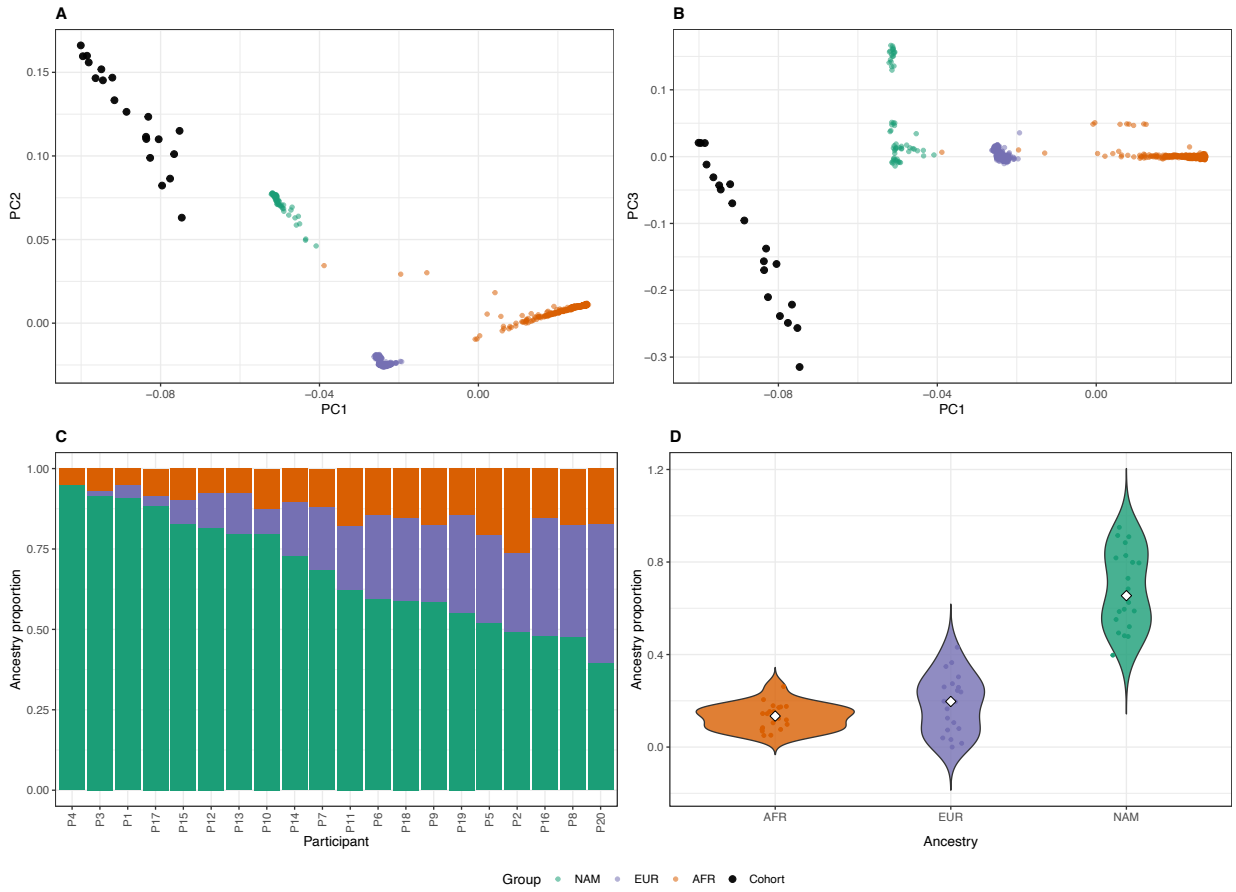


Figure S1. Principal component analysis (PCA) and supervised ADMIXTURE using a pan-Indigenous American reference panel. Reference populations included African (AFR), European (EUR), and Native American (NAM) populations from the Human Genome Diversity Project. Cohort individuals are represented by black circles in PCA space and by individual bars in ADMIXTURE analyses. Panels show: **(A)** PC1 versus PC2 and **(B)** PC1 versus PC3 derived from AFR, EUR, and NAM reference populations; **(C)** supervised ADMIXTURE ancestry estimates for individual participants; and **(D)** ancestry proportion distributions across the cohort. Although cohort individuals clustered with Native American reference populations and exhibited predominantly Indigenous American ancestry, subsequent analyses demonstrated closer clustering with Indigenous Mexican-specific reference populations (Maya and Pima). Therefore, downstream ancestry inference was performed using the Indigenous Mexican (IAM) reference framework.

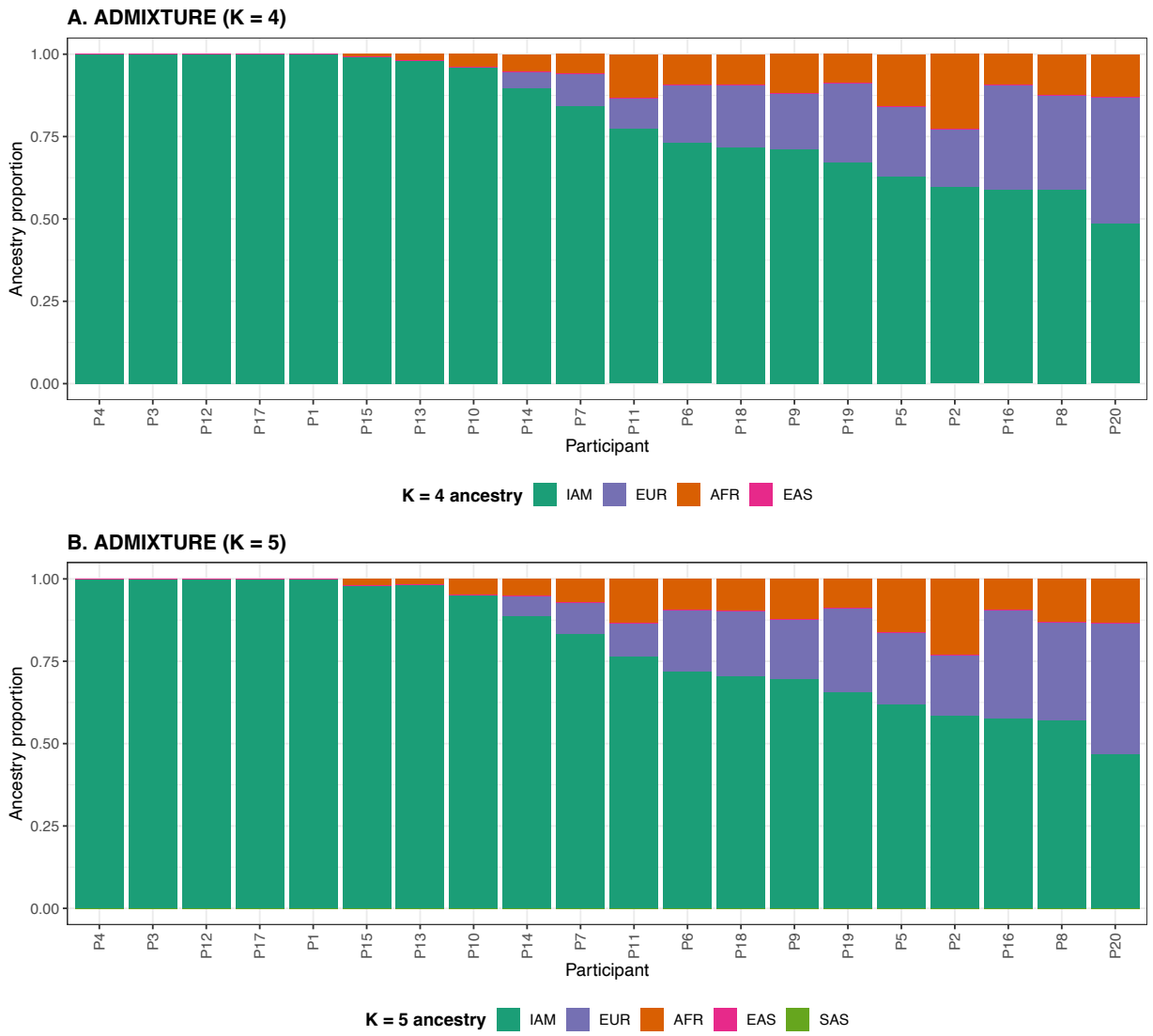


Figure S2. Supervised ADMIXTURE analyses incorporating additional ancestral components. **(A)** ADMIXTURE results assuming four ancestral populations (K = 4), comprising Indigenous Mexican (IAM), European (EUR), African (AFR), and East Asian (EAS) reference populations. **(B)** ADMIXTURE results assuming five ancestral populations (K = 5), additionally incorporating a South Asian (SAS) reference population. Across both models, East Asian and South Asian ancestry contributions were negligible within the cohort, while ancestry estimates for the Indigenous Mexican, European, and African components remained highly consistent with the primary K = 3 analysis. These findings support the use of a simplified three-component model (IAM, EUR, and AFR) for downstream ancestry analyses.

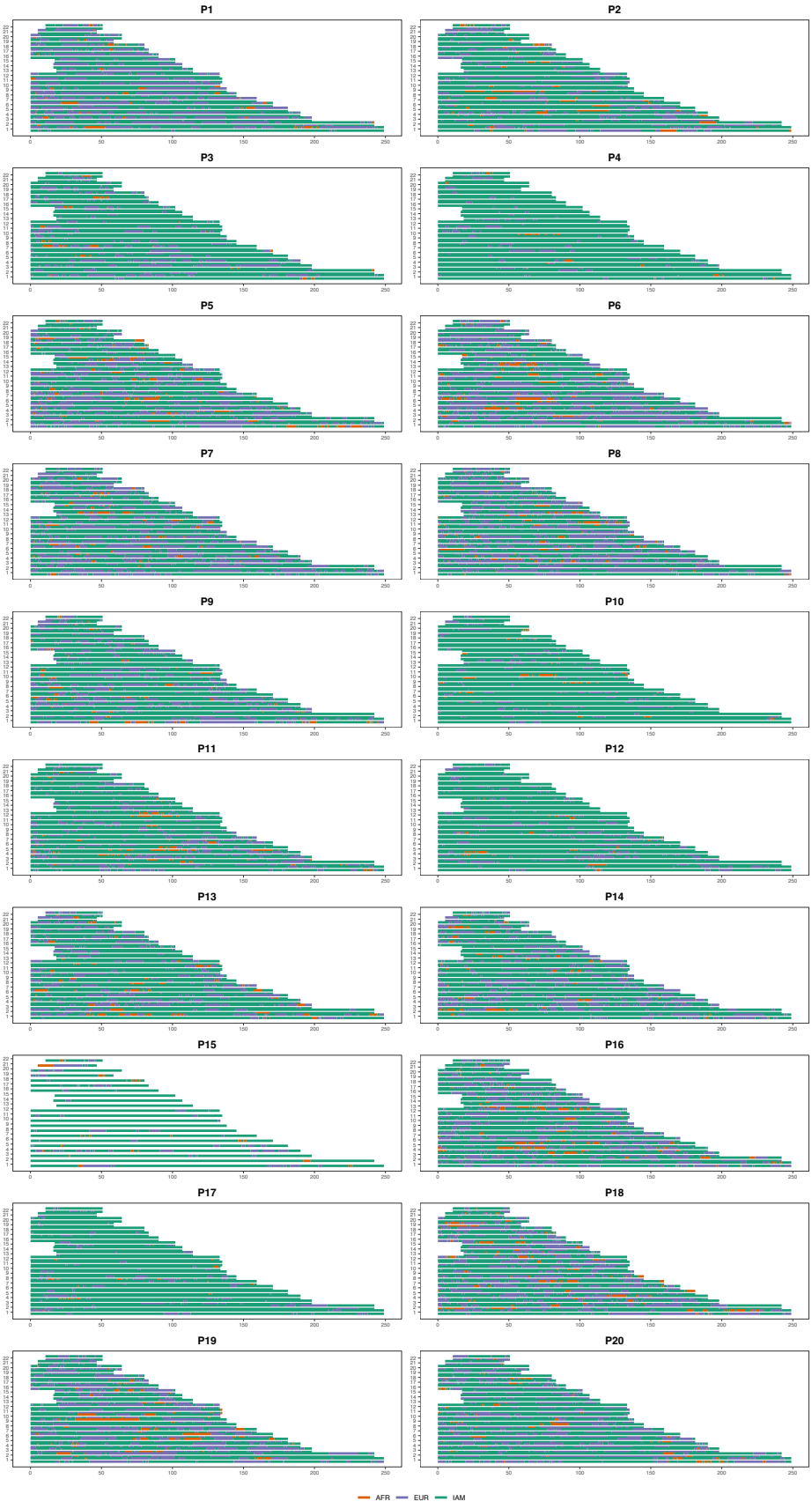

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IAM

Figure S3. Individual local ancestry profiles of *ECEL1* c.110_155del homozygotes. Local ancestry was inferred using RFMix v2.03 for each of the 20 unrelated individuals homozygous for the recurrent *ECEL1* c.110_155del variant. Colored segments represent inferred Indigenous American (IAM; green), European (EUR; purple), and African (AFR; orange) ancestry across chromosomes 1-22. The predominance of IAM ancestry across most genomic regions is consistent with the inferred Indigenous Mexican origin of the cohort.

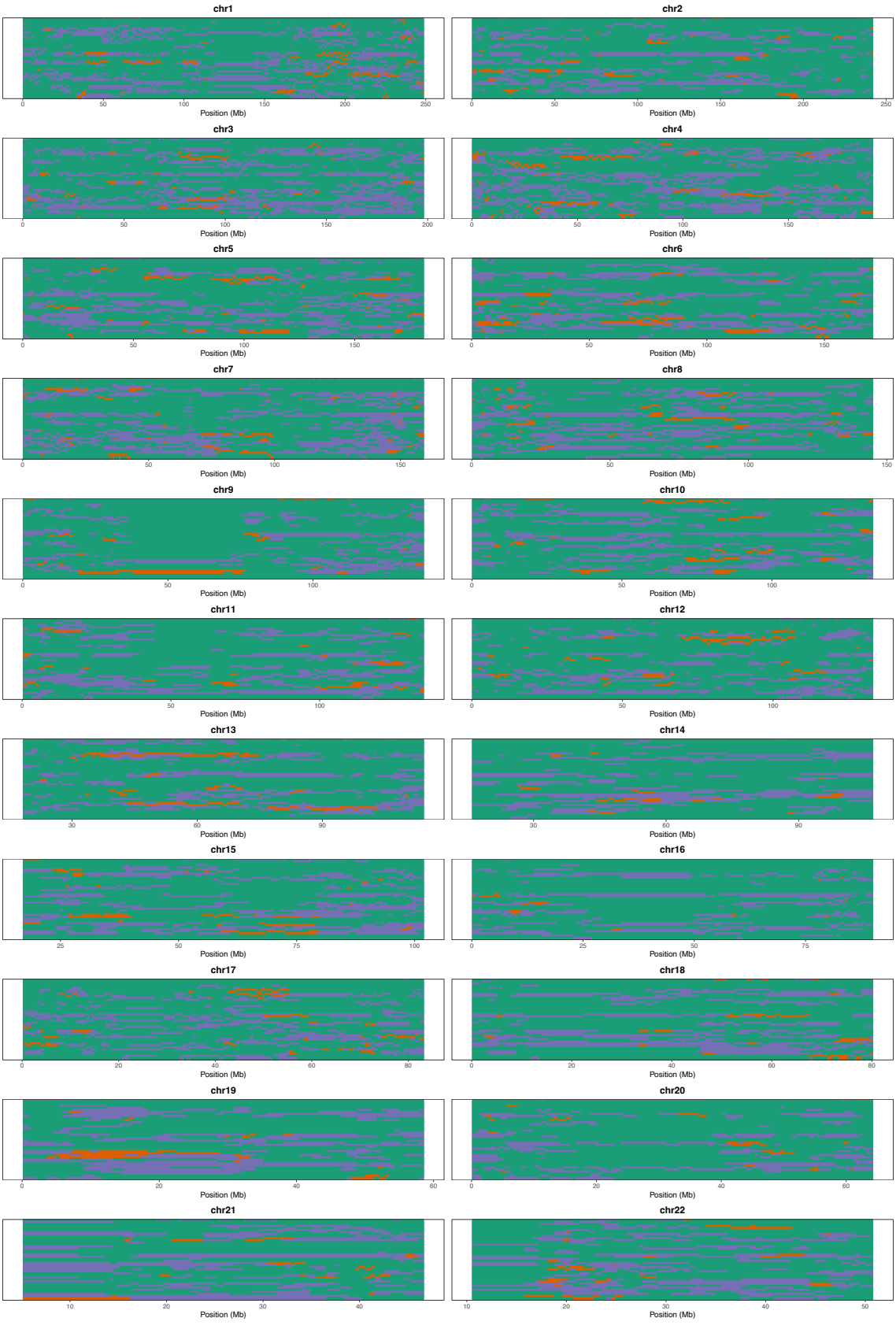

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chr11
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chr16
chr17
chr18
chr19
chr20
chr21
chr22
Position (Mb)
Ancestry
AFR
EUR
IAM

Figure S4. Chromosome-specific local ancestry across *ECEL1* c.110_155del homozygotes. Local ancestry inference was performed using RFMix v2.03. Each panel represents a chromosome (chr1-chr22), with colored segments indicating Indigenous American (IAM; green), European (EUR; purple), and African (AFR; orange) ancestry. The figure demonstrates the predominance of IAM ancestry across the cohort and provides genome-wide context for the Indigenous Mexican ancestral background observed at the chromosome 2 founder haplotype containing *ECEL1* c.110_155del.