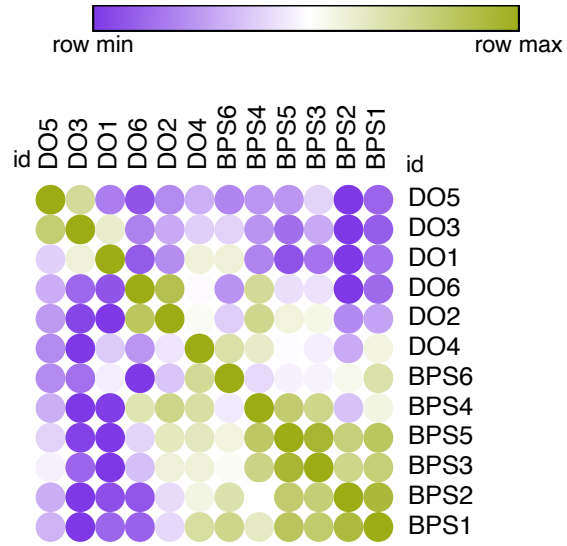
A


row min
row max
id
DO5
DO3
DO1
DO6
DO2
DO4
BPS6
BPS4
BPS5
BPS3
BPS2
BPS1

B

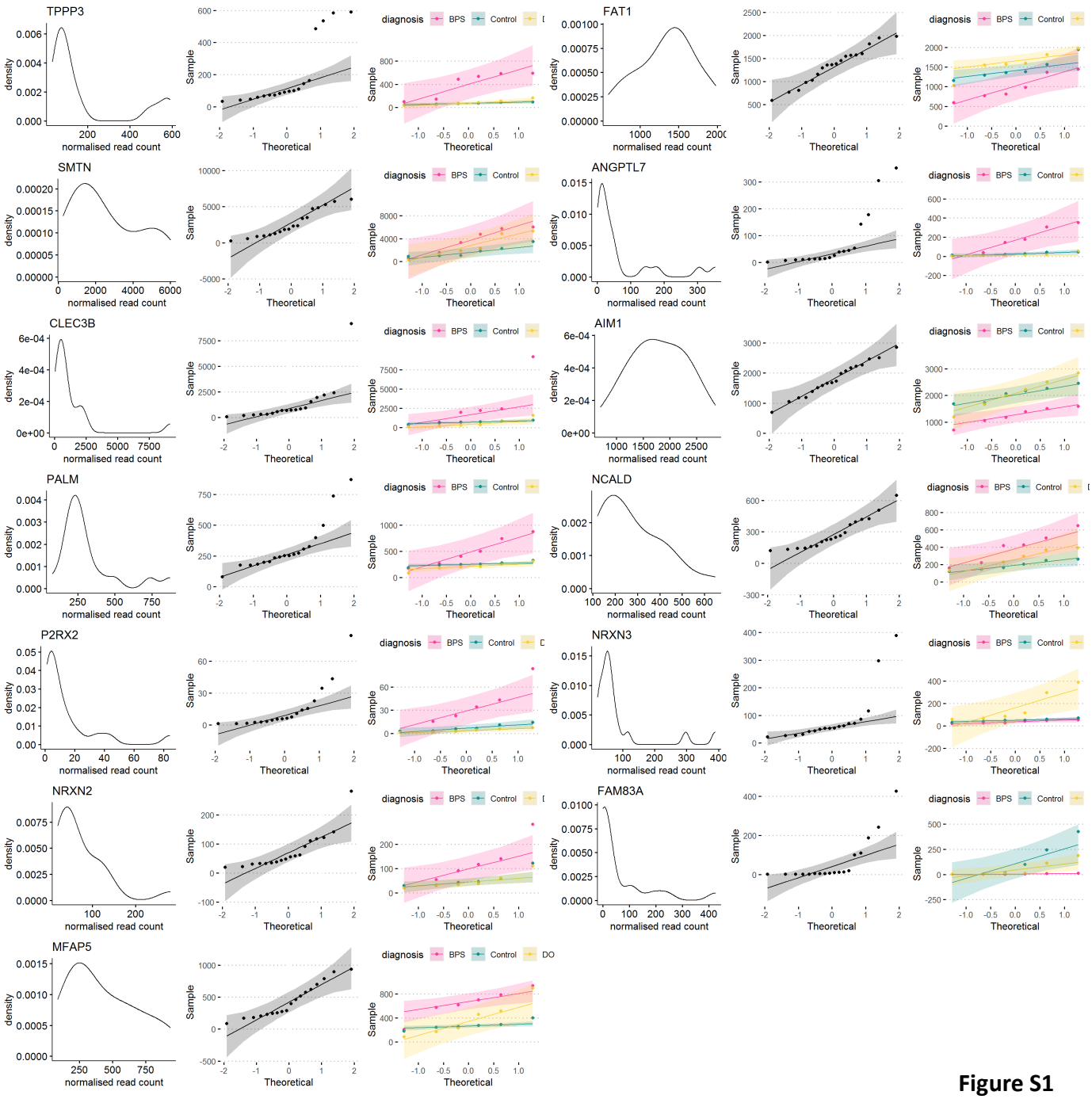
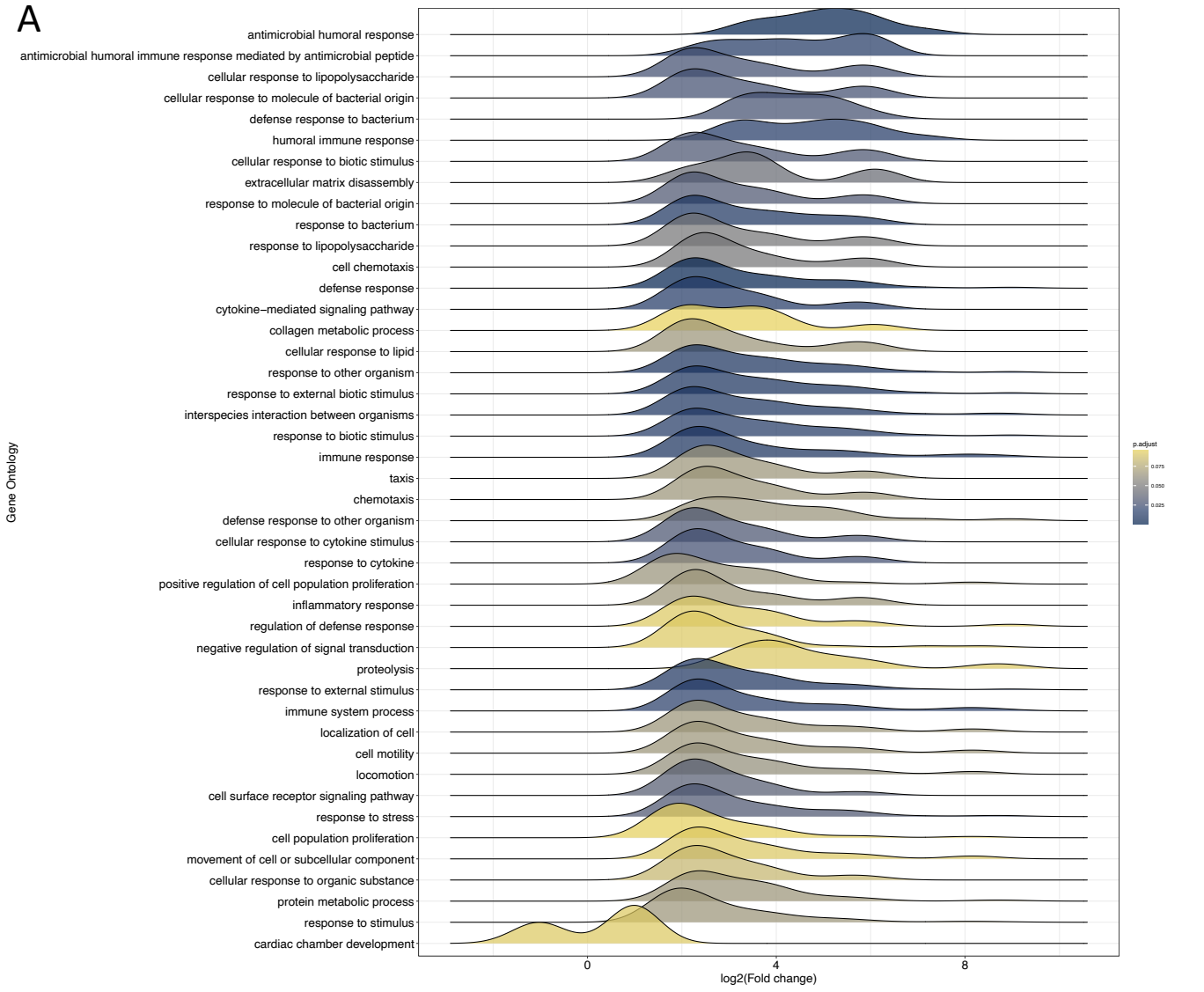

TPPP3
FAT1
SMTN
ANGPTL7
CLEC3B
AIM1
PALM
NCALD
P2RX2
NRXN3
NRXN2
FAM83A
MFAP5
density
normalised read count
Sample
Theoretical
diagnosis
BPS
Control
DO

Figure S1


A
antimicrobial humoral response
antimicrobial humoral immune response mediated by antimicrobial peptide
cellular response to lipopolysaccharide
cellular response to molecule of bacterial origin
defense response to bacterium
humoral immune response
cellular response to biotic stimulus
extracellular matrix disassembly
response to molecule of bacterial origin
response to bacterium
response to lipopolysaccharide
cell chemotaxis
defense response
cytokine−mediated signaling pathway
collagen metabolic process
cellular response to lipid
response to other organism
response to external biotic stimulus
interspecies interaction between organisms
response to biotic stimulus
immune response
taxis
chemotaxis
defense response to other organism
cellular response to cytokine stimulus
response to cytokine
positive regulation of cell population proliferation
inflammatory response
regulation of defense response
negative regulation of signal transduction
proteolysis
response to external stimulus
immune system process
localization of cell
cell motility
locomotion
cell surface receptor signaling pathway
response to stress
cell population proliferation
movement of cell or subcellular component
cellular response to organic substance
protein metabolic process
response to stimulus
cardiac chamber development
Gene Ontology
0
4
8
log2(Fold change)
p.adjust
0.075
0.050
0.025

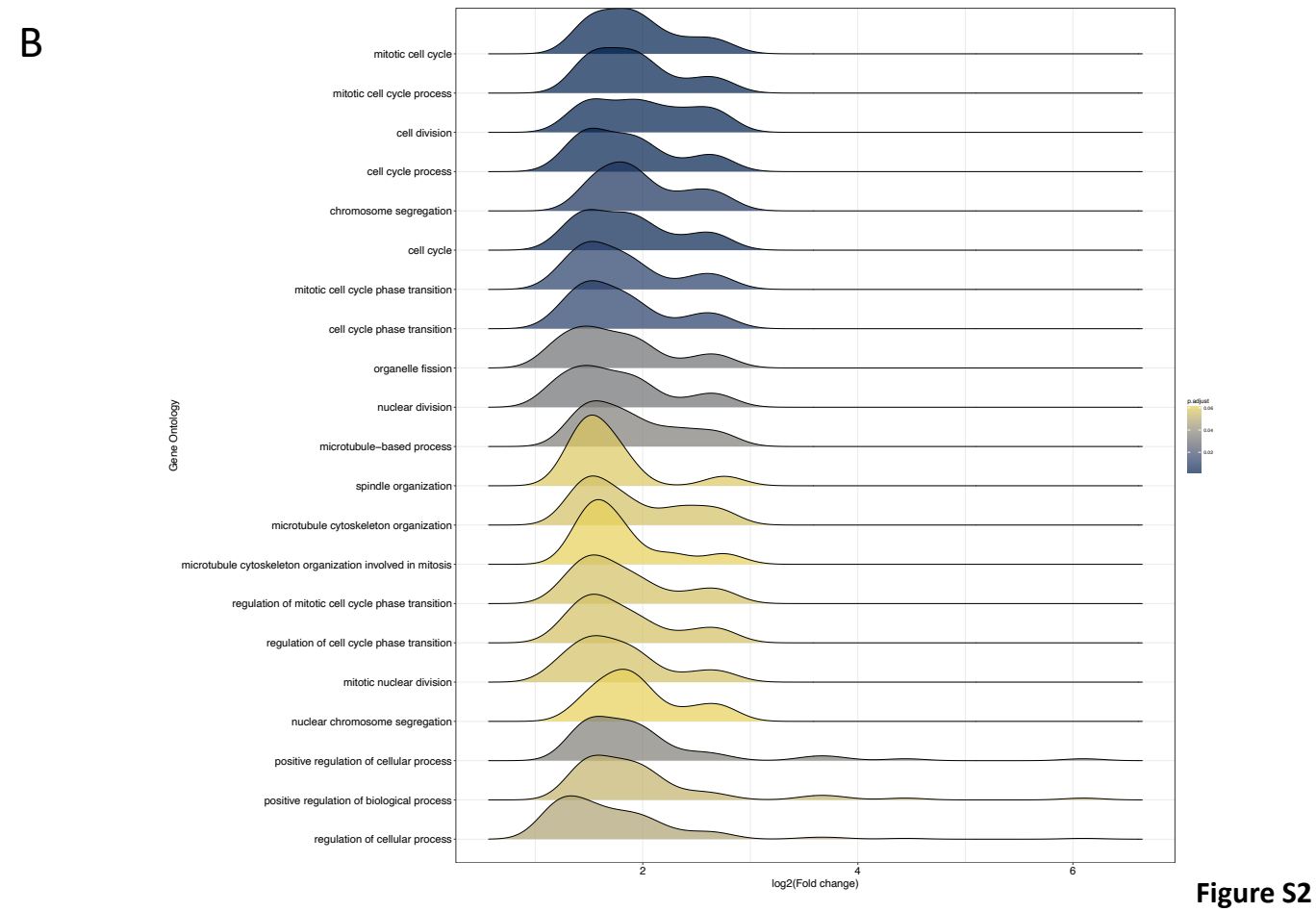

B
mitotic cell cycle
mitotic cell cycle process
cell division
cell cycle process
chromosome segregation
cell cycle
mitotic cell cycle phase transition
cell cycle phase transition
organelle fission
nuclear division
microtubule−based process
spindle organization
microtubule cytoskeleton organization
microtubule cytoskeleton organization involved in mitosis
regulation of mitotic cell cycle phase transition
regulation of cell cycle phase transition
mitotic nuclear division
nuclear chromosome segregation
positive regulation of cellular process
positive regulation of biological process
regulation of cellular process
Gene Ontology
2
4
6
log2(Fold change)
p.adjust

Figure S2

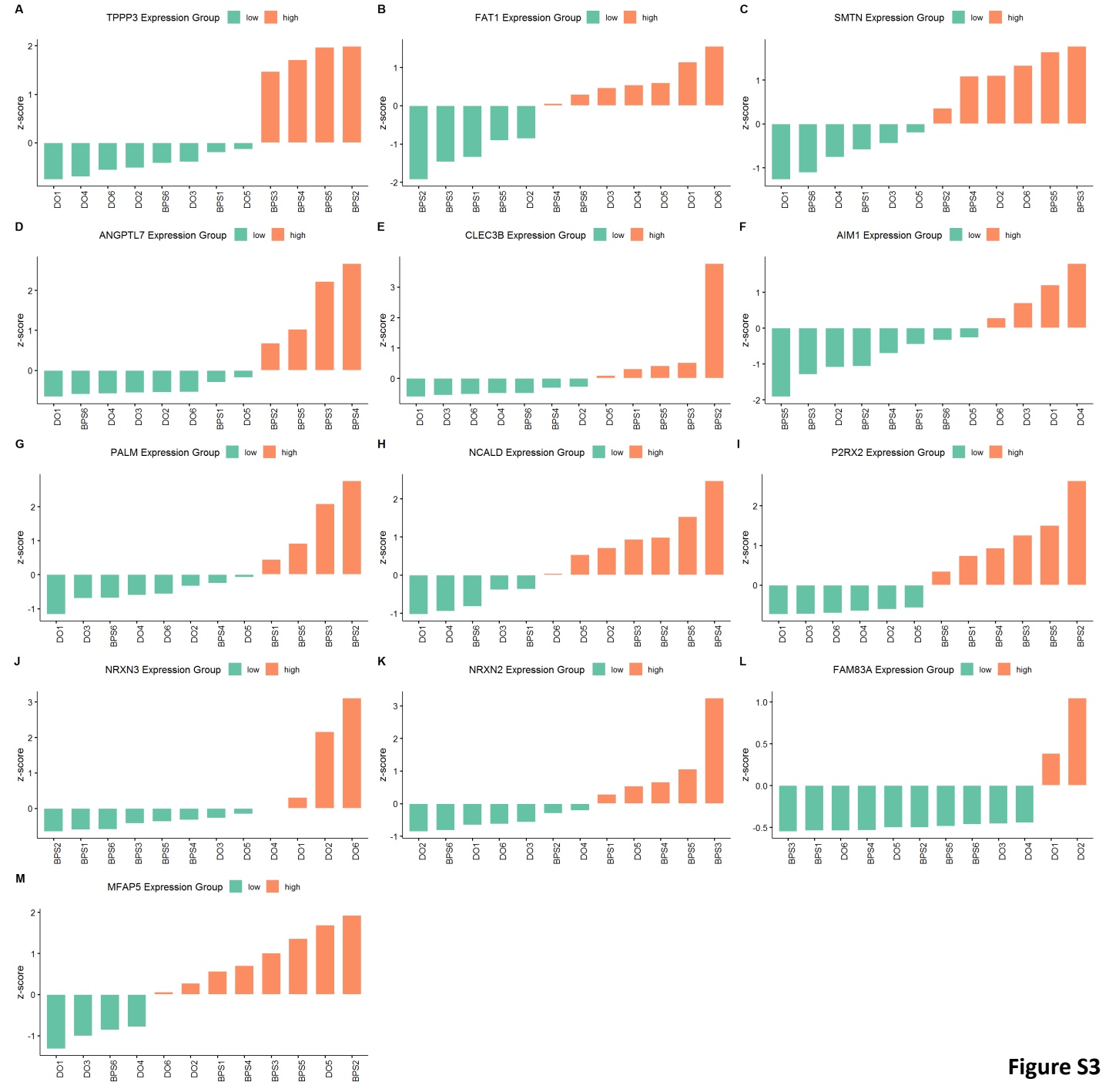

A
TPPP3 Expression Group
low
high
z-score
DO1 DO4 DO6 DO2 BPS6 DO3 BPS1 DO5 BPS3 BPS4 BPS5 BPS2
B
FAT1 Expression Group
low
high
z-score
BPS2 BPS3 BPS1 BPS5 DO2 BPS4 BPS6 DO3 DO4 DO5 DO1 DO6
C
SMTN Expression Group
low
high
z-score
DO1 BPS6 DO4 BPS1 DO3 DO5 BPS2 BPS4 DO2 DO6 BPS5 BPS3
D
ANGPTL7 Expression Group
low
high
z-score
DO1 BPS6 DO4 DO3 DO2 DO6 BPS1 DO5 BPS2 BPS5 BPS3 BPS4
E
CLEC3B Expression Group
low
high
z-score
DO1 DO3 DO6 DO4 BPS6 BPS4 DO2 DO5 BPS1 BPS5 BPS3 BPS2
F
AIM1 Expression Group
low
high
z-score
BPS5 BPS3 DO2 BPS2 BPS4 BPS1 BPS6 DO5 DO6 DO3 DO1 DO4
G
PALM Expression Group
low
high
z-score
DO1 DO3 BPS6 DO4 DO6 DO2 BPS4 DO5 BPS1 BPS5 BPS3 BPS2
H
NCALD Expression Group
low
high
z-score
DO1 DO4 BPS6 DO3 BPS1 DO6 DO5 DO2 BPS3 BPS2 BPS5 BPS4
I
P2RX2 Expression Group
low
high
z-score
DO1 DO3 DO6 DO4 DO2 DO5 BPS6 BPS1 BPS4 BPS3 BPS5 BPS2
J
NRXN3 Expression Group
low
high
z-score
BPS2 BPS1 BPS6 BPS3 BPS5 BPS4 DO3 DO5 DO4 DO1 DO2 DO6
K
NRXN2 Expression Group
low
high
z-score
DO2 BPS6 DO1 DO6 DO3 BPS2 DO4 BPS1 DO5 BPS4 BPS5 BPS3
L
FAM83A Expression Group
low
high
z-score
BPS3 BPS1 DO6 BPS4 DO5 BPS2 BPS5 BPS6 DO3 DO4 DO1 DO2
M
MFAP5 Expression Group
low
high
z-score
DO1 DO3 BPS6 DO4 DO6 DO2 BPS1 BPS4 BPS3 BPS5 DO5 BPS2

Figure S3

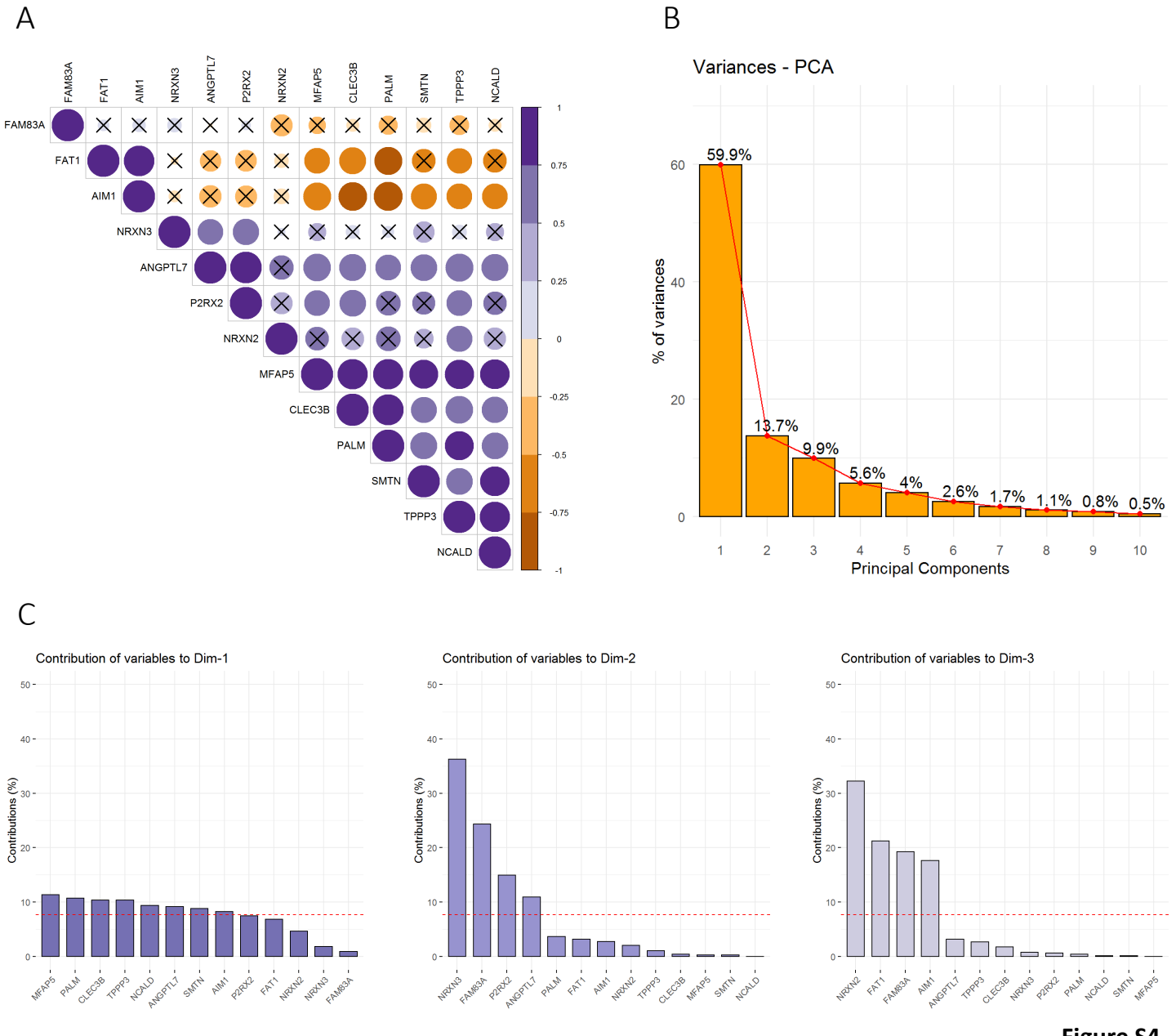

A
FAM83A
FAT1
AIM1
NRXN3
ANGPTL7
P2RX2
NRXN2
MFAP5
CLEC3B
PALM
SMTN
TPPP3
NCALD
1
0.75
0.5
0.25
0
-0.25
-0.5
-0.75
-1
B
Variances - PCA
% of variances
Principal Components
59.9%
13.7%
9.9%
5.6%
4%
2.6%
1.7%
1.1%
0.8%
0.5%
C
Contribution of variables to Dim-1
Contribution of variables to Dim-2
Contribution of variables to Dim-3
Contributions (%)
MFAP5 PALM CLEC3B TPPP3 NCALD ANGPTL7 SMTN AIM1 P2RX2 FAT1 NRXN2 NRXN3 FAM83A
NRXN3 FAM83A P2RX2 ANGPTL7 PALM FAT1 AIM1 NRXN2 TPPP3 CLEC3B MFAP5 SMTN NCALD
NRXN2 FAT1 FAM83A AIM1 ANGPTL7 TPPP3 CLEC3B NRXN3 P2RX2 PALM NCALD SMTN MFAP5

Figure S4

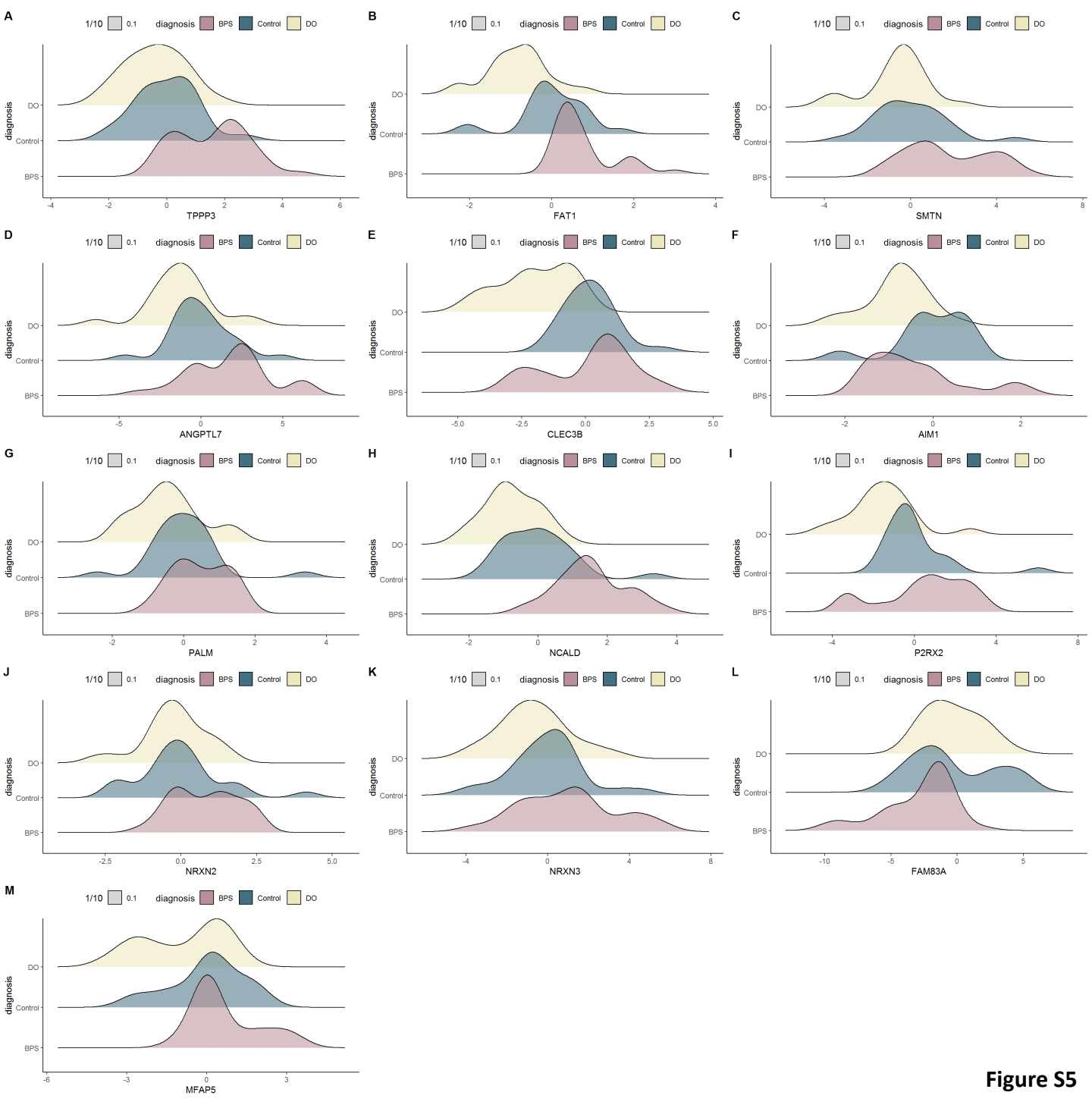

A
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-4 -2 0 2 4 6
TPPP3
B
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-2 0 2 4
FAT1
C
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-4 0 4 8
SMTN
D
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-5 0 5
ANGPTL7
E
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-5.0 -2.5 0.0 2.5 5.0
CLEC3B
F
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-2 0 2
AIM1
G
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-2 0 2 4
PALM
H
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-2 0 2 4
NCALD
I
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-4 0 4 8
P2RX2
J
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-2.5 0.0 2.5 5.0
NRXN2
K
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-4 0 4 8
NRXN3
L
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-10 -5 0 5
FAM83A
M
1/10 0.1 diagnosis BPS Control DO
diagnosis
DO
Control
BPS
-6 -3 0 3
MFAP5

Figure S5

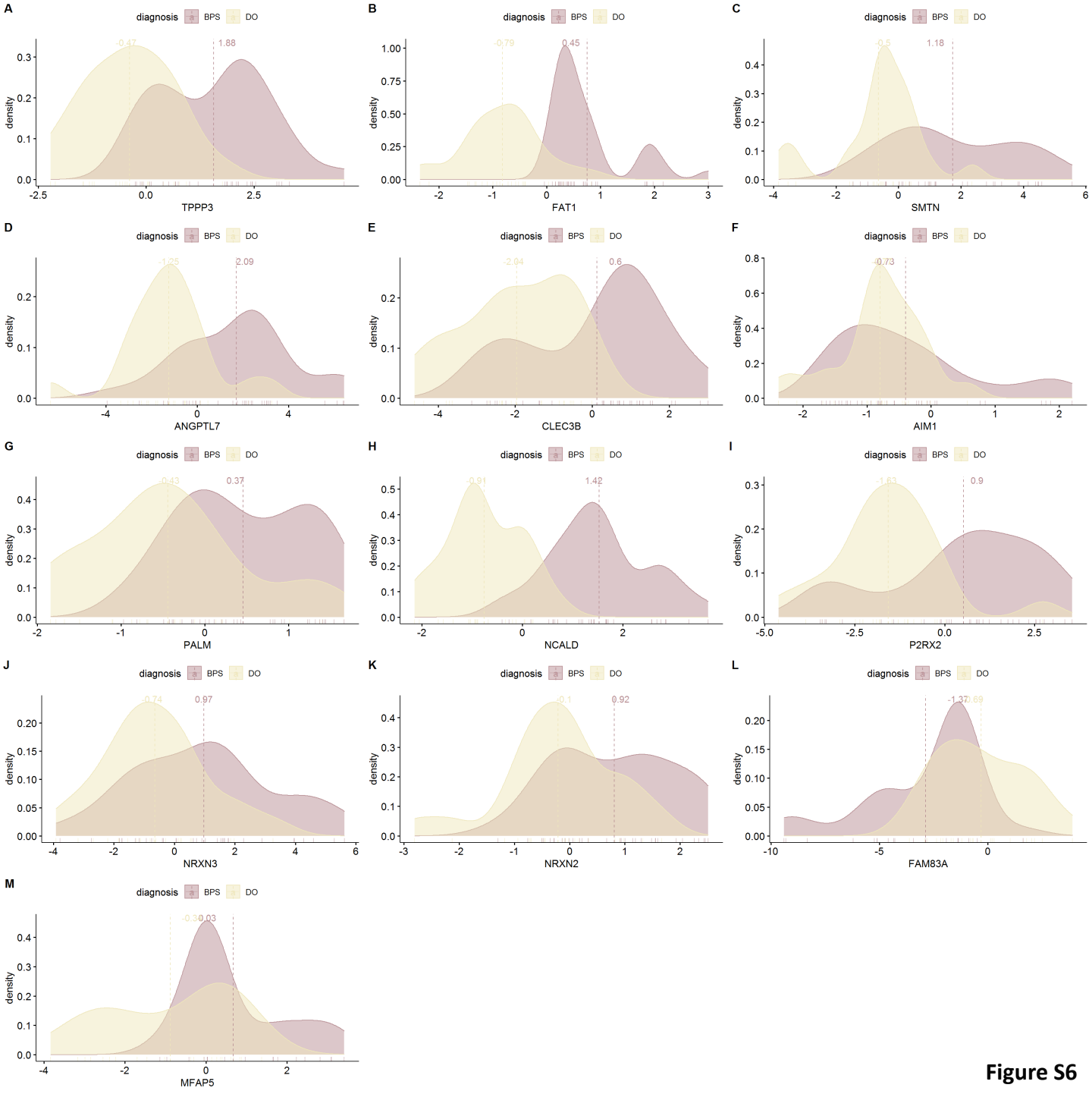

A
diagnosis BPS DO
-0.47
1.88
density
TPPP3
B
diagnosis BPS DO
-0.79
0.45
density
FAT1
C
diagnosis BPS DO
-0.5
1.18
density
SMTN
D
diagnosis BPS DO
-1.25
2.09
density
ANGPTL7
E
diagnosis BPS DO
-2.04
0.6
density
CLEC3B
F
diagnosis BPS DO
-0.73
density
AIM1
G
diagnosis BPS DO
-0.43
0.37
density
PALM
H
diagnosis BPS DO
-0.91
1.42
density
NCALD
I
diagnosis BPS DO
-1.63
0.9
density
P2RX2
J
diagnosis BPS DO
-0.74
0.97
density
NRXN3
K
diagnosis BPS DO
-0.1
0.92
density
NRXN2
L
diagnosis BPS DO
-1.37
-0.69
density
FAM83A
M
diagnosis BPS DO
-0.3
0.03
density
MFAP5

Figure S6

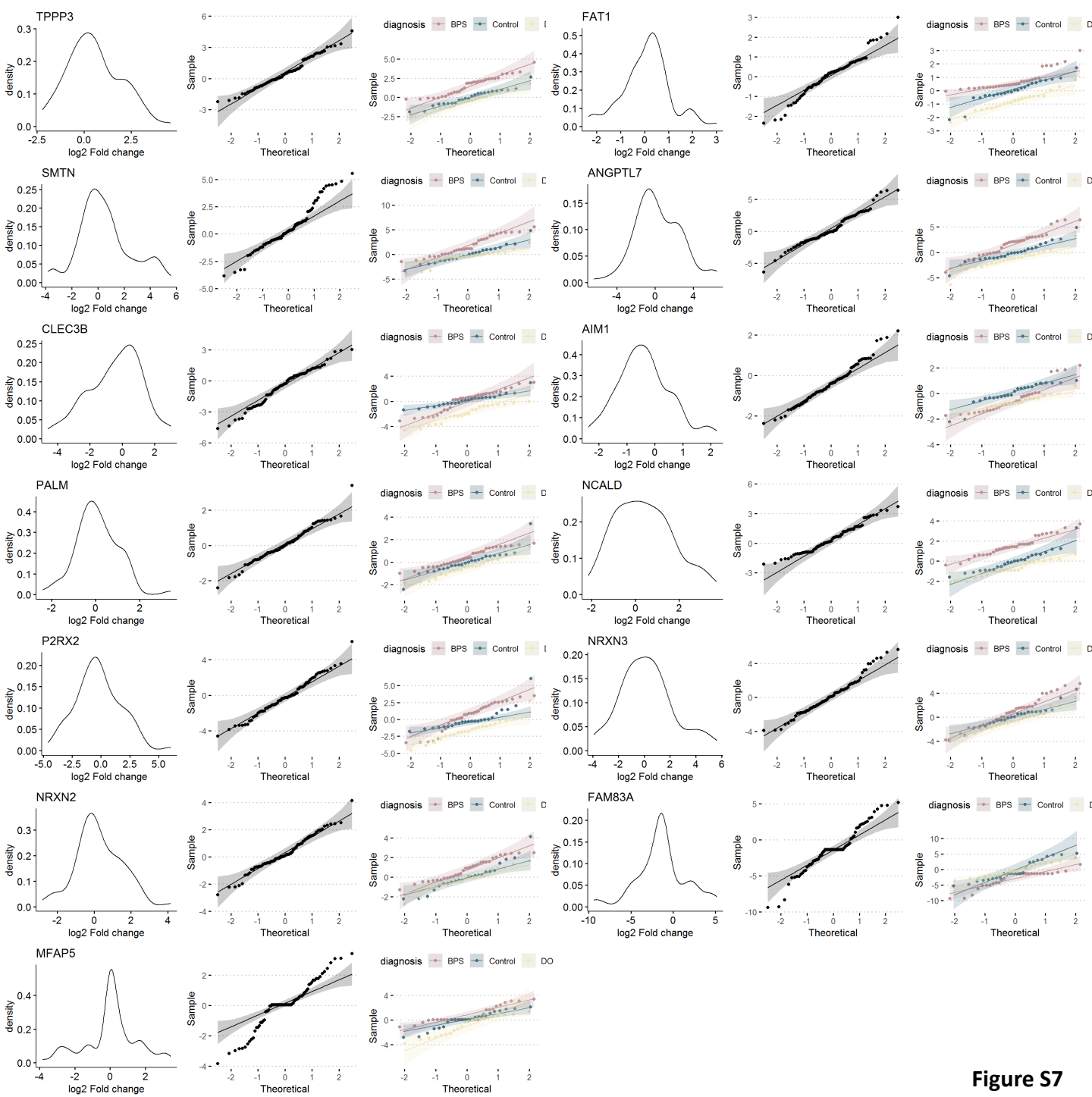

TPPP3
density
log2 Fold change
Sample
Theoretical
diagnosis
BPS
Control
FAT1
SMTN
ANGPTL7
CLEC3B
AIM1
PALM
NCALD
P2RX2
NRXN3
NRXN2
FAM83A
MFAP5
DO

Figure S7

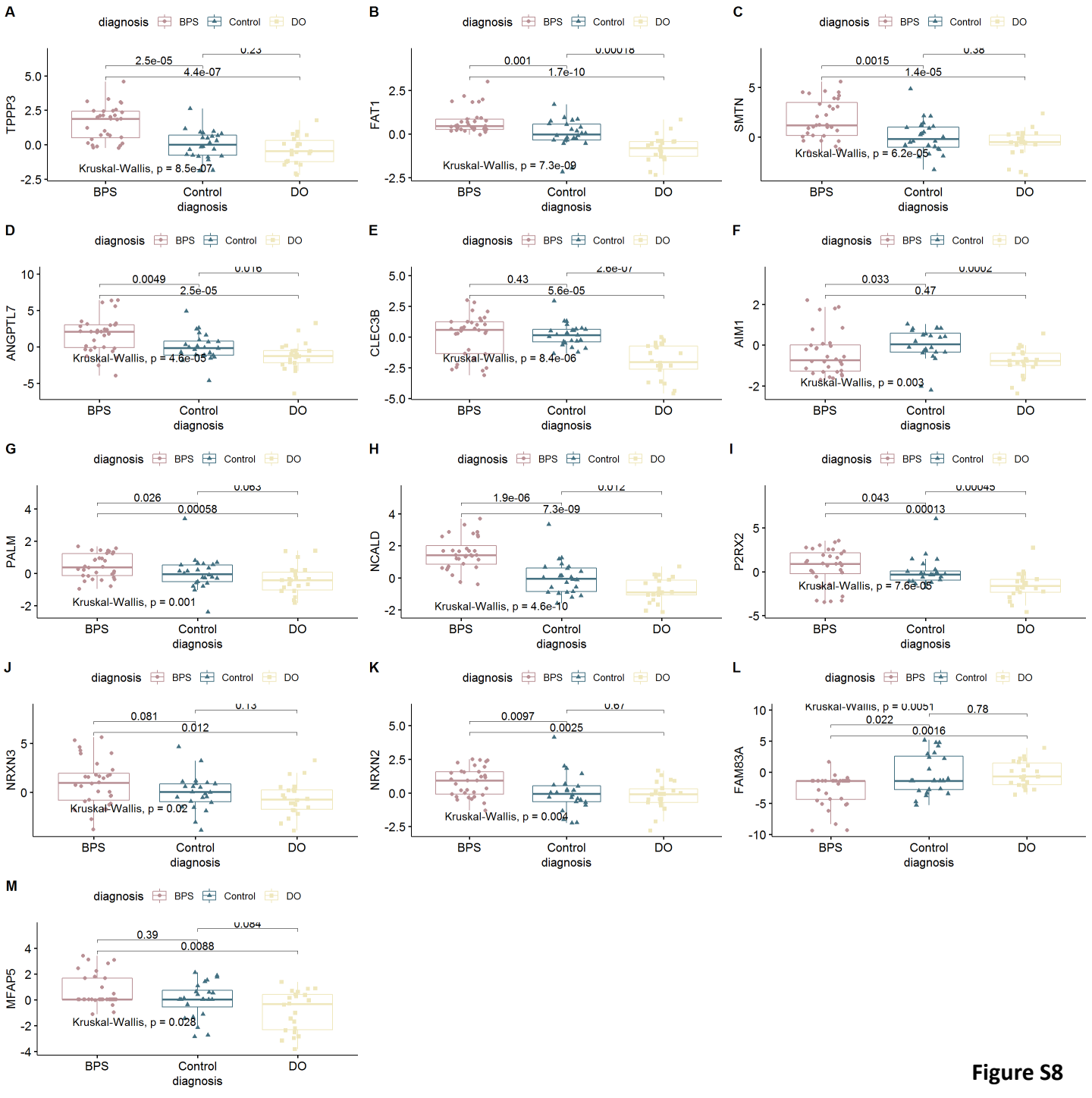

A
diagnosis BPS Control DO
TPPP3
2.5e-05
4.4e-07
Kruskal-Wallis, p = 8.5e-07
BPS Control DO
diagnosis
B
diagnosis BPS Control DO
FAT1
0.001
1.7e-10
Kruskal-Wallis, p = 7.3e-09
BPS Control DO
diagnosis
C
diagnosis BPS Control DO
SMTN
0.0015
1.4e-05
Kruskal-Wallis, p = 6.2e-05
BPS Control DO
diagnosis
D
diagnosis BPS Control DO
ANGPTL7
0.0049
2.5e-05
Kruskal-Wallis, p = 4.6e-05
BPS Control DO
diagnosis
E
diagnosis BPS Control DO
CLEC3B
0.43
5.6e-05
Kruskal-Wallis, p = 8.4e-06
BPS Control DO
diagnosis
F
diagnosis BPS Control DO
AIM1
0.033
0.47
Kruskal-Wallis, p = 0.003
BPS Control DO
diagnosis
G
diagnosis BPS Control DO
PALM
0.026
0.00058
Kruskal-Wallis, p = 0.001
BPS Control DO
diagnosis
H
diagnosis BPS Control DO
NCALD
1.9e-06
7.3e-09
Kruskal-Wallis, p = 4.6e-10
BPS Control DO
diagnosis
I
diagnosis BPS Control DO
P2RX2
0.043
0.00013
Kruskal-Wallis, p = 7.6e-05
BPS Control DO
diagnosis
J
diagnosis BPS Control DO
NRXN3
0.081
0.012
Kruskal-Wallis, p = 0.02
BPS Control DO
diagnosis
K
diagnosis BPS Control DO
NRXN2
0.0097
0.0025
Kruskal-Wallis, p = 0.004
BPS Control DO
diagnosis
L
diagnosis BPS Control DO
FAM83A
0.022
0.0016
0.78
BPS Control DO
diagnosis
M
diagnosis BPS Control DO
MFAP5
0.39
0.0088
Kruskal-Wallis, p = 0.028
BPS Control DO
diagnosis

Figure S8

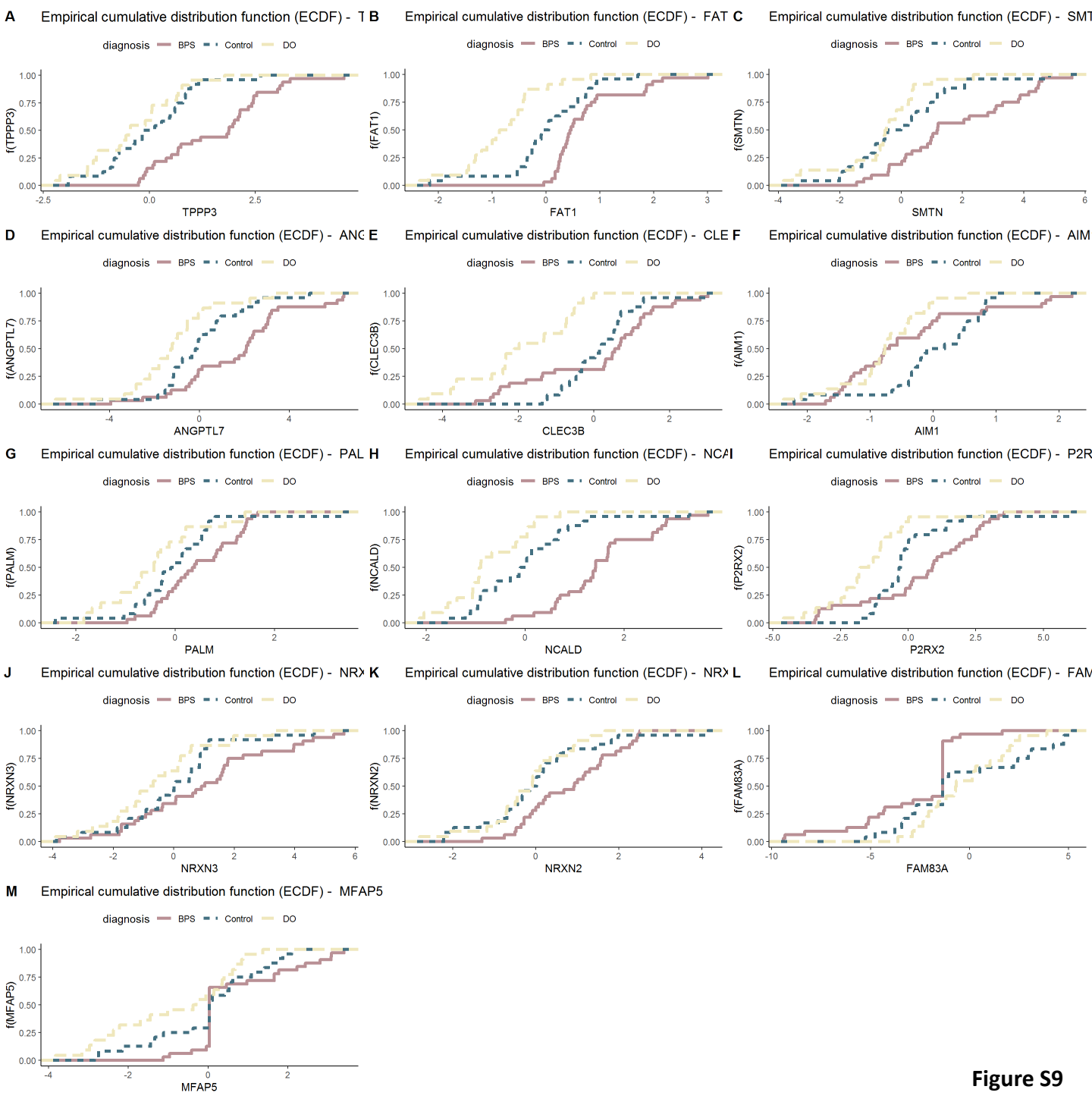

A
Empirical cumulative distribution function (ECDF) - T
B
Empirical cumulative distribution function (ECDF) - FAT
C
Empirical cumulative distribution function (ECDF) - SMT
D
Empirical cumulative distribution function (ECDF) - ANG
E
Empirical cumulative distribution function (ECDF) - CLE
F
Empirical cumulative distribution function (ECDF) - AIM
G
Empirical cumulative distribution function (ECDF) - PAL
H
Empirical cumulative distribution function (ECDF) - NCA
I
Empirical cumulative distribution function (ECDF) - P2R
J
Empirical cumulative distribution function (ECDF) - NRX
K
Empirical cumulative distribution function (ECDF) - NRX
L
Empirical cumulative distribution function (ECDF) - FAM
M
Empirical cumulative distribution function (ECDF) - MFAP5
diagnosis
BPS
Control
DO
f(TPPP3)
TPPP3
f(FAT1)
FAT1
f(SMTN)
SMTN
f(ANGPTL7)
ANGPTL7
f(CLEC3B)
CLEC3B
f(AIM1)
AIM1
f(PALM)
PALM
f(NCALD)
NCALD
f(P2RX2)
P2RX2
f(NRXN3)
NRXN3
f(NRXN2)
NRXN2
f(FAM83A)
FAM83A
f(MFAP5)
MFAP5

Figure S9

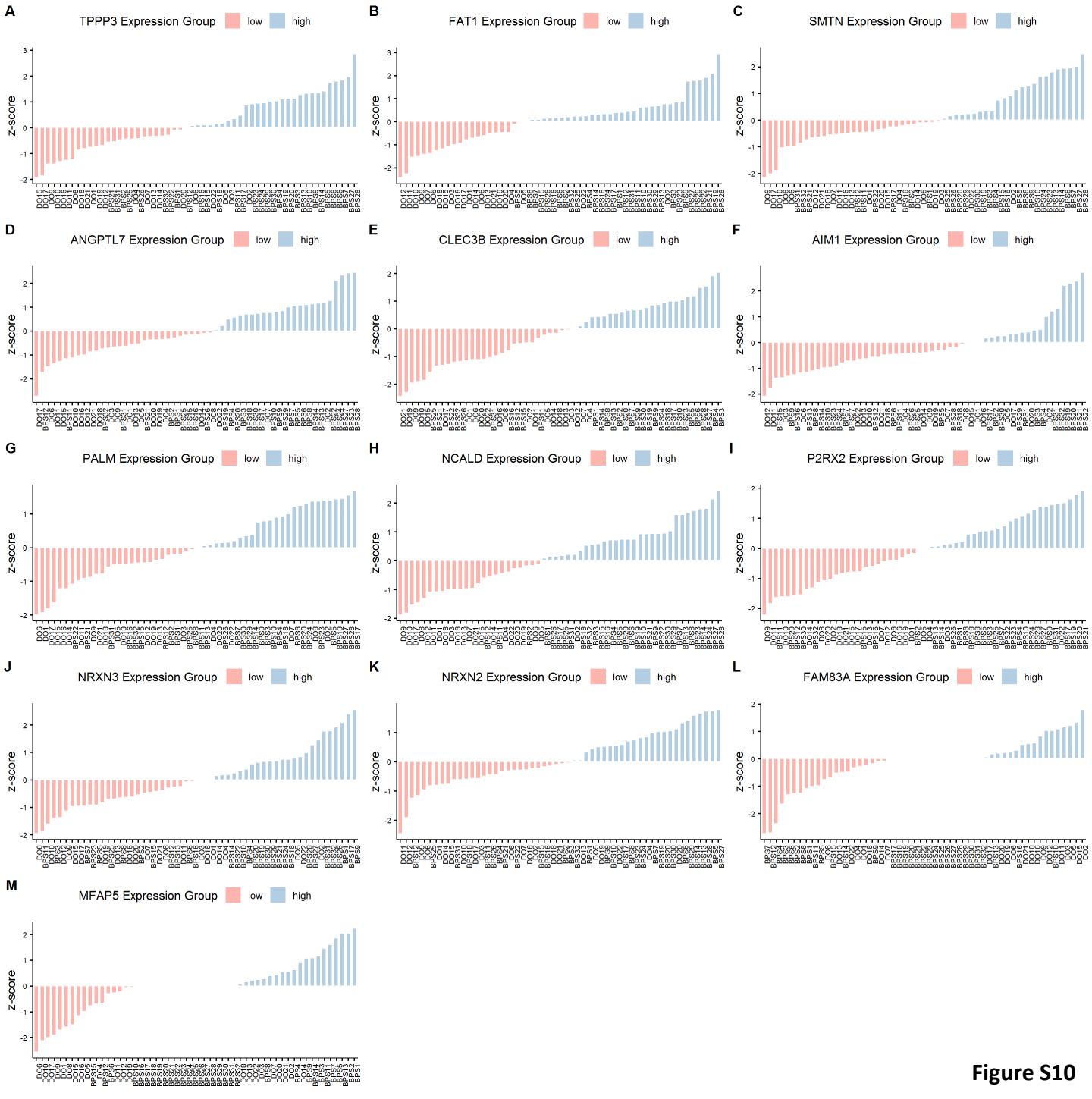

A
TPPP3 Expression Group
low
high
z-score
B
FAT1 Expression Group
low
high
z-score
C
SMTN Expression Group
low
high
z-score
D
ANGPTL7 Expression Group
low
high
z-score
E
CLEC3B Expression Group
low
high
z-score
F
AIM1 Expression Group
low
high
z-score
G
PALM Expression Group
low
high
z-score
H
NCALD Expression Group
low
high
z-score
I
P2RX2 Expression Group
low
high
z-score
J
NRXN3 Expression Group
low
high
z-score
K
NRXN2 Expression Group
low
high
z-score
L
FAM83A Expression Group
low
high
z-score
M
MFAP5 Expression Group
low
high
z-score

Figure S10


A
FAM83A
MFAP5
CLEC3B
ANGPTL7
TPPP3
SMTN
NCALD
PALM
NRXN2
FAT1
AIM1
P2RX2
NRXN3
1
0.75
0.5
0.25
0
-0.25
-0.5
-0.75
-1
B
Variances - PCA
% of variances
Principal Components
48.8%
11.7%
8.5%
6.8%
5.8%
5%
4.7%
2.7%
2%
1.7%
C
Contribution of variables to Dim-1
Contribution of variables to Dim-2
Contribution of variables to Dim-3
Contributions (%)
D
PCA - Biplot
Dim2 (11.7%)
Dim1 (48.8%)
Contrib
GROUP_NAME
BPS
Control
DO

Figure S11

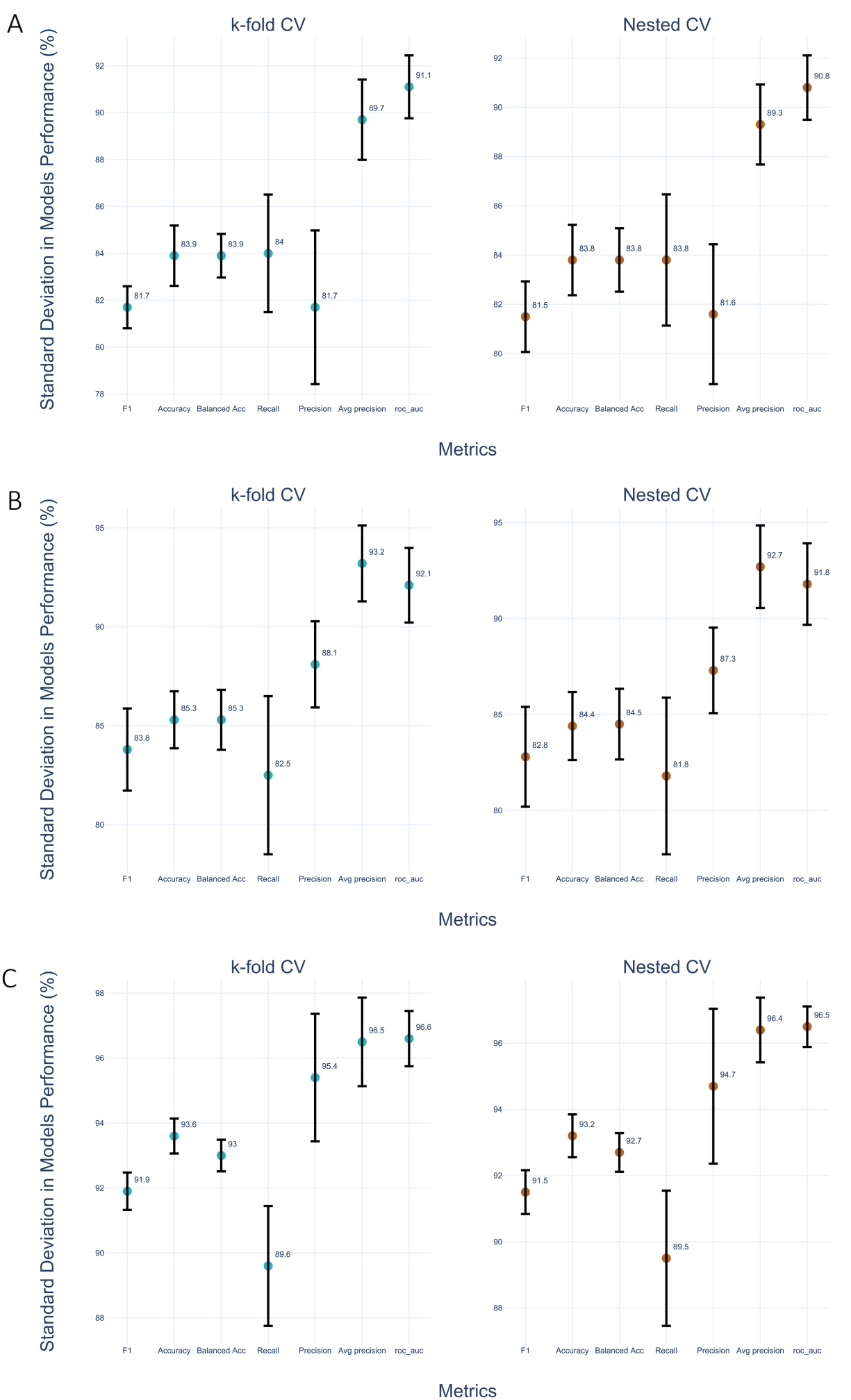

A
k-fold CV
Nested CV
Standard Deviation in Models Performance (%)
92
90
88
86
84
82
80
78
91.1
89.7
83.9
83.9
84
81.7
81.7
F1
Accuracy
Balanced Acc
Recall
Precision
Avg precision
roc_auc
92
90
88
86
84
82
80
90.8
89.3
83.8
83.8
83.8
81.6
81.5
F1
Accuracy
Balanced Acc
Recall
Precision
Avg precision
roc_auc
Metrics
B
k-fold CV
Nested CV
Standard Deviation in Models Performance (%)
95
90
85
80
93.2
92.1
88.1
85.3
85.3
83.8
82.5
F1
Accuracy
Balanced Acc
Recall
Precision
Avg precision
roc_auc
95
90
85
80
92.7
91.8
87.3
84.4
84.5
82.8
81.8
F1
Accuracy
Balanced Acc
Recall
Precision
Avg precision
roc_auc
Metrics
C
k-fold CV
Nested CV
Standard Deviation in Models Performance (%)
98
96
94
92
90
88
96.5
96.6
95.4
93.6
93
91.9
89.6
F1
Accuracy
Balanced Acc
Recall
Precision
Avg precision
roc_auc
96
94
92
90
88
96.4
96.5
94.7
93.2
92.7
91.5
89.5
F1
Accuracy
Balanced Acc
Recall
Precision
Avg precision
roc_auc
Metrics

Figure S12

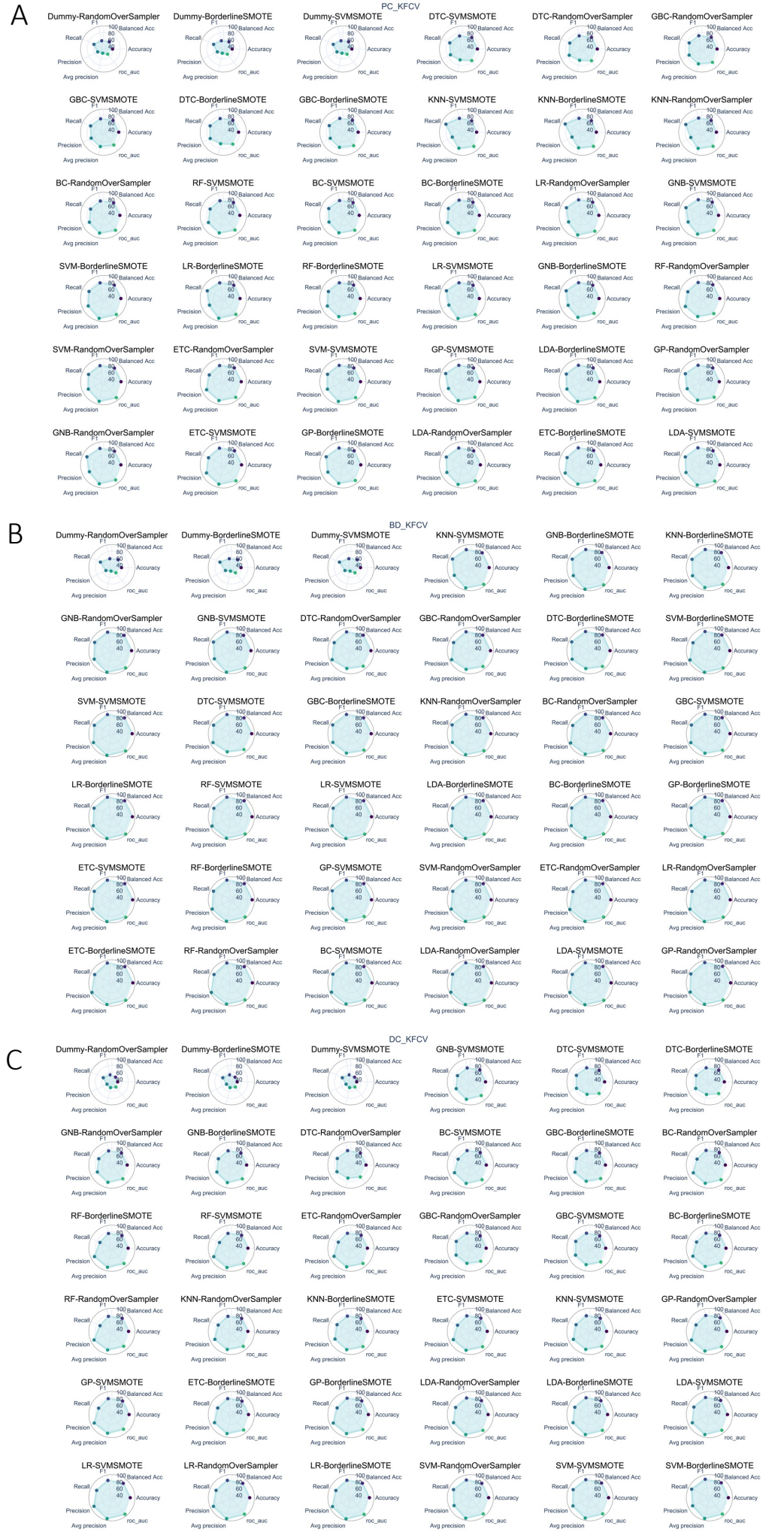
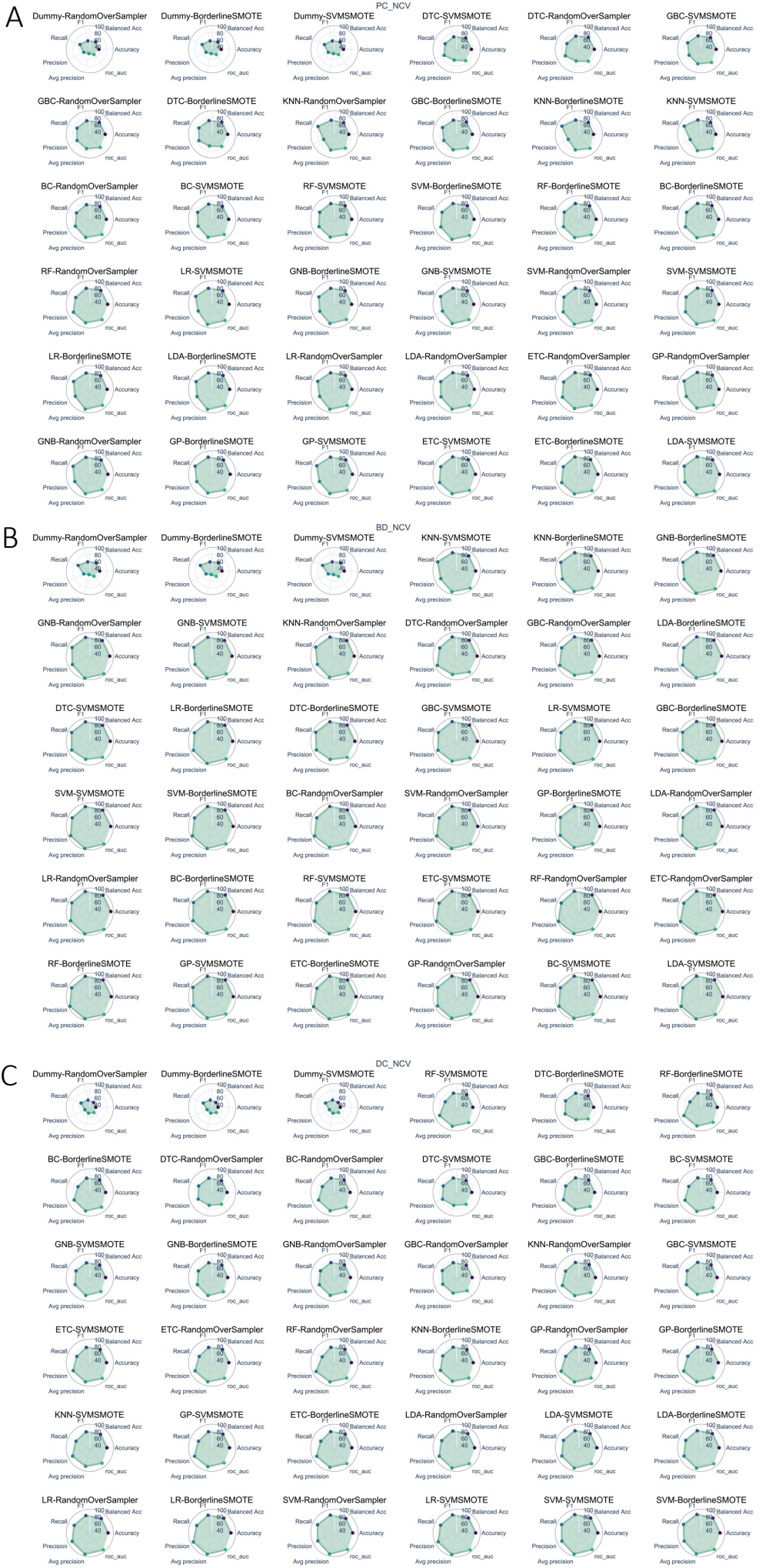

A
PC_KFCV
Dummy-RandomOverSampler
Dummy-BorderlineSMOTE
Dummy-SVMSMOTE
DTC-SVMSMOTE
DTC-RandomOverSampler
GBC-RandomOverSampler
GBC-SVMSMOTE
DTC-BorderlineSMOTE
GBC-BorderlineSMOTE
KNN-SVMSMOTE
KNN-BorderlineSMOTE
KNN-RandomOverSampler
BC-RandomOverSampler
RF-SVMSMOTE
BC-SVMSMOTE
BC-BorderlineSMOTE
LR-RandomOverSampler
GNB-SVMSMOTE
SVM-BorderlineSMOTE
LR-BorderlineSMOTE
RF-BorderlineSMOTE
LR-SVMSMOTE
GNB-BorderlineSMOTE
RF-RandomOverSampler
SVM-RandomOverSampler
ETC-RandomOverSampler
SVM-SVMSMOTE
GP-SVMSMOTE
LDA-BorderlineSMOTE
GP-RandomOverSampler
GNB-RandomOverSampler
ETC-SVMSMOTE
GP-BorderlineSMOTE
LDA-RandomOverSampler
ETC-BorderlineSMOTE
LDA-SVMSMOTE
B
BD_KFCV
Dummy-RandomOverSampler
Dummy-BorderlineSMOTE
Dummy-SVMSMOTE
KNN-SVMSMOTE
GNB-BorderlineSMOTE
KNN-BorderlineSMOTE
GNB-RandomOverSampler
GNB-SVMSMOTE
DTC-RandomOverSampler
GBC-RandomOverSampler
DTC-BorderlineSMOTE
SVM-BorderlineSMOTE
SVM-SVMSMOTE
DTC-SVMSMOTE
GBC-BorderlineSMOTE
KNN-RandomOverSampler
BC-RandomOverSampler
GBC-SVMSMOTE
LR-BorderlineSMOTE
RF-SVMSMOTE
LR-SVMSMOTE
LDA-BorderlineSMOTE
BC-BorderlineSMOTE
GP-BorderlineSMOTE
ETC-SVMSMOTE
RF-BorderlineSMOTE
GP-SVMSMOTE
SVM-RandomOverSampler
ETC-RandomOverSampler
LR-RandomOverSampler
ETC-BorderlineSMOTE
RF-RandomOverSampler
BC-SVMSMOTE
LDA-RandomOverSampler
LDA-SVMSMOTE
GP-RandomOverSampler
C
DC_KFCV
Dummy-RandomOverSampler
Dummy-BorderlineSMOTE
Dummy-SVMSMOTE
GNB-SVMSMOTE
DTC-SVMSMOTE
DTC-BorderlineSMOTE
GNB-RandomOverSampler
GNB-BorderlineSMOTE
DTC-RandomOverSampler
BC-SVMSMOTE
GBC-BorderlineSMOTE
BC-RandomOverSampler
RF-BorderlineSMOTE
RF-SVMSMOTE
ETC-RandomOverSampler
GBC-RandomOverSampler
GBC-SVMSMOTE
BC-BorderlineSMOTE
RF-RandomOverSampler
KNN-RandomOverSampler
KNN-BorderlineSMOTE
ETC-SVMSMOTE
KNN-SVMSMOTE
GP-RandomOverSampler
GP-SVMSMOTE
ETC-BorderlineSMOTE
GP-BorderlineSMOTE
LDA-RandomOverSampler
LDA-BorderlineSMOTE
LDA-SVMSMOTE
LR-SVMSMOTE
LR-RandomOverSampler
LR-BorderlineSMOTE
SVM-RandomOverSampler
SVM-SVMSMOTE
SVM-BorderlineSMOTE
F1
Balanced Acc
Accuracy
roc_auc
Avg precision
Precision
Recall

Figure S13


A
PC_NCV
Dummy-RandomOverSampler
Dummy-BorderlineSMOTE
Dummy-SVMSMOTE
DTC-SVMSMOTE
DTC-RandomOverSampler
GBC-SVMSMOTE
GBC-RandomOverSampler
DTC-BorderlineSMOTE
KNN-RandomOverSampler
GBC-BorderlineSMOTE
KNN-BorderlineSMOTE
KNN-SVMSMOTE
BC-RandomOverSampler
BC-SVMSMOTE
RF-SVMSMOTE
SVM-BorderlineSMOTE
RF-BorderlineSMOTE
BC-BorderlineSMOTE
RF-RandomOverSampler
LR-SVMSMOTE
GNB-BorderlineSMOTE
GNB-SVMSMOTE
SVM-RandomOverSampler
SVM-SVMSMOTE
LR-BorderlineSMOTE
LDA-BorderlineSMOTE
LR-RandomOverSampler
LDA-RandomOverSampler
ETC-RandomOverSampler
GP-RandomOverSampler
GNB-RandomOverSampler
GP-BorderlineSMOTE
GP-SVMSMOTE
ETC-SVMSMOTE
ETC-BorderlineSMOTE
LDA-SVMSMOTE
B
BD_NCV
Dummy-RandomOverSampler
Dummy-BorderlineSMOTE
Dummy-SVMSMOTE
KNN-SVMSMOTE
KNN-BorderlineSMOTE
GNB-BorderlineSMOTE
GNB-RandomOverSampler
GNB-SVMSMOTE
KNN-RandomOverSampler
DTC-RandomOverSampler
GBC-RandomOverSampler
LDA-BorderlineSMOTE
DTC-SVMSMOTE
LR-BorderlineSMOTE
DTC-BorderlineSMOTE
GBC-SVMSMOTE
LR-SVMSMOTE
GBC-BorderlineSMOTE
SVM-SVMSMOTE
SVM-BorderlineSMOTE
BC-RandomOverSampler
SVM-RandomOverSampler
GP-BorderlineSMOTE
LDA-RandomOverSampler
LR-RandomOverSampler
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RF-SVMSMOTE
ETC-SVMSMOTE
RF-RandomOverSampler
ETC-RandomOverSampler
RF-BorderlineSMOTE
GP-SVMSMOTE
ETC-BorderlineSMOTE
GP-RandomOverSampler
BC-SVMSMOTE
LDA-SVMSMOTE
C
DC_NCV
Dummy-RandomOverSampler
Dummy-BorderlineSMOTE
Dummy-SVMSMOTE
RF-SVMSMOTE
DTC-BorderlineSMOTE
RF-BorderlineSMOTE
BC-BorderlineSMOTE
DTC-RandomOverSampler
BC-RandomOverSampler
DTC-SVMSMOTE
GBC-BorderlineSMOTE
BC-SVMSMOTE
GNB-SVMSMOTE
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GNB-RandomOverSampler
GBC-RandomOverSampler
KNN-RandomOverSampler
GBC-SVMSMOTE
ETC-SVMSMOTE
ETC-RandomOverSampler
RF-RandomOverSampler
KNN-BorderlineSMOTE
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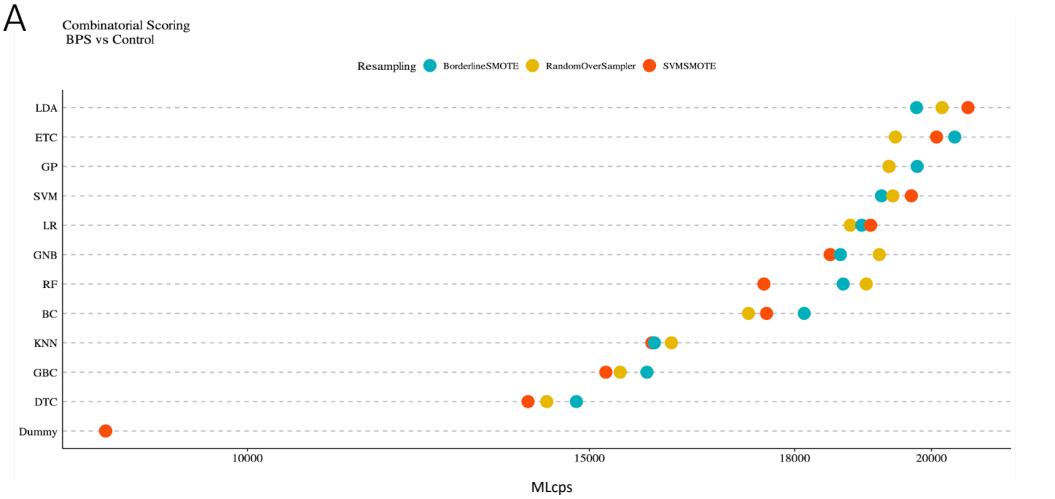
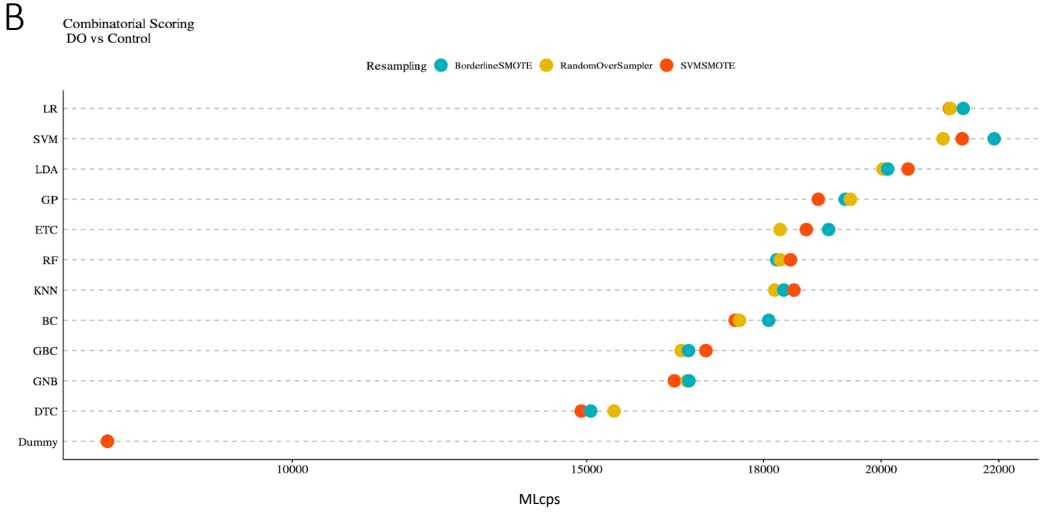
GP-BorderlineSMOTE
KNN-SVMSMOTE
GP-SVMSMOTE
ETC-BorderlineSMOTE
LDA-RandomOverSampler
LDA-SVMSMOTE
LDA-BorderlineSMOTE
LR-RandomOverSampler
LR-BorderlineSMOTE
SVM-RandomOverSampler
LR-SVMSMOTE
SVM-SVMSMOTE
SVM-BorderlineSMOTE
F1
Balanced Acc
Accuracy
roc_auc
Avg precision
Precision
Recall

Figure S14


A
Combinatorial Scoring
BPS vs Control
Resampling
BorderlineSMOTE
RandomOverSampler
SVMSMOTE
LDA
ETC
GP
SVM
LR
GNB
RF
BC
KNN
GBC
DTC
Dummy
10000
15000
18000
20000
MLcps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Combinatorial Scoring
DO vs Control
Resampling
BorderlineSMOTE
RandomOverSampler
SVMSMOTE
LR
SVM
LDA
GP
ETC
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22000
MLcps

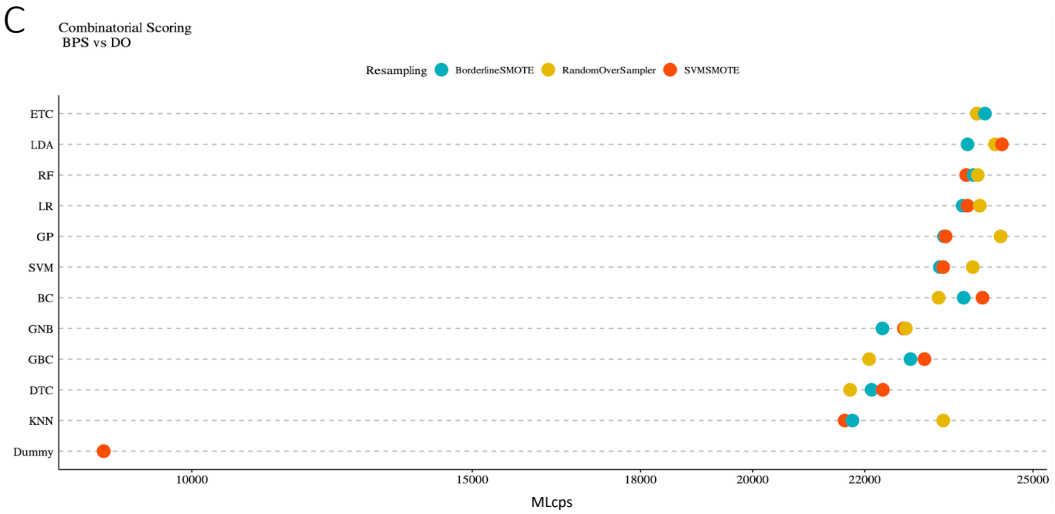
C
Combinatorial Scoring
BPS vs DO
Resampling
BorderlineSMOTE
RandomOverSampler
SVMSMOTE
ETC
LDA
RF
LR
GP
SVM
BC
GNB
GBC
DTC
KNN
Dummy
10000
15000
18000
20000
22000
25000
MLcps

Figure S15

Group	N
Control	24
BPS	32
DO	22

qPCR data

Group pairs

Repeat 1, ..., Repeat 10

Data sets for 3-fold CV

Iteration 1	Test	Train	
Iteration 2	Train	Test	Train
Iteration 3	Train	Train	Test

Iteration 1, ..., Iteration 3

Feature Selection

Recursive feature elimination (RFE)

Estimators for RFE:

Logistic Regression
Linear Discriminant Analysis
Support Vector Machine

In total, 36 different models has been evaluated (12 ML * 3 data sampling algo.)

Data Sampling Methods

Borderline SMOTE
SVM SMOTE
Random Over Sampler

ML Classification Algorithms

Logistic Regression
Linear Discriminant Analysis
Gaussian Naive Bayes
Support Vector Machine
k-nearest neighbors
Decision Tree Classifier
Gaussian Process Classifier
Random Forest Classifier
Bagging Classifier
Extra Trees Classifier
Gradient Boosting Classifier
Dummy Classifier

Model Evaluation Methods

Repeated Stratified k-fold CV
Nested CV

Model Evaluation Metrics

Accuracy
Balanced Accuracy
F1 Score
Precision,
Recall
Average Precision
ROC-AUC

Model 1

Performance scores: F1, Precision, etc.

List of selected Features: Gene A, Gene B, Gene C etc.

Model 2

Performance scores: F1, Precision, etc.

List of selected Features: Gene B, Gene X, Gene A, etc.

Model N

Performance scores: F1, Precision, etc.

List of selected Features: Gene M, Gene B, Gene A etc.

Average Performance

Models Performance
Repeat 1, ... , Repeat 10

Average Performance

Cumulative Performance Score (CPS)

A polygon (radar graph) is created in a polar coordinate space. The vertices of the polygon (labels of the radar graph) are model evaluation metrics (F1,...). The area of the created polygon was measured and reported as a cumulative performance Score (CPS).

Intersection of selected features from top 10 best performing models (based on F1 score)

Potential Biomarkers
Gene A, Gene B, etc

Figure S16

Supplementary Figures - Legends

Figure S1. Similarity matrix and normality test of selected genes in NGS dataset. (A) Similarity matrix for DO and BPS patients using 1390 differentially regulated mRNAs in DO and BPS patients purple color show lower similarity and green color represents higher similarity. (B) Normality test for 13 selected markers. For each gene, the normal plots (histogram), Q-Q plot (quantile-quantile plot) of all patients in a single group and Q-Q plot of each patient group separately is calculated.

Figure S2. Functional enrichment analysis of DEGs based on NGS dataset. (A) Enriched GO (biological processes) in differentially expressed genes (DEGs) between DO and control identified using GSEA methods. X-axis indicates LFC values. The color describes the FDR/adjusted p-value as listed in the color bar notifying whether an enriched term is significant (cutoff <0.05). (**B**) Enriched GO (biological processes) in DEGs between BPS and control identified using GSEA methods.

Figure S3. Deviation Graphs of selected 13 markers in NGS datasets of BPS, DO and controls. Deviation Graphs estimating the cumulative distribution of selected genes. Z-score of 1 denotes that the observation is at a distance of one standard deviation to the right from the centre. (A) TPPP3 (B) FAT1 (C) SMTN (D) ANGPTL7 (E) CLEC3B (F) AIM1 (G) PALM (H) NCALD (I) P2RX2 (J) NRXN3 (K) NRXN2 (L) FAM83A (M) MFAP5

Figure S4. Correlation plot and PCA contribution of selected genes in NGS dataset.

(A) Correlation plot visualizing the relationship between the different attributes. Similarity between observations is defined using the inter-observation distance measures or correlation-based distance measures. The relationships with no significance are visualised by a cross on the correlogram. (B) Scree plot of eigenvalues

showing the percentage of variances explained by each principal component. (C) Barplot of gene contributions in the PCA. A reference dashed line is shown on the barplot corresponding to the expected value if the contribution where uniform. For a given dimension, any gene with a contribution above the reference line could be considered as important in contributing to the dimension.

Figure S5. Log2FC distribution of 13 markers in QPCR dataset. Density ridgeline plot of distribution of BPS, DO and controls for a given gene. (A) TPPP3 (B) FAT1 (C) SMTN (D) ANGPTL7 (E) CLEC3B (F) AIM1 (G) PALM (H) NCALD (I) P2RX2 (J) NRXN3 (K) NRXN2 (L) FAM83A (M) MFAP5

Figure S6. Log2FC distribution of the mean of each 13 markers in QPCR dataset. Density ridgeline plot of distribution of BPS and DO and visualizing the mean of each population.

Figure S7. Normality test and PCA contribution of different markers in QPCR dataset. Normality test for 13 selected markers: the normal plots (histogram), Q-Q plot (quantile-quantile plot) of all patients in a single group and Q-Q plot of each patient group separately is calculated.

Figure S8. Testing the performance of selected 13 markers in QPCR datasets of BPS, DO and controls. Boxplot Statistics visualization (Based on log2FC), pairwise comparisons including p-value. (A) TPPP3 (B) FAT1 (C) SMTN (D) ANGPTL7 (E) CLEC3B (F) AIM1 (G) PALM (H) NCALD (I) P2RX2 (J) NRXN3 (K) NRXN2 (L) FAM83A (M) MFAP5

Figure S9. Empirical cumulative distribution function (ECDF) of selected 13 markers in QPCR datasets of BPS, DO and controls. ECDF reports for any given number (mRNA read count) the percentage of individuals that are below that threshold.

(A) TPPP3 (B) FAT1 (C) SMTN (D) ANGPTL7 (E) CLEC3B (F) AIM1 (G) PALM (H) NCALD (I) P2RX2 (J) NRXN3 (K) NRXN2 (L) FAM83A (M) MFAP5

Figure S10. Deviation Graphs of selected 13 markers in QPCR datasets of BPS, DO and controls. Deviation Graphs estimating the cumulative distribution of selected genes. Z-score of 1 denotes that the observation is at a distance of one standard deviation to the right from the centre. (A) TPPP3 (B) FAT1 (C) SMTN (D) ANGPTL7 (E) CLEC3B (F) AIM1 (G) PALM (H) NCALD (I) P2RX2 (J) NRXN3 (K) NRXN2 (L) FAM83A (M) MFAP5

Figure S11. Performance of selected 13 markers (QPCR datasets of BPS, DO and controls) in PCA (A) Correlogram of the relationship between the different attributes. Relationship with no significance is visualised by a cross (B) Scree plot of eigenvalues showing the percentage of variances explained by each principal component. (C) Barplot of gene contributions. For a given dimension, any gene with a contribution above the reference line could be considered as important in contributing to the dimension. (D) PCA biplot showing the separation samples using QPCR data.

Figure S12. Standard deviation of performance metrics for various models. (**A**) Standard deviation of metrics in BPS vs control, (**B**) DO vs control and (**C**) BPS vs DO.

Figure S13. Models' performance based on k-fold cross-validation (CV) method. Each plot represents an ML model, where the first part of the model's name corresponds to a particular ML algorithm, and the latter part indicates a data resampling method. It displays metric scores for the corresponding model, with a higher shaded area indicating better performance. The models are sorted in increasing order based on the F1 score from the k-fold CV result. (**A**) Thirty-six radar graphs illustrate model performances for BPS vs. Control. (**B**) Thirty-six radar graphs illustrate

model performances for BPS vs. DO. (**C**) Thirty-six radar graphs illustrate model performances for DO vs. Control.

Figure S14. Models' performance based on nested cross-validation (CV) method. Each plot represents an ML model, where the first part of the model's name corresponds to a particular ML algorithm, and the latter part indicates a data resampling method. It displays metric scores for the corresponding model, with a higher shaded area indicating better performance. The models are sorted in increasing order based on the F1 score from the k-fold CV result. (**A**) Thirty-six radar graphs illustrate model performances for BPS vs. Control. (**B**) Thirty-six radar graphs illustrate model performances for BPS vs. DO. (**C**) Thirty-six radar graphs illustrate model performances for DO vs. Control.

Figure S15. MLcps Results. MLcps scores are depicted in Cleveland's dot plot for (**A**) BPS vs. control, (**B**) DO vs. control, and (**C**) BPS vs. DO.

Figure S16. Proposed ML Framework. The proposed pipeline first splits the datasets into k (3) equal-sized bins in a stratified manner, where k-1 bins will be used as training datasets and the remaining bin as a test dataset. Next, it employs the RFECV method for feature selection, three data resampling techniques, and twelve ML algorithms. Then, it evaluates the model performance on the test dataset using the k-fold and nested CV (k=3) method and calculates seven different performance metrics. As part of the k-fold CV methods, it repeats the last two steps for each unique bin. It repeats the complete process ten times and takes the average performance as the final model performance. In the end, the pipeline provides a list of the intersection of selected features from the top 10 best-performing models (based on F1 score) as the final list of selected features.