Reviewer’s report

Title: Breakpoint Associated with a novel 2.3 Mb deletion in the VCFS region of 22q11 and the role of Alu (SINE) in recurring microdeletions.

Version: 1 Date: 17 September 2005

Reviewer: Carrie Bearden

Reviewer’s report:

General
This is an interesting manuscript reporting a novel 2.3 Mb deletion in the DGS/VCFS region in a patient diagnosed with early onset schizophrenia. The authors find that molecular characterization of the sequences in this patient revealed a shared an Alu like sequence of breakpoint regions common to both ends. The authors conclude that this sequence may represent a preferred sequence in the breakpoint regions or LCRs for intra-chromosomal homologous recombination mechanisms, which may result in increased susceptibility of this portion of the chromosome to rearrangements and deletions. However, there are many points of clarification that are needed, particularly with regard to the study goals and hypotheses.

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

While the finding appears interesting, the study goals are not clear from the Introduction or Methods of the paper. It appears that this started out as a study to characterize a large sample of patients, but ended up being a case report. This confusion is evident in the Methods, in which it says that “this report deals with a survey of 379 patients;” but in reality the manuscript only discusses the results for 1 patient.

In addition, while genotyping methods appear adequate, characterization of the sample is particularly lacking here. How was the patient sample ascertained? In particular, what is meant by “patients with suspected schizophrenia?” On what basis was schizophrenia suspected? Given that the authors also mention that these patients had MPA’s, I wonder if they mean that they were schizophrenia patients with suspected chromosomal abnormalities. Also in some places it says ‘suspected schizophrenia’ and other places it says simply “schizophrenia”. Did all the patients who were interviewed meet criteria for schizophrenia? What structured clinical interview was used and who conducted these interviews? I am not sure that this information on the full sample is critical for the major points of the manuscript, which relate only to the single case study. This brings me back to the original point, that the study goals are not adequately characterized.

On p. 7, the authors that their analysis established that “the frequency of the deletion in such a selected population… approximates 11%”. This is not informative without further information regarding the manner in which the sample was selected and ascertained.

The next sentence (“It is worth noting that 30 of the 41 patients showing the deletion were young (<18)" is also not informative without further description about the sample ascertainment. Why is it interesting that the patients with the deletion are young? Were they younger than the patients without the deletion?

In addition, on p. 10 the authors describe the sample as “a population survey of 379 patients …” This would not appear to be an accurate description of the sample.
Also on p. 10 the authors report that they have “identified 1 patient with early onset schizophrenia. Although this represents a frequency of schizophrenia in the del22q11 of only 2.5% this number must be viewed as an underestimate”. The logic of this sentence is totally baffling to me, as earlier in the manuscript, it was stated that the entire sample of 379 patients was selected due to having a diagnosis or “suspected diagnosis” of schizophrenia. In addition, the statement that “the results support a role for 22q11 region in the development of schizophrenia” does not follow from the results as currently described – these results really do not address the role of the deletion in the development of schizophrenia or other psychopathology.

While the patient with this novel deletion is described as having “early onset schizophrenia,” more description about the clinical phenotype of this patient would make this a much more interesting manuscript. Did the patient show characteristic facial morphology and other developmental anomalies associated with 22q11.2 deletions? Without this information the significance of these findings is uncertain.

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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)

Perhaps because English is not the authors’ native language, there are several grammatical and syntactic errors in the manuscript. I would highly recommend that the authors ask a native English speaker to assist with style and grammar editing, in order to improve the clarity of their manuscript.

In the Background, the authors state that “the 22q11.2 region is a hotspot for rearrangements by deletions … with an occurrence rate of 1 in every 4000 live births”. It was my understanding that VCFS, or 22q11.2 Deletion Syndrome (resulting from hemizygous 22q11.2 deletion) alone has an occurrence rate of about 1 in 4000 live births, not including other disorders that may result from chromosomal abnormalities of this region. Please clarify.

It is also not clear whether detailed sequencing of the breakpoints was conducted on all 41 of the deleted patients in the current sample, or only on a few of the patients in the sample. This is important because if it was only conducted on a small proportion of the sample, it is not clear how novel this particular 2.3 Mb deletion is. Perhaps others in the sample had a similar rare form of the deletion.

“A re-assessment of the 41 patients with deletion at 22q11 region identified one unusual patient … with a confirmed diagnosis of early onset schizophrenia.”

This sentence warrants several clarifications. What kind of ‘re-assessment’ was done? On what basis was this patient identified as being “unusual”? And also, how was the diagnosis of early onset schizophrenia made?

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Discretionary Revisions (which the author can choose to ignore)

On p. 3, it would be helpful for the authors to define the differences between SINE and LINE elements, and also to better define Alu elements.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests