Supplementary Materials

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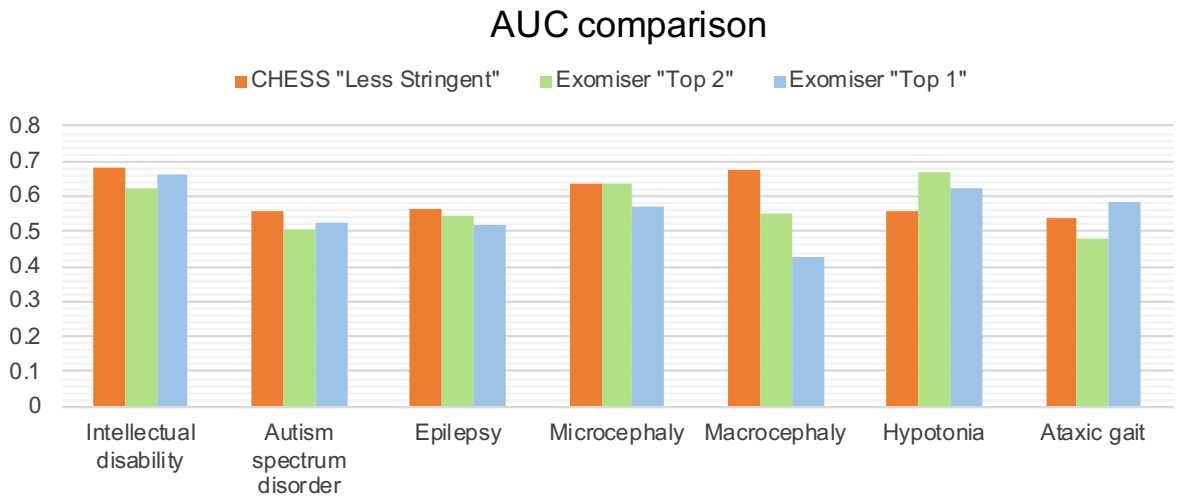
1. **Supplementary Figure S1**

   Comparisons among prediction performances (quantified by AUCs) of CHESS “Less Stringent”, Exomiser “Top 2”, and Exomiser “Top 1”. Performances for all seven disease terms are shown here.



2. **Descriptions on the parameters used before and during the CHESS scoring steps**

   There are several types of parameters used in this analysis:

   (1) The only actual cut-off involved in this analysis was MAF <= 0.05, which was used *before* the CHESS scoring steps. This MAF cut-off was a very loose cut-off, mainly for reducing computation burden. MAF can be set to other values, and would still be fine to continue with the downstream CHESS scoring steps.

   (2) Several pre-set heuristic parameters were used *in* the CHESS scoring steps, namely: the parameters (or weights) for frameshift, missense, and inframe InDel variants. These parameters were set based on best knowledge of the

author on the rare disease genetics—for example, a frameshift variant tended to cause a potentially larger damage to the transcript than a missense variant. These parameters were chosen so that there would be a different emphasis on different types of variants. The choices of the parameters may affect the outcomes. The “del” score, a component of the CHESS scoring step 1, was designed to partially address this issue, by using both the pre-set heuristic parameters and the pre-calculated REVEL score (designed for all missense variants), for the purpose of a more “balanced” measure of the deleteriousness. The actual values of the pre-set parameters are not expected to affect the ability of the scoring system to prioritize variants, as long as the parameters weigh frameshift variants higher than missense or inframe InDel variants (except in rarer cases such as certain ‘gain of function’ missense variants).

3. Descriptions on the adjustments on CHESS submissions

The adjustments on the scores used for submissions were made due to lack of full information, such as gender and family information. **Please note that if in the future CHESS is applied to a dataset with full family information, these adjustments will be irrelevant.** For this CAGI challenge, the reasons for these adjustments have been described here. Generally, a heterozygous variant shared by the patient with one healthy parent would be unlikely the genetic cause of the disease. In the CAGI challenge dataset, it is possible that by chance 50% (or more) of the heterozygous variants were actually shared with healthy parents so that were not the disease cause. That was why the scores of the heterozygous

(estimated “de novo”) were halved. Likewise, in this dataset it was not possible or not easy to determine whether two heterozygous variants were on the same allele. Some of the estimated “compound heterozygous” variants could actually be on the same allele, affecting only one allele instead of both, thus should be given a lower priority. However, the author admits that it was unclear to what extent the scores should be lowered—so the author tried an arbitrary adjustment (the sum of scores of the two involved variants divided by 3), and generated two submissions with lowered “compound heterozygous” scores and one (“Less Stringent”) with the original “compound heterozygous” scores, to be tested in CAGI.

4. Descriptions on Supplementary Data

Supplementary Data contains sn example dataset, scripts for data preprocess and CHESS scoring, and instructions on how to generate the CHESS scoring results. Supplementary Data also contains a version of CHESS for general usage, without the adjustments made for the CAGI challenge submissions.