UNIVERSITI PUTRA MALAYSIA

PREVALENCE AND GENETIC ANALYSES OF SELECTED AGE-RELATED MACULAR DEGENERATION-RELATED POLYMORPHISMS AND THEIR RESPONSES TO INTRAVITREAL RANIBIZUMAB

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By

NUR AFIQAH BINTI MOHAMAD

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Age-related macular degeneration (AMD), a leading cause of vision loss among elderly people is a progressive chronic disease of the central retina associated with environmental and genetic factors. Studies reported that gene polymorphism of various genes were analysed among AMD subjects from different populations with conflicting results. Among those, complement factor, vascular endothelial growth factor (VEGF), high temperature requirement A1 (HTRA1) and age-related maculopathy susceptibility 2 (ARMS2) genes were studied extensively among AMD subjects. In Malaysia the data on intravitreal ranibizumab drug therapy and the genetic association of gene polymorphisms among AMD remains unclear. The current study was initiated to determine the genetic association between the candidate gene polymorphisms in response to ranibizumab and also, the prevalence and changes in treatment patterns of ranibizumab and photodynamic therapy (PDT) among retinal eye disease patients from a tertiary care hospital. Upon ethical approval and consent, a total of 149 AMD and 152 controls were recruited for the prospective study. Moreover, a total number of 821 subjects were recruited for retrospective study using Electronic Medical Record database software from Hospital Selayang, Selangor. Genomic DNA and total RNA were extracted and the genotyping were analyzed using the conventional PCR and PCR-RFLP methods. The gene expression analysis was also performed for *ARMS2* and *HTRA1* genes. The statistical analysis was performed and all the data were analysed with the level of significance was set at $P < 0.05$. The mean age of AMD subjects were 68.6 ± 8.47 and 64.8 ± 10.21 years for the controls. Males were frequent in both AMD (64%) and controls (74%) compared to females. Among AMD, Chinese (57%) were high compared to Malays (34%) and Indians (9%), whereas in controls, Malays were high (42%) compared to Chinese (41%) and Indians (17%). From the retrospective analysis, ranibizumab was the most common (30.8%) drug used as a treatment for AMD, while PDT (84.4%) or combined therapy (58.2%) were used for polypoidal choroidal vasculopathy (a subtype of AMD) patients. A significant difference ($P<0.05$) was observed for the genotypic frequencies of *VEGF +405 G/C, ARMS2 A69S,* and *HTRA1 -625 G/A* gene polymorphisms when compared between

AMD subjects and controls. However, the complement factor H (*CFH) Y402H*, complement component 3 (*C3) R102G*, *VEGF -460 C/T* and *VEGF* Insertion/deletion gene polymorphisms did not show any significant differences ($P>0.05$). The *ARMS2* A69S and *HTRA1* -625 G/A gene polymorphisms in response to the ranibizumab treatment among AMD subjects shows a significant association ($P<0.05$). Moreover, an over-expression of mRNA in the *HTRA1* GG genotype was also reported and could contribute to the non-responders' reaction to ranibizumab. However, no significant association ($P>0.05$) was observed in the *CFH Y402H* gene polymorphism with response to ranibizumab therapy based on both visual and anatomical outcome among AMD subjects. In conclusion,, *Y402H, +405 G/C, A69S, 625 G/A* polymorphisms of the *CFH, VEGF, ARMS2* and *HTRA1* genes, respectively, could be an independent risk factor and can be considered as a genetic susceptibility for the development of AMD among Malaysians.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PREVALENS DAN ANALISIS GENETIK TERHADAP POLIMORFISME YANG BERKAIT DENGAN DEGENERASI MAKULA TERKAIT UMUR DAN TINDAK BALAS TERHADAP INTRAVITREAL RANIBIZUMAB

Oleh

NUR AFIQAH BINTI MOHAMAD

Mei 2018

Pengerusi : Vasudevan Ramachandran, PhD
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Degenerasi makula terkait umur (AMD), punca utama kehilangan penglihatan dalam kalangan warga tua merupakan penyakit kronik progresif pusat retina yang dikaitkan dengan faktor persekitaran dan genetik. Kajian melaporkan polimorfisme gen bagi pelbagai gen yang dianalisis dalam kalangan pesakit AMD daripada populasi berbeza memberikan hasil yang bercanggah. Antaranya adalah gen faktor komplemen, faktor pertumbuhan endotelia vaksular (VEGF), keperluan suhu tinggi A1 (HTRA1) dan kerentanan makulopati berkaitan umur 2 (ARMS2) yang dikaji secara terperinci dalam kalangan subjek AMD. Di Malaysia, data tentang kaitan antara polimorfisme gen dan tindak balasnya terhadap terapi intravitreal ranibizumab dalam kalangan AMD masih tidak jelas. Kajian ini dijalankan untuk menentukan kaitan genetik dan polimorfisme gen bagi gen tercalon serta tindak balasnya terhadap ranibizumab dan juga prevalens serta perubahan corak rawatan ranibizumab dan terapi fotodinamik (PDT) dalam kalangan pesakit retina mata di hospital penjagaan tertiari. Setelah mendapat kelulusan etika dan izin subjek, sebanyak 146 AMD dan 152 kawalan direkrut untuk kajian prospektif. Tambahan lagi, sejumlah 821 subjek direkrut untuk analisis kajian retrospektif menggunakan perisian pangkalan data Rekod Perubatan Elektronik dari Hospital Selayang, Selangor. DNA genomik dan RNA diekstrak daripada sampel darah dan analisis penggenotipan dianalisis dengan menggunakan kaedah PCR kovensional dan analisis PCR-RFLP. Analisis pengekspresan gen juga dijalankan bagi gen *ARMS2* dan *HTRA1*. Analisis statistik dikendalikan dan kesemua data dianalisis dengan signifikan ditetapkan pada $P < 0.05$. Purata umur bagi subjek AMD yang diambil adalah 68.6 ± 8.47 tahun dan 64.8 ± 10.21 tahun bagi kawalan. Lelaki lebih kerap dalam kedua-dua kumpulan AMD (64%) dan kawalan (74%) berbanding wanita. Dikalangan AMD, peratusan Cina (57%) lebih tinggi berbanding Melayu (34%) dan India (9%) manakala bagi peratusan kawalan, Melayu lebih tinggi (42%) berbanding Cina (41%) dan India (17%). Bagi analisis retrospektif, ranibizumab merupakan ubat paling biasa (30.8%) digunakan untuk rawatan AMD, manakala PDT (84.4%) atau rawatan campuran (58.2%) diberikan kepada pesakit vaskulopati polipoidal koroidal

(subjenis AMD). Perbezaan signifikan (P<0.05) dicerap bagi kekerapan genotipik faktor komplementari H (*CFH) Y402H, VEGF -460 C/T, VEGF +405 G/C, ARMS2 A69S,* dan *HTRA1 -625 G/A* polimorfisme gen apabila dibandingkan antara subjek AMD dan kawalan. Namun, komponen komplementari 3 (*C3) R102G* dan penyisipan/penghapusan gen polimorfisme *VEGF* tidak menunjukkan sebarang perbezaan signifikan (P>0.05). Gen polimorfisme *ARMS2* A69S dan *HTRA1* -625 G/A dan tindak balas rawatan ranibizumab terhadap subjek AMD menunjukkan perkaitan yang signifikan (P<0.05). Tambahan lagi, pengekspresan berlebihan mRNA di dalam genotip *HTRA1* GG dilaporkan dan boleh menyumbang kepada tindak balas oleh kumpulan tanpa respons terhadap ranibizumab. Namun, tiada perkaitan signifikan (P>0.05) dicerap dalam polimorfisme gen *CFH Y402H* terhadap rawatan ranibizumab bagi kedua-dua hasil visual dan anatomikal dalam kalangan subjek AMD. Kesimpulannya, polimorfisme *Y402H, +405 G/C, A69S, 625 G/A* bagi gen *CFH, VEGF, ARMS2* dan *HTRA1* boleh menjadi faktor risiko bebas dan boleh dianggap kerentanan genetik bagi perkembangan AMD dalam kalangan warga Malaysia.

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I certify that a Thesis Examination Committee has met on 2nd May 2018 to conduct the final examination of Nur Afiqah Binti Mohamad on her thesis entitled "Prevalence and Genetic Analyses of Selected Age-Related Macular Degeneration-Related Polymorphisms and Their Responses to Intravitreal Ranibizumab" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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CHAPTER 1

INTRODUCTION

Background of the Study

Age-related macular degeneration (AMD) refers to degenerative changes in the retina that have a deep impact on quality of life and independence of affected individuals (Cheung and Eaton 2013). Affected individuals are unlikely to become totally blind, but may become unable to read, write, or drive (Lim *et al.,* 2012). In particular, AMD adversely affects the quality of life in elderly sufferers, increasing the risk of falls and fractures and limiting their ability to drive safely. Rising prevalence rates of this disease are expected as the number and proportion of the aging population grows (Bird 2003). In the Malaysian population, the percentage of people aged 65 years and above is expected to rise from 5.0% in 2010 to 14.5% by 2040; Malaysia is expected to become an aging population, with 7.2% of people defined as elderly (65 years and above) by 2020 (Department of Statistic, Malaysia). An Asian meta-analysis has also shown that the age-specific prevalence of late AMD in Asians is largely similar to that seen in white people (Kawasaki *et al.,* 2010).

AMD is commonly classified into two clinical forms, dry AMD and neovascular/exudative/wet AMD. Most vision loss results from neovascular AMD, which is characterized by the incursion of blood vessels into the sub-retinal spaces (Lim *et al.,* 2012). Although advancing age is the greatest risk factor associated with AMD development, environmental and lifestyle factors may also significantly affect individuals' risk (Chen *et al.,* 2010). Modifiable environmental factors include cigarette smoking, and cardiovascular risk factors such as hypertension and diabetes are also significantly associated with AMD in various populations (Seddon *et al.,* 2005; Chakravarthy *et al.,* 2010; Chen *et al.,* 2010). In addition, genetic variations can also act as risk factors for AMD and are likely to influence differential responses to AMD treatments (Francis 2011; Abedi *et al.,* 2013). Genetic susceptibility can be modified by environmental factors; thus, together, these factors are highly predictive of onset and progression (Seddon *et al.,* 2011).

Polymorphism, a particular genetic variation, occurs when a variation is seen at a specific locus with a frequency of >1% of the population; mutation occurs less frequently (Keats and Sherman 2013). Single nucleotide polymorphisms (SNPs) are the most common genetic polymorphism comprising 90% of human variation. This is defined as a variation in a single base pair of a DNA sequence (Kruglyak and Nickerson 2001). Genetic variants are important because they serve as genetic markers and help determine those genes which confer increased or decreased risk of several diseases, including AMD, within individuals (Leveziel *et al.,* 2011).

The discovery of susceptibility genes for AMD would shed light on the critical biological processes involved in AMD development and progression. SNPs in genes such as *complement factor H (CFH)*, *complement component 3 (C3)*, and *vascular endothelial growth factor (VEGF)* have all been found to predispose individuals to the development of AMD (Janik-Papis *et al.,* 2009; Chen *et al.,* 2010). Such as, *CFH* is a negative regulator of the alternative pathway of the complement system, and thus could play a central role in AMD pathogenesis; multiple SNPs that alter *CFH* function might thus contribute to the development of AMD (Gangnon *et al.,* 2012). Other candidate genes studied in association with AMD include *High-Temperature Requirement A1 (HTRA1)* and *Age-related maculopathy susceptibility 2 (ARMS2)* genes, which have been examined in various population with conflicting results (Kanda *et al.,* 2007; Francis *et al.,* 2008; Kanda *et al.,* 2010; Abbas and Azzazy 2013).

A decade ago, AMD was largely untreatable. However, new pharmaceuticals based on suppression of *VEGF* have substantially changed the management of the disease (Brown *et al.,* 2006; Rosenfeld *et al.,* 2006). The recognition of the key role that *VEGF* plays in choroidal neovascularisation (CNV) pathogenesis led to the development of *VEGF* inhibitors (ranibizumab, bevacizumab, and aflibercept), which are typically given via intravitreal injection (Cook *et al.,* 2008; Stewart 2012). Anti-VEGF helps to slow severe vision loss by reducing the growth of abnormal blood vessels and slowing their leakage; in some cases, this could also improve vision (Bird 2003). Retrospective studies have been conducted to further investigate and survey compliance with and outcomes of anti-VEGF treatments and to investigate responses in AMD patient (Cohen *et al.,* 2013; Korb *et al.,* 2013). Anti-VEGF therapy is also prescribed for other eye diseases such as polypoidal choroidal vasculopathy (PCV) (Kim *et al.,* 2015), diabetic macular oedema (Karadzic *et al.,* 2015), and diabetic retinopathy (Vaziri *et al.,* 2015).

As knowledge of AMD increases, association studies have increasingly been used to study drug responses and susceptibility to adverse drug reactions, resulting in the identification of some novel pharmacogenetic associations (Lee *et al.,* 2009; Hagstrom *et al.,* 2013; Kitchens *et al.,* 2013). Several studies have been conducted on genetic polymorphisms in response to anti-VEGF agents, with conflicting results in various populations (Francis 2011; Kang *et al.,* 2012; Kitchens *et al.,* 2013; Lotery *et al.,* 2013). This study thus mainly focuses on determining the association between genetic polymorphism of susceptibility genes and predispositions to AMD, together with an investigation of variable anti-VEGF treatment responses among AMD subjects.

Problem Statement

AMD is the most common cause of blindness in developed countries and accounts for 8.7% of all blindness worldwide, especially among those aged 60 years and above. The prevalence of AMD is thus likely to increase proportionally to the expected exponential population aging (Kawasaki *et al.,* 2010; Klein and Klein 2013). In Malaysia, the "4th Report of The National Eye Database", reported that an increase in AMD prevalence was expected based on the increasing aging population in Malaysia (Salowi and Goh 2012). Recent findings on the global prevalence of AMD suggest that the largest projected number of AMD cases will be observed among Asians, despite Asians having

a lower AMD prevalence in earlier studies; this is expected to increase more rapidly than in other world regions, as Asians account for more than 60% of the world population (Wong *et al.*, 2014).

Treatments for AMD have begun to emerge since the introduction of intravitreal anti-VEGF therapy that can slow vision loss in AMD patients and improve their quality of life. However, variable treatment responses have been observed and since then, researchers are keen in identifying the causes of this disease to prevent it and delay its progression. It is well known that apart from environmental factors, genetic factors also play a role in susceptibility of AMD. Therefore, several studies have been carried out to determine the candidate genes in predisposition to AMD in various populations with conflicting results (Almeida *et al.*, 2009; Lim *et al.*, 2012; Ratnapriya and Chew, 2013). Most reported data concern polymorphisms in the complement factor, vascular endothelial growth factor A (VEGFA), high temperature requirement A1 (HTRA1) and age-related maculopathy susceptibility 2 (ARMS2) susceptibility genes in association with AMD development. The basis for determining the genetic factor of AMD is to improve the preventive efforts, diagnosis, and treatment through a better understanding the underlying disease mechanisms, and ultimately to enhance the quality of life of elderly people.

Unfortunately, some individuals do not benefit from treatment for AMD and continue to lose vision, particularly on anti-VEGF therapy. The genetic profile of patients is thought to bring about this variability in therapeutic responsiveness. To date, a few studies with limited candidate genetic variants have been performed to investigate the association with response to intravitreal anti-VEGF agents in patients with neovascular AMD. A high possible relationship between polymorphisms of the *CFH, HTRA1* and *ARMS2* gene with the variable response to ranibizumab treatment has been reported in various populations; However, there is still a lack of data available in Malaysia on the genetic and pharmacogenetic associations with AMD. The current study thus provides an opportunity to explore different profiles of genetic variants in relation to their response to AMD treatment compared to the other populations along with ethnic diversity in AMD-associated polymorphisms.

Study Significance

The aim of conducting research is often to examine the association between possible risk factors for a disease and occurrence of the disease. A retrospective cohort study is a type of study that can provide information on the relationship between risk factors and disease. Furthermore, such data can be used to compare prevalences between different populations and also to examine trends or severity over time. The present retrospective study aims to observe patterns of treatment among retinal disease patients and thus determine possible risk factors related to patients receiving these treatments. While many treatment pattern studies have been reported in various countries (Ergun *et al.*, 2004; Curtis *et al.*, 2012; Lad *et al.*, 2014; Parikh *et al.*, 2016), the majority of these have focused on patients of European descent, with fewer studies investigating treatment trends in Asian populations (Koh *et al.*, 2011; Ng *et al.*, 2014; Teo *et al.*, 2014), but it must be recognised that trends in Asia might be different due to heterogeneity; additionally, this heterogeneity might result in a different prevalence of

retinal diseases such as AMD, which in turn would support different treatment trends. Conflicting results have been reported in terms of treatments in Asia, and there is a general lack of information available on treatment patterns of ranibizumab and photodynamic therapy (PDT), especially in Malaysia.

In addition, identifying the susceptibility genes for AMD could also help further understanding of the pathophysiology of the disease. The potential impact of genomic information in terms of selecting suitable treatments for AMD may also aid in recognising those at higher risk of developing the disease and lead to new preventive approaches. This study attempts to determine the frequency of genetic variations in candidate genes that may be associated with the pathogenesis of AMD and variable treatment response to anti-VEGF therapy. Association analyses are performed by comparing cases and controls to study the candidate genes underlying the disease. Possible candidate genes associated with AMD might also influence the variable anti-VEGF treatment response among patients; hence, pharmacogenetic analysis is also performed in this study. Although age, diet, lifestyle, environment, and body condition can influence an individual's response to treatment, knowledge of their genetic makeup might also play a role in providing treatments with greater safety and efficacy, leading to an overall decrease in the cost of health care. Furthermore, pharmacogenetic findings may enable doctors to prescribe the best treatments from the beginning simply by analysing the genetic profile of the individual in question, potentially reducing recovery time.

Conflicting findings are very common in genetic studies, which could be due to confounding factors such as ethnic diversity or different genetic backgrounds in different populations which influence genetic makeup. Regardless of these confounding factors, however, candidate gene analysis provides a better approach for identifying the genotype-phenotype correlations of various populations. Gene expression analysis is also conducted by comparing the expression levels, to further clarify the biological function of the candidate genes. This also provides a better understanding of differential gene expression between normal biology and disease physiology. The expected outcome of the current study could be beneficial in terms of contributing to genetic databases on AMD development in the Malaysian population, while the findings on variable treatment responses to anti-VEGF therapy could also be useful in the future management of the disease. In the future, identifying genetic codes will allow individuals to make environmental and lifestyle changes at an early age to avoid or lessen the severity of developing AMD. The findings in this study could also provide useful information to enable thorough monitoring and appropriate treatments being prescribed to AMD patients, maximising therapy efficacy.

Hypotheses

1. Significant changes occurred in treatment patterns for ranibizumab and PDT between 2010 and 2014 in Malaysia.
2. The environmental risk factors and gene polymorphisms of selected genes highly influence the development of neovascular AMD.
3. There are certain genetic predispositions to treatment responses to anti-VEGF agents among neovascular AMD subjects.

4. Genes are differentially expressed between genotypes of selected gene polymorphisms.

Main Objective

To identify the patterns of treatment of various eye disorders and to identify the environmental and genetic risk factors (gene polymorphisms of the selected genes) for neovascular AMD, in response to anti-VEGF therapy.

Specific Objectives

1. To examine the trends in the use of ranibizumab and PDT in Malaysia.
2. To determine the demographic and environmental risk factors for neovascular AMD subjects.
3. To determine the genotypic and allelic frequencies of the selected gene polymorphisms, *C3 (R102G)* and *VEGF* (*-460 C/T +405 G/C* and insertion/deletion (*I/D*)) in neovascular AMD subjects.
4. To determine the association of genetic variants of *C3 (R102G)* and *VEGF* (*-460 C/T +405 G/C* and *I/D*) genes in neovascular AMD and control subjects.
5. To determine the association of *CFH* (*Y402H*) gene polymorphism on responses to ranibizumab therapy among neovascular AMD subjects.
6. To determine the association of *HTRA1* (*-625 G/A*) and *ARMS2* (*A69S*) gene polymorphism and gene expression pattern on responses to ranibizumab therapy in neovascular AMD subjects.

REFERENCES

Abbas, R. O. and Azzazy, H. M. (2013). Association of single nucleotide polymorphisms in CFH, ARMS2 and HTRA1 genes with risk of age-related macular degeneration in Egyptian patients. *Ophthalmic genetics*, 34(4): 209-216.

Abedi, F., Wickremasinghe, S., Richardson, A. J., Islam, A. F., Guymer, R. H. and Baird, P. N. (2013). Genetic influences on the outcome of anti-vascular endothelial growth factor treatment in neovascular age-related macular degeneration. *Ophthalmology*, 120(8): 1641-1648.

Age-related eye disease study group (AREDS). (2000). Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmology*, 107(12): 2224-2232.

Agrawal, A. and Lynskey, M. T. (2009). Candidate genes for cannabis use disorders: findings, challenges and directions. *Addiction*, 104(4): 518-532.

Akuffo, K. O., Nolan, J., Stack, J., Moran, R., Feeney, J., Kenny, R. A., Peto, T., Dooley, C., O'Halloran, A. M., Cronin, H. and Beatty, S. (2015). Prevalence of age-related macular degeneration in the Republic of Ireland. *The British journal of ophthalmology*, 99(8): 1037-1044.

Alfaro, D. V. (2006). Age-related macular degeneration: a comprehensive textbook, Lippincott Williams & Wilkins.

Almeida, L. N., Carolino, R. M., Sperandio, D. C., Nehemy, M. B. and De Marco, L. A. (2009). The role of molecular genetic factors in age-related macular degeneration. *Arquivos brasileiros de oftalmologia*, 72(4): 567-572.

Ambati, J. and Fowler, B. J. (2012). Mechanisms of age-related macular degeneration. *Neuron*, 75(1): 26-39.

Amle, D., Mir, R., Khaneja, A., Agarwal, S., Ahlawat, R., Ray, P. C. and Saxena, A. (2015). Association of 18bp insertion/deletion polymorphism, at -2549 position of VEGF gene, with diabetic nephropathy in type 2 diabetes mellitus patients of North Indian population. *Journal of diabetes and metabolic disorders*, 14: 19.

Anderson, D. H., Mullins, R. F., Hageman, G. S. and Johnson, L. V. (2002). A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol*, 134(3): 411-431.

Aoki, A., Tan, X., Yamagishi, R., Shinkai, S., Obata, R., Miyaji, T., Yamaguchi, T., Numaga, J., Ito, H. and Yanagi, Y. (2015). Risk Factors for Age-Related Macular Degeneration in an Elderly Japanese Population: The Hatoyama Study. *Investigative ophthalmology & visual science*, 56(4): 2580-2585.

Avery, R. L., Pieramici, D. J., Rabena, M. D., Castellarin, A. A., Nasir, M. A. and Giust, M. J. (2006). Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology*, 113(3): 363-372 e365.

Awata, T., Inoue, K., Kurihara, S., Ohkubo, T., Watanabe, M., Inukai, K., Inoue, I. and Katayama, S. (2002). A common polymorphism in the 5'-untranslated region of the VEGF gene is associated with diabetic retinopathy in type 2 diabetes. *Diabetes*, 51(5): 1635-1639.

Awata, T., Kurihara, S., Takata, N., Neda, T., Iizuka, H., Ohkubo, T., Osaki, M., Watanabe, M., Nakashima, Y., Inukai, K., Inoue, I., Kawasaki, I., Mori, K., Yoneya, S. and Katayama, S. (2005). Functional VEGF C-634G polymorphism is associated with development of diabetic macular edema and correlated with macular retinal thickness in type 2 diabetes. *Biochemical and biophysical research communications*, 333(3): 679-685.

Azab, M., Boyer, D. S., Bressler, N. M., Bressler, S. B., Cihelkova, I., Hao, Y., Immonen, I., Lim, J. I., Menchini, U., Naor, J., Potter, M. J., Reaves, A., Rosenfeld, P. J., Slakter, J. S., Soucek, P., Strong, H. A., Wenkstern, A., Su, X. Y. and Yang, Y. C. (2005). Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration: 2-year results of a randomized clinical trial. *Arch Ophthalmol*, 123(4): 448-457.

Ba, J., Peng, R. S., Xu, D., Li, Y. H., Shi, H., Wang, Q. and Yu, J. (2015). Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis. *Drug design, development and therapy*, 9: 5397-5405.

Baird, P. N., Islam, F. M., Richardson, A. J., Cain, M., Hunt, N. and Guymer, R. (2006). Analysis of the Y402H variant of the complement factor H gene in age-related macular degeneration. *Investigative ophthalmology & visual science*, 47(10): 4194-4198.

Bakri, N. M., Ramachandran, V., Kee, H. F., Subrayan, V., Isa, H., Ngah, N. F., Mohamad, N. A., Mooi, C. S., Mun, C. Y., Ismail, P., Ismail, F., Sukiman, E.

S. and Wan Sulaiman, W. A. (2017). Association of copy number variations in complement factor H-Related genes among age-related macular degenerative subjects. *The Kaohsiung Journal of Medical Sciences*.

Barchitta, M. and Maugeri, A. (2016). Association between Vascular Endothelial Growth Factor Polymorphisms and Age-Related Macular Degeneration: An Updated Meta-Analysis. *Disease markers*, 2016: 8486406.

Barrett, J. C. and Cardon, L. R. (2006). Evaluating coverage of genome-wide association studies. *Nature genetics*, 38(6): 659-662.

Bazyar, N., Azarpira, N., Khatami, S. R. and Galehdari, H. (2012). The investigation of allele and genotype frequencies of human C3 (rs2230199) in south Iranian population. *Molecular biology reports*, 39(9): 8919-8924.

Bertram, K. M., Baglole, C. J., Phipps, R. P. and Libby, R. T. (2009). Molecular regulation of cigarette smoke induced-oxidative stress in human retinal pigment epithelial cells: implications for age-related macular degeneration. *American journal of physiology. Cell physiology*, 297(5): C1200-1210.

Bhutto, I. and Lutty, G. (2012). Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. *Molecular aspects of medicine*, 33(4): 295-317.

Bird, A., Bressler, N., Bressler, S., Chisholm, I., Coscas, G., Davis, M., De Jong, P., Klaver, C., Klein, B. and Klein, R. (1995). An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Survey of ophthalmology*, 39(5): 367-374.

Bird, A. C. (2003). The Bowman lecture. Towards an understanding of age-related macular disease. *Eye (Lond)*, 17(4): 457-466.

Bird, T. D., Jarvik, G. P. and Wood, N. W. (2001). Genetic association studies: genes in search of diseases. *Neurology*, 57(7): 1153-1154.

Black, J. R. and Clark, S. J. (2016). Age-related macular degeneration: genome-wide association studies to translation. *Genetics in medicine : official journal of the American College of Medical Genetics*, 18(4): 283-289.

Blasiak, J., Petrovski, G., Vereb, Z., Facsko, A. and Kaarniranta, K. (2014). Oxidative stress, hypoxia, and autophagy in the neovascular processes of age-related macular degeneration. *BioMed research international*, 2014: 768026.

Bleda, S., De Haro, J., Varela, C., Esparza, L., Ferruelo, A. and Acin, F. (2012). Vascular endothelial growth factor polymorphisms are involved in the late vascular complications in Type II diabetic patients. *Diabetes & vascular disease research*, 9(1): 68-74.

Blumenkranz, M. S., Bressler, N. M., Bressler, S. B., Donati, G., Fish, G. E., Haynes, L. A., Lewis, H., Miller, J. W., Mones, J. M., Potter, M. J., Pournaras, C., Reaves, A., Rosenfeld, P. J., Schachat, A. P., Schmidt-Erfurth, U., Sickenburg, M., Singerman, L. J., Slakter, J. S., Strong, A. and Vannier, S. (2002). Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials--TAP Report no. 5. *Arch Ophthalmol*, 120(10): 1307-1314.

Boekhoorn, S. S., Isaacs, A., Uitterlinden, A. G., van Duijn, C. M., Hofman, A., de Jong, P. T. and Vingerling, J. R. (2008). Polymorphisms in the vascular endothelial growth factor gene and risk of age-related macular degeneration: the Rotterdam Study. *Ophthalmology*, 115(11): 1899-1903.

Botstein, D., White, R. L., Skolnick, M. and Davis, R. W. (1980). Construction of a genetic linkage map in man using restriction fragment length polymorphisms. *American journal of human genetics*, 32(3): 314-331.

Botto, M., Fong, K. Y., So, A. K., Koch, C. and Walport, M. J. (1990). Molecular basis of polymorphisms of human complement component C3. *The Journal of experimental medicine*, 172(4): 1011-1017.

Boyer, D. S., Antoszyk, A. N., Awh, C. C., Bhisitkul, R. B., Shapiro, H. and Acharya, N. R. (2007). Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*, 114(2): 246-252.

Bradley, J., Ju, M. and Robinson, G. S. (2007). Combination therapy for the treatment of ocular neovascularization. *Angiogenesis*, 10(2): 141-148.

Brantley, M. A., Jr., Fang, A. M., King, J. M., Tewari, A., Kymes, S. M. and Shiels, A. (2007). Association of complement factor H and LOC387715 genotypes with response of exudative age-related macular degeneration to intravitreal bevacizumab. *Ophthalmology*, 114(12): 2168-2173.

Brechner, R. J., Rosenfeld, P. J., Babish, J. D. and Caplan, S. (2011). Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 medicare fee-for-service part B claims file. *Am J Ophthalmol*, 151(5): 887-895 e881.

Bressler, N. (2001). Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. *Archives of ophthalmology (Chicago, Ill.: 1960)*, 119(2): 198-207.

Bressler, N. M. (2001). Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. *Arch Ophthalmol*, 119(2): 198-207.

Bressler, N. M., Silva, J. C., Bressler, S. B., Fine, S. L. and Green, W. R. (1994). Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. *Retina*, 14(2): 130-142.

Brogan, I. J., Khan, N., Isaac, K., Hutchinson, J. A., Pravica, V. and Hutchinson, I. V. (1999). Novel polymorphisms in the promoter and 5' UTR regions of the human vascular endothelial growth factor gene. *Human immunology*, 60(12): 1245-1249.

Brown, D. M., Campochiaro, P. A., Singh, R. P., Li, Z., Gray, S., Saroj, N., Rundle, A. C., Rubio, R. G. and Murahashi, W. Y. (2010). Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*, 117(6): 1124-1133 e1121.

Brown, D. M., Kaiser, P. K., Michels, M., Soubrane, G., Heier, J. S., Kim, R. Y., Sy, J. P. and Schneider, S. (2006). Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *The New England journal of medicine*, 355(14): 1432-1444.

Brown, D. M., Michels, M., Kaiser, P. K., Heier, J. S., Sy, J. P. and Ianchulev, T. (2009). Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology*, 116(1): 57-65 e55.

Bruyere, F., Hovens, C. M., Marson, M. N., d'Arcier, B. F., Costello, A. J., Watier, H., Linassier, C. and Ohresser, M. (2010). VEGF polymorphisms are associated with an increasing risk of developing renal cell carcinoma. *The Journal of urology*, 184(4): 1273-1278.

Buentello-Volante, B., Rodriguez-Ruiz, G., Miranda-Duarte, A., Pompa-Mera, E. N., Graue-Wiechers, F., Bekker-Mendez, C., Ayala-Ramirez, R., Quezada, C., Rodriguez-Loaiza, J. L. and Zenteno, J. C. (2012). Susceptibility to advanced age-related macular degeneration and alleles of complement factor H, complement factor B, complement component 2, complement component 3, and age-related maculopathy susceptibility 2 genes in a Mexican population. *Molecular vision*, 18: 2518-2525.

Buraczynska, M., Ksiazek, P., Baranowicz-Gaszczyk, I. and Jozwiak, L. (2007). Association of the VEGF gene polymorphism with diabetic retinopathy in type 2 diabetes patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 22(3): 827-832.

Cameron, D. J., Yang, Z., Tong, Z., Zhao, Y., Praggastis, A., Brinton, E., Harmon, J., Chen, Y., Pearson, E., Bernstein, P. S., Brinton, G., Li, X., Jorgensen, A., Schneider, S., Gibbs, D., Chen, H., Wang, C., Howes, K., Camp, N. J. and Zhang, K. (2008). 10q26 is associated with increased risk of age-related macular degeneration in the Utah population. *Advances in experimental medicine and biology*, 613: 253-258.

Campochiaro, P. A., Soloway, P., Ryan, S. J. and Miller, J. W. (1999). The pathogenesis of choroidal neovascularization in patients with age-related macular degeneration. *Molecular vision*, 5: 34.

Casten, R. J. and Rovner, B. W. (2013). Update on depression and age-related macular degeneration. *Current opinion in ophthalmology*, 24(3): 239-243.

Castillo, M. M., Mowatt, G., Lois, N., Elders, A., Fraser, C., Amoaku, W., Burr, J. M., Lotery, A. J., Ramsay, C. R. and Azuara-Blanco, A. (2014). Optical coherence tomography for the diagnosis of neovascular age-related macular degeneration: a systematic review. *Eye (Lond)*, 28(12): 1399-1406.

Chakravarthy, U., McKay, G. J., de Jong, P. T., Rahu, M., Seland, J., Soubrane, G., Tomazzoli, L., Topouzis, F., Vingerling, J. R., Vioque, J., Young, I. S., Sofat, R., Hingorani, A. D. and Fletcher, A. E. (2013). ARMS2 increases the risk of early and late age-related macular degeneration in the European Eye Study. *Ophthalmology*, 120(2): 342-348.

Chakravarthy, U., Wong, T. Y., Fletcher, A., Piault, E., Evans, C., Zlateva, G., Buggage, R., Pleil, A. and Mitchell, P. (2010). Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC ophthalmology*, 10: 31.

Chan, W.-M. and Lai, T. Y. (2016). Age-related macular degeneration and polypoidal choroidal vasculopathy in Asia. *Hong Kong Journal of Ophthalmology*, 14(1): 14-19.

Chang, W., Noh, D. H., Sagong, M. and Kim, I. T. (2013). Pharmacogenetic association with early response to intravitreal ranibizumab for age-related macular degeneration in a Korean population. *Molecular vision*, 19: 702-709.

Chen, G., Tzekov, R., Li, W., Jiang, F., Mao, S. and Tong, Y. (2015). Pharmacogenetics of Complement Factor H Y402H Polymorphism and Treatment of Neovascular AMD with Anti-VEGF Agents: A Meta-Analysis. *Scientific reports*, 5: 14517.

Chen, S. J., Cheng, C. Y., Peng, K. L., Li, A. F., Hsu, W. M., Liu, J. H. and Chou, P. (2008). Prevalence and associated risk factors of age-related macular degeneration in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Investigative ophthalmology & visual science*, 49(7): 3126-3133.

Chen, X., Rong, S. S., Xu, Q., Tang, F. Y., Liu, Y., Gu, H., Tam, P. O., Chen, L. J., Brelen, M. E., Pang, C. P. and Zhao, C. (2014). Diabetes mellitus and risk of age-related macular degeneration: a systematic review and meta-analysis. *PloS one*, 9(9): e108196.

Chen, Y., Bedell, M. and Zhang, K. (2010). Age-related macular degeneration: genetic and environmental factors of disease. *Molecular interventions*, 10(5): 271-281.

Chen, Y., Zeng, J., Zhao, C., Wang, K., Trood, E., Buehler, J., Weed, M., Kasuga, D., Bernstein, P. S., Hughes, G., Fu, V., Chin, J., Lee, C., Crocker, M., Bedell, M., Salasar, F., Yang, Z., Goldbaum, M., Ferreyra, H., Freeman, W. R., Kozak, I. and Zhang, K. (2011). Assessing susceptibility to age-related macular degeneration with genetic markers and environmental factors. *Arch Ophthalmol*, 129(3): 344-351.

Cheng, C. Y., Yamashiro, K., Chen, L. J., Ahn, J., Huang, L., Cheung, C. M., Miyake, M., Cackett, P. D., Yeo, I. Y., Laude, A., Mathur, R., Pang, J., Sim, K. S., Koh, A. H., Chen, P., Lee, S. Y., Wong, D., Chan, C. M., Loh, B. K., Sun, Y., Davila, S., *et al.* (2015). New loci and coding variants confer risk for age-related macular degeneration in East Asians. *Nature communications*, 6: 6063.

Cheung, C. M., Laude, A., Yeo, I., Tan, S. P., Fan, Q., Mathur, R., Lee, S. Y., Chan, C. M., Tan, G., Lim, T. H., Cheng, C. Y. and Wong, T. Y. (2017). Systemic, Ocular and Genetic Risk Factors for Age-related Macular Degeneration and

Polypoidal Choroidal Vasculopathy in Singaporeans. *Scientific reports*, 7: 41386.

Cheung, C. M., Li, X., Cheng, C. Y., Zheng, Y., Mitchell, P., Wang, J. J. and Wong, T. Y. (2014). Prevalence, racial variations, and risk factors of age-related macular degeneration in Singaporean Chinese, Indians, and Malays. *Ophthalmology*, 121(8): 1598-1603.

Cheung, C. M., Li, X., Mathur, R., Lee, S. Y., Chan, C. M., Yeo, I., Loh, B. K., Williams, R., Wong, E. Y., Wong, D. and Wong, T. Y. (2014). A prospective study of treatment patterns and 1-year outcome of Asian age-related macular degeneration and polypoidal choroidal vasculopathy. *PloS one*, 9(6): e101057.

Cheung, C. M., Tai, E. S., Kawasaki, R., Tay, W. T., Lee, J. L., Hamzah, H. and Wong, T. Y. (2012). Prevalence of and risk factors for age-related macular degeneration in a multiethnic Asian cohort. *Arch Ophthalmol*, 130(4): 480-486.

Cheung, C. M. and Wong, T. Y. (2013). Treatment of age-related macular degeneration. *Lancet*, 382(9900): 1230-1232.

Cheung, L. K. and Eaton, A. (2013). Age-related macular degeneration. *Pharmacotherapy*, 33(8): 838-855.

Chew, E. Y., Clemons, T. E., Agron, E., Sperduto, R. D., Sangiovanni, J. P., Davis, M. D. and Ferris, F. L., 3rd (2014). Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA ophthalmology*, 132(3): 272-277.

Cho, B. J., Heo, J. W., Kim, T. W., Ahn, J. and Chung, H. (2014). Prevalence and risk factors of age-related macular degeneration in Korea: the Korea National Health and Nutrition Examination Survey 2010-2011. *Investigative ophthalmology & visual science*, 55(2): 1101-1108.

Chowers, I., Meir, T., Lederman, M., Goldenberg-Cohen, N., Cohen, Y., Banin, E., Averbukh, E., Hemo, I., Pollack, A., Axer-Siegel, R., Weinstein, O., Hoh, J., Zack, D. J. and Galbinur, T. (2008). Sequence variants in HTRA1 and LOC387715/ARMS2 and phenotype and response to photodynamic therapy in neovascular age-related macular degeneration in populations from Israel. *Molecular vision*, 14: 2263-2271.

Churchill, A. J., Carter, J. G., Lovell, H. C., Ramsden, C., Turner, S. J., Yeung, A., Escardo, J. and Atan, D. (2006). VEGF polymorphisms are associated with

neovascular age-related macular degeneration. *Human molecular genetics*, 15(19): 2955-2961.

Clemons, T. E., Milton, R. C., Klein, R., Seddon, J. M. and Ferris, F. L., 3rd (2005). Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. *Ophthalmology*, 112(4): 533-539.

Cohen, S. Y., Dubois, L., Quentel, G. and Gaudric, A. (2011). Is indocyanine green angiography still relevant? *Retina*, 31(2): 209-221.

Cohen, S. Y., Mimoun, G., Oubraham, H., Zourdani, A., Malbrel, C., Quere, S. and Schneider, V. (2013). Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. *Retina*, 33(3): 474-481.

Coleman, H. R., Chan, C. C., Ferris, F. L., 3rd and Chew, E. Y. (2008). Age-related macular degeneration. *Lancet*, 372(9652): 1835-1845.

Conley, Y. P., Jakobsdottir, J., Mah, T., Weeks, D. E., Klein, R., Kuller, L., Ferrell, R. E. and Gorin, M. B. (2006). CFH, ELOVL4, PLEKHA1 and LOC387715 genes and susceptibility to age-related maculopathy: AREDS and CHS cohorts and meta-analyses. *Human molecular genetics*, 15(21): 3206-3218.

Contreras, A. V., Zenteno, J. C., Fernandez-Lopez, J. C., Rodriguez-Corona, U., Falfan-Valencia, R., Sebastian, L., Morales, F., Ochoa-Contreras, D., Carnevale, A. and Silva-Zolezzi, I. (2014). CFH haplotypes and ARMS2, C2, C3, and CFB alleles show association with susceptibility to age-related macular degeneration in Mexicans. *Molecular vision*, 20: 105-116.

Cook, H. L., Patel, P. J. and Tufail, A. (2008). Age-related macular degeneration: diagnosis and management. *British medical bulletin*, 85: 127-149.

Cooper, D. N., Smith, B. A., Cooke, H. J., Niemann, S. and Schmidtke, J. (1985). An estimate of unique DNA sequence heterozygosity in the human genome. *Human genetics*, 69(3): 201-205.

Cordell, H. J. and Clayton, D. G. (2005). Genetic association studies. *Lancet*, 366(9491): 1121-1131.

Coscas, F., Coscas, G., Souied, E., Tick, S. and Soubrane, G. (2007). Optical coherence tomography identification of occult choroidal neovascularization in age-

related macular degeneration. *American journal of ophthalmology*, 144(4): 592-599.

Cruz-Gonzalez, F., Cabrillo-Estevez, L., Rivero-Gutierrez, V., Sanchez-Jara, A., De Juan-Marcos, L. and Gonzalez-Sarmiento, R. (2016). Influence of CFH, HTRA1 and ARMS2 polymorphisms in the response to intravitreal ranibizumab treatment for wet age-related macular degeneration in a Spanish population. *International journal of ophthalmology*, 9(9): 1304-1309.

Cruz-Gonzalez, F., Cieza-Borrella, C., Cabrillo-Estevez, L., Canete-Campos, C., Escudero-Dominguez, F. and Gonzalez-Sarmiento, R. (2013). VEGF A (rs699947 and rs833061) and VEGFR2 (rs2071559) gene polymorphisms are not associated with AMD susceptibility in a Spanish population. *Current eye research*, 38(12): 1274-1277.

Cui, L., Zhou, H., Yu, J., Sun, E., Zhang, Y., Jia, W., Jiao, Y., Snellingen, T., Liu, X., Lim, A., Wang, N. and Liu, N. (2010). Noncoding variant in the complement factor H gene and risk of exudative age-related macular degeneration in a Chinese population. *Investigative ophthalmology & visual science*, 51(2): 1116-1120.

Curcio, C. A. (2011). Complementing apolipoprotein secretion by cultured retinal pigment epithelium. *Proceedings of the National Academy of Sciences of the United States of America*, 108(46): 18569-18570.

Curtis, L. H., Hammill, B. G., Qualls, L. G., DiMartino, L. D., Wang, F., Schulman, K. A. and Cousins, S. W. (2012). Treatment patterns for neovascular age-related macular degeneration: analysis of 284 380 medicare beneficiaries. *American journal of ophthalmology*, 153(6): 1116-1124 e1111.

Daly, A. K. and Day, C. P. (2001). Candidate gene case-control association studies: advantages and potential pitfalls. *British journal of clinical pharmacology*, 52(5): 489-499.

Daniel, W. W. and Cross, C. L. (1995). Biostatistics: a foundation for analysis in the health sciences.

Davis, M. D., Gangnon, R. E., Lee, L. Y., Hubbard, L. D., Klein, B. E., Klein, R., Ferris, F. L., Bressler, S. B. and Milton, R. C. (2005). The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17. *Arch Ophthalmol*, 123(11): 1484-1498.

Department of Statistic, Malaysia. "Population Projection (Revised), Malaysia, 2010–2040." Retrieved 20.11.2017, from https://www.dosm.gov.my.

Dewan, A., Liu, M., Hartman, S., Zhang, S. S., Liu, D. T., Zhao, C., Tam, P. O., Chan, W. M., Lam, D. S., Snyder, M., Barnstable, C., Pang, C. P. and Hoh, J. (2006). HTRA1 promoter polymorphism in wet age-related macular degeneration. *Science*, 314(5801): 989-992.

Dikmetas, O., Kadayifcilar, S. and Eldem, B. (2013). The effect of CFH polymorphisms on the response to the treatment of age-related macular degeneration (AMD) with intravitreal ranibizumab. *Molecular vision*, 19: 2571-2578.

Donis-Keller, H., Green, P., Helms, C., Cartinhour, S., Weiffenbach, B., Stephens, K., Keith, T. P., Bowden, D. W., Smith, D. R., Lander, E. S. and et al. (1987). A genetic linkage map of the human genome. *Cell*, 51(2): 319-337.

Edwards, D., Forster, J. W., Cogan, N. O. I., Batley, J. and Chagné, D. (2007). Single Nucleotide Polymorphism Discovery. Association Mapping in Plants. N. C. Oraguzie, E. H. A. Rikkerink, S. E. Gardiner and H. N. De Silva. New York, NY, Springer New York**:** 53-76.

Ergun, E., Zawinka, C. and Stur, M. (2004). Incidence of laser photocoagulation and photodynamic therapy with verteporfin at a tertiary retinal center. *Retina*, 24(1): 13-18.

Erikitola, O. C., Crosby-Nwaobi, R., Lotery, A. J. and Sivaprasad, S. (2014). Photodynamic therapy for central serous chorioretinopathy. *Eye (Lond)*, 28(8): 944-957.

Erke, M. G., Bertelsen, G., Peto, T., Sjolie, A. K., Lindekleiv, H. and Njolstad, I. (2012). Prevalence of age-related macular degeneration in elderly Caucasians: the Tromso Eye Study. *Ophthalmology*, 119(9): 1737-1743.

Evans, J. R. (2001). Risk factors for age-related macular degeneration. *Progress in retinal and eye research*, 20(2): 227-253.

Faes, L., Bodmer, N. S., Bachmann, L. M., Thiel, M. A. and Schmid, M. K. (2014). Diagnostic accuracy of the Amsler grid and the preferential hyperacuity perimetry in the screening of patients with age-related macular degeneration: systematic review and meta-analysis. *Eye (Lond)*, 28(7): 788-796.

Farrar, G. J., Chadderton, N., Kenna, P. F. and Millington-Ward, S. (2013). Mitochondrial disorders: aetiologies, models systems, and candidate therapies. *Trends in genetics : TIG*, 29(8): 488-497.

Ferris, F. L., 3rd, Fine, S. L. and Hyman, L. (1984). Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*, 102(11): 1640-1642.

Ferris, F. L., 3rd, Wilkinson, C. P., Bird, A., Chakravarthy, U., Chew, E., Csaky, K. and Sadda, S. R. (2013). Clinical classification of age-related macular degeneration. *Ophthalmology*, 120(4): 844-851.

Fine, S. L., Berger, J. W., Maguire, M. G. and Ho, A. C. (2000). Age-related macular degeneration. *New England Journal of Medicine*, 342(7): 483-492.

Finger, R. P., Wickremasinghe, S. S., Baird, P. N. and Guymer, R. H. (2014). Predictors of anti-VEGF treatment response in neovascular age-related macular degeneration. *Surv Ophthalmol*, 59(1): 1-18.

Flaxman, S. R., Bourne, R. R. A., Resnikoff, S., Ackland, P., Braithwaite, T., Cicinelli, M. V., Das, A., Jonas, J. B., Keeffe, J., Kempen, J. H., Leasher, J., Limburg, H., Naidoo, K., Pesudovs, K., Silvester, A., Stevens, G. A., Tahhan, N., Wong, T. Y. and Taylor, H. R. (2017). Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *The Lancet. Global health*.

Fleiss, J. L., Levin, B. and Paik, M. C. (2004). Comparative Studies: Prospective and Retrospective Sampling. Statistical Methods for Rates and Proportions, John Wiley & Sons, Inc.**:** 144-158.

Fouad, H., Mona, A., Abdel, H., Amira, A. and Abdel, A. (2011). Vascular endothelial growth factor (VEGF) gene insertion/deletion polymorphism and diabetic retinopathy in patients with type 2 diabetes. *J Am Sci*, 7(3): 199-205.

Francis, P. J. (2011). The influence of genetics on response to treatment with ranibizumab (Lucentis) for age-related macular degeneration: the Lucentis Genotype Study (an American Ophthalmological Society thesis). *Transactions of the American Ophthalmological Society*, 109: 115-156.

Francis, P. J., Zhang, H., Dewan, A., Hoh, J. and Klein, M. L. (2008). Joint effects of polymorphisms in the HTRA1, LOC387715/ARMS2, and CFH genes on AMD in a Caucasian population. *Molecular vision*, 14: 1395-1400.

Fraser-Bell, S., Wu, J., Klein, R., Azen, S. P., Hooper, C., Foong, A. W. and Varma, R. (2008). Cardiovascular risk factors and age-related macular degeneration: the Los Angeles Latino Eye Study. *American journal of ophthalmology*, 145(2): 308-316.

Friedman, D. S., O'Colmain, B. J., Munoz, B., Tomany, S. C., McCarty, C., de Jong, P. T., Nemesure, B., Mitchell, P. and Kempen, J. (2004). Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*, 122(4): 564-572.

Fritsche, L. G., Chen, W., Schu, M., Yaspan, B. L., Yu, Y., Thorleifsson, G., Zack, D. J., Arakawa, S., Cipriani, V., Ripke, S., Igo, R. P., Jr., Buitendijk, G. H., Sim, X., Weeks, D. E., Guymer, R. H., Merriam, J. E., Francis, P. J., Hannum, G., Agarwal, A., Armbrecht, A. M., Audo, I., *et al.* (2013). Seven new loci associated with age-related macular degeneration. *Nature genetics*, 45(4): 433-439, 439e431-432.

Fritsche, L. G., Igl, W., Bailey, J. N., Grassmann, F., Sengupta, S., Bragg-Gresham, J. L., Burdon, K. P., Hebbring, S. J., Wen, C., Gorski, M., Kim, I. K., Cho, D., Zack, D., Souied, E., Scholl, H. P., Bala, E., Lee, K. E., Hunter, D. J., Sardell, R. J., Mitchell, P., Merriam, J. E., *et al.* (2016). A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nature genetics*, 48(2): 134-143.

Fryer, R. M., Randall, J., Yoshida, T., Hsiao, L. L., Blumenstock, J., Jensen, K. E., Dimofte, T., Jensen, R. V. and Gullans, S. R. (2002). Global analysis of gene expression: methods, interpretation, and pitfalls. *Experimental nephrology*, 10(2): 64-74.

Fung, A. E., Lalwani, G. A., Rosenfeld, P. J., Dubovy, S. R., Michels, S., Feuer, W. J., Puliafito, C. A., Davis, J. L., Flynn, H. W., Jr. and Esquiabro, M. (2007). An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*, 143(4): 566-583.

Gangnon, R. E., Lee, K. E., Klein, B. E., Iyengar, S. K., Sivakumaran, T. A. and Klein, R. (2012). Effect of the Y402H variant in the complement factor H gene on the incidence and progression of age-related macular degeneration: results from multistate models applied to the Beaver Dam Eye Study. *Arch Ophthalmol*, 130(9): 1169-1176.

Garcia, M., Alvarez, L., Nogacka, A. M., Gonzalez-Iglesias, H., Escribano, J., Fernandez-Vega, B., Fernandez-Vega, A., Fernandez-Vega, L. and Coca-Prados, M. (2015). CFH polymorphisms in a Northern Spanish population

with neovascular and dry forms of age-related macular degeneration. *Acta ophthalmologica*, 93(8): e658-666.

Gass, J. D. (2003). Drusen and disciform macular detachment and degeneration. 1972. *Retina*, 23(6 Suppl): 409-436.

Gemmy Cheung, C. M., Li, X., Cheng, C. Y., Zheng, Y., Mitchell, P., Wang, J. J., Jonas, J. B., Nangia, V. and Wong, T. Y. (2013). Prevalence and risk factors for age-related macular degeneration in Indians: a comparative study in Singapore and India. *Am J Ophthalmol*, 155(4): 764-773, 773 e761-763.

George, G. P., Gangwar, R., Mandal, R. K., Sankhwar, S. N. and Mittal, R. D. (2011). Genetic variation in microRNA genes and prostate cancer risk in North Indian population. *Molecular biology reports*, 38(3): 1609-1615.

Gibbs, D., Yang, Z., Constantine, R., Ma, X., Camp, N. J., Yang, X., Chen, H., Jorgenson, A., Hau, V., Dewan, A., Zeng, J., Harmon, J., Buehler, J., Brand, J. M., Hoh, J., Cameron, D. J., Dixit, M., Tong, Z. and Zhang, K. (2008). Further mapping of 10q26 supports strong association of HTRA1 polymorphisms with age-related macular degeneration. *Vision research*, 48(5): 685-689.

Gomi, F., Ohji, M., Sayanagi, K., Sawa, M., Sakaguchi, H., Oshima, Y., Ikuno, Y. and Tano, Y. (2008). One-year outcomes of photodynamic therapy in age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese patients. *Ophthalmology*, 115(1): 141-146.

Gotoh, N., Yamada, R., Hiratani, H., Renault, V., Kuroiwa, S., Monet, M., Toyoda, S., Chida, S., Mandai, M., Otani, A., Yoshimura, N. and Matsuda, F. (2006). No association between complement factor H gene polymorphism and exudative age-related macular degeneration in Japanese. *Human genetics*, 120(1): 139-143.

Govindaraju, V. K., Bodas, M. and Vij, N. (2017). Cigarette smoke induced autophagy-impairment regulates AMD pathogenesis mechanisms in ARPE-19 cells. *PloS one*, 12(8): e0182420.

Gragoudas, E. S., Adamis, A. P., Cunningham, E. T., Jr., Feinsod, M. and Guyer, D. R. (2004). Pegaptanib for neovascular age-related macular degeneration. *The New England journal of medicine*, 351(27): 2805-2816.

Grizzard, S. W., Arnett, D. and Haag, S. L. (2003). Twin study of age-related macular degeneration. *Ophthalmic epidemiology*, 10(5): 315-322.

Gupta, D., Gupta, V., Singh, V., Prakash, S., Agrawal, S., Chawla, S. and Phadke, S. R. (2016). Vascular endothelial growth factor gene polymorphisms and association with age related macular degeneration in Indian patients. *Meta gene*, 9: 249-253.

Gupta, S. K., Murthy, G. V., Morrison, N., Price, G. M., Dherani, M., John, N., Fletcher, A. E. and Chakravarthy, U. (2007). Prevalence of early and late age-related macular degeneration in a rural population in northern India: the INDEYE feasibility study. *Investigative ophthalmology & visual science*, 48(3): 1007-1011.

Guymer, R. H. and Chong, E. W. (2006). Modifiable risk factors for age-related macular degeneration. *The Medical journal of Australia*, 184(9): 455-458.

Habibi, I., Sfar, I., Chebil, A., Kort, F., Bouraoui, R., Jendoubi-Ayed, S., Makhlouf, M., Abdallah, T. B., El Matri, L. and Gorgi, Y. (2014). Vascular endothelial growth factor genetic polymorphisms and susceptibility to age-related macular degeneration in Tunisian population. *Biomarker research*, 2: 15.

Habibi, I., Sfar, I., Kort, F., Aounallah-Skhiri, H., Chebil, A., Chouchene, I., Bouraoui, R., Limaiem, R., Largheche, L., Jendoubi-Ayed, S., Makhlouf, M., Ben Abdallah, T., Ayed, K., El Matri, L. and Gorgi, Y. (2013). Y402H polymorphism in complement factor H and age-related macular degeneration in the Tunisian population. *Ophthalmic research*, 49(4): 177-184.

Hageman, G. S., Anderson, D. H., Johnson, L. V., Hancox, L. S., Taiber, A. J., Hardisty, L. I., Hageman, J. L., Stockman, H. A., Borchardt, J. D., Gehrs, K. M., Smith, R. J., Silvestri, G., Russell, S. R., Klaver, C. C., Barbazetto, I., Chang, S., Yannuzzi, L. A., Barile, G. R., Merriam, J. C., Smith, R. T., Olsh, A. K., *et al.* (2005). A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, 102(20): 7227-7232.

Hageman, G. S., Luthert, P. J., Victor Chong, N. H., Johnson, L. V., Anderson, D. H. and Mullins, R. F. (2001). An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Progress in retinal and eye research*, 20(6): 705-732.

Hagstrom, S. A., Ying, G.-s., Pauer, G. J. T., Sturgill-Short, G. M., Huang, J., Maguire, M. G. and Martin, D. F. (2014). VEGF-A and VEGFR-2 Gene Polymorphisms and Response to Anti-VEGF Therapy in the Comparison of AMD Treatments Trials (CATT). *JAMA ophthalmology*, 132(5): 521-527.

Hagstrom, S. A., Ying, G. S., Pauer, G. J., Sturgill-Short, G. M., Huang, J., Callanan, D. G., Kim, I. K., Klein, M. L., Maguire, M. G. and Martin, D. F. (2013). Pharmacogenetics for genes associated with age-related macular degeneration in the Comparison of AMD Treatments Trials (CATT). *Ophthalmology*, 120(3): 593-599.

Hahn, P., Acquah, K., Cousins, S. W., Lee, P. P. and Sloan, F. A. (2013). Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among medicare beneficiaries. *Retina*, 33(5): 911-919.

Haines, J. L., Hauser, M. A., Schmidt, S., Scott, W. K., Olson, L. M., Gallins, P., Spencer, K. L., Kwan, S. Y., Noureddine, M., Gilbert, J. R., Schnetz-Boutaud, N., Agarwal, A., Postel, E. A. and Pericak-Vance, M. A. (2005). Complement factor H variant increases the risk of age-related macular degeneration. *Science*, 308(5720): 419-421.

Haines, J. L., Schnetz-Boutaud, N., Schmidt, S., Scott, W. K., Agarwal, A., Postel, E. A., Olson, L., Kenealy, S. J., Hauser, M., Gilbert, J. R. and Pericak-Vance, M. A. (2006). Functional candidate genes in age-related macular degeneration: significant association with VEGF, VLDLR, and LRP6. *Investigative ophthalmology & visual science*, 47(1): 329-335.

Hammond, C. J., Webster, A. R., Snieder, H., Bird, A. C., Gilbert, C. E. and Spector, T. D. (2002). Genetic influence on early age-related maculopathy: a twin study. *Ophthalmology*, 109(4): 730-736.

Hao, X. F., Xie, L. K., Tang, Y. Z., Xie, W. K., Zhang, Z. F., Qi, Y. X., Xiao, W. Z. and Zhang, J. (2015). Association of complement factor H gene polymorphisms with age-related macular egeneration susceptibility. *International journal of clinical and experimental pathology*, 8(3): 3186-3191.

Hata, M., Tsujikawa, A., Miyake, M., Yamashiro, K., Ooto, S., Oishi, A., Nakanishi, H., Takahashi, A. and Yoshimura, N. (2015). Two-year visual outcome of ranibizumab in typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Graefe's archive for clinical and experimental ophthalmology*, 253(2): 221-227.

Havvas, I., Marioli, D. I., Deli, A., Zarkadis, I. K. and Pharmakakis, N. (2014). Complement C3, C2, and factor B gene polymorphisms and age-related macular degeneration in a Greek cohort study. *European journal of ophthalmology*, 24(5): 751-760.

Heier, J. S., Brown, D., Ciulla, T., Abraham, P., Bankert, J. M., Chong, S., Daniel, P. E., Jr. and Kim, I. K. (2011). Ranibizumab for choroidal neovascularization secondary to causes other than age-related macular degeneration: a phase I clinical trial. *Ophthalmology*, 118(1): 111-118.

Heier, J. S., Brown, D. M., Chong, V., Korobelnik, J. F., Kaiser, P. K., Nguyen, Q. D., Kirchhof, B., Ho, A., Ogura, Y., Yancopoulos, G. D., Stahl, N., Vitti, R., Berliner, A. J., Soo, Y., Anderesi, M., Groetzbach, G., Sommerauer, B., Sandbrink, R., Simader, C. and Schmidt-Erfurth, U. (2012). Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*, 119(12): 2537-2548.

Heier, J. S., Campochiaro, P. A., Yau, L., Li, Z., Saroj, N., Rubio, R. G. and Lai, P. (2012). Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology*, 119(4): 802-809.

Herbert, A. P., Kavanagh, D., Johansson, C., Morgan, H. P., Blaum, B. S., Hannan, J. P., Barlow, P. N. and Uhrin, D. (2012). Structural and functional characterization of the product of disease-related factor H gene conversion. *Biochemistry*, 51(9): 1874-1884.

Hicklin, D. J. and Ellis, L. M. (2005). Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 23(5): 1011-1027.

Hirata, F. E., de Vasconcellos, J. P., Medina, F. M., Rim, P. H., Fulco, E. A. and de Melo, M. B. (2015). Association of LOC387715/ARMS2 (rs10490924) Gene Polymorphism with Age-Related Macular Degeneration in the Brazilian Population. *Ophthalmic genetics*, 36(3): 224-228.

Holz, F. G., Strauss, E. C., Schmitz-Valckenberg, S. and van Lookeren Campagne, M. (2014). Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*, 121(5): 1079-1091.

Honda, S., Kurimoto, Y., Kagotani, Y., Yamamoto, H., Takagi, H. and Uenishi, M. (2009). Photodynamic therapy for typical age-related macular degeneration and polypoidal choroidal vasculopathy: a 30-month multicenter study in Hyogo, Japan. *Japanese Journal of Ophthalmology*, 53(6): 593-597.

Hong, N., Shen, Y., Yu, C. Y., Wang, S. Q. and Tong, J. P. (2016). Association of the polymorphism Y402H in the CFH gene with response to anti-VEGF treatment in age-related macular degeneration: a systematic review and meta-analysis. *Acta ophthalmologica*.

Howes, K. A., Liu, Y., Dunaief, J. L., Milam, A., Frederick, J. M., Marks, A. and Baehr, W. (2004). Receptor for advanced glycation end products and age-related macular degeneration. *Investigative ophthalmology & visual science*, 45(10): 3713-3720.

Huang, C., Xu, Y., Li, X. and Wang, W. (2013). Vascular endothelial growth factor A polymorphisms and age-related macular degeneration: a systematic review and meta-analysis. *Molecular vision*, 19: 1211-1221.

Huang, D., Swanson, E. A., Lin, C. P., Schuman, J. S., Stinson, W. G., Chang, W., Hee, M. R., Flotte, T., Gregory, K., Puliafito, C. A. and et al. (1991). Optical coherence tomography. *Science*, 254(5035): 1178-1181.

Huang, E. J., Wu, S. H., Lai, C. H., Kuo, C. N., Wu, P. L., Chen, C. L., Chen, C. Y., King, Y. C. and Wu, P. C. (2014). Prevalence and risk factors for age-related macular degeneration in the elderly Chinese population in south-western Taiwan: the Puzih eye study. *Eye (Lond)*, 28(6): 705-714.

Hughes, A. E., Orr, N., Patterson, C., Esfandiary, H., Hogg, R., McConnell, V., Silvestri, G. and Chakravarthy, U. (2007). Neovascular age-related macular degeneration risk based on CFH, LOC387715/HTRA1, and smoking. *PLoS medicine*, 4(12): e355.

Hyman, L., Schachat, A. P., He, Q. and Leske, M. C. (2000). Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. *Arch Ophthalmol*, 118(3): 351-358.

Ioannidis, J. P., Ntzani, E. E., Trikalinos, T. A. and Contopoulos-Ioannidis, D. G. (2001). Replication validity of genetic association studies. *Nature genetics*, 29(3): 306-309.

Ip, M. S., Domalpally, A., Sun, J. K. and Ehrlich, J. S. (2015). Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. *Ophthalmology*, 122(2): 367-374.

Jager, R. D., Mieler, W. F. and Miller, J. W. (2008). Age-related macular degeneration. *New England Journal of Medicine*, 358(24): 2606-2617.

Jain, R. K., Duda, D. G., Clark, J. W. and Loeffler, J. S. (2006). Lessons from phase III clinical trials on anti-VEGF therapy for cancer. *Nature clinical practice. Oncology*, 3(1): 24-40.

Jakobsdottir, J., Conley, Y. P., Weeks, D. E., Mah, T. S., Ferrell, R. E. and Gorin, M. B. (2005). Susceptibility genes for age-related maculopathy on chromosome 10q26. *American journal of human genetics*, 77(3): 389-407.

Janik-Papis, K., Zaras, M., Krzyzanowska, A., Wozniak, K., Blasiak, J., Szaflik, J. and Szaflik, J. P. (2009). Association between vascular endothelial growth factor gene polymorphisms and age-related macular degeneration in a Polish population. *Experimental and molecular pathology*, 87(3): 234-238.

Joachim, N., Mitchell, P., Burlutsky, G., Kifley, A. and Wang, J. J. (2015). The Incidence and Progression of Age-Related Macular Degeneration over 15 Years: The Blue Mountains Eye Study. *Ophthalmology*, 122(12): 2482-2489.

Johnson, L. V., Leitner, W. P., Staples, M. K. and Anderson, D. H. (2001). Complement activation and inflammatory processes in Drusen formation and age related macular degeneration. *Experimental eye research*, 73(6): 887-896.

Johnston, S. S., Wilson, K., Huang, A., Smith, D., Varker, H. and Turpcu, A. (2013). Retrospective analysis of first-line anti-vascular endothelial growth factor treatment patterns in wet age-related macular degeneration. *Advances in therapy*, 30(12): 1111-1127.

Kabasawa, S., Mori, K., Horie-Inoue, K., Gehlbach, P. L., Inoue, S., Awata, T., Katayama, S. and Yoneya, S. (2011). Associations of cigarette smoking but not serum fatty acids with age-related macular degeneration in a Japanese population. *Ophthalmology*, 118(6): 1082-1088.

Kaiser, P. K., Brown, D. M., Zhang, K., Hudson, H. L., Holz, F. G., Shapiro, H., Schneider, S. and Acharya, N. R. (2007). Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. *American journal of ophthalmology*, 144(6): 850-857.

Kanda, A., Chen, W., Othman, M., Branham, K. E., Brooks, M., Khanna, R., He, S., Lyons, R., Abecasis, G. R. and Swaroop, A. (2007). A variant of mitochondrial protein LOC387715/ARMS2, not HTRA1, is strongly associated with age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, 104(41): 16227-16232.

Kanda, A., Stambolian, D., Chen, W., Curcio, C. A., Abecasis, G. R. and Swaroop, A. (2010). Age-related macular degeneration-associated variants at chromosome 10q26 do not significantly alter ARMS2 and HTRA1 transcript levels in the human retina. *Molecular vision*, 16: 1317-1323.

Kang, H. K., Yoon, M. H., Lee, D. H. and Chin, H. S. (2012). Pharmacogenetic influence of LOC387715/HTRA1 on the efficacy of bevacizumab treatment for age-related macular degeneration in a Korean population. *Korean journal of ophthalmology : KJO*, 26(6): 414-422.

Kang, H. M., Kim, Y. M. and Koh, H. J. (2013). Five-year follow-up results of photodynamic therapy for polypoidal choroidal vasculopathy. *American journal of ophthalmology*, 155(3): 438-447 e431.

Karadzic, J., Kovacevic, I., Ljikar, J., Grgic, Z. and Devecerski, G. (2015). Pharmacological intravitreal treatment for macular edema in branch retinal vein occlusion - three-month results. *Medicinski pregled*, 68(9-10): 295-300.

Katta, S., Kaur, I. and Chakrabarti, S. (2009). The molecular genetic basis of age-related macular degeneration: an overview. *Journal of genetics*, 88(4): 425-449.

Kaur, I., Katta, S., Hussain, A., Hussain, N., Mathai, A., Narayanan, R., Reddy, R. K., Majji, A. B., Das, T. and Chakrabarti, S. (2008). Variants in the 10q26 gene cluster (LOC387715 and HTRA1) exhibit enhanced risk of age-related macular degeneration along with CFH in Indian patients. *Investigative ophthalmology & visual science*, 49(5): 1771-1776.

Kawasaki, R., Wang, J. J., Aung, T., Tan, D. T., Mitchell, P., Sandar, M., Saw, S. M. and Wong, T. Y. (2008). Prevalence of age-related macular degeneration in a Malay population: the Singapore Malay Eye Study. *Ophthalmology*, 115(10): 1735-1741.

Kawasaki, R., Wang, J. J., Ji, G. J., Taylor, B., Oizumi, T., Daimon, M., Kato, T., Kawata, S., Kayama, T., Tano, Y., Mitchell, P., Yamashita, H. and Wong, T. Y. (2008). Prevalence and risk factors for age-related macular degeneration in an adult Japanese population: the Funagata study. *Ophthalmology*, 115(8): 1376-1381, 1381 e1371-1372.

Kawasaki, R., Yasuda, M., Song, S. J., Chen, S. J., Jonas, J. B., Wang, J. J., Mitchell, P. and Wong, T. Y. (2010). The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. *Ophthalmology*, 117(5): 921-927.

Keats, B. J. B. and Sherman, S. L. (2013). Chapter 13 - Population Genetics. Emery and Rimoin's Principles and Practice of Medical Genetics (Sixth Edition). Oxford, Academic Press**:** 1-12.

Keeffe, J., Taylor, H. R., Fotis, K., Pesudovs, K., Flaxman, S. R., Jonas, J. B., Leasher, J., Naidoo, K., Price, H., White, R. A., Wong, T. Y., Resnikoff, S. and Bourne, R. R. (2014). Prevalence and causes of vision loss in Southeast Asia and Oceania: 1990-2010. *The British journal of ophthalmology*, 98(5): 586-591.

Keenan, T. D., Wotton, C. J. and Goldacre, M. J. (2011). Trends over time and geographical variation in rates of intravitreal injections in England. *British Journal of Ophthalmology*: bjophthalmol-2011-300338.

Khotcharrat, R., Patikulsila, D., Hanutsaha, P., Khiaocham, U., Ratanapakorn, T., Sutheerawatananonda, M. and Pannarunothai, S. (2015). Epidemiology of Age-Related Macular Degeneration among the Elderly Population in Thailand. *Journal of the Medical Association of Thailand*, 98(8): 790-797.

Kijlstra, A., La Heij, E. and Hendrikse, F. (2005). Immunological factors in the pathogenesis and treatment of age-related macular degeneration. *Ocular immunology and inflammation*, 13(1): 3-11.

Kim, J. H., Lee, D. W., Choi, S. C., Kim, J. W., Lee, T. G., Kim, C. G. and Cho, H. J. (2015). Intravitreal Anti-vascular Endothelial Growth Factor for Newly Diagnosed Symptomatic Polypoidal Choroidal Vasculopathy with Extrafoveal Polyps. *Korean journal of ophthalmology : KJO*, 29(6): 404-410.

Kim, S. J., Lee, S. J., Kim, N. R. and Chin, H. S. (2012). Association of polymorphisms in C2, CFB and C3 with exudative age-related macular degeneration in a Korean population. *Experimental eye research*, 96(1): 42-47.

Kim, Y. H., Kim, H. S., Mok, J. W. and Joo, C. K. (2013). Gene-gene interactions of CFH and LOC387715/ARMS2 with Korean exudative age-related macular degeneration patients. *Ophthalmic genetics*, 34(3): 151-159.

Kitchens, J. W., Kassem, N., Wood, W., Stone, T. W., Isernhagen, R., Wood, E., Hancock, B. A., Radovich, M., Waymire, J., Li, L. and Schneider, B. P. (2013). A pharmacogenetics study to predict outcome in patients receiving anti-VEGF therapy in age related macular degeneration. *Clin Ophthalmol*, 7: 1987-1993.

Kjeldsen, S. E. (2017). Hypertension and cardiovascular risk: General aspects. *Pharmacological research*, (In press).

Klaver, C. C., Kliffen, M., van Duijn, C. M., Hofman, A., Cruts, M., Grobbee, D. E., van Broeckhoven, C. and de Jong, P. T. (1998). Genetic association of apolipoprotein E with age-related macular degeneration. *American journal of human genetics*, 63(1): 200-206.

Klaver, C. C., Wolfs, R. C., Assink, J. J., van Duijn, C. M., Hofman, A. and de Jong, P. T. (1998). Genetic risk of age-related maculopathy. Population-based familial aggregation study. *Arch Ophthalmol*, 116(12): 1646-1651.

Klein, B. E., Klein, R., Lee, K. E., Moore, E. L. and Danforth, L. (2001). Risk of incident age-related eye diseases in people with an affected sibling : The Beaver Dam Eye Study. *American journal of epidemiology*, 154(3): 207-211.

Klein, R. and Klein, B. E. (2013). The prevalence of age-related eye diseases and visual impairment in aging: current estimates. *Investigative ophthalmology & visual science*, 54(14): ORSF5-ORSF13.

Klein, R., Klein, B. E. and Franke, T. (1993). The relationship of cardiovascular disease and its risk factors to age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology*, 100(3): 406-414.

Klein, R., Klein, B. E., Jensen, S. C. and Meuer, S. M. (1997). The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*, 104(1): 7-21.

Klein, R., Klein, B. E., Knudtson, M. D., Wong, T. Y., Cotch, M. F., Liu, K., Burke, G., Saad, M. F. and Jacobs, D. R., Jr. (2006). Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. *Ophthalmology*, 113(3): 373-380.

Klein, R., Klein, B. E. and Linton, K. L. (1992). Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology*, 99(6): 933-943.

Klein, R., Klein, B. E., Linton, K. L. and DeMets, D. L. (1993). The Beaver Dam Eye Study: the relation of age-related maculopathy to smoking. *American journal of epidemiology*, 137(2): 190-200.

Klein, R., Klein, B. E., Tomany, S. C. and Cruickshanks, K. J. (2003). The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*, 110(6): 1273-1280.

Klein, R., Myers, C. E., Meuer, S. M., Gangnon, R. E., Sivakumaran, T. A., Iyengar, S. K., Lee, K. E. and Klein, B. E. (2013). Risk alleles in CFH and ARMS2 and the long-term natural history of age-related macular degeneration: the Beaver Dam Eye Study. *JAMA ophthalmology*, 131(3): 383-392.

Klein, R., Peto, T., Bird, A. and Vannewkirk, M. R. (2004). The epidemiology of age-related macular degeneration. *American journal of ophthalmology*, 137(3): 486-495.

Klein, R. J., Zeiss, C., Chew, E. Y., Tsai, J. Y., Sackler, R. S., Haynes, C., Henning, A. K., SanGiovanni, J. P., Mane, S. M., Mayne, S. T., Bracken, M. B., Ferris, F. L., Ott, J., Barnstable, C. and Hoh, J. (2005). Complement factor H polymorphism in age-related macular degeneration. *Science*, 308(5720): 385-389.

Kloeckener-Gruissem, B., Barthelmes, D., Labs, S., Schindler, C., Kurz-Levin, M., Michels, S., Fleischhauer, J., Berger, W., Sutter, F. and Menghini, M. (2011). Genetic association with response to intravitreal ranibizumab in patients with neovascular AMD. *Investigative ophthalmology & visual science*, 52(7): 4694-4702.

Koh, A., Lee, W. K., Chen, L. J., Chen, S. J., Hashad, Y., Kim, H., Lai, T. Y., Pilz, S., Ruamviboonsuk, P., Tokaji, E., Weisberger, A. and Lim, T. H. (2012). EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*, 32(8): 1453-1464.

Koh, A., Lim, T. H., Au Eong, K. G., Chee, C., Ong, S. G., Tan, N., Yeo, I. and Wong, D. (2011). Optimising the management of choroidal neovascularisation in Asian patients: consensus on treatment recommendations for anti-VEGF therapy. *Singapore medical journal*, 52(4): 232-240.

Kokame, G. T., Yeung, L., Teramoto, K., Lai, J. C. and Wee, R. (2013). Polypoidal choroidal vasculopathy exudation and hemorrhage: results of monthly ranibizumab therapy at one year. *Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde*, 231(2): 94-102.

Korb, C., Zwiener, I., Lorenz, K., Mirshahi, A., Pfeiffer, N. and Stoffelns, B. (2013). Risk factors of a reduced response to ranibizumab treatment for neovascular age-related macular degeneration--evaluation in a clinical setting. *BMC ophthalmology*, 13: 84.

Krebs, I., Vecsei Marlovits, V., Bodenstorfer, J., Glittenberg, C., Ansari Shahrezaei, S., Ristl, R. and Binder, S. (2013). Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration. *Acta ophthalmologica*, 91(3): e178-183.

Krishnaiah, S., Das, T., Nirmalan, P. K., Nutheti, R., Shamanna, B. R., Rao, G. N. and Thomas, R. (2005). Risk factors for age-related macular degeneration: findings from the Andhra Pradesh eye disease study in South India. *Investigative ophthalmology & visual science*, 46(12): 4442-4449.

Kruglyak, L. and Nickerson, D. A. (2001). Variation is the spice of life. *Nature genetics*, 27(3): 234-236.

Kubista, M., Andrade, J. M., Bengtsson, M., Forootan, A., Jonak, J., Lind, K., Sindelka, R., Sjoback, R., Sjogreen, B., Strombom, L., Stahlberg, A. and Zoric, N. (2006). The real-time polymerase chain reaction. *Molecular aspects of medicine*, 27(2-3): 95-125.

Kwok, P. Y. and Chen, X. (2003). Detection of single nucleotide polymorphisms. *Current issues in molecular biology*, 5(2): 43-60.

Kwon, J. M. and Goate, A. M. (2000). The candidate gene approach. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*, 24(3): 164-168.

Lad, E. M., Hammill, B. G., Qualls, L. G., Wang, F., Cousins, S. W. and Curtis, L. H. (2014). Anti-VEGF treatment patterns for neovascular age-related macular degeneration among medicare beneficiaries. *American journal of ophthalmology*, 158(3): 537-543 e532.

Lambert, N. G., ElShelmani, H., Singh, M. K., Mansergh, F. C., Wride, M. A., Padilla, M., Keegan, D., Hogg, R. E. and Ambati, B. K. (2016). Risk factors and biomarkers of age-related macular degeneration. *Progress in retinal and eye research*, 54: 64-102.

Larsen, M., Schmidt-Erfurth, U., Lanzetta, P., Wolf, S., Simader, C., Tokaji, E., Pilz, S. and Weisberger, A. (2012). Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results. *Ophthalmology*, 119(5): 992-1000.

Lau, L. I., Chen, S. J., Cheng, C. Y., Yen, M. Y., Lee, F. L., Lin, M. W., Hsu, W. M. and Wei, Y. H. (2006). Association of the Y402H polymorphism in

complement factor H gene and neovascular age-related macular degeneration in Chinese patients. *Investigative ophthalmology & visual science*, 47(8): 3242-3246.

Laude, A., Cackett, P. D., Vithana, E. N., Yeo, I. Y., Wong, D., Koh, A. H., Wong, T. Y. and Aung, T. (2010). Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration: same or different disease? *Progress in retinal and eye research*, 29(1): 19-29.

Leal, S., Silva, R., Figueira, J., Cachulo, M. L., Pires, I., de Abreu, J. R. and Cunha-Vaz, J. G. (2010). Photodynamic therapy with verteporfin in polypoidal choroidal vasculopathy: results after 3 years of follow-up. *Retina*, 30(8): 1197-1205.

Lee, A. Y., Raya, A. K., Kymes, S. M., Shiels, A. and Brantley, M. A., Jr. (2009). Pharmacogenetics of complement factor H (Y402H) and treatment of exudative age-related macular degeneration with ranibizumab. *The British journal of ophthalmology*, 93(5): 610-613.

Lee, J. Y., Moon, B. G., Kim, M., Lee, J. E., Park, K. H. and Kim, S. D. (2016). Results of the 2015 Questionnaire Survey of the Korean Retina Society: Current Trends in the Treatment of Vitreoretinal Diseases. *Journal of the Korean ophthalmological society*, 57(7): 1071-1079.

Leveziel, N., Souied, E. H., Richard, F., Barbu, V., Zourdani, A., Morineau, G., Zerbib, J., Coscas, G., Soubrane, G. and Benlian, P. (2007). PLEKHA1-LOC387715-HTRA1 polymorphisms and exudative age-related macular degeneration in the French population. *Molecular vision*, 13: 2153-2159.

Leveziel, N., Tilleul, J., Puche, N., Zerbib, J., Laloum, F., Querques, G. and Souied, E. H. (2011). Genetic factors associated with age-related macular degeneration. *Ophthalmologica*, 226(3): 87-102.

Li, M., Atmaca-Sonmez, P., Othman, M., Branham, K. E., Khanna, R., Wade, M. S., Li, Y., Liang, L., Zareparsi, S., Swaroop, A. and Abecasis, G. R. (2006). CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. *Nature genetics*, 38(9): 1049-1054.

Li, X., Liu, C. L., Li, X. X., Li, Q. C., Ma, L. M. and Liu, G. L. (2015). VEGF Gene Polymorphisms are Associated with Risk of Tetralogy of Fallot. *Medical science monitor : international medical journal of experimental and clinical research*, 21: 3474-3482.

Li, Y., Xu, L., Jonas, J. B., Yang, H., Ma, Y. and Li, J. (2006). Prevalence of age-related maculopathy in the adult population in China: the Beijing eye study. *American journal of ophthalmology*, 142(5): 788-793.

Liang, X. Y., Lai, T. Y., Liu, D. T., Fan, A. H., Chen, L. J., Tam, P. O., Chiang, S. W., Ng, T. K., Lam, D. S. and Pang, C. P. (2012). Differentiation of exudative age-related macular degeneration and polypoidal choroidal vasculopathy in the ARMS2/HTRA1 locus. *Investigative ophthalmology & visual science*, 53(6): 3175-3182.

Lim, L. S., Mitchell, P., Seddon, J. M., Holz, F. G. and Wong, T. Y. (2012). Age-related macular degeneration. *Lancet*, 379(9827): 1728-1738.

Lin, H. J., Chen, W. L., Chen, T. H., Kung, Y. J. and Wan, L. (2014). Vascular Endothelial Growth Factor -460 C/T BstUI Gene Polymorphism is associated with Primary Open Angle Glaucoma. *BioMedicine*, 4: 4.

Lin, J. M., Wan, L., Tsai, Y. Y., Lin, H. J., Tsai, Y., Lee, C. C., Tsai, C. H., Tsai, F. J. and Tseng, S. H. (2008). HTRA1 polymorphism in dry and wet age-related macular degeneration. *Retina*, 28(2): 309-313.

Lin, J. M., Wan, L., Tsai, Y. Y., Lin, H. J., Tsai, Y., Lee, C. C., Tsai, C. H., Tseng, S. H. and Tsai, F. J. (2008). Vascular endothelial growth factor gene polymorphisms in age-related macular degeneration. *American journal of ophthalmology*, 145(6): 1045-1051.

Little, J., Higgins, J. P., Ioannidis, J. P., Moher, D., Gagnon, F., von Elm, E., Khoury, M. J., Cohen, B., Davey-Smith, G., Grimshaw, J., Scheet, P., Gwinn, M., Williamson, R. E., Zou, G. Y., Hutchings, K., Johnson, C. Y., Tait, V., Wiens, M., Golding, J., van Duijn, C., McLaughlin, J., *et al.* (2009). STrengthening the REporting of Genetic Association studies (STREGA)--an extension of the STROBE statement. *European journal of clinical investigation*, 39(4): 247-266.

Liu, Y., Hou, S., Lang, W., Dai, D., Wang, Z., Ji, X., Li, K., Zhang, X., Zou, Y. and Wang, J. (2014). Roles of three common VEGF polymorphisms in the risk of age-related macular degeneration. *Genetic testing and molecular biomarkers*, 18(4): 245-252.

Livak, K. J. and Schmittgen, T. D. (2001). Analysis of relative gene expression data using real-time quantitative PCR and the $2^{-\Delta\Delta CT}$ method. *methods*, 25(4): 402-408.

Lloyd, R., Harris, J., Wadhwa, S. and Chambers, W. (2008). Food and Drug Administration approval process for ophthalmic drugs in the US. *Current opinion in ophthalmology*, 19(3): 190-194.

Lotery, A. J., Gibson, J., Cree, A. J., Downes, S. M., Harding, S. P., Rogers, C. A., Reeves, B. C., Ennis, S. and Chakravarthy, U. (2013). Pharmacogenetic associations with vascular endothelial growth factor inhibition in participants with neovascular age-related macular degeneration in the IVAN Study. *Ophthalmology*, 120(12): 2637-2643.

Lu, H., Shu, X. O., Cui, Y., Kataoka, N., Wen, W., Cai, Q., Ruan, Z. X., Gao, Y. T. and Zheng, W. (2005). Association of genetic polymorphisms in the VEGF gene with breast cancer survival. *Cancer research*, 65(12): 5015-5019.

Lu, Y., Shi, Y., Xue, C., Yin, J. and Huang, Z. (2012). Pooled-analysis of the associations between three polymorphisms in the VEGF gene and age-related macular degeneration. *Molecular biology reports*, 39(6): 6547-6553.

Ly, D. H., Lockhart, D. J., Lerner, R. A. and Schultz, P. G. (2000). Mitotic misregulation and human aging. *Science*, 287(5462): 2486-2492.

Macular Photocoagulation Study Group. (1982). Argon laser photocoagulation for senile macular degeneration. Results of a randomized clinical trial. *Arch Ophthalmol*, 100(6): 912-918.

Macular Photocoagulation Study Group. (1986). Argon laser photocoagulation for neovascular maculopathy. Three-year results from randomized clinical trials. *Arch Ophthalmol*, 104(5): 694-701.

Macular Photocoagulation Study Group. (1991). Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. *Arch Ophthalmol*, 109(8): 1109-1114.

Macular Photocoagulation Study Group. (1991). Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the macular photocoagulation study. *Arch Ophthalmol*, 109(9): 1242-1257.

Madreperla, S. A. (2001). Choroidal hemangioma treated with photodynamic therapy using verteporfin. *Arch Ophthalmol*, 119(11): 1606-1610.

Magnusson, K. P., Duan, S., Sigurdsson, H., Petursson, H., Yang, Z., Zhao, Y., Bernstein, P. S., Ge, J., Jonasson, F., Stefansson, E., Helgadottir, G.,

Zabriskie, N. A., Jonsson, T., Bjornsson, A., Thorlacius, T., Jonsson, P. V., Thorleifsson, G., Kong, A., Stefansson, H., Zhang, K., Stefansson, K. and Gulcher, J. R. (2006). CFH Y402H confers similar risk of soft drusen and both forms of advanced AMD. *PLoS medicine*, 3(1): e5.

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., McCarthy, M. I., Ramos, E. M., Cardon, L. R., Chakravarti, A., Cho, J. H., Guttmacher, A. E., Kong, A., Kruglyak, L., Mardis, E., Rotimi, C. N., Slatkin, M., Valle, D., Whittemore, A. S., Boehnke, M., Clark, A. G., *et al.* (2009). Finding the missing heritability of complex diseases. *Nature*, 461(7265): 747-753.

Martin, D. F., Maguire, M. G., Fine, S. L., Ying, G.-s., Jaffe, G. J., Grunwald, J. E., Toth, C., Redford, M., Ferris, F. L. and Group, C. o. A.-r. M. D. T. T. R. (2012). Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*, 119(7): 1388-1398.\

Martin, D. F., Maguire, M. G., Ying, G. S., Grunwald, J. E., Fine, S. L. and Jaffe, G. J. (2011). Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *The New England journal of medicine*, 364(20): 1897-1908.

Mathew, R. S., Delbaere, K., Lord, S. R., Beaumont, P., Vaegan and Madigan, M. C. (2011). Depressive symptoms and quality of life in people with age- related macular degeneration. *Ophthalmic Physiol Opt*, 31(4): 375-380.

Matsuda, K. (2017). Chapter Two - PCR-Based Detection Methods for Single-Nucleotide Polymorphism or Mutation: Real-Time PCR and Its Substantial Contribution Toward Technological Refinement. *Advances in Clinical Chemistry. G. S. Makowski, Elsevier*. 80: 45-72.

McKay, G. J., Dasari, S., Patterson, C. C., Chakravarthy, U. and Silvestri, G. (2010). Complement component 3: an assessment of association with AMD and analysis of gene-gene and gene-environment interactions in a Northern Irish cohort. *Molecular vision*, 16: 194-199.

McKibbin, M., Ali, M., Bansal, S., Baxter, P. D., West, K., Williams, G., Cassidy, F. and Inglehearn, C. F. (2012). CFH, VEGF and HTRA1 promoter genotype may influence the response to intravitreal ranibizumab therapy for neovascular age-related macular degeneration. *The British journal of ophthalmology*, 96(2): 208-212.

Midena, E. and Vujosevic, S. (2015). Metamorphopsia: An Overlooked Visual Symptom. *Ophthalmic research*, 55(1): 26-36.

Miller, J. W., Le Couter, J., Strauss, E. C. and Ferrara, N. (2013). Vascular endothelial growth factor a in intraocular vascular disease. *Ophthalmology*, 120(1): 106-114.

Mills, R. E., Luttig, C. T., Larkins, C. E., Beauchamp, A., Tsui, C., Pittard, W. S. and Devine, S. E. (2006). An initial map of insertion and deletion (INDEL) variation in the human genome. *Genome research*, 16(9): 1182-1190.

Mitchell, P., Korobelnik, J.-F., Lanzetta, P., Holz, F. G., Pruente, C., Schmidt-Erfurth, U. M., Tano, Y. and Wolf, S. (2009). Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. *British Journal of Ophthalmology*.

Mitchell, P., Wang, J. J., Foran, S. and Smith, W. (2002). Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology*, 109(6): 1092-1097.

Mitchell, P., Wang, J. J., Smith, W. and Leeder, S. R. (2002). Smoking and the 5-year incidence of age-related maculopathy: the Blue Mountains Eye Study. *Arch Ophthalmol*, 120(10): 1357-1363.

Miyazaki, M., Kiyohara, Y., Yoshida, A., Iida, M., Nose, Y. and Ishibashi, T. (2005). The 5-year incidence and risk factors for age-related maculopathy in a general Japanese population: the Hisayama study. *Investigative ophthalmology & visual science*, 46(6): 1907-1910.

Mohamad, N. A., Ramachandran, V., Ismail, P., Isa, H. M., Chan, Y. M., Ngah, N. F., Bakri, N. M., Ching, S. M., Hoo, F. K. and Sulaiman, W. A. W. (2017). R102G polymorphism of the complement component 3 gene in Malaysian subjects with neovascular age-related macular degeneration. *Egyptian Journal of Medical Human Genetics*.

Mohamad, N. A., Ramachandran, V., Ismail, P., Mohd Isa, H., Chan, Y. M., Ngah, N. F., Md Bakri, N., Ching, S. M., Hoo, F. K. and Wan Sulaiman, W. A. (2017). VEGF Polymorphisms Among Neovascular Age-Related Macular Degenerative Subjects in a Multiethnic Population. *Genetic testing and molecular biomarkers*.

Moja, L., Lucenteforte, E., Kwag, K. H., Bertele, V., Campomori, A., Chakravarthy, U., D'Amico, R., Dickersin, K., Kodjikian, L., Lindsley, K., Loke, Y., Maguire, M., Martin, D. F., Mugelli, A., Muhlbauer, B., Puntmann, I., Reeves, B., Rogers, C., Schmucker, C., Subramanian, M. L. and Virgili, G. (2014). Systemic safety of bevacizumab versus ranibizumab for neovascular age-

related macular degeneration. *The Cochrane database of systematic reviews*(9): CD011230.

Mori, K., Horie-Inoue, K., Kohda, M., Kawasaki, I., Gehlbach, P. L., Awata, T., Yoneya, S., Okazaki, Y. and Inoue, S. (2007). Association of the HTRA1 gene variant with age-related macular degeneration in the Japanese population. *Journal of human genetics*, 52(7): 636-641.

Mullis, K. B. (1990). Target amplification for DNA analysis by the polymerase chain reaction. *Annales de biologie clinique*, 48(8): 579-582.

Nakata, I., Yamashiro, K., Nakanishi, H., Akagi-Kurashige, Y., Miyake, M., Tsujikawa, A., Matsuda, F. and Yoshimura, N. (2013). Prevalence and characteristics of age-related macular degeneration in the Japanese population: the Nagahama study. *American journal of ophthalmology*, 156(5): 1002-1009 e1002.

National Eye Database Malaysia. AMD Registry. Retrieved 20.11.2017 from (http://www.acrm.org.my/ned/amd.html).

Ng, E. W. and Adamis, A. P. (2005). Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. *Canadian journal of ophthalmology. Journal canadien d'ophtalmologie*, 40(3): 352-368.

Ng, W. Y., Cheung, C. M., Mathur, R., Chan, C. M., Yeo, I. Y., Wong, E., Lee, S. Y., Loh, B. K., Wong, D. and Wong, T. Y. (2014). Trends in age-related macular degeneration management in Singapore. *Optometry and vision science : official publication of the American Academy of Optometry*, 91(8): 872-877.

Nguyen, Q. D., Brown, D. M., Marcus, D. M., Boyer, D. S., Patel, S., Feiner, L., Gibson, A., Sy, J., Rundle, A. C., Hopkins, J. J., Rubio, R. G. and Ehrlich, J. S. (2012). Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*, 119(4): 789-801.

Ni Dhubhghaill, S. S., Cahill, M. T., Campbell, M., Cassidy, L., Humphries, M. M. and Humphries, P. (2010). The pathophysiology of cigarette smoking and age-related macular degeneration. *Advances in experimental medicine and biology*, 664: 437-446.

Nischler, C., Oberkofler, H., Ortner, C., Paikl, D., Riha, W., Lang, N., Patsch, W. and Egger, S. F. (2011). Complement factor H Y402H gene polymorphism and response to intravitreal bevacizumab in exudative age-related macular degeneration. *Acta ophthalmologica*, 89(4): e344-349.

Nowak, J. Z. (2006). Age-related macular degeneration (AMD): pathogenesis and therapy. *Pharmacological reports : PR*, 58(3): 353-363.

Oishi, A., Kojima, H., Mandai, M., Honda, S., Matsuoka, T., Oh, H., Kita, M., Nagai, T., Fujihara, M. and Bessho, N. (2013). Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results. *American journal of ophthalmology*, 156(4): 644-651. e641.

Ojima, Y., Tsujikawa, A., Otani, A., Hirami, Y., Aikawa, H. and Yoshimura, N. (2006). Recurrent bleeding after photodynamic therapy in polypoidal choroidal vasculopathy. *American journal of ophthalmology*, 141(5): 958-960.

Orlin, A., Hadley, D., Chang, W., Ho, A. C., Brown, G., Kaiser, R. S., Regillo, C. D., Godshalk, A. N., Lier, A., Kaderli, B. and Stambolian, D. (2012). Association between high-risk disease loci and response to anti-vascular endothelial growth factor treatment for wet age-related macular degeneration. *Retina*, 32(1): 4-9.

Owen, C. G., Jarrar, Z., Wormald, R., Cook, D. G., Fletcher, A. E. and Rudnicka, A. R. (2012). The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *The British journal of ophthalmology*, 96(5): 752-756.

Owens, S. L. (1996). Indocyanine green angiography. *The British journal of ophthalmology*, 80(3): 263-266.

Papadopoulos, N., Martin, J., Ruan, Q., Rafique, A., Rosconi, M. P., Shi, E., Pyles, E. A., Yancopoulos, G. D., Stahl, N. and Wiegand, S. J. (2012). Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*, 15(2): 171-185.

Parikh, R., Ross, J. S., Sangaralingham, L. R., Adelman, R. A., Shah, N. D. and Barkmeier, A. J. (2016). Trends of Anti-Vascular Endothelial Growth Factor Use in Ophthalmology Among Privately Insured and Medicare Advantage Patients. *Ophthalmology*.

Park, U. C., Shin, J. Y., Kim, S. J., Shin, E. S., Lee, J. E., McCarthy, L. C., Newcombe, P. J., Xu, C. F., Chung, H. and Yu, H. G. (2014). Genetic factors associated with response to intravitreal ranibizumab in Korean patients with neovascular age-related macular degeneration. *Retina*, 34(2): 288-297.

Park, U. C., Shin, J. Y., McCarthy, L. C., Kim, S. J., Park, J. H., Chung, H. and Yu, H. G. (2014). Pharmacogenetic associations with long-term response to anti-vascular endothelial growth factor treatment in neovascular AMD patients. *Molecular vision*, 20: 1680-1694.

Parmeggiani, F., Romano, M. R., Costagliola, C., Semeraro, F., Incorvaia, C., D'Angelo, S., Perri, P., De Palma, P., De Nadai, K. and Sebastiani, A. (2012). Mechanism of inflammation in age-related macular degeneration. *Mediators of inflammation*, 2012: 546786.

Pedrosa, A. C., Sousa, T., Pinheiro-Costa, J., Beato, J., Falcao, M. S., Falcao-Reis, F. and Carneiro, A. (2017). Treatment of Neovascular Age-Related Macular Degeneration with Anti-VEGF Agents: Predictive Factors of Long-Term Visual Outcomes. *Journal of ophthalmology*, 2017: 4263017.

Pei, X. T., Li, X. X., Bao, Y. Z., Yu, W. Z., Yan, Z., Qi, H. J., Qian, T. and Xiao, H. X. (2009). Association of c3 gene polymorphisms with neovascular age-related macular degeneration in a chinese population. *Current eye research*, 34(8): 615-622.

Pettersson, F. H., Anderson, C. A., Clarke, G. M., Barrett, J. C., Cardon, L. R., Morris, A. P. and Zondervan, K. T. (2009). Marker selection for genetic case-control association studies. *Nature protocols*, 4(5): 743-752.

Phillips, W. B., 2nd, Regillo, C. D. and Maguire, J. I. (1996). Indocyanine green angiography of idiopathic polypoidal choroidal vasculopathy. *Ophthalmic surgery and lasers*, 27(6): 467-470.

Piermarocchi, S., Miotto, S., Colavito, D., Leon, A. and Segato, T. (2015). Combined effects of genetic and non-genetic risk factors affect response to ranibizumab in exudative age-related macular degeneration. *Acta ophthalmologica*, 93(6): e451-457.

Prakash, S., Prasad, N., Sharma, R. K., Faridi, R. M. and Agrawal, S. (2012). Vascular endothelial growth factor gene polymorphisms in North Indian patients with end stage renal disease. *Cytokine*, 58(2): 261-266.

Qian-Qian, Y., Yong, Y., Jing, Z., Xin, B., Tian-Hua, X., Chao, S. and Jia, C. (2015). Nonsynonymous single nucleotide polymorphisms in the complement component 3 gene are associated with risk of age-related macular degeneration: a meta-analysis. *Gene*, 561(2): 249-255.

Qu, Y., Dai, H., Zhou, F., Zhang, X., Xu, X., Bi, H., Pan, X., Wang, H., Jiang, H., Yin, N. and Dang, G. (2011). Vascular endothelial growth factor gene polymorphisms and risk of neovascular age-related macular degeneration in a Chinese cohort. *Ophthalmic research*, 45(3): 142-148.

Quan, Y. L., Zhou, A. Y. and Feng, Z. H. (2012). Association between complementary factor H Y402H polymorphisms and age-related macular degeneration in Chinese: Systematic review and meta-analysis. *International journal of ophthalmology*, 5(2): 242-246.

Rahman, M. T., Uddin, M. S., Sultana, R., Moue, A. and Setu, M. (2013). Polymerase chain reaction (PCR): a short review. *Anwer Khan Modern Medical College Journal*, 4(1): 30-36.

Ratnapriya, R. and Chew, E. Y. (2013). Age-related macular degeneration-clinical review and genetics update. *Clinical genetics*, 84(2): 160-166.

Regillo, C. D., Brown, D. M., Abraham, P., Yue, H., Ianchulev, T., Schneider, S. and Shams, N. (2008). Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*, 145(2): 239-248.

Regillo, C. D., Busbee, B. G., Ho, A. C., Ding, B. and Haskova, Z. (2015). Baseline Predictors of 12-Month Treatment Response to Ranibizumab in Patients With Wet Age-Related Macular Degeneration. *American journal of ophthalmology*, 160(5): 1014-1023 e1012.

Resnikoff, S., Pascolini, D., Etya'ale, D., Kocur, I., Pararajasegaram, R, Pokharel, G.P., Mariotti, S.P. (2004). Global data on visual impairment in the year 2002. *Bull World Health Organ*, 82 (11):844–851.

Reynolds, R., Hartnett, M. E., Atkinson, J. P., Giclas, P. C., Rosner, B. and Seddon, J. M. (2009). Plasma complement components and activation fragments: associations with age-related macular degeneration genotypes and phenotypes. *Investigative ophthalmology & visual science*, 50(12): 5818-5827.

Risch, N. J. (2000). Searching for genetic determinants in the new millennium. *Nature*, 405(6788): 847-856.

Ristau, T., Ersoy, L., Hahn, M., den Hollander, A. I., Kirchhof, B., Liakopoulos, S. and Fauser, S. (2014). Nongenetic risk factors for neovascular age-related macular

degeneration. *Investigative ophthalmology & visual science*, 55(8): 5228-5232.

Rodriguez-Murillo, L. and Salem, R. M. (2013). Insertion/Deletion Polymorphism. Encyclopedia of Behavioral Medicine. M. D. Gellman and J. R. Turner. New York, NY, Springer New York**:** 1076-1076.

Rosenfeld, P. J., Brown, D. M., Heier, J. S., Boyer, D. S., Kaiser, P. K., Chung, C. Y. and Kim, R. Y. (2006). Ranibizumab for neovascular age-related macular degeneration. *The New England journal of medicine*, 355(14): 1419-1431.

Rosenfeld, P. J., Saperstein, D. A., Bressler, N. M., Reaves, T. A., Sickenberg, M., Rosa, R. H., Jr., Sternberg, P., Jr., Aaberg, T. M., Sr. and Aaberg, T. M., Jr. (2004). Photodynamic therapy with verteporfin in ocular histoplasmosis: uncontrolled, open-label 2-year study. *Ophthalmology*, 111(9): 1725-1733.

Ross, R. J., Bojanowski, C. M., Wang, J. J., Chew, E. Y., Rochtchina, E., Ferris, F. L., 3rd, Mitchell, P., Chan, C. C. and Tuo, J. (2007). The LOC387715 polymorphism and age-related macular degeneration: replication in three case-control samples. *Investigative ophthalmology & visual science*, 48(3): 1128-1132.

Ross, R. J., Verma, V., Rosenberg, K. I., Chan, C. C. and Tuo, J. (2007). Genetic markers and biomarkers for age-related macular degeneration. *Expert review of ophthalmology*, 2(3): 443-457.

Roy, H., Bhardwaj, S. and Yla-Herttuala, S. (2006). Biology of vascular endothelial growth factors. *FEBS letters*, 580(12): 2879-2887.

Rudnicka, A. R., Jarrar, Z., Wormald, R., Cook, D. G., Fletcher, A. and Owen, C. G. (2012). Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology*, 119(3): 571-580.

Sachidanandam, R., Weissman, D., Schmidt, S. C., Kakol, J. M., Stein, L. D., Marth, G., Sherry, S., Mullikin, J. C., Mortimore, B. J., Willey, D. L., Hunt, S. E., Cole, C. G., Coggill, P. C., Rice, C. M., Ning, Z., Rogers, J., Bentley, D. R., Kwok, P. Y., Mardis, E. R., Yeh, R. T., Schultz, B., *et al.* (2001). A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*, 409(6822): 928-933.

Sakurada, Y., Yoneyama, S., Imasawa, M. and Iijima, H. (2013). Systemic risk factors associated with polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. *Retina*, 33(4): 841-845.

Salam, A., Mathew, R. and Sivaprasad, S. (2011). Treatment of proliferative diabetic retinopathy with anti-VEGF agents. *Acta ophthalmologica*, 89(5): 405-411.

Salowi, M. A, Goh, P. P. (Eds). (2012). Fourth Report of the National Eye Database 2010, Kuala Lumpur 2012. Retrieved from http://acrm.org.my/ned.

Sandhu, S. S. and Talks, S. J. (2005). Correlation of optical coherence tomography, with or without additional colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes. *The British journal of ophthalmology*, 89(8): 967-970.

SanGiovanni, J. P. and Chew, E. Y. (2014). Clinical applications of age-related macular degeneration genetics. *Cold Spring Harbor perspectives in medicine*, 4(10).

Sayed, K. M., Naito, T., Nagasawa, T., Katome, T. and Mitamura, Y. (2011). Early visual impacts of optical coherence tomographic parameters in patients with age-related macular degeneration following the first versus repeated ranibizumab injection. *Graefe's archive for clinical and experimental ophthalmology*, 249(10): 1449-1458.

Scherer, S. W., Lee, C., Birney, E., Altshuler, D. M., Eichler, E. E., Carter, N. P., Hurles, M. E. and Feuk, L. (2007). Challenges and standards in integrating surveys of structural variation. *Nature genetics*, 39(7 Suppl): S7-15.

Schmidt-Erfurth, U., Miller, J., Sickenberg, M., Bunse, A., Laqua, H., Gragoudas, E., Zografos, L., Birngruber, R., van den Bergh, H., Strong, A., Manjuris, U., Fsadni, M., Lane, A. M., Piguet, B. and Bressler, N. M. (1998). Photodynamic therapy of subfoveal choroidal neovascularization: clinical and angiographic examples. *Graefe's archive for clinical and experimental ophthalmology*, 236(5): 365-374.

Schmidt, S., Hauser, M. A., Scott, W. K., Postel, E. A., Agarwal, A., Gallins, P., Wong, F., Chen, Y. S., Spencer, K., Schnetz-Boutaud, N., Haines, J. L. and Pericak-Vance, M. A. (2006). Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. *American journal of human genetics*, 78(5): 852-864.

Schmittgen, T. D. and Livak, K. J. (2008). Analyzing real-time PCR data by the comparative C(T) method. *Nature protocols*, 3(6): 1101-1108.

Schmittgen, T. D., Zakrajsek, B. A., Mills, A. G., Gorn, V., Singer, M. J. and Reed, M. W. (2000). Quantitative reverse transcription–polymerase chain reaction to study mRNA decay: comparison of endpoint and real-time methods. *Analytical biochemistry*, 285(2): 194-204.

Scholl, H. P., Fleckenstein, M., Fritsche, L. G., Schmitz-Valckenberg, S., Gobel, A., Adrion, C., Herold, C., Keilhauer, C. N., Mackensen, F., Mossner, A., Pauleikhoff, D., Weinberger, A. W., Mansmann, U., Holz, F. G., Becker, T. and Weber, B. H. (2009). CFH, C3 and ARMS2 are significant risk loci for susceptibility but not for disease progression of geographic atrophy due to AMD. *PloS one*, 4(10): e7418.

Schwartz, S. G. and Brantley, M. A., Jr. (2011). Pharmacogenetics and age-related macular degeneration. *Journal of ophthalmology*, 2011: 252549.

Seddon, J. M., Cote, J., Page, W. F., Aggen, S. H. and Neale, M. C. (2005). The US twin study of age-related macular degeneration: relative roles of genetic and environmental influences. *Arch Ophthalmol*, 123(3): 321-327.

Seddon, J. M., Gensler, G., Milton, R. C., Klein, M. L. and Rifai, N. (2004). Association between C-reactive protein and age-related macular degeneration. *Jama*, 291(6): 704-710.

Seddon, J. M., Reynolds, R. and Rosner, B. (2009). Peripheral retinal drusen and reticular pigment: association with CFHY402H and CFHrs1410996 genotypes in family and twin studies. *Investigative ophthalmology & visual science*, 50(2): 586-591.

Seddon, J. M., Reynolds, R., Yu, Y., Daly, M. J. and Rosner, B. (2011). Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors. *Ophthalmology*, 118(11): 2203-2211.

Seddon, J. M., Santangelo, S. L., Book, K., Chong, S. and Cote, J. (2003). A genomewide scan for age-related macular degeneration provides evidence for linkage to several chromosomal regions. *American journal of human genetics*, 73(4): 780-790.

Shah, A. R., Williams, S., Baumal, C. R., Rosner, B., Duker, J. S. and Seddon, J. M. (2016). Predictors of Response to Intravitreal Anti-Vascular Endothelial

Growth Factor Treatment of Age-Related Macular Degeneration. *American journal of ophthalmology*, 163: 154-166 e158.

Sharma, N. K., Gupta, A., Prabhakar, S., Singh, R., Sharma, S. K., Chen, W. and Anand, A. (2013). Association between CFH Y402H polymorphism and age related macular degeneration in North Indian cohort. *PloS one*, 8(7): e70193.

Silva, R. M., Figueira, J., Cachulo, M. L., Duarte, L., Faria de Abreu, J. R. and Cunha-Vaz, J. G. (2005). Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. *Graefe's archive for clinical and experimental ophthalmology*, 243(10): 973-979.

Sivaprasad, S., Adewoyin, T., Bailey, T. A., Dandekar, S. S., Jenkins, S., Webster, A. R. and Chong, N. V. (2007). Estimation of systemic complement C3 activity in age-related macular degeneration. *Arch Ophthalmol*, 125(4): 515-519.

Smailhodzic, D., Muether, P. S., Chen, J., Kwestro, A., Zhang, A. Y., Omar, A., Van de Ven, J. P., Keunen, J. E., Kirchhof, B., Hoyng, C. B., Klevering, B. J., Koenekoop, R. K., Fauser, S. and den Hollander, A. I. (2012). Cumulative effect of risk alleles in CFH, ARMS2, and VEGFA on the response to ranibizumab treatment in age-related macular degeneration. *Ophthalmology*, 119(11): 2304-2311.

Smith, W., Assink, J., Klein, R., Mitchell, P., Klaver, C. C., Klein, B. E., Hofman, A., Jensen, S., Wang, J. J. and de Jong, P. T. (2001). Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology*, 108(4): 697-704.

Smith, W. and Mitchell, P. (1998). Family history and age-related maculopathy: the Blue Mountains Eye Study. *Australian and New Zealand journal of ophthalmology*, 26(3): 203-206.

Smith, W., Mitchell, P. and Leeder, S. R. (1996). Smoking and age-related maculopathy. The Blue Mountains Eye Study. *Arch Ophthalmol*, 114(12): 1518-1523.

Sobrin, L., Ripke, S., Yu, Y., Fagerness, J., Bhangale, T. R., Tan, P. L., Souied, E. H., Buitendijk, G. H., Merriam, J. E., Richardson, A. J., Raychaudhuri, S., Reynolds, R., Chin, K. A., Lee, A. Y., Leveziel, N., Zack, D. J., Campochiaro, P., Smith, R. T., Barile, G. R., Hogg, R. E., Chakravarthy, U., *et al.* (2012). Heritability and genome-wide association study to assess genetic differences between advanced age-related macular degeneration subtypes. *Ophthalmology*, 119(9): 1874-1885.

Sobrin, L. and Seddon, J. M. (2014). Nature and nurture- genes and environment- predict onset and progression of macular degeneration. *Progress in retinal and eye research*, 40: 1-15.

Solomon, S. D., Lindsley, K., Vedula, S. S., Krzystolik, M. G. and Hawkins, B. S. (2014). Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *The Cochrane database of systematic reviews*, 8: CD005139.

Solomon, S. D., Lindsley, K., Vedula, S. S., Krzystolik, M. G. and Hawkins, B. S. (2014). Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *The Cochrane database of systematic reviews*(8): CD005139.

Spaide, R. F., Yannuzzi, L. A., Slakter, J. S., Sorenson, J. and Orlach, D. A. (1995). Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. *Retina*, 15(2): 100-110.

Spencer, K. L., Olson, L. M., Anderson, B. M., Schnetz-Boutaud, N., Scott, W. K., Gallins, P., Agarwal, A., Postel, E. A., Pericak-Vance, M. A. and Haines, J. L. (2008). C3 R102G polymorphism increases risk of age-related macular degeneration. *Human molecular genetics*, 17(12): 1821-1824.

Stadtman, E. R. (2001). Protein oxidation in aging and age-related diseases. *Annals of the New York Academy of Sciences*, 928: 22-38.

Stevens, A., Soden, J., Brenchley, P. E., Ralph, S. and Ray, D. W. (2003). Haplotype analysis of the polymorphic human vascular endothelial growth factor gene promoter. *Cancer research*, 63(4): 812-816.

Stewart, M. W. (2012). Aflibercept (VEGF Trap-eye): the newest anti-VEGF drug. *The British journal of ophthalmology*, 96(9): 1157-1158.

Storkebaum, E. and Carmeliet, P. (2004). VEGF: a critical player in neurodegeneration. *The Journal of clinical investigation*, 113(1): 14-18.

Sundaresan, P., Vashist, P., Ravindran, R. D., Shanker, A., Nitsch, D., Nonyane, B. A., Smeeth, L., Chakravarthy, U. and Fletcher, A. E. (2012). Polymorphisms in ARMS2/HTRA1 and complement genes and age-related macular degeneration in India: findings from the INDEYE study. *Investigative ophthalmology & visual science*, 53(12): 7492-7497.

Sundelin, S., Wihlmark, U., Nilsson, S. E. and Brunk, U. T. (1998). Lipofuscin accumulation in cultured retinal pigment epithelial cells reduces their phagocytic capacity. *Current eye research*, 17(8): 851-857.

Szaflik, J. P., Blasiak, J., Krzyanowska, A., Zaras, M., Janik-Papis, K., Borucka, A. I., Wozniak, K. and Szaflik, J. (2009). Distribution of the C-460T polymorphism of the vascular endothelial growth factor gene in age-related macular degeneration. *Klinika oczna*, 111(4-6): 125-127.

Tan, J. S., Mitchell, P., Kifley, A., Flood, V., Smith, W. and Wang, J. J. (2007). Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol*, 125(8): 1089-1095.

Tan, J. S., Mitchell, P., Smith, W. and Wang, J. J. (2007). Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology*, 114(6): 1143-1150.

Teo, K. Y., Cheung, G. C., Lee, S. Y., Koh, A. C., Ong, S. G. and Wong, T. Y. (2014). Evolving practice patterns in treatment of major retinal diseases in Singapore. *Annals of the Academy of Medicine, Singapore*, 43(3): 192-194.

Teper, S. J., Nowinska, A. and Wylegala, E. (2012). A69S and R38X ARMS2 and Y402H CFH gene polymorphisms as risk factors for neovascular age-related macular degeneration in Poland - a brief report. *Medical science monitor : international medical journal of experimental and clinical research*, 18(2): PR1-3.

Thakkinstian, A., McKay, G. J., McEvoy, M., Chakravarthy, U., Chakrabarti, S., Silvestri, G., Kaur, I., Li, X. and Attia, J. (2011). Systematic review and meta-analysis of the association between complement component 3 and age-related macular degeneration: a HuGE review and meta-analysis. *American journal of epidemiology*, 173(12): 1365-1379.

Tian, J., Yu, W., Qin, X., Fang, K., Chen, Q., Hou, J., Li, J., Chen, D., Hu, Y. and Li, X. (2012). Association of genetic polymorphisms and age-related macular degeneration in Chinese population. *Investigative ophthalmology & visual science*, 53(7): 4262-4269.

Tomita, K., Tsujikawa, A., Yamashiro, K., Ooto, S., Tamura, H., Otani, A., Nakayama, Y. and Yoshimura, N. (2012). Treatment of polypoidal choroidal vasculopathy with photodynamic therapy combined with intravitreal injections of ranibizumab. *American journal of ophthalmology*, 153(1): 68-80 e61.

Tong, Y., Liao, J., Zhang, Y., Zhou, J., Zhang, H. and Mao, M. (2010). LOC387715/HTRA1 gene polymorphisms and susceptibility to age-related macular degeneration: A HuGE review and meta-analysis. *Molecular vision*, 16: 1958-1981.

Topouzis, F., Anastasopoulos, E., Augood, C., Bentham, G. C., Chakravarthy, U., de Jong, P. T., Rahu, M., Seland, J., Soubrane, G., Tomazzoli, L., Vingerling, J. R., Vioque, J., Young, I. S. and Fletcher, A. E. (2009). Association of diabetes with age-related macular degeneration in the EUREYE study. *The British journal of ophthalmology*, 93(8): 1037-1041.

Tosi, G. M., Caldi, E., Neri, G., Nuti, E., Marigliani, D., Baiocchi, S., Traversi, C., Cevenini, G., Tarantello, A., Fusco, F., Nardi, F., Orlandini, M. and Galvagni, F. (2017). HTRA1 and TGF-beta1 Concentrations in the Aqueous Humor of Patients With Neovascular Age-Related Macular Degeneration. *Investigative ophthalmology & visual science*, 58(1): 162-167.

Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. (1999). Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. *Arch Ophthalmol*, 117(10): 1329-1345.

Tufail, A., Patel, P. J., Egan, C., Hykin, P., da Cruz, L., Gregor, Z., Dowler, J., Majid, M. A., Bailey, C., Mohamed, Q., Johnston, R., Bunce, C. and Xing, W. (2010). Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. *BMJ*, 340: c2459.

Ueta, T., Obata, R., Inoue, Y., Iriyama, A., Takahashi, H., Yamaguchi, T., Tamaki, Y. and Yanagi, Y. (2009). Background comparison of typical age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese patients. *Ophthalmology*, 116(12): 2400-2406.

UK Age-Related Macular Degeneration EMR Users Group. (2014). The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. *Ophthalmology*, 121(5): 1092-1101.

Uyama, M., Takahashi, K., Ida, N., Miyashiro, M., Ando, A., Takahashi, A., Yamada, E., Shirasu, J., Nagai, Y. and Takeuchi, M. (2000). The second eye of Japanese patients with unilateral exudative age related macular degeneration. *The British journal of ophthalmology*, 84(9): 1018-1023.

Valones, M. A., Guimaraes, R. L., Brandao, L. A., de Souza, P. R., de Albuquerque Tavares Carvalho, A. and Crovela, S. (2009). Principles and applications of polymerase chain reaction in medical diagnostic fields: a review. *Brazilian journal of microbiology : [publication of the Brazilian Society for Microbiology]*, 40(1): 1-11.

Vassilev, Z. P., Ruigomez, A., Soriano-Gabarro, M. and Garcia Rodriguez, L. A. (2015). Diabetes, cardiovascular morbidity, and risk of age-related macular degeneration in a primary care population. *Investigative ophthalmology & visual science*, 56(3): 1585-1592.

Vaziri, K., Schwartz, S. G., Relhan, N., Kishor, K. S. and Flynn, H. W., Jr. (2015). New Therapeutic Approaches in Diabetic Retinopathy. *The review of diabetic studies : RDS*, 12(1-2): 196-210.

Velilla, S., Garcia-Medina, J. J., Garcia-Layana, A., Dolz-Marco, R., Pons-Vazquez, S., Pinazo-Duran, M. D., Gomez-Ulla, F., Arevalo, J. F., Diaz-Llopis, M. and Gallego-Pinazo, R. (2013). Smoking and age-related macular degeneration: review and update. *Journal of ophthalmology*, 2013: 895147.

Veloso, C. E., Almeida, L. N. and Nehemy, M. B. (2014). CFH Y402H polymorphism and response to intravitreal ranibizumab in Brazilian patients with neovascular age-related macular degeneration. *Revista do Colegio Brasileiro de Cirurgioes*, 41(6): 386-392.

Verteporfin in Photodynamic Therapy Study Group. (2001). Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial--VIP report no. 1. *Ophthalmology*, 108(5): 841-852.

Verteporfin Roundtable Participants. (2005). Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. *Retina*, 25(2): 119-134.

Vierkotten, S., Muether, P. S. and Fauser, S. (2011). Overexpression of HTRA1 leads to ultrastructural changes in the elastic layer of Bruch's membrane via cleavage of extracellular matrix components. *PloS one*, 6(8): e22959.

Vingerling, J. R., Hofman, A., Grobbee, D. E. and de Jong, P. T. (1996). Age-related macular degeneration and smoking. The Rotterdam Study. *Arch Ophthalmol*, 114(10): 1193-1196.

Wang, G., Dubovy, S. R., Kovach, J. L., Schwartz, S. G., Agarwal, A., Scott, W. K., Haines, J. L. and Pericak-Vance, M. A. (2013). Variants at chromosome 10q26 locus and the expression of HTRA1 in the retina. *Experimental eye research*, 112: 102-105.

Wang, J. J., Rochtchina, E., Lee, A. J., Chia, E. M., Smith, W., Cumming, R. G. and Mitchell, P. (2007). Ten-year incidence and progression of age-related maculopathy: the blue Mountains Eye Study. *Ophthalmology*, 114(1): 92-98.

Wang, L., Clark, M. E., Crossman, D. K., Kojima, K., Messinger, J. D., Mobley, J. A. and Curcio, C. A. (2010). Abundant lipid and protein components of drusen. *PloS one*, 5(4): e10329.

Watson, C. J., Webb, N. J., Bottomley, M. J. and Brenchley, P. E. (2000). Identification of polymorphisms within the vascular endothelial growth factor (VEGF) gene: correlation with variation in VEGF protein production. *Cytokine*, 12(8): 1232-1235.

Weber, B. H., Charbel Issa, P., Pauly, D., Herrmann, P., Grassmann, F. and Holz, F. G. (2014). The role of the complement system in age-related macular degeneration. *Deutsches Arzteblatt international*, 111(8): 133-138.

Weeks, D. E., Conley, Y. P., Mah, T. S., Paul, T. O., Morse, L., Ngo-Chang, J., Dailey, J. P., Ferrell, R. E. and Gorin, M. B. (2000). A full genome scan for age-related maculopathy. *Human molecular genetics*, 9(9): 1329-1349.

Weger, M., Renner, W., Steinbrugger, I., Kofer, K., Wedrich, A., Groselj-Strele, A., El-Shabrawi, Y., Schmut, O. and Haas, A. (2007). Association of the HTRA1 -625G>A promoter gene polymorphism with exudative age-related macular degeneration in a Central European population. *Molecular vision*, 13: 1274-1279.

Wen, F., Chen, C., Wu, D. and Li, H. (2004). Polypoidal choroidal vasculopathy in elderly Chinese patients. *Graefe's archive for clinical and experimental ophthalmology*, 242(8): 625-629.

Wilde, C., Patel, M., Lakshmanan, A., Amankwah, R., Dhar-Munshi, S. and Amoaku, W. (2015). The diagnostic accuracy of spectral-domain optical coherence tomography for neovascular age-related macular degeneration: a comparison with fundus fluorescein angiography. *Eye (Lond)*, 29(5): 602-609; quiz 610.

Witmer, A. N., Vrensen, G. F., Van Noorden, C. J. and Schlingemann, R. O. (2003). Vascular endothelial growth factors and angiogenesis in eye disease. *Progress in retinal and eye research*, 22(1): 1-29.

Wong, C. W., Wong, T. Y. and Cheung, C. M. (2015). Polypoidal Choroidal Vasculopathy in Asians. *Journal of clinical medicine*, 4(5): 782-821.

Wong, I. Y., Shi, X., Gangwani, R., Zhao, P., Iu, L. P., Li, Q., Ng, A. and Li, X. (2015). 1-year results of combined half-dose photodynamic therapy and ranibizumab for polypoidal choroidal vasculopathy. *BMC ophthalmology*, 15: 66.

Wong, M. L. and Medrano, J. F. (2005). Real-time PCR for mRNA quantitation. *Biotechniques*, 39(1): 75-88.

Wong, T. Y., Liew, G. and Mitchell, P. (2007). Clinical update: new treatments for age-related macular degeneration. *Lancet*, 370(9583): 204-206.

Wong, W. L., Su, X., Li, X., Cheung, C. M., Klein, R., Cheng, C. Y. and Wong, T. Y. (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *The Lancet. Global health*, 2(2): e106-116.

Woo, S. J., Ahn, J., Morrison, M. A., Ahn, S. Y., Lee, J., Kim, K. W., DeAngelis, M. M. and Park, K. H. (2015). Analysis of Genetic and Environmental Risk Factors and Their Interactions in Korean Patients with Age-Related Macular Degeneration. *PloS one*, 10(7): e0132771.

Woodell, A. and Rohrer, B. (2014). A mechanistic review of cigarette smoke and age-related macular degeneration. *Advances in experimental medicine and biology*, 801: 301-307.

Wu, L., Tao, Q., Chen, W., Wang, Z., Song, Y., Sheng, S., Li, P. and Zhou, J. (2013). Association between polymorphisms of complement pathway genes and age-related macular degeneration in a Chinese population. *Investigative ophthalmology & visual science*, 54(1): 170-174.

Wu, M., Xiong, H., Xu, Y., Xiong, X., Zou, H., Zheng, M., Wang, X. and Zhou, X. (2017). Association between VEGF-A and VEGFR-2 polymorphisms and response to treatment of neovascular AMD with anti-VEGF agents: a meta-analysis. *The British journal of ophthalmology*, 101(7): 976-984.

Wu, P. B., Gu, H., Yang, X. F. and Liu, N. P. (2013). [Association of single nucleotide polymorphism in complement factor I gene with age-related macular degeneration]. *[Zhonghua yan ke za zhi] Chinese journal of ophthalmology*, 49(4): 350-356.

Xu, Y., Guan, N., Xu, J., Yang, X., Ma, K., Zhou, H., Zhang, F., Snellingen, T., Jiao, Y., Liu, X., Wang, N. and Liu, N. (2008). Association of CFH, LOC387715, and HTRA1 polymorphisms with exudative age-related macular degeneration in a northern Chinese population. *Molecular vision*, 14: 1373-1381.

Yamashiro, K., Tomita, K., Tsujikawa, A., Nakata, I., Akagi-Kurashige, Y., Miyake, M., Ooto, S., Tamura, H. and Yoshimura, N. (2012). Factors associated with the response of age-related macular degeneration to intravitreal ranibizumab treatment. *American journal of ophthalmology*, 154(1): 125-136.

Yang, B., Cross, D. F., Ollerenshaw, M., Millward, B. A. and Demaine, A. G. (2003). Polymorphisms of the vascular endothelial growth factor and susceptibility to diabetic microvascular complications in patients with type 1 diabetes mellitus. *Journal of diabetes and its complications*, 17(1): 1-6.

Yang, Z., Camp, N. J., Sun, H., Tong, Z., Gibbs, D., Cameron, D. J., Chen, H., Zhao, Y., Pearson, E., Li, X., Chien, J., Dewan, A., Harmon, J., Bernstein, P. S., Shridhar, V., Zabriskie, N. A., Hoh, J., Howes, K. and Zhang, K. (2006). A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. *Science*, 314(5801): 992-993.

Yannuzzi, L. A. (2011). Indocyanine green angiography: a perspective on use in the clinical setting. *American journal of ophthalmology*, 151(5): 745-751 e741.

Yannuzzi, L. A., Rohrer, K. T., Tindel, L. J., Sobel, R. S., Costanza, M. A., Shields, W. and Zang, E. (1986). Fluorescein angiography complication survey. *Ophthalmology*, 93(5): 611-617.

Yasuda, M., Kiyohara, Y., Hata, Y., Arakawa, S., Yonemoto, K., Doi, Y., Iida, M. and Ishibashi, T. (2009). Nine-year incidence and risk factors for age-related macular degeneration in a defined Japanese population the Hisayama study. *Ophthalmology*, 116(11): 2135-2140.

Yates, J. R., Sepp, T., Matharu, B. K., Khan, J. C., Thurlby, D. A., Shahid, H., Clayton, D. G., Hayward, C., Morgan, J., Wright, A. F., Armbrecht, A. M., Dhillon, B., Deary, I. J., Redmond, E., Bird, A. C. and Moore, A. T. (2007). Complement C3 variant and the risk of age-related macular degeneration. *The New England journal of medicine*, 357(6): 553-561.

Yonekawa, Y., Miller, J. W. and Kim, I. K. (2015). Age-Related Macular Degeneration: Advances in Management and Diagnosis. *Journal of clinical medicine*, 4(2): 343-359.

Yoshida, T., DeWan, A., Zhang, H., Sakamoto, R., Okamoto, H., Minami, M., Obazawa, M., Mizota, A., Tanaka, M., Saito, Y., Takagi, I., Hoh, J. and Iwata, T. (2007). HTRA1 promoter polymorphism predisposes Japanese to age-related macular degeneration. *Molecular vision*, 13: 545-548.

You, Q. S., Xu, L., Yang, H., Li, Y. B., Wang, S., Wang, J. D., Zhang, J. S., Wang, Y. X. and Jonas, J. B. (2012). Five-year incidence of age-related macular degeneration: the Beijing Eye Study. *Ophthalmology*, 119(12): 2519-2525.

Young, R. W. (1987). Pathophysiology of age-related macular degeneration. *Survey of ophthalmologyl*, 31(5): 291-306.

Yuan, D., Liu, X., Yuan, S., Xie, P. and Liu, Q. (2013). Genetic association with response to intravitreal ranibizumab for neovascular age-related macular degeneration in the Han Chinese population. *Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde*, 230(4): 227-232.

Yucel, D., Yilmaz, M., Durukan, A. H. and Ozgul, R. K. (2012). Association of CFH Y402H polymorphism with both forms of advanced age-related macular degeneration in Turkish patients. *Ophthalmic genetics*, 33(3): 144-149.

Zainal, M., Ismail, S. M., Ropilah, A. R., Elias, H., Arumugam, G., Alias, D., Fathilah, J., Lim, T. O., Ding, L. M. and Goh, P. P. (2002). Prevalence of blindness and low vision in Malaysian population: results from the National Eye Survey 1996. *The British journal of ophthalmology*, 86(9): 951-956.

Zarbin, M. A., Casaroli-Marano, R. P. and Rosenfeld, P. J. (2014). Age-related macular degeneration: clinical findings, histopathology and imaging techniques. *Developments in ophthalmology*, 53: 1-32.

Zerbib, J., Richard, F., Puche, N., Leveziel, N., Cohen, S. Y., Korobelnik, J. F., Sahel, J., Munnich, A., Kaplan, J., Rozet, J. M. and Souied, E. H. (2010). R102G polymorphism of the C3 gene associated with exudative age-related macular degeneration in a French population. *Molecular vision*, 16: 1324-1330.

Zhang, M. X., Zhao, X. F., Ren, Y. C., Geng, T. T., Yang, H., Feng, T., Jin, T. B. and Chen, C. (2015). Association between a functional genetic polymorphism (rs2230199) and age-related macular degeneration risk: a meta-analysis. *Genetics and molecular research : GMR*, 14(4): 12567-12576.

Zia, A. and Moses, A. M. (2011). Ranking insertion, deletion and nonsense mutations based on their effect on genetic information. *BMC bioinformatics*, 12: 299.

Zylbermann, R., Landau, D., Rozenman, Y., Abrahami, S. and Pollack, A. (1997). Exudative age-related macular degeneration in patients with diabetic retinopathy and its relation to retinal laser photocoagulation. *Eye (Lond)*, 11 (Pt 6): 872-875.