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Dear Editor,

we are resubmitting revised manuscript entitled "**Analysis of deletion breakpoints from 1,092 humans reveals details of mutation mechanisms**", for consideration for publication in Nature Communications. In this manuscript we derived a confident set of breakpoints for 8,943 structural variants detected in 1,092 human individuals sequenced by the 1000 Genomes Project. Furthermore, we performed a comprehensive analysis of the breakpoints, including comparison in the context of genome functional and epigenetic contents. Our study provides insights into the mutational mechanism leading to the formation of structural variations. In particular, we suggest that structural variations mediated by non-allelic homologous recombination could originate in early embryonic and germ cells without replication and then be passed on through the germline. Furthermore, for structural variants generated by template switching during replication we suggest the existence of particular spatial and temporal configurations of DNA to generate a variant.

Our analysis is of importance not only for the fundamental understanding of mutations in the genome but also for clinical use – in particular, for understanding genetic alterations associated with cancer, senescence, and aging. We, therefore, believe that our manuscript will be of great interest to a broad audience and, especially, to the readers of Nature Communications.

In the revised manuscript we addressed all the reviewers' comments by providing additional info about the breakpoint set, by comparing our breakpoint set with other sets previously published, by correlating breakpoints with DNAse accessibility and nucleosome occupancy, by checking for confounding factors, by rewriting the text, etc. We would like to emphasize that new analyses were consistent with our initials hypothesis and statements. Additionally, we demonstrated the utility of our breakpoint set for structural variant genotyping by utilizing it with the new BreakSeq2 junction-mapping algorithm.

Yours sincerely,

Mark Gerstein
Albert L. Williams Professor   of
Biomedical Informatics