DISCOVERY OF BIOLOGICAL PATHWAYS THAT HAVE A ROLE IN THE ETIOPATHOGENESIS OF MACULAR DEGENERATION BY GENETIC INVESTIGATIONS

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ABSTRACT

DISCOVERY OF BIOLOGICAL PATHWAYS THAT HAVE A ROLE IN THE ETIOPATHOGENESIS OF MACULAR DEGENERATION BY GENETIC INVESTIGATIONS

Macular Degeneration is a common, progressive, multifactorial, and complex eye disorder among people over 50 years old. The etiology of Macular Degeneration is still not known.

The main hypothesis of thesis is that chronic inflammation and oxidative stress are the major factors for the development of AMD. Firstly, the current Literature are reviewed to understand genetic, and nongenetic risk factors of AMD development, transcriptomic of Retina, and molecules that changing with aging. Age, smoking history, gender, race, cardiovascular disease, hypertension, diabetes, hyperlipidemia, kidney disease, and HIV infection status were chosen as non-genetic factors. Genetic factors included ARMS2, C2, C3, CFH, CFI, CX3CR1, IL10RA, IL28B, LIPC, and SYN3.

Secondly, the influence of these factors on early AMD development was investigated by focusing on patients with chronic HIV infection. Based on the idea that patients with acquired immunodeficiency syndrome (AIDS) can be a good model for Aging.

Older age was observed the primary risk factor for AMD development. Smoking, cardiovascular disease, hypertension, diabetes and injection drug use, *CFH*(RS800292), *IL10RA*(RS3135932) and *IL10RA*(RS2229113) were also observed to be significantly associated with AMD. According to pathway enrichment analyses, complement activation pathways, lipid metabolism pathways, cholesterol transport, receptor-mediated endocytosis, and extracellular matrix organization mechanism can be involved in AMD development.

Multivariable models accounting for other variables identified *IL10RA* (RS3135932) and injection drug as risk factors for AMD. For the first time, a significant association between *IL10RA*(RS3135932) and AMD is observed. As a conclusion, chronic inflammation and oxidative stress can be mainly risk factor for AMD development.

ÖZET

MAKÜLER DEJENERASYON ETYOPATOJENİZİNDE ROL ALAN BİYOLOJİK YOLAKLARIN GENETİK İNCELEMELERLE ORTAYA ÇIKARILMASI

Maküler dejenerasyon, 50 yaş üstü kişilerde yaygın görülen, çok faktörlü, kompleks ve kademeli ilerleyen bir hastalıktır. Makuler Dejenerasyonun etiyolojisi hala bilinmemektedir.

Ana hipotezimiz, kronik inflamasyon ve oksidatif stresin YBMD (Yaşa Bağlı Maküler Dejenerasyon) gelişimindeki ana faktörler olduğudur. Öncelikle, YBMD'nin gelişimini anlamak için YBMD ile ilgili çalışmaları, Retina'nın transkriptomisini ve yaşlanma ile değişen molekülleri literatür taraması ile araştırdık. YBMD 'ye etki eden genetik ve genetik olmayan faktörleri incelendi.

Genetik olmayan faktörler olarak yaş, sigara içme öyküsü, cinsiyet, ırk, kardiyovasküler hastalıklar, hipertansiyon, diyabet, hiperlipidemi, böbrek hastalığı, HIV enfeksiyonu seçilmiştir. Genetik faktör olarak, *ARMS2, C2, C3, CFH, CFI, CX3CR1, IL10RA, IL28B, LIPC* ve *SYN3* genleri incelendi.

İkinci olarak, kronik HIV enfeksiyonu olan hasta grubuna odaklanılarak, literatürden elde edilen risk faktörleri incelendi. İkinci hipotezimiz, edinilmiş immün yetmezlik sendromu (AIDS) olan hastaların Yaşlanma Modeli gerektiren çalışmalar için iyi bir model olabileceğidir.

Yaşlılığın YBMD gelişimi için birincil risk faktörü olduğu gözlendi. Sigara, kardiyovasküler hastalıklar, hipertansiyon, diyabet ve uyuşturucu kullanımı, *CFH* (RS800292), *IL10RA* (RS3135932) ve *IL10RA* (RS2229113), YBMD gelişimi ile önemli ölçüde ilişkili olduğu gözlendi. Yapılan genişletilmiş yolak analizlerine göre, YBMD gelişiminde rol alan biyolojik yollar, tamamlayıcı aktivasyon yolları, lipid metabolizması yolları, kolesterol taşınması, reseptör aracılı endositoz ve hücre dışı matris organizasyon mekanizması olabilir.

Çoklu değişken analizlerinde *IL10RA* (RS3135932) ve uyuşturucu kullanımı risk faktörü olarak bulundu. *IL10RA* (RS3135932) ve YBMD arasında ilk kez anlamlı ilişkisi literatürde ilk kez bu çalışmada gösterildi. Sonuç olarak, kronik inflamasyon ve oksidatif stres, YBMD gelişimi için temel risk faktörü olabilir.

DOING WHAT YOU LIKE IS FREEDOM,

LIKING WHAT YOU DO IS HAPPINESS!

Life is too short to wait.

GO and FIND OUT what you like

and what makes you happy.

DEDICATED TO 'ALL' FAMILY MEMBERS

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AMD	Age Related Macular Degeneration
HIV	Human Immunodeficiency Virus
YBMD	Yaşa Bağlı Maküler Dejenerasyon
RPE	Retinal Pigmented Epithelium
VEGFA	Vascular Endothelial Growth Factor A
BMI	Body Mass Index
ROS	Reactive Oxygen Species
PUFA	Polyunsaturated Fatty Acids (PUFA)
POS	Photoreceptor Outer Segments (POS)
Ig	Immunoglobulin
HLA- DR	Human Leucocyte Antigen DR
GWAS	Genome-Wide Association Studies
STRING	Search Tool for the Retrieval of Interacting Genes
PANTHER	Protein Analysis Through Evolutionary Relationships
LSOCA	Longitudinal Study of the Ocular Complications of AIDS
miRNAs	Micro Ribonucleic Acid
PPI	Protein-protein interaction networks
y	mean
mL	miliLitre
HCV	hepatitis C virus
HAART	Highly active retroviral therapy
Ccr5	C-C chemokine receptor type 5
ATP	Adenosine triphosphate

CHAPTER 1

INTRODUCTION

With the global increase in life expectancy, the world's population is also aging over time. Consequently, the prevalence of comorbidities, chronic, and degenerative diseases are also increasing. The study of chronic, degenerative diseases has become popular research subjects (1).

Macular Degeneration is a retinal degenerative, complex, multifactorial, and polygenic disease in the macula region of the eye (2). Macular Degeneration causes visual impairment and blindness and affects the quality of life of millions of patients worldwide (3).

Despite a large literature on the subject, and numerous cohort study studies, the reason for Macular Degeneration is still unknown (4). However, the most critical factor of Macular Degeneration has been suggested to be aging (2, 4). A complex interplay between elderly age; (>60 years) and environmental risk factors, lifestyle, smoking, diet, genetic susceptibility (3), family history, ethnicity, (especially European ancestry) has been suggested to be involved in the development of Macular Degeneration (5).

Age-related macular degeneration (AMD) is the major legal cause of blindness in developed countries (6). The global prevalence rate of AMD is 8.7% within an age range of 45-85 years (7). The prevalence of AMD is expected to reach to about 288 million due to increasing frequency of the aging population by 2040 (8). Except for the wet AMD, there is no direct therapy for AMD. The treatment cost is estimated to be €37,453 per patient per year (9). Visual impairment due to AMD alone accounted for $343 billion reported by the AMD Alliance International in 2010 (10). The global treatment cost of AMD will increase because of the increasing patient number (9, 10).

1.1. Eye

One of the essential unique senses is a vision for humans. The eye is the unique gateway to vision to send visual signals to the brain (11).

The main development of the eye occurs between the 3rd week and the 10th week (12) and forms from ectoderm, neural crest cells, and mesenchyme (13).

Neural tube ectoderm rise to the retina, iris and ciliary body epithelium, optic nerve, smooth muscles of the iris, and some of the vitreous humor (14). The surface ectoderm lens forms the conjunctival and corneal epithelium, eyelids, and lacrimal apparatus (15). The remaining ocular structures are made up of mesenchyme (12).

The eye is composed of three layers that are the outer layer, the middle layer, and the inner layer. The outer layer involves the sclera, which is the white of the eye. The cornea is found in front of the iris, which has a role, like the shutter of a camera, to regulate the amount of light that enters the eye by changing its size, depending on brightness, the colored part of the eye. Behind the cornea, the eye's clear lens is placed to provide focus on things according to close up or far away behind the cornea. There is a clear liquid between the cornea and the lens. The vitreous is a jelly-like material between the lens and retina. Uvea involves blood vessels to nourish the eye in the middle layer of eye structure. The retina is the part of the back of the eye and contains the photoreceptor (light-sensing) cells (rods and cones) that have a role in sending visual signals to the brain (16).

The macula that is near the center of the retina provides the greatest visual acuity such as harp, clear, straight-ahead vision, macula is too unique for primates (17). The fovea dominating (up to 200 000 cone cells/mm2), the center of the macula, contains a massive concentration of photoreceptors with cone cells responsible for visual acuity and color perception (18). The parafoveal area circles the fovea, has rode cells dominate, and authorizes night vision. The choroid layer located behind the retina contains blood vessels that nourish the retina. Bruch's membrane is in the retina between the choroidal choriocapillaris layer and the retinal pigmented epithelium (RPE) layer; to the retina as the 'basement' membrane of the RPE layer that is called the retinal pigmented epithelium (RPE). The role of RPE is to protect that maintain the immune privilege of the eye by inhibiting the passage of immune cells into the retina and nourishing the retina, removing waste products and preventing new blood vessels from growing into the retinal layer, enhancing the clarity of vision by preventing the scattering of the light. Transporters and tight junctions of the RPE cells allow for the selective movement of ions, proteins, and water in and out of the retina (19).

1.2. Aging

Aging is a process and summary of deterioration of the physiological and chemical functions necessary for survival by driven time (20).

Aging is caused by oxidative stress, glycation, telomere shortening, side reactions, mutations, aggregation of proteins(21), a loss of homeostasis of the metabolic process into the organism and disrupted protein homeostasis, metabolic dysfunction, and altered cellular signaling, loss of control of the cellular process, uncontrolled proliferation, accumulation of molecules, interconnected cellular networks (20) and stress buffering mechanisms, and a resultant loss of compensatory reserve leading to accumulation of unrepaired damage (22).

Aging causes mainly changes in body composition, the imbalance between energy availability and demand, dysregulated signaling networks that maintain homeostasis, and neurodegeneration with impaired neuroplasticity (22). These changes ultimately rise in cellular senescence, death, or transformation to uncontrolled proliferation, thereby compromising human health (20).

Thus, Advanced age is the most significant risk factor associated with chronic disease, most cancers, cardiovascular diseases, and neurodegenerative disorders in humans, especially macular Degeneration that is Age Related Macular Degeneration (AMD), multifactorial chronic disease of the eye (20).

According to Literature and statistical data, a common observation supports that human health is in its most stationary state and is associated with a relatively low death rate about the ages of about 20-50 years old (20). The population of males is more affected than females by rising human mortality slightly during this age (23). After fifty years old, the number of significant illnesses also increases linearly (20). The prevalence of dementia (24), diabetes (25), decreasing bone mass and density (26), cancer, cardiovascular disease (27), and visual impairment increases markedly with age (28). At the seventy years of life, mortality rates exponentially increase (20).

1.3. Age Related Macular Degeneration

AMD is a progressive, polygenic, multifactorial, and neurodegenerative disease with complex etiology. Aging is the primary risk factor for AMD development (29).

Genetic and environmental factors have a role in AMD development. Complement activation pathways, lipid metabolism pathways, cholesterol transport, receptor-mediated endocytosis, and extracellular matrix organization mechanism have a role in the development of AMD (30). Environmental risk factors such as smoking, diet, obesity, sunlight exposure, alcohol consumption, and cardiovascular disease increase the risk of AMD (31).

AMD, known as yellow spot disease. Drusen which are yellowish deposits at the level of the RPE are the hallmark of the AMD (32). Drusen is consists of lipids, phospholipids, triglycerides, apolipoproteins, esterified and nonesterified cholesterol, carbohydrates, trace elements, vitronectin, immunoglobulins, amyloid, complement system components, extracellular debris, and cell debris on the Bruch membrane (33). Accumulation of these materials in the macula can have a role as a diffusion barrier so stimulus for inflammation (34). Drusen formation disrupts the connection between the RPE and the choroidal blood supply, so the diffusion of materials such as oxygen, minerals, antioxidants, toxins, and selectively passing of lipids other nutrients passing are blocking (33, 34). Then, Drusens led to hypoxia. The hypoxia causes neovascularization by inducing VEGFA and other pro-angiogenic factors to promote the formation of new vessels. In addition, Drusen deposits and pigmentary changes cause progressive degeneration or loss of the RPE and the neural retina. Visual function impairment is associated with damaged photoreceptors (33).

1.3.1. The Type of Age Related Macular Degeneration

There are two types of AMD, wet and dry forms. AMD is staged as early, intermediate, or late.

Small drusen are the hallmark of stages of AMD. Fewer than 5 small (<63 microns) drusen are called no AMD. Multiple small drusen or some intermediate sized (63-124 microns) drusen shows that is early stage of AMD (35). Causing more or less pigmentation areas called hyperpigmentation or hypopigmentation and drusens are generally diffused. Extensive intermediate sized drusen, more than one large (>125 microns) drusen, or non-central geographic atrophy, with or without pigment changes that are called the intermediate stage of AMD (36).

Late-stage AMD or Advanced AMD is defined by either choroidal neovascularization(wet) or geographic atrophy(dry). Late-stage AMD means leading to central scotomas and permanent loss of visual acuity (visual acuity worse than 20/32) in one eye or two eyes (3). Dry type that is with geographic atrophy of the retinal pigment epithelium with the lack of neovascularization areas. Wet types or exudative; with new blood vessel formations in the choroid, called the choroidal neovascularization areas, further leading to the formation of the disciform scars. The wet type is the heavier form of the disease than the other types because it causes blindness and severe damage to the retina (37).

1.3.2. Symptoms of Age Related Macular Degeneration

Dry macular degeneration develops slower and gradually reveals symptoms without pain (38). General Symptoms of Macular Degeneration are visual distortions, Blurred or "fuzzy" vision, reduced central vision in one or both eyes, increased blurriness of printed words, straight lines, such as sentences on a page, appearing wavy or distorted decreased intensity or brightness of colors, need more bright light and difficulty to adapt light levels, extra sensitivity to glare, in field of vision well-defined blurry spot or a blind spot (38, 39). Thus, people should go to an Eye Doctor when they notice changes; in their central vision, straight lines seeming bent, not see colors and fine detail becomes impaired, need brighter light when reading or doing close-up work, difficulty adapting to low light levels when entering room dimly, a well-defined blurry spot or a blind spot in your field of vision. Over 60-ages, these changes may be the first indication of macular degeneration, particularly (38).

One or both eye can be affected by dry AMD. If one eye of a patient is affected, the patient could not notice any changes in their vision. The other non-affected eye compensates for the weak eye. Thus, patients can not notice their vision changes easily. In this situation, side (peripheral) vision is not affected, so it rarely causes total blindness (40).

Wet (neovascular) macular degeneration is progressed by growing new vessels under the retina and causing to death of macula region cells. The wet type is a relatively sudden change in vision resulting in serious vision loss. Dry AMD can progress to wet (neovascular) macular degeneration by years (41).

1.3.3. Screening And Diagnosis of Age Related Macular Degeneration

To diagnose macular degeneration, one of the comprehensive eye exam tests that Amsler Grid, autofluorescence, Visual Acuity Test or Eye Chart Test, Fundoscopy or Ophthalmoscopy, Fluorescein Angiography, Optical Coherence Tomography (OCT), Tonometry can be detected by an ophthalmologist or an optometrist (42).

1.3.3.1. Amsler Grid

The Amsler grid is used for the presence of AMD.

Early signs of retinal disease can be noticed and be observed changes in vision after an AMD diagnosis.

Amsler grid resembles graph paper in which straight lines intersect at right angles, and a black dot is placed in the center of the grid. One eye of the patient is covered and looks at a black dot in the center of the grid. If there are differences in the grid like the straight lines in the grid appearing wavy or are missing, it might be first sign of AMD (43).

1.3.3.2. Autofluorescence

Autofluorescence photos are used to monitor the retinal pigment epithelium (RPE), the deepest layer of the retina and to study the retina and measure the progression of geographic atrophy that is the death of light-sensitive cells and leading to visual impairment (42).

1.3.3.3. Fundoscopy Or Ophthalmoscopy And Fundus Photography

Special eye drops are used for dilating the pupils to view the back of the retina and allow the doctor to study the retina for signs of disease and to determine optic nerve damage. After dilating the pupil, the doctor aims to check for problems in some parts of the eye that are Retina, Choroid, Blood Vessels and Optic Disk, by using a bright beam of light into the eye. After dilating the pupil, a customized camera is used to photograph for the back of the eye to examine for signs of disease in the Macula, Retina, Optic nerve

by focusing light through the cornea, pupil, and lens. This technique helps the doctor measure changes between visits for patients and sees the disease progression (42).

1.3.3.4. Fluorescein Angiography

Fluorescent dye is used to appear to detect leaking blood vessels by injecting fluorescent dye into your arm and tracing it through the blood vessels in the retina. It is shown like fluorescent patches leakage (44).

1.3.3.5. Optical Coherence Tomography (OCT)

OCT that provides to cross-sectional images of the retina, is a non-invasive technique to image the retina. This technique is used for measuring the different layers and their thicknesses of regions of the retina, revealing the presence of geographic atrophy (44).

1.3.4. The Etiology of AMD

The etiology of AMD is not known, yet. AMD is a multifactorial disease in which susceptibility, progression, and severity are determined by multiple genetic variants and also environmental and lifestyle factors. Advanced age and chronic inflammation, oxidative stress are major factors (45, 46, 47). Cell apoptosis and tissue involution (48), genetic predisposition and epigenetic modifications, smoking, sun exposure (47), heart and vascular disorders (49), hypertension, dyslipidemia/hypercholesterolemia, diabetes, obesity, improper diet, sedentary lifestyle, race are the risk factors for AMD development (47).

Genetic factors strongly modify one's risk for developing AMD, and most of these genetic changes are found in genes of the alternative complement cascade, a component of the immune system. The lack of effective AMD prevention calls for the identification of druggable molecules and pathways (50).

1.3.4.1. Age

AMD is a chronic and progressive disease so advanced age disease. Age is one of the most powerful and invariable factors. Prevalence of AMD spread to an age range of 45–85 years old. At 60 and 80 years old, the risk of developing advanced AMD are at a 3-fold greater than those younger than 60 years (51). The prevalence of late AMD is 1.4% at the age of 70 years, 5.6% at age of 80 and 20% at age of 90 (52).

1.3.4.2. Gender

The gender differences may not be the main risk factor for AMD. But the sex differences can bring different life expectancies, hormone levels, metabolic diseases, and lifestyles. The female gender is more tent to AMD. According to the National Eye Institute, in 2010, 65% of prevalent AMD cases were female patients. The longer life expectancy of women compared, and men may be the reason for the higher prevalence of AMD among women. Because of the longer life expectancy, age-dependent diseases are more detected. Epidemiological data have been crossed regarding the sex-associated risk of AMD. Many studies analyzing the sex-specific risk of AMD have not found directly significant associations between AMD and sex, but there is some evidence to show for increase other factors (53). Munch et al. (54) and Yang et al. (55) reported small drusen are found in males compared to females according to waist circumference, cardiovascular risk factors, BMI, systolic blood pressure, and exercise. Estrogen has a protective role with potential effects via the anti-inflammatory or other regulatory functions of estrogen on AMD development and/or progression for females (56). Sex is not mainly a risk factor, while it can increase other risk factors (53, 57).

1.3.4.3. Race

The prevalence of AMD changes greatly by ethnicity. Early, late, and any age-related macular degeneration is more prevalent in people of European ancestry than those of African ancestry (8). At the age range of 45–85 years, people were diverse by an ethnically diverse population and based on the diversity, the prevalence of AMD varies greatly by ethnicity, with non-Hispanic White Europeans having the greatest disease

burden at 12.3–30% with increasing age. Following this result, the prevalence of AMD with Hispanics is 10.4%, the prevalence of AMD with Africans is 7.5%, and the prevalence of AMD with Asians is 7.4% (4).

1.3.4.4. Smoking

Smoking has pathological effects through different biochemical pathways and is the most important modifiable risk factor for AMD development and progression. Cigarette smoke may cause oxidative damage, vascular changes, and inflammation within cellular changes at the level of the RPE in AMD patients. Smoking causes oxidative stress by reducing the plasma concentration of antioxidants. Because of decreasing the choroidal blood flow and increasing platelet adhesiveness, the risk of hypoxia is increased by smoking (8, 58).

Smoking increases to oxidative stress and the risk for AMD from 1.7 to 3.2-fold in ever smoker and from 1.9 to 4.5- fold in current smokers, and the number of cigarettes directly increase the risk of AMD (58).

1.3.4.5. Oxidative Stress

The eye organ is a special organ has high metabolic activity in Photoreceptors which causes photo-oxidative stress from light exposure. The highest oxygen consumption among all human tissues is in the retina. RPE and photoreceptors of the macula are exposed to high-energy light, and there are many photosensitizers (47) (rhodopsin and lipofuscin) and retinal illumination in photoreceptors and RPE (59). And the macula is a high oxidative stress microenvironment because of the high production of reactive oxygen species (ROS) generation in the Photoreceptors and the RPE. In addition, the cell membranes are rich in polyunsaturated fatty acids (PUFA) in photoreceptors, PUFA is readily oxidized. Phagocytosis of photoreceptor outer segments (POS) driven by RPE cells is accompanied by a respiratory burst and rapid eruption of ROS (47).

Excessive ROS production and accumulation, as well as oxidative stress, and RPE cells, are the critical site of injury in AMD (59). The retina and RPE cells are rich in both enzymatic and nonenzymic antioxidants to decrease the level of ROS (47). However, Aging cause to increase in ROS levels. Augmented levels of ROS and attenuated

antioxidant cell defense systems cause oxidative stress, so the macula has a high oxidative stress microenvironment (59, 60). Damage of photoreceptors, RPE cells, and choriocapillaris in the apoptosis process. Some evidence shows the patients with having systematic oxidative stress, higher ROS production and malfunctioning of the mitochondria, an accumulation of damaged proteins and impairment of autophagy, which is a proteolytic mechanism of efficient antioxidant capability, lipid peroxidation levels are increased. Oxidative stress is highly associated with AMD development (47, 60). With advanced age, the source of ROS production and accumulation of ROS cause chronic low-grade inflammation (pathophysiological parainflammation) and hypoxia, and vice versa (60).

1.3.4.6. Chronic Inflammation

Dysfunction or dysregulation of the immune system cause to damage the blood retina barrier and breach of retinal-immune privilege, leading to the development of retinal lesions in age-related macular degeneration (61). Oxidative stress accumulates little by little for many decades in the macula with aging. Inflammation is secondary to tissue damage and a protective response of the immune system. Thus, the parainflammatory system which has responsible for low levels of tissue stress to maintain homeostasis and restore tissue functionality. Inflammation has a role in the pathogenesis of AMD. The evidence is that myloid A/P, Factor X, prothrombin, and in some instances, Ig, HLA-DR, and complement proteins (*C3, C5, C5b-9, CFH,* and *CRP*) are found in drusen, and second evidence is that macrophages, lymphocytes, and mast cells in AMD lesions or the choroid adjacent to macular lesions (62, 63). The third evidence is polymorphisms of various immune-related genes, such as *CFH, C2/CFB, C3, CX3CR1,* and *TLR3/4*, are associated with AMD risk (63). The final evidence is in experimental animals, by manipulating immune-related genes, AMD-like lesions can be modeled (64).

Dysregulated parainflammation and the pathogenesis of AMD with Aging, oxidative stress products accumulate in the macula. Microglial activation as a parainflammatory response promotes to complement activation with subretinal accumulation. In AMD, the parainflammatory response is dysregulated by genetic predisposition, epigenetic modification, or environmental factors (62). Because of chronic inflammation, various proinflammatory cytokine production or inflammasome

activation damages RPE and the photoreceptors and leads to the development of AMD. During continuous chronic inflammation might be causing scar formation, which can also lead to loss of vision (64).

1.3.4.7. Genetic Factors of AMD and Biological Pathways

Genetic and environmental factors have a role in AMD development. Complement activation pathways, lipid metabolism pathways, cholesterol transport, receptor-mediated endocytosis, and extracellular matrix organization mechanism have a role in the development of AMD (30). In Genome-Wide Association Studies (GWAS) for AMD development, there are 36 genes are identified. *CFH* and *ARMS2* genes have been found to play an important role in AMD. In addition, *APOE, LIPC, CETP42, TIMP3, VEGFA43, C2* genes are thought to play an important role in AMD (65, 66).

ABCA1 is ATP-binding cassette, sub-family A, member 1 and has a role in molecule transport across cell membranes.

ABCA4 is ATP-binding cassette, sub-family A (ABC1), member 4.

ADAMTS9 is *ADAM* metallopeptidase with thrombospondin type 1 Motif, 9 and has a role in regulation of angiogenesis suppression and organ shape during development.

ARMS2 is Age-related maculopathy susceptibility 2.

APOE is Apolipoprotein E and has a role in lipid and cholesterol transport and catabolism.

B3GALTL is Beta 1,3-galactosyltransferase-like and has a role in glycosylation pathway.

CETP is Cholesteryl ester transfer protein and has a role in transport of cholesterol.

CFB is Complement factor B and has a role in alternative complement activation pathway.

CFH is Complement factor H and has a role in Inhibitor of alternative complement pathway.

CFHR1 is Complement factor H-related 1 and has a role in possible overlapping function with *CFH*, complement regulation.

CFHR3 is Complement factor H-related 3 has a role in complement regulation.

CFI is a Complement factor I that has a role in complement cascade regulation.

COL8A1 is Collagen type VIII, alpha1 has a role in main component in basement membrane of the corneal endothelium.

COL10A1 is Collagen, type X, alpha 1 has a role in produced by hypertrophic chondrocytes and located in mineralization zones of hyaline cartilage.

CX3CR1 is Chemokine (C-X3-C motif) receptor 1 has a role in Leukocytes adhesive and migratory function.

C2 is Complement 2 E318D, C3 R1 is Complement 3 R102G and has a role in regulation of complement system activation.

C9 is Complement component 9 and has a role in regulator of the membrane attack formation.

DDR1 is Discodin domain receptor tyrosine kinase 1 and has a role in cell growth, differentiation and metabolism regulator.

ERCC6 is Excision-repair cross-complementing, group 6 and has a role in DNA transcription-coupled excision repair.

FBLN5 is Fibulin 5 and has a role in the extracellular matrix protein that promotes adhesion of endothelial cells.

FBLN6 or *HMCN1* is Fibulin-6 or hemicentin 1 has a role in encodes a large extracellular member of the immunoglobulin superfamily.

FILIP1L is Filamin A interacting protein 1-like has a role in regulation of antiangiogenic activity in endothelial cells.

FRK is Fyn-related kinase has a role in cell growth regulation.

HTRA1 has a role in cell growth and insulin-like growth factors regulator.

IER3 is Immediate early response 3 has a role in regulation of apoptosis.

LIPC is Hepatic lipase C has a role in lipoprotein metabolism.

QRX/*RAXL1* is Retina, and anterior neural fold homeobox-like protein 1 has a role in involved in development of the eye; possible modulation of the photoreceptor specific genes expression.

RAD51B is RAD51 homolog B has a role in the pathway of DNA break repair.

SLC16A8 is Solute carrier family 16, member 8 (monocarboxylic acid transporter) has a role in transport lactate across cell membrane.

TGFBR1 is a Transforming growth factor, beta receptor 1 has a role in regulation of cell growth and division.

TIMP3 is TIMP metalloproteinase inhibitor 3 has a role in extracellular matrix destruction.

TLR3 is (Toll-like receptor 3) and TLR4 is Toll-like receptor 4 and has a role in activation of innate immunity.

TNFRSF10A is Tumor necrosis factor receptor super-family member 10a and has a role in cell apoptosis regulator.

VEGFA is Vascular endothelial growth factor A and has a role in endothelial cell growth regulator; response to angiogenesis (65, 66).

Complement factor H (*CFH*) protein is involved in the regulation of the immune system by controlling the complement system to protect healthy cells. *CFH* inactivates the complement system that has a role in destroying foreign invaders (such as bacteria and viruses), triggering an inflammatory response, and removing residues from cells and tissues when the complement system is not required (67).

The *ARMS2* gene encodes *ARMS2* protein that is a component of the choroidal extracellular matrix of the eye. *ARMS2* is involved in phagocytosis in RPE cells and provide to homeostasis in retina. Mutated *ARMS2* causes to dysfunctional mitochondria (66, 68).

APOE and *ABCA4* cause macular degeneration at an early age. *APOE* has a role in the transport and metabolism of lipids and cholesterol, and response to neuronal injuries. The *ABCA4* gene encodes a light-sensitive specialized protein in the retina that covers the back of the eye. *ABCA4* protein is responsible for converting the light into the brain into electrical signals transmitted to the brain. The mutation of the gene is an example of Mendel's disease called Stargardt macular degeneration (61).

The polymorphism in factor B (*BF)* and complement component 2 (*C2*) genes may trigger AMD or have a protective effect. The products of these genes activate alternative activation pathways and play a role in the regulation of the immune system (69).

Inflammation, lipid transport and metabolism, extracellular matrix remodeling, complement dysregulation, oxidative stress, and autophagy, complement pathway, and proangiogenic/angiogenic molecules have a role in pathological changes to the development of AMD (65, 66).

1.4. Aims & Hypothesis of Thesis

The hypothesis of the thesis is that chronic inflammation and oxidative stress are the major factors for the early development of AMD.

To test this hypothesis, firstly, the genes, proteins, and biological pathways that are potentially involved in AMD development was identified with a systematic review of genome-wide association (GWAS) study results. The gene ontology, protein-protein interactions, biological pathway, and functional annotations of identified genes were conducted.

Secondly, a similar systematic review and detailed ontological and functional annotations were carried out for genes reported to be associated with Aging, and genes that are expressed in the retina. Overlapping genes, biological pathways, and their interactions from these three lists were conducted. Pathways related to chronic inflammation and oxidative stress were identified.

Finally, based on these analyses a smaller set of genes are chosen as candidate genes, and the effects of these genes on early AMD development is investigated in a HIV infected patient cohort, based on the idea that patients with acquired immunodeficiency syndrome (AIDS) can be a good model for accelerated Aging, primarily driven by chronic inflammation and oxidative stress commonly observed in this patient group.

CHAPTER 2

MATERIALS AND METHODS

2.1. Literature Review, Search Strategy and Data Source

2.1.1. AMD Related Biological Pathways

By using an English database (such as NCBI, PubMed, Science, Nature, Nucleic Acids Research), references of this thesis are searched for the relevant articles by hand. The key search terms are used "prevalence", "aging", "biological pathways of an eye", "aids", "age related genes", "incidence," "development," "associated factors," "progression,"' and "age-related macular degeneration", " proteome", "age", "molecules", "biological pathways". Using all these terms, relevant topics are searched through 'All fields' using the connecting 'AND' and 'OR' as appropriate and limited to articles published since 1980 to date.

2.1.2. Age Related Biological Pathways

By using an English database (such as NCBI, PubMed, Science, Nature, Ageing-map, Proteinatlas, Nucleic Acids Research), references of this thesis are searched for the relevant articles by hand. The key search terms are used "prevalence", "aging", "aids", "age related genes", "incidence," "development," "associated factors," "progression", "proteome", "age", "molecules", "biological pathways", "disease". Using all these terms, relevant topics are searched through 'All fields' using the connecting 'AND' and 'OR' as appropriate and limited to articles published since 1980 to date.

2.1.3. Retina Transcriptomic Research

By using an English database (such as NCBI, PubMed, Science, Nature, Proteinatlas, Nucleic Acids Research), references of this thesis are searched for the relevant articles by hand. The key search terms are used "biological pathways of an eye",

"development", "progression,"' and "proteome", "transcriptome in the retina", "proteins in the retina", "molecules", "biological pathways". Using all these terms, relevant topics are searched through 'All fields' using the connecting 'AND' and 'OR' as appropriate and limited to articles published since 1980 to date.

2.2. Gene Ontology and Biological Pathways by using String and Panther Gene Ontology Tools

Protein-protein interaction networks are analyzed by using of STRING 11.5 (Search Tool for the Retrieval of Interacting Genes) (https://string-db.org), for obtaining direct and indirect human protein-protein interaction networks for AMD genes. PANTHER (Protein Analysis Through Evolutionary Relationships) (http://www.pantherdb.org) tool was used to identify gene ontology classifications of genes such as molecular functions, biological process, protein class and pathway. Statistically, significantly overrepresented biological processes and pathways were identified by using both STRING and PANTHER tools. Note: Protein-Protein interactions was performed with minimum required interaction score: 0.04

2.3. Investigation of Effects of Genetic and Nongenetic Factors on Early AMD Development in Patient with AIDS

Firstly, the effects of demographic, health status and clinical factors on Early AMD development was investigated in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) cohort. LSOCA is a cohort of multiethnic patients diagnosed with AIDS, enrolled between 1998 to July 31, 2011 in several HIV clinics throughout the United States. 1825 patients had enrollment photographs and no intraocular infections and form the early AMD study population.

Secondly, 18 variants from 10 genes were analyzed as genetic risk factors for early AMD in patients with AIDS, enrolled in the LSOCA cohort. Effect of Each Genetic variant on Early AMD development was investigated using recessive, dominant and codominant models.

2.4. Statistical Analyses

Categorical variables were analyzed by using the Chi-Square test. The normal distribution assumption was tested for continuous variables by the Shapiro Wilk test. The Wilcoxon rank-sum test was used to compare the distribution of non-normally distributed continuous variables between patients with and without Early AMD.

Each factor with $P<0.05$ were selected and these factors analyzed to associate individually effects on AMD development by Univariate Logistic Regression Analysis. And then, these factors examine with together to Multivariate Analysis to see their effects on AMD development by Multivariate Logistic Regression Analysis.

All statistical analyses were performed using R version 3.5.2 (2018-12-20).

CHAPTER 3

RESULTS AND DISCUSSION

In this thesis, genetic and nongenetic factors for the development of AMD were analyzed in the population with HIV infected.

Macular Degeneration is highly associated with innate immune system, complement activation, lipid metabolism, cholesterol transport, receptor-mediated endocytosis, and extracellular matrix organization, advanced age, chronic inflammation, oxidative stress, lipid metabolism are highly risk factors for AMD. Candidate Genes are selected to investigate effects on Early AMD.

Thus, candidate genes were selected based on expression in Retina. In addition, these candidate genes were selected relationship age related genes and biological pathways that have a role in. The study population had a different metabolism than normal patients. These population have a chronic inflammation and deficient immune system.

3.1. Biological Pathways for Related AMD Genes

3.1.1. Candidate Genes to Investigate Effects of Genetic factors on Early AMD Development in Patient with AIDS

Macular Degeneration is associated with innate immune system, complement activation, lipid metabolism, cholesterol transport, receptor-mediated endocytosis, and extracellular matrix organization. *ARMS2, C2, C3, CFH, CFI, CX3CR1, IL10RA, IL28B (IFNL3), LIPC,* and *SYN3* are selected for investigation of effects of genetic factors on AMD development in Patients with HIV infections. These genes were directly expression in Retina. *C3* and *CFH* were defined Literature in both Age Related Genes, AMD Related Genes and Retinal Genes.

3.1.2. AMD Related Biological Pathways from GWAS Studies and Literature

Total 36 genes *ABCA1, ABCA4, ADAMTS9, APOE, ARMS2, B3GALTL, C2, C3, C9, CETP, CFB, CFH, CFHR1, CFHR3, CFI, COL10A1, COL8A1, CX3CR1, DDR1, ERCC6, FBLN6, FBLN5, FILIP1L, FRK, HTRA1, IER3 , LIPC, QRX, RAD51B, SLC16A8, TGFBR1, TIMP3, TLR3, TLR4, TNFRSF10A, VEGFA*, were found according to Literature for GWAS studies of AMD.

Their PANTHER Protein Class and annotation of genes are represented in Supplement Table 1.

3.1.3. Age Related Biological Pathways from Literature

3071 molecules are found by changing with age, and which 2599 are protein of these molecules (70). Thomas et al. figure out significant changes in metabolism in the organism, organs or specific tissue; levels of 611 molecules decrease, and levels of 555 molecules increase.

The levels of molecules are changed according to life expectancy. These changes cause to alteration of gene expression, epigenetic factors, misfolding of protein, DNA methylation, miRNAs, radicals, accumulation of other molecules, hormones levels, diets, cellular senescence, molecular functions, metabolism of molecules, biological pathways, interactions between cells, proteasome and autophagy systems (70).

Alters essential processes in maintaining cellular protein homeostasis, including the proteasome and autophagy systems, age leads to an accumulation in cellular debris, protein aggregation, and cellular damage and repair mechanisms. After the beginning of these alterations, the balance of metabolism is altered. Biological functions get slower or faster, or nonfunctional. These alterations also increase the aging process. Identifying molecules levels is necessary to decrease the effects of aging and Age Related diseases. Age Related molecules from Literature are shown in Supplement Data Set 1 (70).

3.1.4. Retinal Transcriptome Research Results

According to Literature reviews, 19 083 peptides were found and refer to a total of 3,130 protein groups and 3,436 non-redundant proteins in the normal human retina transcriptomics research. And 158 proteins are found in retina from the curated list of genes that have previously been associated with AMD with PANTHER Protein Class and annotation of genes are represented in Supplement Table 2 (71).

3.1.5. Overlapping of Candidate Genes and Expressed Genes in Retina

Candidate Genes are found in Retinal Transcriptomics. These genes are *ARMS2, C2, C3, CFH, CFI, CX3CR1, IL10RA, IL28B, LIPC* and *SYN3*.

3.1.6. Overlapping of AMD Related Genes and Age Related Genes

58 of AMD Related Genes are found in Age Related Genes. These genes are *ABCA1, ABCA4, ALDH1A1, ANXA4, APOE, ATP5B, ATP5D, C3, CAV1, CFH, CFHR1, CKB, COL14A1, COL1A2, COL3A1, CRP, CRYBA1, CST3, DDR1, EIF4H, ENO2, EPHX1, ERP29, FABP5, FBLN5, FRZB, GFAP, GUK1, HLA-DRA, HLA-DRB1, HNRNPD, IER3, LGALS3, LTF, PKM2, PRELP, PSMB5, RDH5, RTN4, S100A8, S100A9, SAA1, SERPINA1, SERPINA3, SERPINF1, SLC25A11, SLC2A1, TF, TGM2, THY1, TLR3, TLR4, TPD52, TUFM, TXNDC5, VDAC1, VIM, VTN, VWF*. Their changes with age are described in Supplement Table 3.

3.2. Identify Gene Ontology and Biological Pathways by Using STRING and PANTHER tool

Protein-protein interaction networks (PPI) analysis are used for pathway identification, partition functional modules, and annotation of novel protein functions. The PPI network gives a blueprint for systematically analyzing various biological activities, pathways, a signaling sub-network extraction and functional prediction. It represents entities that refers genes (nodes) and their functional co-relationships (edges). Each data type contains a different aspect of the functional role of interested genes. In the

study, we investigated protein-protein interaction using knowledge-based using *STRING 11.5*.

3.2.1. PPI Network of AMD Related Genes

3.2.1.1. PPI Network of Identified Candidate AMD Related Genes

PPI network constructed using 10 genes in STRING as input that results in 18 interactions between 10 nodes based on parameters including database, experimental, co-expression, text mining with the confidence score (1.0e-16), average degree nodes 3.6 and average local clustering coefficient 0.647 in Figure 3.2.1. Their interactions are shown in Supplement Table 5. 9 of them are highly related, but SYN3 did not interact with them.

For 10 genes, the Result of Functional Overrepresentation Panther Pathway Analysis by PANTHER tool significantly did not show any pathways together. However, The result of Reactome Pathway Analysis by PANTHER tool show to their pathways are related with Activation of C3 and C5 (p-value= $7.62e^{-06}$), Regulation of Complement cascade (p-value= $1.95e^{-07}$), Complement cascade (p-value= $2.72e^{-07}$) in Table 3.2.1. The expression of CFH and the expression of C3 increases with age (Supplement Table 3.). These genes have an essential role in the Activation of C3 and C5 and Complement cascade pathways. These pathways could affect by aging.

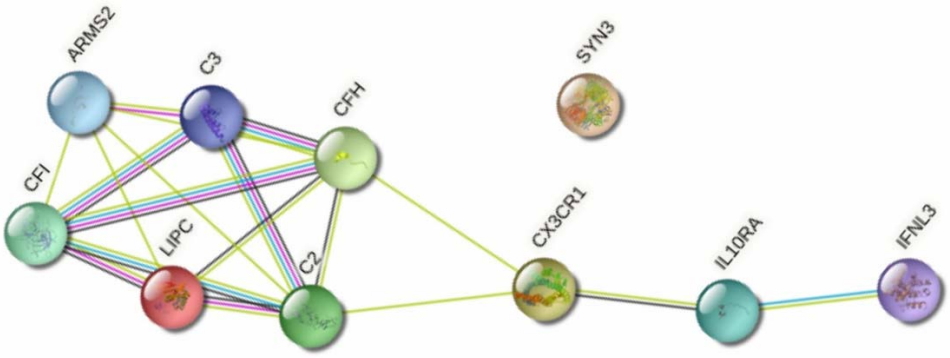

Figure 3.2.1. Overview of PPI Network Constructed Using STRING 11.5 Database for Candidate Genes. The network includes 18 edges (interaction) between 10 nodes respectively based on experiment, co-expression, text mining and co-expression with $1.0e^{-16}$ confidence score as the analysis parameter.

3.2.1.2. PPI Network of AMD Related Genes from GWAS Studies and Candidate Genes

PPI network constructed using genes in *STRING* as input that results in 39 interactions between 169 nodes based on parameters including database, experimental, co-expression, text mining with the confidence score ($1.0e^{-16}$), average degree nodes 9.44 and average local clustering coefficient 0.597 in Figure 3.2.2. Their interactions are shown in Supplement Table 6. Candidate Genes are highly interaction with AMD related genes that are found in GWAS studies. There are 3 Candidate genes different from GWAS studies, one of them is *IL10RA* and is co-expression with *TLR4* and *CX3CR1*. *IL10RA* might be increased or decreased the risk of AMD development.

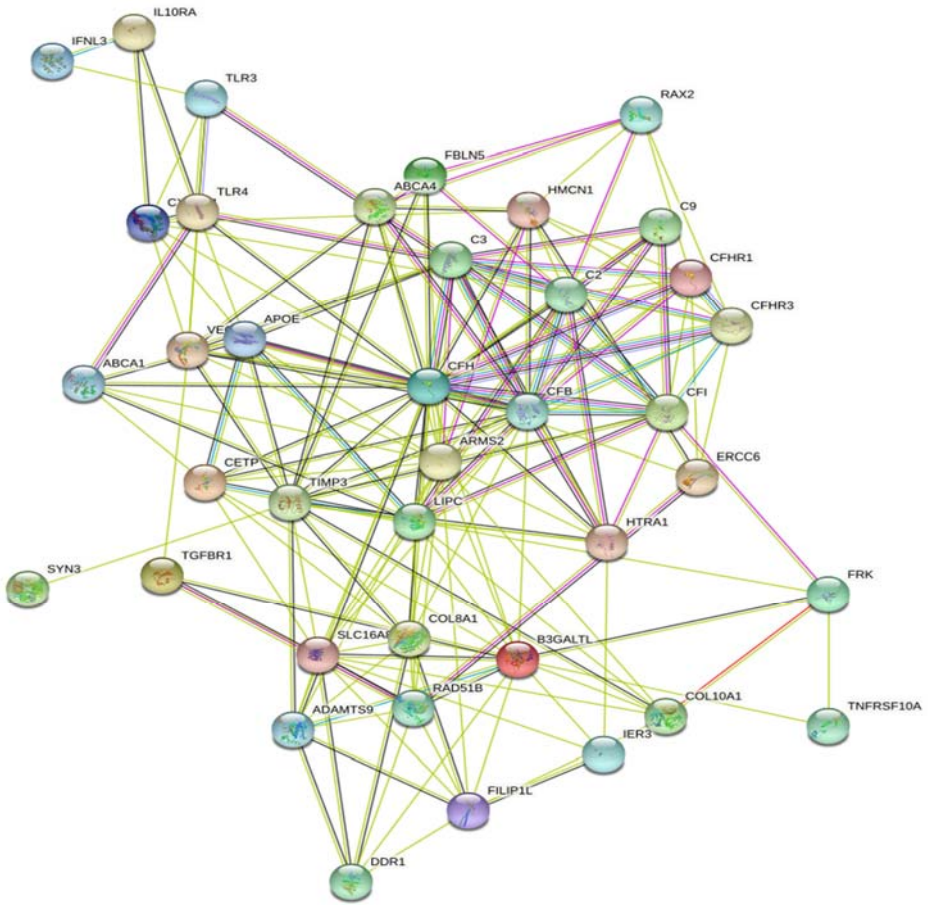

Figure 3.2.2. Overview of PPI Network constructed using STRING 11.5 database for AMD related genes from GWAS studies and candidate genes. The network includes 184 edges (interaction) between 39 nodes respectively based on experiment, co-expression, text mining & co-expression with $1.0e^{-16}$ confidence score as the analysis parameter.

According to AMD related GWAS studies and Candidate genes do not have a role in biological pathways according to The Functional Overrepresentation Panther Pathway analysis by PANTHER. However, Reactome Pathway Analysis by PANTHER show that these genes have a relationship in some biological pathways; Activation of C3 and C5 (p value= $7.42e^{-07}$), Alternative complement activation (p value= $7.27e^{-05}$), Chylomicron clearance (p value= $7.27e^{-05}$), HDL remodeling (p value= $1.89e^{-04}$), Plasma lipoprotein remodeling (p value= $3.27e^{-05}$), NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux (p value= $5.44e^{-05}$), Regulation of Complement cascade (p value= $5.47e^{-11}$), NR1H2 and NR1H3-mediated signaling (p value= $1.02e^{-04}$), Complement cascade (p value= $1.04e^{-10}$), Plasma lipoprotein assembly, remodeling, and clearance (p value= $9.66e^{-06}$), Degradation of the extracellular matrix (p value= $1.55e^{-04}$), Extracellular matrix organization (p value= $2.15e^{-05}$), Innate Immune System (p value= $4.55e^{-06}$). These pathways are related with risk of AMD development.

These pathways and genes that have a role in these biological pathways, might be analyzed to investigate biological pathways for AMD development. Also, signaling pathways could be predict according to these significant pathways which are found in Reactome Pathway Analysis by PANTHER.

Although, there are 13 significant associated pathways in Reactome Pathway Analysis by PANTHER, there are lots of nonsignificant associations of biological pathways. Thus, each gene and biological pathways of genes should be examined by individually. These biological pathways and signaling pathways might help understand the causes of AMD development.

3.2.1.3. PPI Network of AMD Related Genes from Retinal Transcriptomic and GWAS study and Candidate Genes

PPI network constructed using genes in STRING as input that results in 187 interactions between 1309 nodes based on parameters including database, experimental, co-expression, text mining with the confidence score ($1.0e^{-16}$), average degree nodes 9.44 and average local clustering coefficient 0.597 in Figure 3.2.3. PFDN1, RNASE4, TNC, FRZB have not interacted with them.

Results of pathway analysis for these genes are placed in Table 1. and Supplement Table 7. According to these results, these genes are found in many biological pathways.

Reactome pathway analysis shows that several pathways might be caused the development of AMD in Supplement Table 7. The glycolysis pathway involves the metabolism of both glucose and lactate. under hypoxic conditions, glycolysis leads to an increase of lactate production without enough oxygen, and higher lactate levels reflect tissue hypoxia. Hypoxic glycolysis is consistently associated with increased tissue levels of lactate. increased lactate levels may be implicated in the pathogenesis of AMD (72). The reason for the low oxygen level in the retinal tissue might be examined to understand the development of AMD. Plasminogen activating cascade mechanism is related to growth factors that facilitate cell migration, macrophage recruitment during the inflammatory response, promoting the ability of cells to degrade extracellular matrices, tumor cell invasion, and metastasis, wound healing, tissue remodeling, neurite outgrowth, and skeletal myogenesis (73). Blood coagulation is related with angiogenesis (74). Integrin signaling pathways caused to decrease cell migration, cell invasion, and cell proliferation (75). The genes and molecules, that effect on these pathways could be examined.

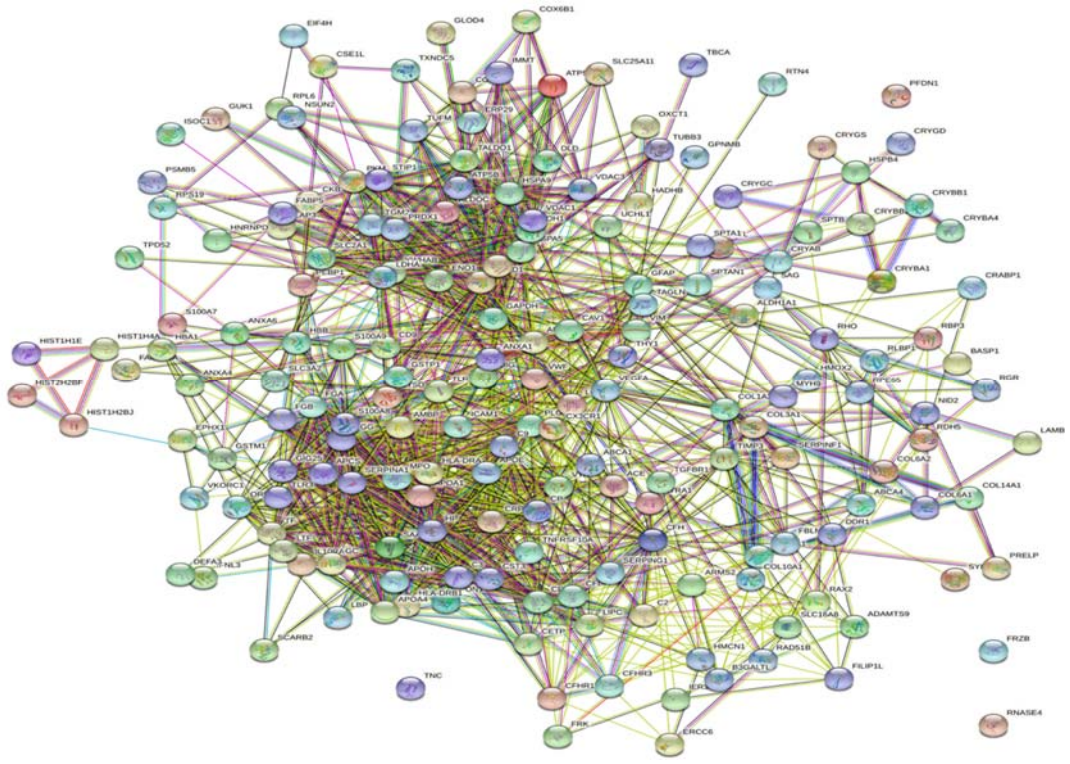

Figure 3.2.3. Overview of PPI Network constructed using STRING 11.5 database for AMD related genes from Retinal Transcriptomics and GWAS studies. The network includes 1309 edges (interaction) between 187 nodes, respectively based on experiment, co-expression, text mining, and co-expression with a $1.0e^{-16}$ confidence score as the analysis parameter.

Table 1. The Result of Functional Overrepresentation Panther Pathway Analysis for both Retinal Transcriptomic and GWAS study and 10 Candidate Genes by PANTHER Tool

PANTHER Pathways	Homo sapiens (REFLIST-20595)	AMD gene list	(expected)	(over/under)	(fold Enrichment)	(raw P-value)	(FDR)
Glycolysis (P00024)	20	4	0.19	+	21.57	$6.36e^{-05}$	$2.65\ e^{-03}$
Plasminogen activating cascade (P00050)	21	4	0.19	+	20.54	$7.51\ e^{-05}$	$2.51\ e^{-03}$
Blood coagulation (P00011)	48	7	0.45	+	15.72	$6.93\ e^{-07}$	$5.78\ e^{-05}$
Integrin signalling pathway (P00034)	193	11	1.79	+	6.15	$3.08\ e^{-06}$	$1.71\ e^{-04}$

3.2.1.4. Overlapping of Age Related Genes and AMD Related Genes

With Advanced Age, there are some changes in gene expression level of genes in Retina, in Supplement Table 3 and Supplement Table 4. The biological pathways are change with age in Table 2.

3.3. To Investigate Effects of Genetic and Nongenetic Factors on Early AMD Development in Patient with AIDS

The effects of demographic, health status, clinical factors, and genetic factors on Early AMD development were investigated in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) cohort, comprising 1825 multiethnic patients diagnosed with AIDS. The prevalence of early AMD in the entire study population was 9.9%.

Table 2. The Result of Functional Overrepresentation Reactome Pathway Analysis for Overlapping AMD Related Genes and Age Related Genes by PANTHER Tool

Reactome pathways	Homo sapiens (REFLIST-20595)	AMD gene list	(expected)	(over/under)	(fold Enrichment)	(raw P-value)
Metal sequestration by antimicrobial proteins (R-HSA-6799990)	6	3	0.03	+	> 100	6.14 e^{-06}
Activation of C3 and C5 (R-HSA-174577)	7	3	0.03	+	> 100	8.74 e^{-06}
Alternative complement activation (R-HSA-173736)	5	2	0.02	+	93.61	3.71 e^{-04}
Chylomicron clearance (R-HSA-8964026)	5	2	0.02	+	93.61	3.71 e^{-04}
Scavenging by Class A Receptors (R-HSA-3000480)	19	3	0.08	+	36.95	1.08 e^{-04}
Regulation of TLR by endogenous ligand (R-HSA-5686938)	19	3	0.08	+	36.95	1.08 e^{-04}
Collagen chain trimerization (R-HSA-8948216)	44	5	0.19	+	26.59	2.05 e^{-06}
Syndecan interactions (R-HSA-3000170)	27	3	0.12	+	26	2.78 e^{-04}
Plasma lipoprotein remodeling (R-HSA-8963899)	30	3	0.13	+	23.4	3.70 e^{-04}
Non-integrin membran e-ECM interactions (R-HSA-3000171)	59	5	0.25	+	19.83	7.78 e^{-06}
NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux (R-HSA-9029569)	36	3	0.15	+	19.5	6.09 e^{-04}
Assembly of collagen fibrils and other multimeric structures (R-HSA-2022090)	60	5	0.26	+	19.5	8.40 e^{-06}
Complement cascade (R-HSA-166658)	122	10	0.52	+	19.18	2.35 e^{-10}
Regulation of Complement cascade (R-HSA-977606)	112	9	0.48	+	18.81	2.30 e^{-09}
Collagen degradation (R-HSA-1442490)	64	5	0.27	+	18.28	1.13 e^{-05}
Collagen biosynthesis and modifying enzymes (R-HSA-1650814)	67	5	0.29	+	17.47	1.39 e^{-05}

(Cont. on Next Page)

Table 2. (cont.)

Integrin cell surface interactions (R-HSA-216083)	84	6	0.36	+	16.72	2.33 e^{-06}
Plasma lipoprotein assembly, remodeling, and clearance (R-HSA-174824)	67	4	0.29	+	13.97	2.39 e^{-04}
Collagen formation (R-HSA-1474290)	89	5	0.38	+	13.15	5.07 e^{-05}
Degradation of the extracellular matrix (R-HSA-1474228)	140	7	0.6	+	11.7	3.12 e^{-06}
Platelet degranulation (R-HSA-114608)	127	6	0.54	+	11.06	2.22 e^{-05}
Post-translational protein phosphorylation (R-HSA-8957275)	107	5	0.46	+	10.94	1.17 e^{-04}
Initial triggering of complement (R-HSA-166663)	87	4	0.37	+	10.76	6.17 e^{-04}
Response to elevated platelet cytosolic Ca2+ (R-HSA-76005)	132	6	0.56	+	10.64	2.74 e^{-05}
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) (R-HSA-381426)	124	5	0.53	+	9.44	2.26 e^{-04}
Extracellular matrix organization (R-HSA-1474244)	299	11	1.28	+	8.61	8.25 e^{-08}
Toll-like Receptor Cascades (R-HSA-168898)	152	5	0.65	+	7.7	5.58 e^{-04}
Platelet activation, signaling and aggregation (R-HSA-76002)	259	7	1.11	+	6.33	1.41 e^{-04}
Signaling by Nuclear Receptors (R-HSA-9006931)	261	7	1.12	+	6.28	1.47 e^{-04}
Neutrophil degranulation (R-HSA-6798695)	478	11	2.04	+	5.39	7.16 e^{-06}
Innate Immune System (R-HSA-168249)	1105	24	4.72	+	5.08	3.15 e^{-11}
Hemostasis (R-HSA-109582)	669	12	2.86	+	4.2	3.07 e^{-05}
Immune System (R-HSA-168256)	2158	33	9.22	+	3.58	2.56 e^{-11}
Signal Transduction (R-HSA-162582)	2728	24	11.66	+	2.06	4.26 e^{-04}

Table 3. Demographic Characteristics of the Study Population of Patients From the Longitudinal Study of the Ocular Complications of AIDS

Character	Subcategories	AMD=0	AMD=1	P
		n=1665	n=184	
Age(y)	median(25%,75%)	43(37-49)	47(42-54)	**$9.33e^{-13}$**
Age (%)	<30	90(5)	8(4)	**$2.35e^{-11}$**
	30–39	479(29)	20(11)	
	40–49	720(44)	74(41)	
	50–59	303(18)	61(34)	
	>60	53(3)	17(9)	
Gender(%)	female	313(19)	40(22)	0.3
	male	1332(81)	140(78)	
Race & Ethnicity (%)	White, nonHispanic	760(46)	68(38)	0.15
	African American	608(37)	80(44)	
	Hispanic	219(13)	24(13)	
	Other	58(4)	8(4)	
Smoking History (%)	Never	524(41)	47(34)	**0.02**
	Former	471(37)	47(34)	
	Current	284(22)	45(32)	
Death(%)	0	1196 (73)	123(68)	0.21
	1	449 (27)	57 (32)	

Demographic characteristics of the study population of patients were examined by age, gender, ethnicity, smoking history, and death in Table 3.

The group had a mean age of 43.4 years, a median age group of 38-49 years, and the lowest age is 13 years old, and the highest age is 73 years old. 8% for participants aged <30 years, 4.0% for participants aged 30–39 years, 9% for participants aged 40–49 years, 17% for participants aged 50–59 years, and 24.3% for participants 60 years of age and over, AMD patients were detected in the population, ($P < .0001$). Age was a significant risk factor for AMD. According to Literature for patients without AIDS, the prevalence of AMD is 8·7% of the worldwide population has age-related macular degeneration between 45–85 years old with increasing chronological age (8).

Compared to this LSOCA Cohort, this AMD prevalence is higher than expected (8). 8% for participants aged 30 years old was very significant differences compared to non-Infected HIV patients. One of the aims is to assess can AIDS patients be used the Accelerated and Accentuated Aging Model. *Accelerated aging* can be defined as an age-related degeneration that arises earlier than expected and increases progressively. *Accentuated aging* can be defined as a rising burden of age-related damage

that will remain stationary over time (76). According to Literature, for <30 years old people, the appearance of AMD is not expected range with 8% of 30 aged population (except Mendelian Gene effects) (2, 3). Also, the prevalence of AMD, 9% for participants aged 40–49 years, 17% for participants aged 50–59 years, and 24.3% for participants 60 years of age and over. These prevalence of AMD in patients with AIDS, is higher than 8·7% of 45-85 aged of the worldwide population (7). AIDS patients could be used the Accelerated and Accentuated Aging Model.

The largest participants for smoking history were "never-smokers" (40.3%), 36.5% were "former-smokers", 23.2% were "current-smokers". 8.2% for participants "never-smokers", 9.1% for participants "former-smokers", 13.7% for participants "current-smokers", the association of smoking and development of AMD was significantly high factor (P = 0.02). Smoking causes vascular inflammation, endothelial dysregulation, oxidative damage, toxic damage, and histopathological changes. Smoking is damage to an ideal macular microenvironment for the development of AMD. Smoking is a proven risk factor for both the development and progression of AMD. In Literature, current smokers have a 2- to 4-fold increase in risk for AMD compared to patients who never smoked (20, 58, 77).

The predominance of participants was male (80.7%), and 19.3% of the population were female. 11.3% of females had AMD, 9.5% of males had AMD development. There was no significant association between gender and AMD development for these patients (P = 0.30).

The majority of participants were white, non-Hispanic (45.4%), African American was followed with 37.7%, 13.3% were Hispanic, and 3.6% were rest of the world. 8.2% of participants were white, non-Hispanic with AMD, 11.6% of participants were African American with AMD, 9.9% of participants were Hispanic with AMD were 12.1% other with AMD patients.

Table 4. Clinical Characteristics of the Study Population of Patients with Acquired Immunodeficiency Syndrome From the LSOCA

Character	Subcategories	amd=0	amd=1	P
		n=1665	n=184	
Time since AIDS diagnosis (y)	Median (25%,75%)	4.27(1.6-7.21)	4.64(1.514-7.43)	0.52
HIV transmission category (%)	Injection drug use	220(13)	37(21)	**0.003**
	Male-to-male sexual contact	915(56)	76(42)	
	Heterosexual contact	417(25)	57(32)	
	other	93(6)	10(6)	
Enrollment CD4þ T cells (cells/mL) (%)	<100	466(29)	53(29)	0.98
	100–199	349(21)	40(22)	
	200–499	600(37)	64(36)	
	>500	215(13)	23(13)	
lowest recorded CD4+ T-cell count (y)	Median (25%,75%)	43 (13 - 112)	55 (20 - 117)	0.17
lowest recorded CD4+ T-cell count (%)	<50	867(53)	86(49)	0.25
	>50	755(47)	90(51)	
CD8+ T-cell count at baseline (y)	Median (25%,75%)	777(497.75-1133.25)	751 (505.5-1033)	0.51
CD4/CD8 T-cell count ratio (y)	Median (25%,75%)	0.25(0.125-0.432)	0.25(0.117-0.41)	0.97
Enrollment HIV load (log10 [copies/mL]) (%)	<2.6	575(37)	52(31)	0.26
	2.6–3.0	272(18)	33(20)	
	>3.0	702(45)	84(50)	
Maximum prior HIV load (log10 [copies/mL]) (y)	median(25%,75%)	5.3 (4.7-5.7)	5.2 (4.7-5.6)	0.22

In the LSOCA cohort, there was no difference in the prevalence of AMD for different racial/ethnic groups (P = 0.15).

According to Literature, white non-Hispanic people have the highest percentage of incident AMD than Hispanic and African participants. In LSOCA, there is no significant result to race group (2, 3, 7, 8).

The death percentage in this population was 27.7%. Moreover, 11.3% of death patients were with AMD.

Clinical and viral measurements for patients with AIDS are measured in Table 4. The largest transmission category for HIV infection was male-to-male sexual contact (54.3%), 26.0% heterosexual transmission, 14.1% injection drug use, and 4.6% other

transmission ways for HIV infection. There was an association between the transmission category for HIV infection and AMD development (P = 0.003). The prevalence of AMD was 14.4% for participants HIV infection by injection drug use, 12.0% for participants HIV infection by heterosexual contact, 7.7% for participants who get HIV infection by men who had sex with men, 5.6% for participants who get HIV infection by transmission ways. The transmission category for HIV infection is essential for viral load. The injection drug user is taken HIV directly when they share needles or syringes with others. Their immune activation and inflammation are greater than other types of transmission categories (78). The mean of time since AIDS diagnosis is 4.971 years, and the median is 4.331 years (25th, 75th percentiles, 1.591 years, 7.252 years) in this patient population. Patients were categorized by <1.55 years, 1.55-4.33 years, 4.34–7.25 years, and >7.25 years. Each category had the same number of patients with HIV infection. The median of the lowest CD4þ T cell count prior to enrollment was 44 cells/mL (25th, 75th percentiles, 13 cells/mL, 113 cells/mL). The median of the lowest CD4þ T cell count prior to enrollment was 55 cells/mL (25th, 75th percentiles, 20 cells/mL, 117.8 cells/mL) in AMD patients. The median of the lowest CD4þ T cell count prior to enrollment was 198.5 cells/mL (25th, 75th percentiles, 81 cells/mL, 360 cells/mL), the median enrollment CD4þ T cell count was 189 cells/mL (25th, 75th percentiles, 83.8 cells/mL, 324 cells/mL) in patients with AMD. Median of the CD8þ T cell count prior to enrollment was 773.0 cells/mL (25th, 75th percentiles, 499.5 cells/mL, 1130.0 cells/mL) Median of the CD8þ T cell count prior to enrollment was 751.0 cells/mL (25th, 75th percentiles, 506 cells/mL, 1033.0 cells/mL) Median of the ratio of CD4þ T cell/CD8þ T cell was 0.2490 (25th, 75th percentiles, 0.1235, 0.4316) in the population. Median of the ratio of CD4þ T cell/CD8þ T cell was 0.246 (25th, 75th percentiles, 0.117, 0.413) in patients with AMD. Median of Enrollment HIV load was 2.700 (log10 [copies/mL]), (25th, 75th percentiles, 1.881(log10 [copies/mL]), 4.602 (log10 [copies/mL])). Median of Enrollment HIV load was 2.997 (log10 [copies/mL]), (25th, 75th percentiles, 2.303(log10 [copies/mL]), 4.628 (log10 [copies/mL])). Median of Enrollment maximum HIV load was 5.282 (log10 [copies/mL]), (25th, 75th percentiles, 4.694 (log10 [copies/mL]), 5.718 (log10 [copies/mL])). Median of Enrollment maximum HIV load was 5.179 (log10 [copies/mL]), (25th, 75th percentiles, 4.683 (log10 [copies/mL]), 5.636 (log10 [copies/mL])). There was a significant association between HIV transmission types with AMD development. The other immunologic and virologic parameters were not significantly different from AMD patients. Viral load and Max Viral load, CD4, CD8

levels might affect by these treatments. Levels of high-sensitivity C-reactive protein (CRP), interleukin (IL)-6, interferon-γ inducible protein (IP)-10, soluble CD14 (sCD14), soluble CD163 (sCD163), and intestinal fatty acid-binding protein (I-FABP) might be examined in future experiments to investigate the immunologic biomarkers which related with inflammation effects on AMD (79).

Advanced age is the number one risk factor for the multiple and complex etiologies underlying the array of human age-related diseases such as; chronic inflammation, most cancers, cardiovascular diseases, and neurodegenerative disorders like AMD (20).

Comorbidities associated chronic disease with aging (Table 5) included cardiovascular disease in 13.7%, hypertension in 20.9%, diabetes in 8.7%, hyperlipidemia in 21.6%, Kidney disease in 6%, HCV infection in 22.3% of the population. 14.0% of patients with cardiovascular disease had AMD (P = 0.02). 13.9% of patients with hypertension had AMD (P = 0.003). 14.5% of patients with diabetes had AMD (P = 0.04). 9.7% of patients with hyperlipidemia had AMD (P = 0.87). 10.8% of patients with Kidney disease had AMD (P = 0.73). 10.7% of patients with HCV infection had AMD (P = 0.065). Cardiovascular disease, hypertension, and diabetes were associated with AMD development (20). There were no significant effects on AMD by treatment of HCV infection.

Table 5. Comorbidities Associated Chronic Disease with Aging of The Study Population of Patients with Acquired Immunodeficiency Syndrome From the Longitudinal Study of the Ocular Complications of AIDS

Disease	Subcategories	AMD=0 n=1665	AMD=1 n=184	P
Cardiovascular disease (%)	0	1146(87)	112(80)	**0.02**
	1	172(13)	28(20)	
Hypertension (%)	0	1315(80)	127(71)	**0.003**
	1	329(20)	53(29)	
Diabetes (%)	0	1509(92)	157(87)	**0.04**
	1	136(8)	23(13)	
Hyperlipidemia (%)	0	1286(78)	142(79)	0.87
	1	355(22)	38(21)	
Kidney disease (%)	0	1546(94)	168(93)	0.73
	1	99(6)	12(7)	
HCV infection status (%)	0	1092(78)	119(76)	0.65
	1	310(22)	37(24)	
Whether a patient is on highly active retroviral therapy at baseline (%)	0	243(15)	33 (18)	0.85
	1	1401(85)	147(82)	
Ever been on HAART before or after study entry (%)	0	102(6)	14(8)	0.41
	1	1543(94)	166(92)	

Table 6. Effects of Treatment of HIV infection on AMD on Study Population of Patients With Acquired Immunodeficiency Syndrome From the Longitudinal Study of the Ocular Complications of AIDS

Drug	subcategories	amd=0 n=1665	amd=1 n=184	P
Non-nucleoside reverse transcriptase inhibitor (%)	0	1014(62)	103(57)	0.24
	1	630(38)	77(43)	
Protease inhibitor (%)	0	623(38)	80(44)	0.09
	1	1021(62)	100(56)	
Fusion (%)	0	1619(98)	176(98)	0.48
	1	25(2)	4(2)	
Ccr5 antogonist (%)	0	1638(1)	180(1)	0.42
	1	6(0)	0(0)	
Integrase inhibitor (%)	0	1606(98)	175(97)	0.70
	1	38(2)	5(3)	
Combivir (%)	0	1350(82)	141(78)	0.21
	1	294(18)	39(22)	

The patients have a treatment for HIV infection. The drug effect on AMD development are shown in Table 5. There is no significant effect on AMD development.

The individual associations of *ARMS2* (RS10490924), *CFH* (RS10801553), *CFH* (RS800292), *CFI* (RS2285714), *C2* (RS9332739), *C2* (RS547154), *C3* (RS2230199), *CX3CR1* (RS3732379_I249V), *CX3CR1* (RS3732378_T280M), *IL10R1* (RS3135932), *IL10R1* (RS2228055), *IL10R1* (RS2229113), *IL10R1* (RS2229114), *IL28B* (RS8099917), *LIPC* (RS10468017), *SYN3* (RS713685), *SYN3* (RS743751), *SYN3* (RS5754221), with AMD were performed with Chi-Square Test in Table 7. Genetic variant in the *CFH* gene RS800292 (A is minor Allele, Genotype is AA, missense variant), (P = 0.04) and *IL10R1* gene RS3135932 (G is minor Allele, Genotype is

Table 7. Genetic variation analysis of Candidate Genes in Patients with AIDS from LSOCA

GENE	Variant/Location	Variant Type	Allele	Minor Allele	Phenotype (Model)	Genotype	AMD=0 n= (%)	AMD=1 n= (%)	P
ARMS2	RS10490924/ 10:122454932	Missense variant	G>T	T	Recessive	(TT)	911 (61)	93 (60)	0.68
					Dominant	(TT/GT)	1408 (95)	150 (96)	0.45
					Codominant	GG	911 (61)	93 (60)	0.60
						GT	497 (33)	57 (37)	
						TT	78 (5)	6 (4)	
C2	RS9332739/ 6:31936027	Missense variant	G>C	C	Recessive	(CC)	1 (0)	0 (0)	
					Dominant	(CC/CG)	92 (6)	4 (3)	0.58
					Codominant	CC	1 (0)	0 (0)	0.16
						CG	91(6)	94(3)	
						GG	1364 (94)	153 (97)	
C2	RS547154/ 6:31943161	Intron variant	G/T	T	Recessive	TT	56(4)	4(3)	0.45
					Dominant	TT/CT	360(24)	39(25)	0.83
					Codominant	TT	56(4)	4(3)	0.66
						CT	304(21)	35(23)	
						CC	1116(76)	116(75)	
C3	RS2230199/ 19:6718376	Missense variant	G/C	C	Recessive	(CC)	36 (2)	3 (2)	0.66
					Dominant	(CC/CG)	337 (23)	34 (22)	0.66
					Codominant	CC	36 (2)	3 (2)	0.86
						CG	301(21)	94(20)	
						GG	1124 (77)	124 (78)	
CFH	RS10801553/ 1:196686613	Intron Variant	A/C	A	Recessive	(AA)	164(12)	18(12)	0.79
					Dominant	(AA/AC)	805(57)	81(55)	0.74
					Codominant	AA	164(12)	18(12)	0.88
						AC	641(45)	63(43)	
						CC	619(43)	66(45)	

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Table 7. (cont.)

CFH	RS800292/ 1:196673103	Missense variant	G/A	A	Recessive	AA	314(22)	45(29)	0.04
					Dominant	AA/AG	879(60)	99(63)	0.51
					Codominant	AA	314(22)	45(29)	0.12
						AG	565(39)	54(34)	
						GG	577(40)	58(37)	
CFI	RS2285714/ 4:109717654	Synonymous variant	C/T	T	Recessive	TT	143(10)	16(10)	0.90
					Dominant	TT/CT	651(46)	62(40)	0.19
					Codominant	TT	143(10)	16(10)	0.34
						CT	508(36)	46(30)	
						CC	778(54)	93(60)	
CX3CR1	RS3732379_I249 V / 3:39265765	missense variant	C/T	T	Recessive	(TT)	69 (5)	3 (2)	0.1
					Dominant	(TT/TC)	505 (35)	54 (34)	0.84
					Codominant	TT	69 (5)	3 (2)	0.24
						CT	436 (30)	51 (32)	
						CC	948 (65)	105 (66)	
CX3CR1	RS3732378_T280 M / 3:39265671	missense variant	G/A	A	Recessive	(AA)	23 (2)	0 (0)	0.1
					Dominant	(AA/AG)	269 (19)	29 (19)	0.99
					Codominant	AA	23 (2)	0 (0)	0.26
						AG	246 (17)	29 (19)	
						GG	1181 (81)	127 (81)	
IL10R1	RS3135932/ 11:117993348	missense variant	A/G	G	Recessive	GG	22(1)	1(1)	0.38
					Dominant	GG/AG	291(19)	15(9)	0.01
					Codominant	GG	22(1)	1(1)	0.006
						AG	269(17)	14(8)	
						AA	1270(81)	155(91)	

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Table 7. (cont.)

IL10R1	RS2228055/ 11:117994131	missense variant	A/G	G	Recessive	GG	4(0)	0(0)	0.63
					Dominant	GG/AG	110(7)	14(8)	0.67
					Codominant	GG	4(0)	0(0)	0.50
						AG	106(7)	14(8)	
						AA	1378(93)	152(92)	
IL10R1	RS2229114/ 11:117999163	missense variant	C/T	T	Recessive	TT	4(0)	0(0)	0.42
					Dominant	TT/CT	84(5)	12(7)	0.39
					Codominant	TT	6(0)	0(0)	0.39
						CT	78(5)	12(7)	
						CC	1476(95)	160(93)	
IL10R1 (IL10RA)	RS2229113/ 11:117998955	missense variant	A/G	A	Recessive	AA	115(8)	7(4)	0.10
					Dominant	AA/AG	658(43)	59(34)	0.03
					Codominant	AA	115(8)	7(4)	0.056
						AG	543(35)	52(30)	
						GG	874(57)	113(66)	
IL28B	RS8099917/ 19:39252525	intergenic variant	T/G	G	Recessive	GG	53(4)	4(3)	0.48
					Dominant	GG/GT	419(29)	51(32)	0.32
					Codominant	GG	53(4)	4(3)	0.36
						GT	366(25)	47(30)	
						TT	1040(71)	106(68)	
LIPC	RS10468017/ 15:58386313	intron variant	C/T	T	Recessive	TT	86(6)	12(8)	0.36
					Dominant	TT/CT	563(38)	57(36)	0.66
					Codominant	TT	86(6)	12(8)	0.49
						CT	477(32)	45(29)	
						CC	914(62)	100(64)	

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Table 7. (cont.)

SYN3	RS713685/ 22:32812451	intron variant	C/T	T	Recessive	(CC)	1307 (88)	133 (85)	0.22
					Dominant	(CC/CT)	1476 (99)	156 (99)	0.87
					Codominant	CC	1307 (88)	133 (85)	0.47
						CT	169 (11)	23 (15)	
						TT	8 (1)	1 (1)	
SYN3	RS743751/ 22:32838192	intron variant	C/G	G	Recessive	CC	1176 (79)	125 (79)	0.85
					Dominant	CC/CG	1454 (98)	158 (99)	0.22
					Codominant	CC	1176 (79)	125 (79)	0.41
						CG	278 (19)	33 (21)	
						GG	30 (2)	1 (1)	
SYN3	RS5754221/22:32 707469	intron variant	T/C	T	Recessive	CC	179(12)	17(11)	0.67
					Dominant	CC/CT	414(27)	41(26)	0.66
					Codominant	CC	179(12)	17(11)	0.89
						CT	235(16)	24(15)	
						TT	1097(73)	118(74)	

GG/AG, missense variant) (P = 0.01) and RS2229113 (A is minor Allele, Genotype is AA/AG, missense variant) (P = 0.03) were highly associated with AMD development.

The results of Univariate Logistic Regression of Individually Significant Association of Risk Factors with AMD Development are shown in Table 8. Age, smoking history and *CFH* are known risk factor for AMD development in the Literature (80).

Age is strongly associated with AMD development with an odds ratio of 0.47 for participants 30-39 years of age (95% CI 0.21, 1.16, P < .082), an odds ratio of 1.16 for participants 40-49 age (95% CI 0.57, 2.67, P < .709), an odds ratio of 2.27 for participants 50-59 years of age (95% CI 1.10, 5.3, P < .006), an odds ratio of 3.61 for participants over than 60 years of age (95% CI 1.50, 9.38, P < .038), compared to participants whose under 30 years of age. Increasing of Age is obviously increased the risk of AMD development. When the compare with under 30 years of aged and over 60 years of aged, AMD development risk is increased 3.61-fold.

Smoking is strongly associated with AMD development with an odds ratio of 1.11 for participants "former-smokers (95% CI 0.73, 1.70, P < .621), an odds ratio of 1.71 for participants "current-smokers" (95% CI 1.14, 2.73, P < .010) compared to participants whose "never-smokers". When the compare with "never-smokers" and "current-smokers", AMD development risk is increased 1.71-fold. Smoking cause to oxidative stress and mutations in genome (58,77). In Literature, current smokers have a 2- to 4-fold increase in risk for AMD compared to patients who never smoked (58, 77, 82).

There is strongly association AMD development with HIV transmission categories in our result. HIV transmission category is strongly associated with AMD development with an odds ratio of 0.49 for participants with male-to-male sexual contact (95% CI 0.33, 0.76, P < .001), an odds ratio of 0.81 for participants with heterosexual contact (95% CI 0.52, 1.28, P < .361) compared to participants with injection drug use. Lifestyle, social economic status, education, diets, drug usage could be related with increasing of AMD development. Viral and clinical measurements might detect chronic inflammation. However, clinical and viral measurements are not associated with AMD development in our results. Thus, HIV viral load levels are not significantly associated with AMD development. Maybe there should be measurements for a different response for HIV infection to measure chronic inflammation. HIV infection categories are significantly associated with AMD development, the reason might be drug usage,

lifestyle, diet cause increase of immune activation and inflammation levels. Thus, immune activation and inflammation levels are high and they increase AMD risk.

Table 8. Univariate Logistic Regression of Individually Significant Association of Risk Factors with AMD in patients with AIDS LSOCA cohort

Category	**Subcategories**	**P**	**OR (95%CI)**
Age (%)	<30	Ref	Ref
	30–39	0.082	0.47 (0.21 - 1.16)
	40–49	0.709	1.16 (0.57- 2.67)
	50–59	0.038	2.27 (1.10 - 5.3)
	>60	0.006	3.61 (1.50 - 9.38)
Smoking history (%)	Never	Ref	Ref
	Former	0.621	1.11 (0.73 - 1.70)
	Current	0.010	1.77 (1.14 - 2.73)
HIV transmission category (%)	Injections drug use	Ref	Ref
	Male-to-male sexual contact	0.001	0.49 (0.33 - 0.76)
	Hetero sexual contact	0.361	0.81 (0.52 - 1.28)
	Other	0.236	0.64 (0.29 - 1.29)
Cardiovascular disease (%)	No	Ref	Ref
	Yes	0.024	1.67 (1.05 - 2.56)
Hypertension (%)	No	Ref	Ref
	Yes	0.003	1.67 (1.18 - 2.34)
Diabetes (%)	No	Ref	Ref
	Yes	0.043	1.63 (0.99 - 2.56)
CFH	RS800292	Ref	Ref
	RS800292/(A-recessive)	0.043	1.46 (1.00 - 2.10)
IL10R1	RS2229113	Ref	Ref
	RS2229113/(A-dominant)	0.030	0.69 (0.50 - 0.96)
	RS3135932	Ref	Ref
	RS3135932 (G-dominant)	0.002	0.42 (0.24 - 0.71)

With Aging, the risk of systematic disease is increased like risk of AMD. Cardiovascular disease, Hypertension, or Diabetes increase the risk of AMD

development, with an odds ratio of 1.67 for participants with Cardiovascular disease (95% CI 1.05, 2.56, P < .024), with an odds ratio of 1.67 for participants with Hypertension (95% CI 1.18, 2.34, P < .003), with an odds ratio of 1.63 for participants with Diabetes (95% CI 0.99, 2.56, P < .043), these diseases are associated with AMD development for elderly people. Probably, the risk factors such as vascular risk factors for development chronic, systematic and metabolic disease are same with AMD development (20-22). Chronic Kidney Disease is an association with AMD based on inflammation, oxidative stress, endothelial dysfunction, and microvascular dysfunction in the Literature (81). In LSOCA cohort, Elevated serum creatinine is measured to detect Chronic Kidney Disease. In our results, there is no any association with AMD and Chronic Kidney Disease. However, measurement of Elevated serum creatinine might be not enough to show their relationship. Some research shows that there is association between Hyperlipidemia and early AMD (83). In our results, there is no any association with AMD and Hyperlipidemia. HCV infection cause to chronic infection and expectation is chronic HCV infection had an increased risk of AMD (84). There is no association with presences or absences of HCV infection. Genetic factors or antiviral treatment drugs decrease effect of HCV infection on patients.

Genetic variant of *CFH* RS800292/(A-recessive) , *IL10R1* RS2229113/(A-dominant) and *IL10R1* RS3135932(G-dominant) are significantly associated with AMD development. CFH RS800292 is increased to AMD development risk with 2-fold. IL10R1 RS2229113/(A-dominant) and IL10R1 RS3135932 (G-dominant) are decreased AMD development risk.

CFH/RS800292 meant 184G>A, I62V, or Val62Ile. A deficiency in complement factor H causes continuous activation of the alternative complement pathway (80) and synthesis of the convertase C3BbB, according to Licht et al. (2006). Hypocomplementemia and complement activation on tissue surfaces lacking endogenous regulators, such as the glomerular basement membrane, arise. The production of dense deposits, thickening of the basement membrane, reduced renal filtration, and progressive loss of renal function are all symptoms of continuous C3 deposition (85, 86).

IL10RA RS3135932 is Exon 4 and RS2229113 is Exon 7. They are missense variant mutation. They are not in ligand binding site but these regions has a role in conformational rearrangements of IL10RA, especially, Exon 4 (87,88). Depend upon confirmational changing, ligand binding efficiency might be decreased. Thus,

immunosuppressive activity of *IL10* is reduced and anti-inflammatory activity increase (88).

Multivariate Logistic Regression of Significant Risk Factors for AMD Development are examined with significant factors which obtained from Chi-Square test in Table 3, Table 4, Table 5, Table 6 and Table 7. There are 2 significant risk factors. One of them is HIV transmission category which is highest risk among injection drug users, and the significant category is also Male-to male sexual contact. AMD development risk is lower in Male-to male sexual contact than injection drug users. The other factor is *IL10R1* RS2229113/(A-dominant) that is decreased AMD development risk. Missense variant mutation on *IL10R1* (Exchange of S138 to G) might be increase anti-inflammatory activity.

There are just 185 patients with AMD. At least 300 patients are needed to get significantly results by statistically. The sample size of patient of AMD is not enough to significant results. Our results might be give an idea to risk factors for AMD development and these risk factors might have a role in AMD development and Progression. However, the risk factors are not certainly proof for AMD development.

Metabolism of Eye is included highly oxidative reactions because of light and vision process. If there is something decrease on repair mechanism or protective molecules, Levels of molecules are easily changed and harmful molecules's level might be increase and It cause to damage of structure of eye. AMD might be progress easily in this condition. Drugs of Treatment of HIV infection is not significantly risk factor for AMD development. These Drugs have a lot side effects, and they can affect easily to eye structure. But there is no any effect on AMD development. Also, their effect is protective against to AMD development. These factors might not have any effect on AMD, to increase or decrease risk.

Genes and biological pathways which are not directly related with AMD development, affects AMD development in these patients. Repair mechanism is not enough to reduce drusen formation. And Drusen Formation rate might be faster than normal patients with AMD. And also, this is early stage of AMD, thus gene effects might be not shown in this stage.

Table 9. Multivariate Logistic Regression of Individually Significant Association of Risk Factors with AMD in patients with AIDS LSOCA cohort

Category	**Subcategories**	**P**	**OR (95%CI)**
Age (%)	<30	Ref	Ref
	30–39	0.269	0.51 (0.16 - 1.92)
	40–49	0.622	1.31 (0.49 - 4.56)
	50–59	0.294	1.81 (0.66 - 6.39)
	>60	0.059	3.37 (1.01 - 13.34)
Smoking history (%)	Never	Ref	Ref
	Former	0.801	0.94 (0.59 - 1.51)
	Current	0.093	1.5 (0.93 - 2.41)
HIV transmission category (%)	Injections drug use	Ref	Ref
	Male-to male sexual contact	0.006	0.47 (0.28 - 0.81)
	Hetero sexual contact	0.322	0.76 (0.44 - 1.32)
	other	0.071	0.38 (0.12 - 1.01)
Cardiovascular disease (%)	No	Ref	Ref
	Yes	0.139	1.46 (0.87 - 2.39)
Hypertension (%)	No	Ref	Ref
	Yes	0.914	0.98 (0.61 - 1.52)
Diabetes (%)	No	Ref	Ref
	Yes	0.95	1.02 (0.52 - 1.86)
CFH	RS800292	Ref	Ref
	RS800292/(A-recessive)	0.4	1.2 (0.77 - 1.85)
IL10R1	RS2229113	Ref	Ref
	RS2229113/(A-dominant)	0.406	0.83 (0.53 - 1.28)
	RS3135932	Ref	Ref
	RS3135932 (G-dominant)	**0.013**	0.38 (0.17 - 0.78)

To conclude, Age is significantly risk factor for AMD development. Aging cause to also chronic inflammation and accumulation of ROS. Chronic inflammation and oxidative stress cause to AMD development. Chronic inflammation and oxidative stress might be the major factors for the early development of AMD. AIDS patients might be used for aging model.

CHAPTER 4

CONCLUSION AND FUTURE DIRECTIONS

Aging is the primary factor for AMD development. Smoking history, Transmission categories of HIV infection, cardiovascular disease, diabetes, and hypertension are significant factors individually. Although AMD is a complex multifactorial disease, missense variant mutations of *IL10R1* genes and missense variant mutations of *CFH* have a considerable role in developing AMD. *IL10R1* gene variants are reported for the first time for the development of AMD.

The population of patients with AIDS showed that HIV infection assesses can AIDS patients be using the Accelerated and Accentuated Aging Model.

Classic AMD gene effects which directly related with AMD development from GWAS studies we could not see because this patient with AIDS, they are not normal people and they have a chronic inflammation. Their immune system is highly induced. It caused to AMD development so we can see it early aged. Also, chronic inflammation effect is over the AMD genes effects. AMD development might be just resulting of complex disease, is not known yet.

In the future, AMD Related gene pathways should be examined according to drusen compositions. Drusen's compositions give an idea about the end of products of these pathways. Understanding the etiopathogenesis of AMD will allow for the development of earlier and more effective therapies. Early therapies and treatments are safer for people than loss of visual acuity and blindness, in addition, they provide to improve the quality of life of patients.

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APPENDICES

APPENDIX A

Dataset

Age Related Molecules from Literature is https://ageing-map.org/atlas/downloads/

APPENDIX B

Supplement Table 1. List of the 36 genes from Literature for development AMD

Gene Symbol	Gene Name	PANTHER Protein Class	Annotation
ABCA1	Phospholipid-transporting ATPase ABCA1	ATP-binding cassette (ABC) transporter (PC00003)	ATP-binding cassette sub-family A member 1; cAMP-dependent and sulfonylurea-sensitive anion transporter. Key gatekeeper influencing intracellular cholesterol transport; Belongs to the ABC transporter superfamily. ABCA family
ABCA4	Retinal-specific phospholipid-transporting ATPase ABCA4;ABCA4	ATP-binding cassette (ABC) transporter (PC00003)	Atp-binding cassette, subfamily a (abc1), member 4; Retinal-specific ATP-binding cassette transporter; In the visual cycle, acts as an inward-directed retinoid flipase, retinoid substrates imported by ABCA4 from the extracellular or intradiscal (rod) membrane surfaces to the cytoplasmic membrane surface are all-trans-retinaldehyde (ATR) and N-retinyl-phosphatidyl-ethanolamine (NR-PE). Once transported to the cytoplasmic surface, ATR is reduced to vitamin A by trans- retinol dehydrogenase (tRDH) and then transferred to the retinal pigment epithelium (RPE) where it is converted to 11-cis [...]
ADAMTS9	A disintegrin and metalloproteinase with thrombospondin motifs 9;ADAMTS9	metalloprotease (PC00153)	A disintegrin and metalloproteinase with thrombospondin motifs 9; Cleaves the large aggregating proteoglycans, aggrecan (at the '1838-Glu-|-Ala-1839' site) and versican (at the '1428- Glu-|-Ala-1429' site). Has a proteas e-independent function in promoting the transport from the endoplasmic reticulum to the Golgi apparatus of a variety of secretory cargos; ADAM metallopeptidases with thrombospondin type 1 motif
APOE	Apolipoprotein E	apolipoprotein (PC00052)	Ag e-related maculopathy susceptibility 2
ARMS2	Ag e-related maculopathy susceptibility protein 2;ARMS2	—	Apolipoprotein E; Mediates the binding, internalization, and catabolism of lipoprotein particles. It can serve as a ligand for the LDL (apo B/E) receptor and for the specific apo-E receptor (chylomicron remnant) of hepatic tissues; Apolipoproteins

(Cont. on Next Page)

Supplement Table 1. (cont.)

B3GALTL	Beta-1,3-glucosyltransferase;B3GLCT	glycosyltransferase (PC00111)	Udp-glucose:o-linked fucose beta-1,3-glucosyltransferase; Beta-1,3-glucosyltransferase; O-glucosyltransferase that transfers glucose toward fucose with a beta-1,3 linkage. Specifically glucosylates O-linked fucosylglycan on TSP typ e-1 domains of proteins, thereby contributing to elongation of O-fucosylglycan
C2	Complement C2;C2	___	Cholesteryl ester transfer protein; Involved in the transfer of neutral lipids, including cholesteryl ester and triglyceride, among lipoprotein particles. Allows the net movement of cholesteryl ester from high density lipoproteins/HDL to triglycerid e-rich very low density lipoproteins/VLDL, and the equimolar transport of triglyceride from VLDL to HDL. Regulates the reverse cholesterol transport, by which excess cholesterol is removed from peripheral tissues and returned to the liver for elimination; Belongs to the BPI/LBP/Plunc superfamily. BPI/LBP family
C3	Complement C3;C3	Protease inhibitor (PC00191)	Complement factor B; Factor B which is part of the alternate pathway of the complement system is cleaved by factor D into 2 fragments: Ba and Bb. Bb, a serine protease, then combines with complement factor 3b to generate the C3 or C5 convertase. It has also been implicated in proliferation and differentiation of preactivated B- lymphocytes, rapid spreading of peripheral blood monocytes, stimulation of lymphocyte blastogenesis and lysis of erythrocytes. Ba inhibits the proliferation of preactivated B-lymphocytes; Belongs to the peptidase S1 family
C9	Complement component C9;C9	___	Complement factor H; Factor H functions as a cofactor in the inactivation of C3b by factor I and also increases the rate of dissociation of the C3bBb complex (C3 convertase) and the (C3b)NBB complex (C5 convertase) in the alternative complement pathway
CETP	Cholesteryl ester transfer protein;CETP	___	Complement factor H-related protein 1; Involved in complement regulation. The dimerized forms have avidity for tissue-bound complement fragments and efficiently compete with the physiological complement inhibitor CFH. Can associate with lipoproteins and may play a role in lipid metabolism
CFB	Complement factor B;CFB	___	Complement factor H-related protein 3; Might be involved in complement regulation
CFH	Complement factor H;CFH	___	Complement factor I; Responsible for cleaving the alpha-chains of C4b and C3b in the presence of the cofactors C4-binding protein and factor H respectively; Belongs to the peptidase S1 family

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Supplement Table 1. (cont.)

CFHR1	Complement factor H-related protein 1;CFHR1	___	Collagen alpha-1 (VIII) chain; Macromolecular component of the subendothelium. Major component of the Descemet's membrane (basement membrane) of corneal endothelial cells. Also component of the endothelia of blood vessels. Necessary for migration and proliferation of vascular smooth muscle cells and thus, has a potential role in the maintenance of vessel wall integrity and structure, in particular in atherogenesis; Collagens
CFHR3	Complement factor H-related protein 3; CFHR3	___	Collagen alpha-1 (X) chain; Type X collagen is a product of hypertrophic chondrocytes and has been localized to presumptive mineralization zones of hyaline cartilage; Collagens
CFI	Complement factor I;CFI	serine protease (PC00203)	CX3C chemokine receptor 1; Receptor for the CX3C chemokine fractalkine (CX3CL1); binds to CX3CL1 and mediates both its adhesive and migratory functions. Acts as coreceptor with CD4 for HIV-1 virus envelope protein (in vitro). Isoform 2 and isoform 3 seem to be more potent HIV-1 coreceptors than isoform 1
COL10A1	Collagen alpha-1 (X) chain;COL10A1	extracellular matrix structural protein (PC00103)	Complement C2; Component C2 which is part of the classical pathway of the complement system is cleaved by activated factor C1 into two fragments: C2b and C2a. C2a, a serine protease, then combines with complement factor C4b to generate the C3 or C5 convertase; Belongs to the peptidase S1 family
COL8A1	Collagen alpha-1 (VIII) chain; COL8A1	extracellular matrix structural protein (PC00103)	Complement C3; C3 plays a central role in the activation of the complement system. Its processing by C3 convertase is the central reaction in both classical and alternative complement pathways. After activation C3b can bind covalently, via its reactive thioester, to cell surface carbohydrates or immune aggregates; C3 and PZP like, alpha-2-macroglobulin domain containing
CX3CR1	CX3C chemokine receptor 1;CX3CR1	___	Complement component C9; Constituent of the membrane attack complex (MAC) that plays a key role in the innate and adaptive immune response by forming pores in the plasma membrane of target cells. C9 is the por e- forming subunit of the MAC; Belongs to the complement C6/C7/C8/C9 family
DDR1	Epithelial discoidin domain-containing receptor 1;DDR1	transmembrane signal receptor (PC00197)	Epithelial discoidin domain-containing receptor 1; Tyrosine kinase that functions as cell surface receptor for fibrillar collagen and regulates cell attachment to the extracellular matrix, remodeling of the extracellular matrix, cell migration, differentiation, survival and cell proliferation. Collagen binding triggers a signaling pathway that involves SRC and leads to the activation of MAP kinases. Regulates remodeling of the extracellular matrix by up-regulation of the matrix metalloproteinases MMP2, MMP7 and MMP9, and thereby facilitates cell migration and wound healing.

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Supplement Table 1. (cont.)

ERCC6	DNA excision repair protein ERCC-6;ERCC6	—	DNA excision repair protein ERCC-6; Essential factor involved in transcription-coupled nucleotide excision repair which allows RNA polymerase II-blocking lesions to be rapidly removed from the transcribed strand of active genes. Upon DNA-binding, it locally modifies DNA conformation by wrapping the DNA around itself, thereby modifying the interface between stalled RNA polymerase II and DNA. It is required for transcription-coupled repair complex formation. It recruits the CSA complex (DCX (ERCC8) complex), nucleotide excision repair proteins and EP300 to the at sites of RNA polymerase I [.
FBLN6	HMCN1	—	Fibulin-5; Essential for elastic fiber formation, is involved in the assembly of continuous elastin (ELN) polymer and promotes the interaction of microfibrils and ELN. Stabilizes and organizes elastic fibers in the skin, lung and vasculature (By similarity). Promotes adhesion of endothelial cells through interaction of integrins and the RGD motif. Vascular ligand for integrin receptors which may play a role in vascular development and remodeling. May act as an adapter that mediates the interaction between FBN1 and ELN; Belongs to the fibulin family
FBLN5	Fibulin-5;FBLN5	extracellular matrix structural protein (PC00103)	Hemicentin-1; Promotes cleavage furrow maturation during cytokinesis in preimplantation embryos. May play a role in the architecture of adhesive and flexible epithelial cell junctions. May play a role during myocardial remodeling by imparting an effect on cardiac fibroblast migration; Fibulins
FILIP1L	Filamin A-interacting protein 1-like;FILIP1L	—	Filamin A-interacting protein 1-like; Acts as a regulator of the antiangiogenic activity on endothelial cells. When overexpressed in endothelial cells, leads to inhibition of cell proliferation and migration and an increase in apoptosis. Inhibits melanoma growth When expressed in tumor- associated vasculature
FRK	Tyrosin e-protein kinase FRK;FRK	—	Tyrosin e-protein kinase FRK; Non-receptor tyrosin e-protein kinase that negatively regulates cell proliferation. Positively regulates PTEN protein stability through phosphorylation of PTEN on 'Tyr-336', which in turn prevents its ubiquitination and degradation, possibly by reducing its binding to NEDD4. May function as a tumor suppressor; SH2 domain containing
HTRA1	Serine protease HTRA1;HTRA1	serine protease (PC00203)	Serine protease HTRA1; Serine protease with a variety of targets, including extracellular matrix proteins such as fibronectin. HTRA1-generated fibronectin fragments further induce synovial cells to up-regulate MMP1 and MMP3 production. May also degrade proteoglycans, such as aggrecan, decorin and fibromodulin. Through cleavage of proteoglycans, may release soluble FGF-glycosaminoglycan complexes that promote the range and intensity of FGF signals in the extracellular space. Regulates the availability of insulin-like growth factors (IGFs) by cleaving IGF-binding proteins. Inhibits signa [...]

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Supplement Table 1. (cont.)

IER3	Radiation-inducible immediat e-early gene IEX-1;IER3	___	Immediate early response 3; Radiation-inducible immediat e-early gene IEX-1; May play a role in the ERK signaling pathway by inhibiting the dephosphorylation of ERK by phosphatase PP2A- PPP2R5C holoenzyme. Acts also as an ERK downstream effector mediating survival. As a member of the NUPR1/RELB/IER3 survival pathway, may provide pancreatic ductal adenocarcinoma with remarkable resistance to cell stress, such as starvation or gemcitabine treatment
LIPC	Hepatic triacylglycerol lipase;LIPC	lipase (PC00143)	Hepatic triacylglycerol lipase; Hepatic lipase has the capacity to catalyze hydrolysis of phospholipids, mono-, di-, and triglycerides, and acyl-CoA thioesters. It is an important enzyme in HDL metabolism. Hepatic lipase binds heparin
QRX	Retina and anterior neural fold homeobox protein 2;RAX2	homeodomain transcription factor (PC00119)	Retina and anterior neural fold homeobox protein 2; May be involved in modulating the expression of photoreceptor specific genes. Binds to the Ret-1 and Bat-1 element within the rhodopsin promoter; PRD class homeoboxes and pseudogenes
RAD51B	DNA repair protein RAD51 homolog 2;RAD51B	DNA metabolism protein (PC00009)	DNA repair protein RAD51 homolog 2; Involved in the homologous recombination repair (HRR) pathway of doubl e-stranded DNA breaks arising during DNA replication or induced by DNA-damaging agents. May promote the assembly of presynaptic RAD51 nucleoprotein filaments. Binds singl e-stranded DNA and doubl e-stranded DNA and has DNA-dependent ATPase activity. Part of the RAD21 paralog protein complex BCDX2 which acts in the BRCA1-BRCA2-dependent HR pathway. Upon DNA damage, BCDX2 acts downstream of BRCA2 recruitment and upstream of RAD51 recruitment. BCDX2 binds predominantly to the intersecti [...]
SLC16A8	Monocarboxylate transporter 3;SLC16A8	transporter (PC00227)	Mfs transporter, mct family, solute carrier family 16 (monocarboxylic acid transporters), member 8; Monocarboxylate transporter 3; Proton-linked monocarboxylate transporter. Catalyzes the rapid transport across the plasma membrane of many monocarboxylates such as lactate, pyruvate, branched-chain oxo acids derived from leucine, valine and isoleucine, and the ketone bodies acetoacetate, beta-hydroxybutyrate and acetate (By similarity); Solute carriers
TGFBR1	TGF-beta receptor typ e-1;TGFBR1	serine/threonine protein kinase receptor (PC00205)	TGF-beta receptor typ e-1; Transmembrane serine/threonine kinase forming with the TGF-beta type II serine/threonine kinase receptor, TGFBR2, the non-promiscuous receptor for the TGF-beta cytokines TGFB1, TGFB2 and TGFB3. Transduces the TGFB1, TGFB2 and TGFB3 signal from the cell surface to the cytoplasm and is thus regulating a plethora of physiological and pathological processes including cell cycle arrest in epithelial and hematopoietic cells, control of mesenchymal cell proliferation and differentiation, wound healing, extracellular matrix production, immunosuppression and carcinogen [...]

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Supplement Table 1. (cont.)

TIMP3	Metalloproteinase inhibitor 3;TIMP3	protease inhibitor (PC00191)	Timp metallopeptidase inhibitor 3; Metalloproteinase inhibitor 3; Complexes with metalloproteinases (such as collagenases) and irreversibly inactivates them by binding to their catalytic zinc cofactor. May form part of a tissu e-specific acute response to remodeling stimuli. Known to act on MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-13, MMP-14 and MMP-15
TLR3	Toll-like receptor 3;TLR3	transmembrane signal receptor (PC00197)	Toll-like receptor 3; Key component of innate and adaptive immunity. TLRs (Toll-like receptors) control host immune response against pathogens through recognition of molecular patterns specific to microorganisms. TLR3 is a nucleotid e-sensing TLR which is activated by doubl e-stranded RNA, a sign of viral infection. Acts via the adapter TRIF/TICAM1, leading to NF-kappa-B activation, IRF3 nuclear translocation, cytokine secretion and the inflammatory response; CD molecules
TLR4	Toll-like receptor 4;TLR4	___	Toll-like receptor 4; Cooperates with LY96 and CD14 to mediate the innate immune response to bacterial lipopolysaccharide (LPS). Acts via MYD88, TIRAP and TRAF6, leading to NF-kappa-B activation, cytokine secretion and the inflammatory response. Also involved in LPS-independent inflammatory responses triggered by free fatty acids, such as palmitate, and Ni (2+). Responses triggered by Ni (2+) require non-conserved histidines and are, therefore, species-specific….
TNFRSF10A	Tumor necrosis factor receptor superfamily member 10A;TNFRSF10A	transmembrane signal receptor (PC00197)	Tumor necrosis factor receptor superfamily member 10A; Receptor for the cytotoxic ligand TNFSF10/TRAIL. The adapter molecule FADD recruits caspas e-8 to the activated receptor. The resulting death-inducing signaling complex (DISC) performs caspas e-8 proteolytic activation which initiates the subsequent cascade of caspases (aspartat e-specific cysteine proteases) mediating apoptosis. Promotes the activation of NF-kappa-B; CD molecules
VEGFA	Vascular endothelial growth factor A;VEGFA	growth factor (PC00112)	Vascular endothelial growth factor A; Growth factor active in angiogenesis, vasculogenesis and endothelial cell growth. Induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels. Binds to the FLT1/VEGFR1 and KDR/VEGFR2 receptors, heparan sulfate and heparin. NRP1/Neuropilin-1 binds isoforms VEGF-165 and VEGF-145. Isoform VEGF165B binds to KDR but does not activate downstream signaling [...]

Supplement Table 2. 158 proteins are found in the retina from the curated list of genes that have previously been associated with AMD with PANTHER Protein Class and annotation of genes.

Gene Symbol	Gene Name	PANTHER Protein Class	Annotation
CRP	C-reactive protein;CRP;ortholog	—	C-reactive protein; Displays several functions associated with host defense: it promotes agglutination, bacterial capsular swelling, phagocytosis and complement fixation through its calcium-dependent binding to phosphorylcholine. Can interact with DNA and histones and may scavenge nuclear material released from damaged circulating cells; Short pentraxins
TUFM	Elongation factor Tu, mitochondrial;TUFM; ortholog	translation elongation factor (PC00222)	Elongation factor Tu, mitochondrial; This protein promotes the GTP-dependent binding of aminoacyl-tRNA to the A-site of ribosomes during protein biosynthesis; Belongs to the TRAFAC class translation factor GTPase superfamily. Classic translation factor GTPase family. EF-Tu/EF-1A subfamily
PLG	Plasminogen;PLG; ortholog	serine protease (PC00203)	Plasminogen; Plasmin dissolves the fibrin of blood clots and acts as a proteolytic factor in a variety of other processes including embryonic development, tissue remodeling, tumor invasion, and inflammation. In ovulation, weakens the walls of the Graafian follicle. It activates the urokinas e-type plasminogen activator, collagenases and several complement zymogens, such as C1 and C5. Cleavage of fibronectin and laminin leads to cell detachment and apoptosis. Also cleaves fibrin, thrombospondin and von Willebrand factor. Its role in tissue remodeling and tumor invasion may be modulated b [...]
APOH	Beta-2-glycoprotein 1;APOH;ortholog	—	Beta-2-glycoprotein 1; Binds to various kinds of negatively charged substances such as heparin, phospholipids, and dextran sulfate. May prevent activation of the intrinsic blood coagulation cascade by binding to phospholipids on the surface of damaged cells; Apolipoproteins
FTL	Ferritin light chain;FTL;ortholog	storage protein (PC00210)	Ferritin light chain; Stores iron in a soluble, non-toxic, readily available form. Important for iron homeostasis. Iron is taken up in the ferrous form and deposited as ferric hydroxides after oxidation. Also plays a role in delivery of iron to cells. Mediates iron uptake in capsule cells of the developing kidney (By similarity); Belongs to the ferritin family
PSMB5	Proteasome subunit beta typ e-5;PSMB5;ortholog	protease (PC00190)	Proteasome subunit beta typ e-5; Component of the 20S core proteasome complex involved in the proteolytic degradation of most intracellular proteins. This complex plays numerous essential roles within the cell by associating with different regulatory particles. Associated with two 19S regulatory particles, forms the 26S proteasome and thus participates in the ATP-dependent degradation of ubiquitinated proteins. The 26S proteasome plays a key role in the maintenance of protein homeost…

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Supplement Table 2. (cont.)

EIF4H	Eukaryotic translation initiation factor 4H;EIF4H;ortholog	translation initiation factor (PC00224)	Eukaryotic translation initiation factor 4H; Stimulates the RNA helicase activity of EIF4A in the translation initiation complex. Binds weakly mRNA; RNA binding motif containing
C10orf58	Peroxiredoxin-like 2A;PRXL2A;ortholog	—	Redox-regulatory protein FAM213A; Involved in redox regulation of the cell. Acts as an antioxidant. Inhibits TNFSF11-induced NFKB1 and JUN activation and osteoclast differentiation. May affect bone resorption and help to maintain bone mass. Acts as a negative regulator of macrophag e-mediated inflammation by inhibiting macrophage production of inflammatory cytokines, probably through suppression of the MAPK signaling pathway; Belongs to the peroxiredoxin-like FAM213 family. FAM213A subfamily
HSPD1	60 kDa heat shock protein, mitochondrial;HSPD1; ortholog	—	Heat shock protein family d (hsp60) member 1; 60 kDa heat shock protein, mitochondrial; Chaperonin implicated in mitochondrial protein import and macromolecular assembly. Together with Hsp10, facilitates the correct folding of imported proteins. May also prevent misfolding and promote the refolding and proper assembly of unfolded polypeptides generated under stress conditions in the mitochondrial matrix. The functional units of these chaperonins consist of heptameric rings of the large subunit Hsp60, which function as a back-to-back double ring. In a cyclic reaction, Hsp60 ring complex [...]
SAG	RING-box protein 2;RNF7;ortholog	ubiquitin-protein ligase (PC00234)	S-arrestin; Arrestin is one of the major proteins of the ros (retinal rod outer segments); it binds to photoactivated- phosphorylated rhodopsin, thereby apparently preventing the transducin-mediated activation of phosphodiesterase
SERPINF1	Pigment epithelium-derived factor;SERPINF1; ortholog	protease inhibitor (PC00191)	Pigment epithelium-derived factor; Neurotrophic protein; induces extensive neuronal differentiation in retinoblastoma cells. Potent inhibitor of angiogenesis. As it does not undergo the S (stressed) to R (relaxed) conformational transition characteristic of active serpins, it exhibits no serine protease inhibitory activity; Serpin peptidase inhibitors
GFAP	Glial fibrillary acidic protein;GFAP;ortholog	—	Glial fibrillary acidic protein; GFAP, a class-III intermediate filament, is a cell- specific marker that, during the development of the central nervous system, distinguishes astrocytes from other glial cells
PRELP	Prolargin;PRELP; ortholog	—	Prolargin; May anchor basement membranes to the underlying connective tissue; Small leucine rich repeat proteoglycans

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Supplement Table 2. (cont.)

RGR	RP e-retinal G protein-coupled receptor;RGR;ortholog	G-protein coupled receptor (PC00021)	RP e-retinal G protein-coupled receptor; Receptor for all-trans- and 11-cis-retinal. Binds preferentially to the former and may catalyze the isomerization of the chromophore by a retinochrom e-like mechanism; Opsin receptors
DEFA3	Neutrophil defensin 3;DEFA3;ortholog	antimicrobial response protein (PC00051)	Neutrophil defensin 3; Defensin 2 and defensin 3 have antibiotic, fungicide and antiviral activities. Has antimicrobial activity against Gram- negative and Gram-positive bacteria. Defensins are thought to kill microbes by permeabilizing their plasma membrane; Defensins, alpha
DLD	Dihydrolipoyl dehydrogenase, mitochondrial;DLD; ortholog	oxidoreductase (PC00176)	Dihydrolipoyl dehydrogenase, mitochondrial; Lipoamide dehydrogenase is a component of the glycine cleavage system as well as an E3 component of three alpha-ketoacid dehydrogenase complexes (pyruvat e-, alpha-ketoglutarat e-, and branched-chain amino acid-dehydrogenase complex). In monomeric form has additional moonlighting function as serine protease. Involved in the hyperactivation of spermatazoa during capacitation and in the spermatazoal acrosome reaction (By similarity)
NSUN2	RNA cytosine C (5)-methyltransferase NSUN2;NSUN2; ortholog	RNA methyltransferase (PC00033)	NOP2/Sun RNA methyltransferase family member 2; tRNA (cytosine (34)-C (5))-methyltransferase; RNA methyltransferase that methylates tRNAs, and possibly RNA polymerase III transcripts. Methylates cytosine to 5- methylcytosine (m5C) at positions 34 and 48 of intron-containing tRNA (Leu) (CAA) precursors, and at positions 48, 49 and 50 of tRNA (Gly) (GCC) precursors. May act downstream of Myc to regulate epidermal cell growth and proliferation. Required for proper spindle assembly and chromosome segregation, independently of its methyltransferase activity
PFDN1	Prefoldin subunit 1;PFDN1;ortholog	chaperone (PC00072)	Prefoldin subunit 1; Binds specifically to cytosolic chaperonin (c-CPN) and transfers target proteins to it. Binds to nascent polypeptide chain and promotes folding in an environment in which there are many competing pathways for nonnative proteins; Prefoldin subunits
CRYBA1	Beta-crystallin A3;CRYBA1;ortholog	—	Beta-crystallin A3; Crystallins are the dominant structural components of the vertebrate eye lens
GAPDH	Glyceraldehyd e-3-phosphate dehydrogenase;GAPDH;ortholog	dehydrogenase (PC00092)	Glyceraldehyd e-3-phosphate dehydrogenase; Has both glyceraldehyd e-3-phosphate dehydrogenase and nitrosylase activities, thereby playing a role in glycolysis and nuclear functions, respectively. Participates in nuclear events including transcription, RNA transport, DNA replication and apoptosis. Nuclear functions are probably due to the nitrosylase activity that mediates cysteine S-nitrosylation of nuclear target proteins such as SIRT1, HDAC2 and PRKDC. Modulates the organization and assembly of the cytoskeleton. Facilitates the CHP1-dependent microtubule and membrane associations throu [...]

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Supplement Table 2. (cont.)

PRDX1	Peroxiredoxin-1;PRDX1;ortholog	peroxidase (PC00180)	Peroxiredoxin-1; Thiol-specific peroxidase that catalyzes the reduction of hydrogen peroxide and organic hydroperoxides to water and alcohols, respectively. Plays a role in cell protection against oxidative stress by detoxifying peroxides and as sensor of hydrogen peroxid e-mediated signaling events. Might participate in the signaling cascades of growth factors and tumor necrosis factor-alpha by regulating the intracellular concentrations of H (2)O (2). Reduces an intramolecular disulfide bond in GDPD5 that gates the ability to GDPD5 to drive postmitotic motor neuron differentiation (By s ..)
TGM2	Protein-glutamine gamma-glutamyl transferase 2;TGM2;ortholog	transferase (PC00220)	Protein-glutamine gamma-glutamyltransferase 2; Catalyzes the cross-linking of proteins and the conjugation of polyamines to proteins; Transglutaminases
CD9	CD9 antigen;CD9;ortholog	—	CD9 antigen; Involved in platelet activation and aggregation. Regulates paranodal junction formation. Involved in cell adhesion, cell motility and tumor metastasis. Required for sperm-egg fusion; Belongs to the tetraspanin (TM4SF) family
SERPINA1	Alpha-1-antitrypsin;SERPINA1; ortholog	protease inhibitor (PC00191)	Alpha-1-antitrypsin; Inhibitor of serine proteases. Its primary target is elastase, but it also has a moderate affinity for plasmin and thrombin. Irreversibly inhibits trypsin, chymotrypsin and plasminogen activator. The aberrant form inhibits insulin-induced NO synthesis in platelets, decreases coagulation time and has proteolytic activity against insulin and plasmin; Belongs to the serpin family
CRYBB1	Beta-crystallin B1;CRYBB1;ortholog		Beta-crystallin B1; Crystallins are the dominant structural components of the vertebrate eye lens; Belongs to the beta/gamma-crystallin family
RDH5	Retinol dehydrogenase 5;RDH5;ortholog	dehydrogenase (PC00092)	11-cis retinol dehydrogenase; Stereospecific 11-cis retinol dehydrogenase, which catalyzes the final step in the biosynthesis of 11-cis retinaldehyde, the universal chromophore of visual pigments. Also able to oxidize 9-cis-retinol and 13-cis-retinol, but not all- trans-retinol. Active in the presence of NAD as cofactor but not in the presence of NADP; Short chain dehydrogenase/reductase superfamily
LBP	Lipopolysaccharid e-binding protein;LBP;ortholog	—	Lipopolysaccharid e-binding protein; Plays a role in the innate immune response. Binds to the lipid A moiety of bacterial lipopolysaccharides (LPS), a glycolipid present in the outer membrane of all Gram-negative bacteria. Acts as an affinity enhancer for CD14, facilitating its association with LPS. Promotes the release of cytokines in response to bacterial lipopolysaccharide; BPI fold containing

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Supplement Table 2. (cont.)

ANXA1	Annexin A1;ANXA1;ortholog	calcium-binding protein (PC00060)	Annexin A1; Plays important roles in the innate immune response as effector of glucocorticoid-mediated responses and regulator of the inflammatory process. Has anti-inflammatory activity. Plays a role in glucocorticoid-mediated down- regulation of the early phase of the inflammatory response. Promotes resolution of inflammation and wound healing. Functions at least in part by activating the formyl peptide receptors and downstream signaling cascades. Promotes ….
TXNDC5	Thioredoxin domain-containing protein 5;TXNDC5;ortholog	chaperone (PC00072)	Thioredoxin domain-containing protein 5; Possesses thioredoxin activity. Has been shown to reduce insulin disulfide bonds. Also complements protein disulfid e- isomerase deficiency in yeast (By similarity)
ANXA5	Annexin A5;ANXA5;ortholog	calcium-binding protein (PC00060)	Annexin A5; This protein is an anticoagulant protein that acts as an indirect inhibitor of the thromboplastin-specific complex, which is involved in the blood coagulation cascade; Annexins
CRYGD	Gamma-crystallin D;CRYGD;ortholog	—	Gamma-crystallin D; Crystallins are the dominant structural components of the vertebrate eye lens
SAA1	Serum amyloid A-1 protein;SAA1;ortholog	—	Serum amyloid A-1 protein; Major acute phase protein; Belongs to the SAA family
TPD52	Tumor protein D52;TPD52;ortholog	—	Tumor protein d52; Belongs to the TPD52 family
EPHX1	Epoxide hydrolase 1;EPHX1;ortholog	hydrolase (PC00121)	Microsomal epoxide hydrolase; Epoxide hydrolase 1; Biotransformation enzyme that catalyzes the hydrolysis of arene and aliphatic epoxides to less reactive and more water soluble dihydrodiols by the trans addition of water (By similarity). May play a role in the metabolism of endogenous lipids such as epoxid e-containing fatty acids
RPS19	40S ribosomal protein S19;RPS19;ortholog	ribosomal protein (PC00202)	40S ribosomal protein S19; Required for pr e-rRNA processing and maturation of 40S ribosomal subunits; Belongs to the eukaryotic ribosomal protein eS19 family
CFH	Complement factor H;CFH;ortholog	—	Complement factor H; Factor H functions as a cofactor in the inactivation of C3b by factor I and also increases the rate of dissociation of the C3bBb complex (C3 convertase) and the (C3b)NBB complex (C5 convertase) in the alternative complement pathway

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Supplement Table 2. (cont.)

HSPA5	Endoplasmic reticulum chaperone BiP;HSPA5;ortholog	___	78 kDa glucos e-regulated protein; Plays a role in facilitating the assembly of multimeric protein complexes inside the endoplasmic reticulum. Involved in the correct folding of proteins and degradation of misfolded proteins via its interaction with DNAJC10, probably to facilitate the release of DNAJC10 from its substrate (By similarity); Belongs to the heat shock protein 70 family
CFHR1	Complement factor H-related protein 1;CFHR1;ortholog	___	Complement factor H-related protein 1; Involved in complement regulation. The dimerized forms have avidity for tissu e-bound complement fragments and efficiently compete with the physiological complement inhibitor CFH. Can associate with lipoproteins and may play a role in lipid metabolism
MPO	Myeloperoxidase;MPO ;ortholog	peroxidase (PC00180)	Myeloperoxidase; Part of the host defense system of polymorphonuclear leukocytes. It is responsible for microbicidal activity against a wide range of organisms. In the stimulated PMN, MPO catalyzes the production of hypohalous acids, primarily hypochlorous acid in physiologic situations, and other toxic intermediates that greatly enhance PMN microbicidal activity; Belongs to the peroxidase family. XPO subfamily
SAG	S-arrestin;SAG; ortholog	scaffold/adaptor protein (PC00226)	S-arrestin; Arrestin is one of the major proteins of the ros (retinal rod outer segments); it binds to photoactivated- phosphorylated rhodopsin, thereby apparently preventing the transducin-mediated activation of phosphodiesterase
SCARB2	Lysosome membrane protein 2;SCARB2; ortholog	membrane trafficking regulatory protein (PC00151)	Lysosome membrane protein 2; Acts as a lysosomal receptor for glucosylceramidase (GBA) targeting; Belongs to the CD36 family
THY1	Thy-1 membrane glycoprotein;THY1; ortholog	cell adhesion molecule (PC00069)	Thy-1 membrane glycoprotein; May play a role in cell-cell or cell-ligand interactions during synaptogenesis and other events in the brain; CD molecules
RTN4	Reticulon-4;RTN4;ortholog	___	Reticulon-4; Developmental neurite growth regulatory factor with a role as a negative regulator of axon-axon adhesion and growth, and as a facilitator of neurite branching. Regulates neurite fasciculation, branching and extension in the developing nervous system. Involved in down-regulation of growth, stabilization of wiring and restriction of plasticity in the adult CNS. Regulates the radial migration of cortical neurons via an RTN4R-LINGO1 containing receptor complex (By similarity). Isoform 2 reduces the anti-apoptotic activity of Bcl-xl and Bcl-2. This is likely consecutive to thei [...]

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Supplement Table 2. (cont.)

HLA-DRB1	HLA class II histocompatibility antigen, DRB1 beta chain;HLA-DRB1;ortholog	major histocompatibility complex protein (PC00149)	HLA class II histocompatibility antigen, DRB1-15 beta chain; Binds peptides derived from antigens that access the endocytic route of antigen presenting cells (APC) and presents them on the cell surface for recognition by the CD4 T-cells. The peptide binding cleft accommodates peptides of 10-30 residues. The peptides presented by MHC class II molecules are generated mostly by degradation of proteins that access the endocytic route, where they are processed by lysosomal proteases and other hydrolases. Exogenous antigens that have been endocytosed by the APC are thus readily available for [...]
GSTT1	Glutathione S-transferase theta-1;GSTT1;ortholog	___	___
ANXA4	Annexin A4;ANXA4;ortholog	calcium-binding protein (PC00060)	Annexin A4; Calcium/phospholipid-binding protein which promotes membrane fusion and is involved in exocytosis; Annexins
SLC25A11	Mitochondrial 2-oxoglutarate/malate carrier protein;SLC25A11 ;ortholog	secondary carrier transporter (PC00258)	Mitochondrial 2-oxoglutarate/malate carrier protein; Catalyzes the transport of 2-oxoglutarate across the inner mitochondrial membrane in an electroneutral exchange for malate or other dicarboxylic acids, and plays an important role in several metabolic processes, including the malat e-aspartate shuttle, the oxoglutarate/isocitrate shuttle, in gluconeogenesis from lactate, and in nitrogen metabolism (By similarity). Maintains mitochondrial fusion and fission events and the organization…
GLOD4	Glyoxalase domain-containing protein 4;GLOD4;ortholog	___	Glyoxalase domain containing 4
TAGLN	Transgelin;TAGLN; ortholog	non-motor actin binding protein (PC00165)	Transgelin; Actin cross-linking/gelling protein (By similarity). Involved in calcium interactions and contractile properties of the cell that may contribute to replicative senescence; Belongs to the calponin family
COL1A2	Collagen alpha-2 (I) chain; COL1A2; ortholog	extracellular matrix structural protein (PC00103)	Collagen alpha-2 (I) chain; Type I collagen is a member of group I collagen (fibrillar forming collagen); Belongs to the fibrillar collagen family

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Supplement Table 2. (cont.)

TALDO1	Transaldolase;TALDO 1;ortholog	aldolase (PC00044)	Transaldolase 1; Transaldolase; Transaldolase is important for the balance of metabolites in the pentos e-phosphate pathway
SPTA1	Spectrin alpha chain, erythrocytic 1;SPTA1;ortholog	___	Spectrin alpha chain, erythrocytic 1; Spectrin is the major constituent of the cytoskeletal network underlying the erythrocyte plasma membrane. It associates with band 4.1 and actin to form the cytoskeletal superstructure of the erythrocyte plasma membrane; EF-hand domain containing
VDAC1	Voltag e-dependent anion-selective channel protein 1;VDAC1;ortholog	voltag e-gated ion channel (PC00241)	Voltag e-dependent anion-selective channel protein 1; Forms a channel through the mitochondrial outer membrane and also the plasma membrane. The channel at the outer mitochondrial membrane allows diffusion of small hydrophilic molecules; in the plasma membrane it is involved in cell volume regulation and apoptosis. It adopts an open conformation at low or zero membrane potential and a closed conformation at potentials above 30-40 mV. The open state has a weak anion selectivity whereas the closed state is cation-selective. May participate in the formation of the permeability transition p [...]
HLA-DRA	HLA class II histocompatibility antigen, DR alpha chain;HLA-DRA;ortholog	major histocompatibility complex protein (PC00149)	Major histocompatibility complex, class ii, dr alpha; HLA class II histocompatibility antigen, DR alpha chain; Binds peptides derived from antigens that access the endocytic route of antigen presenting cells (APC) and presents them on the cell surface for recognition by the CD4 T-cells. The peptide binding cleft accommodates peptides of 10-30 residues. The peptides presented by MHC class II molecules are generated mostly by degradation of proteins that access the endocytic route, where they are processed by lysosomal proteases and other hydrolases. Exogenous antigens that have been end [...]
RHO	Rhodopsin;RHO; ortholog	G-protein coupled receptor (PC00021)	Rhodopsin; Photoreceptor required for imag e-forming vision at low light intensity. Required for photoreceptor cell viability after birth. Light-induced isomerization of 11-cis to all-trans retinal triggers a conformational change leading to G-protein activation and release of all-trans retinal; Belongs to the G-protein coupled receptor 1 family. Opsin subfamily
CRYAB	Alpha-crystallin B chain;CRYAB;ortholog	___	Alpha-crystallin B chain; May contribute to the transparency and refractive index of the lens. Has chaperon e-like activity, preventing aggregation of various proteins under a wide range of stress conditions; Small heat shock proteins
RPL6	60S ribosomal protein L6;RPL6;ortholog	ribosomal protein (PC00202)	60S ribosomal protein L6; Component of the large ribosomal subunit

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Supplement Table 2. (cont.)

CKB	Creatine kinase B-type;CKB;ortholog	amino acid kinase (PC00045)	Creatine kinase B-type; Reversibly catalyzes the transfer of phosphate between ATP and various phosphogens (e.g. creatine phosphate). Creatine kinase isoenzymes play a central role in energy transduction in tissues with large, fluctuating energy demands, such as skeletal muscle, heart, brain and spermatozoa
COL14A1	Collagen alpha-1 (XIV) chain;COL14A1; ortholog	extracellular matrix structural protein (PC00103)	Collagen alpha-1 (XIV) chain; Plays an adhesive role by integrating collagen bundles. It is probably associated with the surface of interstitial collagen fibrils via COL1. The COL2 domain may then serve as a rigid arm which sticks out from the fibril and protrudes the large N-terminal globular domain into the extracellular space, where it might interact with other matrix molecules or cell surface receptors (By similarity); Collagens
SLC3A2	4F2 cell-surface antigen heavy chain;SLC3A2; ortholog	—	4F2 cell-surface antigen heavy chain; Required for the function of light chain amino-acid transporters. Involved in sodium-independent, high-affinity transport of large neutral amino acids such as phenylalanine, tyrosine, leucine, arginine and tryptophan. Involved in guiding and targeting of LAT1 and LAT2 to the plasma membrane. When associated with SLC7A6 or SLC7A7 acts as an arginine/glutamine exchanger, following an antiport mechanism for amino acid transport, influencing arginine release in exchange for extracellular amino acids. Plays a role in nitric oxide synthesis in …
CTSD	Cathepsin D;CTSD;ortholog	—	Cathepsin D; Acid protease active in intracellular protein breakdown. Plays a role in APP processing following cleavage and activation by ADAM30 which leads to APP degradation. Involved in the pathogenesis of several diseases such as breast cancer and possibly Alzheimer disease; Cathepsins
C3	Complement C3;C3;ortholog	protease inhibitor (PC00191)	Complement C3; C3 plays a central role in the activation of the complement system. Its processing by C3 convertase is the central reaction in both classical and alternative complement pathways. After …
RPE65	Retinoid isomerohydrolase;RPE 65;ortholog	oxygenase (PC00177)	Retinoid isomerohydrolase / lutein isomerase; Retinoid isomerohydrolase; Critical isomerohydrolase in the retinoid cycle involved in regeneration of 11-cis-retinal, the chromophore of rod and cone opsins. Catalyzes the cleavage and isomerization of all-trans- retinyl fatty acid esters to 11-cis-retinol which is further oxidized by 11-cis retinol dehydrogenase to 11-cis-retinal for use as visual chromophore. Essential for the production of 11-cis retinal for both rod and cone photoreceptors. Also capable of catalyzing the isomerization of lutein to meso-zeaxanthin an ey e-specific carote [...]

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Supplement Table 2. (cont.)

LDHA	L-lactate dehydrogenase A chain;LDHA;ortholog	dehydrogenase (PC00092)	L-lactate dehydrogenase a chain; Lactate dehydrogenase A; Belongs to the LDH/MDH superfamily. LDH family
CRYAA	Alpha-crystallin A chain ;CRYAA;ortholog	___	Crystallin, alpha A; Contributes to the transparency and refractive index of the lens. Has chaperon e-like activity, preventing aggregation of various proteins under a wide range of stress conditions; Small heat shock proteins
ENO1	Alpha-enolase;ENO1; ortholog	lyase (PC00144)	Alpha-enolase; Multifunctional enzyme that, as well as its role in glycolysis, plays a part in various processes such as growth control, hypoxia tolerance and allergic responses. May also function in the intravascular and pericellular fibrinolytic system due to its ability to serve as a receptor and activator of plasminogen on the cell surface of several cell-types such as leukocytes and neurons. Stimulates immunoglobulin production; Belongs to the enolase family
GC	Vitamin K-dependent gamma-carboxylase ;GGCX; ortholog	___	Vitamin D-binding protein; Involved in vitamin D transport and storage, scavenging of extracellular G-actin, enhancement of the chemotactic activity of C5 alpha for neutrophils in inflammation and macrophage activation
APOA1	Apolipoprotein A-I;APOA1;ortholog	apolipoprotein (PC00052)	Apolipoprotein A-I; Participates in the reverse transport of cholesterol from tissues to the liver for excretion by promoting cholesterol efflux from tissues and by acting as a cofactor for the lecithin ….
ISOC1	Isochorismatase domain -containing protein 1; ISOC1 ; ortholog	hydrolase (PC00121)	Isochorismatase domain-containing protein 1; Isochorismatase domain containing 1
S100A7	Protein S100-A7;S100A7;ortholog	calmodulin-related (PC00061)	S100 calcium binding protein A7; EF-hand domain containing
TIMP3	Metalloproteinase inhibitor 3;TIMP3;ortholog	protease inhibitor (PC00191)	Timp metallopeptidase inhibitor 3; Metalloproteinase inhibitor 3; Complexes with metalloproteinases (such as collagenases) and irreversibly inactivates them by binding to their catalytic zinc cofactor. May form part of a tissu e-specific acute response to remodeling stimuli. Known to act on MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-13, MMP-14 and MMP-15

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Supplement Table 2. (cont.)

ANXA6	Annexin A6;ANXA6;ortholog	calcium-binding protein (PC00060)	Annexin A6; May associate with CD21. May regulate the release of Ca (2+) from intracellular stores; Annexins
FGB	Fibrinogen beta chain;FGB;ortholog	intercellular signal molecule (PC00207)	Fibrinogen beta chain; Cleaved by the protease thrombin to yield monomers which, together with fibrinogen alpha (FGA) and fibrinogen gamma (FGG), polymerize to form an insoluble fibrin matrix. Fibrin has a major function in hemostasis as one of the primary components of blood clots. In addition, functions during the early stages of wound repair to stabilize the lesion and guide cell migration during r e-epithelialization. Was originally thought to be essential for platelet aggregation, based on in vitro studies using anticoagulated blood. However subsequent studies have shown ….
AMBP	Protein AMBP;AMBP;ortholo g	___	Alpha-1-microglobulin/bikunin precursor; Protein AMBP; Inter-alpha-trypsin inhibitor inhibits trypsin, plasmin, and lysosomal granulocytic elastase. Inhibits calcium oxalate crystallization; Lipocalins
FRZB	Secreted frizzled-related protein 3;FRZB;ortholog	transmembrane signal receptor (PC00197)	Secreted frizzled-related protein 3; Soluble frizzled-related proteins (sFRPS) function as modulators of Wnt signaling through direct interaction with Wnts. They have a role in regulating cell growth and differentiation in specific cell types. SFRP3/FRZB appears to be involved in limb skeletogenesis. Antagonist of Wnt8 signaling. Regulates chondrocyte maturation and long bone development
CST3	Cystatin-C;CST3;ortholog		Cystatin-C; As an inhibitor of cysteine proteinases, this protein is thought to serve an important physiological role as a local regulator of this enzyme activity; Belongs to the cystatin family
COL6A2	Collagen alpha-2 (VI) chain;COL6A2;ortholo g	extracellular matrix structural protein (PC00103)	Collagen alpha-2 (VI) chain; Collagen VI acts as a cell-binding protein; Collagens
S100A9	Protein S100-A9;S100A9;ortholog	calmodulin-related (PC00061)	Protein S100-A9; S100A9 is a calcium- and zinc-binding protein which plays a prominent role in the regulation of inflammatory processes and immune response. It can induce neutrophil chemotaxis, adhesion, can increase the bactericidal activity of neutrophils by promoting phagocytosis via activation of SYK, PI3K/AKT, and ERK1/2 and can induce degranulation of neutrophils by a MAPK-dependent mechanism. Predominantly found as calprotectin (S100A8/A9) which has a wide plethora of intra- and extracellular functions. The intracellular functions include: facilitating leukocyte arachidonic acid [...]

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Supplement Table 2. (cont.)

LAMB2	Laminin subunit gamma-1;LAMC1;ortholog	extracellular matrix protein (PC00102)	Laminin subunit beta-2; Binding to cells via a high affinity receptor, laminin is thought to mediate the attachment, migration and organization of cells into tissues during embryonic development by interacting with other extracellular matrix components
MYH9	Myosin-9;MYH9;ortholog	___	Myosin-9; Cellular myosin that appears to play a role in cytokinesis, cell shape, and specialized functions such as secretion and capping. During cell spreading, plays an important role in cytoskeleton reorganization, focal contacts formation (in the margins but not the central part of spreading cells), …
ICAM1	Intercellular adhesion molecule 1;ICAM1;ortholog	___	Intercellular adhesion molecule 1; ICAM proteins are ligands for the leukocyte adhesion protein LFA-1 (integrin alpha-L/beta-2). During leukocyte trans- endothelial migration, ICAM1 engagement promotes the assembly of endothelial apical cups through ARHGEF26/SGEF and RHOG activation; CD molecules
CKB	Choline/ethanolamine kinase;CHKB;ortholog	kinase (PC00137)	Creatine kinase B-type; Reversibly catalyzes the transfer of phosphate between ATP and various phosphogens (e.g. creatine phosphate). Creatine kinase isoenzymes play a central role in energy transduction in tissues with large, fluctuating energy demands, such as skeletal muscle, heart, brain and spermatozoa
CP	Ceruloplasmin;CP; ortholog	oxidase (PC00175)	Ceruloplasmin; Ceruloplasmin is a blue, copper-binding (6-7 atoms per molecule) glycoprotein. It has ferroxidase activity oxidizing Fe (2+) to Fe (3+) without releasing radical oxygen species. It is involved in iron transport across the cell membrane. Provides Cu (2+) ions for the ascorbat e-mediated deaminase degradation of the heparan sulfate chains of GPC1. May also play a role in fetal lung development or pulmonary antioxidant defense (By similarity)
GC	Vitamin D-binding protein;GC;ortholog	transfer/carrier protein (PC00219)	Vitamin D-binding protein; Involved in vitamin D transport and storage, scavenging of extracellular G-actin, enhancement of the chemotactic activity of C5 alpha for neutrophils in inflammation and macrophage activation
APCS	Serum amyloid P-component;APCS; ortholog	___	Serum amyloid P-component; Can interact with DNA and histones and may scavenge nuclear material released from damaged circulating cells. May also function as a calcium-dependent lectin; Belongs to the pentraxin family
VWF	von Willebrand factor;VWF;ortholog	extracellular matrix protein (PC00102)	Von Willebrand factor; Important in the maintenance of hemostasis, it promotes adhesion of platelets to the sites of vascular injury by forming a molecular bridge between sub-endothelial collagen matrix and platelet-surface receptor complex GPIb-IX-V. Also acts as a chaperone for coagulation factor VIII,

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Supplement Table 2. (cont.)

IMMT	MICOS complex subunit MIC60;IMMT;ortholog	___	MICOS complex subunit MIC60; Component of the MICOS complex, a large protein complex of the mitochondrial inner membrane that plays crucial roles in the maintenance of crista junctions, inner membrane architecture, and formation of contact sites to the outer membrane. Plays an important role in the maintenance of the MICOS complex stability and the mitochondrial cristae morphology
STIP1	Stress-induced-phosphoprotein 1;STIP1;ortholog	___	Stress-induced-phosphoprotein 1; Acts as a co-chaperone for HSP90AA1. Mediates the association of the molecular chaperones HSPA8/HSC70 and HSP90 (By similarity); Tetratricopeptide repeat domain containing
VIM	Vimentin;VIM;ortholog	___	Vimentin; Vimentins are class-III intermediate filaments found in various non-epithelial cells, especially mesenchymal cells. Vimentin is attached to the nucleus, endoplasmic reticulum, and mitochondria, either laterally or terminally
HADHB	Trifunctional enzyme subunit beta, mitochondrial; HADHB;ortholog	acyltransferase (PC00042)	hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta
DLD	Probable D-lactate dehydrogenase, mitochondrial;LDHD; ortholog	dehydrogenase (PC00092)	Dihydrolipoyl dehydrogenase, mitochondrial; Lipoamide dehydrogenase is a component of the glycine cleavage system as well as an E3 component of three alpha-ketoacid dehydrogenase complexes (pyruvat e-, alpha-ketoglutarat e-, and branched-chain amino acid-dehydrogenase complex). In monomeric form has additional moonlighting function as serine protease. Involved in the hyperactivation of spermatazoa during capacitation and in the spermatazoal acrosome reaction (By similarity)
ACE	Angiotensin-converting enzyme;ACE;ortholog	metalloprotease (PC00153)	Angiotensin-converting enzyme; Converts angiotensin I to angiotensin II by release of the terminal His-Leu, this results in an increase of the vasoconstrictor activity of angiotensin. Also able to inactivate
CRYGC	Gamma-crystallin C;CRYGC;ortholog	___	Gamma-crystallin C; Crystallins are the dominant structural components of the vertebrate eye lens; Belongs to the beta/gamma-crystallin family
COX5B	Cytochrome c oxidase subunit 5B, mitochondrial; COX5B ;ortholog	oxidase (PC00175)	Cytochrome c oxidase subunit 5B, mitochondrial; This protein is one of the nuclear-coded polypeptide chains of cytochrome c oxidase, the terminal oxidase in mitochondrial electron transport

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Supplement Table 2. (cont.)

COX6B1	Cytochrome c oxidase subunit 6B1 ;COX6B1; ortholog	oxidase (PC00175)	Cytochrome c oxidase subunit 6B1; Connects the two COX monomers into the physiological dimeric form; Mitochondrial complex IV: cytochrome c oxidase subunits
CSE1L	Exportin-2;CSE1L;ortholog	transporter (PC00227)	Exportin-2; Export receptor for importin-alpha. Mediates importin- alpha r e-export from the nucleus to the cytoplasm after import substrates (cargos) have been released into the nucleoplasm. In the nucleus binds cooperatively to importin-alpha and to the GTPase Ran in its active GTP-bound form. Docking of this trimeric complex to the nuclear pore complex (NPC) is mediated through binding to nucleoporins. Upon transit of a nuclear export complex into the cytoplasm, disassembling of the complex and hydrolysis of Ran-GTP to Ran-GDP (induced by RANBP1 and RANGAP1, respectively) cause relea [...]
COL3A1	Collagen alpha-1 (III) chain;COL3A1;ortholo g	extracellular matrix structural protein (PC00103)	Collagen alpha-1 (III) chain; Collagen type III occurs in most soft connective tissues along with type I collagen. Involved in regulation of cortical development. Is the major ligand of ADGRG1 in the developing brain and binding to ADGRG1 inhibits neuronal migration and activates the RhoA pathway by coupling ADGRG1 to GNA13 and possibly GNA12
ENO2	Gamma-enolase;ENO2;ortholog	lyase (PC00144)	Gamma-enolase; Has neurotrophic and neuroprotective properties on a broad spectrum of central nervous system (CNS) neurons. Binds, in a calcium-dependent manner, to cultured neocortical neurons and promotes cell survival (By similarity); Enolases
S100A8	Protein S100-A8;S100A8;ortholog	calmodulin-related (PC00061)	Protein S100-A8; S100A8 is a calcium- and zinc-binding protein which plays a prominent role in the regulation of inflammatory processes and immune response. It can induce neutrophil chemotaxis and adhesion. Predominantly found as calprotectin (S100A8/A9) which has a wide plethora of intra- and extracellular functions. The intracellular functions include: facilitating leukocyte arachidonic acid trafficking and metabolism, modulation of the tubulin-dependent cytoskeleton during migration of phagocytes and activation of the neutrophilic NADPH-oxidase. Activates NADPH- oxidase by facilitat [...]
GUK1	Guanylate kinase;GUK1;ortholog	kinase (PC00137)	Guanylate kinase 1; Guanylate kinase; Essential for recycling GMP and indirectly, cGMP
HBB	Hemoglobin subunit beta;HBB;ortholog	——	Hemoglobin subunit beta; Involved in oxygen transport from the lung to the various peripheral tissues; Belongs to the globin family

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Supplement Table 2. (cont.)

HBA1	Hemoglobin subunit alpha;HBA2;ortholog		Hemoglobin subunit alpha; Involved in oxygen transport from the lung to the various peripheral tissues; Belongs to the globin family
OXCT1	Succinyl-CoA:3-ketoacid coenzyme A transferase1,mitochondrial ; OXCT1;ortholog	transferase (PC00220)	Succinyl-CoA:3-ketoacid coenzyme A transferase 1, mitochondrial; Key enzyme for ketone body catabolism. Transfers the CoA moiety from succinate to acetoacetate. Formation of the enzym e-CoA intermediate proceeds via an unstable anhydride species formed between the carboxylate groups of the enzyme and substrate; Belongs to the 3-oxoacid CoA-transferase family
YWHAB	14-3-3 protein beta/alpha;YWHAB; ortholog	scaffold/adaptor protein (PC00226)	14-3-3 protein beta/alpha; Adapter protein implicated in the regulation of a large spectrum of both general and specialized signaling pathways. Binds to a large number of partners, usually by recognition of a phosphoserine or phosphothreonine motif. Binding generally results in the modulation of the activity of the binding partner. Negative regulator of osteogenesis. Blocks the nuclear translocation of the phosphorylated form (by AKT1) of SRPK2 and antagonizes its stimulatory effect on cyclin D1 expression resulting in blockage of neuronal apoptosis elicited by SRPK2. Negative regulato [...]
HNRNPD	Heterogeneous nuclear ribonucleoprotein D0;HNRNPD;ortholog	Heterogeneous nuclear ribonucleoprotein a/b/d	Heterogeneous nuclear ribonucleoprotein a/b/d; Heterogeneous nuclear ribonucleoprotein D0; Binds with high affinity to RNA molecules that contain AU-rich elements (AREs) found within the 3'-UTR of many proto- oncogenes and cytokine mRNAs. Also binds to doubl e- and singl e- stranded DNA sequences in a specific manner and functions a transcription factor. Each of the RNA-binding domains specifically can bind solely to a singl e-stranded non-monotonous 5'-UUAG-3' sequence and also weaker to the singl e-stranded 5'-TTAGGG-3' telomeric DNA repeat. Binds RNA oligonucleotides with 5'-UUAGGG-3' r [...]
LAP3	Cytosol aminopeptidase;LAP3; ortholog	metalloprotease (PC00153)	Cytosol aminopeptidase; Presumably involved in the processing and regular turnover of intracellular proteins. Catalyzes the removal of unsubstituted N-terminal amino acids from various peptides; Belongs to the peptidase M17 family
VTN	Vitronectin;VTN; ortholog	—	Vitronectin; Vitronectin is a cell adhesion and spreading factor found in serum and tissues. Vitronectin interact with glycosaminoglycans and proteoglycans. Is recognized by certain members of the integrin family and serves as a cell-to-substrate adhesion molecule. Inhibitor of the membran e-damaging effect of the terminal cytolytic complement pathway; Endogenous ligands

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Supplement Table 2. (cont.)

COL6A1	Collagen alpha-1 (VI) chain; COL6A1; ortholog	extracellular matrix structuralprotein (PC00103)	Collagen alpha-1 (VI) chain; Collagen VI acts as a cell-binding protein; Belongs to the type VI collagen family
CRYBA4	Beta-crystallin A4;CRYBA4;ortholog	—	Beta-crystallin A4; Crystallins are the dominant structural components of the vertebrate eye lens; Belongs to the beta/gamma-crystallin family
LGALS3	Galectin-3;LGALS3;ortholog	extracellular matrix protein (PC00102)	Galectin-3; Galactos e-specific lectin which binds IgE. May mediate with the alpha-3, beta-1 integrin the stimulation by CSPG4 of endothelial cells migration. Together with DMBT1, required for terminal differentiation of columnar epithelial cells during early embryogenesis (By similarity). In the nucleus: acts as a pr e-mRNA splicing factor. Involved in acute inflammatory responses including neutrophil activation and adhesion, chemoattraction of monocytes macrophages, opsonization of apoptotic neutrophils, and activation of mast cells; Endogenous ligands
ABCA4	Retinal-specific phospholipid-transporting ATPase ABCA4;ABCA4; ortholog	ATP-binding cassette (ABC) transporter (PC00003)	Atp-binding cassette, subfamily a (abc1), member 4; Retinal-specific ATP-binding cassette transporter; In the visual cycle, acts as an inward-directed retinoid flipase, retinoid substrates imported by ABCA4 from the extracellular or intradiscal (rod) membrane surfaces to the cytoplasmic membrane surface are all-trans-retinaldehyde (ATR) and N-retinyl-phosphatidyl-ethanolamine (NR-PE). Once transported to the cytoplasmic surface, ATR is reduced to vitamin A by trans- retinol dehydrogenase (tRDH) and then transferred to the retinal pigment epithelium (RPE) where it is converted to 11-cis [...]
RNASE4	Ribonuclease 4;RNASE4;ortholog	—	Ribonuclease 4; This RNase has marked specificity towards the 3' side of uridine nucleotides; Ribonuclease A family
SPTB	Spectrin beta chain, erythrocytic;SPTB; ortholog	—	Spectrin beta chain, erythrocytic; Spectrin is the major constituent of the cytoskeletal network underlying the erythrocyte plasma membrane. It associates with band 4.1 and actin to form the cytoskeletal superstructure of the erythrocyte plasma membrane; Pleckstrin homology domain containing
FGG	Fibrinogen gamma chain;FGG;ortholog	intercellular signal molecule (PC00207)	Fibrinogen gamma chain; Together with fibrinogen alpha (FGA) and fibrinogen beta (FGB), polymerizes to form an insoluble fibrin matrix. Has a major function in hemostasis as one of the primary components of blood clots. In addition, functions during the early stages of wound repair to stabilize the lesion and guide cell migration during r e- epithelialization. Was originally thought to be essential for platelet aggregation, based on in vitro studies using anticoagulated blood. However, subsequent studies have shown that it is not absolutely required for thrombus formation in vivo…

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PEBP1	Phosphatidylethanolamin e-binding protein 1;PEBP1;ortholog	protease inhibitor (PC00191)	Phosphatidylethanolamin e-binding protein 1; Binds ATP, opioids and phosphatidylethanolamine. Has lower affinity for phosphatidylinositol and phosphatidylcholine. Serine protease inhibitor which inhibits thrombin, neuropsin and chymotrypsin but not trypsin, tissue type plasminogen activator and elastase (By similarity). Inhibits the kinase activity of RAF1 by inhibiting its activation and by dissociating the RAF1/MEK complex and acting as a competitive inhibitor of MEK phosphorylation
TBCA	Tubulin-specific chaperone A;TBCA ;ortholog	chaperonin (PC00073)	Tubulin-specific chaperone A; Tubulin-folding protein; involved in the early step of the tubulin folding pathway
GSTP1	Glutathione S-transferase P;GSTP1;ortholog	transferase (PC00220)	Glutathione S-transferase P; Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles. Regulates negatively CDK5 activity via p25/p35 translocation to prevent neurodegeneration; Soluble glutathione S-transferases
LAMB2	Laminin subunit beta-2;LAMB2;ortholog	extracellular matrix protein (PC00102)	Laminin subunit beta-2; Binding to cells via a high affinity receptor, laminin is thought to mediate the attachment, migration and organization of cells into tissues during embryonic development by interacting with other extracellular matrix components
LTF	Lactotransferrin;LTF ;ortholog	transfer/carrier protein (PC00219)	Lactotransferrin; Lactoferroxins A, B and C have opioid antagonist activity. Lactoferroxin A shows preference for mu-receptors, while lactoferroxin B and C have somewhat higher degrees of preference for kappa-receptors than for mu-receptors; Transferrins
NID2	Nidogen-2;NID2;ortholog	calmodulin-related (PC00061)	Nidogen (entactin); Nidogen-2; Cell adhesion glycoprotein which is widely distributed in basement membranes. Binds to collagens I and IV, to perlecan and to laminin 1. Does not bind fibulins. It probably has a role in cell-extracellular matrix interactions
ORM1	Alpha-1-acid glycoprotein 1;ORM1;ortholog	___	Alpha-1-acid glycoprotein 1; Functions as transport protein in the blood stream. Binds various ligands in the interior of its beta-barrel domain. Also binds synthetic drugs and influences their distribution and availability in the body. Appears to function in modulating the activity of the immune system during the acut e-phase reaction; Belongs to the calycin superfamily. Lipocalin family
CRYGS	Gamma-crystallin S;CRYGS;ortholog	___	Beta-crystallin S; Crystallins are the dominant structural components of the vertebrate eye lens; Belongs to the beta/gamma-crystallin family

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Supplement Table 2. (cont.)

IDH1	Isocitrate dehydrogenase [NADP] cytoplasmic; IDH1;ortholog	dehydrogenase (PC00092)	Isocitrate dehydrogenase [nadp] cytoplasmic; Isocitrate dehydrogenase 1, cytosolic
CRABP1	Cellular retinoic acid-binding protein 1;CRABP1;ortholog	___	Cellular retinoic acid-binding protein 1; Cytosolic CRABPs may regulate the access of retinoic acid to the nuclear retinoic acid receptors; Belongs to the calycin superfamily. Fatty-acid binding protein (FABP) family
UCHL1	Ubiquitin carboxyl-terminal hydrolase isozyme L1;UCHL1 ;ortholog	cysteine protease (PC00081)	Ubiquitin carboxyl-terminal hydrolase isozyme L1; Ubiquitin-protein hydrolase involved both in the processing of ubiquitin precursors and of ubiquitinated proteins. This enzyme is a thiol protease that recognizes and hydrolyzes a peptide bond at the C-terminal glycine of ubiquitin. Also binds to free monoubiquitin and may prevent its degradation in lysosomes. The homodimer may have ATP-independent ubiquitin ligase activity; Parkinson disease associated genes
GSTM1	Glutathione S-transferase Mu 1; GSTM1;ortholog	transferase (PC00220)	Glutathione S-transferase Mu 1; Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles; Soluble glutathione S-transferases
RLBP1	Retinaldehyd e-binding protein 1; RLBP1;ortholog	transfer/carrier protein (PC00219)	Retinaldehyd e-binding protein 1; Soluble retinoid carrier essential the proper function of both rod and cone photoreceptors. Participates in the regeneration of active 11-cis-retinol and 11-cis-retinaldehyde, from the inactive 11-trans products of the rhodopsin photocycle and in the de novo synthesis of these retinoids from 11-trans metabolic precursors. The cycling of retinoids between photoreceptor and adjacent pigment epithelium cells is known as the 'visual cycle'
ALDOC	Fructos e-bisphosphate aldolase C;ALDOC ;ortholog	aldolase (PC00044)	Fructos e-bisphosphate aldolase, class i; Belongs to the class I fructos e-bisphosphate aldolase family
HMOX2	Heme oxygenase 2;HMOX2;ortholog	oxygenase (PC00177)	Heme oxygenase 2; Heme oxygenase cleaves the heme ring at the alpha methene bridge to form biliverdin. Biliverdin is subsequently converted to bilirubin by biliverdin reductase. Under physiological conditions, the activity of heme oxygenase is highest in the spleen, where senescent erythrocytes are sequestrated and destroyed. Heme oxygenase 2 could be implicated in the production of carbon monoxide in brain where it could act as a neurotransmitter

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ERP29	Endoplasmic reticulum resident protein 29; ERP29;ortholog	membrane traffic protein (PC00150)	Endoplasmic reticulum resident protein 29; Does not seem to be a disulfide isomerase. Plays an important role in the processing of secretory proteins within the endoplasmic reticulum (ER), possibly by participating in the folding of proteins in the ER
HIST1H4A	Histone H4;H4-16; ortholog	histone (PC00118)	Histone cluster 1 H4 family member a; Core component of nucleosome. Nucleosomes wrap and compact DNA into chromatin, limiting DNA accessibility to the cellular machineries which require DNA as a template. Histones thereby play a central role in transcription regulation, DNA repair, DNA replication and chromosomal stability. DNA accessibility is regulated via a complex set of post-translational modifications of histones, also called histone code, and nucleosome remodeling
FGA	Fibrinogen alpha chain; FGA;ortholog		Fibrinogen alpha chain; Cleaved by the protease thrombin to yield monomers which, together with fibrinogen beta (FGB) and fibrinogen gamma (FGG), polymerize to form an insoluble fibrin matrix. Fibrin has a major function in hemostasis as one of the primary components of blood clots. In addition, functions during the early stages of wound repair to stabilize the lesion and guide cell migration during r e-epithelialization. Was originally thought to be essential for platelet aggregation, based on in vitro studies using anticoagulated blood. However, subsequent studies have shown that it i [...]
VDAC3	Voltag e-dependent anion-selective channel protein 3; VDAC3; ortholog	voltag e-gated ion channel (PC00241)	Voltag e-dependent anion-selective channel protein 3; Forms a channel through the mitochondrial outer membrane that allows diffusion of small hydrophilic molecules; Belongs to the eukaryotic mitochondrial porin family
ALDH1A1	Retinal dehydrogenase 1;ALDH1A1;ortholog	dehydrogenase (PC00092)	Aldehyde dehydrogenase 1 family member a1; Retinal dehydrogenase 1; Can convert/oxidize retinaldehyde to retinoic acid. Binds free retinal and cellular retinol-binding protein-bound retinal (By similarity). May have a broader specificity and oxidize other aldehydes in vivo
CRYBB2	Beta-crystallin B2;CRYBB2;ortholog	—	Beta-crystallin B2; Crystallins are the dominant structural components of the vertebrate eye lens; Belongs to the beta/gamma-crystallin family
TNC	Tenascin;TNC;ortholog	extracellular matrix protein (PC00102)	Tenascin; Extracellular matrix protein implicated in guidance of migrating neurons as well as axons during development, synaptic plasticity as well as neuronal regeneration. Promotes neurite outgrowth from cortical neurons grown on a monolayer of astrocytes. Ligand for integrins alpha-8/beta-1, alpha-9/beta-1, alpha-V/beta-3 and alpha-V/beta-6. In tumors, stimulates angiogenesis by elongation, migration and sprouting of endothelial cells; Belongs to the tenascin family

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Supplement Table 2. (cont.)

HP	Haptoglobin;HP; ortholog	serine protease (PC00203)	Haptoglobin-related protein; Haptoglobin; As a result of hemolysis, hemoglobin is found to accumulate in the kidney and is secreted in the urine. Haptoglobin captures, and combines with free plasma hemoglobin to allow hepatic recycling of heme iron and to prevent kidney damage. Haptoglobin also acts as an Antimicrobial; Antioxidant, has antibacterial activity and plays a role in modulating many aspects of the acute phase response. Hemoglobin/haptoglobin complexes are rapidely cleared by the macrophage CD163 scavenger receptor expressed on the surface of liver Kupfer cells through an en [...]
PON1	Serum paraoxonase/ arylesterase 1; PON1; ortholog	___	Serum paraoxonase/arylesterase 1; Hydrolyzes the toxic metabolites of a variety of organophosphorus insecticides. Capable of hydrolyzing a broad spectrum of organophosphate substrates and lactones, and a number of aromatic carboxylic acid esters. Mediates an enzymatic protection of low density lipoproteins against oxidative modification and the consequent series of events leading to atheroma formation; Belongs to the paraoxonase family
VKORC1	Vitamin K epoxide reductase complex subunit 1;VKORC1;ortholog	oxidoreductase (PC00176)	Vitamin-k-epoxide reductase (warfarin-sensitive); Vitamin K epoxide reductase complex subunit 1; Involved in vitamin K metabolism. Catalytic subunit of the vitamin K epoxide reductase (VKOR) complex which reduces inactive vitamin K 2,3-epoxide to active vitamin K. Vitamin K is required for the gamma-carboxylation of various proteins, including clotting factors, and is required for normal blood coagulation, but also for normal bone development
RGR	Ral-GDS-related protein;RGL4;ortholog	guanyl-nucleotide exchange factor (PC00113)	RP e-retinal G protein-coupled receptor; Receptor for all-trans- and 11-cis-retinal. Binds preferentially to the former and may catalyze the isomerization of the chromophore by a retinochrom e-like mechanism; Opsin receptors
TF	Tissue factor;F3;ortholog	transmembrane signal receptor (PC00197)	Serotransferrin; Transferrins are iron binding transport proteins which can bind two Fe (3+) ions in association with the binding of an anion, usually bicarbonate. It is responsible for the transport of iron from sites of absorption and heme degradation to those of storage and utilization. Serum transferrin may also have a further role in stimulating cell proliferation
APOA4	Apolipoprotein A-IV;APOA4;ortholog	apolipoprotein (PC00052)	Apolipoprotein A-IV; May have a role in chylomicrons and VLDL secretion and catabolism. Required for efficient activation of lipoprotein lipase by ApoC-II; potent activator of LCAT. Apoa-IV is a major component of HDL and chylomicrons; Belongs to the apolipoprotein A1/A4/E family
BASP1	Brain acid soluble protein1;BASP1;ortholog	___	Brain abundant membrane attached signal protein 1; Belongs to the BASP1 family

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Supplement Table 2. (cont.)

CAV1	Caveolin-1;CAV1;ortholog	scaffold/adaptor protein (PC00226)	Caveolin-1; May act as a scaffolding protein within caveolar membranes. Interacts directly with G-protein alpha subunits and can functionally regulate their activity (By similarity). Involved in the costimulatory signal essential for T-cell receptor (TCR)- mediated T-cell activation. Its binding to DPP4 induces T-cell proliferation and NF-kappa-B activation in a T-cell receptor/CD3- dependent ….
CRP	Cysteine and glycin e-rich protein 1;CSRP1;ortholog	actin or actin-binding cytoskeletal protein (PC00041)	C-reactive protein; Displays several functions associated with host defense: it promotes agglutination, bacterial capsular swelling, phagocytosis and complement fixation through its calcium-dependent binding to phosphorylcholine. Can interact with DNA and histones and may scavenge nuclear material released from damaged circulating cells; Short pentraxins
FABP5	Fatty acid-binding protein 5;FABP5;ortholog	___	Fatty acid-binding protein, epidermal; High specificity for fatty acids. Highest affinity for C18 chain length. Decreasing the chain length or introducing double bonds reduces the affinity. May be involved in keratinocyte differentiation; Belongs to the calycin superfamily. Fatty-acid binding protein (FABP) family
GPNMB	Transmembrane glycoprotein NMB; GPNMB; ortholog	membran e-bound signaling molecule (PC00152)	Transmembrane glycoprotein NMB; Could be a melanogenic enzyme; Belongs to the PMEL/NMB family
HSPA9	Stress-70 protein, mitochondrial;HSPA9; ortholog	___	Stress-70 protein, mitochondrial; Chaperone protein which plays an important role in mitochondrial iron-sulfur cluster (ISC) biogenesis. Interacts with and stabilizes ISC cluster assembly proteins FXN, NFU1, NFS1 and ISCU. Regulates erythropoiesis via stabilization of ISC assembly. May play a role in the control of cell proliferation and cellular aging (By similarity); Belongs to the heat shock protein 70 family
SERPING1	Plasma protease C1 inhibitor;SERPING1; ortholog	protease inhibitor (PC00191)	Plasma protease C1 inhibitor; Activation of the C1 complex is under control of the C1- inhibitor. It forms a proteolytically inactive stoichiometric complex with the C1r or C1s proteases. May play a potentially crucial role in regulating important physiological pathways including complement activation, blood coagulation, fibrinolysis and the generation of kinins. Very efficient inhibitor of FXIIa. Inhibits chymotrypsin and kallikrein; Serpin peptidase inhibitors
C8G	Complement component C8 gamma chain;C8G; ortholog	___	Complement component C8 gamma chain; C8 is a constituent of the membrane attack complex. C8 binds to the C5B-7 complex, forming the C5B-8 complex. C5-B8 binds C9 and acts as a catalyst in the polymerization of C9. The gamma subunit seems to be able to bind retinol; Complement system

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Supplement Table 2. (cont.)

TF	Serotransferrin;TF; ortholog	transfer/carrier protein (PC00219)	Serotransferrin; Transferrins are iron binding transport proteins which can bind two Fe (3+) ions in association with the binding of an anion, usually bicarbonate. It is responsible for the transport of iron from sites of absorption and heme degradation to those of storage and utilization. Serum transferrin may also have a further role in stimulating cell proliferation
SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1;SLC2A1;ortholog	Glucose transporter subfamily	Solute carrier family 2, facilitated glucose transporter member 1; Facilitative glucose transporter. This isoform may be responsible for constitutive or basal glucose uptake. Has a very broad substrate specificity; can transport a wide range of aldoses including both pentoses and hexoses; Belongs to the major facilitator superfamily. Sugar transporter (TC 2.A.1.1) family.
APOE	Apolipoprotein E;APOE;ortholog	apolipoprotein (PC00052)	Apolipoprotein E; Mediates the binding, internalization, and catabolism of lipoprotein particles. It can serve as a ligand for the LDL (apo B/E) receptor and for the specific apo-E receptor (chylomicron remnant) of hepatic tissues; Apolipoproteins
RBP3	Retinol-binding protein 3;RBP3;ortholog	—	Retinol-binding protein 3; IRBP shuttles 11-cis and all trans retinoids between the retinol isomerase in the pigment epithelium and the visual pigments in the photoreceptor cells of the retina
TUBB3	Tubulin beta-3 chain;TUBB3;ortholog	tubulin (PC00228)	Tubulin beta-3 chain; Tubulin is the major constituent of microtubules. It binds two moles of GTP, one at an exchangeable site on the beta chain and one at a non-exchangeable site on the alpha chain. TUBB3 plays a critical role in proper axon guidance and mantainance; Belongs to the tubulin family
C9	Complement component C9;C9;ortholog	—	Complement component C9; Constituent of the membrane attack complex (MAC) that plays a key role in the innate and adaptive immune response by forming pores in the plasma membrane of target cells. C9 is the por e- forming subunit of the MAC; Belongs to the complement C6/C7/C8/C9 family
HLA-DRA	Ig-like domain-containing protein;HLA-DRA;ortholog	major histocompatibility complex protein (PC00149)	Major histocompatibility complex, class ii, dr alpha; HLA class II histocompatibility antigen, DR alpha chain; Binds peptides derived from antigens that access the endocytic route of antigen presenting cells (APC) and presents them on the cell surface for recognition by the CD4 T-cells. The peptide binding cleft accommodates peptides of 10-30 residues. The peptides presented by MHC class II molecules are generated mostly by degradation of proteins that access the endocytic route, where they are processed by lysosomal proteases and other hydrolases. Exogenous antigens that have been end [...]
SERPINA3	Alpha-1-antichymotrypsin;SERPINA3;ortholog	protease inhibitor (PC00191)	Alpha-1-antichymotrypsin; Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3; Although its physiological function is unclear, it can inhibit neutrophil cathepsin G and mast cell chymase, both of which can convert angiotensin-1 to the active angiotensin-2; Serpin peptidase inhibitors
SPTAN1	Spectrin alpha chain, non-erythrocytic 1;SPTAN1;ortholog	—	Spectrin alpha chain, non-erythrocytic 1; Fodrin, which seems to be involved in secretion, interacts with calmodulin in a calcium-dependent manner and is thus candidate for the calcium-dependent movement of the cytoskeleton at the membrane; EF-hand domain containing

Supplement Table 3. The changing of AMD Related Genes with Aging

Gene	Change name	Change type	Change gender	Age change starts	Age change ends	Process measured	Tissues	Percentage change	P value
ABCA1 (ATP-binding cassette, sub-family A (ABC1), member 1)	Gene expression of ABCA1 increases with age	molecular	female	39	85	Gene Expression Level	Skin	-	-
ABCA4 (ATP-binding cassette, sub-family A (ABC1), member 4)	Gene expression of ABCA4 decreases with age	molecular	female	39	85	Gene Expression Level	Skin	-	-
APOE (apolipoprotein E)	APOE promoter methylation decrease	molecular	male/female	63	92	-	Prefrontal Cortex	-	-
CFH (complement factor H)	complement factor H increases with age	molecular	male/female	20	99	Gene Expression Level	Hippocampus	166.79	None
CFH (complement factor H)	complement factor H increases with age	molecular	male/female	20	99	Gene Expression Level	Parietal Lobe	138.86	None
CFH (complement factor H)	complement factor H increases with age	molecular	male/female	20	99	Gene Expression Level	Frontal Lobe	210.85	None
CFHR1 (complement factor H-related 1)	complement factor H-related 1	molecular	male/female	26	106	Gene Expression Level	Brain	42	7.5767 e-05
CFHR1 (complement factor H-related 1)	complement factor H-related 1 increases with age	molecular	male/female	20	99	Gene Expression Level	Hippocampus	88.04	None
CFHR1 (complement factor H-related 1)	complement factor H-related 1 increases with age	molecular	male/female	20	99	Gene Expression Level	Parietal Lobe	126.47	None
CFHR1 (complement factor H-related 1)	complement factor H-related 1 increases with age	molecular	male/female	20	99	Gene Expression Level	Frontal Lobe	144.16	None
DDR1 (discoidin domain receptor tyrosine kinase 1)	discoidin domain receptor tyrosine kinase 1	molecular	male/female	26	106	Gene Expression Level	Brain	9	0.0004973

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Supplement Table 3. (cont.)

TLR3 (toll-like receptor 3)	toll-like receptor 3 increases with age	molecular	male/female	20	99	Gene Expression Level	Hippocampus	52.96	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Frontal Lobe	150.87	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Parietal Lobe	115.49	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Frontal Lobe	148.44	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Parietal Lobe	46	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Parietal Lobe	114.73	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Frontal Lobe	83.71	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Hippocampus	65.24	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Hippocampus	69.38	None
TLR4 (toll-like receptor 4)	toll-like receptor 4 increases with age	molecular	male/female	20	99	Gene Expression Level	Parietal Lobe	82.15	None
FBLN5 (fibulin 5)	Gene expression of FBLN5 increases with age	molecular	female	39	85	Gene Expression Level	Adipose Tissue	-	-
IER3 (immediate early response 3)	Gene expression of IER3 decreases with age	molecular	female	39	85	Gene Expression Level	Skin	-	-

Supplement Table 4. The Changing of Retinal AMD Related Genes in Homo sapiens or Mus musculus with Aging

Gene	Change name	Organism	Change gender	Age change starts	Age change ends	Tissues	Percentage change	P value
ABCA4 (ATP-binding cassette, sub-family A (ABC1), member 4)	Gene expression of ABCA4 decreases with age	Homo sapiens	female	39	85	Skin	-	-
ALDH1A1 (aldehyde dehydrogenase 1 family, member A1)	aldehyde dehydrogenase 1A1 decreases with age	Homo sapiens	female	6	73	Dermis	-30.3	0.004
Aldh1a1 (aldehyde dehydrogenase family 1, subfamily A1)	aldehyde dehydrogenase family 1, subfamily A1	Mus musculus	male/female	8	24	Muscle	6	0.00056387
ANXA4 (annexin A4)	annexin A4	Homo sapiens	male/female	26	106	Brain	11	0.0008755
APOE (apolipoprotein E)	APOE promoter methylation decrease	Homo sapiens	male/female	63	92	Prefrontal Cortex	-	-
ATP5B (ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide)	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	Homo sapiens	male/female	26	106	Brain	-9	0.00073343
ATP5D (ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit)	Gene expression of ATP5D decreases with age	Homo sapiens	female	39	85	Skin	-	-
C3 (complement component 3)	complement component 3	Mus musculus	male/female	6	22	Liver	5	0.00041991
C3 (complement component 3)	complement component 3	Homo sapiens	male/female	20	75	Skeletal Muscle	16	0.00040967
C3 (complement component 3)	complement component 3 increases with age	Homo sapiens	male/female	20	99	Hippocampus	201.58	None
C3 (complement component 3)	complement component 3 increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	108.42	None
Cav1 (caveolin 1, caveolae protein)	caveolin 1, caveolae protein	Mus musculus	male/female	5	22	Brain	6	0.00081702

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Supplement Table 4. (cont.)

CFH (complement factor H)	complement factor H increases with age	Homo sapiens	male/female	20	99	Hippocampus	166.79	None
CFH (complement factor H)	complement factor H increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	138.86	None
CFH (complement factor H)	complement factor H increases with age	Homo sapiens	male/female	20	99	Frontal Lobe	210.85	None
CFHR1 (complement factor H-related 1)	complement factor H-related 1	Homo sapiens	male/female	26	106	Brain	42	7.5767 e-05
CFHR1 (complement factor H-related 1)	complement factor H-related 1 increases with age	Homo sapiens	male/female	20	99	Hippocampus	88.04	None
CFHR1 (complement factor H-related 1)	complement factor H-related 1 increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	126.47	None
CFHR1 (complement factor H-related 1)	complement factor H-related 1 increases with age	Homo sapiens	male/female	20	99	Frontal Lobe	144.16	None
CKB (creatine kinase, brain)	Gene expression of CKB decreases with age	Homo sapiens	female	39	85	Adipose Tissue	-	-
CKB (creatine kinase, brain)	creatine kinase, brain	Homo sapiens	male/female	27	92	Kidney	-10	0.00059379
COL14A1 (collagen, type XIV, alpha 1)	Gene expression of COL14A1 decreases with age	Homo sapiens	female	39	85	Skin	-	-
COL1A2 (collagen, type I, alpha 2)	Gene expression of COL1A2 decreases with age	Homo sapiens	female	39	85	Skin	-	-
COL1A2 (collagen, type I, alpha 2)	Gene expression of COL1A2 decreases with age	Homo sapiens	female	39	85	Adipose Tissue	-	-
COL3A1 (collagen, type III, alpha 1)	Gene expression of COL3A1 decreases with age	Homo sapiens	female	39	85	Skin	-	-
CRP (C-reactive protein, pentraxin-related)	blood CRP level increase	Homo sapiens	male/female	26	87	Plasma	-	-

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Supplement Table 4. (cont.)

Cryba1 (crystallin, beta A1)	crystallin, beta A1	Mus musculus	male/female	3	23	Hematological System	95	4.8219 e-05
CST3 (cystatin C)	Gene expression of CST3 decreases with age	Homo sapiens	female	39	85	Skin	-	-
EIF4H (eukaryotic translation initiation factor 4H)	eukaryotic translation initiation factor 4H	Homo sapiens	male/female	20	75	Skeletal Muscle	2	1.2424 e-05
ENO2 (enolase 2 (gamma, neuronal))	Gene expression of ENO2 increases with age	Homo sapiens	female	39	85	Skin	-	-
EPHX1 (epoxide hydrolase 1, microsomal (xenobiotic))	Gene expression of EPHX1 decreases with age	Homo sapiens	female	39	85	Skin	-	-
ERP29 (endoplasmic reticulum protein 29)	Gene expression of ERP29 decreases with age	Homo sapiens	female	39	85	Skin	-	-
Fabp5 (fatty acid binding protein 5, epidermal)	fatty acid binding protein 5, epidermal	Mus musculus	male/female	2	24	Visual Apparatus	259	0.00064797
Gfap (glial fibrillary acidic protein)	glial fibrillary acidic protein	Mus musculus	male/female	5	30	Anatomical System	11	7.0715 e-05
Gfap (glial fibrillary acidic protein)	glial fibrillary acidic protein	Mus musculus	male/female	2	15	Hippocampus	4	0.00082018
GUK1 (guanylate kinase 1)	guanylate kinase 1	Homo sapiens	male/female	26	106	Brain	-5	0.00096105
HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Hippocampus	317.66	None
HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Temporal Lobe	146.66	None
HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	241.65	None

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Supplement Table 4. (cont.)

HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Frontal Lobe	146.81	None
HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Temporal Lobe	150.4	None
HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Hippocampus	324.53	None
HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	303.68	None
HLA-DRA (major histocompatibility complex, class II, DR alpha)	major histocompatibility complex, class II, DR alpha increases with age	Homo sapiens	male/female	20	99	Frontal Lobe	135.28	None
HLA-DRB1 (major histocompatibility complex, class II, DR beta 1)	major histocompatibility complex, class II, DR beta 1 increases with age	Homo sapiens	male/female	20	99	Hippocampus	193.49	None
HLA-DRB1 (major histocompatibility complex, class II, DR beta 1)	major histocompatibility complex, class II, DR beta 1 increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	90.28	None
HLA-DRB1 (major histocompatibility complex, class II, DR beta 1)	major histocompatibility complex, class II, DR beta 1 increases with age	Homo sapiens	male/female	20	99	Frontal Lobe	82.98	None
HLA-DRB1 (major histocompatibility complex, class II, DR beta 1)	major histocompatibility complex, class II, DR beta 1 increases with age	Homo sapiens	male/female	20	99	Hippocampus	204.16	None

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Supplement Table 4. (cont.)

HLA-DRB1 (major histocompatibility complex, class II, DR beta 1)	major histocompatibility complex, class II, DR beta 1 increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	111.08	None
HNRNPD (heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa))	Gene expression of HNRNPD increases with age	Homo sapiens	female	39	85	Skin	-	-
Lgals3 (lectin, galactose binding, soluble 3)	lectin, galactose binding, soluble 3	Mus musculus	male/female	2	24	Visual Apparatus	141	0.00051188
LTF (lactotransferrin)	lactotransferrin	Homo sapiens	male/female	27	92	Kidney	115	1.1943 e-05
Ltf (lactotransferrin)	lactotransferrin	Mus musculus	male/female	2	15	Hippocampus	23	0.00066771
Pkm2 (pyruvate kinase, muscle)	pyruvate kinase, muscle	Mus musculus	male/female	8	24	Muscle	-3	0.00059594
PRELP (proline/arginin e-rich end leucin e-rich repeat protein)	Gene expression of PRELP decreases with age	Homo sapiens	female	39	85	Skin	-	-
PSMB5 (proteasome (prosome, macropain) subunit, beta type, 5)	Gene expression of PSMB5 decreases with age	Homo sapiens	female	39	85	Skin	-	-
RDH5 (retinol dehydrogenase 5 (11-cis/9-cis))	Gene expression of RDH5 increases with age	Homo sapiens	female	39	85	Skin	-	-
RTN4 (reticulon 4)	Gene expression of RTN4 decreases with age	Homo sapiens	female	39	85	Skin	-	-
RTN4 (reticulon 4)	reticulon 4	Homo sapiens	male/female	26	106	Brain	-8	0.00018221
S100a8 (S100 calcium binding protein A8 (calgranulin A))	S100 calcium binding protein A8 (calgranulin A)	Mus musculus	male/female	3	23	Hematological System	-40	0.00052108
S100A8 (S100 calcium binding protein A8)	S100 calcium binding protein A8 increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	1228.24	None
S100A8 (S100 calcium binding protein A8)	S100 calcium binding protein A8 increases with age	Homo sapiens	male/female	20	99	Temporal Lobe	530.64	None

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Supplement Table 4. (cont.)

S100A8 (S100 calcium binding protein A8)	S100 calcium binding protein A8 increases with age	Homo sapiens	male/female	20	99	Hippocampus	1115.4	None
S100A8 (S100 calcium binding protein A8)	S100 calcium binding protein A8 increases with age	Homo sapiens	male/female	20	99	Frontal Lobe	921.38	None
S100a9 (S100 calcium binding protein A9 (calgranulin B))	S100 calcium binding protein A9 (calgranulin B)	Mus musculus	male/female	2	15	Hippocampus	33	0.00063436
S100A9 (S100 calcium binding protein A9)	S100 calcium binding protein A9 increases with age	Homo sapiens	male/female	20	99	Parietal Lobe	228.96	None
S100A9 (S100 calcium binding protein A9)	S100 calcium binding protein A9 increases with age	Homo sapiens	male/female	20	99	Frontal Lobe	92.75	None
Saa1 (serum amyloid A 1)	serum amyloid A 1	Mus musculus	male/female	3	23	Hematological System	118	0.00077718
SERPINA12 (serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 12)	serine (or cysteine) proteinase inhibitor; clade A (alpha-1 antiproteinase; antitrypsin); member 12 decreases with age	Homo sapiens	female	6	73	Dermis	-15.2	None
SERPINA12 (serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 12)	serine (or cysteine) proteinase inhibitor; clade A (alpha-1 antiproteinase; antitrypsin); member 12 increases with age	Homo sapiens	male/female	21	85	Mesenchymal Stem Cell	52.7	None
SERPINA1 (serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1)	Gene expression of SERPINA1 decreases with age	Homo sapiens	female	39	85	Skin	-	-
SERPINA3 (serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3)	Gene expression of SERPINA3 decreases with age	Homo sapiens	female	39	85	Skin	-	-

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Supplement Table 4. (cont.)

SERPINF1 (serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member)	serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member	Homo sapiens	male/female	26	106	Brain	-7	0.00061035
Slc25a11 (solute carrier family 25 (mitochondrial carrier oxoglutarate carrier), member 11)	solute carrier family 25 (mitochondrial carrier oxoglutarate carrier), member 11	Mus musculus	male/female	8	24	Muscle	-1	0.00086092
SLC2A1 (solute carrier family 2 (facilitated glucose transporter), member 1)	Gene expression of SLC2A1 increases with age	Homo sapiens	female	39	85	Skin	-	-
SLC2A1 (solute carrier family 2 (facilitated glucose transporter), member 1)	glucose transporter 1 activity decreases	Homo sapiens	male/female	-1	-1	Blood Brain Barrier	-	-
Slc2a1 (solute carrier family 2 (facilitated glucose transporter), member 1)	solute carrier family 2 (facilitated glucose transporter), member 1	Mus musculus	male/female	2	15	Hippocampus	6	0.00024775
TF (transferrin)	Gene expression of TF decreases with age	Homo sapiens	female	39	85	Skin	-	-
TGM2 (transglutaminase 2 (C polypeptide, protein-glutamin e-gamma-glutamyltransferase))	transglutaminase 2 (C polypeptide, protein-glutamin e-gamma-glutamyltransferase)	Homo sapiens	male/female	26	106	Brain	18	0.00017443
THY1 (Thy-1 cell surface antigen)	Gene expression of THY1 decreases with age	Homo sapiens	female	39	85	Skin	-	-
THY1 (Thy-1 cell surface antigen)	Gene expression of THY1 decreases with age	Homo sapiens	female	39	85	Adipose Tissue	-	-
TPD52 (tumor protein D52)	Gene expression of TPD52 increases with age	Homo sapiens	female	39	85	Adipose Tissue	-	-

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Supplement Table 4. (cont.)

Tpd52l1 (tumor protein D52-like 1)	tumor protein D52-like 1	Mus musculus	male/female	2	15	Hippocampus	2	0.00058224
SLC22A18 (solute carrier family 22, member 18)	tumor suppressing subtransferable candidate 5 increases with age	Homo sapiens	female	6	73	Dermis	16.9	0.001
TUFM (Tu translation elongation factor, mitochondrial)	Gene expression of TUFM decreases with age	Homo sapiens	female	39	85	Skin	-	-
TXNDC5 (thioredoxin domain containing 5 (endoplasmic reticulum))	Gene expression of TXNDC5 decreases with age	Homo sapiens	female	39	85	Skin	-	-
VDAC1 (voltag e-dependent anion channel 1)	voltag e-dependent anion channel 1	Homo sapiens	male/female	26	106	Brain	-10	1.6337 e-05
VIMP (VCP-interacting membrane protein)	Gene expression of VIMP decreases with age	Homo sapiens	female	39	85	Skin	-	-
Vtn (vitronectin)	vitronectin	Mus musculus	male/female	5	30	Anatomical System	4	0.00064497
VWF (von Willebrand factor)	Hypomethylation of VWF is positively correlated with age	Homo sapiens	male/female	25	92	Blood	-	-
Frzb (frizzled-related protein)	frizzled-related protein	Mus musculus	male/female	8	24	-	-12	0.00035437

Supplement Table 5. PIP Network Analysis for 10 Candidate Genes with STRING

#node1	node2	neighborhood_on_chromosome	gene_fusion	phylogenetic_cooccurrence	homology	coexpression	experimentally_determined_interaction	database_annotated	Automated_textmining	combined_score
ARMS2	C3	0	0	0	0	0	0.3	0	0.662	0.75
ARMS2	LIPC	0	0	0	0	0	0	0	0.739	0.74
ARMS2	C2	0	0	0	0	0	0	0	0.77	0.77
ARMS2	CFH	0	0	0	0	0	0	0	0.916	0.92
ARMS2	CFI	0	0	0	0	0	0	0	0.682	0.68
C2	C3	0	0	0	0	0.148	0.3	0.8	0.762	0.97
C2	LIPC	0	0	0	0	0.065	0.06	0	0.514	0.53
C2	CX3CR1	0	0	0	0	0	0	0	0.43	0.43
C2	CFH	0	0	0	0	0.063	0	0	0.783	0.79
C2	CFI	0	0	0	0	0.099	0	0.65	0.737	0.91
C3	CFI	0	0	0	0	0.139	0.97	0.8	0.971	1
C3	CFH	0	0	0	0	0.118	0.98	0.8	0.989	1
CFH	LIPC	0	0	0	0	0.095	0	0	0.666	0.68
CFH	CX3CR1	0	0	0	0	0	0	0	0.417	0.42
CFH	CFI	0	0	0	0	0.12	0.87	0.6	0.93	1
CFI	LIPC	0	0	0	0	0.139	0.06	0	0.428	0.5
CX3CR1	IL10RA	0	0	0	0	0.198	0	0	0.43	0.52
IFNL3	IL10RA	0	0	0	0	0	0	0.6	0.54	0.81

Supplement Table 6. PIP Network Analysis for AMD Genes from GWAS Studies and Candidate Genes with STRING

#node1	node2	neighborhood_on_chromosome	gene_fusion	phylogenetic_ cooccurrence	homology	coexpression	experimentally_ determined_ interaction	database_ annotated	Automated .textmining	combined_score
ABCA1	CETP	0	0	0	0	0	0	0	0.847	0.847
ABCA1	APOE	0	0	0	0	0.063	0	0	0.983	0.983
ABCA1	LIPC	0	0	0	0	0.062	0	0	0.716	0.722
ABCA1	CFH	0	0	0	0	0.087	0	0	0.425	0.452
ABCA1	TLR4	0	0	0	0	0.107	0.056	0	0.521	0.561
ABCA1	ARMS2	0	0	0	0	0	0	0	0.498	0.497
ABCA4	TIMP3	0	0	0	0	0.065	0	0	0.427	0.441
ABCA4	HMCN1	0	0	0	0	0.089	0	0	0.404	0.434
ABCA4	CFH	0	0	0	0	0.062	0	0	0.556	0.565
ABCA4	CFB	0	0	0	0	0.069	0.056	0	0.39	0.417
ABCA4	RAX2	0	0	0	0	0	0.057	0	0.457	0.466
ABCA4	ARMS2	0	0	0	0	0	0	0	0.561	0.561
ADAMTS9	COL8A1	0	0	0	0	0	0	0	0.522	0.522
ADAMTS9	TIMP3	0	0	0	0	0.118	0	0	0.421	0.468
ADAMTS9	SLC16A8	0	0	0	0	0	0	0	0.535	0.535
ADAMTS9	B3GALTL	0	0	0	0	0	0	0.9	0.707	0.969
ADAMTS9	FILIP1L	0	0	0	0	0.065	0	0	0.499	0.511
ADAMTS9	CFH	0	0	0	0	0.061	0	0	0.39	0.402
ADAMTS9	DDR1	0	0	0	0	0.049	0	0	0.407	0.412
ADAMTS9	ARMS2	0	0	0	0	0	0	0	0.517	0.517
ADAMTS9	RAD51B	0	0	0	0	0	0	0	0.597	0.597
APOE	CETP	0	0	0	0	0.062	0	0.72	0.827	0.95
APOE	C3	0	0	0	0	0.138	0	0	0.563	0.607
APOE	TIMP3	0	0	0	0	0.076	0	0	0.423	0.444
APOE	CFB	0	0	0	0	0.08	0	0	0.47	0.491
APOE	VEGFA	0	0	0	0	0	0	0	0.594	0.594
APOE	ARMS2	0	0	0	0	0	0	0	0.6	0.6
APOE	CFH	0	0	0	0	0.054	0.297	0	0.66	0.754
APOE	TLR4	0	0	0	0	0	0	0	0.756	0.756
APOE	LIPC	0	0	0	0	0.062	0	0.9	0.722	0.971
ARMS2	CETP	0	0	0	0	0	0	0	0.681	0.681
ARMS2	C3	0	0	0	0	0	0.297	0	0.662	0.752
ARMS2	COL8A1	0	0	0	0	0	0	0	0.602	0.602
ARMS2	TIMP3	0	0	0	0	0	0	0	0.595	0.595
ARMS2	HMCN1	0	0	0	0	0	0.27	0	0.877	0.906
ARMS2	LIPC	0	0	0	0	0	0	0	0.739	0.739

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Supplement Table 4. (cont.)

ARMS2	C2	0	0	0	0	0	0	0	0.77	0.77
ARMS2	CFHR1	0	0	0	0	0	0	0	0.662	0.662
ARMS2	SLC16A8	0	0	0	0	0	0	0	0.6	0.6
ARMS2	COL10A1	0	0	0	0	0	0	0	0.494	0.493
ARMS2	B3GALTL	0	0	0	0	0	0	0	0.596	0.596
ARMS2	FBLN5	0	0	0	0	0	0	0	0.469	0.469
ARMS2	FILIP1L	0	0	0	0	0	0	0	0.405	0.405
ARMS2	CFHR3	0	0	0	0	0	0	0	0.653	0.653
ARMS2	CFH	0	0	0	0	0	0	0	0.916	0.916
ARMS2	HTRA1	0	0	0	0	0	0	0	0.77	0.77
ARMS2	CFI	0	0	0	0	0	0	0	0.682	0.682
ARMS2	CFB	0	0	0	0	0	0	0	0.844	0.844
ARMS2	RAD51B	0	0	0	0	0	0	0	0.556	0.556
ARMS2	VEGFA	0	0	0	0	0	0	0	0.556	0.556
B3GALTL	CETP	0	0	0	0	0	0	0	0.455	0.455
B3GALTL	TNFRSF10A	0	0	0	0	0	0	0	0.406	0.406
B3GALTL	IER3	0	0	0	0	0	0	0	0.517	0.517
B3GALTL	COL8A1	0	0	0	0	0	0	0	0.595	0.595
B3GALTL	LIPC	0	0	0	0	0	0	0	0.519	0.519
B3GALTL	SLC16A8	0	0	0	0	0.062	0	0	0.68	0.687
B3GALTL	COL10A1	0	0	0	0	0	0	0	0.47	0.47
B3GALTL	FRK	0	0	0	0	0.064	0	0	0.393	0.407
B3GALTL	TGFBR1	0	0	0	0	0.064	0	0	0.42	0.433
B3GALTL	CFB	0	0	0	0	0	0	0	0.456	0.456
B3GALTL	CFH	0	0	0	0	0	0	0	0.458	0.457
B3GALTL	DDR1	0	0	0	0	0	0	0	0.518	0.518
B3GALTL	RAD51B	0	0	0	0	0.109	0	0	0.591	0.62
B3GALTL	FILIP1L	0	0	0	0	0	0	0	0.632	0.632
C2	C3	0	0	0	0	0.148	0.296	0.8	0.762	0.967
C2	C9	0	0	0	0	0.146	0.176	0	0.604	0.697
C2	HMCN1	0	0	0	0	0	0	0	0.608	0.608
C2	LIPC	0	0	0	0	0.065	0.057	0	0.514	0.534
C2	CX3CR1	0	0	0	0	0	0	0	0.43	0.43
C2	CFHR1	0	0	0	0	0	0	0	0.519	0.519
C2	FBLN5	0	0	0	0	0	0.056	0	0.52	0.527
C2	RAX2	0	0	0	0	0	0.057	0	0.54	0.547
C2	CFHR3	0	0	0	0	0	0	0	0.561	0.561
C2	HTRA1	0	0	0	0	0.062	0.056	0	0.566	0.582
C2	CFB	0	0	0	0.882	0.172	0	0.6	0.801	0.687
C2	CFH	0	0	0	0	0.063	0	0	0.783	0.788
C2	CFI	0	0	0	0	0.099	0	0.65	0.737	0.91
C3	TLR3	0	0	0	0	0.062	0.087	0	0.369	0.412
C3	HTRA1	0	0	0	0	0.089	0	0	0.405	0.434
C3	VEGFA	0	0	0	0	0.073	0	0	0.459	0.477
C3	TLR4	0	0	0	0	0.062	0.087	0	0.583	0.611
C3	C9	0	0	0	0	0.18	0.078	0	0.627	0.693
C3	CFHR3	0	0	0	0	0	0.27	0.6	0.936	0.979

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Supplement Table 4. (cont.)

C3	CFHR1	0	0	0	0	0	0.973	0.6	0.955	0.999
C3	CFI	0	0	0	0	0.139	0.974	0.8	0.971	0.999
C3	CFH	0	0	0	0	0.118	0.982	0.8	0.989	0.999
C3	CFB	0	0	0	0	0.311	0.977	0.8	0.989	0.999
C9	CFB	0	0	0	0	0.146	0.157	0	0.519	0.623
C9	CFH	0	0	0	0	0.262	0	0	0.519	0.629
C9	CFI	0	0	0	0	0.1	0.077	0	0.609	0.647
CETP	COL8A1	0	0	0	0	0	0	0	0.4	0.4
CETP	SLC16A8	0	0	0	0	0	0	0	0.421	0.42
CETP	CFB	0	0	0	0	0.085	0	0	0.52	0.542
CETP	CFH	0	0	0	0	0.087	0	0	0.6	0.619
CETP	LIPC	0	0	0	0	0.09	0	0.54	0.859	0.936
CFB	COL8A1	0	0	0	0	0	0	0	0.456	0.456
CFB	TIMP3	0	0	0	0	0.088	0	0	0.409	0.437
CFB	HMCN1	0	0	0	0	0.065	0	0	0.41	0.424
CFB	LIPC	0	0	0	0	0.065	0.057	0	0.604	0.621
CFB	CFHR1	0	0	0	0	0	0.297	0	0.756	0.821
CFB	SLC16A8	0	0	0	0	0	0	0	0.407	0.407
CFB	CFHR3	0	0	0	0	0	0	0.6	0.732	0.888
CFB	CFH	0	0	0	0.543	0.158	0.297	0.8	0.884	0.923
CFB	HTRA1	0	0	0	0	0.088	0.056	0	0.53	0.56
CFB	CFI	0	0	0	0	0.133	0	0.65	0.833	0.944
CFB	VEGFA	0	0	0	0	0.098	0	0	0.369	0.406
CFH	COL8A1	0	0	0	0	0.14	0	0	0.501	0.552
CFH	TIMP3	0	0	0	0	0.111	0	0	0.518	0.553
CFH	HMCN1	0	0	0	0	0.068	0	0	0.505	0.518
CFH	LIPC	0	0	0	0	0.095	0	0	0.666	0.684
CFH	CFHR1	0	0	0	0.96	0.325	0.932	0	0.874	0.954
CFH	SLC16A8	0	0	0	0	0	0	0	0.466	0.465
CFH	FBLN5	0	0	0	0	0.131	0	0	0.478	0.527
CFH	ERCC6	0	0	0	0	0	0	0	0.537	0.537
CFH	CX3CR1	0	0	0	0	0	0	0	0.417	0.416
CFH	CFHR3	0	0	0	0.946	0.065	0.229	0.9	0.87	0.925
CFH	TLR4	0	0	0	0	0.162	0	0	0.323	0.409
CFH	VEGFA	0	0	0	0	0.062	0	0	0.593	0.601
CFH	HTRA1	0	0	0	0	0.102	0	0	0.714	0.733
CFH	CFI	0	0	0	0	0.12	0.87	0.6	0.93	0.996
CFHR1	HMCN1	0	0	0	0	0	0	0	0.442	0.442
CFHR1	ERCC6	0	0	0	0	0	0	0	0.412	0.412
CFHR1	RAX2	0	0	0	0	0	0	0	0.416	0.416
CFHR1	CFI	0	0	0	0	0	0	0	0.708	0.708
CFHR1	CFHR3	0	0	0	0.919	0.905	0	0.6	0.915	0.963
CFHR3	HMCN1	0	0	0	0	0	0	0	0.457	0.457
CFHR3	ERCC6	0	0	0	0	0	0	0	0.414	0.414
CFHR3	RAX2	0	0	0	0	0	0	0	0.43	0.43
CFHR3	CFI	0	0	0	0	0	0	0.6	0.681	0.866
CFI	TIMP3	0	0	0	0	0.069	0	0	0.629	0.64

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Supplement Table 4. (cont.)

CFI	LIPC	0	0	0	0	0.139	0.057	0	0.428	0.495
CFI	HTRA1	0	0	0	0	0	0.056	0	0.433	0.442
CFI	FRK	0	0	0	0	0	0.056	0	0.42	0.429
COL10A1	TIMP3	0	0	0	0	0.053	0	0	0.407	0.414
COL10A1	LIPC	0	0	0	0	0	0	0	0.453	0.453
COL10A1	SLC16A8	0	0	0	0	0	0	0	0.432	0.432
COL10A1	FILIP1L	0	0	0	0	0	0	0	0.406	0.406
COL10A1	FRK	0	0.001	0	0	0	0	0	0.436	0.436
COL8A1	DDR1	0	0	0	0	0.062	0	0	0.394	0.407
COL8A1	TIMP3	0	0	0	0	0.09	0	0	0.457	0.484
COL8A1	LIPC	0	0	0	0	0	0	0	0.503	0.503
COL8A1	RAD51B	0	0	0	0	0	0	0	0.513	0.513
COL8A1	FILIP1L	0	0	0	0	0.084	0	0	0.533	0.554
COL8A1	SLC16A8	0	0	0	0	0	0	0	0.574	0.574
CX3CR1	IL10RA	0	0	0	0	0.198	0	0	0.43	0.523
CX3CR1	HMCN1	0	0	0	0	0	0	0	0.43	0.43
CX3CR1	TLR3	0	0	0	0	0	0	0	0.421	0.42
CX3CR1	VEGFA	0	0	0	0	0	0	0	0.502	0.502
CX3CR1	TLR4	0	0	0	0	0.099	0	0	0.619	0.642
DDR1	SLC16A8	0	0	0	0	0.072	0	0	0.475	0.492
DDR1	FILIP1L	0	0	0	0	0	0	0	0.475	0.475
DDR1	RAD51B	0	0	0	0	0	0	0	0.405	0.405
ERCC6	HMCN1	0	0	0	0	0.066	0	0	0.401	0.416
ERCC6	RAD51B	0	0	0	0	0.062	0.185	0	0.351	0.461
FBLN5	TIMP3	0	0	0	0	0.126	0	0	0.394	0.448
FBLN5	VEGFA	0	0	0	0	0.062	0	0	0.44	0.453
FBLN5	RAX2	0	0	0	0	0	0.059	0	0.457	0.467
FILIP1L	IER3	0	0	0	0	0.062	0	0	0.476	0.488
FILIP1L	SLC16A8	0	0	0	0	0	0	0	0.595	0.595
FILIP1L	RAD51B	0	0	0	0	0	0	0	0.566	0.566
FRK	TNFRSF10A	0	0	0	0	0	0	0	0.49	0.49
FRK	LIPC	0	0	0	0	0	0	0	0.404	0.404
HMCN1	RAX2	0	0	0	0	0	0	0	0.54	0.54
HTRA1	IER3	0	0	0	0	0	0	0	0.682	0.682
HTRA1	TIMP3	0	0	0	0	0.338	0	0	0.325	0.535
HTRA1	LIPC	0	0	0	0	0	0	0	0.404	0.404
IER3	SLC16A8	0	0	0	0	0	0	0	0.476	0.476
IFNL3	IL10RA	0	0	0	0	0	0	0.6	0.54	0.808
IFNL3	TLR3	0	0	0	0	0	0	0	0.549	0.549
IL10RA	TLR4	0	0	0	0	0.141	0	0	0.467	0.522
LIPC	TIMP3	0	0	0	0	0	0	0	0.491	0.491
LIPC	RAD51B	0	0	0	0	0	0	0	0.408	0.408
LIPC	SLC16A8	0	0	0	0	0	0	0	0.637	0.637
RAD51B	SLC16A8	0	0	0	0	0.062	0	0	0.575	0.584
RAD51B	TGFBR1	0	0	0	0	0.049	0.078	0	0.389	0.418
SLC16A8	TIMP3	0	0	0	0	0	0	0	0.413	0.412
SLC16A8	TGFBR1	0	0	0	0	0	0	0	0.481	0.481

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Supplement Table 4. (cont.)

SYN3	TIMP3	0	0	0	0	0	0	0	0.683	0.683
TGFBR1	VEGFA	0	0	0	0	0	0	0	0.525	0.525
TIMP3	VEGFA	0	0	0	0	0.092	0	0	0.665	0.683
TLR3	TLR4	0	0	0	0.592	0.062	0	0	0.956	0.427
TLR3	VEGFA	0	0	0	0	0	0	0	0.469	0.469
TLR4	VEGFA	0	0	0	0	0	0	0	0.65	0.65

Supplement Table 7. The Functional Overrepresentation Reactome Pathway Analysis for Both Retinal Transcriptomic and AMD GWAS Study and 10 Candidate Genes by PANTHER

Reactome pathways	Homo sapiens - REFLIST (20595)	Client Text Box Input (191)	Client Text Box Input (expected)	Client Text Box Input (over/under)	Client Text Box Input (fold Enrichment)	Client Text Box Input (raw P-value)	Client Text Box Input (FDR)
Defective ABCA1 causes Tangier disease (R-HSA-5682113)	2	2	0.02	+	> 100	4.98 e-04	1.54 e-02
Metal sequestration by antimicrobial proteins (R-HSA-6799990)	6	4	0.06	+	71.88	1.39 e-06	1.13 e-04
Activation of C3 and C5 (R-HSA-174577)	7	3	0.06	+	46.21	8.74 e-05	3.38 e-03
Alternative complement activation (R-HSA-173736)	5	2	0.05	+	43.13	1.71 e-03	4.54 e-02
Chylomicron clearance (R-HSA-8964026)	5	2	0.05	+	43.13	1.71 e-03	4.49 e-02
Scavenging by Class B Receptors (R-HSA-3000471)	5	2	0.05	+	43.13	1.71 e-03	4.44 e-02
Regulation of TLR by endogenous ligand (R-HSA-5686938)	19	7	0.18	+	39.73	2.81 e-09	4.94 e-07
HDL remodeling (R-HSA-8964058)	9	3	0.08	+	35.94	1.58 e-04	5.64 e-03
Chylomicron remodeling (R-HSA-8963901)	10	3	0.09	+	32.35	2.04 e-04	7.06 e-03
Chylomicron assembly (R-HSA-8963888)	10	3	0.09	+	32.35	2.04 e-04	6.96 e-03
GRB2:SOS provides linkage to MAPK signaling for Integrins (R-HSA-354194)	14	4	0.13	+	30.81	1.91 e-05	9.92 e-04
p130Cas linkage to MAPK signaling for integrins (R-HSA-372708)	15	4	0.14	+	28.75	2.40 e-05	1.22 e-03
Scavenging by Class A Receptors (R-HSA-3000480)	19	5	0.18	+	28.38	2.29 e-06	1.75 e-04
The canonical retinoid cycle in rods (twilight vision) (R-HSA-2453902)	23	6	0.21	+	28.13	2.22 e-07	2.30 e-05
Retinoid cycle disease events (R-HSA-2453864)	13	3	0.12	+	24.88	3.92 e-04	1.26 e-02
Diseases associated with visual transduction (R-HSA-2474795)	13	3	0.12	+	24.88	3.92 e-04	1.24 e-02
Plasma lipoprotein assembly (R-HSA-8963898)	18	4	0.17	+	23.96	4.44 e-05	2.03 e-03
Signaling by high-kinase activity BRAF mutants (R-HSA-6802948)	35	6	0.32	+	18.48	1.91 e-06	1.51 e-04
Plasma lipoprotein remodeling (R-HSA-8963899)	30	5	0.28	+	17.97	1.61 e-05	8.77 e-04
Collagen chain trimerization (R-HSA-8948216)	44	7	0.41	+	17.15	4.08 e-07	3.88 e-05

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Supplement Table 7. (cont.)

Integrin cell surface interactions (R-HSA-216083)	84	13	0.78	+	16.69	5.24 e-12	1.71 e-09
Formation of Fibrin Clot (Clotting Cascade) (R-HSA-140877)	39	6	0.36	+	16.59	3.36 e-06	2.40 e-04
MAP2K and MAPK activation (R-HSA-5674135)	39	6	0.36	+	16.59	3.36 e-06	2.33 e-04
Integrin signaling (R-HSA-354192)	26	4	0.24	+	16.59	1.57 e-04	5.69 e-03
Gluconeogenesis (R-HSA-70263)	33	5	0.31	+	16.34	2.44 e-05	1.21 e-03
Syndecan interactions (R-HSA-3000170)	27	4	0.25	+	15.97	1.79 e-04	6.29 e-03
Common Pathway of Fibrin Clot Formation (R-HSA-140875)	22	3	0.2	+	14.7	1.51 e-03	4.27 e-02
RA biosynthesis pathway (R-HSA-5365859)	22	3	0.2	+	14.7	1.51 e-03	4.22 e-02
Chaperone Mediated Autophagy (R-HSA-9613829)	22	3	0.2	+	14.7	1.51 e-03	4.16 e-02
Non-integrin membran e-ECM interactions (R-HSA-3000171)	59	8	0.55	+	14.62	1.80 e-07	1.96 e-05
Platelet degranulation (R-HSA-114608)	127	17	1.18	+	14.43	2.16 e-14	1.24 e-11
Paradoxical activation of RAF signaling by kinase inactive BRAF (R-HSA-6802955)	45	6	0.42	+	14.38	7.11 e-06	4.39 e-04
Signaling by RAS mutants (R-HSA-6802949)	45	6	0.42	+	14.38	7.11 e-06	4.27 e-04
Signaling by moderate kinase activity BRAF mutants (R-HSA-6802946)	45	6	0.42	+	14.38	7.11 e-06	4.16 e-04
Signaling downstream of RAS mutants (R-HSA-9649948)	45	6	0.42	+	14.38	7.11 e-06	4.06 e-04
MET activates PTK2 signaling (R-HSA-8874081)	30	4	0.28	+	14.38	2.58 e-04	8.67 e-03
Pyruvate metabolism (R-HSA-70268)	30	4	0.28	+	14.38	2.58 e-04	8.55 e-03
Platelet Aggregation (Plug Formation) (R-HSA-76009)	38	5	0.35	+	14.19	4.51 e-05	1.98 e-03
Response to elevated platelet cytosolic Ca2+ (R-HSA-76005)	132	17	1.22	+	13.89	3.85 e-14	1.46 e-11
Collagen degradation (R-HSA-1442490)	64	8	0.59	+	13.48	3.18 e-07	3.16 e-05
Assembly of collagen fibrils and other multimeric structures (R-HSA-2022090)	60	7	0.56	+	12.58	2.70 e-06	1.99 e-04
Signaling by Retinoic Acid (R-HSA-5362517)	43	5	0.4	+	12.54	7.72 e-05	3.15 e-03
Post-translational protein phosphorylation (R-HSA-8957275)	107	12	0.99	+	12.09	1.03 e-09	2.14 e-07
ECM proteoglycans (R-HSA-3000178)	76	8	0.7	+	11.35	1.05 e-06	9.26 e-05
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) (R-HSA-381426)	124	13	1.15	+	11.3	4.37 e-10	9.98 e-08
Collagen biosynthesis and modifying enzymes (R-HSA-1650814)	67	7	0.62	+	11.27	5.30 e-06	3.46 e-04

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Supplement Table 7. (cont.)

Visual phototransduction (R-HSA-2187338)	97	10	0.9	+	11.12	5.50 e-08	7.40 e-06
NCAM signaling for neurite out-growth (R-HSA-375165)	59	6	0.55	+	10.97	2.93 e-05	1.42 e-03
Amyloid fiber formation (R-HSA-977225)	79	8	0.73	+	10.92	1.38 e-06	1.17 e-04
MET promotes cell motility (R-HSA-8875878)	40	4	0.37	+	10.78	7.04 e-04	2.14 e-02
Complement cascade (R-HSA-166658)	122	12	1.13	+	10.61	4.06 e-09	6.63 e-07
Regulation of Complement cascade (R-HSA-977606)	112	11	1.04	+	10.59	1.86 e-08	2.66 e-06
Binding and Uptake of Ligands by Scavenger Receptors (R-HSA-2173782)	104	10	0.96	+	10.37	1.01 e-07	1.21 e-05
Signaling by BRAF and RAF fusions (R-HSA-6802952)	64	6	0.59	+	10.11	4.48 e-05	2.01 e-03
Plasma lipoprotein assembly, remodeling, and clearance (R-HSA-174824)	67	6	0.62	+	9.66	5.68 e-05	2.36 e-03
Degradation of the extracellular matrix (R-HSA-1474228)	140	12	1.3	+	9.24	1.70 e-08	2.59 e-06
Oncogenic MAPK signaling (R-HSA-6802957)	72	6	0.67	+	8.99	8.25 e-05	3.31 e-03
Metabolism of fat-soluble vitamins (R-HSA-6806667)	48	4	0.45	+	8.99	1.33 e-03	3.83 e-02
Collagen formation (R-HSA-1474290)	89	7	0.83	+	8.48	2.96 e-05	1.41 e-03
Extracellular matrix organization (R-HSA-1474244)	299	23	2.77	+	8.29	2.91 e-14	1.33 e-11
Signaling by PDGF (R-HSA-186797)	54	4	0.5	+	7.99	1.99 e-03	5.05 e-02
Pyruvate metabolism and Citric Acid (TCA) cycle (R-HSA-71406)	54	4	0.5	+	7.99	1.99 e-03	5.00 e-02
Platelet activation, signaling and aggregation (R-HSA-76002)	259	18	2.4	+	7.49	1.01 e-10	2.87 e-08
Scavenging of heme from plasma (R-HSA-2168880)	76	5	0.7	+	7.09	9.05 e-04	2.69 e-02
Interleukin-4 and Interleukin-13 signaling (R-HSA-6785807)	111	7	1.03	+	6.8	1.11 e-04	4.14 e-03
Toll-like Receptor Cascades (R-HSA-168898)	152	9	1.41	+	6.38	1.86 e-05	9.87 e-04
Glucose metabolism (R-HSA-70326)	86	5	0.8	+	6.27	1.53 e-03	4.15 e-02
Antimicrobial peptides (R-HSA-6803157)	91	5	0.84	+	5.92	1.93 e-03	4.96 e-02
Neutrophil degranulation (R-HSA-6798695)	478	23	4.43	+	5.19	2.48 e-10	6.29 e-08
RAF/MAP kinase cascade (R-HSA-5673001)	232	10	2.15	+	4.65	8.47 e-05	3.33 e-03
MAPK1/MAPK3 signaling (R-HSA-5684996)	237	10	2.2	+	4.55	1.00 e-04	3.82 e-03
Signaling by Nuclear Receptors (R-HSA-9006931)	261	11	2.42	+	4.54	4.55 e-05	1.96 e-03
FLT3 Signaling (R-HSA-9607240)	250	10	2.32	+	4.31	1.53 e-04	5.62 e-03

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Supplement Table 7. (cont.)

Innate Immune System (R-HSA-168249)	1105	44	10.25	+	4.29	3.28 e-16	2.49 e-13
Hemostasis (R-HSA-109582)	669	26	6.2	+	4.19	1.26 e-09	2.39 e-07
G alpha (i) signalling events (R-HSA-418594)	402	15	3.73	+	4.02	7.69 e-06	4.28 e-04
MAPK family signaling cascades (R-HSA-5683057)	276	10	2.56	+	3.91	3.28 e-04	1.07 e-02
Metabolism of carbohydrates (R-HSA-71387)	286	9	2.65	+	3.39	1.68 e-03	4.52 e-02
Diseases of signal transduction (R-HSA-5663202)	366	11	3.39	+	3.24	7.62 e-04	2.29 e-02
Immune System (R-HSA-168256)	2158	64	20.01	+	3.2	1.62 e-17	1.85 e-14
Vesicl e-mediated transport (R-HSA-5653656)	725	21	6.72	+	3.12	5.48 e-06	3.48 e-04
Cytokine Signaling in Immune system (R-HSA-1280215)	823	23	7.63	+	3.01	3.39 e-06	2.28 e-04
Disease (R-HSA-1643685)	1126	31	10.44	+	2.97	7.57 e-08	9.60 e-06
Signaling by Interleukins (R-HSA-449147)	447	12	4.15	+	2.89	1.15 e-03	3.36 e-02
Transport of small molecules (R-HSA-382551)	719	19	6.67	+	2.85	5.30 e-05	2.24 e-03
Signaling by Receptor Tyrosine Kinases (R-HSA-9006934)	457	12	4.24	+	2.83	1.38 e-03	3.93 e-02
Metabolism of proteins (R-HSA-392499)	1977	41	18.33	+	2.24	9.62 e-07	8.78 e-05
Post-translational protein modification (R-HSA-597592)	1388	27	12.87	+	2.1	3.94 e-04	1.23 e-02
Signal Transduction (R-HSA-162582)	2728	53	25.3	+	2.09	1.47 e-07	1.68 e-05
Metabolism (R-HSA-1430728)	2079	39	19.28	+	2.02	3.05 e-05	1.42 e-03
Unclassified (UNCLASSIFIED)	9941	27	92.19	-	0.29	4.60 e-23	1.05 e-19