Reviewer's report

Title: Atypical X-linked Agammaglobulinemia caused by a Novel BTK Mutation in a selective IgM Deficiency Patient.

Version: 3 Date: 12 July 2013

Reviewer: Leopoldo Santos-Argumedo

Reviewer's report:

The phenotype of the case presented in this article is very interesting because it is a selective IgM deficiency with normal levels of IgG and IgA. In addition, the patient presented autoimmunity, described as "Lupus-like Nephritis" in the abstract (which is not described as such in the rest of the manuscript). The authors detected immune complexes in a kidney biopsy, and the patient was treated with several immunosuppressive drugs, apparently succeeding with mycophenolate to treat the autoimmunity.

The manuscript describes a clinical phenotype that is totally different from what is known of XLA. The only data that correlates with XLA is the low proportion of B cells in peripheral blood; however, other humoral deficiencies (such as common variable immunodeficiency) can be also manifested with low levels of B cells. The incidence of autoimmunity in XLA is very low, and rheumatoid arthritis is the autoimmune manifestation most often associated with XLA. The description of Lupus-like phenotype is very interesting and I may recommend its publication. Unfortunately for the authors, this "mutation" has not been described by any other group, what remains to be determined without a doubt is whether this is actually a pathological mutation and not a polymorphism. There is no additional data that support the idea that this mutation affects the expression of Btk in mononuclear cells from the patients, or perhaps there is no information about the functionality of mutated BTK, assessed for example as alteration in the phosphorylation (tyrosine 223) in monocytes after activating via TLRs. Any of these data, or even better, both of them, could contribute to the hypothesis that the genetic change found is actually a mutation affecting the expression and/or activation of Btk and therefore its functionality.

Moreover, few studies have also shown decreased levels of IgM, with normal IgG; for example, a paper from Basile N., et al (J Clin Immunol (2009) 29:123–129) describes a patient (#12) from a cohort of 49 XLA patients, having normal levels of IgG with decrease in IgM. However, the mutation found in this patient is very frequent in XLA and this patient does not have autoimmunity. In summary, it seems to me that this very interesting clinical phenotype must be accompanied by a clear demonstration of loss of function of Btk in order to sustain the finding.

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

Quality of written English: Acceptable

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