Reviewer's report

Title: A missense founder mutation in VLDLR is associated with Dysequilibrium Syndrome without the quadrupedal locomotion

Version: 2 Date: 16 April 2012

Reviewer: Jillian Parboosingh

Reviewer's report:

Dysequilibrium syndrome (DES) resulting from mutations in VLDLR (DES-VLDLR) is a rare genetic disorder with only six families and patients in the Hutterite population being described in the literature. Consequently few mutations have been identified. This paper describes the presence of a homozygous novel missense VLDLR mutation in two families of Omani descent with clinical features consistent with DES-VLDLR. This is the first report of homozygosity for a missense mutation. Pathogenicity is assumed based on its conservation of the amino acid, in silico prediction programs, its predicted role in disulfide bonding and thus likelihood of resulting in a misfolded protein, and absence from in-house exome databases. In addition, the authors claim to have expanded the phenotype associated with DES, however it is up to the reader to discern this as the authors indicate “all affected children in this report had typical features of this disorder”. They provide a comprehensive summary of all the reported cases to date which highlights the similarities of their patients and the other cases. The only difference as indicated by this table being the lack of speech. The authors did not emphasize or discuss this additional clinical feature leaving the reader wondering about the conclusion. The title of this paper indicates the finding of a founder mutation. The identification of the same mutation in two families with no known relationship both of Omani descent is suggestive of a founder mutation.

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

1) The title indicates that a founder mutation has been identified. If the authors have identified a shared haplotype to support this claim, they are encouraged to report it. Otherwise, the title should reflect the lack of certainty – “potential founder mutation”.

2) The authors need to make explicit and discuss how the patients described in this manuscript expand the phenotype.

3) The abstract states that “massive parallel sequencing in patients from two unrelated consanguineous families” was used. However two methods were described in the Materials and Methods section: homozygosity mapping followed by candidate gene analysis and sequencing was used to identify the mutation in family 1; exome sequencing was used for family 2. The abstract should be changed to reflect methods used.
4) In the Materials and Methods section, the individual(s) from family 1 who were genotyped and sequenced should be indicated.

5) In the Materials and Methods section DNA methodologies, the authors indicate that for family 2, variants identified in the exome were “intersected with identity-by-descent blocks identified by HomozygosityMapper”. Clarification of whether the exome variants were used as input into the software or prior SNP genotyping performed is needed.

6) Mutation nomenclature used is inconsistent and does not reflect current guidelines (http://www.hgvs.org/mutnomen/). The mutation found should be described as c.2117G>T at the nucleotide level. Other mutations have also been incorrectly described, such as c.1342C.T. Some mutations described at the protein level are lacking the “p.” The RefSeq accession number used to describe the mutation should be listed. The methods section describes sequencing a 17 exon gene yet the longest VLDLR transcript is 19 exons (NM_003383.3). This may be a typographical error but if not, the authors should confirm that the previously reported mutations listed in the paper are consistent with this transcript.

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

1) References should reflect the BMC Medical Genetics reference style.

2) All genes should be italicized.

3) In the background section of the Abstract, “disequilibrium” should be replaced with “dysequilibrium”.

4) On page 6, under the heading “Identification of a pathogenic missense mutation”, the term “freeze” half way down the paragraph to describe the hg19 build should be replaced with “build”. In the same paragraph, the term “transversion” is incorrectly used as it applies only to the nucleotide change and not the amino acid substitution. Suggested change “This alteration resulted in a c.2117G>T nucleotide change and a p.C706F amino acid substitution”.

5) Throughout there are grammatical errors. While the message is conveyed, it would be improved, by having someone for whom English is his/her first language edit it.

6) On page 6 in the “Discussion”, the opening brackets are missing for references 6, 10, 11.

7) In the final paragraph of the “Discussion”, the word “seizures” is incorrectly spelled (seizers).

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

None.

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

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.