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Author/s:

Altshuler, DM;Durbin, RM;Abecasis, GR;Bentley, DR;Chakravarti, A;Clark, AG;Donnelly, P;Eichler, EE;Flicek, P;Gabriel, SB;Gibbs, RA;Green, ED;Hurles, ME;Knoppers, BM;Korbel, JO;Lander, ES;Lee, C;Lehrach, H;Mardis, ER;Marth, GT;McVean, GA;Nickerson, DA;Schmidt, JP;Sherry, ST;Wang, J;Wilson, RK;Gibbs, RA;Boerwinkle, E;Doddapaneni, H;Han, Y;Korchina, V;Kovar, C;Lee, S;Muzny, D;Reid, JG;Zhu, Y;Wang, J;Chang, Y;Feng, Q;Fang, X;Guo, X;Jian, M;Jiang, H;Jin, X;Lan, T;Li, G;Li, J;Li, Y;Liu, S;Liu, X;Lu, Y;Ma, X;Tang, M;Wang, B;Wang, G;Wu, H;Wu, R;Xu, X;Yin, Y;Zhang, D;Zhang, W;Zhao, J;Zhao, M;Zheng, X;Lander, ES;Altshuler, DM;Gabriel, SB;Gupta, N;Gharani, N;Toji, LH;Gerry, NP;Resch, AM;Flicek, P;Barker, J;Clarke, L;Gil, L;Hunt, SE;Kelman, G;Kulesha, E;Leinonen, R;McLaren, WM;Radhakrishnan, R;Roa, A;Smirnov, D;Smith, RE;Streeter, I;Thormann, A;Toneva, I;Vaughan, B;Zheng-Bradley, X;Bentley, DR;Grocock, R;Humphray, S;James, T;Kingsbury, Z;Lehrach, H;Sudbrak, R;Albrecht, MW;Amstislavskiy, VS;Borodina, TA;Lienhard, M;Mertes, F;Sultan, M;Timmermann, B;Yaspo, M-L;Mardis, ER;Wilson, RK;Fulton, L;Fulton, R;Sherry, ST;Ananiev, V;Belaia, Z;Beloslyudtsev, D;Bouk, N;Chen, C;Church, D;Cohen, R;Cook, C;Garner, J;Hefferon, T;Kimelman, M;Liu, C;Lopez, J;Meric, P;O'Sullivan, C;Ostapchuk, Y;Phan, L;Ponomarov, S;Schneider, V;Shekhtman, E;Sirotkin, K;Slotta, D;Zhang, H;McVean, GA;Durbin, RM;Balasubramaniam, S;Burton, J;Danecek, P;Keane, TM;Kolb-Kokocinski, A;McCarthy, S;Stalker, J;Quail, M;Schmidt, JP;Davies, CJ;Gollub, J;Webster, T;Wong, B;Zhan, Y;Auton, A;Campbell, CL;Kong, Y;Marcketta, A;Gibbs, RA;Yu, F;Antunes, L;Bainbridge, M;Muzny, D;Sabo, A;Huang, Z;Wang, J;Coin, LJM;Fang, L;Guo, X;Jin, X;Li, G;Li, Q;Li, Y;Li, Z;Lin, H;Liu, B;Luo, R;Shao, H;Xie, Y;Ye, C;Yu, C;Zhang, F;Zheng, H;Zhu, H;Alkan, C;Dal, E;Kahveci, F;Marth, GT;Garrison, EP;Kural, D;Lee, W-P;Leong, WF;Stromberg, M;Ward, AN;Wu, J;Zhang, M;Daly, MJ;DePristo, MA;Handsaker, RE;Altshuler, DM;Banks, E;Bhatia, G;del Angel, G;Gabriel, SB;Genovese, G;Gupta, N;Li, H;Kashin, S;Lander, ES;McCarroll, SA;Nemesh, JC;Poplin, RE;Yoon, SC;Lihm, J;Makarov, V;Clark, AG;Gottipati, S;Keinan, A;Rodriguez-Flores, JL;Korbel, JO;Rausch, T;Fritz, MH;Stuetz, AM;Flicek, P;Beal, K;Clarke, L;Datta, A;Herrero, J;McLaren, WM;Ritchie, GRS;Smith, RE;Zerbino, D;Zheng-Bradley, X;Sabeti, PC;Shlyakhter, I;Schaffner, SF;Vitti, J;Cooper, DN;Ball, EV;Stenson, PD;Bentley, DR;Barnes, B;Bauer, M;Cheetham, RK;Cox, A;Eberle, M;Humphray, S;Kahn, S;Murray, L;Peden, J;Shaw, R;Kenny, EE;Batzer, MA;Konkel, MK;Walker, JA;MacArthur, DG;Lek, M;Sudbrak, R;Amstislavskiy, VS;Herwig, R;Mardis, ER;Ding, L;Koboldt, DC;Larson, D;Ye, K;Gravel, S;Swaroop, A;Chew, E;Lappalainen, T;Erich, Y;Gymrek, M;Willems, TF;Simpson, JT;Shriver, MD;Rosenfeld, JA;Bustamante, CD;Montgomery, SB;De La Vega, FM;Byrnes, JK;Carroll, AW;DeGorter, MK;Lacroute, P;Maples, BK;Martin, AR;Moreno-Estrada, A;Shringarpure, SS;Zakharia, F;Halperin, E;Baran, Y;Lee, C;Cerveira, E;Hwang, J;Malhotra, A;Plewczynski, D;Radew, K;Romanovitch, M;Zhang, C;Hyland, FCL;Craig,

DW;Christoforides, A;Homer, N;Izatt, T;Kurdoglu, AA;Sinari, SA;Squire, K;Sherry, ST;Xiao, C;Sebat, J;Antaki, D;Gujral, M;Noor, A;Ye, K;Burchard, EG;Hernandez, RD;Gignoux, CR;Haussler, D;Katzman, SJ;Kent, WJ;Howie, B;Ruiz-Linares, A;Dermitzakis, ET;Devine, SE;Goncalo, RA;Kang, HM;Kidd, JM;Blackwell, T;Caron, S;Chen, W;Emery, S;Fritsche, L;Fuchsberger, C;Jun, G;Li, B;Lyons, R;Scheller, C;Sidore, C;Song, S;Sliwerska, E;Taliun, D;Tan, A;Welch, R;Wing, MK;Zhan, X;Awadalla, P;Hodgkinson, A;Li, Y;Shi, X;Quitadamo, A;Lunter, G;McVean, GA;Marchini, JL;Myers, S;Churchhouse, C;Delaneau, O;Gupta-Hinch, A;Kretzschmar, W;Iqbal, Z;Mathieson, I;Menelaou, A;Rimmer, A;Xifara, DK;Oleksyk, TK;Fu, Y;Liu, X;Xiong, M;Jorde, L;Witherspoon, D;Xing, J;Eichler, EE;Browning, BL;Browning, SR;Hormozdiari, F;Sudmant, PH;Khurana, E;Durbin, RM;Hurles, ME;Tyler-Smith, C;Albers, CA;Ayub, Q;Balasubramaniam, S;Chen, Y;Colonna, V;Danecek, P;Jostins, L;Keane, TM;McCarthy, S;Walter, K;Xue, Y;Gerstein, MB;Abyzov, A;Balasubramanian, S;Chen, J;Clarke, D;Fu, Y;Harmanci, AO;Jin, M;Lee, D;Liu, J;Mu, XJ;Zhang, J;Zhang, Y;Li, Y;Luo, R;Zhu, H;Alkan, C;Dal, E;Kahveci, F;Marth, GT;Garrison, EP;Kural, D;Lee, W-P;Ward, AN;Wu, J;Zhang, M;McCarroll, SA;Handsaker, RE;Altshuler, DM;Banks, E;Del Angel, G;Genovese, G;Hartl, C;Li, H;Kashin, S;Nemesh, JC;Shakir, K;Yoon, SC;Lihm, J;Makarov, V;Degenhardt, J;Korbel, JO;Fritz, MH;Meiers, S;Raeder, B;Rausch, T;Stuetz, AM;Flicek, P;Casale, FP;Clarke, L;Smith, RE;Stegle, O;Zheng-Bradley, X;Bentley, DR;Barnes, B;Cheetham, RK;Eberle, M;Humphray, S;Kahn, S;Murray, L;Shaw, R;Lameijer, E-W;Batzer, MA;Konkel, MK;Walker, JA;Ding, L;Hall, I;Ye, K;Lacroute, P;Lee, C;Cerveira, E;Malhotra, A;Hwang, J;Plewczynski, D;Radew, K;Romanovitch, M;Zhang, C;Craig, DW;Homer, N;Church, D;Xiao, C;Sebat, J;Antaki, D;Bafna, V;Michaelson, J;Ye, K;Devine, SE;Gardner, EJ;Abecasis, GR;Kidd, JM;Mills, RE;Dayama, G;Emery, S;Jun, G;Shi, X;Quitadamo, A;Lunter, G;McVean, GA;Chen, K;Fan, X;Chong, Z;Chen, T;Witherspoon, D;Xing, J;Eichler, EE;Chaisson, MJ;Hormozdiari, F;Huddleston, J;Malig, M;Nelson, BJ;Sudmant, PH;Parrish, NF;Khurana, E;Hurles, ME;Blackburne, B;Lindsay, SJ;Ning, Z;Walter, K;Zhang, Y;Gerstein, MB;Abyzov, A;Chen, J;Clarke, D;Lam, H;Mu, XJ;Sisu, C;Zhang, J;Zhang, Y;Gibbs, RA;Yu, F;Bainbridge, M;Challis, D;Evani, US;Kovar, C;Lu, J;Muzny, D;Nagaswamy, U;Reid, JG;Sabo, A;Yu, J;Guo, X;Li, W;Li, Y;Wu, R;Marth, GT;Garrison, EP;Leong, WF;Ward, AN;del Angel, G;DePristo, MA;Gabriel, SB;Gupta, N;Hartl, C;Poplin, RE;Clark, AG;Rodriguez-Flores, JL;Flicek, P;Clarke, L;Smith, RE;Zheng-Bradley, X;MacArthur, DG;Mardis, ER;Fulton, R;Koboldt, DC;Gravel, S;Bustamante, CD;Craig, DW;Christoforides, A;Homer, N;Izatt, T;Sherry, ST;Xiao, C;Dermitzakis, ET;Abecasis, GR;Kang, HM;McVean, GA;Gerstein, MB;Balasubramanian, S;Habegger, L;Yu, H;Flicek, P;Clarke, L;Cunningham, F;Dunham, I;Zerbino, D;Zheng-Bradley, X;Lage, K;Jespersen, JB;Horn, H;Montgomery, SB;DeGorter, MK;Khurana, E;Tyler-Smith, C;Chen, Y;Colonna, V;Xue, Y;Gerstein, MB;Balasubramanian, S;Fu, Y;Kim, D;Auton, A;Marcketta, A;Desalle, R;Narechania, A;Sayres, MAW;Garrison, EP;Handsaker, RE;Kashin, S;McCarroll, SA;Rodriguez-Flores, JL;Flicek, P;Clarke, L;Zheng-Bradley, X;Erlich, Y;Gymrek, M;Willems, TF;Bustamante, CD;Mendez, FL;Poznik, GD;Underhill, PA;Lee, C;Cerveira, E;Malhotra, A;Romanovitch, M;Zhang, C;Abecasis, GR;Coin, L;Shao, H;Mittelman, D;Tyler-Smith, C;Ayub, Q;Banerjee, R;Cerezo, M;Chen, Y;Fitzgerald, T;Louzada, S;Massaia, A;McCarthy, S;Ritchie, GR;Xue, Y;Yang, F;Gibbs, RA;Kovar, C;Kalra, D;Hale, W;Muzny, D;Reid, JG;Wang, J;Dan, X;Guo, X;Li, G;Li, Y;Ye, C;Zheng, X;Altshuler, DM;Flicek, P;Clarke, L;Zheng-Bradley, X;Bentley, DR;Cox, A;Humphray, S;Kahn, S;Sudbrak, R;Albrecht, MW;Lienhard, M;Larson, D;Craig, DW;Izatt, T;Kurdoglu, AA;Sherry, ST;Xiao, C;Haussler, D;Abecasis, GR;McVean, GA;Durbin, RM;Balasubramaniam, S;Keane, TM;McCarthy, S;Stalker, J;Chakravarti, A;Knoppers, BM;Abecasis, GR;Barnes, KC;Beiswanger, C;Burchard, EG;Bustamante, CD;Cai, H;Cao, H;Durbin, RM;Gerry, NP;Gharani, N;Gibbs, RA;Gignoux, CR;Gravel, S;Henn, B;Jones, D;Jorde, L;Kaye, JS;Keinan, A;Kent, A;Kerasidou, A;Li, Y;Mathias, R;McVean,

GA;Moreno-Estrada, A;Ossorio, PN;Parker, M;Resch, AM;Rotimi, CN;Royal, CD;Sandoval, K;Su, Y;Sudbrak, R;Tian, Z;Tishkoff, S;Toji, LH;Tyler-Smith, C;Via, M;Wang, Y;Yang, H;Yang, L;Zhu, J;Bodmer, W;Bedoya, G;Ruiz-Linares, A;Cai, Z;Gao, Y;Chu, J;Peltonen, L;Garcia-Montero, A;Orfao, A;Dutil, J;Martinez-Cruzado, JC;Oleksyk, TK;Barnes, KC;Mathias, RA;Hennis, A;Watson, H;McKenzie, C;Qadri, F;LaRocque, R;Sabeti, PC;Zhu, J;Deng, X;Sabeti, PC;Asogun, D;Folarin, O;Happi, C;Omoniwa, O;Stremlau, M;Tariyal, R;Jallow, M;Joof, FS;Corrah, T;Rockett, K;Kwiatkowski, D;Kooner, J;Tran, TH;Dunstan, SJ;Nguyen, TH;Fonnie, R;Garry, R;Kanneh, L;Moses, L;Sabeti, PC;Schieffelin, J;Grant, DS;Gallo, C;Poletti, G;Saleheen, D;Rasheed, A;Brook, LD;Felsenfeld, A;McEwen, JE;Vaydylevich, Y;Green, ED;Duncanson, A;Dunn, M;Schloss, JA;Wang, J;Yang, H;Auton, A;Brooks, LD;Durbin, RM;Garrison, EP;Kang, HM;Korbel, JO;Marchini, JL;McCarthy, S;McVean, GA;Abecasis, GR

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A global reference for human genetic variation

The 1000 Genomes Project Consortium*

Abstract

The 1000 Genomes Project set out to provide a comprehensive description of common human genetic variation by applying whole-genome sequencing to a diverse set of individuals from multiple populations. Here we report completion of the project, having reconstructed the genomes of 2,504 individuals from 26 populations using a combination of low-coverage whole-genome sequencing, deep exome sequencing, and dense microarray genotyping. We characterized a broad spectrum of genetic variation, in total over 88 million variants (84.7 million single nucleotide polymorphisms (SNPs), 3.6 million short insertions/deletions (indels), and 60,000 structural variants), all phased onto high-quality haplotypes. This resource includes >99% of SNP variants with a frequency of >1% for a variety of ancestries. We describe the distribution of genetic variation across the global sample, and discuss the implications for common disease studies.

The 1000 Genomes Project has already elucidated the properties and distribution of common and rare variation, provided insights into the processes that shape genetic diversity, and advanced understanding of disease biology^{1,2}. This resource provides a benchmark for surveys of human genetic variation and constitutes a key component for human genetic studies, by enabling array design^{3,4}, genotype imputation⁵, cataloguing of variants in regions of interest, and filtering of likely neutral variants^{6,7}.

In this final phase, individuals were sampled from 26 populations in Africa (AFR), East Asia (EAS), Europe (EUR), South Asia (SAS), and the Americas (AMR) (Fig. 1a; see Supplementary Table 1 for population descriptions and abbreviations). All individuals were sequenced using both whole-genome sequencing (mean depth = 7.4×) and targeted exome sequencing (mean depth = 65.7×). In addition, individuals and available first-degree relatives (generally, adult offspring) were genotyped using high-density SNP microarrays. This provided a cost-effective means to discover genetic variants and estimate individual genotypes and haplotypes^{1,2}.

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Correspondence and requests for materials should be addressed to A.A. (adam.auton@gmail.com) or G.R.A. (goncalo@umich.edu).

*Lists of participants and their affiliations appear in the online version of the paper.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

Supplementary Information is available in the online version of the paper.

Author Contributions Details of author contributions can be found in the author list.

The authors declare competing financial interests: details are available in the online version of the paper.

Data set overview

In contrast to earlier phases of the project, we expanded analysis beyond bi-allelic events to include multi-allelic SNPs, indels, and a diverse set of structural variants (SVs). An overview of the sample collection, data generation, data processing, and analysis is given in Extended Data Fig. 1. Variant discovery used an ensemble of 24 sequence analysis tools (Supplementary Table 2), and machine-learning classifiers to separate high-quality variants from potential false positives, balancing sensitivity and specificity. Construction of haplotypes started with estimation of long-range phased haplotypes using array genotypes for project participants and, where available, their first degree relatives; continued with the addition of high confidence bi-allelic variants that were analysed jointly to improve these haplotypes; and concluded with the placement of multi-allelic and structural variants onto the haplotype scaffold one at a time (Box 1). Overall, we discovered, genotyped, and phased 88 million variant sites (Supplementary Table 3). The project has now contributed or validated 80 million of the 100 million variants in the public dbSNP catalogue (version 141 includes 40 million SNPs and indels newly contributed by this analysis). These novel variants especially enhance our catalogue of genetic variation within South Asian (which account for 24% of novel variants) and African populations (28% of novel variants).

To control the false discovery rate (FDR) of SNPs and indels at $<5\%$, a variant quality score threshold was defined using high depth ($>30\times$) PCR-free sequence data generated for one individual per population. For structural variants, additional orthogonal methods were used for confirmation, including microarrays and long-read sequencing, resulting in $\text{FDR} < 5\%$ for deletions, duplications, multi-allelic copy-number variants, Alu and L1 insertions, and $<20\%$ for inversions, SVA (SINE/VNTR/Alu) composite retrotransposon insertions and NUMTs⁸ (nuclear mitochondrial DNA variants). To evaluate variant discovery power and genotyping accuracy, we also generated deep Complete Genomics data (mean depth = $47\times$) for 427 individuals (129 mother–father–child trios, 12 parent–child duos, and 16 unrelateds). We estimate the power to detect SNPs and indels to be $>95\%$ and $>80\%$, respectively, for variants with sample frequency of at least 0.5%, rising to $>99\%$ and $>85\%$ for frequencies $>1\%$ (Extended Data Fig. 2). At lower frequencies, comparison with $>60,000$ European haplotypes from the Haplotype Reference Consortium⁹ suggests 75% power to detect SNPs with frequency of 0.1%. Furthermore, we estimate heterozygous genotype accuracy at 99.4% for SNPs and 99.0% for indels (Supplementary Table 4), a threefold reduction in error rates compared to our previous release², resulting from the larger sample size, improvements in sequence data accuracy, and genotype calling and phasing algorithms.

A typical genome

We find that a typical genome differs from the reference human genome at 4.1 million to 5.0 million sites (Fig. 1b and Table 1). Although $>99.9\%$ of variants consist of SNPs and short indels, structural variants affect more bases: the typical genome contains an estimated 2,100 to 2,500 structural variants ($\sim 1,000$ large deletions, ~ 160 copy-number variants, ~ 915 Alu insertions, ~ 128 L1 insertions, ~ 51 SVA insertions, ~ 4 NUMTs, and ~ 10 inversions), affecting ~ 20 million bases of sequence.

The total number of observed non-reference sites differs greatly among populations (Fig. 1b). Individuals from African ancestry populations harbour the greatest numbers of variant sites, as predicted by the out-of-Africa model of human origins. Individuals from recently admixed populations show great variability in the number of variants, roughly proportional to the degree of recent African ancestry in their genomes.

The majority of variants in the data set are rare: ~64 million autosomal variants have a frequency <0.5%, ~12 million have a frequency between 0.5% and 5%, and only ~8 million have a frequency >5% (Extended Data Fig. 3a). Nevertheless, the majority of variants observed in a single genome are common: just 40,000 to 200,000 of the variants in a typical genome (1–4%) have a frequency <0.5% (Fig. 1c and Extended Data Fig. 3b). As such, we estimate that improved rare variant discovery by deep sequencing our entire sample would at least double the total number of variants in our sample but increase the number of variants in a typical genome by only ~20,000 to 60,000.

Putatively functional variation

When we restricted analyses to the variants most likely to affect gene function, we found a typical genome contained 149–182 sites with protein truncating variants, 10,000 to 12,000 sites with peptide-sequence-altering variants, and 459,000 to 565,000 variant sites overlapping known regulatory regions (untranslated regions (UTRs), promoters, insulators, enhancers, and transcription factor binding sites). African genomes were consistently at the high end of these ranges. The number of alleles associated with a disease or phenotype in each genome did not follow this pattern of increased diversity in Africa (Extended Data Fig. 4): we observed ~2,000 variants per genome associated with complex traits through genome-wide association studies (GWAS) and 24–30 variants per genome implicated in rare disease through ClinVar; with European ancestry genomes at the high-end of these counts. The magnitude of this difference is unlikely to be explained by demography^{10,11}, but instead reflects the ethnic bias of current genetic studies. We expect that improved characterization of the clinical and phenotypic consequences of non-European alleles will enable better interpretation of genomes from all individuals and populations.

Sharing of genetic variants among populations

Systematic analysis of the patterns in which genetic variants are shared among individuals and populations provides detailed accounts of population history. Although most common variants are shared across the world, rarer variants are typically restricted to closely related populations (Fig. 1a); 86% of variants were restricted to a single continental group. Using a maximum likelihood approach¹², we estimated the proportion of each genome derived from several putative ‘ancestral populations’ (Fig. 2a and Extended Data Fig. 5). This analysis separates continental groups, highlights their internal substructure, and reveals genetic similarities between related populations. For example, east–west clines are visible in Africa and East Asia, a north–south cline is visible in Europe, and European, African, and Native-American admixture is visible in genomes sampled in the Americas.

To characterize more recent patterns of shared ancestry, we first focused on variants observed on just two chromosomes (sample frequency of 0.04%), the rarest shared variants

within our sample, and known as f_2 variants². As expected, these variants are typically geographically restricted and much more likely to be shared between individuals in the same population or continental group, or between populations with known recent admixture (Extended Data Fig. 6a, b). Analysis of shared haplotype lengths around f_2 variants suggests a median common ancestor ~296 generations ago (7,410 to 8,892 years ago; Extended Data Fig. 6c, d), although those confined within a population tend to be younger, with a shared common ancestor ~143 generations ago (3,570 to 4,284 years ago)¹³.

Insights about demography

Modelling the distribution of variation within and between genomes can provide insights about the history and demography of our ancestor populations¹⁴. We used the pairwise sequentially Markovian coalescent (PSMC)¹⁴ method to characterize the effective population size (N_e) of the ancestral populations (Fig. 2b and Extended Data Fig. 7). Our results show a shared demographic history for all humans beyond ~150,000 to 200,000 years ago. Further, they show that European, Asian and American populations shared strong and sustained bottlenecks, all with $N_e < 1,500$, between 15,000 to 20,000 years ago. In contrast, the bottleneck experienced by African populations during the same time period appears less severe, with $N_e > 4,250$. These bottlenecks were followed by extremely rapid inferred population growth in non-African populations, with notable exceptions including the PEL, MXL and FIN.

Due to the shared ancestry of all humans, only a modest number of variants show large frequency differences among populations. We observed 762,000 variants that are rare (defined as having frequency <0.5%) within the global sample but much more common (>5% frequency) in at least one population (Fig. 3a). Several populations have relatively large numbers of these variants, and these are typically genetically or geographically distinct within their continental group (LWK in Africa, PEL in the Americas, JPT in East Asia, FIN in Europe, and GIH in South Asia; see Supplementary Table 5). Drifted variants within such populations may reveal phenotypic associations that would be hard to identify in much larger global samples¹⁵.

Analysis of the small set of variants with large frequency differences between closely related populations can identify targets of recent, localized adaptation. We used the F_{ST} -based population branch statistic (PBS)¹⁶ to identify genes with strong differentiation between pairs of populations in the same continental group (Fig. 3b). This approach reveals a number of previously identified selection signals (such as *SLC24A5* associated with skin pigmentation¹⁷, *HERC2* associated with eye colour¹⁸, *LCT* associated with lactose tolerance, and the *FADS* cluster that may be associated with dietary fat sources¹⁹). Several potentially novel selection signals are also highlighted (such as *TRBV9*, which appears particularly differentiated in South Asia, *PRICKLE4*, differentiated in African and South Asian populations, and a number of genes in the immunoglobulin cluster, differentiated in East Asian populations; Extended Data Fig. 8), although at least some of these signals may result from somatic rearrangements (for example, via V(D)J recombination) and differences in cell type composition among the sequenced samples. Nonetheless, the relatively small number of

genes showing strong differentiation between closely related populations highlights the rarity of strong selective sweeps in recent human evolution²⁰.

Sharing of haplotypes and imputation

The sharing of haplotypes among individuals is widely used for imputation in GWAS, a primary use of 1000 Genomes data. To assess imputation based on the phase 3 data set, we used Complete Genomics data for 9 or 10 individuals from each of 6 populations (CEU, CHS, LWK, PEL, PJL, and YRI). After excluding these individuals from the reference panel, we imputed genotypes across the genome using sites on a typical one million SNP microarray. The squared correlation between imputed and experimental genotypes was >95% for common variants in each population, decreasing gradually with minor allele frequency (Fig. 4a). Compared to phase 1, rare variation imputation improved considerably, particularly for newly sampled populations (for example, PEL and PJL, Extended Data Fig. 9a). Improvements in imputations restricted to overlapping samples suggest approximately equal contributions from greater genotype and sequence quality and from increased sample size (Fig. 4a, inset). Imputation accuracy is now similar for bi-allelic SNPs, bi-allelic indels, multi-allelic SNPs, and sites where indels and SNPs overlap, but slightly reduced for multi-allelic indels, which typically map to regions of low-complexity sequence and are much harder to genotype and phase (Extended Data Fig. 9b). Although imputation of rare variation remains challenging, it appears to be most accurate in African ancestry populations, where greater genetic diversity results in a larger number of haplotypes and improves the chances that a rare variant is tagged by a characteristic haplotype.

Resolution of genetic association studies

To evaluate the impact of our new reference panel on GWAS, we re-analysed a previous study of age-related macular degeneration (AMD) totalling 2,157 cases and 1,150 controls²¹. We imputed 17.0 million genetic variants with estimated $R^2 > 0.3$, compared to 14.1 million variants using phase 1, and only 2.4 million SNPs using HapMap2. Compared to phase 1, the number of imputed common and intermediate frequency variants increased by 7%, whereas the number of rare variants increased by >50%, and the number of indels increased by 70% (Supplementary Table 6). We permuted case-control labels to estimate a genome-wide significance threshold of $P < \sim 1.5 \times 10^{-8}$, which corresponds to ~ 3 million independent variants and is more stringent than the traditional threshold of 5×10^{-8} (Supplementary Table 7). In practice, significance thresholds must balance false positives and false negatives^{22–24}. We recommend that thresholds aiming for strict control of false positives should be determined using permutations. We expect thresholds to become more stringent when larger sample sizes are sequenced, when diverse samples are studied, or when genotyping and imputation is replaced with direct sequencing. After imputation, five independent signals in four previously reported AMD loci^{25–28} reached genome-wide significance (Supplementary Table 8). When we examined each of these to define a set of potentially causal variants using a Bayesian Credible set approach²⁹, lists of potentially functional variants were $\sim 4\times$ larger than in HapMap2-based analysis and 7% larger than in analyses based on phase 1 (Supplementary Table 9). In the *ARMS2/HTRA1* locus, the most strongly associated variant was now a structural variant (estimated imputation $R^2 = 0.89$)

that previously could not be imputed, consistent with some functional studies³⁰. Deep catalogues of potentially functional variants will help ensure that downstream functional analyses include the true candidate variants, and will aid analyses that integrate complex disease associations with functional genomic elements³¹.

The performance of imputation and GWAS studies depends on the local distribution of linkage disequilibrium (LD) between nearby variants. Controlling for sample size, the decay of LD as a function of physical distance is fastest in African populations and slowest in East Asian populations (Extended Data Fig. 10). To evaluate how these differences influence the resolution of genetic association studies and, in particular, their ability to identify a narrow set of candidate functional variants, we evaluated the number of tagging variants ($r^2 > 0.8$) for a typical variant in each population. We find that each common variant typically has over 15–20 tagging variants in non-African populations, but only about 8 in African populations (Fig. 4b). At lower frequencies, we find 3–6 tagging variants with 100 kb of variants with frequency $<0.5\%$, and differences in the number of tagging variants between continental groups are less marked.

Among variants in the GWAS catalogue (which have an average frequency of 26.6% in project haplotypes), the number of proxies averages 14.4 in African populations and 30.3–44.4 in other continental groupings (Supplementary Table 10). The potential value of multi-population fine-mapping is illustrated by the observation that the number of proxies shared across all populations is only 8.2 and, furthermore, that 34.9% of GWAS catalogue variants have no proxy shared across all continental groupings.

To further assess prospects for fine-mapping genetic association signals, we performed expression quantitative trait loci (eQTL) discovery at 17,667 genes in 69 samples from each of 6 populations (CEU, CHB, GIH, JPT, LWK, and YRI)³². We identified eQTLs for 3,285 genes at 5% FDR (average 1,265 genes per population). Overall, a typical eQTL signal comprised 67 associated variants, including an indel as one of the top associated variants 26–40% of the time (Fig. 4c). Within each discovery population, 17.5–19.5% of top eQTL variants overlapped annotated transcription factor binding sites (TFBSs), consistent with the idea that a substantial fraction of eQTL polymorphisms are TFBS polymorphisms. Using a meta-analysis approach to combine pairs of populations, the proportion of top eQTL variants overlapping TFBSs increased to 19.2–21.6% (Fig. 4d), consistent with improved localization. Including an African population provided the greatest reduction in the count of associated variants and the greatest increase in overlap between top variants and TFBSs.

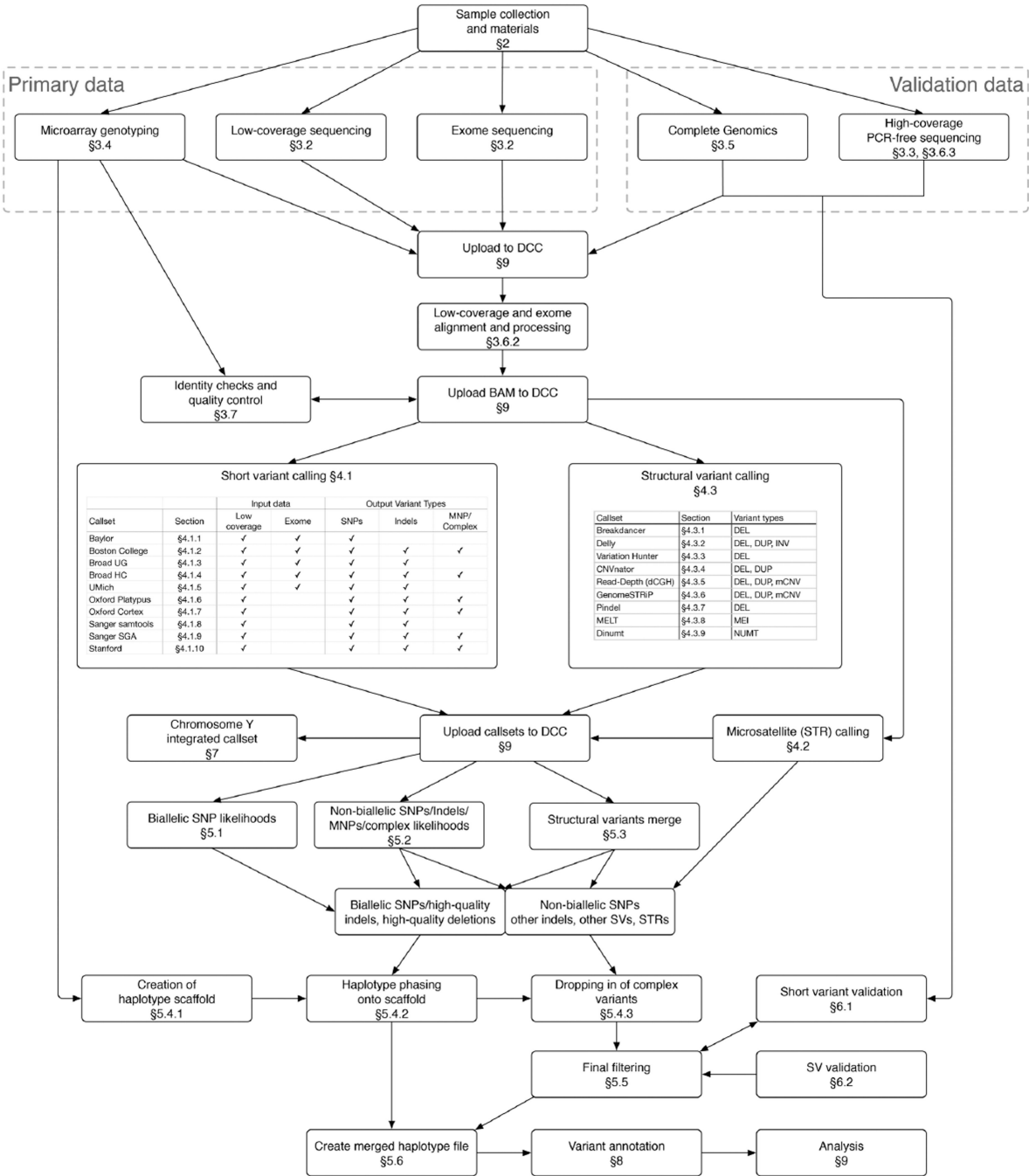
Discussion

Over the course of the 1000 Genomes Project there have been substantial advances in sequence data generation, archiving and analysis. Primary sequence data production improved with increased read length and depth, reduced per-base errors, and the introduction of paired-end sequencing. Sequence analysis methods improved with the development of strategies for identifying and filtering poor-quality data, for more accurate mapping of sequence reads (particularly in repetitive regions), for exchanging data between analysis tools and enabling ensemble analyses, and for capturing more diverse types of

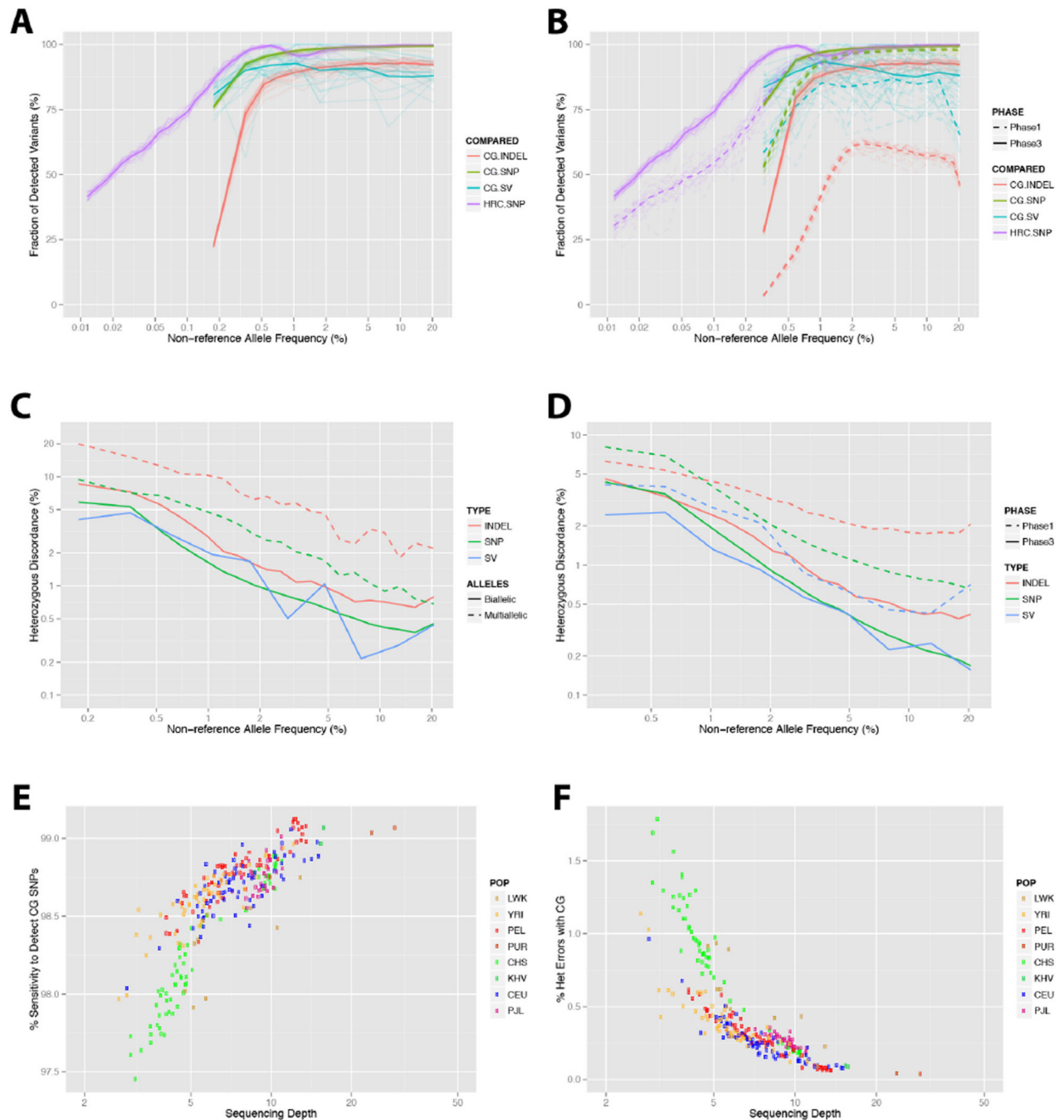
variants. Importantly, each release has examined larger numbers of individuals, aiding population-based analyses that identify and leverage shared haplotypes during genotyping. Whereas our first analyses produced high-confidence short-variant calls for 80–85% of the reference genome¹, our newest analyses reach ~96% of the genome using the same metrics, although our ability to accurately capture structural variation remains more limited³³. In addition, the evolution of sequencing, analysis and filtering strategies means that our results are not a simple superset of previous analysis. Although the number of characterized variants has more than doubled relative to phase 1, ~2.3 million previously described variants are not included in the current analysis; most missing variants were rare or marked as low quality: 1.6 million had frequency <0.5% and may be missing from our current read set, while the remainder were removed by our filtering processes.

These same technical advances are enabling the application of whole genome sequencing to a variety of medically important samples. Some of these studies already exceed the 1000 Genomes Project in size^{34–36}, but the results described here remain a prime resource for studies of genetic variation for several reasons. First, the 1000 Genomes Project samples provide a broad representation of human genetic variation—in contrast to the bulk of complex disease studies in humans, which primarily study European ancestry samples and which, as we show, fail to capture functionally important variation in other populations. Second, the project analyses incorporate multiple analysis strategies, callsets and variant types. Although such ensemble analyses are cumbersome, they provide a benchmark for what can be achieved and a yardstick against which more practical analysis strategies can be evaluated. Third, project samples and data resulting from them can be shared broadly, enabling sequencing strategies and analysis methods to be compared easily on a benchmark set of samples. Because of the wide availability of the data and samples, these samples have been and will continue to be used for studying many molecular phenotypes. Thus, we predict that the samples will accumulate many types of data that will allow connections to be drawn between variants and both molecular and disease phenotypes.

Extended Data



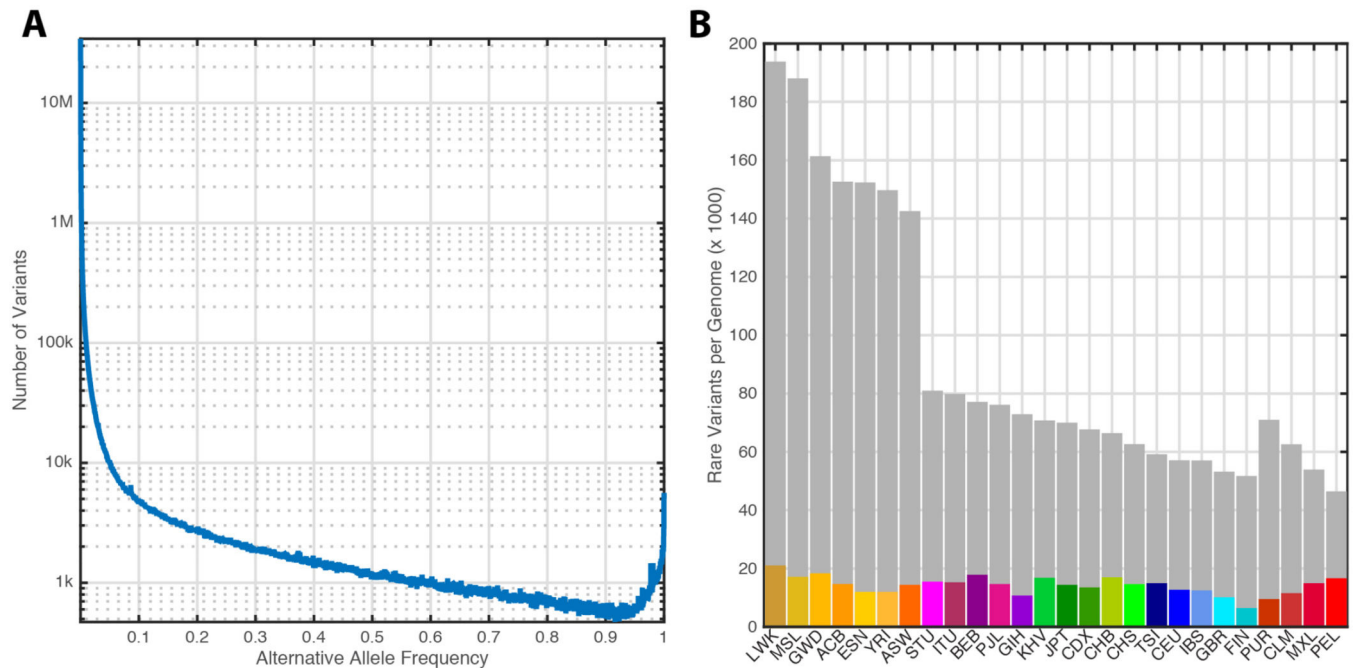
Extended Data Figure 1. Summary of the callset generation pipeline
Boxes indicate steps in the process and numbers indicate the corresponding section(s) within the Supplementary Information.



Extended Data Figure 2. Power of discovery and heterozygote genotype discordance

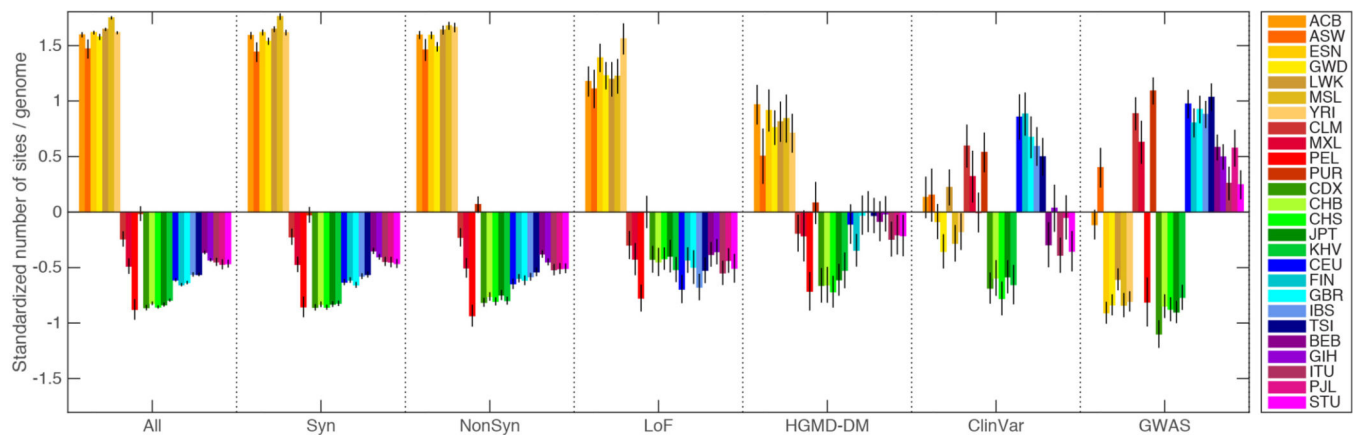
a, The power of discovery within the main data set for SNPs and indels identified within an overlapping sample of 284 genomes sequenced to high coverage by Complete Genomics (CG), and against a panel of >60,000 haplotypes constructed by the Haplotype Reference Consortium (HRC)⁹. To provide a measure of uncertainty, one curve is plotted for each chromosome. **b**, Improved power of discovery in phase 3 compared to phase 1, as assessed in a sample of 170 Complete Genomics genomes that are included in both phase 1 and phase 3. **c**, Heterozygote discordance in phase 3 for SNPs, indels, and SVs compared to 284

Complete Genomics genomes. **d**, Heterozygote discordance for phase 3 compared to phase 1 within the intersecting sample. **e**, Sensitivity to detect Complete Genomics SNPs as a function of sequencing depth. **f**, Heterozygote genotype discordance as a function of sequencing depth, as compared to Complete Genomics data.



Extended Data Figure 3. Variant counts

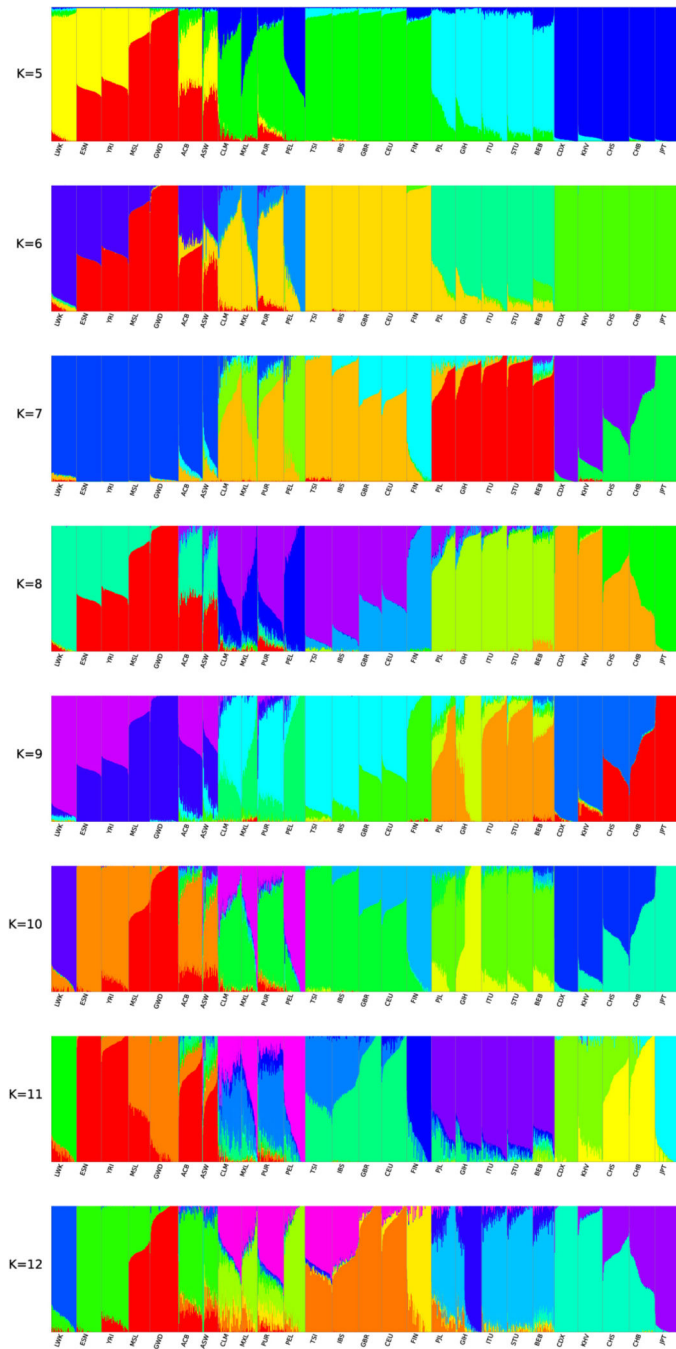
a, The number of variants within the phase 3 sample as a function of alternative allele frequency. **b**, The average number of detected variants per genome with whole-sample allele frequencies <0.5% (grey bars), with the average number of singletons indicated by colours.



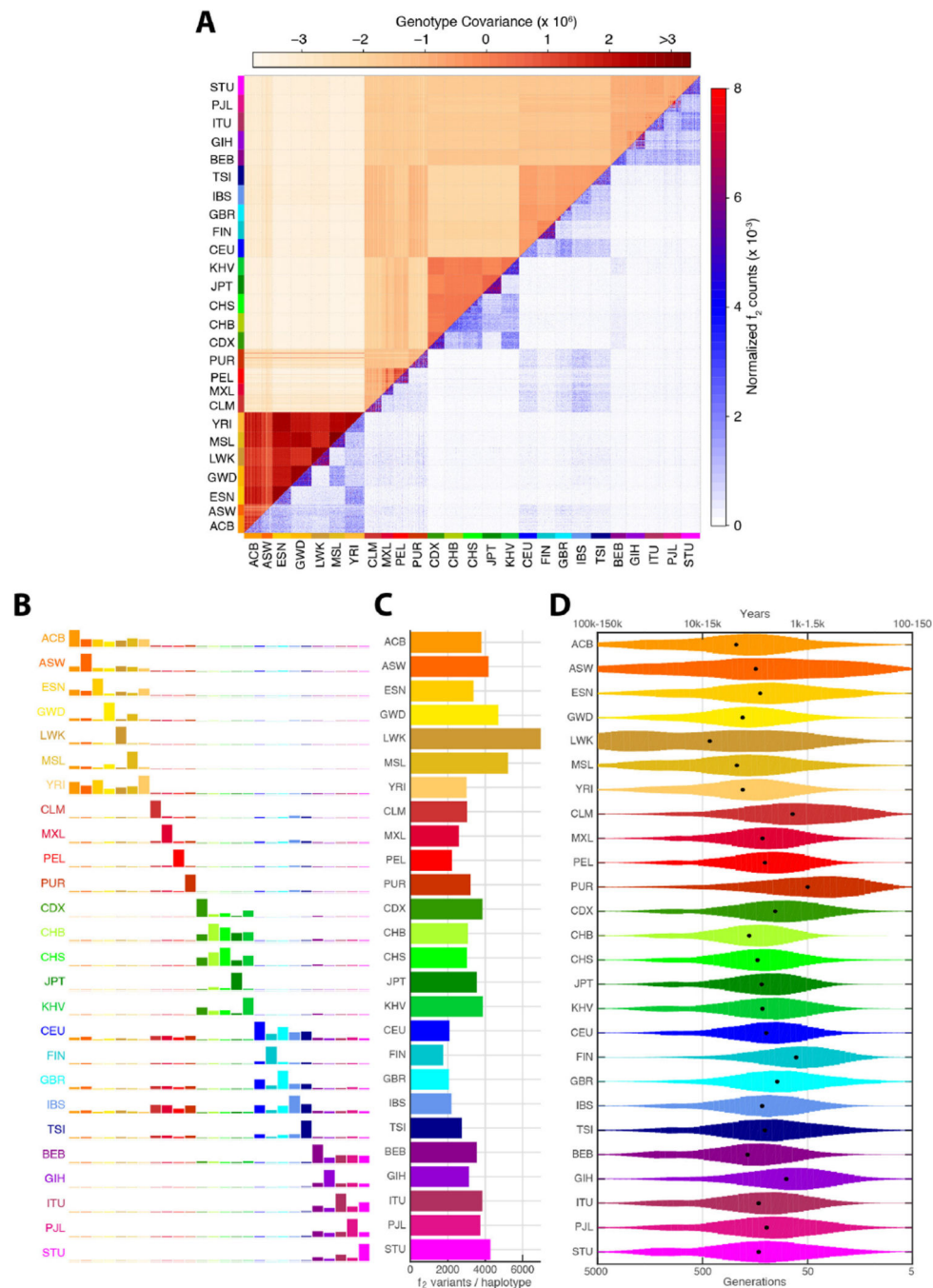
Extended Data Figure 4. The standardized number of variant sites per genome, partitioned by population and variant category

For each category, z-scores were calculated by subtracting the mean number of sites per genome (calculated across the whole sample), and dividing by the standard deviation. From left: sites with a derived allele, synonymous sites with a derived allele, nonsynonymous sites

with a derived allele, sites with a loss-of-function allele, sites with a HGMD disease mutation allele, sites with a ClinVar pathogenic variant, and sites carrying a GWAS risk allele.

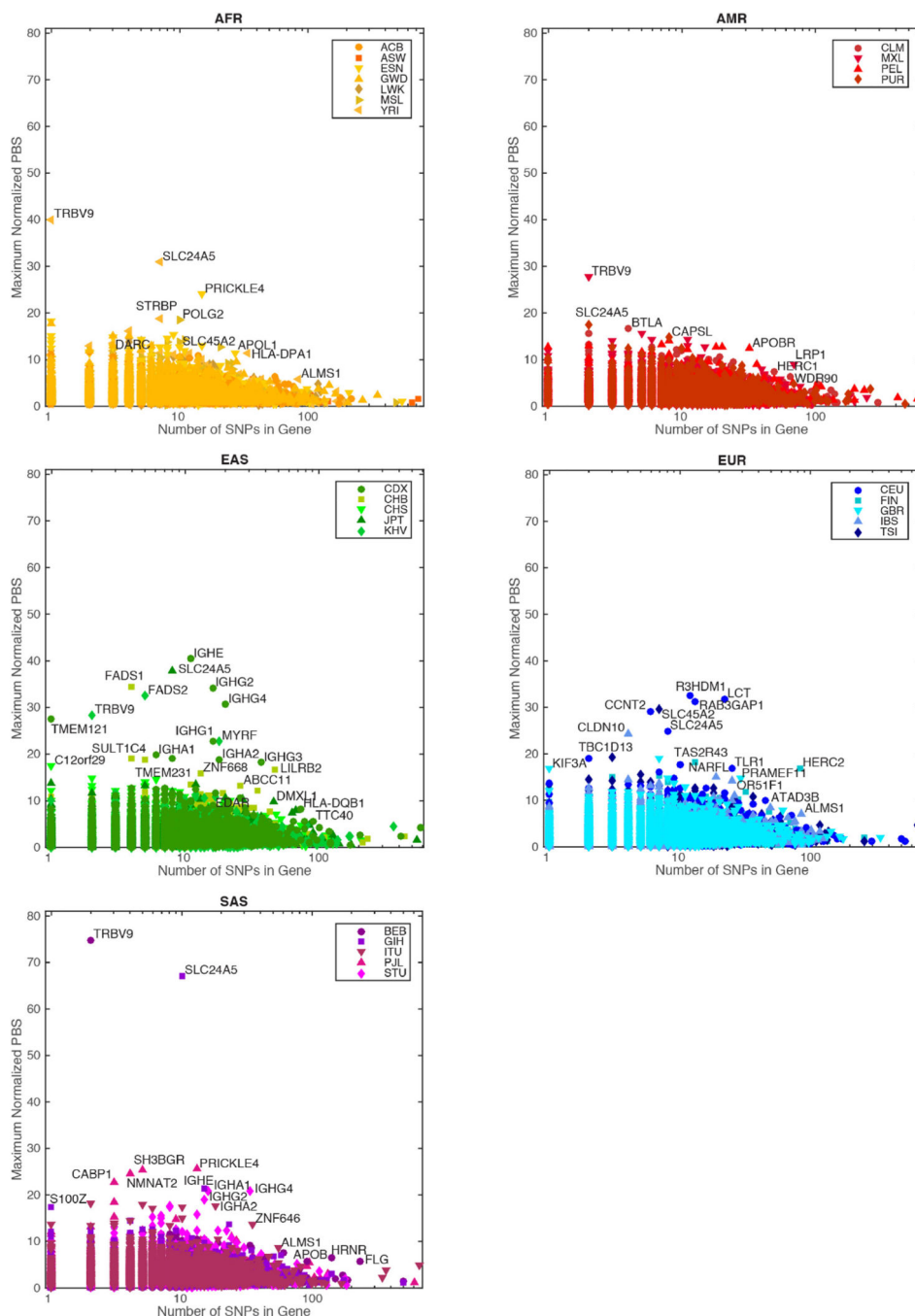


Extended Data Figure 5. Population structure as inferred using the admixture program for $K = 5$ to 12



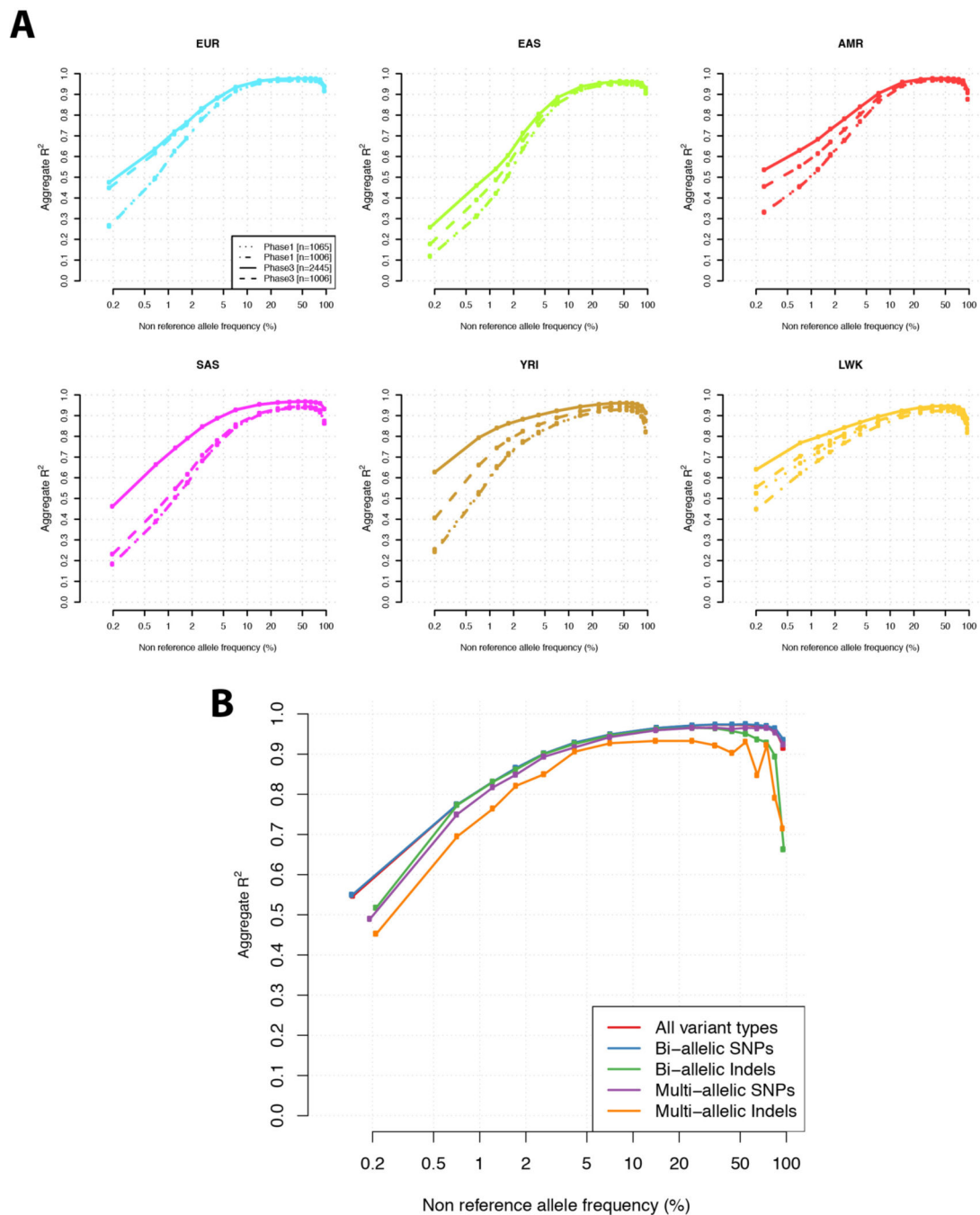
Extended Data Figure 6. Allelic sharing

a, Genotype covariance (above diagonal) and sharing of f_2 variants (below diagonal) between pairs of individuals. **b**, Quantification of average f_2 sharing between populations. Each row represents the distribution of f_2 variants shared between individuals from the population indicated on the left to individuals from each of the sampled populations. **c**, The average number of f_2 variants per haploid genome. **d**, The inferred age of f_2 variants, as estimated from shared haplotype lengths, with black dots indicating the median value.



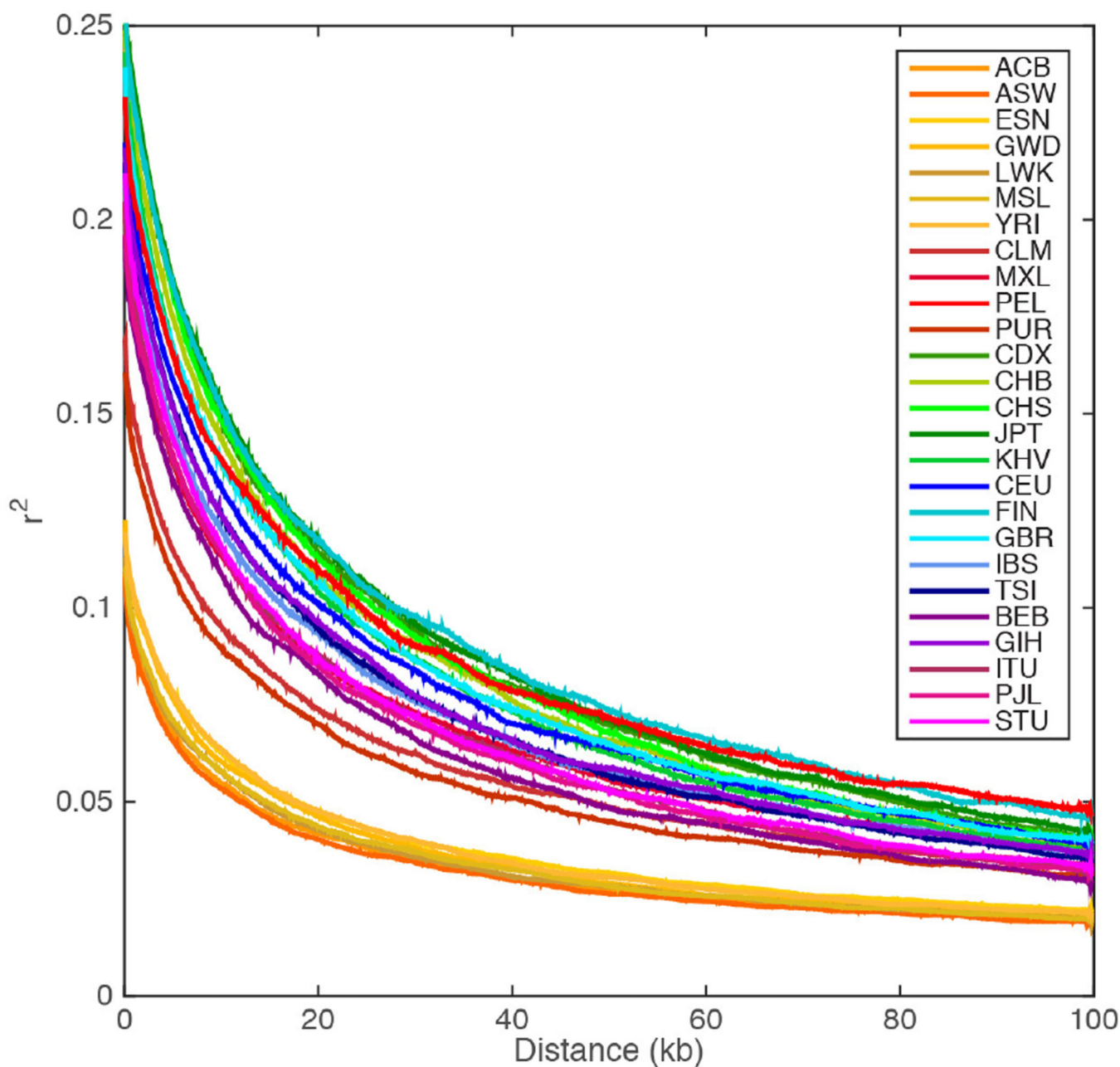
Extended Data Figure 8. Genes showing very strong patterns of differentiation between pairs of closely related populations within each continental group

Within each continental group, the maximum PBS statistic was selected from all pairwise population comparisons within the continental group against all possible out-of-continent populations. Note the x axis shows the number of polymorphic sites within the maximal comparison.



Extended Data Figure 9. Performance of imputation

a, Performance of imputation in 6 populations using a subset of phase 3 as a reference panel ($n = 2,445$), phase 1 ($n = 1,065$), and the corresponding data within intersecting samples from both phases ($n = 1,006$). **b**, Performance of imputation from phase 3 by variant class.



Extended Data Figure 10. Decay of linkage disequilibrium as a function of physical distance

Linkage disequilibrium was calculated around 10,000 randomly selected polymorphic sites in each population, having first thinned each population down to the same sample size (61 individuals). The plotted line represents a 5 kb moving average.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

The 1000 Genomes Project Consortium (Participants are arranged by project role, then by institution alphabetically, and finally alphabetically within institutions except for Principal Investigators and Project Leaders, as indicated.)

Corresponding authors Adam Auton¹, Gonalo R. Abecasis²

Steering committee: David M. Altshuler³ (Co-Chair), Richard M. Durbin⁴ (Co-Chair), Gonçalo R. Abecasis², David R. Bentley⁵, Aravinda Chakravarti⁶, Andrew G. Clark⁷, Peter Donnelly^{8,9}, Evan E. Eichler^{10,11}, Paul Flicek¹², Stacey B. Gabriel¹³, Richard A. Gibbs¹⁴, Eric D. Green¹⁵, Matthew E. Hurles⁴, Bartha M. Knoppers¹⁶, Jan O. Korbel^{12,17}, Eric S. Lander¹³, Charles Lee^{18,19}, Hans Lehrach^{20,21}, Elaine R. Mardis²², Gabor T. Marth²³, Gil A. McVean^{8,9}, Deborah A. Nickerson¹⁰, Jeanette P. Schmidt²⁴, Stephen T. Sherry²⁵, Jun Wang^{26,27,28,29,30}, Richard K. Wilson²²

Production group: Baylor College of Medicine Richard A. Gibbs¹⁴ (Principal Investigator), Eric Boerwinkle¹⁴, Harsha Doddapaneni¹⁴, Yi Han¹⁴, Viktoriya Korchina¹⁴, Christie Kovar¹⁴, Sandra Lee¹⁴, Donna Muzny¹⁴, Jeffrey G. Reid¹⁴, Yiming Zhu¹⁴; **BGI-Shenzhen** Jun Wang^{26,27,28,29,30} (Principal Investigator), Yuqi Chang²⁶, Qiang Feng^{26,27}, Xiaodong Fang^{26,27}, Xiaosen Guo^{26,27}, Min Jian^{26,27}, Hui Jiang^{26,27}, Xin Jin²⁶, Tianming Lan²⁶, Guoqing Li²⁶, Jingxiang Li²⁶, Yingrui Li²⁶, Shengmao Liu²⁶, Xiao Liu^{26,27}, Yao Lu²⁶, Xuedi Ma²⁶, Meifang Tang²⁶, Bo Wang²⁶, Guangbiao Wang²⁶, Honglong Wu²⁶, Renhua Wu²⁶, Xun Xu²⁶, Ye Yin²⁶, Dandan Zhang²⁶, Wenwei Zhang²⁶, Jiao Zhao²⁶, Meiru Zhao²⁶, Xiaole Zheng²⁶; **Broad Institute of MIT and Harvard** Eric S. Lander¹³ (Principal Investigator), David M. Altshuler³, Stacey B. Gabriel¹³ (Co-Chair), Namrata Gupta¹³; **Coriell Institute for Medical Research** Neda Gharani³¹, Lorraine H. Toji³¹, Norman P. Gerry³¹, Alissa M. Resch³¹; **European Molecular Biology Laboratory, European Bioinformatics Institute** Paul Flicek¹² (Principal Investigator), Jonathan Barker¹², Laura Clarke¹², Laurent Gil¹², Sarah E. Hunt¹², Gavin Kelman¹², Eugene Kulesha¹², Rasko Leinonen¹², William M. McLaren¹², Rajesh Radhakrishnan¹², Asier Roa¹², Dmitriy Smirnov¹², Richard E. Smith¹², Ian Streeter¹², Anja Thormann¹², Iliana Toneva¹², Brendan Vaughan¹², Xiangqun Zheng-Bradley¹²; **Illumina** David R. Bentley⁵ (Principal Investigator), Russell Grocock⁵, Sean Humphray⁵, Terena James⁵, Zoya Kingsbury⁵; **Max Planck Institute for Molecular Genetics** Hans Lehrach^{20,21} (Principal Investigator), Ralf Sudbrak³² (Project Leader), Marcus W. Albrecht³³, Vyacheslav S. Amstislavskiy²⁰, Tatiana A. Borodina³³, Matthias Lienhard²⁰, Florian Mertes²⁰, Marc Sultan²⁰, Bernd Timmermann²⁰, Marie-Laure Yaspo²⁰; **McDonnell Genome Institute at Washington University** Elaine R. Mardis²² (Co-Principal Investigator) (Co-Chair), Richard K. Wilson²² (Co-Principal Investigator), Lucinda Fulton²², Robert Fulton²²; **US National Institutes of Health** Stephen T. Sherry²⁵ (Principal Investigator), Victor Ananiev²⁵, Zinaida Belaia²⁵, Dimitriy Beloslyudtsev²⁵, Nathan Bouk²⁵, Chao Chen²⁵, Deanna Church³⁴, Robert Cohen²⁵, Charles Cook²⁵, John Garner²⁵, Timothy Hefferon²⁵, Mikhail Kimelman²⁵, Chunlei Liu²⁵, John Lopez²⁵, Peter Meric²⁵, Chris O'Sullivan³⁵, Yuri Ostapchuk²⁵, Lon Phan²⁵, Sergiy Ponomarov²⁵, Valerie Schneider²⁵, Eugene Shekhtman²⁵, Karl Sirotkin²⁵, Douglas Slotta²⁵, Hua Zhang²⁵; **University of Oxford** Gil A. McVean^{8,9} (Principal Investigator); **Wellcome Trust Sanger Institute** Richard M. Durbin⁴ (Principal Investigator), Senduran Balasubramaniam⁴, John Burton⁴, Petr Danecek⁴, Thomas M. Keane⁴, Anja Kolb-Kokocinski⁴, Shane McCarthy⁴, James Stalker⁴, Michael Quail⁴

Analysis group: Affymetrix Jeanette P. Schmidt²⁴ (Principal Investigator), Christopher J. Davies²⁴, Jeremy Gollub²⁴, Teresa Webster²⁴, Brant Wong²⁴, Yiping Zhan²⁴; **Albert Einstein College of Medicine** Adam Auton¹ (Principal Investigator), Christopher L.

Campbell¹, Yu Kong¹, Anthony Marcketta¹; **Baylor College of Medicine** Richard A. Gibbs¹⁴ (Principal Investigator), Fuli Yu¹⁴ (Project Leader), Lilian Antunes¹⁴, Matthew Bainbridge¹⁴, Donna Muzny¹⁴, Aniko Sabo¹⁴, Zhuoyi Huang¹⁴; **BGI-Shenzhen** Jun Wang^{26,27,28,29,30} (Principal Investigator), Lachlan J. M. Coin²⁶, Lin Fang^{26,27}, Xiaosen Guo²⁶, Xin Jin²⁶, Guoqing Li²⁶, Qibin Li²⁶, Yingrui Li²⁶, Zhenyu Li²⁶, Haoxiang Lin²⁶, Binghang Liu²⁶, Ruibang Luo²⁶, Haojing Shao²⁶, Yinlong Xie²⁶, Chen Ye²⁶, Chang Yu²⁶, Fan Zhang²⁶, Hancheng Zheng²⁶, Hongmei Zhu²⁶; **Bilkent University** Can Alkan³⁶, Elif Dal³⁶, Fatma Kahveci³⁶; **Boston College** Gabor T. Marth²³ (Principal Investigator), Erik P. Garrison⁴ (Project Lead), Deniz Kural³⁷, Wan-Ping Lee³⁷, Wen Fung Leong³⁸, Michael Stromberg³⁹, Alistair N. Ward²³, Jiantao Wu³⁹, Mengyao Zhang⁴⁰; **Broad Institute of MIT and Harvard** Mark J. Daly¹³ (Principal Investigator), Mark A. DePristo⁴¹ (Project Leader), Robert E. Handsaker^{13,40} (Project Leader), David M. Altshuler³, Eric Banks¹³, Gaurav Bhatia¹³, Guillermo del Angel¹³, Stacey B. Gabriel¹³, Giulio Genovese¹³, Namrata Gupta¹³, Heng Li¹³, Seva Kashin^{13,40}, Eric S. Lander¹³, Steven A. McCarroll^{13,40}, James C. Nemesh¹³, Ryan E. Poplin¹³; **Cold Spring Harbor Laboratory** Seungtae C. Yoon⁴² (Principal Investigator), Jayon Lihm⁴², Vladimir Makarov⁴³; **Cornell University** Andrew G. Clark⁷ (Principal Investigator), Srikanth Gottipati⁴⁴, Alon Keinan⁷, Juan L. Rodriguez-Flores⁴⁵; **European Molecular Biology Laboratory** Jan O. Korbel^{12,17} (Principal Investigator), Tobias Rausch^{17,46} (Project Leader), Markus H. Fritz⁴⁶, Adrian M. Stütz¹⁷; **European Molecular Biology Laboratory, European Bioinformatics Institute** Paul Flicek¹² (Principal Investigator), Kathryn Beal¹², Laura Clarke¹², Avik Datta¹², Javier Herrero⁴⁷, William M. McLaren¹², Graham R. S. Ritchie¹², Richard E. Smith¹², Daniel Zerbino¹², Xiangqun Zheng-Bradley¹²; **Harvard University** Pardis C. Sabeti^{13,48} (Principal Investigator), Ilya Shlyakhter^{13,48}, Stephen F. Schaffner^{13,48}, Joseph Vitti^{13,49}; **Human Gene Mutation Database** David N. Cooper⁵⁰ (Principal Investigator), Edward V. Ball⁵⁰, Peter D. Stenson⁵⁰; **Illumina** David R. Bentley⁵ (Principal Investigator), Bret Barnes³⁹, Markus Bauer⁵, R. Keira Cheetham⁵, Anthony Cox⁵, Michael Eberle⁵, Sean Humphray⁵, Scott Kahn³⁹, Lisa Murray⁵, John Peden⁵, Richard Shaw⁵; **Icahn School of Medicine at Mount Sinai** Eimear E. Kenny⁵¹ (Principal Investigator); **Louisiana State University** Mark A. Batzer⁵² (Principal Investigator), Miriam K. Konkel⁵², Jerilyn A. Walker⁵²; **Massachusetts General Hospital** Daniel G. MacArthur⁵³ (Principal Investigator), Monkol Lek⁵³; **Max Planck Institute for Molecular Genetics** Ralf Sudbrak³² (Project Leader), Vyacheslav S. Amstislavskiy²⁰, Ralf Herwig²⁰; **McDonnell Genome Institute at Washington University** Elaine R. Mardis²² (Co-Principal Investigator), Li Ding²², Daniel C. Koboldt²², David Larson²², Kai Ye²²; **McGill University** Simon Gravel⁵⁴; **National Eye Institute, NIH** Anand Swaroop⁵⁵, Emily Chew⁵⁵; **New York Genome Center** Tuuli Lappalainen^{56,57} (Principal Investigator), Yaniv Erlich^{56,58} (Principal Investigator), Melissa Gymrek^{13,56,59,60}, Thomas Frederick Willems⁶¹; **Ontario Institute for Cancer Research** Jared T. Simpson⁶²; **Pennsylvania State University** Mark D. Shriver⁶³ (Principal Investigator); **Rutgers Cancer Institute of New Jersey** Jeffrey A. Rosenfeld⁶⁴ (Principal Investigator); **Stanford University** Carlos D. Bustamante⁶⁵ (Principal Investigator), Stephen B. Montgomery⁶⁶ (Principal Investigator), Francisco M. De La Vega⁶⁵ (Principal Investigator), Jake K. Byrnes⁶⁷, Andrew W. Carroll⁶⁸, Marianne K. DeGorter⁶⁶, Phil Lacroute⁶⁵, Brian K. Maples⁶⁵, Alicia R. Martin⁶⁵, Andres Moreno-Estrada^{65,69}, Suyash S. Shringarpure⁶⁵, Fouad Zakharia⁶⁵; **Tel-Aviv University** Eran Halperin^{70,71,72} (Principal

Investigator), Yael Baran⁷⁰; **The Jackson Laboratory for Genomic Medicine** Charles Lee^{18,19} (Principal Investigator), Eliza Cerveira¹⁸, Jaeho Hwang¹⁸, Ankit Malhotra¹⁸ (Co-Project Lead), Dariusz Plewczynski¹⁸, Kamen Radew¹⁸, Mallory Romanovitch¹⁸, Chengsheng Zhang¹⁸ (Co-Project Lead); **Thermo Fisher Scientific** Fiona C. L. Hyland⁷³; **Translational Genomics Research Institute** David W. Craig⁷⁴ (Principal Investigator), Alexis Christoforides⁷⁴, Nils Homer⁷⁵, Tyler Izatt⁷⁴, Ahmet A. Kurdoglu⁷⁴, Shripad A. Sinari⁷⁴, Kevin Squire⁷⁶; **US National Institutes of Health** Stephen T. Sherry²⁵ (Principal Investigator), Chunlin Xiao²⁵; **University of California, San Diego** Jonathan Sebat^{77,78} (Principal Investigator), Danny Antaki⁷⁷, Madhusudan Gujral⁷⁷, Amina Noor⁷⁷, Kenny Ye⁷⁹; **University of California, San Francisco** Esteban G. Burchard⁸⁰ (Principal Investigator), Ryan D. Hernandez^{80,81,82} (Principal Investigator), Christopher R. Gignoux⁸⁰; **University of California, Santa Cruz** David Haussler^{83,84} (Principal Investigator), Sol J. Katzman⁸³, W. James Kent⁸³; **University of Chicago** Bryan Howie⁸⁵; **University College London** Andres Ruiz-Linares⁸⁶ (Principal Investigator); **University of Geneva** Emmanouil T. Dermitzakis^{87,88,89} (Principal Investigator); **University of Maryland School of Medicine** Scott E. Devine⁹⁰ (Principal Investigator); **University of Michigan** Gonçalo R. Abecasis² (Principal Investigator) (Co-Chair), Hyun Min Kang² (Project Leader), Jeffrey M. Kidd^{91,92} (Principal Investigator), Tom Blackwell², Sean Caron², Wei Chen⁹³, Sarah Emery⁹², Lars Fritsche², Christian Fuchsberger², Goo Jun^{2,94}, Bingshan Li⁹⁵, Robert Lyons⁹⁶, Chris Scheller², Carlo Sidore^{2,97,98}, Shiya Song⁹¹, Elzbieta Sliwerska⁹², Daniel Taliun², Adrian Tan², Ryan Welch², Mary Kate Wing², Xiaowei Zhan⁹⁹; **University of Montréal** Philip Awadalla^{62,100} (Principal Investigator), Alan Hodgkinson¹⁰⁰; **University of North Carolina at Chapel Hill** Yun Li¹⁰¹; **University of North Carolina at Charlotte** Xinghua Shi¹⁰² (Principal Investigator), Andrew Quitadamo¹⁰²; **University of Oxford** Gerton Lunter⁸ (Principal Investigator), Gil A. McVean^{8,9} (Principal Investigator) (Co-Chair), Jonathan L. Marchini^{8,9} (Principal Investigator), Simon Myers^{8,9} (Principal Investigator), Claire Churchhouse⁹, Olivier Delaneau^{9,87}, Anjali Gupta-Hinch⁸, Warren Kretschmar⁸, Zamin Iqbal⁸, Iain Mathieson⁸, Androniki Menelaou^{9,103}, Andy Rimmer⁸⁷, Dionysia K. Xifara^{8,9}; **University of Puerto Rico** Taras K. Oleksyk¹⁰⁴ (Principal Investigator); **University of Texas Health Sciences Center at Houston** Yunxin Fu⁹⁴ (Principal Investigator), Xiaoming Liu⁹⁴, Momiao Xiong⁹⁴; **University of Utah** Lynn Jorde¹⁰⁵ (Principal Investigator), David Witherspoon¹⁰⁵, Jinchuan Xing¹⁰⁶; **University of Washington** Evan E. Eichler^{10,11} (Principal Investigator), Brian L. Browning¹⁰⁷ (Principal Investigator), Sharon R. Browning¹⁰⁸ (Principal Investigator), Fereydoun Hormozdizadeh¹⁰, Peter H. Sudmant¹⁰; **Weill Cornell Medical College**, Ekta Khurana¹⁰⁹ (Principal Investigator); **Wellcome Trust Sanger Institute** Richard M. Durbin⁴ (Principal Investigator), Matthew E. Hurles⁴ (Principal Investigator), Chris Tyler-Smith⁴ (Principal Investigator), Cornelis A. Albers^{110,111}, Qasim Ayub⁴, Senduran Balasubramanian⁴, Yuan Chen⁴, Vincenza Colonna^{4,112}, Petr Danecek⁴, Luke Jostins⁸, Thomas M. Keane⁴, Shane McCarthy⁴, Klaudia Walter⁴, Yali Xue⁴; **Yale University** Mark B. Gerstein^{113,114,115} (Principal Investigator), Alexej Abyzov¹¹⁶, Suganthi Balasubramanian¹¹⁵, Jieming Chen¹¹³, Declan Clarke¹¹⁷, Yao Fu¹¹³, Arif O. Harmanci¹¹³, Mike Jin¹¹⁵, Donghoon Lee¹¹³, Jeremy Liu¹¹⁵, Xinmeng Jasmine Mu^{13,113}, Jing Zhang^{113,115}, Yan Zhang^{113,115}

Structural variation group: BGI-Shenzhen Yingrui Li²⁶, Ruibang Luo²⁶, Hongmei Zhu²⁶; **Bilkent University** Can Alkan³⁶, Elif Dal³⁶, Fatma Kahveci³⁶; **Boston College** Gabor T. Marth²³ (Principal Investigator), Erik P. Garrison⁴, Deniz Kural³⁷, Wan-Ping Lee³⁷, Alistair N. Ward²³, Jiantao Wu²³, Mengyao Zhang²³; **Broad Institute of MIT and Harvard** Steven A. McCarroll^{13,40} (Principal Investigator), Robert E. Handsaker^{13,40} (Project Leader), David M. Altshuler³, Eric Banks¹³, Guillermo del Angel¹³, Giulio Genovese¹³, Chris Hartl¹³, Heng Li¹³, Seva Kashin^{13,40}, James C. Nemesh¹³, Khalid Shakir¹³; **Cold Spring Harbor Laboratory** Seungtae C. Yoon⁴² (Principal Investigator), Jayon Lihm⁴², Vladimir Makarov⁴³; **Cornell University** Jeremiah Degenhardt⁷; **European Molecular Biology Laboratory** Jan O. Korbel^{12,17} (Principal Investigator) (Co-Chair), Markus H. Fritz⁴⁶, Sascha Meiers¹⁷, Benjamin Raeder¹⁷, Tobias Rausch^{17,46}, Adrian M. Stütz¹⁷; **European Molecular Biology Laboratory, European Bioinformatics Institute** Paul Flicek¹² (Principal Investigator), Francesco Paolo Casale¹², Laura Clarke¹², Richard E. Smith¹², Oliver Stegle¹², Xiangqun Zheng-Bradley¹²; **Illumina** David R. Bentley⁵ (Principal Investigator), Bret Barnes³⁹, R. Keira Cheetham⁵, Michael Eberle⁵, Sean Humphray⁵, Scott Kahn³⁹, Lisa Murray⁵, Richard Shaw⁵; **Leiden University Medical Center** Eric-Wubbo Lameijer¹¹⁸; **Louisiana State University** Mark A. Batzer⁵² (Principal Investigator), Miriam K. Konkel⁵², Jerilyn A. Walker⁵²; **McDonnell Genome Institute at Washington University** Li Ding²² (Principal Investigator), Ira Hall²², Kai Ye²²; **Stanford University** Phil Lacroute⁶⁵; **The Jackson Laboratory for Genomic Medicine** Charles Lee^{18,19} (Principal Investigator) (Co-Chair), Eliza Cerveira¹⁸, Ankit Malhotra¹⁸, Jaehoo Hwang¹⁸, Dariusz Plewczynski¹⁸, Kamen Radew¹⁸, Mallory Romanovitch¹⁸, Chengsheng Zhang¹⁸; **Translational Genomics Research Institute** David W. Craig⁷⁴ (Principal Investigator), Nils Homer⁷⁵; **US National Institutes of Health** Deanna Church³⁴, Chunlin Xiao²⁵; **University of California, San Diego** Jonathan Sebat⁷⁷ (Principal Investigator), Danny Antaki⁷⁷, Vineet Bafna¹¹⁹, Jacob Michaelson¹²⁰, Kenny Ye⁷⁹; **University of Maryland School of Medicine** Scott E. Devine⁹⁰ (Principal Investigator), Eugene J. Gardner⁹⁰ (Project Leader); **University of Michigan** Gonçalo R. Abecasis² (Principal Investigator), Jeffrey M. Kidd^{91,92} (Principal Investigator), Ryan E. Mills^{91,92} (Principal Investigator), Gargi Dayama^{91,92}, Sarah Emery⁹², Goo Jun^{2,94}; **University of North Carolina at Charlotte** Xinghua Shi¹⁰² (Principal Investigator), Andrew Quitadamo¹⁰²; **University of Oxford** Gerton Lunter⁸ (Principal Investigator), Gil A. McVean^{8,9} (Principal Investigator); **University of Texas MD Anderson Cancer Center** Ken Chen¹²¹ (Principal Investigator), Xian Fan¹²¹, Zechen Chong¹²¹, Tenghui Chen¹²¹; **University of Utah** David Witherspoon¹⁰⁵, Jinchuan Xing¹⁰⁶; **University of Washington** Evan E. Eichler^{10,11} (Principal Investigator) (Co-Chair), Mark J. Chaisson¹⁰, Fereydoun Hormozdizadeh¹⁰, John Huddleston^{10,11}, Maika Malig¹⁰, Bradley J. Nelson¹⁰, Peter H. Sudmant¹⁰; **Vanderbilt University School of Medicine** Nicholas F. Parrish⁹⁵; **Weill Cornell Medical College** Ekta Khurana¹⁰⁹ (Principal Investigator); **Wellcome Trust Sanger Institute** Matthew E. Hurles⁴ (Principal Investigator), Ben Blackburne⁴, Sarah J. Lindsay⁴, Zemin Ning⁴, Klaudia Walter⁴, Yujun Zhang⁴; **Yale University** Mark B. Gerstein^{113,114,115} (Principal Investigator), Alexej Abyzov¹¹⁶, Jieming Chen¹¹³, Declan Clarke¹¹⁷, Hugo Lam¹²², Xinneng Jasmine Mu^{13,113}, Cristina Sisu¹¹³, Jing Zhang^{113,115}, Yan Zhang^{113,115}

Exome group: Baylor College of Medicine Richard A. Gibbs¹⁴ (Principal Investigator) (Co-Chair), Fuli Yu¹⁴ (Project Leader), Matthew Bainbridge¹⁴, Danny Challis¹⁴, Uday S. Evani¹⁴, Christie Kovar¹⁴, James Lu¹⁴, Donna Muzny¹⁴, Uma Nagaswamy¹⁴, Jeffrey G. Reid¹⁴, Aniko Sabo¹⁴, Jin Yu¹⁴; **BGI-Shenzhen** Xiaosen Guo^{26,27}, Wangshen Li²⁶, Yingrui Li²⁶, Renhua Wu²⁶; **Boston College** Gabor T. Marth²³ (Principal Investigator) (Co-Chair), Erik P. Garrison⁴, Wen Fung Leong²³, Alistair N. Ward²³; **Broad Institute of MIT and Harvard** Guillermo del Angel¹³, Mark A. DePristo⁴¹, Stacey B. Gabriel¹³, Namrata Gupta¹³, Chris Hartl¹³, Ryan E. Poplin¹³; **Cornell University** Andrew G. Clark⁷ (Principal Investigator), Juan L. Rodriguez-Flores⁴⁵; **European Molecular Biology Laboratory, European Bioinformatics Institute** Paul Flicek¹² (Principal Investigator), Laura Clarke¹², Richard E. Smith¹², Xiangqun Zheng-Bradley¹²; **Massachusetts General Hospital** Daniel G. MacArthur⁵³ (Principal Investigator); **McDonnell Genome Institute at Washington University** Elaine R. Mardis²² (Principal Investigator); Robert Fulton²², Daniel C. Koboldt²²; **McGill University** Simon Gravel⁵⁴; **Stanford University** Carlos D. Bustamante⁶⁵ (Principal Investigator); **Translational Genomics Research Institute** David W. Craig⁷⁴ (Principal Investigator), Alexis Christoforides⁷⁴, Nils Homer⁷⁵, Tyler Izatt⁷⁴; **US National Institutes of Health** Stephen T. Sherry²⁵ (Principal Investigator), Chunlin Xiao²⁵; **University of Geneva** Emmanouil T. Dermitzakis^{87,88,89} (Principal Investigator); **University of Michigan** Gonçalo R. Abecasis² (Principal Investigator), Hyun Min Kang²; **University of Oxford** Gil A. McVean^{8,9} (Principal Investigator); **Yale University** Mark B. Gerstein^{113,114,115} (Principal Investigator), Suganthi Balasubramanian¹¹⁵, Lukas Habegger¹¹³

Functional interpretation group: Cornell University Haiyuan Yu⁴⁴ (Principal Investigator); **European Molecular Biology Laboratory, European Bioinformatics Institute** Paul Flicek¹² (Principal Investigator), Laura Clarke¹², Fiona Cunningham¹², Ian Dunham¹², Daniel Zerbino¹², Xiangqun Zheng-Bradley¹²; **Harvard University** Kasper Lage^{13,123} (Principal Investigator), Jakob Berg Jespersen^{13,123,124}, Heiko Horn^{13,123}; **Stanford University** Stephen B. Montgomery⁶⁶ (Principal Investigator), Marianne K. DeGorter⁶⁶; **Weill Cornell Medical College**, Ekta Khurana¹⁰⁹ (Principal Investigator); **Wellcome Trust Sanger Institute** Chris Tyler-Smith⁴ (Principal Investigator) (Co-Chair), Yuan Chen⁴, Vincenza Colonna^{4,112}, Yali Xue⁴; **Yale University** Mark B. Gerstein^{113,114,115} (Principal Investigator) (Co-Chair), Suganthi Balasubramanian¹¹⁵, Yao Fu¹¹³, Donghoon Kim¹¹⁵

Chromosome Y group: Albert Einstein College of Medicine Adam Auton¹ (Principal Investigator), Anthony Marcketta¹; **American Museum of Natural History** Rob Desalle¹²⁵, Apurva Narechania¹²⁶; **Arizona State University** Melissa A. Wilson Sayres¹²⁷; **Boston College** Erik P. Garrison⁴; **Broad Institute of MIT and Harvard** Robert E. Handsaker^{13,40}, Seva Kashin^{13,40}, Steven A. McCarroll^{13,40}; **Cornell University**: Juan L. Rodriguez-Flores⁴⁵; **European Molecular Biology Laboratory, European Bioinformatics Institute** Paul Flicek¹² (Principal Investigator), Laura Clarke¹², Xiangqun Zheng-Bradley¹²; **New York Genome Center** Yaniv Erlich^{56,58}, Melissa Gymrek^{13,56,59,60}, Thomas Frederick Willems⁶¹; **Stanford University** Carlos D. Bustamante⁶⁵ (Principal Investigator) (Co-Chair), Fernando L. Mendez⁶⁵, G. David Poznik¹²⁸, Peter A. Underhill⁶⁵; **The Jackson**

Laboratory for Genomic Medicine Charles Lee^{18,19}, Eliza Cerveira¹⁸, Ankit Malhotra¹⁸, Mallory Romanovitch¹⁸, Chengsheng Zhang¹⁸; **University of Michigan** Gonçalo R. Abecasis² (Principal Investigator); **University of Queensland** Lachlan Coin¹²⁹ (Principal Investigator), Haojing Shao¹²⁹; **Virginia Bioinformatics Institute** David Mittelman¹³⁰; **Wellcome Trust Sanger Institute** Chris Tyler-Smith⁴ (Principal Investigator) (Co-Chair), Qasim Ayub⁴, Ruby Banerjee⁴, Maria Cerezo⁴, Yuan Chen⁴, Thomas W. Fitzgerald⁴, Sandra Louzada⁴, Andrea Massaia⁴, Shane McCarthy⁴, Graham R. Ritchie⁴, Yali Xue⁴, Fengtang Yang⁴

Data coordination center group: Baylor College of Medicine Richard A. Gibbs¹⁴ (Principal Investigator), Christie Kovar¹⁴, Divya Kalra¹⁴, Walker Hale¹⁴, Donna Muzny¹⁴, Jeffrey G. Reid¹⁴; **BGI-Shenzhen** Jun Wang^{26,27,28,29,30} (Principal Investigator), Xu Dan²⁶, Xiaosen Guo^{26,27}, Guoqing Li²⁶, Yingrui Li²⁶, Chen Ye²⁶, Xiaole Zheng²⁶; **Broad Institute of MIT and Harvard** David M. Altshuler³; **European Molecular Biology Laboratory, European Bioinformatics Institute** Paul Flicek¹² (Principal Investigator) (Co-Chair), Laura Clarke¹² (Project Lead), Xiangqun Zheng-Bradley¹²; **Illumina** David R. Bentley⁵ (Principal Investigator), Anthony Cox⁵, Sean Humphray⁵, Scott Kahn³⁹; **Max Planck Institute for Molecular Genetics** Ralf Sudbrak³² (Project Lead), Marcus W. Albrecht³³, Matthias Lienhard²⁰; **McDonnell Genome Institute at Washington University** David Larson²²; **Translational Genomics Research Institute** David W. Craig⁷⁴ (Principal Investigator), Tyler Izatt⁷⁴, Ahmet A. Kurdoglu⁷⁴; **US National Institutes of Health** Stephen T. Sherry²⁵ (Principal Investigator) (Co-Chair), Chunlin Xiao²⁵; **University of California, Santa Cruz** David Haussler^{83,84} (Principal Investigator); **University of Michigan** Gonçalo R. Abecasis² (Principal Investigator); **University of Oxford** Gil A. McVean^{8,9} (Principal Investigator); **Wellcome Trust Sanger Institute** Richard M. Durbin⁴ (Principal Investigator), Senduran Balasubramaniam⁴, Thomas M. Keane⁴, Shane McCarthy⁴, James Stalker⁴

Samples and ELSI group: Aravinda Chakravarti⁶ (Co-Chair), Bartha M. Knoppers¹⁶ (Co-Chair), Gonçalo R. Abecasis², Kathleen C. Barnes¹³¹, Christine Beiswanger³¹, Esteban G. Burchard⁸⁰, Carlos D. Bustamante⁶⁵, Hongyu Cai²⁶, Hongzhi Cao^{26,27}, Richard M. Durbin⁴, Norman P. Gerry³¹, Neda Gharani³¹, Richard A. Gibbs¹⁴, Christopher R. Gignoux⁸⁰, Simon Gravel⁵⁴, Brenna Henn¹³², Danielle Jones⁴⁴, Lynn Jorde¹⁰⁵, Jane S. Kaye¹³³, Alon Keinan⁷, Alastair Kent¹³⁴, Angeliki Kerasidou¹³⁵, Yingrui Li²⁶, Rasika Mathias¹³⁶, Gil A. McVean^{8,9}, Andres Moreno-Estrada^{65,69}, Pilar N. Ossorio^{137,138}, Michael Parker¹³⁵, Alissa M. Resch³¹, Charles N. Rotimi¹³⁹, Charmaine D. Royal¹⁴⁰, Karla Sandoval⁶⁵, Yeyang Su²⁶, Ralf Sudbrak³², Zhongming Tian²⁶, Sarah Tishkoff¹⁴¹, Lorraine H. Toji³¹, Chris Tyler-Smith⁴, Marc Via¹⁴², Yuhong Wang²⁶, Huanming Yang²⁶, Ling Yang²⁶, Jiayong Zhu²⁶

Sample collection: British from England and Scotland (GBR) Walter Bodmer¹⁴³; **Colombians in Medellín, Colombia (CLM)** Gabriel Bedoya¹⁴⁴, Andres Ruiz-Linares⁸⁶; **Han Chinese South (CHS)** Zhiming Cai²⁶, Yang Gao¹⁴⁵, Jiayou Chu¹⁴⁶; **Finnish in Finland (FIN)** Leena Peltonen†; **Iberian Populations in Spain (IBS)** Andres Garcia-Montero¹⁴⁷, Alberto Orfao¹⁴⁷; **Puerto Ricans in Puerto Rico (PUR)** Julie Dutil¹⁴⁸, Juan C. Martinez-Cruzado¹⁰⁴, Taras K. Oleksyk¹⁰⁴; **African Caribbean in Barbados (ACB)**

Kathleen C. Barnes¹³¹, Rasika A. Mathias¹³⁶, Anselm Hennis^{149,150}, Harold Watson¹⁵⁰, Colin McKenzie¹⁵¹; **Bengali in Bangladesh (BEB)** Firdausi Qadri¹⁵², Regina La Rocque¹⁵², Pardis C. Sabeti^{13,48}; **Chinese Dai in Xishuangbanna, China (CDX)** Jiayong Zhu²⁶, Xiaoyan Deng¹⁵³; **Esan in Nigeria (ESN)** Pardis C. Sabeti^{13,48}, Danny Asogun¹⁵⁴, Onikepe Folarin¹⁵⁵, Christian Happi^{155,156}, Omonwunmi Omoniwa^{155,156}, Matt Stremlau^{13,48}, Ridhi Tariyal^{13,48}; **Gambian in Western Division –Mandinka (GWD)** Muminatou Jallow^{8,157}, Fatoumatta Sisay Joof^{8,157}, Tumani Corrah^{8,157}, Kirk Rockett^{8,157}, Dominic Kwiatkowski^{8,157}; **Indian Telugu in the UK (ITU) and Sri Lankan Tamil in the UK (STU)** Jaspal Kooner¹⁵⁸; **Kinh in Ho Chi Minh City, Vietnam (KHV)** Trần Tĩnh Hiền¹⁵⁹, Sarah J. Dunstan^{159,160}, Nguyen Thuy Hang¹⁵⁹; **Mende in Sierra Leone (MSL)** Richard Fonniet¹⁶¹, Robert Garry¹⁶², Lansana Kanneh¹⁶¹, Lina Moses¹⁶², Pardis C. Sabeti^{13,48}, John Schieffelin¹⁶², Donald S. Grant^{161,162}; **Peruvian in Lima, Peru (PEL)** Carla Gallo¹⁶³, Giovanni Poletti¹⁶³; **Punjabi in Lahore, Pakistan (PJL)** Danish Saleheen^{164,165}, Asif Rasheed¹⁶⁴

Scientific management: Lisa D. Brooks¹⁶⁶, Adam L. Felsenfeld¹⁶⁶, Jean E. McEwen¹⁶⁶, Yekaterina Vaydylevich¹⁶⁶, Eric D. Green¹⁵, Audrey Duncanson¹⁶⁷, Michael Dunn¹⁶⁷, Jeffery A. Schloss¹⁶⁶, Jun Wang^{26,27,28,29,30}, Huanming Yang^{26,168}

Writing group: Adam Auton¹, Lisa D. Brooks¹⁶⁶, Richard M. Durbin⁴, Erik P. Garrison⁴, Hyun Min Kang², Jan O. Korbel^{12,17}, Jonathan L. Marchini^{8,9}, Shane McCarthy⁴, Gil A. McVean^{8,9}, Gonçalo R. Abecasis²¹

Department of Genetics, Albert Einstein College of Medicine, Bronx, New York 10461, USA. ²Center for Statistical Genetics, Biostatistics, University of Michigan, Ann Arbor, Michigan 48109, USA. ³Vertex Pharmaceuticals, Boston, Massachusetts 02210, USA. ⁴Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, CB10 1SA, UK. ⁵Illumina United Kingdom, Chesterford Research Park, Little Chesterford, Nr Saffron Walden, Essex CB10 1XL, UK. ⁶McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA. ⁷Center for Comparative and Population Genomics, Cornell University, Ithaca, New York 14850, USA. ⁸Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK. ⁹Department of Statistics, University of Oxford, Oxford OX1 3TG, UK. ¹⁰Department of Genome Sciences, University of Washington School of Medicine, Seattle, Washington 98195, USA. ¹¹Howard Hughes Medical Institute, University of Washington, Seattle, Washington 98195, USA. ¹²European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SD, UK. ¹³The Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, Massachusetts 02142, USA. ¹⁴Baylor College of Medicine, Human Genome Sequencing Center, Houston, Texas 77030, USA. ¹⁵US National Institutes of Health, National Human Genome Research Institute, 31 Center Drive, Bethesda, Maryland 20892, USA. ¹⁶Centre of Genomics and Policy, McGill University, Montreal, Quebec H3A 1A4, Canada. ¹⁷European Molecular Biology Laboratory, Genome Biology Research Unit, Meyerhofstr. 1, Heidelberg, Germany. ¹⁸The Jackson Laboratory for Genomic Medicine, 10 Discovery Drive, Farmington, Connecticut 06032, USA. ¹⁹Department of Life Sciences, Ewha Womans University, Ewhayeodae-gil, Seodaemun-gu, Seoul, South Korea 120-750. ²⁰Max

Planck Institute for Molecular Genetics, D-14195 Berlin-Dahlem, Germany. ²¹Dahlem Centre for Genome Research and Medical Systems Biology, D-14195 Berlin-Dahlem, Germany. ²²McDonnell Genome Institute at Washington University, Washington University School of Medicine, St Louis, Missouri 63108, USA. ²³USTAR Center for Genetic Discovery & Department of Human Genetics, University of Utah School of Medicine, Salt Lake City, Utah 84112, USA. ²⁴Affymetrix, Santa Clara, California 95051, USA. ²⁵US National Institutes of Health, National Center for Biotechnology Information, 45 Center Drive, Bethesda, Maryland 20892, USA. ²⁶BGI-Shenzhen, Shenzhen 518083, China. ²⁷Department of Biology, University of Copenhagen, Ole Maaløes Vej 5, 2200 Copenhagen, Denmark. ²⁸Princess Al Jawhara Albrahim Center of Excellence in the Research of Hereditary Disorders, King Abdulaziz University, Jeddah 80205, Saudi Arabia. ²⁹Macau University of Science and Technology, Avenida Wai long, Taipa, Macau 999078, China. ³⁰Department of Medicine and State Key Laboratory of Pharmaceutical Biotechnology, University of Hong Kong, 21 Sassoon Road, Hong Kong. ³¹Coriell Institute for Medical Research, Camden, New Jersey 08103, USA. ³²European Centre for Public Health Genomics, UNU-MERIT, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands. ³³Alacris Theranostics, D-14195 Berlin-Dahlem, Germany. ³⁴Personalis, Menlo Park, California 94025, USA. ³⁵US National Institutes of Health, National Human Genome Research Institute, 50 South Drive, Bethesda, Maryland 20892, USA. ³⁶Department of Computer Engineering, Bilkent University, TR-06800 Bilkent, Ankara, Turkey. ³⁷Seven Bridges Genomics, 1 Broadway, 14th floor, Cambridge, Massachusetts 02142, USA. ³⁸Department of Agronomy, Kansas State University, Manhattan, Kansas 66506, USA. ³⁹Illumina, San Diego, California 92122, USA. ⁴⁰Department of Genetics, Harvard Medical School, Cambridge, Massachusetts 02142, USA. ⁴¹SynapDx, Four Hartwell Place, Lexington, Massachusetts 02421, USA. ⁴²Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA. ⁴³Seaver Autism Center and Department of Psychiatry, Mount Sinai School of Medicine, New York, New York 10029, USA. ⁴⁴Department of Biological Statistics and Computational Biology, Cornell University, Ithaca, New York 14853, USA. ⁴⁵Department of Genetic Medicine, Weill Cornell Medical College, New York, New York 10044, USA. ⁴⁶European Molecular Biology Laboratory, Genomics Core Facility, Meyerhofstrasse 1, 69117 Heidelberg, Germany. ⁴⁷Bill Lyons Informatics Centre, UCL Cancer Institute, University College London, London WC1E 6DD, UK. ⁴⁸Center for Systems Biology and Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, Massachusetts 02138, USA. ⁴⁹Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, Massachusetts 02138, USA. ⁵⁰Institute of Medical Genetics, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK. ⁵¹Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1498, New York, New York 10029-6574, USA. ⁵²Department of Biological Sciences, Louisiana State University, Baton Rouge, Louisiana 70803, USA. ⁵³Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. ⁵⁴McGill University and Genome Quebec Innovation Centre, 740, Avenue du Dr. Penfield, Montreal, Quebec H3A 0G1, Canada. ⁵⁵National Eye Institute, National Institutes of Health, Bethesda, Maryland 20892, USA. ⁵⁶New York Genome Center, 101 Avenue of the Americas, 7th floor, New York, New York 10013, USA. ⁵⁷Department of Systems

Biology, Columbia University, New York, NY 10032, USA. ⁵⁸Department of Computer Science, Fu Foundation School of Engineering, Columbia University, New York, New York, USA. ⁵⁹Harvard–MIT Division of Health Sciences and Technology, Cambridge, Massachusetts 02139, USA. ⁶⁰General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA. ⁶¹Whitehead Institute for Biomedical Research, Nine Cambridge Center, Cambridge, Massachusetts 02142, USA. ⁶²Ontario Institute for Cancer Research, MaRS Centre, 661 University Avenue, Suite 510, Toronto, Ontario, M5G 0A3, Canada. ⁶³Department of Anthropology, Penn State University, University Park, Pennsylvania 16802, USA. ⁶⁴Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey 08903, USA. ⁶⁵Department of Genetics, Stanford University, Stanford, California 94305, USA. ⁶⁶Departments of Genetics and Pathology, Stanford University, Stanford, California 94305-5324, USA. ⁶⁷Ancestry.com, San Francisco, California 94107, USA. ⁶⁸DNAnexus, 1975 West El Camino Real STE 101, Mountain View California 94040, USA. ⁶⁹Laboratorio Nacional de Genómica para la Biodiversidad (LANGEBIO), CINVESTAV, Irapuato, Guanajuato 36821, Mexico. ⁷⁰Blavatnik School of Computer Science, Tel-Aviv University, Tel-Aviv 69978, Israel. ⁷¹Department of Microbiology, Tel-Aviv University, Tel-Aviv 69978, Israel. ⁷²International Computer Science Institute, Berkeley, California 94704, USA. ⁷³Thermo Fisher Scientific, 200 Oyster Point Boulevard, South San Francisco, California 94080, USA. ⁷⁴The Translational Genomics Research Institute, Phoenix, Arizona 85004, USA. ⁷⁵Life Technologies, Beverly, Massachusetts 01915, USA. ⁷⁶Department of Human Genetics, David Geffen School of Medicine at UCLA, Los Angeles, California 90024, USA. ⁷⁷Department of Psychiatry, University of California, San Diego, La Jolla, California 92093, USA. ⁷⁸Department of Cellular and Molecular Medicine, University of California, San Diego, La Jolla, California 92093, USA. ⁷⁹Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York 10461, USA. ⁸⁰Departments of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, California 94158, USA. ⁸¹Institute for Quantitative Biosciences (QB3), University of California, San Francisco, 1700 4th Street, San Francisco, California 94158, USA. ⁸²Institute for Human Genetics, University of California, San Francisco, 1700 4th Street, San Francisco, California 94158, USA. ⁸³Center for Biomolecular Science and Engineering, University of California, Santa Cruz, Santa Cruz, California 95064, USA. ⁸⁴Howard Hughes Medical Institute, Santa Cruz, California 95064, USA. ⁸⁵Department of Human Genetics, University of Chicago, Chicago, Illinois 60637, USA. ⁸⁶Department of Genetics, Evolution and Environment, University College London, London WC1E 6BT, UK. ⁸⁷Department of Genetic Medicine and Development, University of Geneva Medical School, 1211 Geneva, Switzerland. ⁸⁸Institute for Genetics and Genomics in Geneva, University of Geneva, 1211 Geneva, Switzerland. ⁸⁹Swiss Institute of Bioinformatics, 1211 Geneva, Switzerland. ⁹⁰Institute for Genome Sciences, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. ⁹¹Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan 48109, USA. ⁹²Department of Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA. ⁹³Department of Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania 15224, USA. ⁹⁴The University of Texas Health Science Center at Houston, Houston, Texas 77030, USA. ⁹⁵Vanderbilt University School of Medicine, Nashville, Tennessee 37232,

USA. ⁹⁶University of Michigan Sequencing Core, University of Michigan, Ann Arbor, Michigan 48109, USA. ⁹⁷Istituto di Ricerca Genetica e Biomedica, CNR, Monserrato, 09042 Cagliari, Italy. ⁹⁸Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, 07100 Sassari, Italy. ⁹⁹University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, Texas 75390, USA. ¹⁰⁰Department of Pediatrics, University of Montreal, Ste. Justine Hospital Research Centre, Montreal, Quebec H3T1C5, Canada. ¹⁰¹Department of Genetics, Department of Biostatistics, Department of Computer Science, University of Chapel Hill, North Carolina 27599, USA. ¹⁰²Department of Bioinformatics and Genomics, College of Computing and Informatics, University of North Carolina at Charlotte, 9201 University City Boulevard, Charlotte, North Carolina 28223, USA. ¹⁰³Department of Medical Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands. ¹⁰⁴Department of Biology, University of Puerto Rico at Mayagüez, Mayagüez, Puerto Rico 00680, USA. ¹⁰⁵Eccles Institute of Human Genetics, University of Utah School of Medicine, Salt Lake City, Utah 84112, USA. ¹⁰⁶Department of Genetics, Rutgers University, Piscataway, New Jersey 08854, USA. ¹⁰⁷Department of Medicine, Division of Medical Genetics, University of Washington, Seattle, Washington 98195, USA. ¹⁰⁸Department of Biostatistics, University of Washington, Seattle, Washington 98195, USA. ¹⁰⁹Department of Physiology and Biophysics, Weill Cornell Medical College, New York, New York 10065, USA. ¹¹⁰Department of Human Genetics, Radboud Institute for Molecular Life Sciences and Donders Centre for Neuroscience, Radboud University Medical Center, Geert Grooteplein 10, 6525 GA Nijmegen, The Netherlands. ¹¹¹Department of Molecular Developmental Biology, Faculty of Science, Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University, 6500 HB Nijmegen, The Netherlands. ¹¹²Institute of Genetics and Biophysics, National Research Council (CNR), 80125 Naples, Italy. ¹¹³Program in Computational Biology and Bioinformatics, Yale University, New Haven, Connecticut 06520, USA. ¹¹⁴Department of Computer Science, Yale University, New Haven, Connecticut 06520, USA. ¹¹⁵Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut 06520, USA. ¹¹⁶Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota 55905, USA. ¹¹⁷Department of Chemistry, Yale University, New Haven, Connecticut 06520, USA. ¹¹⁸Molecular Epidemiology Section, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center 2333 ZA, The Netherlands. ¹¹⁹Department of Computer Science, University of California, San Diego, La Jolla, California 92093, USA. ¹²⁰Beyster Center for Genomics of Psychiatric Diseases, University of California, San Diego, La Jolla, California 92093, USA. ¹²¹Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77230, USA. ¹²²Bina Technologies, Roche Sequencing, Redwood City, California 94065, USA. ¹²³Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. ¹²⁴Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, Kemitorvet Building 208, 2800 Lyngby, Denmark. ¹²⁵Sackler Institute for Comparative Genomics, American Museum of Natural History, New York, New York 10024, USA. ¹²⁶Department of Invertebrate Zoology, American Museum of Natural History, New York, New York 10024, USA. ¹²⁷School of Life Sciences, Arizona State University, Tempe, Arizona 85287-4701, USA. ¹²⁸Program in Biomedical Informatics, Stanford University, Stanford, California

94305, USA. ¹²⁹Institute for Molecular Bioscience, University of Queensland, St Lucia, QLD 4072, Australia. ¹³⁰Virginia Bioinformatics Institute, 1015 Life Sciences Drive, Blacksburg, Virginia 24061, USA. ¹³¹Division of Allergy and Clinical Immunology, School of Medicine, Johns Hopkins University, Baltimore, Maryland 21205, USA. ¹³²Department of Ecology and Evolution, Stony Brook University, Stony Brook, New York 11794, USA. ¹³³Centre for Health, Law and Emerging Technologies, University of Oxford, Oxford OX3 7LF, UK. ¹³⁴Genetic Alliance, London N1 3QP, UK. ¹³⁵The Ethox Center, Nuffield Department of Population Health, University of Oxford, Old Road Campus, OX3 7LF, UK. ¹³⁶Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA. ¹³⁷Department of Medical History and Bioethics, Morgridge Institute for Research, University of Wisconsin-Madison, Madison, Wisconsin 53706, USA. ¹³⁸University of Wisconsin Law School, Madison, Wisconsin 53706, USA. ¹³⁹US National Institutes of Health, Center for Research on Genomics and Global Health, National Human Genome Research Institute, 12 South Drive, Bethesda, Maryland 20892, USA. ¹⁴⁰Department of African & African American Studies, Duke University, Durham, North Carolina 27708, USA. ¹⁴¹Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA. ¹⁴²Department of Psychiatry and Clinical Psychobiology & Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona, 08035 Barcelona, Spain. ¹⁴³Cancer and Immunogenetics Laboratory, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DS, UK. ¹⁴⁴Laboratory of Molecular Genetics, Institute of Biology, University of Antioquia, Medellín, Colombia. ¹⁴⁵Peking University Shenzhen Hospital, Shenzhen, 518036, China. ¹⁴⁶Institute of Medical Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Kunming 650118, China. ¹⁴⁷Instituto de Biología Molecular y Celular del Cáncer, Centro de Investigación del Cáncer/IBMCC (CSIC-USAL), Institute of Biomedical Research of Salamanca (IBSAL) & National DNA Bank Carlos III, University of Salamanca, 37007 Salamanca, Spain. ¹⁴⁸Ponce Research Institute, Ponce Health Sciences University, Ponce 00716, Puerto Rico. ¹⁴⁹Chronic Disease Research Centre, Tropical Medicine Research Institute, Cave Hill Campus, The University of the West Indies. ¹⁵⁰Faculty of Medical Sciences, Cave Hill Campus, The University of the West Indies. ¹⁵¹Tropical Metabolism Research Unit, Tropical Medicine Research Institute, Mona Campus, The University of the West Indies. ¹⁵²International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh. ¹⁵³Xishuangbanna Health School, Xishuangbanna 666100, China. ¹⁵⁴Irrua Specialist Teaching Hospital, Edo State, Nigeria. ¹⁵⁵Redeemers University, Ogun State, Nigeria. ¹⁵⁶Harvard T. H. Chan School of Public Health, Boston, Massachusetts 02115, USA. ¹⁵⁷Medical Research Council Unit, The Gambia, Atlantic Boulevard, Fajara, P.O. Box 273, Banjul, The Gambia. ¹⁵⁸NHLI, Imperial College London, Hammersmith Hospital, London SW7 2AZ, UK. ¹⁵⁹Centre for Tropical Medicine, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam. ¹⁶⁰Peter Doherty Institute of Infection and Immunity, The University of Melbourne, 792 Elizabeth Street, Melbourne VIC 3000, Australia. ¹⁶¹Kenema Government Hospital, Ministry of Health and Sanitation, Kenema, Sierra Leone. ¹⁶²Tulane University Health Sciences Center, New Orleans, Louisiana 70112, USA. ¹⁶³Laboratorios de Investigación y Desarrollo, Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia, Peru. ¹⁶⁴Center for Non-Communicable Diseases, Karachi, Pakistan. ¹⁶⁵Department of Epidemiology and Biostatistics, Perelman School of

Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA. ¹⁶⁶US National Institutes of Health, National Human Genome Research Institute, 5635 Fishers Lane, Bethesda, Maryland 20892, USA. ¹⁶⁷Wellcome Trust, Gibbs Building, 215 Euston Road, London NW1 2BE, UK. ¹⁶⁸James D. Watson Institute of Genome Sciences, Hangzhou 310008, China.

‡Deceased

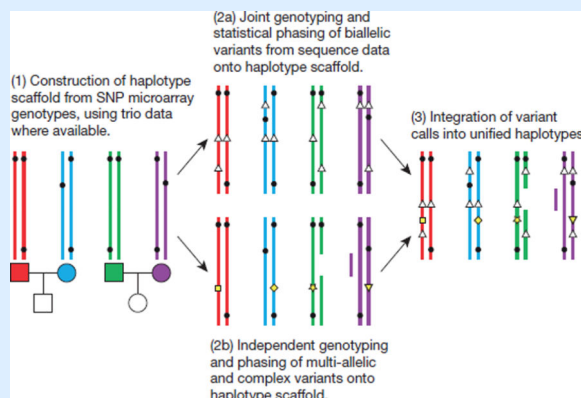
References

1. The 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature*. 2010; 467:1061–1073. [PubMed: 20981092]
2. The 1000 Genomes Project Consortium. An integrated map of genetic variation from 1,092 human genomes. *Nature*. 2012; 491:56–65. [PubMed: 23128226]
3. Voight BF, et al. The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet*. 2012; 8:e1002793. [PubMed: 22876189]
4. Trynka G, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nature Genet*. 2011; 43:1193–1201. [PubMed: 22057235]
5. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nature Genet*. 2012; 44:955–959. [PubMed: 22820512]
6. Xue Y, et al. Deleterious- and disease-allele prevalence in healthy individuals: insights from current predictions, mutation databases, and population-scale resequencing. *Am. J. Hum. Genet*. 2012; 91:1022–1032. [PubMed: 23217326]
7. Jung H, Bleazard T, Lee J, Hong D. Systematic investigation of cancer-associated somatic point mutations in SNP databases. *Nature Biotechnol*. 2013; 31:787–789. [PubMed: 24022151]
8. Sudmant PH, et al. An integrated map of structural variation in 2,504 human genomes. *Nature*. <http://dx.doi.org/10.1038/nature15394> (this issue).
9. The Haplotype Reference Consortium. (<http://www.haplotype-reference-consortium.org/>).
10. Simons YB, Turchin MC, Pritchard JK, Sella G. The deleterious mutation load is insensitive to recent population history. *Nature Genet*. 2014; 46:220–224. [PubMed: 24509481]
11. Do R, et al. No evidence that selection has been less effective at removing deleterious mutations in Europeans than in Africans. *Nature Genet*. 2015; 47:126–131. [PubMed: 25581429]
12. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. *Genome Res*. 2009; 19:1655–1664. [PubMed: 19648217]
13. Mathieson I, McVean G. Demography and the age of rare variants. *PLoS Genet*. 2014; 10:e1004528. [PubMed: 25101869]
14. Li H, Durbin R. Inference of human population history from individual whole-genome sequences. *Nature*. 2011; 475:493–496. [PubMed: 21753753]
15. Moltke I, et al. A common Greenlandic *TBC1D4* variant confers muscle insulin resistance and type 2 diabetes. *Nature*. 2014; 512:190–193. [PubMed: 25043022]
16. Yi X, et al. Sequencing of 50 human exomes reveals adaptation to high altitude. *Science*. 2010; 329:75–78. [PubMed: 20595611]
17. Lamason RL, et al. SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science*. 2005; 310:1782–1786. [PubMed: 16357253]
18. Eiberg H, et al. Blue eye color in humans may be caused by a perfectly associated founder mutation in a regulatory element located within the *HERC2* gene inhibiting *OCA2* expression. *Hum. Genet*. 2008; 123:177–187. [PubMed: 18172690]
19. Mathias RA, et al. Adaptive evolution of the *FADS* gene cluster within Africa. *PLoS ONE*. 2012; 7:e44926. [PubMed: 23028684]
20. Hernandez RD, et al. Classic selective sweeps were rare in recent human evolution. *Science*. 2011; 331:920–924. [PubMed: 21330547]

21. Chen W, et al. Genetic variants near *TIMP3* and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. *Proc. Natl Acad. Sci. USA*. 2010; 107:7401–7406. [PubMed: 20385819]
22. Wakefield J. Bayes factors for genome-wide association studies: comparison with *P*-values. *Genet. Epidemiol.* 2009; 33:79–86. [PubMed: 18642345]
23. Wakefield J. Commentary: genome-wide significance thresholds via Bayes factors. *Int. J. Epidemiol.* 2012; 41:286–291. [PubMed: 22345299]
24. Sham PC, Purcell SM. Statistical power and significance testing in large-scale genetic studies. *Nature Rev. Genet.* 2014; 15:335–346. [PubMed: 24739678]
25. Gold B, et al. Variation in factor B(*BF*) and complement component 2 (*C2*) genes is associated with age-related macular degeneration. *Nature Genet.* 2006; 38:458–462. [PubMed: 16518403]
26. Klein RJ, et al. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005; 308:385–389. [PubMed: 15761122]
27. Rivera A, et al. Hypothetical *LOC387715* is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Hum. Mol. Genet.* 2005; 14:3227–3236. [PubMed: 16174643]
28. Yates JR, et al. Complement C3 variant and the risk of age-related macular degeneration. *N. Engl. J. Med.* 2007; 357:553–561. [PubMed: 17634448]
29. Maller JB, et al. Bayesian refinement of association signals for 14 loci in 3 common diseases. *Nature Genet.* 2012; 44:1294–1301. [PubMed: 23104008]
30. Fritsche LG, et al. Age-related macular degeneration is associated with an unstable *ARMS2* (*LOC387715*) mRNA. *Nature Genet.* 2008; 40:892–896. [PubMed: 18511946]
31. The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012; 489:57–74. [PubMed: 22955616]
32. Stranger BE, et al. Patterns of *cis* regulatory variation in diverse human populations. *PLoS Genet.* 2012; 8:e1002639. [PubMed: 22532805]
33. Chaisson MJ, et al. Resolving the complexity of the human genome using single-molecule sequencing. *Nature*. 2015; 517:608–611. [PubMed: 25383537]
34. Gudbjartsson DF, et al. Large-scale whole-genome sequencing of the Icelandic population. *Nature Genet.* 2015; 47:435–444. [PubMed: 25807286]
35. The UK10K Consortium. The UK10K project identifies rare variants in health and disease. *Nature*. 2015 <http://dx.doi.org/10.1038/nature14962>.
36. Sidore C, et al. Genome sequencing elucidates Sardinian genetic architecture and augments association analyses for lipid and blood inflammatory markers. *Nature Genet.* 2015 <http://dx.doi.org/10.1038/ng3368>.
37. Delaneau O, Marchini J. The 1000 Genomes Project Consortium. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. *Nature Commun.* 2014; 5:3934. [PubMed: 25653097]
38. O'Connell J, et al. A general approach for haplotype phasing across the full spectrum of relatedness. *PLoS Genet.* 2014; 10:e1004234. [PubMed: 24743097]
39. Menelaou A, Marchini J. Genotype calling and phasing using next-generation sequencing reads and a haplotype scaffold. *Bioinformatics*. 2013; 29:84–91. [PubMed: 23093610]

BOX 1**Building a haplotype scaffold**

To construct high quality haplotypes that integrate multiple variant types, we adopted a staged approach³⁷. (1) A high-quality ‘haplotype scaffold’ was constructed using statistical methods applied to SNP microarray genotypes (black circles) and, where available, genotypes for first degree relatives (available for ~52% of samples; Supplementary Table 11)³⁸. (2a) Variant sites were identified using a combination of bioinformatic tools and pipelines to define a set of high-confidence bi-allelic variants, including both SNPs and indels (white triangles), which were jointly imputed onto the haplotype scaffold. (2b) Multi-allelic SNPs, indels, and complex variants (represented by yellow shapes, or variation in copy number) were placed onto the haplotype scaffold one at a time, exploiting the local linkage disequilibrium information but leaving haplotypes for other variants undisturbed³⁹. (3) The biallelic and multi-allelic haplotypes were merged into a single haplotype representation. This multi-stage approach allows the long-range structure of the haplotype scaffold to be maintained while including more complex types of variation. Comparison to haplotypes constructed from fosmid suggests the average distance between phasing errors is ~1,062 kb, with typical phasing errors stretching ~37kb (Supplementary Table 12).



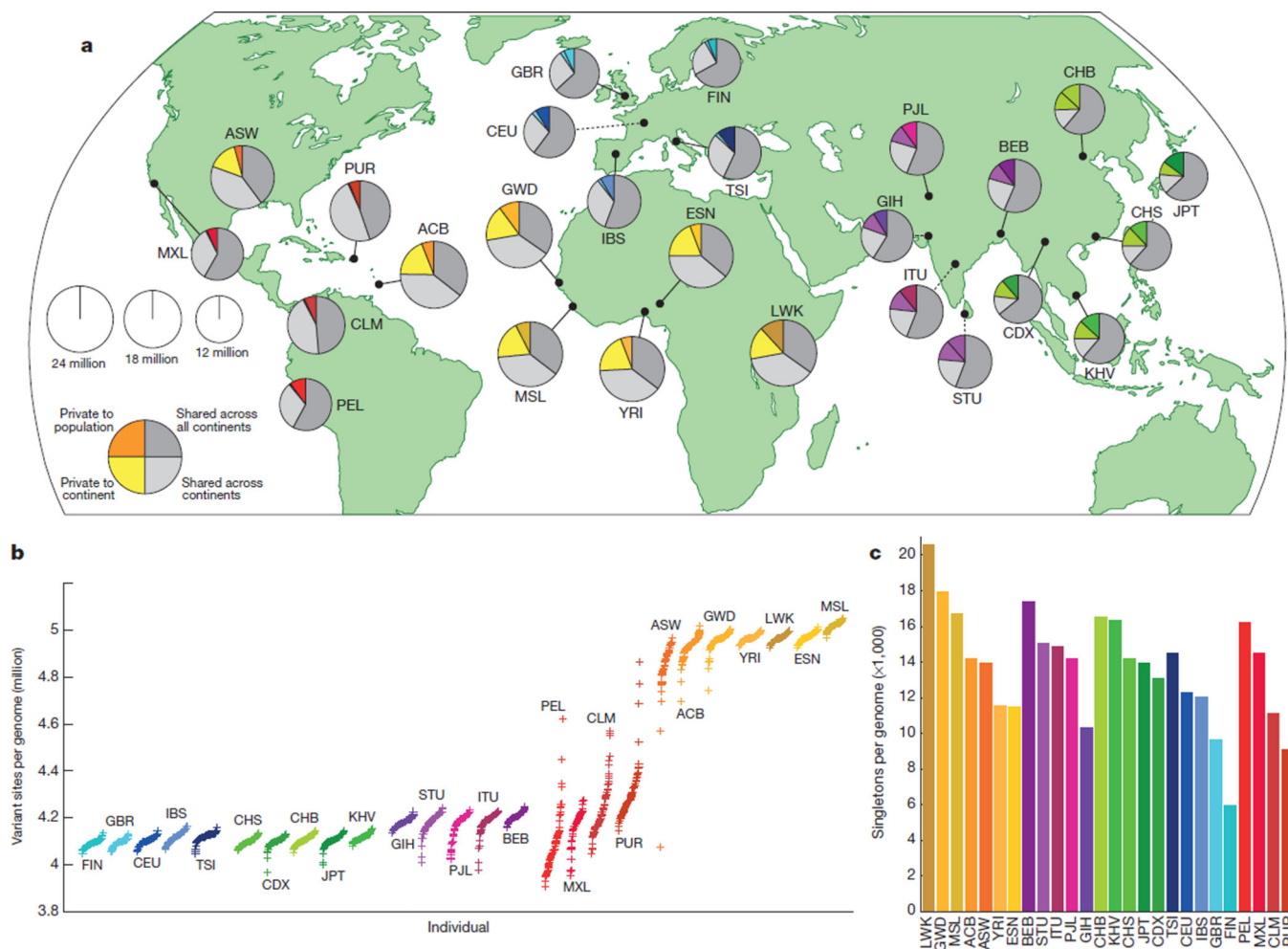


Figure 1. Population sampling

a, Polymorphic variants within sampled populations. The area of each pie is proportional to the number of polymorphisms within a population. Pies are divided into four slices, representing variants private to a population (darker colour unique to population), private to a continental area (lighter colour shared across continental group), shared across continental areas (light grey), and shared across all continents (dark grey). Dashed lines indicate populations sampled outside of their ancestral continental region. **b**, The number of variant sites per genome. **c**, The average number of singletons per genome.

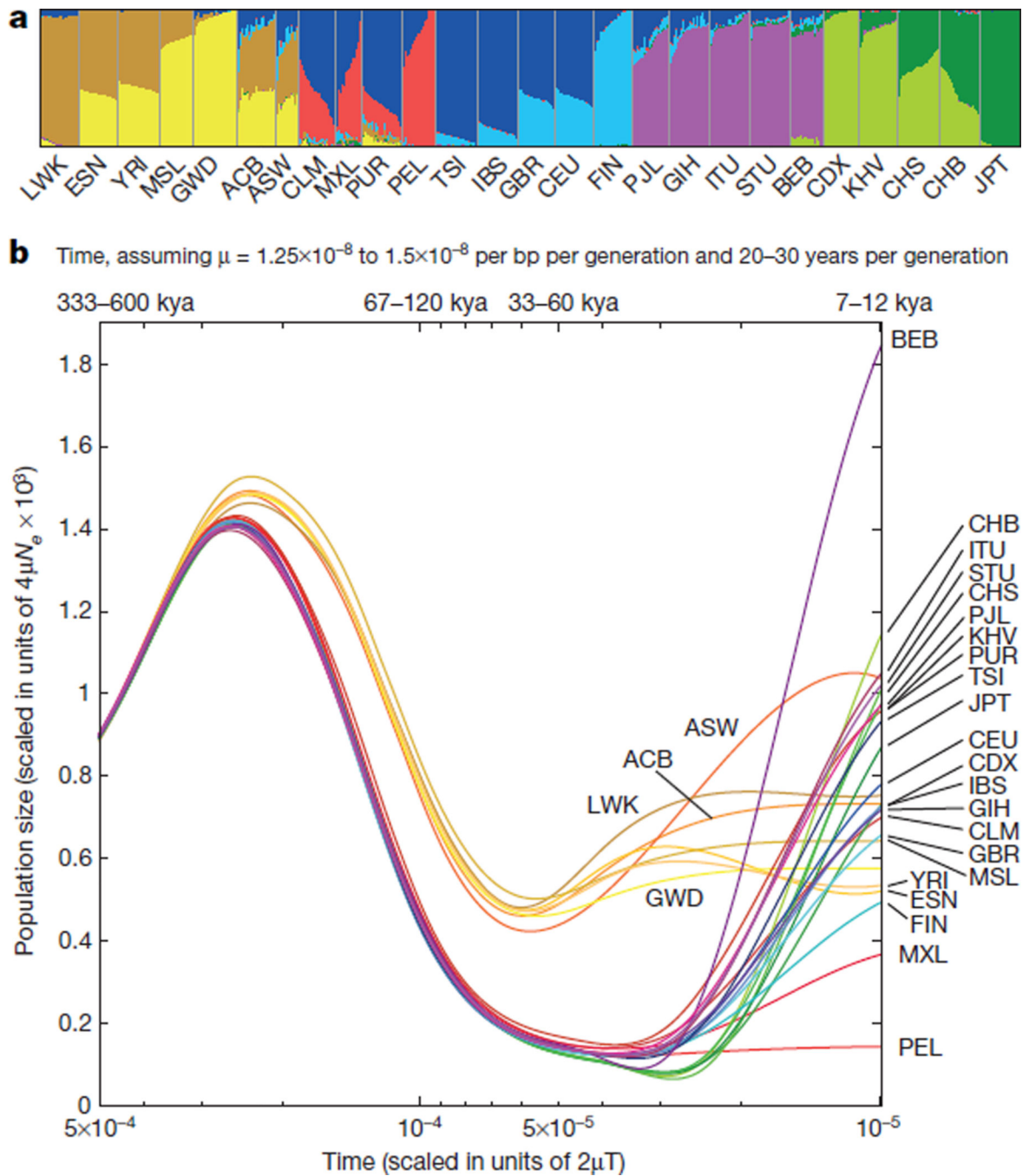


Figure 2. Population structure and demography

a, Population structure inferred using a maximum likelihood approach with 8 clusters. **b**, Changes to effective population sizes over time, inferred using PSMC. Lines represent the within-population median PSMC estimate, smoothed by fitting a cubic spline passing through bin midpoints.

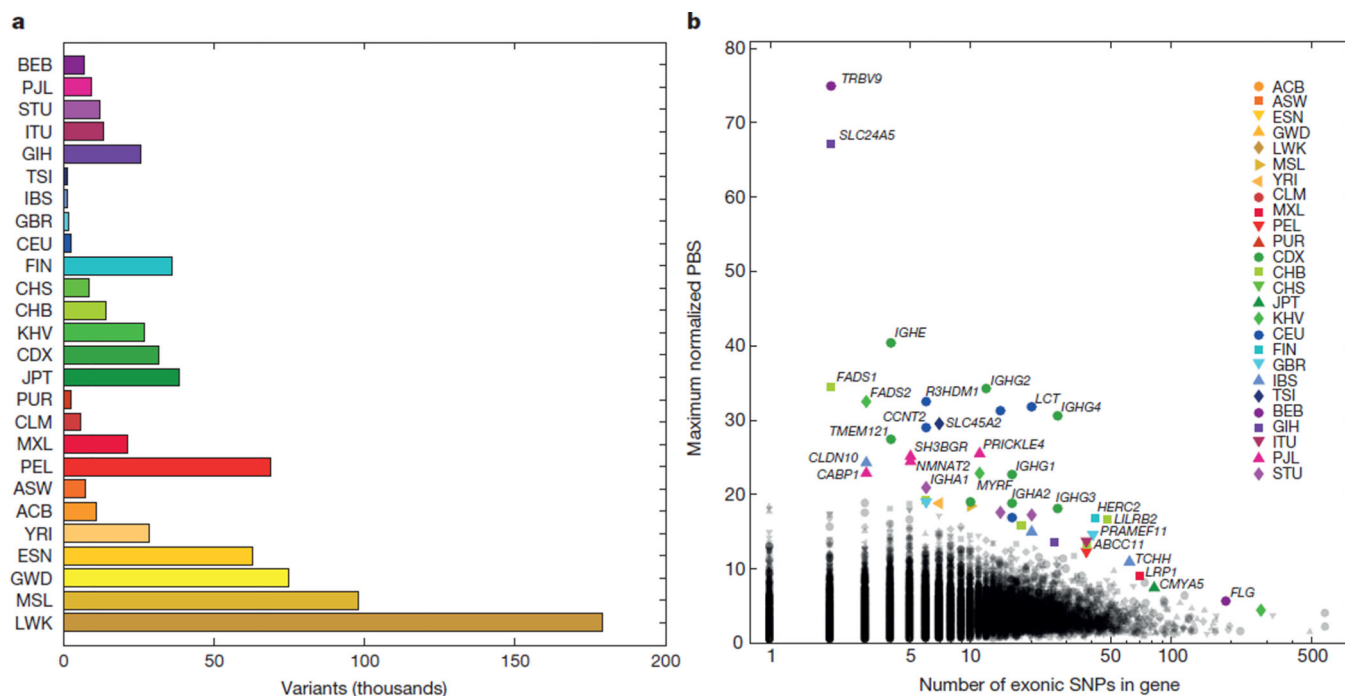


Figure 3. Population differentiation

a, Variants found to be rare (<0.5%) within the global sample, but common (>5%) within a population. **b**, Genes showing strong differentiation between pairs of closely related populations. The vertical axis gives the maximum obtained value of the F_{ST} -based population branch statistic (PBS), with selected genes coloured to indicate the population in which the maximum value was achieved.

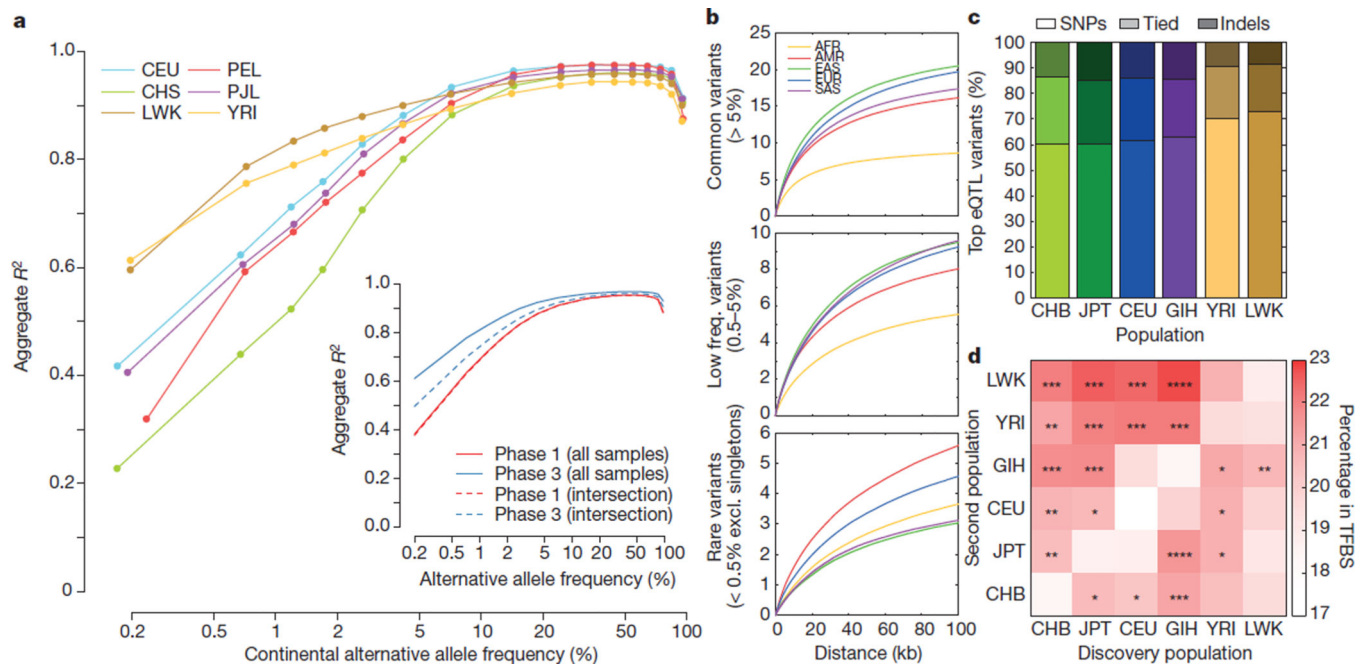


Figure 4. Imputation and eQTL discovery

a, Imputation accuracy as a function of allele frequency for six populations. The insert compares imputation accuracy between phase 3 and phase 1, using all samples (solid lines) and intersecting samples (dashed lines). **b**, The average number of tagging variants ($r^2 > 0.8$) as a function of physical distance for common (top), low frequency (middle), and rare (bottom) variants. **c**, The proportion of top eQTL variants that are SNPs and indels, as discovered in 69 samples from each population. **d**, The percentage of eQTLs in TFBS, having performed discovery in the first population, and fine mapped by including an additional 69 samples from a second population (* $P < 0.01$, ** $P < 0.001$, *** $P < 0.0001$, McNemar's test). The diagonal represents the percentage of eQTLs in TFBS using the original discovery sample.

Table 1

Median autosomal variant sites per genome

	AFR		AMR		EAS		EUR		SAS	
Samples	661		347		504		503		489	
Mean coverage	8.2		7.6		7.7		7.4		8.0	
	Var. sites	Singletons	Var. sites	Singletons	Var. sites	Singletons	Var. sites	Singletons	Var. sites	Singletons
SNPs	4.31M	14.5k	3.64M	12.0k	3.55M	14.8k	3.53M	11.4k	3.60M	14.4k
Indels	625k	-	557k	-	546k	-	546k	-	556k	-
Large deletions	1.1k	5	949	5	940	7	939	5	947	5
CNVs	170	1	153	1	158	1	157	1	165	1
MEI (Alu)	1.03k	0	845	0	899	1	919	0	889	0
MEI (L1)	138	0	118	0	130	0	123	0	123	0
MEI (SVA)	52	0	44	0	56	0	53	0	44	0
MEI (MT)	5	0	5	0	4	0	4	0	4	0
Inversions	12	0	9	0	10	0	9	0	11	0
Nonsynon	12.2k	139	10.4k	121	10.2k	144	10.2k	116	10.3k	144
Synon	13.8k	78	11.4k	67	11.2k	79	11.2k	59	11.4k	78
Intron	2.06M	7.33k	1.72M	6.12k	1.68M	7.39k	1.68M	5.68k	1.72M	7.20k
UTR	37.2k	168	30.8k	136	30.0k	169	30.0k	129	30.7k	168
Promoter	102k	430	84.3k	332	81.6k	425	82.2k	336	84.0k	430
Insulator	70.9k	248	59.0k	199	57.7k	252	57.7k	189	59.1k	243
Enhancer	354k	1.32k	295k	1.05k	289k	1.34k	288k	1.02k	295k	1.31k
TFBSs	927	4	759	3	748	4	749	3	765	3
Filtered LoF	182	4	152	3	153	4	149	3	151	3
HGMD-DM	20	0	18	0	16	1	18	2	16	0
GWAS	2.00k	0	2.07k	0	1.99k	0	2.08k	0	2.06k	0
ClinVar	28	0	30	1	24	0	29	1	27	1

See Supplementary Table 1 for continental population groupings. CNVs, copy-number variants; HGMD-DM, Human Gene Mutation Database disease mutations; k, thousand; LoF, loss-of-function; M, million; MEI, mobile element insertions.