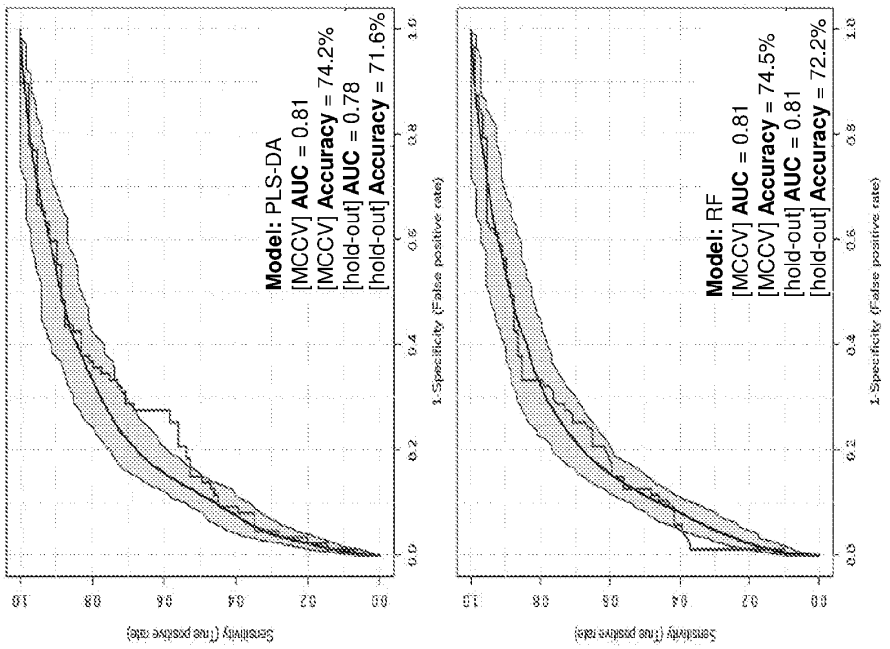

Model: PLS-DA
[MCCV] AUC = 0.81
[MCCV] Accuracy = 74.2%
[hold-out] AUC = 0.78
[hold-out] Accuracy = 71.6%
Model: RF
[MCCV] AUC = 0.81
[MCCV] Accuracy = 74.5%
[hold-out] AUC = 0.81
[hold-out] Accuracy = 72.2%
Sensitivity (True positive rate)
1-Specificity (False positive rate)

Fig. 1

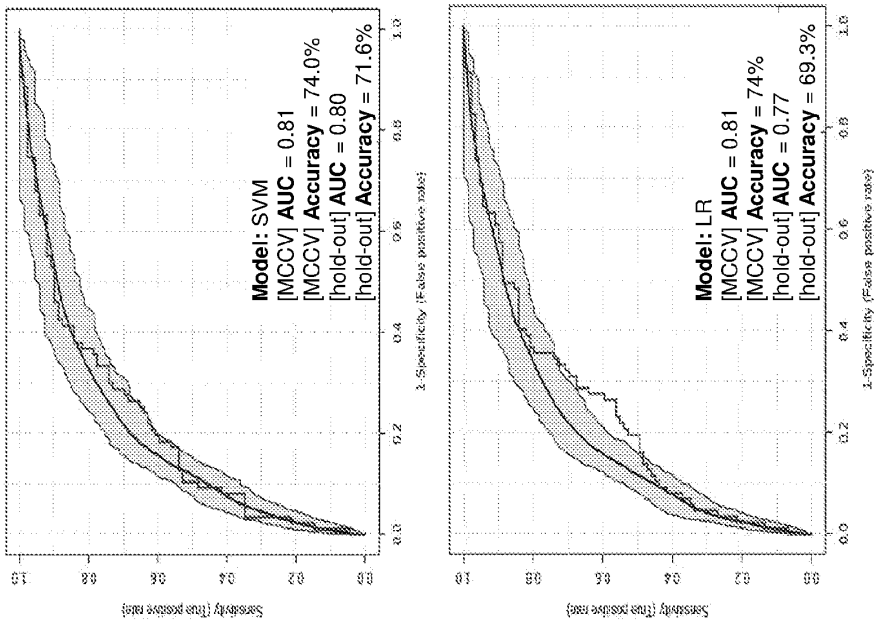
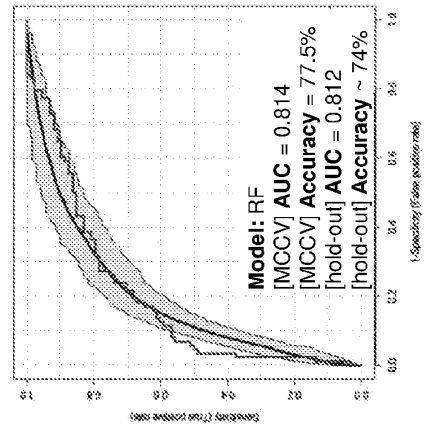
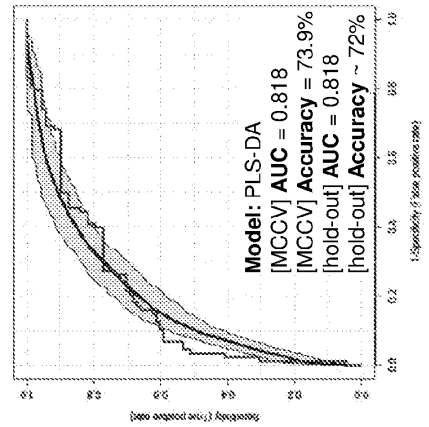
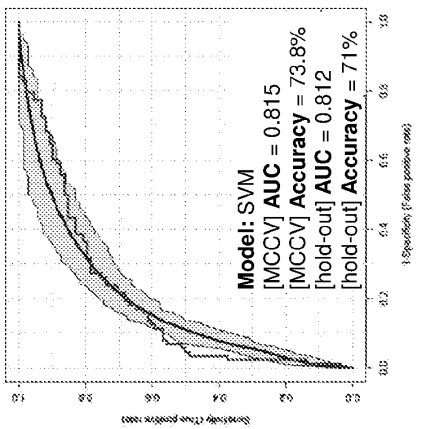
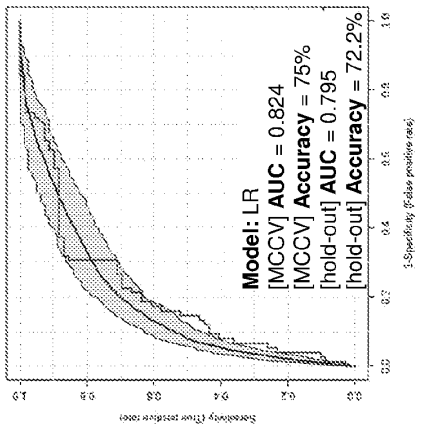

Model: SVM
[MCCV] AUC = 0.81
[MCCV] Accuracy = 74.0%
[hold-out] AUC = 0.80
[hold-out] Accuracy = 71.6%
Model: LR
[MCCV] AUC = 0.81
[MCCV] Accuracy = 74%
[hold-out] AUC = 0.77
[hold-out] Accuracy = 69.3%
Sensitivity (True positive rate)
1-Specificity (False positive rate)

Fig. 2


Model: RF
[MCCV] AUC = 0.814
[MCCV] Accuracy = 77.5%
[hold-out] AUC = 0.812
[hold-out] Accuracy ~ 74%


Model: PLS-DA
[MCCV] AUC = 0.818
[MCCV] Accuracy = 73.9%
[hold-out] AUC = 0.818
[hold-out] Accuracy ~ 72%


Model: SVM
[MCCV] AUC = 0.815
[MCCV] Accuracy = 73.8%
[hold-out] AUC = 0.812
[hold-out] Accuracy = 71%


Model: LR
[MCCV] AUC = 0.824
[MCCV] Accuracy = 75%
[hold-out] AUC = 0.795
[hold-out] Accuracy = 72.2%

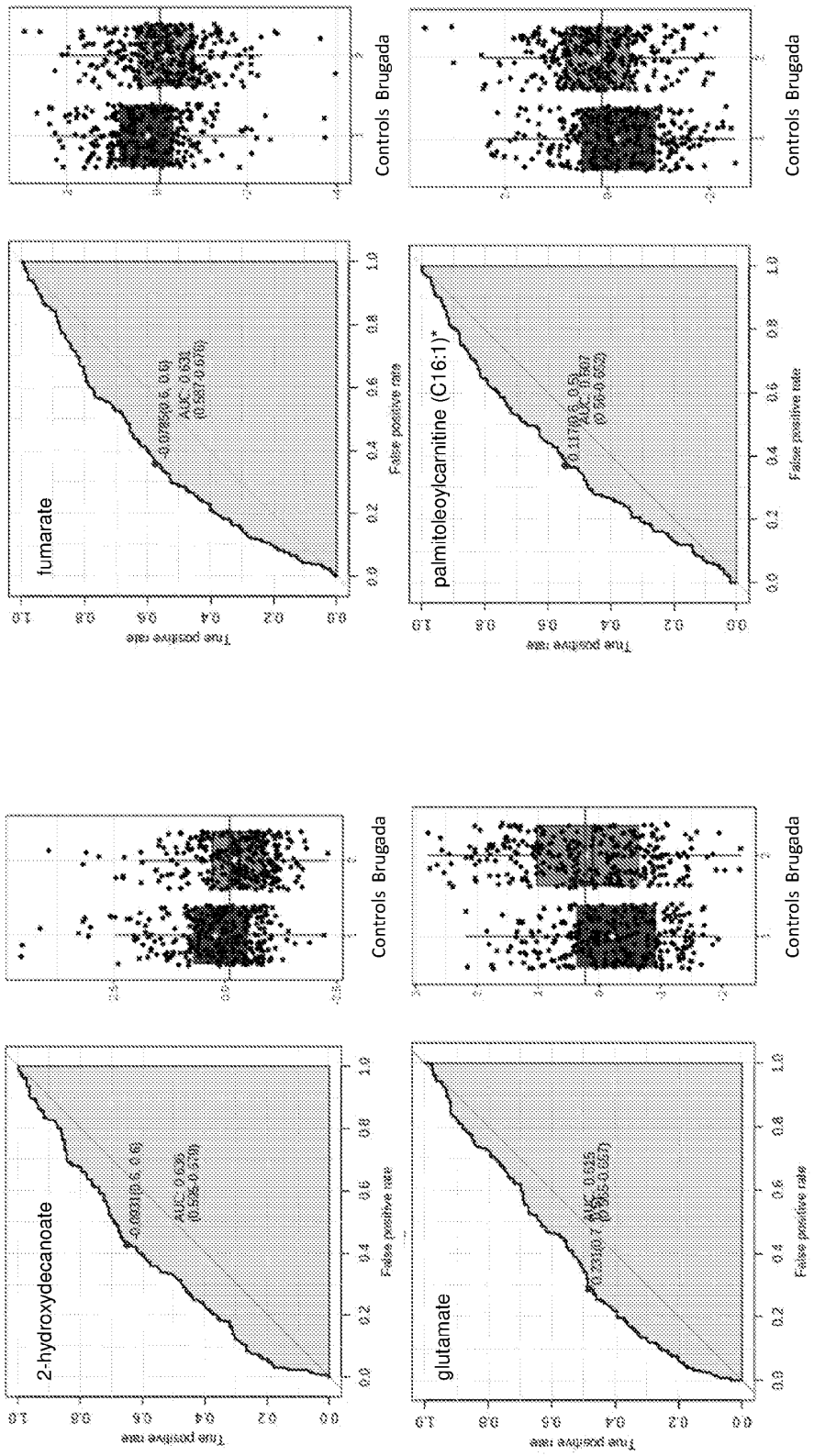

fumarate
palmitoleoylcarnitine (C16:1)*
2-hydroxydecanoate
glutamate
True positive rate
False positive rate
Controls
Brugada

Fig. 3A

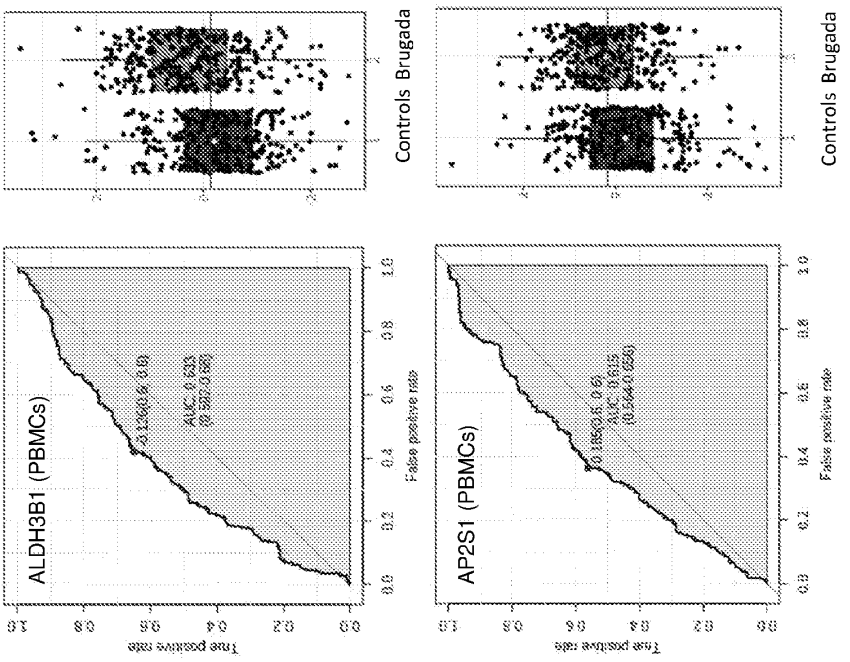
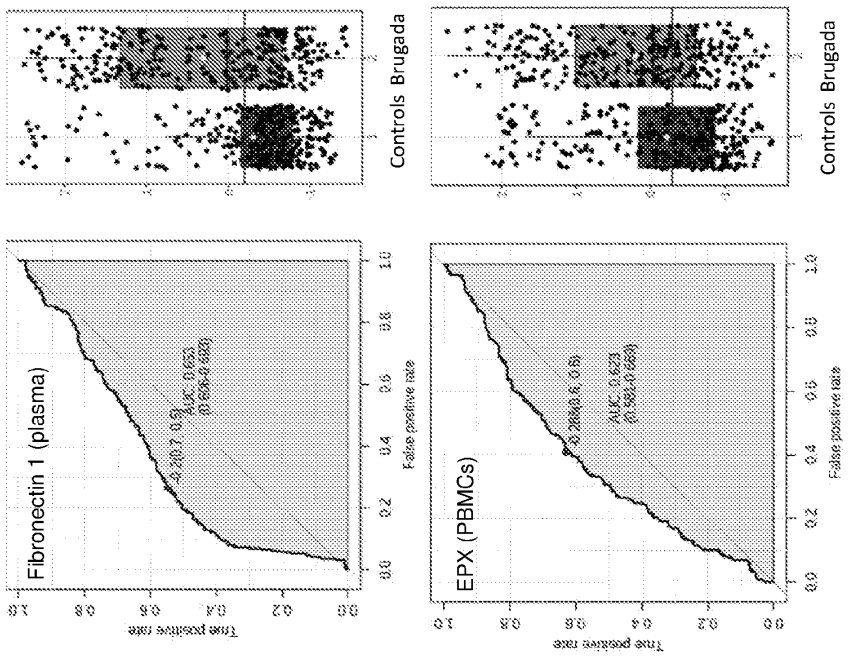

ALDH3B1 (PBMCs)
AP2S1 (PBMCs)
True positive rate
False positive rate
Controls
Brugada

Fig. 3B


Fibronectin 1 (plasma)
EPX (PBMCs)
True positive rate
False positive rate
Controls
Brugada

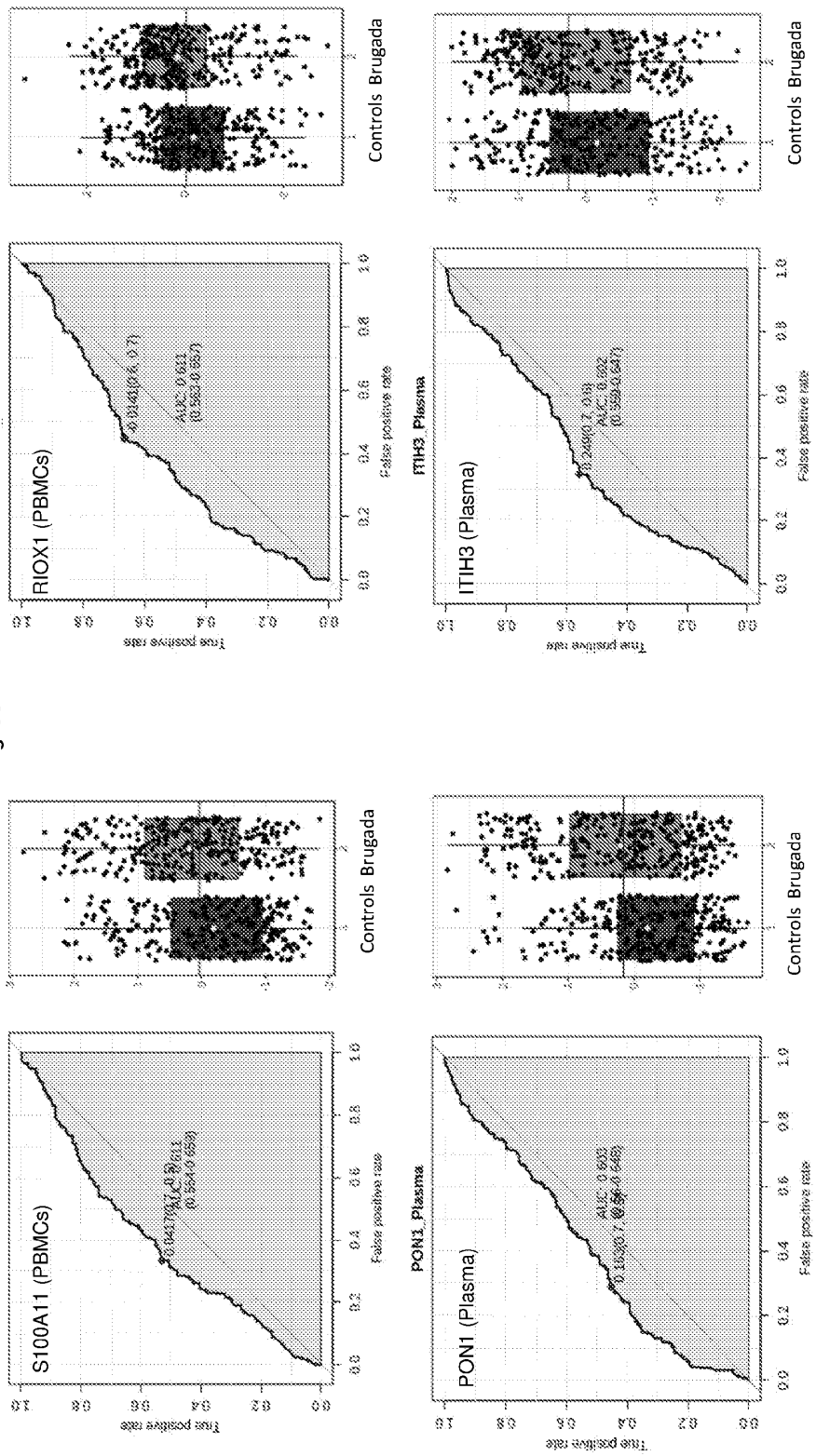

RIOX1 (PBMCs)
ITIH3 (Plasma)
S100A11 (PBMCs)
PON1 (Plasma)
True positive rate
False positive rate
Controls
Brugada

Fig. 3C

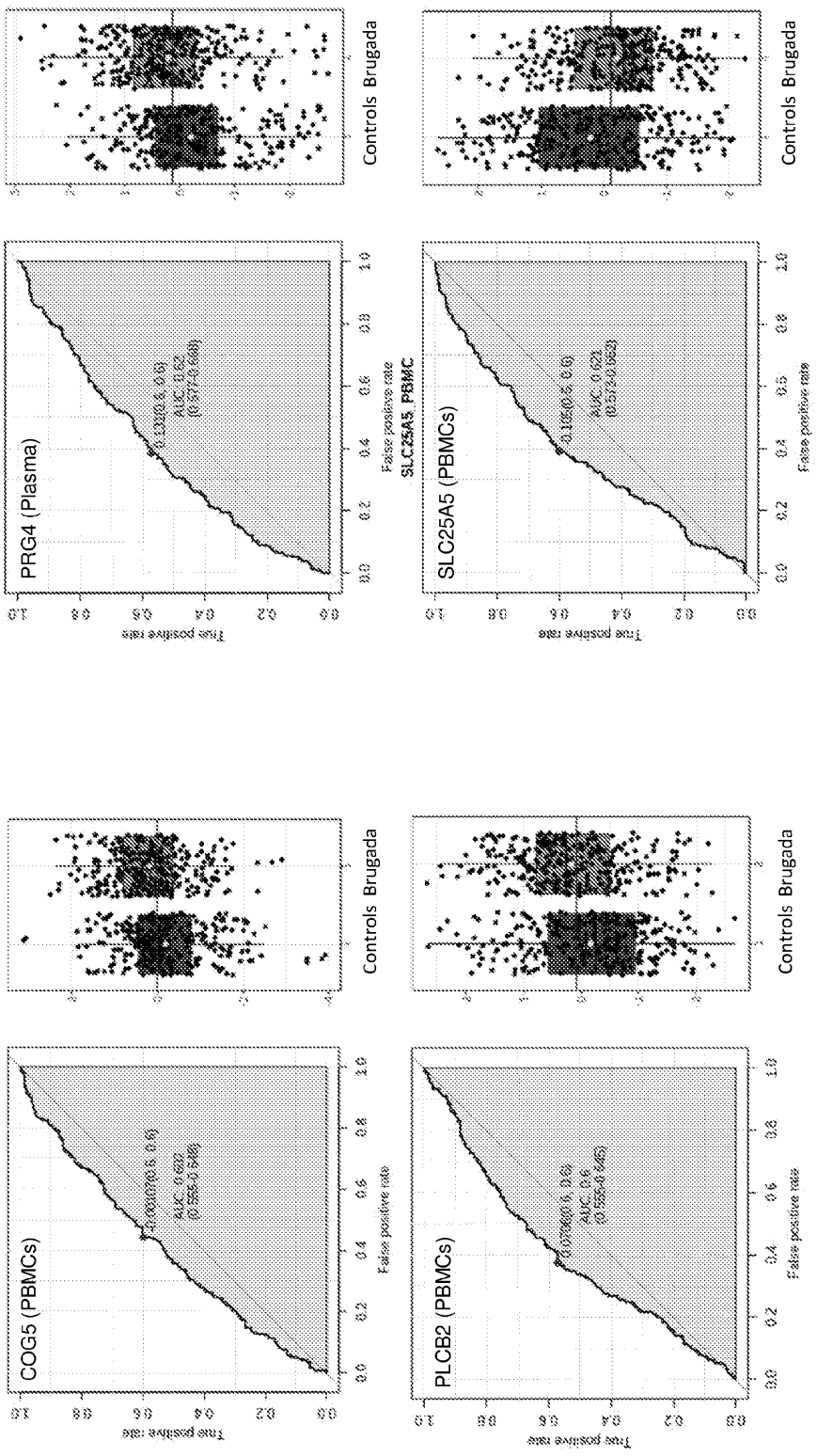
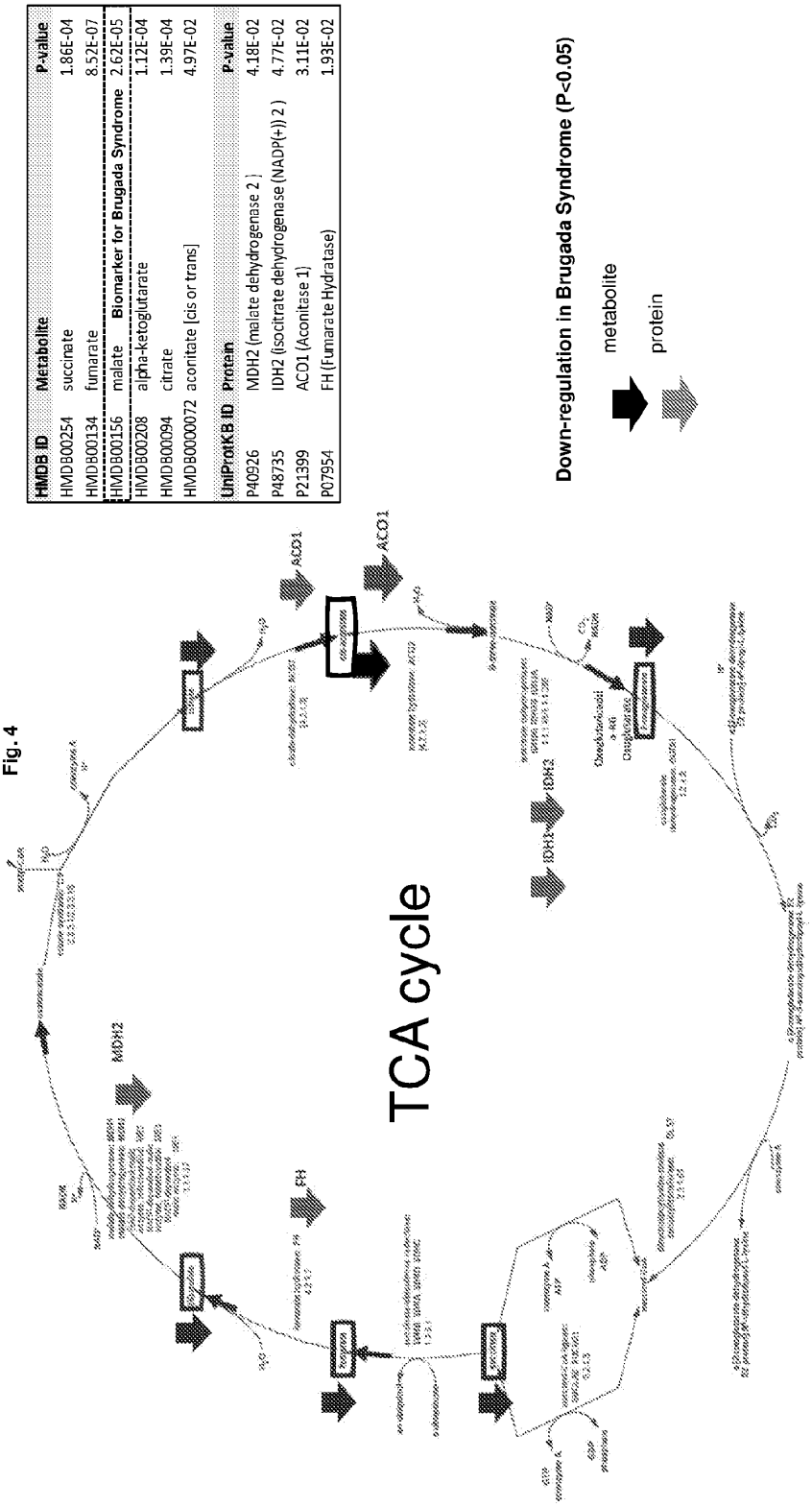

PRG4 (Plasma)
SLC25A5 (PBMCs)
COG5 (PBMCs)
PLCB2 (PBMCs)
True positive rate
False positive rate
Controls
Brugada

Fig. 3D

Fig. 4

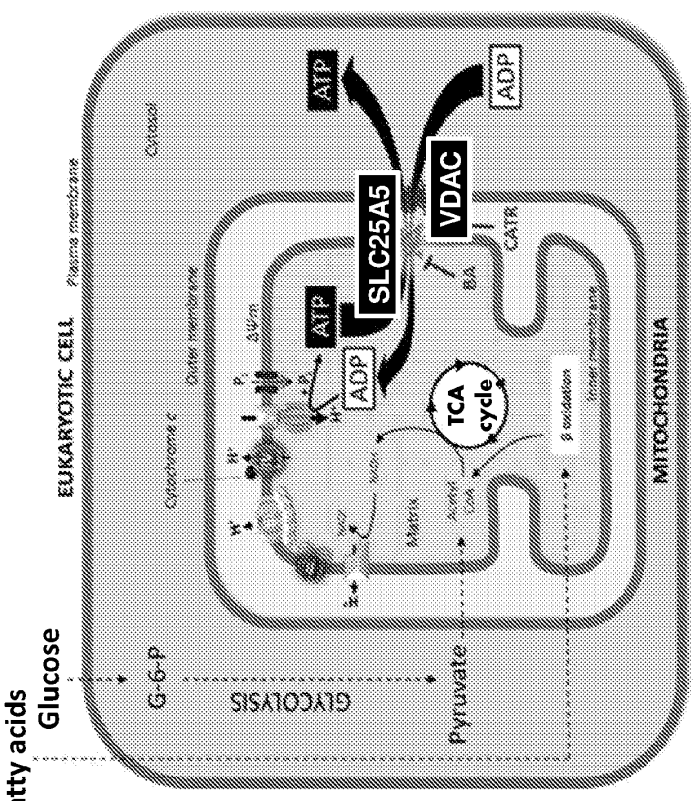


HMDB ID	Metabolite	P-value
HMDB00254	succinate	1.86E-04
HMDB00134	fumarate	8.52E-07
HMDB00156	malate	2.62E-05

Biomarker for Brugada Syndrome		
HMDB00208	alpha-ketoglutarate	1.12E-04
HMDB00094	citrate	1.39E-04
HMDB0000072	aconitate [cis or trans]	4.97E-02

UniProtKB ID	Protein	P-value
P40926	MDH2 (malate dehydrogenase 2)	4.18E-02
P48735	IDH2 (isocitrate dehydrogenase (NADP(+)) 2)	4.77E-02
P21399	ACO1 (Aconitase 1)	3.11E-02
P07954	FH (Fumarate Hydratase)	1.93E-02

Fig. 5



UniProtKB ID	Protein	Description	Log_2 FC (fold change)	P-value
P05141	SLC25A5	solute carrier family 25 member 5	-0.133	1.45E-08
P21796	VDAC1	voltage dependent anion channel 1	-0.032	5.31E-03

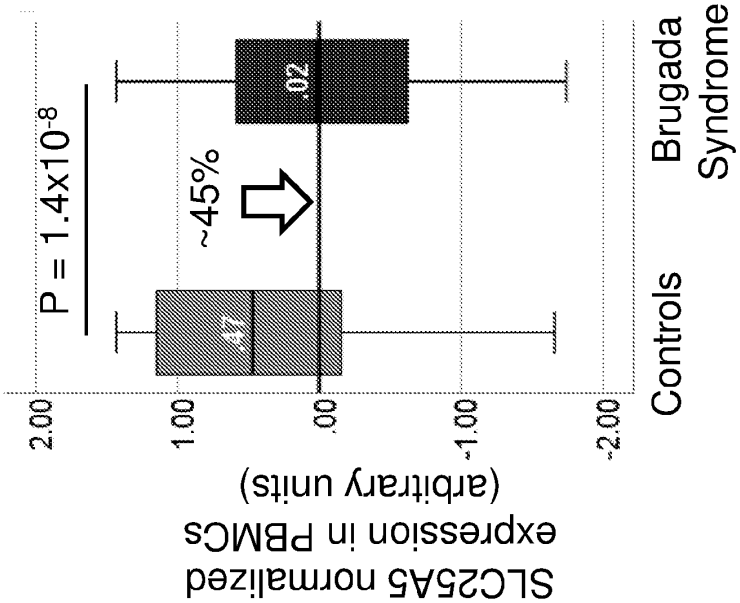
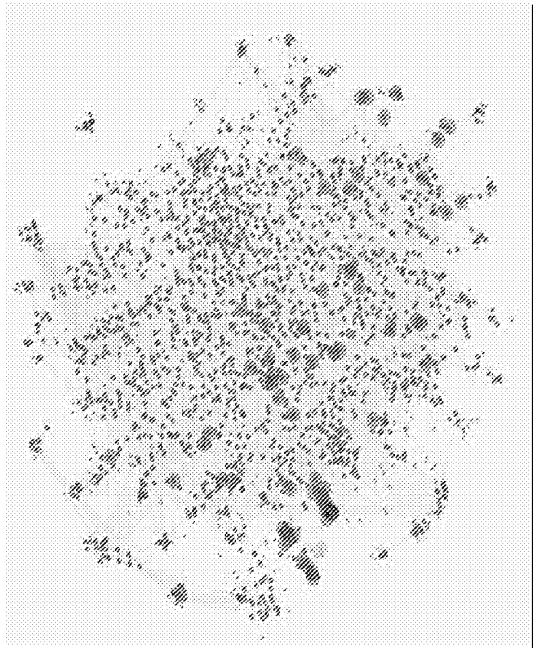


Fig. 6

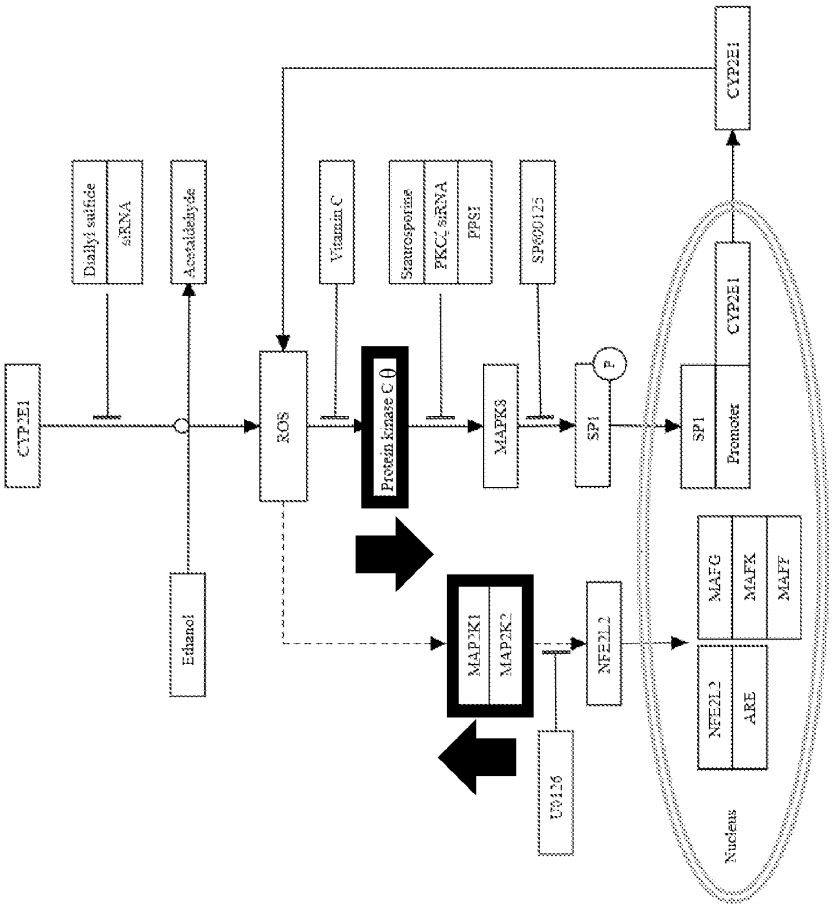


proteins form “Metabolic Pathways” (KEGG)

up-regulated proteins		Log_2FC
ARG1	arginase 1	0.28
CDA	cytidine deaminase	0.26
NAMPT	nicotinamide phosphoribosyltransferase	0.26
BST1	bone marrow stromal cell antigen 1	0.26
LPCAT2	lysophosphatidylcholine acyltransferase 2	0.25
ASL	argininosuccinate lyase	0.25
PKM	pyruvate kinase M1/2	0.25
ALDH3A2	aldehyde dehydrogenase 3 family member A2 **Biomarker for Brugada Syndrome**	0.24
ALOX5	arachidonate 5-lipoxygenase	0.23
ADSS2	adenylosuccinate synthase 2	0.23
PGD	phosphogluconate dehydrogenase	0.23
PAPSS1	3'-phosphoadenosine 5'-phosphosulfate synthase 1	0.23
BPGM	bisphosphoglycerate mutase	0.23
ATP6V0D1	ATPase H+ transporting V0 subunit d1	0.23
SDHC	succinate dehydrogenase complex subunit C	0.22
PLCB3	phospholipase C beta 3 **Biomarker for Brugada Syndrome**	0.22
NANS	N-acetylneuraminate synthase	0.22
GNS	glucosamine (N-acetyl)-6-sulfatase	0.22
GAA	glucosidase alpha, acid	0.22
DPYD	dihydropyrimidine dehydrogenase	0.22
ADO	2-aminoethanethiol dioxygenase	0.22
RPIA	ribose 5-phosphate isomerase A	0.22
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	0.22
IMPA2	inositol monophosphatase 2	0.21
PGAM1	phosphoglycerate mutase 1	0.21
HMOX1	heme oxygenase 1	0.21
GUSB	glucuronidase beta	0.21
NAPRT	nicotinate phosphoribosyltransferase	0.21
ATP6V1G1	ATPase H+ transporting V1 subunit G1	0.21
GALK1	galactokinase 1	0.20
PLCG2	phospholipase C gamma 2	0.20
AKR1A1	aldo-keto reductase family 1 member A1	0.20
G6PD	glucose-6-phosphate dehydrogenase	0.20
GYS1	glycogen synthase 1	0.20
DTYMK	deoxythymidylate kinase	0.20
BCKDHB	branched chain keto acid dehydrogenase E1 subunit beta	0.20
PGK1	phosphoglycerate kinase 1	0.20
HEXA	hexosaminidase subunit alpha	0.20
TPI1	triosephosphate isomerase 1	0.20
PANK2	pantothenate kinase 2	0.20
ALDH1A1	aldehyde dehydrogenase 1 family member A1	0.20
POLR3B	RNA polymerase III subunit B	0.20
ATP6V1B2	ATPase H+ transporting V1 subunit B2	0.20
AGL	amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase	0.20
CHKB	choline kinase beta	0.20
LPCAT1	lysophosphatidylcholine acyltransferase 1	0.20
PI4KA	phosphatidylinositol 4-kinase alpha	0.19
SMS	spermine synthase	0.19
IDH1	isocitrate dehydrogenase (NADP(+)) 1	0.19
MTHFD1	methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase	0.19
PCYT1A	phosphate cytidylyltransferase 1, choline, alpha	0.19
ATP6V1A	ATPase H+ transporting V1 subunit A	0.19

down-regulated proteins		Log_2FC
RPN1	ribophorin I	-0.03
IDH2	isocitrate dehydrogenase (NADP(+)) 2	-0.04
SHMT2	serine hydroxymethyltransferase 2	-0.04
NDUFV2	NADH-ubiquinone oxidoreductase core subunit V2	-0.04
MDH2	malate dehydrogenase 2	-0.04
PFKP	phosphofructokinase, platelet	-0.05
GOT2	glutamic-oxaloacetic transaminase 2	-0.05
DGUOK	deoxyguanosine kinase	-0.06
COX15	cytochrome c oxidase assembly homolog COX15	-0.06
AKR1C3	aldo-keto reductase family 1 member C3	-0.07
PLA2G4F	phospholipase A2 group IVF	-0.07
XDH	xanthine dehydrogenase	-0.07
ACSL4	acyl-CoA synthetase long chain family member 4	-0.07
HPSE	heparanase	-0.08
ATP5MC3	ATP synthase membrane subunit c locus 3	-0.08
HLCS	holocarboxylase synthetase	-0.08
UQCRQ	ubiquinol-cytochrome c reductase complex III subunit VII	-0.08
NDUFB8	NADH-ubiquinone oxidoreductase subunit B8	-0.09
PSAT1	phosphoserine aminotransferase 1	-0.09
PLCE1	phospholipase C epsilon 1	-0.09
NT5E	5'-nucleotidase ecto	-0.12
REV3L	REV3 like, DNA directed polymerase zeta catalytic subunit	-0.12
ATP5MG	ATP synthase membrane subunit g	-0.13
CHSY3	chondroitin sulfate synthase 3	-0.13
CPS1	carbamoyl-phosphate synthase 1	-0.14
LAMA5	laminin subunit alpha 5	-0.15
ITPKB	inositol-trisphosphate 3-kinase B	-0.16

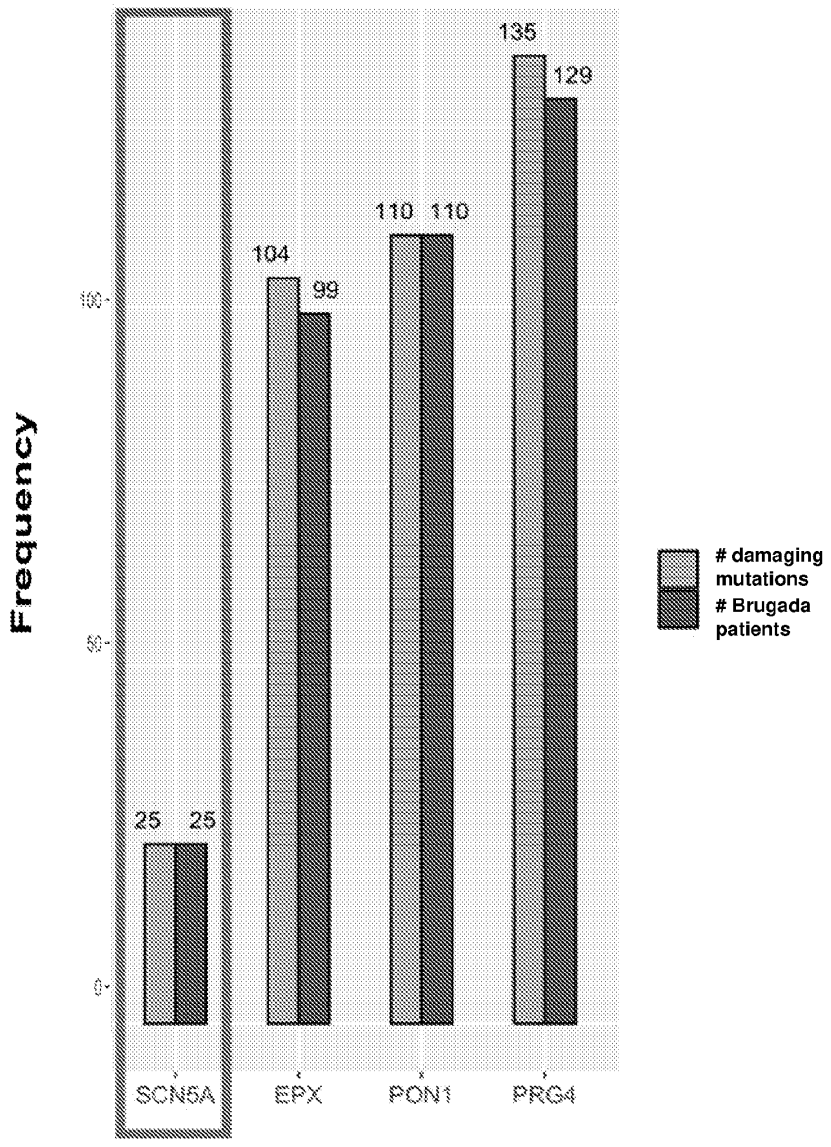
Fig. 7



Dysregulated proteins

UniProtKB ID	Protein	Description	Log_2 FC (fold change)	P-value
Q02750	MAP2K1	mitogen-activated protein kinase kinase 1	0.070	2.54E-03
P36507	MAP2K2	mitogen-activated protein kinase kinase 2	0.066	1.62E-05
Q04759	PRKCQ	protein kinase C theta	-0.056	1.66E-03

Fig. 8


Frequency
150
50
0
25
25
104
99
110
110
135
129
SCN5A
EPX
PON1
PRG4
damaging mutations
Brugada patients
Genes encoding for biomarker proteins