

FIGURE 1A

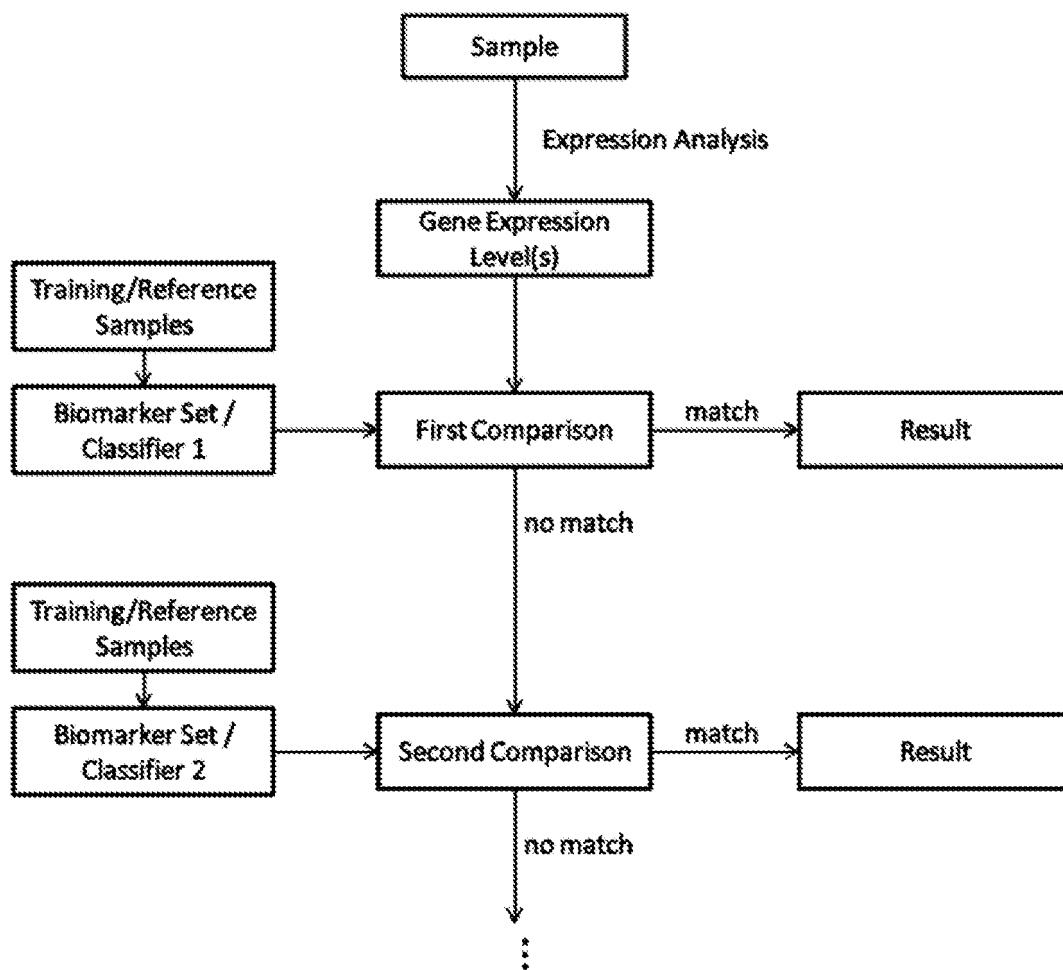


Fig.1B

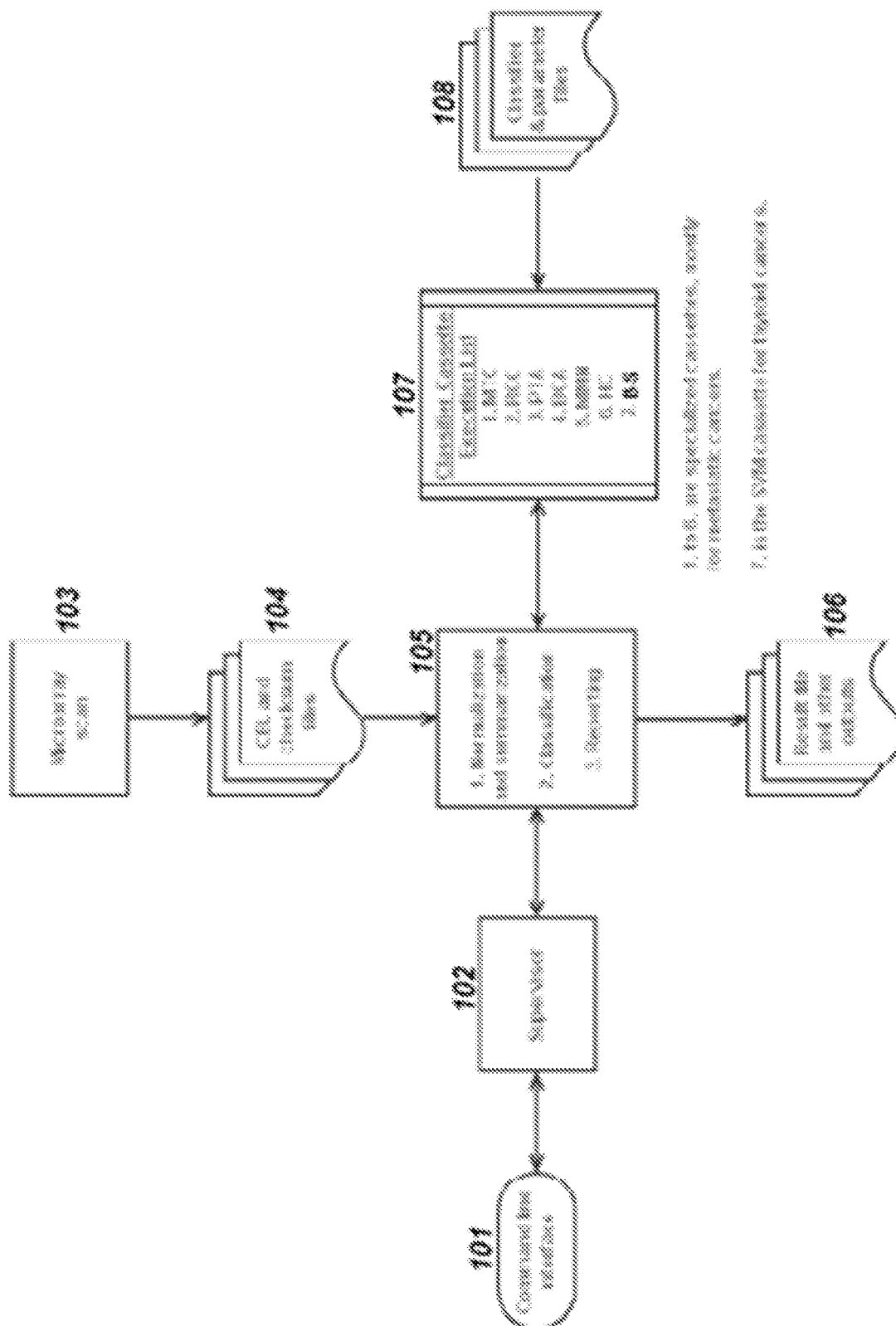


FIGURE 1B

Fig.1C

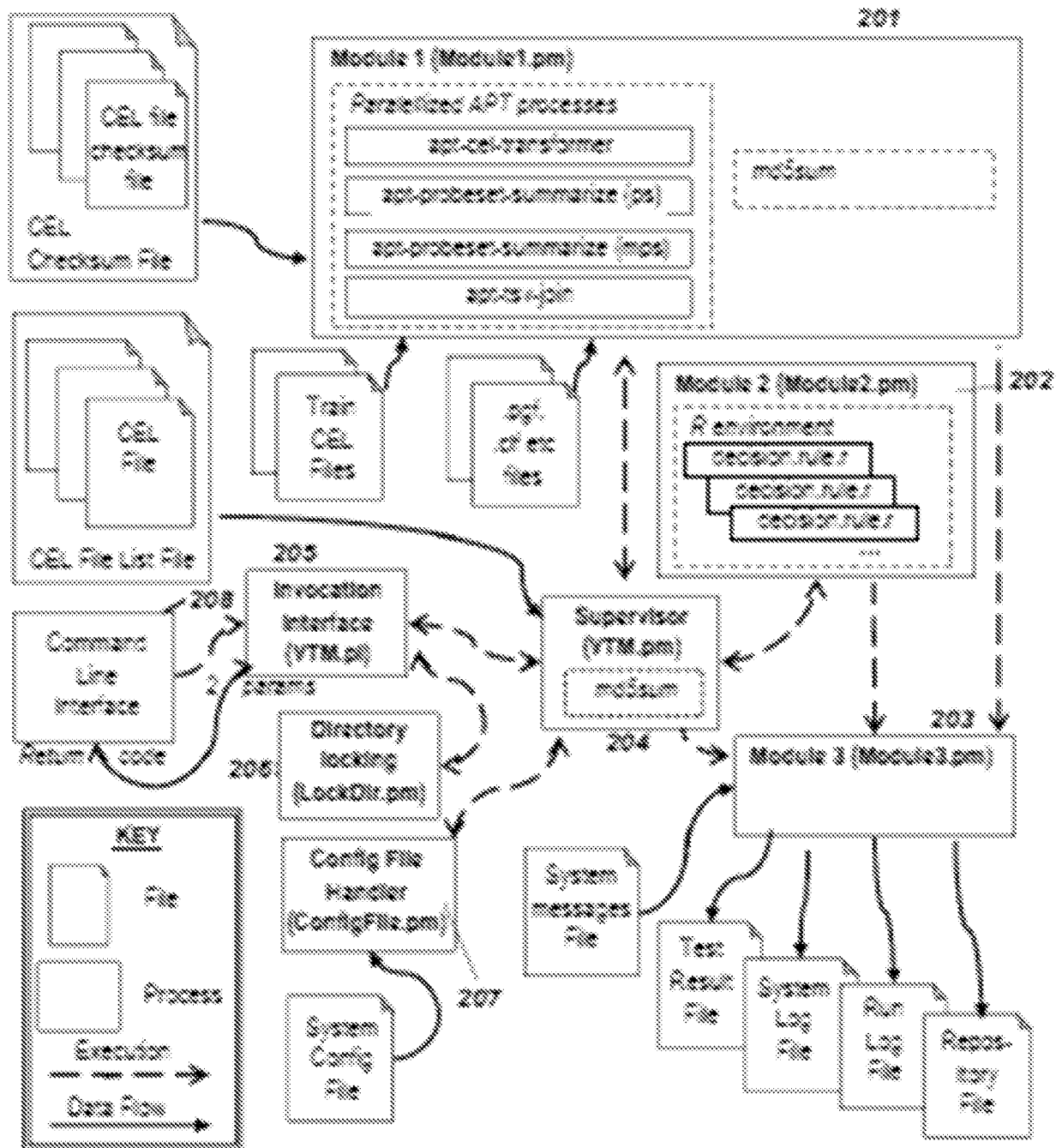


Fig.2

Gene Biomarker Panels for Diagnosing a Thyroid Condition

- | | |
|----|---|
| 1 | Normal Thyroid (NML) |
| 2 | Lymphocytic, Autoimmune Thyroiditis (LCT) |
| 3 | Nodular Hyperplasia (NHP) |
| 4 | Follicular Thyroid Adenoma (FA) |
| 5 | Hurthle Cell Thyroid Adenoma (HA) |
| 6 | Parathyroid (non thyroid tissue) (PTA) |
| 7 | Anaplastic Thyroid Carcinoma (ATC) |
| 8 | Follicular Thyroid Carcinoma (FC) |
| 9 | Hurthle Cell Thyroid Carcinoma (HC) |
| 10 | Papillary Thyroid Carcinoma (PTC) |
| 11 | Follicular Variant of Papillary Carcinoma (FVPTC) |
| 12 | Medullary Thyroid Carcinoma (MTC) |
| 13 | Renal Carcinoma metastasis to the Thyroid (RCC) |
| 14 | Melanoma metastasis to the Thyroid (MMN) |
| 15 | B cell Lymphoma metastasis to the Thyroid (BCL) |
| 16 | Breast Carcinoma metastasis to the Thyroid (BCA) |

Fig.3

FIGURE 3

Optimized Gene Classification Panels of Diagnostic Utility in Thyroid FNA

Classification Panel	Subtype-specific Classifier Components	Number of Markers Per Panel
1	MTC	5
2	RCC	5
3	PTA	5
4	BCA	5
5	MMN	5
6	HA & HC ¹	33
7	Benign/Suspicious ²	142

¹ denotes the combination of two panels -HA and HC- into a single panel.

² denotes the combination of eight panels -FA, FC, NHP, PTC, FVPTC, LCT, HA, HC- into a single panel.

Fig.4A

TCID	GENE	Gene Description	Classification Panel
3364127	CALCA	calcitonin-related polypeptide alpha	MTC
3834341	CEACAM5	carcinoembryonic antigen-related cell adhesion molecule 5	MTC
3594003	SCG3	secretogranin III	MTC
2583400	SCN2A	sodium channel, voltage-gated, type II, alpha subunit	MTC
2583400	SCN9A	sodium channel, voltage-gated, type IX, alpha subunit	MTC
3803614	SVT4	synaptotagmin IV	MTC
2923928	FABP7	fatty acid binding protein 7, brain	RCC
3393446	FXRD2	FXRD domain containing ion transport regulator 2	RCC
2883317	HAVCR1	hepatitis A virus cellular receptor 1	RCC
2883317	LOC100101266	hepatitis A virus cellular receptor 1 pseudogene	RCC
3428225	NR1H4	nuclear receptor subfamily 1, group H, member 4	RCC
2479698	PREPL	prolyl endopeptidase-like	RCC
2479698	SLC3A1	solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport), member 1	RCC
3159734	DMRT2	doublesex and mab-3 related transcription factor 2	PTA
2941690	GCM2	glial cells missing homolog 2 (Drosophila)	PTA
3363686	KIDINS220	kinase D-interacting substrate, 220kDa	PTA
3484893	KL	klotho	PTA
3363686	PTH	parathyroid hormone	PTA
2894790	SYCP2L	synaptonemal complex protein 2-like	PTA
3039830	AQR3	anterior gradient homolog 3 (Xenopus laevis)	BCA
3264997	C10orf81	chromosome 10 open reading frame 81	BCA
2926802	MYB	v-myb myeloblastosis viral oncogene homolog (avian)	BCA
3912079	SYCP2	synaptonemal complex protein 2	BCA
2430163	VTCN1	V-set domain containing T cell activation inhibitor 1	BCA
3811949	CDH19	cadherin 19, type 2	MMN

Fig.4B

TCID	GENE	Gene Description	Classification Panel
3161261	MLANA	melan-A	MMN
3935486	S100B	S100 calcium binding protein B	MMN
3437336	SILV	silver homolog (mouse)	MMN
3343832	TYR	tyrosinase (oculocutaneous albinism IA)	MMN
3343832	TYRL	tyrosinase-like (pseudogene)	MMN
2366348	AFF3	AF4/FMR1 family, member 3	HA & HC, Benign/Suspicious
2988982	ADMP2	aminoacyl tRNA synthetase complex-interacting multifunctional protein 2	HA & HC, Benign/Suspicious
3169331	ALDH1B1	aldehyde dehydrogenase 1 family, member B1	HA & HC, Benign/Suspicious
2984616	BRP44L	brain protein 44-like	HA & HC, Benign/Suspicious
2822492	C5orf30	chromosome 5 open reading frame 30	HA & HC, Benign/Suspicious
3326633	CD44	CD44 molecule (Indian blood group)	HA & HC, Benign/Suspicious
2750627	CPE	carboxypeptidase E	HA & HC, Benign/Suspicious
3042001	CYCS	cytochrome c, somatic	HA & HC, Benign/Suspicious
3122678	DEFB1	defensin, beta 1	HA & HC, Benign/Suspicious
2739308	EGF	epidermal growth factor (beta-urogastrone)	HA & HC, Benign/Suspicious
2988882	EIF2AK1	eukaryotic translation initiation factor 2-alpha kinase 1	HA & HC, Benign/Suspicious
3603932	FAH	fumarylacetoacetate hydrolase (fumarylacetoacetase)	HA & HC, Benign/Suspicious
2970897	FEK	lyn-related kinase	HA & HC, Benign/Suspicious
3212008	FERMD3	FERM domain containing 3	HA & HC, Benign/Suspicious
3302990	GOT1	glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)	HA & HC, Benign/Suspicious
3417703	HSD17B6	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	HA & HC, Benign/Suspicious
2877508	HSPA9	heat shock 70kDa protein 9 (mortalin)	HA & HC, Benign/Suspicious

Fig.4C

TCID	GENE	Gene Description	Classification Panel
2708922	IGF2BP2	insulin-like growth factor 2 mRNA binding protein 2	HA & HC, Benign/Suspicious
2604998	IQCA1	IQ motif containing with AAA domain 1	HA & HC, Benign/Suspicious
3724543	ITGB3	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	HA & HC, Benign/Suspicious
3397774	KCNJ1	potassium inwardly-rectifying channel, subfamily J, member 1	HA & HC, Benign/Suspicious
2604998	LOC100129258	hypothetical protein LOC100129258	HA & HC, Benign/Suspicious
3009299	MDH2	malate dehydrogenase 2, NAD (mitochondrial)	HA & HC, Benign/Suspicious
3654699	NUFR1	nuclear protein, transcriptional regulator, 1	HA & HC, Benign/Suspicious
4020633	ODZ1	odt, odd On ten-m homolog 1(Drosophila)	HA & HC, Benign/Suspicious
3970833	PDHA1	pyruvate dehydrogenase (lipoamide) alpha 1	HA & HC, Benign/Suspicious
2377094	PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2	HA & HC, Benign/Suspicious
3278198	PHYH	phytanoyl-CoA 2-hydroxylase	HA & HC, Benign/Suspicious
2880051	PPP2R2B	protein phosphatase 2 (formerly 2A), regulatory subunit B, beta isoform	HA & HC, Benign/Suspicious
3939862	PVALB	parvalbumin	HA & HC, Benign/Suspicious
2688499	PVRL2	policivirus receptor-related 2 (herpesvirus entry mediator B)	HA & HC, Benign/Suspicious
2604998	RPL3	ribosomal protein L3	HA & HC, Benign/Suspicious
2964231	REACD	Ras-related GTP binding D	HA & HC, Benign/Suspicious
2798538	SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	HA & HC, Benign/Suspicious
2798538	SDHALP1	succinate dehydrogenase complex, subunit A, flavoprotein pseudogene 1	HA & HC, Benign/Suspicious
2798538	SDHALP2	succinate dehydrogenase complex, subunit A, flavoprotein pseudogene 2	HA & HC, Benign/Suspicious

Fig.4D

TCID	GENE	Gene Description	Classification Panel
2798538	SDHAP3	succinate dehydrogenase complex, subunit A, flavoprotein pseudogene 3	HA & HC, Benign/Suspicious
2428301	SLC16A1	solute carrier family 16, member 1 (monocarboxylic acid transporter 1)	HA & HC, Benign/Suspicious
2877508	SNORD63	small nucleolar RNA, C/D box 63	HA & HC, Benign/Suspicious
2562529	ST3GAL5	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	HA & HC, Benign/Suspicious
2688499	ZBED2	zinc finger, BED-type containing 2	HA & HC, Benign/Suspicious
3450861	ABCD2	ATP-binding cassette, sub-family D (ALD), member 2	Benign/Suspicious
3341061	ACER3	alkaline ceramidase 3	Benign/Suspicious
2796353	ACSL1	acyl-CoA synthetase long-chain family member 1	Benign/Suspicious
3373733	AHNAK	AHNAK nucleoprotein	Benign/Suspicious
2439354	AIM2	absent in melanoma 2	Benign/Suspicious
3768474	ARSG	arylsulfatase G	Benign/Suspicious
3214845	ASPN	asporin	Benign/Suspicious
3006572	AUTS2	autism susceptibility candidate 2	Benign/Suspicious
3902489	BCL3L1	BCL2-like 1	Benign/Suspicious
2668717	BTLA	B and T lymphocyte associated	Benign/Suspicious
2708835	C11orf72	chromosome 11 open reading frame 72	Benign/Suspicious
2730303	C4orf7	chromosome 4 open reading frame 7	Benign/Suspicious
3239387	CC2D2B	coiled-coil and C2 domain containing 2B	Benign/Suspicious
3204285	CCL19	chemokine (C-C motif) ligand 19	Benign/Suspicious
3338192	CCND1	cyclin D1	Benign/Suspicious
3010503	CD36	CD36 molecule (thrombospondin receptor)	Benign/Suspicious
2326463	CD52	CD52 molecule	Benign/Suspicious
2633741	CD96	CD96 molecule	Benign/Suspicious
2373338	CFH	complement factor H	Benign/Suspicious
2373336	CFHR1	complement factor H-related 1	Benign/Suspicious
2710599	CLDN1	claudin 1	Benign/Suspicious
2657808	CLDN16	claudin 16	Benign/Suspicious

Fig.4E

TCID	GENE	Gene Description	Classification Panel
2377283	CR2	complement component (3d/Epstein Barr virus) receptor 2	Benign/Suspicious
3242353	CREM	cAMP responsive element modulator	Benign/Suspicious
2490351	CTNNA2	catenin (cadherin-associated protein), alpha 2	Benign/Suspicious
2732508	CXCL13	chemokine (C-X-C motif) ligand 13	Benign/Suspicious
2834645	DAB2	disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)	Benign/Suspicious
2321911	DDI2	DDI1, DNA-damage inducible 1, homolog 2 (S. cerevisiae)	Benign/Suspicious
2642791	DNAJC13	Deaf (Hsp40) homolog, subfamily C, member 13	Benign/Suspicious
2584018	DPP4	dipeptidyl-peptidase 4	Benign/Suspicious
3032647	DPP6	dipeptidyl-peptidase 6	Benign/Suspicious
2981874	DYNLT1	dynein, light chain, Yctex-type 1	Benign/Suspicious
2638676	EAF2	ELL associated factor 2	Benign/Suspicious
3832832	EMR3	egf-like module containing, mucin-like, hormone receptor-like 3	Benign/Suspicious
3142381	FABP4	fatty acid binding protein 4, adipocyte	Benign/Suspicious
2396730	FBXO2	F-box protein 2	Benign/Suspicious
3338192	FLJ42258	FLJ42258 protein	Benign/Suspicious
2526806	FN1	Fibronectin 1	Benign/Suspicious
2598261	FN1	Fibronectin 1	Benign/Suspicious
3839910	FPR2	formyl peptide receptor 2	Benign/Suspicious
3486096	FREM2	FRA51 related extracellular matrix protein 2	Benign/Suspicious
3393479	FXYS6	FXYS domain containing ion transport regulator 6	Benign/Suspicious
2378068	G0S2	G0/G1 switch 2	Benign/Suspicious
2884845	GABRB2	gamma-aminobutyric acid (GABA) A receptor, beta 2	Benign/Suspicious
3083793	GALNT4	galactose-3-O-sulfotransferase 4	Benign/Suspicious
3031556	GIMAP2	GTPase, GIMAP family member 2	Benign/Suspicious
3861948	GMFG	glia maturation factor, gamma	Benign/Suspicious
3540862	GPHN	gephyrin	Benign/Suspicious
3982612	GPR174	G protein-coupled receptor 174	Benign/Suspicious
2809793	GZMK	granzyme K (granzyme 3, tryptase II)	Benign/Suspicious
2638676	HCG11	HLA complex group 11	Benign/Suspicious
2332609	HNRNPA3	heterogeneous nuclear ribonucleoprotein A3	Benign/Suspicious
3373735	IGHG1	immunoglobulin heavy constant gamma 1 (G1m marker)	Benign/Suspicious
2806468	IL7R	interleukin 7 receptor	Benign/Suspicious

Fig.4F

TCID	GENE	Gene Description	Classification Panel
2377283	CR2	complement component (3d/Epstein Barr virus) receptor 2	Benign/Suspicious
3242353	CREM	cAMP responsive element modulator	Benign/Suspicious
2490351	CTNNA2	catenin (cadherin-associated protein), alpha 2	Benign/Suspicious
2732508	CXCL13	chemokine (C-X-C motif) ligand 13	Benign/Suspicious
2834645	DAB2	disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)	Benign/Suspicious
2321911	DDI2	DDI1, DNA-damage inducible 1, homolog 2 (S. cerevisiae)	Benign/Suspicious
2642791	DNAJC13	Deaf (Hsp40) homolog, subfamily C, member 13	Benign/Suspicious
2584018	DPP4	dipeptidyl-peptidase 4	Benign/Suspicious
3032647	DPP6	dipeptidyl-peptidase 6	Benign/Suspicious
2981874	DYNLT1	dynein, light chain, Yctex-type 1	Benign/Suspicious
2638676	EAF2	ELL associated factor 2	Benign/Suspicious
3832832	EMR3	egf-like module containing, mucin-like, hormone receptor-like 3	Benign/Suspicious
3142381	FABP4	fatty acid binding protein 4, adipocyte	Benign/Suspicious
2396730	FBXO2	F-box protein 2	Benign/Suspicious
3338192	FLJ42258	FLJ42258 protein	Benign/Suspicious
2526806	FN1	Fibronectin 1	Benign/Suspicious
2598261	FN1	Fibronectin 1	Benign/Suspicious
3839910	FPR2	formyl peptide receptor 2	Benign/Suspicious
3486096	FREM2	FRA1 related extracellular matrix protein 2	Benign/Suspicious
3393479	FXND6	FXND domain containing ion transport regulator 6	Benign/Suspicious
2378068	G0S2	G0/G1 switch 2	Benign/Suspicious
2884845	GABRB2	gamma-aminobutyric acid (GABA) A receptor, beta 2	Benign/Suspicious
3083793	GALNT4	galactose-3-O-sulfotransferase 4	Benign/Suspicious
3031556	GIMAP2	GTPase, GIMAP family member 2	Benign/Suspicious
3861948	GMFG	glia maturation factor, gamma	Benign/Suspicious
3540862	GPHN	gephyrin	Benign/Suspicious
3982612	GPR174	G protein-coupled receptor 174	Benign/Suspicious
2809793	GZMK	granzyme K (granzyme 3, tryptase II)	Benign/Suspicious
2638676	HCG11	HLA complex group 11	Benign/Suspicious
2332609	HNRNPA3	heterogeneous nuclear ribonucleoprotein A3	Benign/Suspicious
3373735	IGHG1	immunoglobulin heavy constant gamma 1 (G1m marker)	Benign/Suspicious
2806468	IL7R	interleukin 7 receptor	Benign/Suspicious

Fig.4G

YCID	GENE	Gene Description	Classification Panel
3875642	PLCB1	phospholipase C, beta 1 (phosphoinositide-specific)	Benign/Suspicious
2456811	PLEK	pleckstrin	Benign/Suspicious
3246888	PRKG1	protein kinase, cGMP-dependent, type I	Benign/Suspicious
3874731	PRNP	prion protein	Benign/Suspicious
2685304	PROS1	protein S (alpha)	Benign/Suspicious
2373842	PTPNC	protein tyrosine phosphatase, receptor type, C	Benign/Suspicious
3270270	PTPRE	protein tyrosine phosphatase, receptor type, E	Benign/Suspicious
3264210	PYGL	phosphorylase, glycogen, liver	Benign/Suspicious
2362351	PYHIN1	pyrin and HIN domain family, member 1	Benign/Suspicious
3443464	PZP	pregnancy-zone protein	Benign/Suspicious
2372312	RGS13	regulator of G-protein signaling 13	Benign/Suspicious
3110393	REMS2	regulating synaptic membrane exocytosis 2	Benign/Suspicious
3893793	RNF24	ring finger protein 24	Benign/Suspicious
2721939	ROS1	c-ras oncogene 1, receptor tyrosine kinase	Benign/Suspicious
2442008	RXRG	retinoid X receptor, gamma	Benign/Suspicious
3494629	SCEL	scellin	Benign/Suspicious
2904483	SCUBE3	signal peptide, CUB domain, EGF-like 3	Benign/Suspicious
3039667	SEMA3D	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3D	Benign/Suspicious
3365136	SERGEF	secretion regulating guanine nucleotide exchange factor	Benign/Suspicious
3577612	SERPINA1	serpin peptidase inhibitor, clade A (alpha-1 antitrypsin), member 1	Benign/Suspicious
3577612	SERPINA2	serpin peptidase inhibitor, clade A (alpha-1 antitrypsin), member 2	Benign/Suspicious
3759006	SHC1	SHC (Src homology 2 domain containing) transforming protein 1	Benign/Suspicious
2440258	SLAMF6	SLAM family member 6	Benign/Suspicious
3622934	SLC24A3	solute carrier family 24, member 3	Benign/Suspicious
3183522	SLC31A1	solute carrier family 31 (copper transporters), member 1	Benign/Suspicious
2721959	SLC34A2	solute carrier family 34 (sodium phosphate), member 2	Benign/Suspicious
3761939	SLC35B1	solute carrier family 35, member B1	Benign/Suspicious
3373843	SLC43A3	solute carrier family 43, member 3	Benign/Suspicious
3759006	SLC4A1	solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group)	Benign/Suspicious
2730746	SLC4A4	solute carrier family 4, sodium bicarbonate cotransporter, member 4	Benign/Suspicious

Fig.4H

TCID	GENE	Gene Description	Classification Panel
2777714	SNCA	synuclein, alpha (non A4 component of amyloid precursor)	Benign/Suspicious
2834282	STK32A	serine/threonine kinase 32A	Benign/Suspicious
3341497	THRSS	thyroid hormone responsive (SPOT14 homolog, rat)	Benign/Suspicious
3976341	TIMP1	TIMP metalloproteinase inhibitor 1	Benign/Suspicious
3772661	TIMP2	TIMP metalloproteinase inhibitor 2	Benign/Suspicious
2491271	TMSB10	thymosin beta 10	Benign/Suspicious
3648391	TNFRSF17	tumor necrosis factor receptor superfamily, member 17	Benign/Suspicious
3441849	TNFRSF1A	tumor necrosis factor receptor superfamily, member 1A	Benign/Suspicious
2412668	TXNDC12	thioredoxin domain containing 12 (endoplasmic reticulum)	Benign/Suspicious
3353914	VWFA5A	von Willebrand factor A domain containing 5A	Benign/Suspicious
3976766	WAS	Wiskott-Aldrich syndrome (eczema-thrombocytopenia)	Benign/Suspicious
3768474	WIP1	WD repeat domain, phosphoinositide interacting 1	Benign/Suspicious
2817731	ZFYVE16	zinc finger, FYVE domain containing 16	Benign/Suspicious
4027585	unknown		Benign/Suspicious

Fig.5

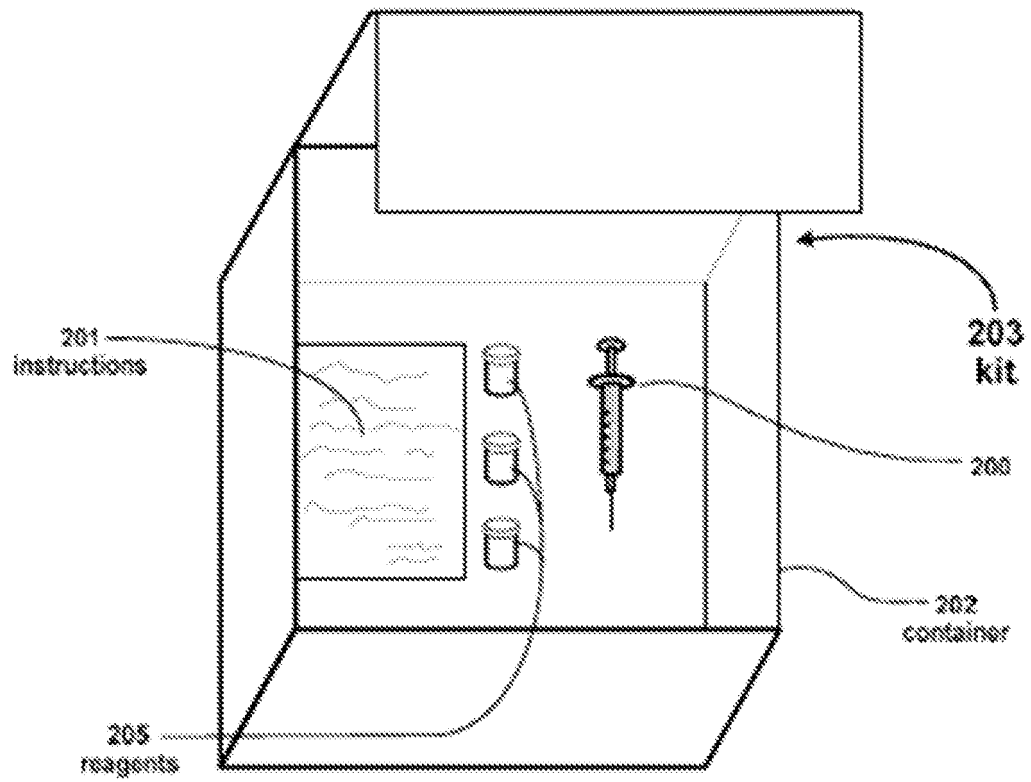


Fig.6

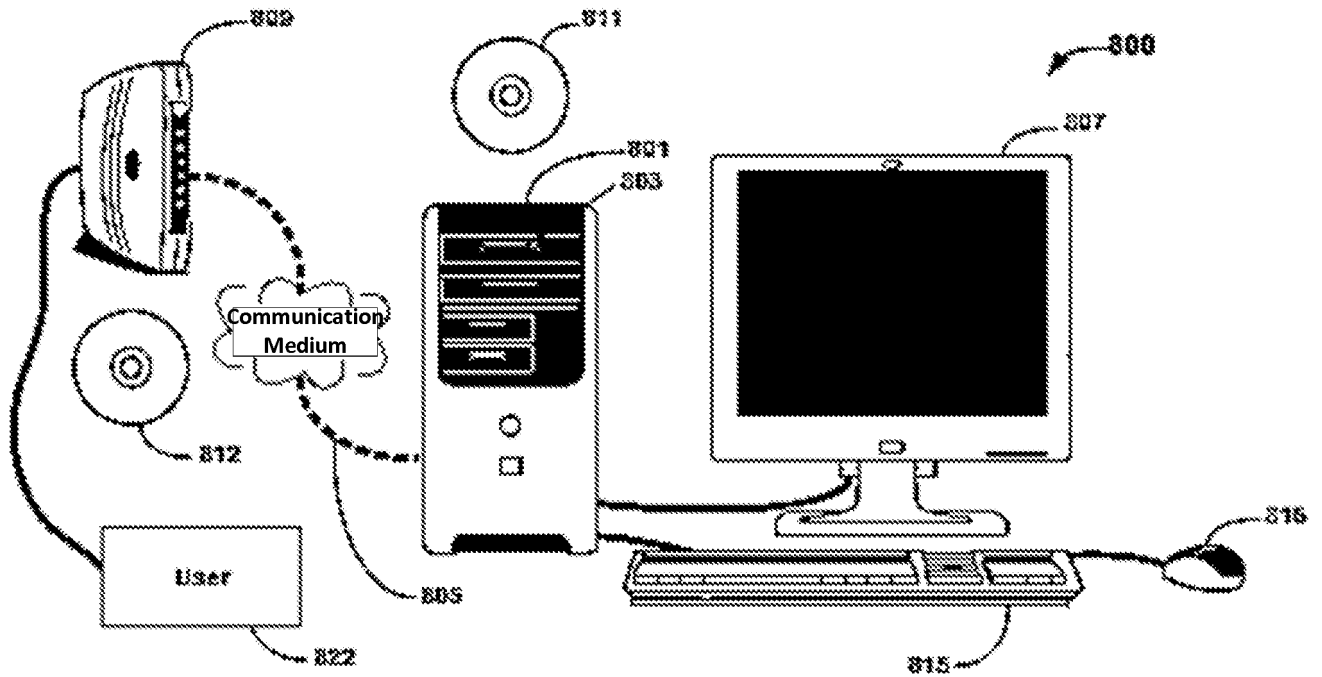


Fig.7

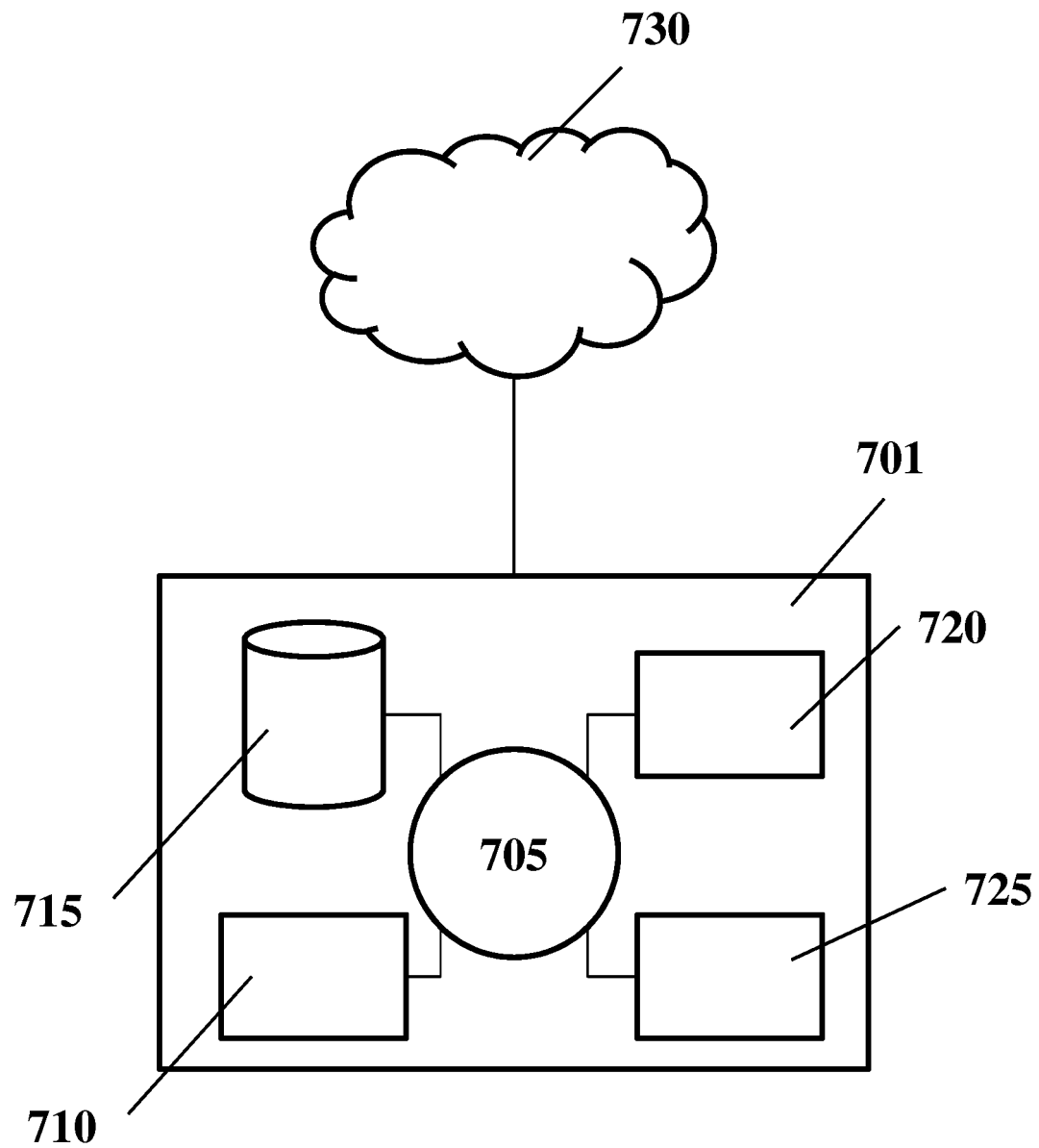


Fig.8

SLC4A1

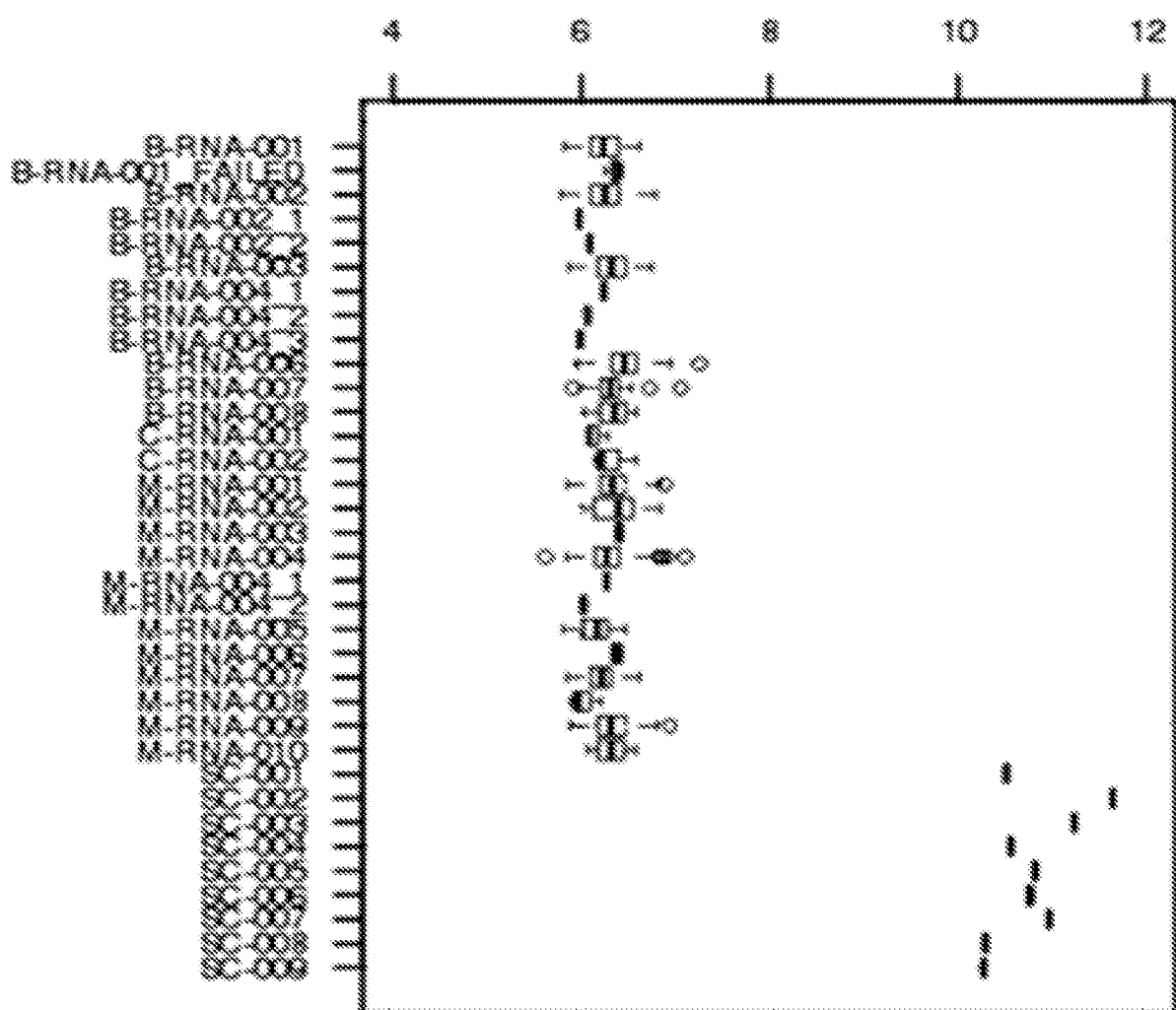


Fig.9

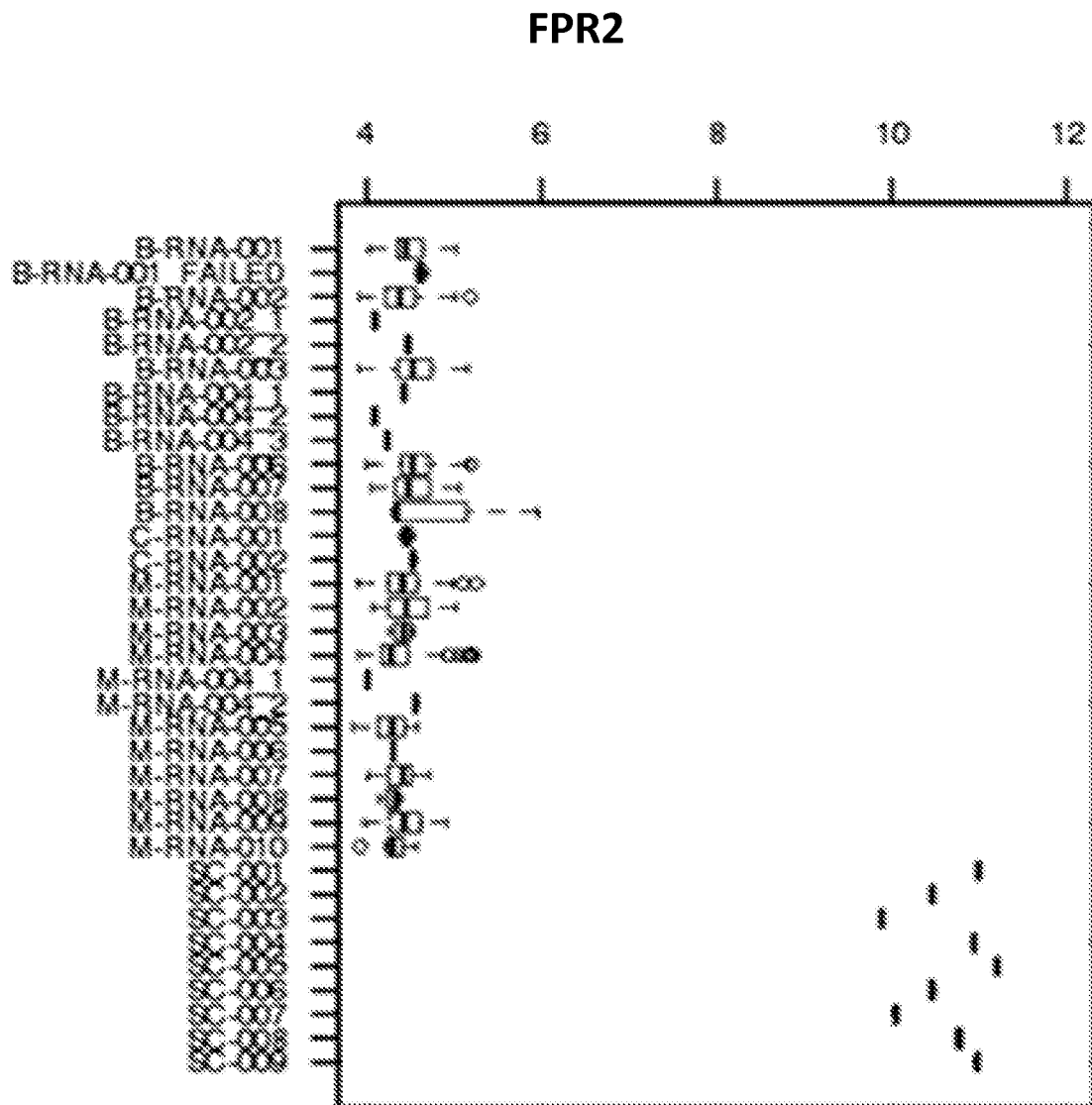


Fig.10

EMR3

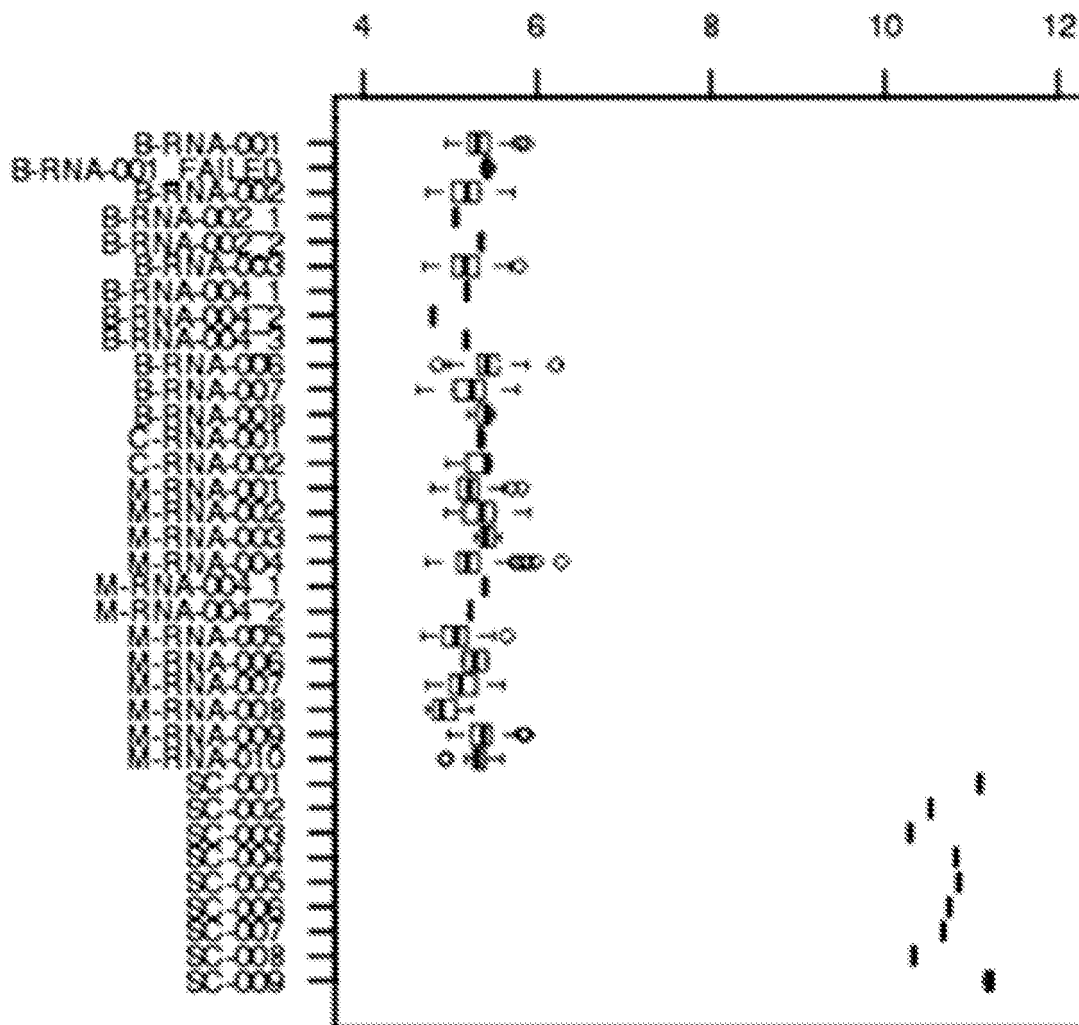


Fig.11

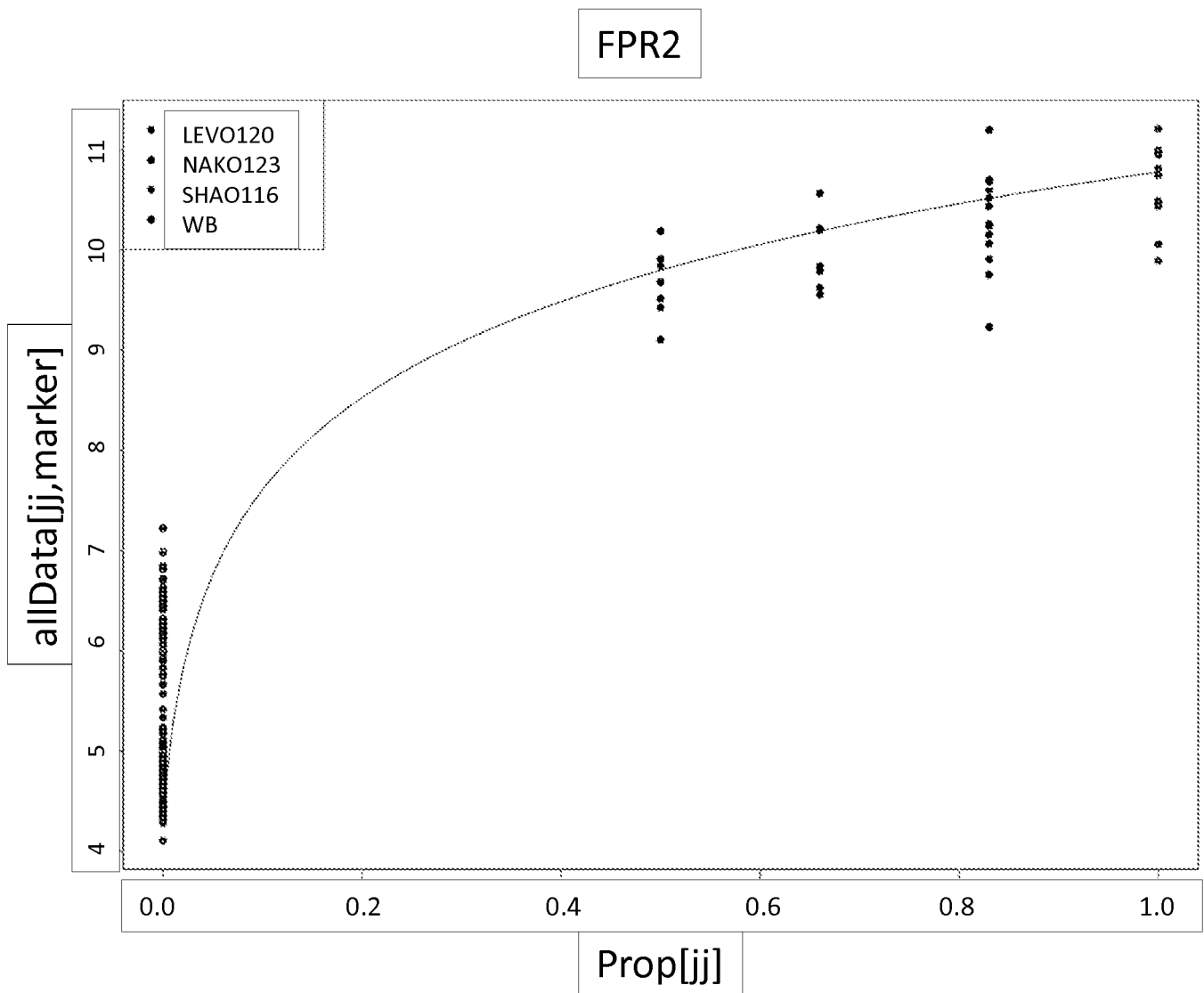


Fig.12

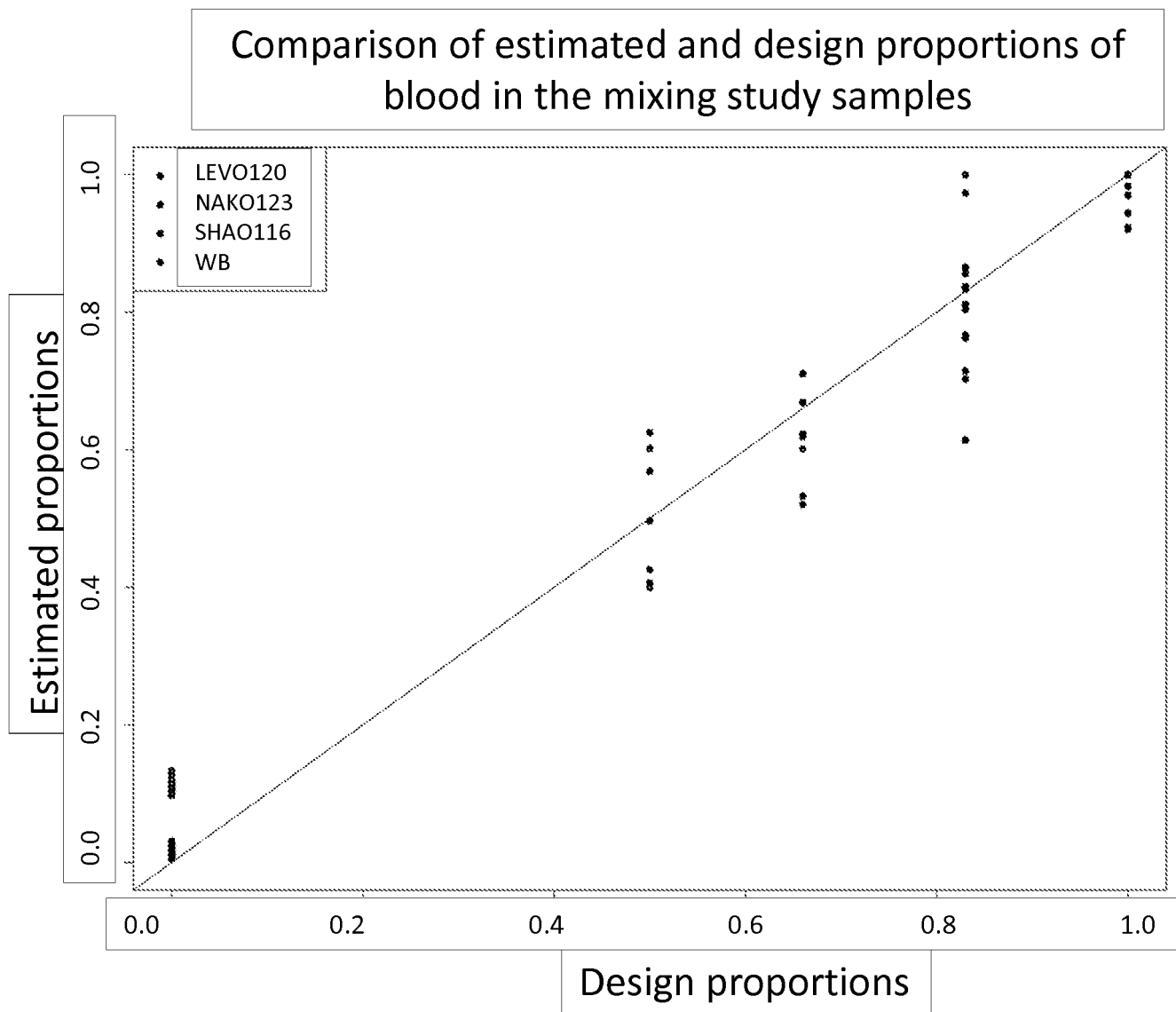


Fig.13

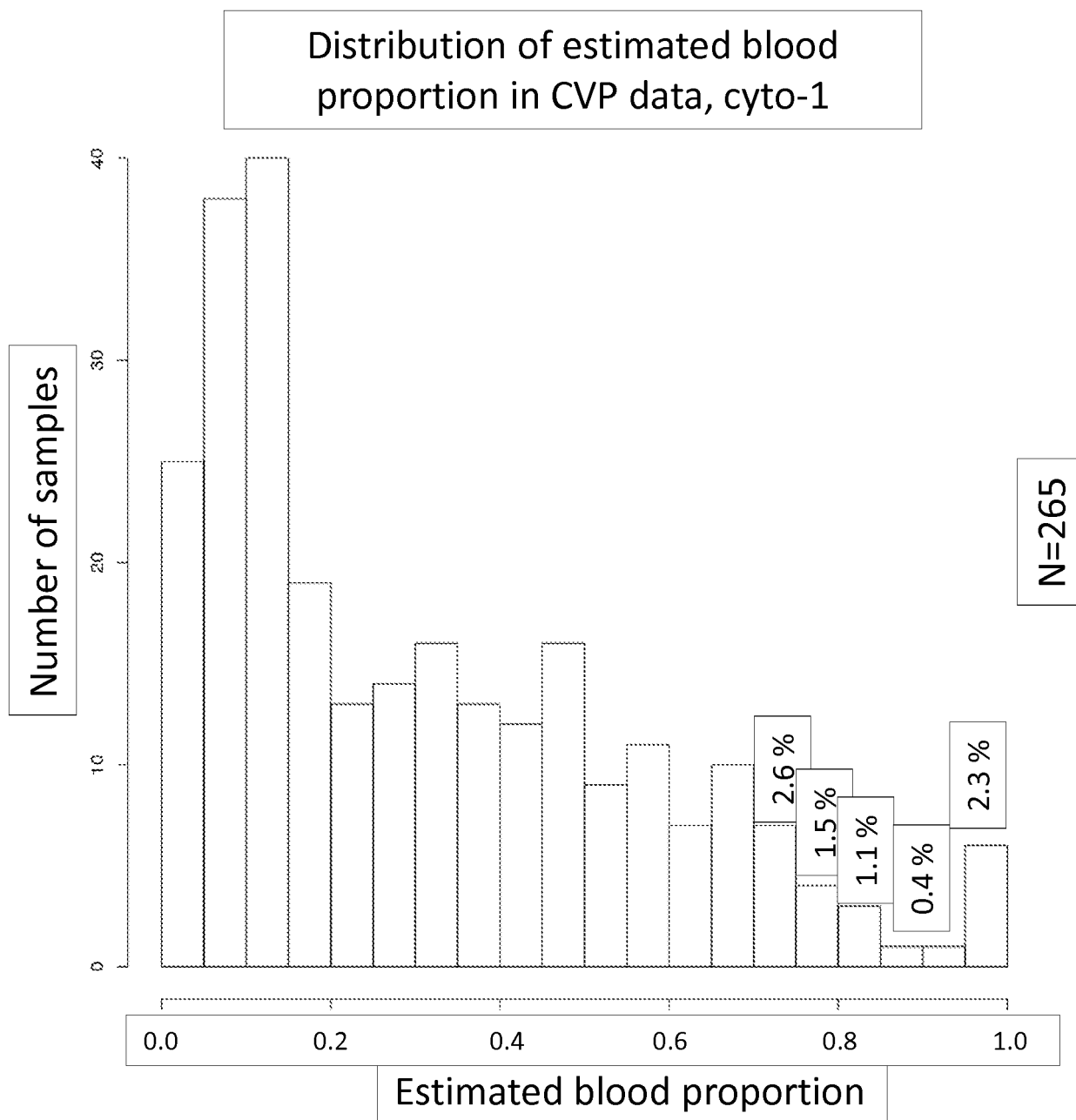


Fig.14A

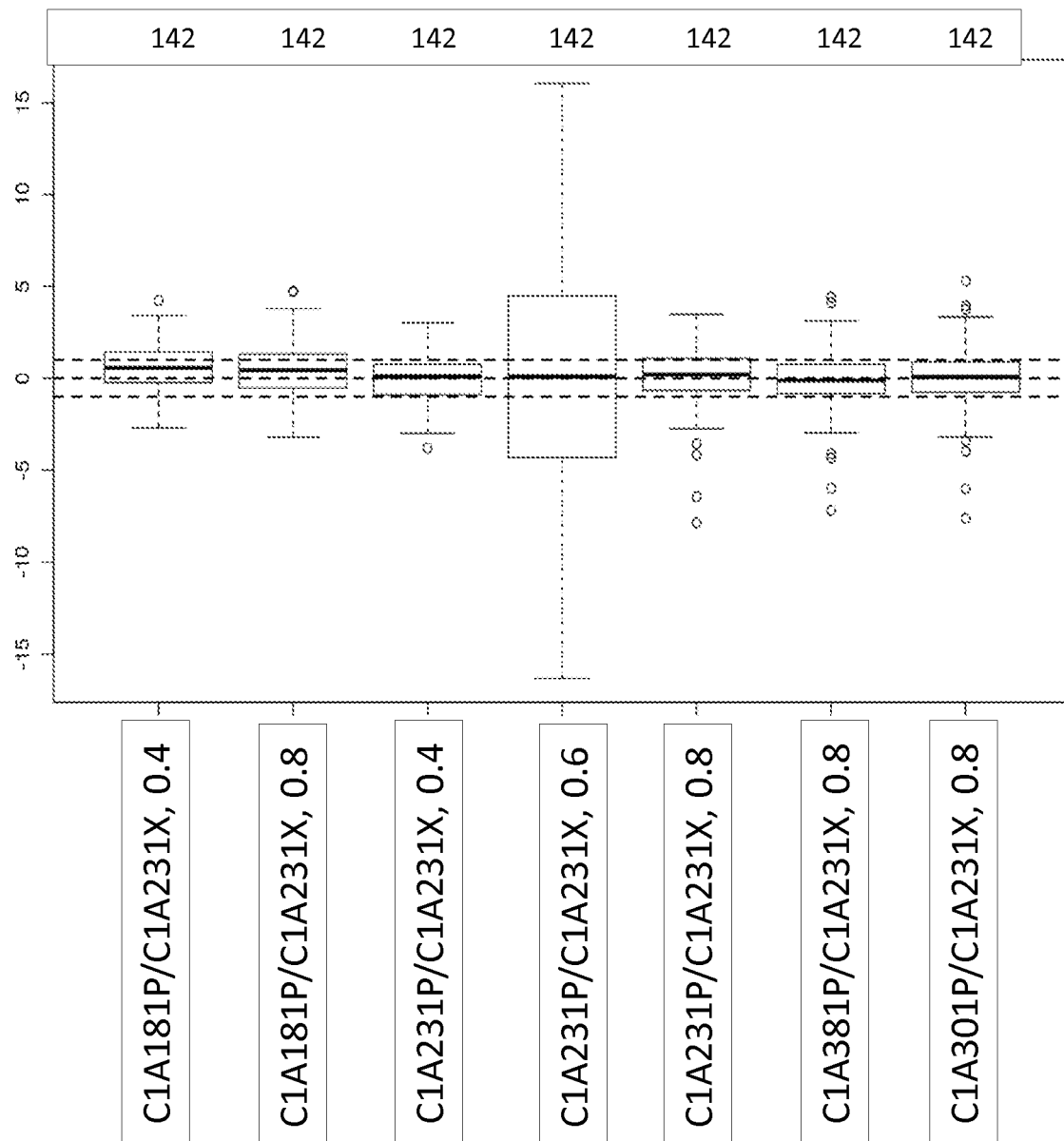


Fig.14B

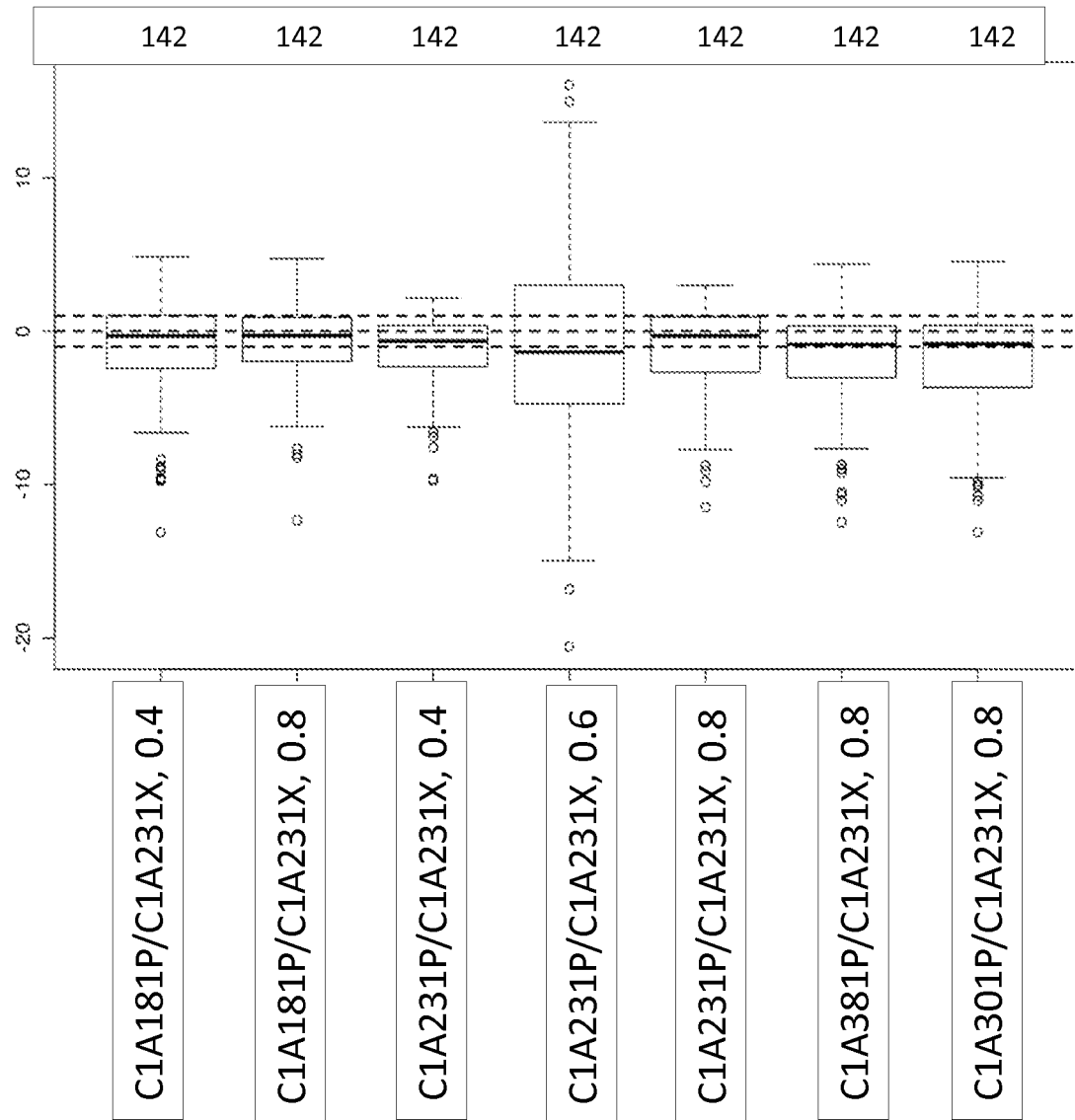


Fig.15

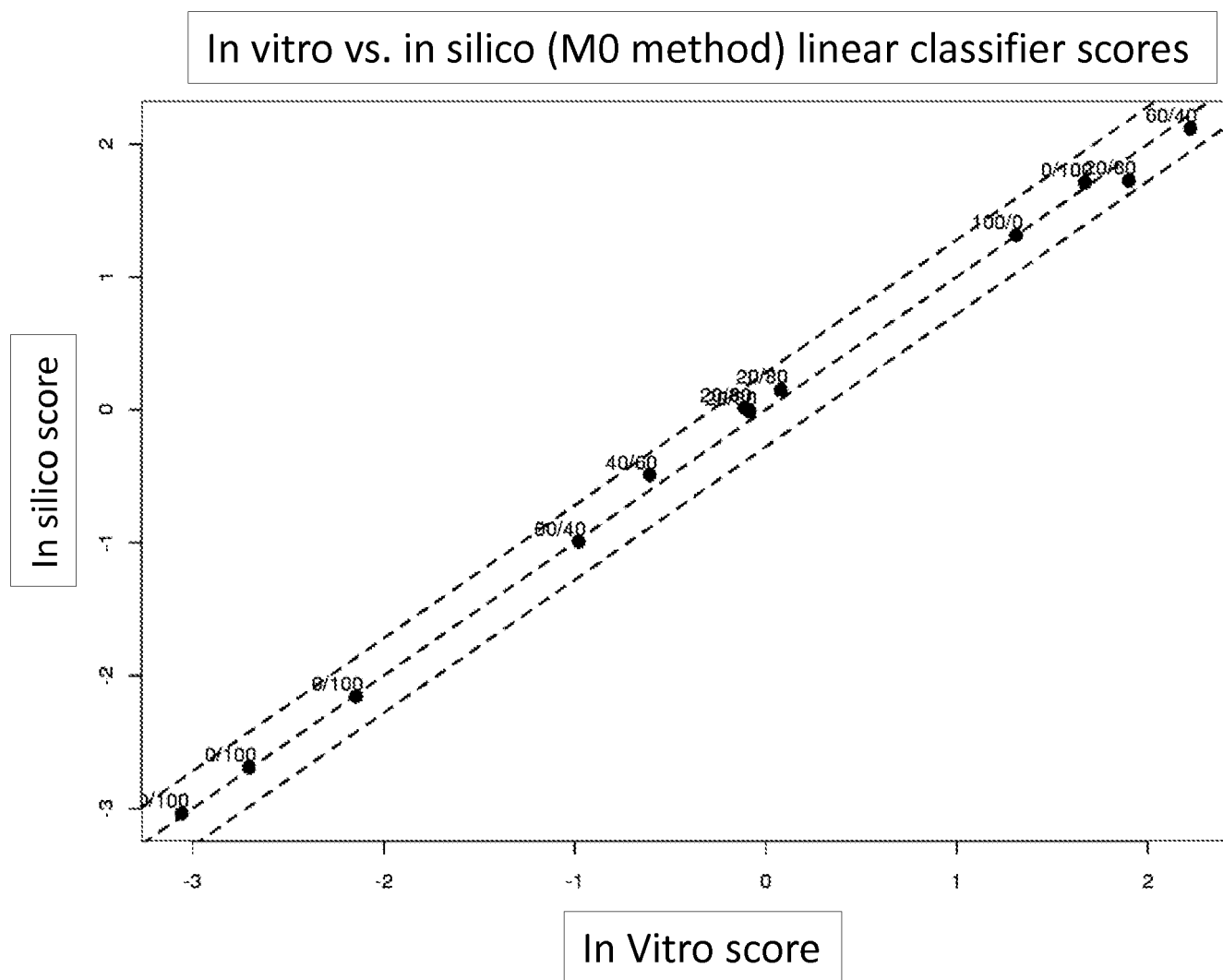


Fig.16

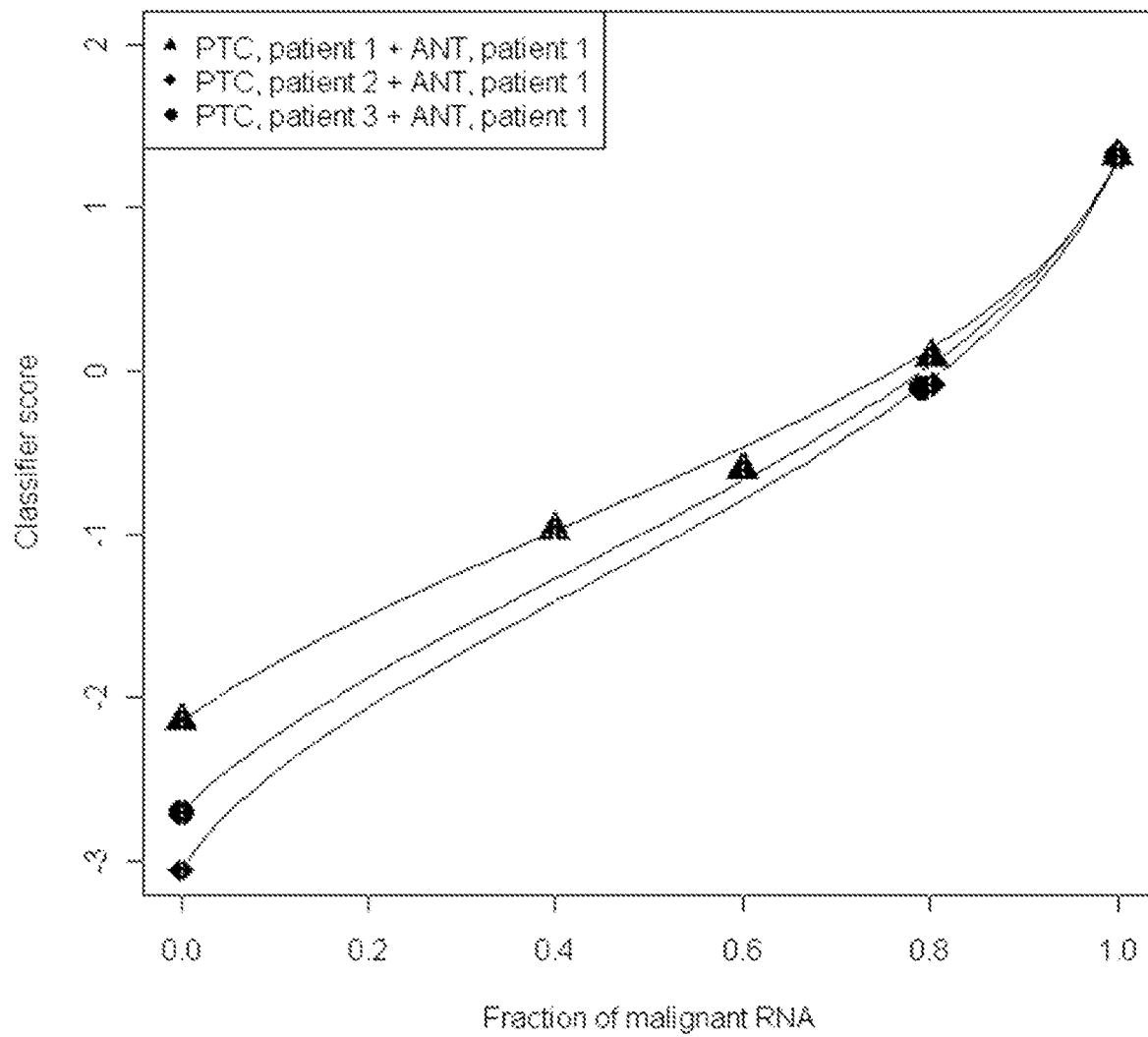


Fig.17

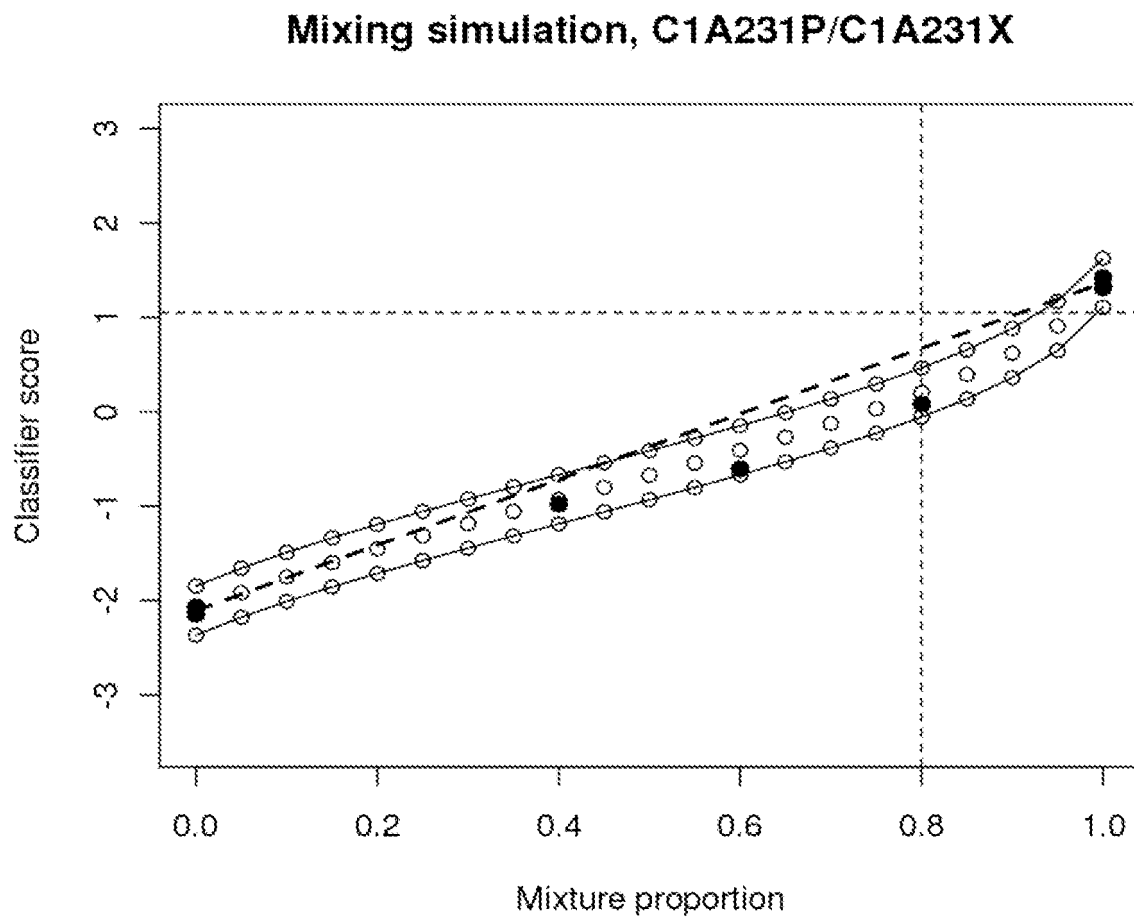


Fig.18

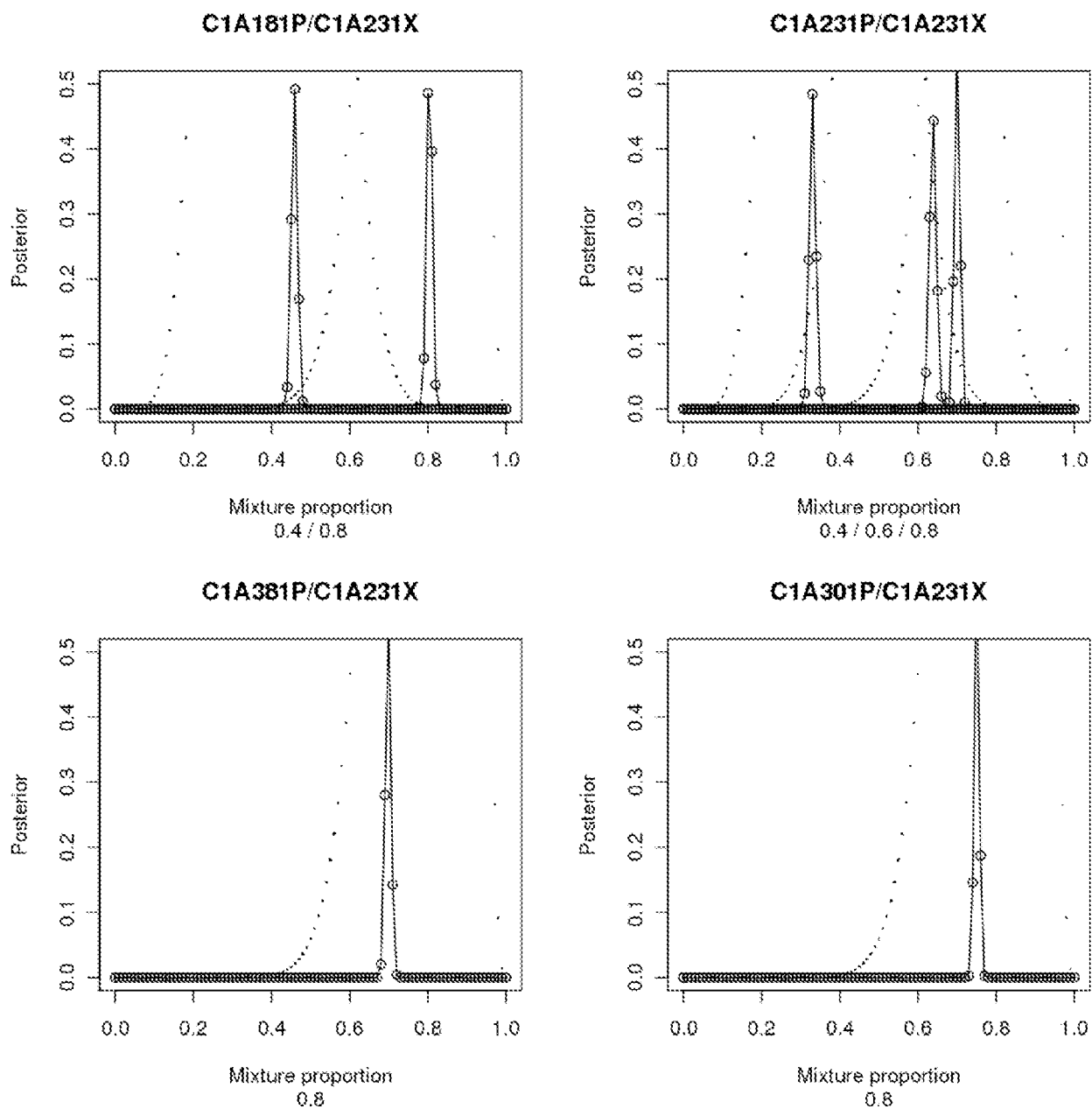
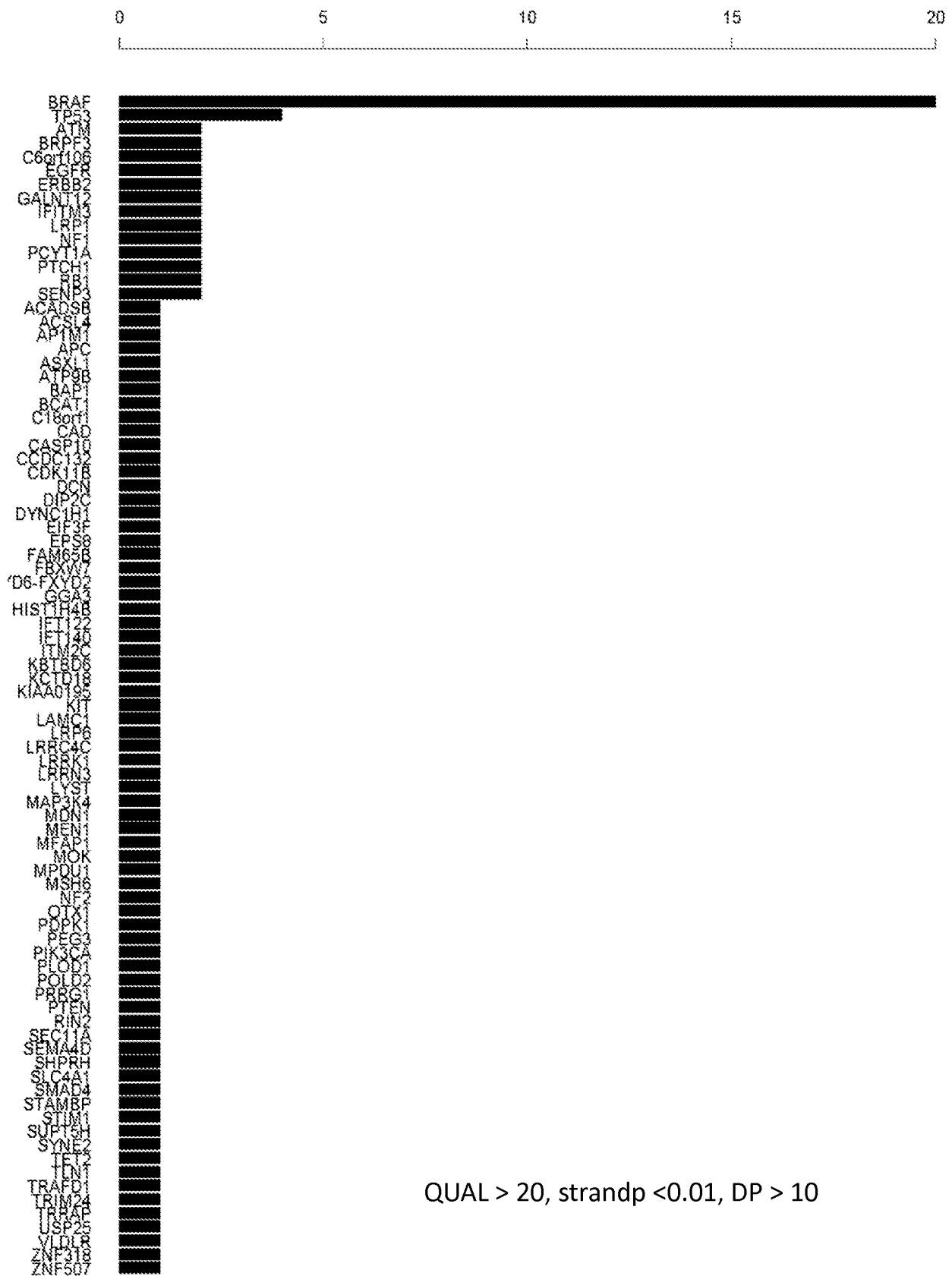


Fig.19



QUAL > 20, strandp < 0.01, DP > 10

Fig.20

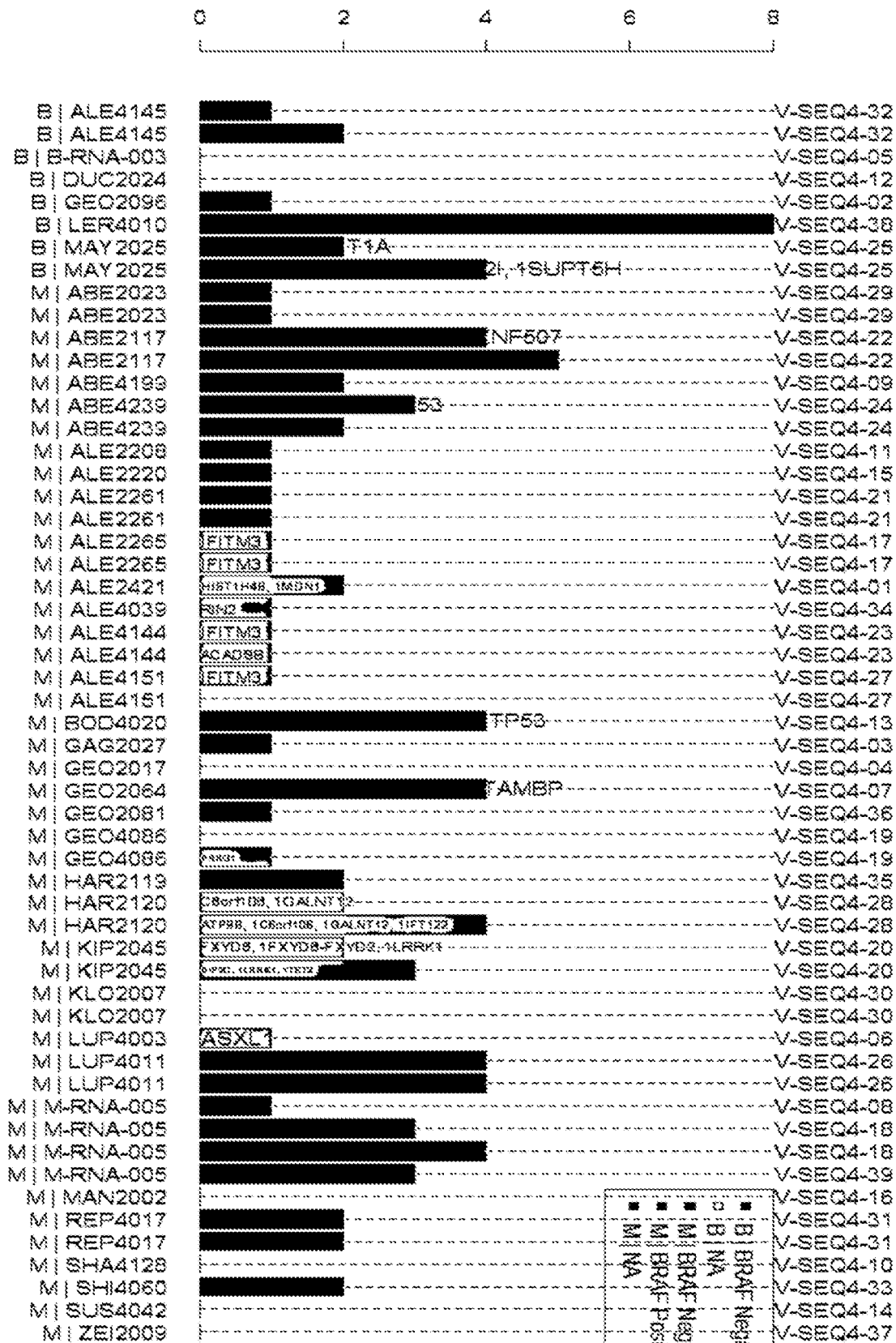


Fig.21

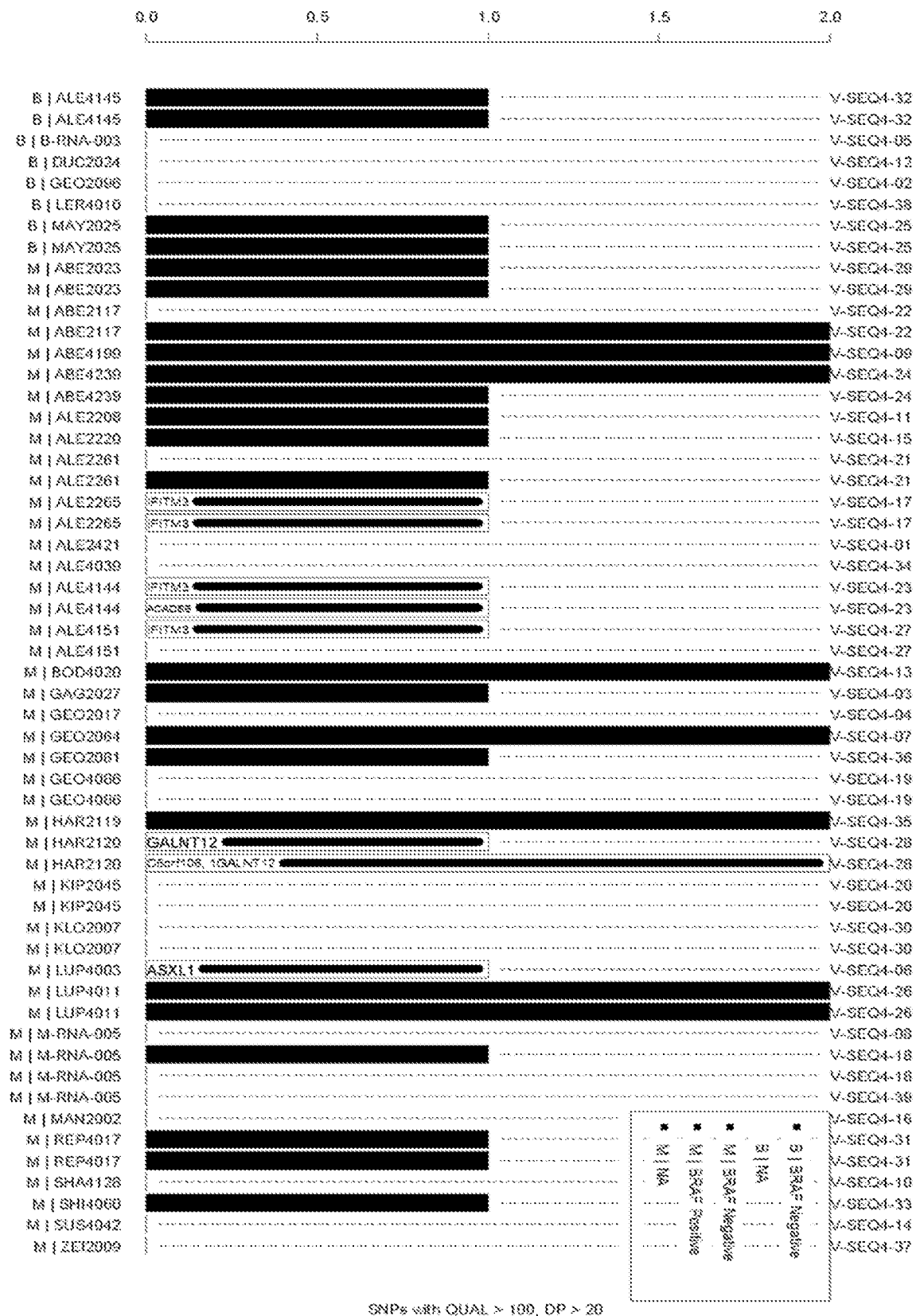


Fig.22

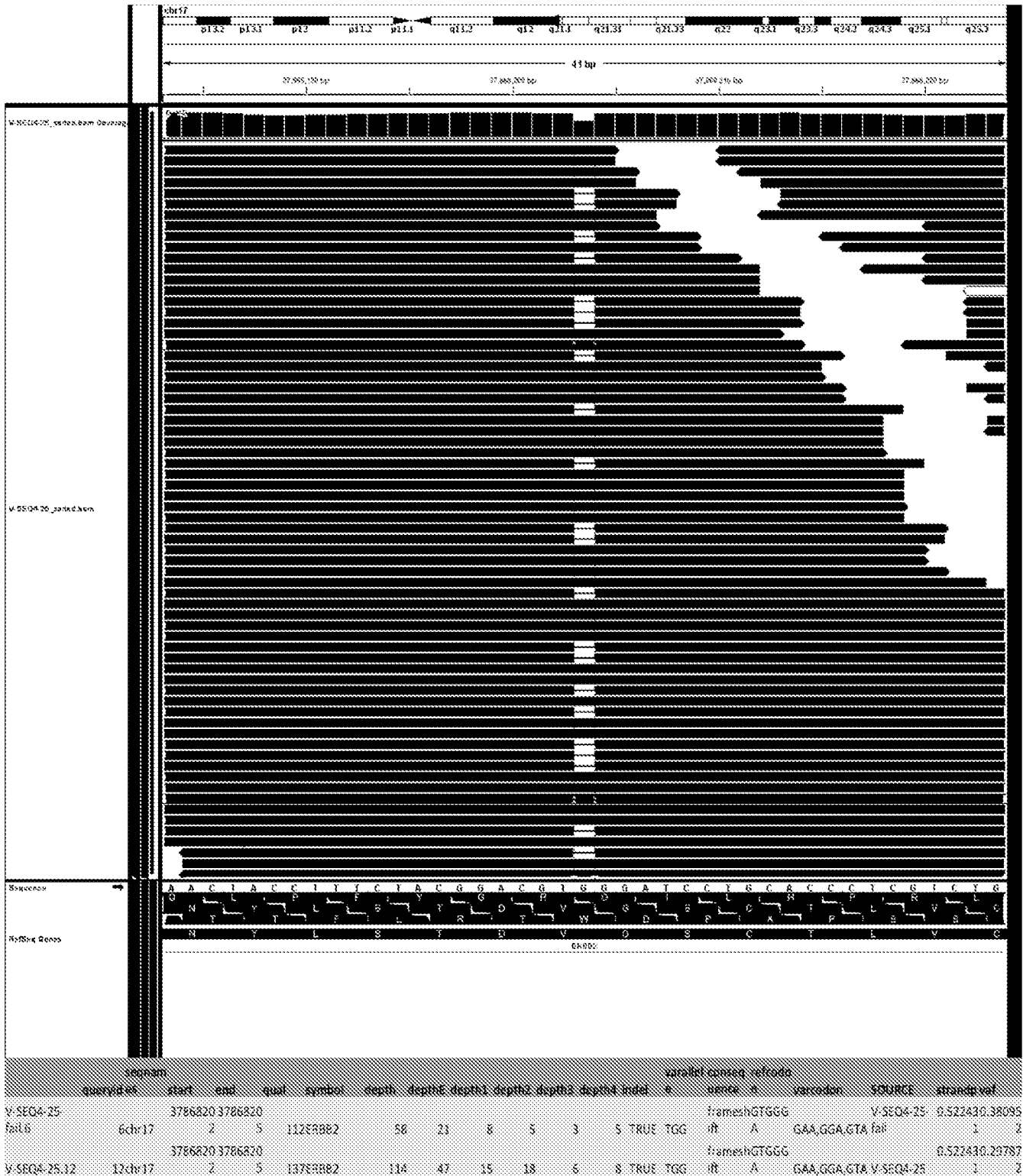


Fig.23

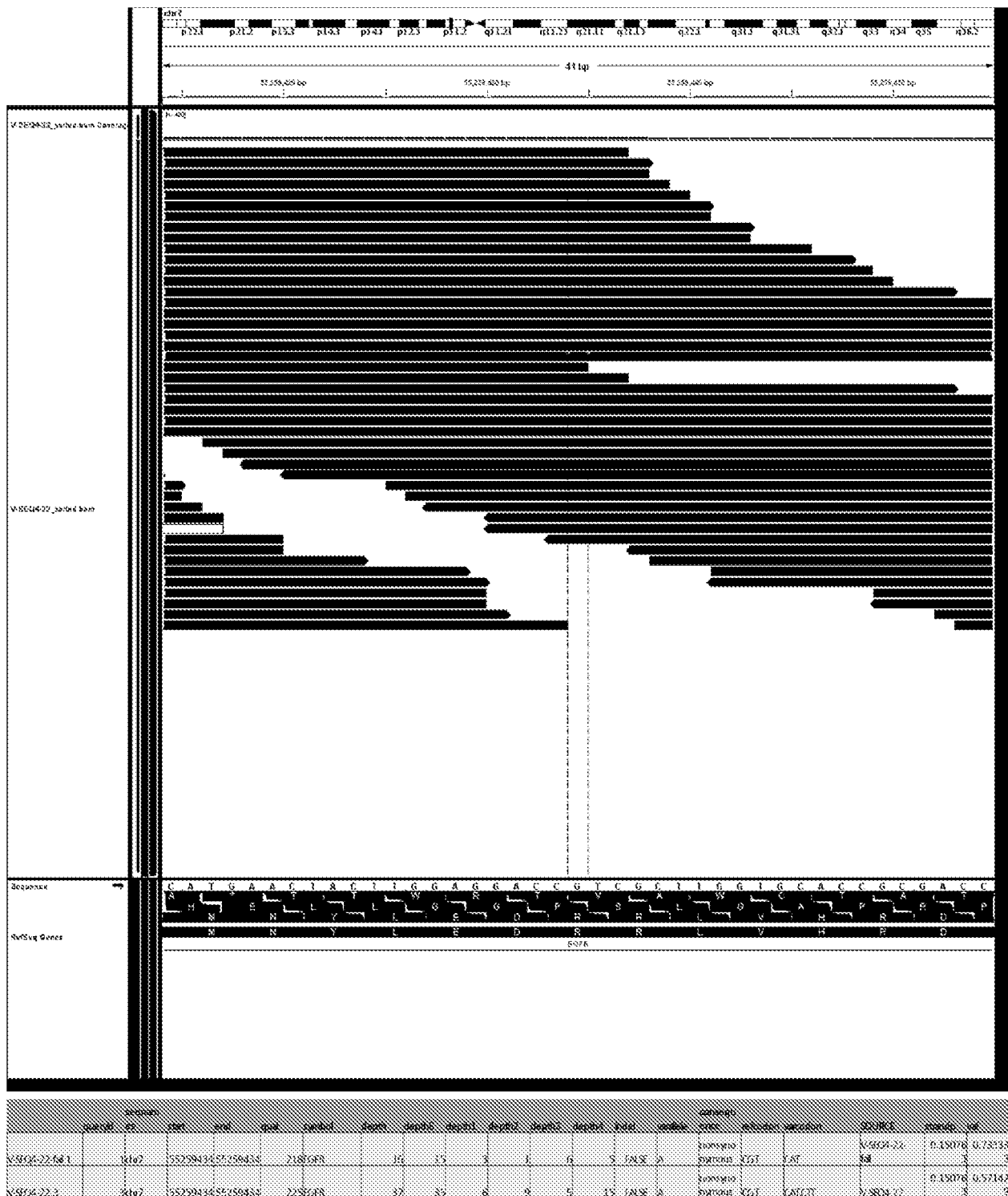


Fig.24A

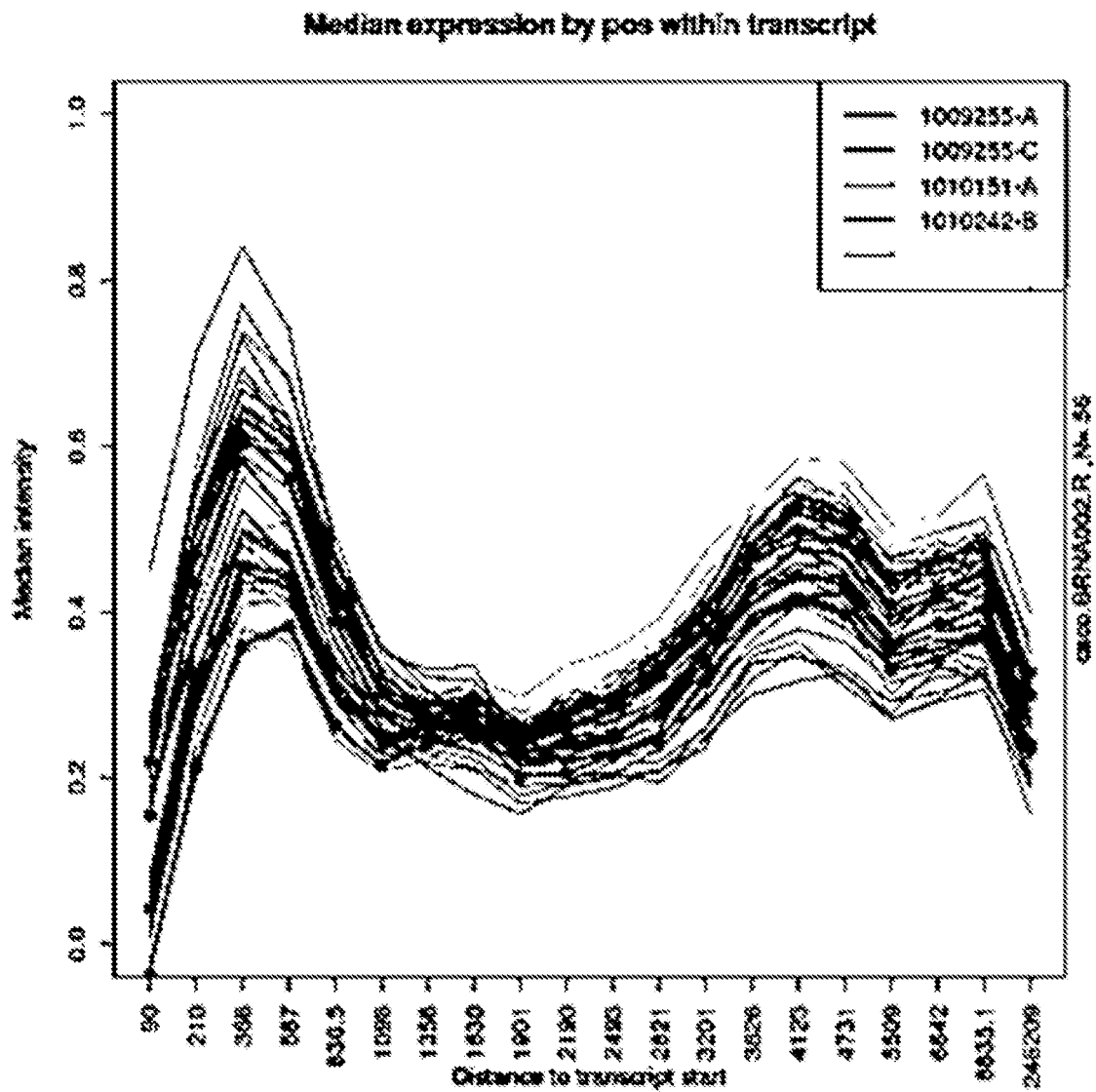


Fig.24B

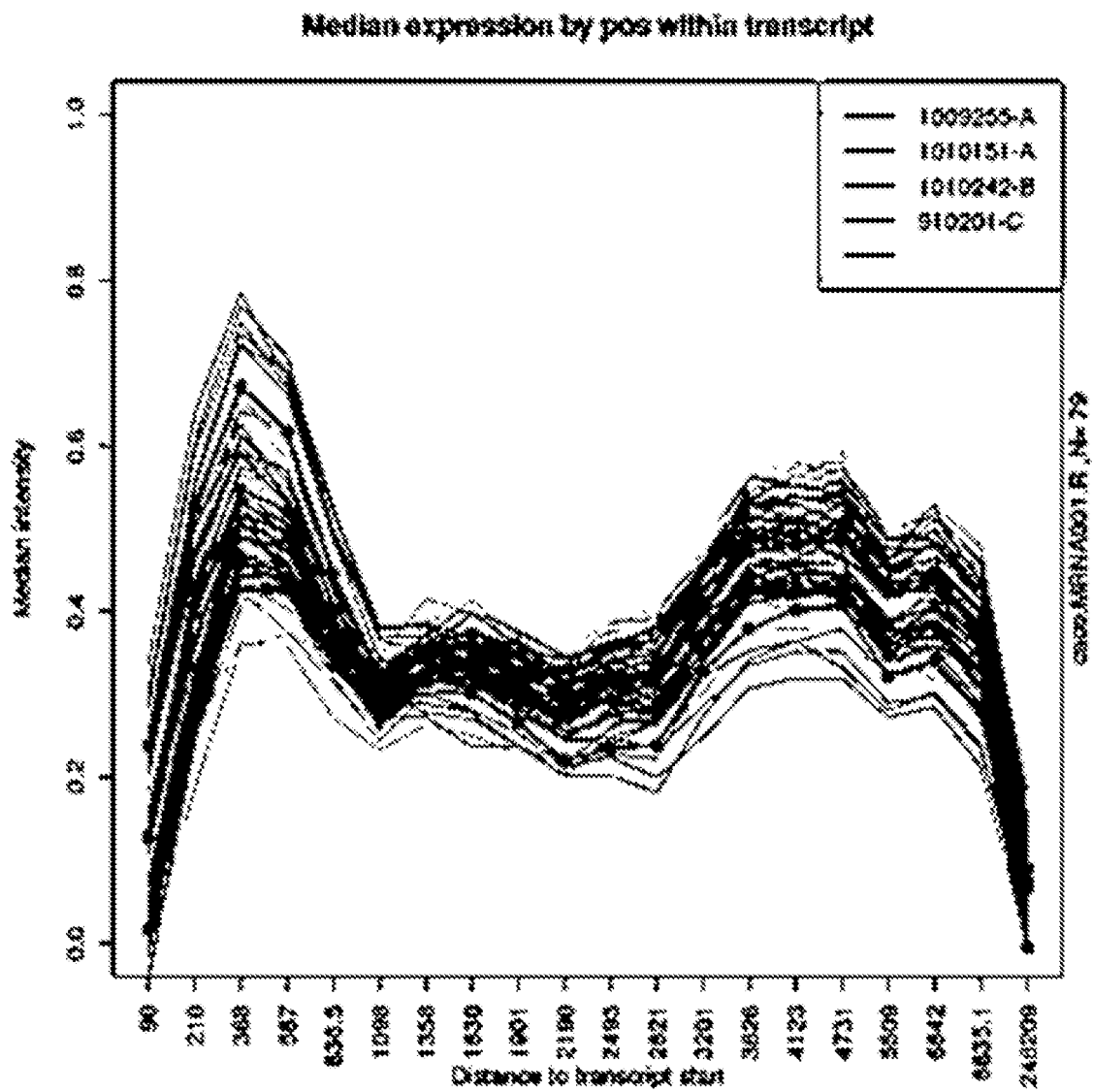


Fig.24C

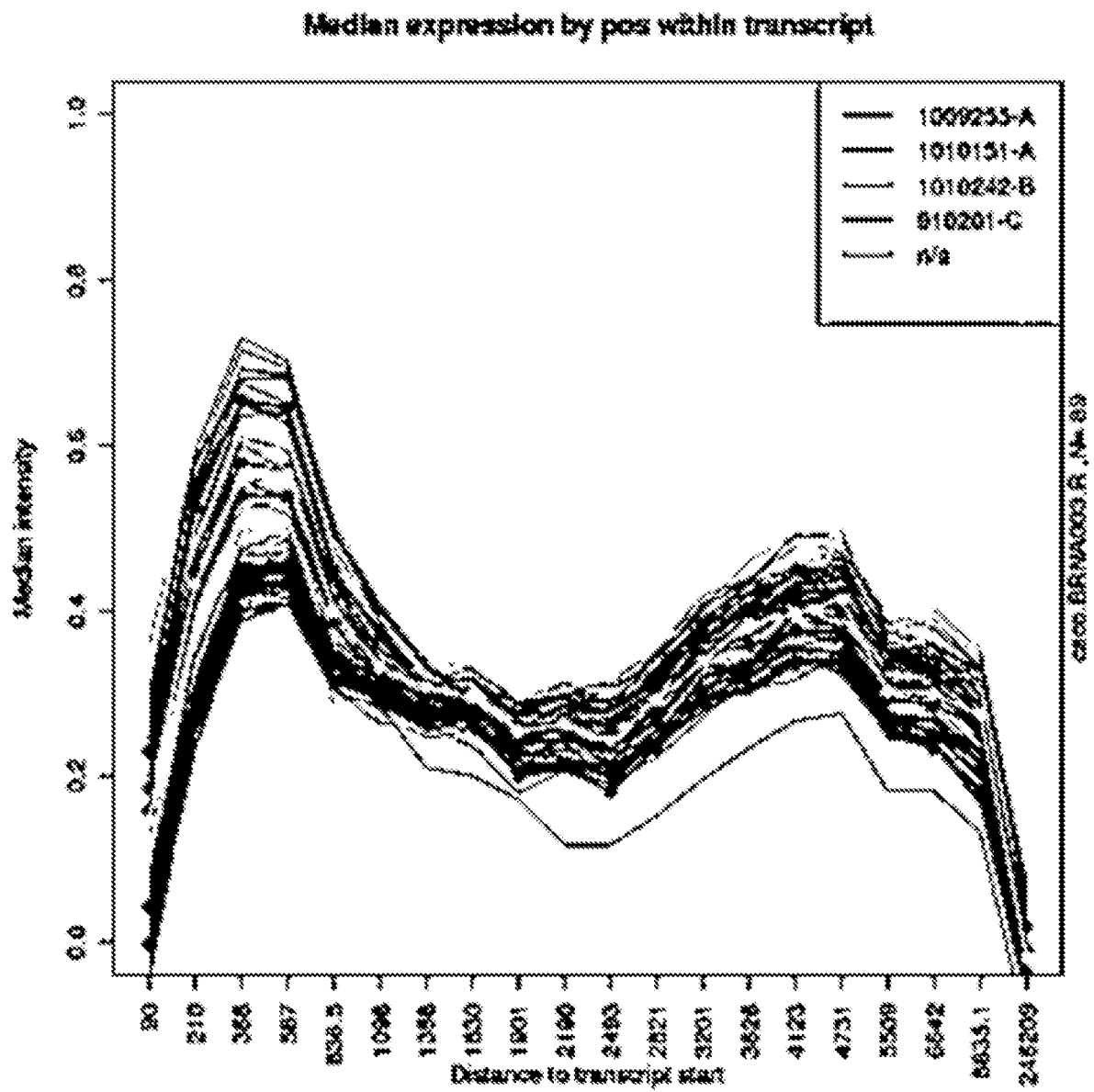


Fig.24D

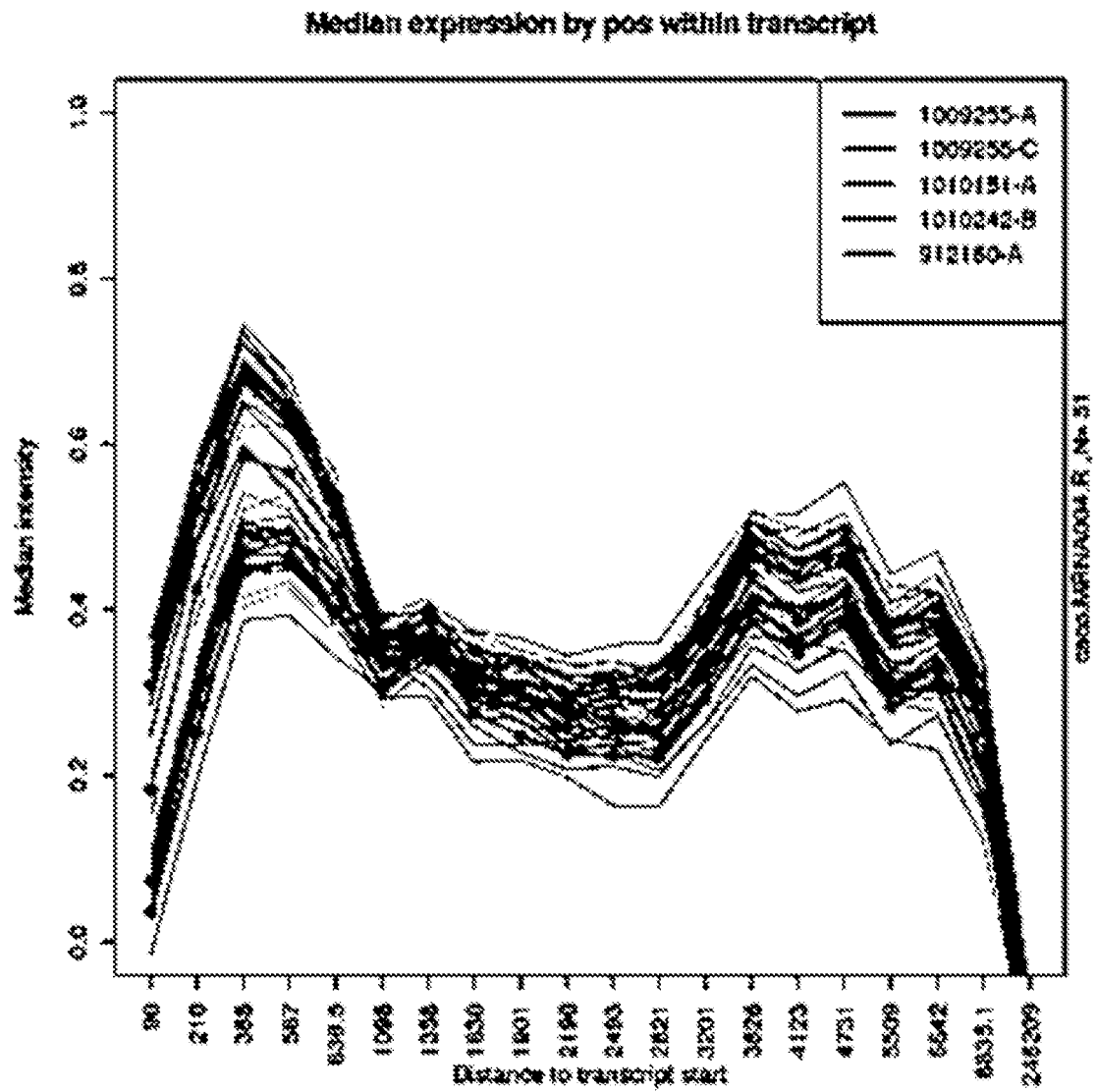


Fig.25A

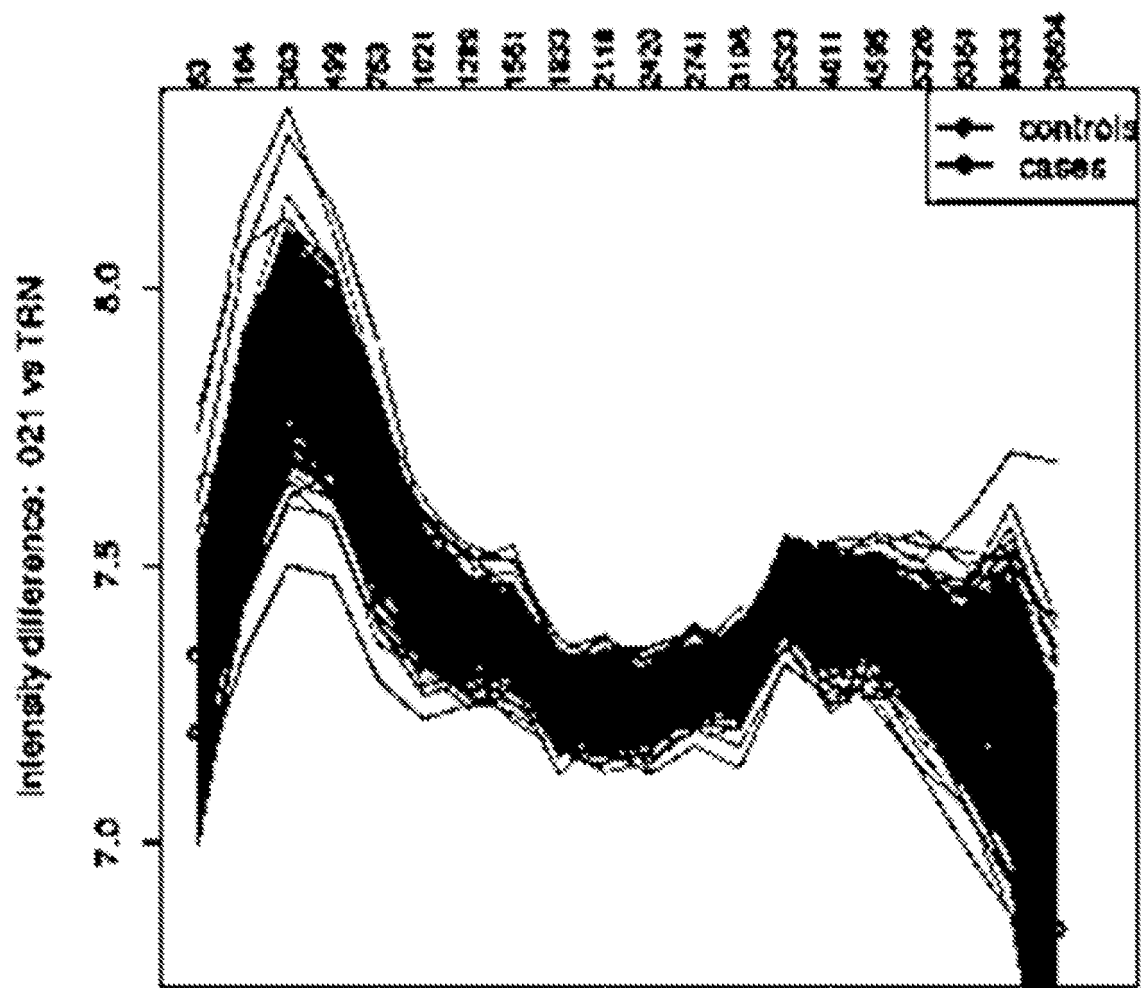


Fig.25B

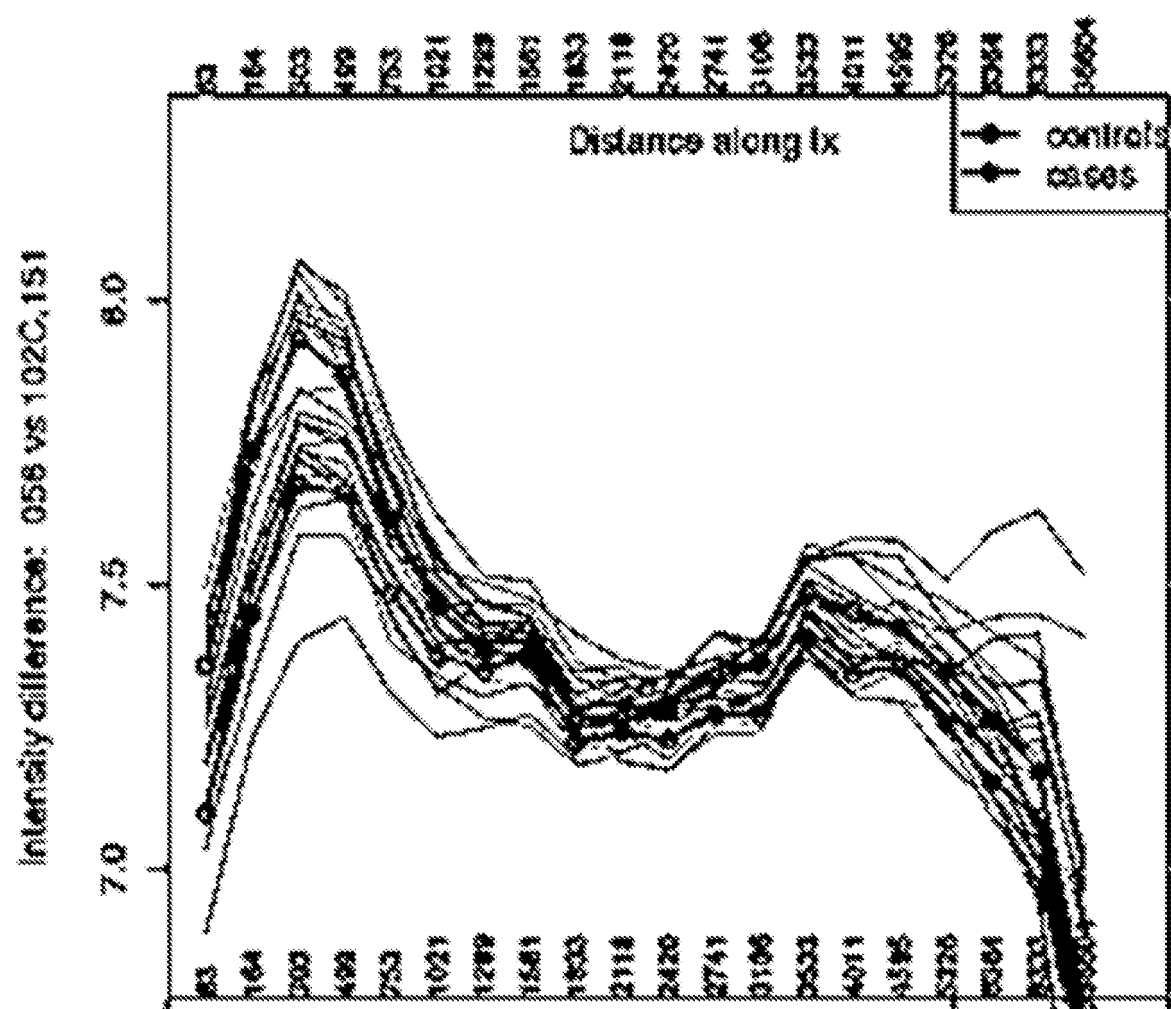


Fig.25C

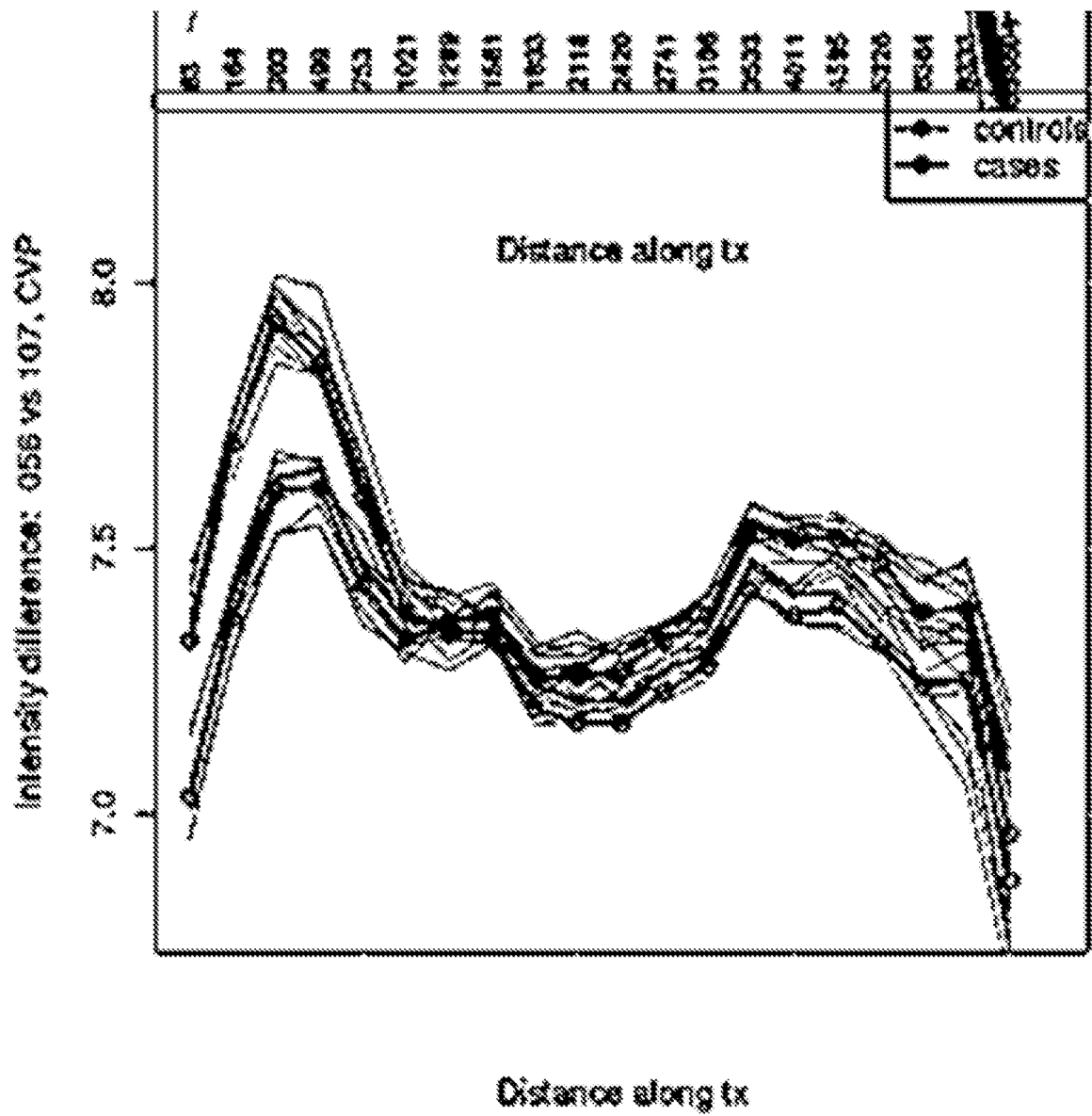


Fig.25D

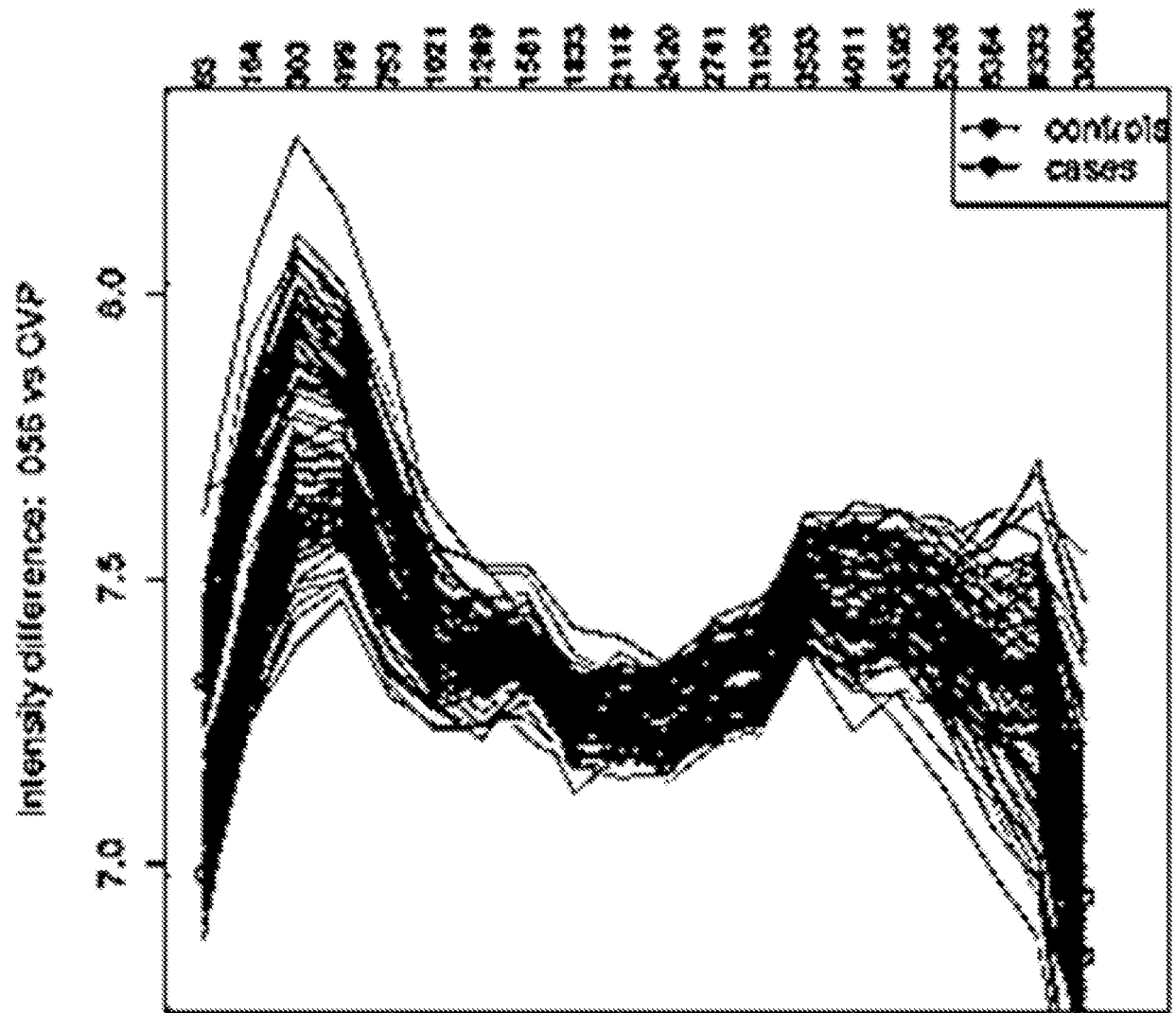


Fig.25E

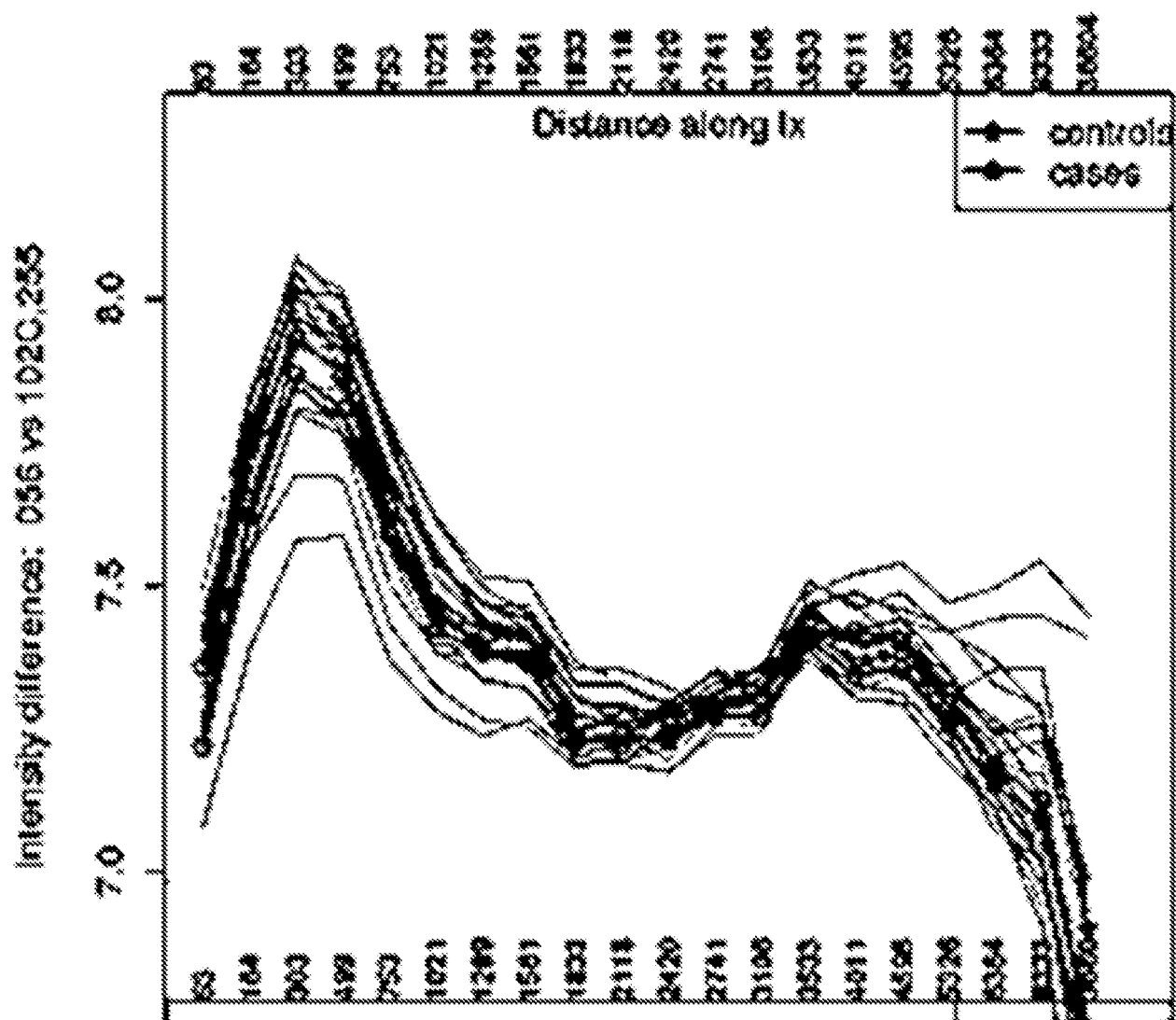


Fig.25F

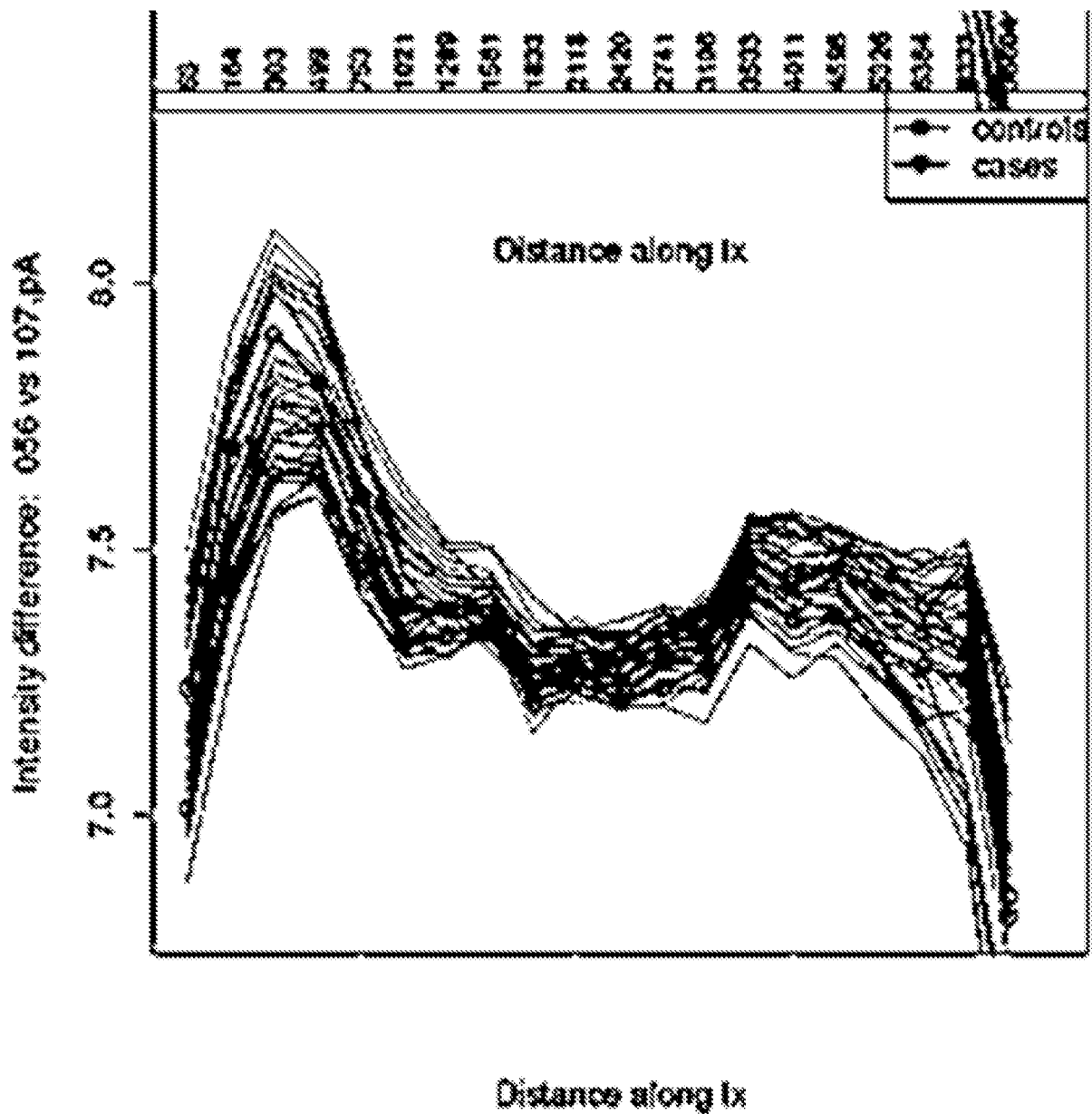


Fig.25G

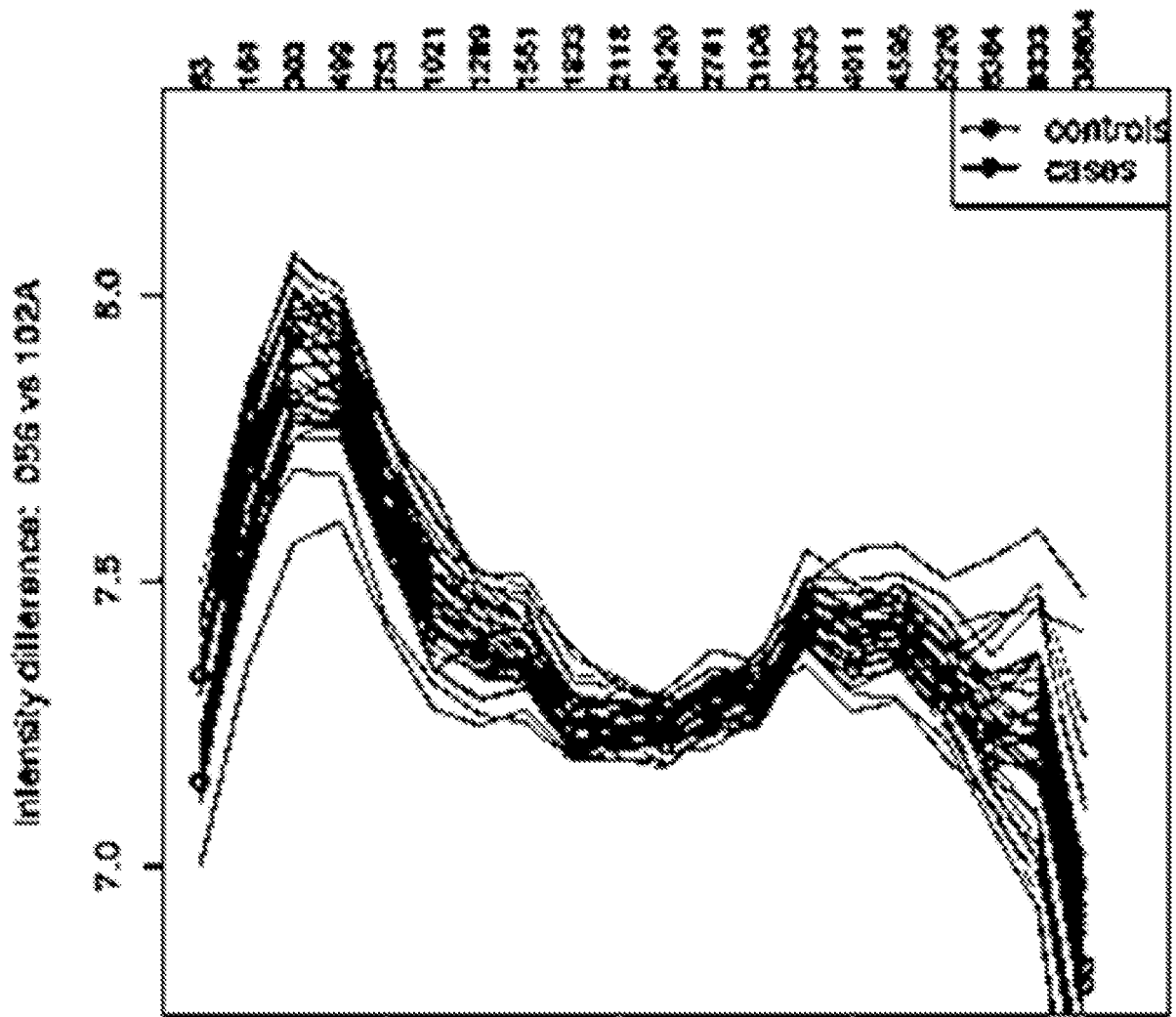
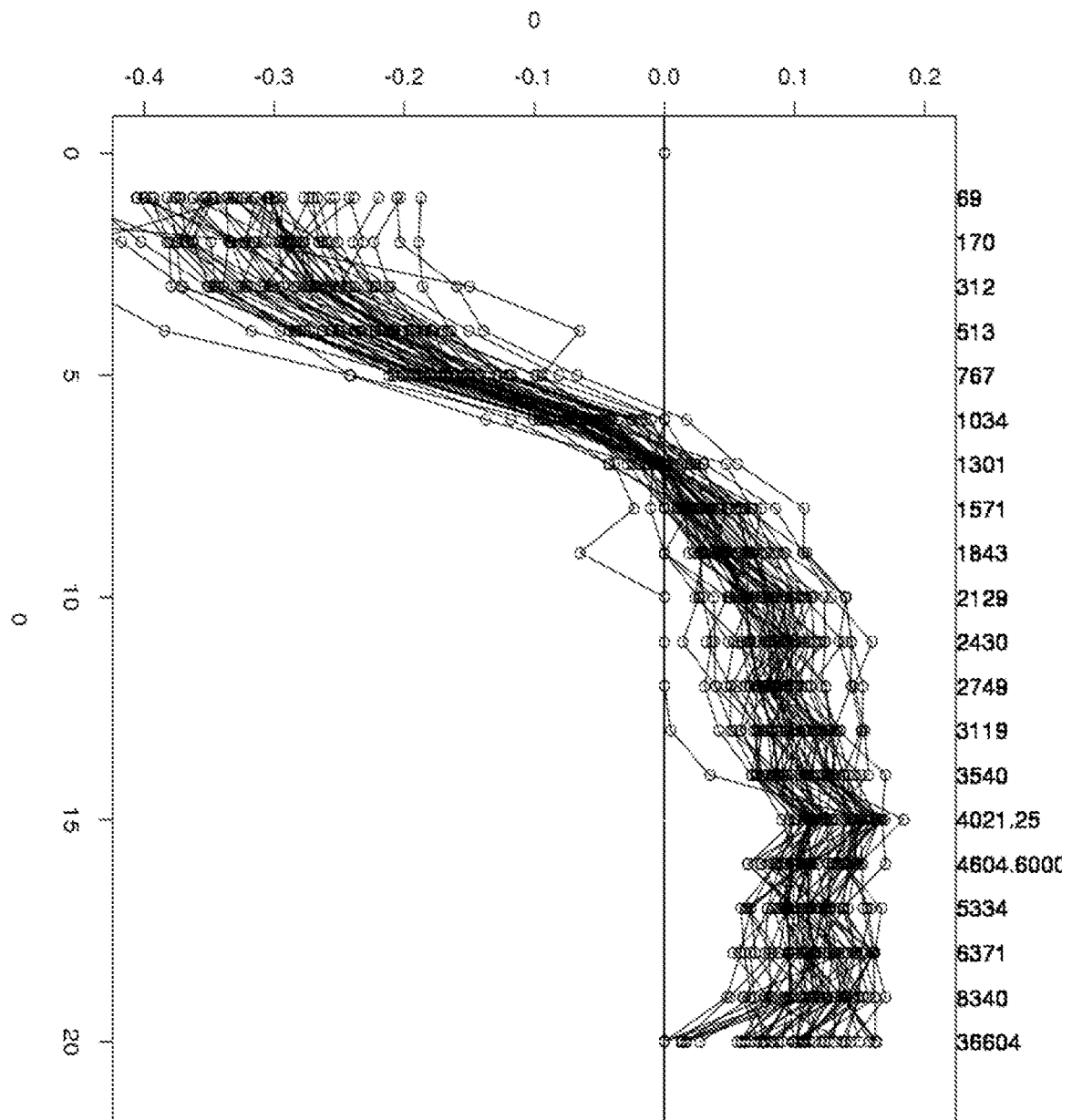


Fig.26



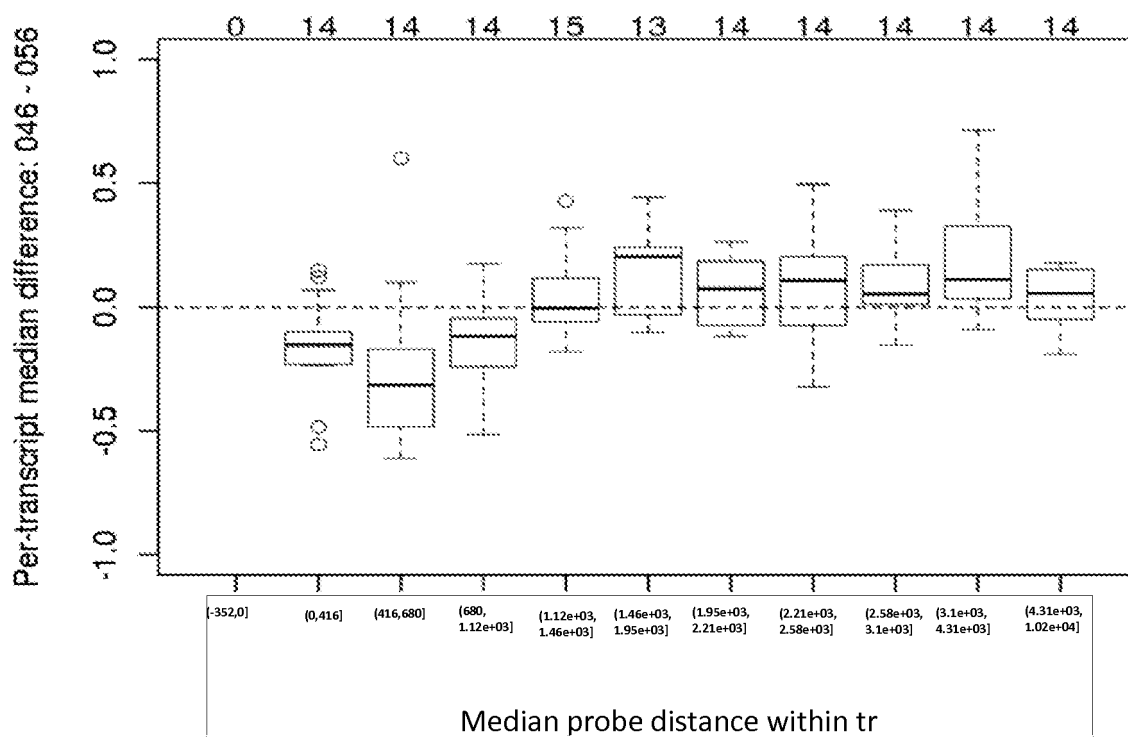


Fig.27A

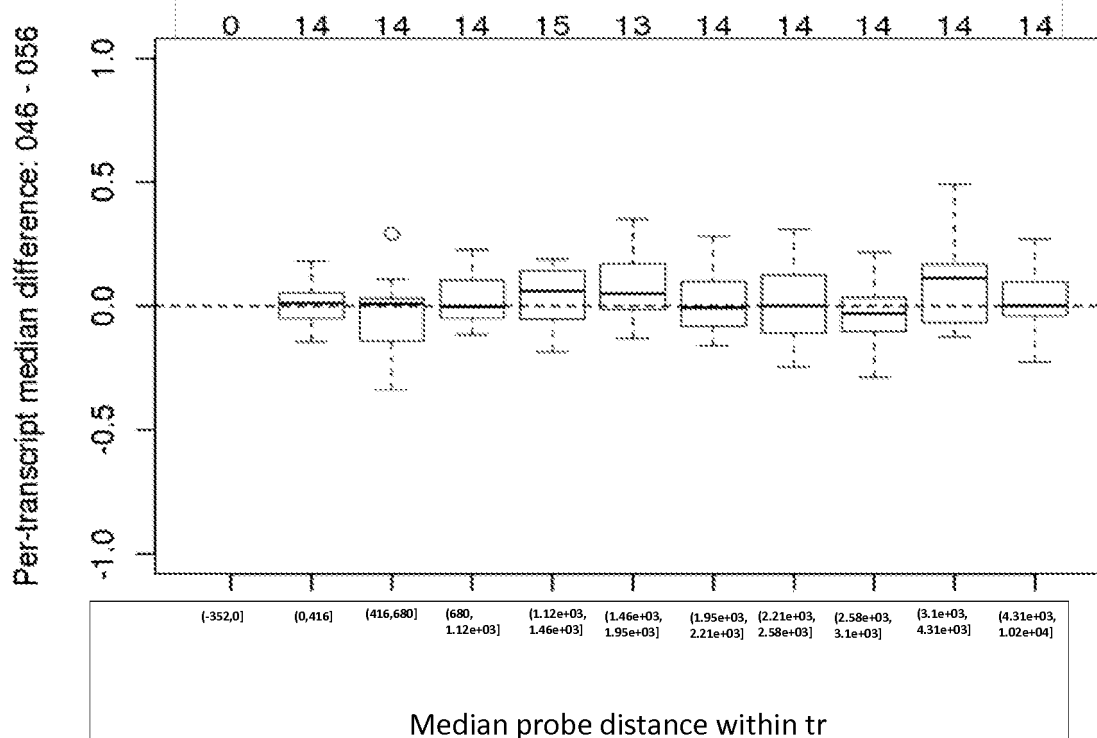


Fig. 27B

Fig.28

Classification results: ROC curve

Training set excl 021 samples, updated labels

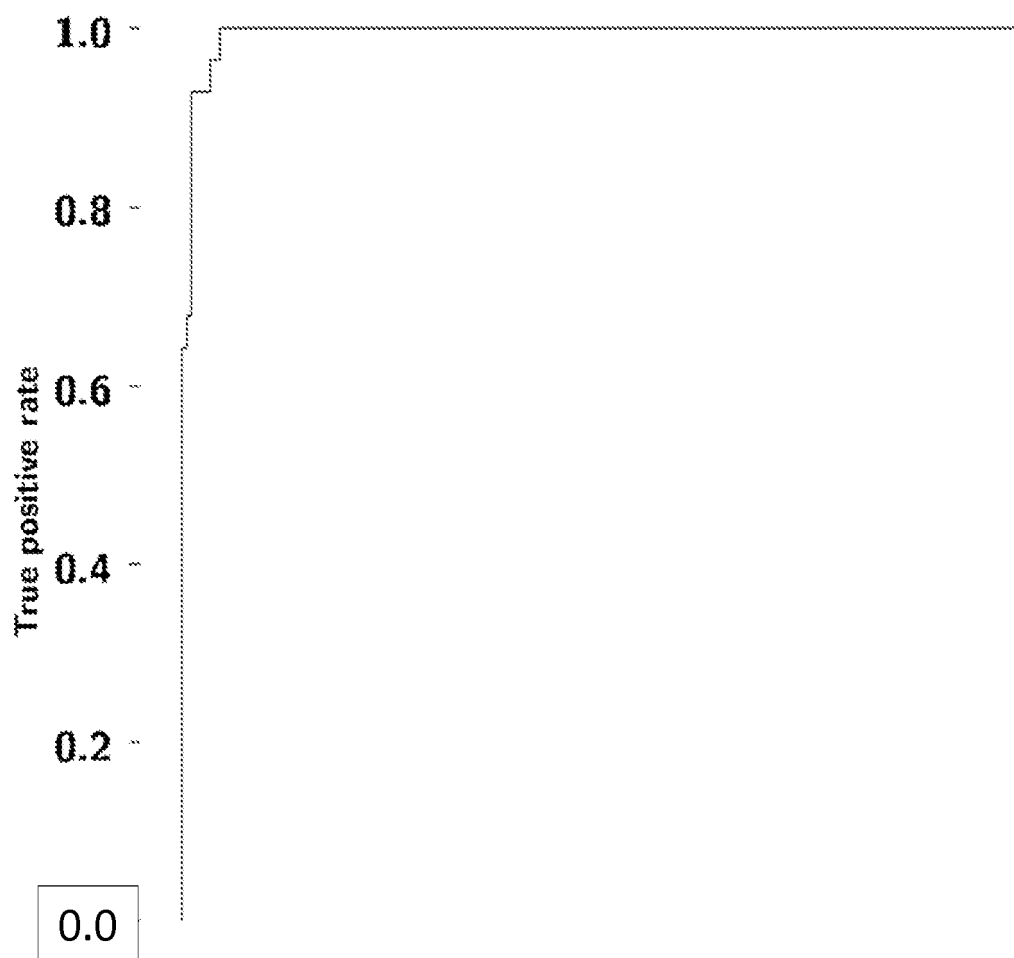


Fig.29

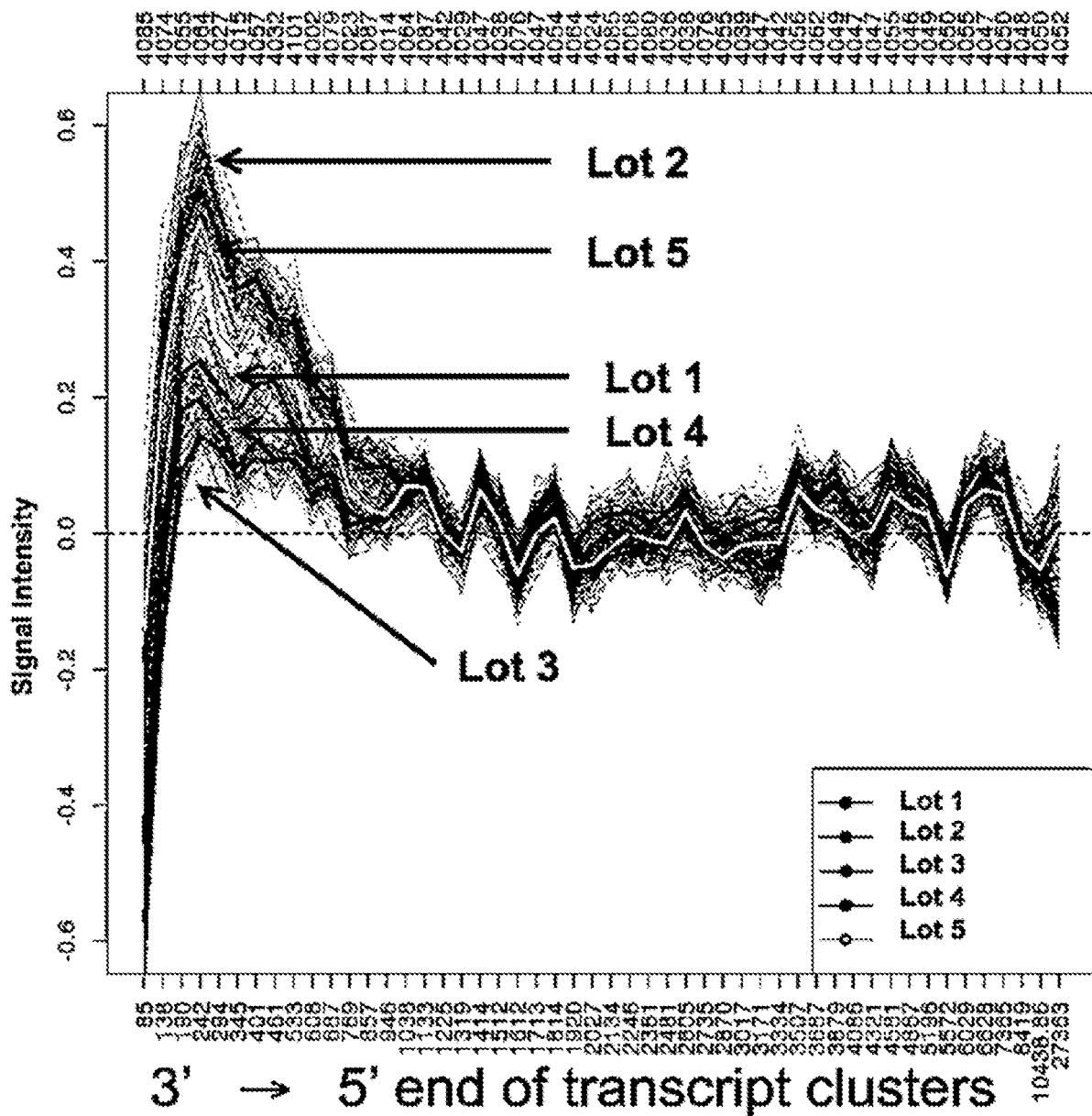


Fig.30

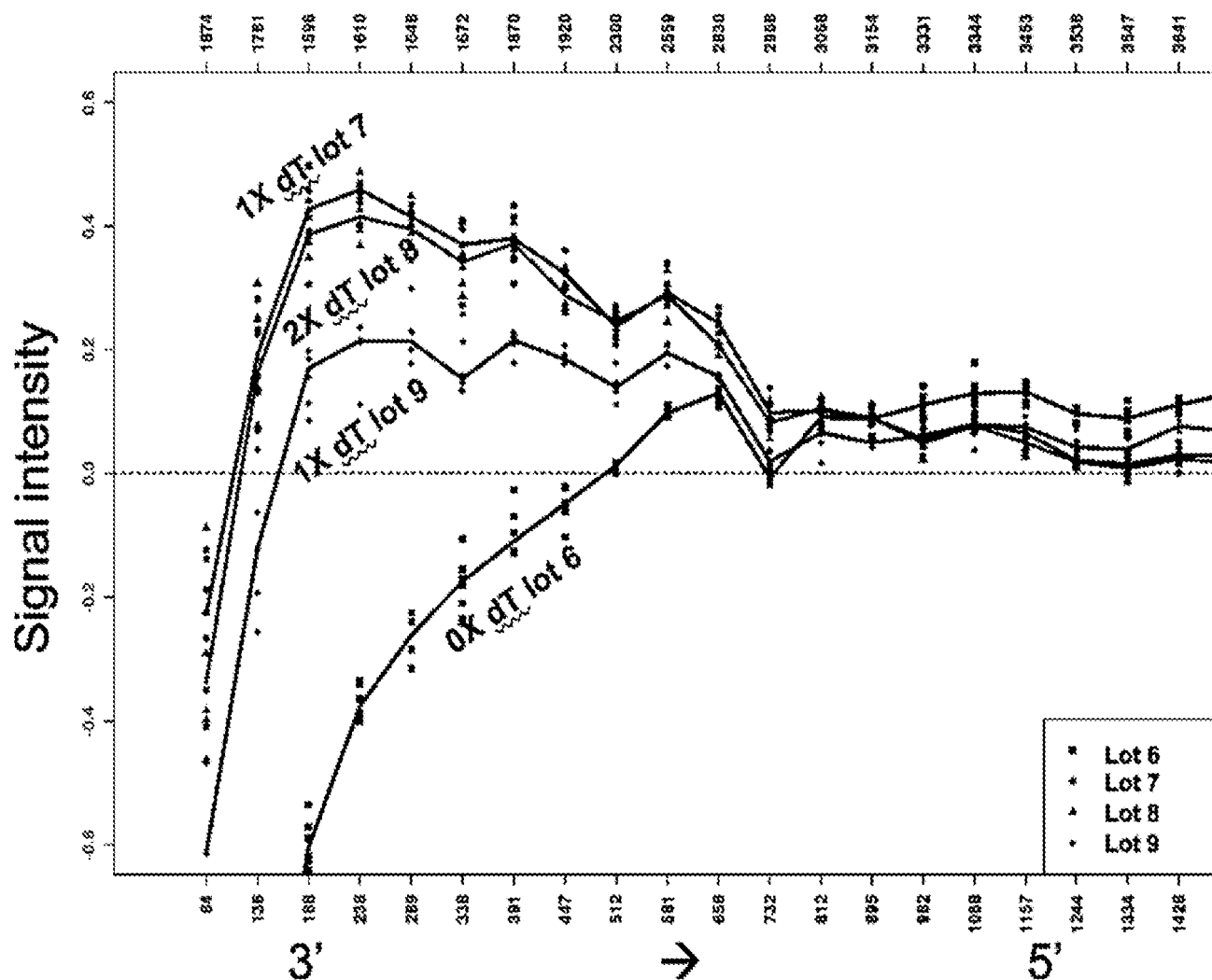
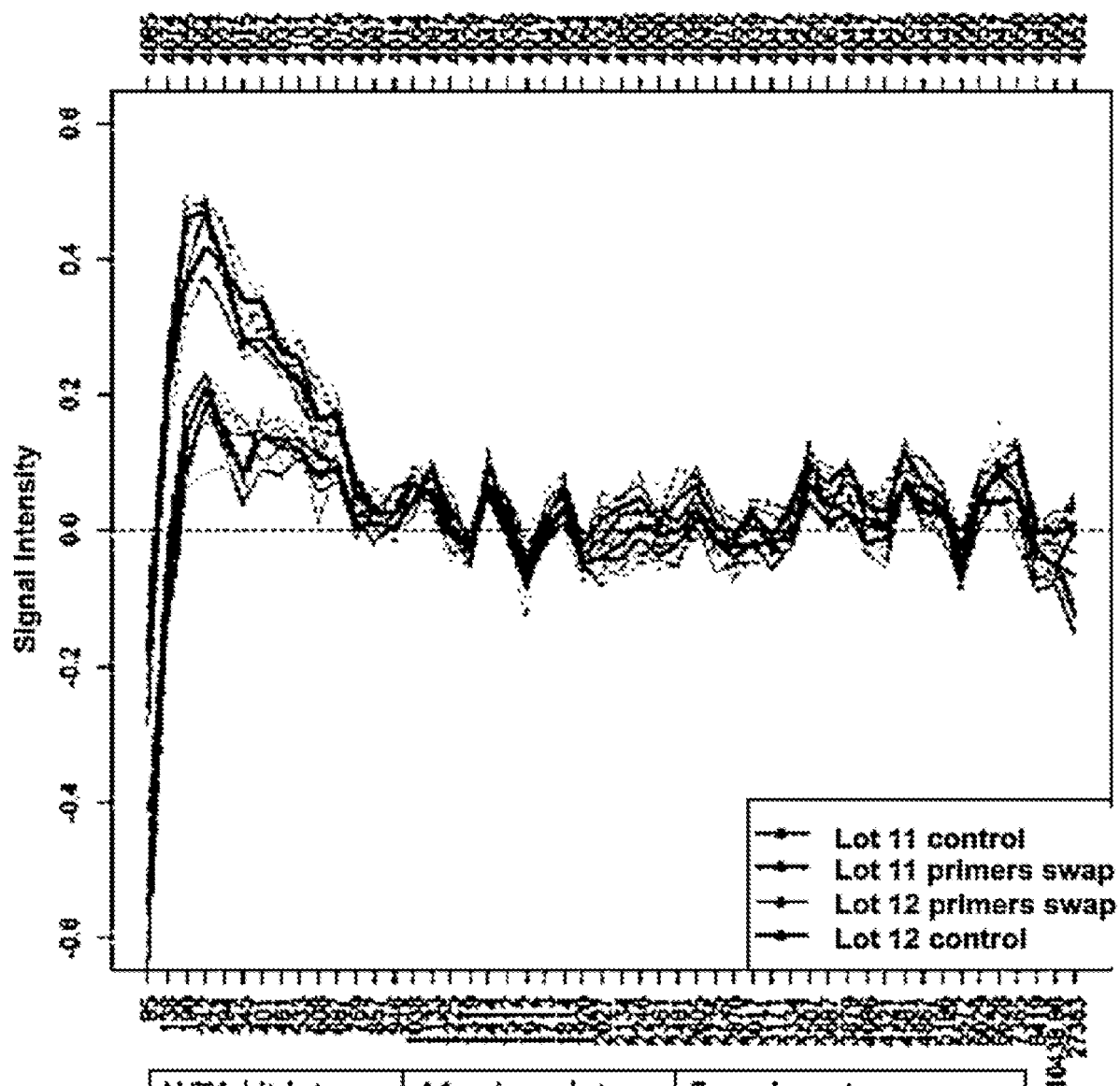


Fig.31



WTA kit lot	A1 primer lot	Experiment name
Lot 11	Lot 11	Lot 11 Control
Lot 11	Lot 12	Lot 11 swap
Lot 12	Lot 12	Lot 12 Control
Lot 12	Lot 11	Lot 12 swap

Fig.32

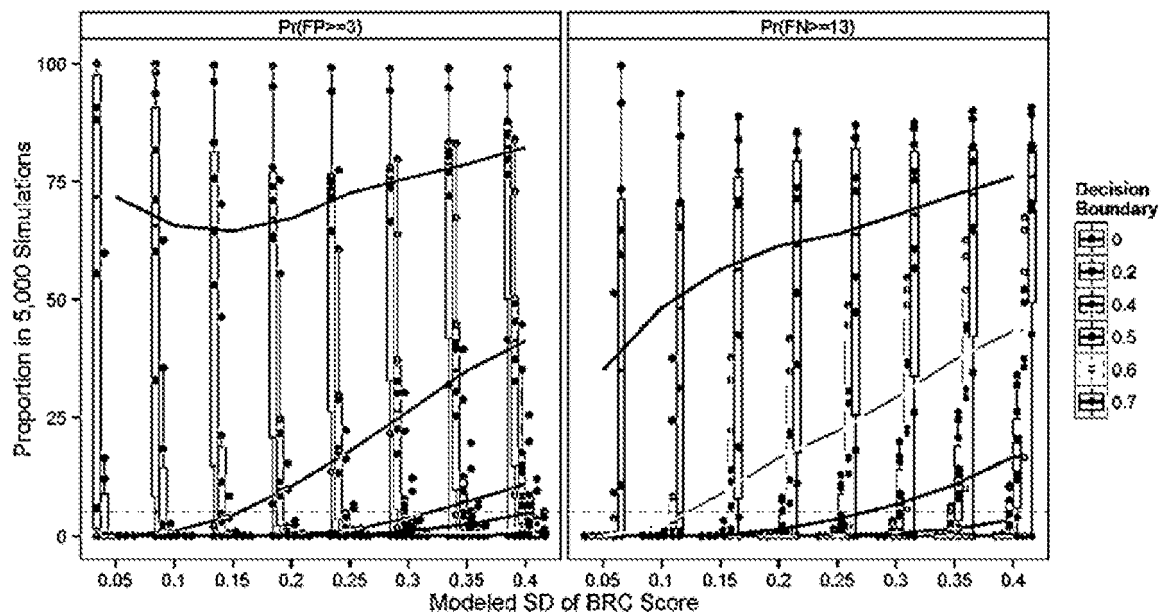


Fig.33

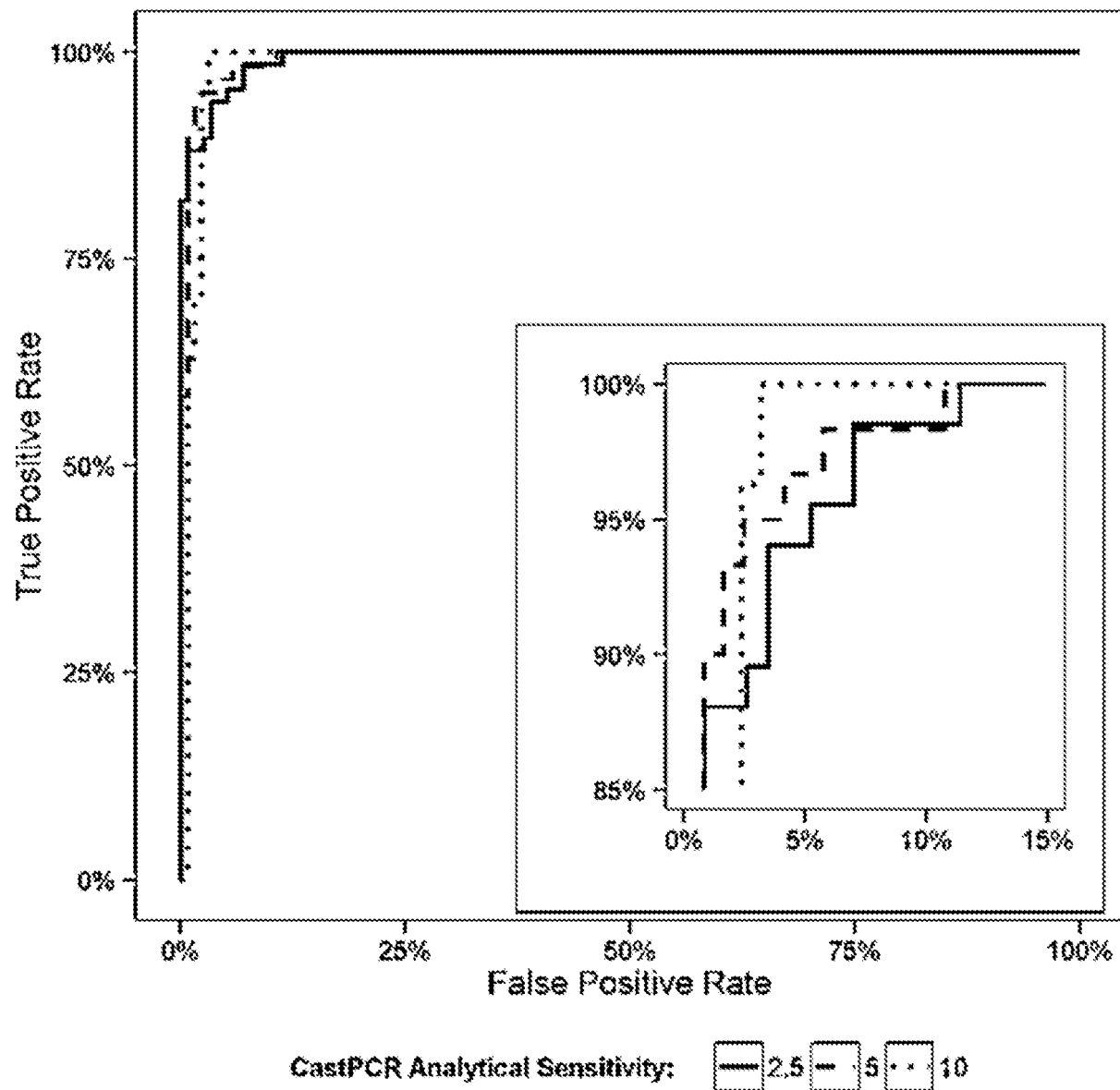


Fig.34

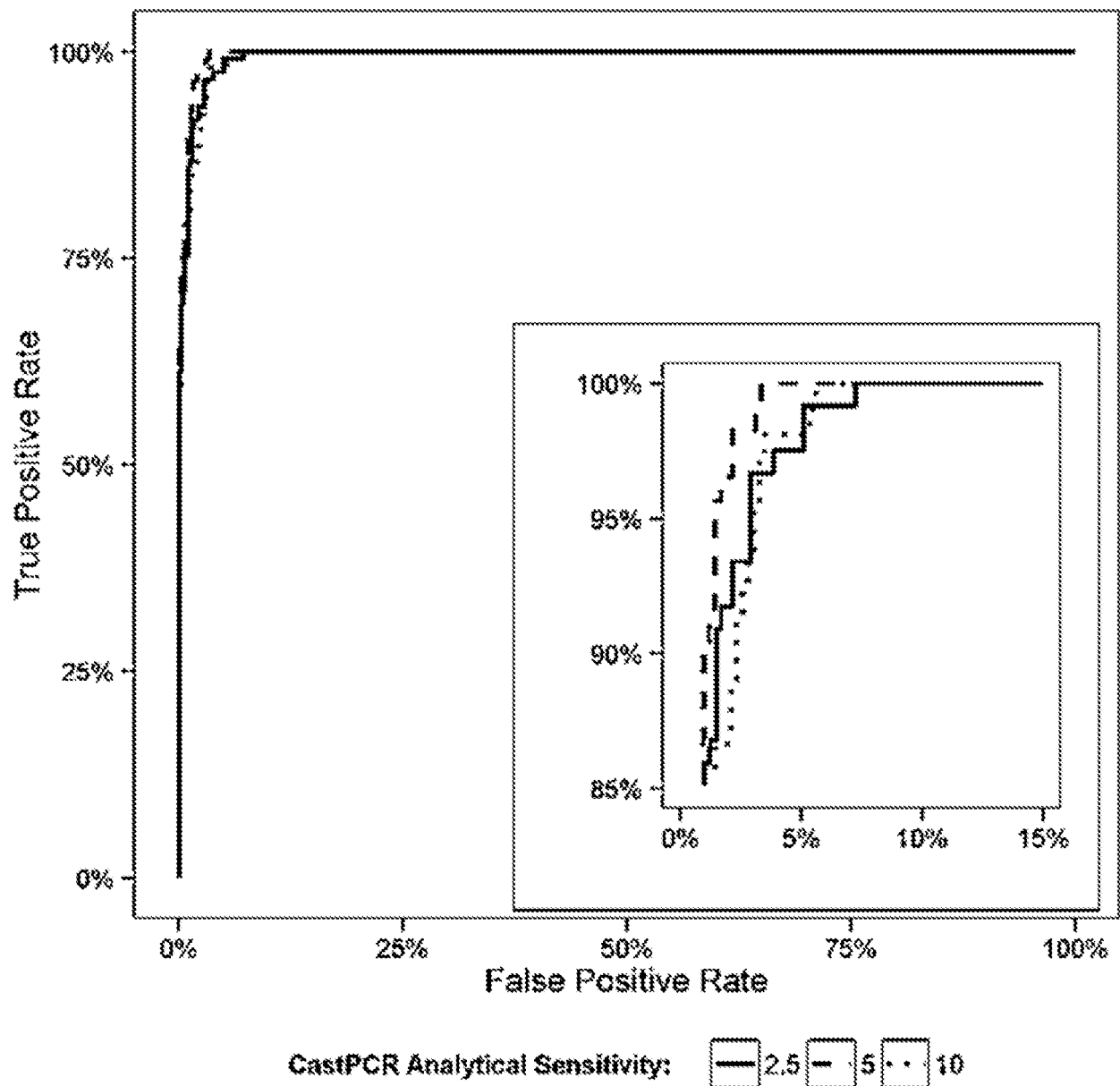


Fig.35

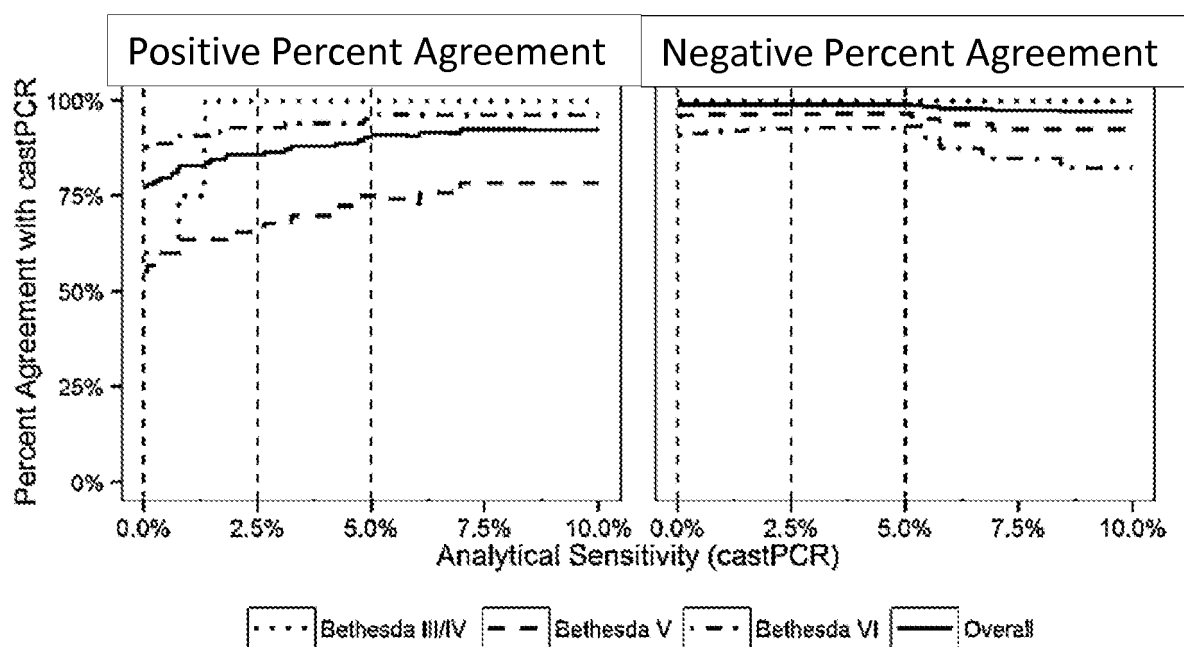


Fig.36

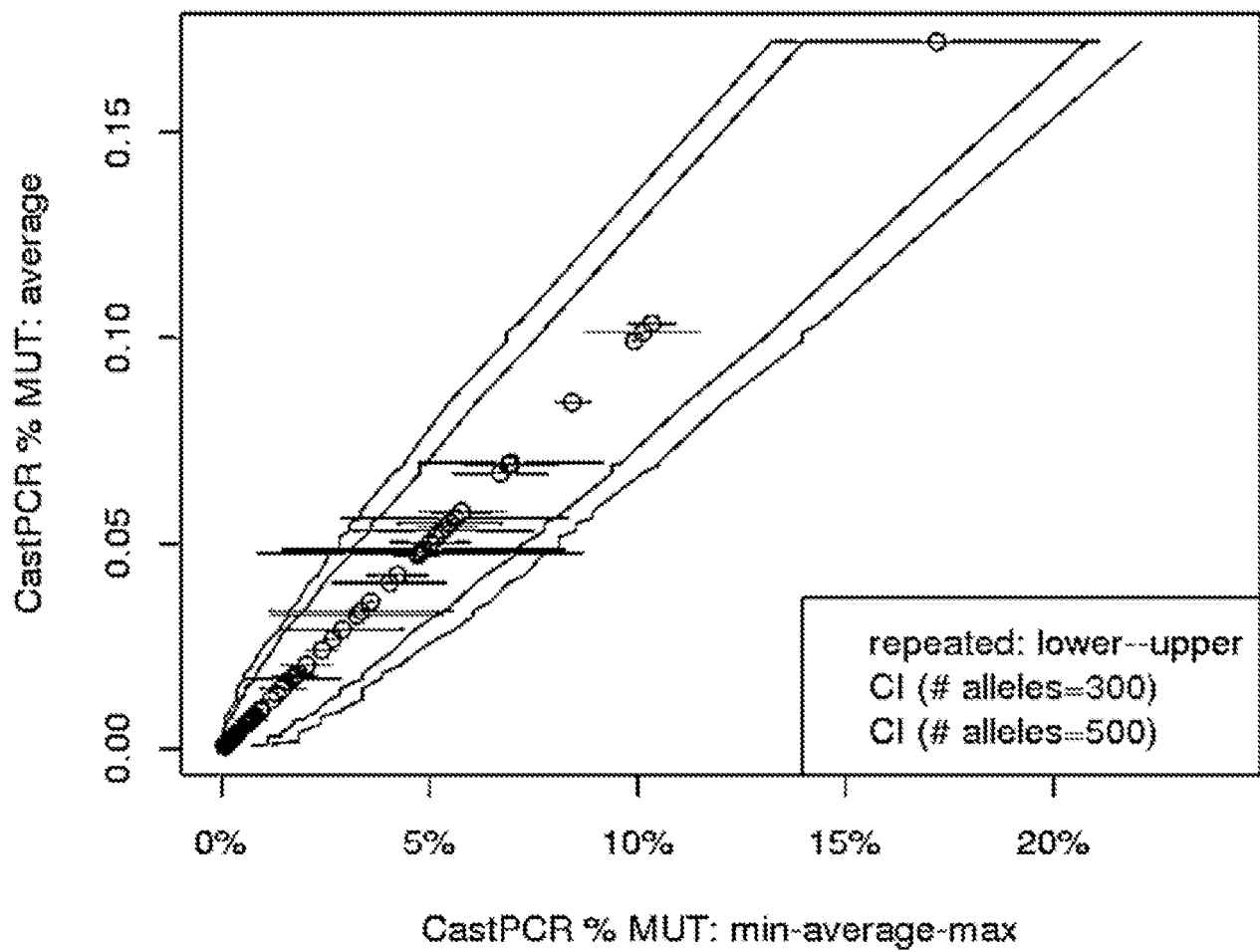


Fig.37

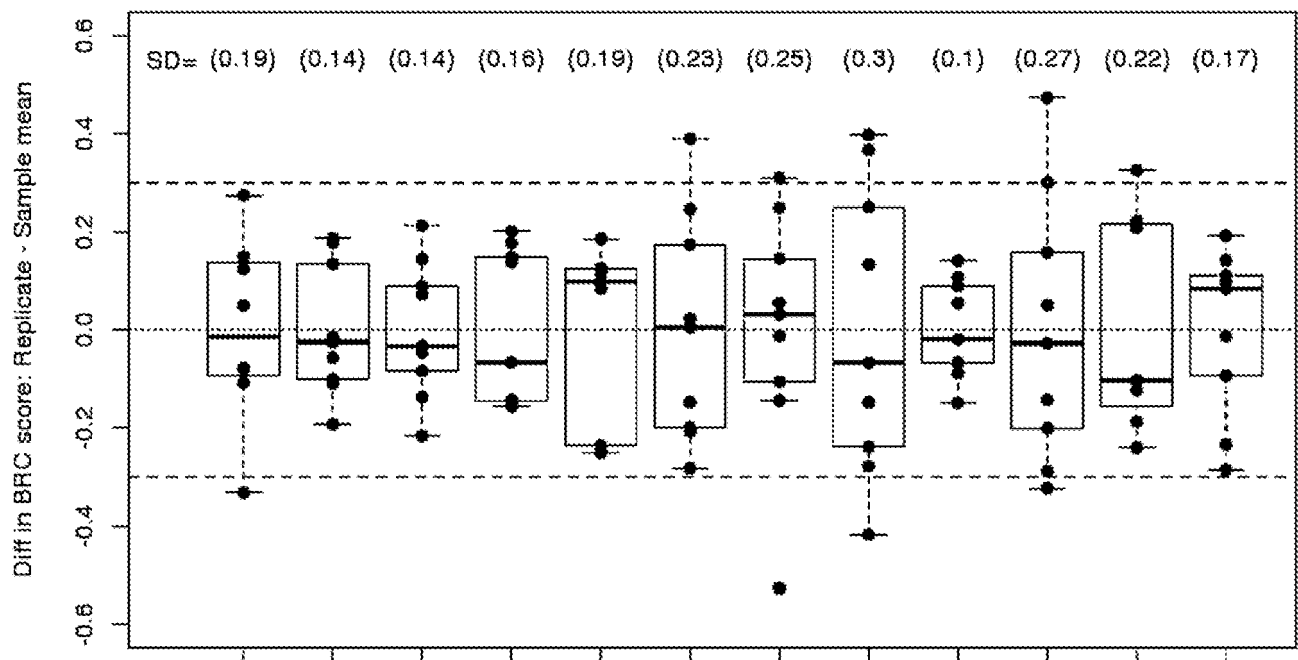


Fig.38A

RNAseq

207 DE genes

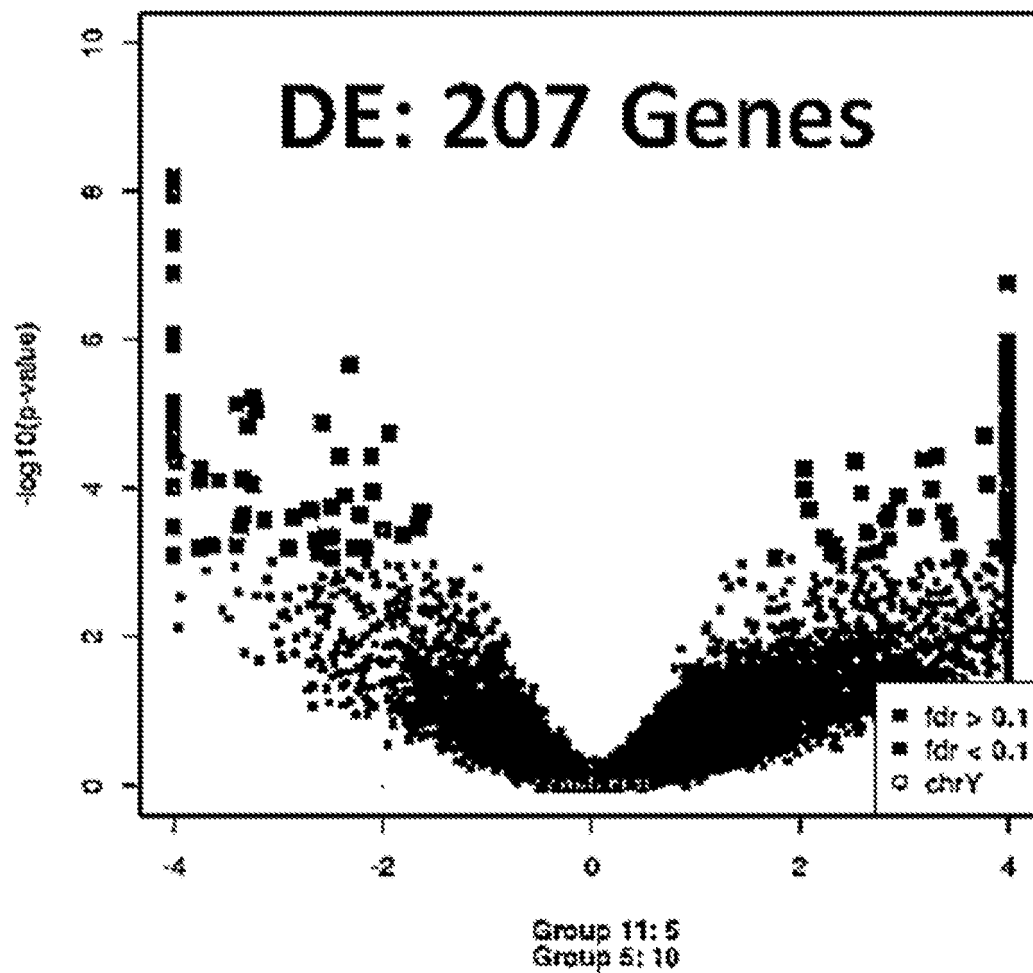


Fig.38B

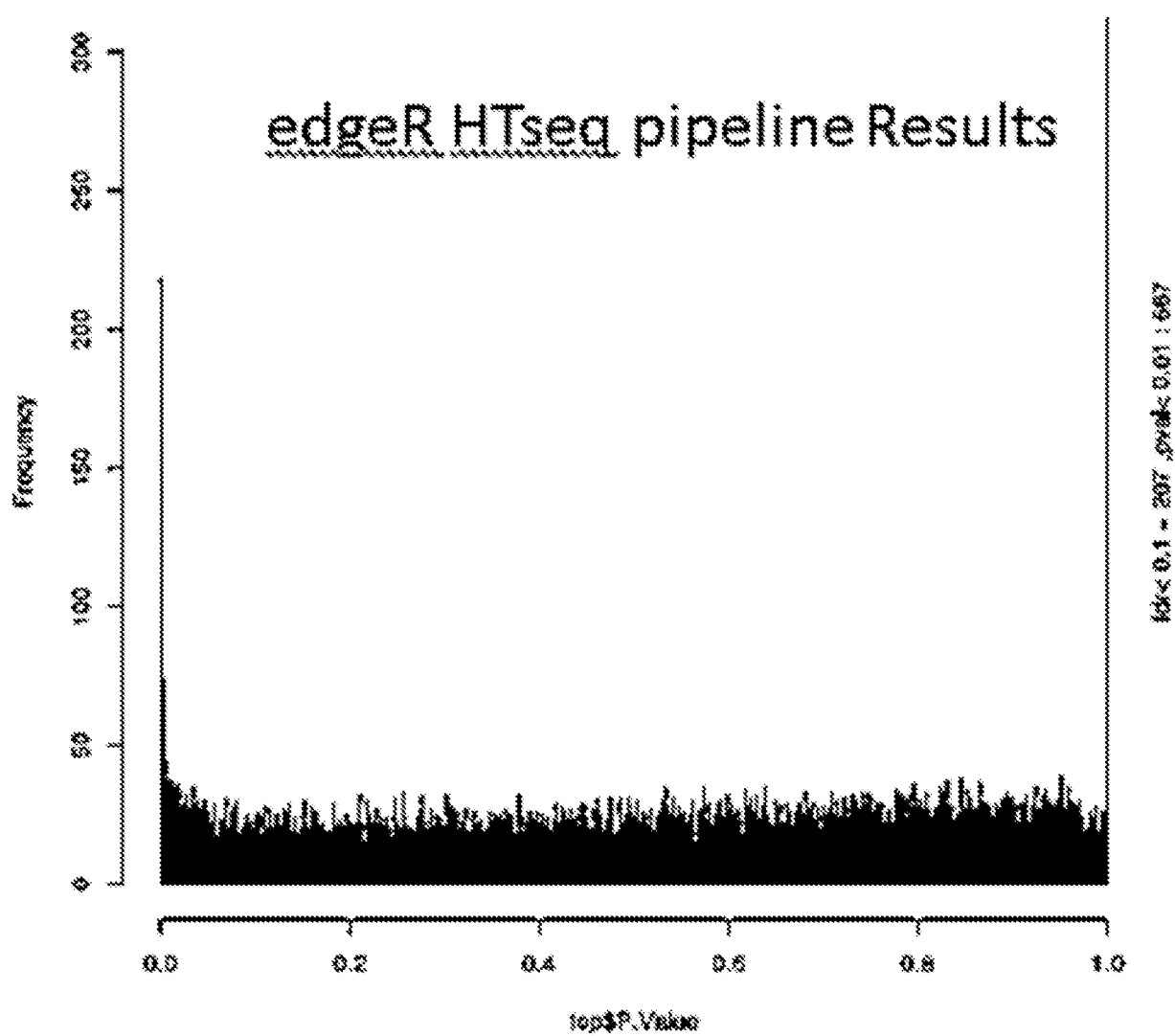


Fig.38C

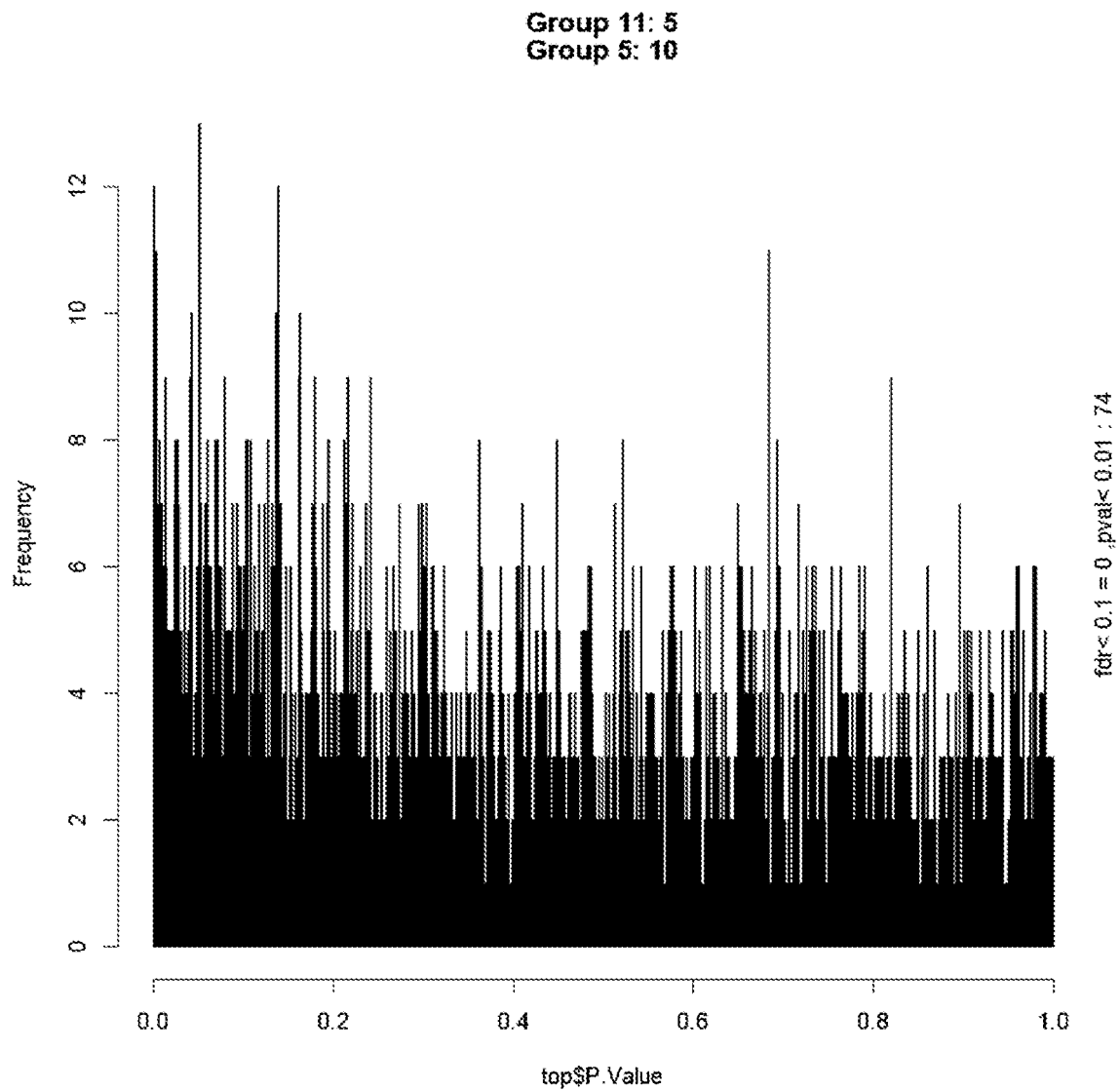


Fig.38D

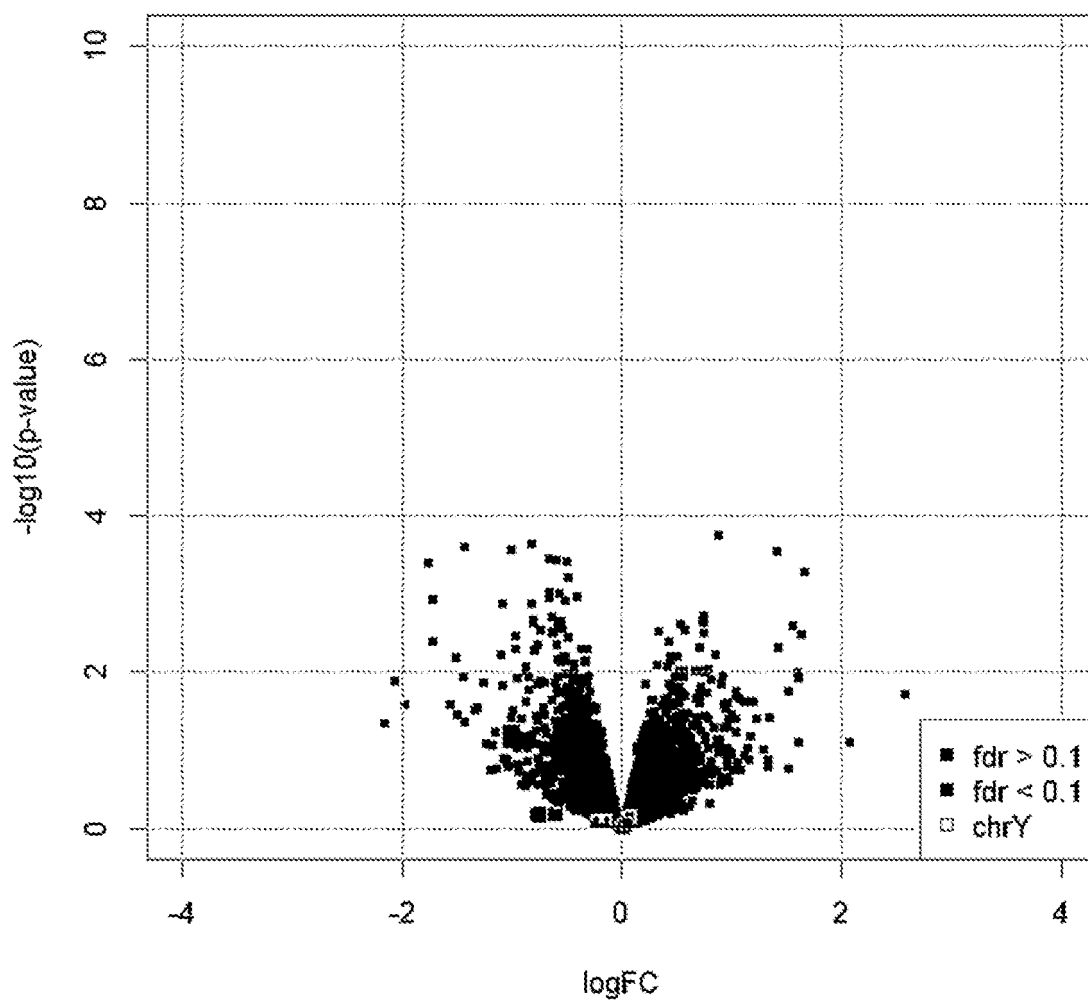


Fig.38E

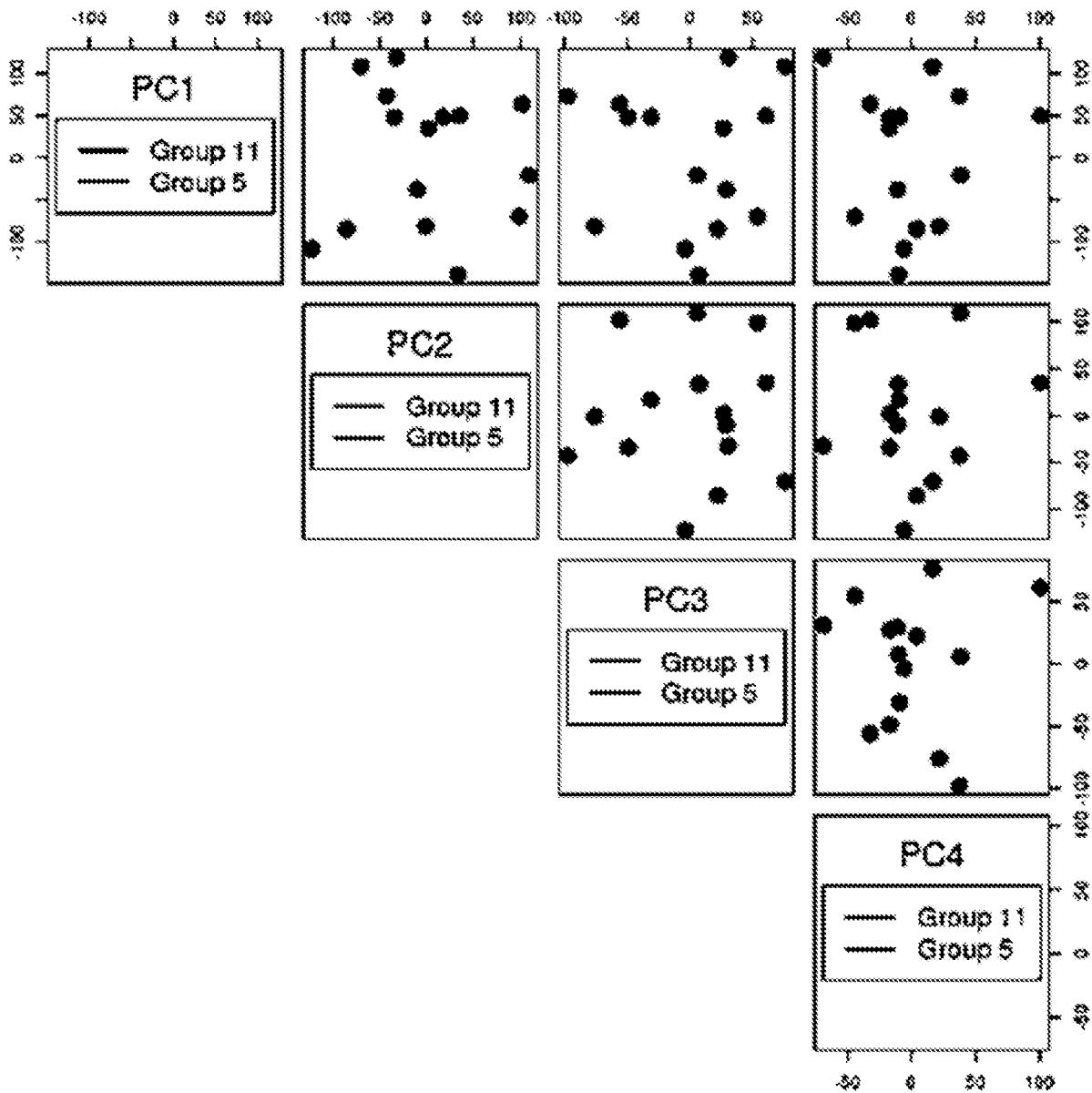


Fig.38F

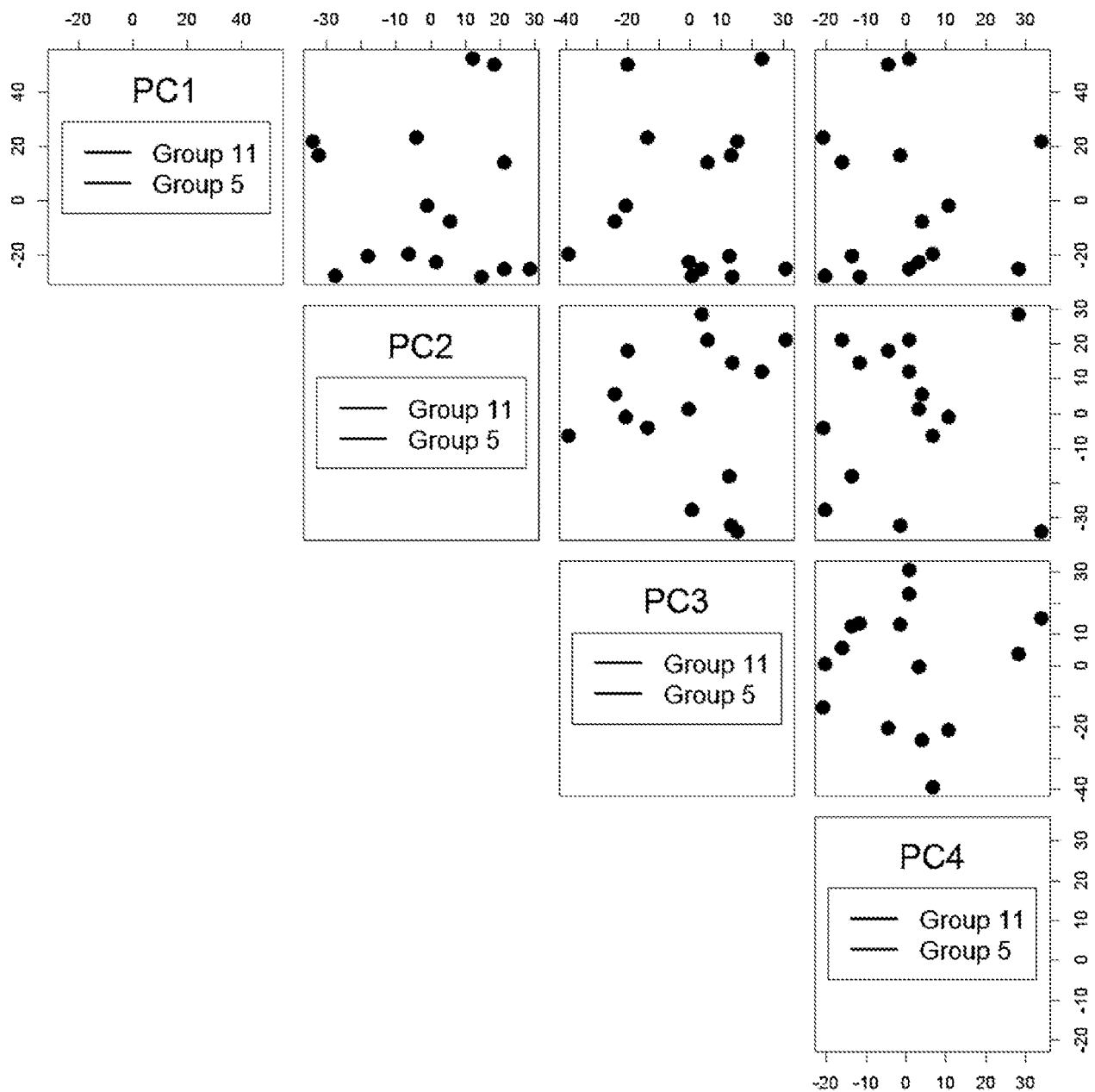


Fig.39A

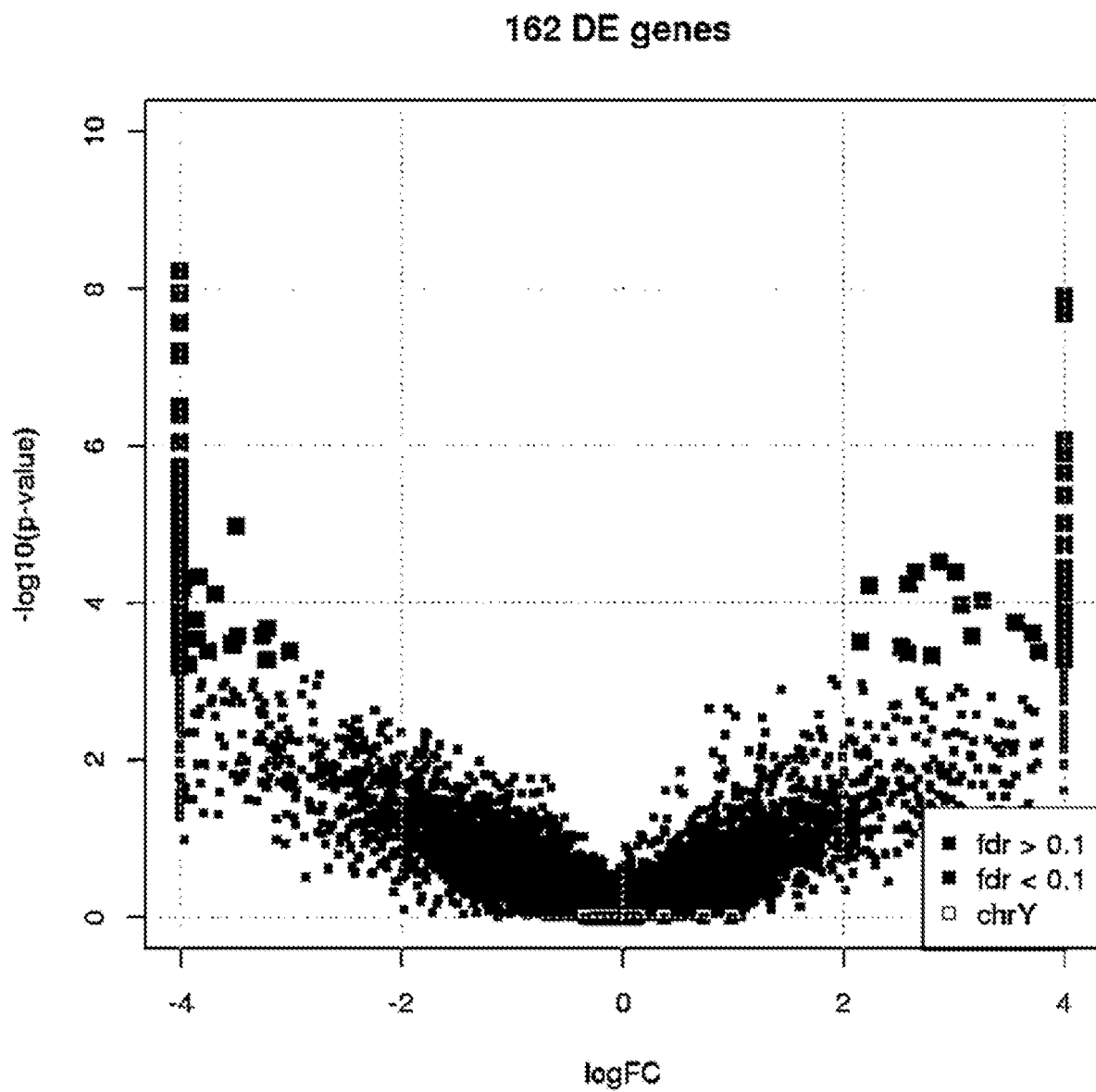


Fig.39B

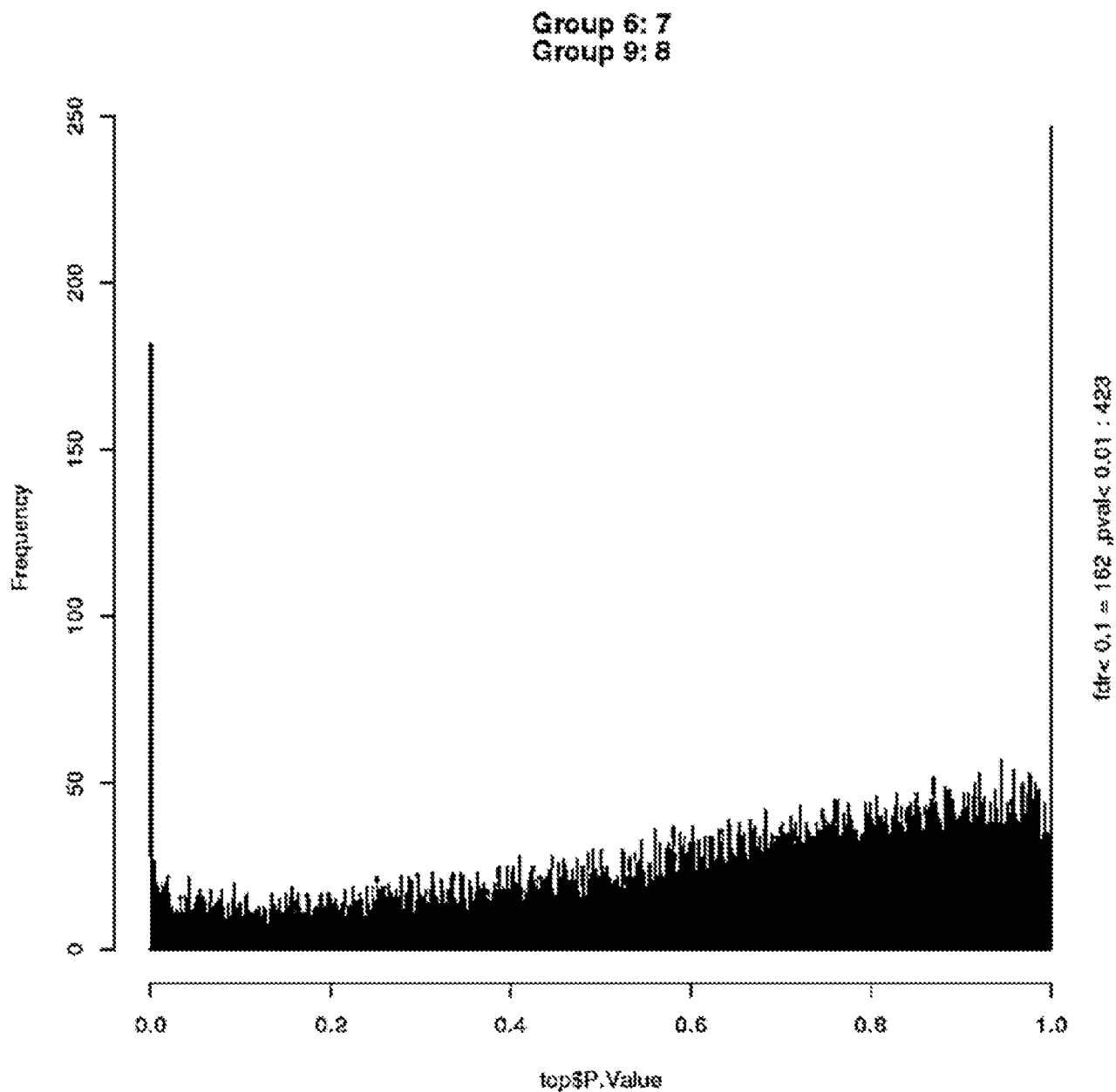


Fig.39C

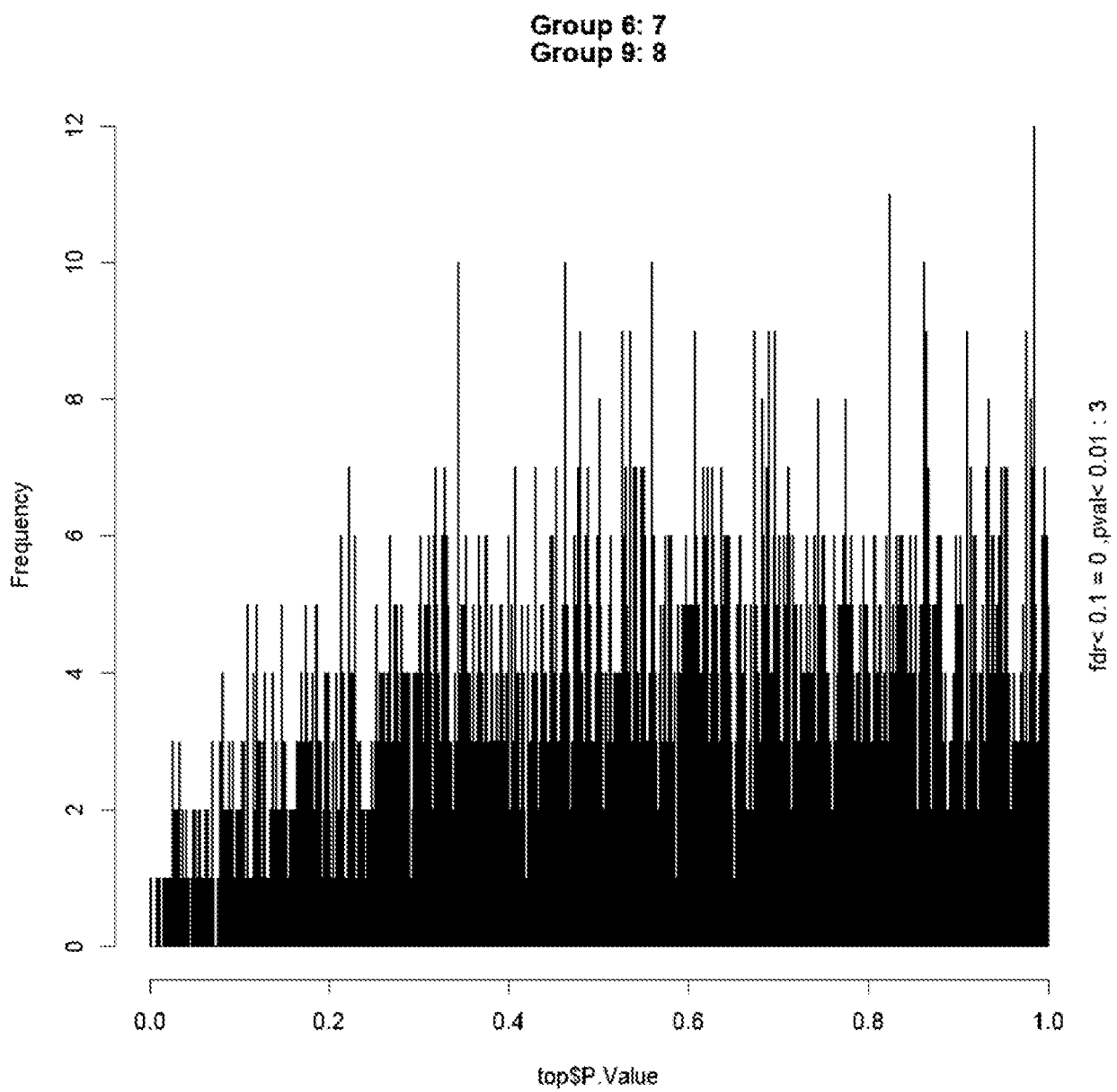


Fig.39D

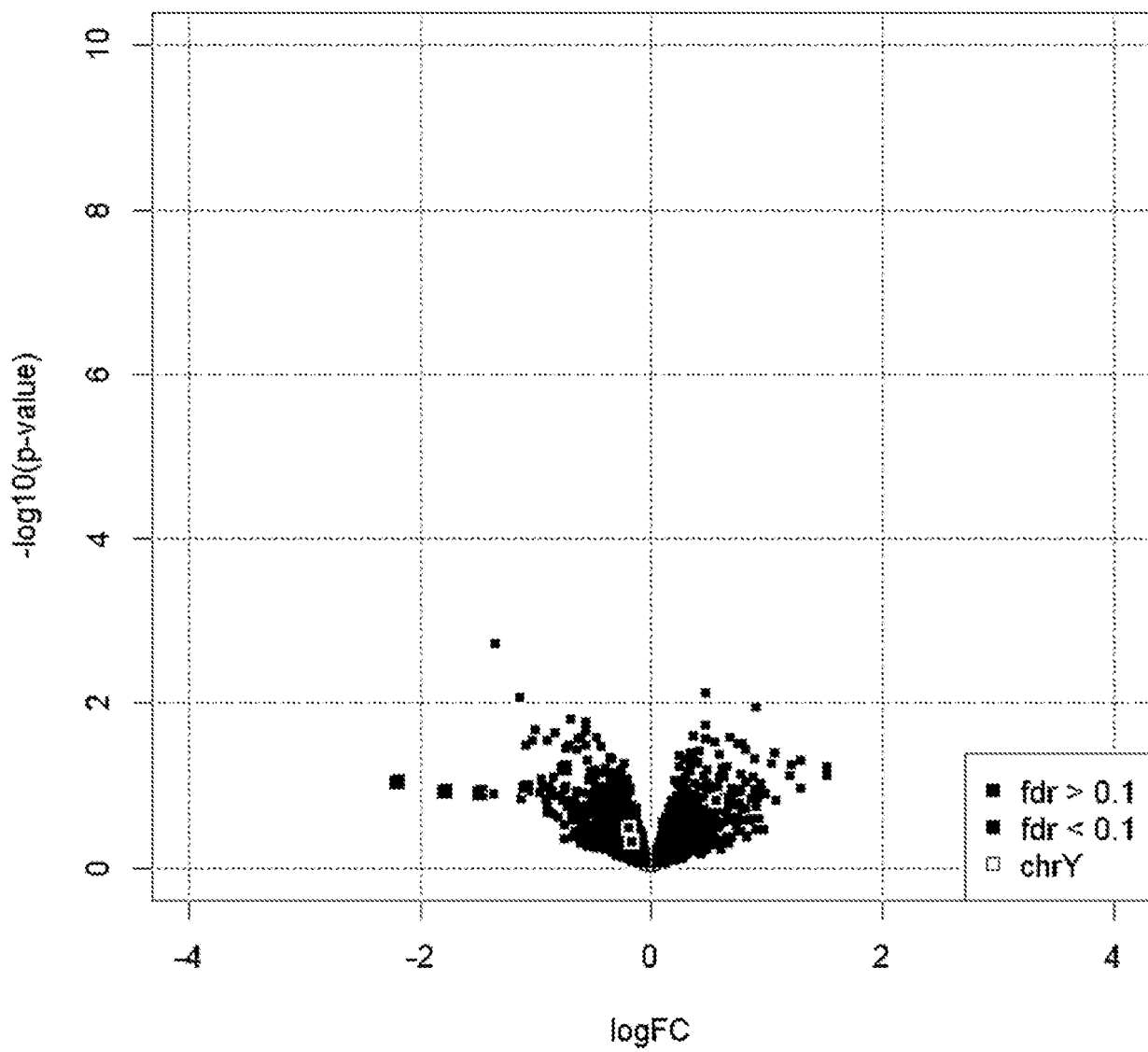


Fig.39E

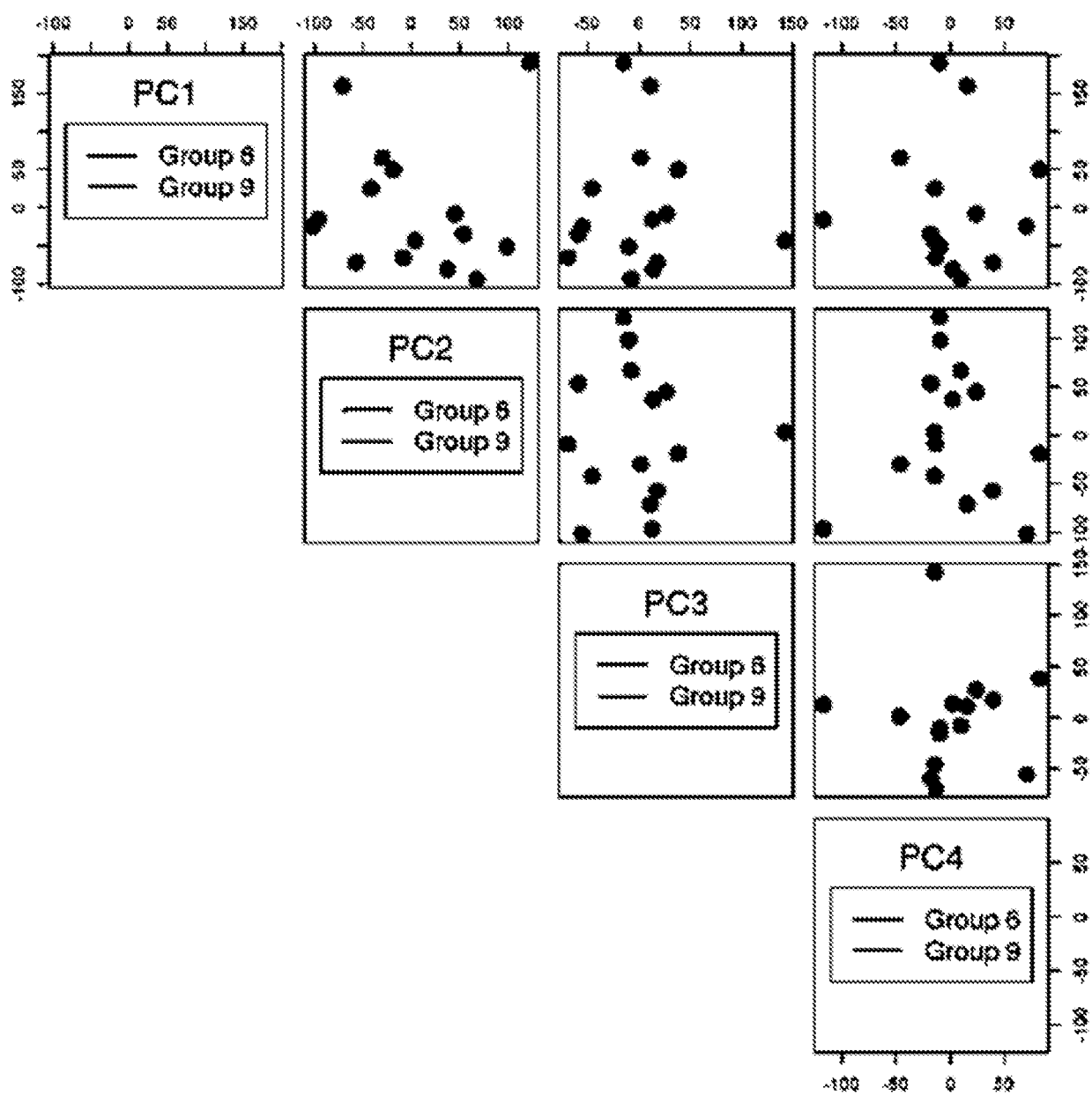


Fig.39F

