Dr. Tiago Faial, PhD
Chief Editor
Nature Genetics

Bonn, 18 November 2025

Dear Dr. Faial:

We are pleased to submit our manuscript entitled "***Genome-wide profiling of short tandem repeat somatic instability reveals associations with age, sex and brain-related traits***" to be considered for publication as an Article in *Nature Genetics.*

Tandem repeats represent one of the most prevalent classes of genetic variation in humans, with short tandem repeats (STRs) alone constituting an estimated ~7% of the human genome. Since the discovery of a CCG repeat expansion as the cause of fragile X syndrome in 1991, STR expansions have been found to cause over 60 different disorders, the majority of which are characterized by pronounced brain pathology. Emerging evidence indicates that **age-associated somatic instability of STR expansions represents a key mechanism in the pathogenesis of repeat expansion disorders (*e.g., Scahill et al. Nat Med, 2025; 31(3):807–818, Handsaker et al. Cell, 2025; 188(3):623-639).*** However, currently no computational methods exist for the systematic study of STR somatic instability. Here, **we addressed this critical unmet need by developing an efficient, haplotype-resolved genotyping algorithm for high-throughput genome-wide profiling of somatic STR variations from either whole genome or targeted sequencing data.** Importantly, we have implemented this algorithm in a versatile and user-friendly bioinformatic tool, *searchSTR*, which we intend to make freely available to the scientific community upon publication of the paper.

Apart from an increased accuracy and speed for calling STR genotypes, the most distinguishing feature of *searchSTR* is its **ability to estimate STR somatic instability, which is beyond the reach of other existing state-of-the-art STR genotyping tools** such as *ExpansionHunter*. This capability enabled us to systematically assess the association of STR somatic instability at many functionally relevant genomic loci with a range of biologically highly relevant traits, including age, sex, magnetic resonance imaging-derived measures of brain structure as well as biofluid markers of neurodegeneration. To this end, we applied our approach to whole genome sequencing data from 3,202 individuals of the 1000 Genomes Project as well as targeted deep-sequencing data from 2,974 participants of the Rhineland Study, a deeply phenotyped population-based prospective cohort study in Bonn, Germany. **This approach enabled us to generate the first comprehensive multiancestry genome-wide reference panel of STR somatic instability, covering more than 1.4 million STRs across 26 populations. Fascinatingly, we also found that STR somatic instability at many genomic loci was robustly associated with age, sex, brain morphology and markers of neurodegeneration in the general population.**

We are convinced that these groud-breaking results will be of great interest to the broad and diverse readership of *Nature Genetics*, and could be highly relevant to geneticists, clinicians as well as basic researchers alike who are interested in understanding the role of STRs and their somatic instability in health and disease.

We confirm that this paper has been read and approved by all the co-authors. We had full access to all of the data and have the right to publish any and all of the data. In parallel to this submission, we have also uploaded a pre-print version of the manuscript to the medRxiv pre-print server (DOI: 10.1101/2025.11.13.25340159). There are no financial conflicts of interest

to be disclosed. Correspondence and phone calls about the paper should be directed to the undersigned.

We thank you for your consideration and look forward to your reply.

With kind regards, on behalf of all authors,

Ahmad Aziz

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