Online Repository Methods

1 Multi-ethnic genome-wide and HLA association study of total serum IgE

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2 Studies

A total of N=21,901 participants of diverse ancestry from asthma, atopic dermatitis and population-based or other disease studies were included in our total serum IgE (tIgE) GWAS (Table E1, Figure 1).

2.1 WGS studies

Six studies from the National Institutes of Health (NIH) National Heart, Lung and Blood Institute (NHLBI) Trans-Omics for Precision Medicine (TOPMed) program, for which whole-genome sequence (WGS) data and measures of tIgE were available, were included in our study: The Genetics of Cardiometabolic Health in the Amish (Amish) study is a community-based study of the Old Order Amish community of Lancaster, Pennsylvania, focused largely on cardiometabolic health [1]; the Barbados Asthma Genetics Study (BAGS) investigates genetic risk for asthma in Barbados where asthma prevalence is as high as 20% [2]; the Genetic Epidemiology of COPD (COPDGene) study of genetic risk for chronic obstructive pulmonary disease (COPD) [3]; the Genetic Epidemiology of Asthma in Costa Rica (CRA) study of genetic risk for asthma in Costa Rica where asthma prevalence is as high as 24% [4]; the Framingham Heart Study (FHS), a multigenerational study of genetic risk for cardiovascular and other diseases [5,6]; and the Severe Asthma Research Program (SARP), a comprehensive study of adults and children with severe asthma [7]. More information about these studies is available at the NHLBI TOPMed website and in the cited publications.

2.2 GWAS array studies

Five studies from the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA), for which tIgE measures and GWAS array data were available, were included in our study: The Brazilian Immunogenetics of Asthma and Schistosomiasis (BIAS) study, a whole-population ascertainment designed study of asthma and schistosomiasis in the rural district of Conde, Bahia [8]; the Chicago Asthma Genetics (CAG) study [9] that recruited participants from adult and/or pediatric asthma clinics at University of Chicago Hospital; the Genomic Research on Asthma in the African Diaspora (GRAAD) consortium that recruited African American children and adults from the Baltimore-Washington DC metropolitan area [10]; the Jamaican Adolescent Asthma Study (JAAS), a cross-sectional study on the prevalence of asthma and allergies in Jamaican adolescents [11]; and the Proyecto Genes Candidatos en Asma (PGCA) study, a population-based asthma study conducted by the Institute for Immunological Research of The University of Cartagena (Colombia) [12]. More information on these studies is available in the CAAPA asthma GWAS publication [13]. In addition, GWAS array data and tIgE measures from the Genetic susceptibility to Asthma and pollution in Peru (GASP) study [14], GWAS array data (obtained from the NHLBI Framingham SNP Health Association Resource (SHARe) resource in dbGAP phs000342) and tIgE measures for FHS participants for whom WGS data were not available [6], and GWAS array data and tIgE from African American, European and Hispanic/Latino participants from the Atopic Dermatitis Research Network (ADRN) [15] were also included in our study.

2.3 Ethics statement

2.3.1 Amish

All study protocols were approved by the institutional review board at the University of Maryland Baltimore. Informed consent was obtained from each study participant.

2.3.2 ADRN

All samples used for this study were obtained following written informed consent from participants. The University of Colorado, Johns Hopkins University, National Jewish Health, Oregon Health & Science University, University of California San Diego, Boston Children's Hospital, Northwestern University, Ann & Robert H. Lurie Children's Hospital of Chicago, University of Rochester Medical Center, Children's Hospital Los Angeles, Children's Hospital of Philadelphia, and Mount Sinai School of Medicine Institutional Review Boards approved the conduct of this study.

2.3.3 BAGS, SARP and CAAPA

NIH guidelines for conducting human genetic research were followed. The Institutional Review Boards (IRB) of Johns Hopkins University (GRAAD and BAGS), Wake Forest University (SARP), the University of Chicago (CAG), University of the West Indies, Mona, Jamaica and Cave Hill Campus, Barbados (BAGS), the Universidad Católica de Honduras in San Pedro Sula (HONDAS), Federal University of Bahia (BIAS and ProAR), the University of Cartagena (PGCA), all reviewed and approved this study. All participants provided written informed consent.

2.3.4 COPDGene

All COPDGene participants provided written informed consent, and the study was approved by the Institutional Review Boards of the participating clinical centers.

2.3.5 CRA

All Genetics of Asthma in Costa Rica parents provided informed consent and all children provided assent for participation in the study and the study was approved by the Institutional Review Board of the Hospital de Ninos in San Juan, Costa Rica and by the Institutional Review Board of Brigham and Women's Hospital, Boston MA.

2.3.6 FHS

The Framingham Heart Study was approved by the Institutional Review Board of the Boston University Medical Center. All study participants provided written informed consent.

2.3.7 GASP

The institutional review boards at the Johns Hopkins University School of Medicine (Baltimore, Maryland) and AB PRISMA (Lima, Peru) approved this study, and all subjects/parents provided written consent.

3 Genotyping

3.1 TOPMed studies

Whole genome sequencing with mean read coverage of 30X was performed by TOPMed sequencing centers and is described in detail at https://www.nhlbiwgs.org/topmed-whole-genome-sequencing-methods-freeze-8. Reads were mapped to the GRCh38 human genome reference sequence using analytical pipelines that ensure functional equivalence, which in turn enabled harmonized variant calling across sequenced data sets [16]. TOPMed freeze 8 CRAM files were used to call HLA alleles for SARP, and freeze 5b CRAM files were used to call HLA alleles for all other TOPMed studies. The TOPMed freeze 8 genotype call set was used for GWAS. See https://www.nhlbiwgs.org/topmed-whole-genome-sequencing-methods-freeze-8 for more details on the TOPMed sequence alignment and variant calling pipelines.

3.1.1 Quality control

Initial sample level quality control performed by the TOPMed Informatics Research Center (IRC) for inclusion in the TOPMed freeze 8 genotype call set required estimated DNA sample contamination below 10% (estimated using the *verifyBamId* software [17]), and 95% or more of the genome covered to 10x or greater.

Variants with a Hardy-Weinberg disequilibrium p-value less than 10^{-6} in the direction of excess heterozygosity, after accounting for population structure, and variants that have Mendelian inconsistencies in 5% or more of families, were filtered by the TOPMed IRC from the freeze 8 genotype call set. In addition, the TOPMed IRC calculated Mendelian consistency scores for variants using known familial relatedness and duplicates, and used these scores to train a Support Vector Machine (SVM) classifier between known variant sites (SNPs found to be polymorphic either in the 1000 Genomes Omni2.5 array or in HapMap 3.3, with additional evidence of being polymorphic in the sequenced samples) and Mendelian inconsistent variants. Variants were labelled as passed or failed based on their SVM scores. Only variants that passed this SVM filter were included for GWAS.

The TOPMed Data Coordinating Center (DCC) performed additional analysis to verify concordance between annotated sex and genetic sex inferred from sequence data and concordance between prior SNP array genotypes and WGS-derived genotypes. The DCC also compared observed and expected relatedness from pedigrees by estimating kinship coefficients between pairs of individuals by applying the GENESIS R package software on a set of linkage disequilibrium (LD) pruned (r^2 <0.1) autosomal SNV markers that passed the quality control filters as described above (~638k variants with MAF > 1% and missing call rate < 1%). Identified discrepancies were resolved by the DCC in collaboration with the contributing studies. We additionally used the kinship analysis released by the DCC to identify duplicate sample pairs, and removed samples such that only one sample per subject was retained for inclusion in our tIgE GWAS.

3.2 GWAS array studies

Non-TOPMed studies were genotyped on the following platforms: CAG was genotyped on the Illumina HumanHap1M chip and the African Diaspora Power Chip (ADPC) [18] and GRAAD was genotyped on the Illumina HumanHap 650Y and ADPC, as described in Supplementary Notes 4 and 5 of the CAAPA asthma GWAS paper [2]. BIAS, JAAS and PGCA were genotyped on Illumina's Multi-Ethnic Genotyping Array (MEGA), described in Supplementary Note 9 of the CAAPA asthma GWAS paper [2]. GASP was genotyped on the MEGA (Ayobami and Brunetti et al. [14]), FHS was genotyped on the Affymetrix GeneChip Human Mapping 500K Array Set [6], and ADRN was genotyped on the MEGA (all African American and Hispanic/Latino subjects, 49% European subjects), and the Illumina OMNI 2.5 array chip (51% of the European ancestry subjects).

3.2.1 Quality control

Genotype quality control for the BIAS, CAG, GRAAD, JAAS and PGCA studies are detailed in Supplementary Notes 4, 5 and 9 of the CAAPA GWAS publication [2] and details for GASP are described in the GWAS reported by Ayobami and Brunetti et al [14].

Variants and samples annotated in the dbGAP NHLBI Framingham SNP Health Association Resource (SHARe) deposition as failing quality control were removed from the data set. In addition, only those GWAS array samples with SHARe identifier not present in the FHS TOPMed WGS data were retained. LD pruned variants present in both the FHS TOPMed WGS and GWAS array data set were then used to estimate the proportion of genetic material shared identical by descent (using the *plink* software and "–genome" option) between pairs of individuals in the FHS TOPMed WGS and GWAS array data sets, to verify the absence of duplicate FHS samples.

For ADRN, preliminary SNP QC was performed by GenomeStudio, using the recommended Illumina thresholds for call frequency, cluster separation, mean normalized intensity for genotype clusters, and mean and standard deviations of the normalized theta values for homozygous clusters. Samples with excess heterozygosity, gender discrepancies and high missingness were removed from the data sets. Any samples that had unexpected relatedness based on identity-by-descent checks were excluded. Principal Component Analysis was performed by ancestry group and samples that were 6 standard deviations away from the mean on PC1 and PC2 were identified as outliers and were removed. SNPs that failed on Hardy-Weinberg equilibrium per ancestry group, and had high missingness, were removed. In addition, genotyping of the African American samples were run in two different batches. Sample and SNP QC was performed separately for these two batches after which the data was merged. Because no control subjects were included in the first batch, association tests were run between AD cases from the first batch and AD cases from the second batch; SNPs that had a P value less than 0.01 (N=97,052) were considered to be different due to the technical variation between the batches and were removed prior to imputation.

3.2.2 Imputation

Each of the GWAS array data sets were imputed separately to the TOPMed release 2 imputation panel on the TOPMed Imputation Server (https://imputation.biodatacatalyst.nhlbi.nih.gov) using the steps outlined at https://github.com/mdaya/topmed_imputation. ADRN European ancestry subjects were also imputed separately by genotype platform (MEGA vs. OMNI), after which the MEGA and OMNI imputed data sets were merged.

4 Asthma and atopic dermatitis definition

Asthma was defined and harmonized in TOPMed studies by study-specific analysts, based on a self-reported history of ever having asthma (BAGS[10], CRA[19], COPDGene[20]). All SARP participants were considered asthmatic.

Diagnosis of asthma in studies included in CAAPA have previously been described [2]. Briefly, BIAS identified individuals with asthma using a modified ISAAC questionnaire [21,22]. CAG defined asthma based on phycisian diagnosis, and all asthma cases met objective criteria of bronchial hyperresponsiveness after a methacholine challenge or reversibility to an inhaled bronchodilator [9]. GRAAD used standardized questionnaires administered by a clinical coordinator to determine whether a subject has a history of both self-reported and physician- diagnosed asthma (asthma case), or had no history of

asthma (healthy control). Asthma status was determined in JAAS by questionnaire and/or medical records [11]. In PGCA, asthma was defined using a standardized GINA 2005 questionnaire previously tested [23,24] in patients with a history of physician-diagnosed asthma [25,26].

In GASP, asthma was defined based on physician diagnosis of asthma and asthma symptoms or taking asthma medications within the past year; controls were children without asthma symptoms or the use of asthma medications in the past year, normal FEV1/FVC and FEV1 > 80%. More details are provided in the GWAS by Ayobami and Brunetti et al. [14].

In the ADRN, atopic dermatitis cases were defined based on phycisian diagnosis using standard diagnostic criteria, with the additional requirement that subjects less than four years of age presented with atopic dermatitis for at least six months (to avoid misdiagnosis). The non-atopic control subjects were defined as having no individual or family history of atopy and average total IgE less than 100 ng/ml.

5 Ancestry group definition

Ancestry groups for single ancestry studies (European ancestry: Amish, FHS; African ancestry: BAGS, CAG, GRAAD, JAAS; Hispanic/Latino ancestry: CRA, BIAS, GASP, PGCA) were defined according to the ancestry group or country of origin ascertained for these studies. We note that the Amish, FHS, CAG and GRAAD are US-based studies; the Amish is a European descent population isolate [1], the FHS study recruited participants of European descent [5], and the CAG and GRAAD studies recruited African American individuals [2]. BAGS and JAAS are African descent populations from the Caribbean, while the CRA, BIAS, GASP and PGCA study participants are from Central and South American countries (Costa Rica, Brazil, Peru and Colombia, respectively). For COPDGene, SARP and ADRN - multi-ancestry studies that are based in the US - participants were grouped according to self-reported identity. In this study, we did not perform any additional verification of ancestry group by e.g. principal component analysis, but as described below, included principal components of genetic ancestry to account for population structure, and assessed the GWAS test statistic distribution for evidence of residual population structure.

6 GWAS analysis

As expected, mean tIgE is higher in asthmatics and participants with atopic dermatitis, compared to control groups and population-based studies (Figure 1, Table E1) [27,28]. In addition, also according to expectation, mean tIgE is higher in the African ancestry group compared to the European and Hispanic/Latino ancestry groups (Figure 1, Table E1) [29]. Due to this heterogeneity of tIgE distribution, GWAS strata were defined by study, disease group, ancestry group and genotyping platform (WGS data vs GWAS array data); each row in Table E1 corresponds to a GWAS stratum. GWAS was performed separately for each stratum and results were then combined via meta-analysis. This approach allowed for the easy integration of WGS and GWAS array data into a combined analysis, and for assessing and contrasting variant effects by disease and ancestry group. An overview of the analysis approach is shown in Figure E1.

Linear mixed effects models implemented in the *SevenBridges GENESIS Single Variant Association Test* pipeline available on Biodata Catalyst (https://biodatacatalyst.nhlbi.nih.gov/platforms/seven-bridges) and published on Dockstore at https://dockstore.org/organizations/SevenBridges/collections/genesispipelines were used to perform GWAS. *PC-relate* was used to estimate a kinship matrix excluding other sources of variance such as population structure [30], and *PC-AiR* to calculate principal components accounting for cryptic and known relatedness between subjects [31]. The kinship matrix and principal components were calculated using a data set of autosomal LD pruned variants, selected by the TOPMed DCC across the entire TOPMed freeze 8 genotype call set (638,486 SNPs with r^2 <0.1, MAF > 1% and missing call rate < 1%). Within each GWAS strata, a second MAF > 1%, imputation quality filter for GWAS array data (Rsq >= 0.9) and LD pruning step was applied, to ensure that only uncorrelated high genotype quality variants with appreciable frequencies particular to the analysis strata were used for kinship estimation and principal component analysis. The number of markers included to calculate the kinship matrix and perform principal component analysis are shown by GWAS stratum in Figure E2. Prior to performing single variant association tests, the GENESIS pipeline fits a null model with no SNP genotype terms. GENESIS then estimates single variant association p-values using a score test, which tests for model fit improvement if a SNP is added to the null model. To fit the null model, tIgE IU/ml measurements were log10 transformed, and age, sex and principal components from PC-AiR were included as fixed effect covariates. The number of principal components selected by the elbow method to include as covariates are shown by GWAS stratum in Figure E2. tIgE measurement batch was included as additional covariate for BAGS and COPDGene, and genotyping batch was included as additional covariate for the ADRN strata (African ancestry atopic dermatitis, European ancestry atopic dermatitis and European ancestry non-atopic controls). The PC-relate kinship matrix was included as a random effect in the null model. The null linear mixed effect model was fit using the Gaussian family of distributions. Visual summaries generated by the GENESIS pipeline were used to assess projected phenotype values (phenotype values adjusted for the fixed effect covariates, random effects, and heterogeneous residual variances) for normality and outlier observations, before proceeding to run single variant association tests. Only variants with imputation accuracy

Rsq >= 0.7 and MAF >= 1% were included in the association tests. QQ and manhattan plots generated by the GENESIS pipeline were used to visually assess whether the observed test statistic distribution deviated from the expected null test statistic distribution. No evidence of inflated test statistics was observed in any of the GWAS strata (lambda ranging between 0.79 and 1.05, with median value 1.00).

GWAS results were combined using MR-MEGA [32]. MR-MEGA uses multi-dimensional scaling to infer genetic axes of variation across studies from allele frequencies, and models allelic effect across studies using a linear regression model of the allelic effect of each study along each genetic axis of variation, weighting the contribution of a study by the inverse variance of the allelic effect from the study. The model is described in detail in the Materials and Methods section of the MR-MEGA publication [32]. Two axes of genetic variation were specified for the MR-MEGA software configuration, as this would be sufficient to distinguish the three continental ancestral contributions (African, European, American) present in our study. A plot of the genetic coordinates of each of the GWAS strata is shown in Figure E3. Separation between continental European/American and African ancestry is reflected by the first axis, while the second axis separate continental American ancestry; we note the diverse aggregate ancestry spectrum represented in the Hispanic/Latino studies. A QQ plot was used to visually assess whether the observed MR-MEGA test statistic distribution deviated from the expected null test statistic distribution (Figure E4). P-values $< 5 \times 10^{-9}$ were considered genome-wide significant [33]. The Bayes Factor returned by MR-MEGA was used to construct 99% credible sets per GWAS locus that reached genome-wide significance, as follows (Table E2): The posterior probability of association for each SNP (the ratio of its Bayes Factor over the sum of the Bayes Factors of all SNPs +- 1MB from the lead variant) was first calculated. SNPs were then ranked according to their Bayes Factors, and SNPs were selected for inclusion in the 99% credible set until their cumulative posterior probability attained or exceeded 0.99. Because MR-MEGA estimates the effect size of a variant along genetic axes of variation and not the effect size of the variant itself, effect sizes of variants (across all studies, by ancestry group, and by disease group) were estimated using inverse-variance meta-analysis (METAL software package). The p-value for ancestry heterogeneity (Table E2) and forest plots grouped by ancestry (Figure E5) were used to assess evidence of different effects by ancestry, and the p-value for residual heterogeneity (Table E2) and forest plots grouped by disease group (Figure E6) were used to assess evidence of different effects by disease group. For the MHC region, locus zoom plots by ancestry were used to additionally assess association signals by ancestry (Figure E7).

7 Co-localization

To estimate the probability of a shared common causal variant in a given region controlling tIgE levels and expression of a gene, we performed co-localization analysis using the R coloc package [34] and gene expression data available through the Genotype-Tissue Expression (GTEx) database (multiple tissues) and the eQTLGen Consortium (eQTLGen) for the regions summarized in Table E2 but excluding the MHC. Because co-localization assumes similar patterns of LD in the datasets tested [34,35], betas and standard errors of the beta from the European ancestry tIgE inverse-variance meta-analysis and eQTLs from the GTEx European ancestry analysis (gene-tissue pairs with FDR < 0.05 for the lead tIgE variant and variants +-2MB from the lead variant) were assayed for colocalization. The eQTLGen dataset is predominantly of European ancestry, and here the MAF, p-value, and number of observations were assayed for colocalization with the European ancestry tIgE inverse-variance meta-analysis betas and standard errors (all eGenes +-2MB from the lead tIgE variant). Co-localization also assumes a single causal variant; for this reason, we first performed joint association analysis of the European ancestry inverse-variance meta-analysis using GCTA-COJO and a LD reference panel calculated from the TOPMed European ancestry subjects. The MHC region was excluded from this analysis due to the complex LD structure in this region [36]. The GCTA-COJO analysis confirmed a single causal variant in each of the tIgE association regions.

Posterior probabilities of one common causal variant (PPH4) > 0.5 were considered evidence for co-localization. Several GTEx gene-tissue pairs showed strong evidence of co-localization with *FCER1A* (transcript ID ENSG00000179639.1, tissues Heart Atrial Appendage, Breast Mammary Tissue, Artery Tibial, Thyroid, Heart Left Ventricle, Whole Blood, Nerve Tibial, Colon Sigmoid, Lung, Skin Not Sun Exposed Suprapubic, Colon Transverse, Artery Aorta, Skin Sun Exposed Lower leg, Esophagus Muscularis, Esophagus Gastroesophageal Junction, Adipose Subcutaneous, Adipose Visceral Omentum, Muscle Skeletal, all PPH4 > 0.9, largest PPH4=0.9986 in Adipose Visceral Omentum). *IL13* showed strong co-localization in GTEx Testis (the only tissue with *IL13* expression data, transcript ID ENSG00000169194.9, PPH4=0.9961), and *STAT6* showed strong co-localization in GTEx Cultured Fibroblasts (the GTEx tissue with the lowest variability in *STAT6* expression, perhaps explaining why co-localization was not observed for other tissues, transcript ID ENSG00000166888.11, PPH4=0.9984)

8 HLA association analysis

8.1 HLA allele calling

8.1.1 WGS data

HLA-LA [37] was used to call HLA alleles from WGS reads. Briefly, HLA-LA extracts reads from CRAM files that map to the HLA-region, aligns the reads to a graph reference, and uses the graph alignment to quantify the probability of HLA-allele calls. Calls with HLA-LA variables Q1 < 0.9, perfectG != 1, AverageCoverage < 20 were set to missing; the call rate (proportion of non-missing calls) per HLA gene and by study after performing this step is shown in Figure E8. HLA-LA call quality was further assessed by comparing the concordance between samples that were sequenced in duplicate (Figure E9) and assessing Mendelian consistency in trios (Figure E10). Based on this analysis, all HLA-DRB3 calls were removed (low call rate and high trio Mendelian error rate across all studies), HLA-DPA1 calls were set to missing in all BAGS samples (high trio Mendelian error rate), and HLA-A calls were set to missing in all BAGS and CRA samples (high trio Mendelian error rate). After performing these steps, the mean call rate across all HLA genes was 0.901, the mean discordance between duplicate samples was 0.004, and the mean proportion of trios with inconsistent HLA genotypes was 0.007.

8.1.2 GWAS array data

The HIBAG R Bioconductor package [38] was used to call HLA alleles for the GWAS array data set, using HIBAG's pre-trained models. As the multi-ethnic pre-trained models have been reported to work at least as well as the ethnic-specific models [38], for studies genotyped on Illumina's MEGA (ADRN, BIAS, GASP, JAAS, PGCA), the Illumina MEGA multi-ethnic 4 digit models were used (InfiniumMEGA-Broad-HLA4-hg19), for FHS, the Affymetrix 500K multi-ethnic 4 digit models were used (Affy500K-Broad-HLA4-hg19), and for the ADRN Illumina OMNI 2.5 data set, the Illumina OMNI 2.5 multi-ethnic 4 digit models were used (Affy500K-Broad-HLA4-hg19). As CAG and GRAAD genotype data are from both Illumina HumanHap and ADPC arrays, the generic African 4 digit models (African-HLA4-hg19) were used. Genotype calls with posterior probabilities less than 0.5 was set to missing, as per the HIBAG publication recommendation [38]. The call rate (proportion of non-missing genotype calls) per GWAS array data set and HLA gene is summarized in Figure E11. Due to a low call rate in GRAAD (this study was genotyped on Illumina HumanHap 650Y, an early generation GWAS array, perhaps explaining the low call rate), GRAAD was excluded from subsequent association analysis.

8.2 Tests for association

To identify associations between specific HLA-alleles and tIgE, HLA-allele calls from the TOPMed WGS data sets were used for discovery and HLA-allele calls from the GWAS array data sets were used for replication. A dominant allele model was employed, i.e. testing for association between being a carrier vs. non-carrier of a specific HLA allele and tIgE. Analysis strata were defined using the same strategy as for GWAS, and GENESIS linear mixed effect models were fit separately to each stratum as for GWAS, but using a dominant allele coding. Only alleles with carrier frequency of at least 0.5% in an analysis stratum were tested for association. Results were combined using inverse-variance meta-analysis (METAL software package). A Bonferroni correction of 155 tests (the number of alleles tested across all discovery strata) was applied to the combined discovery results to identify alleles to carry forward for replication (Table 1). An additional exploratory analysis to identify ancestry-specific associations combined discovery and replication data sets by ancestry group. The frequencies of alleles with replicated associations (HLA-A*02:01, HLA-DQA1:03:01, HLA-DQB1:03:02) were compared against frequencies of reference ancestry groups in the Allele Frequencies Net Database and by genotyping platform (Figure E12). A consistent lower allele frequency in GWAS array data sets compared to WGS data was observed for HLA-DQA1:03:01 (of note, lower frequencies in African ancestry groups called from GWAS array data compared to WGS data, lower allele frequency in FHS GWAS array data compared to FHS WGS data), suggesting potential bias in this allele call. Forest plots grouped by ancestry (Figure E13) were used to assess evidence of different effects by ancestry and forest plots grouped by disease group (Figure E14) were used to assess evidence of different effects by disease group.

9 Software

Software pipelines used in this analysis were run on BioData Catalyst powered by Seven Bridges (https://biodatacatalyst.nhlbi.nih.gov/pl
bridges) and custom pipelines have been published on Dockstore (https://dockstore.org/search?search=mdaya).

10 NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium

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