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

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### 39 Abstract

#### 40

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 guantitative 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. 56

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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 diseaseassociated loci resolved to single-variant resolution<sup>1-3</sup>. Since non-causal variants tagging causal 68 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 in the field, including in several seminal studies<sup>4,5</sup>. This approach, however, assumes no 78 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 causal<sup>6</sup>. 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 variants<sup>7</sup>, 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 populationspecific results. Bayesian methods<sup>8,9</sup> provide a principled way to fine-map causal variants across 86 populations and have been employed in the analyses of several complex traits or diseases<sup>8–12</sup>. 87 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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Recently, Wang et al. proposed a single-population fine-mapping method, SUm of SIngle Effects 93 (SuSiE)<sup>13</sup>, which improved the calibration, computational efficiency and interpretation of statistical 94 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 Biobank<sup>14</sup> and Taiwan Biobank<sup>15</sup>, and to fine-map schizophrenia genetic risk loci 101 across European and East Asian ancestries.

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#### 103 104 **RESULTS**

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# 106 Overview of SuSiEx

SuSiEx extends the single-population fine-mapping model, SuSiE<sup>13</sup>, by integrating population-107 specific GWAS summary statistics and LD reference panels from multiple populations. In SuSiE, 108 109 the genetic influence on a trait or disease within a genomic locus is modeled as the summation 110 of several distinct effects, each contributed by a single causal variant, which naturally allows for 111 the modeling of multiple association signals and assigns each inferred putative causal variant to 112 a credible set with a posterior inclusion probability (PIP) (Figure 1). Building on this framework, 113 SuSiEx couples each single effect by assuming that the causal variants are shared across 114 populations (i.e., we report a single PIP rather than population-specific PIPs for each variant in a 115 credible set), while allowing them to have varying effect sizes (including null effects) across 116 ancestries. In addition, SuSiEx allows for a variant to be missing in an ancestry (e.g., due to its 117 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 118 variable selection in regression<sup>16,17</sup> and applies the iterative Bayesian stepwise selection<sup>13</sup> to 119 120 model fitting. Further modeling and computational details for SuSiEx are discussed in Methods.

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Compared with the meta-analysis-based fine-mapping approach<sup>4,5</sup>, SuSiEx explicitly models 122 123 population-specific GWAS summary statistics and LD patterns (Figure 1; Extended Data Figure 124 1a), which is expected to improve the fine-mapping resolution and more accurately control the 125 false positive rates, while allowing for heterogeneous effect sizes and retaining population-specific 126 causal variants (Extended Data Figure 1c). Compared with post hoc analysis to combine single-127 population fine-mapping results<sup>7</sup>, SuSiEx leverages the sample size, genetic correlation and LD 128 diversity across ancestries to improve the resolution of fine-mapping, especially for loci that are 129 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<sup>9,18</sup> and 130 131 MsCAIVAR<sup>8</sup>, SuSiEx infers distinct credible sets for each causal signal (Figure 1), facilitating the 132 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 133 134 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 locus, genetic correlations across populations ( $r_q$ ) and SNP heritability ( $h^2$ ) (Methods). To examine 149 the impact of these genetic parameters on fine-mapping results, we defined a standard simulation 150 setting with  $n_{csl} = 1$ ,  $r_a = 0.7$  and  $h^2 = 0.1\%$ , and then varied these parameters to produce a range 151 152 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 reached genome-wide significance in population-specific GWAS (P<5x10<sup>-8</sup>); in cross-population 156 157 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-

mapping in large genomic loci; (v) Robustness: the proportion of runs in which the fine-mappingalgorithm 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<sup>19,20</sup>.

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A widely used approach in recent multi-ancestry genetic studies<sup>4</sup> is to apply a single-population 187 188 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-analysis<sup>6</sup>. 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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Figure 2: The performance of SuSiEx in simulations. Simulated data were generated under 200 201 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 different sample sizes for fine-mapping. b, The number of true causal variants mapped to 203 PIP >95%. c, The coverage of credible sets (the proportion of credible sets that contain a true 204 205 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 discoveries<sup>7</sup>. 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<sup>9,18</sup> and MsCAVIAR<sup>8</sup>, using the standard simulation setting (Supplementary Table 2). We noted that neither of the two methods is capable of analyzing all common variants 238 239 (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 MsCAIVAR 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  $(r_q)$  can be less than one for many complex traits and diseases<sup>21</sup>. SuSiEx accounts for imperfect genetic correlation by 298 299 allowing for varying genetic effects across populations. Using simulated data with  $r_a$  of 0.4, 0.7, 300 and 1.0, we confirmed that SuSiEx was robust to a range of  $r_a$  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  $(n_{csl})$  per locus can differ across the genome for a given trait or disease<sup>1,22-24</sup>. We set the heritability per locus to 0.05%, 0.1%, 0.2%, 0.3%, 0.4% 303 304 and 0.5%, and for a given per-locus heritability, varied  $n_{csl}$  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  $n_{csl}$  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  $n_{csl}$  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 studies<sup>25–28</sup>, 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<sup>6,29–31</sup>. 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).

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# 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)<sup>14</sup> 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<sup>15,32</sup>. We selected 25 guantitative 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.

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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 ( $P = 3.7 \times 10^{-6}$ ; two-sided t test), and reduced the average size of credible sets from 29.4 to 27.2 (P = 0.015; two-356 357 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 associated with total bilirubin at PIP >99%, a missense variant of TRIM5 (rs11601507). This 361 362 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

identified a two-variant credible set associated with albumin that failed to reach genome-wide significance in any population (Figure 5b; Extended Data Figure 5). The lead variant in the credible set is an intron variant of *ALOX5AP* with PIP 97.4%. This variant was fine-mapped to be an eQTL variant regulating the expression of *ALOX5AP* in whole blood (PIP >99%), artery aorta (PIP = 86.1%) and spleen (PIP = 77.9%) (Figure 5b; Extended Data Figure 5)<sup>33</sup>. In both examples, SuSiEx identified putative causal variants and resolved a genetic locus to its gene target that 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 guality of variant calling and imputation may be negatively affected<sup>34</sup>. This variant is also represented in fewer than 50% of individuals in gnomAD v2.1.1 genomes<sup>35</sup>, 384 385 and violates Hardy-Weinberg equilibrium.

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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 gnomAD<sup>35</sup>; 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 guality 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.

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401 We used Ensembl Variant Effect Predictor (VEP)<sup>36</sup> 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

high/moderate impact SNPs with PIP greater than 95%, while only 23 were detected in the three
 single-population fine-mapping analyses. In particular, *IQGAP2* and *PIEZO1* carried 3 missense
 wariante appariated with multiple blaced biamarkers with PIPs >05%

410 variants associated with multiple blood biomarkers with PIPs >95%.

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•  $PIP_{SuSiEx} > 0.95, \max(PIP_{single-pop}) < 0.5$  •  $PIP_{SuSiEx} > 0.95, \max(PIP_{single-pop}) < 0.8$  •  $PIP_{SuSiEx} < 0.5, \max(PIP_{single-pop}) > 0.95$ 

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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 to PIP >95% in single-credible-set loci. e, The maximum PIP from SuSiEx versus the maximum 416 417 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

Lastly, we compared the per-allele effect sizes of high-confidence putative causal variants (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.





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 Europan), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations 443 following the LocusZoom<sup>37</sup> 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<sub>10</sub>(p-value) 446 of each SNP. The gray horizontal dash line represents the genome-wide significance threshold 447 (5x10<sup>-8</sup>). 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 ( $N_{case} = 53,251, N_{control} =$ 77,127) and EAS ( $N_{case}$  = 14,004,  $N_{control}$  = 16,757) ancestries from the Psychiatric Genomics 456 457 Consortium (PGC), and fine-mapped the same 250 autosomal loci in the recent PGC publication<sup>4</sup>. 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 results, which applied a single-population fine-mapping method, FINEMAP<sup>38</sup>, to meta-analyzed 461 462 GWAS summary statistics and sample size weighted LD<sup>4</sup>. 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 the GWAS, likely due to inaccurate reference panel<sup>39</sup>. Furthermore, SuSiEx substantially 468 469 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).







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<sub>10</sub>(p-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

- 485 **DISCUSSION**
- 486

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 the correlation of SNP effect sizes across samples. A recent study proposed SuSiE-inf<sup>40</sup>, which 507 508 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 work<sup>39</sup> 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 continues to expand in global biobanks<sup>41</sup> and disease-focused consortia. Lastly, it remains 537 538 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

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

$$\boldsymbol{y}_{s} = \boldsymbol{X}_{s}\boldsymbol{\beta}_{s} + \boldsymbol{\epsilon}_{s}, \qquad \boldsymbol{\epsilon}_{s} \sim N(\boldsymbol{0}, \sigma_{s}^{2}\boldsymbol{I}), \qquad s = 1, 2, \dots, S,$$
$$\boldsymbol{\beta}_{s} = \sum_{l=1}^{L} \boldsymbol{b}_{sl}, \qquad \boldsymbol{b}_{sl} = \boldsymbol{\gamma}_{l} \boldsymbol{b}_{sl}, \qquad \boldsymbol{\gamma}_{l} \sim Mult(1, \boldsymbol{\pi}), \qquad \boldsymbol{b}_{sl} = N(\boldsymbol{0}, \tau_{sl}^{2}),$$

559

558

where for an population s (e.g., European, Asian or African),  $y_s$  is a vector of standardized 560 561 phenotypes (zero mean and unit variance) from  $N_s$  individuals,  $X_s = [x_{s1}, x_{s2}, ..., x_{sM}]$  is an 562  $N_s \times M$  matrix of standardized genotypes (each column  $x_{si}$  is mean centered and has unit 563 variance) in a genomic region that harbors at least one strong association signal,  $\beta_s$  is a vector 564 of SNP effect sizes, and  $\epsilon_s$  is a vector of residuals with i.i.d. elements, each following a normal distribution with zero mean and variance  $\sigma_s^2$ . We assume that  $\beta_s$  is the sum of *L* single-effect 565 vectors  $\boldsymbol{b}_{sl}$ , l = 1, 2, ..., L, each has exactly one non-zero element (equals to  $b_{sl}$ ). The position of 566 567 the non-zero element is determined by the binary vector  $\gamma_l$ , which follows a multinomial distribution.  $\boldsymbol{\pi} = [\pi_1, \pi_2, ..., \pi_M]^T$  is a vector that gives the prior probability of a SNP being causal, 568 and  $\tau_{sl}^2$  is the prior variance on the effect size  $b_{sl}$  of the causal SNP. We note that all populations 569 share the same underlying causal SNPs ( $\gamma_l$  does not depend on s), but the effect sizes of a causal 570 571 SNP across populations are allowed to be different ( $b_{sl}$  depends on s). 572

573 **Model fitting**. Assuming  $\sigma_s^2$  and  $\tau_{sl}^2$  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  $\boldsymbol{b}_{sl}$ , denoted as  $\overline{\boldsymbol{b}}_{sl}$  (e.g.,  $\overline{\boldsymbol{b}}_{sl} = 0$  for all *s* and *l*), 576 the fitting procedure involves iteratively updating  $\boldsymbol{b}_{sl}$ , given estimates of other effects  $\boldsymbol{b}_{sl'}$ ,  $l' \neq l$ , 577 until convergence:

578

580

579 ◊ Compute residuals:

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

581  $\diamond$  Compute the posterior inclusion probabilities (PIPs): 585  $\alpha_{li} = \Pr(\gamma_{li} = 1 | \mathbf{r}_{sl}, \mathbf{X}_{s}) = \frac{\pi_{j} \prod_{s=1}^{S} BF(\mathbf{r}_{sl}, \mathbf{r}_{sl})}{\mathbf{T}_{sl} \mathbf{T}_{sl} \mathbf{T}_$ 

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

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

583 
$$\hat{b}_{slj} = (\boldsymbol{x}_{sj}^{\mathrm{T}} \boldsymbol{x}_{sj})^{-1} \boldsymbol{x}_{sj}^{\mathrm{T}} \boldsymbol{r}_{sl} = N_{s}^{-1} \boldsymbol{x}_{sj}^{\mathrm{T}} \boldsymbol{r}_{sl}, v_{sj}^{2} = \sigma_{s}^{2} (\boldsymbol{x}_{sj}^{\mathrm{T}} \boldsymbol{x}_{sj})^{-1} = \sigma_{s}^{2} N_{s}^{-1}, z_{slj} = \delta_{slj}^{2} (\boldsymbol{v}_{sj}^{\mathrm{T}} \boldsymbol{x}_{sj})^{-1} = \delta_{slj}^{2$$

586  $\Diamond$  Update the posterior distribution for  $b_{sl}$ :

587

590

 $b_{sl}|\gamma_{lj} = 1, \boldsymbol{r}_{sl}, \boldsymbol{x}_{sj} \sim N\left(\mu_{slj}, \phi_{slj}^2\right),$ where  $\phi_{slj}^2 = \left(v_{sj}^{-2} + \tau_{sl}^{-2}\right)^{-1}, \mu_{slj} = \left(\phi_{slj}^2 / v_{sj}^2\right) \hat{b}_{slj}.$ 

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

$$\overline{\boldsymbol{b}}_{sl} = \mathrm{E}[\boldsymbol{b}_{sl}|\boldsymbol{r}_{sl},\boldsymbol{X}_{s}] = \boldsymbol{\alpha}_{l} \circ \boldsymbol{\mu}_{sl},$$

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

593

594 **Credible sets**. The PIPs  $\alpha_l$  can be used to compute a level- $\rho$  credible set  $CS(\alpha_l; \rho)$ , which has a probability no less than  $\rho$  of containing at least one causal SNP. Specifically, let  $(i_1, i_2, ..., i_M)$ 595 denote the indices that sort  $\alpha_{lj}$  in decreasing order, i.e.,  $\alpha_{li_1} > \alpha_{li_2} > \cdots > \alpha_{li_M}$ , and let  $S_k =$ 596  $\sum_{i=1}^{k} \alpha_{li_i}$ . Then  $CS(\boldsymbol{\alpha}_l; \rho) \coloneqq \{i_1, i_2, \dots, i_{k_0}\}$ , where  $k_0 = \min\{k: S_k \ge \rho\}$ . When L exceeds the 597 598 number of detectable effects in the data, some  $\alpha_l$  become diffuse and the corresponding credible sets will be large, containing many uncorrelated SNPs. Such credible sets have no inferential 599 600 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  $\hat{\beta}_{sj} = (\mathbf{x}_{sj}^{\mathrm{T}}\mathbf{x}_{sj})^{-1}\mathbf{x}_{sj}^{\mathrm{T}}\mathbf{y}_{s} = N_{s}^{-1}\mathbf{x}_{sj}^{\mathrm{T}}\mathbf{y}_{s}$  denote the marginal 604 least squares effect size estimate of SNP *j* in the ethnic group *s*, and  $\mathbf{D}_{s} = [\mathbf{d}_{s1}, \mathbf{d}_{s2}, ..., \mathbf{d}_{sM}] =$ 605  $\mathbf{X}_{s}^{\mathrm{T}}\mathbf{X}_{s}/N_{s}$  denote the LD matrix for ethnic group *s*, which can be estimated using an LD reference 606 panel. Note that  $\mathbf{x}_{sj}^{\mathrm{T}}\mathbf{r}_{sl} = \mathbf{x}_{sj}^{\mathrm{T}}\mathbf{y}_{s} - \mathbf{x}_{sj}^{\mathrm{T}}\sum_{l'\neq l}\mathbf{X}_{s}\mathbf{\overline{b}}_{sl'} = N_{s}\hat{\beta}_{sj} - N_{s}\sum_{l'\neq l}\mathbf{d}_{sj}^{\mathrm{T}}\mathbf{\overline{b}}_{sl'}$ . Therefore, IBSS can 607 be turned into a summary statistics based algorithm.

## 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 HAPGEN2<sup>42</sup> with ancestry-matched 1000 Genomes Project (1KG) Phase III<sup>43</sup> superpopulation 620 samples as the reference panel. We grouped CEU, IBS, FIN, GBR and TSI into the EUR 621 622 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  $n_{csl}$  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(0,  $\Sigma_{3\times3}$ ), where  $\Sigma_{3\times3}$  was defined as,  $\Sigma_{ij} = 1$ ,

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 correlations  $(r_a)$ , per-locus heritability  $(h^2)$ , and the number of causal variants  $(n_{csl})$  per locus. We 642 defined a standard simulation setting using  $n_{csl} = 1$ ,  $r_q = 0.7$  and  $h^2 = 0.1\%$ . We then varied  $r_q$  ( $r_q$ 643 = 0.4 and 1.0) to reflect different levels of cross-population genetic correlations, varied  $h^2$  ( $h^2$  = 644 645 0.05%, 0.2%, 0.3%, 0.4% and 0.5%) to reflect different per-locus heritability values, and varied 646  $n_{csl}$  ( $n_{csl}$  = 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.

Association analysis and LD calculation. We used the linear regression implemented in
 PLINK<sup>44</sup> to generate GWAS summary statistics, and calculated in-sample LD for each genomic
 locus. To evaluate the impact of LD mismatch on fine-mapping results, we additionally calculated
 LD matrices using subpopulation samples within the EUR and AFR superpopulations.

656

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

We compared SuSiEx, SuSiE, PAINTOR and MsCAVIAR using the standard simulation setting. 658 659 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 associated variants from GWAS, respectively. PAINTOR provides two model fitting options, 663 664 "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 panel and PLINK<sup>44</sup>. To include loci that reached genome-wide significance (P <5E-8) only in the 689 690 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 PLINK<sup>44</sup>. Multi-allelic variants and indels were excluded to avoid potential strand 701 flipping and alignment errors.

702

**Fine-mapping.** We applied SuSiEx to the 25 quantitative traits to integrate GWAS summary statistics derived from the three populations. We filtered out credible sets that did not contain any genome-wide significant variant (p <5E-8) in any population-specific GWAS or cross-population 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 method<sup>7</sup>. Specifically, for a given pair of overlapping 711 credible sets in a genomic locus, we computed the PIP-weighted Jaccard similarity index, defined

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

variant *i* from the two credible sets. Pairs of credible sets with a similarity index greater than 0.1
were aligned. If one credible set can be aligned with multiple credible sets, the set with the highest
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 analysis<sup>4</sup>. We fine-mapped the same 255 loci defined in the PGC publication. We calculated LD by applying LD-Store v1.1<sup>39</sup> to 721 each cohort and locus, and then calculated an effective sample size weight LD matrix<sup>45</sup> across 722 723 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: <u>https://mathgen.stats.ox.ac.uk/impute/1000GP\_Phase3.html;</u>
- 732 Genetic map for each subpopulation:
- 733 <u>https://ftp.1000genomes.ebi.ac.uk/vol1/ftp/technical/working/20130507\_omni\_recombination\_rat</u>
   734 es;
- 735 PanUKBB summary statistics: <u>https://pan.ukbb.broadinstitute.org/downloads;</u>
- 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 (<u>https://www.twbiobank.org.tw/new\_web\_en/</u>);

- 739 PGC schizophrenia GWAS: <u>https://pgc.unc.edu/for-researchers/download-results</u>
- 740

741 CODE AVAILABILITY

- The code used in this study is available from the following websites:
- 743 SuSiEx: https://github.com/getian107/SuSiEx;
- 744 PAINTOR: <u>https://github.com/gkichaev/PAINTOR\_V3.0;</u>
- 745 MsCAVIAR: <u>https://github.com/nlapier2/MsCAVIAR;</u>
- 746 HAPGEN2: https://mathgen.stats.ox.ac.uk/genetics\_software/hapgen/hapgen2.html;
- 747 PLINK1.9: <u>https://www.cog-genomics.org/plink;</u>
- 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
- obtained informed consent from all participants for research use of the collected data. Access
- to, and use of, TWB data in the present work was approved by the EGC of TWB (approval
- number: TWBR10907-05) and the Institutional Review Board of National Health Research
- 758 Institutes, Taiwan (approval number: EC1090402-E).
- 759

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# 773 COMPETING INTERESTS

W.S. and C.S. are employees of Digital Health China Technologies Corp. Ltd.. M.J.D. is a founder
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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 style<sup>17</sup>. 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 Europan), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations. For association statistics, the left y-axis represents the -log<sub>10</sub>(p-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.



**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 Europan), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations following the LocusZoom<sup>37</sup> 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  $-\log_{10}(p-value)$  of each SNP. The gray horizontal dash line represents the genome-wide significance threshold ( $5x10^{-8}$ ). 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 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 Europan), African (Pan-UKBB African) and East Asian (Taiwan biobank) populations following the LocusZoom<sup>37</sup> 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  $-\log_{10}(p-value)$  of each SNP. The gray horizontal dash line represents the genome-wide significance threshold ( $5x10^{-8}$ ). 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 gnomAD<sup>33</sup>; 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 <a href="https://useast.ensembl.org/info/genome/variation/prediction/predicted\_data.html">https://useast.ensembl.org/info/genome/variation/prediction/predicted\_data.html</a>. 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.