Author's response to reviews

Title: FLAGS, Frequently Mutated Genes in Public Exomes

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Tim Sands PhD
Executive Editor, BMC Medical Genomics

Re: Manuscript submission

Dear Dr. Sands,

We are pleased to submit the manuscript entitled “FLAGS, Frequently Mutated Genes in Public Exomes” for consideration as a research article in BMC Medical Genomics. Our work directly addresses a challenge of distinguishing true pathogenic variants from rare benign variants and therefore fits well with the genome-scale analysis of exomes and whole-genomes. We believe this work rises to the standard expected and will be of broad interest to the readers of the journal.

Dramatic improvements in DNA-sequencing technologies and computational analyses have led to wide use of whole exome sequencing (WES) to identify the genetic basis of Mendelian disorders. As rare/novel genetic variants continue to be uncovered, there is a major challenge in distinguishing true pathogenic variants from rare benign mutations. We experienced this challenge in our efforts to identify causes of rare Mendelian disorders; namely, we noticed occurrence of either rare or novel, likely functional variants that pass all of our prioritization filters, but recurrently affect the same set of genes. Since we study a diverse spectrum of rare disorders, we found it extremely unlikely that our patients would recurrently have the same genetic cause. Therefore, we used publicly available exome cohorts, together with the dbSNP database, to derive a list of genes that most frequently exhibit rare (<1%) non-synonymous/splice-site variants in general populations. We termed these genes FLAGS for FrequentLy MutAted GeneS. We analyzed the properties of these genes and provide an example how this list of genes could be used to further prioritize variants as more likely to be pathogenic. Also, we demonstrated an overlap between FLAGS and the rare-disease causing genes recently discovered through WES studies, and the need for replication studies and rigorous statistical and biological analyses when associating FLAGS to rare disease. We found that the rate at which genes accumulate rare mutations is beneficial information for prioritizing candidates, and propose that clinical reports associating any disease/phenotype to FLAGS be evaluated with extra caution.

Our work is of interest to informaticians and clinicians alike working with exome and whole genome studies for disease diagnosis, and aligned with the research scope targeted
by BMC Medical Genomics.

I look forward to your response.

Yours sincerely,

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