

1 Fine-mapping across diverse ancestries drives the discovery of putative 2 causal variants underlying human complex traits and diseases

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38

39 **Abstract**

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41 Genome-wide association studies (GWAS) of human complex traits or diseases often implicate
42 genetic loci that span hundreds or thousands of genetic variants, many of which have similar
43 statistical significance. While statistical fine-mapping in individuals of European descent has made
44 important discoveries, cross-population fine-mapping has the potential to improve power and
45 resolution by capitalizing on the genomic diversity across ancestries. Here we present SuSiEx,
46 an accurate and computationally efficient method for cross-population fine-mapping, which builds
47 on the single-population fine-mapping framework, Sum of Single Effects (SuSiE). SuSiEx
48 integrates data from an arbitrary number of ancestries, explicitly models population-specific allele
49 frequencies and LD patterns, accounts for multiple causal variants in a genomic region, and can
50 be applied to GWAS summary statistics when individual-level data is unavailable. We
51 comprehensively evaluated SuSiEx using simulations, a range of quantitative traits measured in
52 both UK Biobank and Taiwan Biobank, and schizophrenia GWAS across East Asian and
53 European ancestries. In all evaluations, SuSiEx fine-mapped more association signals, produced
54 smaller credible sets and higher posterior inclusion probability (PIP) for putative causal variants,
55 and retained population-specific causal variants.

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59 INTRODUCTION

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61 Genome-wide association studies (GWAS) of human complex traits or diseases often implicate
62 genetic loci that span hundreds or thousands of genetic variants, many of which have similar
63 statistical significance. These loci may contain one or a handful of causal variants, while the
64 associations of other variants are driven by their linkage disequilibrium (LD) with the causal
65 variant(s). Statistical fine-mapping refines a GWAS locus to a smaller set of likely causal variants
66 to facilitate interpretation and computational and experimental functional studies. Fine-mapping
67 studies in samples of European ancestry have made important advances, with some disease-
68 associated loci resolved to single-variant resolution¹⁻³. Since non-causal variants tagging causal
69 signals have marginally different effects across populations due to differences in LD patterns,
70 cross-population fine-mapping, which integrates data from multiple populations and capitalizes
71 on the genomic diversity across ancestries (e.g., smaller LD blocks in African populations), holds
72 the promise to further improve fine-mapping resolution.

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74 Cross-population fine-mapping analysis can be broadly classified into three categories, namely
75 the meta-analysis-based approach, the *post hoc* combining approach, and Bayesian statistical
76 methods (Figure 1). The meta-analysis-based approach applies single-population fine-mapping
77 methods to meta-analyzed GWAS summary statistics and LD matrices, and has been widely used
78 in the field, including in several seminal studies^{4,5}. This approach, however, assumes no
79 heterogeneity in effect sizes and LD patterns across populations, which is often not true and may
80 lead to false positives and miscalibration of the inferred probability of a variant being causal⁶. The
81 *post hoc* combining approach analyzes data from each population independently and integrates
82 single-population fine-mapping results *post hoc*. While conducive to identifying population-
83 specific causal variants⁷, this approach fails to leverage the increased sample size, potential
84 genetic correlations and LD diversity across populations to facilitate loci discovery and improve
85 fine-mapping resolution, and may be sensitive to the choice of methods that combine population-
86 specific results. Bayesian methods^{8,9} provide a principled way to fine-map causal variants across
87 populations and have been employed in the analyses of several complex traits or diseases⁸⁻¹².
88 That said, current cross-population Bayesian fine-mapping methods often suffer from inflated
89 false positive rates, poor computational scalability, and inability to distinguish multiple causal
90 signals in the same genomic locus, impeding their applications to emerging biobank-scale
91 datasets of diverse ancestries.

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93 Recently, Wang *et al.* proposed a single-population fine-mapping method, SUM of SIngle Effects
94 (SuSiE)¹³, which improved the calibration, computational efficiency and interpretation of statistical
95 fine-mapping. Here, we extend the SuSiE model to a cross-population fine-mapping method,
96 SuSiEx, which integrates multiple population-specific GWAS summary statistics and LD panels
97 to enable more powerful and accurate fine-mapping. We evaluated the calibration, power,
98 resolution and computational scalability of SuSiEx along with alternative fine-mapping methods
99 via extensive simulations. We further used SuSiEx to fine-map 25 quantitative traits shared
100 between the UK Biobank¹⁴ and Taiwan Biobank¹⁵, and to fine-map schizophrenia genetic risk loci
101 across European and East Asian ancestries.

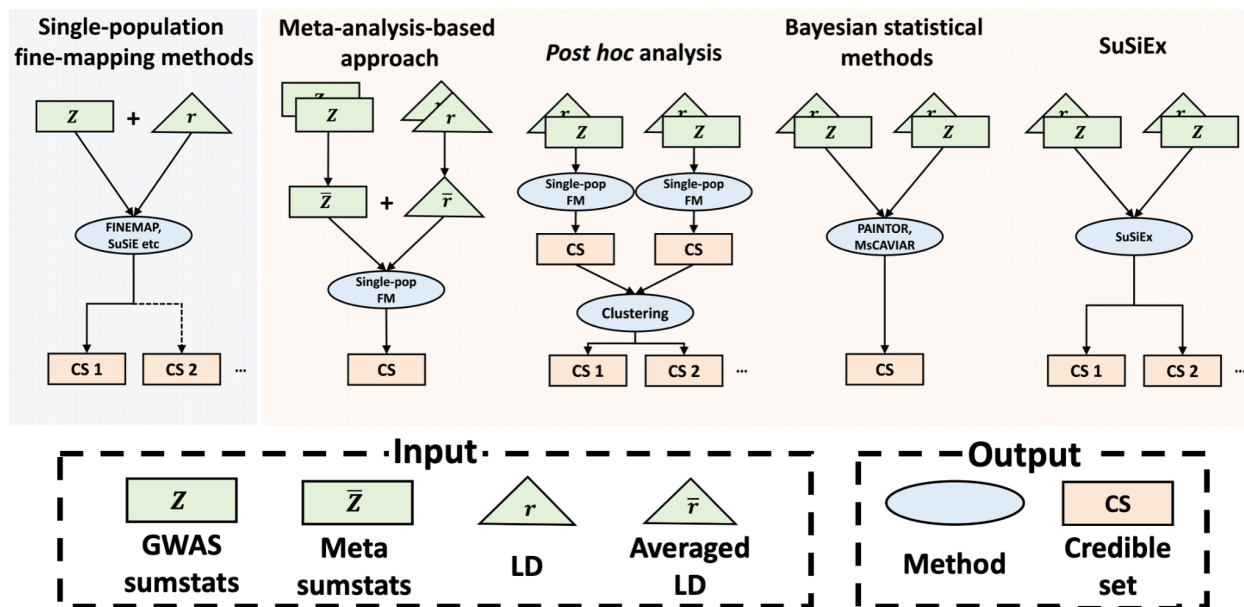
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RESULTS

Overview of SuSiEx

SuSiEx extends the single-population fine-mapping model, SuSiE¹³, by integrating population-specific GWAS summary statistics and LD reference panels from multiple populations. In SuSiE, the genetic influence on a trait or disease within a genomic locus is modeled as the summation of several distinct effects, each contributed by a single causal variant, which naturally allows for the modeling of multiple association signals and assigns each inferred putative causal variant to a credible set with a posterior inclusion probability (PIP) (Figure 1). Building on this framework, SuSiEx couples each single effect by assuming that the causal variants are shared across populations (i.e., we report a single PIP rather than population-specific PIPs for each variant in a credible set), while allowing them to have varying effect sizes (including null effects) across ancestries. In addition, SuSiEx allows for a variant to be missing in an ancestry (e.g., due to its low allele frequency), in which case the ancestry does not contribute to the PIP estimate, effectively reducing the total sample size. Similar to SuSiE, SuSiEx builds on the Bayesian variable selection in regression^{16,17} and applies the iterative Bayesian stepwise selection¹³ to model fitting. Further modeling and computational details for SuSiEx are discussed in Methods.

Compared with the meta-analysis-based fine-mapping approach^{4,5}, SuSiEx explicitly models population-specific GWAS summary statistics and LD patterns (Figure 1; Extended Data Figure 1a), which is expected to improve the fine-mapping resolution and more accurately control the false positive rates, while allowing for heterogeneous effect sizes and retaining population-specific causal variants (Extended Data Figure 1c). Compared with *post hoc* analysis to combine single-population fine-mapping results⁷, SuSiEx leverages the sample size, genetic correlation and LD diversity across ancestries to improve the resolution of fine-mapping, especially for loci that are under-powered to fine-map in individual datasets (Figure 1; Extended Data Figure 1b). Compared with other Bayesian cross-population fine-mapping methods such as PAINTOR^{9,18} and MsCAIVAR⁸, SuSiEx infers distinct credible sets for each causal signal (Figure 1), facilitating the interpretation of fine-mapping results, and is orders of magnitudes more scalable computationally (discussed later), enabling the analysis of large, complex loci and biobank-scale datasets across many complex traits and diseases.



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 137 **Figure 1: Overview of fine-mapping methods.** An illustration of the inputs and outputs for
 138 single-population and cross-population fine-mapping methods, the latter of which includes meta-
 139 analysis-based approaches, *post hoc* combining approaches, previously published Bayesian fine-
 140 mapping methods as well as SuSiEx.

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 145 **SuSiEx outperformed single-population and naive cross-population fine-mapping**
 146 **methods in simulations**

147 We conducted a series of simulations to systematically evaluate the performance of SuSiEx.
 148 Specifically, we generated simulation data under different numbers of causal variants (n_{cs}) per
 149 locus, genetic correlations across populations (r_g) and SNP heritability (h^2) (Methods). To examine
 150 the impact of these genetic parameters on fine-mapping results, we defined a standard simulation
 151 setting with $n_{cs} = 1$, $r_g = 0.7$ and $h^2 = 0.1\%$, and then varied these parameters to produce a range
 152 of local genetic architectures (Supplementary Tables 1 & 2). Given a set of genetic parameters,
 153 we further assessed the impact of different population (European - EUR; African - AFR; East
 154 Asian - EAS) and discovery sample size combinations (Supplementary Table 3) on fine-mapping
 155 results. Throughout the simulation study, in single-population fine-mapping, we analyzed loci that
 156 reached genome-wide significance in population-specific GWAS ($P < 5 \times 10^{-8}$); in cross-population
 157 fine-mapping, we analyzed loci that reached genome-wide significance in at least one of the
 158 population-specific GWAS or in the cross-population fixed-effect meta-analysis. We assessed the
 159 performance of different fine-mapping methods using an array of metrics: (i) Coverage/Calibration:
 160 the proportion of credible sets that include at least one true causal variant across simulation
 161 replicates; (ii) Power: the number of true causal variants identified (i.e., covered by a credible set);
 162 (iii) Resolution: the size of credible sets and the number of fine-mapped variants with high
 163 confidence (e.g., PIP >95%); (iv) Scalability: the computational cost/feasibility to perform fine-

164 mapping in large genomic loci; (v) Robustness: the proportion of runs in which the fine-mapping
165 algorithm converges and returns sensible results (defined later).

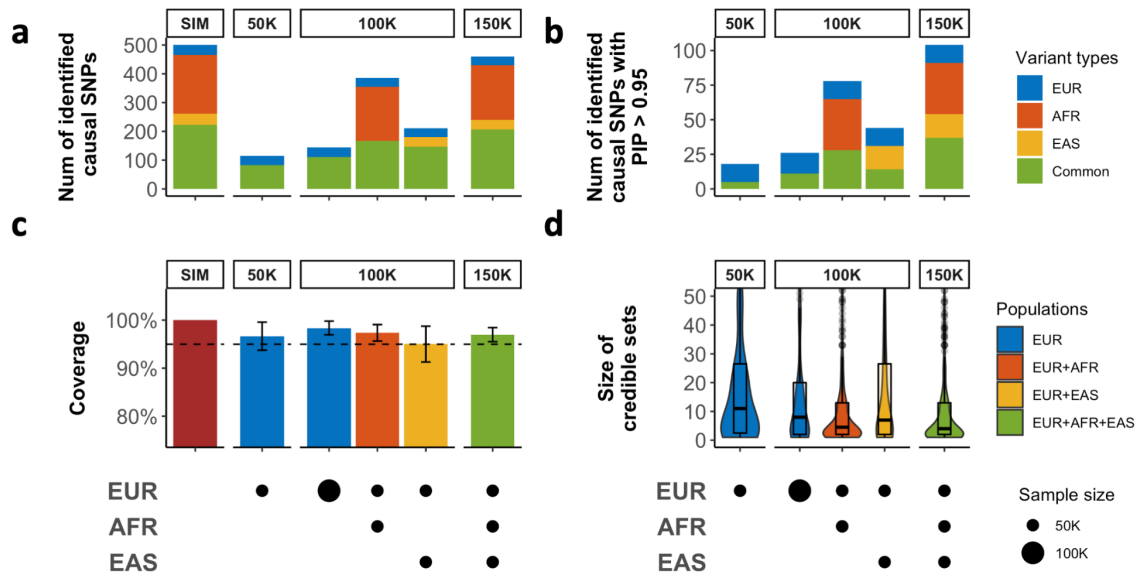
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167 As expected, in the standard simulation setting (Figure 2; Supplementary Figures 1 & 2),
168 compared with single-population fine-mapping even with the same total sample size, integrating
169 data across populations using SuSiEx led to better power (i.e., more true causal variants being
170 identified; Figure 2a), had higher resolution (i.e., smaller credible sets and more causal variants
171 with high PIP; Figure 2b & 2d) and retained population-specific causal variants (Figure 2a & 2b).
172 Meanwhile, SuSiEx had well controlled coverage at 95%, regardless of the populations from
173 which data were combined (Figure 2c). The magnitude of improvements in power and resolution
174 is a result of both the increase in the total sample size and the LD diversity in the discovery
175 samples (Figure 2; Supplementary Table 4). For example, adding 50K EUR individuals to an
176 existing EUR sample of 50K individuals increased the number of identified causal variants with
177 PIP >95% from 18 to 26 and reduced the median size of the credible set from 11 to 8. The yield
178 of causal variants with PIP >95% was much greater (increased from 18 to 78) and the median
179 size of the credible set was much smaller (reduced from 11 to 5) if the added 50K individuals were
180 of AFR instead of EUR ancestry, demonstrating the importance of genetic diversity in cross-
181 population fine-mapping. The inclusion of 50K individuals of EAS ancestry also provided a greater
182 yield of causal variants with PIP >95% (increased from 18 to 44) and smaller credible sets
183 (reduced from 11 to 7) relative to adding 50K EUR samples, although the advantages were less
184 pronounced than when the AFR samples were added, due to the smaller LD blocks in the African
185 ancestries^{19,20}.

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187 A widely used approach in recent multi-ancestry genetic studies⁴ is to apply a single-population
188 fine-mapping method to meta-analyzed GWAS summary statistics and LD matrices (e.g., using a
189 sample size weighted approach). Despite of its convenience, this method can be miscalibrated
190 and does not unleash the full potential of genomic diversity, likely due to its over-simplified
191 modeling of LD across populations, the presence of population-specific variants, and the strong
192 assumption on cross-population effect size heterogeneity in fixed-effect meta-analysis⁶. We
193 confirmed, using the standard simulation setting, that fine-mapping using meta-analyzed GWAS
194 and sample size weighted LD suffered substantial loss in both power and coverage
195 (Supplementary Figures 3 & 4; Supplementary Table 5). In contrast, SuSiEx, through explicit and
196 flexible modeling of population-specific association statistics and LD, identified many more causal
197 variants (Supplementary Figure 4a) and was well calibrated (Supplementary Figure 4b).

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 200 **Figure 2: The performance of SuSiEx in simulations.** Simulated data were generated under
 201 the standard parameter setting (Methods). **a**, The number of identified true causal variants (true
 202 causal variants covered by a credible set) when integrating data from different populations with
 203 different sample sizes for fine-mapping. **b**, The number of true causal variants mapped to
 204 PIP >95%. **c**, The coverage of credible sets (the proportion of credible sets that contain a true
 205 causal variant). The dashed line indicates 95% coverage and error bars indicate 95% confidence
 206 intervals. **d**, Distribution of the size of credible sets. The upper and lower bounds of the box
 207 indicate the 75th and 25th percentiles, respectively. The middle line in the box indicates the
 208 median. In **a-d**, top labels of each subpanel indicate the total sample size, and the bottom panels
 209 indicate the sample size from each population. In **a** and **b**, we defined variants with MAF >0.5%
 210 only in one population as specific to that population, and all other variants as “shared” (i.e., shared
 211 variants across populations).

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 215 Another recently proposed strategy uses *post hoc* analysis to combine single-population fine-
 216 mapping results, which has been applied to multiple large-scale biobanks with promising
 217 biological discoveries⁷. However, this approach does not make use of subthreshold association
 218 signals, and does not leverage LD diversity to improve the resolution of fine-mapping. In
 219 simulations, SuSiEx found more true causal variants especially when the GWAS sample size is
 220 moderate or small, as expected for current non-EUR GWAS (Supplementary Table 5). For
 221 example, when analyzing 50K EUR and 20K AFR individuals under the standard simulation
 222 setting, the *post hoc* approach identified a smaller number of causal variants compared with
 223 SuSiEx (159 vs. 175). Although the numbers of true causal variants discovered by both
 224 approaches become closer when the GWAS sample sizes become larger, SuSiEx still
 225 outperformed *post hoc* analysis in resolution. In simulations, SuSiEx always identified more true
 226 causal variants with high PIP (50% or 95%) than *post hoc* analysis (Supplementary Figure 5 and
 227 Supplementary Table 5). For example, when analyzing 200K EUR and 200K AFR individuals
 228 under the standard simulation setting, the *post hoc* approach identified a smaller number of causal

229 variants with PIP > 95% compared with SuSiEx (140 vs. 161). And the median size of the credible
230 set was 10 vs. 8 when combining data from 50K EUR and 20K AFR individuals for *post hoc* and
231 SuSiEx respectively, and 4 vs. 2 when analyzing 200K EUR and 200K AFR individuals
232 (Supplementary Table 5).

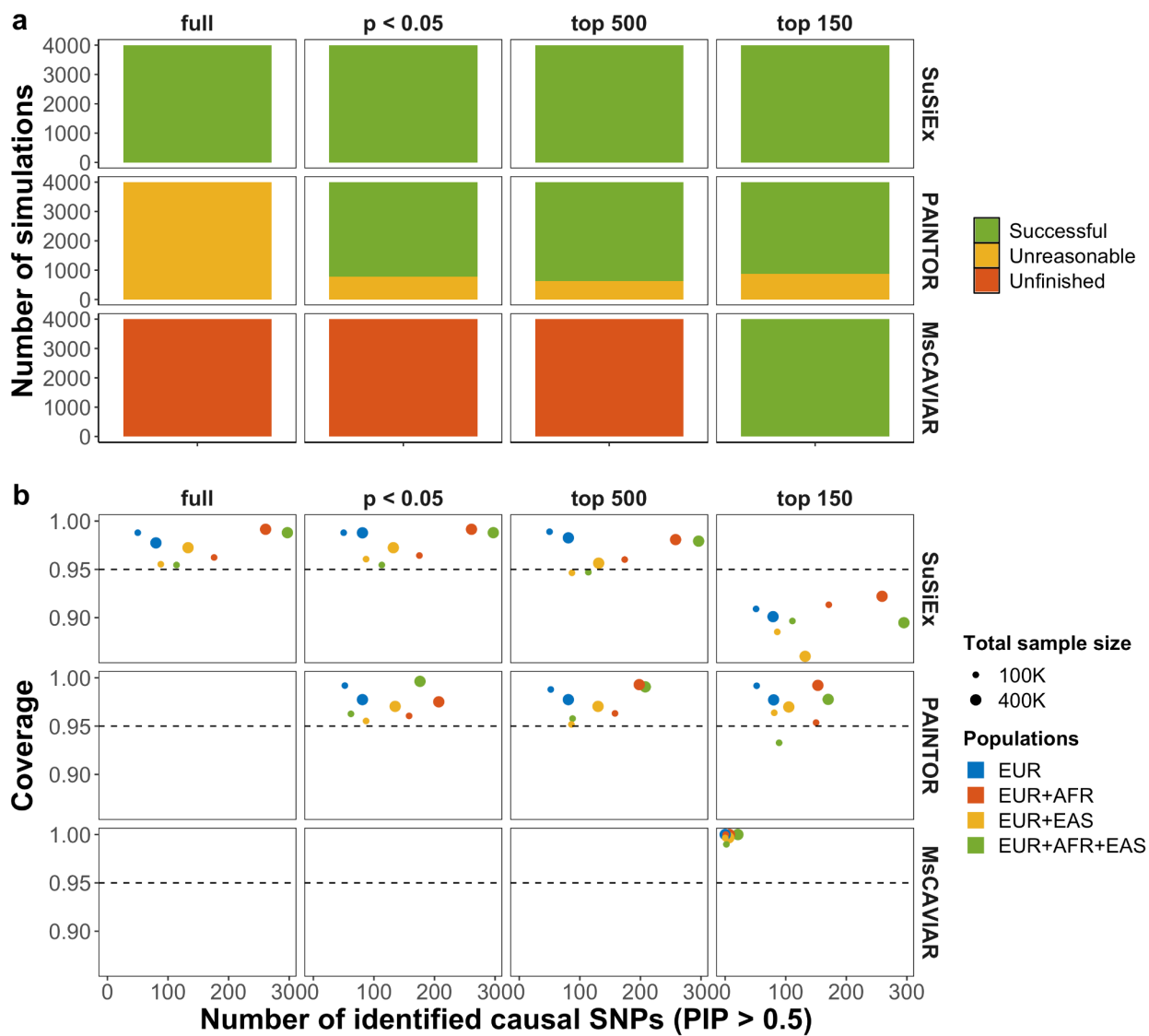
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234 **SuSiEx outperformed existing Bayesian cross-population fine-mapping methods in** 235 **simulations**

236 We further compared SuSiEx with two published Bayesian cross-population fine-mapping
237 methods, PAINTOR^{9,18} and MsCAVIAR⁸, using the standard simulation setting (Supplementary
238 Table 2). We noted that neither of the two methods is capable of analyzing all common variants
239 (MAF >1% in EUR, EAS or AFR) in a 1 Mb locus (6,548 variants per locus on average; Figure 3a,
240 left column). In particular, MsCAVIAR is not computationally scalable and cannot complete
241 analyzing a genetic locus within 24 hours, while PAINTOR always returned unreasonable results,
242 in which the sum of PIP across variants in a genomic locus >5 or <0.1. We note that in the
243 standard simulation setting, the number of true causal variants was set to one in each locus, and
244 thus a sum of PIP >5 or <0.1 appears “unreasonable” and may indicate severe model fitting issues
245 such as failure to converge. We then filtered the discovery summary statistics to fewer variants to
246 enable performance evaluation across methods. Specifically, we created three input datasets with
247 increasingly stringent selection criteria: “p < 0.05”, “top 500” and “top 150”, corresponding to
248 marginal P <0.05, the top 500 and the top 150 most associated variants, respectively. With these
249 filtered input datasets, the “enumerate” mode of PAINTOR, with the number of causal variants
250 set to one (which matched the simulation parameter, and was thus a favorable setting for
251 PAINTOR), still returned unreasonable results (sum of PIP >5 or <0.1) for approximately 25% of
252 the analyses (Figure 3a), while the “MCMC” mode of PAINTOR returned unreasonable results for
253 almost all the analyses, with zero PIP for every variant (Supplementary Table 6). The “enumerate”
254 mode of PAINTOR was also highly sensitive to the parameter “maximum number causal SNPs”,
255 which is typically unknown *a priori* and difficult to set in practice (Extended Data Figure 2). The
256 other Bayesian fine-mapping method, MsCAIVAR, was only able to analyze the smallest input
257 dataset (“top 150”), as larger dataset took more than 24 hours per locus (Figure 3a), although the
258 results were generally “reasonable” (Extended data Figure 2; Supplementary Table 6).

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 262 **Figure 3: Comparison of SuSiEx, PAINTOR and MsCAVIAR in simulations.** **a**, The job
 263 completion summary (scalability and robustness) for Bayesian fine-mapping methods using
 264 different numbers of input variants. PAINTOR was run using the “enumerate” mode with “-
 265 enumerate=1” (which matched the simulation parameter). Unfinished: jobs taking longer than 24
 266 hours wall time. Unreasonable: jobs returning unreasonable results, defined as the sum of PIP
 267 across variants in the genomic locus >5 or <0.1 (1 is expected). Successful: jobs completed within
 268 24 hours of wall time and returned reasonable results. **b**, Number of identified true causal variants
 269 with PIP >50% (x-axis) versus the coverage of credible sets (y-axis) for different input datasets
 270 and fine-mapping methods. Only simulation runs that were completed within 24 hours and
 271 returned reasonable results were included.

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276 For each method, we then focused on simulation runs that returned reasonable PIP estimates.
277 PAINTOR, with the “enumerate” mode and the number of causal variants set to one, had
278 calibrated results at 95% coverage and identified a similar number of high-PIP causal variants to
279 SuSiEx in the EUR-only and EUR + EAS fine-mapping (PIP >50%; Figure 3b). MsCAVIAR,
280 however, identified much fewer causal variants with PIP >50% (Figure 3b). This is because
281 MsCAVIAR tends to return large credible sets containing almost all the variants in the input
282 dataset, each having a small PIP (Supplementary Table 7). SuSiEx outperformed PAINTOR and
283 MsCAVIAR in the number of causal variants identified with PIP >50%, when AFR samples were
284 included in the discovery GWAS (Figure 3b), suggesting that SuSiEx can leverage genomic
285 diversity to fine-map more causal variants with high accuracy. For example, when combining
286 200K EUR and 200K AFR samples, SuSiEx identified 261 unique causal variants with PIP >50%
287 using the full GWAS summary statistics, comparing with 209 identified by PAINTOR and 7
288 identified by MsCAVIAR across the four input datasets (Figure 3b; Supplementary Table 7). We
289 note that the coverage for SuSiEx was well calibrated in most settings but dropped below 95%
290 when the top 150 most associated variants were used as input, likely due to information loss from
291 variant filtering. As using the full GWAS summary statistics as input was computationally tractable
292 and yielded optimal results for SuSiEx, we do not consider this a limitation for SuSiEx and do not
293 recommend any prefiltering of variants when using SuSiEx in practice.

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295 **SuSiEx is robust to varying cross-population genetic architectures**

296 We further examined the calibration, power and resolution of SuSiEx by varying key parameters
297 in the standard simulation setting. The cross-population genetic correlation (r_g) can be less than
298 one for many complex traits and diseases²¹. SuSiEx accounts for imperfect genetic correlation by
299 allowing for varying genetic effects across populations. Using simulated data with r_g of 0.4, 0.7,
300 and 1.0, we confirmed that SuSiEx was robust to a range of r_g values, with good calibration and
301 similar power and resolution (Supplementary Figures 6-10; Supplementary Table 8). The local
302 heritability (h^2) and the number of causal variants (n_{csi}) per locus can differ across the genome for
303 a given trait or disease^{1,22-24}. We set the heritability per locus to 0.05%, 0.1%, 0.2%, 0.3%, 0.4%
304 and 0.5%, and for a given per-locus heritability, varied n_{csi} from 1 to 5 with each genetic effect
305 drawn from a normal distribution (Methods). As expected, SuSiEx performed better when h^2
306 increased (Supplementary Figures 11-15; Supplementary Table 9) and n_{csi} decreased
307 (Supplementary Figures 16-20; Supplementary Table 10), which corresponds to higher per-
308 variant heritability and thus larger statistical power. Nonetheless, SuSiEx was always well
309 calibrated at 95% coverage (Supplementary Figures 12 & 17), and was able to capture multiple
310 causal variants in the same locus as n_{csi} increased.

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312 We additionally assessed the robustness of SuSiEx under model misspecifications. SuSiEx
313 assumes that causal variants are shared across populations. While a reasonable assumption for
314 most genetic associations underlying human complex traits and diseases as supported by recent
315 studies²⁵⁻²⁸, SuSiEx allows for different effect sizes (including null effects) of a causal variant
316 across populations, and thus can accommodate violations of this modeling assumption. We
317 empirically evaluated the robustness of SuSiEx by simulating variants that had non-zero effect
318 sizes in one population but were null in other populations. We found that adding null data had little
319 impact on fine-mapping results (Supplementary Figure 21 and Supplementary Table 11),

320 confirming the robustness of SuSiEx to model misspecifications. Lastly, we note that in-sample
321 LD is preferred in fine-mapping as it matches the correlation pattern between variants in the
322 discovery GWAS sample. Unfortunately, in-sample LD is not always available, especially in large-
323 scale GWAS comprising multiple cohorts. Using an external LD reference panel from a genetically
324 close population can be a pragmatic solution despite its limitations^{6,29-31}. Here, we evaluated the
325 impact of LD mismatch on SuSiEx. Consistent with previous findings, analysis using in-sample
326 LD produced excellent calibration and power, while using external LD led to coverage and power
327 loss as the genetic distance between the external reference panel and the discovery sample
328 increased (Supplementary Figure 4 and Supplementary Table 12).

329

330 **SuSiEx increased the power and resolution of fine-mapping in biobank analysis**

331 Encouraged by simulation results, we applied SuSiEx to data from the Pan-UKBB project and the
332 Taiwan Biobank (TWB). The Pan-UKBB project is a multi-ancestry resource derived from the UK
333 Biobank (UKBB)¹⁴ by analyzing six continental ancestry groups across 7,228 phenotypes. We
334 included summary statistics of EUR and AFR (N_{EUR} up to 419,807; N_{AFR} up to 6,570,
335 Supplementary Table 13) ancestries from Pan-UKBB. We additionally included TWB, one of the
336 largest biomedical databases in East Asia ($N_{EAS} = 92,615$) with close to 100,000 study
337 samples^{15,32}. We selected 25 quantitative traits shared between Pan-UKBB and TWB
338 (Supplementary Table 13), and defined 13,420 genomic loci that reached genome-wide
339 significance in at least one of the single-population association analysis or the meta-analysis
340 across the three populations (Methods; Supplementary Table 14). We then performed single-
341 population fine-mapping using SuSiE, and cross-population fine-mapping using SuSiEx,
342 combining EUR, AFR and EAS data.

343

344 SuSiEx identified 14,400 credible sets across 9,826 loci, while single-population fine-mapping
345 identified 12,784, 48, and 1,475 credible sets for the EUR, AFR and EAS populations, respectively
346 (Supplementary Table 14). Aligning credible sets across analyses (Methods) led to 2,953 (20.5%)
347 credible sets identified by SuSiEx that were not identified by single-population fine-mapping
348 (Supplementary Table 14). Among the 14,400 credible sets, 1,413 (9.8%) credible sets reached
349 genome-wide significance in the meta-analysis but not in any population-specific GWAS (as
350 indexed by the maximum PIP variant), and thus would have been missed if fine-mapping was
351 only conducted in single populations (Supplementary Table 14; Extended Data Figure 3b as an
352 example). In addition to identifying and mapping more genetic associations through integrating
353 data from multiple populations, SuSiEx also improved fine-mapping resolution. Relative to single-
354 population fine-mapping in the EUR population, adding AFR and EAS data increased the average
355 of the maximum PIP for a variant across all aligned credible sets from 0.44 to 0.47 ($P = 3.7 \times 10^{-6}$;
356 two-sided t test), and reduced the average size of credible sets from 29.4 to 27.2 ($P = 0.015$; two-
357 sided t test; Figure 4a & 4b; Supplementary Table 15; Extended Data Figure 3a as an example).
358 Additionally, cross-population fine-mapping identified 2,485 putative causal variants with PIP >95%
359 (Figure 4c; Supplementary Table 16), among which 575 were not discovered by any single-
360 population fine-mapping. For example, SuSiEx identified a credible set containing a single variant
361 associated with total bilirubin at PIP >99%, a missense variant of *TRIM5* (rs11601507). This
362 credible set failed to reach genome-wide significance in any population and was thus missed in
363 single-population fine-mapping (Figure 5a and Extended Data Figure 4). Similarly, SuSiEx

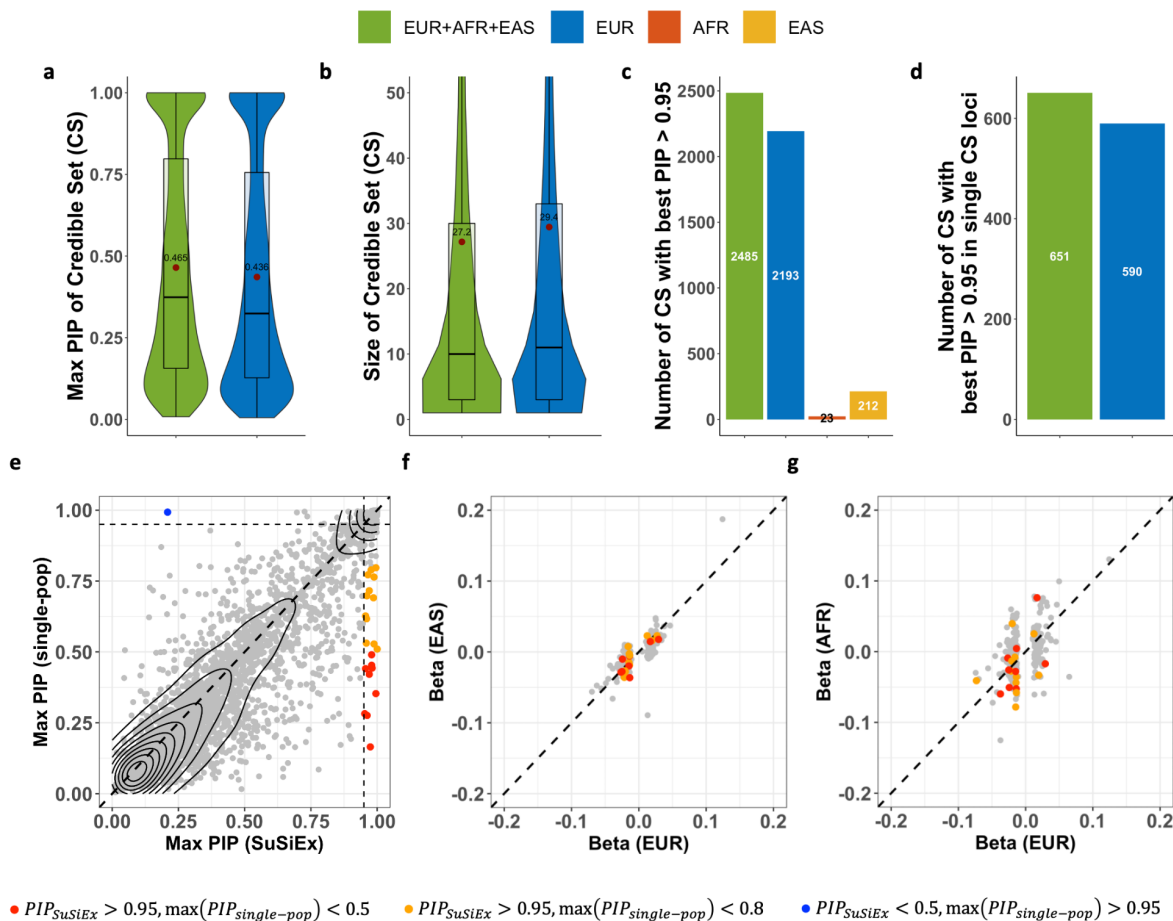
364 identified a two-variant credible set associated with albumin that failed to reach genome-wide
365 significance in any population (Figure 5b; Extended Data Figure 5). The lead variant in the credible
366 set is an intron variant of *ALOX5AP* with PIP 97.4%. This variant was fine-mapped to be an eQTL
367 variant regulating the expression of *ALOX5AP* in whole blood (PIP >99%), artery aorta (PIP =
368 86.1%) and spleen (PIP = 77.9%) (Figure 5b; Extended Data Figure 5)³³. In both examples,
369 SuSiEx identified putative causal variants and resolved a genetic locus to its gene target that
370 would have been missed if only single-population fine-mapping was performed.

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372 Next, we restricted the comparison to loci that were mapped to a single credible set by both single-
373 and cross-population fine-mapping such that our results were not affected by multiple causal
374 variants in LD and the algorithm of credible set alignment. In these single-credible-set loci, SuSiEx
375 continued to outperform single-population fine-mapping in power and resolution, identifying more
376 credible sets with high confidence (best PIP >95%; Figure 4d), and improving the maximum PIP
377 of a credible set in general relative to single-population fine-mapping ($P = 6.4e-5$; two-sided t test;
378 Figure 4e). In particular, SuSiEx improved the maximum PIP of 30 credible sets from <80% to >95%
379 (Figure 4e; orange and red dots), among which 9 were improved from <50% to >95% (Figure 4e;
380 red dots). We note that the maximum PIP for one credible set dropped substantially, from 99% to
381 21%, in the cross-population fine-mapping (Figure 4e; blue dot). Further investigation of this locus
382 revealed that the putative causal variant (12-67643414-T-A) is located in a low complexity
383 genomic region, where the quality of variant calling and imputation may be negatively affected³⁴.
384 This variant is also represented in fewer than 50% of individuals in gnomAD v2.1.1 genomes³⁵,
385 and violates Hardy-Weinberg equilibrium.

386
387 Biobank analyses further confirmed that SuSiEx can retain population-specific causal variants
388 (Extended Data Figure 3c as an example). Despite a dominating EUR sample size, SuSiEx
389 recaptured 83% of the findings from single-population fine-mapping. A non-trivial proportion of
390 credible sets from single-population fine-mapping that were not captured by SuSiEx may be
391 driven by quality issues, defined as (i) the best PIP variant is in the low complexity region (LCR);
392 (ii) the best PIP variant is in allelic imbalance or violates Hardy Weinberg equilibrium in gnomAD³⁵;
393 or (iii) the best PIP variant is multi-allelic or colocalizes with indels at the same genomic position,
394 which might influence imputation quality. For example, 17.5% (29/166) of the putative causal
395 variants with PIPs dropped by 10-20% in cross-population fine-mapping relative to single-
396 population fine-mapping had quality issues, compared with 41.2% (7/17) of the variants with PIPs
397 dropped by >40% (Extended Data Figure 6). These results suggest that, through the joint
398 modeling of multiple populations and datasets, SuSiEx provides the additional benefit of
399 identifying and removing likely low-quality findings from single-population analyses.

400
401 We used Ensembl Variant Effect Predictor (VEP)³⁶ to annotate each variant into high, moderate
402 or low functional impact, as well as modifiers. As the inferred PIPs increased, the proportion of
403 variants with high impact clearly increased (Extended Data Figure 7), suggesting that confidently
404 fine-mapped variants were enriched among mutations of functional importance. In total, we
405 identified 2,286 high or moderate impact variants in 95% credible sets located in 1,630 genes.
406 Among these variants, 425 had a PIP greater than 50% (Supplementary Table 17), and 275 had
407 a PIP greater than 95% (Supplementary Table 18). There were 28 genes containing at least two

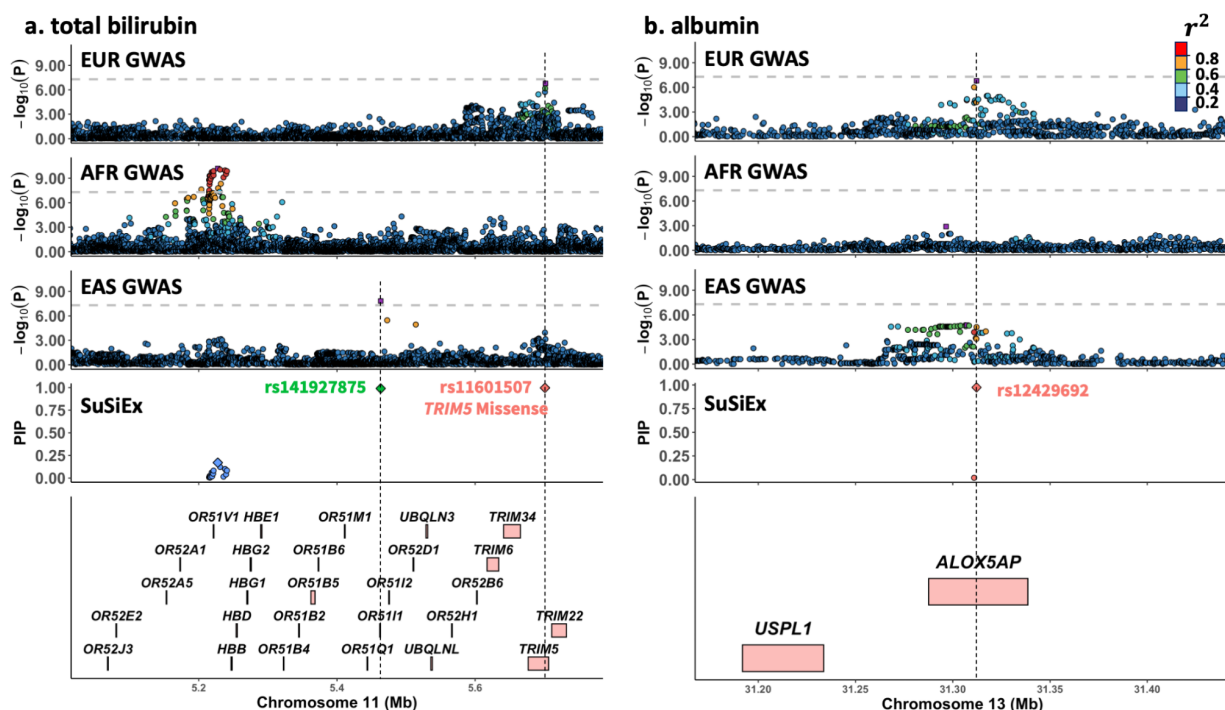
408 high/moderate impact SNPs with PIP greater than 95%, while only 23 were detected in the three
 409 single-population fine-mapping analyses. In particular, *IQGAP2* and *PIEZO1* carried 3 missense
 410 variants associated with multiple blood biomarkers with PIPs >95%.
 411



412
 413 **Figure 4: Cross-population fine-mapping analysis in biobanks.** **a**, The distribution of the
 414 maximum PIP from all credible sets. **b**, The distribution of the size of all credible sets. **c**, The
 415 number of variants mapped to PIP >95% for all credible sets. **d**, The number of variants mapped
 416 to PIP >95% in single-credible-set loci. **e**, The maximum PIP from SuSiEx versus the maximum
 417 value of the maximum PIP in the three single-population fine-mapping using SuSiE. Only genomic
 418 loci with a single credible set aligned across analyses were included. **f** and **g**, The marginal per-
 419 allele effect size of the maximum PIP variant in EUR vs. EAS and EUR vs. AFR populations. We
 420 included variants in single-credible-set loci with PIP >95% estimated by SuSiEx and minor allele
 421 frequencies >5% in all populations. In **a-b**, red dots indicate the mean, the middle line in the box
 422 indicates the median, and the upper and lower bounds of the box indicate the 75th and 25th
 423 percentiles, respectively.

424
 425
 426 Lastly, we compared the per-allele effect sizes of high-confidence putative causal variants
 427 (PIP >95% in single- or cross-population fine-mapping) located in single-credible-set loci among

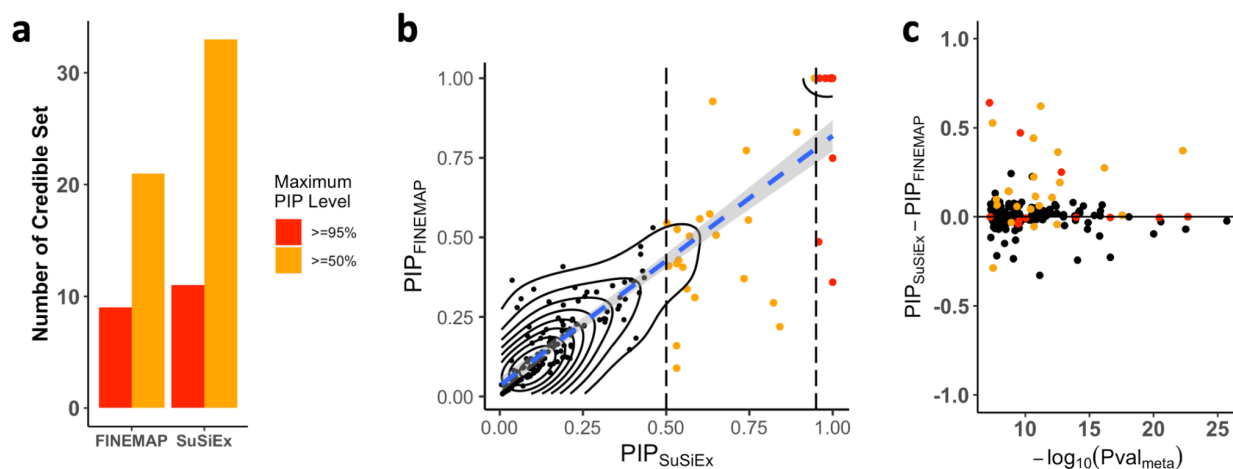
428 EUR, AFR and EAS populations (Figure 4f & 4g). As no secondary association was found in these
 429 loci, we used marginal effect sizes in the comparison. Overall, the effect sizes were highly
 430 concordant between EUR and EAS populations ($r = 0.82$) but less consistent between EUR and
 431 AFR populations ($r = 0.21$), likely reflecting the larger uncertainties of the effect size estimates in
 432 AFR samples due to the limited GWAS sample size. We suggest the nature and cause of such
 433 inconsistency should be subject to a more thorough investigation with expanded non-European
 434 resources. At the current state, the imperfect genetic correlations across populations suggested
 435 the importance of accounting for variants with varying population-specific effect sizes in fine-
 436 mapping models.
 437



438
 439 **Figure 5. SuSiEx identified variants missed in single-population fine-mapping.** Each sub-
 440 figure consists of five panels, which are aligned vertically, with the x-axis representing the
 441 genomic position. The top three panels visualize GWAS association statistics of the European
 442 (Pan-UKBB European), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations
 443 following the LocusZoom³⁷ style. The second to bottom panel visualizes the fine-mapping results
 444 from SuSiEx, which integrated GWAS summary statistics from the three populations. The bottom
 445 panel shows gene annotations. For GWAS panels, the left y-axis represents the $-\log_{10}(p\text{-value})$
 446 of each SNP. The gray horizontal dash line represents the genome-wide significance threshold
 447 (5×10^{-8}). The purple rectangle for each locus represents the lead (most associated) variant.
 448 Variants are colored by descending LD with the lead variant (ordered red, orange, green, light
 449 blue, and dark blue dots). For fine-mapping panels, different colors were used to distinguish
 450 different credible sets. The diamond represents the maximum PIP variant of each credible set. **a**,
 451 Association with total bilirubin on chr11: 5,100,000-5,700,000. **b**, Association with albumin on
 452 chr13: 31,150,000-31,450,000.
 453

454 **SuSiEx identified additional putative causal candidates for schizophrenia**

455 We applied SuSiEx to schizophrenia GWAS summary statistics of EUR ($N_{case} = 53,251$, $N_{control} =$
456 $77,127$) and EAS ($N_{case} = 14,004$, $N_{control} = 16,757$) ancestries from the Psychiatric Genomics
457 Consortium (PGC), and fine-mapped the same 250 autosomal loci in the recent PGC publication⁴.
458 SuSiEx successfully identified 215 credible sets out of 193 loci (not all loci converged to a credible
459 set, as in all fine-mapping analyses), among which 11 had a SNP with PIP >95% (Figure 6a;
460 Supplementary Tables 19 & 20). As expected, SuSiEx outperformed published PGC fine-mapping
461 results, which applied a single-population fine-mapping method, FINEMAP³⁸, to meta-analyzed
462 GWAS summary statistics and sample size weighted LD⁴. Specifically, SuSiEx mapped 57% (33
463 vs. 21) more signals to a single variant with PIP >50% in single-credible-set loci (Figure 6). Most
464 of the SuSiEx-improved credible sets had a marginally genome-wide significant signal (P-value
465 between $5E-8$ and $1E-15$; Figure 6b & 6c). SuSiEx also produced credible sets for three loci that
466 could not be resolved by FINEMAP in the original analysis. In these loci, FINEMAP inferred five
467 independent credible sets, each containing a single variant that was not statistically significant in
468 the GWAS, likely due to inaccurate reference panel³⁹. Furthermore, SuSiEx substantially
469 increased the resolution of fine-mapping by reducing the average size of credible sets from 87.1
470 to 60.3 ($P = 0.015$; paired two-sided t test), and increasing the average of maximum PIP across
471 credible sets from 0.25 to 0.27 ($P = 0.012$; paired two-sided t test).
472



473
474 **Figure 6: Fine-mapping of schizophrenia risk loci across European and East Asian**
475 **populations. a**, The number of putative causal variants mapped to PIP >50% and >95% by
476 FINEMAP and SuSiEx in single-credible-set loci. **b**, The maximum PIP for each credible set within
477 single-credible-set loci, estimated by SuSiEx and FINEMAP. **c**, The difference of the maximum
478 PIP, estimated by SuSiEx and FINEMAP (y-axis), within each single-credible-set locus, plotted
479 against the $-\log_{10}(p\text{-value})$ of the most associated variant in the cross-population meta-analysis.
480 In **b** and **c**, red dots represent credible sets with a maximum PIP >95% estimated by SuSiEx;
481 orange dots represent credible sets with a maximum PIP >50% estimated by SuSiEx.
482

483
484
485
486

DISCUSSION

487 We presented SuSiEx, a cross-population fine-mapping method which links multiple population-
488 specific sum of single effects (SuSiE) models by assuming the sharing of underlying causal
489 variants. Through flexible and accurate modeling of varying population-specific causal effect sizes
490 and LD patterns, SuSiEx improves the power and resolution of fine-mapping while producing well-
491 calibrated false positive rates and retaining the ability to identify population-specific causal
492 variants. We showed, via comprehensive simulation studies, that SuSiEx is highly computationally
493 efficient, outperforms alternative cross-population fine-mapping methods in calibration, power and
494 resolution, and is robust to model misspecifications. In particular, as the two state-of-the-art
495 Bayesian cross-population fine-mapping methods, PAINTOR is sensitive to the predefined (yet
496 unknown) number of causal variants, while MsCAVIAR is computationally intractable when the
497 total number of input variants is greater than a few hundreds. Moreover, neither method has the
498 capacity to analyze summary statistics from a comprehensive set of common variants in loci
499 greater than 1MB. SuSiEx overcomes these limitations and offers effective and efficient cross-
500 population fine-mapping that can be applied on biobank-scale datasets for the first time.

501
502 SuSiEx is designed to flexibly integrate genomic data from multiple populations, where effect
503 sizes and/or LD patterns can be different. For two or more GWAS conducted in independent
504 samples from the same population where effect sizes and LD patterns are highly concordant, we
505 recommend a fixed-effect meta-analysis to combine these GWAS, which is often more statistically
506 powerful than modeling these GWAS separately in SuSiEx without imposing any assumptions on
507 the correlation of SNP effect sizes across samples. A recent study proposed SuSiE-inf⁴⁰, which
508 incorporates a term of infinitesimal effects in addition to a small number of single-variant causal
509 effects, and showed that the new model can produce more calibrated fine-mapping results. While
510 the calibration of SuSiEx was excellent in simulation studies, expanding the SuSiEx model to
511 include this feature in the future may improve the fine-mapping of complex traits and diseases
512 that have a highly polygenic architecture.

513
514 We note that throughout this work we tried to use in-sample LD reference panels for fine-mapping.
515 Mismatch between the LD of the discovery sample and the reference panel may produce spurious
516 credible sets and causal signals, especially in genomic loci that harbor strong association signals.
517 This has been shown in prior work³⁹ and our simulations studies, and is a limitation of all fine-
518 mapping methods. We therefore recommend using in-sample LD for SuSiEx whenever possible,
519 and applying aggressive filtering of low-quality variants and secondary credible sets in complex
520 genomic loci if external LD reference panels have to be used.

521
522 There are several limitations of SuSiEx and the present study. First, we restricted our analyses to
523 SNPs to avoid potential strand flippings and alignment errors when analyzing indels across
524 biobanks. This may produce false positives if fine-mapped SNP(s) are proxies for causal indels
525 or structural variations (SV). Second, we did not incorporate functional annotations into SuSiEx.
526 Adding functional priors to the model may improve fine-mapping resolution when multiple variants
527 in strong LD have similar statistical significance, and may aid prioritization of follow-up functional
528 studies. That said, the biology underlying the observed variant-phenotype association may be
529 complex, and the modeling of functional data may be error-prone and inflate false positive rates.
530 Extending the Bayesian framework of SuSiEx to leverage functional or other omics data by

531 introducing a proper prior to the model can be a promising future direction. Third, our cross-
532 population fine-mapping in biobanks had an encouraging but modest improvement over the
533 resolution of credible sets identified by European-only analyses, which was largely due to the
534 limited discovery sample size of the African GWAS. However, we have shown that the largest
535 improvements of SuSiEx come with the most diverse datasets, and thus expect that SuSiEx will
536 become increasingly useful as the scale of genomic research in underrepresented populations
537 continues to expand in global biobanks⁴¹ and disease-focused consortia. Lastly, it remains
538 unclear how SuSiEx would perform in admixed samples, in which the local ancestry (and thus the
539 causal variants and their effect sizes) may vary from individual to individual. Developing and
540 evaluating statistical fine-mapping methods in populations with complex genetic ancestries is an
541 important future direction.

542
543 In summary, SuSiEx provides robust, accurate and scalable fine-mapping that integrates GWAS
544 summary statistics from diverse populations. Together with the ability to distinguish multiple
545 causal variants within a genomic region, SuSiEx enables the analysis of large, complex genomic
546 loci and aids the interpretation of fine-mapping results. Future work that combines SuSiEx with
547 the rapidly expanding non-European genomic resources may facilitate the discovery of
548 functionally-important disease-causing variants computationally and experimentally.

549

550

551 METHODS

552

553 Cross-population Sum of Single Effect (SuSiEx) model

554 **Model description.** We extend the “Sum of Single Effects” (SuSiE) regression model to fine-
555 mapping studies across multiple populations:

556

$$557 \mathbf{y}_s = \mathbf{X}_s \boldsymbol{\beta}_s + \boldsymbol{\epsilon}_s, \quad \boldsymbol{\epsilon}_s \sim N(\mathbf{0}, \sigma_s^2 \mathbf{I}), \quad s = 1, 2, \dots, S,$$

$$558 \boldsymbol{\beta}_s = \sum_{l=1}^L \mathbf{b}_{sl}, \quad \mathbf{b}_{sl} = \boldsymbol{\gamma}_l b_{sl}, \quad \boldsymbol{\gamma}_l \sim \text{Mult}(\mathbf{1}, \boldsymbol{\pi}), \quad b_{sl} = N(0, \tau_{sl}^2),$$

559

560 where for an population s (e.g., European, Asian or African), \mathbf{y}_s is a vector of standardized
561 phenotypes (zero mean and unit variance) from N_s individuals, $\mathbf{X}_s = [\mathbf{x}_{s1}, \mathbf{x}_{s2}, \dots, \mathbf{x}_{sM}]$ is an
562 $N_s \times M$ matrix of standardized genotypes (each column \mathbf{x}_{sj} is mean centered and has unit
563 variance) in a genomic region that harbors at least one strong association signal, $\boldsymbol{\beta}_s$ is a vector
564 of SNP effect sizes, and $\boldsymbol{\epsilon}_s$ is a vector of residuals with i.i.d. elements, each following a normal
565 distribution with zero mean and variance σ_s^2 . We assume that $\boldsymbol{\beta}_s$ is the sum of L single-effect
566 vectors \mathbf{b}_{sl} , $l = 1, 2, \dots, L$, each has exactly one non-zero element (equals to b_{sl}). The position of
567 the non-zero element is determined by the binary vector $\boldsymbol{\gamma}_l$, which follows a multinomial
568 distribution. $\boldsymbol{\pi} = [\pi_1, \pi_2, \dots, \pi_M]^T$ is a vector that gives the prior probability of a SNP being causal,
569 and τ_{sl}^2 is the prior variance on the effect size b_{sl} of the causal SNP. We note that all populations
570 share the same underlying causal SNPs ($\boldsymbol{\gamma}_l$ does not depend on s), but the effect sizes of a causal
571 SNP across populations are allowed to be different (b_{sl} depends on s).

572

573 **Model fitting.** Assuming σ_s^2 and τ_{sl}^2 are known, the SuSiEx model can be fitted using a simple
 574 extension of the iterative Bayesian stepwise selection (IBSS) algorithm. Specifically, with an
 575 initialization of the posterior mean effect size of \mathbf{b}_{sl} , denoted as $\bar{\mathbf{b}}_{sl}$ (e.g., $\bar{\mathbf{b}}_{sl} = 0$ for all s and l),
 576 the fitting procedure involves iteratively updating \mathbf{b}_{sl} , given estimates of other effects $\mathbf{b}_{sl'}, l' \neq l$,
 577 until convergence:

578

579 \diamond Compute residuals:

$$580 \quad \mathbf{r}_{sl} = \mathbf{y}_s - \sum_{l' \neq l} \mathbf{X}_s \mathbf{b}_{sl'}, \quad s = 1, 2, \dots, S.$$

581 \diamond Compute the posterior inclusion probabilities (PIPs):

$$585 \quad \alpha_{lj} = \Pr(\gamma_{lj} = 1 | \mathbf{r}_{sl}, \mathbf{X}_s) = \frac{\pi_j \prod_{s=1}^S \text{BF}(\mathbf{r}_{sl}, \mathbf{x}_{sj})}{\sum_{j'}^M \pi_{j'} \prod_{s=1}^S \text{BF}(\mathbf{r}_{sl}, \mathbf{x}_{sj'})}, \quad j = 1, 2, \dots, M,$$

$$582 \quad \text{where } \text{BF}(\mathbf{r}_{sl}, \mathbf{x}_{sj}) = \frac{p(\mathbf{r}_{sl} | \mathbf{x}_{sj})}{p(\mathbf{r}_{sl} | \mathbf{x}_{sj}, \mathbf{b}_{sl} = 0)} = \sqrt{\frac{v_{sj}^2}{\tau_{sl}^2 + v_{sj}^2}} \exp\left(\frac{z_{slj}^2}{2} \frac{v_{sj}^2}{\tau_{sl}^2 + v_{sj}^2}\right),$$

$$583 \quad \hat{\mathbf{b}}_{slj} = (\mathbf{x}_{sj}^T \mathbf{x}_{sj})^{-1} \mathbf{x}_{sj}^T \mathbf{r}_{sl} = N_s^{-1} \mathbf{x}_{sj}^T \mathbf{r}_{sl}, \quad v_{sj}^2 = \sigma_s^2 (\mathbf{x}_{sj}^T \mathbf{x}_{sj})^{-1} = \sigma_s^2 N_s^{-1}, \quad z_{slj} =$$

$$584 \quad \hat{\mathbf{b}}_{slj} / v_{sj}.$$

586 \diamond Update the posterior distribution for \mathbf{b}_{sl} :

$$588 \quad \mathbf{b}_{sl} | \gamma_{lj} = 1, \mathbf{r}_{sl}, \mathbf{x}_{sj} \sim N(\mu_{slj}, \phi_{slj}^2),$$

$$587 \quad \text{where } \phi_{slj}^2 = (v_{sj}^{-2} + \tau_{sl}^{-2})^{-1}, \quad \mu_{slj} = (\phi_{slj}^2 / v_{sj}^2) \hat{\mathbf{b}}_{slj}.$$

589 \diamond Compute the posterior mean for \mathbf{b}_{sl} :

$$590 \quad \bar{\mathbf{b}}_{sl} = \mathbb{E}[\mathbf{b}_{sl} | \mathbf{r}_{sl}, \mathbf{X}_s] = \boldsymbol{\alpha}_l \circ \boldsymbol{\mu}_{sl},$$

591 Where $\boldsymbol{\alpha}_l = [\alpha_{l1}, \alpha_{l2}, \dots, \alpha_{lM}]^T$, $\boldsymbol{\mu}_{sl} = [\mu_{sl1}, \mu_{sl2}, \dots, \mu_{slM}]^T$, and \circ is element-wise
 592 multiplication.

593

594 **Credible sets.** The PIPs α_l can be used to compute a level- ρ credible set $CS(\boldsymbol{\alpha}_l; \rho)$, which has a
 595 probability no less than ρ of containing at least one causal SNP. Specifically, let (i_1, i_2, \dots, i_M)
 596 denote the indices that sort α_{lj} in decreasing order, i.e., $\alpha_{li_1} > \alpha_{li_2} > \dots > \alpha_{li_M}$, and let $S_k =$
 597 $\sum_{j=1}^k \alpha_{li_j}$. Then $CS(\boldsymbol{\alpha}_l; \rho) := \{i_1, i_2, \dots, i_{k_0}\}$, where $k_0 = \min\{k: S_k \geq \rho\}$. When L exceeds the
 598 number of detectable effects in the data, some α_l become diffuse and the corresponding credible
 599 sets will be large, containing many uncorrelated SNPs. Such credible sets have no inferential
 600 value and can be discarded if they have purity below a threshold (e.g., 0.5), where purity is defined
 601 as the smallest absolute correlation among all pairs of variants within the credible set.

602

603 **Using GWAS summary statistics.** Let $\hat{\beta}_{sj} = (\mathbf{x}_{sj}^T \mathbf{x}_{sj})^{-1} \mathbf{x}_{sj}^T \mathbf{y}_s = N_s^{-1} \mathbf{x}_{sj}^T \mathbf{y}_s$ denote the marginal
 604 least squares effect size estimate of SNP j in the ethnic group s , and $\mathbf{D}_s = [\mathbf{d}_{s1}, \mathbf{d}_{s2}, \dots, \mathbf{d}_{sM}] =$
 605 $\mathbf{X}_s^T \mathbf{X}_s / N_s$ denote the LD matrix for ethnic group s , which can be estimated using an LD reference
 606 panel. Note that $\mathbf{x}_{sj}^T \mathbf{r}_{sl} = \mathbf{x}_{sj}^T \mathbf{y}_s - \mathbf{x}_{sj}^T \sum_{l' \neq l} \mathbf{X}_s \bar{\mathbf{b}}_{sl'} = N_s \hat{\beta}_{sj} - N_s \sum_{l' \neq l} \mathbf{d}_{sj}^T \bar{\mathbf{b}}_{sl'}$. Therefore, IBSS can
 607 be turned into a summary statistics based algorithm.

608

609

610 **The multi-step model fitting approach.** To determine the maximum number of single effects L ,
611 we designed a heuristic, multi-step model fitting approach. Specifically, we start with $L = 5$ and fit
612 the SuSiEx model. If the model does not converge, we sequentially reduce L by 1 until the
613 algorithm converges. If the model converges with $L = 5$ and returns 5 credible sets, suggesting
614 that more than 5 credible sets may exist, we set $L = 10$ and rerun the model fitting algorithm. If
615 the model does not converge with $L = 10$, we sequentially reduce L by 1 until the algorithm
616 converges.

617

618 **Simulations**

619 **Genomic data.** We simulated individual-level genotypes of EUR, EAS and AFR populations using
620 HAPGEN2⁴² with ancestry-matched 1000 Genomes Project (1KG) Phase III⁴³ superpopulation
621 samples as the reference panel. We grouped CEU, IBS, FIN, GBR and TSI into the EUR
622 superpopulation, CDX, CHB, CHS, JPT and KHV into the EAS superpopulation, and ESN, MSL,
623 LWK, GWD and YRI into the AFR superpopulation. To calculate the genetic map (cM) and
624 recombination rate (cM/Mb) for each superpopulation, we downloaded the maps and rates for
625 their constituent subpopulations (Data availability), linearly interpolated the genetic map and
626 recombination rate at each position (Code availability), and averaged the genetic maps and
627 recombination rates across the subpopulations in each superpopulation. We simulated 400,000
628 EUR samples, 200,000 EAS samples and 200,000 AFR samples, and confirmed that the allele
629 frequencies and LD patterns of the simulated genotypes were highly similar to those of the 1KG
630 reference panels. We randomly selected 100 1MB regions from chromosome 1 (Supplementary
631 Table 1), and filtered for bi-allelic common (MAF >1%) SNPs in at least one of the three
632 superpopulations.

633

634 **Phenotypic data.** We randomly selected n_{csi} causal variants within each genomic locus. The
635 allelic effect sizes of each selected causal variant for the EUR, EAS and AFR populations were
636 generated under a multivariate normal distribution $N(\mathbf{0}, \Sigma_{3 \times 3})$, where $\Sigma_{3 \times 3}$ was defined as, $\Sigma_{ij} = I$,
637 if $i = j$, and $\Sigma_{ij} = r_g$, if $i \neq j$ where r_g is the genetic correlation between populations. For each locus,
638 we then generated the phenotype by adding a normally distributed noise term to the genetic
639 component to produce the given per-locus heritability h^2 .

640

641 To assess SuSiEx in a wide range of settings, we generated simulation data with varying genetic
642 correlations (r_g), per-locus heritability (h^2), and the number of causal variants (n_{csi}) per locus. We
643 defined a standard simulation setting using $n_{csi} = 1$, $r_g = 0.7$ and $h^2 = 0.1\%$. We then varied r_g (r_g
644 = 0.4 and 1.0) to reflect different levels of cross-population genetic correlations, varied h^2 ($h^2 =$
645 0.05%, 0.2%, 0.3%, 0.4% and 0.5%) to reflect different per-locus heritability values, and varied
646 n_{csi} ($n_{csi} = 2, 3, 4, 5$) with $h^2 = 0.5\%$ to reflect the scenario of multiple causal variants in a genomic
647 locus. To evaluate the robustness of SuSiEx to model misspecification, we simulated 200K EUR
648 and 200K AFR samples with no causal variants, and included these null data in cross-population
649 fine-mapping. For each parameter setting, we replicated the simulation five times for each locus
650 (Supplementary Table 2), producing 500 simulation runs.

651

652 **Association analysis and LD calculation.** We used the linear regression implemented in
653 PLINK⁴⁴ to generate GWAS summary statistics, and calculated in-sample LD for each genomic
654 locus. To evaluate the impact of LD mismatch on fine-mapping results, we additionally calculated
655 LD matrices using subpopulation samples within the EUR and AFR superpopulations.

656

657 **Fine-mapping analysis with SuSiEx, SuSiE, PAINTOR, and MsCAVIAR.**

658 We compared SuSiEx, SuSiE, PAINTOR and MsCAVIAR using the standard simulation setting.
659 SuSiEx and SuSiE were performed and evaluated on additional settings beyond the standard
660 simulations. As PAINTOR and MsCAVIAR are not computationally scalable to full GWAS
661 summary statistics, we restricted the analysis to three filtered sets of variants: “ $p < 0.05$ ”, “top 500”
662 and “top 150”, corresponding to marginal p-values < 0.05 , the top 500 and the top 150 most
663 associated variants from GWAS, respectively. PAINTOR provides two model fitting options,
664 “MCMC” and “enumerate”. The “MCMC” mode automatically learns the number of causal variants
665 in a locus while the “enumerate” mode requires pre-setting the maximum number of causal
666 variants. We ran PAINTOR using “-mcmc”, “-enumerate=1”, “-enumerate=2” and “-enumerate=3”.
667 All other parameters were set to default. We set the maximum runtime to 24 hours in our high-
668 performance computing (HPC) system, the maximum memory to 8 GB, and the number of CPUs
669 to one. For SuSiEx, we used the multi-step model fitting approach described above to determine
670 the number of causal variants. Credible sets that did not contain any genome-wide significant
671 variant (marginal $P < 5E-8$) in any single-population GWAS nor cross-population meta-GWAS
672 were filtered out. We ran MsCAVIAR with the default parameters and set the confidence level of
673 credible sets as 0.95.

674

675 **Biobank analysis**

676 **Cohorts.** GWAS summary statistics of 25 quantitative traits, available from both the UK Biobank
677 (UKBB) and Taiwan Biobank (TWB), were used in our biobank fine-mapping analysis
678 (Supplementary Table 13). European (EUR; N_{EUR} up to 419,807) and African (AFR; N_{AFR} up to
679 6,570) GWAS summary statistics were obtained from the Pan-ancestry genetic analysis of the
680 UK Biobank (Pan-UKBB). East Asian GWAS summary statistics were obtained from the Taiwan
681 Biobank (EAS; $N_{EAS} = 92,615$).

682

683 **Loci definition.** We used a 6-way LD clumping-based method to define the genomic loci, using
684 1KG data as the LD reference for clumping. CEU, GBR, TSI, FIN and IBS were combined as the
685 reference for the EUR population; ESN, GWD, LWK, MSL and YRI were combined as the
686 reference for the AFR population; CHB, CHS, CDX, JPT and KHV were combined as the
687 reference for the EAS population. We extracted all variants with $MAF > 0.5\%$, and for each of the
688 25 traits, performed the LD clumping in the three populations using the corresponding reference
689 panel and PLINK⁴⁴. To include loci that reached genome-wide significance ($P < 5E-8$) only in the
690 meta-analysis, we further performed clumping for the meta-GWAS across the three populations,
691 using the three reference panels, respectively. For each clumping, we set the p-value threshold
692 of the leading variant as $5e-8$ (--clump-p1) and the threshold of the tagging variant as 0.05 (--
693 clump-p2), and set the LD threshold as 0.1 (--clump-r2) and the distance threshold as 250 kb (--
694 clump-kb). We then took the union of the 6-way LD clumping results and extended the boundary

695 of each merged region by 100 kb upstream and downstream. Finally, we merged adjacent loci if
696 the LD (r^2) between the leading variants was larger than 0.6 in any LD reference panel.

697

698 **In-sample LD calculation.** We used the in-sample LD of the three populations in the fine-
699 mapping analysis. We extracted all variants with MAF >0.5% from each population and calculated
700 the LD using PLINK⁴⁴. Multi-allelic variants and indels were excluded to avoid potential strand
701 flipping and alignment errors.

702

703 **Fine-mapping.** We applied SuSiEx to the 25 quantitative traits to integrate GWAS summary
704 statistics derived from the three populations. We filtered out credible sets that did not contain any
705 genome-wide significant variant ($p < 5E-8$) in any population-specific GWAS or cross-population
706 meta-GWAS.

707

708 **Credible set alignment.** To compare the results between single-population and cross-population
709 fine-mapping, we aligned the inferred credible sets across the four sets of analyses using a
710 weighted Jaccard similarity index-based method⁷. Specifically, for a given pair of overlapping
711 credible sets in a genomic locus, we computed the PIP-weighted Jaccard similarity index, defined
712 as $\sum_i \min(x_i, y_i) / \sum_i \max(x_i, y_i)$, where x_i and y_i are PIP values (or zero if missing) for the same
713 variant i from the two credible sets. Pairs of credible sets with a similarity index greater than 0.1
714 were aligned. If one credible set can be aligned with multiple credible sets, the set with the highest
715 similarity was selected.

716

717 **Cross-population fine-mapping in schizophrenia cohorts.**

718 Schizophrenia GWAS summary statistics of European (EUR; $N_{case} = 53,251$, $N_{control} = 77,127$) and
719 East Asian (EAS; $N_{case} = 14,004$, $N_{control} = 16,757$) ancestries were obtained from the recently
720 published Psychiatric Genomics Consortium (PGC) schizophrenia analysis⁴. We fine-mapped the
721 same 255 loci defined in the PGC publication. We calculated LD by applying LD-Store v1.1³⁹ to
722 each cohort and locus, and then calculated an effective sample size weight LD matrix⁴⁵ across
723 cohorts for the EUR and EAS populations, respectively (Code availability; LDmergeFM). We
724 applied SuSiEx to integrate EUR and EAS schizophrenia GWAS summary statistics to perform
725 cross-population fine-mapping. Credible set level was set to 99%. Credible sets that did not
726 contain any genome-wide significant variant (marginal $P < 5E-8$) in single-population GWAS or
727 cross-population meta-GWAS were filtered out.

728

729 DATA AVAILABILITY

730 Publicly available data are available from the following sites:

731 1KG Phase 3 reference panels: https://mathgen.stats.ox.ac.uk/impute/1000GP_Phase3.html;

732 Genetic map for each subpopulation:

733 [https://ftp.1000genomes.ebi.ac.uk/vol1/ftp/technical/working/20130507_omni_recombination_rat](https://ftp.1000genomes.ebi.ac.uk/vol1/ftp/technical/working/20130507_omni_recombination_rates)
734 [es](https://ftp.1000genomes.ebi.ac.uk/vol1/ftp/technical/working/20130507_omni_recombination_rates);

735 PanUKBB summary statistics: <https://pan.ukbb.broadinstitute.org/downloads>;

736 TWB data used in this study contain protected health information and are thus under controlled
737 access. Application to access such data can be made to the TWB

738 (https://www.twbiobank.org.tw/new_web_en/);

739 PGC schizophrenia GWAS: <https://pgc.unc.edu/for-researchers/download-results>

740

741 **CODE AVAILABILITY**

742 The code used in this study is available from the following websites:

743 SuSiEx: <https://github.com/getian107/SuSiEx>;

744 PAINTOR: https://github.com/gkichaev/PAINTOR_V3.0;

745 MsCAVIAR: <https://github.com/nlapier2/MsCAVIAR>;

746 HAPGEN2: https://mathgen.stats.ox.ac.uk/genetics_software/hapgen/hapgen2.html;

747 PLINK1.9: <https://www.cog-genomics.org/plink>;

748 LDmergeFM: <https://github.com/Pintaius/LDmergeFM>

749

750 **ETHICS**

751 Collection of the UKBB data was approved by the Research Ethics Committee of the UKBB.

752 UKBB individual-level data used in the present work were obtained under application no. 32568.

753 Collection of the TWB data was approved by the Ethics and Governance Council (EGC) of TWB and the Department of Health and Welfare, Taiwan (Wei-Shu-I-Tzu no.1010267471). TWB

754 obtained informed consent from all participants for research use of the collected data. Access

755 to, and use of, TWB data in the present work was approved by the EGC of TWB (approval

756 number: TWBR10907-05) and the Institutional Review Board of National Health Research

757 Institutes, Taiwan (approval number: EC1090402-E).

758

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771

772 **COMPETING INTERESTS**

774 W.S. and C.S. are employees of Digital Health China Technologies Corp. Ltd.. M.J.D. is a founder

775 of Maze Therapeutics. C.Y.C. is an employee of Biogen. H.H. received consultancy fees from

776 Ono Pharmaceutical and honorarium from Xian Janssen Pharmaceutical.

777

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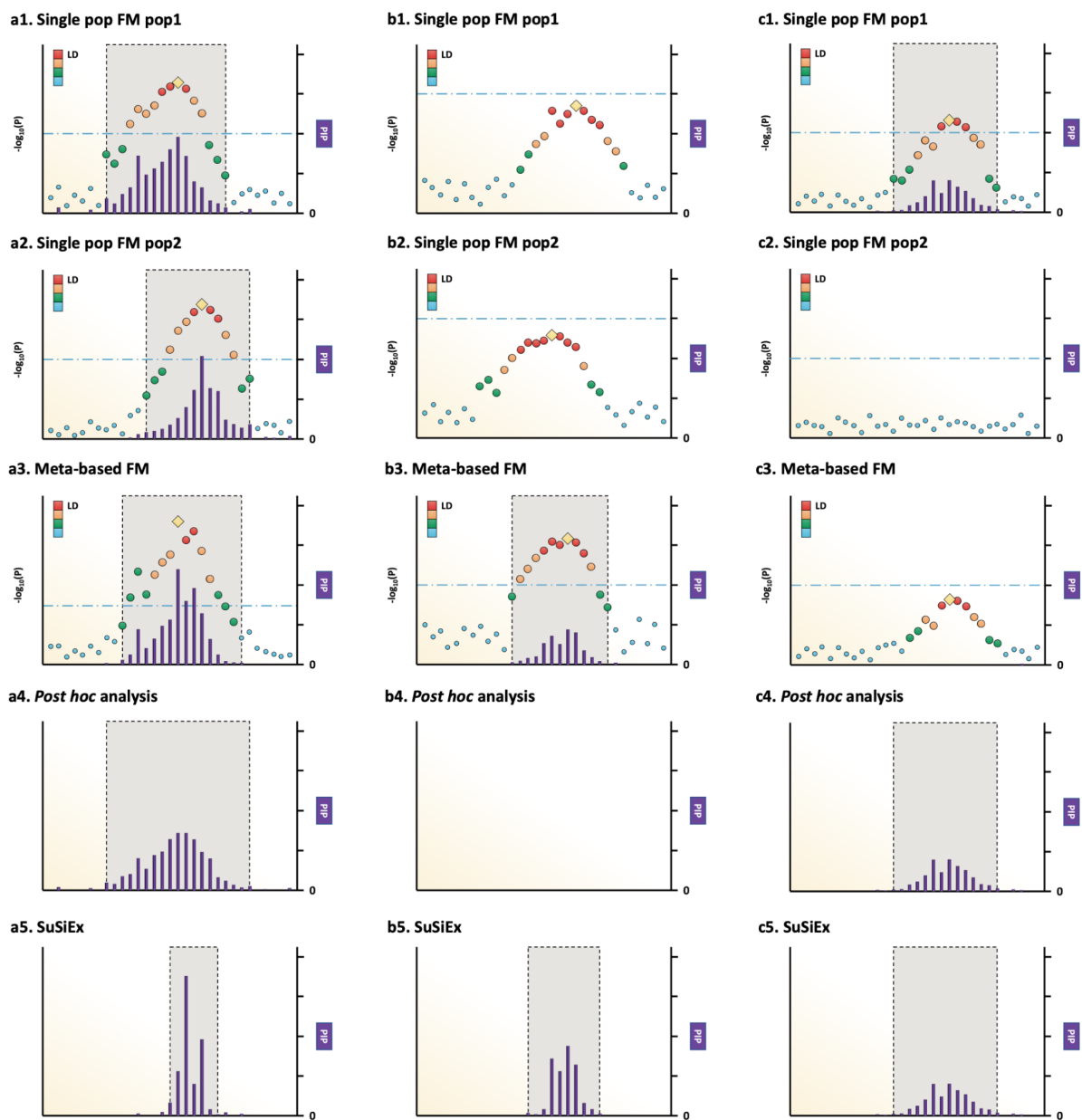
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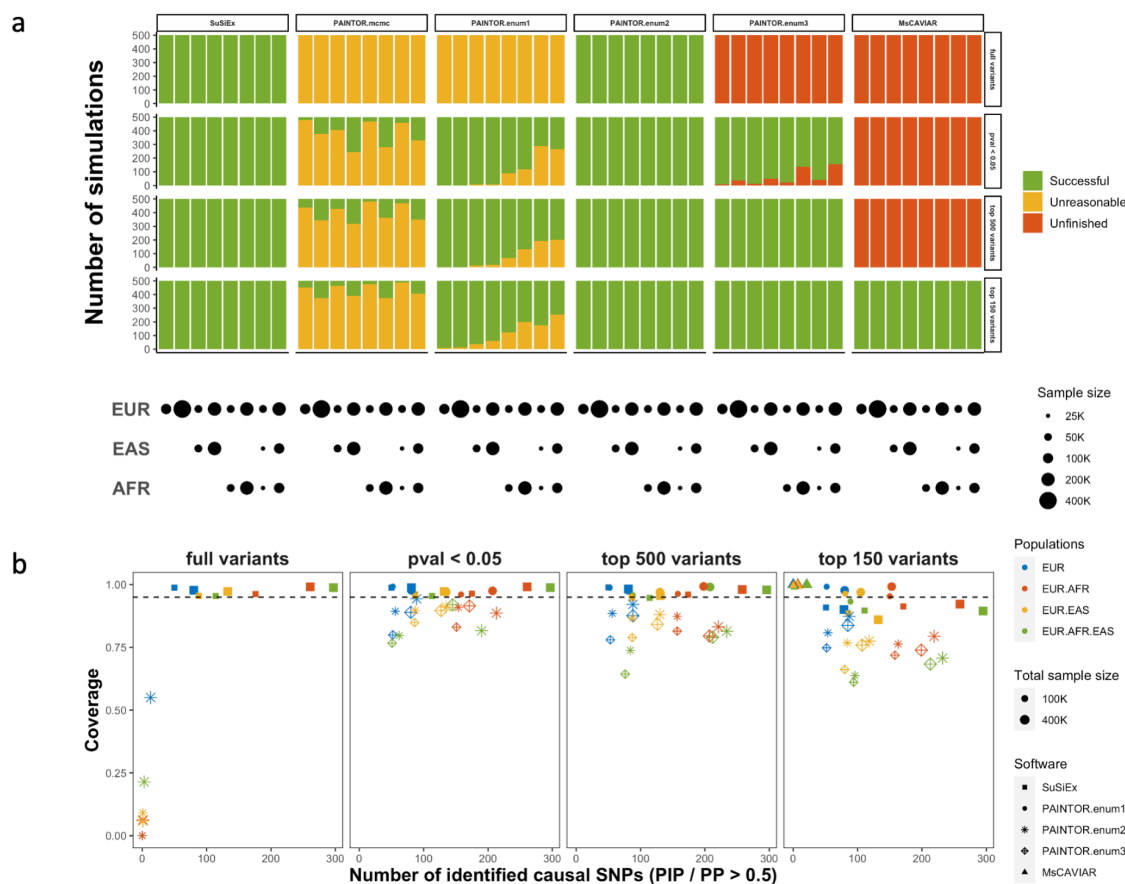
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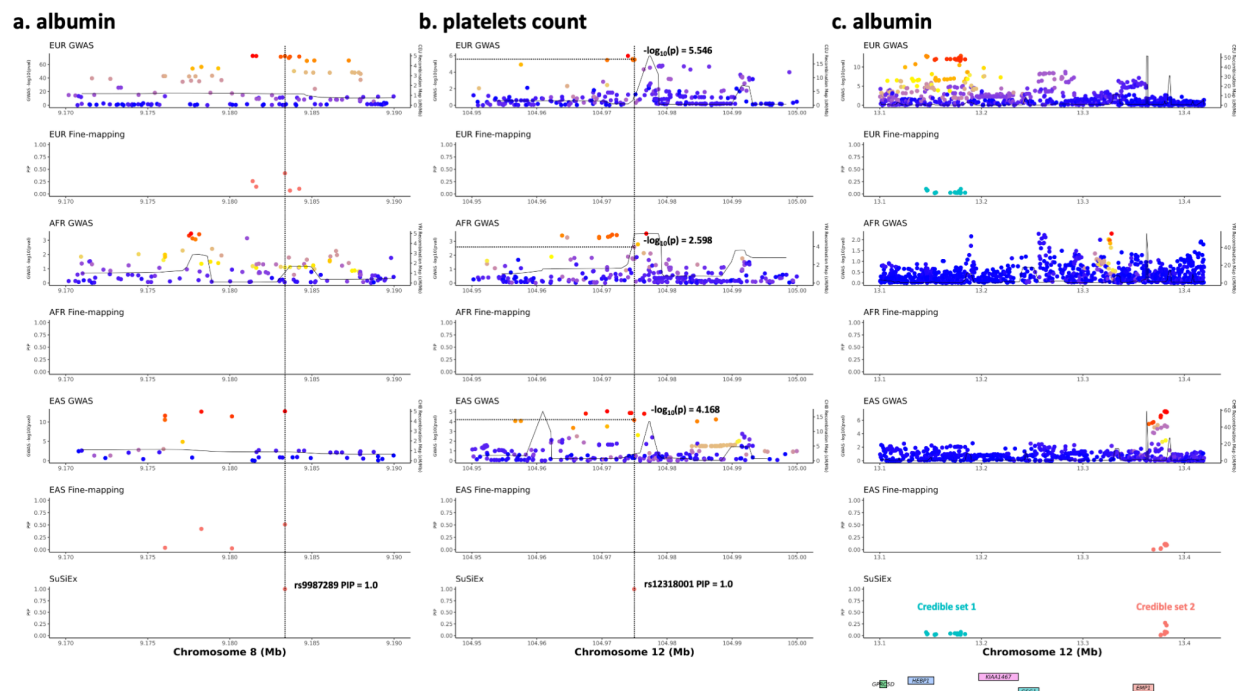


Extended Data Figure 1: Schematic illustration of meta-based, *post hoc* and SuSiEx fine-mapping methods. All panels were created following the LocusZoom style¹⁷. Variant positions are shown on the x axis. The gold diamond for each locus represents the lead (most associated) variant. The association strengths for other variants are colored by descending degrees of linkage disequilibrium (LD) with the lead variant (ordered red, orange, green, and blue dots). The purple bars represent the posterior inclusion probability (PIP) inferred by fine-mapping methods. The light gray boxes represent the credible set estimated by fine-mapping. **a1-a5**, Example of a strong causal signal shared across populations. **b1-b5**, Example of a weak causal signal shared across populations. **c1-c5**, Example of a population-specific causal signal.



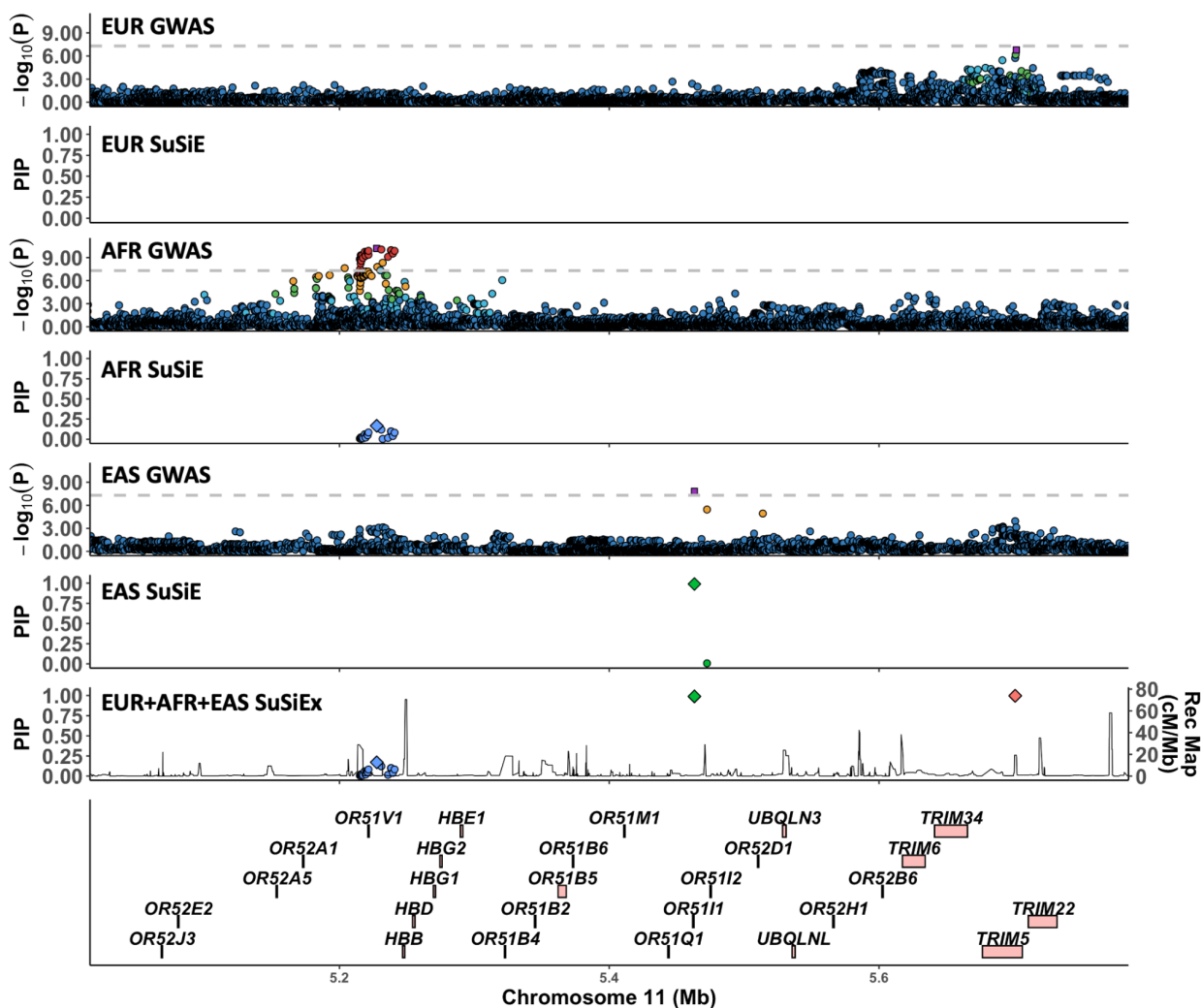
Extended Data Figure 2: Comparison of SuSiEx, PAINTOR and MsCAVIAR in simulations.

a, The job completion summary for the three Bayesian fine-mapping methods using different parameters and input datasets. Red stands for jobs taking longer than 24 hours. Yellow stands for jobs returning unreasonable results, defined as the sum of PIP across variants in the genomic locus >5 or <0.1 (1 is expected). Green stands for jobs that were completed within 24 hours and returned reasonable results. **b**, Number of identified true causal SNPs with $PIP > 0.5$ (x-axis) versus the coverage of credible sets (y-axis) for different input datasets and fine-mapping methods. Color represents the combination of discovery populations; size of the symbols represents the total discovery sample size, and the shape of the symbols represents different methods and parameters. Only simulation runs that were completed within 24 hours and returned reasonable results were included.

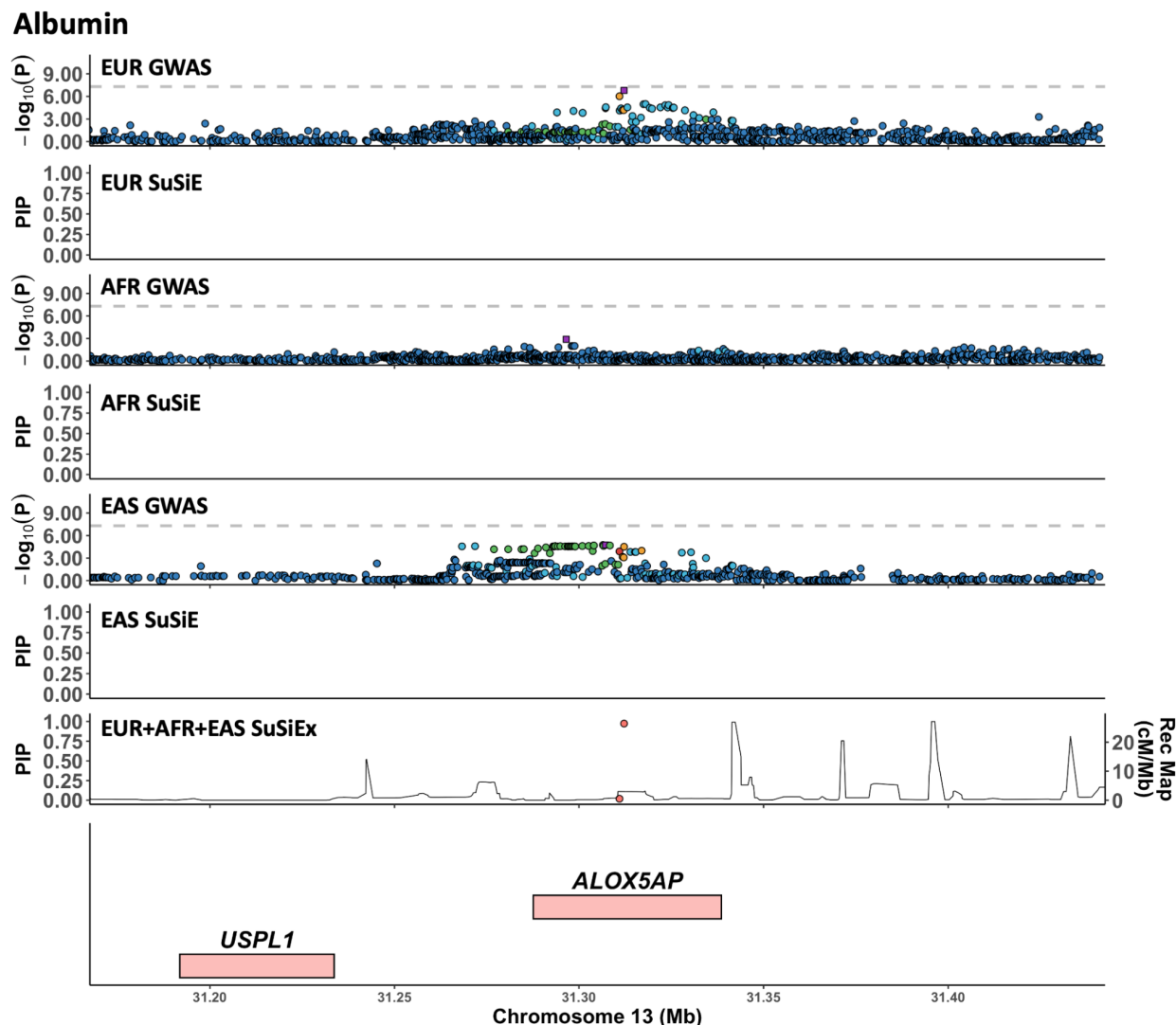


Extended Data Figure 3: Examples of the improvement of SuSiEx over single-population fine-mapping in biobank analysis. Each of the three sub-figures consists of eight panels, which are aligned vertically, with the x-axis representing the genomic position. The top six panels visualize GWAS association statistics and single-population fine-mapping results of the European (Pan-UKBB European), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations. For association statistics, the left y-axis represents the $-\log_{10}(p\text{-value})$ of each SNP. The color stands for the descending degrees of LD with the lead SNP (from red, orange to blue). The right y-axis represents the recombination rate in the centimorgan per Megabase. The solid line indicates the population-specific recombination maps obtained from the 1000 Genomes Project. Different colors were used to distinguish different credible sets in the fine-mapping results. The second to bottom panel visualizes results from SuSiEx. The bottom panel shows gene annotations if any. **a**, Association with albumin on chr8:9,170,000-9,190,000, an example of a strong causal signal shared across populations. **b**, Association with platelets count on chr12:104,900,000-105,050,000, an example of a weak causal signal shared across populations. **c**, Association with albumin on chr12:13,100,000-13,400,000, an example of population-specific causal signals.

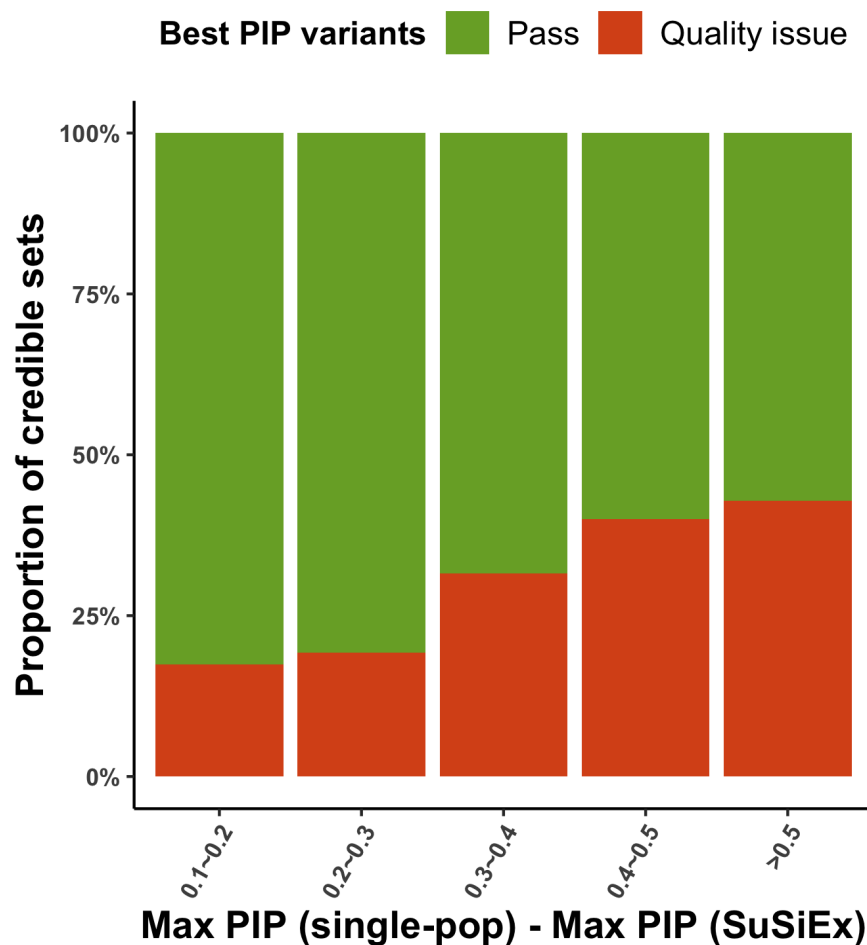
Total bilirubin



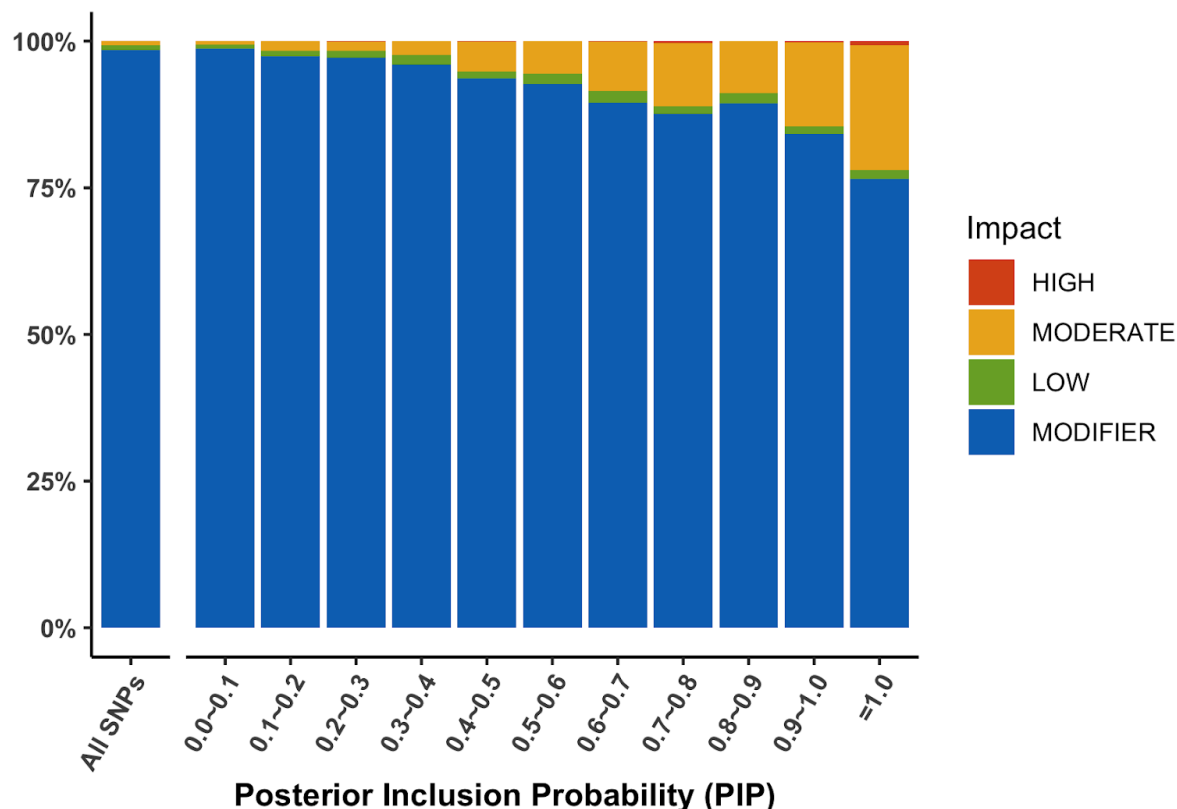
Extended Data Figure 4: Association with total bilirubin on chr11: 5,100,000-5,700,000. Panels are aligned vertically, with the x-axis representing the genomic position. The top six panels visualize GWAS association statistics and single-population fine-mapping results of the European (Pan-UKBB European), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations following the LocusZoom³⁷ style. The second to bottom panel visualizes the fine-mapping results from SuSiEx, which integrated GWAS summary statistics from the three populations. The bottom panel shows gene annotations. For GWAS panels, the left y-axis represents the $-\log_{10}(\text{p-value})$ of each SNP. The gray horizontal dash line represents the genome-wide significance threshold (5×10^{-8}). The purple rectangle for each locus represents the lead (most associated) variant. Variants are colored by descending LD with the lead variant (ordered red, orange, green, light blue, and dark blue dots). For fine-mapping panels, different colors were used to distinguish different credible sets. The diamond represents the maximum PIP variant of each credible set. The left y-axis represents the PIP from fine-mapping and the right y-axis represents the recombination map obtained from the 1000 Genomes Project (for the SuSiEx panel, the average recombination rate across three populations was used).



Extended Data Figure 5: Association with albumin on chr13: 31,150,000-31,450,000. Panels are aligned vertically, with the x-axis representing the genomic position. The top six panels visualize GWAS association statistics and single-population fine-mapping results of the European (Pan-UKBB European), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations following the LocusZoom³⁷ style. The second to bottom panel visualizes the fine-mapping results from SuSiEx, which integrated GWAS summary statistics from the three populations. The bottom panel shows gene annotations. For GWAS panels, the left y-axis represents the $-\log_{10}(\text{p-value})$ of each SNP. The gray horizontal dash line represents the genome-wide significance threshold (5×10^{-8}). The purple rectangle for each locus represents the lead (most associated) variant. Variants are colored by descending LD with the lead variant (ordered red, orange, green, light blue, and dark blue dots). For fine-mapping panels, different colors were used to distinguish different credible sets. The diamond represents the maximum PIP variant of each credible set. The left y-axis represents the PIP from fine-mapping and the right y-axis represents the recombination map obtained from the 1000 Genomes Project (for the SuSiEx panel, the average recombination rate across three populations was used).



Extended Data Figure 6: Proportion of variants showing quality issues binned by the drop in PIP from single- to multi-population fine-mapping. Quality issues were defined as (i) the best PIP variant is in the low complexity region; (ii) the best PIP variant is in allelic imbalance or violates Hardy Weinberg equilibrium in gnomAD³³; or (iii) the best PIP variant is multi-allelic or colocalizes with indels at the same genomic position, which might influence imputation quality.



Extended Data Figure 7: Proportion of variants with high/moderate functional impact in cross-population biobank fine-mapping analyses. The functional impact of each variant was annotated using VEP, with the definition and classification of functional impact obtained from https://useast.ensembl.org/info/genome/variation/prediction/predicted_data.html. The high impact category includes transcript ablation, splice acceptor variants, splice donor variants, etc; moderate impact includes missense variants, protein-altering variants, etc; low impact includes synonymous variants, splice region variants, etc; modifier impact includes introns and intergenic variants among others.