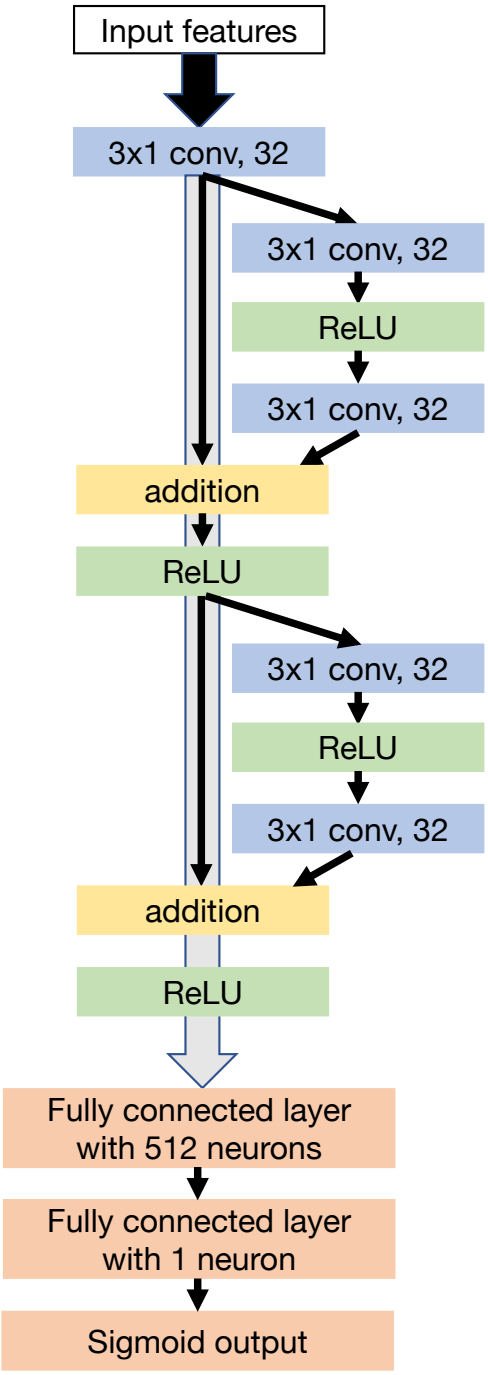
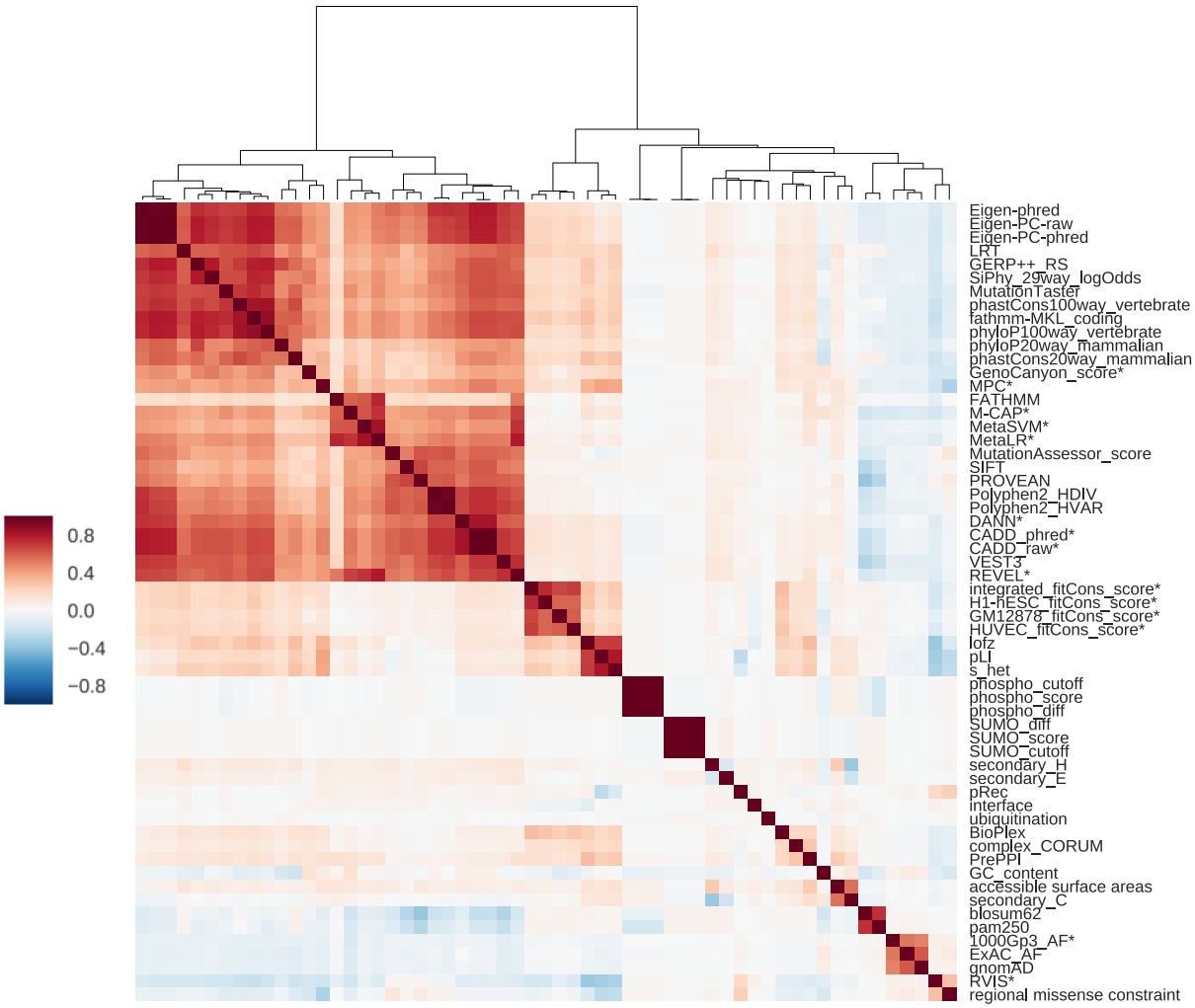
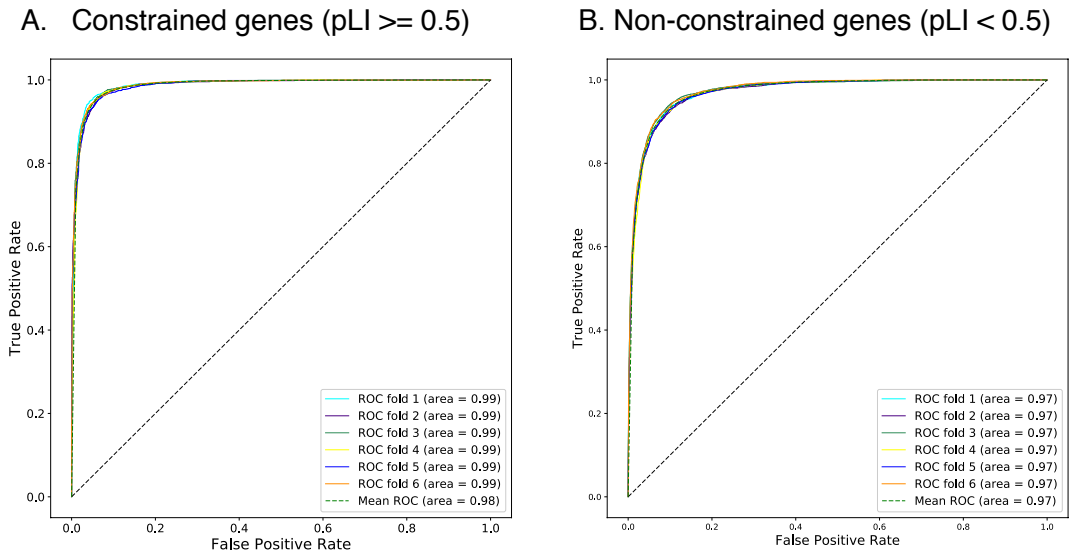


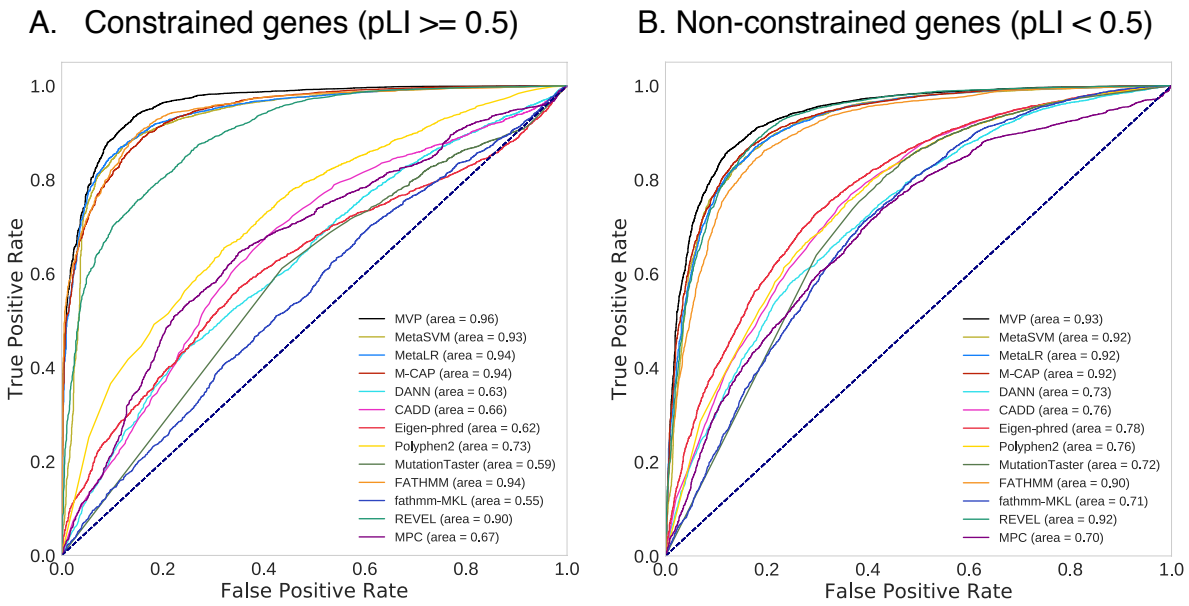
Supplementary Figure S1. MVP ResNet architecture. Building blocks are arranged as shown. Parameters and dimensions of input and output is indicated in the brackets. Blue boxes are convolutional filters, green boxes are ReLU activation, yellow boxes are addition of 2 layers output, orange boxes are fully connected layers.



Supplementary Figure S2. Heatmap and hierarchical clustering of features correlation among features and published methods in the training dataset. Color key indicates the level of pearson correlation between features and predictors. Columns are ordered by hierarchical clustering. Predictors followed with * are not used in training.



Supplementary Figure S3. ROC curves for MVP score with 6-fold cross validation in the training dataset. (A) Performance evaluation in constrained genes. (B) Performance evaluation in non-constrained genes. The performance of MVP in each fold is evaluated by the ROC curve and AUC score indicated in parenthesis. Higher AUC score indicates better performance.



Supplementary Figure S4. ROC curves for existing prediction scores and the MVP score in VariBench testing data sets. (A) Performance evaluation in constrained genes. (B) Performance evaluation in non-constrained genes. The performance of each predictor is evaluated by the ROC curve and AUC score indicated in parenthesis. Higher AUC score indicates better performance.

Supplementary Table S1. Estimated number of pathogenic missense de novo mutations using published methods by recommended parameters.

		Congenital heart disease (CHD)		Autism spectrum disorder (ASD)	
	threhold to define pathogenic missense variants	# of risk variants	True positive rate	# of risk variants	True positive rate
All missense		268	0.17	287	0.13
Polyphen (HDIV)	> 0.5	176	0.22	195	0.18
SIFT	< 0.05	162	0.18	201	0.16
CADD	> 15	202	0.17	252	0.15
Meta-SVM	> 0	123	0.33	110	0.23
M-CAP	> 0.025	217	0.25	203	0.18
REVEL	> 0.5	136	0.33	164	0.29

Supplementary Table S6. Synonymous rate ratio in cases verses controls of de novo mutations.

	Synonymous variants counts	Rate ratio to controls
Autism spectrum disorder(ASD)	1026	1.027
Congenital heart disease(CHD)	701	1.049
Simons Simplex Collection unaffected siblings (controls)	483	N/A