Reviewer's report

Title: The Estrogen Receptor 1 locus associated with migraine susceptibility is restricted to the 3' end of the gene

Version: 2 Date: 17 November 2005

Reviewer: Amanda Shearman

Reviewer's report:

General
The authors previously reported an association of the Estrogen Receptor alpha (ESR1) exon 8 G594A polymorphism and migraine susceptibility in two independent cohorts. Here they report negative results for two further ESR1 polymorphisms: a T/C PvuII polymorphism in intron 1 and the C325G polymorphism in exon 4. The manuscript is well written and carefully presented.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The SNP database contains hundreds of ESR1 SNPs in multiple linkage disequilibrium blocks. Thus the current title and conclusions that migraine susceptibility is restricted to the 3 prime end of the gene should be worded more specifically. The need for studies with a high density of polymorphisms to follow your previous important findings of ESR1 association with migraine might be mentioned. The context of your work/Discussion may be strengthened by consideration of prior reports of the polymorphisms you studied with other phenotypes with established relationships with migraine, for example, estrogen level and stroke (Schuit SC, de Jong FH, Stolk L, Koek WN, van Meurs JB, Schoofs MW, Zillikens MC, Hofman A, van Leeuwen JP, Pols HA, Uitterlinden AG. Estrogen receptor alpha gene polymorphisms are associated with estradiol levels in postmenopausal women. Eur J Endocrinol. 2005;153:327-34; Shearman AM, Cooper JA, Kotwinski PJ, Humphries SE, Mendelsohn ME, Housman DE, Miller GJ. Estrogen Receptor a gene variation and risk of stroke. Stroke 2005, 36:2281-2). You should discuss your ESR1 PvuII CC frequencies, for example, 27% in males with migraine, and 19% in control males, 30 % in migraine without aura (MO) and 20% in migraine with aura (MA). Test specifically for association of PvuII CC with migraine in men. Consider your results in the context of ESR1 variation providing a common basis for the relationship between migraine and stroke.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
None

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Discretionary Revisions (which the author can choose to ignore)
None

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
**Statistical review:** No

**Declaration of competing interests:**

I am an MIT employee. A patent application titled "Estrogen Receptor Alpha Gene Variation and Disease" was filed through the MIT Technology Licensing Office and listed my name among others. I have received no compensation for this. Otherwise I have no competing interests.