Medical data and machine learning improve power of stroke genome-wide association studies

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Abstract

Genome-wide association studies (GWAS) may require enrollment of up to millions of participants to power variant discovery. This requires manual curation of cases and controls with large-scale collaborations. Biobanks connected to electronic health records (EHR) can facilitate these studies by using data from clinical care systems, like billing diagnosis codes, as phenotypes. These systems, however, do not define adjudicated cases and controls. We developed QTPhenProxy, a machine learning model that adds nuance to cohort classification by assigning everyone in a cohort a probability of having the study disease. We then ran a GWAS using the probabilities as a quantitative trait. With an order of magnitude fewer cases than the largest stroke GWAS, our method outperformed previous methods at replicating known variants in stroke and discovered a novel variant in *ABCG8* associated with intracerebral hemorrhage in the UK Biobank that replicated in the MEGASTROKE GWA meta-analysis. QTPhenProxy expands

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traditional phenotyping to improve the power of GWAS.

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1. Introduction

Large genetic repositories connected to electronic health records (EHR) promise the ability to perform thousands of genetic studies using data routinely captured in clinical practice. High-throughput identification of cases and controls can be difficult, however, due to time-consuming chart review and incompleteness of medical records. Current disease genome-wide association studies develop case-control sets in which power relies on a large amount of pure cases, and the missingness of EHR data could prevent some cases from discovery in a high-throughput manner (McCarthy et al., 2008; Weiskopf et al., 2013; DeBoever et al., 2019). In addition, extreme case-control imbalance in biobanks can lead to increased type 1 error when running linear mixed model genome-wide association analysis (Zhou et al., 2018). An incorporation of additional accessible EHR data could improve case curation sensitivity. In addition, many diseases such as stroke result from a combination of gene and environmental interactions, and there is significant overlap with co-morbidities in genome-wide significant variants (Malik et al., 2018a). Therefore, it is difficult to confirm every person without the event a control, suggesting the utility of a disease likelihood assignment (McCarthy et al., 2008; Yang et al., 2009).

The definition of the disease phenotype influences the success of detecting a genetic signal since power is generally calculated by number of cases and controls

(Maher, 2008; Zaykin and Zhivotovsky, 2005). We propose that including EHR information about comorbidities (Kohane, 2011) and other health information about our subject to trait assignment can improve the power of GWAS. Past studies have shown that incorporating diagnosis count improved the power of genetic studies, and the addition of patient questionnaires and genetic correlations to hospital records improved detection of cases for genome-wide association studies (Sinnott et al., 2018; DeBoever et al., 2019; Liu et al., 2017; Ruderfer et al., 2019). Incorporating EHR data to develop a probability of suicide attempt also improved the power of its genome-wide association study (Ruderfer et al., 2019). We argue that including several modalities of health data to estimate assignment of case probability can improve the power of genomic studies. For example, the most successful genome-wide association study for stroke required 40,585 cases and 406,111 controls (Malik et al., 2018a). We hypothesize that we can discover genome-wide significant variants associated with stroke with a fraction of those cases (4,354) by incorporating EHR information of 337,147 participants in the UK Biobank Cohort into a stroke phenotype score to be used as quantitative trait.

In this study, we use machine learning methods to expand sample cohorts by assigning every patient a probability of disease. We hypothesize that the output of a supervised machine learning classifier, trained on the EHR data of a small number of known cases and controls, can be used as a proxy variable for stroke and will be an efficient strategy for expanding cohort size (See Graphical Abstract). We demonstrate that our quantitative proxy trait can improve power over its respective binary trait in ischemic stroke. We also show that the new variants discovered are known in similar cardiovascular and neurological diseases. We find up to 7 LD independent loci that pass genome-wide significance and conditional

analysis, and the majority of the associated genes are known to be associated with stroke or cardiovascular disease. For stroke and its subtypes ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage, QTPhenProxy recovered known and discovered new stroke variants, such as in *ABCG8*, with an order of magnitude fewer cases than traditional genome-wide association studies.

2. Methods

2.1. QTPhenProxy Phenotyping Model.

We gathered clinical features of primary ICD10 diagnosis codes, OCPS4 procedure codes (UK Biobank code 42100), medications (UK Biobank code 20003), race/ethnicity (UK Biobank code 1001), and age. 2018 served as the age end point. We mapped the OCPS4 procedure codes (UK Biobank code 240) to SNOMED-CT codes and the UK Biobank medication codes to RxNorm codes by name (National Library of Medicine, 2019b,a). We also gathered data of self reported and first occurrence of all stroke, ischemic stroke, sub-arachnoid stroke, and intracerebral hemorrhage. We made a large matrix in which each extracted EHR feature was a binary variable based on the presence or absence of the feature. We dichotomized age as greater than or equal or less than 50 years. For each disease, we then defined the cases from the ICD10 code combinations described in the UK Biobank's phenotyping algorithm (Schnier et al., 2017). We then trained 5 different classifiers: 1) logistic regression with elastic net penalty, 2) logistic regression with L1 penalty, 3) random forest, 4) adaboost, 5) gradient boosting classifiers on 50% of the cases and an equal number of controls. Controls were identified as subjects without any ICD10 codes within the same category as the Clinical Modification Clinical Classifications Software tool (Healthcare Cost and Utilization Project).

We then applied the trained algorithm to the whole UK Biobank, resulting in a model probability or quantitative trait proxy for each subject and each disease. For comparison, another phenotype file with binary assignment of case and control for each disease was prepared as well. Table 1 shows the number of cases available for each disease.

2.2. Evaluation of QTPhenProxy Model Performance.

To evaluate the performance of the QTPhenProxy model, we determined its ability to recover cases when the defining ICD10 codes are removed. We trained 50% of the cases and an equal number of controls on the clinical features described above using the EN and RF classifiers. We chose these classifiers because of their overall high performance and their probability assignment distributions were continuous (Figure 1, Supplementary Figure A.1). We removed the ICD10 codes used to define the cases and controls in our feature set. We then tested the model on all other subjects in the UK Biobank, which included known cases and self-reported cases that did not have an ICD10 code for the disease. We then evaluated the recovery of 1) cross-validation and 2) the holdout test set through Precision at top 50, 100, 500, and number of cases, area under the receiver operating curve, area under the precision recall curve, and maximum F1 score.

2.3. Genotyping and Imputation.

UK Biobank subjects that were of White British descent, in the UK Biobank PCA calculations and therefore without 3rd degree and above relatedness, and without aneuploidy were used in this study, totalling 337147 subjects (181,032 females and 156,115 males) (UK Biobank; Bycroft et al., 2018). Of the nearly 500,000 participants, approximately 50,000 subjects were genotyped on the UK

BiLEVE Array by Affymetrix while the rest were genotyped using the Applied Biosystems UK Biobank Axiom Array, with over 800,000 markers. The arrays share 95% marker coverage. Initially, we ran a QC extracting markers with an MAF>0.5%, INFO score > 0.3, and hardy-weinberg equilibrium test mid-p value > 10^{-10} using all subjects, which we will refer to as QC1. QC1 was run for GWAS of all 18 diseases. We then re-ran the QC, which we will refer to as QC2, more stringently by extracting markers with an MAF>1%, INFO score > 0.8, and hardy-weinberg equilibrium test mid-p value > 10^{-5} using Plink2 (Chang et al., 2015). UKBB version 3 Imputation combined the Haplotype Research Consortium with the UK10K haplotype resource using the software IMPUTE4 (UK Biobank).

2.4. Genome-wide Association Analysis.

The binary trait and QTPhenProxy probabilities were compared by running two separate association analyses. For both analyses, covariates included age at 2018, sex, first 10 principal components, and the genotyping array the sample was carried out on. In QC1, the original PCs determined by the UKBiobank QC were used. In QC2, we calculated the PCs using the method described in 2.11. QC2 GWAS was only run for stroke, ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage GWAS. For the binary trait GWAS, a logistic regression was run adjusted with the aforementioned covariates. For comparison, the QTPhenProxy probabilities were quantile normalized and run under a linear regression adjusting for the same covariates. We also permuted the probabilities within the phenotyping files and ran additional GWAS 10 times to ensure the signal was correlated with the phenotype.

117 *2.5. Mapping variants to known disease variant marker sets and mapping marker*
 118 *sets to disease systems.*

119 The EBI-GWAS catalogue has a database of all published GWAS (Buniello et al.,
 120 2019). We extracted over 2,000 disease marker sets conducted on populations with
 121 European ancestry. MedDRA is a standardized medical vocabulary developed by
 122 International Council for Harmonisation of Technical Requirements for Pharma-
 123 ceuticals for Human Use (ICH) (Brown, 1999). All terms in the vocabulary can be
 124 mapped to its highest system level, which includes 27 different organ systems
 125 and other general and lab studies such as social circumstance and investigations.
 126 Using the NCBO annotator, we mapped the names of the EBI-GWAS disease
 127 marker sets to the MedDRA System Organ Classes level (Whetzel et al., 2011).

128 *2.6. Assessing the specificity of the QTPhenProxy-derived variants.*

129 To assess the disease specificity of the genome-wide significant variants, we
 130 first calculated the proportion of genome-wide significant variants in each of the
 131 EBI-GWAS disease marker sets. We then aggregated the marker sets together by
 132 System Organ Class to evaluate the systems enriched for genome-wide significant
 133 variants. We ordered the marker sets in each class by proportion of genome-wide
 134 significant variants and divided by the number of marker sets in each class. We
 135 also compared the proportion of variants of varying significance of the marker
 136 sets related to each disease with 1) the other marker sets related to the same
 137 System Organ Class as the disease and 2) all other marker sets. We stratified each
 138 comparison by significance value, between 0.05 and 5E-08.

139 2.7. Evaluation of recovery of known variants

140 For each disease, we gathered EBI-GWAS marker sets that contained the
141 disease in its name. These represent known variants of each disease. We then
142 extracted the p-value from either the binary trait logistic regression or QTPhen-
143 Proxy linear regression. We then ran a t-test comparing the negative log base
144 10 p-values of the binary trait with QTPhenProxy GWAS. We also ran a t-test
145 comparing the difference between the binary and QTPhenProxy log base 10 p val-
146 ues for the known ischemic stroke variants and an equivalent number of random
147 variants.

148 2.8. Refinement of discovered variants by QTPhenProxy using conditional analysis

149 At each LD-independent locus, the SNP with lowest p-value may not be the
150 variant that causes the most phenotypic variation within the area (Yang et al., 2012).
151 Therefore, we applied GCTA-COJO, a conditional analysis that takes into account
152 lead SNPs and the LD structure of a sample of the population, to our genome-
153 wide association results (Yang et al., 2012). We randomly sampled 10,000 subjects
154 from the UKBiobank for the linkage disequilibrium calculation (Wells et al., 2019).
155 From the GCTA-COJO results, we then mapped each locus to its nearest gene
156 using dbSNP and the UCSC Genome Browser accessed at <http://genome.ucsc.edu/>
157 (National Center for Biotechnology Information, National Library of Medicine;
158 Kent et al., 2002). For intergenic loci, we chose the 1-2 nearest genes that were at
159 most 10,000 KB away.

160 2.9. Correlation of QTPhenProxy GWAS beta coefficients to Binary trait GWAS Odds 161 Ratio

162 We calculated the Pearson correlation between the beta-coefficients of the
163 QTPhenProxy GWAS and log of the odds ratios of the Binary trait GWAS. In order
164 to account for noise, we calculated the correlation with variants with different
165 levels of significance in the QTPhenProxy models. P-value cutoffs included 1,
166 0.05, 0.0005, 5e-06, and 5e-08.

167 2.10. Simulation of Conversion of QTPhenProxy trait to Binary trait and Conversion 168 of beta coefficients to odds ratios

169 Based on the scale difference between binary and quantitative traits, the odds
170 ratios are not directly comparable. We decided to simulate a method to convert
171 beta coefficients from QTPhenProxy to Odds ratios. We did this by simulating a
172 quantitative trait, converting it to a binary trait, and testing the correlation of a
173 simulated marker variant's significance between the two methods. Using SOLAR,
174 a software package for estimating heritability using identity by descent calculations,
175 we simulated a quantitative trait with one quantitative trait locus with two
176 alleles and a nearby marker locus with two alleles (Almasy and Blangero, 1998).
177 We first removed all related individuals with a resulting cohort of 4,195 subjects.
178 For the simulation, we varied the frequency for the causal minor allele and a
179 marker minor allele from 0.05-0.45 in increments of 0.010, the mean quantitative
180 trait value for the heterozygous genotype from 5-45 in increments of 10 and the
181 homozygous genotypes' $mean \pm 50$, the standard deviation of the quantitative
182 trait from 5-20 in increments of 4, and the recombinant fraction from 0.01-0.10 in
183 increments of 0.02. After simulating the quantitative trait distribution, we then
184 normalized the trait to several distributions: standard normal, normal distribution

185 with mean 0 and standard deviation 10, and mean 50 and standard deviation 10.
 186 We compared distributions because we quantile normalized our QTPhenProxy
 187 trait values before running the genome-wide associations studies. We then con-
 188 verted each simulation to a binary trait using liability thresholding (Risch, 1990).
 189 Liability thresholding was implemented as follows: We determined a quantitative
 190 trait value as a threshold based off the prevalence of the simulated trait, which
 191 we varied from 2.5-20% in increments of 5%. Any subjects above this threshold is
 192 labeled a case, and the rest controls in the binary trait phenotype. We then ran
 193 linear or logistic regressions using the python package statsmodels between the
 194 simulated quantitative trait or the binary trait and the subjects' genotypes for the
 195 marker and causal loci (Seabold and Perktold, 2010). We developed a conversion
 196 formula for the beta coefficients to odds ratios by linearly regressing the correla-
 197 tion between the simulated effect sizes. We then converted the beta-coefficients
 198 to odds ratios of the UK Biobank GWAS results by multiplying the beta coefficient
 199 by the average slope and intercept and then taking the exponential of the result.

200 2.11. PCA

201 In order to confirm the cases were well distributed within the data and to
 202 determine the number of principal components to use as covariates, we conducted
 203 PCA. For each of the four diseases, we first pruned the variants used for PCA by
 204 running a sliding window of size 100 kbps, 5 variant step size, and r^2 threshold of
 205 0.1. We then combined the chromosomes, extracting only the pruned variants,
 206 using plink2 and cat-bgen software (Band and Marchini, 2018). We then ran pca
 207 with plink2 (Chang et al., 2015) and evaluated the PCs to be used as covariates
 208 using a skree plot. Within the main PCs, we plotted them against each other,
 209 highlighting the distribution of the cases.

210 2.12. LD Score Regression and evaluation of genomic inflation

211 We determined the lambda genomic correction and LD score regression coef-
212 ficient using the software LDSC (Bulik-Sullivan et al., 2015). We used the disease
213 GWAS summary statistics and European LD scores pre-computed from 1000
214 genomes by the Alkes group (Bulik-Sullivan et al., 2015). QQ plots were plotted
215 using qqman (Turner, 2014). To determine the relationship between genomic
216 inflation and minor allele frequency, we binned all variants in the stroke gwas by
217 minor allele frequency into 30 bins. We then calculated the genomic inflation of
218 the p-values of the variants in each bin.

219 2.13. Genetic Correlation of QTPhenProxy with MEGASTROKE and Coronary Artery 220 Disease GWAS

221 We measured the genetic correlation of the QTPhenProxy EN stroke and
222 stroke subtype models using both QC1 and QC2 quality control and the results
223 from the binary classification of stroke with a large stroke study as well as other
224 stroke-related risk factors using LDSC software (Bulik-Sullivan et al., 2015). We
225 gathered summary statistics from the MEGASTROKE meta-analysis of GWA data
226 on stroke and stroke subtypes, including Acute Ischemic Stroke (AIS) (Malik et al.,
227 2018a). We compared our results to these summary statistics and measured its
228 genetic correlation with the same risk factor GWAS compared in MEGASTROKE
229 (Malik et al., 2018a). Specifically, we measured the genetic correlation with the
230 following risk factors: Coronary Artery Disease (CAD) (Nikpay et al., 2015), T2D
231 (Xue et al., 2018), Atrial Fibrillation (AF) (Nielsen et al., 2018), White matter
232 hyperintensities (WMH) (Traylor et al., 2019), and Low-density lipoprotein (LDL)
233 (Willer et al., 2013). Further information about the resources of these risk factors
234 can be found in Supplementary Information. Finally, we used LD Hub (Zheng et al.,

235 2017), a database server by the Broad Institute that calculates genetic correlations
 236 with hundreds of available traits. To measure the genetic correlation between the
 237 QTPhenProxy EN stroke model and a wide variety of trait GWAS, from stroke-
 238 related to many that are unrelated to the pathophysiology of stroke, we ran LD
 239 Hub to calculate the genetic correlation between the QTPhenProxy Stroke QC1
 240 GWAS and 597 trait GWAS run by the Neale lab in the UK Biobank cohort (Neale,
 241 2018).

242 3. Results

243 3.1. *QTPhenProxy has high model performance.*

244 We trained models with 5 different classifier types and all stroke, ischemic
 245 stroke, intracerebral hemorrhage, and subarachnoid hemorrhage as defined by
 246 the UK Biobank Algorithmically Defined Outcomes rubric (Schnier et al., 2017).
 247 Random forest models overall showed the best area under the receiver operating
 248 curve and adaboost models gave the best area under the precision recall curve on
 249 the hold-out test set (Supplementary Tables B.1 and B.3). Overall stroke, followed
 250 by ischemic stroke showed high precision at top 50 patients ordered by probability
 251 (Figure 1, Table 1, Supplementary Table B.2). We chose the probabilities from
 252 the EN and RF models to run the genome-wide association analyses because the
 253 distribution of their probabilities was continuous and included values from 0-1
 254 (Figure 1, Supplementary Figure A.1).

255 3.2. *Novel and known variants are recovered by QTPhenProxy in higher numbers 256 traditional binary method using the QC1 markers and principal components.*

257 The binary trait logistic regression genome-wide association study for stroke,
 258 ischemic stroke, and subarachnoid hemorrhage recovered no variants with genome-

259 wide significance. Binary trait logistic regression genome-wide association study
260 for intracerebral hemorrhage recovered 2 variants with genome-wide significance.
261 Quantitative trait linear regression using QTPhenProxy probabilities for stroke
262 recovered 120 genome-wide significant SNPs with 16 LD-independent loci and
263 1215 genome-wide significant SNPs with 39 LD-independent loci, for ischemic
264 stroke recovered 202 genome-wide significant SNPs with 15 LD-independent
265 loci, and 1266 genome-wide significant SNPs with 46 LD-independent loci, for
266 subarachnoid hemorrhage recovered 69 genome-wide significant SNPs with 4 LD-
267 independent loci, and 722 genome-wide significant SNPs with 40 LD-independent
268 loci, and for intracerebral hemorrhage recovered 146 genome-wide significant
269 SNPs with 8 LD-independent loci, and 1059 genome-wide significant SNPs with
270 54 LD-independent loci using the EN and RF classifiers, respectively (Table 1).
271 We show the comparison of genome-wide significant variants between the QT-
272 PhenProxy EN model and Binary trait GWAS for stroke in a Hudson plot (Figure
273 2) (Lucas). Out of known ischemic stroke variants, both models also recovered
274 3 known variants with genome-wide significance, and the EN model recovered
275 21/49 of the known variants, equivalent to a sensitivity of 0.428, while the tradi-
276 tional binary trait recovered 15/49, (sensitivity=0.306), and RF model recovered
277 14/49 (sensitivity=0.286) with nominal p-value of 0.05 (Table 1). For all stroke, sen-
278 sitivity of known stroke variants was 0.333 using the EN model, 0.261 using the RF
279 model, and 0.202 using the binary trait. Subarachnoid hemorrhage did not have a
280 specific EBI-GWAS disease marker set, and the EBI-GWAS disease marker set for
281 intracerebral hemorrhage only consisted of one variant. The difference in p-values
282 between the binary and QTPhenProxy for known ischemic stroke variants was
283 significantly increased compared to the same number of random variants using

the EN classifier (two sample t test, $t=2.43$, $p=0.0184$ for EN classifier and $t=1.74$, $p=0.0876$ for RF classifier). In addition, QTPhenProxy with EN classifier showed a significant decrease in p-value of all known ischemic stroke variants compared to traditional binary method (two sample t-test, $t=-2.1$ $p=0.0367$) while QTPhenProxy with RF classifier did not show a significant decrease ($t=-1.48$, $p=0.144$). The difference in p-values between the binary and QTPhenProxy for known all stroke variants was significantly increased compared to the same number of random variants for the EN classifier ($t=2.80$, $p=0.00638$) but not significant for the RF classifier ($t=0.737$, $p=0.463$). In addition, QTPhenProxy with EN classifier showed a decrease in p-value of all known stroke variants compared to traditional binary method (two sample t-test, $t=-1.87$ $p=0.0639$) while QTPhenProxy with RF classifier did not show a significant decrease ($t=-1.05$, $p=0.298$).

3.3. *Novel and known variants are recovered by QTPhenProxy in higher numbers traditional binary method using the QC2 markers and principal components.*

The binary trait logistic regression genome-wide association study for stroke, ischemic stroke, and subarachnoid hemorrhage recovered no variants with genome-wide significance. Binary trait logistic regression genome-wide association study for intracerebral hemorrhage recovered 2 variants with genome-wide significance. Quantitative trait linear regression using QTPhenProxy probabilities for stroke recovered 7 LD-independent loci, 3 LD-independent loci, for ischemic stroke, 3 LD-independent loci for subarachnoid hemorrhage, and 3 LD-independent loci for intracerebral hemorrhage using the EN classifier. We show the comparison of genome-wide significant variants between the EN and Binary in a Hudson plot (Figure 2) (Lucas). Out of known ischemic stroke variants, both models also recovered 3 known variants with genome-wide significance, and the EN model

309 recovered 16/49 of the known variants, equivalent to a sensitivity of 0.326, while
310 the traditional binary trait recovered 15/49, (sensitivity=0.306), and RF model
311 recovered 15/49 (sensitivity=0.306) with nominal p-value of 0.05 (Figure 3). For
312 all stroke, sensitivity of known stroke variants was 0.265 using the EN model,
313 0.220 using the RF model, and 0.220 using the binary trait (Supplementary Figure
314 A.5). The t-tests referred to in 3.2 did not show significance.

315 *3.4. Conditional analysis identifies novel variants with genome-wide significance* 316 *using the QC1 markers and principal components.*

317 Conditional analysis of the GWAS with QC1 quality control for the QTPhen-
318 Proxy EN model for all stroke identified 13 candidate variants with genome-wide
319 significance, all which are novel, though some of the nearest genes to these loci
320 have been identified in previous studies through nearby loci. There were 12 loci
321 identified for the stroke subtype ischemic stroke, 3 loci for subarachnoid hemor-
322 rhage, and 9 loci for intracerebral hemorrhage (Table 2). Several loci overlapped
323 across stroke and some subtypes. Position 46705193 on chromosome 11, which is
324 in an intronic section of *ARHGAP1* (National Center for Biotechnology Informa-
325 tion, National Library of Medicine), showed genome-wide significance in stroke,
326 ischemic stroke, and intracerebral hemorrhage. A missense mutation at locus
327 rs6025 in the *F5* gene showed genome-wide significance across stroke, intracere-
328 bral hemorrhage, and locus rs1894692, which is near the *F5* gene (National Center
329 for Biotechnology Information, National Library of Medicine), showed genome
330 wide significance in ischemic stroke. Additional loci that showed genome-wide
331 significance in both all stroke and ischemic stroke included those that are intronic
332 to *LPA* and *NOS3* and nearby to *APOC1P1/APOC1* and *CDKN2A/CDKN2B* (National
333 Center for Biotechnology Information, National Library of Medicine). Finally, all

stroke and intracerebral hemorrhage shared additional loci that showed genome-wide significance after conditional analysis, which were nearby LOC105377992 and *RPS4X9* (National Center for Biotechnology Information, National Library of Medicine). All stroke genome-wide significant variants also included intronic loci in the *MTA3*, *SOX7*, *ABO*, *FURIN*, and *PLCB1* genes (National Center for Biotechnology Information, National Library of Medicine). Ischemic stroke genome-wide significant variants included intronic loci in the *LPAL2* gene, intergenic loci in the *PITX2*, *LDLR*, and an insertion mutation in the *ABO* gene (National Center for Biotechnology Information, National Library of Medicine). Subarachnoid hemorrhage genome-wide significant variants included an intronic locus in the *ABO* gene. Finally, intracerebral hemorrhage genome-wide significant variants included a missense mutation loci in the *ABCG8* gene, and intronic loci in the *NOS3* and *XKR6* genes (National Center for Biotechnology Information, National Library of Medicine). The variants near or in LOC105377992, *NOS3*, *CDKN2A/CDKN2B*, *LPA*, *LDLR*, *ABCG8*, and *RPS4X9* were below nominal significance of 0.05 in the MEGASTROKE stroke and ischemic stroke GWAS of European ancestry (Table 3) (Malik et al., 2018a).

3.5. Conditional analysis identifies novel variants with genome-wide significance using the QC2 markers and principal components.

Conditional analysis of the GWAS with QC2 quality control for the QTPhen-Proxy EN model for all stroke identified 7 candidate variants with genome-wide significance, all which are novel, though some of the nearest genes to these loci have been identified in previous studies through nearby loci. There were 3 loci identified for the stroke subtype ischemic stroke, 3 loci for subarachnoid hemorrhage, and 3 loci for intracerebral hemorrhage (Table 3). Almost all of

the genome-wide significant variants overlapped with those found running the GWAS using QC1 quality control. New variants that were genome-wide significant for all stroke included a deletion variant that was intergenic to the gene *ATP5MC1P3*, an intronic variant of the *MRSA* gene, and a 3'UTR variant in *KCNJ4* (National Center for Biotechnology Information, National Library of Medicine). In addition, several genome-wide significant variants in the MEGASTROKE stroke and ischemic stroke GWAS were near the variants that were genome-wide significant in the QTPhenProxy EN GWAS. Almost all of those nearby MEGASTROKE genome-wide significant variants replicated to at least nominal significance of 0.05 in the QTPhenProxy EN GWAS (Table 4).

3.6. *Effect sizes of QTPhenProxy and traditional binary trait analysis are correlated.*

We determined the correlation between the effect sizes of the binary trait GWAS and QTPhenProxy GWAS. Pearson correlation of the beta coefficients and log of the odds ratios increased when restricting to variants with small p-values (max $r^2=0.58$ for GWAS with QC2 control, max $r^2=0.70$ for GWAS with QC1 control) (Figure 4, Supplementary Figure A.6). Too few variants, such as with p-values $> 5e-08$ resulted in a decreased Pearson correlation.

3.7. *Genome-wide significant variants are enriched in related EBI-GWAS marker sets.*

From the over 2,000 EBI-GWAS disease variant marker sets mapped to organ systems, we calculated the proportion of markers in each set that was found to be at genome-wide significance by our QTPhenProxy model with QC2 markers and principal components. We found that the organ systems with markers sets with the highest proportion of genome-wide significant variants for stroke included

vascular disorders, investigations, psychiatric disorders, and general disorders and administration site conditions (Figure A.5, Supplementary Figure 3). The enriched disease marker sets in the Investigations class included the lab values lipoprotein A levels, lipoprotein a levels adjusted for apolipoprotein A isoforms, blood protein levels, and white blood cell counts. The enriched disease marker sets in the General disorders and administration site conditions included aortic valve stenosis and allergy, while the Psychiatric disorders enriched marker sets were response to statins (LDL change) and venous thromboembolism. For ischemic stroke, the top enriched disease marker sets included those described for stroke and also activated partial thromboplastin time, coagulation factor levels, protein biomarkers, soluble levels of adhesion molecules, pancreatic cancer, and urinary metabolites.

3.8. LD score regression intercept and genomic inflation are similar across stroke and its subtypes.

Using QC1 quality control, the genomic inflation for QTPhenProxy EN model for Stroke was 1.133, while using the QC2 quality control the genomic inflation for the same model was 1.134. For binary traits using QC2 quality control, genomic inflation for stroke was 1.027. Using the QC2 quality control model, the QTPhenProxy EN model genomic inflation for Ischemic stroke was 1.118, for subarachnoid hemorrhage was 1.122, and for intracerebral hemorrhage was 1.114. LD score regression intercept for QTPhenProxy EN model with QC2 quality control for stroke was 1.037 ± 0.0088 , for ischemic stroke, 1.031 ± 0.0077 , for subarachnoid hemorrhage, 1.012 ± 0.008 , and for intracerebral hemorrhage, 1.051 ± 0.0081 . We found that more common variants, or those with higher minor allele frequencies, had higher genomic inflation than rarer variants (Figure 4).

408 3.9. Genetic Correlation of QTPhenProxy Models' GWAS with MEGASTROKE GWAS 409 and Risk Factor GWAS

410 We measured a genetic correlation of 0.60 (p-value 1.4E-19) between the QT-
411 PhenProxy EN Model for stroke, QC2 quality control, and the MEGASTROKE
412 all stroke GWAS, and a genetic correlation of 0.49 (p-value 2.2E-12) between
413 the QTPhenProxy EN Model for ischemic stroke, QC2 quality control, GWAS
414 and the MEGASTROKE acute ischemic stroke GWAS (Malik et al., 2018a). We
415 also found significant and large positive genetic correlations between QTPhen-
416 Proxy EN Stroke and Ischemic Stroke Models and QTPhenProxy RF Stroke Model
417 GWAS and coronary artery disease, type 2 diabetes mellitus, atrial fibrillation, and
418 white matter hyperintensities (Supplementary Table B.4). We found significant
419 and large negative correlations between subarachnoid hemorrhage and coro-
420 nary artery disease, type 2 diabetes mellitus, atrial fibrillation and low density
421 lipoprotein levels GWAS. Calculating genetic correlation calculations between
422 the traditional binary GWAS for UK Biobank and MEGASTROKE GWAS and risk
423 factors GWAS resulted in error due to low heritability (below 1E-03) estimated for
424 the UK Biobank GWAS or invalid values encountered during genetic correlation
425 calculation. After running genetic correlations on 1) the QTPhenProxy EN Model
426 for stroke, QC1 quality control, GWAS and 597 trait GWAS run by the Neale lab
427 on the UK Biobank data set, and 2) the QTPhenProxy EN Model for stroke, QC2
428 quality control, GWAS and 804 trait GWAS, including the same 597 UKBB traits,
429 we found 117 and 118 traits, respectively, with bonferroni significant genetic
430 correlations (see Supplementary Information). We found the top 50 significant
431 genetic correlations for both models to be in traits associated with cardiovascu-
432 lar and kidney diseases, blood pressure and cardiovascular disease medications,

anthropomorphic measurements such as waist circumference and BMI, physical activity, education, and family history (See Supplementary Information). We found the highest negative genetic correlations in traits that state no vascular or heart problems, no medications for cholesterol, blood pressure, or diabetes, and father's age at death. The insignificant and smallest magnitude of genetic correlations were with traits that included asthma, some cancer diagnoses, bone disorders and fractures, alcohol use, amyloidosis, asthma, type of transportation used, and asthma (See Supplementary Information).

3.10. *Simulation of conversion of quantitative trait to binary trait shows correlation of effect sizes to empirical data.*

Based on the scale difference between binary and quantitative traits, the odds ratios are not directly comparable. We simulated the effect of a quantitative trait locus and nearby marker both on the original quantitative trait and the binary trait converted from the quantitative trait using liability thresholding. We found high correlation of effect sizes between the beta coefficients and log odds ratios of the quantitative trait variants with p-value < 0.005 and their respective binary trait variant effect sizes (Pearson correlation, $r^2=0.82$). Lower p-values were not tested because of too few qualifying variants. After standard normalizing the quantitative trait, we also found the slope of the correlation between it and the log binary trait to be stable across the parameters, with a mean of 1.63 for each parameter except for marker allele frequency (1.35) and prevalence (1.77) (Supplementary Figure A.7).

455 4. Discussion

456 4.1. *QTPhenProxy can identify patients with stroke using EHR data other than the* 457 *disease diagnosis code.*

458 For all stroke and its subtype ischemic stroke, the machine learning models
459 trained to assign QTPhenProxy probabilities performed well (greater than 90%
460 AUROC, greater than 30% maximum F1 score, 74-97% precision at 50). The
461 models trained on subarachnoid hemorrhage and intracerebral hemorrhage cases
462 performed similarly with AUROC but not as well with maximum F1 score and
463 precision at 50. This may be due to the number of cases the two subtypes have to
464 train on, which was an order of magnitude smaller (600 cases versus 3300-4300
465 cases). Importantly, we only trained on half of the cases and tested on the other
466 half, which equates to 300-2200 cases, depending on the disease definition. From
467 this small training set, we were able to assign a probability of disease to all 500,000
468 subjects in the UK Biobank. This training set is a fraction of the over 40,000 cases
469 required to power the most recent genome-wide association study for stroke
470 (MEGASTROKE).

471 4.2. *QTPhenProxy discovers many new variants and recovers known disease variants* 472 *to genome-wide significance*

473 Using QTPhenProxy resulted in 3-13 loci with genome-wide significance.
474 In contrast, traditional binary trait GWAS using all disease cases resulted in
475 the discovery of 0 genome-wide significant loci for stroke, ischemic stroke, and
476 subarachnoid hemorrhage and 3 loci for intracerebral hemorrhage. In addition
477 to new loci discovery, QTPhenProxy recovered known disease variants to a
478 significance level of 0.05 with a sensitivity better than binary trait GWAS. In

479 addition to recovering known variants, overall the effect size of the known variants
480 in the binary trait GWAS was correlated with QTPhenProxy effect sizes for
481 variants with low p-values. These results suggest that the QTPhenProxy method
482 can recover relevant variants with fewer cases than traditional methods for stroke.

483 *4.3. Simulation of quantitative trait and corresponding binary trait further supported*
484 *the correlation of effect sizes between the two methods.*

485 Our simulations showed high correlation between quantitative trait beta
486 coefficients and binary trait log odds ratio, which is similar to our empirical
487 findings in the UK Biobank. We also show that the correlation slope is relatively
488 stable across all the different simulation parameters, suggesting that there is a
489 set correlation between quantitative traits and binary traits created from them.
490 Further simulation will need to determine the effects of multiple loci on correlation
491 between quantitative and corresponding binary trait.

492 *4.4. Variants discovered for stroke are enriched in disease marker sets for vascular and*
493 *neurological disease, and variants discovered for other diseases were enriched*
494 *for disease and system specific markers.*

495 As a specificity measure for the variants discovered by QTPhenProxy, we
496 found the EN model had the highest proportion of overlapping variants with
497 EBI-GWAS marker sets related to vascular disorders and associated lab values. QT-
498 PhenProxy variants improves the power of detecting variants related to diseases
499 that are co-morbid or risk factors for stroke.

500 4.5. *QTPhenProxy* has high genetic correlation with the MEGASTROKE GWAS and 501 *stroke-related risk factor* GWAS

502 We found high genetic correlation (0.60-0.64) between the MEGASTROKE
503 stroke and ischemic stroke GWAS and the *QTPhenProxy* models. The high
504 genetic correlation between MEGASTROKE and *QTPhenProxy* suggests that
505 both studies highlight shared genetic underpinnings, which we confirmed by
506 finding large positive genetic correlations between the *QTPhenProxy* stroke and
507 ischemic stroke models and risk factor GWAS that had large positive genetic
508 correlations with MEGASTROKE (Malik et al., 2018a). We found large negative
509 genetic correlations between the *QTPhenProxy* sub-arachnoid hemorrhage GWAS
510 and the risk factors. We also were unable to find genetic correlations between the
511 traditional binary GWAS of stroke, ischemic stroke, intracerebral hemorrhage,
512 and sub-arachnoid hemorrhage and MEGASTROKE or the risk factors, most likely
513 due to the small number of cases (581-4354) in each cohort. Finally, we found
514 the least significant genetic correlations between the *QTPhenProxy* models and
515 traits that are not stroke-related, such as bone disorders, cancer, and cataracts,
516 while the most significant were cardiovascular-related. These findings suggest
517 that our models do highlight genetic associations related to the pathophysiology
518 of stroke. Although there is concern that this method may highlight genetic
519 associations related to risk factors of stroke rather than stroke itself, we show
520 that our models' GWAS are highly correlated with the MEGASTROKE GWAS and
521 have similar correlations with risk factor GWAS highlighted by the study. These
522 results suggest that *QTPhenProxy* models develop a phenotypic score ascertained
523 for stroke and its subtypes.

524 4.6. Low LD score regression intercepts relative to genomic inflation suggests high 525 polygenicity.

526 Our genome-wide association studies using QTPHENProxy had moderate
527 genomic inflation, slightly above 1.1, but low LD score regression intercepts
528 near 1.0. The corresponding binary trait GWAS had genomic inflation below
529 1.05, suggesting minimal population stratification. Since the population for the
530 binary trait GWAS was the same as those used for QTPHENProxy, this suggests
531 that polygenicity, rather than population stratification, is the cause for genomic
532 inflation. Polygenicity, or the contribution of small effects of many genes to a
533 phenotype, may be the more likely cause (Bulik-Sullivan et al., 2015). In addition,
534 Bulik-sullivan et. al. argue that genomic inflation can increase with sample size
535 when there is polygenicity, and LD score regression intercept is more robust
536 in distinguishing inflated p-values from polygenicity. As seen in (Howrigan
537 et al., 2017), increased genomic inflation with common variants over rare variants
538 suggests polygenicity. We show a similar upward trend in Figure 4. Another sign
539 of true signal over inflated signal is the evidence of causal variants in linkage
540 disequilibrium, as seen in a manhattan or hudson plot (Howrigan et al., 2017).
541 Figure 2 shows genome-wide significant variants in linkage disequilibrium with
542 each other. Finally, this study reports results from using two different quality
543 controls in the genome-wide association analysis, QC1, and more stringent, QC2.
544 Results using QC1 showed more variants with genome-wide significance and
545 discovered more new variants for stroke than the QC2 GWAS. This may lead one
546 to believe that more stringent quality control led to reduced inflation of p-values.
547 However, the genomic inflation of the p-values from the QC1 GWAS was the
548 same as the genomic inflation of the p-values from the QC2 GWAS (1.134 vs 1.133)

549 with the QC2 GWAS having a slightly higher LD score regression intercept value
550 (1.0288 vs 1.0369). This suggests that the p-values from the QC1 GWAS may not
551 be overly inflated.

552 4.7. *QTPhenProxy replicates known stroke variants and discovers variants within* 553 *cardiovascular disease genes.*

554 Several of the genes discovered by the QTPhenProxy GWAS, using QC1 or
555 QC2 quality control have been associated with stroke, including *NOS3*, *FURIN*,
556 *PITX2*, *CDK2NB*, *LDLR*, and *ABO* (Malik et al., 2018a,b). *NOS3*, in particular was
557 discovered through meta-analysis of the MEGASTROKE results with the UK
558 Biobank (Malik et al., 2018b). We were able to replicate this association using
559 only the QTPhenProxy method on the UK Biobank, and not traditional binary
560 trait analysis. *NOS3* has been shown to be related to hypertension either through
561 salt excretion regulation in the kidney (Gao Yang et al., 2018) or regulation of
562 vascular relaxation in endothelial cells (Farah et al., 2018). Other discovered
563 genes by QTPhenProxy are also associated with related cardiovascular diseases.
564 *F5* gene codes for an essential coagulation factor, and mutations that can lead
565 to increased thrombosis or hemorrhage, depending on the mutation (Asselta
566 and Peyvandi, 2009; Kujovich, 2011; Hinds et al., 2016). *LPA* codes for a protein,
567 lipoprotein-A, that can contribute to atherosclerosis (The Emerging Risk Factors
568 Collaboration, 2009; Wang Long et al., 2016). Mutations in the *PLCB1* gene, which
569 encodes for phospholipase synthesis, have been found in epilepsy and seizures
570 (Schoonjans et al., 2016). *LDLR* gene codes for the low-density lipoprotein re-
571 ceptor, which is involved in cholesterol production (Brown and Goldstein, 1979),
572 and the *APOC1/APOC1P1* genes code for parts of apolipoprotein C1, which are
573 involved in high density lipoprotein metabolism (Erqou et al., 2010). *ARHGAP1*, a

gene coding for Rho GTPase activating protein 1 has been associated with cancer phenotypes and activation of hypoxic and inflammatory pathways (Fessler et al., 2004; Hashimoto et al., 2018; Zhang et al., 2019). *ABCG8* gene has been associated with combined gwas of lipids and inflammation, lipid levels, and gallstone disease (Ligthart et al., 2016). In addition, it is known to code for a cholesterol transporter. *EYST3* and *XKR6* gene mutations have been associated with coronary artery disease and ischemic stroke respectively in Asian populations, and *MRAS* gene mutations have been associated with coronary artery disease in two populations (Jiang et al., 2011; Zheng et al., 2019; Song et al., 2019; Erdmann et al., 2009). These results suggest that QTPhenProxy has replicated genome-wide significant mutations in genes known to be related with stroke and discovered those associated with related risk factors such as coronary artery neurological diseases. Out of the 13 newly discovered variants with genome-wide significance, five are intronic or nearby genes that have been found in previous studies (MEGASTROKE), and five more have been discovered in previous GWAS studies of related cardiovascular diseases. The variants within and near the *F5* gene had the highest genetic signal for stroke and all of its subtypes, even though it was not replicated in the MEGASTROKE GWAS. Out of all the new variants discovered by the QTPhenProxy EN model using the GWAS QC2 quality control, the rs11887534 variant, a missense mutation within the *ABCG8* gene, replicated to a p-value significance of 6.85E-04 in the MEGASTROKE stroke GWAS of over 40,000 European ancestry subjects. Using a tenth of the number of cases, QTPhenProxy discovered a variant within a new gene that replicated in MEGASTROKE, and discovered variants within known stroke genes.

598 4.8. Limitations

599 There are several limitations with this method. First, out of the five machine
600 learning models used in QTPhenProxy, only two provided probabilities along
601 a continuous scale. Adaboost, gradient boosting, and logistic regression using
602 L1 penalty models, although with high performance, assigned probabilities in
603 discrete bins. These distributions violate the the genome-wide association linear
604 regression assumption of normal distribution of the quantitative trait. Although
605 the probabilities produced by EN and RF models were not initially normally
606 distributed, they were continuous, and could be adjusted with quantile normal-
607 ization. In addition, the GWAS results from QTPhenProxy using the RF model
608 resulted in many more hits than the EN model, and reduced sensitivity to known
609 disease variants. Further study will be required to understand why one model
610 gave more sensitive and specific results than the other, and whether there was
611 p-value inflation in the random forest models. QTPhenProxy also may be par-
612 ticularly suited for stroke because the training model for phenotyping patients
613 was optimized for stroke (Thangaraj et al., 2019). Since stroke is an acute event
614 than can be identified with high accuracy in the electronic health record, this
615 method may not translate as well to other diseases, such as chronic illnesses.
616 A final limitation discussion point is whether QTPhenProxy models highlight
617 genetic associations with risk factors for stroke rather than stroke itself. We
618 have shown, from replicating known stroke variants to finding large positive and
619 significant genetic correlations with MEGASTROKE and related traits, that our
620 models improve the power of genetic associations for stroke, and not just a few
621 specific risk factors.

622 4.9. Conclusions

623 We have developed a method, QTPhenProxy, that we have shown improves
624 the power of genome-wide association studies in stroke and three of its subtypes:
625 ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage with an
626 order of magnitude fewer cases than required for traditional genome-wide associ-
627 ation studies of the same diseases. Converting dichotomous traits to quantitative
628 ones could result in improvement of power by incorporating electronic health
629 record information for subjects who may have genetic susceptibility to stroke
630 but may not have experience a stroke yet. Previous studies have shown that for
631 diseases with low prevalence, there can be a reduction of power using logistic
632 regression for binary trait GWAS compared to linear regression for quantitative
633 trait GWAS (Zaitlen et al., 2012). Recently, (Abraham et al., 2019) showed that
634 the inclusion of ischemic stroke risk factors' genome-wide significant SNPs in
635 polygenic risk score improves prediction of ischemic stroke. This supports our
636 idea that inclusion of risk factor information into the phenotype can help detect
637 genetically susceptible subjects. We show that with as few as 2200 stroke subjects
638 we can recover known variants of stroke and discover new variants that have
639 been linked to cardiovascular and nervous system diseases. This method could
640 be useful for studies with a small set of cases and without access to large meta-
641 analyses. We also have suggested new variants that warrant further replication
642 in other groups. QTPhenProxy shows the benefits of incorporating electronic
643 health record data to convert traditional binary traits to quantitative in improving
644 GWAS power.

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660 DIAGRAM (DIABetes Genetics Replication And Meta-analysis), ENIGMA (En-
661 hancing Neuro Imaging Genetics through Meta Analysis), EAGLE (EARly Genetics
662 Lifecourse Epidemiology Eczema Consortium, excluding 23andMe), EGG (Early
663 Growth Genetics Consortium), GABRIEL (A Multidisciplinary Study to Identify
664 the Genetic and Environmental Causes of Asthma in the European Community),
665 GCAN (Genetic Consortium for Anorexia Nervosa), GEFOS (GENetic Factors for
666 OSteoporosis Consortium), GIANT (Genetic Investigation of ANthropometric
667 Traits), GIS (Genetics of Iron Status consortium), GLGC (Global Lipids Genetics
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6. Author Contributions

Conceptualization: P.T. and N.T., methodology: P.T. and N.T., software: P.T. and N.T., formal analysis: P.T., U.G., and N.T., investigation: P.T. and N.T., resources: P.T. and N.T., data curation: P.T., U.G., and N.T., writing-original draft: P.T. and N.T., writing- review and editing: P.T., U.G., and N.T., visualization: P.T. and N.T., Supervision: N.T., Funding Acquisition: P.T. and N.T.

7. Declaration of Interests

The authors declare no competing interests.

690 8. Figures

Figure 1: **Precision at top 50, 100, 500, and N cases probabilities assigned by machine learning algorithms on hold out test set and probability distributions.** A. All Stroke, B. Ischemic Stroke, C. Sub-arachnoid Hemorrhage, D. Intracerebral Hemorrhage. Left panel: Precision of each algorithm. Circles represent precision for the Logistic Regression model with L1 penalty (LR), squares: Random Forest model (RF), triangles: Adaboost model (AB), cross: Gradient boosting model (GB), and star Logistic Regression model with Elastic Net penalty (EN). Middle Panel: EN probability distributions, Right panel: RF Probability distributions

Figure 2: QQ Plots and Hudson plot of QTPhenProxy genome-wide association analysis, EN Model with Binary trait genome-wide association analysis for Stroke, (Top) using QC1 quality control and (Bottom) using QC2 quality control. A. and D. Q-Q Plot for QT-PhenProxy, EN Model GWAS. B. and E. Q-Q Plot for Binary trait GWAS. C. and F. Top manhattan plot is for QTPhenProxy, bottom plot for binary trait. Variants with p-value $< 5e-08$ are highlighted in pink, and the dashed lines are at the same value.

Figure 3: QTPhenProxy recovers known ischemic stroke variants and variants specific to related organ systems. Results from QTPhenProxy GWAS with QC2 quality control. (A) Horizontal axis shows Ischemic Stroke variants catalogued in EBI-GWAS that have shown genome-wide significance in previous studies. Black markers represent p-values of variants recovered by QTPhenProxy models (square=RF, Triangle=EN). (B) X-axis is the top percentile of marker sets in each category, Y-axis is the proportion of variants in marker sets that overlap with QTPhenProxy genome-wide significant variants. Each shape corresponds to a disease category. In color are top disease categories: Square=Investigations, Triangle=Vascular disorders, Cross=Nervous system disorders, X=General disorders and administration site conditions, Star=cardiac disorders, and Diamond=Blood and lymphatic system disorders.

Figure 4: Correlation between beta and odds ratio effect sizes for variants at varying degrees of significance and Genomic Inflation within bins of variants with similar minor allele frequencies for QTPhenProxy EN Model for Stroke with QC2 quality control. (A-E) Correlation between QTPhenProxy, EN Model for Stroke GWAS and Binary trait GWAS effect size, QC2 quality control. X-axis is QTPhenProxy GWAS beta-coefficients, Y-axis is log base 10 of the Binary GWAS odds ratios. Pearson correlation is recorded in top right corner. From left to right, top to bottom, variants included decreases by restricting p-value. (F) Genomic Inflation within bins of variants with similar minor allele frequencies for QTPhenProxy EN Model for Stroke with QC2 quality control. Light blue line shows the genomic inflation of each bin of variants, green line shows 1.0 genomic inflation, and blue bars show numbers of SNPs (variants) in each bin, binned by $\log_{10}(\text{MAF})$, or log(minor allele frequency.)

9. Tables

Disease	N Cases	Binary Hits	Bin Sens	RF Hits	RF Sens	EN Hits	EN Sens
Stroke	4354	0	0.217	1215	0.217	120	0.261
IscStroke	3308	0	0.312	1266	0.312	202	0.333
SAHStroke	665	0	NA	722	NA	69	NA
ICHStroke	581	2	NA	1059	NA	146	NA

Table 1: **Number of genome-wide significant loci and proportion of known stroke variants that reach nominal significance for each model.** *IscStroke*: Ischemic Stroke, *SAHStroke*: Subarachnoid Hemorrhage, *ICHStroke*: Intracerebral Hemorrhage, *N Cases*: number of cases, *hits*: Number of genome-wide significant loci, *sens*: sensitivity measure for each model GWAS and binary trait GWAS, measures what proportion of known stroke variants reach genome-wide significance in each association test. *RF*: Random Forest model, *EN*: Logistic Regression with elastic net penalty model.

Phenotype	rsID	Chr.	Gene	Location	R/R allele	RAF	Beta	Converted OR	P value
Stroke	rs6025	1q24.2	<i>F5</i>	missense	T/C	0.0231	0.0492 (0.0421-0.0564)	1.09 (1.08-1.10)	4.87e-12
Stroke	rs8179838	2p21	<i>MTA3</i>	intronic	T/C	0.621	0.0126 (0.0104-0.0149)	1.02 (1.02-1.03)	9.63e-09
Stroke	rs6923947	6q22.32	<i>LOC105377992</i>	intergenic	A/G	0.447	0.0123 (0.0101-0.0144)	1.02 (1.02-1.02)	1.19e-08
Stroke	rs55730499	6q25.3	<i>LPA</i>	intronic	T/C	0.0817	0.0273 (0.0234-0.0312)	1.05 (1.04-1.06)	2.70e-12
Stroke	rs3918226	7q36.1	<i>NOS3</i>	intronic	T/C	0.0814	0.0263 (0.0223-0.0302)	1.05 (1.04-1.05)	3.44e-11
Stroke	rs6991641	8p23.1	<i>SOX7</i>	intronic	G/C	0.403	0.013 (0.0108-0.0152)	1.02 (1.02-1.03)	3.29e-09
Stroke	rs1333049	9p21.3	<i>CDKN2A-CDKN2B</i>	intergenic	C/G	0.481	0.0129 (0.0108-0.0151)	1.02 (1.02-1.03)	1.41e-09
Stroke	9:136138765	9q34.3	<i>ABO</i>	intronic	G/GC...	0.184	0.0155 (0.0128-0.0183)	1.03 (1.02-1.03)	2.05e-08
Stroke	11:46705193	11p11.2	<i>ARHGAP1</i>	intronic	C/CT	0.28	0.0143 (0.0119-0.0167)	1.02 (1.02-1.03)	4.10e-09
Stroke	rs59065675	15q26.1	<i>FURIN</i>	intronic	C.../C	0.47	0.0127 (0.0105-0.0149)	1.02 (1.02-1.03)	5.00e-09
Stroke	rs814573	19q13.32	<i>APOC1-APOC1P1</i>	intergenic	T/A	0.188	0.0156 (0.0128-0.0184)	1.03 (1.02-1.03)	2.97e-08
Stroke	20:862958	20p12.3	<i>PLCB1</i>	intronic	TA/T	0.76	0.0138 (0.0113-0.0164)	1.02 (1.02-1.03)	4.73e-08

IscStroke	rs1894692	1q24.2	<i>F5-SLC19A2</i>	intergenic	G/A	0.0218	0.0546 (0.0478-0.0614)	1.1 (1.09-1.11)	8.22e-16
IscStroke	rs369787256	4q25	<i>PITX2-MIR297</i>	intergenic	C/T	0.0905	0.0223 (0.0188-0.0257)	1.04 (1.03-1.05)	1.17e-10
IscStroke	rs55730499	6q25.3	<i>LPA</i>	intronic	T/C	0.0817	0.0272 (0.0236-0.0307)	1.05 (1.04-1.05)	2.49e-14
IscStroke	rs117733303	6q25.3	<i>LPAL2</i>	intronic	G/A	0.0187	0.0428 (0.0356-0.05)	1.08 (1.06-1.09)	2.69e-09
IscStroke	rs3918226	7q36.1	<i>NOS3</i>	intronic	T/C	0.0814	0.0209 (0.0173-0.0246)	1.04 (1.03-1.04)	6.81e-09
IscStroke	rs2205258	8q23.3	<i>LOC107986968</i>	intronic	C/T	0.83	0.0151 (0.0125-0.0177)	1.03 (1.02-1.03)	6.76e-09
IscStroke	rs8176719	9q34.2	<i>ABO</i>	insertion	TC/T	0.34	0.0145 (0.0124-0.0165)	1.02 (1.02-1.03)	2.17e-12
IscStroke	rs1333049	9p21.3	<i>CDKN2A-CDKN2B</i>	intergenic	C/G	0.481	0.0132 (0.0112-0.0151)	1.02 (1.02-1.03)	1.31e-11
IscStroke	11:46705193	11p11.2	<i>ARHGAP1</i>	intronic	C/CT	0.28	0.0122 (0.01-0.0145)	1.02 (1.02-1.02)	3.22e-08
IscStroke	rs814573	19q13.32	<i>APOC1-APOC1P1</i>	intergenic	T/A	0.188	0.0172 (0.0146-0.0198)	1.03 (1.02-1.03)	1.85e-11
IscStroke	rs118068660	19p13.2	<i>LDLR</i>	intergenic	C/T	0.901	0.0193 (0.0159-0.0227)	1.03 (1.03-1.04)	1.43e-08
IscStroke	rs12151925	20p12.2	<i>LOC101929413-FAT1P1</i>	intergenic	C/T	0.222	0.0129 (0.0105-0.0152)	1.02 (1.02-1.03)	4.26e-08
SAHStroke	rs6025	1q24.2	<i>F5</i>	missense	T/C	0.0231	0.0673 (0.0593-0.0753)	1.12 (1.11-1.14)	4.61e-17
SAHStroke	rs36058710	9q34.2	<i>ABO</i>	intronic	CT/C	0.287	0.0166 (0.0139-0.0194)	1.03 (1.02-1.03)	1.03e-09
SAHStroke	rs34850248	12q12	<i>LINC02400</i>	intergenic	A/AC	0.0714	0.0268 (0.0221-0.0314)	1.05 (1.04-1.06)	9.95e-09
ICHStroke	rs6025	1q24.2	<i>F5</i>	missense	T/C	0.0231	0.0480 (0.0411-0.0549)	1.09 (1.07-1.1)	2.85e-12
ICHStroke	rs11887534	2p21	<i>ABCG8</i>	missense	G/C	0.935	0.0271 (0.0229-0.0313)	1.05 (1.04-1.06)	7.90e-11
ICHStroke	rs372302634	3q22.3	<i>ESYT3-MRAS</i>	intergenic	T/T...	0.457	0.0121 (0.01-0.0142)	1.02 (1.02-1.02)	8.51e-09
ICHStroke	rs6923947	6q22.32	<i>LOC105377992</i>	intergenic	A/G	0.447	0.0127 (0.0106-0.0148)	1.02 (1.02-1.03)	9.5e-10
ICHStroke	rs2077111	6q22.33	<i>RPS4XP9</i>	intergenic	G/A	0.447	0.012 (0.00995-0.0141)	1.02 (1.02-1.02)	8.89e-09
ICHStroke	rs1808593	7q36.1	<i>NOS3</i>	intronic	G/T	0.25	0.0131 (0.0107-0.0155)	1.02 (1.02-1.03)	4.14e-08
ICHStroke	rs7013277	8p23.1	<i>XKR6</i>	intronic	C/A	0.396	0.0116 (0.00947-0.0137)	1.02 (1.02-1.02)	4.6e-08
ICHStroke	11:46705193	11p11.2	<i>ARHGAP1</i>	intronic	C/CT	0.28	0.0133 (0.011-0.0156)	1.02 (1.02-1.03)	1.35e-08

Table 2: **Genome-wide significant variants discovered by QTPhenProxy, EN Model, using QC1 quality control.** Cytogenic position was determined using Kent et al. (2002). *rsID*: variant id, *Chr*: cytogenic position, *Location*: location of variant relative to the gene, *R/R*: risk/reference, *RAF*: risk allele frequency in population, *Beta*: Beta coefficient *OR*: Odds Ratio, 95% Confidence Intervals

Phenotype	rsID	Chr.	Gene	P value	MEGASTROKE P value
Stroke	rs1894692	1q24.2	<i>F5-SLC19A2</i>	6.87E-10	0.435

Stroke	rs8179838	2p21	<i>MTA3</i>	8.36E-06	0.515
Stroke	rs769407520	3q22.3	<i>ATP5MC1P3</i>	2.50E-08	not found
Stroke	rs6923947	6q22.32	<i>LOC105377992</i>	4.58E-07	0.04332
Stroke	rs55730499	6q25.3	<i>LPA</i>	6.85E-10	0.05915
Stroke	rs3918226	7q36.1	<i>NOS3</i>	6.45E-09	0.00134
Stroke	8:10206921	8p23.1	<i>MSRA</i>	4.62E-08	not found
Stroke	rs1333049	9p21.3	<i>CDKN2A-CDKN2B</i>	5.02E-06	1.85E-07
Stroke	9:136138765	9q34.3	<i>ABO</i>	9.73E-09	not found
Stroke	11:46705193	11p11.2	<i>ARHGAP1</i>	7.06E-07	not found
Stroke	rs59065675	15q26.1	<i>FURIN</i>	4.06E-07	not found
Stroke	rs814573	19q13.32	<i>APOC1-APOC1P1</i>	2.52E-05	0.412
Stroke	20:862958	20p12.3	<i>PLCB1</i>	1.95E-06	not found
Stroke	rs2269608	22q13.1	<i>KCNJ4</i>	4.23E-08	0.212
IscStroke	rs1894692	1q24.2	<i>F5-SLC19A2</i>	1.90E-11	0.229
IscStroke	rs369787256	4q25	<i>PITX2-MIR297</i>	3.69E-06	not found
IscStroke	rs55730499	6q25.3	<i>LPA</i>	1.26E-09	0.0316
IscStroke	rs117733303	6q25.3	<i>LPAL2</i>	0.000119	0.422
IscStroke	rs3918226	7q36.1	<i>NOS3</i>	3.59E-06	0.00118
IscStroke	rs2205258	8q23.3	<i>LOC107986968</i>	7.16E-06	0.415
IscStroke	9:1361387	9q34.2	<i>ABO</i>	4.99E-10	not found
IscStroke	rs1333049	9p21.3	<i>CDKN2A-CDKN2B</i>	3.01E-06	1.09E-06
IscStroke	11:46705193	11p11.2	<i>ARHGAP1</i>	3.85E-05	not found
IscStroke	rs814573	19q13.32	<i>APOC1-APOC1P1</i>	2.20E-06	0.716
IscStroke	rs118068660	19p13.2	<i>LDLR</i>	1.28E-06	1.14E-05

IscStroke	rs12151925	20p12.2	<i>LOC101929413-FAT1P1</i>	0.000107	0.104
SAHStroke	rs6025	1q24.2	<i>F5</i>	6.34E-18	0.453
SAHStroke	rs36058710	9q34.2	<i>ABO</i>	1.59E-10	not found
SAHStroke	rs34850248	12q12	<i>LINC02400</i>	7.18E-09	not found
ICHStroke	rs6025	1q24.2	<i>F5</i>	1.52E-10	0.453
ICHStroke	rs11887534	2p21	<i>ABCG8</i>	4.29E-08	6.85E-04
ICHStroke	rs372302634	3q22.3	<i>ESYT3-MRAS</i>	4.03E-08	not found
ICHStroke	rs6923947	6q22.32	<i>LOC105377992</i>	1.47E-07	0.00433
ICHStroke	rs2077111	6q22.33	<i>RPS4XP9</i>	1.96E-06	0.0372
ICHStroke	rs1808593	7q36.1	<i>NOS3</i>	2.96E-06	0.565
ICHStroke	rs7013277	8p23.1	<i>XKR6</i>	2.06E-05	0.156
ICHStroke	11:46705193	11p11.2	<i>ARHGAP1</i>	3.59E-06	not found

Table 3: **Genome-wide significant variants discovered by QTPhenProxy, EN Model, using QC2 quality control.** Also includes QC2 p-value for genome-wide significant variants from QC1 GWAS and p-values for variants from the MEGASTROKE stroke or ischemic stroke european GWAS Malik et al. (2018a). Cytogenic position was determined using Kent et al. (2002). *rsID*: variant id, *Chr*: cytogenic position

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Phenotype	Gene	rsID	QTPhenProxy p-value
Stroke	<i>LPA</i>	rs56393506	1.09E-08
Stroke	<i>NOS</i>	rs1799983	not found
Stroke	<i>CDKN2B-CDKN2A</i>	rs7859727	6.94E-05
Stroke	<i>ABO</i>	rs635634	1.07E-07
Stroke	<i>FURIN</i>	rs4932370	2.55E-05
Stroke	<i>COL4A1</i>	rs9521634	0.00375
Stroke	<i>LOC105372798</i>	rs720470	0.88
Ischemic stroke	<i>PITX2-MIR297</i>	rs13143308	not found
Ischemic stroke	<i>LPA</i>	rs56393506	2.50E-09
Ischemic stroke	<i>NOS3</i>	rs1799983	not found
Ischemic stroke	<i>CDKN2B-CDKN2A</i>	rs7859727	5.95E-05
Ischemic stroke	<i>ABO</i>	rs635634	7.93E-09
Ischemic stroke	<i>LDLR</i>	rs8103309	0.171
Subarachnoid Hemorrhage	<i>ABO</i>	rs635634	2.22E-06
Intracerebral Hemorrhage	<i>NOS3</i>	rs1799983	not found

Table 4: QTPhenProxy EN Model GWAS using QC2 quality control P-value of variants that were genome-wide significant in MEGASTROKE Stroke and Ischemic Stroke GWAS.

696 Appendix A. Supplementary Figures

Figure A.1: Model probability distributions assigned by machine learning algorithms, related to Figure 1. A. All Stroke, B. Ischemic Stroke, C. Sub-arachnoid Hemorrhage, D. Intracerebral Hemorrhage. First panel: Logistic Regression model with Elastic Net penalty probability distribution, Second panel: Random Forest probability distribution, Third panel: Logistic Regression model with L1 penalty probability distribution, Fourth panel: Adaboost probability distribution, Fifth panel: Gradient boosting probability distribution

Figure A.2: QQ Plots and Hudson plot of QTPhenProxy genome-wide association analysis, EN Model with Binary trait genome-wide association analysis for Ischemic Stroke, (Top) using QC1 quality control and (Bottom) using QC2 quality control, related to Figure 2. A. and D. Q-Q Plot for QTPhenProxy, EN Model GWAS. B. and E. Q-Q Plot for Binary trait GWAS. C. and F. Top Manhattan plot is for QTPhenProxy, bottom plot for binary trait. Variants with $p\text{-value} < 5e-8$ are highlighted in pink, and the dashed lines are at the same value.

Figure A.3: QQ Plots and Hudson plot of QTPhenProxy genome-wide association analysis, EN Model with Binary trait genome-wide association analysis for Subarachnoid Hemorrhage, (Top) using QC1 quality control and (Bottom) using QC2 quality control, related to Figure 2. A. and D. Q-Q Plot for QTPhenProxy, EN Model GWAS. B. and E. Q-Q Plot for Binary trait GWAS. C. and F. Top manhattan plot is for QTPhenProxy, bottom plot for binary trait. Variants with p-value < 5e-08 are highlighted in pink, and the dashed lines are at the same value.

Figure A.4: QQ Plots and Hudson plot of QTPhenProxy genome-wide association analysis, EN Model with Binary trait genome-wide association analysis for Intracerebral Hemorrhage, (Top) using QC1 quality control and (Bottom) using QC2 quality control, related to Figure 2. A. and D. Q-Q Plot for QTPhenProxy, EN Model GWAS. B. and E. Q-Q Plot for Binary trait GWAS. C. and F. Top manhattan plot is for QTPhenProxy, bottom plot for binary trait. Variants with p-value < 5e-08 are highlighted in pink, and the dashed lines are at the same value.

Figure A.5: QTPhenProxy recovers known stroke variants and variants specific to related organ systems, related to Figure 3. Results from QTPhenProxy GWAS with QC2 quality control. (A) Horizontal axis shows Stroke variants catalogued in EBI-GWAS that have shown genome-wide significance in previous studies. Black markers represent p-values of variants recovered by QTPhenProxy models (square=RF, Triangle=EN). (B) X-axis is the top percentile of marker sets in each category, Y-axis is the proportion of variants in marker sets that overlap with QTPhenProxy genome-wide significant variants. Each shape corresponds to a disease category. In color are top disease categories: Square=Investigations, Triangle=Vascular disorders, Cross=Nervous system disorders, X=General disorders and administration site conditions, Star=cardiac disorders, and Diamond=Blood and lymphatic system disorders.

Figure A.6: Correlation between beta and odds ratio effect sizes for variants at varying degrees of significance, related to Figure 4. (A-E) Correlation between QTPhenProxy, EN Model for Stroke GWAS and Binary trait GWAS effect size, QC1 quality control. X-axis is QTPhenProxy GWAS beta-coefficients, Y-axis is log base 10 of the Binary GWAS odds ratios. Pearson correlation is recorded in top right corner. From left to right, top to bottom, variants included decreases by restricting p-value.

Figure A.7: **Slope of correlation between beta from simulated quantitative trait and log(odds ratio) of simulated binary trait with varying simulation parameters.** Left panels calculate slope with all variants, right panels calculate slope with variants with p-value < 0.005. (A) varies the transformation of the probability distribution, where $N(0,1)$ is a normal distribution with mean 0, variance 1, $N(0,10)$ is a normal distribution with mean 0, variance 10, $N(10,50)$ is a normal distribution with mean 10, variance 50, *norm* is normalized by the maximum value, and *orig* is the original distribution. (B) varies the prevalence of the trait, (C) varies the causal allele frequency, (D) varies the recombination fraction between the causal allele and marker allele, and (E) varies the marker minor allele frequency.

697 **Appendix B. Supplementary Tables**

Disease	Model	AUROC	AUPRC	Maximum F1
Ischemic Stroke	rf	0.953(0.000279)	0.248(0.00201)	0.326(0.00229)
	ab	0.950(0.000504)	0.246(0.00465)	0.316(0.00335)
	lr	0.946(0.000409)	0.239(0.0021)	0.322(0.00196)
	gb	0.952(0.000686)	0.210(0.00479)	0.294(0.00319)
	en	0.943(0.000362)	0.209(0.00193)	0.295(0.00199)
SAH Stroke	rf	0.875(0.000746)	0.144(0.00299)	0.242(0.00423)
	ab	0.859(0.00186)	0.171(0.0062)	0.271(0.00807)
	lr	0.850(0.00115)	0.151(0.00419)	0.291(0.00509)
	gb	0.863(0.00149)	0.113(0.00379)	0.203(0.00513)
	en	0.863(0.000958)	0.109(0.00377)	0.198(0.00497)
ICH Stroke	rf	0.903(0.000924)	0.0483(0.00143)	0.116(0.00253)
	ab	0.900(0.00171)	0.0480(0.00196)	0.114(0.00305)
	lr	0.879(0.00145)	0.0270(0.000709)	0.0762(0.00137)
	gb	0.900(0.00123)	0.0365(0.00125)	0.0935(0.00227)
	en	0.903(0.00118)	0.0329(0.000755)	0.0861(0.00146)
Stroke	rf	0.899(0.000404)	0.326(0.0016)	0.375(0.00147)
	ab	0.906(0.000711)	0.335(0.00423)	0.380(0.00262)
	lr	0.905(0.000528)	0.314(0.00143)	0.368(0.00154)
	gb	0.903(0.00047)	0.292(0.00245)	0.355(0.00151)
	en	0.896(0.000448)	0.282(0.00113)	0.350(0.000962)

Table B.1: **Phenotyping Models Performance.** *rf*: Random Forest, *ab*= Adaboost, *lr*=Logistic regression with L1 penalty, *gb*=Gradient Boosting, *en*=Logistic Regression with elastic net penalty models. *AUROC*: Area under the Receiver Operating Curve, *AUPRC*: Area under Precision-Recall curve. 95% confidence intervals shown in parentheses

Disease	Model	Prec at 50	Prec at 100	Prec at 500	Prec at N
IscStroke	rf	0.739(0.0132)	0.682(0.0105)	0.544(0.00575)	0.322(0.00246)
	ab	0.71(0.0192)	0.674(0.0154)	0.527(0.0117)	0.309(0.00405)
	lr	0.801(0.0143)	0.672(0.00997)	0.483(0.00560)	0.314(0.00205)
	gb	0.609(0.0305)	0.544(0.0246)	0.425(0.0179)	0.282(0.00714)
	en	0.74(0.0141)	0.63(0.00946)	0.435(0.00476)	0.29(0.00197)
SAHStroke	rf	0.607(0.0178)	0.55(0.0106)	0.308(0.00623)	0.235(0.00381)
	ab	0.627(0.0185)	0.538(0.0144)	0.329(0.0102)	0.266(0.00801)
	lr	0.535(0.0187)	0.5(0.0147)	0.356(0.00722)	0.271(0.00630)
	gb	0.532(0.0203)	0.442(0.0176)	0.249(0.00759)	0.197(0.00557)
	en	0.543(0.0188)	0.441(0.0136)	0.244(0.00773)	0.192(0.00523)
ICHStroke	rf	0.263(0.013)	0.216(0.00968)	0.124(0.00328)	0.110(0.00265)
	ab	0.203(0.0185)	0.171(0.0124)	0.108(0.00400)	0.0997(0.00352)
	lr	0.109(0.0121)	0.100(0.00713)	0.0742(0.00252)	0.0677(0.0027)
	gb	0.137(0.0146)	0.123(0.00838)	0.0908(0.00279)	0.0834(0.00240)
	en	0.123(0.0110)	0.115(0.00761)	0.0835(0.00262)	0.0768(0.00204)
Stroke	rf	0.974(0.00548)	0.941(0.00506)	0.822(0.00339)	0.374(0.0015)
	ab	0.940(0.0120)	0.910(0.0120)	0.813(0.0131)	0.378(0.00265)

lr	0.929(0.00793)	0.872(0.00678)	0.775(0.00413)	0.365(0.00164)
gb	0.868(0.0324)	0.818(0.0309)	0.696(0.0180)	0.351(0.00166)
en	0.848(0.00829)	0.836(0.00706)	0.694(0.00394)	0.345(0.000996)

Table B.2: **Precision at top 50, 100, 500, and N cases probabilities of phenotyping models.**

rf: Random Forest, *ab*= Adaboost, *lr*=Logistic regression with L1 penalty, *gb*=Gradient Boosting, *en*=Logistic Regression with elastic net penalty models. *Prec*: Precision. 95% confidence intervals

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Disease	Model	Sensitivity	Specificity	PPV	NPV
Ischemic Stroke	rf	0.347(0.00483)	0.996(0.000133)	0.00185(2.58e-05)	0.997(2.52e-05)
	ab	0.369(0.00744)	0.995(0.000256)	0.00196(3.99e-05)	0.997(3.86e-05)
	lr	0.362(0.00528)	0.995(0.000127)	0.00192(2.82e-05)	0.997(2.76e-05)
	gb	0.368(0.00868)	0.994(0.000354)	0.00196(4.67e-05)	0.997(4.50e-05)
	en	0.332(0.00624)	0.995(0.000195)	0.00177(3.35e-05)	0.996(3.24e-05)
SAH Stroke	rf	0.215(0.00503)	0.999(5.47e-05)	0.000354(8.28e-06)	0.999(8.21e-06)
	ab	0.272(0.00924)	0.999(7.14e-05)	0.000447(1.52e-05)	0.999(1.51e-05)
	lr	0.266(0.00764)	0.999(6.34e-05)	0.000437(1.26e-05)	0.999(1.25e-05)
	gb	0.204(0.00598)	0.999(9.43e-05)	0.000336(9.86e-06)	0.999(9.75e-06)
	en	0.201(0.00597)	0.999(0.000126)	0.000330(9.85e-06)	0.999(9.68e-06)
ICH Stroke	rf	0.133(0.00715)	0.998(0.000140)	0.000174(9.40e-06)	0.999(9.22e-06)
	ab	0.167(0.0113)	0.998(0.000219)	0.000220(1.49e-05)	0.999(1.47e-05)
	lr	0.177(0.0211)	0.995(0.000742)	0.000233(2.79e-05)	0.999(2.69e-05)
	gb	0.141(0.00950)	0.998(0.000268)	0.000185(1.25e-05)	0.999(1.22e-05)
	en	0.146(0.0123)	0.997(0.000398)	0.000192(1.62e-05)	0.999(1.57e-05)

Stroke	rf	0.377(0.00414)	0.989(0.000286)	0.00648(7.24e-05)	0.989(6.74e-05)
	ab	0.390(0.00559)	0.989(0.000379)	0.00671(9.76e-05)	0.990(9.17e-05)
	lr	0.399(0.00499)	0.987(0.000408)	0.00688(8.81e-05)	0.990(8.1e-05)
	gb	0.388(0.00462)	0.986(0.000373)	0.00670(8.15e-05)	0.989(7.51e-05)
	en	0.393(0.00425)	0.985(0.000336)	0.00678(7.51e-05)	0.990(6.90e-05)

Table B.3: **Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of phenotyping models.** *rf*: Random Forest, *ab*= Adaboost, *lr*=Logistic regression with L1 penalty, *gb*=Gradient Boosting, *en*=Logistic Regression with elastic net penalty models. *PPV*: Positive Predictive Value, *NPV*: Negative Predictive Value. 95% confidence intervals shown in parentheses

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Risk Factor GWAS	Phenotype	Model GWAS	Sample Cohort	GC(SE)	Z score	P value
CAD	Stroke	EN QTPhenProxy-QC1	UK Biobank	0.54(0.06)	8.53	1.44E-17
CAD	Stroke	EN QTPhenProxy-QC2	UK Biobank	0.46(0.07)	7.12	1.04E-12
CAD	Stroke	RF QTPhenProxy-QC1	UK Biobank	0.54(0.04)	13.38	8.40E-41
CAD	Stroke	Binary	MEGASTROKE	0.43(0.07)	6.11	1.03E-09
CAD	Stroke	Binary-QC1	UK Biobank	error-h2 is low (-0.0009)		
CAD	Stroke	Binary-QC2	UK Biobank	error-h2 is low (-0.0012)		
CAD	IscStroke	EN QTPhenProxy-QC1	UK Biobank	0.59(0.06)	9.16	5.29E-20
CAD	IscStroke	EN QTPhenProxy-QC2	UK Biobank	0.44(0.07)	6.74	1.60E-11
CAD	IscStroke	Binary	MEGASTROKE	0.43(0.07)	6.41	1.44E-10
CAD	IscStroke	Binary-QC1	UK Biobank	error-h2 is low (-8.5864e-05)		
CAD	IscStroke	Binary-QC2	UK Biobank	error-h2 is low (-0.0005)		
CAD	ICHStroke	EN QTPhenProxy-QC1	UK Biobank	0.10(0.08)	1.25	0.21
CAD	ICHStroke	EN QTPhenProxy-QC2	UK Biobank	0.04(0.08)	0.54	0.59

CAD	ICHStroke	EN QTPhenProxy-QC1	UK Biobank	-0.19(0.40)	-0.48	0.63
CAD	ICHStroke	EN QTPhenProxy-QC2	UK Biobank	-0.22(0.45)	-0.49	0.62
CAD	SAHStroke	EN QTPhenProxy-QC1	UK Biobank	-0.40(0.06)	-6.46	1.05E-10
CAD	SAHStroke	EN QTPhenProxy-QC2	UK Biobank	-0.37(0.06)	-5.98	2.19E-09
CAD	SAHStroke	Binary-QC1	UK Biobank	error-invalid value		
CAD	SAHStroke	Binary-QC2	UK Biobank	error-invalid value		
T2DM	Stroke	EN QTPhenProxy-QC1	UK Biobank	0.40(0.04)	9.11	8.50E-20
T2DM	Stroke	EN QTPhenProxy-QC2	UK Biobank	0.42(0.04)	9.46	3.11E-21
T2DM	Stroke	RF QTPhenProxy-QC1	UK Biobank	0.59(0.03)	22.67	9.69E-114
T2DM	Stroke	Binary	MEGASTROKE	0.34(0.04)	7.63	2.40E-14
T2DM	Stroke	Binary-QC1	UK Biobank	error-h2 is low (-0.0005)		
T2DM	Stroke	Binary-QC2	UK Biobank	error-h2 is low (-0.0009)		
T2DM	IscStroke	EN QTPhenProxy-QC1	UK Biobank	0.37(0.05)	7.69	1.44E-14
T2DM	IscStroke	EN QTPhenProxy-QC2	UK Biobank	0.37(0.04)	8.30	1.03E-16
T2DM	IscStroke	Binary	MEGASTROKE	0.31(0.05)	6.89	5.51E-12
T2DM	IscStroke	Binary-QC1	UK Biobank	error-h2 is low (-0.0006)		
T2DM	IscStroke	Binary-QC2	UK Biobank	error-h2 is low (-0.0011)		
T2DM	ICHStroke	EN QTPhenProxy-QC1	UK Biobank	0.21(0.06)	3.47	0.00
T2DM	ICHStroke	EN QTPhenProxy-QC2	UK Biobank	0.24(0.06)	4.21	2.57E-05
T2DM	ICHStroke	Binary-QC1	UK Biobank	0.12(0.16)	0.77	0.44
T2DM	ICHStroke	Binary-QC2	UK Biobank	0.11(0.16)	0.71	0.48
T2DM	SAHStroke	EN QTPhenProxy-QC1	UK Biobank	-0.54(0.04)	-13.96	2.69E-44
T2DM	SAHStroke	EN QTPhenProxy-QC2	UK Biobank	-0.54(0.04)	-13.77	3.79E-43
T2DM	SAHStroke	Binary-QC1	UK Biobank	error-invalid value		
T2DM	SAHStroke	Binary-QC2	UK Biobank	error-invalid value		
AF	Stroke	EN QTPhenProxy-QC1	UK Biobank	0.26(0.05)	5.75	9.15E-09
AF	Stroke	EN QTPhenProxy-QC2	UK Biobank	0.26(0.04)	6.01	1.81E-09

AF	Stroke	RF QTPhenProxy-QC1	UK Biobank	0.33(0.03)	12.78	2.20E-37
AF	Stroke	Binary	MEGASTROKE	0.39(0.04)	9.86	5.96E-23
AF	Stroke	Binary-QC1	UK Biobank	0.95(2.03)	0.47	0.64
AF	Stroke	Binary	QC2	error-invalid value		
AF	IscStroke	EN QTPhenProxy-QC1	UK Biobank	0.29(0.04)	6.75	1.44E-11
AF	IscStroke	EN QTPhenProxy-QC2	UK Biobank	0.27(0.04)	6.34	2.33E-10
AF	IscStroke	Binary	MEGASTROKE	0.36(0.04)	9.59	8.93E-22
AF	IscStroke	Binary-QC1	UK Biobank	0.76(1.80)	0.42	0.67
AF	IscStroke	Binary-QC2	UK Biobank	error-invalid value		
AF	ICHStroke	EN QTPhenProxy-QC1	UK Biobank	0.17(0.05)	3.39	0.00
AF	ICHStroke	EN QTPhenProxy-QC2	UK Biobank	0.18(0.06)	3.16	0.00
AF	ICHStroke	Binary-QC1	UK Biobank	0.50(1.07)	0.47	0.64
AF	ICHStroke	Binary-QC2	UK Biobank	0.51(1.01)	0.50	0.61
AF	SAHStroke	EN QTPhenProxy-QC1	UK Biobank	-0.25(0.04)	-6.28	3.46E-10
AF	SAHStroke	EN QTPhenProxy-QC2	UK Biobank	-0.24(0.04)	-6.21	5.18E-10
AF	SAHStroke	Binary-QC1	UK Biobank	error-invalid value		
AF	SAHStroke	Binary-QC2	UK Biobank	error-invalid value		
LDL	Stroke	EN QTPhenProxy-QC1	UK Biobank1	0.09(0.05)	1.95	0.05
LDL	Stroke	EN QTPhenProxy-QC2	UK Biobank	0.11(0.05)	2.22	0.03
LDL	Stroke	RF QTPhenProxy-QC1	UK Biobank	0.13(0.03)	4.17	2.99E-05
LDL	Stroke	Binary	MEGASTROKE	0.03(0.05)	0.69	0.49
LDL	Stroke	Binary-QC1	UK Biobank	error-invalid value		
LDL	Stroke	Binary-QC2	UK Biobank	error-h2 is low (-0.0012)		
LDL	IscStroke	EN QTPhenProxy-QC1	UK Biobank	0.11(0.06)	1.88	0.06
LDL	IscStroke	EN QTPhenProxy-QC2	UK Biobank	0.12(0.05)	2.28	0.02
LDL	IscStroke	Binary	MEGASTROKE	0.05(0.05)	1.14	0.25
LDL	IscStroke	Binary-QC1	UK Biobank	error-invalid value		

LDL	IscStroke	Binary-QC2	UK Biobank	error-h2 is low (-0.0002)		
LDL	ICHStroke	EN QTPhenProxy-QC1	UK Biobank	0.06(0.06)	1.12	0.26
LDL	ICHStroke	EN QTPhenProxy-QC2	UK Biobank	0.03(0.05)	0.56	0.57
LDL	ICHStroke	Binary-QC1	UK Biobank	-0.25(0.50)	-0.49	0.62
LDL	ICHStroke	Binary-QC2	UK Biobank	-0.29(0.64)	-0.45	0.65
LDL	SAHStroke	EN QTPhenProxy-QC1	UK Biobank	-0.18(0.04)	-4.30	1.70E-05
LDL	SAHStroke	EN QTPhenProxy-QC2	UK Biobank	-0.17(0.04)	-4.19	2.74E-05
LDL	SAHStroke	Binary-QC1	UK Biobank	error-h2 is low (-0.0003)		
LDL	SAHStroke	Binary-QC2	UK Biobank	error-invalid value		
WMH	Stroke	EN QTPhenProxy-QC1	UK Biobank	0.50(0.14)	3.64	0.00
WMH	Stroke	EN QTPhenProxy-QC2	UK Biobank	0.41(0.11)	3.61	0.00
WMH	Stroke	RF QTPhenProxy-QC1	UK Biobank	0.31(0.08)	3.89	9.89E-05
WMH	Stroke	Binary	MEGASTROKE	0.42(0.11)	3.74	0.00
WMH	Stroke	Binary-QC1	UK Biobank	error-h2 is low (0.0005)		
WMH	Stroke	Binary-QC2	UK Biobank	error-invalid value		
WMH	IscStroke	EN QTPhenProxy-QC1	UK Biobank	0.54(0.13)	4.09	4.35E-05
WMH	IscStroke	EN QTPhenProxy-QC2	UK Biobank	0.37(0.10)	3.68	0.00
WMH	IscStroke	Binary	MEGASTROKE	0.36(0.10)	3.47	0.00
WMH	IscStroke	Binary-QC1	UK Biobank	error-h2 is low (0.0005)		
WMH	IscStroke	Binary-QC2	UK Biobank	error-invalid value		
WMH	ICHStroke	EN QTPhenProxy-QC1	UK Biobank	0.29(0.14)	2.10	0.04
WMH	ICHStroke	EN QTPhenProxy-QC2	UK Biobank	0.46(0.17)	2.78	0.01
WMH	ICHStroke	Binary-QC1	UK Biobank	0.49(1.21)	0.41	0.68
WMH	ICHStroke	Binary-QC2	UK Biobank	0.54(1.10)	0.49	0.63
WMH	SAHStroke	EN QTPhenProxy-QC1	UK Biobank	0.00(0.11)	0.04	0.97
WMH	SAHStroke	EN QTPhenProxy-QC2	UK Biobank	0.00(0.11)	-0.02	0.99
WMH	SAHStroke	Binary-QC1	UK Biobank	error-h2 is low (0.0009)		

WMH	SAHStroke	Binary-QC2	UK Biobank	error-invalid value
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Table B.4: **Genetic Correlation of Stroke Risk Factor GWAS with QTPhenProxy Models and MEGASTROKE.** GC: Genetic Correlation, SE: Standard Error, CAD: Coronary Artery Disease, T2DM: Type 2 Diabetes Mellitus, AF: Atrial Fibrillation, LDL: Low-Density Lipoproteins WMH: White Matter Hyperintensities

701

702 *Appendix B.1. Supplementary Information Table Titles*

- 703 1. LD Hub GC correlation results of QTPhenProxy Stroke EN Model, QC1
- 704 quality control.
- 705 2. LD Hub GC correlation results of QTPhenProxy Stroke EN Model, QC2
- 706 quality control.
- 707 3. GWAS resources for Supplementary Table B.4.

708 *Appendix B.2. Data and Code Availability Statements*

709 The EBI-GWAS marker set- MedDRA mappings and code generated in this

710 study will be made publicly available online at <https://github.com/pthangaraj/QTPhenProxy>.

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Train

UK Biobank
337,147 patients

EHR Data	
Patient 1 codes ...	...
Patient 2 codes ...	...
Patient 3 codes ...	...
Patient 4 codes ...	...

Supervised ML Classifiers

Predictions

Stroke?
0.986
0.246
0.997
0.112
0.496
0.356
0.877
0.012
0.960

Assign Stroke Probabilities to
UK Biobank Patients after training
Machine Learning models on
EHR Data

Predictions
(Quantitative Trait)

Stroke?
0.986
0.246
0.997
0.112
0.496
0.356
0.877
0.012
0.960

+

QTPhenProxy GWAS

+

Diagnosis Code
(Binary Trait)

Stroke?
1
0
1
0
0
0
1
0
1

Binary GWAS

Use Stroke Probabilities
as Quantitative Trait,
Compare GWAS to
Binary Trait GWAS