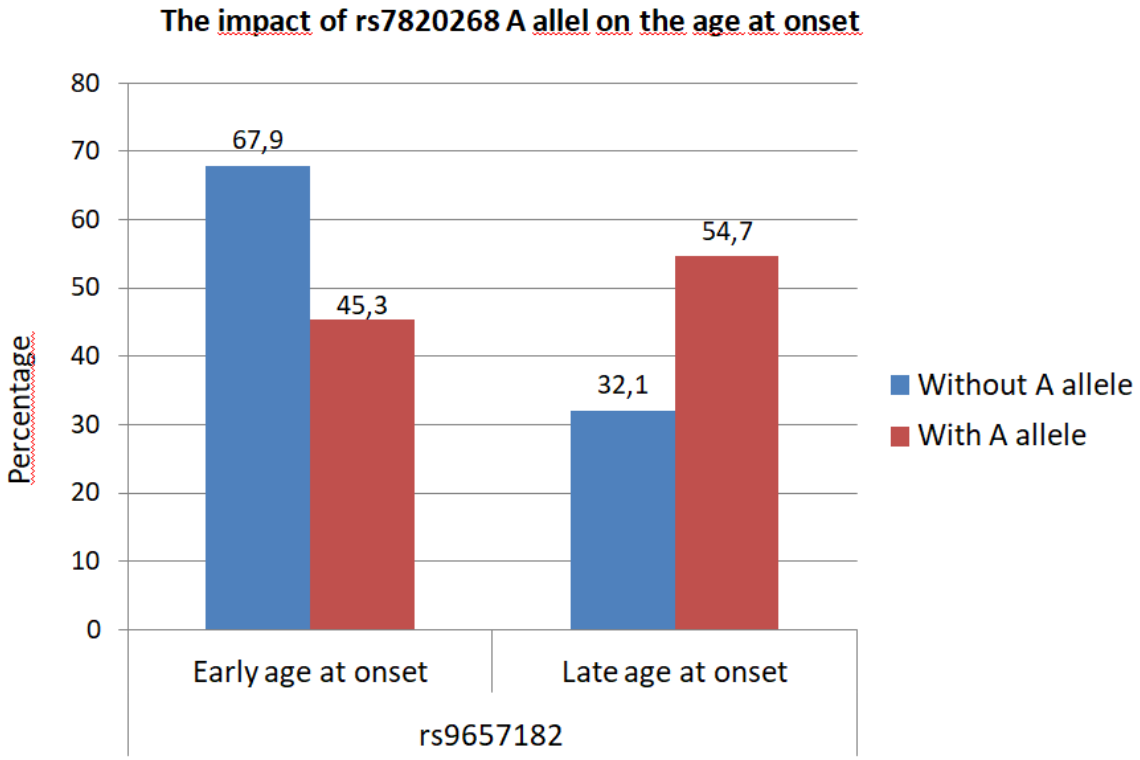


**Figure 2B.** The impact of the A allel of the IDO1 rs9657182SNP on the age at onset of PD.

The genotype distribution rs9657182 was 29 GG, 48 GA and 28 AA in the PD group, and 23 GG, 70 GA and 36 AA in the control group. The allele frequency results did not show remarkable differences, with 50.5% G allele in the PD group vs 45% G allele in the controls, and 49.5% A allele in the PD group vs 55% A allele in the control group (Table 2). This SNP variant is likewise not associated with PD (genotype: p=0.186, G allele: p=0.832, A allele: p=0.073), but it affects the age at disease onset (genotype: p=0.091, G allele: p=0.131, A allele: p=0.042) (Table 3). Similarly, the A allele seems to be a factor affecting the age at onset of PD (Table 3), as carrying the allele associates with late onset (≥ 60 years; 54.7% vs 45.3%), and non-carrying associates with earlier onset (< 60 years; 67.9% vs 32.1%) (OR = 2.546, 95% CI = 1.020–6.351, p = 0.042 for AA + AG vs. GG) (Figure 2B).

Three investigated SNPs of the IDO1 gene were not significantly correlated with PD patients, compared to healthy controls. However, the age-dependent subgroup analysis revealed that rs7820268 SNP or rs9657182 SNP carriers onset PD later in life compared to noncarriers, suggesting the rs7820268 or rs9657182 SNPs potentially delyed the disease onset of PD.

## 4. Discussion

DA receptors, catechol-O-methyltransferase, monoamine oxidase B, NMDA receptors, adenosine A2A receptors, and cholinergic receptors are main targets of PD medication approved for clinical use. The drugs frequently cause serious side effects, become less effectual during treatment, and eventually lead to development of drug-resistant PD such as L-DOPA-resistant PD [32,33]. Thus, a search for novel therapeutic targets is under extensive research. Intervention in KP of TRP metabolism has been shed light on in search of novel drugs for neurodegenerative and psychiatric diseases. Glutamate and acetylcholine are main neurotransmitters responsible for cognition and behavior in which bioactive KYNs mediate neurotoxic, neuromodulatory, and immunological response in reaction to pathological insults [3,34].

The decreased concentrations of L-KYN and KYNA in the frontal cortex, putamen and SNpc, and elevated concentrations of 3-HK in the putamen and SNpc were observed in postmortem brain of PD patients [35]. In addition to the central nervous system, peripheral samples showed

abnormalities such as the increased activity of kynurenine aminotransferase (KAT) and elevated KYNA levels in red blood cells, which may be a protective response [36]. Natural product curcumin was reported to relieve pain and stress through the KYN metabolic pathway [37]. The KP is proposed to be a potential target for treatment of Alzheimer's diseases and schizophrenia [26,38]. Psychedelic psilocybin was reported to relieve depressive and anxiety symptoms of patients with terminal illness [39]. The action is considered at least partly through the KP. Furthermore, delivery of active agents to the brain through the blood-brain barrier is under extensive research [40]. Other in vitro and in vivo studies showed therapeutic opportunities through elevated levels of KYNA in PD [41-43].

However, no study reported a role of the gene polymorphism of KYN enzymes in PD pathogenesis. SNP variants of KMO were investigated. SNP variants of enzymes of the KP in PD were studied previously. SNP analysis of KMO in PD and healthy controls were compared and a subgroup analysis was conducted according to age of onset. Four loci of SNPs did not reveal any significance between PD and healthy controls and between subgroups of age of onset [44]. This study revealed that three SNPs of IDO1 were not associated with PD, but the rs7820268 and the rs9657182 SNPs affected the age of onset of PD. The A alleles carriers were associated with late age of onset, whereas non-carries were associated with early age of onset of PD. The A allele of rs7820268 SNP associated with later onset, whereas non-carriers of the allele were associated with earlier onset (Figure 2A). Another DNA strand the T allele of the SNP was shown to impair CD8+ Treg function [29]. The allele may lead to beneficial immunosuppressive effects in the rs7820268 SNP carriers in PD. The rs9657182 SNP is linked to moderate or severe IFN-$\alpha$-induced depressive symptoms in Caucasian patients with chronic hepatitis C. The SNP is located in the linkage disequilibrium block encompassing 20 kilobases upstream of IDO1 as well as includes at least six additional polymorphisms that may contain binding sites for immunoregulatory proteins or may have epigenetic regulatory function [30]. In addition, a downstream metabolite kynurenic acid was found an antidepressant in animal mode of depression [45]. Indoximod is a methylated TRP that inhibits IDO to maintain or elevate TRP levels important to T cell function. Interestingly, a case study reported that indoximod induced parkinsonism in a patient treated for metastatic breast cancer.

Age is the most important risk factors for neurodegenerative diseases. Age-related risk of leptin metabolism disturbance, especially in obese people was associated with partial pathomechanism of neurodegenerative diseases [46]. Beneficial use of nutraceutical inositols was proposed for age-prone disturbances of energy metabolism and mitochondrial function [47]. In addition, genetic, environmental, infectious, nutritional, and lifestyle are initiation factors which play a role of pathogenesis of PD. Mutations in the genes *SNCA, PRKN, LRRK2, PINK1, DJ-1, VPS35* and *GBA* have been shown to be important risk factors for PD [48]. The frequency of the L444P mutation of the GBA gene was found higher in the PD patients and associated with the early onset of PD [49].

Long interspersed element-1 (LINE-1) is a class I transposable element that has been linked to the various diseases including PD. Higher germline variations and increasing somatic variations of LINE-1 loci were associated with PD. Thus, polymorphism and accumulation of retrotransposition competent LINE-1s were considered to contribute to pathogenesis of PD [50]. The brain cytoplasmic 200 long-noncoding RNA 1 is coded in the *BCYRN1*. The rs13388259 Intergenic polymorphism *BCYRN1* gene was associated with PD [51]. A large-scale meta-analysis of genome-side association (GSA) studies identified SNP variants of several loci associated with PD. *GBA*, *GAK/DGKQ*, *SNCA*, and *HLA* were identified as secondary independent risk factors. Furthermore, substantial cumulative risk was reported by risk profile analysis [52]. GSA generated polygenic risk scores (PRS) for prediction of risk and progression of Parkinson's disease (PD), to search PD-related biological pathways from large-scale pathway specific-genetic risk profiling, and to identify causal PD genes and potential therapeutic targets [53]. Furthermore, increasing evidence suggests that epigenetic mechanisms play a role in regulation of PD-associated genes, including DNA methylation, histone modifications, and microRNAs (miRNSs) [54]. miRNAs are short non-coding RNAs responsible for gene expression at the post-transcriptional level. Altered miRNAs have been linked to mitochondrial dysfunction and oxidative stress in ageing and neurodegenerative diseases [55]. miR-133b, miR-7, miR153, miR-433, miR-433, miR-205, and miR-124 are of interest as possible biomarkers in PD [56].

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Furthermore, differential monitoring of the redox status was proposed to build a personalized treatment for patients with multifactorial neurologic diseases [57]

This study had several limitations including its relatively small sample size, the small number of SNP loci, heterogeneity of the study subjects, and the collection of blood samples at a single center. Furthermore, enzyme activities of IDO1, IDO2, and TDO were not measured. Thus, it was not known if IDO2 and/or TDO compensated the polymorphic variants of IDO1. Prospective studies in larger patient number, with the larger number of SNP loci, and data with IDO2 and TDO activities are needed to validate our findings.

## 5. Conclusion

This study explored the potential role of IDO1 gene polymorphisms in PD. None of three IDO1 SNPs investigated in this study were significantly associated with PD; however, two IDO1 SNPs showed correlated with the age onset of PD, suggesting that the gene polymorphisms may not play a direct role in pathogenesis of PD, but may influence the disease onset probably as secondary risk factors. The further investigation is expected in search of roles of gene polymorphism in risk, onset, prognosis, progression of PD including SNPs, structural variants, and the disease-related pathways.

**Author Contributions:** Conceptualization, N.T. and L.V.; methodology, N.T. and K.M.; software, N.T.; validation, N.T.; formal analysis, N.T. and K.M.; investigation, N.T.; resources, N.T., R. M.T., Z.S and F.S.; data curation, N.T. and K.B. ; writing—original draft preparation, N.T.; writing—review and editing, M.T.; visualization, N.T.; supervision, P.K. and L.V.; project administration, N.T.; funding acquisition, L.V. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

**Abbreviations**

| | |
|---|---|
| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| CSF | cerebrospinal fluid |
| DA | dopamine |
| 3-HAA | 3-hydroxyanthranillic acid |
| 3-HK | 3-hydroxykynurenine |
| IDO | indoleamine 2,3-dioxygenase |
| IFN | Interferon |
| KAT | kynurenine aminotransferases |
| KMO | kynurenine 3-monooxygenase |
| KP | kynurenine pathway |
| KYNA | kynurenic acid |
| NMDA | *N*-methyl-D-aspartate |
| PD | Parkinson's disease |
| QUIN | quinolinic acid |
| ROS | reactive oxygen species |
| SNP | single nucleotide polymorphisms |
| TDO | tryptopan 2,3-dioxygenase |
| TRP | tryptophan |

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