Reviewer’s report

Title: A novel Bruton’s tyrosine kinase gene (BTK) missense mutation in a Chinese family with X-linked agammaglobulinemia

Version: 2
Date: 28 June 2014

Reviewer: Pamela Lee

Reviewer’s report:

The authors reported a case of XLA with classical presentation. The case is straightforward without diagnostic issues. A novel BTK mutation was identified and its pathogenicity is analyzed by bioinformatics tools.

Minor Essential Revisions
1. BTK, when referring to the gene, should be in italics
2. Page 2, line 43: ‘that’ is duplicated
3. Page 3, line 58: ‘increased transparency of the bilateral lobes’ - authors please specify the finding with standard radiological term
4. Page 3, line 59: should be Streptococcus pneumoniae in italics
5. Page 3, line 61: lymphadenectasis should either be replaced by lymphadenopathy or lymphadenitis, whichever is appropriate
6. Page 3, line 66: the abbreviations of blood biochemistry are not standard and should be given in full (HBDH, TP, A, G)
7. Page 3, line 68: give reference range for ferritin
8. Page 3, line 72: delete the word ‘suspected’
9. Page 3, line 86: the affected family member is a cousin, not a sibling according to the family tree. And the individuals in the family tree should be labelled with the corresponding number in each generation (I, II, III)
10. Page 5, line 114: specify incidence as live births or live male births
11. Page 5, line 128: specify unit of molecular mass. The standard unit is kilodalton (kDa)

Discretionary Revisions
1. Page 2, line 34: ‘The incidence of XLA is the highest among the PIDs’ - this is probably not true, now with universal newborn screening for SCID the collective incidence of SCID probably exceeds that of XLA. This piece of information is not essential to this report and can be omitted.
2. Screening of BTK mutation for the patient’s family members was performed and male relative (III-2) was found to be affected. Is he symptomatic? How old is this relative (cousin) when BTK mutation was found? What is his immunological profile (Ig G/A/M, % B-cells)? It would be interesting if this cousin has mild or
relatively milder symptoms so that he was not previously investigated, and adds importance to genetic confirmation of BTK mutation in family screening and diagnosis of affected family members.

3. The administration of IVIG described by the authors is suboptimal for the management of patients with XLA. IVIG is recommended to be given 3-4 weekly, and dosage should be adjusted according to the trough level and clinical symptoms.

Reference: Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, J Allergy Clin Immunol 2006;117: S525-53

4 The most comprehensive database for BTK gene variations is the BTKbase, Version 8.53 last updated 17 June, 2013 contains 1254 public entries. This should be mentioned in addition to Human Gene Mutation Database.

http://structure.bmc.lu.se/idbase/BTKbase/index.php?content=index/IDbases

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.

Declaration of competing interests:

I declare that I have no competing interests