We would like to thank the reviewer for his or her thorough critique of our paper. Briefly, the reviewer raised four major points, which we have rephrased here for brevity and clarity:

1. **Define gene activity and distinguish it from protein activity**
2. **Unpublished data**
3. **How are functional regions associated with sequence requirements?**
4. **Is there insight into *dpy-22* biology?**

We have tried to address **points 1** and **4** through a major rewriting of the manuscript and the addition of 5 figures and 2 tables. The manuscript we submitted previously was extremely short; we have increased the length substantially to carefully explain each concept in detail. We have tried to be specific about the fact that "gene activity" refers to the combined effects of mRNA copy number, translational efficiency, protein stability, protein localization and protein activity (among other factors). Necessarily, this definition of "gene activity" or "gene dosage" means that it can be impacted in many ways at many different steps. This presents an important caveat in any genetic study, which may be supplemented with biochemical or cell biological assays to definitively identify the detailed mechanism causing a change in "gene activity" of a mutant allele. However, we should point out that these assays can be challenging and time-consuming to perform, and may not be feasible for all genes. In this sense, the genetic analysis of an allelic series should be seen as a valuable first step towards a thorough characterization of the gene of interest. Similarly, we have expanded our explanations for the boundaries of the functional regions. We have also tried to be explicit about what constitutes a functional region, and that functional regions could represent short motifs that confer localization (such as an NLS) or independently folding protein domains with complex biochemical activities (such as enzymatic functions), and we have added a sentence explaining that our interpretation of functional regions is with regards to the protein, but that functional regions could also reflect impacts on RNA stability, translation or localization. Finally, we have modified the manuscript to be in the appropriate format for *Genetics*, both in terms of references and in layout. We have also uploaded our supplementary data using figshare.

We addressed the critique of **unpublished data** by removing the *dpy-7* and the *dpy-10* data, which were also not deemed highly relevant to the study. We do mention the use of unpublished wild-type controls used to infer batch effects.

To address the question of **biological insight**, we sequenced mutants of *let-60* (loss and gain of function mutants of the *C. elegans* ras homologue) and *bar-1* (loss of function of a wnt pathway gene encoding a beta-catenin). We used these mutants to define transcriptomic signatures of each pathway, then asked whether we could detect these signatures in the *dpy-22* mutants. These data have been deposited in the GEO repository along with the *dpy-22* sequences. We also performed gene enrichment analyses on each phenotypic class to try to gain biological insight into them.

Minor deficiencies
In addition, the reviewer pointed out a number of minor deficiencies which we have tried to address. Briefly:
1. The non-complementation of *bx93* to *sy622* in a *let-23* sensitized background should be presented in the introduction.

2. Include information on the direction and magnitude of expression changes for the transcripts within each phenotypic class within each mutant analyzed, together with a graph showing the degree to which the direction of change is similar between mutants.
3. Stress the caveats.
4. Ascribe biological meaning to classes.
5. Frequent references to a *biorXiv* manuscript.

We have modified the manuscript to introduce the non-complementation between *dpy-22* alleles in a sensitized background. We have also included information on direction and magnitude of expression changes. We have added a paragraph in the conclusion stressing the caveats in interpretation of the phenotypic classes. We have also added enrichment analyses to the phenotypic classes for greater biological meaning. Finally, the *biorXiv* manuscript has since been published in *PNAS*, so we have updated the reference to reflect this.