Original Article

Drug Repurposing for Age-Related Macular Degeneration (AMD) Based on Gene Co-Expression Network Analysis

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Abstract

Background: Age-related macular degeneration (AMD) is a lesser-known eye disease in the world that gradually destroys a person's vision by creating dark spots in the center of vision.

Material and Methods: Samples of AMD-related genes were extracted from the NCBI, then the gene expression network (GCN) was extracted. In addition, pathway enrichment analysis was performed to investigate the role of co-expressed genes in AMD. Finally, the drug-gene interaction network was plotted.

Results: The results of this work based on bioinformatics showed that many genes are involved in AMD disease, the most important of which are the genes of TYROBP, LILRB2, LCP2, PTPRC, CFH, SPARC, HTR5A.

Overexpression of these genes can be considered as basic biomarkers for this disease, we separated some of which we had from the gene co-expression network and some from the results of genes ontology (genes that have a P value ≤ 0.05). The most important drugs were isolated from the drug-gene network based on degree, which included 5 drugs including ocriplasmin, collagenase clostridium histolyticum, topiramate, primidone, butalbital.

Conclusion: Among the genes we found, three genes of CFH, TYROBP, SPARC seem to be more important than the others. Among drugs, ocriplasmin, topiramate, primidone can play a more important role based on the degree in the drug-gene network, because all steps are performed with different bioinformatics methods, clinical trials must confirm or reject the results.

Keywords: Age-Related Macular Degeneration; AMD; Co-Expression Network; Drug Repurposing.

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Introduction

Age- related macular degeneration (AMD or ARMD) is a persistent progressive disease of the central retina and one of the main causes of vision loss around the world. Most vision loss in the late stages of the disease occurs due to one of two processes: "wet type " macular degeneration which is associated with increasing age and leakage of blood vessels below the retina and the "dry type," in which parts of the macula become thinner with age, and small masses of a protein called drusen grow, and over time, central vision weakens and disappears [1]. The dry type is more common and about 90 % of patients get this type. The wet type is usually associated with more severe vision loss [2]. Macular degeneration is more common in people over 65 and women are more likely to get the disease. Most cases of this disease occur with age or can be a complication of some drugs. Heredity also appears to play a role in the disease. In age-related macular degeneration, the choroid blood vessels penetrate the retina, leaking blood and fats into this area, leading to fibrous ulcers. In geographical atrophy, progressive atrophy of the retinal pigment epithelium, the choriocapillary region (plate created by the choroid), and light receptors are involved, which are the final stages of AMD [3, 4]. The greatest loss of vision due to macular degeneration is due to aging due to these advanced forms of the disease.

Symptoms: Macular degeneration can cause gradual or sudden loss of vision. Seeing straight lines as wavy, blurred vision, or seeing dark spots in the center of vision can in many cases be the first signs of macular degeneration. Sometimes in the early stages patient may have no symptoms [1, 5, 6]. The ophthalmologist diagnoses the early signs of the disease on examination, this is usually done through a visual field test [1, 6].

Causes of the disease: The exact explanation for this disease isn't yet known. The dry type could also be caused by aging and thinning of the macular tissue, deposition of pigments within the macula, or a mixture of both. In the wet type, new blood vessels grow under the retina and blood and fluid leak from them. This leak causes the death of retinal cells and causes blind spots in the central vision [7]. Factors that increase the chances of getting the disease include: Family history, smoking, high blood pressure, hyperactivity and obesity. Many researchers and ophthalmologists believe that certain foods, such as zinc, lutein, xyxantine, and vitamins A, C, and E, help reduce the risk of disease or slow the progression of dry AMD. Fats may also play a role, a study published in the august 2001 issue of the Journal of Ophthalmology concluded that omega-3 fatty acids, which are abundant in fish, have a protective effect against macular degeneration [2, 8]. On the other hand, consuming omega-6 fatty acids found in vegetable oils increases the risk. Some cases of macular degeneration are a complication of toxic drugs such as chloroquine (an anti-malarial drug) or phenothiazines (a class of psychiatric drugs).

Treatment of macular degeneration: There is no definitive cure for this disease, but there are treatments to prevent the patient from progressing or even improving vision.

Vitamins and minerals: Research has shown that taking vitamins and antioxidants such as beta-carotene in the amount of 15 mg per day, taking vitamin A, vitamin C in 500 mg per day and taking vitamin E in the amount of 400 units may protect against destruction macular degeneration [9]. A recent study of 3,600 patients showed that taking vitamins C, E, beta-carotene, and zinc (80 mg daily) reduced the

risk of developing the disease in some patients by up to 28 %. It should be noted that smokers should not take beta-carotene pills because the risk of lung cancer in these people and those who have just quit smoking increases with beta-carotene [10].

Pharmacological treatment: A decade ago, age-related macular degeneration was largely incurable. However, new drugs based on suppression of vascular endothelial growth factor (VEGF) have fundamentally changed disease management.

Visudyne is the first drug to be used for the wet type. In this treatment, the drug is injected into the patient›s hand and then activated using a non-thermal laser. Activation of the drug causes a chemical reaction that destroys abnormal blood vessels. One in six patients treated sees better, which is twice as many as those who do not [10].

In 2006, clinical trials showed that monthly injections of ranibizumab (Lucentis, Genentech / Novartis) prevented vision loss in approximately 95 % of patients on a monthly basis and significantly improved vision in these patients by up to 40 %.

Another drug, bevacizumab (Avastin, Genetek), elaborated for the systemic treatment of colorectal cancer and related to the main molecule ranibizumab, is now highly used as an alternative further. Bevacizumab at aglance is very popular because it seems to have the same effect as ranibizumab but is much cheaper [11].

In 2011, an important trial showed that bevacizumab and ranibizumab were equally effective over a 1-year period. Moreover to treatment, significant advances have been made in understanding the epidemiology, risk factors, and genetics of age-related macular degeneration [10].

Laser treatment: Laser photocoagulation improves patients with wet type by destroying and isolating new blood vessels and preventing blood and fluid leakage. In this method, the laser site remains like a wound on the retina and causes blind spots in the patient's vision. Researchers are exploring ways to reduce wounds as well as treat the dry form of the disease with laser [4, 12].

Blood Filtration: In this method, which was invented by the Japanese about 2 decades ago, different blood flow in the membrane reduces the amount of some proteins and fatty acids that are high in amount and may be harmful. This technique has been utilized in a spread of diseases, but a replacement type called Rheopheresis has been tested to treat dry AMD. Rheopherhresis has not yet been approved by the US Food and Drug Administration (FDA) but is commercially available in Canada and Europe [13].

Implantable Telescope: This is a small telescopic device that magnifies the image and projects it on the retina. Enlarging the image reduces the proportion of the damaged part of the macula to the size of the image, resulting in smaller spots in the central view. The Implantable Miniature Telescope was invented in the late 1990s and is currently being tested on 200 patients. Although there have been many advances in AMD treatment recently, lost vision is irreversible. For patients who have lost their sight, there are devices that help improve vision by using magnifying lenses and high light. Some of these devices transmit the image to the more peripheral parts of the retina and outside the macula [14].

Innovation in systems biology has brought us a variety of computational tools and analytical means [15-17]. This approach successfully helps researchers to investigate molecular mechanisms of inhibition and activation of the genes and transcription factors, predict drug-

target interactions, and detect novel molecular biomarkers of phenotypes. Proposing of the novel panels for early detection of diseases, drug discovery, finding macromolecules interaction in the cells, are attractive subjects in systems biology studies [18-22].

The aim of this article is to identify important genes in AMD disease by drawing a gene co-expression network. In this project, finally 5 new drugs were proposed to treat of this disease.

Material and Methods

Dataset and analyses

Patient gene Sample collection

In the first level of this study, AMD-related genes samples were extracted from NCBI[1] (GEO2R section of this site is used to compare two or more sample groups to identify genes that have been expressed under different experimental conditions, the results of which are tabulated genes based on importance) [23] , with access code GSE29801[24] ,in this level AMD-related genes collected from patients includes all types of AMD (dry or wet AMD) in men and women samples compared with healthy specimens.

Gene co-expression network

In this stage of study disease genes were taken to STRING database[2] to draw gene co-expression network (GCN) [25-27]. For more reasonable results, among the genes associated with AMD disease, only genes with P value ≤ 0.01 were selected, bringing the total to 2,000 genes. Since at the cellular level, different functions are regulated based on how groups of proteins are placed together, this regenerated network was plotted by cytoscape software [28], large network of gene co-expression was shown (figure1), that important networks had to be separated from the main network. To get the most important protein networks, subnetworks were extracted that included 5 independent gene co-expression subnetworks from the main network (Figure 2).

Gene Ontology and Reactome Pathway Enrichment Analysis

To analyze biological pathways and prove the role of genes found in AMD disease, David Database [29] was used. the pathways with P value < 0.05 were selected as significant on the studied gene list.

We performed the ontology for each cluster by using this method, in this way, the genes of each cluster were prioritized for us, information about the biological processes (BP), cellular component (CC), molecular function (MF) of the genes of each cluster was sorted according to the P value (< 0.05) and FDR index. Most samples had an acceptable P value (close to zero or < 0.05). Complete information about the DAVID ontology and reactome pathway of all five clusters are available in the supplementary file S4.

Drug-gene interaction network

In order to study the drugs involved in AMD disease, we needed to draw an interaction network for drugs and themes target genes, as in the previous steps. To do this, drugs related to the five-cluster genes obtained from the Dgidb drug database [30] were collected and the large network between the drug and its target genes was drawn. To select the most important drugs by using the degree option, this time we drew drug-gene network for 5 of the most

1 https://www.ncbi.nlm.nih.gov/geo/geo2r/

2 https://string-db.org/

important drugs based on their degree.

Results

In this research study Samples were extracted from NCBI (GEO2R), with access code GSE29801[16], in this level AMD-related genes collected from 142 patients (includes all types of AMD in men and women samples) with 2,000 disease-interfering genes with P value ≤ 0.01. The total number of samples in this study was 293 of which 142 samples were patients between 10 and 90 years old (includes retinal and choroidal specimens of patient's with dry or wet AMD in both sexes of men and women in different ages) in return 151 healthy specimens. Complete information on the number of samples is available in the S1 supplementary file.

We extracted a list of disease-related genes that are most commonly expressed in the development of AMD disease for review in various bioinformatics databases. The laboratory samples by the Santa Barbara Center for the Study of Macular Degeneration have been located on this site with the consent of the people tested. Our project method is based on information obtained from biological databases and bioinformatics techniques.

Dataset and analyses

In this study, AMD-related genes collected from142 patients with 2,000 disease-

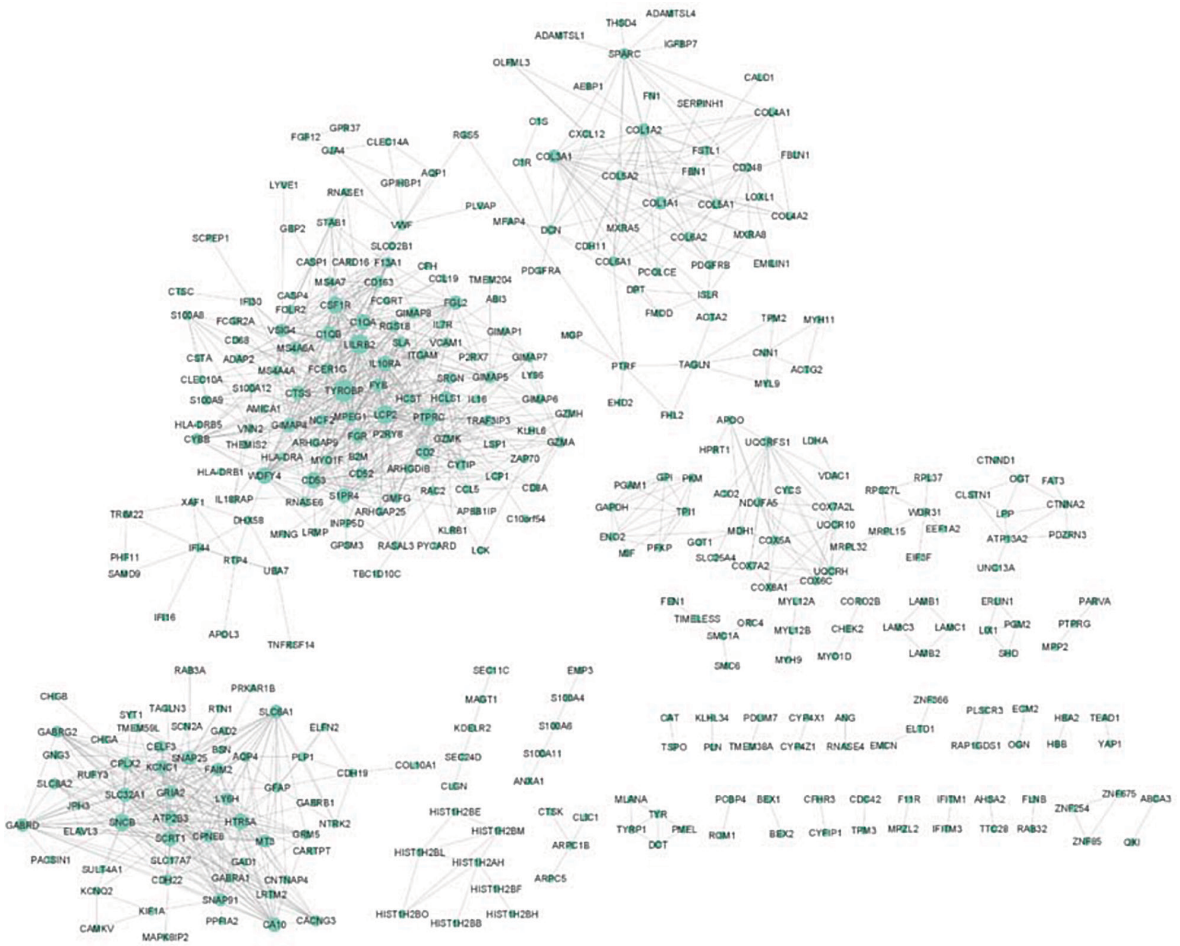

Figure 1: The main gene co-expression network drawn by cytoscape software. Blue rectangles are proteins (genes). Larger nodes mean more degrees in a bipartite network

interfering genes from GEO2R database were taken to a STRING database to draw gene co-expression network (GCN)., number of 2000 disease genes have been selected based on the definition of a string database, so that it is not possible to draw an expression network for more than 2000 genes in this database. For more reasonable results, among the genes associated with AMD disease, only genes with a P value ≤ 0.01 were selected, bringing the total to 2,000 genes. Since at the cellular level, different functions are regulated based on how groups of proteins are placed together, this regenerated network was plotted by cytoscape software, in this step large GCN network obtained (figure1). To get the most important protein networks, subnetworks were extracted that included 5 independent gene co-expression subnetworks from the main network by cluster viz plugin in cytoscape software (figure2).

Gene co-expression network is actually a set of genes that are involved in a particular disease or biological activity in the body. Because the development of genetic diseases is a complex process, study on one gene will not be effective and a group of genes involved in the disease should be examined in groups. That›s why we first drew the gene co-expression network. It was necessary to cluster a large network for careful examination. To cluster the large network, the Cluster viz plugin (whit FAG-EC algorithm) was used in Cytoscape software [31].

Genes related to all five subnetworks along with their degree, the amount of degree actually indicates the number of links between that gene and other co-expression genes, shown in the supplementary file S2.

The genes with the highest degree belonged to cluster 2 (TYROBP with53 degrees, LILRB2 with45 degrees, LCP2 with 41 degrees and PTPRC with 37degrees).

GO enrichment analysis

At this stage, to study biological pathways of 5 subnetworks have been obtained we used DAVID database[3] [29]. In this site, the biological pathways in which the genes of the subnetworks had the most role and function were reported based on the two indicators of P value (≤ 0.05) and FDR (≤ 0.05). According to P value and FDR, the three pathways immune system process (contains 73genes), signaling (contains 119genes) and biological adhesion (contains 49 genes) were the most important based on gene ontology. Results of ontology the genes of all 5 subnetworks are available in the supplementary file S5.

Drug-gene Interaction network

In this step, we took the genes of all five subnetworks (figure2), which contained 224 different genes (supplementary file S3) to the DGIdb [4]database (drug-gene interaction data base) [32], this database identifies the exact link between genes and the drugs that affect them. After collecting data related to drugs and genes, an interactive network was drawn between them in Cytoscape software. As in the previous steps, this network was very large and the most important drugs had to be extracted from the network, to limit the large network (figure3), degree option (higher degrees indicate that a particular drug targets more genes from the disease) was used in Cytoscape software. Based on the degree from the thousands of drugs, we selected five drugs with the highest degree in the drug-gene network for further study (figure4).

After drawing the drug-gene network for 224 genes in all five subnets by Cytoscape software, we have identified the 5 drugs with the highest

3 https://david.ncifcrf.gov/

4 https://www.dgidb.org/about

Table 1: Biological pathways for the three pathways with the highest P value and FDR

Biological processes	FDR	P Value	Genes
GO:0002376~immune system process	2.81E-12	2.56E-13	*ITGAM, NCF2, CLEC10A, LRMP, AQP4, IFI30, CTSS, PYCARD, IL18RAP, FCGRT, DHX58, TBC1D10C, RAC2, VSIG4, B2M, CTSC, TRIM22, FCER1G, CYBB, IL16, CARTPT, FGR, APBB1IP, ZAP70, TYROBP, CD8A, LCK, MFNG, HCLS1, LCP2, HPRT1, LCP1, S100A9, HCST, S100A8, C1QB, CSF1R, C1QA, CFH, C1S, KLRB1, C1R, LY96, RASAL3, CPLX2, FYB, IFI16, INPP5D, CCL5, S100A12, TNFRSF14, S1PR4, CHGA, VCAM1, GZMA, FN1, LILRB2, GZMH, CD2, P2RX7, COL1A1, COL3A1, PTPRC, FCGR2A, CXCL12, COL1A2, THEMIS2, KLHL6, CD248, FOLR2, XAF1, IL7R, FBN1*
GO:0023052~signaling	2.02E-08	3.68E-09	*SPARC, RAB3A, NCF2, CPNE6, SLA, FAIM2, IFI30, SLC8A2, PYCARD, IL18RAP, FCGRT, DHX58, ARHGDIB, TBC1D10C, BSN, B2M, TRIM22, PPFIA2, PDGFRB, PDGFRA, CYBB, CARTPT, MAPK8IP2, GABRG2, TYROBP, COL4A2, COL4A1, CD8A, MFNG, KCNQ2, S100A9, S100A8, GRIA2, CSF1R, KLRB1, LY96, FBLN1, CPLX2, RASAL3, INPP5D, S100A12, TNFRSF14, VCAM1, SYT1, GOT1, FN1, MT3, ARHGAP25, SNAP91, GFAP, COL1A1, PTPRC, CXCL12, COL1A2, CYCS, SCN2A, XAF1, IL7R, FBN1, ARHGAP9, SNAP25, GABRB1, ITGAM, LSP1, SLC6A1, CTSS, GRM5, JPH3, STAB1, RAC2, CTSC, SRGN, CD53, FCER1G, SLC32A1, DCN, FGR, APBB1IP, ZAP70, LCK, HCLS1, LCP2, LCP1, SLC25A4, HCST, CNTNAP4, RGS18, C1QA, FSTL1, FYB, P2RY8, GNG3, IFI16, TMEM204, CCL5, SLC17A7, SNCB, GABRD, CACNG3, S1PR4, APOL3, CHGA, NTRK2, GABRA1, IL10RA, GAD1, GAD2, ATP2B3, LILRB2, HTR5A, LYVE1, CD2, P2RX7, COL3A1, FCGR2A, THEMIS2, KLHL6, PLP1, FMOD*
GO:0022610~biological adhesion	1.02E-07	2.79E-08	*ITGAM, PYCARD, ISLR, ARHGDIB, STAB1, RAC2, EMILIN1, VSIG4, B2M, PPFIA2, PDGFRA, FCER1G, C10ORF54, APBB1IP, ZAP70, CD8A, LCK, COL6A2, COL6A1, CDH11, LCP1, S100A9, S100A8, CNTNAP4, CDH19, CSTA, DPT, FBLN1, RASAL3, CALD1, CCL5, CDH22, IGFBP7, TNFRSF14, VCAM1, FN1, LILRB2, LYVE1, CD2, P2RX7, COL1A1, MFAP4, COL3A1, PTPRC, CXCL12, THEMIS2, COL5A1, IL7R, FBN1*

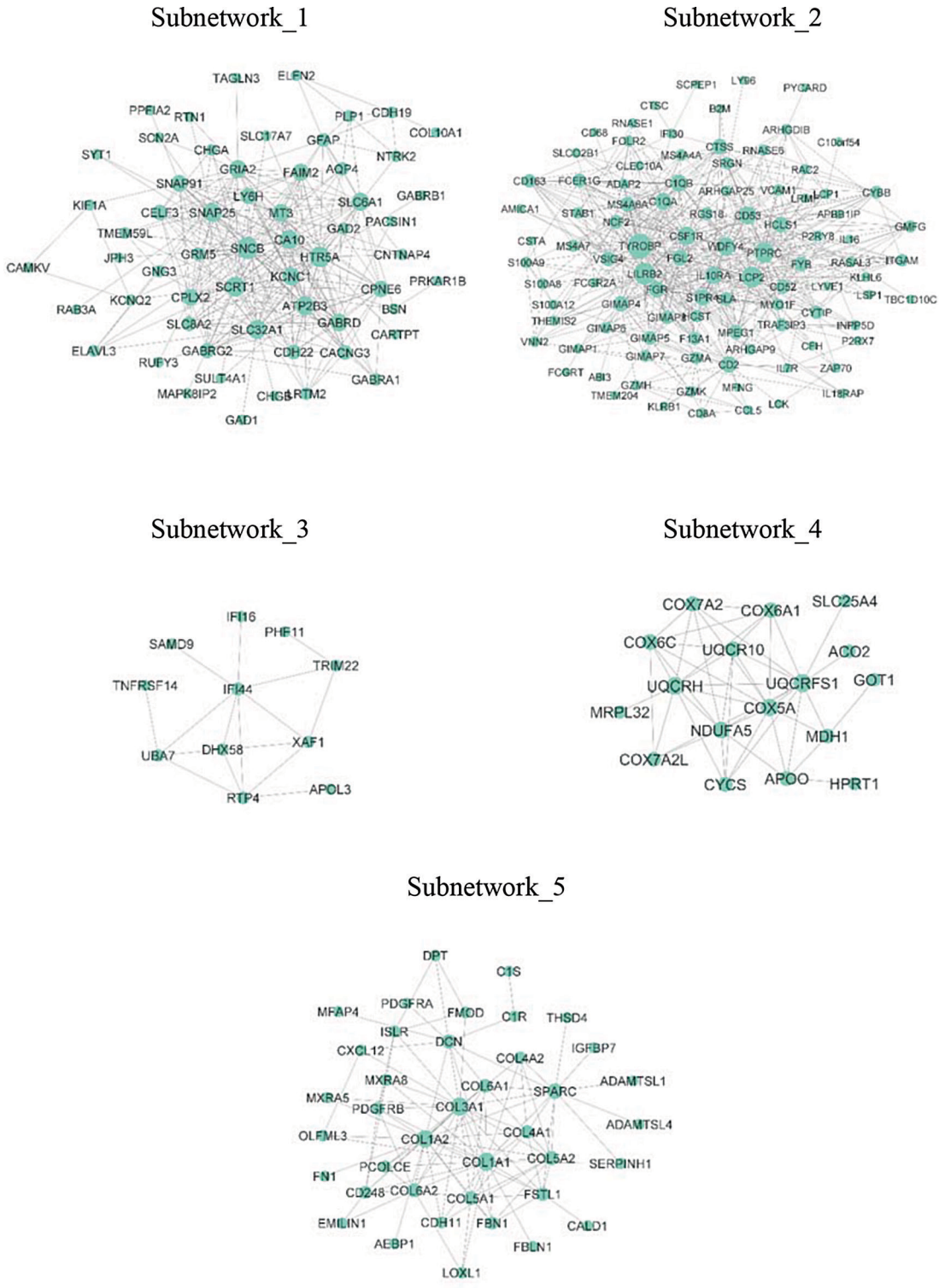

Figure 2: five subnetworks derived from the main gene co-expression network. Proteins (genes) in these networks are marked with blue rectangles. Blue rectangles are proteins (genes). Larger nodes mean more degrees in a bipartite network

degree in the network as candidate drugs for AMD eye disease (Whether the effect of these drugs is inhibitory or antagonists has been investigated in the discussion section).

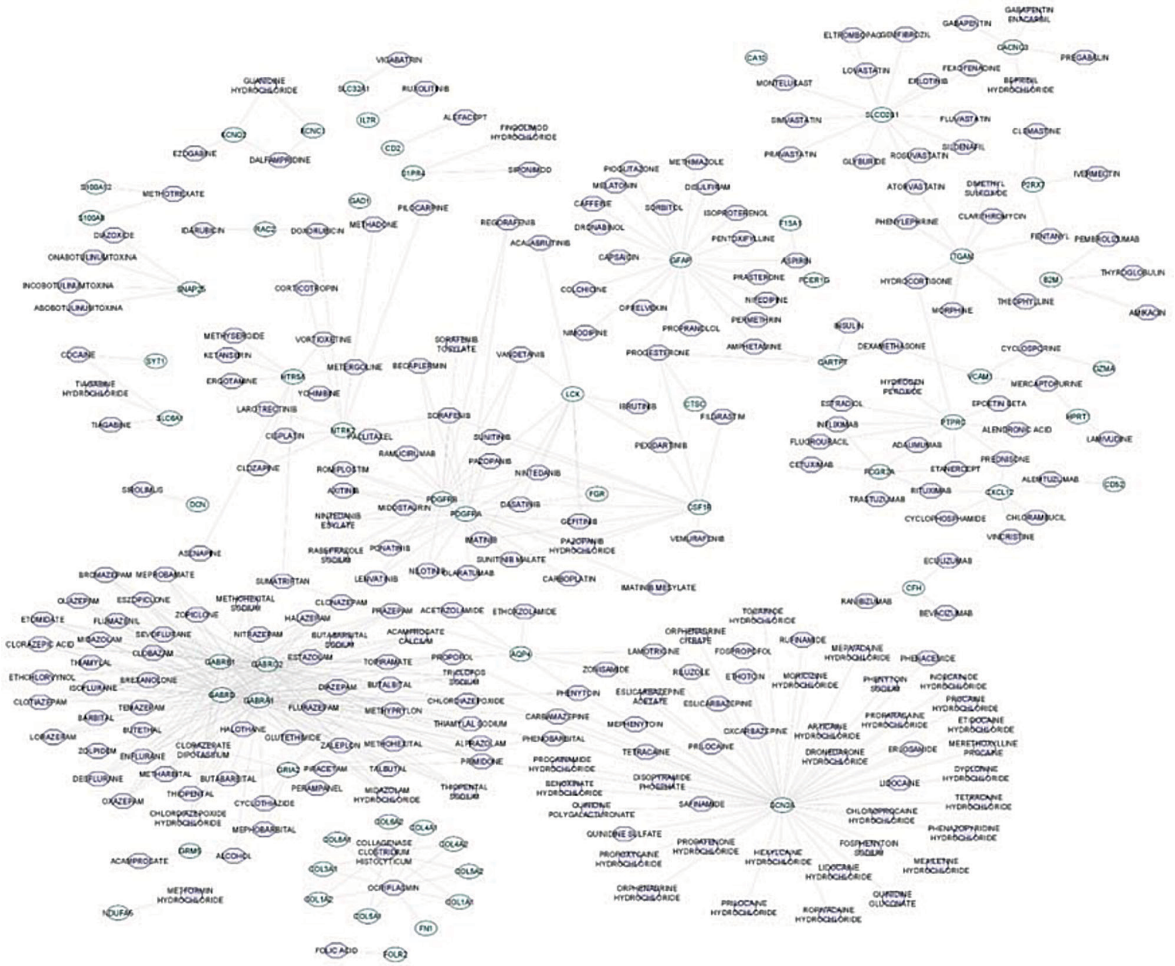

Figure 3: Large Drug-Gene Binary Network. Drugs in this network are marked with green octagons and genes are marked with blue rectangles

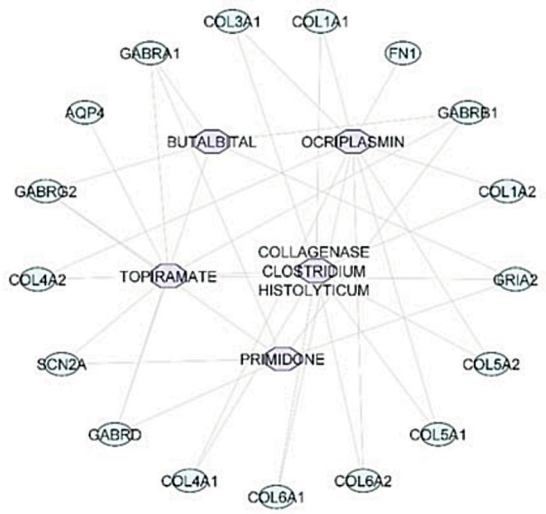

Figure 4: five drugs with the highest degree (importance) in the drug-gene network. Drugs are marked with green octagons and genes are marked with blue rectangles

Among the large number of drugs, five drugs include Ocriplasmin with degrees 10, collagenase clostridium histolyticum with degrees 9, topiramate with degrees 7, primidone with degrees 6, butalbital with degrees 5 are the most important drugs in this network.

Discussion

In this article, after collecting information about Age-related macular degeneration (AMD) disease genes from the string database, co-expression network was plotted for the proteins of this disease in cytoscape software. After drawing the gene expression

network, we sorted genes of this disease by degrees' indicator. In fact, the degree in this network tells us how much protein a gene in this disease is involved with, according to cell biochemistry, the more proteins or genes involved in a protein complex, the more likely it is that a particular protein or gene is involved in the disease. After that, we were able to introduce four key genes (TYROBP, LILRB2, LCP2 and PTPRC) in our network, use the gene ontology by the David Database to find more genes, and identified several genes and biological pathways. After the gene ontology, interactive network for drug-gene was also drawn by using the DGIdb drug database in cytoscape software, in this section, we also introduced 5 drugs (Ocriplasmin collagenase clostridium, histolyticum, topiramate, primidone, butalbital) with high degree in drug-gene network as new drugs for the treatment of AMD.

We examined the genes we identified as candidates for AMD eye disease (Age-related macular degeneration) one by one in order of importance. Among the genes of 5 different subnetworks, previously drawn for this disease (Figure 2), we studied the TYROBP, LILRB2, LCP2 and PTPRC genes for further investigation.

In our study, the TYROBP gene had the highest degree [53] in co-expression network, which in various studies has shown the role of this gene in AMD disease, especially its dry type [33].

In Mr. Waksmunski- 2020article, the role of the LCP2 gene in AMD is mentioned [34]. The role of PTPRC gene in two articles related to AMD eye disease, especially the role of this gene in eye inflammation is mentioned [35, 36]. Regarding LILRB2gene, although no information was found related to AMD disease, due to the high degree of this gene in the network, it is recommended that clinical studies be performed to prove its role in eye disease.

We found in previous studies that the CFH gene, which is also listed in our ontology results (table 1), is one of the most important genes involved in AMD disease. Findings indicate that an individual's response to AREDS supplements may be related to CFH genotype. This could have clinical relevance by predicting treatment outcome and potentially preventing unwanted side effects in those that might not benefit. Corroboration of these analyses is needed before considering modification of current management [37]. Given the putative roles of SPARC in cell-matrix interactions and cellular differentiation, reduction of the protein in RPEc with age may impinge upon common pathologies that involve the ageing chorioretinal interface like age-related degeneration [38, 39].

Another gene mentioned in ontology, which is also present in the table of genes of each cluster and their degree (supplementary file S5), is the SPARC gene, whose role in AMD is well defined. Regarding the HTR5A gene with degree 31on co-expression network, it has been suggested that specific HTRA1 alleles may predict the development of AMD [40].

Ocriplasmin treatment seems to be generally safe and well tolerated and fine resulted [41, 42]. Although collagenase clostridium histolyticum is most commonly used in the treatment of Dupuytren's contracture disease (a painless thickening and tightening of tissue [cord] beneath the skin within the palm of the hand, which can make it difficult to straighten one or more fingers), however, considering that this is the second most important drug out of the 5 drugs introduced by us, it is necessary to conduct clinical studies for the usability and effectiveness of this drug in the treatment or rejection of treat AMD.

Another drug in our study was topiramate,

which has a lot of information about the use of this drug in the treatment of AMD in various studies. Topiramate appeared to induce the growth of novel nerve fibers and relieve symptoms of peripheral neuropathy while also improving components of metabolic syndrome [43, 44]. The next drug is primidone which is mostly used in the treatment of seizures. Due to the rank of this drug, it is recommended to evaluate its use in the treatment of AMD in clinical studies. Last drug to be studied is butalbital, which has a pain reliever and relaxant role that is not unrelated to AMD in relieving ocular inflammation. However, its clinical role in the treatment of AMD should be investigated.

Conclusion

In this study, we nominated 5 drugs as the most important among the many drugs in the drug-gene network, most important of which was Ocriplasmin, which detailed research before us also confirmed the therapeutic ability of this drug in AMD.

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Footnotes and Financial Disclosures

Conflict of interest

The authors have no conflict of interest with the subject matter of the present manuscript.