Author’s response to reviews

Title: IKZF1 Genetic variants rs4132601 and rs11978267 and Acute Lymphoblastic Leukemia Risk in Tunisian children: a case-control study

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Author’s response to reviews:

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Editor-in-Chief
BMC Medical Genetics

Dear Editor,

Please find attached a revised version of the manuscript entitled:

Association of IKZF1 gene polymorphisms rs4132601 T/G and rs11978267 A/G with Acute Lymphoblastic Leukemia in a Tunisian paediatric cohort: a case-control study
By Sana Mahjoub, Vera Chayeb, Hedia Zitouni, Rabeb El Ghali, Haifa Regaieg, Wassim Y. Almawi, Touhami Mahjoub (Touhami Mahjoub, senior and corresponding author), which we submit for consideration for publication in BMC Medical Genetics, after having addressed the reviewers’ comments. Attached also is our point-by-point response to the reviewers’ comments. To facilitate the reviewing process, all changes made were marked in red.

None of the authors has any potential financial conflict of interest related to this manuscript

All authors have carefully examined and approved the changes made to the manuscript, and understand and accept that in the event of its publication, all copyright shall be transferred to BMC Medical Genetics. The manuscript is not currently under consideration/review by another journal. Please address all correspondence pertaining to the manuscript to the senior author, Dr. T. Mahjoub, at the address shown below. We look forward to hear from you in due course.

Sincerely,

MGTC-D-19-00191

RESPONSE TO REVIEWERS’ COMMENTS

Reviewer: 1. Title: term "association" seems not represent your research design (case-control). Case control study usually is done to seek the risk (Odd Ratio) not association study design, consider your conclusion. Please revise your title and incorporate your aim of study throughout your manuscript.

Authors: Will do.

Changes: The title has been altered to « Genetic variants of IKZF1 rs4132601 and rs11978267 and risk of Acute Lymphoblastic Leukemia in Tunisian children: a case-control study". 
Reviewer: 2. Abstract conclusion: Please revise with more assertive words such as "IKZF1 gene polymorphisms rs4132601 T/G and rs11978267 A/G are the risk factor of ALL in a Tunisian paediatric cohort"

Authors: Answer: It was done in the texte.

Changes: The Abstract was re-written, in light of the Reviewer’s comment. (from line 19 to line 45)

Reviewer: 3. How to write human gene name: please using italic style for human gene name (IKZF1 gene), revise it.

Authors: Will do.

Changes: The italic designation of the gene (IKZF1) was done for throughout the text.

Section Result ; Abstract : line 19
Section Background : line 30 ; 45 ;48
Section SNPgenotyping : line 45
Section Association Studies : line 4, 7
Section Correlation Studies : line 49
Section Haplotypes Analysis : line 10
Section Discussion : page1 Line 53, 58, 60 ; page2 line 38 ; 50 ; page 3 line 32 ; 45 page 4 line 30,34,40

Reviewer: 4. All abbreviation should be spell out in the first appearance. Example: Hardy Weinberg Equilibrium (HWE).

Authors: Noted.

Changes: It was done in the section abbreviations.

Section Statical Analysis : line 30 ; line 35
Reviewer: 5. Background: a. "...genetic etiology dominates in younger age due to lower exposure environmental factors compared to adult". How can you so sure about the less exposure in younger age? How about if they live in very bad environment? Cancer in younger age usually due to germline/inherited genetic susceptibility (risk factor).

Authors: Will do.

Changes: As young subjects are less likely to be exposed to environmental factors, this was not part of our results, but was reported elsewhere in literature (see references 13, 24 and 26).

Reviewer: 5. Background. b. "The heritable susceptibility to ALL is proved proven".

Authors: This was altered with the editing of the manuscript.

Changes: Not applicable.

Reviewer: Background. c. IKAROS is a potential regulator of lymphocyte and differentiation (17), and immune system development. Please be aware of punctuation in scientific article, review throughout your manuscript. See also in your Method subtitle Subjects: ...cytochemical reactions (myeloperoxidase form ALM and esterase for ALL).(, space) immunophenotyping 2.2. SNP Genotyping (enter into new paragraph) Total genomic DNA was...

Authors: Will do.

Changes: Appropriate modifications were made in the text.

Reviewer: 6. Grammar/syntax error: this study has already been done a while ago. Please read carefully especially your method and result, and revise accordingly. Example: ...we have collected we had collected; ...ALL classification is (was) made; The guardian of both patients and controls of all participants/subjects are (were) informed; Data is was performing...; Total genomic DNA was isolated in (??) from...; Immunophenotyping is done Immunophenotyping was done....

Authors: Noted.

Changes: Grammar/syntax errors were noted and corrected in the revised text.

Section Methods: line 5 (we collected) ; line 8 (were identified)

Section Association Studies: line 40 (there were no significant association....)
Reviewer: 7. SNP Genotyping: "genotyping of both rs4132601 and rs1197867 were missed for 3 and 17 respectively". I do not get you idea. What are going to say? Are those from cases and control or what? Did they finally excluded?

Authors: What we meant was: Genotyping of both rs4132601 (3 subjects) and rs11978267 (17 patients) could not be performed because of poor DNA quality.

Changes: Appropriate modifications per the Reviewer’s comment were made in the text.

Reviewer: 8. Association Study:...minor allele frequencies were at the limit of significancy (P=0.086). I do not think we can say limit of significancy, we should say not significantly associated.

Authors: True as stated by the Reviewer.

Changes: Appropriate changes were made in the Abstract and Results sections per the Reviewer’s comment.

Reviewer: 9. Table 1. Note: bold types are indicates significant association p> 0.05 (p value < 0.05 considered as significant association was stated in your statistical analysis).

Authors: Yes, it was a typographical error.

Changes: The typographical error in Table 1 was amended.

WBC (Cases: 69.31 ± 57.7)

Reviewer: 10. There is discrepancy between abstract and result (haplotype analysis) of GA haplotype analysis values (p values, OR and 95%CI). Which one is correct? Be careful with number.

Authors: Will do.

Changes: Association of 2-locus haplotypes with ALL risk was adjusted in Abstract and Results sections.
Reviewer: 11. Page 10 line 5: ..... (??) leukemia (MLL). Typo?? review throughout your manuscript. Leukemia (MLL) gene rearrangements in their leukemia cells, is with poor prognostic [42] in both ALL and AML infant cases.

Authors: MLL (Mixed Lineage Leukemia) is distinct from ALL.

Changes: None for now.

Reviewer 2:

Reviewer 1. Faculty of Medecine Ibn Jazzar, University of Sousse, Sousse, Tunisia
Authors Will do
Change Hematology Department; Faculty of Medecine Ibn Jazzar University of Sousse, Tunisia.

Reviewer: 2. could you explain this number of patients regarding your statement that there was 25 new ALL diagnosed in Tunisia. During this period of the study, shoud be around 125 patients.

Authors 25 new ALL diagnosed in Tunisia, this was not part of our results, but was reported elsewhere in literature.

Reviewer 3. if this number of patients meets the number needed for analyzing

Authors NO; 125 is the number of patients with ALL type B. Genotyping of both rs4132601 (3 subjects of 170) and rs11978267 (17 patientsof 170) could not be performed because of poor DNA quality. (see the text)

Authors I declare that I have no competing interests