Supplemental Materials

for

Prioritization of regulatory variants with tissue-specific function in the non-coding regions of human genome

Shengcheng Dong[1] and Alan P. Boyle[1,2*]

1. Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI

2. Department of Human Genetics, University of Michigan, Ann Arbor, MI

Supplemental Tables

Supplemental Table S1. Number of allele specific TF binding (ASB) training SNVs in 6 cell lines.

Cell type name	# of ASB SNVs	# of control SNVs
GM12878	1,848	12,382
A549	215	1,357
H1hESC	1,464	6,525
HepG2	2,717	24,479
K562	767	12,635
MCF7	653	8,034

Supplemental Table S2. Feature list in random forest models of TURF.

Generic features	
TF binding sites from ChIP-seq	Binary variable
DNase I hypersensitive sites from DNase-seq	Binary variable
DNase footprints	Binary variable
DNase footprints with matched TF ChIP-seq peaks	Binary variable
TF motifs from PWM matching	Binary variable
TF motifs from PWM matching with matched TF ChIP-seq peaks	Binary variable
Information content change of two alleles in PWM matching	Numerical variable
Information content change of two alleles in PWM matching with matched TF ChIP-seq peaks	Numerical variable
eQTLs	Binary variable
Quantiles (25%,50%,75% and 100%) and variance of ChIP-seq signals across all available ChIP-seq experiments from ENCODE	Numerical variables
Functional significance score from *DeepSEA*	Numerical variable
Tissue-specific features (in final ensemble model)	
H3K4me1 peaks from ChIP-seq	Binary variable
H3K4me3 peaks from ChIP-seq	Binary variable
H3K27ac peaks from ChIP-seq	Binary variable
H3K36me3 peaks from ChIP-seq	Binary variable
H3K27me3 peaks from ChIP-seq	Binary variable
DNase I hypersensitive sites from DNase-seq	Binary variable
DNase footprints	Binary variable

Supplemental Table S3. Feature importance of TURF generic scores. The importance is calculated based on mean decrease of impurity from the random forest model.

Feature name	Importance
CHIP	0.124607
DNASE	0.033935
PWM	0.018686
FOOTPRINT	0.008609
EQTL_2	0.004167
PWM_matched	0.005055
FOOTPRINT_matched	0.001454
IC_change	0.050415
IC_matched_change	0.021396
funsig	0.122206
ChIP_var	0.149313
ChIP_max	0.167037
ChIP_quantile1	0.097849
ChIP_quantile2	0.090261
ChIP_quantile3	0.105011

Supplemental Table S4. Comparison of performance on cell type-specific predictions for MPRA variants and ASB SNVs.

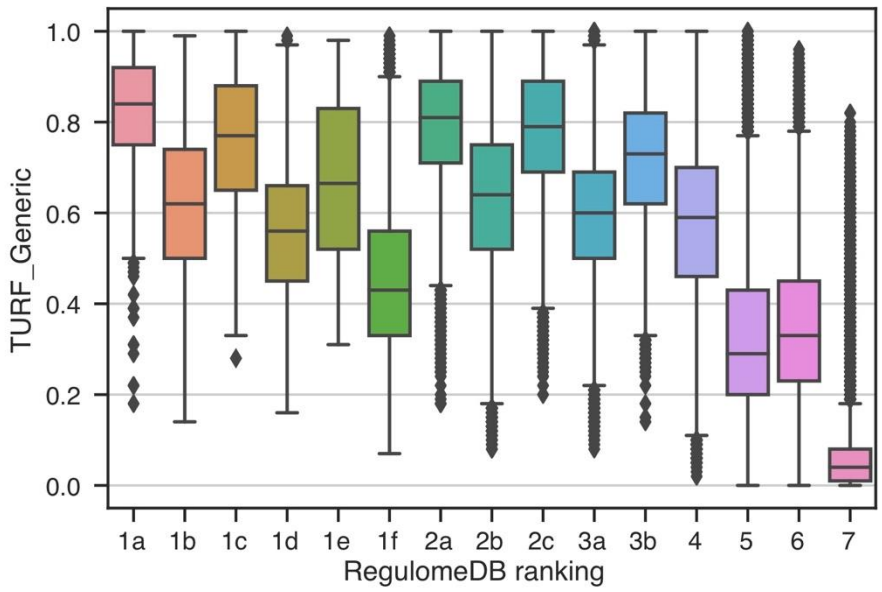
Method	AUPR	AUROC	Correlation
Test on MPRA variants in E116 (GM12878)			
TURF_Tissue-Specific	0.548	0.731	0.450
TURF_Generic	0.536	0.740	0.447
GenoNet	0.536	0.723	0.442
DeepSEA	0.451	0.671	0.115
GenoSkyline	0.394	0.673	0.352
CADD	0.240	0.566	0.082
TURF_Ensemble (trained from ASB SNVs)	0.484	0.724	0.393
Test on MPRA variants in E118 (HepG2)			
TURF_Tissue-Specific	0.571	0.765	0.423
TURF_Generic	0.502	0.733	0.372
GenoNet	0.572	0.757	0.429
DeepSEA	0.401	0.667	0.166
GenoSkyline	0.326	0.628	0.225
CADD	0.332	0.607	0.152
TURF_Ensemble (trained from ASB SNVs)	0.479	0.728	0.357
Test on MPRA variants in E123 (K562)			
TURF_Tissue-Specific	0.441	0.681	0.344
TURF_Generic	0.400	0.664	0.294
GenoNet	0.420	0.706	0.340
DeepSEA	0.290	0.607	0.099

GenoSkyline	0.284	0.659	0.274
CADD	0.212	0.539	0.046
TURF_Ensemble (trained from ASB SNVs)	0.329	0.676	0.253
Test on ASB SNVs in GM12878			
TURF_Ensemble	0.511	0.894	0.538
TURF_Tissue-Specific	0.510	0.882	0.537
TURF_Generic	0.284	0.822	0.390
GenoSkyline	0.246	0.743	0.340
DeepSEA	0.222	0.688	0.190
GenoNet	0.129	0.685	0.158
Test on ASB SNVs in HepG2			
TURF_Ensemble	0.355	0.857	0.406
TURF_Tissue-Specific	0.353	0.831	0.401
TURF_Generic	0.221	0.797	0.323
DeepSEA	0.226	0.611	0.138
GenoSkyline	0.212	0.582	0.133
GenoNet	0.161	0.654	0.134
Test on ASB SNVs in K562			
TURF_Ensemble	0.316	0.847	0.376
TURF_Tissue-Specific	0.313	0.815	0.366
TURF_Generic	0.193	0.782	0.301
GenoNet	0.140	0.644	0.113
GenoSkyline	0.090	0.628	0.144
DeepSEA	0.062	0.572	0.054

Test on ASB SNVs in A549

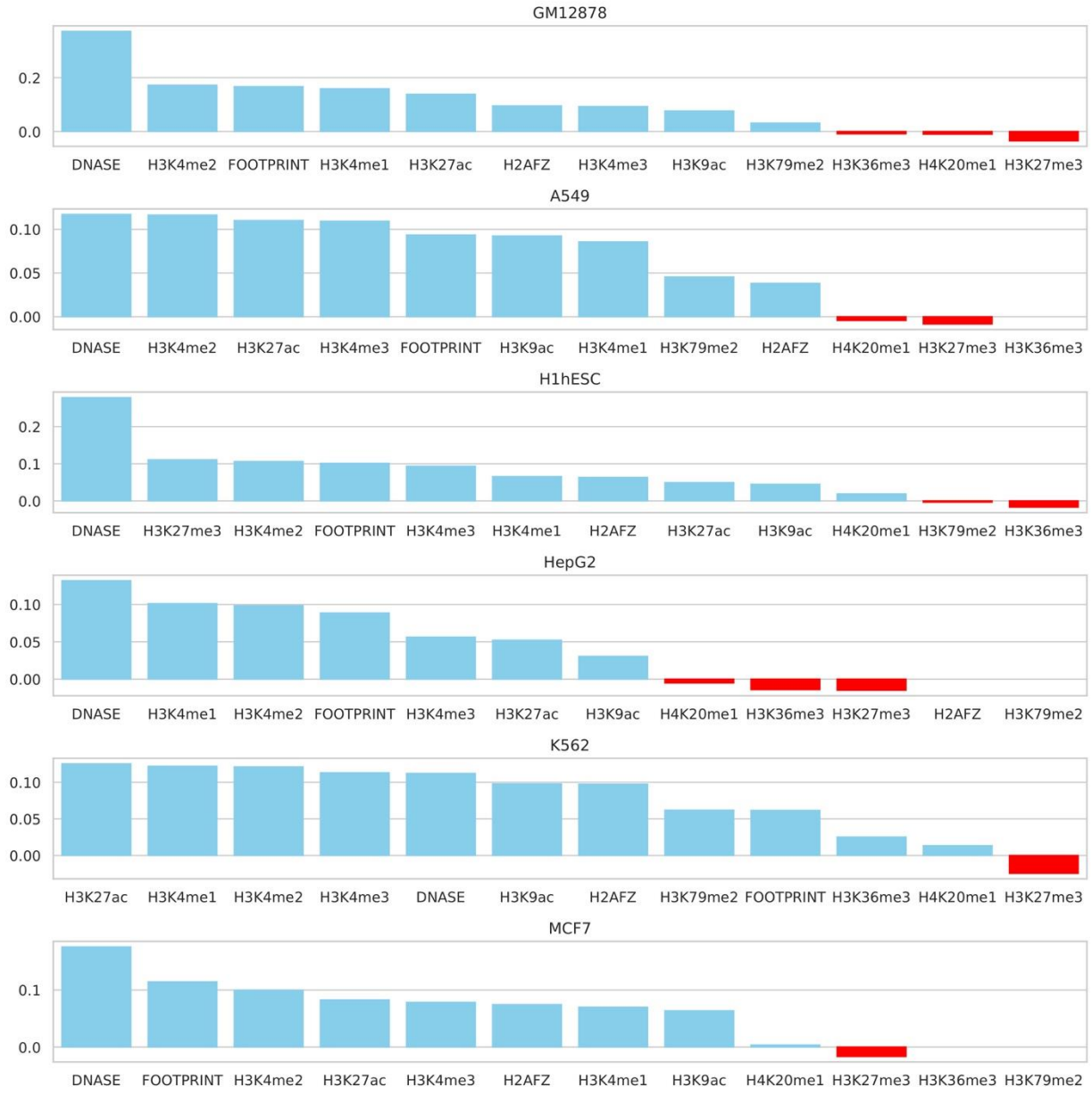
TURF_Ensemble	0.313	0.872	0.369
TURF_Tissue-Specific	0.315	0.833	0.369
TURF_Generic	0.158	0.796	0.256
DeepSEA	0.052	0.760	0.119
GenoNet	0.030	0.690	0.094
GenoSkyline	0.022	0.632	0.049

Supplemental Figures

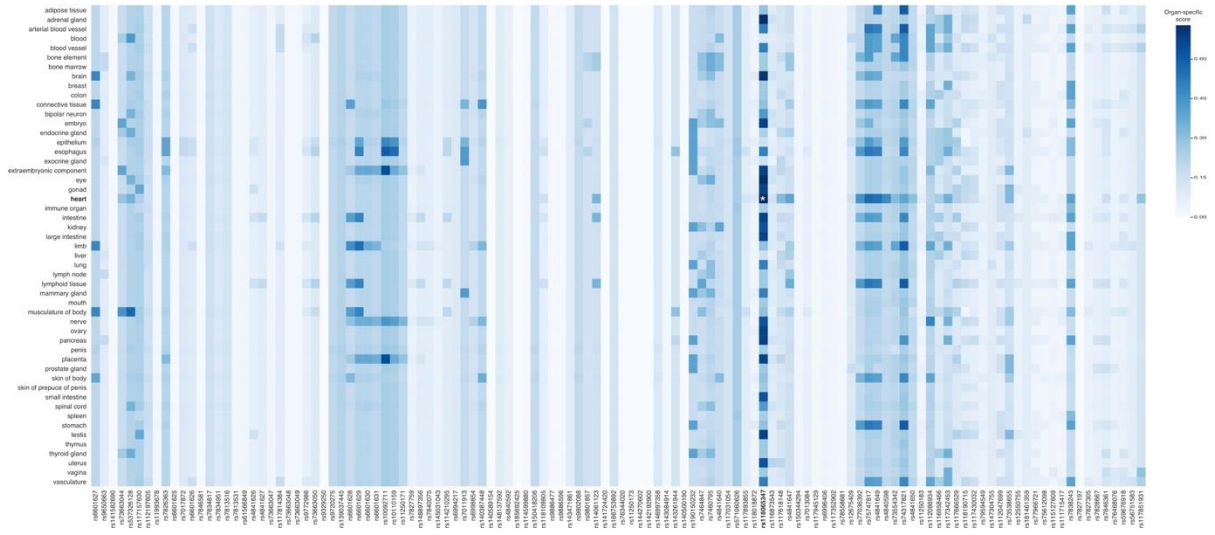


Supplemental Figure S1. Boxplot of TURF generic scores VS RegulomeDB ranking scores on 10,422,004 common SNVs from dbSNP153. X axis represents the original ranking scores from RegulomeDB v1.1, y axis represents the TURF generic scores from random forest model.

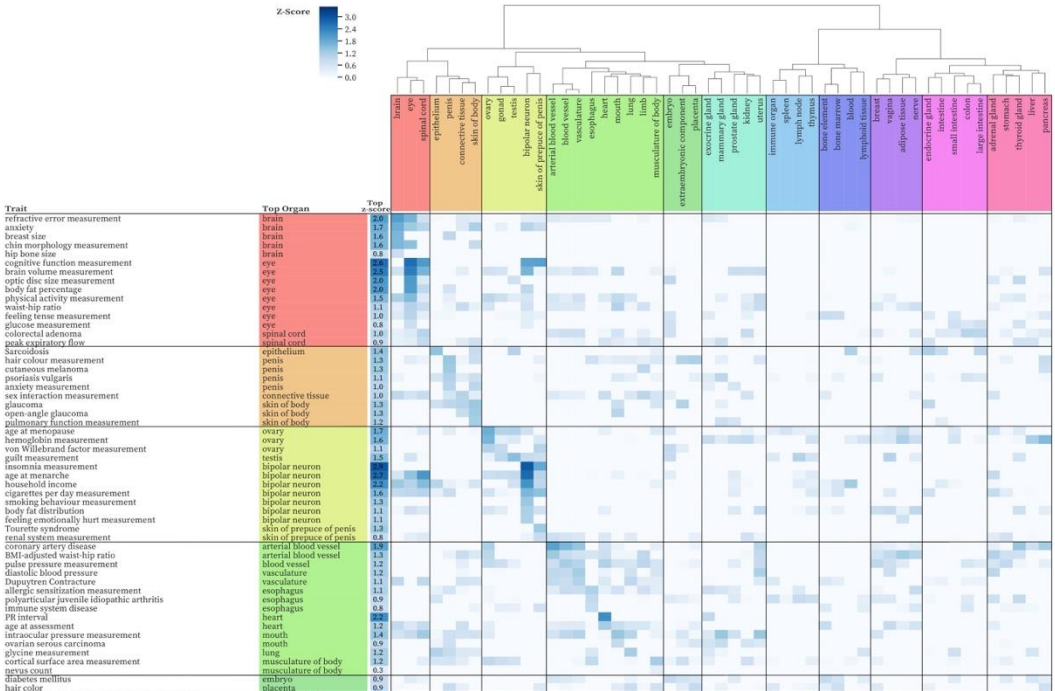
Supplemental Figure S2. Pearson correlation of labels and tissue-specific features in three MPRA datasets (E116: GM12878; E118: HepG2; E123: K562). Blue bars represent positive correlations while red bars represent negative correlations.



Supplementary Figure 3. Pearson correlation of labels and tissue-specific features in 6 ASB datasets. Blue bars represent positive correlations while red bars represent negative correlations.

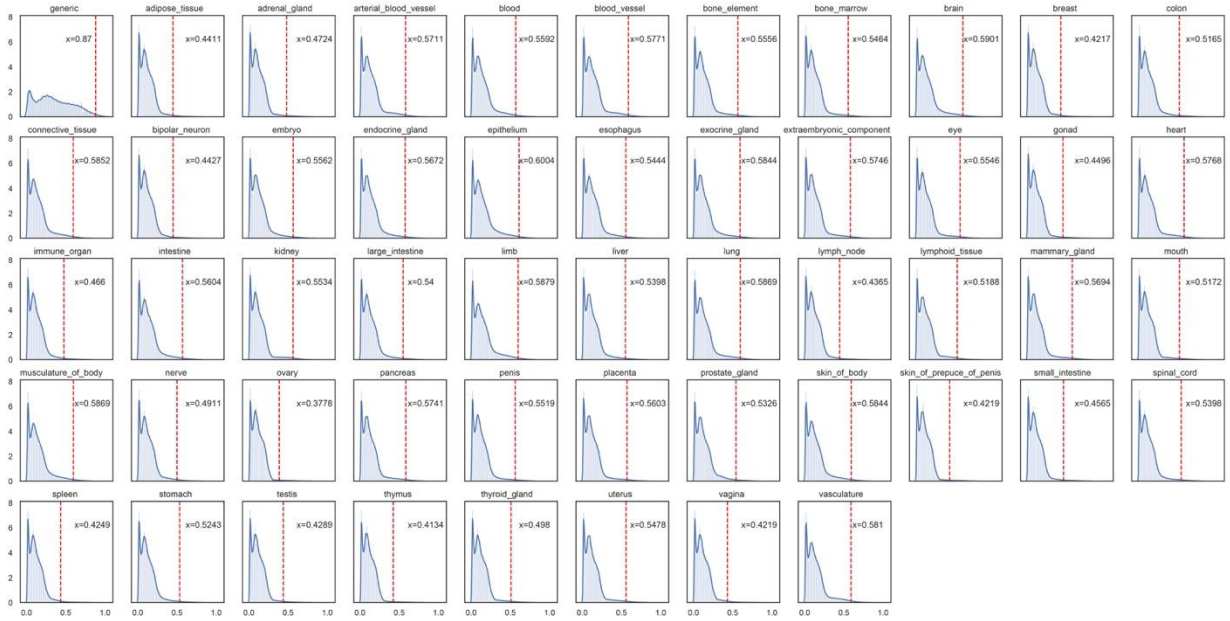


Supplemental Figure S4. Organ-specific scores of variants in the *GATA4* locus. rs118065347 has the top organ-specific score in heart compared to other candidate SNPs found through genome-wide association scan on bicuspid aortic valve cases. rs118065347 was shown to have hear-specific regulatory functionality from a previous study Yang et al. 2017.



Trait	Top Organ	Top z-score
refractive error measurement	brain	2.0
anxiety	brain	1.7
breast size	brain	1.6
chin morphology measurement	brain	1.6
hip bone size	brain	0.8
cognitive function measurement	eye	2.6
brain volume measurement	eye	2.5
optic disc size measurement	eye	2.0
body fat percentage	eye	2.0
physical activity measurement	eye	1.5
waist-hip ratio	eye	1.1
feeling tense measurement	eye	1.0
glucose measurement	eye	0.8
colorectal adenoma	spinal cord	1.0
peak expiratory flow	spinal cord	0.9
Sarcoidosis	epithelium	1.4
hair colour measurement	penis	1.3
cutaneous melanoma	penis	1.3
psoriasis vulgaris	penis	1.1
anxiety measurement	penis	1.0
sex interaction measurement	connective tissue	1.0
glaucoma	skin of body	1.3
open-angle glaucoma	skin of body	1.3
pulmonary function measurement	skin of body	1.2
age at menopause	ovary	1.7
hemoglobin measurement	ovary	1.6
von Willebrand factor measurement	ovary	1.1
guilt measurement	testis	1.5
insomnia measurement	bipolar neuron	2.9
age at menarche	bipolar neuron	2.2
household income	bipolar neuron	2.2
cigarettes per day measurement	bipolar neuron	1.6
smoking behaviour measurement	bipolar neuron	1.3
body fat distribution	bipolar neuron	1.1
feeling emotionally hurt measurement	bipolar neuron	1.1
Tourette syndrome	skin of prepuce of penis	1.3
renal system measurement	skin of prepuce of penis	0.8
coronary artery disease	arterial blood vessel	1.9
BMI-adjusted waist-hip ratio	arterial blood vessel	1.3
pulse pressure measurement	blood vessel	1.2
diastolic blood pressure	vasculature	1.2
Dupuytren Contracture	vasculature	1.1
allergic sensitization measurement	esophagus	1.1
polyarticular juvenile idiopathic arthritis	esophagus	0.9
immune system disease	esophagus	0.8
PR interval	heart	2.2
age at assessment	heart	1.2
intraocular pressure measurement	mouth	1.4
ovarian serous carcinoma	mouth	0.9
glycine measurement	lung	1.2
cortical surface area measurement	musculature of body	1.2
nevus count	musculature of body	0.3
diabetes mellitus	embryo	0.9
hair color	placenta	0.9
longitudinal alcohol consumption measurement	exocrine gland	2.3
HMG CoA reductase inhibitor use measurement	exocrine gland	1.4
insulin measurement	exocrine gland	1.1
balding measurement	prostate gland	1.8
blood urea nitrogen measurement	kidney	2.4
glomerular filtration rate	kidney	2.1
magnesium measurement	kidney	1.4
mean arterial pressure	kidney	1.3
homocysteine measurement	kidney	1.0
heel bone mineral density	uterus	2.3
atrial fibrillation	uterus	1.3
cardiovascular disease	uterus	1.1
autoimmune disease	immune organ	2.3
autoimmune thyroid disease	immune organ	2.0
psoriatic arthritis	immune organ	2.0
basophil count	spleen	2.3
monocyte count	spleen	2.2
granulocyte percentage of myeloid white cells	spleen	2.1
monocyte percentage of leukocytes	spleen	2.1
leukocyte count	spleen	2.0
neutrophil count	spleen	1.9
lymphocyte percentage of leukocytes	spleen	1.9
celiac disease	spleen	1.8
myeloid white cell count	spleen	1.7
allergic rhinitis	spleen	1.7
granulocyte count	spleen	1.6
red blood cell distribution width	spleen	1.6
Eczema	spleen	1.5
apolipoprotein B measurement	spleen	1.4
mean corpuscular hemoglobin concentration	spleen	1.2
HbA1c measurement	spleen	1.1
systemic scleroderma	spleen	1.1
multiple sclerosis	lymph node	2.9
systemic lupus erythematosus	lymph node	2.7
adult onset asthma	lymph node	2.6
chronic lymphocytic leukemia	lymph node	2.4
atopic asthma	lymph node	2.4
eosinophil count	lymph node	2.4
eosinophil percentage of granulocytes	lymph node	2.2
neutrophil percentage of granulocytes	lymph node	2.2
eosinophil percentage of leukocytes	lymph node	2.0
allergy	lymph node	1.9
family history of Alzheimer's disease	lymph node	1.8
albumin:globulin ratio measurement	lymph node	1.7
inflammatory bowel disease	lymph node	1.6
serum non-albumin protein measurement	lymph node	1.6
Vitiligo	lymph node	1.5
alkaline phosphatase measurement	lymph node	1.4
platelet component distribution width	lymph node	1.4
Hodgkins lymphoma	lymph node	1.3
Inhalant adrenergic use measurement	lymph node	1.3
rheumatoid factor negative	lymph node	0.9
oligoarticular juvenile idiopathic arthritis	lymph node	0.8
Thyroid preparation use measurement	thymus	2.4
lymphocyte count	thymus	2.2
hypothyroidism	thymus	2.2
ulcerative colitis	thymus	1.8
psoriasis	thymus	1.6
keratinocyte carcinoma	thymus	1.4
basal cell carcinoma	thymus	1.2
respiratory system disease	thymus	0.9
lower urinary tract symptom	bone element	1.3
platelet count	bone marrow	2.0
mean corpuscular hemoglobin	bone marrow	1.7
mean corpuscular volume	bone marrow	1.7
platelet crit	bone marrow	1.5
mean platelet volume	bone marrow	1.3
central corneal thickness	breast	1.5
bladder carcinoma	breast	0.4
body height	vagina	3.0
appendicular lean mass	vagina	2.0
blood protein measurement	vagina	1.8
birth weight	vagina	1.7
erythrocyte count	vagina	1.7
reticulocyte count	vagina	1.5
neutrophil percentage of leukocytes	adipose tissue	1.3
high density lipoprotein cholesterol measurement	adipose tissue	1.3
macula measurement	nerve	1.3
Progressive supranuclear palsy	nerve	1.2
triglyceride measurement	intestine	1.5
corneal topography	intestine	1.1
apolipoprotein A 1 measurement	small intestine	1.9
P wave duration	small intestine	0.8
ankylosing spondylitis	colon	2.0
sclerosing cholangitis	colon	1.9
Crohn's disease	colon	1.8
N-glycan measurement	colon	1.2
cataract	large intestine	0.9
Agents acting on the renin-angiotensin system use measurement	adrenal gland	1.9
systolic blood pressure	adrenal gland	1.7
creatine kinase measurement	adrenal gland	1.4
Diuretic use measurement	adrenal gland	1.4
narcolepsy with cataplexy	stomach	0.7
eye measurement	thyroid gland	1.0
hematocrit	thyroid gland	0.8
low density lipoprotein cholesterol measurement	liver	2.1
total cholesterol measurement	liver	2.1
alcohol drinking	liver	2.1
C-reactive protein measurement	liver	2.0
gallstones	liver	1.8
fibrinogen measurement	liver	1.1
esophageal carcinoma	liver	0.2
Calcium channel blocker use measurement	pancreas	1.8
idiopathic pulmonary fibrosis	pancreas	1.4
Drugs used in diabetes use measurement	pancreas	1.0

Supplemental Figure S5. Enrichment of regulatory variants with high organ-specific scores over variants associated with diverse traits. Only organ-trait pairs with z-scores higher than 0 and passing multiple test correction (FDR threshold of 5%) are shown.



Supplemental Figure S6. Distribution of TURF generic and organ-specific scores on 3,102,261 GM12878 SNVs. The red vertical dashed line represents the 99th percentile score in each subplot.