Evaluating the Association between Migraine Disease and the Development of Neurodegenerative Conditions in Women: A Literature Review

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Introduction

It is a well-researched fact that the prevalence of migraine disease is disproportionately higher in women than in men, with prevalence rates of 17.1% and 5.6% respectively[1, 2]. It is also true that women have a higher lifetime risk of developing Alzheimer's Disease than men, with women having a 1 in 5 risk and men having a 1 in 10 risk[3, 4, 5]. Estrogen is thought to play a protective role in neurovascular diseases, as demonstrated by studies of menstrual migraines (which occur when estrogen levels are lowest in a woman's menstrual cycle) and the improvement of migraine during pregnancy (due to estrogen levels remaining high throughout gestation)[6, 7, 8, 9, 10]. Similar studies have been conducted to examine estrogen's role in neurodegeneration, using animal models (which found that brain estrogen protects against beta amyloid plaque formation) and by studying the effects of HRT, which may delay AD onset when administered at the beginning of natural estrogen decline and reduce the risk of developing AD or any other neurodegenerative diseases in women[11, 12, 13, 14, 15, 16]. These findings strongly suggest that estrogen levels play a role in both migraine and AD pathology. Previous meta-analyses and multiple cohort studies indicate that migraine disease may be associated with cognitive impairment, increasing the risk of all-cause dementia and AD[17, 18, 19, 20].

Utilizing data from cohort and genome-wide association studies (GWAS), this study aims to examine the estrogen receptor alpha and aromatase genes (ESR1 and CYP19A1, respectively) and their accompanying single nucleotide polymorphisms (five for ESR1 and five for CYP19A1) involved in both migraine and AD pathology. Furthermore, these finding will be used to demonstrate whether or not women with these gene variants are at a higher risk for developing migraine disease and/or Alzheimer's disease.

Methods

The search for articles was limited to those published after 1995 in the following databases: PubMed, EBSCO, and Google Scholar, with the criteria ("migraine" OR "Alzheimer's" OR "estrogen" OR "ESR1" OR "CYP19A1").

Results

SNP	Migraine Association	Alzheimer's Association	Source
rs2234693	Risky*	Risky	**Ghosh et al., 2012; Ranjan et al., 2024; Bertram et al., 2007; Cheng et al., 2014**
rs1801132	No association	Risky	**Ranjan et al., 2024; Ma et al., 2009;**
rs2228480	Risky	No association	**Ranjan et al., 2024; Tiberio et al., 2023**
rs9340799	Risky	Risky	**Ranjan et al., 2024; Bertram et al., 2007**
rs2077647	No association	Risky	**Corominas et al., 2009; Ma et al., 2009**
rs10046	Risky*	Risky*	**Ghosh et al., 2012; CoSkun at al., 2016; Song et al., 2019; Janicki et al., 2014**
rs4646	Protective	Risky*	**Ghosh et al., 2012; Janicki et al., 2014**
rs1143704	No association	Risky*	**Janicki et al., 2014**
rs767199	No association	Risky*	**Janicki et al., 2014**
rs727479	No association	Protective	**Janicki et al., 2014**

*Asterisks indicate studies that found increased risk for women with variants of the indicated alleles

Discussion

This review helped to identify three single nucleotide polymorphisms, rs2234693, rs9340799, and rs10046, (2 of the ESR1 gene and 1 of the CYP19A1 gene) that are associated with an increased risk in both migraine disease and Alzheimer's disease. Some sources did not find a significant association between rs9340799 and migraine disease in certain ethnic groups, indicating that further research is needed to prove or disprove the association. Of those three, rs10046 demonstrated a significantly increased risk for women of both migraine disease and Alzheimer's disease.

Many GWAS did not stratify by sex and therefore could not be used to establish whether or not the SNPs that were discussed resulted in altered risk for women. Future research should continue to examine the different ways these gene variants affect each demographic being studied.

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