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Genetic roots of neuropsychiatric symptoms in Parkinson's disease

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Abstract
The literature review presents current data on the effect of the COMT, MAO-A, MAO-B, DAT, DRD2, VMAT2, TPH2 and SNCA genes on the course of Parkinson's disease, the effectiveness of therapy and their connection with a number of mental disorders. The work studies 77 articles and monographs devoted to the problems of genetics, neurology and psychiatry, published in the period from 1972 to 2018. Timely recognition of the genetic features of the course of the disease will optimize drug therapy, predict the development of early complications of the disease, such as cognitive decline, affective, obsessive-compulsive, psychotic disorders, as well as impulse-control disorders. Genetic prediction is also particularly relevant in the aspect of preparing and selecting patients for surgeries for deep brain stimulation.
Key words: Parkinson's disease, neurology, genetics, psychiatry.

Parkinson's disease is a neurodegenerative disease with a wide range of both motor and non-motor manifestations. The variability of the clinical picture due to various combinations of motor and non-motor symptoms is quite large, which requires finding new ways to optimally manage and predict the effectiveness of treatment, as well as determine the leading symptoms of disability.

Accumulation of new knowledge regarding neuropathology, neurochemistry and neuroimaging has led to consideration of the severity of the disease with a focus on "the overall severity of non-motor symptoms" [1,2] moving away from an isolated assessment of motor status [3].

It should be emphasized that in many cases the non-motor manifestations of a disease, in particular of neuropsychiatric rank, constitute a significant difficulty in managing patients, leading to neurochemical collisions when it is necessary to simultaneously correct affective, cognitive, motor and autonomic status. Based on this, the prediction of the development of neuropsychiatric symptoms in patients with PD is of great practical interest. One of these possibilities was the results of genetic studies of recent years, which revealed commonality of some changes in genome of psychiatric and neurodegenerative diseases. The resulting neurochemical cascades determine occurrence of mixed neuropsychiatric symptom complexes. The ability to study functioning of a gene in a continuous process during neurodegeneration and in conditions of exacerbation / remission of mental disorder provides a more holistic picture of the syndromes of neurotransmitter dysregulation as a single continuum, which despite the determining phenotypic differences between neurological and mental diseases, is determined by polygenetic factors.

Presumably, this equifinality effect is determined by both the direct influence of gene polymorphisms and the compensatory resources of the brain [3], which makes it possible to predict the variability and accentuation of the clinical picture of diseases with genetic intersections.

In particular, PD has been shown to develop dementia or mild cognitive impairment with a mutation in the glucocerebrosidase (GBA) gene, as well as the development of depression and sleep disorders during a mutation in the LRRK2 gene [5]. However, the most interesting are mutations, not only participating in the development of neuropsychiatric symptoms, but also changing the response to drug therapy (Table 1).

The evolution of views on the causes of the emergence of PD reflects the development of technology in the world and science [6]. The study of the genesis of PD became possible after appearance of methods of local toxic destruction of the black substance in primates, which formed basis of the theory of oxidative stress and influence of free radicals on the functioning of mitochondria. Traditionally, the most common targets for studying the genesis of PD are disorders of autophagy of nerve cells, as well as changes in the function of lysosomes and mitochondria, and a large number of researches have been devoted to the study of these aspects of PD appearance [7].

The development of genetics and the identification of the first PARK gene in 1977 shifted the emphasis in the study to the aspect of influencing the dynamics and clinical picture of PD genomic polymorphisms of -synuclein. The influence of the APPL2, NUCKS1, LAG3, SNCA Rep1 263, LRRK2 gene polymorphisms on the functioning of α-synuclein and the phenotypic features of mental and neurodegenerative diseases is

discussed in the world scientific literature. Identification of the genetic basis of familial cases of PD allowed identification of genetic predictors of the sporadic form of PD. Associated with hereditary forms of PD are the PARK1, PARK2, PARK5 genes, mutations of which cause disturbances in the ubiquintin-proteasome pathway of protein degradation, and PARK7, the mitochondrial nuclear protein gene, normally involved in the process of cell apoptosis [8-10].

The emergence of the possibility of sequencing individual DNA regions made it possible to introduce viral models for the occurrence of PD and intensively study the peculiarities of local expression of gene mutations that are involved in the occurrence of certain diseases, the dynamics of the spread of gene polymorphisms in the brain. The following areas of research into the genomic characteristics of PD seem to be relevant: the study of the features of the genes that determine the functioning of mitochondria and the effect of mutations in mitochondrial DNA on neuron activity and the release of neurotransmitters into the synaptic cleft; the effect of -synuclein variations on the functional state of the cell; the effect of gene mutations of lysosomal proteins on DNA repair, protein utilization, cell apoptosis; features of dopamine receptors, dopamine transfer proteins and proteins associated with dopamine cleavage [8-11].

The genetic method of learning is also used in psychiatry. The material of the meta-analysis of M. Nagel et al. (2018) presents promising areas for the study of the genesis of mental diseases: gene polymorphisms that influence the formation and functioning of dopaminergic, serotonergic neurons, GABAergic secondary projection spine neurons [12].

Due to the nosological diversity of mental diseases, it becomes possible to compare the genetic functioning of neurons during illness and remission on one group of cells, for example, when studying addiction disorders and recurrent depressive disorders, which is impossible due to irreversible changes in the spectrum model of neurodegenerative diseases.

The emergence of genetic research methods in a new way sanctifies the genesis of neurological and mental diseases, in which, despite the phenotypic differences, common polygenetic factors have been identified.

The study of the genome in psychiatry is characterized by a shift in attention to "positive" manifestations of mental disorders (psychosis, anxiety, depression, psychomotor agitation) [13-15] In neurology, however, there is a shift in emphasis on the loss or irreversible deterioration in the quality of a function (movement disorders, irreversible changes in personality structure, cognitive decline) [16].

The study of protective factors of both neurological and mental diseases seems promising. For example, the PARK16 locus responsible for DNA repair and timely utilization of non-functional proteins, including the genes rs823128 (NUCKS1), rs1572931 (RAB29), rs823156 (SLC41A1) is considered protective against PD [17], but not studied with respect to other diseases.

Another promising direction of studying the genetic features of mental and neurological diseases is the comparison of the genomic profile of diseases that reduce the likelihood of each other. In particular, the study of the SNAP25 genes SLC6A3, DAT1, DRD4, HTR1B, TPH2, SLC6A2, CDH13 did not show similar polymorphisms in patients with attention deficit disorder and PD, although both diseases are based on one or another pathology of the dopamine system homeostasis of the brain [18]. Despite the negative results, such information may shed light on the genesis of both psychiatric and neurological diseases. The comparison of the genetic and neurophysiological features of schizophrenia and PD seems to be promising. A sequential manifesto in one patient of these two diseases is a rare phenomenon and is an ambiguous task for a clinician [19]. In particular, it was shown on the model of application of typical antipsychotics, not only the effect on the D2 receptors of the brain, but also an increase in oxidative stress leads to the appearance of parkinsonism symptoms in psychiatric patients [20].

At first glance, schizophrenia and the spectrum of endogenous diseases and PD have a different genesis and different topical localization of the lesions of the long dopaminergic systems of the central nervous system: PD at the stage of motor symptoms will be characterized by predominant dysfunction of the nigrostriatal pathways of the mesostriatal system, while at schizophrenia there is a malfunction of mesolimbic and mesostriatal systems [21]. On the other hand, both diseases lead to deterioration of social functioning and a significant increase in economic costs, cognitive decline, narrowing the range of interests and simplifying cognitive activity, increasing dependence on others, in both diseases there can be deceptions of perception, delusions, affective and anxiety disorders [22].

Despite various violations of the cognitive sphere in the form of a violation of associative processes in schizophrenia and predominantly mental disorders against the background of increased rigidity of thinking in PD, there are a number of common cognitive characteristics (working, verbal memory, pace of performance, motor skills, speech fluency, planning) that undergo changes with the progression of both conditions [23,24], each of the diseases has its own most probable predictor genes: if for PD these are the genes responsible for supporting bruising genome integrity, protein utilization and timely apoptosis, dopaminergic neuroblasts, middle spine neurons, serotonergic neurons, vesicular leptomeningeal cells, radial glial cells, oligodendrocyte [12] progenitor are the most likely predictor genes for schizophrenia.

In the aspect of dopamine dysregulation, PD is comparable to the group of impulse-control disorders and a tendency to addictions. For example, a number of studies have shown an inverse correlation between smoking and PD [25]. The adherence to smoking also reflects the brain's ability to plasticize the release of dopamine in response to external influences, for example, stimulation with nicotine through an action on the acetylcholine system. The acetylcholine system is characterized by a variety of receptor subtypes (9 different types of α and β subunits), differing in localization and degree of permeability, and genetic features. The most sensitive to nicotine are α7-containing receptors located on the bodies and terminals of dopaminergic neurons in the ventral tegmental area and the compact part of the substantia nigra, which allows nicotine to directly influence and alter the impulse release of dopamine. The effect of nicotine is also noted on the prefrontal cortex, in which dopamine determines the executive function, motivation, plasticity of behavior and decision making for actions not only on the acetylcholine receptors, but on the glutamatergic and GABA system. Thus, the inverse correlation of PD and states of impulse-control disturbances or dependencies on surfactants is not only a statistically important indicator, but also shows new directions of approaches to treatment of PD and sheds light on aspects of PD genesis that were poorly understood before [26,27]

Materials and methods

In the review, 77 works were used, 75 of them were articles on genetics, clinical features of PD and mental diseases, 2 monographs on PD and psychiatry. 57 were published in the period from 2008 to 2018, 16 in the period from 1997 to 2007, 3 in the period from 1972 to 1995. 34 on the topic of the clinic and the genetic characteristics of PD.

42 articles were research papers (7,539 patients), as well as 7 studies on animal models and 2 studies performed in the laboratory by genome sequencing or creating a hybrid DNA model.

In neurological articles (13 papers), in addition to clinical observation, the most commonly used tests were UPDRS, QUIP score (Questionnaire for Impulsive Disorders in Parkinson's Disease-Rating Scale), MMSE (Mini-Mental State Examination), CES-D (Center for Epidemiologic Studies Depression Scale).

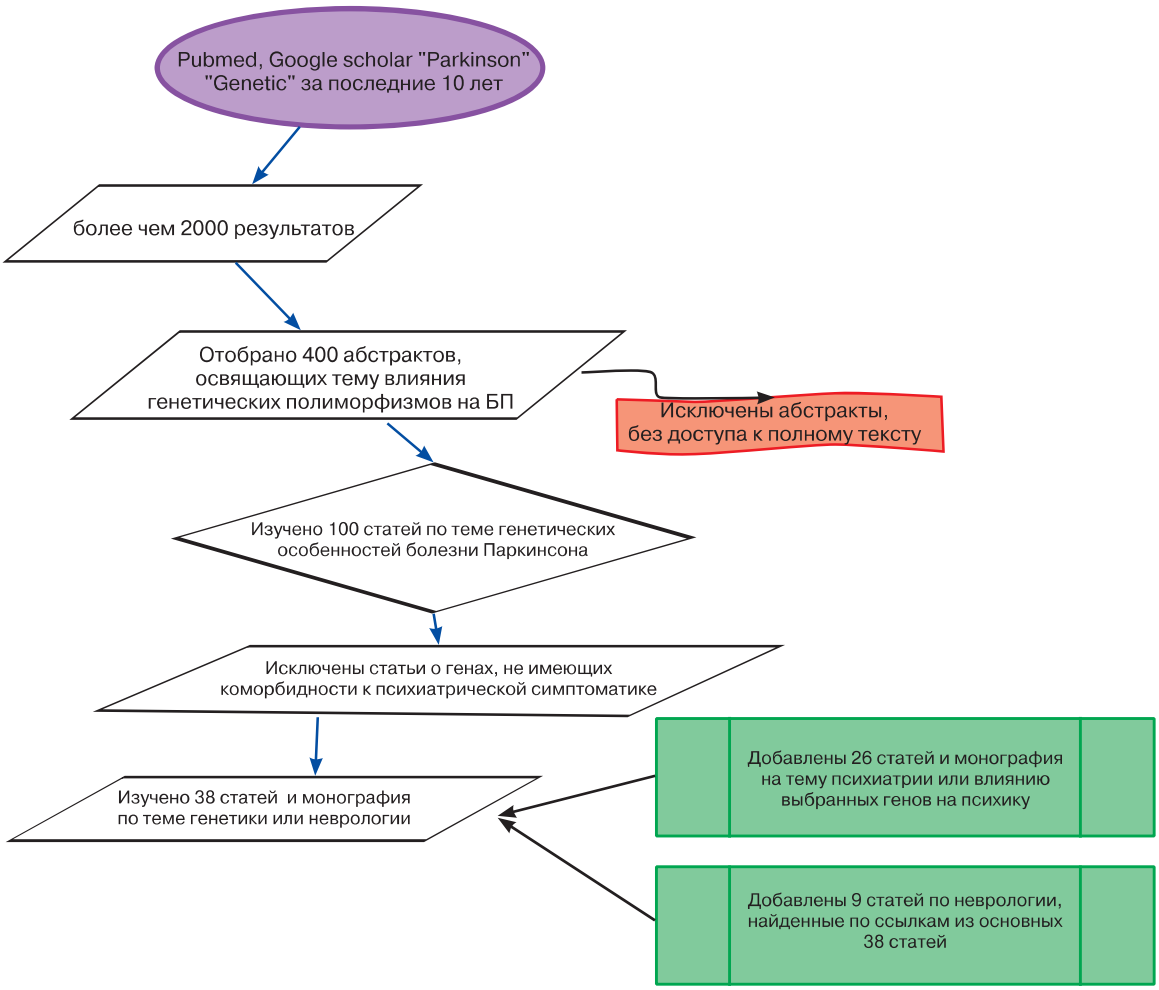

Рисунок. Схема отбора литературы.

Psychiatric articles (29 papers) noted the use of WAIS-R tests (Silverstein's method with scores from the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised), SCID-IV (Structured Clinical Interview for DSM-IV), ToM (test used to evaluate social cognition), Thematic Apperception Test , PANSS, CBCL/6–18 (Child Behavior Checklist for the age range of 6–18 years old), HAM-D (Hamilton Depression Rating Scale), CDSS (Calgary depression scale for schizophrenia), MINI (Mini International Neuropsychiatric Interview) , HAMD-17 (Hamilton Rating Scale for Depression), HAMA (Hamilton Anxiety Scale).

The study used 43 literature reviews, 7 - meta-analyzes: 3 reviews on genetics, 7 reviews and 2 meta-analyzes on psychiatry, 16 reviews and 5 meta-analyzes on the topic of PD.

Further, the review examined current studies highlighting some of the genetic features of Parkinson's disease (PD) and the genetic relationship between PD and a number of mental illnesses.

1. COMT - Catechol-O-methyltransferase catalyzes the breakdown of catecholamines: dopamine, epinephrine, norepinephrine. COMT polymorphisms in the cortico-striatal pathways of the brain are involved in the formation of early dementia in PD, regardless of the progression of motor disorders [28]. Antipsychotic medication was present in 30% of patients with a view to curing mental symptoms years before the onset of motor manifestations of PD, which subsequently delayed the verification of PD by expanding the scope of diagnostic search [29].

The appearance of mental disorders long before the manifestation of the first motor symptoms of PD is consecrated within the framework of two theories. On the one hand, the concept of H. Braak ("Braakhypothesis" 2003) presents mental disorders in the premorbid period as a manifestation of the first two stages of PD formation, during which the serotonergic nuclei of the brain stem seam is affected long before the substance is damaged. According to another point of view, affective pathology in the premorbid period of PD is caused by the pathology of a neurobiological substrate common to both mental and neurological diseases [30].

In addition to PD, the 22q11.2 deletion syndrome (COMT gene) was studied on a model of mental illness: 24% of carriers of COMT polymorphism show symptoms of a psychotic register in a history, 31.4% have affective and anxiety disorders. [31,32]. The effect of the deletion of the COMT gene is also noted in patients with schizophrenia, in whom the 22q11.2 locus polymorphism occurs in 1% of cases and determines the phenotype of patients. Patients with schizophrenia who carry a 22q11.2 deletion phenotypically differ in the early onset of the disease from 12 to 26 years, a lesser severity of negative disorders, a tendency to explosive reactions and impulsive actions [33]. The 22q11.2 deletion carriers are also distinguished by the features of cognitive function: 40% had moderate mental retardation, poor results in tests for motor skills, verbal skills and social intelligence [34].

Thus, common to carriers of COMT gene polymorphisms, both PD patients and psychiatric patients, will have symptoms of early cognitive decline, a history of mental illness and subsequent antipsychotic or dopaminergic therapy, which reflects a metabolic catecholamine caused by the genetic characteristics of the COMT enzyme.

2. MAO - (monoamine oxidase), an enzyme that participates in the catabolism of both endogenous and exogenous monoamines and is encoded by an X-linked gene, which causes uneven phenotypic manifestations of MAO depending on the sex of the patient [11,12]. MAO is divided into two subspecies: MAO A is a fermenting adrenaline, noradrenaline, serotonin, histamine, dopamine, and highly specialized MAO-B, the substrates for which are phenylethylamine and dopamine. MAO-B polymorphisms, which slow down or accelerate the function of monoamine oxidase, cause dyskinesia at the peak of the levodopa dose, accelerate cognitive decline. [35].

The participation of the rs1137070 and rs3741049 polymorphisms (A / A allele) of the MAO enzyme was noted in the formation of depressive disorders, including those that are not sensitive to placebo [36,37], bipolar affective disorders [38], schizophrenia [39], and borderline personality disorder [40], and the formation of attention deficit disorder in adolescents [41,42]. Genetic variations of MAO, together with SERT, and to a lesser extent COMT, determined the phenotypic features of depressive patients with schizophrenia in the form of aggression, impulsivity, speedy increase of negative symptoms.

Common to PD and mental disorders in the disruption of the functioning of MAO are a rapid decline in cognitive function, the paradox of the action of drugs (dopaminergic drugs, antidepressants) [43], as well as a predisposition to occurrence of affective disorders throughout life.

3. DRD1, DRD2, DRD3 - dopamine receptor genes. Polymorphism of the gene encoding D2 receptors (rs1800497) is associated with a decrease in the density of dopamine receptors in the striatum, which leads to the formation of parkinsonian symptoms [44]. DRD2 (rs1800497) and DRD1 (rs4532 and rs4867798) polymorphism carriers, despite being well tolerated by dopamine replacement therapy, are at risk of impulse control disorders, due to the effect of dopaminergic therapy on the ventral striatum, the most associated with the symptoms of the pathological search for positive reinforcement [45.46].

Studies in the general population showed the involvement of DRD2 mutations in the formation of behavioral control disorders and addictive disorders: according to O.H. Della Torre (2018) DRD2 polymorphism (rs6277) determines the personality characteristics of children: a tendency to conflict and ignoring social norms. A decrease in the density of DRD2 / 3 receptors in the striatum is observed among adults with impaired learning function (dependence on positive reinforcement) [47,48].

4. DAT is a transmembrane transporter of dopamine, which reverses it from the synaptic cleft into the cytosol of the cell and it is associated with a large number of neuropsychiatric disorders. Recessive polymorphism of the DAT gene with a variant number of tandem repeats (DAT1-VNTR) of the 3'-region is often found in PD [49].

Polymorphisms DAT1-VNTR, rs27072, rs27048 and rs2963238 were found in 24% of patients with alcoholism in a study on the European population, they lead to more severe alcoholic palimpsests and the formation of dependence, in particular to methylphenidate, the DAT blocker, which has a psycho-stimulating effect. [50, 51]. The DAT gene together with the COMT genes, dopamine (DRD1, DRD2, DRD3, DRD4) and serotonin receptors, serotonin transporters (HTR2A, 5HTT), and glutamate receptors (GRIN2B), is involved in the formation of obsessive-compulsive behavior in PD [52]

5. 5TPH2 (tryptophan hydroxylase) - an enzyme involved in the synthesis of serotonin and melatonin, together with VMAT2 determine the functioning of the serotonin system in PD, while the relationship between the serotonin transporter SERT and PD was refuted in L. Gao meta-analysis (2014), created on the basis of 9 studies of the genetic characteristics of PD and the association of PD with depression. Tryptophan hydroxylase participates in the first stage of serotonin synthesis, catalyzes the addition of the –HO group (hydroxylation) to 5-hydroxytryptophan, affects the transcription of serotonin receptor RNA (5HT) and is predominantly (up to 50%) localized in the striatum and prefrontal cortex [53,54]. Normally, the activity of 5HT receptors inhibits the action of dopamine in the ventral part of the tire and the accessory brain nucleus [55], while the level of serotonin decreases, a decrease in the tonic inhibitory effect on dopamine and impaired fronto-striatal pathways is observed, which is reflected in impulsive behavior and a decrease in criticism to errors and increased search behavior [56,57].

The study of TPH2 mutations in PD is most relevant in terms of impulsive behavior and abuse of dopaminergic drugs. TPH2 mutations (rs1352250, rs6582078 SNPs, GGA haplotype) determined the severity of additive behavior in PD, which is not corrected with a decrease in the dosage of drugs [58].

Interconnection TPH2 and impulsive behavior also proved to psychiatric samples: polymorphisms rs6582078 and rs1352250 predisposed to risky behavior and acceptance of impulsive solutions [59], affective carriers of rs7305115 A / G and G / G alleles are at risk of suicide attempt [60].

6. SNCA - the gene encoding alpha-synuclein, presynaptic chaperone, is the dominant gene and is found in familial forms of PD with dominant inheritance. The repeated SNCA polymorphism is called REP1; in the presence of a long SNCA Rep1 263 allele, the risk of developing PD increases: the risk of oxidative stress increases. Reduced SNCA transcription, although a protective factor for PD, increases the risk of alcohol abuse, which in turn increases the likelihood of polymorphisms [61].

Although the study of SNCA pathology is associated with the motor sphere, it is important to pay attention to the non-motor aspects of PD: SNCA carriers (Rep1 263) were distinguished by a quick early onset of the disease, an increase in dementia and the presence of hallucinations that occurred and develop independently of the dynamics of the motor symptoms. [62].

7. VMAT2 is an integral membrane protein that transports and packs monoamines: dopamine, norepinephrine, serotonin and histamine, from the cell cytosol to synaptic vesicles, and is involved in the breakdown of toxic cytosolic unpackaged dopamine, which becomes vulnerable to creating active oxygen forms [63]. In the nigrostriatal and mesolimbic pathways, VMAT2 is involved in the vesicular release of GABA. On the basis of the amplified DNA of two African and European ethnic groups, polymorphisms were detected, these groups increase the synthesis of VMAT2 (rs60543597, rs12412905), which is a protective factor for PD [64]. S.P. Alter study (2016), conducted in mice, showed that a decrease in the expression of the VMAT2 gene (SLC18A2) does not affect the degradation of serotonergic cells, but increases the sensitivity of 5-HT1A autoreceptors, most common in the human CNS [65,66]. A partial decrease in VMAT2 production ("VMAT2 knockout") negatively affects the elimination of endogenous neurotoxins and stimulates the development of oxidative stress, an important stage in the pathogenesis of PD [67; 68]. The decrease in VMAT2 production was correlated with the appearance of non-depressive apathy, with PD on a mouse brain model in the form of reducing the need for home improvement and reducing interest in sugar, while maintaining the results of the swimming test within the norm, which indicates the absence of an affective component in the behavior. [69]. VMAT2 gene mutations are found in most narcological, psychiatric and neurological diseases, as well as being one of the nine defining gene markers for schizophrenia (CHGB, SLC18A2, SLC25A27, ESD, C4A / C4B, TCP1, CHL1, CTNNA2) [70].

8. GABA (GABA) - γ-Aminobutyric acid inhibitory neurotransmitter central nervous. GABA has an inhibitory effect on the release of dopamine and noradrenaline in the frontal lobes, while the activity of the GABA neurons themselves is under the control of serotonin: activation of 5-HT2C receptors leads to an increase in GABA activity and a decrease in dopamine in the frontal lobes. This mechanism probably explains both the appearance of apathy with long-term therapy with antidepressants from the SSRI group, and the anti-apathetic action of 5-HT2C inhibitors (Fluoxetini, Agomelatini) [71,72].

According to https://www.snpedia.com, a resource reporting information about polymorphisms in the human genome, in humans, the GABA function is encoded in 29 genes on different chromosomes, with many variants of polymorphisms that encode for synthesis, degradation, transport, and GABA receptors.

he involvement of GABA in the pathogenesis of PD is traced at all stages of the formation of the dis-

Table

Variants of gene mutations that affect the therapy and phenotypic features of Parkinson's disease are promising for study in clinical practice

Substrate	Polymorphism	Chromosome	Phenotypic features	Clinical manifestation	Tests	The number of patients examined	Author
COMT	rs6269 rs4633 rs4818 rs4680	22	Change COMT activity	The rapid increase of cognitive defect	MMSE	409	Lin C.H., 2018
COMT	COMT H/H	22	High COMT activity	The need for high doses of levodopa	-	162	Sampaio T.F., 2018
COMT	COMT L/L	22	Low COMT activity	The need for high doses of levodopa	-	162	Sampaio T.F., 2018
COMT	22q11.2 делеция	22	Change COMT activity	The presence of mental disorders before the manifestation of PD, the high prevalence of mental non-motor disorders against the background of the reception Levodopa	-	Systematic review of 45 clinical cases	Boot E., 2015
MAO-B	MAO-B A/A	X-chromosome	MAO-B activity decrease	The emergence of dyskinesia on the background of the peak dose of Levodopa	-	95 patients	Białecka M., 2004
MAO-B	MAO-B G/G	X-chromosome	Increased MAO-B activity	The need for high doses of levodopa	-	95 patients	Białecka M., 2004
DAT	rs3836790 rs28363170	5	Increase in the main concentration of dopamine transporter	Best effect L -DOPA on motor functions (gait) UPDRS	UPDRS	61 patients	Moreau C., 2015
DRD2	rs1800497 (Taq1 Apolymorphism A1 / A1 A1 / A2)	11	Decreased baseline dopamine in the striatum	Increased risk of impulse-control disorders inpatients with a dopaminergic therapy	UPDRS CES-D MMSE QUIP	11 пациентов	McDonel K.E., 2018
VMAT2	rs60543597, rs12412905	10	Increase VMAT2 output	Reducing the risk of PD	-	Amplified DNA of African and European samples	Glatt C.E., 2006
TPH2	rs1352250, rs6582078, GGA haplotype	12	Reduced TPH2 production	Increased risk of impulse control disorders	Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale QUIP MMSE 154 patient	154 patients	Gao L., 2014
SNCA	SNCA (Rep1 263)	4	Enhancement of SNCA expression	Increased risk of early onset of PD, complicated by psychotic events and an increase in dementia	-	426 patients	Corrado L., 2018

ease. In the early stages of the disease, the pathology of GABA affects functioning of posterior nuclei of the vagus nerve, nucleus of the glossopharyngeal nerve, locus coeruleus, hypothalamus, mesolimbic and nigrostriatal dopaminergic systems, which clinically manifested in violations of the gastrointestinal tract, loss or change in sense of smell, sleep disorders and the emergence of anxiety, anhedonia, apathy, hypomimia and difficulty in motivating movement [73,74]. At the stages of the first motor symptoms of GABA disease, there is an imbalance of GABA in the central nervous system: an increase in GABA in the striatopallidal complex promotes the development of bradykinesia and rigidity, reduces tremor and postural instability. During the collapse of the GABA system, there is a decrease in cognitive and motor function due to the effect on the striato-hippocampal and thalamocortical system [75].

At the moment, there is a certain lack of information on the effect of mutations of GABA genes on mental and neurodegenerative diseases.

9. PINK1 is a recessive gene that affects the functioning of the Parkin gene, the activity of which determines the timely autophagy of depolarized mitochondria. In the clinical case, L. Ephraty et al., (2007) of a familial PD disease in PINK1 mutation carriers were brothers 25 and 33 years old, they had an early manifestation of the disease in the form of anxiety-depressive disorder with antisocial behavior and impulse-control disorders. The parents of the patients had behavioral disorders and a tendency to affective diseases without signs of parkinsonism [76].

Prospects for the study of genetic features, comorbid mental pathology, with PD in clinical practice.

Evaluation of genetic features in order to determine a patient's treatment strategy is a common practice worldwide [77]. The study of such enzymes as COMT, MAO-A, MAO-B, DAT, DRD2, VMAT2, TPH2 and SNCA is a promising direction for personalized treatment of PD.

An important aspect of the study of genetic features in clinical practice is the determination of the prospects for the operation of deep brain stimulation (DBS). In a study by E. Lohmann et al. (2008) patients of PD were treated with Parkin gene carriers in comparison with the sporadic form of PD and the heterozygous form of PD [78]. The Parkin gene encodes ubiquitin ligase, which regulates mitochondrial DNA recovery, mitochondrial division, timely elimination of non-functional proteins, is characterized by recessive inheritance, i.e. for complete phenotypic manifestation, two mutations in the carrier DNA are necessary. Parkin mutation carriers are characterized by early onset of the disease, slow progression and good response to dopaminergic therapy drugs [79] 24 months after surgery, homozygous Parkin carriers were characterized by lower doses of dopaminergic therapy, but they had worse results on testing the cognitive decline on the MATTIS scale.

Thus, the assessment of genetic features in order to determine a patient's treatment strategy is a common practice throughout the world [77, 80]. The study of such enzyme genes as COMT, MAO-A, MAO-B, DAT, DRD2, VMAT2, TPH2 and SNCA is a promising direction in developing personalized therapy strategies based not only on the assessment of clinical status, but also on their endophenotype, as well as reflects the transition from the nosological approach to the study of both mental and neurological disorders to the dimensional one.

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