Differentially Expressed Genes Associated with Estrogen Receptor Pathway in Cerebral Aneurysms

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Introduction

Rupture of an intracranial aneurysm remains one of the most devastating neurosurgical vascular disease. While many genetic variations have been implicated in this disease, there is evidence to support a difference in incidence and rate of aneurysmal rupture between man and women, and also between pre- and post-menopausal women.

Estrogen is thought to play a role in the protection against the development of cerebral aneurysms and has been shown to be associated with the regulation of arterial cell wall matrix, mediation of inflammation, and regulation of proteolytic and apoptotic pathways. The objective of the study is to identify differentially expressed genes in the downstream estrogen receptor pathway that may be associated with development of aneurysms.

Methods

We performed a search of databases of expression array on GEO with keywords "intracranial aneurysm" or "cerebral aneurysm" and limited the search to homo sapiens. We obtained a total of 22 results, each of which was reviewed for eligibility , and a final 6 sets of gene expression microarray data were identified (Fig 1). Data from these six Gene Expression Omnibus (GEO) databases with gene expression profiles of cerebral aneurysm tissue were analyzed (GSE6551, GSE15629, GSE26969, GSE46337, GSE54083, GSE75436). A random-effects model was used for the meta-analysis.

Results

A total of 98 genes were found to be associated with the estrogen receptor signaling pathway, of which 94 were present in all 6 GEO databases. A heatmap of the gene expression of the 94 genes are shown in Figure 2. After multiple-testing adjustment, 4 genes were identified to be significantly associated with intracranial aneurysms, of which two were down-regulated (PIK3R1, fold change [FC] 0.41, FDR=6.1x10-5; ADCY9, FC 0.55, FDR=2.3x10-4), and two were up-regulated (HBEGF FC 1.46, FDR=4.9x10-4; ADCY7 FC 2.11, FDR=6.0x10-3).

Fig 1. GEO expression database selection

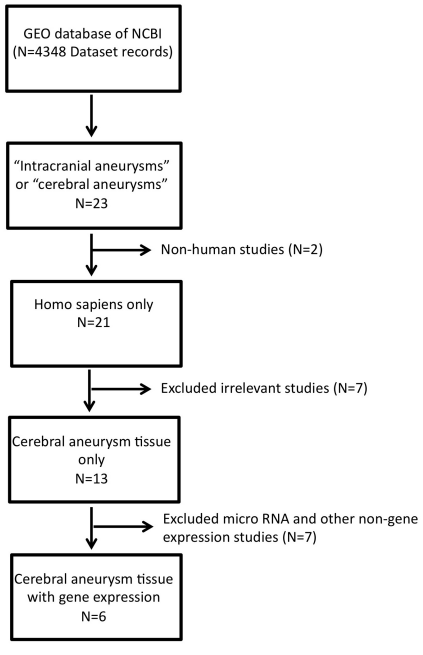
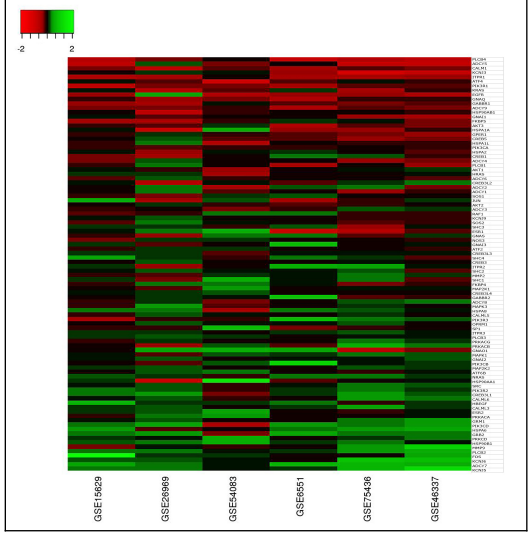


Fig 2. Differentially expressed genes in the estrogen receptor pathway associated with the development of cerebral aneurysms.



Conclusions

In this study, we performed a meta-analysis of gene expression studies to identify potential differentially expressed genes assocated with the estrogen receptor signaling pathway. The analysis of 6 GEO databases revealed four differential expressed genes (PIK3R1, HBEGF, ADCY7, ADCY9) in cerebral aneurysm tissue that are associated with the estrogen receptor pathway. Furthermore, PIK3R1 expression is significantly reduced in sub-group analysis in men and women. Our meta-analysis approach is a preliminary investigation into identification of candidate genes for subsequent study of the estrogen receptor pathway and its association with the development of cerebral aneurysms.

Learning Objectives

By the conclusion of this session, participants should be able to:

1) Understand the estrogen pathway plays a role in the protection against the development of aneurysms

2) Identify downstream genes which may be associated with cerebral aneurysm development

References

1. Lin B, Chen W, Ruan L, et al. Sex differences in aneurysm morphologies and clinical outcomes in ruptured anterior communicating artery aneurysms: a retrospective study. BMJ Open. Apr 15 2016;6(4):e009920.
2. Harrod CG, Batjer HH, Bendok BR. Deficiencies in estrogen-mediated regulation of cerebrovascular homeostasis may contribute to an increased risk of cerebral aneurysm pathogenesis and rupture in menopausal and postmenopausal women. Med Hypotheses. 2006;66(4):736-756.
3. Stober T, Sen S, Anstatt T, Freier G, Schimrigk K. Direct evidence of hypertension and the possible role of post-menopause oestrogen deficiency in the pathogenesis of berry aneurysms. J Neurol. 1985;232(2):67-72.
4. Hamdan A, Barnes J, Mitchell P. Subarachnoid hemorrhage and the female sex: analysis of risk factors, aneurysm characteristics, and outcomes. J Neurosurg. Dec 2014;121(6):1367-1373.
5. Harrod CG, Batjer HH, Bendok BR. Deficiencies in estrogen-mediated regulation of cerebrovascular homeostasis may contribute to an increased risk of cerebral aneurysm pathogenesis and rupture in menopausal and postmenopausal women. Med Hypotheses. 2006;66(4):736-756.
6. Tada Y, Makino H, Furukawa H, et al. Roles of estrogen in the formation of intracranial aneurysms in ovariectomized female mice. Neurosurgery. Dec 2014;75(6):690-695; discussion 695.
7. Crago EA, Sherwood PR, Bender C, Balzer, J, Ren D, Poloyac SM. Plasma Estrogen Levels Are Associated With Severity of Injury and Outcomes After Aneurysmal Subarachnoid Hemorrhage. Biol Res Nurs. Oct 2015;17(5):558-566.