Reviewer's report

Title: Homozygosity for a mis-sense mutation in the 67kDa isoform of glutamate decarboxylase in a family with autosomal recessive spastic cerebral palsy: parallels with Stiff-Person Syndrome and other movement disorders.

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Reviewer: lisbeth tranebjaerg

Reviewer's report:

General

The paper describes the possibility for a newly detected missense mutation in GAD-1 gene, which occurs in homozygosity to be the genetic cause of CP in two Pakistani families with CP. This work follows the mapping of the disease locus as reported by some of the present authors in AJHG 1999 by Hale et al to 2q24. The paper describes the narrowing of the locus to 0,5 cM and the investigation of the most attractive candidate gene, GAD-1 , in this region. The paper is clearly written with an extensive interesting discussion and well documented methods, and references.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The most critical problem with the results is that the lack of demonstration of frameshift mutation predicted to lead to truncated protein (in other unrelated patients/families), and the lack of in vitro assays to detect the possible functional deleterious consequences of this missense mutation cannot be considered a direct proof of this sequence variation to be the cause of the disease. As the authors point out, a more complicated genetic mechanism may be in action and it may turn out to be very difficult to show the subtle steps in this underlying mechanism. The authors would have a much stronger case if the reported the planned transfection studies in neuronal cells in their report. Until they in some other way can more specifically correlate the sequence change to a functional change, it remains an association which deserves attention for possibly being the cause.

In the paper, they explain in too little details the findings in the two families. On page 9, they say (surprisingly in the light of the AR nature of the disorder) that they found no obligate carriers to be heterozygous for this missense mutation, and on page 15 they say oppositely that the mutation segregated with AR CP in 4 affected children.

They should describe which family members were actually sequenced and give the full results , and it would be expected that parents and some sibs would turn out to be carriers due to the autosomal recessive inheritance. In the light of the present state of the uncertain causal relationship of the findings, however attractive they seem , and however interesting their review-like long discussion is, that the paper could be shortened considerably.

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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)

Errors to be corrected: the numbering of the figures and tables do not fit with the legends for those. This is a source of confusion for the reader.

Dispositionary Revisions (which the author can choose to ignore)