Dear sir or madam,

We would be very grateful if you would consider our revised manuscript for publication in *BMC Medical Genetics*. We have addressed all of the reviewers’ comments which are dealt with point-by-point below.

Best wishes,

Yours sincerely,

Adam & Sreeram

Dr. Adam E Handel & Dr. Sreeram V Ramagopalan,
Wellcome Trust Centre for Human Genetics,
University of Oxford,
UK
Reviewer: Greg Singer
Reviewer's report:
Overview:
I enjoyed this brief article very much; although I have been aware of the inheritance of epigenetic traits, I had never put this into the context of Lamarckian evolution, and I believe the authors are correct to do so. I don’t think there is any argument that genetic (i.e., Darwinian) evolution is of greater importance than epigenetic inheritance, but the latter may indeed play an important role and I agree that there are social and medical implications—especially when “the sins of the father are laid upon the children.”
It would have been possible—and perhaps preferable—for the authors to perform a more thorough review of epigenetic inheritance, but I believe the examples they cite are sufficient to make their case.
Minor Essential Revisions:
Abstract: To say that Lamarckian ideas are treated with derision is too strong, in my opinion. Rather, in my experience biologists generally treat Lamarck’s hypothesis as a reasonable one given the limited information he had access to at the time.
We have changed this in accordance with the reviewer’s suggestions.
Background: The authors ought to update their text so that it refers to 2009 rather than to “this year”. In addition, I think to say that Lamarck’s work garners “no praise” is too strong and would prefer the passage to read “little praise”.
We have changed this in accordance with the reviewer’s suggestions.
P. 3: I’m not sure that it’s correct to say that Lamarck’s Philosophie Zoologique was “recently” reviewed by Gould—a man who has been (sadly) dead since 2002. I suppose it’s all relative, but I’d recommend alternative phrasing.
We have duly rephrased this.
P. 6: Spelling error: “conumdra” should be “conundrums”. I agree that “conundra” sounds like it should be right, but the English language is hardly consistent in this respect!
We have corrected this.

Reviewer: Arthur L Beaudet
Reviewer's report:
Discretionary Revisions
This is a relatively concise review of possible roles of epigenetics in human disease. In this regard, it is not novel, but it is reasonably well written. It is difficult to know if the strong link to and defense of Lamarck strengthens or weakens the review, but it does distinguish the emphasis here as contrasted to other reviews.
Other similar reviews are PMID: 20074974 and PMID: 19808797. Perhaps these or similar could be cited.
We have cited the suggested reviews in the body of the manuscript.
The abstract has the following sentence. “These centre on the tendency for complexity to increase in organisms over time and the direct transmission of phenotypic traits from parents to offspring.” The meaning of “These” is not clear. Does it refer to these criticisms?

We have clarified this with the insertion of “theories”.

The following occurs; of C-G dinucleotides. It should be CpG dinucleotides.

We have corrected this.

The following sentence occurs. “It is likely that transgenerational transmission of epigenetic alterations is mediated by small molecules of RNA called microRNA that are capable of inducing sequence specific changes in the epigenome [10].” The nature of this phenomenon is not clear. It may represent a form of RNA inheritance or it may involve a change in chromatin. By Adrian Bird’s definition of epigenetics as involving a change in chromatin, RNA inheritance would not be epigenetics. By other definitions of epigenetics, RNA-mediated inheritance would be included in epigenetics. This sentence should be worded in a way that takes into account that a change in chromatin has not been demonstrated.

MicroRNA is clearly important as a potential mechanism for epigenetic transgenerational transmission but we have emphasised that this has not yet been definitively associated with chromatin modifications.