Author’s response to reviews

Title: Prevalence of Clinically Actionable Disease Variants in Exceptionally Long-Lived Families

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Author’s response to reviews:

We thank the reviewers and the editor for their review of the manuscript. Please find below a point-by-point response to all the reviewer and editorial comments.

Editorial Comments:

1 - Please include a Conclusions heading for the Conclusions section.
Response: We have added a Conclusions heading for the Conclusions section in the main manuscript.

2 - Please provide a list of all the abbreviations used in the manuscript. This list should be placed just before the Declarations section. All abbreviations should still be defined in the text at first use.
Response: We have now provided a list of all the abbreviations used in the manuscript.
3 - In the Funding section of the Declarations please indicate the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. If no specific funding was received for this study, please clearly indicate this in the Funding section.

Response: We have included a statement about the role of the funding body in the study design and writing the manuscript.

4 - Please include a statement in the Authors’ contributions section to the effect that all authors have read and approved the manuscript, and ensure that this is the case.

Response: We have now included a statement in the Authors’ contribution section that states that all authors have read and approved the manuscript.

5 - Please include an Acknowledgements section in the Declarations.

Response: We have included an Acknowledgements section in the Declarations.

6 - At this stage, please upload your proofread manuscript as a single, final, clean version that does not contain any tracked changes, comments, highlights, strikethrough or text in different colours. All relevant tables/figures/additional files should also be clean versions. Figures (and additional files) should remain uploaded as separate files. Please ensure that all figures, tables and additional/supplementary files are cited within the text. Should you wish to respond to these revision requests, please include the information in the designated input box only.

Response: We have uploaded a single, final, clean version without any track changes or text in different colours.
Reviewer reports:

Chang Zeng (Reviewer 1):

Paige Carlson and colleagues report on utilizing data from LLFS to evaluate the prevalence of pathogenic variants associated with Mendelian-inherited disorders and compare the allele frequencies with that from public databases.

The authors may want to consider the following aspects:

1. Because this study primarily focuses on Caucasian population, it would be helpful to provide the demographic and clinical features of the general population in public databases (age, gender, ethnicity and disease history etc.)?

Response: We have included the details of the gnomAD databases as requested by the reviewer. However, since data on age of the participants in gnomAD is available only for a subset of participants (https://gnomad.broadinstitute.org/faq), we did not include information on the age distribution in the revised manuscript.

The revised “Variant Classification” section includes the following sentences with the new information: “The prevalence of the annotated variants was found using public genome variant databases such as gnomAD v2, which consists of exome and genome data from 141,456 individuals sequenced as part of various disease-specific and population genetic studies. Approximately 55% of individuals included in gnomAD v2 were of European ancestry and 46% of individuals were women.”

2. Of these 464 genes, how many genes are on the ACMG list of secondary genetic findings?

Response: As stated in the “Sequencing of Variants” section, 7 ACMG genes were included in the list of 464 genes.

3. How many variants have been annotated? It is not clear how many variants have been filtered or kept in each step?

Response: We have revised the results section to included the information requested by the reviewer.
The revised section now includes the following sentences with the new information: Among 1372 variants identified in the 25 genes, 283 nonsynonymous and stop-gain variants were identified for further review after excluding common variants (variants present in &gt;0.5% of the general population). Of the 283 variants, seven (2.4%) were stop-gain variants and 276 (97.6%) were nonsynonymous variants. Nine variants (3.2%) were classified as likely pathogenic or pathogenic, 241 variants (85.1%) were classified as variants of uncertain significance (VUS), and the remaining variants were classified as likely benign (11.7%).