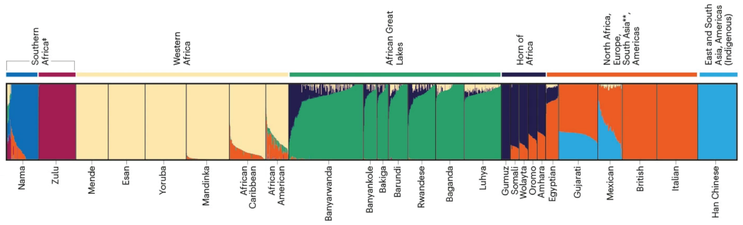
Structural variant discovery and characterization from *de novo* assembly of Khoe-Sān genomes

Zoeb N. Jamal[1*], Daniela C. Soto[1*], Kristin Hardy[1*], Mohamed Abuelanin[1], William Palmer[1], Javier Prado-Martinez[2], Paul Norman[3], Marlo Moller[4], Brenna M. Henn[1], Megan Y. Dennis[1]

[1]Genome Center, University of California, Davis, CA. [2]Institute of Evolutionary Biology, PRBB, Barcelona, Spain.
[3]University of Colorado, Biomedical Informatics, Aurora, CO. [4]Stellenbosch University, Molecular Biology and Human Genetics, Stellenbosch, South Africa.

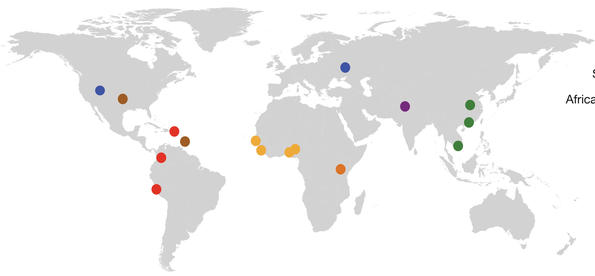
Background

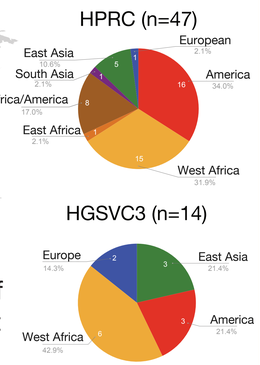
- Long read sequencing (LRS) of large cohorts is enhancing our understanding of the genomic variation landscape
- Genetic diversity within African populations can exceed that between continental groups, yet many remain underrepresented



Carlson et al. 2022 PMID: 36261568

- This gap suggests ample genetic diversity is missing in large datasets

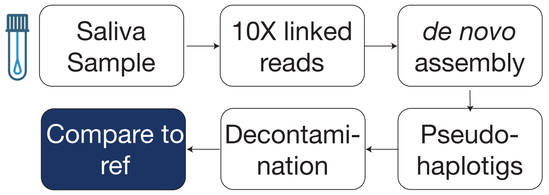


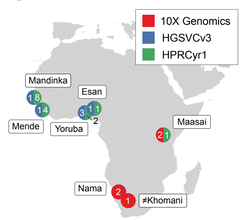


- In particular, the Khoe-Sān indigenous peoples of Southern Africa carry some of the most divergent haplotypes in extant human lineages

Methods

- We performed 10X genomics long range sequencing and de novo assembly for 3 Khoe-Sān individuals (2 Nama, 1 ≠Khomani San)

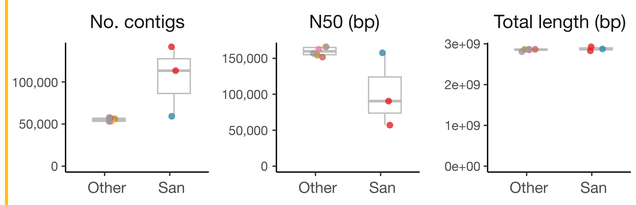




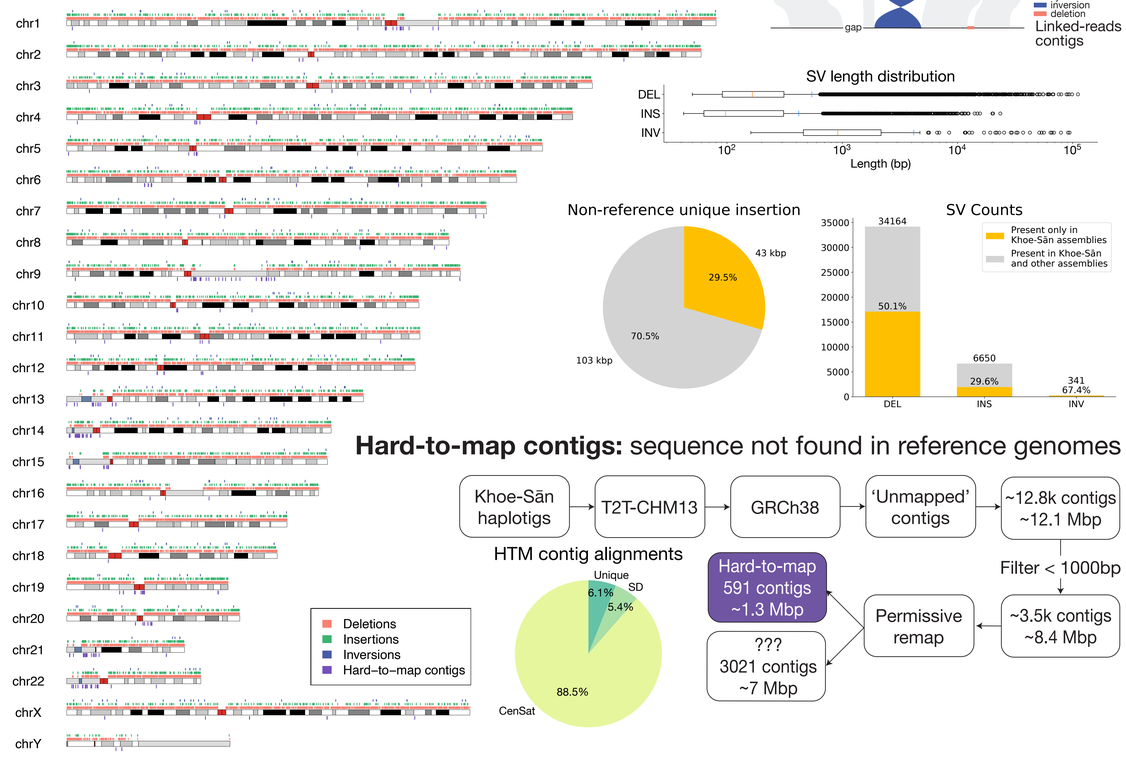
- We called structural variants (SVs) against T2T-CHM13 for these Khoe-Sān genomes and other 10X linked-read assemblies
- Used whole genome short read sequencing (SRS) data from a cohort of 93 Khoe-Sān individuals to genotype discovered SVs and investigate copy number variability
- Used VEP to query the impact of genotyped SVs

Results

Assembly statistics: *de novo* assembly compared to other 10X linked read assemblies

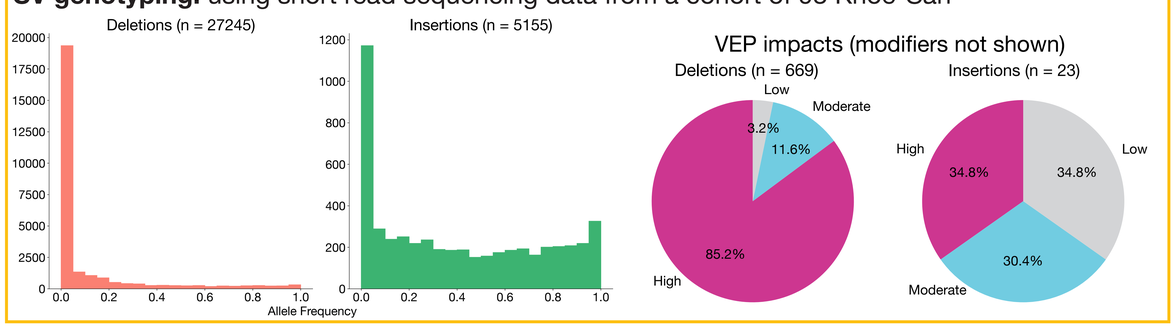


Structural variation: assembly to reference comparison

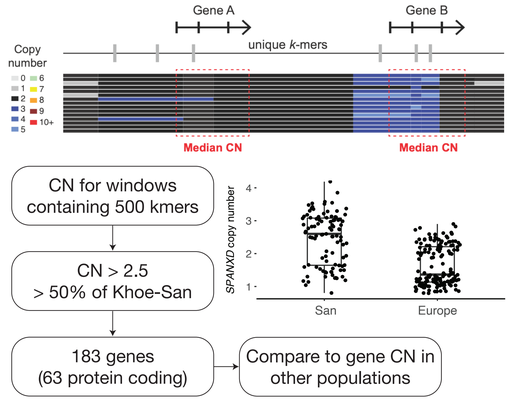


Hard-to-map contigs: sequence not found in reference genomes

SV genotyping: using short read sequencing data from a cohort of 93 Khoe-Sān



Copy number variation: using short reads from 93 Khoe-Sān individuals



Conclusions

- A lack of diversity in African genomes in LRS projects limits us from exploring human genetic variation
- We generated 10X linked-read and de novo assembly for 3 Khoe-Sān individuals
- We found ~7Mbp not mapping to human reference genomes, even after relaxing parameters
- We ascertained allele frequencies of many novel structural variants through genotyping in SRS Khoe-Sān samples
- We detected copy number variations that may differ from other human populations

Future directions

- Robust investigation of non-mapping contigs, namely aligning short read Khoe-Sān datasets to them
- Genotype discovered SVs in other populations from the HGDP, and identify Khoe-Sān specific variants
- Calculate F_{ST} and V_{ST} between Khoe-Sān and HGDP to study stratification
- Further explore high impact variants highlighted by VEP
- Leverage long haplotypes to investigate structurally complex loci, including HLA
- Assess improved mappability for Khoe-Sān individuals using new assemblies

References

Carlson et al. 2022 PMID: 36261568, Chen et al. 2019 PMID: 31856913
Shen and Kidd. 2020 PMID: 32013076

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