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Bioinformatic analysis of biological pathways in coronary heart disease and Alzheimer's disease

Chasovskikh N.Y., Chizhik E.E.

Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation

ABSTRACT

Aim. Using bioinformatic tools, to perform a pathway enrichment analysis in Alzheimer's disease and coronary heart disease (CHD).

Materials and methods. Genes contributing to susceptibility to CHD and Alzheimer's disease were obtained from the public database DisGeNET (Database of Gene – Disease Associations). A pathway enrichment analysis was performed in the ClueGO Cytoscape plug-in (version 3.6.0) using hypergeometric distribution and the KEGG and Reactome databases.

Results. The identified genes contributing to susceptibility to Alzheimer's disease and CHD are included in 69 common signaling pathways, grouped into the following subgroups: cell death signaling pathways (1); signaling pathways regulating immune responses (2); signaling pathways responsible for fatty acid metabolism (3); signaling pathways involved in the functioning of the nervous system (4), cardiovascular system (5), and endocrine system (6).

Conclusion. Following the performed analysis, we identified possible associations between processes involving genetic factors and their products in CHD and Alzheimer's disease. In particular, we assumed that susceptibility genes involved in the implementation of these pathways regulate apoptosis, production of inflammatory cytokines and chemokines, lipid metabolism, β-amyloid formation, and angiogenesis.

Keywords: coronary heart disease, Alzheimer's disease, ClueGO Cytoscape plug-in, susceptibility genes, pathway enrichment analysis

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Биоинформационный анализ биологических путей при ишемической болезни сердца и болезни Альцгеймера

Часовских Н.Ю., Чижик Е.Е.

Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Цель исследования – провести анализ обогащения биологических путей при болезни Альцгеймера и ишемической болезни сердца (ИБС) с помощью биоинформационных инструментов.

✉ *Chizhik Evgenia E.,* evgenika06@gmail.com

Гены предрасположенности к ИБС и гены предрасположенности к болезни Альцгеймера извлечены из публичной базы данных DisGeNET (база данных ассоциаций генов и заболеваний). Анализ обогащения биологических путей проведен в плагине ClueGO Cytoscape version 3.6.0 при помощи гипергеометрического теста с использованием баз данных KEGG и REACTOME.

Выявленные гены предрасположенности к болезни Альцгеймера и ИБС включены в 69 общих сигнальных путей, объединенных в следующие подгруппы: сигнальные пути, участвующие в гибели клеток (1); сигнальные пути, вовлеченные в процессы иммунной системы (2); сигнальные пути, ответственные за метаболизм жирных кислот (3); сигнальные пути, принимающие участие в функционировании нервной системы (4), сердечно-сосудистой системы (5), эндокринной системы (6).

В результате проведенного анализа выявлены возможные общие процессы, в которые вовлечены генетические факторы и их продукты при ишемической болезни сердца и болезни Альцгеймера. В частности, предполагается, что гены предрасположенности, участвующие в реализации данных путей, регулируют процессы апоптоза, наработки воспалительных цитокинов и хемокинов, метаболизма липидов, формирования β-амилоида, ангиогенеза.

Ключевые слова: ишемическая болезнь сердца, болезнь Альцгеймера, ClueGO Cytoscape, гены предрасположенности, анализ обогащения путей

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

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INTRODUCTION

Currently, Alzheimer's disease (AD) is a serious health problem. According to the estimates by Alzheimer's Disease International in 2019, more than 50 million people suffer from this disease worldwide [1]. Numerous studies on the genetic basis of AD have identified genes contributing to the development of this disease [2, 3]. Besides, the results of genetic association studies of various diseases showed that AD manifestations can be combined with other pathologies, for example, with cardiovascular diseases, such as myocardial infarction [4] and atrial fibrillation [5]. According to M.K.Aronson et al., who studied the association between dementia and coronary heart disease (CHD) in elderly patients, CHD, especially long-term, is associated with a smaller cortical thickness and brain volume (according to magnetic resonance imaging data) [6]. In addition, a number of epidemiological studies showed that patients with CHD have higher incidence of AD [7, 8].

However, the association between AD and CHD remains debatable, since data of some studies suggest that CHD is associated with cognitive impairment [9], while other studies suggest that there is no relationship between these conditions [10]. For example, the Rotterdam Study (a prospective cohort study that started in 1990 in the Netherlands and is aimed at finding the causes of chronic diseases common among elderly people and increasing with the population aging) showed that unrecognized (asymptomatic) myocardial infarction was associated with a risk of developing AD, whereas recognized MI was not [5, 11].

In 2014, G. Liu et al. integrated data of three GWAS using a gene-based meta-analysis to identify new risk factors for AD. The pathway analysis was performed using the Kyoto Encyclopedia of Genes and Genomes and the gene ontology database [12]. The authors revealed for the first time the involvement of signaling pathways associated with cardiovascular diseases, cellular processes, and infectious diseases in the development of AD. However, there are no other studies describing joint processes of signal transduction in AD and CHD. Thus, a pathway enrichment analysis, which makes it possible to assess the involvement of susceptibility genes in possible mechanisms of simultaneous presentation of these pathologies, is of particular interest.

The aim of this work was to identify signaling and metabolic pathways involved in the processes of signal transduction in both AD and CHD.

Genes contributing to susceptibility to CHD and AD were extracted from the public database DisGeNET [13]. DisGeNET is a platform containing a complete catalog of genes and their variants related to human diseases. The catalog combines data from expert databases, such as CTD, UniProt, ClinVar, Orphanet, GWAS, GAD, with information obtained by the scientific literature analysis [13]. The pathway enrichment analysis presumably involved in the mechanisms of simultaneous presentation of CHD and AD was carried out in the ClueGO Cytoscape plug-in (version 3.6.0) [14] using the KEGG [15] and Reactome [16] databases.The studied susceptibility genes for CHD and AD in the ClueGO Cytoscape plug-in were presented in the form of clusters 1 and 2, respectively. For the analysis, the hypergeometric test with $p < 0.05$ and kappa K = 0.4 was used.

Susceptibility gene sets for AD and CHD were formed on the basis of the DisGeNET data analysis. For AD, the set consisted of 446 genes, and for CHD – 324 protein-coding genes. Following the pathway enrichment analysis, we revealed 90 pathways which include susceptibility genes for AD, 28 pathways which include susceptibility genes for CHD, and 69 pathways associated with both diseases (the latter are presented in the Table).

These pathways were grouped into the following blocks by their involvement in biological processes and functioning of body systems: cell death signaling pathways (1); signaling pathways regulating immune responses (2); signaling pathways responsible for fatty acid metabolism (3); signaling pathways involved in the functioning of the nervous system (4), cardiovascular system (5), and endocrine system (6). In addition, pathways that include genes required for implementing physiological processes and changes in typical pathological processes (such as inflammation and hypoxia) were considered separately.

Table

Common biological pathways associated with CHD and AD

Biological pathways	Genes that are common to diseases and are included in the signaling pathway
1. Cell death signaling pathways	
Apoptosis	*NFKB1*, *TNF*
Necroptosis	*IL1A*, *IL1B*, *TLR4*, *TNF*
TNF signaling pathway	*CCL2*, *IL1B*, *IL6*, *MMP3*, *MMP9*, *NFKB1*, *PTGS2*, *TNF*
p53 signaling pathway	*SERPINE1*
2. Signaling pathways regulating immune responses	
Hematopoietic cell lineage	*IL1A*, *IL1B*, *IL6*, *IL6R*, *TNF*
Innate immunity	*AGER*, *CFH*, *CRP*, *F2*, *IGF2R*, *IL1B*, *MMP9*, *MPO*, *NFKB1*, *NOS3*, *OLR1*, *PLA2G2A*, *PLCG2*, *TLR4*
Signaling by interleukins	*AGER*, *CCL2*, *CCR5*, *HMOX1*, *ICAM1*, *IL10*, *IL18*, *IL1A*, *IL1B*, *IL1RN*, *IL6*, *IL6R*, *IRS1*, *MMP3*, *MMP9*, *NFKB1*, *PTGS2*, *TGFB1*, *TNF*, *VEGFA*
Complement cascade	*CFH*, *CRP*, *F2*
Fc γ R-mediated phagocytosis	PLCG2
Phagosome	*MPO*, *OLR1*, *TLR4*
Cell surface interactions at the vascular wall	*F2*, *OLR1*, *TGFB1*
Leukocyte transendothelial migration	*MMP9*, *PLCG2*
Interleukin (IL)-4 and IL-13 signaling pathways	*CCL2*, *HMOX1*, *IL10*, *IL18*, *IL1A*, *IL1B*, *IL6*, *IL6R*, *MMP3*, *MMP9*, *PTGS2*, *TGFB1*, *TNF*, *VEGFA*
IL-17 signaling pathway	*CCL2*, *IL1B*, *IL6*, *MMP3*, *MMP9*, *NFKB1*, *PTGS2*, *TNF*
PI3K-Akt signaling pathway	*BDNF*, *IL6*, *IL6R*, *IRS1*, *NFKB1*, *NOS3*, *TLR4*, *VEGFA*
Fc ε RI-mediated signaling pathway	*PLCG2*
C-type lectin receptor signaling pathway	*IL10*, *IL1B*, *IL6*, *NFKB1*, *PLCG2*, *PTGS2*, *TNF*
Toll-like receptor signaling pathway	*IL1B*, *IL6*, *NFKB1*, *TLR4*, *TNF*
Clathrin-mediated endocytosis	*IGF2R*, *LDLR*
3. Signaling pathways responsible for fatty acid metabolism	
Plasma lipoprotein assembly	*ABCA1*, *APOA1*, *APOE*
Plasma lipoprotein remodeling	*ALB*, *APOA1*, *APOE*, *CETP*, *LPL*

Table (continued)

Biological pathways	Genes that are common to diseases and are included in the signaling pathway
Plasma lipoprotein assembly, remodeling, and clearance	*ABCA1*, *ALB*, *APOA1*, *APOE*, *CETP*, *LDLR*, *LPL*, *NPC1*
Cholesterol metabolism	*ABCA1*, *APOA1*, *APOE*, *CETP*, *LDLR*, *LPA*, *LPL*, *LRP1*, *NPC1*, *SORT1*
Ether lipid metabolism	*PLA2G1B*, *PLA2G2A*
Fat digestion and absorption	*ABCA1*, *APOA1*, *PLA2G1B*, *PLA2G2A*
Bile secretion	*ABCB1*, *HMGCR*, *LDLR*
Sphingolipid signaling pathway	*NFKB1*, *NOS3*, *TNF*
4. Signaling pathways involved in the functioning of the nervous system	
Signaling by NTRKs	*BDNF*, *IRS1*
Signaling by NTRK2 (TRKB)	*BDNF*
Neurotrophin signaling pathway	*BDNF*, *IRS1*, *NFKB1*, *PLCG2*, *SORT1*
Amyloid fibril formation	*APOA1*
Axon guidance	*MMP9*, *UNC5C*
Serotonergic synapse	*PTGS2*
Neurotransmitter clearance	*ALDH2*
Endocrine and other factor-regulated calcium reabsorption	*ESR1*, *VDR*
5. Signaling pathways involved in the functioning of the cardiovascular system	
VEGFA – VEGFR2 Pathway	*NOS3*, *VEGFA*
Signaling by VEGF	*NOS3*, *VEGFA*
Complement and coagulation cascades	*F2*, *PLG*, *SERPINE1*
Platelet activation, signaling, and aggregation	*ALB*, *APOA1*, *F2*, *PLCG2*, *PLG*, *SERPINE1*, *TGFB1*, *VEGFA*
Platelet activation	*F2*, *NOS3*, *PLCG2*
Signaling by PDGF	*PLG*
Fluid shear stress and atherosclerosis	*CCL2*, *HMOX1*, *IL1A*, *IL1B*, *MMP9*, *NFKB1*, *NOS3*, *TNF*, *VEGFA*
Platelet homeostasis	*NOS3*
Apelin signaling pathway	*NOS3*, *SERPINE1*
Aldosterone synthesis and secretion	*AGT*, *LDLR*
6. Signaling pathways involved in the functioning of the endocrine system	
Ovarian steroidogenesis	*LDLR*, *PTGS2*
Peptide hormone metabolism	*ACE*, *AGT*
Aldosterone-regulated sodium reabsorption	*IRS1*
7. Signaling pathways involved in processes in normal conditions and in pathology	
Signal transduction	*AGT*, *APOA1*, *APOE*, *BDNF*, *CCR5*, *ESR1*, *ESR2*, *F2*, *IL6*, *IL6R*, *IRS1*, *LDLR*, *LPL*, *LRP1*, *MMP3*, *MMP9*, *NFKB1*, *NOS3*, *NR3C1*, *PLCG2*, *PLG*, *PPARG*, *SERPINE1*, *TGFB1*, *TNF*, *VEGFA*
Cellular responses to stress	*IL1A*, *IL6*, *NFKB1*, *NR3C1*, *VEGFA*
Signaling by receptor tyrosine kinases	*BDNF*, *ESR1*, *IRS1*, *MMP9*, *NOS3*, *PLG*, *VEGFA*
FOXO-mediated transcription	*NR3C1*
FoxO signaling pathway	*IL10*, *IL6*, *IRS1*, *TGFB1*
MAPK signaling pathway	*BDNF*, *IL1A*, *IL1B*, *NFKB1*, *TGFB1*, *TNF*, *VEGFA*
Phospholipase D signaling pathway	*AGT*, *F2*, *PLCG2*
TGF-β signaling pathway	*TGFB1*, *TNF*
HIF-1 signaling pathway	*HMOX1*, *IL6*, *IL6R*, *NFKB1*, *NOS3*, *PLCG2*, *SERPINE1*, *TLR4*, *VEGFA*
Biological oxidation	*ALDH2*, *HPGDS*
Extracellular matrix organization	*MMP3*, *MMP9*, *PLG*, *SERPINE1*, *TGFB1*
Degradation of the extracellular matrix	*MMP3*, *MMP9*, *PLG*
Focal adhesion	*VEGFA*

Table (continued)

Biological pathways	Genes that are common to diseases and are included in the signaling pathway
Regulation of insulin-like growth factor (IGF) transport and uptake by insulin-like growth factor binding proteins (IGFBPs)	*ALB*, *APOA1*, *APOE*, *F2*, *IL6*, *PLG*
RAS signaling pathway	*BDNF*, *NFKB1*, *PLA2G1B*, *PLA2G2A*, *PLCG2*, *VEGFA*
G-α(i) signaling events	*AGT*, *APOA1*, *APOE*, *LDLR*, *LPL*, *LRP1*
Circadian clock	*NR3C1*, *SERPINE1*
ABC transporters	*ABCA1*, *ABCB1*
SUMOylation of intracellular receptors	*ESR1*, *NR3C1*, *PPARG*, *VDR*
G-α (q) signaling events	*AGT*, *F2*, *MMP3*
Glycolysis / gluconeogenesis	*ALDH2*

CELL DEATH SIGNALING PATHWAYS

These pathways include genes associated with AD and CHD. The TNF signaling pathway [KEGG:04668] initiates apoptotic or necroptotic pathway implementation. Namely, TNFR1 signaling pathway triggers the NF-κB signaling pathway, as well as apoptosis and necroptosis [17]. In addition, apoptosis can be triggered following the implementation of the p53 signaling pathway [18]. The necroptosis signaling pathway [KEGG:04217] is involved in the pathogenesis of many diseases, including neurological diseases, ischemic injury, and viral infections [19].

Changes in the regulation and activation of these pathways are of great importance for the development of both CHD and AD. However, the role of apoptosis in AD is ambiguous. Some researchers report that AD activates caspases, in particular caspase-6, which initiates apoptosis in the brain [20]. Other researchers argue that the theory of apoptotic cell death in AD and the clinical presentation of the disease are incompatible, since cells that are to undergo apoptosis die within a few days, maintaining a high level of caspase-3, which should lead to acute and massive neuronal loss. In this case, clinical symptoms of AD should be identified at an early stage of the disease, and not decades after its onset [21]. It is also known that apoptosis is a key component in the CHD pathogenesis [22].

SIGNALING PATHWAYS REGULATING IMMUNE RESPONSES

The signaling pathway of the hematopoietic cell lineage [KEGG:04640] reflects the transition of blood cells from hematopoietic stem cells to mature blood cells, including immune cells. It is known that an increase in the total number of leukocytes and in each of their subtypes separately makes it possible to predict the development of CHD. In addition, almost all cellular elements of blood, including leukocytes, erythrocytes, and platelets, are involved in the pathogenesis of atherosclerosis [23]. It is also known that platelets are involved in the development of the amyloid precursor protein, and their functional similarity with neurons makes it possible to use platelets as a model for AD studies [24].

Signaling by interleukins (ILs) [R-HSA:449147] is associated with their pleiotropic effect on cells (which affects tissue growth and repair, hematopoietic stem cell homeostasis, as well as multiple lines of body defense against pathogens) [25]. For example, IL-1β is the main mediator in the implementation of the acute phase response at the level of the entire body, as well as in the development of a local inflammatory response [26]. It is known that impaired coronary circulation with myocardial ischemia increases its concentration in the blood [27]. What is more, an increased level of this interleukin is observed in AD, which is associated with inflammation during the disease progression [28].

IL-4 and IL-13 signaling [R-HSA:6785807] in the central nervous system is associated with the neuroprotective effect of IL-4 and IL-13, which suppress the production of inflammatory mediators. It was confirmed by the results of the experiment with an animal AD model [29].

IL-17 signaling pathway [KEGG:04657] includes a family of cytokines consisting of IL-17A-F and plays an important role in acute and chronic inflammatory responses [30]. The IL-17 family cytokines transmit signals through their respective

receptors and activate downstream pathways, which include NF-κB, MAPK, and C/EBP, inducing the expression of antimicrobial peptides, cytokines, and chemokines [31].

Phagocytosis is an important process in the implementation of the protective function of the body against infectious pathogens. The Fc γ R-mediated phagocytosis pathway [KEGG:04666] implements this function via γ receptors on Fc cells, opsonized by antibodies that recognize foreign substances. Cross-linking of Fc-γ receptors initiates a series of signals mediated by tyrosine phosphorylation of several proteins, which, in turn, lead to the formation of phagosomes following cytoskeletal actin rearrangement and membrane remodeling [32]. The phagosome signaling pathway [KEGG:04145] is triggered when specific receptors on the surface of phagocytes recognize ligands on the surface of foreign particles. The acquisition of lysosomal proteases by phagosomes during maturation and the release of reactive oxygen species are important for the breakdown of foreign substances contained in them [33].

The Fc ε-RI signaling pathway [KEGG:04664] in mast cells identified by the bioinformatic analysis is initiated by antigen interaction with IgE bound to the extracellular domain of the Rc ε-RI α-chain. Mast cells activate the release of preformed granules containing biogenic amines and proteoglycans. Activation of phospholipase A2 causes the release of membrane lipids with subsequent development of lipid mediators, such as leukotrienes, namely LTC4, LTD4, LTE4, and prostaglandins, in particular PDG2. Cytokines are secreted; the most important cytokines are TNF-α, IL-4, and IL-5 [34, 35].

The C-type lectin receptor signaling pathway [KEGG:04625] is responsible for the functioning of CLRs as pattern recognition receptors (PRRs) for pathogen-derived ligands in dendritic cells, macrophages, neutrophils, etc. After ligand binding, CLRs stimulate intracellular signaling cascades, which induce the production of inflammatory cytokines and chemokines, and therefore trigger innate and adaptive immunity to pathogens [36].

The involvement of common susceptibility genes for the studied diseases in the above biological pathways can affect:

the production of cytokines and chemokines involved in inflammation in nervous and cardiovascular systems. Microglia have been shown to play the key role in the activation of inflammation. The amount of microglia increases in people with AD and in the experimental model of AD in transgenic mice [37]. *In vitro* studies showed that cytokines secreted by microglial cells, in particular IL-1β, IL-6, TNF-α, and INF-γ, and chemokines can increase the immune response [37]. It is also known that many cytokines, for example, IL-12, IL-23, IL-6, and IL-1β, are involved both in neurodegeneration and in neuroinflammation mediated by leukocyte invasion of the brain [38]. In CHD, an increase in the levels of IL-6 and C-reactive protein indicates an increase in the damage to coronary arteries [39, 40];

a change in the immune response when exposed to pathogens. In the experimental model of AD in mice, it was found that the administration of microbial mimics, apart from inducing a strong systemic inflammatory response, enhances neurodegeneration [41]. In CHD, various pathogenic microorganisms can reside in the atherosclerotic plaque and support the local inflammatory response [42]. However, regardless of the pathogens found in the plaque, systemic inflammation develops due to the release of cytokines. For example, periodontal pathogens, such as P. gingivalis and Actinomycetemcomitans, promote Th17 responses in both the spleen and atherosclerotic plaques, which, in turn, increases the release of a variety of powerful cytokines, such as IL-1β, IL-6, and IL-17 [42].

SIGNALING PATHWAYS RESPONSIBLE FOR FATTY ACID METABOLISM

The identified common susceptibility genes for the studied diseases are also involved in plasma lipoprotein assembly [R-HSA:8963898] and plasma lipoprotein remodeling [R-HSA:8963899]. Very-low-density lipoproteins (VLDL) are produced in the liver and transport triacylglycerol synthesized there to other tissues in the body. High-density lipoproteins (HDL) are generated mainly in the liver and transport several types of lipids between tissues and other lipoproteins [43]. Plasma lipoprotein remodeling is a sequence of events that begins with circulating chylomicrons acquiring apolipoprotein C and E molecules; interacting with endothelial lipases, they often lose most of their triacylglycerol. Under the effect of the described changes, they

become chylomicron remnants, which bind to LDL receptors, primarily on the surface of liver cells. As chylomicrons circulate, VLDLs are exposed to lipoprotein lipases located on the endothelium of blood vessels and secreting fatty acids and glycerol. Then they are absorbed by tissues, and VLDLs are converted first into intermediate-density lipoproteins (IDL) and then into low-density lipoproteins (LDL) [44]. HDL remodeling includes conversion of HDL-bound cholesterol to cholesterol esters (spherical HDL remodeling), transfer of HDL into target cells with regeneration of pre-βHDL, and conversion of pre-β HDL to discoidal HDL [45].

Impaired functioning of the identified biological pathway of cholesterol metabolism [KEGG:04979] can lead to an increased risk of various endocrine disorders and cardiovascular diseases [46]. Common susceptibility genes for CHD and AD *PLA2G1B, PLA2G2A* are involved in the implementation of ester metabolism [KEGG:00565].

The identified pathways of fat digestion and absorption [KEGG:04975] and bile secretion [KEGG:04976] are pathways that are involved in lowering cholesterol levels. The sphingolipid signaling pathway [KEGG:04071] reflects the role of sphingomyelin and its metabolic products as second messengers in various metabolic processes.

Thus, a change in lipid metabolism with the participation of these signaling and metabolic pathways can violate the state of the vascular wall, lead to infiltration of arterial walls with atherogenic lipoproteins, formation of sclerotic plaques and stenosis, and formation of blood clots, and be a key component in the pathogenesis of CHD [47].

In the brain in AD, impaired lipid metabolism, namely, an increase in cholesterol levels, promotes the integration of β-amyloid into the cell membrane, which ultimately increases the level of cytosolic calcium in astrocytes and leads to neuronal death [48]. A high level of plasma cholesterol under certain conditions can destroy the blood – brain barrier, which allows systemic macrophages to penetrate into the brain parenchyma and initiate neuroinflammation [49]. A high level of LDPs enhances BACE-1 activity, affects the amyloid precursor protein, and impairs synaptic activity [49]. Besides, apolipoprotein E, which acts as a cholesterol transporter, can bind to cell surface receptors and allow for the production of cholesterol oxidation products [50]. Disturbances in sphingolipid metabolism, in particular, its hydrolysis, can lead to the formation of ceramide, which causes apoptosis of brain cells in AD [51].

SIGNALING PATHWAYS INVOLVED IN THE FUNCTIONING OF THE NERVOUS SYSTEM

The susceptibility genes for CHD and AD are involved in signaling via NTRK2 (TRKB) [RHSA:9006115] and in the neurotrophin signaling pathway [KEGG:04722], where signaling via NTRK2 (TRKB) [RHSA:9006115] is a component of the identified NTRK pathway [R-HSA:166520]. NTRK signaling pathway transduces signal from neurotrophins (NGF, BDNF, NTF3, and NTF4) via NTRK tyrosine kinase receptors, which have a preferred neurotrophin ligand, and via the p75NTR death receptor, which interacts with all neurotrophins [52].

The identified biological pathway for amyloid fibril formation [R-HSA:977225] was originally described as a nucleation-dependent polymerization mechanism [53], but now it is thought to be more complex, with multiple events outside the pathway leading to the formation of multiple oligomeric structures, in addition to fibrils [54].

Thus, the signaling pathways considered in this block affect the formation of amyloid fibrils and signal transmission via neurotrophins, which can mediate changes in the nervous system in AD and in the cardiovascular system in CHD.

In AD, the amyloid fibril formation pathway is responsible for the formation of β-amyloid (Aβ), which underlies the amyloid cascade hypothesis in AD. It suggests that $A\beta_{42}$ fragments accumulate in the brain with age [55]. Neurotrophic factors modulate synaptic plasticity and are involved in memory formation; their reduced levels, for example, BDNF, can contribute to the degeneration and progressive atrophy of neurons in the brain affected by AD [56].

In patients with AD, the level of $A\beta_{42}$ is increased and the accumulation of this protein in the myocardium is also observed [57, 58]. Circulating $A\beta_{40}$ aggravates atherosclerosis and predicts disease progression and cardiovascular mortality in patients with diagnosed CHD [58].

SIGNALING PATHWAYS INVOLVED IN THE FUNCTIONING OF THE CARDIOVASCULAR SYSTEM

The biological pathway VEGFA – VEGFR2 [R-HSA:4420097] is an integral part of VEGF signaling [R-HSA:194138] and is related to angiogenesis. VEGFA signaling via VEGFR2 is the main pathway that activates angiogenesis through induction of proliferation, survival, sprouting, and migration of endothelial cells, as well as by increasing endothelial permeability [59]. Dysfunction of VEGF is associated with inflammatory diseases, including atherosclerosis [60, 61].

The identified biological pathway of complement and coagulation cascades [KEGG:04610] combines the complement system and blood coagulation. The main consequences of complement activation are opsonization of pathogens, recruitment of inflammatory and immunocompetent cells, and direct destruction of pathogens [62].

The biological pathways of platelet activation, signaling, and aggregation [R-HSA:76002] and platelet activation [KEGG:04611] are analogs and are implemented using common susceptibility genes for CHD and AD. Activation of integrin αIIbβ3 (glycoprotein IIb / IIIa), the most common platelet receptor, enhances adhesion and leads to platelet interaction and aggregation [63].

Susceptibility genes for the studied diseases are involved in PDGF signaling [R-HSA:186797]. Platelet-derived growth factor (PDGF) is a potent stimulator of growth and motility of connective tissue cells (fibroblasts, smooth muscle cells), capillary endothelial cells, and neurons. PDGF binds and activates α and β protein tyrosine kinase (PTK) receptors, which, in turn, dimerize and undergo autophosphorylation. Phosphorylation sites then recruit downstream effectors for signal transduction into the cell [64].

The biological pathway of platelet hemostasis [R-HSA:418346] is regulated by susceptibility genes for CHD and AD. Under normal conditions, vascular endothelium supports vasodilation, inhibits platelet adhesion and activation, inhibits coagulation, enhances fibrin breakdown, and is anti-inflammatory in nature. In acute vascular injury, vasoconstrictor mechanisms predominate, and the endothelium becomes prothrombotic, procoagulant, and proinflammatory. This is achieved by reducing endothelial dilating agents (adenosine, NO, and prostacyclin), as well as through the direct effect of ADP, serotonin, and thromboxane on vascular smooth muscle cells, which causes their contraction. Under normal conditions, laminar flow induces COX-2 expression and prostacyclin (PGI2) synthesis, which, in turn, stimulates endothelial nitric oxide synthase (eNOS) activity. PGI2 and NO counteract platelet activation and aggregation, as does CD39 ecto-ADPase, which reduces platelet activation and recruitment by metabolizing platelet-released ADP [65].

Thus, susceptibility genes common for AD and CHD are involved in signal transduction, which affects angiogenesis, blood coagulation, and production of inflammatory cytokines. Impairment of these processes plays an essential role in the development of CHD and AD.

Elevated levels of VEGF, a hypoxia-induced vascular endothelial growth factor, have been found in blood vessel walls, perivascular deposits, astrocytes, and the intrathecal space of patients with AD and are consistent with chronic cerebral hypoperfusion and hypoxia that have been observed in these individuals [66]. Also, in addition to VEGF, cerebral vessels in AD release molecules that can affect angiogenesis, including IL-1β, IL-6, IL-8, TNF, TGFβ, MCP1, thrombin, angiopoietin 2, integrins αVβ3 and αVβ5, and HIF1α [66].

SIGNALING PATHWAYS INVOLVED IN THE FUNCTIONING OF THE ENDOCRINE SYSTEM

Peptide hormone metabolism [R-HSA:2980736] includes modification of peptide hormones after secretion and their degradation by extracellular proteases. For example, insulin metabolism proceeds in 4 stages: formation of intramolecular disulfide bonds, formation of proinsulin – zinc – calcium complexes, proteolytic cleavage of proinsulin by PCSK1 (PC1/3) and PCSK2 to form insulin, and translocation of granules through the cytosol to the plasma membrane. During the metabolism of angiotensinogen to angiotensin, renin cleaves angiotensinogen to form angiotensin I. The two C-terminal amino acid residues of angiotensin I are then removed by an angiotensin-converting enzyme (ACE) located on the surface of endothelial cells to form angiotensin II – an active peptide that causes

vasoconstriction, sodium and chloride resorption, potassium excretion, water retention, and aldosterone secretion. [67].

The biological pathway of aldosterone-regulated sodium reabsorption [KEGG:04960] reflects the role of aldosterone in sodium and potassium metabolism by binding to epithelial mineralocorticoid receptors in renal collecting duct cells located in the distal nephron, promoting sodium reabsorption and potassium excretion [68].

The pathway enrichment analysis also identified pathways that are ubiquitous under normal conditions; changes in the regulation of these pathways are observed in a large number of different diseases. This group included the following pathways: signal transduction [R-HSA:162582], cellular responses to stress [R-HSA:2262752], signaling by receptor tyrosine kinases [R-HSA:9006934], MAPK signaling pathway [KEGG:04010], FoxO signaling pathway [KEGG:04068] and FOXO-mediated transcription [R-HSA:9614085], phospholipase D signaling pathway [KEGG:04072], TGF-β signaling pathway [KEGG:04350], HIF-1 signaling pathway [KEGG:04066], biological oxidations [R-HSA:211859], extracellular matrix organization [R-HSA:1474244], degradation of the extracellular matrix [R-HSA:1474228], focal adhesion [KEGG:04510], regulation of insulin-like growth factor (IGF) transport and uptake by insulin-like growth factor binding proteins (IGFBPs) [R-HSA:381426], RAS signaling pathway [KEGG:04014].

The role of the *ApoE4* gene in the development of the diseases under study should be described separately. A study investigating the association between postmortem neuropathology of AD and CHD revealed a significant association in carriers of the ApoE4 allele [69]. Apolipoprotein E (ApoE), which is involved in AD susceptibility, regulates lipid transport and metabolism [44]. Also, in 2018, an article was published by W. Chen et al., who considered the *ApoE4* gene as a target for the treatment of CHD and AD. It was shown that mutation in the apolipoprotein E gene leads to impaired cholesterol metabolism, which can result in the development of CHD and AD; mutation in the *ABCA1* gene leads to the same result [6].

The obtained results are consistent with those in a study that investigated gene variants promoting inflammation and cholesterol metabolism due to acute myocardial infarction and AD. As a result, it was found that acute myocardial infarction and AD have common genetic prerequisites associated with cholesterol metabolism and upregulation of inflammation [70].

Thus, the study of signaling and metabolic pathways demonstrated that the genes contributing to AD and CHD are involved in processes associated with cell death, maintenance of inflammation, and fatty acid metabolism, as well as with the functioning of the nervous, cardiovascular, and endocrine systems.

CONCLUSION

As a result of the study, 69 biological pathways common for AD and CHD were identified. Among them, pathways involved in cell death; associated with the innate immunity; responsible for fatty acid metabolism; as well as for signal transduction processes that affect the functioning of the nervous, cardiovascular, and endocrine systems, can play an important role in changing intra- and intercellular interactions in cellular homeostasis. The obtained results suggest the presence of a number of mechanisms of influence in genetic factors of AD and CHD that affect the development of these diseases.

Based on the involvement of signaling pathways in the processes described above, it can be assumed that susceptibility genes involved in the implementation of these pathways regulate the following processes:

– apoptosis of both neurons and cardiomyocytes;

– production of inflammatory cytokines and chemokines, and, as a result, maintenance of inflammation;

– lipid metabolism, which, when changed, can form sclerotic plaques on the blood vessel walls and lead to the development of CHD; under certain conditions, neuroinflammation in the brain can occur;

– formation of β-amyloid, both in the brain and in the myocardium;

– angiogenesis, in particular, the level of VEGF in the walls of blood vessels increases in AD.

The results of this study provide a deeper understanding of the molecular genetic mechanisms of the combined development of the studied diseases

and their proper treatment. The results of this study are prerequisites for further study of these pathologies.

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Authors information

Chasovskikh Nataliya Yu. – Dr. Sci. (Med.), Professor, Acting Head of the Medical and Biological Cybernetics Division, Siberian State Medical University, Tomsk, nch03@mail.ru, https://orcid.org/0000-0001-6077-0347

Chizhik Evgenia E. – Teaching Assistant, Medical and Biological Cybernetics Division, Siberian State Medical University, Tomsk, evgenika06@gmail.com

(✉) **Chizhik Evgenia E.,** evgenika06@gmail.com

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