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Ph.D. School in Biology

Genetic analysis of neurological disorders with different age characteristics

Summary of the Ph.D. thesis

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1. Introduction

1.1. Description of Parkinson’s disease and the kyurenine pathway

Parkinson's disease (PD) may occur at any age, even in a very young adult age, but PD of unknown origin ("idiopathic") is a disease of the elderly population over 60 years of age. It is slightly more common in men. It is estimated that 16-20,000 patients live in Hungary.

The kynurenine system is the main pathway of tryptophan degradation in the human brain. The majority of tryptophan is utilized here, while a smaller proportion is transported to the serotonin system or used as building blocks for new proteins (Schwarcz 1993). At the end of the enzymatic pathway, nicotinamide adenine dinucleotide (NAD) and NAD phosphate are formed.

The literature has previously suggested a relationship between PD and altered kynurenine and serotonin pathways. Lower levels of serotonin (5-HT), kynurenine (KYN), and kynurenic acid were measured in the frontal cortex, putamen, and substantia nigra pars compacta regions in patients with PD compared to healthy controls (Ogawa et al. 1992), furthermore 3-hydroxy-kynurenine (3-HK) levels were higher in the patient group (Ogawa et al. 1992). Differences in the enzymatic pathway have also been detected in two Parkinson's animal models too (Knyihar-Csillik et al. 2004; Luchowski et al. 2002; Knyihar-Csillik et al. 2006). No study has been investigated kynurenine enzymes polimorphisms in PD before, so our group has aimed to investigate single nucleotide polymorphisms (SNPs) of the kynurenine-3-monooxygenase (KMO) enzyme, which is one of the key enzymes of the cascade.

1.2. Relationship between amiotrophic lateral sclerosis and vitamin D

Amyotrophic lateral sclerosis (ALS) can also occur at any age (genetic involvement plays a crucial role in the onset of the disease at young ages), but sporadic cases occur most often between the ages of 40 and 60. The incidence of the disease is 5.40 per 100,000 people, which means 540 new cases per year in Hungary (based on its 10 million population).

Vitamin D is synthesized in the skin from its prohormone by sunlight. The active form of vitamin D is 1α-25- (OH) 2D, which binds to its nuclear receptor (VDR) and thus modulates the transcription of genes that affect among others mineral homeostasis. Vitamin D regulates serum calcium levels, which can affect various immune functions (Basit 2013) too. In ALS, one of the possible causes of the vulnerability of motor neurons is their lower levels of calcium binding proteins (parvalbumin and calbindin-D28K). Vitamin D is responsible for also the biosynthesis of neutrophic factors and inducible nitric oxide synthase, and increases glutathione levels. All of these play a role in the pathomechanism of ALS and other

neurological diseases. Vitamin D generally reduces inflammatory processes, which play a significant role in neurodegeneration by modulating antigen presentation and affecting T cell proliferation and phenotype. The VDR gene encodes the vitamin D3 nuclear hormone receptor. There is significant literature on the relationship between the VDR gene and certain neurological disorders (Torok et al. 2013; Chen et al. 2017; Abdollah Zadeh et al. 2017; Bettencourt et al. 2017; Laczmanski et al. 2015); but data is limited in case of ALS (Kamel et al. 2003). Therefore, our group aimed to study four polymorphisms of the VDR gene in ALS. Our aim was to investigate the role of their alleles in the development and the age at onset of the disease.

1.3. Multiple sclerosis and the CCR5 locus

Multiple sclerosis (MS) affects around 2.5 million people worldwide. The disease is a progressive disease, the most common neurological disorder in the young adult population. Women are more affected and more likely to develop the disease. Typically, the first symptoms appear between the ages of 20 and 50. The number of patients in Hungary is about 7-8000.

It is widely known that central nervous system inflammation in MS is accompanied by loss of the myelin sheath, axonal damage and gliosis, which together cause progressive neurological dysfunction.

Chemokines (chemoattractant cytokines) and chemokine receptors play a key role in inflammatory processes. They can direct the migration of immune cells, including T cells through the blood-brain barrier, which is thought to be one of the first steps towards the development of MS (Matsui 2013; Jatczak-Pawlik et al., 2016).

The chemokine receptor V (CCR5) has been showed increased receptor expression in inflammatory brain regions in both the human MS experiments and in experimental autoimmune encephalomyelitis (animal model of MS) (Baranzini et al. 2000; Simpson et al. 2000). 2000; Zang et al. 2000). The most studied polymorphism of the CCR5 gene is the 32 bp deletion of the gene, which results in a frame shift mutation in exon 1. The role of the deletion in the development of MS remains questionable due to the many contradictory results. So our group aimed to investigate this deletion in a large sample population, which has not been studied yet.

2. Materials and methods

2.1 Biobank: blood collection and storage

First we have created a biobank at the Department of Neurology, Faculty of Medicine, University of Szeged. Blood samples were stored in four -80 ° C freezers. Later, the biobank was also approved by the local National Public Health and Medical Officer Service and the University of Szeged, Albert Szentgyörgyi Clinical Center Regional Ethics Committee for Human Biomedical Research.

The collection, cataloging and storage of samples was carried out in accordance with law XXI of 2008 (which regulates the protection of human genetic data, the rules of human genetic studies and research, and the operation of biobanks).

The collections were gathered from patients from the clinic who had given written informed consent (MS, PD, Huntington's disease, epilepsy, stroke, ALS and migraine patients) and their healthy, non-blood relatives (husband-wife).

Later, we also organized additional sample collections from local, national and international cooperations.

2.2. Patient and control samples in the three genetic analyzes

Our study protocols were approved by the Medical Council, Scientific and Research Ethics Committee for PD, ALS (470663/2013 / ECU (556/2013)) and MS (No.35764 / 2012 / ECU (566 / PI12)) and are in line with the Helsinki Declaration.

Patient and control data for the three studies are presented in three tables (Tables 1-3). In all three cases, we worked with gender and age-matched patient and control groups.

Groups (N)	Male	Female	Average age (SD)	Median	Min	Max	Age at onset (SD)
Parkinson's patients (105)	48	57	66.42 ± 9.236	68	34	84	58.81 ± 10.970
Controls (131)	60	71	65.21 ± 8.072	63	53	87	-

Table 1. Summary of the sociodemographic data of the Parkinson's disease and the kynurenine system study. N: element number, SD: standard deviation

Groups (N)	Male	Female	Average age (SD)	Median	Min	Max	Age at onset (SD)	Median of the age at onset
ALS patients (75)	28	47	60.3±11.0	61	33	86	58.9±11.8	60
Controls (97)	36	61	60.1±11.3	62	33	84	-	-

Table 2. Summary of sociodemographic data from the ALS study. N: element number, SD: standard deviation

Groups (N)	Male (%)	Female (%)	Average age (SD)	EDSS score (SD)	Age at onset (SD)
MS patients (428)	106 (24.8)	322 (75.2)	43.74±11.97	2.54±1.92	32.17±9.80
Controls (831)	204 (24.6)	626 (75.4)	44.34±13.20	-	-

Table 3. Sociodemographic data of the multiple sclerosis study. N: Element Number, SD: Standard Deviation, EDSS: Disability Status Scale

2.3. DNA isolation

Peripheral blood samples were collected from patients with PD, ALS, and MS and their healthy non-blood relatives after written consent. These samples were used to isolate genomic DNA. The hereditary material was isolated from white blood cells from blood tissue according to the Miller's method (Miller, Dykes, and Polesky 1988). The purified genomic DNA was stored at -20 and -80 ° C in the Biobank of the Department of Neurology until further use.

2.4. Genotyping

Taqman probe polymerase chain reaction method was used in the PD and the MS study. Fluorescently labeled Taqman probes and the primers were provided by Nucleotest Bio Ltd. (Budapest, Hungary). A specific master mix was used for genotyping. Experimental work was

performed using the BioRad CFX96 C1000 real-time PCR machine, and data analysis was evaluated using BioRad software for this machine.

In case of the ALS study the alleles were isolated by restriction fragment length polymorphism assays. The enzymes used for digestion were supplied by Thermo Scientific Baltic (Vilnius, Lithuania).

2.5. Statistics

Data was evaluated using SPSS software version 20. A Chi-square test was used to examine the distribution of genotypes and alleles, and a *t*-test to compare means between the two groups in all three analyses.

The odds ratio (OR) and the 95% confidence interval (CI) were calculated to examine the relationship between VDR and ALS risk. A value of $P < 0.05$ was considered significant.

In MS experiments, analysis of variance was used when the mean of more than two groups was to be considered, and bidirectional analysis of variance when more than two grouping criteria were used.

The observed genotype frequencies were consistent with the Hardy-Weinberg equilibrium (HWE) between patient and control groups.

3. Results

3.1. Parkinson's disease

The investigated four KMO polymorphisms (rs2050518, rs6661244, rs2275163, rs1053230) were not associated with PD, nor did they influence the onset of the disease.

3.2. Amiotrofic lateral sclerosis

One of the four tested SNP (BsmI, TaqI, FokI and ApaI) ApaI showed a significant association with ALS. In case of ApaI genotype distribution between patient and control group was significant association ($\chi2 = 11.09$; $P = 0.004$). The frequency (AA + AC) vs CC of genotypes containing the A allele was significantly higher in ALS patients than in the control group ($\chi2 = 10.807$, df = 1, $P = 0.001$, OR: 4.143 and 95% CI = 1.699–10.100). (Table 4, Figure 1). Furthermore, the A allele was significantly associated with the ALS patient group ($\chi2 = 5.352$, df = 1, $P = 0.021$).

None of the investigated polymorphisms influenced disease onset and gender distribution in the patient group.

Table 4. Summary of the results of the ALS study.

rs7975232 (ApaI)	AA (%)	AC (%)	CC (%)	p	A (%)	C (%)	p
ALS patients	25 (33.3%)	43 (57.3%)	7 (9.3%)	0.004	93 (62%)	57 (38%)	0.021
Controls	28 (28.9%)	40 (41.2 %)	29 (29.9%)		96 (49.5%)	98 (50.5%)	
Age at onset ≤60 year	10 (26.3%)	23 (60.5%)	5 (13.2%)	0.289			
Age at onset >60 year	15 (41%)	20 (54%)	2 (5%)				
Male	12 (42.9%)	13 (46.4%)	3 (10.7%)	0.327			
Female	13 (27.7%)	30 (63.8%)	4 (8.5%)				

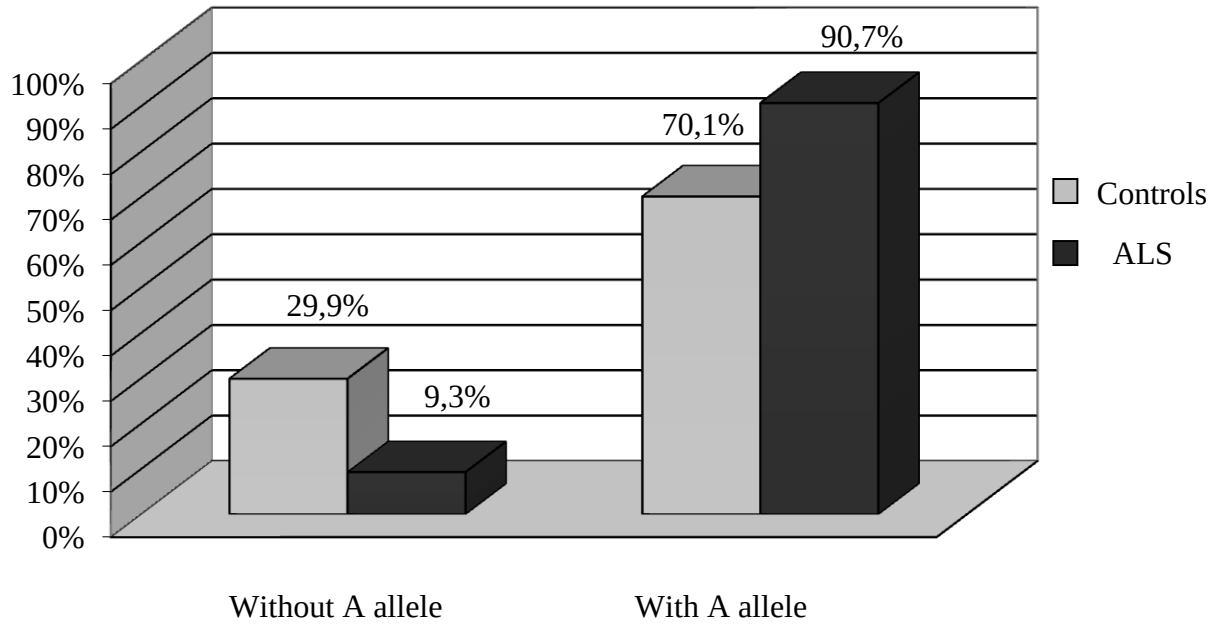

Figure 1. Distribution of the ApaI A allele in the ALS and control groups.

3.3. Multiple sclerosis

Of the 428 MS patients, 352 were homozygous wild type, 71 were heterozygous and 5 were homozygous for the Δ32 deletion. Thus, the frequency of the Δ32 allele was 9.46%. We identified 670 wild type, 146 heterozygotes and 12 homozygous Δ32 deletion genotypes in the healthy control group. The lower allele frequency in the group was 10.26%. No significant differences were found between the patient and control groups in a the genotype distribution (OR = 1.092, 95% CI = 0.807-1.478, p = 0.568 wt / wt / wt / Δ32, Δ32 / Δ32) or in the allele

frequencies (OR) = 0.914, 95% CI = 0.692-1.207, p = 0.525), or in allele distribution (p = 0.817). We then examined the genotype distribution and the allele frequency by gender, but no significant difference was found. The genotype distribution has no effect on the form of the disease (p = 0.440). We aimed to clarify that the genotypes or the alleles have any effect on the severity of the disease (EDSS) or the age at disease onset. The genotype distribution did not affect the EDSS score (F = 0.282; p = 0.755) or the age at onset of the disease (F = 0.416; p = 0.660). Neither the deletion nor the wild-type allele affected the EDSS (wt allele: F = 0.032, p = 0.858; Δ32 allele: F = 0.564; p = 0.453), or the age at disease onset (wt allele: F = 0.010, p = 0.921; Δ32 allele: F = 0.821, p = 0.365).

Because not only genetic predisposition, but also environmental factors are critical in the development of MS, we collected data from our patients about their alcohol consuming and smoking habits and body mass index (BMI). We examined whether these environmental factors together with the wild-type and deletion allele affect the EDSS or the age at disease onset. In our study, none of the investigated combinations were significant in the patient population for the EDSS and the age at disease onset. Our results show that there is no correlation between the CCR5 Δ32 allele and the MS predisposition in the Csongrad County and Northern Bácska populations.

In our last study, we studied only the role of the environmental factors alone on age at onset and the severity of MS. First, the effect of alcohol on EDSS and age at onset of disease was analysed. There was no significant difference in EDSS, however, alcohol had a significant negative effect on age at disease onset (P = 0.019). The individuals with MS predisposed to alcohol may have earlier onset of the disease (Table 5). Thereafter, smoking habits were compared with severity and age at onset of the disease. In this study, no significant value was obtained (P = 0.721. P = 0.229). Finally, BMI data were analyzed to determine whether they affect EDSS or age at onset (Table 6). In this study, we found a significant difference in the age at onset of disease (p = 0.007). The table shows that the increase in BMI (from lean to obese) increases the age at onset of the disease too.

Table 5. Effect of the alcohol consumption on the EDSS and the age at disease onset.

Alcohol	EDSS (N)	p	Age at onset (N)	p
no	2.584±1.948 (391)	0.125	32.49±9.667 (391)	0.019
yes	2.069±1.604 (36)		28.50±10.676 (36)	

Table 6. Effect of body mass index on the EDSS and the age at disease onset.

BMI	EDSS (N)	p	Age at onset (N)	p
lean	2.460±1.936 (25)	0.686	28.48±7.875 (25)	0.007
normal weight	2.541±1.975 (233)		31.46±10.359 (233)	
overweight	2.669±2.004 (118)		32.97±8.899 (118)	
obese	2.280±1.464 (50)		35.70±8.945 (50)	

4. Summary

The present thesis summarizes the genetic analysis of selected, disease specific SNPs of three neurological disorders: PD, MS and ALS.

The first major step of the project was to create a biobank at the Department of Neurology in Szeged (Faculty of Medicine, University of Szeged). We had to ensure that all the materials are purchased and all the official licenses are provided which was necessary for collecting and storing human blood samples.

Our goal was to investigate the chronic, progressive PD which affects mostly the elderly population. In our first study we enrolled 105 PD patients and 131 control subjects. Our aim was to carry out the tests on a large age-matched control and patient group. We also considered it to be important to draw attention to the relationship between the PD and the kynurenine pathway which had not previously been genetically studied. In our study, four

KMO gene SNPs were investigated: rs2050518, rs6661244, rs2275163 and rs1053230. DNA extraction from white blood cells was performed using the Miller isolation, while genotyping was done by Taqman probe based polymerase chain reactions. To evaluate the data, a Chi-square test and a t-test were applied in the SPSS software. The observed genotype frequencies were consistent with the Hardy-Weinberg equilibrium in the PD and the control group.
Based on our results, none of the four analyzed KMO polymorphisms were related to the PD and neither did they influence the age of onset. Thus, the genetic relationship between the PD and the kynurenine system is still not supported. The studied SNPs are unlikely to have an effect on the function of the KMO gene, nor are they part of the regulatory protein binding sites that are relevant to PD.

Amytrophic Lateral Sclerosis (ALS) is a fatal, progressive, neurodegenerative disorder that affects nerve cells in the brain and spinal cord. Previous studies have shown that affected neurons show low expression of calcium binding proteins. The level of these can be raised with Vitamin D supplementation. The active form of vitamin D is 1α-25-(OH)2D, which binds to its nuclear receptor (VDR) in the cell and is able to modulate the transcription of the regulated genes and it can influence the mineral homeostasis. It is also important to note that vitamin D regulates serum calcium levels, which contribute to different immune functions. A study ten years ago found that the level of 25-hydroxy vitamin D is lower in ALS patients. Recently another study investigated the effect of Vitamin D supplementation in ALS which was able to slightly slow down the disease progression. It has recently been reported that chronic vitamin D treatment increases the mRNA level of VDR gene in rat brain neurons after glutamate-induced neurotoxicity. Therefore our group aimed to study the polymorphisms of the VDR gene in ALS. The VDR encodes the nuclear hormone receptor of vitamin D3. The relationship between the VDR gene and some neurological disorders has been described in the literature, but only few articles have been published in the context of ALS. In our study we collected blood samples of 75 sporadic ALS patients (approximately 20% of the Hungarian ALS population) and 97 of age-sex matched healthy controls. The examined SNPs were as follows: rs1544410 (BsmI), rs7975232 (ApaI), rs731236 (TaqI), and rs2228570 (FokI). Since no previous data were available on the possible connection between the polymorphisms of the VDR gene and the disease, our goal was to provide new insight into the role of vitamin D in ALS. After the collection of the blood samples we isolated genomic DNA using the Miller's salting method. For the isolation of alleles, the restriction fragment length polymorphism (RFLP) technique was used. In the statistical part of the study, Chi-square test and t-test were used. For examining the relationship between the risk of the gene and the disease, the odds

ratio and the 95% confidence interval were calculated. The obtained genotype frequencies were consistent in the control and patient group with the Hardy-Weinberg equilibrium.A significant difference was found in the genotype distribution of ApaI SNP between the patient and the control group, meaning that the frequency (AA+AC) vs. CC of the genotypes containing A alleles was significantly higher in ALS patients than in the control group. Furthermore, the A allele was significantly associated with the ALS patient group. However, the two studied alleles did not affect the disease age of onset or the gender distribution in the ALS group. This work is the first genetic evidence that the VDR gene can play a role in ALS. Kamel et al.-previously investigated the BsmI SNP of the VDR gene, but this was not related to the pathology or the pathogenic lead level. In our study we support this observation since we did not find any significant relationship between the BsmI SNP and the disease either. No significant difference was found in the case of the FokI or TaqI SNP in the ALS control group.

Multiple sclerosis (MS) is an autoimmune neurological disorder of the central nervous system affecting mainly the young population. This disease is the most common neurological disorder of young adults and in half of the cases it causes disability due to irreversible tissue damage. The trigger of the disease is the inflammation of the white matter in the central nervous system, which results in damage to the neurons and the myelin surrounding them. Chemokines (chemoattractant cytokines) and chemokine receptors play a key role in inflammatory processes as they direct migration of immune cells, including T-cells through the blood-brain barrier, which is presumably the first step to the development of the disease. Previously published data suggest an upregulation in the CCR5 chemokine receptor expression in inflammatory brain regions derived from human samples and there are similar results in the animal model of the disease, in experimental autoimmune encephalomyelitis. The most studied mutation of the CCR5 gene is a Δ32 bp deletion, which shows contradictory results in the connection with MS. Our aim was to carry out this investigation on a large patient and control population that has not been included in a similar study before in connection to the disease. We planned to study the potential effect of the allele on the Expensive Disability Status Scale (EDSS) and on the age of onset. We considered it important to test the effect of lifestyle and environmental factors in parallel with carrying the allele, so alcohol consumption, smoking and BMI data were also registered. Finally, 428 patients with relapsing-remitting or secunder progressive disease and 831 healthy controls were included in the survey. After the DNA isolation (Miller's salting method) a Taqman probe allele discrimination method was utilized to identify the alleles. In the statistical analysis, Chi-

squared test was used to compare genotype and allele distribution, and t-test was used to compare the averages of two groups. The variance analysis was used when the average of more than two groups had to be taken into account, while the bidirectional variance analysis was utilized when more than two categorization criteria were analysed. The observed genotype frequencies were consistent with the Hardy-Weinberg equilibrium in both the MS and control groups. There was no significant difference between the MS patient and the control group either in genotype distribution or in allele frequencies. The rs333 polymorphism did not affect the EDSS score or the age of onset of the disease. Neither the deletion nor the wild type allele did affect the EDSS or the age of onset. In the combined study none of the wild or the deletion allele in combination with smoking, alcohol consumption, and body mass index (BMI) proved to be significant in the patient group for the EDSS or the disease initiation. Our results show that there is no correlation between the CCR5 Δ32 allele and MS susceptibility in the Csongrád County and North Bácska populations. This study did not identify any relationship between the Δ32 deletion of the CCR5 gene and the MS. According to our results deletion does not mean a greater risk of developing the disease, it cannot be called a biomarker, since it does not occur in a larger number in the patient group. It has no protective role, because it does not appear in a larger number in the control group. Furthermore, it is not a prognostic factor, as it does not affect either the EDSS value or the age of onset. We obtained our results on a large number of patient and the second largest number of control group. Our results were confirmed by a recent meta-analysis study which study re-summarized and re-analyzed data. In that study summarized data were collected and analyzed again from other studies to involve larger sample number. The studies of the alcohol consumption, smoking habits and body mass index in case of MS have shown two significant results. The alcohol consumption has been shown to be a risk factor for earlier MS onset, while the high body mass index had a protective effect on the age at onset of the disease.

Publication list

ΣIF: 34,203

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