Unstable Angina is a Mixed Th17 and Th1 immune disorder

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Abstract

Unstable angina is common clinical manifestation of atherosclerosis. However, the detailed pathogenesis of unstable angina is still not known. Here, I propose that unstable angina is a mixed TH17 and TH1 immune disorder. By using microarray analysis, I find out that TH1 and TH17 related cytokine, cytokine receptor, chemokines, complement, immune-related transcription factors, anti-bacterial genes, Toll-like receptors, and heat shock proteins are all up-regulated in peripheral leukocytes of unstable angina. In addition, H-ATPase, glycolytic genes, platelet and RBC related genes are also up-regulated in peripheral leukocytes of during unstable angina. It also implies that atherosclerosis is a mixed TH17 and TH1 autoimmune disease. If we know the etiology of unstable angina as well as atherosclerosis better,

we can have better methods to control and prevent this detrimental illness.

Introduction

Atherosclerosis is a very popular disease, especially in developed countries. It is the top death-causing disease in industrial countries. Coronary artery disease (CAD) is the most important clinical symptom of atherosclerosis. Typical angina and unstable angina are common manifestations of CAD. Atherosclerosis is thought to be an inflammatory disorder. However, the detailed pathogenesis of angina is not known. Here, I use microarray analysis of peripheral leukocytes to describe unstable angina is a mixed TH1 and TH17 immune disorder.

Materials and methods

Study samples

I use microarray dataset from Gene Omnibus website (GEO). The dataset serial number is GSE. This dataset includes peripheral leukocytes from patients of acute myocardial infarction and unstable angina. Here, I compare the RNA expression profile of leukocytes from unstable angina patients to that from health normal control. This dataset is GSE29111 from Dr. Milo and Rothman's study group. The healthy normal controls are from dataset of a Huntington's disease blood biomarker study population. The dataset is GSE8762 from Dr. Runne H.'s study group. This second study was published in PNAS,2007, 104(36):14424.

RMA normalization

Affymetrix HG-U133A 2.0 genechip was used in both samples. RMA express software(UC Berkeley, Board Institute) is used to do normalization and to rule out the outliners of the above dataset. I rule out the potential outliners of samples due to the following criteria:

1. Remove samples which have strong deviation in NUSE plot
2. Remove samples which have broad spectrum in RLE value plot
3. Remove samples which have strong deviation in RLE-NUSE mutiplot
4. Remove samples which exceed 99% line in RLE-NUSE T2 plot

By the exclusion criteria above, I removed GSM721017 from unstable angina samples and GSM217774 from healthy normal controls. Then, Genespring XI software was

done to analysis the significant expressed genes between ARDS and healthy control leukocytes. P value cut-off point is less than 0.05. Fold change cut-off point is >2.0 fold change. Benjamini-hochberg corrected false discovery rate was used during the analysis. Totally, a genelist of 6020 genes was generated from the HGU133A2.0 chip with 18400 transcripts including 14500 well-characterized human genes.

Results

Toll-like receptor up-regulation in unstable angina

During the microarray analysis of peripheral blood leukocytes of unstable angina patients, I find out that Toll-like receptor genes are up-regulated.(Table1) These genes include TLR 1,2,4,6,8, TIRAP, TTRAP, TRAF6, TANK, TICAM2, and TOLIP. It is worth noting that TLR1 is 7 fold up-regulated, TLR4 is 13 fold up-regulated, TLR8 is 6 fold up-regulated, and TANK is 6 fold up-regulated. Since TLR 1,2,4,6,8 are related to the activation of antibacterial TH1 or TH17(TH22) immunity, we can say that TH1(anti-intracellular bacteria) or TH17(TH22)(anti-extracellular bacteria) immunity is triggered during unstable angina.

Heat shock protein up-regulation in unstable angina

In the peripheral leukocyte of unstable angina patients, mRNAs of many heat shock proteins are up-regulated. These genes include HSPA6, HSPA1A/A1B, HSPA13, HSPB11, DNAJA4, DNAJB9, DNAJB2, DNAJB4, DNAJC6, DNAJA2, DNAJC27, DNAJC3, and DNAJC25. (Table2) Among them, HSPA1A/HSPA1B is 5.6 fold up-regulated and DNAJC6 is 4.8 fold up-regulated. However, few certain heat shock protein genes are down-regulated including HSP90AA1, DNAJC1, DNAJC2, DNAJC3, and DNAJC7. In addition, these genes are only 2-3 fold down-regulated. HSP70 can bind to TLRs to initiate anti-bacterial immunity. Thus, anti-bacterial TH1 or TH17(TH22) is likely to be activated at unstable angina.

TH1 and TH17 related transcription factor up-regulation during unstable angina

Then, we will look at TH1 and TH22(TH17) related transcription factor regulation during unstable angina.(Table 3) TH1 related transcription factors, STAT1, ETS2, RARA, RXRA, IRF2, MNDA, MYADM, IDO1, and MMD, are up-regulated during unstable angina. Up-regulated TH17 related transcription factors include SMAD1, SMAD4,

SMAD2, SMAD5, SMAD7, RARA, RXRA, STAT5B, SOCS3, IKZF3, FOSL2, and FOXO3. Besides, negative regulator of TH17 immunity, ETS1, is down-regulated in unstable angina. In addition, THαβ related transcription factors are down-regulated including MAFB, suppressor of IKKe, and BCL6. STAT1 is the key downstream mediator of IFNg. ETS2 can up-regulate IL-12 production. Retinoic acid (for RXRA and RARA) can promote TH1 and TH17 immunity. IRF2 can promote TH1 immunity via IFNg. IDO is the downstream mediator of IFNg. MNDA, MYADM, and MMD are all macrophage differentiation factors. SMADs and STAT5B are downstream mediators of TGFb, a key cytokine of TH17 immunity. SOCS3, IKZF3, FOSL2, and FOXO3 can all promote TH17 immunity.

TH1 and TH17 related chemokine up-regulation during unstable angina

In this microarray analysis, we can see many chemokine genes are up-regulated during unstable angina. (Table 4) Most important of all, majority of these chemokine genes are TH1 and TH17 related chemokines. The up-regulated chemokine as well as chemokine receptors include CXCL1, CCR1, CXCL6, CCR2, CCR6, CCR3, DARC, CCL23, CCRL2, CXCR7, CXCL5, CKLF, IL8RB, IL8RA, IL8, S100A11, S100B, S100A9, S100P, and S100A12. Among these genes, CXCL1 is 8 fold up-regulated, CCR3 is 18 fold up-regulated, CXCL5 is 8 fold up-regulated, IL8RB is 38 fold up-regulated, and S100P is 50 fold up-regulated. TH1 related chemokine or chemokine receptors include CCR1, CCR2, CCR6, CCR3, CCL23, and CXCR7. TH17 related chemokine or chemokine receptors include CXCL1, CXCL6, CXCL5, IL8RB, IL8RA, IL8, and S100 proteins.

TH1 and TH17 related prostaglandin and leukotriene during unstable angina

In peripheral leukocytes of unstable angina patients, many prostaglandin and leukotriene genes are up-regulated. (Table 5) These up-regulated genes include HPGD, PTGS1, PTGS2, LTB4R, ALOX5AP, ALOX5, ALOX12, PLA2G12A, and PLAA. Prostaglandin and leukotriene B4 are mainly neutrophil chemoattractants. Thus, up-regulation of these genes suggests that TH17 related chemotaxis is up-regulated during unstable angina.

TH1 and TH17 related cytokine up-regulation in unstable angina

During unstable angina, many TH1 and TH17 related cytokines are up-regulated. (Table 6) Up-regulated TH1 cytokines include TGFA, IL-18(IFNG inducing factor), and IFNG. Up-regulated TH17 related cytokines include IL-8 and IL-1B. It is worth noting

that IL1B is 11 fold up-regulated. Down-regulated cytokines in unstable angina include IL-34, IL-23A, IL-32, and TGFB1. It is important to know that IL1 beta is the key cytokine in TH17 (TH22) anti-extracellular bacteria immunity. IFN gamma is the key enzyme in TH1 anti-intracellular bacteria immunity. Thus, both TH17 and TH1 immunity are up-regulated during unstable angina.

TH1 and TH17 related cytokine receptor expression in unstable angina

In this microarray study, I find out that many cytokine receptor gene expressions are changed during unstable angina. (Table 7) Up-regulated cytokine is usually accompanying with down-regulated its cytokine receptor in certain specific immunological pathway. Down-regulation of IL-6 receptor (IL-6ST) implies that TH17 immunological pathway is activated. Down-regulation of IFNg receptor implies that TH1 immunological pathway is also activated. Up-regulation of IL-13 and IL-5 receptors suggest that TH2 immunological pathway is not activated. Up-regulation of IL-10 and type 1 interferon receptors suggests that THαβ immunological pathway is not activated. Significant up-regulation of IL-1 receptors suggests that TH22 immunological pathway is not activated. And, up-regulation of TGFB1 receptor suggests that Treg pathway is not activated.

Anti-bacterial complement up-regulation during unstable angina

Complements are important for anti-bacterial innate immunity including TH1 and TH17 immunity. Here, we show that majority of complement genes are up-regulated during unstable angina. (Table 8) These complement genes include CD59, CD55, CFD, C4BPA, CR1, C4A/B, CD46, C1QBP, ITGAX, C1RL, C5AR1, and CR1/1L. The only down-regulated complement gene is C1QA. It means that the whole complement machinery is up-regulated during unstable angina.

Other anti-bacterial related gene up-regulation in unstable angina

In table 9, many other important anti-bacterial genes are up-regulated during unstable angina. These genes include CSF3R, FPR1, CSF2RB, SCARF1, CSF2RA, DEFA4, NCF4, NCF2, FPR2, MRC2, DEFB106A, and PTX3. It is worth noting that CSF2RB is 10 fold up-regulated, DEFA4 is 11 fold up-regulated, and FPR2 is 38 fold up-regulated. These neutrophil or anti-bacterial related genes suggest the activation of TH1 and TH17 host immunological pathways in unstable angina.

Glycolytic genes up-regulation during unstable angina

In table 10, the whole set of glycolytic pathway is up-regulated in unstable angina. Hypoxia can drive the activation of the anaerobic glycolysis. Thus, it is reasonable that glycolytic enzymes are up-regulated during the hypoxia status of the attack of unstable angina. These up-regulated genes include PGK1, PFKFB3, HK2, PYGL, BPGM, PDK3, PFKFB2, GAPDH, ENO1, PDK2, PDK4, PGK1, and PFKFB4. It is worth noting that BPGM(2,3-bisphosphoglycerate mutase) is 19 fold up-regulated. The product of BPGM is 2,3-bisphosphoglycerate, which combines with hemoglobin, can cause a decrease in affinity for oxygen. Thus, the presence of 2,3-bisphosphoglycerate helps oxyhemoglobin to unload oxygen to help unstable angina patients.

H^+-ATPase gene up-regulation during unstable angina

In table 11, we can see many H^+-ATPases are up-regulated during unstable angina. These genes include ATP6V0B, ATP6V0C, ATP6V1B2, ATP6V0E1, ATP6AP2, ATP6V1A, ATP6V1C1, ATP6V0A2, and ATP6V1D. These ATPases are proton pumps which can generate H^+ by using ATP. In addition, several carbonic anhydrases are also up-regulated including CA1, CA2, and CA4. Carbonic anhydrases can catalyze H_2CO_3 formation from CO_2 and H_2O. Thus, acidosis can result during the attack of unstable angina.

Coagulation gene up-regulation during unstable angina

In table 12, majority of coagulation related genes are up-regulated in peripheral leukocytes of unstable angina patients. These genes include THBS1, VWF, THBD, F2R, F5, F8, F2RL1, ITGA2B, PROS1, GP5, PTAFR, PLAUR, TFP1, ITGB3, PDGFD, HPSE, GP6, PEAR1, and TBXAS1. Only few coagulation related genes are down-regulated including GP1BB and CD36. Most important of all, F2RL1 is 18 fold up-regulated.

RBC related genes are up-regulated during unstable angina

In table 13, majority of RBC related genes are up-regulated during unstable angina. These up-regulated genes include EPB41, GYPE, ANK1, HP/HPP, NFE2, ALAS2, GYPA, HBG1/HBG2, EPOR, RHCE/RHD, ANKRD12, GYPB, HEBP1, ERAF, HBQ1, AK2RIN2, ANKRDS2, HEMGN, ANKRD50, HBM, and HBD. A few genes are down-regulated including HMOX1 and ANKRD10. It is worth noting that many hemoglobin genes are up-regulated including HBG1, HBG2, HBQ1, HBM, and HBD. Among them, HBG1/2 is

20 fold up-regulated, HBM is 60 fold up-regulated, HEMGN is 49 fold up-regulated, HBQ1 is 18 fold up-regulated, ERAF is 33 fold up-regulated, GYPA is 27 fold up-regulated, and ALAS2 is 36 fold up-regulated. Heme oxygenase (HMOX1) can degrade heme and it is down-regulated in unstable angina.

Discussion

Atherosclerosis is a very common and detrimental disease, especially in many developed countries. It is usually among the top three leading causes of mortality. Inflammatory process is thought to be related to the etiology of atherosclerosis. C reactive protein (CRP) is found to be related to the course of atherosclerosis. Abnormal T cell activation has been found in atherosclerosis.(Liuzzo, Kopecky et al. 1999) However, detailed relationship between inflammation and atherosclerosis is remained to be unlocked. Unstable angina is a clinical manifested syndrome of atherosclerosis. Thus, I use microarray analysis of peripheral leukocytes to study the relationship of specific inflammation and unstable angina.

Host immunity against bacteria includes TH1(anti-intracellular bacteria) and TH17(anti-extracellular bacteria). It is observed that Chlamydia pneumonia is noted in endothelium of atherosclerosis lesion(Benagiano, Azzurri et al. 2003, Benagiano, Munari et al. 2012). Thus, immunity against intracellular bacteria is likely to be activated in atherosclerosis. In addition, Helicobacter pylori infection is also related to atherosclerosis. Thus, anti-extracellular TH17 immunity is also likely to be activated during atherosclerosis(Ng, Burris et al. 2011). In addition, TH1 and TH17 immunological pathways are also related to important risk factors for atherosclerosis: Diabetes mellitus and hypertension.(Gao, Jiang et al. 2010, Xie, Wang et al. 2010) In addition, CRP, the TH17 inflammatory factor, is elevated in atherosclerosis. Macrophage, the main TH1 effector cell, is accumulated in atherosclerotic plaques(Laurat, Poirier et al. 2001). In addition, deficiency of Treg cells promotes the progression of atherosclerosis.(Gotsman, Grabie et al. 2006, Mor, Planer et al. 2007) Besides, TH2 and THαβ immunological pathway activation such as IL-10 up-regulation can reduce the development of atherosclerosis.(Liuzzo, Kopecky et al. 1999, Pinderski 2002) These evidences all suggest that TH1 and TH17 immunity plays an important role in the pathophysiology of atherosclerosis.

In this study, I find out the evidences that immunity plays a very important role in the pathogenesis of unstable angina. First of all, anti-bacterial Toll-like receptors are up-regulated during unstable angina. These Toll-like receptors include TLR 1,2,4,6,8.

It is worth noting that TLR 1,2,4,6 are for triggering anti-extracellular bacteria TH17 immunity. TLR8 is for triggering anti-intracellular bacteria TH1 immunity. Thus, both TH1 and TH17 immunity are initiated during unstable angina.

In addition, heat shock proteins which are responsible for triggering anti-bacterial immunity are also up-regulated during unstable angina attack. Heat shock protein 70 (HSP70) can bind to Toll-like receptor 2 and Toll-like receptor 4 to trigger TH17 immunity. In this study, I find out that HSP70 genes are up-regulated including HSPA1A, HSPA6, and HSPA13. This means anti-bacterial immunity is activated during unstable angina.

Then, we look at immune-related transcription factor expression in unstable angina. Strikingly, we find out many TH1 and TH17 related immune transcription factor up-regulation in unstable angina patients' peripheral leukocytes. STAT1 is the key downstream transcription factor of TH1 immunity. The key TH1 cytokine, IFN gamma, can mediate its function mainly by activating STAT1. In addition, STAT5B and SMAD proteins are major effector genes of TGF beta signaling. TGF beta is the key cytokine to initiate TH17 immunity. Thus, both TH1 and TH17 are likely to be activated during unstable angina. In addition, TH17 negative regulator, ETS1, is down-regulated in unstable angina(Moisan, Grenningloh et al. 2007). Retinoic acid related transcription factors, which promote TH1 and TH17 immunity, are up-regulated during unstable angina.(Mucida, Park et al. 2007) Aiolos(IKZF3), which can activate TH17 immunity, is also up-regulated in unstable angina.(Quintana, Jin et al. 2012)

Chemokine genes are differentially regulated in unstable angina. Most important of all, TH17 and TH1 related chemokine and chemokine receptor genes are up-regulated. These strikingly up-regulated chemokine related genes include CXCL1, CCR3, CXCL5, IL8RB, and S100P. CCR3 is TH1 immunity related chemokine receptor. CXCL1, CXCL5, and S100P are TH17 immunity related chemokines. And, IL8RB is TH17 related chemokine receptor. Besides, prostaglandin and leukotriene B4 related genes are also up-regulated during unstable angina. This also shows that TH17 anti-bacterial immunity is activated at unstable angina.

Then, we look at cytokine and cytokine receptor gene expression profiles of peripheral leukocytes during unstable angina. We find out that IL-18, TGFA, IFNG, IL1B, and IL8 are up-regulated. Among them, IL-18, TGFA, and IFNG are key TH1 related cytokines. IL8 and IL1B are key TH17 related cytokines. Besides, many cytokine receptors are also differentially regulated at unstable angina. These

up-regulated cytokine receptors include IL-1R, IL-13R, IL-5R, IL10R, IFNaR, IL1R, and TGFB1R. And, down-regulated cytokine receptors are IL6ST and IFNgR. Specific immunological pathway is usually associated with down-regulation of its effector cytokine receptors. Thus, TH1 activation is related to interferon gamma receptor down-regulation, and TH17 activation is related to interleukin 6 receptor down-regulation. In addition, TH2, THαβ, Treg, and TH22 immune pathways are not triggered. These results also support my hypothesis.

Complements are important in mediating host killing of intracellular bacteria as well as extracellular bacteria. In this study, we can see that majority of complement machinery is activated including CD59, CD55, CFD, C4BPA, CR1, C4A/B, CD46, C1QBP, ITGAX, C1RL, C5AR1, and CR1/1L. This means anti-bacterial TH1 or TH17 immunity is triggered during unstable angina. Besides, other important anti-bacterial host defense genes are also up-regulated. These up-regulated anti-bacterial genes include CSF3R, FPR1, CSF2RB, SCARF1, CSF2RA, DEFA4, NCF4, NCF2, FPR2, MRC2, DEFB106A, and PTX3. These genes include neutrophil and macrophage growth factors, pattern recognition receptor, defensin, neutrophil cytosolic factors, and pentraxin. These all suggest that TH1 or TH17 anti-bacterial immunity is activated during unstable angina.

By using microarray analysis, we can also understand the complications of unstable angina. Glycolysis, acidosis, hypoxia, and coagulation anomaly are frequently reported in unstable angina. First of all, we look at the glycolytic mediating enzymes in unstable angina. Strikingly, we find out all glycolytic enzyme genes are up-regulated including PGK1, PFKFB3, HK2, PYGL, BPGM, PDK3, PFKFB2, GAPDH, ENO1, PDK2, PDK4, PGK1, and PFKFB4. Among them, BPGM is 19 fold up-regulated. BPGM can help to unload oxygen from oxy-hemoglobins. Thus, it can help to alleviate the hypoxic syndrome during unstable angina. It can be explained as a host compensatory mechanism responding to the attack of unstable angina. More, we find out that many ATPase genes are up-regulated during unstable angina including ATP6V0B, ATP6V0C, ATP6V1B2, ATP6V0E1, ATP6AP2, ATP6V1A, ATP6V1C1, ATP6V0A2, and ATP6V1D. Several carbonic anhydrase enzyme genes are also up-regulated including CA1, CA2, and CA4. In my previous malaria genomic research, I find out a co-expression of glycolytic enzymes and ATPases. Here, I also find out acidosis at unstable angina can be due to up-regulation of these proton pumps (H^+-ATPase) and H_2CO_3 producing carbonic anhydrases.

Finally, we look at RBC and platelet related gene expression profiles during unstable angina. Strikingly, we find out that majority of RBC and platelet related genes are

up-regulated during unstable angina. Up-regulated platelet/coagulation related genes include THBS1, VWF, THBD, F2R, F5, F8, F2RL1, ITGA2B, PROS1, GP5, PTAFR, PLAUR, TFP1, ITGB3, PDGFD, HPSE, GP6, PEAR1, and TBXAS1. Platelet function is triggering blood coagulation, and overactivation of coagulation related genes can be related to the pathophysiology of atherosclerosis induced unstable angina with coronary artery occlusion. Up-regulated RBC related genes include EPB41, GYPE, ANK1, HP/HPP, NFE2, ALAS2, GYPA, HBG1/HBG2, EPOR, RHCE/RHD, ANKRD12, GYPB, HEBP1, ERAF, HBQ1, AK2RIN2, ANKRDS2, HEMGN, ANKRD50, HBM, and HBD. We can see many hemoglobin genes are up-regulated at unstable angina. Unstable angina is caused by lack of oxygen support for cardiac muscle. Thus, up-regulated RBC related genes including hemoglobin genes can help to alleviate the hypoxia status during unstable angina. It can be viewed as a host compensatory mechanism at the attack of unstable angina.

In summary, microarray analysis of peripheral leukocytes from unstable angina patients can help to explain the pathogenesis of unstable angina. From the above evidences, unstable angina can be viewed as a mix TH1 and TH17 inflammatory disorder with up-regulated TH1/TH17 chemokines, cytokines, transcription factors, Toll-like receptors, heat shock proteins, complements, leukotrienes, prostaglandins, defensins, pentraxins, and other effector molecules. In addition, overactivation of platelet related genes, glycolytic enzymes, and H^+-ATPases can help to explain the pathophysiology of unstable angina with coagulation hyperactivity and metabolic acidosis. Finally, up-regulation of RBC related genes should be a host compensatory mechanism to increase oxygen delivery during unstable angina.

Figure legends

Figure 1. RMA express plot for selecting samples in normal healthy controls.
1-A NUSE boxplot for normal control
1-B RLE boxplot for normal control
1-C RLE-NUSE multiplot for normal control
1-D RLE-NUSE T2 plot for normal control

Figure 2. RMA express plot for selecting samples in unstable angina patients.
2-A NUSE boxplot for unstable angina patients
2-B RLE boxplot for unstable angina patients
2-C RLE-NUSE multiplot for unstable angina patients
2-D RLE-NUSE T2 plot for unstable angina patients

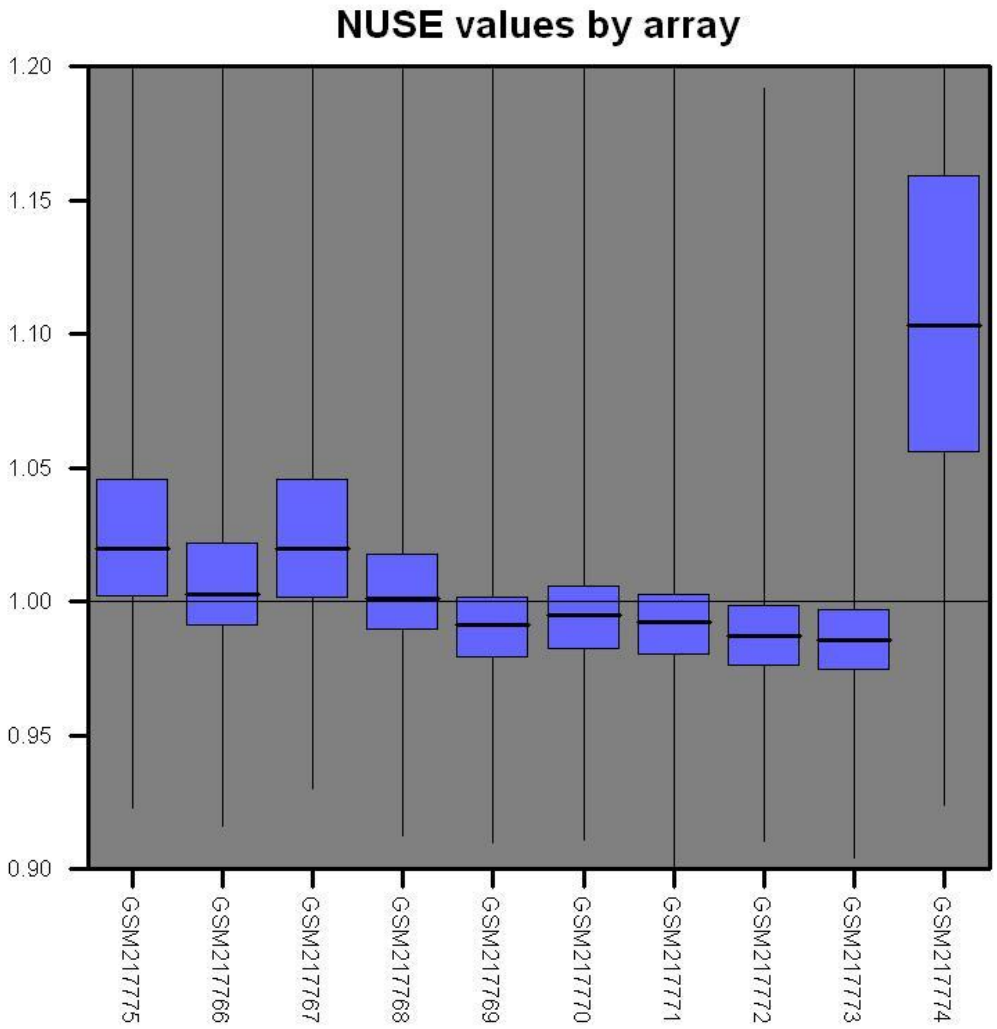
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Figure 1-A

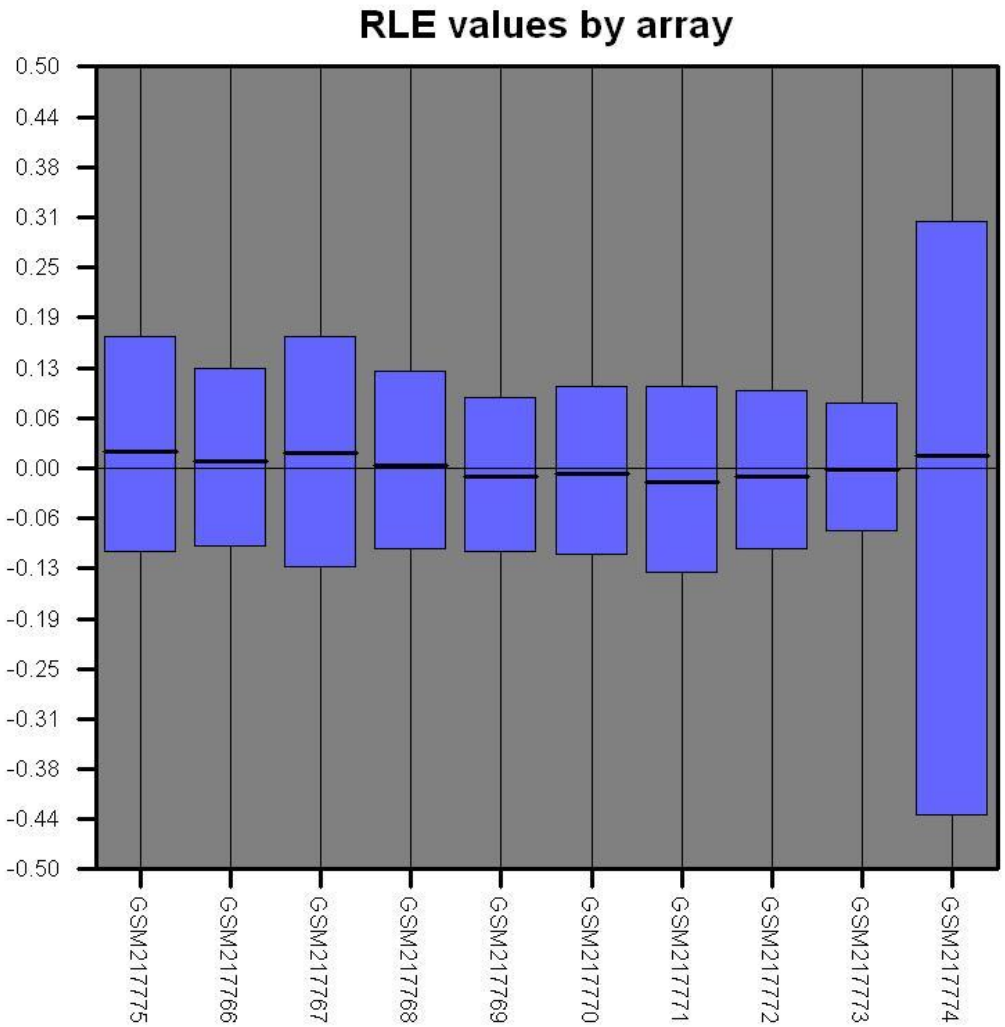
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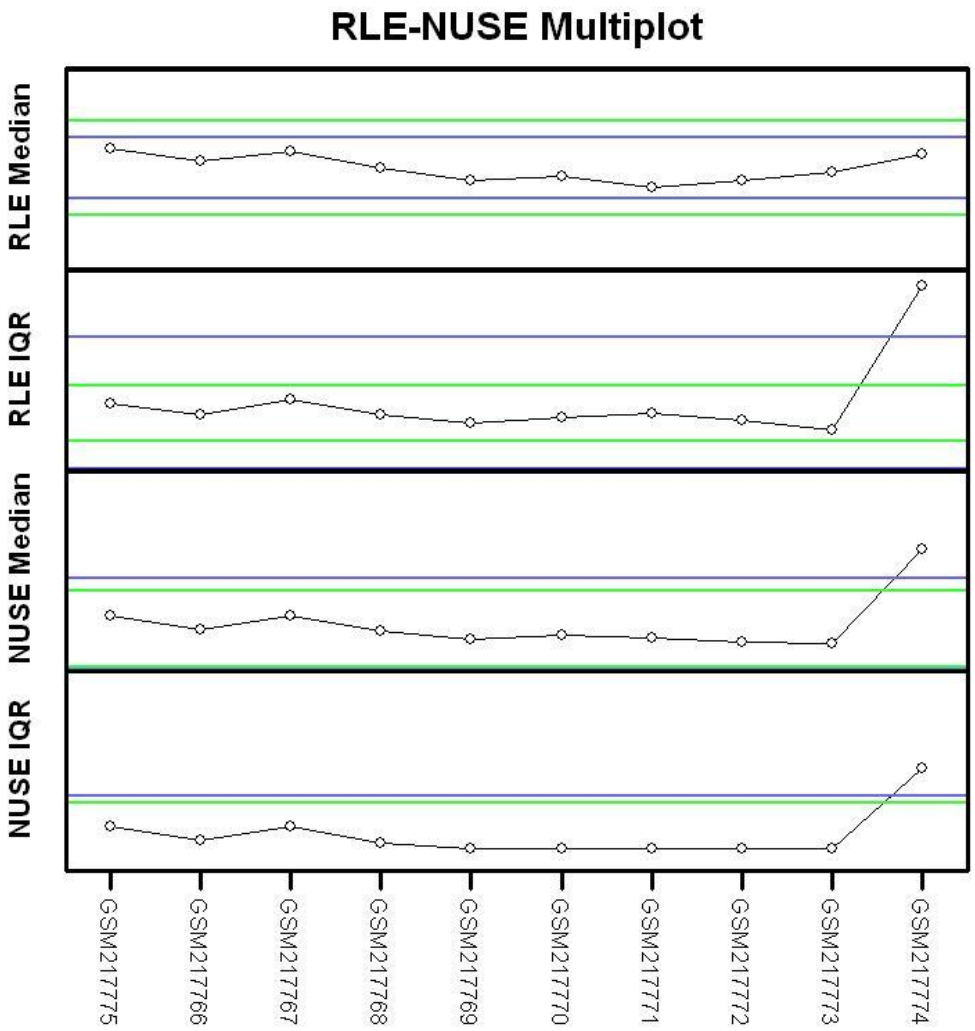
Figure 1-B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RLE IQR
NUSE Median
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Figure 1-C

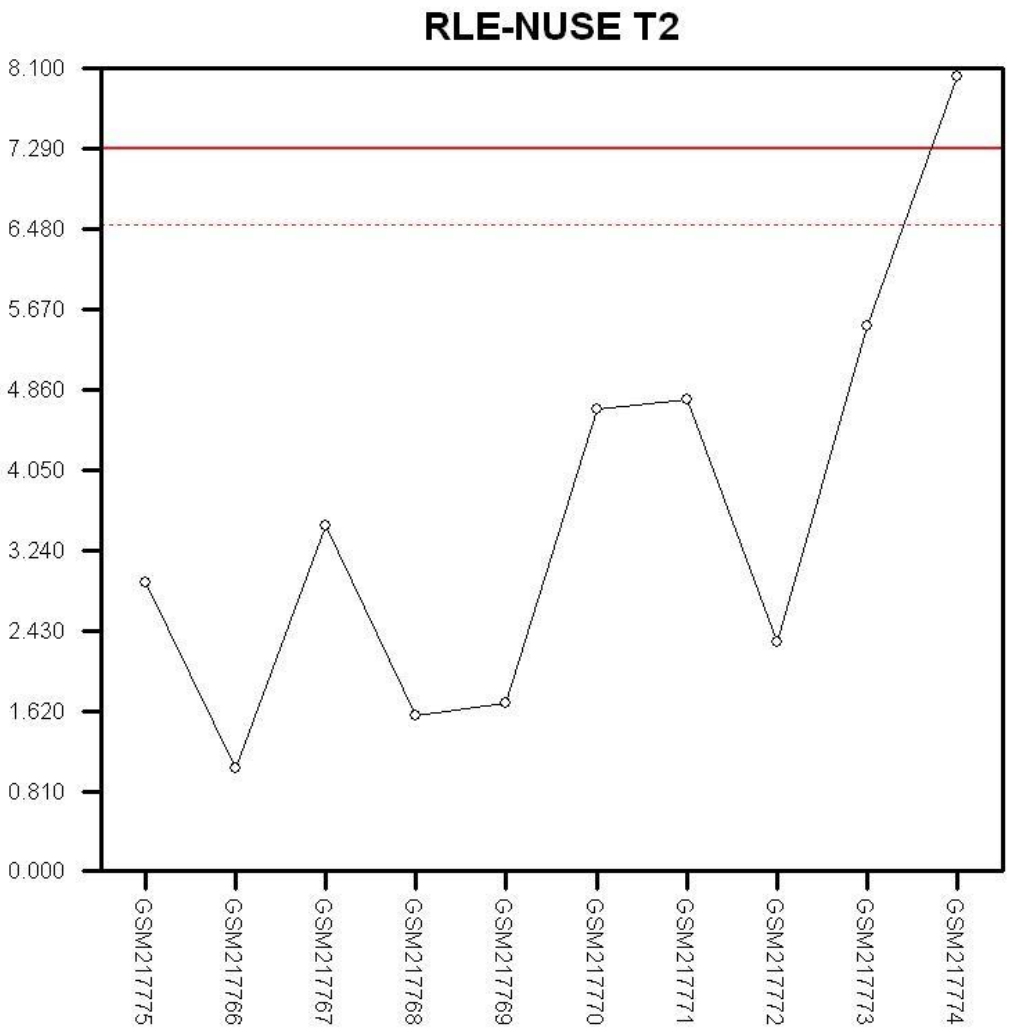
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Figure 1-D

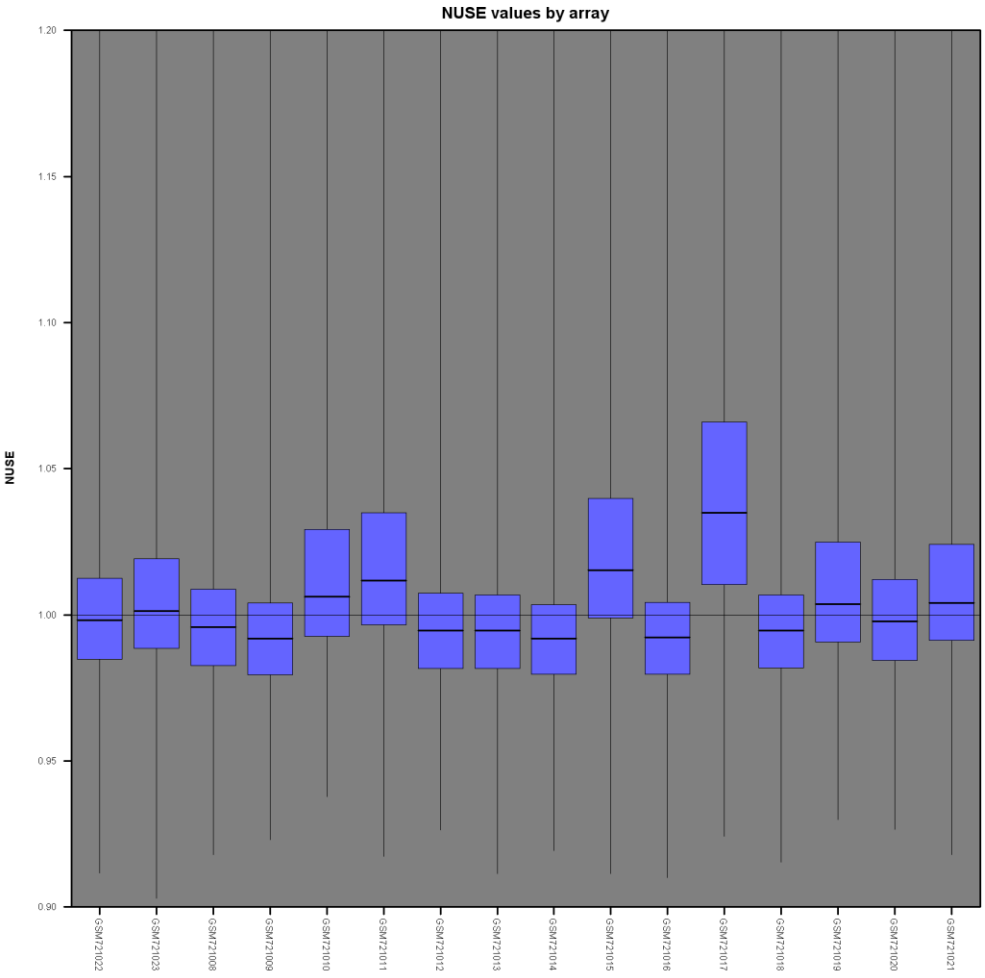
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Figure 2-A

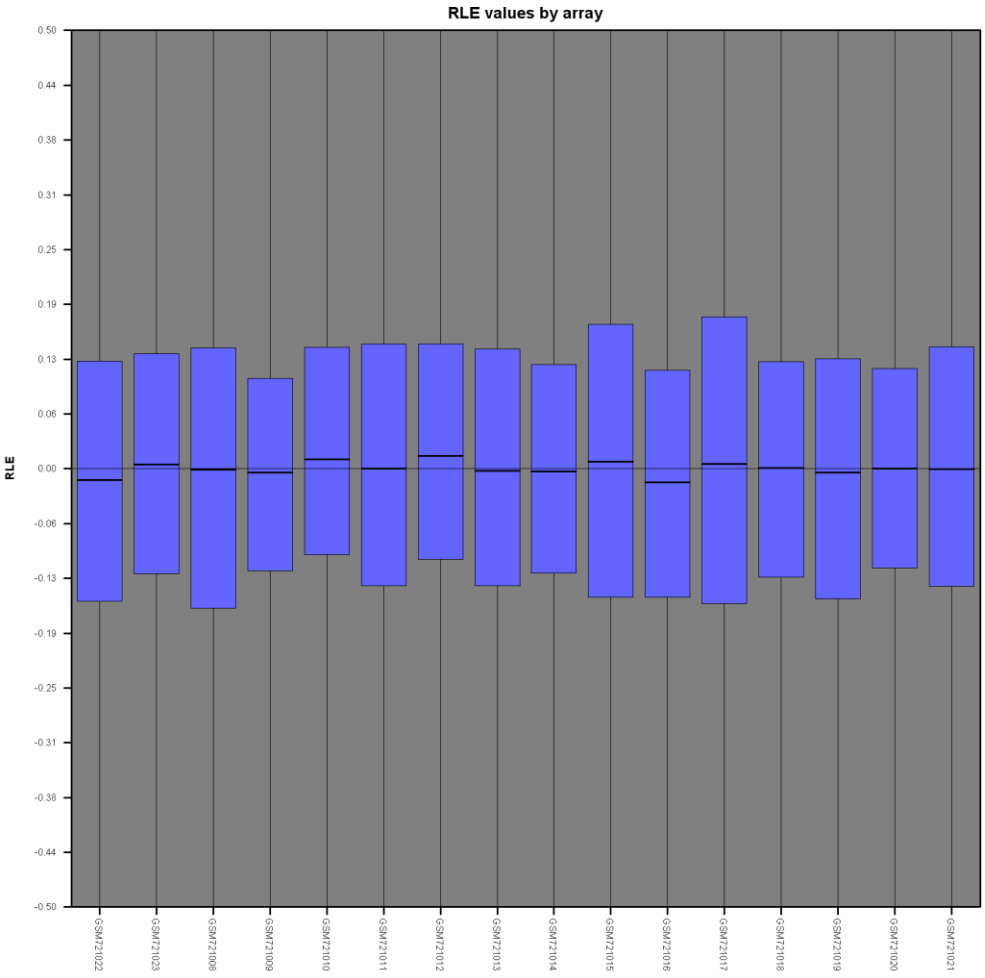
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Figure 2-B

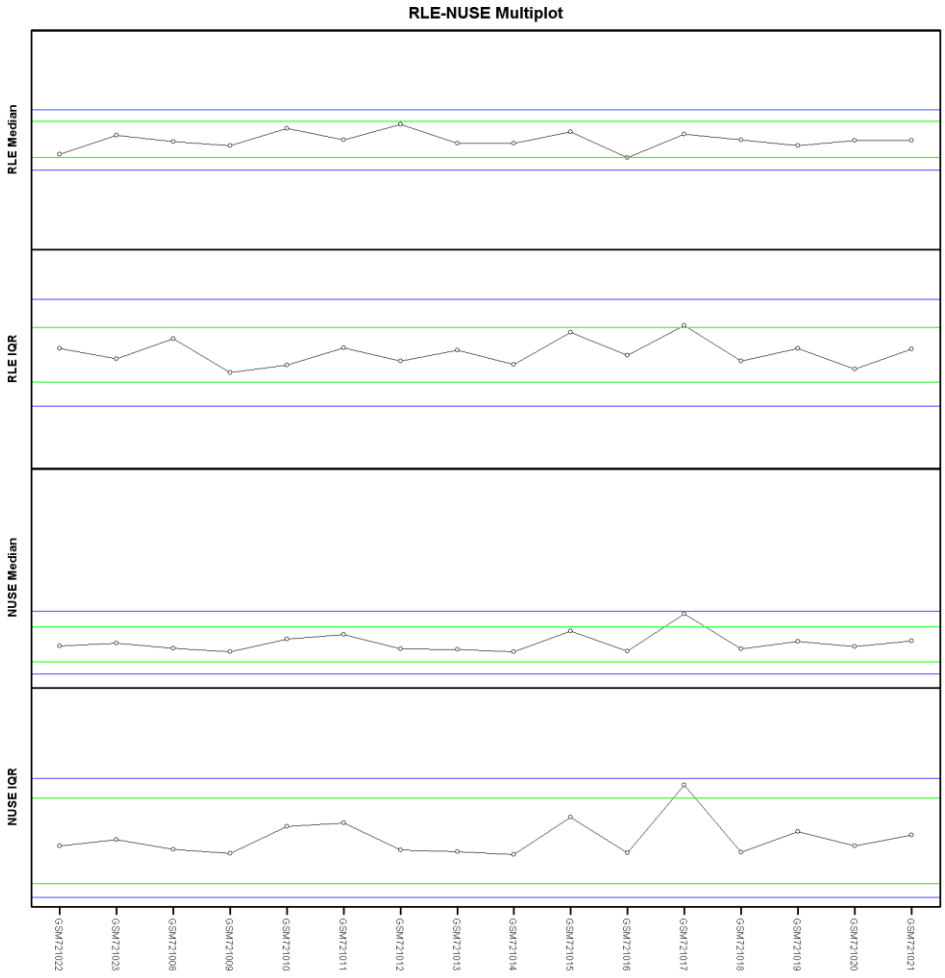
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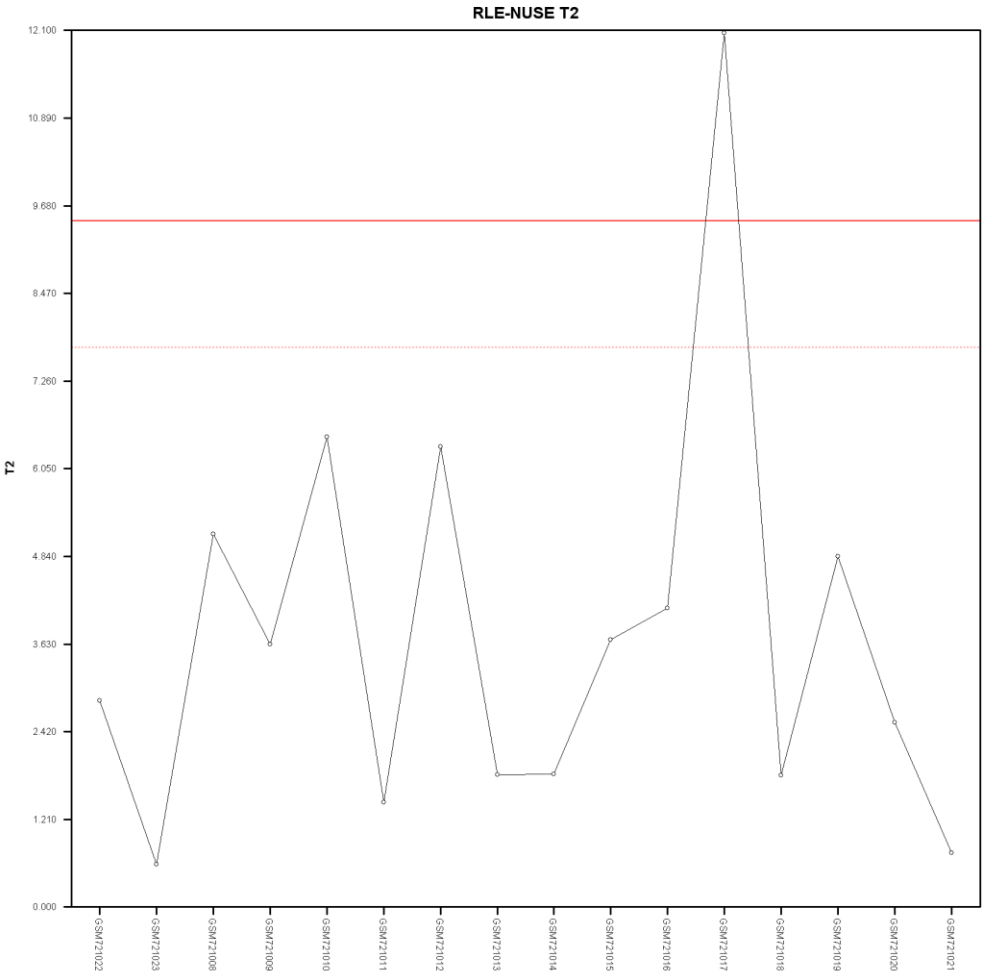
Figure 2-C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3.630
2.420
1.210
0.000
GSMTZ1022
GSMTZ1023
GSMTZ1008
GSMTZ1009
GSMTZ1010
GSMTZ1011
GSMTZ1012
GSMTZ1013
GSMTZ1014
GSMTZ1015
GSMTZ1016
GSMTZ1017
GSMTZ1018
GSMTZ1019
GSMTZ1020
GSMTZ1021

Figure 2-D

Table 1.

Toll-like-receptor

Probe Set ID	Pvalue	Arrow	Fold	Gene
204924_at	6.07E-05	up	2.711394	TLR2
207446_at	1.82E-06	up	2.196196	TLR6
210176_at	1.61E-09	up	7.237305	TLR1
220832_at	1.16E-08	up	6.489917	TLR8
221060_s_at	6.35E-07	up	5.706266	TLR4
224341_x_at	5.14E-06	up	5.151984	TLR4
229560_at	6.43E-05	up	3.756611	TLR8
232068_s_at	2.04E-10	up	13.17082	TLR4
1552798_a_at	7.63E-07	up	3.467543	TLR4
202266_at	1.91E-07	up	2.636574	TTRAP
209451_at	5.11E-09	up	5.10644	TANK
210458_s_at	2.56E-10	up	6.495119	TANK
211828_s_at	1.66E-08	down	-2.46097	TNIK
217930_s_at	8.09E-10	up	3.414113	TOLLIP
239431_at	1.01E-05	up	2.18973	TICAM2
1552360_a_at	1.28E-09	up	2.909597	TIRAP
213817_at	6.28E-04	up	2.556772	IRAK3
205558_at	2.29E-09	up	2.273412	TRAF6

Table 2. Heat shock protein

Probe Set ID	Pvalue	Arrow	Fold	Gene
211968_s_at	5.02E-09	down	-3.03611	HSP90AA1
213418_at	1.09E-04	up	2.462545	HSPA6
117_at	2.01E-06	up	3.369852	HSPA6
200799_at	1.78E-05	up	2.131275	HSPA1A
200800_s_at	7.79E-05	up	2.27759	HSPA1A/B
202557_at	1.48E-05	up	2.020725	HSPA13
202581_at	7.23E-10	up	5.616055	HSPA1A/B
203960_s_at	1.04E-05	up	2.114942	HSPB11
1554333_at	4.79E-05	up	4.757214	DNAJA4
1554334_a_at	2.40E-04	up	3.128753	DNAJA4
1554462_a_at	6.27E-08	up	2.534985	DNAJB9
1558080_s_at	2.64E-06	down	-3.33239	DNAJC3
202416_at	1.77E-09	down	-2.93756	DNAJC7
202500_at	6.74E-09	up	3.785045	DNAJB2
202842_s_at	1.22E-06	up	2.269558	DNAJB9
202843_at	5.11E-09	up	2.767084	DNAJB9
203810_at	4.20E-08	up	2.99098	DNAJB4
204720_s_at	2.13E-06	up	4.809938	DNAJC6
208810_at	8.05E-09	up	2.512607	DNAJB6
208811_s_at	1.66E-06	up	2.526036	DNAJB6
209015_s_at	2.35E-07	up	2.843226	DNAJB6
209157_at	3.03E-08	up	2.647895	DNAJA2
213097_s_at	3.59E-10	down	-2.68168	DNAJC2
222620_s_at	5.74E-07	down	-2.89806	DNAJC1
223504_at	2.84E-05	up	2.296595	DNAJC27
225061_at	1.83E-04	up	3.17514	DNAJA4
225284_at	4.93E-05	up	2.162836	DNAJC3
226859_at	5.59E-09	up	2.031987	DNAJC25
226994_at	2.89E-07	up	2.197155	DNAJA2

Table 3. Transcription factors

Probe Set ID	Pvalue	Arrow	Fold	Gene
M97935_MB_at	5.29E-06	up	3.250345	STAT1
201328_at	8.13E-06	up	2.391284	ETS2
201329_s_at	2.07E-04	up	2.834679	ETS2
202527_s_at	2.47E-08	up	3.925728	SMAD4
203077_s_at	2.05E-09	up	2.499254	SMAD2
203140_at	2.67E-08	up	4.672891	BCL6
203275_at	3.53E-10	up	2.53243	IRF2
203749_s_at	1.45E-09	up	2.776926	RARA
204131_s_at	3.18E-07	up	5.362668	FOXO3
204132_s_at	7.42E-10	up	9.790864	FOXO3/B
204790_at	3.32E-06	up	2.693902	SMAD7
205841_at	8.44E-05	up	2.228473	JAK2
210655_s_at	2.51E-08	up	6.194851	FOXO3/B
211027_s_at	1.09E-07	down	-2.20832	IKBKB
212550_at	7.95E-10	up	2.703492	STAT5B
214447_at	2.18E-06	down	-2.71117	ETS1
217804_s_at	7.97E-10	down	-2.29951	ILF3
218880_at	2.81E-07	up	2.718907	FOSL2
222670_s_at	7.29E-04	down	-2.03266	MAFB
223287_s_at	8.80E-09	down	-4.59015	FOXP1
224889_at	1.75E-10	up	8.903059	FOXO3
224891_at	3.03E-07	up	4.554951	FOXO3
225223_at	1.74E-06	up	2.836291	SMAD5
225262_at	0.018247	up	2.013291	FOSL2
227798_at	1.70E-05	up	2.374207	SMAD1
228026_at	1.18E-06	up	3.017289	RP5-1000E10.4
228188_at	5.50E-07	up	4.339457	FOSL2
228758_at	1.45E-05	up	3.365109	BCL6
240613_at	4.95E-10	down	-6.16447	JAK1
1552611_a_at	2.95E-05	up	2.774677	JAK1
1565703_at	1.20E-06	up	2.179628	SMAD4
204959_at	1.12E-06	up	5.577443	MNDA
210029_at	1.19E-05	up	3.981845	IDO1
211027_s_at	1.09E-07	down	-2.20832	IKBKB
214105_at	7.95E-08	down	-2.10317	SOCS3
221092_at	8.50E-04	up	2.294967	IKZF3

223287_s_at	8.80E-09	down	-4.59015 FOXP1
223937_at	5.84E-07	down	-2.23877 FOXP1
225223_at	1.74E-06	up	2.836291 SMAD5
225673_at	1.62E-06	up	2.660096 MYADM
202426_s_at	5.52E-11	up	7.436708 RXRA
228026_at	1.18E-06	up	3.017289 RP5-1000E10.4
235444_at	2.78E-08	down	-2.21648 FOXP1
244523_at	7.85E-07	up	2.832237 MMD

Table 4 Chemokine

Probe Set ID	Pvalue	Arrow	Fold	Gene
204470_at	4.05E-11	up	7.821242	CXCL1
205098_at	1.50E-05	up	3.999256	CCR1
205099_s_at	0.001392	up	2.339561	CCR1
206336_at	4.69E-10	up	3.787778	CXCL6
206337_at	2.90E-06	down	-2.92756	CCR7
206978_at	0.011513	up	2.081589	CCR2
206983_at	1.38E-04	up	2.189831	CCR6
207794_at	0.00177	up	2.296914	CCR2
208304_at	4.74E-11	up	17.6996	CCR3
208335_s_at	2.21E-06	up	3.161269	DARC
210548_at	0.001164	up	2.080932	CCL23
211434_s_at	1.17E-05	up	2.202749	CCRL2
212977_at	8.10E-06	up	2.406206	CXCR7
214974_x_at	2.32E-06	up	7.833923	CXCL5
215101_s_at	2.78E-06	up	8.043318	CXCL5
219161_s_at	4.00E-11	up	5.634878	CKLF
221058_s_at	1.44E-08	up	2.639918	CKLF
223451_s_at	7.77E-11	up	4.474447	CKLF
223454_at	4.20E-06	up	3.074875	CXCL16
1568934_at	2.01E-06	up	2.647086	CX3CR1
204470_at	4.05E-11	up	7.821242	CXCL1
207008_at	1.99E-12	up	38.26742	IL8RB
207094_at	1.25E-14	up	12.5119	IL8RA
211506_s_at	3.18E-04	up	2.965578	IL8
202859_x_at	0.02858	up	2.698248	IL8
208540_x_at	2.08E-06	up	2.709116	S100A11/P
209686_at	0.022845	up	2.555998	S100B
238909_at	5.34E-06	down	-2.86673	S100A10
203535_at	4.97E-06	up	3.946168	S100A9
204351_at	5.64E-10	up	50.28864	S100P
205863_at	1.63E-04	up	4.381631	S100A12

Table 5 Prostaglandin/leukotriene

Probe Set ID	Pvalue	Arrow	Fold	Gene
211548_s_at	4.79E-08	up	3.603627	HPGD
211549_s_at	1.36E-05	up	2.012863	HPGD
238669_at	2.01E-04	up	2.296154	PTGS1
1554997_a_at	9.37E-04	up	3.008369	PTGS2
203913_s_at	4.41E-09	up	4.03641	HPGD
203914_x_at	2.93E-07	up	3.450221	HPGD
204748_at	8.71E-06	up	7.748884	PTGS2
236172_at	1.25E-09	up	3.392918	LTB4R
204174_at	1.11E-10	up	7.512037	ALOX5AP
204446_s_at	2.35E-06	up	2.195747	ALOX5
207206_s_at	3.90E-05	up	2.604373	ALOX12
214366_s_at	2.90E-04	up	2.121638	ALOX5
221027_s_at	0.00175	up	2.000762	PLA2G12A
228084_at	4.11E-04	up	2.14738	PLA2G12A
235394_at	9.50E-06	up	2.173632	PLAA
242323_at	5.76E-07	up	2.319156	PLA2G12A

Table 6. Cytokine

Probe Set ID	Pvalue	Arrow	Fold	Gene
237046_x_at	4.92E-08	down	-2.01547	IL34
1568513_x_at	5.20E-07	down	-3.14638	IL23A
202859_x_at	0.02858	up	2.698248	IL8
203828_s_at	2.70E-07	down	-4.22368	IL32
205067_at	2.91E-09	up	11.1993	IL1B
206295_at	2.08E-07	up	2.190391	IL18
39402_at	3.79E-08	up	9.375368	IL1B
203085_s_at	2.46E-12	down	-4.47642	TGFB1
209651_at	1.04E-05	up	3.862509	TGFB1I1
205016_at	3.08E-13	up	12.56279	TGFA
210354_at	4.89E-05	up	2.295556	IFNG
230681_at	3.27E-05	down	-2.09638	TBRG1

Table 7. Cytokine receptor

Probe Set ID	Pvalue	Arrow	Fold	Gene
239522_at	1.63E-07	down	-2.13821	IL12RB1
201887_at	2.63E-04	up	2.493641	IL13RA1
201888_s_at	3.50E-07	up	5.265817	IL13RA1
202948_at	3.01E-13	up	10.59575	IL1R1
204116_at	1.72E-13	down	-4.5043	IL2RG
205403_at	1.14E-14	up	37.11373	IL1R2
205798_at	0.001876	down	-2.04842	IL7R
206618_at	3.97E-05	up	2.889916	IL18R1
209575_at	6.50E-10	up	3.094987	IL10RB
210744_s_at	5.37E-04	up	2.377707	IL5RA
210904_s_at	6.93E-13	up	10.38528	IL13RA1
211372_s_at	8.57E-13	up	23.53884	IL1R2
211517_s_at	0.001136	up	2.419155	IL5RA
211612_s_at	5.00E-09	up	8.944053	IL13RA1
212196_at	9.43E-05	down	-2.08387	IL6ST
226333_at	4.08E-13	up	2.730188	IL6R
224793_s_at	4.59E-05	up	2.229928	TGFBR1
225661_at	1.28E-12	up	5.958052	IFNAR1
225669_at	8.99E-08	up	3.14582	IFNAR1
204191_at	2.17E-07	up	2.336802	IFNAR1
242903_at	1.66E-09	down	-10.0312	IFNGR1

Table 8. Complement

Probe Set ID	Pvalue	Arrow	Fold	Gene
200983_x_at	2.01E-10	up	5.126428	CD59
200984_s_at	3.96E-10	up	5.39977	CD59
200985_s_at	7.88E-08	up	3.902797	CD59
201925_s_at	5.64E-10	up	4.165688	CD55
201926_s_at	7.26E-08	up	2.685217	CD55
205382_s_at	3.05E-04	up	3.283973	CFD
205654_at	0.025737	up	2.728636	C4BPA
206244_at	1.59E-08	up	5.148756	CR1
208451_s_at	1.33E-05	up	3.146097	C4A/4B
208488_s_at	2.21E-06	up	2.838257	CR1
208783_s_at	4.44E-10	up	2.762472	CD46
208910_s_at	8.91E-07	up	2.772785	C1QBP
210184_at	3.36E-07	up	2.689394	ITGAX
212463_at	2.39E-08	up	2.387086	CD59
217552_x_at	1.26E-08	up	5.06804	CR1
218232_at	0.001617	down	-2.31401	C1QA
218983_at	5.79E-11	up	4.443039	C1RL
220088_at	6.89E-05	up	4.115375	C5AR1
239205_s_at	5.31E-11	up	15.49001	CR1/1L
239206_at	2.42E-09	up	12.87955	CR1L
244313_at	8.98E-10	up	9.401143	CR1
1555950_a_at	8.18E-09	up	3.116447	CD55

Table 9 anti-bacterial genes

Probe Set ID	Pvalue	Arrow	Fold	Gene
203591_s_at	5.40E-05	up	2.953523	CSF3R
205118_at	1.40E-06	up	6.013851	FPR1
205119_s_at	1.17E-07	up	8.646483	FPR1
205159_at	4.60E-08	up	10.71302	CSF2RB
206995_x_at	9.73E-09	up	5.092197	SCARF1
207085_x_at	1.37E-06	up	3.863292	CSF2RA
207269_at	9.38E-06	up	11.51901	DEFA4
207677_s_at	4.04E-08	up	5.465464	NCF4
209949_at	2.90E-05	up	2.761298	NCF2
210340_s_at	2.92E-06	up	3.513592	CSF2RA
210772_at	3.39E-13	up	38.75074	FPR2
210773_s_at	1.67E-11	up	22.8151	FPR2
211287_x_at	5.85E-07	up	2.873763	CSF2RA
37408_at	1.83E-05	up	2.611298	MRC2
1552411_at	1.45E-06	up	2.029896	DEFB106A/B
1553297_a_at	1.38E-05	up	2.481309	CSF3R
206157_at	9.63E-08	up	3.038519	PTX3

Table 10 Glycolytic enzymes

Probe Set ID	Pvalue	Arrow	Fold	Gene
217356_s_at	1.45E-07	up	3.485421	PGK1
202464_s_at	1.88E-05	up	3.848975	PFKFB3
202934_at	7.47E-04	up	2.054129	HK2
202990_at	4.01E-07	up	4.853299	PYGL
203502_at	2.42E-08	up	19.10826	BPGM
206348_s_at	4.04E-08	up	2.488083	PDK3
209992_at	1.30E-07	up	2.552616	PFKFB2
M33197_5_at	4.35E-06	up	2.191367	GAPDH
217294_s_at	9.10E-05	up	3.210724	ENO1
217356_s_at	1.45E-07	up	3.485421	PGK1
213724_s_at	2.15E-05	up	2.269032	PDK2
225207_at	0.04755	up	2.020549	PDK4
227068_at	5.94E-05	up	2.026827	PGK1
228499_at	1.41E-06	up	2.453812	PFKFB4

Table11 ATPase

Probe Set ID	Pvalue	Arrow	Fold	Gene
200078_s_at	1.87E-05	up	2.165182	ATP6V0B
200954_at	7.36E-08	up	3.458313	ATP6V0C
201089_at	2.00E-05	up	3.342557	ATP6V1B2
201171_at	2.74E-08	up	3.750572	ATP6V0E1
201444_s_at	8.20E-06	up	2.14297	ATP6AP2
201971_s_at	4.37E-04	up	2.028055	ATP6V1A
202872_at	1.07E-10	up	6.460473	ATP6V1C1
202874_s_at	2.48E-10	up	4.5579	ATP6V1C1
205704_s_at	3.66E-05	up	2.185279	ATP6V0A2
208898_at	5.55E-05	up	2.130803	ATP6V1D
208899_x_at	3.59E-08	up	2.716261	ATP6V1D
214149_s_at	8.54E-11	up	7.664084	ATP6V0E1
36994_at	4.81E-09	up	2.599531	ATP6V0C
205950_s_at	5.00E-08	up	42.28005	CA1
206208_at	2.02E-09	up	3.94974	CA4
206209_s_at	1.82E-12	up	8.938537	CA4
209301_at	2.90E-04	up	2.461168	CA2

Table 12. Coagulation genes

Probe Set ID	Pvalue	Arrow	Fold	Gene
201108_s_at	2.84E-05	up	3.303681	THBS1
201109_s_at	7.13E-05	up	2.95573	THBS1
201110_s_at	5.89E-08	up	6.730528	THBS1
202112_at	8.64E-07	up	2.154882	VWF
203887_s_at	2.66E-10	up	13.1587	THBD
203888_at	1.55E-09	up	5.29251	THBD
203989_x_at	3.03E-05	up	3.24114	F2R
204713_s_at	3.02E-06	up	2.665104	F5
204714_s_at	2.58E-06	up	3.393421	F5
205756_s_at	1.71E-07	up	2.887461	F8
206429_at	4.35E-06	up	2.168341	F2RL1
206493_at	0.012261	up	2.018667	ITGA2B
207808_s_at	6.13E-06	up	3.830064	PROS1
207815_at	9.67E-06	up	8.676992	PF4V1
207926_at	1.53E-05	up	2.539035	GP5
209769_s_at	1.05E-08	down	-2.30101	GP1BB
211661_x_at	1.44E-06	up	5.09946	PTAFR
211924_s_at	1.35E-07	up	4.396324	PLAUR
213258_at	9.09E-06	up	3.442621	TFPI
213506_at	1.11E-10	up	18.07023	F2RL1
214866_at	5.24E-08	up	3.066191	PLAUR
215240_at	1.86E-07	up	4.259491	ITGB3
219304_s_at	0.001786	up	2.10823	PDGFD
219403_s_at	0.002328	up	2.352545	HPSE
220336_s_at	3.37E-04	up	2.506245	GP6
222881_at	1.96E-06	up	2.9733	HPSE
228618_at	2.78E-05	up	2.611937	PEAR1
231029_at	2.14E-09	up	4.807453	F5
236345_at	1.63E-13	up	8.191023	TBXAS1
237252_at	1.11E-05	up	2.237747	THBD
242197_x_at	6.23E-05	down	-4.4414	CD36

Table 13 RBC genes

Probe Set ID	Pvalue	Arrow	Fold	Gene
207793_s_at	5.29E-06	up	3.527715	EPB41
207854_at	5.69E-04	up	2.700479	GYPE
208352_x_at	5.02E-08	up	5.233521	ANK1
208353_x_at	1.46E-08	up	8.199239	ANK1
208470_s_at	4.92E-04	up	2.42323	HP /// HPR
209930_s_at	7.44E-07	up	6.157681	NFE2
211560_s_at	5.08E-08	up	36.1193	ALAS2
211820_x_at	5.24E-10	up	17.19674	GYPA
211821_x_at	5.49E-09	up	27.56794	GYPA
213515_x_at	8.72E-07	up	13.31291	HBG1 /// HBG2
215054_at	4.51E-10	up	3.067622	EPOR
37986_at	2.17E-09	up	2.737781	EPOR
215819_s_at	1.12E-07	up	4.649047	RHCE /// RHD
216317_x_at	0.001298	up	2.167189	RHCE
216563_at	3.75E-05	up	2.423975	ANKRD12
216833_x_at	1.03E-06	up	7.30822	GYPB /// GYPE
218450_at	1.29E-04	up	2.919147	HEBP1
203665_at	1.99E-04	down	-2.47673	HMOX1
219672_at	1.22E-08	up	33.80057	ERAF
220807_at	2.56E-10	up	18.14282	HBQ1
223143_s_at	0.001106	up	2.024285	AKIRIN2
223542_at	4.16E-06	up	2.408006	ANKRD32
223669_at	9.14E-08	up	20.2901	HEMGN
223670_s_at	4.73E-11	up	49.78136	HEMGN
225051_at	6.51E-05	up	2.198623	EPB41
225735_at	1.10E-06	up	2.178783	ANKRD50
226663_at	5.93E-06	down	-2.50174	ANKRD10
240336_at	3.15E-12	up	61.68572	HBM
1554481_a_at	4.42E-06	up	5.047096	EPB41
204419_x_at	3.33E-06	up	20.09402	HBG1 /// HBG2
204848_x_at	1.85E-06	up	17.25642	HBG1 /// HBG2
206834_at	0.011457	up	3.600573	HBD
213515_x_at	8.72E-07	up	13.31291	HBG1 /// HBG2

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