Author’s response to reviews

Title: f-treeGC: A questionnaire-based family tree-creation software for genetic counseling and genome cohort studies

Authors:
Tomoharu Tokutomi (tktmtnhr@iwate-med.ac.jp)
Akimune Fukushima (akimunef@iwate-med.ac.jp)
Kayono Yamamoto (kyamamot@iwate-med.ac.jp)
Yasushi Bansho (bansho@holonic-systems.com)
Tsuyoshi Hachiya (thachiya@iwate-med.ac.jp)
Atsushi Shimizu (ashimizu@iwate-med.ac.jp)

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Author’s response to reviews:
Matteo Pasini, Ph.D.
Editor-in-Chief
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Subject: Submission of revised manuscript, reference ID MGTC-D-16-00303R2

Dear Dr. Pasini,

Thank you very much for your review of our manuscript entitled “f-treeGC: A questionnaire-based family tree-creation software system for use in genetic counseling and genome cohort studies” by T. Tokutomi et al. (ID MGTC-D-16-00303R2).
The reviewers’ comments were constructive and helpful. We have considered each of their comments carefully and revised our manuscript accordingly. Please find enclosed our revised manuscript. The major changes include modification of the comparison of the pedigree symbols used and addition of verification of the software and the interview sheet. Other corrections are listed in the attached letter.

We hope that you will find this revised manuscript satisfactory.

Yours sincerely,

Akimune Fukushima, MD., Ph.D.
Department of Clinical Genetics, School of Medicine, Iwate Medical University
19-1 Uchimaru, Morioka, Iwate 020-8505, Japan
Tel: +81-19-651-5111
Fax: +81-19-907-3711
E-mail: akimunef@iwate-med.ac.jp

Response to Reviewer 1

Dear Dr. Wei-Min Chen,

Thank you for your comments. We have modified our manuscript according to your suggestion, as follows:

#1. The major weakness of this manuscript is the authors failed to show in a more rigorous way the exact differences/advantages between this software and other pedigree drawing tools. What are the main advantages? The only comparison appears in the DISCUSSION section, instead of RESULT section which is more standard. For the comparisons, the authors imply existing pedigree drawing software tools 1) require specialized knowledge of clinical genetics 2) are not fully compliant with international recommendations 3) do not automatically draw pedigrees based on questionnaires 4) are not for multiple families. Is it true that all three existing software tools are so bad? I think this kind of comparison is not rigorous and quite likely the statements are false. Please be more detailed on the comparison. A peer reviewed manuscript should be more than a user manual.
We agree with this criticism. We have focused on the comparison of the pedigree symbols used objectively and added this to the Results section (page 13, line 216, Table 2); further, we have clarified the section describing the main advantages of this software (page 32, line 336).

#2. Several references have a non-standard format. It's likely those software tools have their associated manuscripts for the purpose of citation.

Thank you for your pointing out this lapse in formatting. We have changed the citation format of these software tools to that of the GA4GH family history tools catalog.

Response to Reviewer 2

Dear Dr. Lori Ann Orlando,

Thank you for your comments. We have modified our manuscript according to your suggestions, as follows:

#1. If you are limited to only 4 medical conditions per person how can this be enough data to adequately link to genomic information for analyses? In most countries the average number of medical problems (except for the very young) exceed 4. Is this different for your country? If so please provide data to support that. Even in this case it would limit the usefulness of the tool to your country.

We agree with this criticism. We have changed this to 16 medical conditions per person (page 10, line 171). Of course, 16 conditions are also not sufficient; however, this is now comparable with the 16 diseases/conditions offered by the My Family Health Portrait tool.

#2. How can the data be analyzed in relationship to genomic data if it is not codified in some way. It seems from the description that the problems are entered as free text. That creates problems with analysis as chronic kidney disease could be entered in any number of different manner making it practically impossible to evaluate across individuals what conditions are present and compare to genome findings across populations. There are any number of data standards that could be used to help resolve this issue or you could use drop down lists to prevent items from being coded differently. Other solutions exist but I think if you want to say that this tool will facilitate large scale genome studies this has to be addressed.
Thank you for your suggestion. The purpose of using f-treeGC in genome cohort studies for the biobank is to accurately and rapidly collect genealogical information and create pedigree charts, and subsequently facilitate screening of families. We have changed the medical conditions per person from 4 to 16 (page 11, line 174). In the future, we aim to add a search function for family health conditions from free text using Human Phenotype Ontology or artificial intelligence.

#3. Address the question of patient lack of knowledge regarding their family history. If the data is collected at the point of care without any guidance to patients about talking with relatives and what type of information they should ask about- the amount and accuracy of the family history is limited. This should be addressed - by further developing the tool or by listing it as a limitation as it is a huge barrier to the quality of family history data.

We agree with this criticism. We have mentioned this limitation and introduced a section describing our efforts at generating public awareness regarding the knowledge of one’s family health history through a genetics workshop mentored by medical geneticists or genetic counselors. This workshop is held before recruiting participants for the cohort study of the Tohoku Medical Megabank project (page 30, line 303).

#4. The authors however make significant claims about the accuracy and the facile nature of the tool without providing any data to support their statement. The manuscript guidelines for software recommend comparison to existing tools and I would strongly urge that this the tool be evaluated in a way that allows comparison of the features to existing tools. Even without a direct comparison some metrics regarding the tool could be provided.

We agree with this criticism. We have focused on the comparison of the pedigree symbols used objectively and added this to the Results section (page 13, line 216, Table 2); further, we have clarified the section describing the main advantages of this software (page 32, line 336).

#5. Who has used the tool? Where has it been implemented? How many patient's histories have been collected with it? How much data was collected? How long did it take (mean and range) to collect the data in clinical setting?

Thank you for your extremely relevant questions. The targeted clinical populations are users of primary and specialty health care facilities. f-treeGC may be used for collecting family health histories and creating pedigrees for individuals participating in primary care programs, genetic counseling, or genome cohort studies (page 29, line 285). We used f-treeGC for genetic counseling carried out at our institution, collecting approximately 100 patient histories and corresponding data, which would take around twenty minutes when performed by a genetic
counselor in a clinical setting. In contrast, the present software took about one minute per person to input two clinical scenarios during the verification experiment (N = 56) (page 21, line 238; Table 4; page 31, line 327).