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.

**Version:** 1  Date: 30 June 2004

**Reviewer:** Hans-Michael Meinck

### Reviewer's report:

**General**

This interesting paper presents evidence that a missense mutation of the gene encoding GAD67 segregates with a form of familial spastic paraplegia with an autosomal recessive trait. As a clinician and neurophysiologist, I will not discuss the methods and results. I have, however, the following questions and comments:

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

Abstract (Conclusions section): What are the exact neurological sequelae of circulating anti-GAD-Abs? As to my knowledge, this issue is a matter of hypotheses and speculations. Do the authors mean that GAD has neuroprotective effects by reducing the level of the excitatory neurotransmitter glutamate? I regard such a wide-ranging hypothesis as beyond the scopes of this communication.

Background (first line): The term CP is used for a certain group of disorders that affect the brain, not the nervous system as a whole.

Methods (Features and Pedigrees section): Information on the clinical syndrome is scanty. More details on the neurological and mental status and the course (progressive?) are requested. On p 13 (2nd paragraph) epilepsy is stated to occur in both pedigrees, please specify. Do the affected individuals have abnormal startle? MRI and EEG studies would be informative to the reader.

Discussion (p 13, 2nd paragraph). Please specify the type of epilepsy.

(p. 14, top paragraph): Clinically, SPS is by no means similar to spastic CP, "continuous contraction...involuntary alpha motor unit firing at rest" is not an electrophysiological sign of spasticity.

(p. 14, 2nd paragraph): Hyperekplexia by no means has a pathophysiology similar to spastic CP. It is, moreover, not clear whether SPS "arises as a result of autoantibodies" against GAD or gephyrin (or amphiphysin), or is associated with these autoantibodies as an epiphenomenon.

**Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**

Abstract (Methods section): Glutamate is both an amino acid and a neurotransmitter. I guess that it is not the neurotransmitter, but the amino acid that is converted into GABA (see also p 11, 3rd paragraph line 3).

Abstract (Results section): "Auto-antibodies ... Batten disease" is no result.

**Discretionary Revisions (which the author can choose to ignore)**
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

None