Parkinson's disease is a TH17 dominant autoimmune disorder against accumulated alpha-synuclein

By Wan-Chung Hu (Wan-Jiung Hu)

Postdoctorate
Genomic Research Center
Academia Sinica
128 Academia Road section 2
Nangang 115, Taipei
Taiwan

Previous institutes:

Department of Neurology
Taipei Mackay Memorial Hospital (Medical Center)

Graduate Institute of Immunology
National Taiwan University College of Medicine

Department of International Health (Vaccine science track)
Johns Hopkins University Bloomberg School of Public Health

Abstract

Parkinson's disease is a very common neurodegenerative disorder. Patients usually undergo destruction of substantia nigra to develop typical symptoms such as resting tremor, hypokinesia, and rigidity. However, the exact mechanism of Parkinson's disease is still unknown, so it is called idiopathic Parkinsonism. According to my microarray analysis of peripheral blood leukocytes and substantia nigra brain tissue, I propose that Parkinson's disease is actually a TH17 dominant autoimmune disease. The autoantigen is mainly alpha-synuclein. After knowing the exact disease pathophysiology, we can develop better drugs to prevent or control the detrimental disorder.

About the author

Wan-Jiung Hu is a MD PhD. His former name is Wan-Chung Hu. His MD degree was

awarded from National Taiwan University. His PhD degree was awarded from Vaccine science track of Department of International Health of Johns Hopkins University. His PhD thesis was using microarray to identify the host immunological pathway after malaria infection. His first first-author paper: “Common and divergent immune response signaling pathways discovered in peripheral blood mononuclear cell gene expression patterns in presymptomatic and clinically apparent malaria” is published in Infection and Immunity in 2006 October. Thus, he first proposed the THαβ immunity which is host immunity against viruses. A subsequent paper in 2008 called it TH9 immunity. However, TH9 immunity is not a good name since IL-9 is a TH2 cytokine. He was trained as a neurology resident in Department of Neurology of Taipei Mackay Memorial Hospital of Taiwan. Currently, he is doing postdoc research in Genomic Research Center of Academia Sinica, Taiwan. His current research topic is cancer immunotherapy. Besides, he is doing functional genomics studies. The author would like to publish this manuscript. If journal editors are interested in this paper, please feel free to contact me.

Introduction

Parkinson’s disease is the second most common neurodegenerative disorder. Primary Parkisonism is also called idiopathic Parkinson’s disease because its exact etiology is still unknown. After the destruction of substantia nigra of midbrain, patients will develop resting tremor, cogwheel rigidity, hypokinesia, and postural instability. Patients’ life expectancy is much shorter than normal healthy population. Even it is a very common and detrimental illness, the etiology and pathogenesis is still a puzzle. By using microarray analysis of peripheral blood leukocytes and substantia nigra brain tissue, I find out that idiopathic Parkinsonism is actually a TH17 dominant autoimmune disease. Summary of all previous literatures also support that Parkinson’s disease is a TH17 autoimmune illness.

Materials and methods

Microarray datasets of Parkinson’s disease

In this paper, I incooperate two microarray datasets for analysis. The fist one is peripheral blood mononuclear cell gene expression profiles in Parkinson’s disease patient. The dataset GSE6613 is available in GEO website. Dr. C.R. Scherzer published the research results of peripheral blood biomarkers for Parkinson’s disease in PNAS. The second dataset(GSE7621) is substantia nigra gene expression profiles in

Parkinson's disease. Substantia nigra is the major affected brain area of Parkinson's disease.

Statistical analysis

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
After the analysis of RMA express, we select 47 Parkinson's disease and 19 healthy controls. We remove GSE153479, GSE153497, and GSE153508 in healthy control due to RNA express analysis. We remove GSE153411, GSE153421, GSE153454 in Parkinsonism group. (Figure 1 and Figure 2) Then, we use Genespring to find out statistically significant expressed genes in substantia nigra and peripheral leukocytes of Parkinson's disease.

Validation by RT-PCR

Since this study is a secondary dataset analysis, I don't have samples in hand to do wet bench validation such as RT-PCR. However, in Dr. Scherzer's paper, he performed RT-PCR to confirm his result of microarray experiment by using RT-PCR. He found that the gene ST13, a HSP70 cofactor, is down-regulated in Parkinsonism compared to that in Healthy control due to microarray analysis. Then, he used quantitative real-time PCR assays based on precise fluorogenic 5' nuclease chemistry in a large set of 39 Parkinsonism patients and 12 age-, sex-, and blood count- matched healthy controls. He used the housekeeping gene glyceraldehydes-3-phosphate dehydrogenase to control for input RNA and the comparative threshold cycle method for analysis. The RT-PCR results confirmed that ST13 is lower in Parkinsonism patients. Thus, it states that the microarray platform of Dr. Scherzer's experiments is valid and reliable.

Results

Heat shock protein, Toll-like receptor, Caspases, and TH17 related gene up-regulation in substantia nigra of Parkinson's disease patients

In the first dataset, we selected 816 genes of substantia nigra of Parkinson's disease compared to healthy control with fold change>1.5 and Benjamin adjusted false discovery rate<0.05. Then, we selected immune-related genes from this 816 genelist.(Table1) We find out that heat shock protein genes are almost all up-regulated in Parkinson's disease including HSP40, HSP70, HSP90, HSP27, and HSP105. In addition, TLR5 and TLR7 are up-regulated as well. Based on several references, TLR5 and TLR7 can recognize heat shock protein to trigger TH17 immunity. Several toll-like signaling molecules are also up-regulated in Parkinson's disease. In addition, many TH17 related transcription factors are up-regulated in Parkinson's disease including CEBPbeta, CEBPgamma, and FOS(AP1). STAT1, the key transcription factor for TH1 and TH9 immunity, is downregulated in Parkinson's disease patients. Key TH17 cytokine receptors are also up-regulated including IL-17 receptor and TGF beta receptor. And, TH2 cytokine receptor-IL13 receptor is down-regulated in Parkinson's disease substantia nigra. Finally, the key downstream effector molecule caspase1 of TH17 cytokine IL-1 is up-regulated in Parkinson's patients. This caspase 1 up-regulation may closely related to the neuron death triggered by TH17 cytokine IL-1.

TH17 related molecules are up-regulated in peripheral leukocytes of Parkinson's disease patients

In our second analysis, we find out that 505 significantly expressed genes in peripheral leukocytes of Parkinson's patients with fold change>1.1 and unadjusted false discovery rate P<0.05. Then, we pick 103 immune related genes out of the 505 genelist. (Table2) We find out that many Th17 related molecules are up-regulated in WBC of Parkinson's disease patients.

First of all, many TH17 driven transcription factors are up-regulated in leukocytes of Parkinsonism patients. NFKB1A, CEBPD, FOS(AP-1), retinoic receptor alpha, and suppressor of IKK epsilon are up-regulated. They are master transcription factors for TH17 immunity. Retinoic receptor alpha is related to the differentiation of main TH17 effector cells-Neutrophils. Besides, the TH9 (THαβ) related transcription factor IRF8 is down-regulated.

Second, many TH17 effector molecules are also up-regulated in peripheral leukocytes of Parkinson's disease. S100A11, LPS induced TNF factor, TNF alpha induced protein2, CD32, G-CSF, lysosomal mannosidase, MMP9, CD16b, type II interleukin 1 receptor,

interleukin 8 receptor alpha & beta, TNF receptor 9 & 1A & 10C, TNF factor 14, casapase8, S100A11P, CD93 (c1q receptor), cathepsin Z, HLA-G, leukocyte immunoglobulin-like receptors, type1 thrombospondin containing 7A, complement receptor1, IgG Fc receptor transporter alpha, and complement 5a receptor are all up-regulated after Parkinson's disease. These up-regulated molecules highly suggest that TH17 immunological pathway is triggered in Parkinsonism. In addition, Fas inhibitory gene and BCL2 are down-regulated that suggest apoptotic signals are up-regulated in Parkinson's disease.

Lymphocyte related genes and immune genes other than TH17 pathway are down-regulated in leukocytes of Parkinson's disease. Generally, neutrophils are up-regulated and lymphocytes are down-regulated in TH17 immunity. Thus, this result can also help to point out Parkinson's disease is a TH17 dominant autoimmune disease. These lymphocyte related genes include ILF2, CD22, CD3E, BLNK, ILF3, TCR alpha, TCR zeta, LAT, ITK, LY9, BANK1, and TCR delta. TH1, TH9, and TH2 immune genes are down-regulated including GBP1, IRF8, CD44, KIR3DL2, HEBP1, HEBP2, and TRAF3. IL-32 which can suppress NFkB and STAT3(TH17 transcription factor) is also down-regulated in leukocytes of Parkinson's disease.

Unlike the up-regulation of heat shock proteins in substantia nigra, heat shock protein genes in peripheral leukocytes are down-regulated in Parkinson's disease patients. These heat shock protein related genes include HSP90AB1 and ST13. In addition, the main autoantigen of Parkinsonism-alpha synuclein gene is down-regulated in leukocytes of Parkinson's disease patients as well. There might be some negative feedback machinery for these down-regulated disease related genes.

Discussion

Idiopathic Parkinson's disease is a very common neurodegenerative disorder, but its etiology is still unknown. Although there are a few cases of familial Parkinson's diseases, sporadic Parkinson's diseases are still the major population of this disorder. Parkinson's disease is found to be associated with several risk factors such as MPTP exposure, heavy metal such as Manganese exposure, pesticides such as rotenone or paraquet exposure, herbicides such as Agent Orange exposure, and Influenza virus infection.(Betarbet, Sherer et al. 2000) Estrogen, anti-oxidants, caffeine, and NSAID have protective roles from Parkinson's disease.(Ross, Abbott et al. 2000; Chen, Zhang et al. 2003; Sawada and Shimohama 2003) Here, I propose that Parkinson's disease is actually a TH17 dominant autoimmune disease which can explain the above

evidences.

Alpha synuclein is the major accumulated protein forming inclusion bodies in substantia nigra neurons of Parkinson's patients. In familial Parkinsonism, autoantibody against mutation of alpha synuclein can contribute to the disease pathogenesis.(Papachroni, Ninkina et al. 2007) Alpha synuclein is a kind of acute response amyloid protein which can be up-regulated by Th17 cytokine IL-1 during some bacterial infection.(Griffin, Liu et al. 2006) Similar to other neurodegenerative diseases such as Alzheimer's disease, the accumulation of alpha synuclein can up-regulate molecular chaperons such as heat shock protein 60 or heat shock protein 70 to trigger toll-like receptor driven TH17 immunity. Heat shock proteins released by neuron or glia cells can activate TLR2/4/5/7 of immune cells to trigger TH17 cytokines or chemokines.(Asea, Kraeft et al. 2000) Neuron or glia cells can also posse Toll-like receptor to trigger TH17 cytokine such as IL-6 or TNF alpha release in neuron or glia cells.(Alvarez-Erviti, Couch et al. 2011) These cytokines can be autocrine to enhance more Th17 cytokine release. More immune effector cells will be recruited and release more TH17 cytokines and chemokines. TH17 cytokine IL-1 can in turns up-regulate more alpha synuclein in neuron or glia. That is a vicious cycle. In addition, TH17 cytokines such as IL-1, TNFα, and IL-6 can act on neuron cells to undergo Wallerian-like degeneration.(Saha and Pahan 2003) That is the pathophysiology of Parkinson's disease. This pathogenesis is very similar to other neurodegenerative disorders such as Alzheimer's disease and Huntington's disease.

Witebsky's postulates are the standard criteria to decide if a disorder is an autoimmune disease. There are three requirements in Witebsky's postulates: 1. Direct evidence from transfer of pathogenic antibody or T cells 2. Indirect evidence based on reproduction of the autoimmune disease in experimental animal 3. Circumstantial evidence from clinical clues. First, in an Acta Neurology paper, injection of IgG antibody from Parkinsonism patients can cause substantia nigra destruction and Parkinson-like disease in rats.(Chen, Le et al. 1998) In a Brain paper, all Parkinsonism patients have IgG autoantibody recognizing dopaminergic neurons.(Orr, Rowe et al. 2005) In addition, Fc gamma receptors are up-regulated in lymphocytes and microglia of Parkinson disease patients. In an Experimental Neurology paper, injection of autoreactive IgG antibody isolated from Parkinsonism patients can also cause substantia nigra destruction in mice.(He, Le et al. 2002) In a paper from Journal of Neuroinflammation, serum antibodies from Parkinsonism patients can react with neuron membrane of mice dopaminergic cell line.(Huber, Mondal et al. 2006) In the presence of microglia, the serum antibodies can also

suppress the production of dopamine from the mice dopaminergic cell line. In a JCI paper, CD4 T cell infiltration is found in postmortem Parkinson disease brain tissue and is related to neurodegeneration.(Brochard, Combadiere et al. 2009) In another paper of Journal of Neuroinflammation, complement activation is noted at substantia nigra isolated from expired Parkinsonian patients compared to normal control.(Loeffler, Camp et al. 2006) In a review paper, elevated autoantibodies and complements are found in serum and CSF of Parkinsonians. In addition, anti-alpha synuclein autoantibody is noted in familial Parkinsonism patients. Cytokine IL-1, TNF, and IL-6 are also increased in the serum, CSF, and substantia nigra of Parkinson disease patients. CD4 T cells are also increased in serum of Parkinson disease patients. In Parkinsonism's substantia nigra, up-regulation of TH17 effector molecule iNOS and cycloxygenase are found.(Gatto, Carreras et al. 1996) As for the second criteria, autoreactive CD4 T cell infiltration is found in brain of mice Parkinsonism model, and these CD4 T cells contribute to neurodegeneration. In rat Parkinsonism model, CD4(+)CD25(+) Treg cells have neuroprotective roles and TH17 cells are detrimental(Reynolds, Stone et al. 2010). In mice Parkinsonism model, overexpression of human alpha synuclein can lead to microglia activation and adaptive immune reaction.(Zhang, Wang et al. 2005) In a Brain paper, local and systemic IL-1 can exacerbate neurodegeneration and motor symptoms in animal models of Parkinsonism.(Pott Godoy, Tarelli et al. 2008) In a Brain Research paper, IL-1 elevation induced by MPTP cause neurodegeneration in MPTP Parkinsonism mice models.(Bian, Li et al. 2009) In a Glia paper, TH17 effector cells-neutrophil infiltration in substantia nigra causes Parkinsonism-like symptoms. In addition, mice deficient in TNF receptor are protected from Parkinsonism symptoms. Systemic and local injection of extracellular bacteria product LPS can produce neurodegeneration including Parkisonism symptoms.(Meredith, Sonsalla et al. 2008) Key TH9 (THαβ) cytokine IL-10 has protective role in rat model of Parkinsonism.(Johnston, Su et al. 2008) It is worth noting that alpha synuclein knockout mice didn't develop Parkinsonism after MPTP injection.(Dauer, Kholodilov et al. 2002) MPTP can cause alpha synuclein up-regulation and aggregation in substantia nigra.(Vila, Vukosavic et al. 2000) Thus, alpha synclein is the major mediator of MPTP induced Parkinsonism. Autoimmune against alpha synuclein is the most likely pathogenesis. As for criteria 3, there is association between Parkinson's disease and HLA haplotypes.(Hamza, Zabetian et al. 2010; Nalls, Plagnol et al. 2011) Besides, polymorphisms of TH17 related cytokines such as IL-1α, IL-1β, TNF-α, TNF receptor, IL-1 receptor antagonist, CD14 receptor, and IL-6 are related to the risk of Parkinson's disease.(Wahner, Sinsheimer et al. 2007) Elevated serum or CSF key TH17 cytokine IL-1 and IL-6 is also associated with the increasing risk of Parkinson's disease.(Blum-Degen, Muller et al.

1995) Autoimmune seborrheic dermatitis is associated with the risk of Parkinsonism. Anti-inflammatory caffeine, NASID, or estrogen intakes have protective role for the Parkinson's disease development.(Giraud, Caron et al. 2010) Fetal stem cell transplant is newly used for Parkinson's disease treatment. However, graft rejection is noted and there is only short-term beneficial effect not long-term therapeutic effect for the fetal stem cell transplant.(Spencer, Robbins et al. 1992; Bjorklund, Dunnett et al. 2003; Bachoud-Levi, Gaura et al. 2006; Krystkowiak, Gaura et al. 2007) It is because there are still autoreactive immune cells attacking alpha synuclein positive neuron cells. Thus, the new transplant will still be rejected by the abnormal host immune system. These evidences all point out that idiopathic Parkinson's disease is an autoimmune disorder.

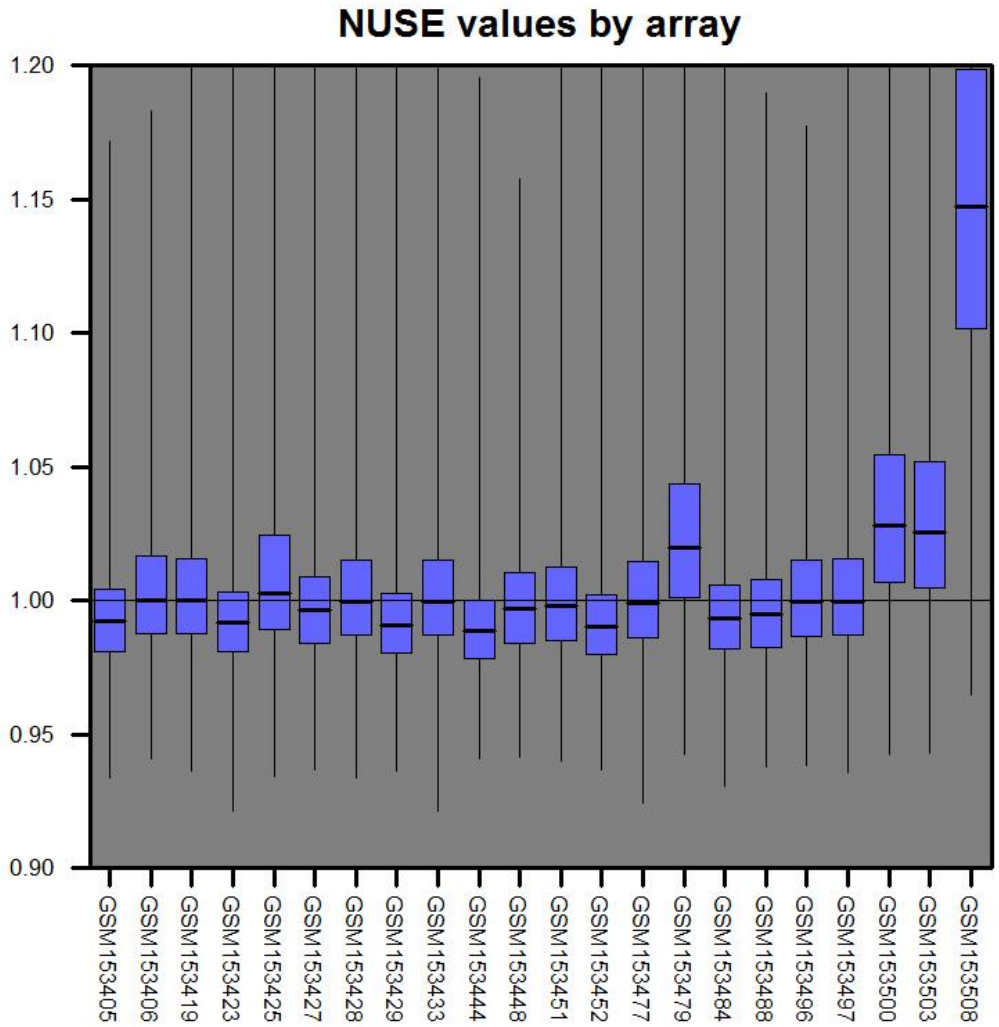
Parkinson's disease is TH17 dominant autoimmune disorder against alpha synuclein. Current treatment strategies include dopamine supplement and fetal stem cell transplant. However, these therapeutic methods could not solve the underlying pathogenesis of Parkinson's disease and stop the disease progression. We should use anti-inflammatory agents such as NSAID to treat. In addition, we need to develop new strategy to induce tolerance for alpha synuclein to stop Parkinson's disease. I sincerely hope we can control this detrimental illness in the future.

Figure legends

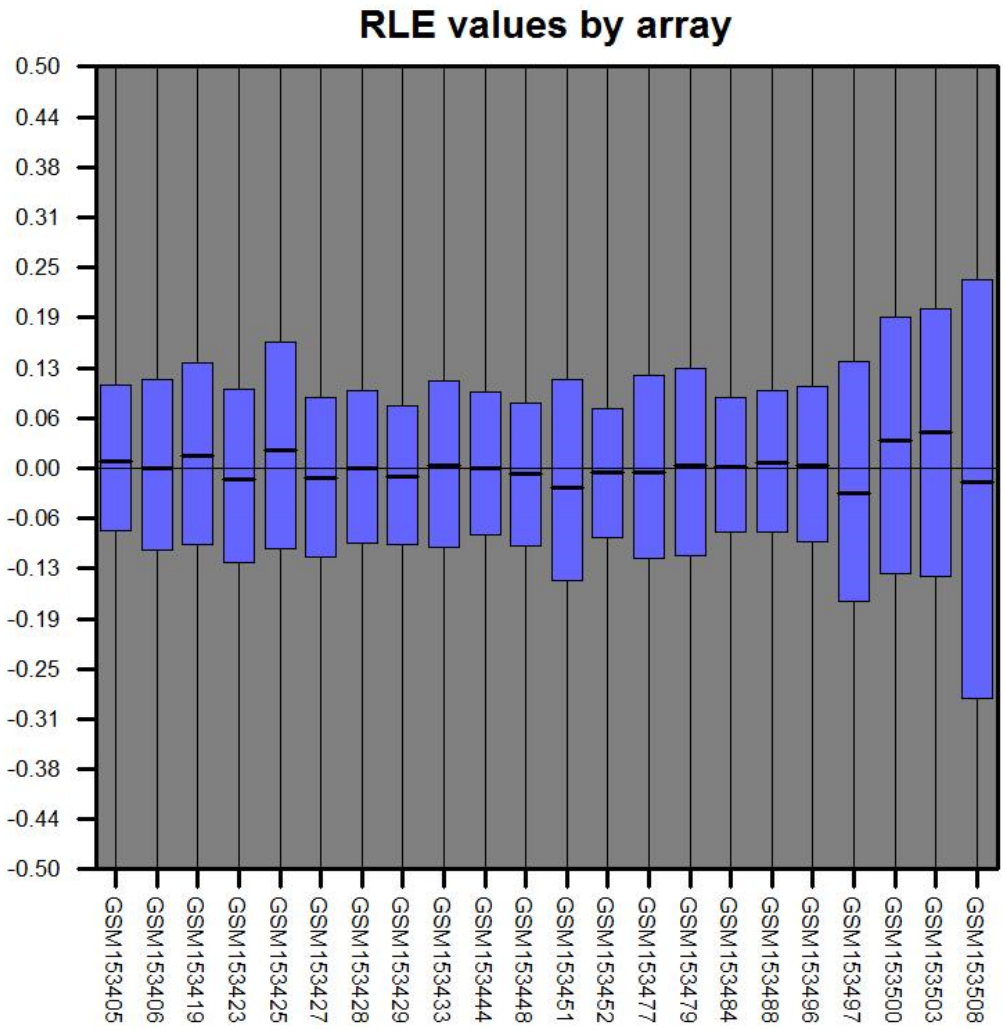
Figure 1. RMA express plot for selecting samples in normal healthy controls.
1-A NUSE boxplot for normal control
1-B RLE boxplot for normal control
1-C RLE-NUSE multiplot for normal control
1-D RLE-NUSE T2 plot for normal control

Figure 2. RMA express plot for selecting samples in Parkinson's disease patients.
2-A NUSE boxplot for Parkinson's disease patients
2-B RLE boxplot for Parkinson's disease patients
2-C RLE-NUSE multiplot for Parkinson's disease patients
2-D RLE-NUSE T2 plot for Parkinson's disease patients

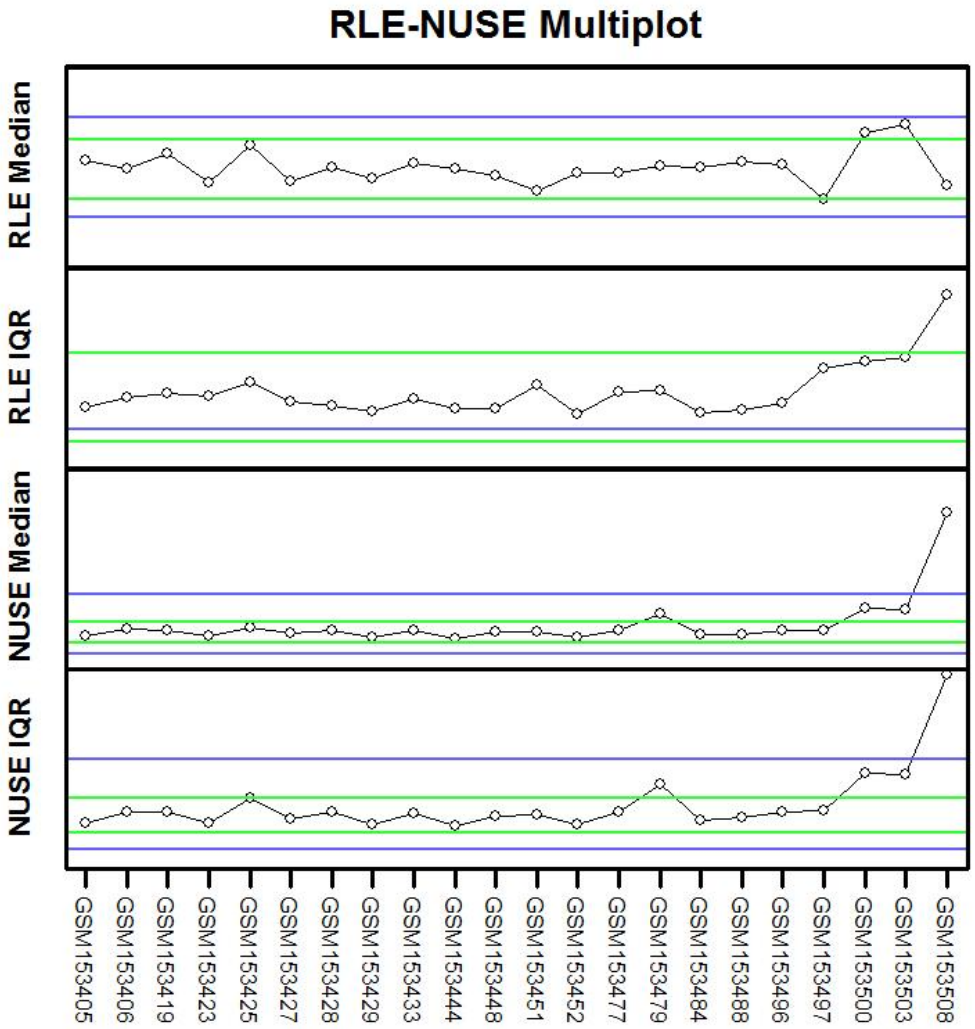
Figure 1



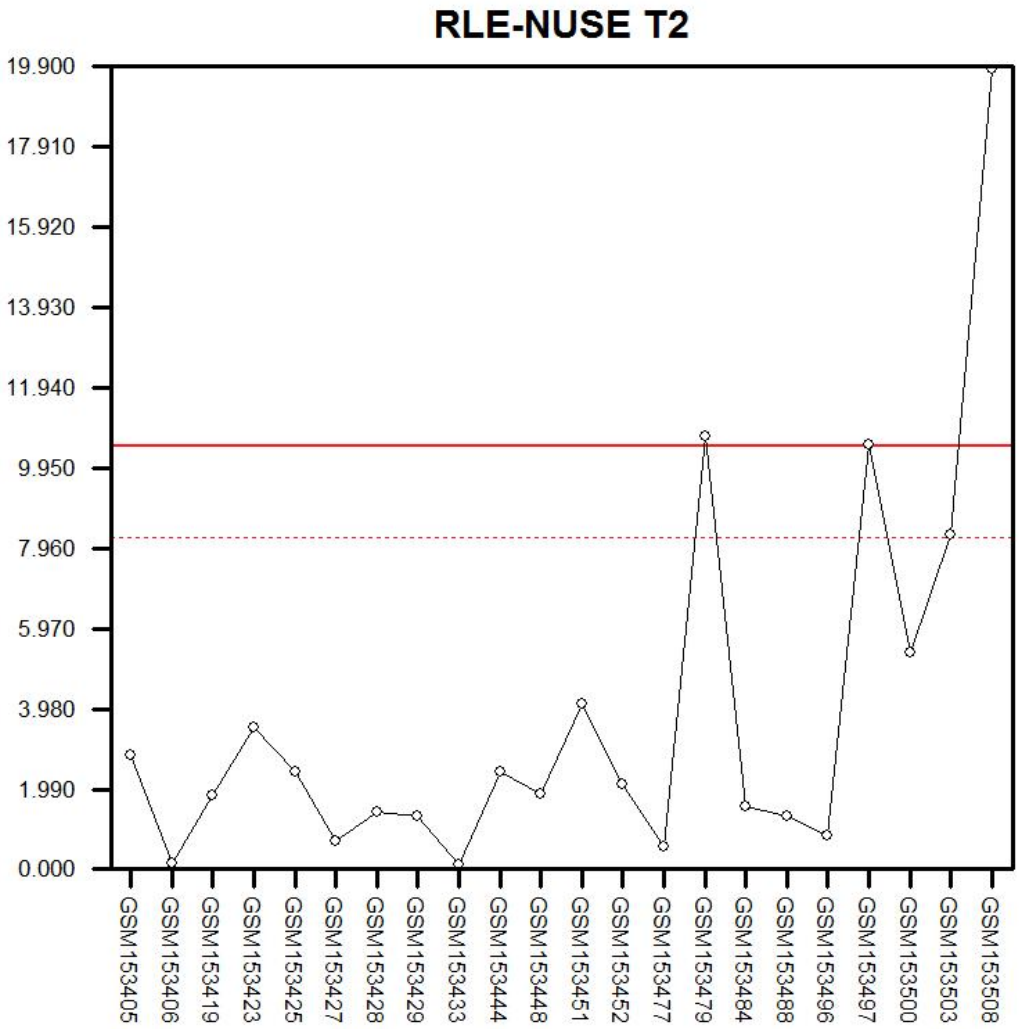
1-A



1-B

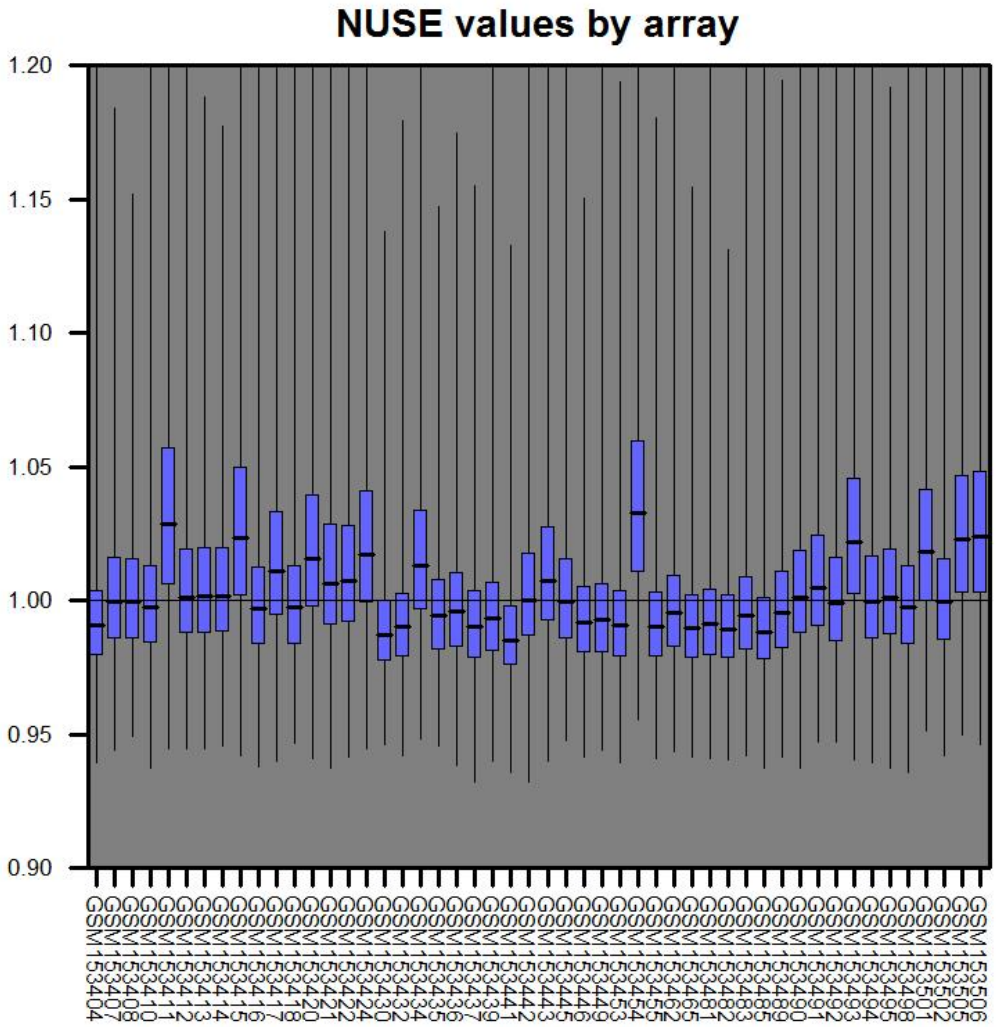


1-C

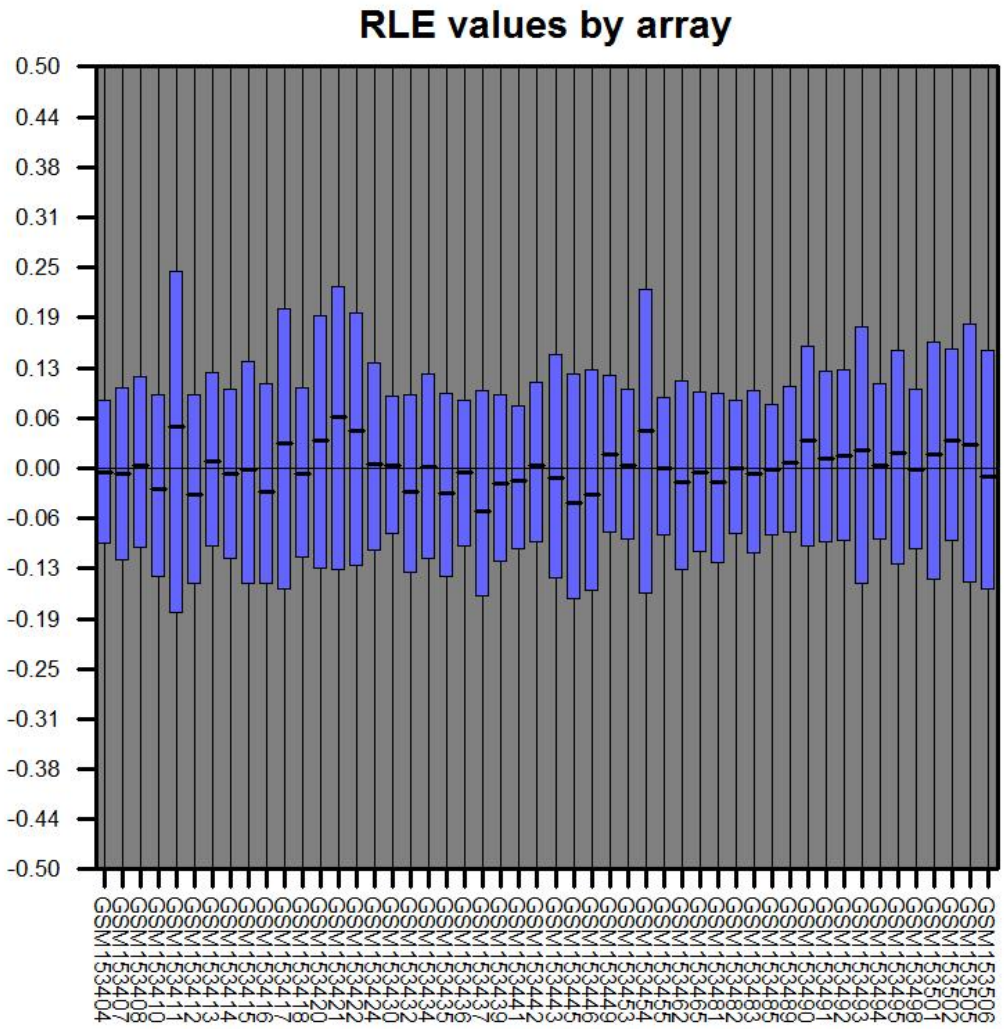


1-D

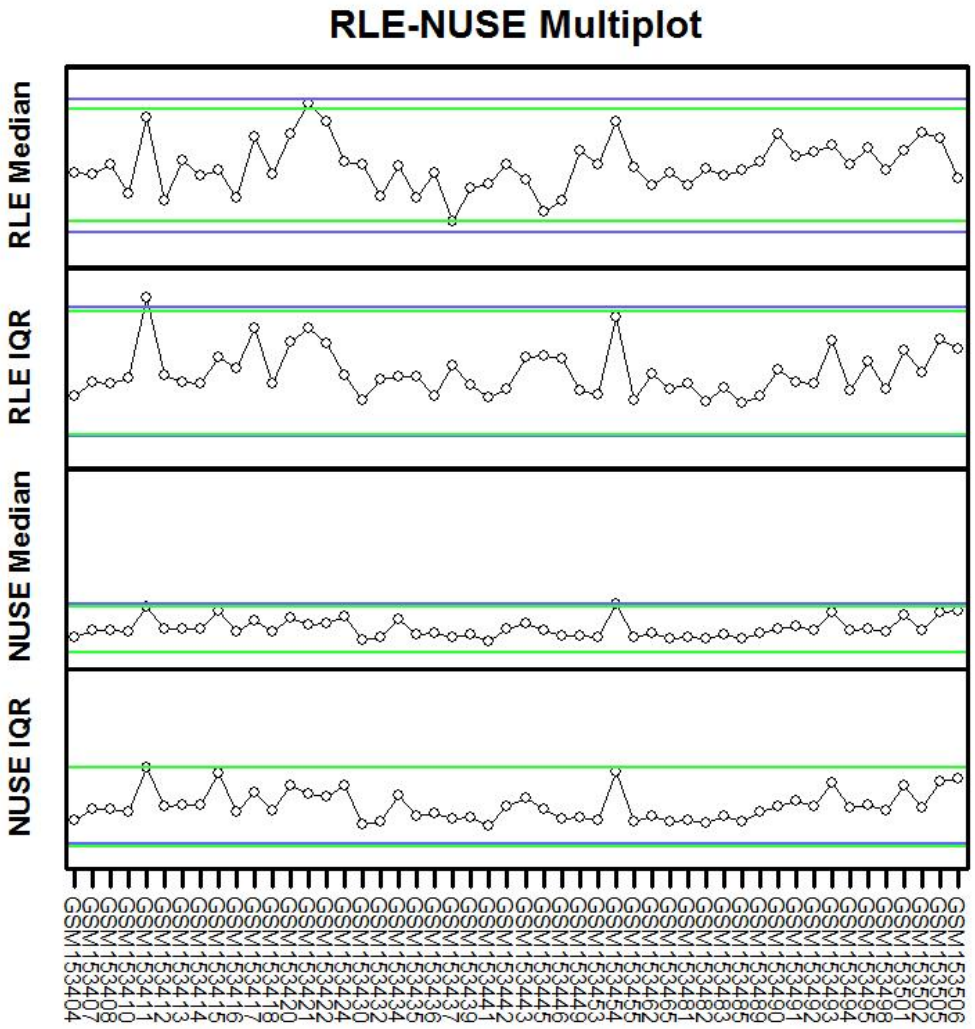
Figure 2



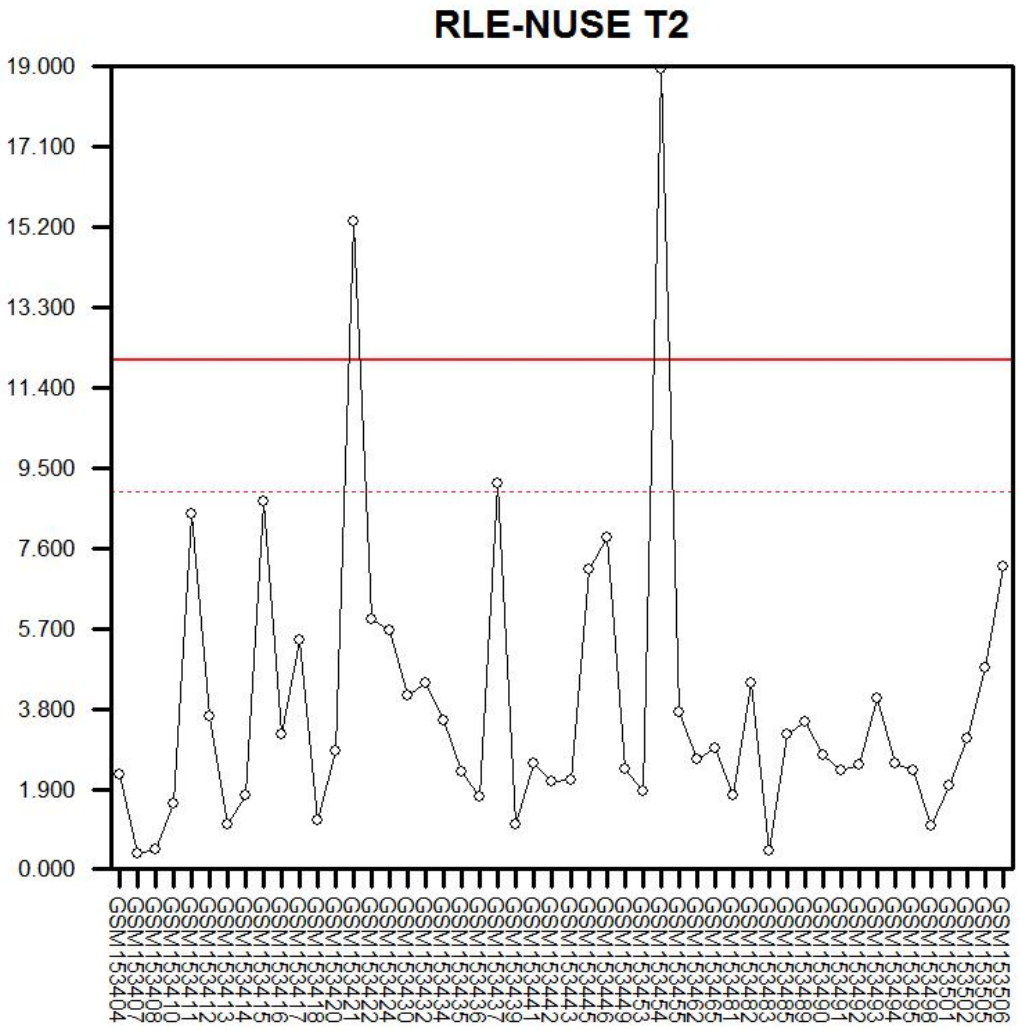
2-A



2-B



2-C



2-D

Table 1. Heat shock protein and TH17-related gene up-regulation in substantia nigra of Parkinson's disease patients

Probeset	Pvalue	Arrow	Fold	Gene	Description
Heat Shock					
200666_s_at	0.046436	up	1.591286	DNAJB1	Hsp40B1
200799_at	0.016182	up	1.942031	HSPA1A	heat shock 70kDa protein 1A
200800_s_at	0.009898	up	2.568059	HSPA1A/B	heat shock 70kDa protein 1A 1B
200881_s_at	0.025109	up	1.5808	DNAJA1	Hsp40A1
201491_at	0.00584	up	1.565841	AHSA1	activator of heat shock 90kDa
201841_s_at	0.041056	up	1.93935	HSPB1	heat shock 27kDa protein 1
202581_at	0.008943	up	2.568776	HSPA1A/B	heat shock 70kDa protein1A /1B
206976_s_at	0.015495	up	1.938839	HSPH1	heat shock 105kDa/110kDa 1
209015_s_at	0.001648	up	2.366288	DNAJB6	Hsp40B 6
210189_at	0.001899	up	1.692562	HSPA1L	heat shock 70kDa protein 1-like
221782_at	0.013571	down	1.539068	DNAJC10	Hsp40C10
227808_at	0.01902	down	1.660796	DNAJC15	Hsp40C15
230148_at	0.001627	up	1.813061	AHSA2	activator of heat shock 90kDa
Toll-like					
210166_at	0.014399	up	1.605882	TLR5	toll-like receptor 5
220146_at	0.046749	up	1.506414	TLR7	toll-like receptor 7
228234_at	0.002924	up	1.602183	TICAM2	toll-like receptor adaptor 2
231779_at	0.014626	up	1.588289	IRAK2	IL-1 receptor-as kinase 2
Transcription factor					
M97935MBat	0.014721	down	1.52548	STAT1	signal transducer and activator1
212501_at	0.047435	up	1.659838	CEBPB	CCAAT/enhancer binding beta
225527_at	0.00591	up	1.503377	CEBPG	CCAAT/enhancerbinding gamma
228188_at	0.012176	up	2.218706	FOSL2	FOS-like antigen 2
203574_at	0.043302	up	1.816873	NFIL3	nuclear factor, interleukin 3
Caspase					
206011_at	0.036084	up	1.51373	CASP1	caspase 1
209970_x_at	0.040759	up	1.542726	CASP1	caspase 1
Cytokine receptor					
219255_x_at	0.012304	up	1.755705	IL17RB	interleukin 17 receptor B
224156_x_at	0.017114	up	1.627902	IL17RB	interleukin 17 receptor B
224361_s_at	0.020254	up	1.631049	IL17RB	interleukin 17 receptor B
206172_at	0.023187	down	1.60825	IL13RA2	interleukin 13 receptor, alpha 2
236561_at	0.028704	up	1.605665	TGFBR1	TGF, beta receptor 1

Table 2. TH17 related gene up-regulation in peripheral leukocytes of Parkinson's disease patients

Probe Set	Fold	Arrow	p-value	Gene
200052_s_at	1.188939	down	0.009691	ILF2
200064_at	1.141238	down	0.015928	HSP90AB1
200660_at	1.184608	up	0.025142	S100A11
200704_at	1.161244	up	0.010052	LITAF
200706_s_at	1.168248	up	0.043356	LITAF
200986_at	1.17499	down	0.02649	SERPING1
201244_s_at	1.164101	up	0.044455	RAF1
201315_x_at	1.132939	up	0.030281	IFITM2
201502_s_at	1.200774	up	0.017593	NFKBIA
202201_at	1.200977	down	0.021401	BLVRB
202270_at	1.28927	down	0.022318	GBP1
202379_s_at	1.223381	up	0.016804	NKTR
202388_at	1.256398	up	0.00215	RGS2
202509_s_at	1.107859	up	0.013255	TNFAIP2
202877_s_at	1.125594	up	0.037677	CD93
203041_s_at	1.200253	up	0.01719	LAMP2
203140_at	1.211998	up	0.013618	BCL6
203430_at	1.122783	up	0.043456	HEBP2
203561_at	1.141576	up	0.033892	FCGR2A
203591_s_at	1.21527	up	0.003722	CSF3R
203685_at	1.214759	down	0.01472	BCL2
203778_at	1.104544	up	0.024774	MANBA
203828_s_at	1.177826	down	0.036371	IL32
203936_s_at	1.261711	up	0.026599	MMP9
203973_s_at	1.265417	up	0.007709	CEBPD
204007_at	1.119838	up	0.018176	FCGR3B
204057_at	1.11098	down	0.03413	IRF8
204466_s_at	1.481427	down	0.022285	SNCA
204467_s_at	1.244787	down	0.049072	SNCA
204489_s_at	1.11089	down	0.006604	CD44
204581_at	1.121758	down	0.016833	CD22
204666_s_at	1.105866	up	2.69E-04	RP5-1000E10.4
205403_at	1.313192	up	0.002585	IL1R2
205456_at	1.104177	down	0.0124	CD3E
206420_at	1.246161	up	0.009528	IGSF6

207008_at	1.262777	up	0.010445 IL8RB
207094_at	1.125419	up	0.023716 IL8RA
207104_x_at	1.10934	up	0.036019 LILRB1
207314_x_at	1.115032	down	0.044444 KIR3DL2
207536_s_at	1.121413	up	0.003446 TNFRSF9
207643_s_at	1.168614	up	0.009971 TNFRSF1A
207655_s_at	1.123825	down	0.048559 BLNK
207697_x_at	1.153652	up	0.00905 LILRB2
207827_x_at	1.351602	down	0.019893 SNCA
207907_at	1.15163	up	2.80E-04 TNFSF14
208405_s_at	1.251242	down	0.041759 CD164
208485_x_at	1.117304	up	0.0214 CFLAR
208540_x_at	1.108202	up	0.042068 S100A11/P
208666_s_at	1.213137	down	1.26E-04 ST13
208667_s_at	1.248621	down	3.96E-04 ST13
208931_s_at	1.150311	down	0.019467 ILF3
209189_at	1.164217	up	0.021235 FOS
209508_x_at	1.140008	up	0.007207 CFLAR
209671_x_at	1.184911	down	0.016073 TRA@ /// TRAC
209723_at	1.28675	down	0.007788 SERPINB9
209939_x_at	1.17078	up	0.009053 CFLAR
210031_at	1.174872	down	0.027308 CD247
210042_s_at	1.265922	up	0.048335 CTSZ
210225_x_at	1.137269	up	0.003548 LILRB3
210514_x_at	1.105079	up	0.040499 HLA-G
210563_x_at	1.152512	up	0.007233 CFLAR
210564_x_at	1.141197	up	0.011338 CFLAR
210754_s_at	1.254778	up	0.018888 LYN
210776_x_at	1.100981	down	0.009593 TCF3
210784_x_at	1.20723	up	7.90E-04 LILRA6 /// LILRB3
210943_s_at	1.309776	up	0.003924 LYST
210972_x_at	1.199937	down	0.030357 TRA@
211005_at	1.149716	down	0.009554 LAT /// SPNS1
211133_x_at	1.118174	up	0.010374 LILRA6 /// LILRB3
211135_x_at	1.184438	up	0.001229 LILRB3
211163_s_at	1.210836	up	0.005458 TNFRSF10C
211316_x_at	1.20165	up	0.003518 CFLAR
211339_s_at	1.215744	down	0.025145 ITK

211372_s_at	1.208659	up	0.009117	IL1R2
211546_x_at	1.339729	down	0.017353	SNCA
211862_x_at	1.13062	up	0.014222	CFLAR
211902_x_at	1.185072	down	0.006675	TRA@
212414_s_at	1.224381	down	0.018298	N-PAC /// SEPT6
213318_s_at	1.150105	down	0.031006	BAT3
213894_at	1.100305	up	0.002152	THSD7A
214359_s_at	1.19457	down	0.037662	HSP90AB1
214486_x_at	1.186758	up	0.001419	CFLAR
214574_x_at	1.107749	up	0.041912	LST1
215338_s_at	1.139026	up	0.007906	NKTR
215967_s_at	1.108165	down	0.012386	LY9
216300_x_at	1.126279	up	0.002184	RARA
217412_at	1.122067	down	0.016503	TRD@
217433_at	1.12529	up	0.00102	TACC1
217550_at	1.114039	up	0.030685	ATF6
217552_x_at	1.105204	up	0.047014	CR1
217724_at	1.163798	down	0.039041	SERBP1
217775_s_at	1.149285	down	0.003501	RDH11
218450_at	1.16605	down	0.043368	HEBP1
218831_s_at	1.131095	up	0.022043	FCGRT
219528_s_at	1.187628	down	0.032716	BCL11B
219667_s_at	1.197731	down	0.014477	BANK1
220088_at	1.18788	up	0.040003	C5AR1
220938_s_at	1.101576	up	8.66E-04	GMEB1
221478_at	1.437751	down	0.006494	BNIP3L
221571_at	1.120485	down	0.011251	TRAF3
221602_s_at	1.161923	down	0.001686	FAIM3
222218_s_at	1.143145	up	0.031853	PILRA

References

Alvarez-Erviti, L., Y. Couch, et al. (2011). "Alpha-synuclein release by neurons activates the inflammatory response in a microglial cell line." Neurosci Res **69**(4): 337-342.

Asea, A., S. K. Kraeft, et al. (2000). "HSP70 stimulates cytokine production through a CD14-dependant pathway, demonstrating its dual role as a chaperone and cytokine." Nat Med **6**(4): 435-442.

Bachoud-Levi, A. C., V. Gaura, et al. (2006). "Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study." Lancet Neurol **5**(4): 303-309.

Betarbet, R., T. B. Sherer, et al. (2000). "Chronic systemic pesticide exposure reproduces features of Parkinson's disease." Nat Neurosci **3**(12): 1301-1306.

Bian, M. J., L. M. Li, et al. (2009). "Elevated interleukin-1beta induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine aggravating dopaminergic neurodegeneration in old male mice." Brain Res **1302**: 256-264.

Bjorklund, A., S. B. Dunnett, et al. (2003). "Neural transplantation for the treatment of Parkinson's disease." Lancet Neurol **2**(7): 437-445.

Blum-Degen, D., T. Muller, et al. (1995). "Interleukin-1 beta and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients." Neurosci Lett **202**(1-2): 17-20.

Brochard, V., B. Combadiere, et al. (2009). "Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease." J Clin Invest **119**(1): 182-192.

Chen, H., S. M. Zhang, et al. (2003). "Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease." Arch Neurol **60**(8): 1059-1064.

Chen, S., W. D. Le, et al. (1998). "Experimental destruction of substantia nigra initiated by Parkinson disease immunoglobulins." Arch Neurol **55**(8): 1075-1080.

Dauer, W., N. Kholodilov, et al. (2002). "Resistance of alpha -synuclein null mice to the parkinsonian neurotoxin MPTP." Proc Natl Acad Sci U S A **99**(22): 14524-14529.

Gatto, E. M., M. C. Carreras, et al. (1996). "Neutrophil function, nitric oxide, and blood oxidative stress in Parkinson's disease." Mov Disord **11**(3): 261-267.

Giraud, S. N., C. M. Caron, et al. (2010). "Estradiol inhibits ongoing autoimmune neuroinflammation and NFkappaB-dependent CCL2 expression in reactive astrocytes." Proc Natl Acad Sci U S A **107**(18): 8416-8421.

Griffin, W. S., L. Liu, et al. (2006). "Interleukin-1 mediates Alzheimer and Lewy body

pathologies." J Neuroinflammation **3**: 5.

Hamza, T. H., C. P. Zabetian, et al. (2010). "Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease." Nat Genet **42**(9): 781-785.

He, Y., W. D. Le, et al. (2002). "Role of Fcgamma receptors in nigral cell injury induced by Parkinson disease immunoglobulin injection into mouse substantia nigra." Exp Neurol **176**(2): 322-327.

Huber, V. C., T. Mondal, et al. (2006). "Serum antibodies from Parkinson's disease patients react with neuronal membrane proteins from a mouse dopaminergic cell line and affect its dopamine expression." J Neuroinflammation **3**: 1.

Johnston, L. C., X. Su, et al. (2008). "Human interleukin-10 gene transfer is protective in a rat model of Parkinson's disease." Mol Ther **16**(8): 1392-1399.

Krystkowiak, P., V. Gaura, et al. (2007). "Alloimmunisation to donor antigens and immune rejection following foetal neural grafts to the brain in patients with Huntington's disease." PLoS One **2**(1): e166.

Loeffler, D. A., D. M. Camp, et al. (2006). "Complement activation in the Parkinson's disease substantia nigra: an immunocytochemical study." J Neuroinflammation **3**: 29.

Meredith, G. E., P. K. Sonsalla, et al. (2008). "Animal models of Parkinson's disease progression." Acta Neuropathol **115**(4): 385-398.

Nalls, M. A., V. Plagnol, et al. (2011). "Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies." Lancet **377**(9766): 641-649.

Orr, C. F., D. B. Rowe, et al. (2005). "A possible role for humoral immunity in the pathogenesis of Parkinson's disease." Brain **128**(Pt 11): 2665-2674.

Papachroni, K. K., N. Ninkina, et al. (2007). "Autoantibodies to alpha-synuclein in inherited Parkinson's disease." J Neurochem **101**(3): 749-756.

Pott Godoy, M. C., R. Tarelli, et al. (2008). "Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease." Brain **131**(Pt 7): 1880-1894.

Reynolds, A. D., D. K. Stone, et al. (2010). "Regulatory T cells attenuate Th17 cell-mediated nigrostriatal dopaminergic neurodegeneration in a model of Parkinson's disease." J Immunol **184**(5): 2261-2271.

Ross, G. W., R. D. Abbott, et al. (2000). "Association of coffee and caffeine intake with the risk of Parkinson disease." JAMA **283**(20): 2674-2679.

Saha, R. N. and K. Pahan (2003). "Tumor necrosis factor-alpha at the crossroads of neuronal life and death during HIV-associated dementia." J Neurochem **86**(5): 1057-1071.

Sawada, H. and S. Shimohama (2003). "Estrogens and Parkinson disease: novel approach for neuroprotection." Endocrine **21**(1): 77-79.

Spencer, D. D., R. J. Robbins, et al. (1992). "Unilateral transplantation of human fetal mesencephalic tissue into the caudate nucleus of patients with Parkinson's disease." N Engl J Med **327**(22): 1541-1548.

Vila, M., S. Vukosavic, et al. (2000). "Alpha-synuclein up-regulation in substantia nigra dopaminergic neurons following administration of the parkinsonian toxin MPTP." J Neurochem **74**(2): 721-729.

Wahner, A. D., J. S. Sinsheimer, et al. (2007). "Inflammatory cytokine gene polymorphisms and increased risk of Parkinson disease." Arch Neurol **64**(6): 836-840.

Zhang, W., T. Wang, et al. (2005). "Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease." FASEB J **19**(6): 533-542.