Reviewer's report

Title: Systematic mutation analysis of KIAA0767 and KIAA1646 in chromosome 22q-linked periodic catatonia

Version: 1 Date: 17 July 2005

Reviewer: George Kirov

Reviewer's report:

General
The authors present results on their systematic screen of candidate genes in a linkage region of periodic catatonia. This is a sub-type of schizophrenia described by Leonhard and is one of the more easily recognised Leonhardian subtypes, which has also shown to have a dominant transmission. The authors have been recruiting families with periodic catatonia for years and have no doubt accumulated the largest such collection in the world. Even for psychiatrists who are not familiar with Leonhard’s classification, this still represents a valid collection of families affected with catatonic schizophrenia, and I am not aware of any other similar collection. As these families showed positive lod-scores in two samples, the community of psychiatric geneticists have been interested in the results of this group for some time.

The paper is generally well written and clear. It is unfortunate that the authors have not found the causative mutations in their linkage regions. The paper is however a useful update on the work of this group and shows the readers some of the difficulties in finding genes for psychiatric disorders, even when a clear phenotype and large multiply affected families are available.

I have only a few minor points that could make things clearer to the readers. (under Minor Essential Revisions)

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
none

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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)
I would like to see a bit more information as to why a mutation at MLC1 is now considered excluded. We now know that mutations at this gene cause megalencephalic leukoencephalopathy with subcortical cysts, but this does not yet completely exclude the possibility that other mutations in this gene cannot cause a different phenotype. If the authors can provide any new information, they should do this, or at least they can provide the readers with their reasoning for confidently excluding this gene. In this context the authors should cite the article by Meyer et al. A missense mutation in a novel gene encoding a putative cation channel is associated with catatonic schizophrenia in a large pedigree. Mol Psychiatry. 2001 May;6(3):302-6. This is the paper that originally reported that mutation, although at that time the link with megalencephalic leukoencephalopathy was not yet known. This will help the readers follow better the whole story, which deserves more than a single sentence. Many groups tried to replicate this finding at the time, at least one of them (Devaney et al 2002) published their results, perhaps these negative findings could also be cited here.
In the supplementary table the positions of the SNPs are given according to NT_011523.1. These are the same positions as given by the UCSC Genome Browser May 2004 Assembly. It will avoid some confusion if in the legend to the table the authors state that the position is according to that assembly (http://www.genome.ucsc.edu/) although both are correct. The tables could also be slightly simplified. The last column contains on each line the numbers of the 4 linked pedigrees. It might look better to make one column for the genotype of the individual from each family, including one for the control. This adds columns but the overall text in the table will be smaller, and I think, a bit clearer.

Finally some minor stylistic comments:
Page 5 the sentence “…were already not deposited in current databases…”, should read “were not yet deposited…”

P7: the sentence “…both were neither found segregating…” should read “…neither were found to segregate…”

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential 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:
I declare that I have no competing interests