The Association Between Genetic Polymorphisms in Estrogen Receptor Genes and the Risk of Ocular Disease: A Meta-Analysis

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Abstract

Objectives: To evaluate the association between estrogen receptor (ER) genes polymorphisms and the risk of ocular disease.

Materials and Methods: A meta-analysis was performed of all available studies that investigated the association between ER gene polymorphisms and the risk of ocular disease.

Results: Studies that were selected based on inclusion criteria reported 5 and 4 single-nucleotide polymorphisms (SNPs) identified in the ESR1 (ERα) (rs2234093, rs12154178, rs1884054, rs1801132, and rs9340799) and ESR2 (ERβ) (rs1268656, rs7159462, rs1256031, and rs986938) genes, respectively. The pooled result showed a significant association between ESR2 rs1256031 gene polymorphism and ocular disease (odds ratio: 0.55, 95% confidence interval: 0.41-0.74, p<0.0001).

Conclusion: The recessive genotype of ESR2 rs1256031 gene polymorphism had a protective effect against ocular disease, which supports the hypothesis that the estrogen-signaling pathway through ERβ plays a pivotal role in the pathogenesis of ophthalmic disorders.

Keywords: Estrogen receptor, gene, polymorphism, ocular disease

Introduction

Estradiol (E2) is a female sex steroid hormone and considered a major form of estrogen.1 E2 biosynthesis is regulated by rate-limiting enzyme aromatase, which is encoded by the cyp19a1 gene.2,3,5 Although the ovary is known as the main site of E2 production, local E2 synthesis is also observed in several tissues including the brain, adipocytes, bone, liver, and retina.6,7 Some evidence suggests an association between gonadal hormones and several diseases that are not related to the reproductive organs, such as diabetes, obesity, and myocardial infarction.4,8,9 However, little is known about the role of E2 in relation to the eye.

In mammals, expression of cyp19a1 is detected in the inner nuclear layer, outer plexiform layer, outer nuclear layer, and photoreceptors, while estrogen receptor (ER) is localized in almost all retina layers, cornea, lens, conjunctiva, lacrimal and meibomian glands7,10, implying that E2 synthesis and its signaling are necessary for the eye. It has been reported that E2 exerts a neuroprotective effect in the retina and optic nerve.11 Moreover, E2 seems to be involved in several eye pathologies such as glaucoma, myopia, age-related maculopathy (ARM), and cataract.12,13,14,15 Furthermore, the prevalence of dry eye disease is predominantly found in females, particularly in the menopausal and postmenopausal age group.16 Together, these support the notion that estrogen is a contributing factor to the development of ocular disease.

DNA polymorphisms are different DNA sequences that commonly occur among individuals and populations. The
most common type of DNA polymorphism is the single nucleotide polymorphism (SNP), which is characterized by a single nucleotide change in the DNA sequence. Interestingly, however, alterations in DNA sequences may be directly or indirectly correlated with the development of disease through the modification of its expression and functional effect.\textsuperscript{17} Estrogen-mediated effects are mainly modulated by ER\textalpha{} and ER\textbeta{}, which are encoded by the \textit{ESR1} and \textit{ESR2} genes, respectively.\textsuperscript{18} The association between genetic polymorphisms of \textit{ER} genes and the risk of disease has been reported extensively, particularly in cancer.\textsuperscript{19,20} Two common SNPs have been identified in \textit{ESR1} (rs223469, rs9340799) and \textit{ESR2} (rs1256031, rs4986938).\textsuperscript{21,22} Thus, SNPs in \textit{ESR} genes may directly or indirectly affect normal physiological functions of estrogen and may affect the risk of ocular disease. Therefore, in the present study, a meta-analysis of all eligible studies was performed to provide an accurate estimation of the association between ER polymorphisms and the risk of ocular disease.

Methods

A literature search was conducted from PubMed, Google Scholar, Scopus, and Web of Science. Keywords such as ER, polymorphisms, and ocular disease were used in combination. The literature search was updated until September 2019. The selection criteria were as follows: (1) evaluating the associations between \textit{ER} gene polymorphisms and the risk of ocular disease and (2) case-control design. The genotypic frequency for the \textit{ER} polymorphisms was tested by Hardy-Weinberg equilibrium (HWE). Associations between the \textit{ER} polymorphisms and risk of ocular disease were estimated by calculating pooled odds ratios (OR) and 95% confidence interval (CI). The random-effect model was used to allow heterogeneity. Heterogeneity was evaluated with Q-test and $I^2$. Egger's regression test was used to assess publication bias. P value of <0.05 was indicative of statistical significance.

Results

From the literature search, 5 studies were selected based on inclusion criteria. The characteristics of the selected studies are shown in Table 1. Mabuchi et al.\textsuperscript{23} recruited 425 glaucoma patients (220 males and 205 females) with the average age of 63.55, while Kosior-Jarecka et al.\textsuperscript{21} enrolled 235 glaucoma patients (72 males and 163 females) with an average age of 75.7. Seitzman et al.\textsuperscript{14} and Imbert et al.\textsuperscript{22} recruited only female participants with an average age of 65 and 62.2, respectively. A study by Škiline\v{c}i\v{c} et al.\textsuperscript{15} did not provide information regarding the gender and age of the participants. However, the study evaluated...
estrogen-related polymorphism in age-related cataracts. All of the studies used age- and gender-matched controls. Thus, this current study mainly consisted of menopausal female participants.

Five and 4 SNPs occurred in the \textit{ESR1} (rs2234093, rs12154178, rs1884054, rs1801132, and rs9340799) and \textit{ESR2} (rs1268656, rs7159462, rs1256031, and rs4986938) genes, respectively. All SNPs complied with the HWE (p>0.05). Finally, only 3 studies were included in our meta-analysis of the association between \textit{ESR1} (rs2234093 and rs9340799) and \textit{ESR2} (rs1256031 and rs4986938) polymorphisms with ocular disease. The pooled results on the association between ER polymorphisms and the risk of ocular disease are shown in Table 2. There was no significant association between \textit{ESR1} gene polymorphisms and risk of ocular disease. However, the recessive model of \textit{ESR2} rs1256031 gene polymorphism showed a 45% decrease in odds ratio (OR: 0.55, 95% CI: 0.41-0.74, p=0.0001, with low heterogeneity I$^2$=15%), suggesting a protective effect of recessive genotype in \textit{ESR2} rs1256031 against ocular disease. No publication bias was observed for the association of ER polymorphisms and risk of ocular disease (p\_Egger test\textgreater0.05).

### Discussion

In this study, 4 ocular diseases (primary open-angle glaucoma, dry eye, cataract, and ARM) were included in the analysis. Interestingly, such cases are mostly correlated with increased age. Indeed, low estrogen levels are observed in menopausal women and have been associated with increased cytokine production and ocular disease.\textsuperscript{23,24} Moreover, menopausal women treated with hormone replacement therapy show a reduction of intraocular pressure\textsuperscript{25,26}, which suggests a protective effect of estrogen. However, there is a conflicting result in regards to \textit{cyp19a1} polymorphism. A woman with \textit{cyp19a1} (rs10046) polymorphism has a higher susceptibility to myopia\textsuperscript{24}, while there is no evidence of \textit{cyp19a1} polymorphism being associated with the risk of cataract.\textsuperscript{35} Furthermore, Nishikawa et al.\textsuperscript{27} provided evidence that there is no change in sex steroid hormone levels in patients with vitreoretinal disease. Nonetheless, the role of estrogen on ocular disease needs further investigation.

Because the action of estrogen depends on the interaction with its receptors, understanding ER genetic variations become important to evaluate the association of ER polymorphisms and the risk of ocular disease. This report indicated that the recessive model of \textit{ESR2} rs1256031 gene polymorphism was correlated

### Table 2. Meta-analysis for the association between ER polymorphisms and the risk of ocular disease

| Model          | Number of studies | OR     | 95% CI    | I$^2$ (%) | p value |
|----------------|-------------------|--------|-----------|-----------|---------|
| \textit{ESR1} rs2234093 |                   |        |           |           |         |
| Allele model   | 3                 | 1.05   | 0.89-1.24 | 0         | 0.61    |
| Dominant model | 2                 | 1.37   | 0.92-2.04 | 0         | 0.12    |
| Recessive model| 2                 | 0.86   | 0.60-1.22 | 0         | 0.39    |
| Homozygous model| 2                | 2.53   | 1.11-6.08 | 78        | 0.57    |
| Heterozygous model| 2             | 0.93   | 0.64-1.36 | 0         | 0.05    |
| \textit{ESR1} rs9340799 |               |        |           |           |         |
| Allele model   | 2                 | 0.99   | 0.82-1.19 | 0         | 0.90    |
| \textit{ESR2} rs1256031 |              |        |           |           |         |
| Allele model   | 2                 | 1.16   | 0.97-1.40 | 0         | 0.10    |
| Dominant model | 2                 | 1.29   | 0.99-1.68 | 0         | 0.06    |
| Recessive model| 2                 | 0.55   | 0.41-0.74 | 15        | <0.0001*|
| Homozygous model| 2                | 0.75   | 0.53-1.07 | 0         | 0.11    |
| Heterozygous model| 2             | 0.85   | 0.44-1.64 | 77        | 0.63    |
| \textit{ESR2} rs4986938 |             |        |           |           |         |
| Allele model   | 2                 | 1.15   | 0.83-1.59 | 54        | 0.40    |
| Dominant model | 2                 | 1.2    | 0.93-1.56 | 0         | 0.37    |
| Recessive model| 2                 | 0.93   | 0.35-2.44 | 66        | 0.09    |
| Homozygous model| 2                | 0.86   | 0.34-2.19 | 62        | 0.11    |
| Heterozygous model| 2            | 1.09   | 0.48-2.49 | 52        | 0.15    |

*For \textit{ESR1} rs9340799 polymorphism was made only the comparison of allele model due to genotype frequency is not provided from one study. *p<0.05, OR: Odds ratio, CI: Confidence interval
with a reduction of ocular disease risk, which has been also reported as a protective factor in developing type 2 diabetes mellitus.28 Mice lacking ERβ are more susceptible to in vivo injury to RPE cells29, which supports a protective effect of ERβ. It has been reported that the expression of ERβ is more abundant than ERα in the central nervous system29,30, including the retina. Moreover, the expression of ERβ is relatively more constant than ERα in the human eye31, suggesting a prominent role of ERβ in regulating normal physiological function in the eye.

Study Limitations

There are limitations to this study. First, the number of studies included in the meta-analysis was relatively small due to the limited availability of published papers. From 5 published papers, only 3 were suitable for further analysis, while the rest evaluated different SNPs. Second, major and minor alleles might have different roles in the risk of ocular disease, resulting in heterogeneity of the studies. Third, although this study was mainly generated from the pooled data of menopausal women, some studies enrolled both male and female participants, which may affect the pooled estimate. Thus, these findings should be interpreted with caution.

Conclusion

In summary, the current meta-analysis suggests that ESR2 rs1256031 gene polymorphism is significantly associated with the risk of ocular disease. The recessive genotype of ESR2 rs1256031 gene polymorphism was associated with a reduced risk of developing ocular disease. It is expected that more studies will become available, which may help the accurate estimation of the relationship of ER with ocular disease to verify this conclusion.

Ethics

Peer-review: Internally and externally peer reviewed.

Financial Disclosure: The author declared that this study received no financial support.

References

1. Hutchinson CV, Walker JA, Davidson C. Oestrogen, ocular function and low-level vision: a review. J Endocrinol. 2014;223:R9-18.
2. Ulhaq ZS, Kishida M. Brain Aromatase Modulates Serotonergic Neuron by Regulating Serotonin Levels in Zebrafish Embryos and Larvae. Front Endocrinol (Lausanne). 2018;9:230.
3. Ulhaq ZS. Brain aromatase modulates cardiac functions in embryonic zebrafish. International Journal of Veterinary Science and Medicine. 2019.
4. Ulhaq ZS. Estrogen-serotonin interaction and its implication on insulin resistance. Alexandria Journal of Medicine. 2019:53:76-81.
5. Ulhaq ZS. Aromatase and neurogeneration. Malang Neurol J. 2019;5:15-30.
6. Barakat R, Oakley O, Kim H, Jin J, Ko CJ. Extra-gonadal sites of estrogen biosynthesis and function. BMR Rep. 2016;49:488-496.
7. Cascio C, Russo D, Drago G, Galizzi G, Pasantino R, Guarnieri R, Guarnieri P. 17beta-estradiol synthesis in the adult male rat retina. Exp Eye Res. 2007;85:166-172.
8. Newton KM, LaCroix AZ, Heckbert SR, Abraham L, McCulloch D, Barlow W. Estrogen therapy and risk of cardiovascular events among women with type 2 diabetes. Diabetes Care. 2003;26:2810-2816.
9. Liscano F, Guzman G. Estrogen Deficiency and the Origin of Obesity during Menopause. Biomed Res Int. 2014;2014:757461.
10. Kazama S, Kazama JJ, Ando N. Eye diseases in women. Fukushima J Med Sci. 2019;65:30-36.
11. Nuzzi R, Scalabrin S, Becco A, Panzica G. Sex Hormones and Optic Nerve Disorders: A Review. Front Neurosci. 2019;13:57.
12. Mabuchi F, Sakurada Y, Kashiwagi K, Yamazaga T, Iijima H, Tsukahara S. Estrogen receptor beta gene polymorphism and intraocular pressure elevation 2 in female patients with primary open-angle glaucoma. Am J Ophthalmol. 2010;149:826-830.
13. Chen ZT, Wang J, Liao YT, Shih YF, Lin LL. Polymorphisms in steroidogenesis genes, sex steroid levels, and high myopia in the Taiwanese population. Mol Vis. 2011;17:2297-2310.
14. Seitzman RL, Mahajan VB, Mangione C, Cauley JA, Ernstrom KE, Stone KL, Cummings SR, Hochberg MC, Hillier TA, Simsner JS, Yu E Cofman AL. Estrogen receptor alpha and matrix metalloproteinase 2 polymorphisms and age-related maculopathy in older women. Am J Epidemiol. 2008;167:1217-1225.
15. Škúlič D, Nilson S, Seibt Paliér M, Tasa G, Juronen E, Behemp A, Carlsson JO, Petersen A, Zetterberg H, Zetterberg M. Estrogen-related Polymorphisms in Estonian Patients with Age-related Cataract. Ophthalmic Genet. 2015;36:188-191.
16. Peck T, Olakovsky L, Aggarwal S. Dry Eye Syndrome in Menopause and Perimenopausal Age Group. J Midlife Health. 2017;8:51-54.
17. Figtree GA, Noonan JF, Bhindi R, Collins P. Estrogen receptor polymorphisms: significance to human physiology, disease and therapy. Recent Pat DNA Gene Seq. 2009;3:164-171.
18. Kovats S. Estrogen receptors regulate innate immune cells and signaling pathways. Cell Immunol. 2015:294:63-69.
19. Chae YK, Huang Y, Strickland P, Hoffman SC, Helzlsouer K. Genetic polymorphisms of estrogen alpha and beta and the risk of developing prostate cancer. PLoS One. 2009;4:e6523.
20. Cai Q, Shu XO, Jin E, Dai Q, Wen W, Ceng J, Gao YT, Zheng W. Genetic polymorphisms in the estrogen receptor alpha gene and risk of breast cancer: results from the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev. 2003;12:853-859.
21. Koseer-Jarzecz E, Sagan M, Wrobel-Dudzi ska D, ukasik U, Aung T, Khor CC, Keck J, arnowski T. Estrogen receptor gene polymorphisms and their influence on clinical status of Caucasian patients with primary open angle 3 glaucoma. Ophthalmic Genet. 2019;40:323-328.
22. de Voogel S, Wolfs RC, Jansens NM, Uitterlinden AG, Pols HA, Hofman A, de Jong PT. Estrogen receptors alpha and beta and the risk of open-angle glaucoma: the Rotterdam Study. Arch Ophthalmol. 2008;126:110-114.
23. Imbert Y, Fouilks GN, Brennan MD, Jumablatt MM, John G, Shah H, Newton C, Pooranfar F, Young WW Jr. MUC1 and estrogen receptor alpha gene polymorphisms in dry eye patients. Exp Eye Res. 2009;89:354-368.
24. Chen ZT, Wang J, Liao YT, Shih YF, Lin LL. Polymorphisms in steroidogenesis genes, sex steroid levels, and high myopia in the Taiwanese population. Mol Vis. 2011;17:2297-2310.
25. Alintiwa O, Caglar Y, Üyküel N, Demirci A, Karabaş L. The effects of menopause and hormone replacement therapy on quality and quantity of tear, intraocular pressure and ocular blood flow. Ophthalmologica. 2004;218:120-129.
26. Ulhaq, ZS (In press). The association of estrogen-signaling pathways and susceptibility to open-angle glaucoma. Beni-Suef univ J Basic Appl Sci. doi: 10.1186/s4088-020-0035-8.
27. Nishikawa Y, Morishita S, Horie T, Fukumoto M, Sato T, Kida T, Oku H, Sugawa J, Ikeda T, Nakamura K. A comparison of sex steroid concentration levels in the vitreous and serum of patients with vitreoretinal diseases. PLoS One. 2017;12:e0180933.
28. Herrera-Lopez EE, Castelan-Martinez OD, Suarez-Sanchez F, Gomez-Zamudio JH, Peralta-Romero JJ, Cruz M, Valladares-Salgado A. The rs1256031 of estrogen receptor β gene is associated with type 2 diabetes. Diabetes Metab Syndr. 2018;12:631-633.
29. Elliot SJ, Catanuto P, Espinosa-Heidmann DG, Fernandez P, Hernandez E, Saloupis P, Kotach K, Karl M, Cousins SW. Estrogen receptor beta protects against in vivo injury in RPE cells. Exp Eye Res. 2010;90:10-16.

30. Wu WF, Tan XJ, Dai YB, Krishnan V, Warner M, Gustafsson JA. Targeting estrogen receptor β in microglia and T cells to treat experimental autoimmune encephalomyelitis. Proc Natl Acad Sci USA. 2013;110:3543-3548.

31. Munaut C, Lambert V, Noel A, Frankenne F, Deprez M, Foidart JM, Rakic JM. Presence of oestrogen receptor type beta in human retina. Br J Ophthalmol. 2001;85:877-882.