Reviewer's report

Title: Global gene expression studies in clonal cell cultures from Rett syndrome females with eight different MECP2 mutationse

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Reviewer: Rudolf Jaenisch

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after discretionary revisions

In this work global gene expression was studied in cloned fibroblasts derived from Rett patients. Using standard test and analysis procedures it was found that the expression of a number of genes was altered in mutant fibroblasts when compared with controls. However, when the authors attempted to confirm the significance of candidate gene dysregulation in multiple and independently derived subclones from the same patient, they failed to find any expression changes that were correlated with the MECP2 mutation. Rather, the expression level of the candidate genes varied considerably within and between mutant and control cells, a result that precluded drawing firm conclusions regarding the role of MECP2 in gene regulation.

Biochemical evidence has implicated MECP2 as a general transcriptional repressor predicting that cells from Rett patients should show derepression of many genes. Indeed, some published data comparing a few brains of patients with unrelated control samples yielded this predicted result. The present work strongly argues that the validity of these conclusions may need to be reassessed. The strength of this work is in the well controlled experimental design: mutant and control clones were derived from the same patient and thus allowed comparison of multiple genetically identical samples that differed solely in their MECP2 genotype. Furthermore, the gene chip based expression data were confirmed by quantitative RT-PCR analyses. The study raises two cautions regarding the interpretation of global expression analyses: (i) Sufficient data points need to be included in any analysis to reach significance. This has not been the case in some published results that detected "significant" changes in Rett tissues. (ii) Cloned cells may alter gene expression levels as a consequence of tissue culture and may, therefore, not be a good source for such analyses. In any case, the present results do not provide support for the current model of MECP2 action. They raise the possibility that either other methyl-binding proteins compensate for the loss of MECP2 or that current models need to be revised.

Rett syndrome is a complex and important disease and little progress has been made as to understand its molecular basis. The data in this manuscript serve as a caution against uncritical interpretation of expression profiling. Although the results are essentially negative I strongly recommend publication in BMC Medical Genetics as they will stimulate new experimental approaches.
Competing interests:
None declared.