**The discovery of integrated gene networks for autism and related disorders.**

1. The authors indicate that the M1 and M2 Best modules are (iteratively) the sets of genes significantly enriched in mutations. However, for comparison of their findings with previously published module sets, they use the M1\_extended and M2\_extended sets only (detailed venn diagram shown in supplementary). While the \*extended sets are all the genes in the top 1 percentile scored modules (excluding the \*best set), it is confusing that the validation of the method’s results is being done using the auxiliary modules and not the core modules as suggested by the algorithm. They similarly only use the extended sets in the pathway enrichment analysis – based on this, what is the actual output to be used for analysis from MAGI? Are the ‘best’ modules not really the reference points for future study?
2. The algorithm furthermore excludes all genes observed in the ith  Best *and* Extended sets when it seeds in the i+1th iteration. While it might make sense to exclude the ith Best module’s set of genes in the next iteration (and so uncover additional LoF+missense enriched gene sets), I don’t see any logical justification for excluding the ‘extended’ set in the next iteration as well. This seems especially harsh given how the ‘extended’ set is derived in the ith iteration in the first place (top 1 percentile, and no other thresholding/filter relative to the score of the Mi\_Best module).

**Sharing and Specificity of Co-expressioin Networks across 35 Human Tissues**

1. It is quite clear early on in the results that the essential mechanisms are driving the ‘hubs’ in each tissue. Referring to the methods section, in the Gene Set Selection process, the authors point out that they filtered out all probes that were ‘[…] constant across any tissue’ by requiring non-zero gene expression in atleast 1/5 of the samples. I am not clear as to how this meets the requirement of filtering out constant-valued genes/probes, and wonder if this is actually the reason for the overwhelming emphasis on essential genes’ hubs in their results?
2. It is also surprising that (unlike the paper last week, where a high sample size was able to counter influence of essential gene systems, after applying Lasso regression to induce a sparse distribution), their L1 parameterization is not able to correct for this flaw. Could this be because of the fact that the network optimization using the L1 sparsity penalty is done in a tissue-specific manner instead of across the entire cohort?