Opazo et al. present a phylogenetic analysis of the relationships and origin among DRD receptors. Overall, the manuscript is well-written and results are nicely supported. Comments are as follows:

Major Comments

1. Line 103: The authors state that “bioinformatics procedures” were used to generate the dataset. This is not a suitable description of methods. Authors should explain in much more detail how they generated their dataset, including any databases queried used and “seed” search sequences (i.e. if BLAST or similar tool was used). Specific steps should be precisely explained and any scripts used in this step should be included with or linked to the paper.
2. While the tree appears well-supported based on bootstrap, it is not clear how many tree searches were performed. To reliably obtain a supported phylogeny, it is crucial to do more than one iteration due to the heuristics needed in searching massive tree space, *especially* given the historic difficulty in resolving DRD relationships within the two major clades. If more than one search was done, please state. Otherwise, authors should more exhaustively search tree space to ensure reliability (50-100 runs would be good).
3. Line 282, the authors refer to “simulated mutagenesis” (also in legend of Fig 9). I see no evidence for any such analysis in this paper. What do they mean here? Is an an analysis from the paper presenting the DRD structure? This must be expanded upon greatly. It would merit an additional Methods section at the very least.
4. The authors describe “divergence” on two occasions among receptor sequences. I am not sure that this word is used correctly. It seems that these calculations (also, please describe the calculations!) were conducted naively with alignment similarity. Such a quantity would refer to **distance**, not divergence, which would require a more thorough evolutionary analysis to consider substitution events rather than just pairwise differences. As such, this procedure should be substantially clarified or redone, depending what the authors wish to convey.
5. Much of the background for DRD receptors is presented in the first paragraph of “Results/Discussion”, namely lines 145-156. I strongly recommend moving this content to the Introduction.
6. A minor but critical fix: The receptor DRD2L is shown in Fig 3, but the text throughout the paper should a lower-case “L”, which I thought was either a “1” (one) or capital “i” until encountering this figure. Please change all to DRD2L (unless lower-case is more standard in the field, then use all lower) for consistency and readability of this ambiguous letter.

Minor Comments

1. Figures in general need some clarifications. As a general principle, a reader should be able to figure out exactly what is in each figure based on the legend alone without having to search for corresponding text. I recommend the following steps be taken to increase clarity:

    a. Figures 2 and 3: Describe what the colors and line types mean. Specifically there is a tan-ish color in the synteny plots that does not appear to be either a DRD receptor or a flanking gene, and some genes are shown as dashed lines. Are these genes which have been lost?
    b. Figure 5: Consider adding colors to the check and X marks for ease of visualization, but also retain the shapes to assist with any color blind readers. Further, something is not aligned properly with the cyclostome sequences check/X marks.
    c. Figure 9: The legend should explicitly state the PDB ID and source.
    d. Figure 10: The caption here is excessive and contains much of the content presented in the main text. This should be distilled.
2. Line 55, Huntington’s should be uppercase
3. Line 130, should be “used as” (not “use as”)
4. The authors tend to duplicate citations, specifically as back-to-back “Yamamoto et al. (2015) (Yamamoto et al., 2015)”. Only the first should be presented.