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Dear Dr. Cho,

Thank you for the invitation to revise and resubmit the manuscript. We are heartened that reviewers #1 and #3 find our responses satisfactory and have endorsed our manuscript for publication in *Nature Communications*. However, we are rather surprised by reviewer #2's comments.

The publications that we cited in our responses are a selection of the most current work performed by authorities in the field and peer-reviewed by colleagues in the community. The main point we are trying make is not to show the 'correctness' of these methods, but to point to the broader reality that there is at present a diversity of methods in the community. For example, while the GTEx consortium [1] did attempt to correct for allelic mapping bias, they performed their alignment on the human reference genome and allele-specific detection using binomial tests, not accounting for over-dispersion. On the other hand, Ding *et al.* [2] performed their alignment on the human reference genome and allele-specific detection using binomial tests, but did *not* correct for allelic mapping bias. Given the plurality of current approaches, the fact that the reviewer is insisting on his/her points of view suggests his/her prejudice for a particular 'right' approach, where there is no firm consensus.

In our endeavor to mine the wealth of existing datasets, we have come to appreciate and acknowledge this diversity, and thus have advocated for the need to uniformly process these datasets. Our allele-specific detection approach has already been extensively discussed and ultimately utilized in the ENCODE, Epigenomics Roadmap and 1000 Genomes Project consortia. The ENCODE consortium has utilized an earlier version of our approach in its 2012 publication [3]. It is also currently being utilized by the Epigenomics Roadmap consortium in their allele-specific analyses. Moreover, our approach is used in the analyses of the 1000 Genomes Project Structural Variants group. Specifically, the personal genome construction is especially useful in structural variant analyses since it is able to incorporate indels and structural variants; the other methods are only limited to single nucleotide variants. The manuscript from

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the Structural Variant Group of the 1000 Genomes Project consortium has just been recently peer-reviewed and accepted by *Nature*.

Furthermore, building a personal genome not only reduces the reference bias as mentioned by reviewer #2, but, as we show in our new analyses and responses, it is also less affected by the type of allelic bias that was highlighted in Degner *et al* [4] and van de Geijn *et al* [5].

We agree that allele-specific analyses are challenging. Therefore, there is a plethora of approaches, with corresponding pros and cons, developed to address various concerns. Reviewer #2 has made some reasonable suggestions, thus we have made significant efforts in trying to incorporate his and *all* the reviewers' comments. While we have also tried to add new analyses and responses in this round of review to address specifically reviewer #2's concerns, we fear an insistence on his/her single approach in performing allele-specific detection when there are multiple ways. Nonetheless, we are encouraged by the other reviewers' endorsements of our current manuscript and indeed, strongly believe that our approach and resource will generate considerable interest in the community. Hence, we do hope to seek your understanding and do take into consideration this cover letter when making your decision.

**Deleted:** van de Geijn *et al* [4]. The manuscript from the Structural Variant Group of the 1000 Genomes Project consortium, which included analyses from our approach, has just been recently peer-reviewed and accepted by *Nature*.

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Yours sincerely,

Mark Gerstein

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[1] The GTEx Consortium (2015). *Science*. 348(6235):648-60

[2] Ding, Z. *et al.* (2014). *PLoS Genet.* 10(11):e1004798

[3] Djebali *et al.* (2012). *Nature*. 489(7414):101-8

[4] Degner *et al.* (2009). *Bioinformatics*. 25(24):3207-12

[5] van de Geijn *et al.* (2015). *bioRxiv*. doi: <http://dx.doi.org/10.1101/011221>

**Deleted:** [4

**We list a number of suitable reviewers for the paper:**

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