**ANNOTATION**

Doctor of Philosophy (PhD) theses
in the specialty 6D110100 – "Medicine" Aralbayeva Assel
on the topic: "**Clinical and genetic features of Parkinson disease in the Republic of Kazakhstan**"

**The relevance of research.** Parkinson's disease (PD) is an urgent medical and socially significant problem worldwide. This is because PD is the most common neurodegenerative idiopathic neurological disease, second only to Alzheimer's disease. [KowalS.L., DallT.M., ChakrabartiR. etal. The current and projected economic burden of Parkinson's disease in the United States // MovDisord. – 2013. – Vol. 28. – P. 311-318, Dorsey E.R., Constantinescu R., Thompson J.P. et al. Projected number of people with Parkinson's disease in the most populous nations, 2005 through 2030 // Neurology. – 2007. – Vol. 68. – P. 384-386].

According to the latest WHO data (2016), the global incidence in number ranged from 9.7 to 13.8 per 100,000 population per year, and the prevalence is from 65.6 to 187 per 100,000 population [KowalS.L., DallT.M., ChakrabartiR. etal. The current and projected economic burden of Parkinson's disease in the United States // MovDisord. – 2013. – Vol. 28. –p.313; Dorsey E.R., Constantinescu R., Thompson J.P. et al. Projected number of people with Parkinson's disease in the most populous nations, 2005 through 2030 // Neurology. – 2007. – Vol. 68. – p.385].

In the US, the economic cost of BP in 2010 was estimated at 14.4 billion dollars, while by 2030 it is predicted that only medical expenses will increase by 1.7 times [KowalS.L., DallT.M., ChakrabartiR. Et al. The current and projected economic burden of Parkinson's disease in the United States // MovDisord. – 2013. – Vol. 28. –p.311; Dorsey E.R., Constantinescu R., Thompson J.P. et al. Projected number of people with Parkinson's disease in the most populous nations, 2005 through 2030 // Neurology. – 2007. – Vol. 68. – p.384].

Dorsey E.R. et al. (2007), predict that by 2030 the number of people with PD in the world will be about 9 million people [DorseyE.R., ConstantinescuR., ThompsonJ.P. et al. Projected number of people with Parkinson's disease in the most populous nations, 2005 through 2030 // Neurology. – 2007. – Vol. 68. – p.384], and suggest that differences in prevalence will depend not only on genetic predisposition, but also on environmental factors, ethnic differences.

Despite the social, economic, and emotional burden this disease imposes, there are as yet no treatments that have either prevented its progression or provided restoration of damaged nervous systems. The lack of knowledge has undoubtedly contributed to the fact that so far the world has not been successful in efforts to develop more effective treatments. [ChengH.C.,UlaneC.M., BurkeR.E. Clinical Progression in Parkinson's Diseaseand the Neurobiology of Axons // Annals of Neurology. – 2010. – Vol. 67(6). – P. 715-725].

The development and progression of PD is associated with the degeneration of dopaminergic (DA) neurons in the brain. Progressive degeneration of dopamine-containing pigment neurons in the substantia nigra leads to the development of motor symptoms of bradykinesia, muscle rigidity and tremor, in combination with postural

disturbances that join in the steady progression of the disease. [TagliaferroP., KarevaT., OoT.F. etal. An early axonopathy in a hLRRK2(R1441G) transgenic model of Parkinson's disease // Neurobiol Dis. – 2015. – Vol. 82. – P. 359-371].

The literature provides various estimates of the dopaminergic neurons loss (about 40% on average) in the substantia nigra by the time the first motor signs of the disease appear, the duration of which depends on many factors [BurkeR.E.O'Malley K. Axon Degeneration in Parkinson's Disease // Exp Neurol. – 2013. – Vol. 246. – P. 72-83,Pfeiffer R.F. Non-motor symptoms in Parkinson's disease // Parkinsonism RelatDisord. – 2016. – Vol. 22, Suppl 1. – P. S119-S122].

According to HirschE.C. et al. (2013) cell death in Parkinson's disease is caused by a multifactorial cascade of pathogenic events, they suggest that axons and their terminalia take the brunt of damage in PD, it is the ongoing degeneration of axons that is the determining factor in the clinical progression of the disease [HirschE.C., JennerP., Przedborski S. Pathogenesis of Parkinson's disease // Mov. Disord. – 2013. – Vol. 28. – P. 24-30].

TagliaferroP., BurkeR. (2016) suggest that axons are involved at an early stage and that the pathogenesis of PD is explained mainly by this mechanism, and not only by the loss of neurons. The formation of the pathophysiological model of PD, namely the early involvement of axons, is based mainly on experimental studies. [TagliaferroP., BurkeR. Retrograde Axonal Degeneration in Parkinson Disease // Journal of Parkinson's Disease. – 2016. – Vol. 6, Issue 1. – P. 1-15].

It has been proven that there is a preclinical non-motor phase, before the first clinical motor extrapyramidal symptoms, which lasts on average up to 20 years, which indicates the existence of compensatory mechanisms in the early stages of PD. With increasing awareness of the presence of non-motor symptoms (NMS) in PD the realization has come that these non-motor features play an extremely important and sometimes dominant role in the treatment and diagnosis of the disorder. Despite this, there remains a reluctance to formally address and treat the non-motor symptoms of PD, leading to deterioration in the quality of life of patients [PfeifferR.F. Non-motor symptoms in Parkinson's disease // ParkinsonismRelatDisord. – 2016. – Vol. 22, Suppl 1. – p.120; HirschE.C., JennerP., PrzedborskiS. Pathogenesis of Parkinson'sdisease // Mov. Disord. – 2013. – Vol. 28. – p.25; TagliaferroP., BurkeR. Retrograde Axonal Degeneration in Parkinson Disease // Journal of Parkinson's Disease. – 2016. – Vol. 6, Issue 1.–p.11]. NMS in PD play an important role in the development of this neurodegenerative movement disorder. According to some authors, the identification of non-motor symptoms will allow the development of more effective strategies to slow or stop the progression of the disease. [MehndirattaM., GargR.K., PandeyS.J. Non motor symptom complex of Parkinson's disease - anunder-recognized entity // AssocPhysiciansIndia. – 2011. – Vol. 59, Issue 313. – P. 302-308]. NMS are sometimes present before diagnosis and almost inevitably appear as the disease progresses. According to the literature, patients with PD are diagnosed with one to several non-motor symptoms during the course of the disease. [MehndirattaM., GargR.K., PandeyS.J. Non motor symptom complex of Parkinson's disease - anunder-recognizedentity // AssocPhysiciansIndia. – 2011. – Vol. 59, Issue 313. – p.303]. Many of these symptoms appear months or even years before a diagnosis of PD is made. Despite their high prevalence and impact on the

burden of disease, they often go undiagnosed due to factors such as lack of complaints from patients or insufficient interviewing by physicians.

A number of researchers have concluded that non-dopaminergic (NDP) and non-motor symptoms often dominate the clinical picture of progressive PD and contribute to severe disability, lead to a deterioration in the quality of life and a reduction in life expectancy. [LeggioL., VivarelliS. etal. microRNAs in Parkinson's Disease: From Pathogenes is to Novel Diagnostic and Therapeutic Approaches // International Journal of Molecular Sciences. – 2017. – Vol. 18(12). – P. 2698-12698-30, Sauerbier A., Jitkritsadakul O., Titova N. et al. Non-Motor Symptoms Assessed by Non-Motor Symptoms Questionnaire and Non-Motor Symptoms Scale in Parkinson's Disease in Selected Asian Populations // Neuroepidemiology. – 2017. – Vo. 49. – P. 1-17]. Unlike dopaminergic symptoms of the disease, for which treatment is available, non-motor symptoms are often poorly recognized and treated inadequately.

We conducted a literature review using PubMed. Despite numerous studies of NMS in PD, the problem of visual impairment is not well understood. Common symptoms that were assessed in these studies were mainly: fatigue, attention, mood, apathy, sleep disturbance, constipation, memory impairment and nocturia. Some authors suggest that phenotypic heterogeneity due to NMS is present in Asian patients compared to Western PD populations and there may be differences in estimated NMS. [BraakH., DelTrediciK., BratzkeHetal. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages) // J Neurol. – 2002. – Vol. 249, Suppl 3. – P. 1-5].

The search for articles and currently available publications that refer to and evaluate NMS in PD patients living in Asian countries using approved questionnaires and rating scales is small, there are no such works in Kazakhstan.

As the search for successful disease-modifying treatments progresses, it is logical to consider how this can be applied to patients in terms of motor control, indeed prior to the development of motor dysfunctions, with the obvious goal of delaying and even preventing the onset of dysfunctions. [Sauerbier A., Jitkritsadakul O., TitovaN. Et al. Non-Motor Symptoms Assessed by Non-Motor Symptoms Questionnaire and Non-Motor Symptoms Scale in Parkinson's Disease in Selected Asian Populations // Neuroepidemiology. – 2017. – Vo. 49. –p.9; Braak H., Del Tredici K., Bratzke H et al. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages) // J Neurol. – 2002. – Vol. 249, Suppl 3.–p.2].

Currently available treatments for Parkinson's disease do not address many of the debilitating non-motor manifestations of the disease, including cognitive decline and autonomic failure. [BraakH., DelTrediciK., BratzkeHetal. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages) // J Neurol. – 2002. – Vol. 249, Suppl 3.–p.3].

Thus, for PD, as for many other adult-onset neurodegenerative disorders, there is an urgent need for therapy that will prevent the progressive degenerative process.

Therefore, in recent years there has been a significant increase in interest in NMS, including visual impairment as an early premotor marker of PD.

Evaluation often overlooks non-motor visual symptoms and signs associated with PD, which can negatively affect daily function and quality of life. Visual

disturbances are common in PD patients, but they receive little attention in both research and clinical practice, resulting in reduced quality of life and disability. A wide range of visual impairment threatens the ability of patients to receive optimal benefit from visual feedback. Of particular importance is the fact that patients with PD often compensate for their motor deficits by visually orienting their movements. Increasing awareness and early recognition of visual problems in PD may allow timely individualized treatment, leading to increased patient safety, greater independence, and a better quality of life. Visual dysfunction, which is one of the non-motor manifestations that adversely affect the quality of life of a patient with PD, has not been sufficiently studied to date [BraakH., DelTrediciK., BratzkeHetal. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages) // J Neurol. – 2002. – Vol. 249, Suppl 3. –p.4].

In many countries, the assessment of NMS in PD is now part of the standard of good clinical practice. But these questions are not included in the current clinical protocol for the diagnosis and treatment of Parkinson's disease of the Ministry of Health and Social Development of the Republic of Kazakhstan dated November 29, 2016 Protocol No. 16, approved by the Joint Commission on the Quality of Medical Services. There are no algorithms for diagnosing visual non-motor manifestations, visual and spatial perception, cognitive disorders for possible early correction and improving the quality of life of patients with PD. Physician awareness of NMS remains low and PD is still largely regarded as a motor syndrome only.

Thus, the identification of NMS in the early stages of PD is a critical goal to be achieved in order to develop future neuroprotective therapies for risk groups aimed at delaying or limiting the ongoing degeneration process. Improvement of the methods for visual spatial assessment is a promising way to improve the accuracy of early diagnosis and treatment monitoring.

In addition, it should be noted that an active search is currently underway for PD biomarkers that can predict the development of the disease, determine the rate of disease progression, and evaluate the effectiveness of ongoing therapy.

The current knowledge of the underlying genetics of PD, collected over the past two decades, has provided researchers with an incredible amount of information about the various biological pathways involved in the pathogenesis of PD [NuytemansK.,TheunsJ., CrutsM. etal. Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update // Human Mutation. – 2010. – Vol. 31, №7. – P. 763-780].

More than 500 different DNA variants have been identified in five disease genes associated with PD; α-synuclein (SNCA), parkin (PARK2), putative PTEN-induced kinase 1 (PINK1), DJ-1 (PARK7), and leucine-rich repeat kinase 2 (LRRK2). These genetic variants include about 82% simple mutations and about 18% copy number variations. The biological significance of the putative pathogenic mutations is clear. There is a need for a comprehensive genetic screening of patients with Parkinson's disease, followed by a study of the functional significance of the observed genetic variants [NuytemansK.,TheunsJ., CrutsM. Et al. Genetic etiology of Parkinson's disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update // Human Mutation. – 2010. – Vol. 31, №7. – p.765].

An active study of the role of a class of small RNAs, miRNA (RNA inhibiting RNA) with a length of 19-25 nucleotides and a size of 6-9 nanometers, in the functioning of both a single cell and the whole organism as a whole is being carried out [Filatova Ye.V., Aliyeva A.Kh. , Shadrina M.I. et al. Micro-RNA: a possible role in the pathogenesis of Parkinson's disease // Biochemistry. - 2012. - Vol. 77, No. 8. – pp. 981-988]. Currently, pharmacological treatments for neurodegenerative diseases are limited, but scientists are on the cusp of developing promising new therapies, including molecular-specific therapies [ArshadA.R., SulaimanS.A., SaperiA.A. etal. MicroRNAs and Target Genes As Biomarkers for the Diagnosis of Early Onset of Parkinson Disease // Front. Mol. Neurosci. – 2017. – Vol. 10. – P. 352-1-352-20]. Methods developed within cognitive neuroscience that can reveal the integrity of neural systems can be adapted for clinical use. A number of miRNAs have been identified that may be directly or indirectly involved in the development of PD. It has been shown that the expression of these genes can be regulated by various miRNAs and influence the development of pathology [ArshadA.R., SulaimanS.A., SaperiA.A. etal. MicroRNAs and Target Genes As Biomarkers for the Diagnosis of Early Onset of Parkinson's Disease // Front. Mol. Neurosci. – 2017. – Vol. 10. – P. 352-1-352-20-p.352]. In this regard, determination of disease staging markers is of particular interest in research on Parkinson's disease. Such studies have not been performed in Central Asia and Kazakhstan.

**The aim of the study:** to study the clinical and genetic features of Parkinson's disease in the Republic of Kazakhstan**.**

**Research objectives:**

1. To study the characteristics of non-motor symptoms, including visual and cognitive symptoms in patients with PD, using neuropsychological tests and visual spatial assessment methods.
2. To identify the impact of visual and cognitive non-motor symptoms on the course of PD, as well as to determine the correlation with age, gender, time of onset, stage and duration of the disease, as well as motor disorders in the study groups.
3. To reveal the existence of a relationship between the frequency of miRNA binding sites occurrence with mRNA target genes in PD.
4. To create databases of candidate genes involved in the development of PD and miRNA databases to determine the effect of miRNA on the expression of candidate genes

**Scientific novelty:**

1. For the first time, the characteristics of non-motor symptoms, including visual and cognitive ones, were studied in Kazakh patients with PD, using neuropsychological tests and methods of visual spatial assessment.
2. The most accurate early and late non-motor visual impairments in patients with PD were identified, the relationship of visual and cognitive non-motor symptoms in patients with Parkinson's disease was determined with age, onset time, stage and duration of the disease, as well as motor and other non-motor disorders.

3. A database of candidate genes involved in the development of PD and miRNA databases were created to determine their effect on the expression of candidate genes involved in the development of the disease.
4. Associations of miRNAs and target genes, which are recommended as markers for the diagnosis of Parkinson's disease, have been identified for the first time.
5. For the first time, miRNA features that can affect the expression of PD candidate genes have been identified, which must be taken into account when developing biomarkers that adequately reflect the interaction of miRNA with mRNA in PD.

**The main points for defense:**

1. Among PD patients, a high prevalence of non-motor dysfunctions (96.2%) is revealed, while 87.8% had at least one of the non-motor visual symptoms, 18.3% of them had symptoms in the early period for several months and years before a confirmed diagnosis of PD.
2. Visual non-motor symptoms are detected at any stage of the disease, the rate of their progression differs from motor symptoms by independence. Symptoms such as difficulty in reading, weakness and fatigue of the eyes, blurring of the image can be considered as a clinical marker in the early stages and even in the pre-motor stage of the disease.
3. With the progression of the disease, non-motor visual symptoms are more often combined with cognitive disorders, important factors that determine the severity of the patient's condition. Statistically significant correlations of disease duration (5 years or more) were observed in patients with visual hallucinations ($p<0.01$), color perception disorders ($p<0.05$), and activity according to the Schwab-England scale. Identified visual non-motor symptoms prevail in patients with akinetic-rigid form of PD disease, with anxiety disorders.
4. miRNAs from different miRNA bases can bind to mRNAs of PD candidate genes. Associations of miRNAs and target genes that can serve as markers for the diagnosis of Parkinson's disease have been determined.
5. Quantitative characteristics of the miRNA interaction and target genes that can competitively influence the expression of candidate PD genes have been identified, which must be taken into account when developing biomarkers that adequately reflect the interaction of miRNA with mRNA in PD.

**Practical significance of the work:**

1. A prospective cohort study revealed non-motor symptoms, including visual and cognitive symptoms in patients, as prognostic factors that determine the outcome of the disease, which can be used to optimize the diagnosis and treatment of PD.
2. The most accurate early and late non-motor visual disturbances in patients with PD were determined.
3. The "Method for early diagnosis of Parkinson's disease" developed by us (Patent for utility model No. 5656 dated December 11, 2020) is recommended for use in clinical practice. It improves the diagnosis of motor and non-motor disorders in the early stages of PD.
4. Databases of candidate genes involved in the development of PD and miRNA databases were created to determine their effect on the expression of candidate

genes involved in the development of PD, which in the future can be used to develop molecular laboratory methods for diagnosing and treating PD.

**Approbation of the research:**

1. Scientific and practical conference with international participation "Spring School of the Kazakhstan National Association of Neurologists "Neuroscience" (Almaty, 2018 - April 27-28);
2. The 3rd international educational forum "Neurology Update in Kazakhstan" (Almaty, 2019 - April 4-5);
3. International educational forum "Neurology Update in Kazakhstan 2021" (Almaty, 2021 - April 23-34);
4. At an international conference Parkinson and Movement Disorders Society: Therapeutic Milestones in Parkinson's Disease (Venice, 2020 – 18-20 March);
5. The 2nd International Scientific and Practical Internet Conference "Science and Education in the XXI CENTURY" dedicated to the 20th anniversary of Astana (October 30-31, 2018);
6. At the World Online Congress of the International Association of Parkinsonism and Related Diseases (IAPRD XXV World Congress on PRD June 7–10, 2020).
7. I-Russian-Kazakh neurological forum "Modern aspects of neurology: problems and solutions" February 12-13, 2021.

**Publications:**

*1 article - in a publication indexed in the Scopus information base:*

1. Evolutionary changes in the interaction of miRNA with mRNA of candidate genes for Parkinson's disease. Frontiers in Genetics.March 2021. Vol.12 Article 647288. Scopus Cite Score 2020 – 2,7. IF – 3,258.

*3 articles - in publications recommended by the Committee for Control in the Sphere of Education and Science of the Republic of Kazakhstan:*

1. Motor and non-motor manifestations in patients with Parkinson's disease. Bulletin of KazNMU. -2019.- No.1- pp. 201-204. ISSN 2524-0684 (Print). ISSN 2524-0692 (Online). The citation index of the RSCI 2019 is 403.
2. Parkinson's disease. Bulletin of KazNMU. -2019.- No. 1- pp.199-201. ISSN 2524-0684 (Print). ISSN 2524-0692 (Online). The citation index of the RSCI 2019 is 403.
3. Determination of the motor symptoms severity in Parkinson's disease. Bulletin of KazNMU. -2019.- No. 4- pp. 138-140. ISSN 2524-0684 (Print). ISSN 2524-0692 (Online). The citation index of the RSCI 2019 is 403.

*8 theses - in the collections of foreign international conferences (including foreign ones - 5):*

1. Association of miRNA and target genes of Parkinson's disease. Biological Markers in fundamental and clinical medicine. Collection of abstracts. 2018.- VOL. 2. -№ 2. - P. 9 -11. ISSN 2570-5911 (print), ISSN 2570-5903 (on-line). DOI: 10.29156
2. The microRNA in Parkinson's disease. Parkinsonism and Related disorders, Volume79|supplement 1|e79, IAPRD XXV World Congress on PRD October 2020. https://doi.org/10.1016/j.parkreldis.2020.06.287.
3. Determination of non-motor symptoms in Parkinson's disease. 26th Annual Meeting of the European Charcot Foundation. The role of long-term clinical

studies in defining DMTs' profile. (15 - 17 November, 2018). -Baveno, Italy. (26th Annual Meeting Mobile Application).
4. Dementia in Parkinson's disease. 34World Congress of Internal Medicine. (18-21 October, 2018) - Cape Town, South Africa. Abstract book. - 2018.-P.119.
5. Determining the stage of Parkinson's disease on the scale of Hoehn and Yahr. Movement Disorders,Volume7|IssueS2|March2020, Abstracts of the ES SUMMIT: Therapeutic Milestones in Parkinsons Disease. Venice, Italy. March 18-20,2020 №85
6. Determining cognitive function in Parkinson's disease using a Mini Mental Examination (MMSE). 27$^{th}$Annual Meeting of the European Charcot Foundation. The role of B-lymphocytes in Multiple Sclerosis (21/11/2019-23/11/2019). - Baveno, Italy. (27th Annual Meeting Mobile Application).
7. Dementia in Parkinson's disease. II International scientific and practical Internet conference "Science and education in the XXI CENTURY" dedicated to the 20$^{th}$ anniversary of Astana (October 30-31, 2018): Materials of the II International scientific and practical Internet conference "Science and education in XXI CENTURY" -2018.-pp.-37-39.
8. Non-Motor Visual Disorders In Kazakhtan Patients With Parkinson's Disease Journal of Interdisciplinary Approaches to Medicine,Volume2|issue 1|ISSN 2709-2968 eISSN 2709-2976 December 2021.

**Objects and subjects of study:** this is a prospective study of outpatients observed in various polyclinics in one of the major cities of Kazakhstan, Almaty city. At the first stage of the study, a continuous sample was used to analyze 595 outpatients referred from 11 polyclinics of one of the major cities of Kazakhstan, Almaty, in stages from November 01, 2018 to January 31, 2020. All patients or their legal representatives provided written informed consent to participation in our study. The study was approved by the ethical committee of "National Medical University" JSC Protocol No. 9 (73) dated September 28, 2018.

The diagnosis of PD was established on the basis of generally accepted criteria in accordance with the international classification of diseases (ICD-10, WHO 1992) based on the results of a clinical examination and data from additional research methods. The work was guided by the diagnostic criteria of the international neurological community - Parkinson's Disease Society Brain Bank**.**

All patients were consulted by ophthalmologists of polyclinics and, if necessary, by doctors from the Kazakh Research Institute of Eye Diseases. To obtain reliable results, patients with significant ophthalmic diseases were excluded from the study. Subsequently, 106 patients were selected for the study by the method of exclusion.

In total, a group of 106 patients with PD (64 women and 42 men) was formed using MDS-UPDRS. 61.9% of the surveyed respondents are of Asian race, and 38.4% are of European race. The comparison group consisted of 55 neurological healthy subjects of the appropriate age and gender, from the database of clinics in Almaty, regardless of nationality. The total number of those examined, taking into account the comparison group, was 161 people. Socio-demographic and clinical characteristics were studied.

Patients were asked questions about various MS and NMS using the Unified PD Severity Scale (UPDRS), the Hoehn-Yar Movement Disorder Scale. Neuropsychological Methods for Assessment of Visual-Spatial Disorders and Cognitive Status.

Study of the interaction of miRNAs with mRNA of PD candidate genes. Identification of miRNA associations and their target genes using the MirTarget program on the supercomputer of Al-Farabi KazNU.

The study protocol was approved by the local ethical committee of S.Zh. Asfendiyarov KazNMU.

The work was carried out on the basis of the city polyclinic No. 4 in Almaty (the contract dated September 03, 2018).

**Conclusions:**

1. Among PD patients, a high prevalence of non-motor dysfunctions (96.2%) is revealed, while 87.7% had at least one of the non-motor visual symptoms, 18.3% of them had symptoms in the early period for several months and years until a definite diagnosis of PD. Visual and cognitive non-motor symptoms are detected at any stage of the disease, the rate of their progression differs from motor symptoms in independence. Early visual NM Symptoms in patients with PD are characterized by difficulty in reading, weakness and fatigue of the eyes, blurred images.
2. The results of the study showed that such NMS as hyposmia, hypersalivation, sleep problems, nocturia, constipation and hyperhidrosis in the early stages of the disease, and in 11.3% of patients preceded motor manifestations. The diagnosis of NMS in PD has been complicated by the fact that patients with PD often do not understand certain manifestations of these symptoms.
3. In 39.6% of patients in the late stages of PD in subgroups with 2.5-4 stages of the disease according to Hoehn-Yar, non-motor manifestations dominated as more important and disabling than motor fluctuations, presenting certain difficulties for patients and attendants.
4. Statistically significant correlations of disease duration (5 years or more) were observed in patients with visual hallucinations ($p<0.01$), color perception disorders ($p<0.05$), which adversely affect the activity of patients according to the Schwab-England scale, and determine the outcome of the disease. Visual dysfunction is combined with cognitive impairment. The revealed visual non-motor symptoms prevail in patients with the akinetic-rigid form of PD, equally in men and women.
5. In our study, there were no significant differences between men and women in the assessment of visual non-motor disorders and in the performance of tests to detect cognitive disorders (MMSE MoCa NMSQ Yerkes test, clock test, Poppelreiter test).
6. PD candidate genes that are miRNA targets have been identified. Quantitative characteristics of miRNA interaction with mRNA of PD candidate genes were determined. The organization of miRNA binding sites into clusters with overlapping nucleotide sequences has been established. This organization of binding sites reduces the mRNA length and leads to competition between miRNAs when interacting with clusters in the 5'UTR, CDS, and 3'UTR. Polysite binding for one

miRNA and multiple binding sites for two or more miRNAs in one mRNA are identified.

7. In addition to single associations of miRNA and genes, associations of one gene and several miRNAs were found that bind to the mRNA of this gene; association of one miRNA binding to mRNA of several genes; association of several miRNAs binding to mRNAs of several genes. Associations of miRNAs with PD candidate genes with free energy interactions greater than -130 kJ/mol are recommended for the development of PD diagnostic markers.

**Practical recommendations:**

1. Patients with PD should be carefully monitored using the NMSQ questionnaire, as well as Visual Impairment in Parkinson's Disease for early detection of visual dysfunctions associated with non-motor manifestations of PD.
2. To organize full-fledged care for patients with PD, specialized rooms are needed at city regional polyclinics (following the example of specialized rooms for multiple sclerosis, demyelinating and autoimmune diseases of the nervous system)
3. To carry out mandatory monitoring of cognitive impairment according to the MMSE, MoCa test scales, as well as identify anxiety disorders.
4. It is advisable to use associations between miRNAs and their target genes as biomarkers for PD diagnosing.
5. Validated biomarkers for PD diagnosing can form the basis for the development of therapeutic agents for Parkinson's disease
6. Recommend revision of the clinical protocol for the diagnosis and treatment of Parkinson's disease, taking into account non-motor symptoms.

**Research materials are introduced into practical healthcare:**

1. The use of the unified Parkinson's disease assessment scale of the International Movement Disorders Society for the assessment of motor and non-motor symptoms in patients with Parkinson's disease (MDS-UPDRS) has been introduced into the work of City Policlinic No. 4 in Almaty (Appendix A).
2. The use of the Mini-Mental State Examination scale for assessing the state of cognitive functions and mental status (short mental status assessment scale) in patients with Parkinson's disease in clinical practice has been introduced into the work of City Policlinic No. 4 in Almaty (Appendix B).
3. A certificate on state registration for a utility model, "Method for early diagnosis of Parkinson's disease", registered in the State Register of Industrial Designs of the Republic of Kazakhstan on December 11, 2020, patent No. 5656 (Appendix C) was received.
4. The results of the dissertation research are used in the educational process of the Higher Medical School of KazNU named after Al-Farabi

**Personal contribution of the dissertation candidate:**

Dissertation student was directly involved in the diagnosis and determination of the tactics of management and treatment of patients with PD. As part of the dissertation work, all studies with data interpretation and observation in dynamics were carried out directly with the participation of the author. In addition, the author

assessed the neurological status using the appropriate scales. The author independently conducted a literary search on this issue, collecting a database, pre-processing the material, and interpreting the results. The dissertation student participated in molecular genetics research and statistical analysis. The dissertation was written by the author independently, with the formulation of the main provisions, scientific novelty, conclusions and recommendations.

**Structure and scope of the dissertation work**. The volume of the dissertation is 127 pages of typewritten text, including the title page, content, normative references, definitions, designations and abbreviations, introduction, main body, opinion, conclusions, practical recommendations and a list of sources used. There are appendices on 27 pages at the end of the dissertation.

The scientific work is illustrated by 42 figures, 13 tables, and 14 appendices. Information on the literature used for the dissertation writing contains 273 sources, in Russian and English.