

Genome-wide patterns of population structure and admixture in West Africans and African Americans

Katarzyna Bryc^a, Adam Auton^a, Matthew R. Nelson^b, Jorge R. Oksenberg^c, Stephen L. Hauser^c, Scott Williams^d, Alain Froment^e, Jean-Marie Bodo^f, Charles Wambebe^g, Sarah A. Tishkoff^{h,1,2}, and Carlos D. Bustamante^{a,1,3}

^aDepartment of Biological Statistics and Computational Biology, Cornell University, Ithaca, NY 14853; ^bGlaxoSmithKline, Research Triangle Park, NC 27709; ^cDepartment of Neurology, University of California, San Francisco, CA 94143; ^dDepartment of Molecular Physiology and Biophysics, Center for Human Genetics Research, Vanderbilt University, Nashville, TN 37232; ^eUnité Mixte de Recherche 208, Institut de recherche pour le développement (IRD)-Muséum national d'Histoire naturelle (MNHN), Musée de l'Homme, 75116 Paris, France; ^fMinistère de la Recherche Scientifique et de l'Innovation, BP 1457, Yaoundé, Cameroon; ^gInternational Biomedical Research in Africa, Abuja, Nigeria; and ^hDepartments of Genetics and Biology, University of Pennsylvania, Philadelphia, PA 19104

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Quantifying patterns of population structure in Africans and African Americans illuminates the history of human populations and is critical for undertaking medical genomic studies on a global scale. To obtain a fine-scale genome-wide perspective of ancestry, we analyze Affymetrix GeneChip 500K genotype data from African Americans ($n = 365$) and individuals with ancestry from West Africa ($n = 203$ from 12 populations) and Europe ($n = 400$ from 42 countries). We find that population structure within the West African sample reflects primarily language and secondarily geographical distance, echoing the Bantu expansion. Among African Americans, analysis of genomic admixture by a principal component-based approach indicates that the median proportion of European ancestry is 18.5% (25th–75th percentiles: 11.6–27.7%), with very large variation among individuals. In the African-American sample as a whole, few autosomal regions showed exceptionally high or low mean African ancestry, but the X chromosome showed elevated levels of African ancestry, consistent with a sex-biased pattern of gene flow with an excess of European male and African female ancestry. We also find that genomic profiles of individual African Americans afford personalized ancestry reconstructions differentiating ancient vs. recent European and African ancestry. Finally, patterns of genetic similarity among inferred African segments of African-American genomes and genomes of contemporary African populations included in this study suggest African ancestry is most similar to non-Bantu Niger-Kordofanian-speaking populations, consistent with historical documents of the African Diaspora and trans-Atlantic slave trade.

Africa | human genomics | population genetics

Studies of African genetic diversity have greatly informed our understanding of human origins and history (1, 2), have identified genes under natural selection across evolutionary time (3), and hold great potential for elucidating the genetic bases of disease susceptibility and drug response among diverse human populations (4, 5). The study of African population structure is also critical for reconstructing patterns of African ancestry among African Americans and for enabling genome-wide association mapping of complex disease susceptibility and pharmacogenomic response in African-American populations (6–9).

Africa contains over 2,000 ethnolinguistic groups and harbors great genetic diversity (2, 10–17), but little is known about fine-scale population structure at a genome-wide level. This is, in part, because previous studies of high-density SNP and haplotype variation among global human populations (defined as studies with at least 100,000 SNP markers) have included few African populations (10, 12, 13, 18), whereas detailed studies of genetic structure among African populations have used a modest number of markers (2) (~1,500 microsatellites and indels). Nonetheless, recent studies of microsatellite and DNA sequence variation suggest a significant population structure exists within sub-Saharan Africa, with geography, language, and mode of

subsistence (e.g., hunter-gatherer, pastoralist, agriculturalist) as potential key factors (2, 12, 13, 19). Given that high-density genotype data have revealed discernible population structure within other continental populations (e.g., Europe, East Asia) and even among geographical regions within countries (e.g., Switzerland, Finland, United Kingdom) (20–24), there is strong reason to believe that high-density genotype data from African and African-American populations can elucidate patterns of genetic structure among these populations further.

We have thus genotyped on the Affymetrix GeneChip 500K array set 146 individuals from 11 populations in West and South Africa (Fig. S1 and Table S1) who speak Nilo-Saharan, Afro-Asiatic, and Niger-Kordofanian languages and integrated these data with our previous studies of human genomic diversity, including 57 Yorubans from Ibadan, Nigeria, genotyped as part of the International Haplotype Map project, 365 African Americans from throughout the United States, and 400 individuals of European ancestry (10, 25). Our study focuses on analysis of fine-scale population structure among the West African samples and its implication for high-resolution inference of admixture in African Americans. We use principal component analysis (PCA) to infer axes of genetic variation within Africa and examine individual and population clustering using the clustering algorithm FRAPPE (26). Next, we compare the West African, European, and African-American samples and seek to identify the set of West African populations closest to the ancestral population of African Americans. Finally, based on the results of the other two analyses, we evaluate individual patterns of European and African ancestry along each chromosome for each African-American subject in our dataset using a computationally efficient PCA-based method that infers admixture proportions based on high-density genome-wide data.

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¹S.A.T. and C.D.B. contributed equally to this work.

²To whom correspondence may be addressed at: Departments of Biology and Genetics, 428 Clinical Research Building, 415 Curie Boulevard, University of Pennsylvania, Philadelphia, PA 19104–6145. E-mail: tishkoff@mail.med.upenn.edu.

³To whom correspondence may be addressed at: Department of Biological Statistics, Computational Biology, 102J Weill Hall, Cornell University, Ithaca, NY 14853. E-mail: cdb28@cornell.edu.

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Results

Genetic Structure of West African Populations. Our study focused on West African populations, because previous genetic and historical studies suggest that region was the source for most of the ancestry of present-day African Americans (2, 27, 28). Among the sampled West African populations, Wright's measure of population differentiation [autosomal F_{ST} (29)] was low (1.2%), suggesting quite recent common ancestry of all individuals in our sample or, alternatively, a large effective population size for the structured population from which the sample was drawn, with a large degree of gene flow among subpopulations. Nonetheless, we observed substantial variation in pairwise F_{ST} among sampled populations, suggesting genetic heterogeneity among the groups (Table 1). Differences in pairwise F_{ST} may reflect variation in effective population size or migration rates among the populations potentially attributable to isolation by distance or heterogeneity in geographical or cultural barriers to gene flow. For example, the Fulani appear to be genetically distinct from all other West African populations we sampled (average pairwise $F_{ST} = 3.91\%$). Likewise, we found that the Bulala, Xhosa, and Mada populations consistently exhibited pairwise F_{ST} above 1% when compared with any other population, whereas the non-Bantu Niger-Kordofanian populations of the Igbo, Brong, and Yoruba exhibited little genetic differentiation from one another (average $F_{ST} < 0.4\%$). These results suggest that there are clear and discernible genetic differences among some of the West African populations, whereas others appear to be nearly indistinguishable even when comparing over 300,000 genetic markers.

To investigate whether we could reliably distinguish ancestry among individuals from these populations, we used two approaches tailored for high-density genotype data. One, FRAPPE, implements a maximum likelihood method to infer genetic ancestry of each individual, wherein the individuals are assumed to have originated from K ancestral clusters (26). Fig. 1A and Fig. S2 summarize FRAPPE results when the number of clusters, K , is varied from $K = 2$ to $K = 7$. The small number of clusters was consistent with the small overall level of population differentiation among these populations. We next undertook PCA of the matrix of individual genotype values (i.e., the matrix with entries "0," "1," or "2" generated by tallying the number of copies of a given allele across all SNPs in a panel for all individuals genotyped) (30).

Patterns of population structure were consistent between the two approaches (Figs. S2–S5). For example, in the FRAPPE analysis, the Fulani population was distinguished at $K = 2$, with Bulala, Mada, and Kaba populations showing some genetic similarity with the Fulani. PCA, likewise, separated the Fulani from other populations along the first principal component (PC1) (Fig. 1B). The two subsequent principal components, PC2 and PC3, reflect the geographical distribution of the populations. PC2 showed a Chadic and Nilo-Saharan dimension extending

into inland Africa from the coast, distinguishing the Bulala, Mada, and Kaba populations. These populations belong to the Nilo-Saharan and Afro-Asiatic (Chadic) linguistic groups and live further inland. Analysis of the African populations, excluding the Fulani, gave a PC1 and PC2 that resemble the second and third principal components of the PCA with the Fulani (Fig. 1C). Rotating the PC1 and PC2 axes from the PCA without the Fulani reveals the similarity of the genetic and geographical maps (Fig. 1C and D).

At $K = 3$, the FRAPPE algorithm clusters the Bulala into their own group and suggests genetic similarity of the Mada, Kaba, and Hausa, potentially indicating differentiation of Nilo-Saharan- and Afro-Asiatic-speaking populations from Niger-Kordofanian-speaking populations. At $K = 4$, all individuals from the Bantu-speaking Xhosa of South Africa cluster into a single group and individuals from the Bantu-speaking populations (Fang, Bamoun, and Kongo) exhibit considerable shared membership in this cluster. At $K = 5$, the Mada are distinguishable as a unique group, with modest genetic similarity with the Hausa and Kaba as well as with most of the Niger-Kordofanian populations. These results suggest that although these populations are quite closely related genetically, it is possible to detect meaningful population substructure given sufficient marker density [see also ref. (2)]. It is important to note that there is likely further substructure and diversity within these populations. Because we sample a modest number of individuals from each population ($n = 13$, on average, per population), we are not likely to have captured all the genetic variation within each population, region, or linguistic family. To compare patterns of haplotype structure and discern differences in demographic history among the African populations, we estimated linkage disequilibrium (LD) between all pairs of markers in the data for all populations (see *SI Text* and Fig. S6). All the African populations showed low levels of LD (even at closely linked sites) and a rapid decay of LD with distance genome-wide relative to populations of European ancestry.

Genome-Wide Patterns of Admixture in African Americans. To understand the genetic structure of the African-American population better and to determine African-American ancestry, we used FRAPPE to evaluate African Americans together with European and African individuals genotyped on the same marker set. At $K = 2$, African populations (blue) were distinguished from European populations (red), with African Americans showing highly variable levels of European and West African ancestry (Fig. 1E and F). For the African Americans, estimated mean West African ancestry was 77%, consistent with prior studies (2, 28, 31–34). Analysis at $K = 4$ revealed additional substructure in a North-South cline within Europe and clusters coinciding with the linguistic and geographical substructure within Africa (see *SI Text*, Tables S2–S4, and Figs. S7 and S8 for

Table 1. F_{ST} distances between African populations

	Igbo	Brong	Yoruba	Kongo	Bamoun	Xhosa	Fang	Hausa	Kaba	Mada	Bulala
Brong	0.350%	—									
Yoruba	0.084%	0.200%	—								
Kongo	0.282%	0.425%	0.291%	—							
Bamoun	0.293%	0.448%	0.318%	0.175%	—						
Xhosa	1.448%	1.636%	1.251%	1.106%	1.277%	—					
Fang	0.415%	0.594%	0.432%	0.150%	0.247%	1.165%	—				
Hausa	0.397%	0.560%	0.420%	0.588%	0.546%	1.796%	0.691%	—			
Kaba	0.516%	0.510%	0.471%	0.501%	0.484%	1.498%	0.567%	0.619%	—		
Mada	1.296%	1.336%	1.300%	1.282%	1.276%	2.319%	1.380%	1.299%	0.968%	—	
Bulala	1.862%	1.905%	1.879%	1.736%	1.806%	2.646%	1.929%	1.773%	1.280%	0.931%	—
Fulani	3.905%	3.684%	4.034%	3.770%	3.996%	4.133%	4.063%	3.761%	3.811%	3.967%	3.920%

Bold face font is used to emphasize the genetic similarity of the Igbo, Brong and Yoruba.

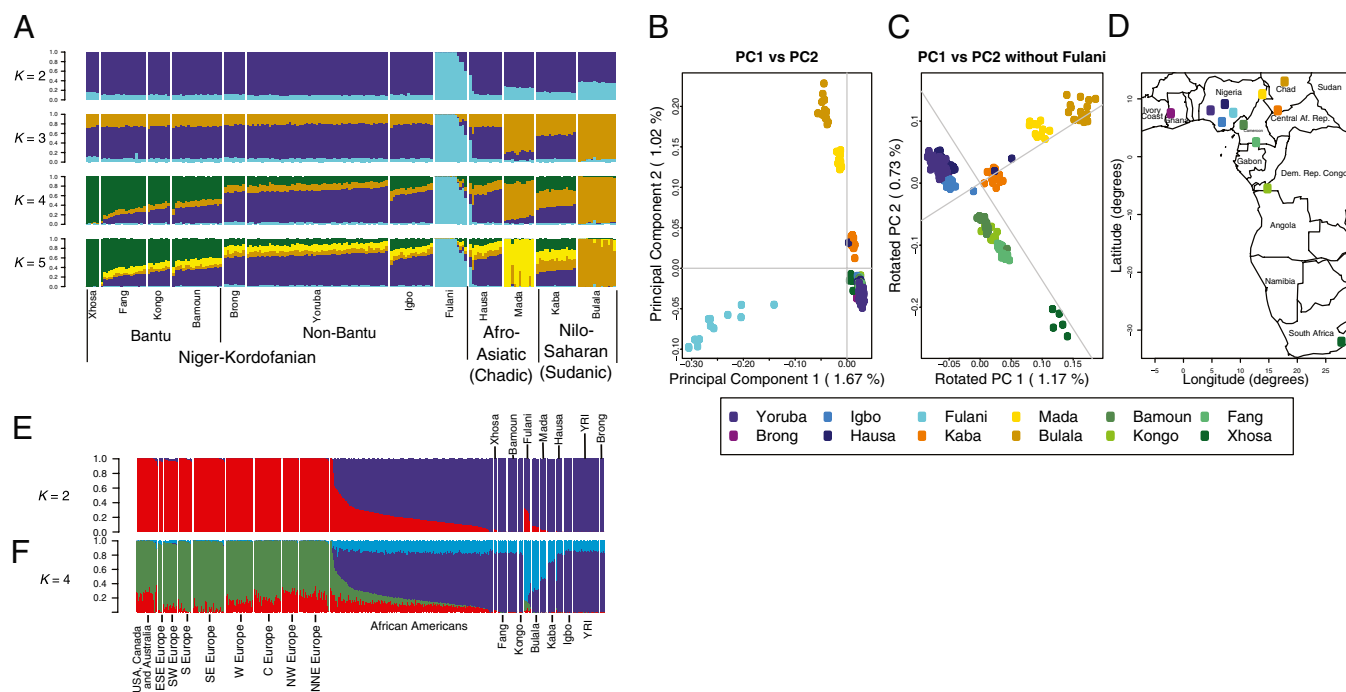


Fig. 1. Population structure within West Africa and relation to language and geography. (A) FRAPPE analysis of the West African populations. Individuals are represented as thin vertical lines partitioned into segments corresponding to the inferred membership in $K = 2$ through $K = 5$ genetic clusters as indicated by the colors (see Figs. S2–S5 for additional results). (B) Principal components 1 and 2 of the African individuals. (C) Principal components 1 and 2 of the African individuals, excluding the Fulani population, wherein the components have been rotated to emphasize further similarity with geography. (D) Approximate locations of sampled populations in Africa. (E and F) FRAPPE clustering of Europeans, African Americans, and West Africans. Individuals are represented as thin vertical lines partitioned into K segments corresponding to the inferred membership of the genetic clusters indicated by the colors. Values for $K = 2$ (E) and $K = 4$ (F) are shown for comparison between the two analyses.

additional FRAPPE and population genetic analyses). PCA of the genotype value matrix of the European, West African, and African-American samples revealed the primary axis of variation (PC1) to correspond with “European” vs. “West African” ancestry (see Fig. 2A) and explained $\sim 9.8\%$ of the genetic variance. Specifically, we observed two centroids in the data, with all the individuals of European ancestry exhibiting negative loadings along PC1, whereas all the West African individuals exhibited positive loadings. African Americans exhibited a wide range of loadings along PC1, presumably attributable to differences in European vs. West African ancestry. PC2 corresponds to population substructure within West Africa and largely mirrors the patterns discussed above.

Estimation of Admixture in Local Genomic Regions. We reconstructed estimated European or West African ancestry for every African American in our dataset at every position in the genome using a PCA-based algorithm (Fig. 2A). Our method is a generalization of the approach of Paschou et al. (35) and estimates genome-wide proportion of West African ancestry for a given individual as $P = b/(a + b)$, where b and a are the chord distances from the European and West African centroids, respectively, for the given individual along PC1. Our generalization involves undertaking the PC1 distance analysis on a grid of points along the genome (as opposed to genome-wide) centered on 15 SNP windows and using a Hidden Markov Model (HMM) for inference of ancestry state (i.e., having “0,” “1,” or “2” chromosomes of recent African origin; see *SI Text*, Fig. 2B, and Fig. S9). An ancestry plot summarizing the number of segments of European (i.e., “0”), West African (i.e., “2”), or admixed (i.e., “1”) ancestry for a representative African-American individual with 73.5% West African ancestry is illustrated in Fig. 2C. There is a great deal of variation among the ancestry plots of the 365 self-

identified African Americans in the study, ranging from an estimate of over 99% West African ancestry to an estimate of less than 1% West African ancestry (Fig. 2F). Some patterns reflected a high level of West African ancestry and only one or two ancestry-switching events per chromosome, suggesting very recent direct African ancestry (Fig. 2D). Other patterns reflected only European and admixed ancestry throughout the genome, suggesting one parent of European ancestry and one parent of African-American ancestry (Fig. 2E).

An interesting question one can address with these kinds of data is whether regions of the genome show substantially high European or West African ancestry across all individuals in the sample [e.g., as may be the case if a particular allele from one of the ancestral populations was under strong selection (36–39)]. For our analysis, we considered genomic regions as potential candidates for increased European or West African ancestry if the mean ancestry for the region across the 365 African-American individuals was 3 SDs above or below the genome-wide average of West African ancestry (78.1%). Using this approach, we found that several genomic regions of autosomal chromosomes 5, 6, and 11 could be considered outliers from the genome-wide distribution of ancestry, although these differences were not significant after correction for multiple tests. In Fig. 2G, we show mean ancestry across two example chromosomes that do not show any outlier regions (chromosomes 1 and 12) and one chromosome showing a region falling outside the 3 SD criteria (chromosome 11). Mean ancestry estimates for all chromosomes can be found in Fig. S10, and a precise listing of molecular regions for the three outlier regions may be found in Table S4. In contrast to the autosomes, the X chromosome shows significantly high West African ancestry along the majority of the chromosome, consistent with a gender-biased model of admixture with excess European male and West African female ancestry (Fig. 2G).

A concern in estimating admixture is the effect of choice of ancestral populations. Often, the true ancestral population is no longer available for sampling; thus, using a proxy may introduce bias when evaluating the admixed population. For example, individual admixture estimates in Latin Americans have been shown to depend on the ancestral populations evaluated (42). Some studies estimating admixture proportions in African Americans have used a single ancestral African population, the Yoruba (39), and our data provide an effective means of testing whether other populations may serve as better proxies for the ancestral population of African Americans and whether using the Yoruba biases inferences. Comparison of the inferred West African segments of African-American genomes with contemporary West African populations (Table S3) reveals that the ancestry of the West African component of African Americans is most similar to the profile from non-Bantu Niger-Kordofanian-speaking populations, which include the Igbo, Brong, and Yoruba, with F_{ST} values to African segments of the African Americans ranging from 0.074 to 0.089%. That these F_{ST} values are all nearly identical (and quite small), coupled with the small pairwise F_{ST} values of the Igbo, Yoruba, and Brong populations (Table 1), suggests that considering the set of West African populations sampled, any of these three populations may serve as a proxy for the ancestral population of the African Americans and that, in fact, all three are likely to have contributed ancestry to present-day African Americans (43). This is wholly in line with historical documents showing that the Igbo and Yoruba are 2 of the 10 most frequent ethnicities in slave trade records, although it is important to note that other African populations not sampled, including those from Sierra Leone, Senegal, Guinea Bissau, and Angola, may also serve as good (or potentially even better) proxies for the ancestral population of some African Americans (44).

That some individuals who self-identify as African American show almost no West African ancestry and others show almost complete West African ancestry has implications for pharmacogenomics studies and assessment of disease risk. Although individuals with very low West African or very low European ancestry may be expected by chance after several generations of admixture, these individuals are most likely descendants of individuals of European ancestry or recent African immigrants, respectively. Assuming these individuals are not simply mislabeled, it appears that the range of genetic ancestry captured under the term *African American* is extremely diverse, which suggests caution should be used in prescribing treatment based on differential guidelines for African Americans (45).

We found regions on chromosomes 5, 6, and 11 that show deviations from the overall mean West African ancestry. These regions do not overlap with those previously suggested to be under selection (39), and about a dozen genes are found across these regions. Whether these genes or regions are potentially under selection in African Americans merits further investigation.

In conclusion, we believe the data presented here speak to several important points. First, patterns of genomic diversity within Africa are complex and reflect deep historical, cultural, and linguistic impacts on gene flow among populations. These patterns are discernible using high-density genotype data and allow us to differentiate closely related populations along linguistic and geographical axes, even with limited sample sizes from many of our populations. Second, admixture can be reconstructed for local genomic regions efficiently at a high density of genetic markers. For this study, we tailored the method to admixed populations with two ancestral source populations, but the approach is generalizable to multiple populations. Application of the method to

genome-wide patterns of genomic variation in African Americans reveals the rich mosaic structure of admixture in this population. We find that we can distinguish African ancestry among West African populations to a large degree (e.g., Bantu from non-Bantu Niger-Kordofanian populations) but that some populations (e.g., Igbo, Yoruba, and, to a lesser extent, Brong) are so closely related genetically that their contribution to patterns of African ancestry in African Americans is not reliably distinguishable. We believe that increasing the density of markers and, more importantly, sequencing directly in these populations to identify ancestry-informative markers may make this possible in the future.

Materials and Methods

Datasets. We genotyped 225 individuals from 11 African populations [see the article by Tishkoff et al. (2) for sampling locations] on the Affymetrix GeneChip 500K array set and incorporated data from the Yoruban population of Ibadan, Nigeria, from the HapMap project, thinned to the same SNP set (10). European samples were from the GlaxoSmithKline Population Reference Sample (POPRES) project, a resource of nearly 6,000 control individuals from North America, Europe, and Asia (25) genotyped on the Affymetrix GeneChip 500K array set. For our analyses, we extracted a subset of 400 individuals from Europe, randomly sampling 15 individuals from each European country represented in POPRES when possible and 15 individuals each from the United States, Canada, and Australia. We include 365 African Americans from this dataset (see *SI Text* and ref. 25). Written informed consent was provided by the study participants and approved by the proper institutional review boards, and permits were obtained for collection of African populations as described by Tishkoff et al. (2).

Population Structure Analyses. FRAPPE implements an efficient maximum likelihood version of the Bayesian clustering algorithm, STRUCTURE (26, 46, 47). After thinning markers to have Pearson product-moment correlation of allele frequency, r^2 , less than 0.5 in 50 SNP windows, shifted and recalculated every 5 SNPs, we ran FRAPPE on all 204,457 remaining markers for 5,000 iterations. Clusters at $K = 6$ and higher did not correspond to known linguistic or population substructures (Fig. S2). We ran PCA using the program *smartpca* from the package *eigenstrat* (30) on a reduced dataset of 251,253 SNPs, where $r^2 < 0.8$ in 50 SNP windows. F_{ST} was calculated using a C++ implementation of Weir and Cockerham's weighted equations (29). Minor allele frequency (MAF) was thresholded at >0.1 in the populations being compared for all comparisons, except when calculating distances between African Americans and each of the African populations. To reduce the SNP ascertainment biases associated with SNP discovery in the Yoruba, we used only markers with a MAF >0.1 in Europeans for the F_{ST} estimates.

Admixture Analysis. Our local genomic PCA admixture method normalizes the genotype matrix of all individuals using the procedure as in *eigenstrat* (30). Each chromosome is divided into 15 SNP nonoverlapping windows. The score for an individual for a given window is the product of an individual's normalized and scaled genotypes across this window with the corresponding segment of the PC1 eigenvector (see *SI Text* for more details of the procedure). Windows that have one or more missing genotypes for an individual are not given a score and are omitted by the HMM. This gives a vector of scores for each individual across all chromosomes. We assume that ancestral population scores are drawn from a normal distribution and use the ancestral population sample means and variances as the estimated parameters for the distribution (see *SI Text* for mathematical details of the model and validation).

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