On the fraught inference of historical human generation times

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Abstract

Wang *et al.* (2023) recently proposed an approach to infer the history of human generation intervals from changes in mutation profiles over time. As the relative proportions of different mutation types depend on the ages of parents, *stratifying*binning variants by the time they arose allows for the inference of average paternal and maternal generation times at past times. Applying this approach to published allele age estimates, Wang *et al.* (2023) inferred long-lasting sex differences in average generation times and surprisingly found that ancestral generation times of West African populations remained substantially higher than those of Eurasian populations extending tens of thousands of generations into the past. Here we *show*argue KRT: Thinking about tone here – show is softer. that the results and interpretations in Wang *et al.* (2023) are primarily driven by noise and biases in input data and a lack of validation using independent approaches for estimating allele ages. With the recent development of methods to reconstruct genome-wide gene genealogies, coalescence times, and allele ages, we caution that downstream analyses may be strongly influenced by uncharacterized biases in their output.

Recent years have seen the rapid development of methods for reconstructing genealogical structures of large cohorts KRT: is it clear that this means "unrelated"/ "randomly sampled" individuals and would not be confused with pedigrees? (Speidel *et al.*, 2019; Wohns *et al.*, 2022; Hubisz *et al.*, 2020), which are comprised of a series of gene genealogies (or trees) along the genome. Reconstructed genealogies (or informative summaries of them) have the potential to transform population genetic inference,. *as biological and evolutionary processes impact the shape and correlation of gene trees and the distribution of variation that arises in the lineages they represent.*Biological and evolutionary processed determine the structure of these genealogies, including the location of mutations. In particular, the age of a variant can be estimated by mapping its mutation to the *portion*branch of the *gene tree in which it is inferred to have occurred*genealogy consistent with the observed data. (Albers and McVean, 2020).

The past few years have also seen efforts to sequence large sets of pedigrees, providing increased resolution of important parameters of genome biology, including direct measurements of mutation rates and profiles. Through high-coverage sequencing of multiple generations of families, *de novo* mutations can be determined as maternally or paternally inherited,. *and with*With a large enough sample size (meoises), both the number of mutations and proportions of mutation types (i.e., the *mutation spectrum* of A→C, A→G, etc. mutation types) can be correlated with parental age and sex (Jónsson *et al.*, 2017; Halldorsson *et al.*, 2019). These two sets of inferences, the estimated ages of mutations and the parental age- and sex-dependence of the mutation spectrum, can be combined to infer the history of average maternal and paternal generation intervals for human populations of diverse ancestries (Macià *et al.*, 2021; Wang *et al.*, 2023). In order to avoid overfitting, this approach requires making a number of assumptions about the constancy of the mutational process over time and its similarity across populations (Harris, 2015; Mathieson and Reich, 2017; Harris and Pritchard, 2017; DeWitt *et al.*, 2021), and of negligible effects of selection and biased gene conversion (cite) on shaping the profile of segregating mutation types.

KRT: first 2 sentences can be merged? *This approach has recently been criticized (*Gao et al.*, 2022).*Gao *et al.* (2022) have recently criticized this approach. *Notably,* Gao et al. *(2022)*They show that observed changes in the mutation spectrum over time cannot be explained by changes in maternal and paternal generation intervals alone*, as specific mutational signatures would require unique and divergent generation time histories to simultaneously explain them.*. Male and female generation times are required to change in different directions within the same time interval in order to explain the data for different classes of mutation. Gao *et al.* (2022) also point out that pedigree-based estimates of the *de novo* mutation spectrum do not agree with the mutation spectrum among young variants in existing population-level datasets, potentially biasing such approaches. KRT: Need to explain why they may be expected to agree: young mutations = closer to the present (but with massive variance) They argue that factors other than changes in generation intervals, including genetic modifiers and environmental exposure, must explain observed variation in mutation profiles.

In this note, we examine both the results and conclusions of Wang *et al.* (2023). We first consider the reported inferred generation time histories and find that they are inconsistent with current understanding of human population history, in particular population structure within Africa. In exploring the source of this inconsistency, we show that allele age estimates are not just noisy, but age-stratified mutation spectra reconstructed using independent methods do not agree, with mutation profiles diverging in opposing directions. Thus, the results from Wang *et al.* (2023) do not reproduce when applying different estimates of allele ages from the same population samples. We further discuss the disagreement between the mutation rate profile found in pedigree studies and from young variants, the source of which is not well understood and complicates their comparison. In conclusion, we suggest that downstream analyses using estimated allele ages and mutation profiles should more carefully validate their results and such results should be interpreted with a heavy dose of skepticism. KRT: This last sentence needs softening – we need to strike a balance between yelling "garbage in, garbage out" and implying that Jerome, Simon, etc., are the problem here.

Long-lasting differences in population-specific generation intervals

Applying the proposed inference approach to multiple populations of different continental ancestries, Wang *et al.* (2023) estimated that the ancestors of European, East Asian, and South Asian populations included in the 1000 Genomes Project Consortium *et al.* (2015) dataset (1KGP) have a history of significantly reduced average generation times compared to West African populations. These differences extend to over 10,000 generations, the time period highlighted in this study KRT: Does "this study" refer to this document or to Wang et al.?. In discussing this *result*inference the authors state, "[T]he difference among populations beyond 2000 generations ago reflects population structure in humans before their dispersal out of Africa, a structure that is not fully captured by the 1000 Genomes AFR sample. This implies that the simple labels of 'African' and 'non-African' for these populations conceal differences in generation times that existed on our ancestral continent." Indeed, a number of recent genetic studies suggest that human population structure within Africa extending hundreds of thousands of years into the past has *in part* shaped present-day genetic variation (Hammer *et al.*, 2011; Hsieh *et al.*, 2016; Hey *et al.*, 2018; Ragsdale and Gravel, 2019; Lorente-Galdos *et al.*, 2019; Durvasula and Sankararaman, 2020).

However, in extending their analysis deeper into the past, Wang *et al.* (2023) find that ancestral generation intervals do not converge until many 10s of thousands of generations ago. Assuming an average generation time of 25–30 years, this corresponds to well over one million years. This observation would require some portion of the ancestries of Eurasian and West African populations to have remained isolated for many hundreds of thousands of years, for those structured ancestral populations to have had large differences in average generation times over the course of this history, and for those groups to have contributed substantively to different contemporary human populations. While such a scenario of very long-lasting isolation among ancestral populations is not impossible, it is not supported by genetic (Ragsdale *et al.*, 2022) or archaeological (Scerri *et al.*, 2018) evidence, which rather suggest at least periodic connectivity of ancestral human populations within Africa.

Genetic studies have estimated the Eurasian–West African divergence (i.e., the time of recent shared ancestry) at only ≈ 75ka (thousand years ago) (e.g., Pagani *et al.*, 2015; Bergström *et al.*, 2020). While population genetic studies vary considerably in estimated split times, even those that infer deeper human divergences place the Eurasian–West African divergence at 100–150ka (e.g., Schlebusch *et al.*, 2017). If such estimated divergence times represent the majority of ancestry of the two groups (while allowing for a smaller portion to be due to long-lasting structure), then the shared portion of ancestry should be subject to the same generation intervals prior to the divergence time. Any differences in the mutation spectrum from those epochs would be driven by differences in generation times affecting the minority of ancestry that remained isolated.

KRT: References to SI material and figures are missing from this paragraph and the next. As a simple test of such a scenario, we considered a model of archaic admixture within Africa, allowing for some proportion of admixture from a diverged lineage into West African populations (such as ≈ 10% as inferred by Durvasula and Sankararaman (2020), see Supporting Information). At 10,000 generations ago, paternal and maternal generation intervals in the ancestors of Eurasians were inferred to both be ≈ 20 years, while the ancestral African generation intervals were at least 28 and 23 (see Figure S4 in Wang *et al.* (2023)). Using the same mutation model (Jónsson *et al.*, 2017), we can determine the generation intervals in the isolated lineage that is needed to result in a mutation spectrum matching that of the inferred generation times.

KRT: How easy is it to vary these parameters? Is there any way to "throw them a bone" and find something anywhere close to reasonable? We assume that ancestry proportions of 10% and 90% from the diverged and Eurasian-shared lineages result in surviving variation from those epochs having similar proportions of contributions (in effect, ignoring differences in total mutation rate and demographic effects that may distort the magnitude of the contributed mutation spectra). With 10% admixture into West Africans from a diverged lineage, the mean paternal age of conception would need to be 92 and the mean maternal age 48. These are unreasonably long generation times for *Homo* species. With 20% admixture from this diverged lineage (which is larger than has been proposed or inferred in previous genetic studies), mean ages would still need to be 58 and 34.

Therefore, even assuming a model of long-lasting population structure with strict isolation within Africa, we find the reconstructed generation time intervals over the past 10,000 years from Wang *et al.* (2023) to be incompatible with plausible life histories of early humans. Given this, it is natural to ask what may be causing such mis-inference. Below we show that multiple sources of uncertainty, namely noise and bias in allele age inference and incosistencies in trio-base estimates of mutation profiles, confound inferences of generation times from age-stratified mutation spectra.

Inconsistencies in inferred mutation spectra over time

KRT: This paragraph is not about accurate dating. *Accurate dating of variant ages is central to the inference of generation intervals from time-stratified mutation spectra.* Wang *et al.* (2023) used published allele ages from `GEVA` (Albers and McVean, 2020). `GEVA` estimates allele ages by considering the number of mutations that have accumulated on the ancestral haplotype carrying the focal variant, as well as the effect of recombination in reducing the size of that ancestral haplotype. Singletons are excluded from analysis and are not assigned an age. Partitioning variants by their estimated ages shows that the mutation spectrum has changed over time, assuming that the observed spectrum of segregating variation is not biased with respect to the spectrum of *de novo* mutations occuring during that time (Figure 1A and see Figure 1C in Wang *et al.* (2023)).

In fitting generation time histories to data from the past 10,000 generations, we find that the inferred generation times provide a poor fit to the data (Figure 1D). The relative proportions of the predicted mutation spectrum trend in opposite directions for some mutation classes, confirming the concern from Gao *et al.* (2022) that a single generation time history cannot simultaneously explain each of the six mutation class frequency changes. For alleles older than 10,000 generations, the mutation spectrum fluctuates by large amounts (Figure S5). While estimated allele ages from the distant past have decreased accuracy (Albers

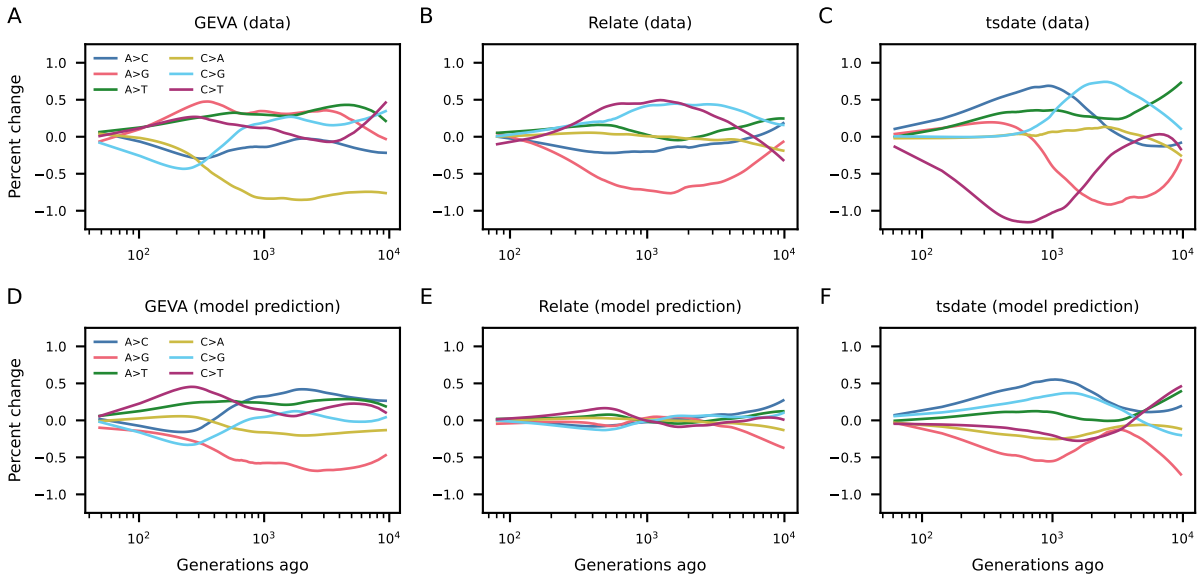

Figure 1: **Time-stratified mutation spectra are inconsistent and poorly fit by historical generation time changes.** (A-C) Three methods for estimating allele ages provide incongruous mutation spectrum histories. (D-F) In fitting historical generation intervals to each observed mutation spectrum profile, none of the mutation spectrum histories observed in the data are recovered by the predicted spectra using the inferred generation time histories. Trajectories are smoothed using LOESS regression.

and McVean, 2020; Wang *et al.*, 2023), the large differences in proportions suggests a bias in `GEVA`'s reported dates that correlates with mutation type.

Accurate dating of variant ages is central to the inference of generation intervals from time-stratified mutation spectra. Given the poor fit of the model to the `GEVA` data and the known uncertainty in age estimation for older variants, we attempted to reproduce the inferred generation time histories using allele age estimates from independent sources, `Relate` (Speidel *et al.*, 2019) and `tsdate` (Wohns *et al.*, 2022), both state-of-the-art genealogical reconstruction methods able to scale to modern sample sizes. KRT: Added this b/c it addresses "why not argweaver?" The ages of variants dated by at least two of the methods are only moderately correlated (`GEVA` and `Relate`: $r^2 \approx 0.28$, `GEVA` and `tsdate`: $r^2 \approx 0.33$, `tsdate` and `Relate`: $r^2 \approx 0.64$; Figure 2A-C and see Figure S20 from Wohns *et al.* (2022)). KRT: The next sentence could read as a bit sarcastic. KRT: The stuff about bias and mutation class should be a new paragraph – we are moving from high-level correlation to specific details. Despite the low to moderate correlation, we would hope that differences are *unbaised*unbiased with respect to mutation type. However, allele ages provided by each method *result in unalike mutation*disagree at the level of individual mutation spectrum histories (Figures 1A-C and S2–S4), with mutation spectrum changes often trending in opposite directions over the same time periods. In turn, these divergent spectrum histories provide qualitatively different inferred generation time histories (Figures S9–S11). *Notably, none*None of them provide a reasonable fit to the data (Figure 1D-F).

KRT: Somewhere around here we may want to mention the paper on performance of age estimators from the Nielsen group?

Published allele ages from both Albers and McVean (2020) (`GEVA`) and Speidel *et al.* (2019) (`Relate`) used the same input dataset: the phase 3 release of 1KGP. However, they differ in the total number of variants that were assigned ages (roughly 30 million and 48 million, respectively). KRT: We should say why, to the best we are able. tsdate dates EVERYTHING because it requires that the original data can

be reconstructed. relate makes assumptions leading to some variants not being dated. More? Of those variants, 25 million variants were dated by each, with the remaining uniquely assigned an age by one or the other method. When comparing mutation spectrum histories restricted to variants dated by both `GEVA` and `Relate`, the two methods still predict very different mutation profile trajectories (Figure S8). In comparing the proportions of mutation types assigned ages by both methods or uniquely by one, we find that those proportions differ considerably (Figure 2D). For example, `GEVA` provides age estimates for relatively more A→G mutations and fewer C→G mutations, while `Relate` provides age estimates for relatively more C→T and fewer A→G mutations. This owes to methodological differences in evaluating whether a particular variant can be reliably dated, which may have both bioinformatic (e.g., genotyping and phasing error) and biological (e.g., recurrent mutations) causes. Therefore, when comparing mutation spectra that are conditioned on variants being dated by a particular method, it is not apparent which method, if any, provides unbiased estimates of age-stratified mutation spectra.

Mutation spectra differ between *de novo* mutations and young alleles

The large disagreements in mutation spectrum histories between multiple variant age-estimation methods are concerning for down-stream inferences that rely on them. Independent of biases in allele age estimate, there are further problems in comparing age-stratified mutation spectra to those estimated from pedigree studies (Jónsson *et al.*, 2017; Halldorsson *et al.*, 2019). As Wang *et al.* (2023) acknowledge, the spectrum of *de novo* mutations identified in Icelandic trios (Jónsson *et al.*, 2017) differs from the spectrum of young segregating variation (e.g., variants estimated to be less than 100 generations old, Figure 2E and Table S1). Gao *et al.* (2022) argue that these differences are unlikely to be driven by biological processes.

For some mutation classes, the relative proportion of *de novo* mutations in the trio-based study differs from the young-variant spectrum by up to 0.02, which would imply a large over- or under-count of different mutation types. This is the equivlent of 10s of thousands of SNPs in the most recent bin, with the exact number depending on the variant-dating method. `GEVA`, `tsdate` and `Relate`, while their estimated mutation spectra differ at older times, very closely agree for mutations inferred to be less than 100 generations old (Table S1). In discussing this discrepancy, Wang *et al.* (2023) state, "We found that the mutation spectrum from the large pedigree study consistently differed from the variant spectrum inferred from the 1000 Genomes Project data, possibly because we removed singletons from the polymorphism dataset to reduce errors." *Rather*however, `GEVA` does not provide estimates of allele ages for singletons, so this suggested source of discrepancy cannot be checked with their published allele ages. Both `tsdate` and `Relate` report allele ages for singletons, and their inclusion does not strongly affect the mutation spectrum for very young variants (Table S1), though it does impact the mutation profiles in older time periods (Figures S6, S7). Reported ages from `GEVA` and `Relate` both used the low-coverage phase 3 1KGP data while `tsdate` used the more recent independently sequenced high-coverage 1KGP data (Byrska-Bishop *et al.*, 2022), so the accuracy of the mutation spectrum among young variants is unlikely to be driven by differences in coverage.

To account for the differences between the *de novo* spectrum from pedigree studies (Jónsson *et al.*, 2017) and the spectrum among young variants, Wang *et al.* (2023) subtracted this difference from each historical mutation spectrum. This choice "has the effect of assuming that parental ages in the pedigreed mutation dataset reflect generation times in the most recent historical bin" (Wang *et al.*, 2023). However, the average generation time among present-day Icelanders may not reflect average generation times in world-wide populations over the past 3-5 thousand years, represented by the most recent time bin in their analysis. Still more concerning is that we do not know the source of the discrepancy between the Iceland and 1KGP mutation spectra. Without knowing this, it is unclear that simply substracting the differences between them properly accounts for it. Instead, mutation class-specific genotyping differences *likely*may distort the underlying mutation model, potentially driving deviations in predicted mutation profiles in unexpected ways.

What could be driving the large disagreement between the spectrum of *de novo* mutations from Icelandic pedigrees and that of young variants in the 1KGP dataset? First, there could be true differences in the

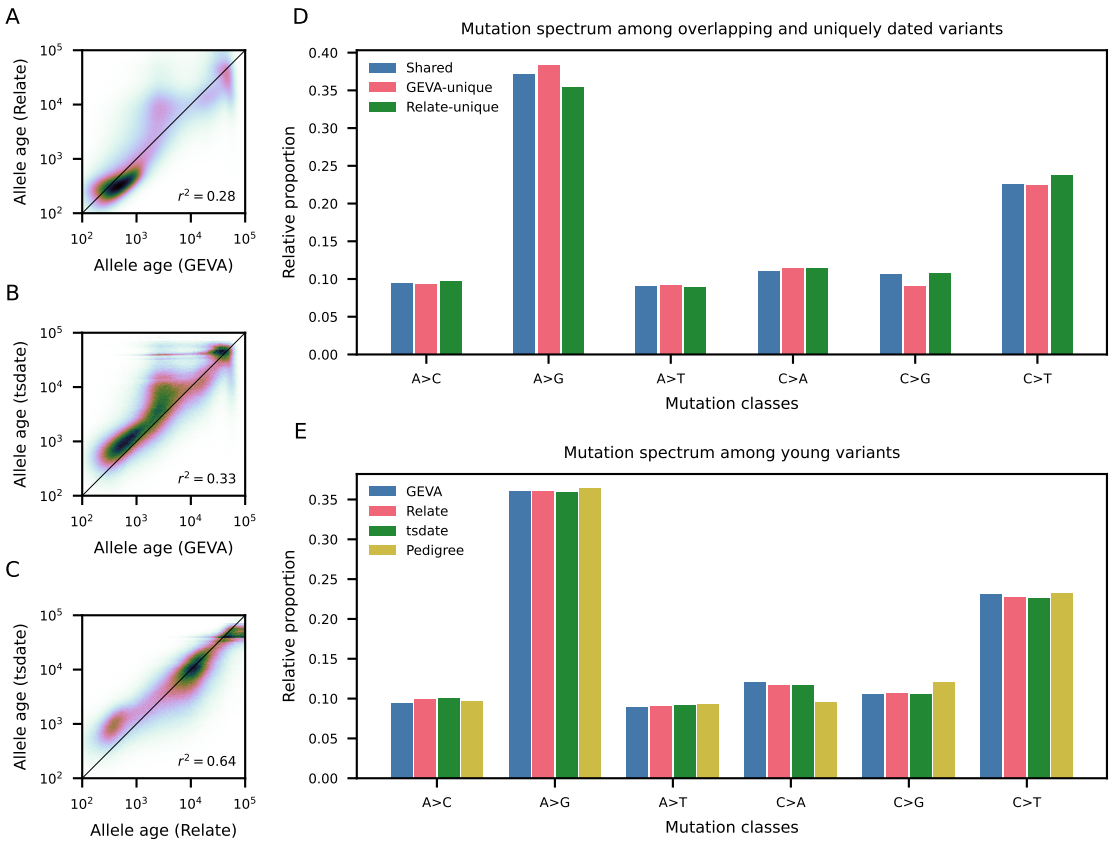

Figure 2: KRT: Is a legend scale needed for panels A-C? It may be visually ugly, but it is also expected. **Comparing allele ages and mutation spectra across data sources.** (A-C) Allele age estimates are only moderately correlated between methods. Shown here are allele age estimates for variants that were assigned ages by two or more of `GEVA`, `Relate` and `tsdate`. (D) The proportions of mutation types uniquely dated by `GEVA` and `Relate` differ from the variant proportions among mutations dated by both methods, indicating biases in the mutation types that are kept and discarded. Here, we compared `GEVA` and `Relate` (instead of `tsdate`) because allele ages were obtained from the same input data, namely phase three of the 1KGP. (E) While the mutation spectrum among young variants dated to < 100 generations is similar between age estimation methods, the pedigree-based estimate of the *de novo* mutation spectrum (Jónsson *et al.*, 2017) differs, in particular for C→A and C→G mutations.

mutation spectrum between the Iceland cohort and 1KGP populations, although this *is*seems unlikely, as populations of different ancestries in 1KGP have more similar recent mutation spectra to each other than to the Iceland *de novo* spectrum (including the EUR populations, Table S2). If the differences are real, then the Icelandic pedigree data is an inappropriate calibration for the mutation spectrum in other populations. Second, there could be differences in selective pressures between mutations of different classes, although selection would need to be very strong for some classes compared to others in order to see the observed difference among young variants. Third, the signal may be driven by genotyping error or bioinformatics choices, though the agreement between high- and low-coverage 1KGP datasets suggests that genotyping error does not have a strong effect in the 1KGP data. Instead, filtering and bioinformatics choices in the pedigree approach are the likely culprit (Bergeron *et al.*, 2022). Until the source of these differences are understood and properly accounted for, population-genetic inferences should avoid calibration using mutation rates and profiles from pedigree studies.

Conclusions

KRT: This is another place where we need careful wording – we want to reiterate that genealogical reconstruction is great, but also that it is an evolving field (maybe cite Nielsen group paper here, arguing that all of the methods need improvement). With genome-wide genealogical reconstruction methods in their infancy, we should be cautious of unexpected and subtle biases that can impact downstream analyses. In the case of generation time inference (Wang *et al.*, 2023), we showed that patterns of variation that were attributed to biological processes (variation in generation times) are predominantly driven by nonbiological artifacts in the input data. This highlights the need for increased scrutiny and validation of methods using genealogical reconstruction approaches in downstream inferences, as these issues would have been identified by attempting to reproduce their inferences using available independent allele age estimates. Large-scale reconstruction of gene genealogies, dating mutations, and T_{MRCA} inference are all exciting developments, but these methods are quite new and will likely advance considerably in the coming years. As existing methods show very different accuracies and bias even under overly-idealized conditions (Brandt *et al.*, 2022), we should continue to evaluate their performance and be cautious in their use in downstream analyses.

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