Dear Angela:

Thank you for your email from May 31st. We have included a detailed analysis in response to the comments from the statistics reviewer #4 showing the robustness of our analysis; all suggested perturbations to the analysis give very similar results and our conclusions remain identical. The analysis is described in our point-by-point response to the reviewers and in a statistical analysis section now included as Supplementary Discussion in **Supplementary File 1**. As you discussed with Nevan, the experiments suggested by reviewer #2 in their one remaining comment would not only add no meaningful new information to a manuscript that already has an overwhelming amount of multiple datasets but would also lead to a considerable, many month delay as we collect even more data. Nevertheless, a “leave-data-out” analysis suggested by reviewer #4 (included in the Supplementary Discussion in **Supplementary File 1**, “Withholding mutants” sectionnicely confirms that our model is (i) robust to leaving out mutations and (ii) is capable of classifying each left-out mutation into the correct functional group. This is akin to reviewer #2’s comment to test the model in analogy with crystallography (“*This would be like leaving out 20% of the reflections when solving a crystal structure and using the structural model to predict the reflections”).*

Together with the positive comments from reviewers #1 and #3, as well as our formatting changes, including shortening the text by ~940 words, we hope that the manuscript is now acceptable for publication in *Nature*.

With many thanks to you and the reviewers for thoughtful comments,

Tanja & Nevan