

## Functional analysis and signaling pathway enrichment analysis of genes associated with Alzheimer's disease and Parkinson's disease

Chasovskikh N.Yu., Grechishnikova A.Yu., Smirnov D.V.

*Siberian State Medical University (SSMU)  
2, Moscow Trakt, Tomsk, 634050, Russian Federation*

### ABSTRACT

We identified significant functions of susceptibility-genes and performed an analysis of pathway enrichment for Alzheimer's disease, Parkinson's disease and for both of them. Genes were extracted from a Catalog of Published Genome-Wide Association Studies (GWAS). We uploaded genes into Cytoscape version 3.2.1. ClueGO plugin was used for functional and pathway enrichment analysis of genes based on the hypergeometric test. Two databases, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and REACTOME, were selected for analysis.

The identified susceptibility genes are involved in the synthesis regulation and accumulation of toxic proteins,  $\beta$ -amyloid and  $\alpha$ -synuclein, and lead to apoptosis of neurons. We have defined 14 shared functions: collagen catabolic process, cellular response to retinoic acid, regulation of calcium-mediated signaling, negative regulation of cell projection organization, negative regulation of neuron projection development, glial cell activation, microglial cell activation, macrophage activation, regulation of cholesterol metabolism, clathrin-mediated endocytosis, regulation of protein oligomerization, regulation of dendritic spine development, kinesin binding and clathrin binding. Also, we have defined 3 shared signaling pathways: trans-Golgi Network Vesicle Budding, Clathrin derived vesicle budding, Intestinal immune network for IgA production. These pathways contain genes susceptible to Alzheimer's disease and Parkinson's disease. The results suggest the metabolic, neuronal and immunological factors participate in the development of Parkinson's disease and Alzheimer's disease.

**Key words:** Parkinson's disease, Alzheimer's disease, GWAS, ClueGO Cytoscape, functional annotation of genes.

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## Функциональная аннотация и анализ обогащения сигнальных путей генов, ассоциированных с болезнью Альцгеймера и болезнью Паркинсона

Часовских Н.Ю.<sup>1</sup>, Гречишникова А.Ю.<sup>1</sup>, Смирнов Д.В.<sup>1</sup>

<sup>1</sup> Сибирский государственный медицинский университет (СибГМУ)  
Россия, 634050, г. Томск, Московский тракт, 2

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✉ Grechishnikova Aleksandra Yu., e-mail: grechishnikova.al@mail.ru.

**РЕЗЮМЕ**

**Цель исследования.** Охарактеризовать *in silico* функции генов предрасположенности и провести анализ обогащения сигнальных путей при болезни Паркинсона и болезни Альцгеймера.

**Материалы и методы.** Гены, ассоциированные с болезнью Паркинсона и болезнью Альцгеймера, были получены на основе анализа информации из каталога GWAS (каталог ассоциаций однонуклеотидных полиморфизмов с заболеваниями). Оценка принадлежности генов к биологическому процессу, молекулярным функциям, к иммунной системе в терминах генной онтологии осуществлялась с помощью алгоритма, реализованного в плагине ClueGO Cytoscape version 3.2.1. Анализ обогащения путей был выполнен при помощи плагина ClueGO Cytoscape с использованием KEGG и REACTOME и с применением гипергеометрического теста.

**Результаты.** Выявленные гены предрасположенности к болезни Паркинсона и болезни Альцгеймера участвуют в регуляции синтеза и накопления токсичных белков  $\beta$ -амилоида и  $\alpha$ -синуклеина, приводя к апоптозу нейронов. Установлено наличие 14 общих функций (процесс катаболизма коллагена, клеточный ответ на ретиноевую кислоту, регуляция кальций-опосредованного сигналинга, негативная регуляция защиты клеточной организации, негативная регуляция развития нейронов, активация глиальных клеток, активация микроглиальных клеток, активация макрофагов, регуляция метаболизма холестерина, клатрин-зависимый эндоцитоз, регуляция олигомеризации белка, регуляция развития дендритного отростка, связывание кинезина, связывание клатрина) и три общих сигнальных пути (везикуло-опосредованный транспорт, клатрин-производное почкование везикул, обеспечение продукции иммуноглобулина A), в которые вовлечены гены предрасположенности к болезни Альцгеймера и болезни Паркинсона.

**Заключение.** Полученные результаты свидетельствуют об участии метаболических (гены *MMP12*, *COL13A1*, *APOE*, *DGKQ*); нейрональных (гены *CLU*, *MAPT*, *SNCA*, *STAP1*, *RNF6*, *GAK*, *INPP5F*, *MAP4K4*) и иммунологических факторов (гены *LA-DQB1*, *HLA-DRA*, *AICDA*) в механизмах развития болезни Паркинсона и болезни Альцгеймера.

**Ключевые слова:** болезнь Паркинсона, болезнь Альцгеймера, GWAS, ClueGO Cytoscape, гены предрасположенности.

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**INTRODUCTION**

Neurological diseases are in the top three most common diseases in the world. Parkinson's disease (PD) comes second next to Alzheimer's disease (AD), which affects 1-2% of people over 65 years old [1].

In the recent years, progress in understanding biochemical and molecular mechanisms of these diseases has been made. Nevertheless, issues of their co-occurrence need to be studied further. A significant role here is played by genetic predisposition to the disease and environmental factors.

Patients with Alzheimer's disease and Parkinson's disease often obtain overlapping clinical presentations and brain neuropathology.

$\beta$ -amyloid and  $\alpha$ -synuclein accumulation happens in substantia nigra of the human brain in PD, and in hippocampus in AD. It makes the brain unable to produce sufficient amount of dopamine [2,3].

Methods that include identification of genes responsible not only for particular disorders, but also for susceptibility to various diseases, are used in research of molecular mechanisms of neurological diseases. This susceptibility can be expressed by changes in genes, included in the most important biological processes, molecular functions and signaling and metabolic pathways. Occurring disorders of cellular homeostasis lead to the activation of pathological process mechanisms [4].

The search for genes functions and biological pathways that allow researchers to characterize general molecular genetic mechanisms is of specific interest in studying the co-occurrence of diseases. Existing bioinformatics tools allow for characterizing the participation of genes in the development of pathological process and evaluating their role in regulating intracellular signaling and cellular homeostasis [5]. Such tools include the Gene Ontology initiative.

**Aim.** In silico characterization of susceptibility genes functions and signaling pathways enrichment analysis for Parkinson's disease and Alzheimer's disease.

## MATERIALS AND METHODS

Susceptibility to Parkinson's and Alzheimer's diseases genes were obtained with Catalog of Published Genome-Wide Association Studies (GWAS). It is a supervised resource that contains results of genome wide search of disease-associated single nucleotide polymorphism [6]. A ClueGO Cytoscape version 3.2. plugin was used to evaluate genes involvement in biological process, molecular functions and immune system in genetic ontology terms [7].

2 is the minimum number of groups required to form functional groups. Hypergeometric test with  $p < 0.05$  and  $K = 0.4$  was used to evaluate functional links between genes [8].

Pathways enrichment analysis was conducted with ClueGO Cytoscape plugin and KEGG and REACTOME databases. Hypergeometric test with  $p < 0.05$  was also used for it. Specificity level of 60% was chosen, meaning that enriched pathway must include more than 60% of susceptibility genes of a disease in order to be ranked with this disease. Additionally enriched pathways were clustered into groups with similar biological significance and content of susceptibility genes.

## RESULTS AND DISCUSSION

A list of susceptibility genes was formed for each disease. For Parkinson's disease it consists of 119 following genes: *CLRN3*, *CTC1*, *CCDC82*, *TMC3-AS1*, *TMC3*, *COL13A1*, *LRRK2*, *SP-PL2C*, *MAPT*, *MCCC1*, *FAM47E-STBD1*, *TMEM175*, *SREBF1*, *SLC41A1*, *RIT2*, *WNT3*, *MGC57346-CRHR1*, *ASS1P14*, *HLA-DRB1*, *GBA*, *SYT10*, *GAK*, *GCH1*, *MCCC1*, *RAB29*,

*NUCKS1*, *RAD1P1*, *FAM47E*, *BST1*, *RIT2*, *CCDC62*, *OR5AZ1P*, *SH3GL2*, *SYT17*, *NDUFAF2*, *CA8*, *HSD17B1P1*, *OR5BD1P*, *WNT9A*, *COL5A2*, *IGSF11*, *RN7SL383P*, *RPA2P1*, *MDGA2*, *UNC13B*, *HLA-DRA*, *GAK*, *RAB25*, *ACMSD*, *LAMTOR2*, *MCCC1*, *TMEM175*, *BST1*, *MGC57346-CRHR1*, *CCDC62*, *MGC57346*, *DLG2*, *STAP1*, *RPL9P21*, *SEMA5A*, *EIF2AP4*, *BST1*, *SLC2A13*, *PLEKHM1*, *SNCA*, *PAX7*, *BRINP1*, *DGKQ*, *TAS1R2*, *LHFPL2*, *TRPS1*, *KLHDC1*, *TPM1*, *DSG3*, *PRRG4*, *ATF6*, *QSER1*, *AAK1*, *AGAP1*, *SPTSSB*, *PINK1*, *ZNF165*, *GBF1*, *CAB39L*, *RPL13AP3*, *MED13*, *ITGA2B*, *POLRMT1*, *HMGN2P18*, *RAB29*, *NUCKS1*, *SIPA1L2*, *VDAC2P4*, *KTN1*, *MCCC1*, *TMEM175*, *BST1*, *KRTCAP2*, *HLA-DQB1*, *MTCO3P1*, *GPNMB*, *INPP5F*, *DLG2*, *CCDC62*, *GCH1*, *GPHN*, *TMEM229B*, *BCKDK*, *RIT2*, *TMPRSS9*, *DDRKG1*, *ITPKB*, *MAP4K4*, *SCN2A*, *SP-PL2B*, *IP6K2*, *ITIH1*, *CAMK2D*, *NDUFAF2*.

For Alzheimer's disease – of 57 genes: *DSTNP5*, *WDR1*, *SLC2A9*, *PCDH7*, *RNF6*, *ATP8A2P3*, *DCHS2*, *SEPT5*, *TST*, *TEX33*, *RANP7*, *SALL4P5*, *CLDN18*, *HSPA8P9*, *STK32B*, *ZC-CHC10*, *EN2*, *CIR1P1*, *TOMM40*, *PINK1*, *MTATP6P30*, *PVRL2*, *EXOC4*, *PARVB*, *PHF14*, *RPL26P32*, *ST18*, *AICDA*, *RPL5P26*, *MS4A2*, *SLC24A4*, *BCAM*, *CHRNA2*, *ZFP3*, *ZNF232*, *ACE*, *FBXL7*, *IGSF23*, *MS4A3*, *YWHAZP9*, *IGSF23*, *CEACAM19*, *BLOC1S3*, *EXOC3L2*, *BCL3*, *PPP1R37*, *APOC1*, *APOE*, *CLU*, *MMP3*, *GBA*, *PICALM*, *LRRK2*, *RELN*, *DISC1*, *TREM2*, *PAX2*.

An analysis of these lists revealed that products of *SNCA*, *MAPT* and *PINK1* genes when interacting with each other can contribute to the co-occurrence of Parkinson's disease and Alzheimer's disease. In particular, amyloid beta ( $A\beta$ ), changes of which underlie proteopathy of Alzheimer's disease, stimulates aggregation of alpha-synuclein ( $\alpha$ S), protein encoded by *SNCA* gene. *MAPT* gene promotes oligomers and alpha-synuclein fibrils production. Alpha-synuclein expression pattern influences manifestation of Parkinson's disease. Thus, *MAPT*-mediated interaction between  $A\beta$  and  $\alpha$ -synuclein can concern patients with Alzheimer's disease and Parkinson's disease [9].

*PINK1* gene encodes mitochondrial protein kinase. *PINK1* mutations lead to mitochondrial

dysfunction, thus, causing early-onset Alzheimer's disease [10]. It was revealed that *PINK1* in AD is associated with classic senile plaques, vascular amyloid deposition and reactive astrocytes, related to typical lesions of Alzheimer's [11].

Study of AD susceptibility gene functions allowed to create two main groups. The first group of genes (*GPNMB*, *MAP4K4*, *NDUFAF2*, *SREBF1*) is responsible for processes of negative regulation of insulin secretion, such as decrease in speed, frequency and the degree of insulin secretion from secretory granules (GO:0090278; GO:0046676). Genes of the second group (*GAK*, *LRRK2*, *SH3GL2*, *SNCA*, *SYT10*, *SYT17*, *UN-*

*C13B*) influence transport and secretion of neurotransmitters (GO:0099504, GO:0051588).

The study revealed that genes associated with AD were joined in one main group (*ABCA7*, *APOE*, *CLU*, *PICALM*). This group is in charge of production, regulation and metabolism of Alzheimer's amyloid precursor protein. Alzheimer's amyloid precursor protein is the main component of amyloid plaques in AD (GO:1900221, GO:0042987, GO:1902993).

Functional analysis discovered 14 shared gene functions, which characterize biological processes and molecular functions in the diseases (table 1).

Table 1

| Functions associated with AD and PD                                |                                                         |                                                                                                                      |
|--------------------------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| Marker                                                             | Genes from the functional group                         |                                                                                                                      |
|                                                                    | Alzheimer's disease                                     | Parkinson's disease                                                                                                  |
| Collagen catabolic process [GO:0030574]                            | <i>MMP12</i> , <i>MMP3</i>                              | <i>COL13A1</i> , <i>COL5A2</i> , <i>CTSB</i>                                                                         |
| Cellular response to retinoic acid [GO: 0071300]                   | <i>PAX2</i>                                             | <i>BRINP1</i> , <i>LTK</i> , <i>SREBF1</i> , <i>WNT3</i> , <i>WNT9A</i>                                              |
| Regulation of calcium-mediated signaling [GO: 0050848]             | <i>TREM2</i>                                            | <i>BST1</i> , <i>CAMK2D</i> , <i>LRRK2</i> , <i>RIT2</i>                                                             |
| Negative regulation of cell projection organization [GO: 0031345]  | <i>APOE</i> , <i>RNF6</i>                               | <i>GAK</i> , <i>INPP5F</i> , <i>MAP4K4</i> , <i>RAB29</i> , <i>RIT2</i> , <i>SEMA5A</i> , <i>STAP1</i> , <i>WNT3</i> |
| Negative regulation of neuron projection development [GO: 0010977] | <i>APOE</i> , <i>RNF6</i>                               | <i>GAK</i> , <i>INPP5F</i> , <i>MAP4K4</i> , <i>RAB29</i> , <i>RIT2</i> , <i>SEMA5A</i> , <i>WNT3</i>                |
| Glial cell activation [GO: 0061900]                                | <i>CLU</i>                                              | <i>MAPT</i> , <i>SNCA</i> , <i>STAP1</i>                                                                             |
| Microglial cell activation [GO: 001774]                            | <i>CLU</i>                                              | <i>MAPT</i> , <i>SNCA</i> , <i>STAP1</i>                                                                             |
| Macrophage activation [GO: 0042116]                                | <i>CLU</i> , <i>MAPT</i>                                | <i>MAPT</i> , <i>SNCA</i> , <i>STAP1</i>                                                                             |
| Regulation of cholesterol metabolic process [GO: 0090181]          | <i>APOE</i>                                             | <i>DGKQ</i> , <i>FDFT1</i> , <i>SREBF1</i>                                                                           |
| Clathrin-dependent endocytosis [GO: 0072583]                       | <i>PICALM</i>                                           | <i>GAK</i> , <i>INPP5F</i> , <i>SH3GL2</i> , <i>SNCA</i>                                                             |
| Regulation of protein oligomerization [GO: 0032459]                | <i>APOE</i> , <i>CLU</i> , <i>GBA</i> , <i>MMP3</i>     | <i>GBA</i>                                                                                                           |
| Regulation of dendritic spine development [GO: 0060998]            | <i>APOE</i> , <i>DISC1</i> , <i>LRRK2</i> , <i>RELN</i> | <i>LRRK2</i>                                                                                                         |
| Kinesin binding [GO: 0019894]                                      | <i>DISC1</i>                                            | <i>KTN1</i> , <i>RAB29</i> , <i>SNCA</i>                                                                             |
| Clathrin binding [GO: 0030276]                                     | <i>PICALM</i>                                           | <i>LRRK2</i> , <i>SYT10</i> , <i>SYT17</i>                                                                           |

The results of the functional analysis demonstrate that shared functions of AD and PD susceptibility genes are connected with the influence on neurons and nervous system functions. For example, microglial activation is a distinctive feature of neuroinflammation, typical for both, Alzheimer's disease and Parkinson's disease. Changes in the regulation of neuronal development can increase or decrease their sensitivity and, thus, lead to disorder in cell response to irritants [12].

Studied gene products enforce processes of collagen disorganization in extracellular matrix. This promotes neuronal dysfunction [13, 14]. Change in cellular response to retinoic acid can disturb cell proliferation and differentiation functions and cause changes cell state and activity. In particular, retinoic acid has neuroprotective effect on dopaminergic neurons in Parkinson's disease [15].

Influence on calcium-mediated signaling induces change in calcium concentration in endo-

plasmic reticulum. High  $\text{Ca}^{2+}$  concentration may lead to synaptic deficit and contribute to amyloid plaque accumulation in Alzheimer's disease [16].

The following analysis of signaling pathways enrichment and metabolic pathways has shown that PD susceptibility genes are specifically involved in pathways R-HSA:202165, R-HSA:202291, R-HSA:202427 and R-HSA:2130378. These pathways are engaged into transfer of histocompatibility complex (MHC) class II and activation of Lck (lymphocyte kinase) which phosphorylates immunoreceptor tyrosine-based inhibitory motif (ITIM) in T-cell receptor (TCR) family. TCR is responsible for specifically bind antigen recognition and triggers cellular response [17].

Gene associated with AD specifically enrich pathways concerned with regulation of cholesterol metabolism. Cholesterol takes part in regulation of  $\beta$ -amyloid products (KEGG:04979; R-HSA:174824; R-HSA:8963898) [18].

The analysis of pathways enrichment identified significant pathways shared by AD and PD ( $p < 0.05$ ). These pathways are responsible for the following processes (table 2):

Vesicle-mediated transport (R-HSA:199992). It provides directed movement of substances from Golgi complex to other cell parts, including organelles and plasma membrane.

Clathrin-derived vesicle budding (R-HSA:421837). It is a transport vesicle formation under the effect of clathrin and adaptor proteins on the Golgi membrane.

Immunoglobulin A (IgA) production with intestinal immune network (KEGG:04672). It is a production of a large number of non-inflammatory antibodies for IgA.

The conducted study of signaling and metabolic pathways demonstrate that genes associated with PD and AD specifically enrich pathways, which contribute to synthesis and accumulation of toxic proteins. These toxic proteins are  $\beta$ -amyloid and  $\alpha$ -synuclein which lead to neuronal apoptosis. Studied genes also influence products of non-inflammatory antibodies to immunoglobulin A (IgA), thus, providing active protection from microorganisms and toxins.

## CONCLUSION

Three components influencing development mechanisms of Parkinson's disease and Alzheimer's disease can be formulated based on the analysis of AD and PD susceptibility genes participation in molecular functions and signaling and metabolic pathways:

Metabolic component including collagen catabolism, cholesterol metabolism, clathrin-mediated endocytosis (MMP12, COL13A1, APOE, DGKQ)

Neuronal reactions such as glial cells activation, negative neuronal regulation, vesicle-mediated transport in synapses and calcium-mediated signaling (CLU, MAPT, SNCA, STAP1, RNF6, GAK, INPP5F, MAP4K4)

Immunological component that is macrophage and microglial activation and influence on Immunoglobulin A production (LA-DQB1, HLA-DRA, AICDA)

Future use of this data may help to determine (in silico and by experiment) main molecular genetic development mechanisms and possible ways of therapeutic correction of Alzheimer's disease and Parkinson's disease.

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Table 2

| Enriched pathways specific for Parkinson's disease and Alzheimer's disease |                                      |                     |
|----------------------------------------------------------------------------|--------------------------------------|---------------------|
| Marker                                                                     | Genes included in biological pathway |                     |
|                                                                            | Parkinson's disease                  | Alzheimer's disease |
| Vesicle-mediated transport                                                 | <i>GAK, GBF1, SH3GL2</i>             | <i>BLOC1S3</i>      |
| Clathrin-derived vesicle budding                                           | <i>GAK, GBF1, SH3GL2</i>             | <i>BLOC1S3</i>      |
| Immunoglobulin A (IgA) production with intestinal immune network           | <i>HLA-DQB1, HLA-DRA, HLA-DRB1</i>   | <i>AICDA</i>        |

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## Authors information

Chasovskikh Nataliya Yu., Dr. Sci. (Med.), Professor, Department of Medical and Biological Cybernetics, SSMU, Tomsk. ORCID 0000-0001-6077-0347.

Grechishnikova Aleksandra Yu., Assistant, Department of Medical and Biological Cybernetics, SSMU, Tomsk.

Smirnov Dmitrii V., Student, Department of Medicine and Biology, SSMU, Tomsk.

(✉) Grechishnikova Aleksandra Yu., e-mail: grechishnikova.al@mail.ru.

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