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Environmental and genetic risk factors for Parkinson's disease

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ABSTRACT

Aim. To analyze risk factors in the group of patients with Parkinson's disease (PD) and compare them with the literature data.

Materials and methods. The study included 439 patients with PD and 354 controls, comparable by gender and age. For each individual, a registration card was filled in containing demographic, epidemiological, clinical, and neuropsychological data. The severity of the disease was studied according to the MDS-UPDRS scale; the stage of PD was determined according to the Hoehn and Yahr scale. Cognitive functions were assessed by the MoCA test and MMSE. The length of the (CAG)n repeat region in the *HTT* gene was determined using fragment analysis on the ABI 3730 DNA analyzer. The obtained results were analyzed using GeneMapper Software v4.1 (Applied Biosystems, USA).

Results. When comparing patients with PD and the control group, the odds ratio (OR) for PD in individuals with traumatic brain injury was 3.13 (95% confidence interval (CI): 2,27–4.34; $p = 4.94 \times 10^{-13}$), which showed the significance of this risk factor for PD. Consumption of coffee in the anamnesis distinguished the group of PD patients from the control group (OR = 0.41 (95% CI: 0.30–0.56); $p < 0.0001$), confirming its neuroprotective effect. Analysis of the variability in the length of the (CAG)n repeat regions in the *HTT* gene showed that patients whose genotype contained an allele with 17 repeats in combination with any allele other than an allele containing 18 repeats had a protective effect (OR = 0.50 (95% CI: 0.27–0.92); $p = 0.025$). All genotypes containing an allele with 18 repeats were predisposed to PD (OR = 2.57 (95% CI: 1.66–4.28); $p = 0.007$). The predisposing effect of the allele to PD, unrelated to the expansion of CAG repeats in the *HTT* gene, was revealed for the first time.

Conclusion. Traumatic brain injury and the allele with 18 CAG repeats in the *HTT* gene are risk factors for PD. Coffee consumption can be attributed to protective factors in relation to PD.

Keywords: Parkinson's disease, risk factors, coffee, traumatic brain injury, *HTT* gene

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. The patients gave an informed consent to examination, neuropsychological testing, and sampling of venous blood. The study was approved by the local Ethics Committee at Siberian State Medical University (Protocol No. 7813 of 27.05.2019).

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Средовые и генетические факторы риска болезни Паркинсона

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РЕЗЮМЕ

Цель. Проанализировать факторы риска в группе пациентов с болезнью Паркинсона (БП) и сопоставить их с литературными данными.

Материалы и методы. В исследование были включены 439 пациентов с БП и 354 индивида группы контроля, сопоставимых по полу и возрасту. На каждого индивидуума заполнена регистрационная карта, содержащая информацию о демографических, эпидемиологических, клинических и нейропсихологических данных. Тяжесть заболевания исследовалась по шкале MDS-UPDRS; стадия БП – согласно шкале Hoehn – Yahr. Когнитивные функции оценивались по MoCA-тесту и MMSE. Длину (CAG)n-повтора в гене *HTT* определяли с помощью фрагментного анализа на платформе ABI Genetic Analyzer 3730. Анализ полученных результатов проводился с помощью GeneMapper Software v4.1 (Applied Biosystems, США).

Результаты. При сравнении пациентов с БП и контрольной выборки отношение шансов развития БП у индивидов с травмой головы составило 3,13 (95% CI: 2,27–4,34; $p = 4{,}94 \times 10^{-13}$), показав значимость этого фактора риска БП. Употребление в анамнезе кофе отличает группу пациентов с БП от группы контроля (OR = 0,41 (95% CI: 0,30–0,56); $p < 0{,}0001$), подтверждая его нейропротективное действие. Анализ вариабельности длины (CAG)*n*-повторов в гене *HTT* показал, что пациенты, в генотипе которых присутствует аллель, содержащий 17 повторов в сочетании с любым другим аллелем, кроме аллеля, содержащего 18 повторов, обладает протективным эффектом (OR = 0,50 (95% CI: 0,27–0,92); $p = 0{,}025$). Все генотипы, содержащие аллель с 18 повторами, предрасполагают к БП (OR = 2,57 (95% CI: 1,66–4,28); $p = 0{,}007$). Предрасполагающий эффект аллеля, не связанный с экспансией CAG-повторов гена *HTT*, к БП выявлен впервые.

Заключение. Черепно-мозговая травма и аллель $(CAG)_{18}$-повторов гена *HTT* являются факторами риска для развития БП. Употребление кофе можно отнести к протективным факторам в отношении БП.

Ключевые слова: болезнь Паркинсона, факторы риска, кофе, черепно-мозговая травма, *HTT*

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование выполнено при частичной грантовой поддержке научно-исследовательских проектов, выполняемых молодыми учеными («Роль генов репарации в патогенезе болезни Паркинсона, болезни Гентингтона и нормального (здорового) старения», 2021–2023 гг.). Работа выполнена при частичном финансировании Министерства науки и высшего образования (госзадание № 122020300041-7).

Соответствие принципам этики. Обследование, нейропсихологическое тестирование и забор венозной крови всех лиц проводились только после подписания информированного согласия. Исследование одобрено локальным этическим комитетом СибГМУ (протокол № 7813 от 27.05.2019).

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INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease, described by James Parkinson in 1817 in the essay about "shaking palsy" [1]. Degeneration of dopaminergic neurons in the substantia nigra and formation of Lewy bodies are pathological markers of PD [2]. Lewy bodies are cytoplasmic inclusions that contain insoluble aggregates of α-synuclein. However, pathological process is not restricted to the substantia nigra, it affects other brain regions and involves non-dopaminergic neurons.

PD is characterized by multifactorial etiology, which includes environmental and genetic components. Lifestyle and environmental factors [3] and multiple genetic variants have modifying effects both on predisposition to PD [4] and on the rate of PD progression [5–7]. Such factors as age, male gender [8], contact with pesticides [9], head injuries, depression, osteoporosis, therapy with beta-adrenergic antagonists or melanoma in the medical history [10] are associated with an increased risk for PD. At the same time, physical activity [11], coffee consumption [12], and long-term intake of nonsteroidal anti-inflammatory drugs, calcium channel blockers, and statins are associated with a decreased risk for PD [3]. Some studies revealed a decrease in the frequency of PD among people with alcohol abuse [11] and among smokers [13]. The latter two associations are controversial and can be caused by peculiarities of study group formation.

Monogenic forms of PD are encountered approximately in 5–10 % of PD cases. At least 18 different genes, mutations in which lead to PD, have been currently described [14]. The main pathogenic variants are found in genes encoding α-synuclein (SNCA), leucin-rich repeat kinase 2 (LRRK2), glucocerebrosidase (GBA), and parkin E3 ubiquitin protein ligase (PRKN) [15]. Nonetheless, PD mostly has sporadic nature, and the majority of PD patients do not have mutations in these genes [2, 16].

Moreover, the most frequent genetic mutations contributing to PD have incomplete penetrance, which indicates the presence of modifying factors. Twin studies have shown that inheritance of PD is 30%, which indicates that an increased risk for PD is associated with environmental and lifestyle factors [17]. The *HTT* gene is one of the possible modifier genes; expansion in its (CAG)n repeat regions (more than 36 repeats) results in Huntington's disease (HD). The length of repeat regions is assumed to be a physiological modifier for the adenosine diphosphate (ADP) / adenosine triphosphate (ATP) ratio, which implies a common pathological component in both diseases (PD and HD). Moreover, single cases with atypical PD were described in the literature: PD patients with pronounced clinical manifestations have some neurophysiological features typical of HD. Such patients have intermediate alleles in the *HTT gene* – $(CAG)_{27}$ and $(CAG)_{29}$ – which do not exceed the pathological (CAG)n repeat length in HD [18, 19]. Therefore, we considered the length of (CAG)n repeats in the *HTT* gene as one of the risk factors for PD.

The aim of the study was to evaluate the role of environmental and genetic factors in PD development.

MATERIALS AND METHODS

A group of PD patients was recruited at the Neurology and Neurosurgery Division of Siberian State Medical University. The diagnosis was established according to the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease [20]. We examined 439 PD patients (179 males and 260 females) and 354 healthy individuals as a control group (143 males and 211 females). All these individuals were included in the study. The control group consisted of healthy individuals without neurodegenerative pathology. The study groups were comparable by age (66.3 ± 7.3 and 66.2 ± 9.1 years, $p > 0.05$) and sex (1:1.45 and 1:1.47, respectively).

All study participants underwent clinical neurological and neuropsychological testing. An individual registration card was filled in for each participant containing demographic, epidemiological, and clinical data. Information about risk factors for PD (head injury, exposure to toxic chemicals, smoking, coffee consumption) was obtained from interviews with the participants and their relatives (individuals with pronounced cognitive impairments were not included in the study). The above factors were taken into account only if they preceded PD symptoms.

The severity of the disease was assessed using the MDS-UPDRS scale; the stage of PD was determined according to the Hoehn and Yahr scale (1967) [21]. Cognitive functions were examined according to the Montreal Cognitive Assessment (MoCA) test [22] and MMSE [23].

The study complied with the principles of the Good Clinical Practice (GCP) and the Declaration of Helsinki. The study was approved by the local Ethics Committee at Siberian State Medical University.

Molecular and genetic testing was performed at the Center for Collective Use of Research Equipment and Experimental Biological Material "Medical Genomics" of the Research Institute of Medical Genetics, Tomsk NRMC. The length of (CAG)n repeats in the *HTT* gene was examined by the fragment analysis on the ABI Genetic Analyzer 3730 according to the earlier described method [24]. The obtained results were analyzed using GeneMapper Software v4.1. (Applied Biosystems).

Statistical data processing was performed using Statistica 10 software. Calculation of odds ratio (OR) and 95% confidence interval (95% CI) was performed using the online tool at https://www.medcalc.org/calc/odds_ratio.php.

RESULTS

Association of traumatic brain injury with Parkinson's disease. According to the literature data, traumatic brain injury (TBI) was studied as one of the risk factors for a range of neurodegenerative diseases [25]. Some studies have shown that head injury can cause neuroinflammation, affecting neurons either directly [26, 27] or indirectly – via blood – brain barrier impairment [28, 29].

Among the examined 439 PD patients, 208 (47.4%) individuals reported the presence of TBI in the medical history (42 females and 166 males, the average age was 66.2 ± 9.2 years). In the control group, only 79 (22.3%) individuals (18 females and 61 males, the average age was 65.5 ± 8.8 years) reported TBI in the past medical history (Fig.1).

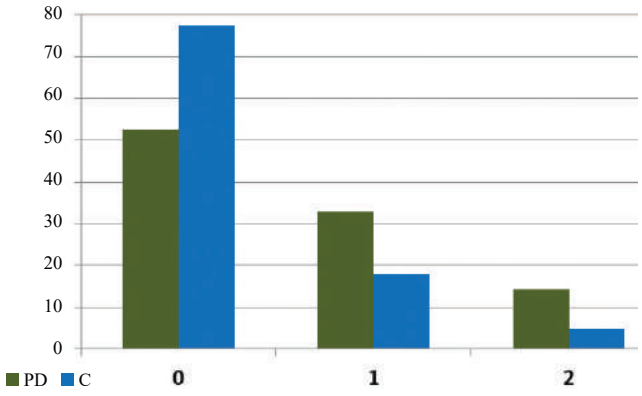

Fig. 1. Frequency of TBI in the past medical history of individuals with PD and the control group (C), %; 0 – no TBI; 1 – the presence of TBI without a loss of consciousness; 2 – the presence of TBI with a loss of consciousness

Comparing the frequency of TBI in PD patients and the control group, OR for PD in individuals with TBI was 3.13 (95 % CI: 2.27–4.34; p = 4.94 × 10^{-13}). Therefore, TBI is a significant risk factor for PD. 63 (14.3%) of PD patients and 17 (4.8%) individuals from the control group reported TBI with a loss of consciousness. The odds for development of PD increase in individuals with more severe TBI (TBI with a loss of consciousness). The OR for the development of PD in individuals with TBI with a loss of consciousness, compared with individuals without TBI, was 4.41 (95% CI: 2.44–8.07; $p = 7.39 \times 10^{-8}$). The average age of disease debut did not differ significantly between PD patients with and without TBI (66.2 ± 9.2 years vs. 67.8 ± 11.8 years, p = 0.82).

Exposure to toxic chemicals. Numerous studies that included populations from all over the world have shown that exposure to pesticides and farming or living in rural areas are considered risk factors for the development of PD [16]. Occupational hazards and accidental exposure to such pesticides as paraquat, rotenone, 2,4-dichlorophenoxyacetic acid, and some dithiocarbamates and organochlorines (for residents living near the areas treated with these pesticides) are associated with an increased risk of PD development [30]. Genetically determined impairments in individuals exposed to toxic chemicals may affect their health increasing the risk of PD manifestation [31]. And on the contrary, compliance with hygiene rules and healthy diet can protect from adverse effects of environmental factors and reduce the effect of pesticide exposure [32, 33].

Among the studied individuals, 116 patients (26.4%) reported exposure to toxic chemicals for more than 5 years: gasoline and petroleum products 8.7% (38), paints and organic solvents 8.0% (35), pesticides and fertilizers 4.3% (19), metals and ionizing radiation 3.6% (16); 8 individuals (1.8%) among the PD patients were welders with work experience of 10 ± 6 years. Nevertheless, comparing the group of PD patients and the control group in terms of exposure to toxic chemicals did not reveal significant differences (OR = 0.79 95 % CI: 0.58–1.08; p = 0.1409).

Lifestyle factors. Some lifestyle factors are associated with a decreased risk of PD development. The strongest association was found between a decreased risk of PD and cigarette smoking individuals and (according to other studies) other tobacco users. It is assumed that nicotine plays the central role in this association. However, a recently finished clinical trial did not reveal a modifying effect of a nicotine patch on manifestations and progression of the disease in PD patients [34, 35].

In the current study, about 42% (n = 184) of patients have never smoked, 53% (n = 233) of patients used to smoke, and 5% (n = 22) of patients are current smokers. In the control group, the values were 50.3% (n = 178), 43.5% (n = 154), and 6.2% (n = 22), respectively. No significant differences were revealed between smoking and non-smoking individuals (p = 0.6594).

In 2007, Dr. Xiang Gao published the first large, prospective study, which lasted 16 years, on the effect of diet and eating habits on the risk of PD development [36]. It was shown that coffee and caffeine consumption were linked with a decreased risk of PD development. This effect was more pronounced in men, was dose-dependent, and might depend on genetic factors. Similarly, some studies showed a decreased risk of PD in individuals drinking strong tea [37, 38].

Among the examined PD patients, only 20.5 % (n = 90) of individuals drink coffee, and about 38.7% (n = 137) of people drink coffee in the control group (OR = 0.41 (95%CI: 0.30–0.56); $p < 0.0001$). At the same time, about 16% of PD patients regularly drink coffee for more than 10 years. These results are consistent with the data obtained by the Xiang Gao et al. [36].

Alcohol consumption in the studied groups was evaluated at the time of the study and in the anamnesis in terms of the frequency of consumption of beer, wine, fortified wine, sweet liqueur or strong alcohol in grams per day (g / day) based on the standard volume of the container for a particular drink. Division into groups was the following: < 0.1 g / day (people who do not drink alcohol, I), 0.1–4.9 g / day (II), 5.0–14.9 g / day (III), 15.0–29.9 g / day (IV), 30.0–59.9 g / day (V), and ≥ 60 g / day (VI). For patients with PD, the following values were identified: 15% (I), 18% (II), 34% (III), 20% (IV), 10% (V), and ≥3% (VI). For the control group, the values were the following: 13% (I), 19% (II), 35% (III), 20% (IV), 10% (V), and ≥3% (VI) ($p > 0.05$). At the same time, the average amount of consumed alcohol did not differ between the groups: 3.01 ± 1.29 and 3.02 ± 1.26 (p = 0.9501).

Length of (CAG)n-repeats in the HTT gene. Despite incontrovertible evidence of the pathophysiological role of mitochondria in PD and their key role in cell signaling pathways, identification of mitochondrial dysfunction as a cause or effect of neurodegeneration is still a challenging task for researchers [39].

Earlier, we showed the associations of *NBN*, *ATM*, and *MLH1* genes with PD. Protein deficiency in these genes can also lead to mitochondrial dysfunction. Frequent alleles and genotypes of non-synonymous substitution of rs1801516 in *ATM* and rs1799977 in *MLH1* predispose to PD development; at the same time, heterozygotes exert a protective effect. A rare allele and genotype of promoter substitution in *NBN* (rs1805800) is also a risk allele for PD [40].

In the current study, we analyzed the length of (CAG)n repeats in the *HTT* gene in PD patients and healthy individuals. In both groups, we found a comparable number of alleles (16 and 17 in PD patients and in the control group, respectively) and a comparable length range (12–32 (CAG)n repeats in PD patients and 12–30 (CAG)n repeats in the control group) (Fig.2). Intermediate alleles $(CAG)_{26\text{-}35}$ were identified in both groups with alleles of normal length: $(CAG)_{16\text{-}19}$ in PD patients and $(CAG)_{15\text{-}24}$ in the control group. The frequency of intermediate alleles was 2.38% and 5.58% in the PD patients and in the control group, respectively.

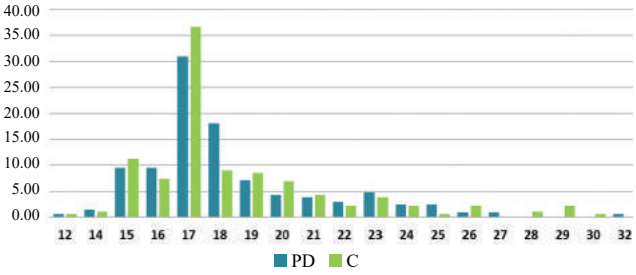

Fig. 2. Frequency of (CAG)n repeat regions in the HTT gene in patients with PD and in the control group, %

The distribution of alleles in both studied groups was similar, about 80% of alleles had 15–20 repeats (Fig.3); the $(CAG)_{17}$ allele was the most frequent in both groups (30.95% and 36.70% in PD patients and healthy individuals, respectively). However, the $(CAG)_{18}$ allele in PD patients was significantly more frequent than in the control group (OR = 2.22 (95%CI: 1.66–4.28), $\chi 2$ = 6.09, p = 0.014). Therefore, a risk allele was identified (18 repeats); the allele with 17 repeats was 5.75% more frequent in the control group; however, these differences were not significant (p = 0.269).

Since there was a great number of genotypes in each sample (38 in each group), we have grouped genotypes for the further analysis. The "18 / all" group included all genotypes which had one allele with 18 (CAG)n repeats and the other allele with any number of repeats except for 17. The genotype combining alleles with 17 and 18 repeats was studied

separately. The "17 / all" group included all genotypes which had one allele with 17 repeats and the other allele with any number of repeats, expect for 18. All remaining genotypes were included in the group "all / all". The "17 / all" genotype had a protective effect (OR = 0.50 (95%CI: 0.27–0.92), $\chi 2 = 5.05$, $p = 0.025$). At the same time, genotypes with 18 alleles were more prevalent in PD patients: "18 / all" was 2.98 times more frequent, and "17 / 18" was 1.47 times more frequent than in the control group. Therefore, we considered these genotypes together. The frequency of the genotype containing 18 alleles in combination with any other allele (including the allele with 17 repeats) in the group of PD patients was 36.19%, in the group of healthy individuals – 18.09%; the OR for these genotypes was 2.57 (95%CI: 1.66–4.28; $\chi 2 = 7.25$; $p = 0.007$).

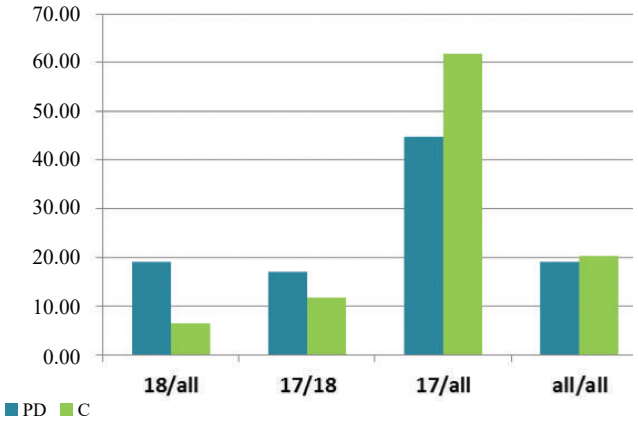

Fig. 3. Genotype frequencies for (CAG)n repeats in the HTT gene in patients with PD and in the control group

The obtained results indicate that the allele containing 17 (CAG)n repeats has a protective effect in combination with any allele, except for the one containing 18 repeats. In turn, all genotypes with 18 (CAG)n repeats predispose to PD. The predisposing effect to PD of the normal length allele in the *HTT* gene was identified in this study for the first time. It is hard to state how this association can manifest itself in the pathological phenotype, as there are no data on the involvement of normal alleles in the pathology. It is possible that the revealed associations can be explained by the involvement of the polyglutamine tract in the *HTT* gene in the regulation of energy production by mitochondria. I.S. Seong et al. showed in 2005 that the ADP / ATP ratio suggests the participation of not only pathological alleles, but also normal ones in this process [41]. Therefore, changes in the energy production function of mitochondria may contribute to the phenotypic manifestations of PD.

CONCLUSION

Our study in PD patients confirms modifying effects of lifestyle factors on PD progression, and changes in lifestyle can improve health-related quality of life of patients.

Coffee consumption in the anamnesis significantly distinguishes PD patients from healthy individuals. The obtained data suggest a possible neuroprotective effect of caffeine, which contributes to maintenance of cognitive and physical functioning, improving the quality of life of PD patients and their relatives. Caffeine is known as a psychostimulant and antioxidant, which boosts attention. According to the conducted studies, caffeine is able to protect low-density lipoproteins from oxidation and decrease oxidative DNA damage. Additionally, caffeine is an adenosine A2A-receptor antagonist and exerts a neuroprotective effect, decreasing dopamine deficiency [42]. The use of caffeine in animal models of PD led to a decrease in oxidative stress and restoration of dopamine level in the midbrain and the striatum, which, in turn, prevented reduction of motor activity and muscle strength and normalized the norepinephrine level [43].

TBI was widely studied as a risk factor of many neurodegenerative diseases [44]. Some studies have shown that TBI is accompanied by neuroinflammation, affecting neurons either directly [45-47] or indirectly – via blood – brain barrier impairment [48]. Moreover, individuals with TBI had elevated levels of α-synuclein in the cerebrospinal fluid [49]. The literature data suggest a possible association between TBI and PD, which was shown in our study.

The advantages of this study include personal interviews with patients, registered clinical and environmental data, a comprehensive neurological examination, and a sample size. However, we should consider some limitations when interpreting the results of the study. Due to the retrospective design of our study, we should take into account the recall bias: TBI in the past medical history was identified following interviews with patients, and PD patients may be more prone to recalling elements, which can justify their condition. Despite this, a previously conducted study showed high consistency between the assessment of medical history by the patient and TBI registered in the medical record [50].

Therefore, PD is a complex disease, the development of which is affected by both environmental and

molecular genetic factors that require further in-depth study. Reducing the burden of PD can be achieved through a two-pronged strategy: implementing interventions to correct modifiable risk factors, such as behavioral or environmental factors, and developing drugs aimed at correcting the functioning of protein products in genes associated with PD.

REFERENCES

1. Obeso J.A., Stamelou M., Goetz C.G., Poewe W., Lang A.E., Weintraub D. et al. Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy. *Mov. Disord.* 2017;32(9):1264–1310. DOI: 10.1002/mds.27115.
2. Poewe W., Seppi K., Tanner C.M., Halliday G.M., Brundin P., Volkmann J. et al. Parkinson disease. *Nat. Rev. Dis. Primers.* 2017;3:17013. DOI: 10.1038/nrdp.2017.13.
3. Ascherio A., Schwarzschild M.A. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol.* 201615(12):1257–1272. DOI: 10.1016/S1474-4422(16)30230-7.
4. Dong X., Liao Z., Gritsch D., Hadzhiev Y., Bai Y., Locascio J.J. et al. Enhancers active in dopamine neurons are a primary link between genetic variation and neuropsychiatric disease. *Nat. Neurosci.* 2018;21(10):1482–1492. DOI: 10.1038/s41593-018-0223-0.
5. Liu G., Boot B., Locascio J.J., Jansen I.E., Winder-Rhodes S., Eberly S. et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's. *Ann. Neurol.* 2016;80(5):674–685. DOI: 10.1002/ana.24781.
6. Domínguez-Baleón C., Ong J.S., Scherzer C.R., Rentería M.E., Dong X. Understanding the effect of smoking and drinking behavior on Parkinson's disease risk: a Mendelian randomization study. *Sci. Rep.* 2021;11(1):13980. DOI: 10.1038/s41598-021-93105-y.
7. Liu G., Locascio J.J., Corvol J.C., Boot B., Liao Z., Page K. et al. Prediction of cognition in Parkinson's disease with a clinical-genetic score: a longitudinal analysis of nine cohorts. *Lancet Neurol.* 2017Aug.;16(8):620–629. DOI: 10.1016/S1474-4422(17)30122-9.
8. Balestrino R., Schapira A.H.V. Parkinson disease. *Eur. J. Neurol.* 2020;27(1):27–42. DOI: 10.1111/ene.14108.
9. Wang A., Costello S., Cockburn M., Zhang X., Bronstein J., Ritz B. Parkinson's disease risk from ambient exposure to pesticides. *Eur. J. Epidemiol.* 2011;26(7):547–555. DOI: 10.1007/s10654-011-9574-5.
10. Rybkina V.L., Azizova T.V. The risk factors for Parkinson's Disease. *The Neurological Journal*. 2017;22(6):287–294 (in Russ.). DOI: 10.18821/1560- 9545-2017-22-6-287-294.
11. Bettiol S.S., Rose T.C., Hughes C.J., Smith L.A. Alcohol Consumption and Parkinson's Disease Risk: A Review of Recent Findings. *J. Parkinsons Dis.* 2015;5(3):425–442. DOI: 10.3233/JPD-150533.
12. Costa J., Lunet N., Santos C., Santos J., Vaz-Carneiro A. Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. *J. Alzheimers Dis.* 2010;20(1):S221–238. DOI: 10.3233/JAD-2010-091525.
13. Gallo V., Vineis P., Cancellieri M., Chiodini P., Barker R.A., Brayne C. et al. Exploring causality of the association between smoking and Parkinson's disease. *Int. J. Epidemiol.* 2019;48(3):912–925. DOI: 10.1093/ije/dyy230.
14. Cherian A., Divya K.P. Genetics of Parkinson's disease. *Acta. Neurol. Belg.* 2020;120(6):1297–1305. DOI: 10.1007/s13760-020-01473-5.
15. Cook L., Schulze J., Naito A., Alcalay R.N. The role of genetic testing for arkinson's disease. *Curr. Neurol. Neurosci. Rep.* 2021;21(4):17. DOI: 10.1007/s11910-021-01100-7.
16. Simon D.K., Tanner C.M., Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. *Clin. Geriatr. Med.* 2020;36(1):1–12. DOI: 10.1016/j.cger.2019.08.002.
17. Goldman S.M., Marek K., Ottman R., Meng C., Comyns K., Chan P. et al. Concordance for Parkinson's disease in twins: A 20-year update. *Ann. Neurol.* 2019;85(4):600–605. DOI: 10.1002/ana.25441.
18. Jot S. Parkinsonism with a Hint of Huntington's from 29 CAG repeats in HTT. *Brain Sci.* 2019;9(10):245. DOI: 10.3390/brainsci9100245.
19. Nikitina M.A., Bragina E.Yu., Nazarenko M.S., Zhukova N.G., Gomboeva D.E., Nurzhanova K.F., Tsentr N.V., Alifirova V.M. Atypical course of Parkinson's disease with clinical manifestations of Huntington's disease in a patient with an allele of 27 CAG repeats in the HTT gene. *Bulletin of Siberian Medicine*. 2020;19(4):235–240 (in Russ.). DOI: 10.20538/1682-0363-2020-4-235-240.
20. Postuma R.B., Berg D., Stern M., Poewe W., Olanow C.W., Oertel W. et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord.* 2015;30(12):1591–1601. DOI: 10.1002/mds.26424.
21. Hoehn M.M., Yahr M.D. Parkinsonism: onset, progression and mortality. *Neurology.* 196717(5):427–442. DOI: 10.1212/wnl.17.5.427.
22. Freud T., Vostrikov A., Dwolatzky T., Punchik B., Press Y. Validation of the Russian version of the MoCA test as a cognitive screening instrument in cognitively asymptomatic older individuals and those with mild cognitive impairment. *Front. Med. (Lausanne).* 2020;7:447. DOI: 10.3389/fmed.2020.00447.
23. Folstein M.F., Folstein S.E., McHugh P.R. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 1975;12(3):189–198. DOI: 10.1016/0022-3956(75)90026-6.
24. Bastepe M., Xin W. Huntington disease: molecular diagnostics approach. *Curr. Protoc. Hum. Genet.* 2015;87:9.26.1–9.26.23. DOI: 10.1002/0471142905.hg0926s87.
25. Crane P.K., Gibbons L.E., Dams-O'Connor K., Trittschuh E., Leverenz J.B., Keene C.D. et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. *JAMA Neurol.* 2016;73(9):1062–1069. DOI: 10.1001/jamaneurol.2016.1948.
26. Ramlackhansingh A.F., Brooks D.J., Greenwood R.J., Bose S.K., Turkheimer F.E., Kinnunen K.M. et al. Inflammation after trauma: microglial activation and traumatic brain injury. *Ann. Neurol.* 2011;70(3):374–383. DOI: 10.1002/ana.22455.
27. Loane D.J., Kumar A., Stoica B.A., Cabatbat R., Faden A.I. Progressive neurodegeneration after experimental brain trau-

ma: association with chronic microglial activation. *J. Neuropathol. Exp. Neurol.* 2014;73(1):14–29. DOI: 10.1097/NEN.0000000000000021.
28. Nicoletti A., Vasta R., Mostile G., Nicoletti G., Arabia G., Iliceto G. et al. Head trauma and Parkinson's disease: results from an Italian case-control study. *Neurol. Sci.* 2017;38(10):1835–1839. DOI: 10.1007/s10072-017-3076-5.
29. Stoll G., Jander S., Schroeter M. Detrimental and beneficial effects of injury-induced inflammation and cytokine expression in the nervous system. *Adv. Exp. Med. Biol.* 2002;513:87–113. DOI: 10.1007/978-1-4615-0123-7_3.
30. Chia S.J., Tan E.K., Chao Y.X. Historical perspective: models of Parkinson's disease. *Int. J. Mol. Sci.* 2020;21(7):2464. DOI: 10.3390/ijms21072464.
31. Carmona A., Zogzas C.E., Roudeau S., Porcaro F., Garrevoet J., Spiers K.M. et al. SLC30A10 mutation involved in Parkinsonism results in manganese accumulation within nanovesicles of the Golgi apparatus. *ACS Chem. Neurosci.* 2019;10(1):599–609. DOI: 10.1021/acschemneuro.8b00451.
32. Aloizou A.M., Siokas V., Sapouni E.M., Sita N., Liampas I., Brotis A.G. et al. Parkinson's disease and pesticides: Are microRNAs the missing link? *Sci. Total. Environ.* 2020;744:140591. DOI: 10.1016/j.scitotenv.2020.140591.
33. Dardiotis E., Xiromerisiou G., Hadjichristodoulou C., Tsatsakis A.M., Wilks M.F., Hadjigeorgiou G.M. The interplay between environmental and genetic factors in Parkinson's disease susceptibility: the evidence for pesticides. *Toxicology.* 2013;307:17–23. DOI: 10.1016/j.tox.2012.12.016.
34. Breckenridge C.B., Berry C., Chang E.T., Sielken R.L. Jr., Mandel J.S. Association between Parkinson's disease and Cigarette Smoking, Rural Living, Well-Water Consumption, Farming and Pesticide Use: Systematic Review and Meta-Analysis. *PLoS One.* 2016;11(4):e0151841. DOI: 10.1371/journal.pone.0151841.
35. Martino R., Candundo H., Lieshout P.V., Shin S., Crispo J.A.G., Barakat-Haddad C. Onset and progression factors in Parkinson's disease: A systematic review. *Neurotoxicology.* 2017;61:132–141. DOI: 10.1016/j.neuro.2016.04.003.
36. Gao X., Chen H., Fung T.T., Logroscino G., Schwarzschild M.A., Hu F.B. et al. Prospective study of dietary pattern and risk of Parkinson disease. *Am. J. Clin. Nutr.* 2007;86(5):1486–1494. DOI: 10.1093/ajcn/86.5.1486.
37. Delamarre A., Meissner W.G. Epidemiology, environmental risk factors and genetics of Parkinson's disease. *Presse Med.* 2017;46(2-1):175–181. DOI: 10.1016/j.lpm.2017.01.001.
38. Paul K.C., Chuang Y.H., Shih I.F., Keener A., Bordelon Y., Bronstein J.M. et al. The association between lifestyle factors and Parkinson's disease progression and mortality. *Mov. Disord.* 2019;34(1):58–66. DOI: 10.1002/mds.27577.
39. Prasuhn J., Davis R.L., Kumar K.R. Targeting mitochondrial impairment in Parkinson's disease: challenges and opportunities. *Front. Cell Dev. Biol.* 2021;8:615461. DOI: 10.3389/fcell.2020.615461.
40. Nikitina M., Babushkina N., Bragina E., Alifirova V., Gomboeva D., Koroleva E. et al. The role of repair genes in the pathogenesis of Parkinson's disease. *J. Neurol. Sci.* 2021;429:119480.
41. Seong I.S., Ivanova E., Lee J.M., Choo Y.S., Fossale E., Anderson M. et al. HD CAG repeat implicates a dominant property of huntingtin in mitochondrial energy metabolism. *Hum. Mol. Genet.* 2005;14(19):2871–2880. DOI: 10.1093/hmg/ddi319.
42. Chen J.F., Xu K., Petzer J.P., Staal R., Xu Y.H., Beilstein M. et al. Neuroprotection by caffeine and A(2A) adenosine receptor inactivation in a model of Parkinson's disease. *J. Neurosci.* 2001;21(10):RC143. DOI: 10.1523/JNEUROSCI.21-10-j0001.2001.
43. Khadrawy Y.A., Salem A.M., El-Shamy K.A., Ahmed E.K., Fadl N.N., Hosny E.N. Neuroprotective and therapeutic effect of caffeine on the rat model of Parkinson's disease induced by rotenone. *J. Diet Suppl.* 2017;14(5):553–572. DOI: 10.1080/19390211.2016.1275916.
44. Crane P.K., Gibbons L.E., Dams-O'Connor K., Trittschuh E., Leverenz J.B., Keene C.D. et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. *JAMA Neurol.* 2016;73(9):1062–1069. DOI: 10.1001/jamaneurol.2016.1948.
45. Ramlackhansingh A.F., Brooks D.J., Greenwood R.J., Bose S.K., Turkheimer F.E., Kinnunen K.M. et al. Inflammation after trauma: microglial activation and traumatic brain injury. *Ann. Neurol.* 2011Sept.;70(3):374-83. DOI: 10.1002/ana.22455.
46. Loane D.J., Kumar A., Stoica B.A., Cabatbat R., Faden A.I. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. *J. Neuropathol. Exp. Neurol.* 2014;73(1):14–29. DOI: 10.1097/NEN.0000000000000021.
47. Schmidt O.I., Heyde C.E., Ertel W., Stahel P.F. Closed head injury-an inflammatory disease? *Brain Res. Brain Res. Rev.* 2005;48(2):388–399. DOI: 10.1016/j.brainresrev.2004.12.028.
48. Stoll G., Jander S., Schroeter M. Detrimental and beneficial effects of injury-induced inflammation and cytokine expression in the nervous system. *Adv. Exp. Med. Biol.* 2002;513:87–113. DOI: 10.1007/978-1-4615-0123-7_3.
49. Mondello S., Buki A., Italiano D., Jeromin A. α-Synuclein in CSF of patients with severe traumatic brain injury. *Neurology.* 2013;80(18):1662–1668. DOI: 10.1212/WNL.0b013e3182904d43.
50. Goldman S.M., Tanner C.M., Oakes D., Bhudhikanok G.S., Gupta A., Langston J.W. Head injury and Parkinson's disease risk in twins. *Ann. Neurol.* 2006;60(1):65–72. DOI: 10.1002/ana.20882.

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