Reviewer's report

Title: Epigenetic mechanisms in migraine: a promising avenue?

Version: 1 Date: 28 October 2012

Reviewer: Gretchen E Tietjen

Reviewer's report:

This is a well written concise review of the potential role of epigenetic mechanisms in the pathogenesis and treatment of migraine. It covers an important topic in a complicated, evolving field of research.

Minor essential revisions--

1. There should be consistency in citing references. For some reviews it is cited [reviewed in 18], for other reviews (eg references 20, 21) it is not.

2. In the section of the epigenetic effects of estrogen, it is probably known to most readers that women have much higher prevalence of migraine than men, and that female reproductive hormones likely play a role, but this should be mentioned. Some may know that estrogen lowers the threshold for CSD, and that drops in estrogen (with menses and postpartum) precipitate attacks. Given this, the second paragraph of the section on environmental factors is unclear with regards to the example it gives in FHM mice. It is my understanding that the investigators found that, as with humans, female mice were more susceptible to spreading depression than male mice. This difference was reversed (ie less susceptible, ie increased threshold for CSD induction) if the female mice had their ovaries removed, and then partially restored by replacement of the hormone estrogen (ie. decreased threshold). In the second sentence of the second paragraph under environment factors, eliminate the word “patients” or change to humans.

Discretionary revisions

1. In the first sentence I suggest changing from “1 to 3 day” to “4 to 72 hours”, since many attacks last less than 1 day

2. In the paragraph of early life stress, it suggest mentioning that early life stress also increases risk of developing important migraine comorbidities, such as depression, and of developing alterations in the immune system, such as inflammation, since these are discussed as separate entities in the following sections.

3. Following the section on Genetic risk factors for migraine affecting epigenetic modifications, the concept that heritability of epigenetic changes may potentially extend trans-generationally should be mentioned, especially since genes for the common forms of migraine have been elusive, despite the fact that it is appears
in most cases to be an inherited condition.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no competing interests