PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Postnatal epigenetic modification of glucocorticoid receptor gene in preterm infants: a prospective cohort study
AUTHORS	Kantake, Masato; Yoshitake, Hiroshi; Ishikawa, Hitoshi; Araki, Yoshihiko; Shimizu, Toshiaki

VERSION 1 - REVIEW

REVIEWER	Satoshi Kusuda Tokyo Women's Medical University Tokyo Japan
REVIEW RETURNED	02-May-2014

GENERAL COMMENTS	Ref 33 "Matsumoto" should be "Masumoto". This paper describes the epigenetic modification of glucocorticoid receptor in neonates. The discussion are very clear after revision. Furthermore, the results are very interesting. General comments: 1. Abstract This study just showed the difference in an epigenetic modification among the infants after birth. Factors which can explain this difference is not clear yet. It is difficult to indicate the stress as a causal relationship. Furthermore, the implication of the gene modification is not known at the moment. Please change the “Conclusion”. 2. Discussion Please focus on the study results, and limit the speculation on the development of adult diseases. Please mention the limitation of the study, not in “Conclusion”. Minor comments: The change shown in the preterm infants could be seen even in infants who did not need admission in NICU. How to exclude the possibility that these changes came from just evolutionary changes in preterm infants?

REVIEWER	Eleanor Molloy DEpartment of PAediatrics, Trinity College Dublin, Ireland
REVIEW RETURNED	22-May-2014

GENERAL COMMENTS	The authors compare term and preterm methylation rate of the glucocorticoid receptor gene. The differences found between term and preterm infants was associated with “environmental stress”. This is an interesting paper and I have previously reviewed it. The authors have significantly altered and improved their description of the methods especially the clinical definitions. Abstract In the abstract the authors could explain the relevance of glucocorticoid receptor gene polymorphism. Methods What is the definition of “maternal contact”. Although the criteria mention <37weeks for preterms they only used < 35 weeks as a cutoff. Several of the definitions were unconventional including: birth asphyxia Apgar <7 at 5 mins. In addition Late circulatory collapse is not well-recognised and what was the baseline blood pressure. The reference for LCC should be included in methods. The conventional definition of CLD is not usually Xray findings and additional oxygen at 28 days and could the authors reference it. The authors mention that ROP is defined by an oculist but not by conventional definitions. Systemic inflammation needs a definition and reference. 10uL of blood seems a very tiny amount for DNA extraction and further explanation of methods would be helpful. Results: Comments such as preterm infants have significantly lower gestational age and birthweight may be redundant. Table1 : the demographics could be described in the text rather than in a table Table 2: Difficult to interpret and could perhaps be written in text instead Discussion The authors mention an adverse environment but this has not been described earlier. The association with “child maltreatment induced DNA methylation” needs further explanation.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Ref 33 "Matsumoto" should be "Masumoto".
This paper describes the epigenetic modification of glucocorticoid receptor in neonates. The discussion are very clear after revision. Furthermore, the results are very interesting.

Our response:

According to the reviewer's assignment, we have corrected the author's name in Ref 33.

Reviewer: 2

The authors compare term and preterm methylation rate of the glucocorticoid receptor gene. The differences found between term and preterm infants was associated with "environmental stress". This is an interesting paper and I have previously reviewed it. The authors have significantly altered and improved their description of the methods especially the clinical definitions.

Our response: none