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<153>ABCB7	Class 4	Homo sapiens ATP binding cassette transporter mRNA, complete cds	Identification of genes expressed in human CD34(+) hematopoietic stem/progenitor cells by expressed sequence tags and efficient full-length cDNA cloning	ABC transporter	AF038950
<983>HSPA1A	Class 4	Homo sapiens heat shock 70kD protein 1 (HSPA1A), mRNA; Heat shock 70kD protein 1	Human major histocompatibility complex contains genes for the major heat shock protein HSP70	hsp	NM_005345
<215>CCR5	Class 4	Human CC chemokine receptor 5 (CCR5) mRNA, complete cds	Molecular cloning and functional characterization of a novel human CC chemokine receptor (CCR5) for RANTES, MIP-1beta, and MIP-1alpha	Signal	U54994
<809>DAXX	Class 4	Homo sapiens Fas-binding protein Daxx mRNA, complete cds	Cloning and expression of primate Daxx cDNAs and mapping of the human gene to chromosome 6p21.3 in the MHC region	Signal	AF015956
<720>DOK1	Class 4	Docking protein 1, 62kD (downstream of tyrosine kinase 1)	p62(dok): a constitutively tyrosine-phosphorylated, GAP-associated protein in chronic myelogenous leukemia progenitor cells	Gap-juncton	U70987
<383>SMARCA3	Class 4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 3	Characterization of a helicase-like transcription factor involved in the expression of the human plasminogen activator inhibitor-1 gene	ATPase	Z46606
<345>MSH2	Class 4	Human DNA mismatch repair protein MSH2	Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer	DNAREPAIR	U04045
<1192>MAP2K1	Class 4	Homo sapiens ERK activator kinase (MEK1) mRNA	ERK activator kinase; MEK kinase	Signal	L11284
<166>TOPBP1	Class 4	Homo sapiens mRNA for DNA topoisomerase II binding protein, complete cds	A DNA-topoisomerase-II-binding protein with eight repeating regions similar to DNA-repair enzymes and to a cell-cycle regulator	topoisomerase	AB019397
<254>NR3C1	Class 4	Human glucocorticoid receptor alpha mRNA, complete cds	glucocorticoid receptor; glucocorticoid receptor-alpha	glucocorticoids (Cortisol)	M10901
<150>HSPCA	Class 4	Homo sapiens Hsp89-alpha-delta-N mRNA; Heat shock 90kD protein 1, alpha	Cloning and sequence analysis of Hsp89alphaDeltaN, a new member of the hsp90 gene family	hsp	AF028832
<391>TAF2F	Class 4	TATA box binding protein (TBP)-associated factor, RNA polymerase II, F, 55kD	Cloning of an intrinsic human TFIID subunit that interacts with multiple transcriptional activators	polymerase, TF	U18062
<213>TSC22	Class 4	Human putative regulatory protein TGF-beta-stimulated clone 22 homolog (TSC22)	Cloning of the human homologue of the TGF beta-stimulated clone 22 gene	GF	U35048
<1339>AKR1B1	Class 4	Homo sapiens aldo-keto reductase family 1, member B1 (aldose reductase)	The aldo-keto reductase superfamily. cDNAs and deduced amino acid sequences of human aldehyde and aldose reductases	hyperosmotic stress	NM_001628
<564>ADPRT	Class 4	Human poly(ADP-ribose) polymerase mRNA (ADPRT), PARP	human fibroblast poly(ADP-ribose) polymerase	Signal	M18112

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<423>HDAC1	Class 4	Human mRNA for RPD3 protein, Histone deacetylase 1	Isolation and mapping of a human gene (RPD3L1) that is homologous to RPD3, a transcription factor in <i>Saccharomyces cerevisiae</i>	Signal, TF	D50405
<112>RAB11A	Class 4	Homo sapiens rab11a GTPase mRNA, complete cds.	Human rab11a: transcription, chromosome mapping and effect on the expression levels of host GTP-binding proteins	oncogene	AF000231
<406>TCEB1L	Class 4	transcription elongation factor B (SIII), polypeptide 1-like	A conserved mammalian embryonic mRNA with homology to RNA polymeraseII elongation factor	polymerase, TF	Z47087
<354>PCNA	Class 4	Homo sapiens proliferating cell nuclear antigen (PCNA) mRNA	Cloning and sequence of the human nuclear protein cyclin: Homology with DNA-binding proteins	CellCycle, Signal	NM_002592
<460>ATP6H	Class 4	ATPase, H+ transporting, lysosomal (vacuolar proton pump) 9kD	Identification and characterization of a novel 9.2-kDa membrane sector-associated protein of vacuolar proton-ATPase from chromaffin granules	ATPase	Y15286
<487>IL16	Class 4	Homo sapiens putative IL-16 protein precursor, mRNA, complete cds	Molecular and functional analysis of a lymphocyte chemoattractant factor: association of biologic function with CD4 expression	Cytokine	M90391
<1224>TPR	Class 4	H.sapiens tpr mRNA; Translocated promoter region (to activated MET oncogene)	The human tpr gene encodes a protein of 2094 amino acids that has extensive coiled-coil regions and an acidic C-terminal domain	oncogene	X66397
<788>NTF5	Class 4	Human neurotrophin-4 (NT-4) gene; neurotrophin 5 (neurotrophin 4/5) (NTF5)	nerve growth factor; neurotrophin-4	GF	M86528
<511>MCM3	Class 4	minichromosome maintenance deficient (<i>S. cerevisiae</i>) 3	hRif beta subunit; p102 protein; P1 protein; DNA replication licensing factor	polymerase	D38073
<1281>IRS4	Class 4	Homo sapiens insulin receptor substrate 4 (IRS4)	A novel 160-kDa phosphotyrosine protein in insulin-treated embryonic kidney cells is a new member of the insulin receptor substrate family	Insulin	NM_003604
<495>TP53BP1	Class 4	Human clone 53BP1 p53-binding protein mRNA, partial cds.	Two cellular proteins that bind to wild-type but not mutant p53	suppressor	U09477
<1289>ADCY7	Class 4	Homo sapiens adenylate cyclase 7 (ADCY7)	Prediction of the coding sequences of unidentified human genes. I. The coding sequences of 40 new genes (KIAA0001-KIAA0040) deduced by analysis of randomly sampled cDNA clones from human immature myeloid cell line KG-1 (supplement)	Signal	NM_001114
<386>MSH6	Class 4	Human DNA mismatch repair protein MSH6; mutS alpha 160-kDa subunit; G/T mismatch binding protein (GTMBP; GTBP)	hMSH2 forms specific mispair-binding complexes with hMSH3 and hMSH6	DNArepair	U54777
<1275>COX10	Class 4	Homo sapiens COX10 (yeast) homolog, cytochrome c	Isolation of a human cDNA for heme A:farnesyltransferase by functional	mitochondria & stress	NM_001303

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		oxidase assembly protein (heme A: farnesyltransferase)	complementation of a yeast cox10 mutant		
<1295>COX11	Class 4	Homo sapiens COX11 (yeast) homolog, cytochrome c oxidase assembly protein (COX11)	Identification and characterization of human cDNAs specific to BCS1, PET112, SCO1, COX15, and COX11, five genes involved in the formation and function of the mitochondrial respiratory chain	mitochondria & stress	NM_004375
<261>IL2RB	Class 4	Human interleukin 2 receptor beta chain (p70-75) mRNA, complete cds	interleukin; interleukin 2 receptor beta-chain	Cytokine, Signal	M26062
<394>ATRX	Class 4	Alpha thalassemia/mental retardation syndrome X-linked	ATRX encodes a novel member of the SNF2 family of proteins: mutations point to a common mechanism underlying the ATR-X syndrome	ATPase	U72938
<1268>AKAP11	Class 4	A kinase (PRKA) anchor protein 11 (AKAP11); Homo sapiens mRNA for KIAA0629 protein, partial cds	The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro	Signal	AB014529
<1272>YWHAH	Class 4	Human 14-3-3n protein mRNA; Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide	14-3-3 protein; activator; protein kinase-dependent activator of tryptophan hydroxylase; protein kinase-dependent activator of tyrosine hydroxylase	Tyrosine Hydroxylase	L20422
<244>KRAS2	Class 4	Human K-ras oncogene protein mRNA (KRAS2)	K-ras oncogene	oncogene	M54968
<1327>NRF	Class 4	Homo sapiens transcription factor NRF	Constitutive silencing of IFN-beta promoter is mediated by NRF (NF-kappaB-repressing factor), a nuclear inhibitor of NF-kappaB	mitochondria & stress	NM_017544
<671>POLR2H	Class 4	Human RNA polymerase II subunit (hsRPB8) mRNA; polymerase (RNA) II (DNA directed) polypeptide H	ix human RNA polymerase subunits functionally substitute for their yeast counterparts	polymerase	U37689
<113>ING1	Class 4	Homo sapiens growth inhibitor p33ING1 (ING1) mRNA, complete cds	Extension of the replicative life span of human diploid fibroblasts by inhibition of the p33ING1 candidate tumor suppressor	Signal, suppressor	AF001954
<723>CDC25B	Class 4	Human cdc25B mRNA, complete cds.	B-type cyclin; mitotic cyclin; tyrosine phosphatase	CellCycle	M81934
<521>CASP10	Class 4	Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds	CPP32, a novel human apoptotic protein with homology to C. elegans cell death protein CED-3 and mammalian interleukin-1-beta converting enzyme	apoptosis, Signal	U60519
<1073>C11ORF13	Class 4	Human DNA-binding protein (HRC1) mRNA; Chromosome 11 open reading frame 13	The HRAS1 gene cluster: two upstream regions recognizing transcripts and a third encoding a gene with a leucine zipper	TF	M91083
<269>ABCB1	Class 4	Homo sapiens P-glycoprotein (PGY1) mRNA (MDR1)	P-glycoprotein; drug resistance protein; transport protein	glucocorticoids (Cortisol)	M14758
<889>PSMC4	Class 4	Proteasome (prosome, macropain) 26S subunit, ATPase, 4	Cloning and expression analysis of a novel human gene homologous to mouse proteasomal ATPase (Tat-binding protein 7)	ATPase	AF020736
<603>HSBP1	Class	Homo sapiens heat shock	Negative regulation of the heat shock	hsp	AF068754

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	4	factor binding protein 1 HSBP1 mRNA; Heat shock factor binding protein 1	transcriptional response by HSBP1		
<199>ALDH9	Class 4	Human gamma- aminobutyraldehyde dehydrogenase mRNA	Human gamma-aminobutyraldehyde dehydrogenase (ALDH9): cDNA sequence, genomic organization, polymorphism, chromosomal localization, and tissue expression	ALDH	U34252
<231>CD2	Class 4	Human T-cell surface antigen CD2 (T11) mRNA, complete cds	CD2 surface antigen; T-cell antigen; glycoprotein; immunoglobulin super gene family	Signal	M14362
<741>EPOR	Class 4	Human erythropoietin receptor mRNA, complete cds	erythropoietin receptor	Cytokine, Signal	M60459
<880>ABCB6	Class 4	Homo sapiens clone 24410 ABC transporter mRNA, partial cds	FLI_CDNA	ABC transporter	AF070598
<910>MST1R	Class 4	H.sapiens RON mRNA for tyrosine kinase; Macrophage stimulating 1 receptor (c-met- related tyrosine kinase)	met oncogene; receptor protein-tyrosine kinase; RON gene; transmembrane protein	Signal	X70040
<221>MADH2	Class 4	Human mad protein homolog (hMAD-2) mRNA; JV18- 1.MADR2 OR SMAD2	Receptor-associated Mad homologues synergize as effectors of the TGF-beta response	Signal, TF	U68018
<917>TNFRSF1A	Class 4	H.sapiens TNF-R mRNA for tumor necrosis factor receptor type 1.	TNF-R gene; tumor necrosis factor receptor 1	Cytokine, Signal	X55313
<963>TIM	Class 4	Human guanine nucleotide regulatory protein (tim1) mRNA, complete cds.	Expression cDNA cloning of a novel oncogene with sequence similarity to regulators of small GTP-binding proteins	oncogene	U02082
<118>PSMC6	Class 4	Proteasome (prosome, macropain) 26S subunit, ATPase, 6	Human SUG2	ATPase	AF006305
<1343>AP1S2	Class 4	Homo sapiens adaptor-related protein complex 1, sigma 2 subunit (AP1S2)	Identification and characterization of novel clathrin adaptor-related proteins	AP-1	NM_003916
<548>ISGF3G	Class 4	Human IFN-responsive transcription factor subunit mRNA; Interferon-stimulated transcription factor 3, gamma (48kD); p48	DNA-binding protein; IFN-alpha responsive transcription factor; ISGF3- gamma protein	Signal, TF	M87503
<594>PRKCBP1	Class 4	Homo sapiens protein kinase C-binding protein RACK7 mRNA, partial cds; Protein kinase C binding protein 1	Protein Kinase C-Binding Protein	Signal	U48251
<46>CRADD	Class 4	Human death domain containing protein CRADD mRNA; CASP2 and RIPK1 domain containing adaptor with death domain	CRADD, a novel human apoptotic adaptor molecule for caspase-2, and FasL/tumor necrosis factor receptor- interacting protein RIP	apoptosis, Signal	U84388
<954>CDK4	Class 4	Human (clone PSK-J3) cyclin-dependent protein kinase mRNA; cyclin- dependent kinase 4 (CDK4)	cyclin-dependent protein kinase, type 4; kinase; protein kinase; protein-serine kinase	CellCycle, Signal	M14505

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<317>IRF2	Class 4	Human mRNA for interferon regulatory factor-2 (IRF-2).	interferon regulatory factor 2	Cytokine	X15949
<186>PRKCN	Class 4	Homo sapiens EPK2 mRNA for serine/threonine kinase; Protein kinase C, nu	PKCnu, a new member of the protein kinase C family, composes a fourth subfamily with PKCmu	Signal	AB015982
<116>IL1RL1	Class 4	Homo sapiens mRNA for ST2 protein	immunoglobulin superfamily	Cytokine	D12763
<329>SKIL	Class 4	Human sno oncogene mRNA for snoN protein, ski-related	alternative splicing; oncogene; sno oncogene	oncogene, Signal	X15219
<343>NR4A2	Class 5	H.sapiens mRNA for NOT	immediate early gene; steroid-thyroid hormone; transcription factor	NR4, TF	X75918
<1231>TNFAIP3	Class 5	Human tumor necrosis factor alpha inducible protein A20 mRNA complete cds	The A20 cDNA induced by tumor necrosis factor alpha encodes a novel type of zinc finger protein	Cytokine, Signal	M59465
<252>GADD45A	Class 5	Human growth arrest and DNA-damage-inducible protein (gadd45) mRNA	DNA-damage-inducible protein; growth arrest inducible protein	DNA-damage-inducible	M60974
<182>TCF8	Class 5	Human mRNA for transcription factor AREB6; Transcription factor 8 (represses interleukin 2 expression)	DNA binding protein; transcription factor; zinc-finger protein	Cytokine, Signal, TF	D15050
<1361>ATF3	Class 5	Human activating transcription factor 3 (ATF3) mRNA	DNA-binding protein; activating transcription factor 3; transcription factor.	ATF/CREB	L19871
<1306>SGK	Class 5	Homo sapiens serum/glucocorticoid regulated kinase	Cloning and characterization of a putative human serine/threonine protein kinase transcriptionally modified during anisotonic and isotonic alterations of cell volume	hyperosmotic stress	NM_005627
<777>SCYA3	Class 5	Human macrophage inflammatory protein (GOS19-1) mRNA, Small inducible cytokine subfamily A (Cys-Cys), member 3; Mip-1a	Three human homologs of a murine gene encoding an inhibitor of stem cell proliferation	Cytokine, Signal	M23452
<255>DTR	Class 5	Human heparin-binding EGF-like growth factor mRNA (HBEGF); diphtheria toxin receptor (DTR)	heparin-binding EGF-like growth factor	GF	M60278
<251>CDC42	Class 5	Human GTP-binding protein (G25K) mRNA, complete cds	G25K gene; GTP-binding protein G25K	CellCycle	M35543
<793>NFKBIE	Class 5	Human I kappa B epsilon (IkbE) mRNA, complete cds	I kappa B epsilon, a novel member of the I kappa B family, controls RelA and cRel NF-kappa B activity	Signal	U91616
<267>NFKBIA	Class 5	Homo sapiens MAD-3 mRNA encoding Ikb-like activity, complete cds, IkbAlpha	Characterization of an immediate-early gene induced in adherent monocytes which encodes Ikb-like activit	Signal	M69043
<546>FGF5	Class 5	Human fibroblast growth factor-5 (FGF-5) mRNA, complete cds	fibroblast growth factor-5	GF	M37825
<275>PDGFRA	Class 5	Human platelet-derived growth factor receptor alpha	platelet-derived growth factor receptor	GF, Signal	M21574

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		(PDGFRA) mRNA; CD140A antigen			
<652>BRCA1	Class 5	Human breast and ovarian cancer susceptibility (BRCA1)	A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1	Signal, suppressor	U14680
<627>BAG4	Class 5	Homo sapiens silencer of death domains (SODD) mRNA; BCL2-associated athanogene 4	Prevention of Constitutive TNF Receptor 1 Signaling by Silencer of Death Domains	Signal	AF111116
<1194>RIPK2	Class 5	Homo sapiens serine/threonine kinase RICK (RICK) mRNA; RIP2	RICK, a novel protein kinase containing a caspase recruitment domain, interacts with CLARP and regulates CD95-mediated apoptosis	apoptosis, Signal	AF027706
<1183>IFNA16	Class 5	Human leukocyte interferon-alpha mRNA, complete cds, clone pIFN105	interferon	Cytokine, Signal	M28585
<320>TNFAIP6	Class 5	Tumor necrosis factor, alpha-induced protein 6	adhesion receptor CD44; hyaluronate binding protein; tumor necrosis factor inducible gene.	Cytokine, Signal	M31165
<540>CYP4B1	Class 5	Human lung cytochrome P450 (IV subfamily) BI protein, complete cds	cytochrome; cytochrome P450; cytochrome P450 IVBI	P450	J02871
<1365>CPE	Class 5	Homo sapiens carboxypeptidase E (CPE)	Human carboxypeptidase E. Isolation and characterization of the cDNA, sequence conservation, expression and processing in vitro	differentiation	NM_001873
<815>TNFRSF10C	Class 5	Homo sapiens TRAIL receptor 3 mRNA, complete cds	Characterization of two receptors for TRAIL	Cytokine	AF016267
<342>ARHI	Class 5	Homo sapiens putative tumor suppressor NOEY2 mRNA; Ras homolog gene family, member I	NOEY2 (ARHI), an imprinted putative tumor suppressor gene in ovarian and breast carcinomas	Signal, suppressor	U96750
<854>THRB	Class 5	Human c-erb-A mRNA for thyroid hormone receptor	cellular oncogene; erbA cellular oncogene; erbA oncogene; hormone receptor; steroid hormone receptor; thyroid hormone receptor.	oncogene	X04707
<662>SULTX3	Class 5	Homo sapiens sulfotransferase-like protein mRNA	Molecular cloning and expression of novel sulphotransferase-like cDNAs from human and rat brain	sulfotransferase	AF188698
<347>PRKCM	Class 5	H.sapiens mRNA for protein kinase C mu; Protein kinase C, mu	PKC μ is a novel, atypical member of the protein kinase C family	Signal	X75756
<313>KITLG	Class 5	Human stem cell factor mRNA; (SCF); mast cell growth factor (MGF); c-kit ligand (KITLG)	stem cell factor	GF	M59964
<892>NR1I2	Class 5	Homo sapiens orphan nuclear receptor PXR mRNA, complete cds	The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions	NR1(PXR)	AF061056
<1225>CYP3A4	Class	Homo sapiens cytochrome	Establishment of transgenic cell line	p450	AF182273

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	5	P450-3A4 (CYP3A4) mRNA, complete cds	CHL-3A4 and its metabolic activation		
<282>TFAP2C	Class 5	Human transcription factor ERF-1 mRNA; Transcription factor AP-2 gamma (activating enhancer-binding protein 2 gamma)	Identification of ERF-1 as a member of the AP2 transcription factor family	TF	U85658
<335>NR5A2	Class 5	Homo sapiens hepatocytic transcription factor (hB1F) mRNA, complete cds	Cloning and characterization of a novel human hepatocyte transcription factor, hB1F, which binds and activates enhancer II of hepatitis B virus	NR5, TF	U80251
<333>UGT2B4	Class 5	Human mRNA for liver microsomal UDP-glucuronosyltransferase (UDPGT).	transferase; UDP-glucuronosyltransferase	UGT	Y00317
<695>CRYBA4	Class 5	Human beta-A4 crystallin (CRYBA4) mRNA	Sequence analysis of betaA3, betaB3, and betaA4 crystallins completes the identification of the major proteins in young human lens	sulfotransferase	U59057
<1437>GHSR	Class 5	Homo sapiens growth hormone secretagogue receptor (GHSR)	A receptor in pituitary and hypothalamus that functions in growth hormone release	GH	NM_004122
<1252>IL10	Class 5	Human interleukin 10 (IL10) mRNA	cytokine synthesis inhibitory factor; interleukin 10	Cytokine	M57627
<1146>PEMT	Class 5	Homo sapiens mRNA for phosphatidylethanolamine N-methyltransferase, complete cds	phosphatidylethanolamine N-methyltransferase	methytransferase	AB029821
<1112>ILF1	Class 5	Human mRNA for transcription factor ILF	ilf gene; transcription factor	Cytokine, TF	X60787
<984>CDK5R1	Class 5	H.sapiens p35 mRNA for regulatory subunit of cdk5 kinase	p35 is a neural-specific regulatory subunit of cyclin-dependent kinase 5	CellCycle	X80343
<694>ATP2B3	Class 5	ATPase, Ca++ transporting, plasma membrane 3	Primary structure of human plasma membrane Ca(2+)-ATPase isoform 3	ATPase	U57971
<862>CSF3	Class 5	Human mRNA for granulocyte colony-stimulating factor (G-CSF).	colony stimulating factor; glycoprotein; signal peptide	Cytokine, Signal	X03438
<316>TGFB2	Class 5	Human transforming growth factor-beta-2 mRNA; glioblastoma -derived T-cell suppressor factor (G-TSF); bsc-1 cell growth inhibitor; polyargin; cetermin	alternative splicing; transforming growth factor	GF	M19154
<1102>NR2F1	Class 5	Human mRNA for chicken ovalbumin upstream promoter transcription factor (COUP-TF).	DNA-binding protein; steroid receptor; transcription factor	NR2, TF	X16155
<1334>MAPK13	Class 5	Homo sapiens stress-activated protein kinase 4 (SAPK4) mRNA, complete cds	Novel homologues of CSBP/p38 MAP kinase: activation, substrate specificity and sensitivity to inhibition by pyridinyl imidazoles	Stress	AF004709

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<376>AADAC	Class 5	Human arylacetamide deacetylase mRNA	arylacetamide deacetylase; esterase; lipase	esterase	L32179
<624>SCYA13	Class 5	Human monocyte chemotactic protein-4 precursor (MCP-4) mRNA; Small inducible cytokine subfamily A (Cys-Cys), member 13	Monocyte chemotactic protein-4 (MCP-4), a Novel Human CC Chemokine	Cytokine	U59808
<1084>PNMT	Class 5	Human phenylethanolamine N-methyltransferase mRNA, complete cds	epinephrine biosynthesis; phenylethanolamine N-methyltransferase	Phenylethanolamine-N-methyl transferase	J03727
<1206>GNA13	Class 5	Human guanine nucleotide regulatory protein (G13) mRNA; Guanine nucleotide binding protein (G protein), alpha 13	guanine nucleotide regulatory protein	Signal	L22075
<1223>ALDH7	Class 5	Human aldehyde dehydrogenase ALDH7 mRNA	Cloning of a cDNA encoding human ALDH7, a new member of the aldehyde dehydrogenase family	ALDH	U10868
<1212>CYP1A2	Class 5	Homo sapiens cytochrome P450, subfamily I (aromatic compound-inducible), polypeptide 2 (CYP1A2) mRNA	Human P(3)450: cDNA and complete protein sequence, repetitive Alu sequences in the 3' nontranslated region, and localization of genoto chromosome 15	P450	NM_000761
<1088>SCYA24	Class 5	Human myeloid progenitor inhibitory factor-1 MPIF-2 mRNA	Molecular and functional characterization of two novel human C-C chemokines as inhibitors of two distinct classes of myeloid progenitors	Cytokine	U85768
<1029>TRAF4	Class 5	H.sapiens MLN62 mRNA (TNF receptor-associated factor 4)	overexpressed in breast carcinoma	Cytokine	X80200
<1237>KARP1	Class 5	Ku86 autoantigen related protein 1	KARP-1: a novel leucine zipper protein expressed from the Ku86 autoantigen locus is implicated in the control of DNA-dependent protein kinase activity	Signal	AF039597
<615>CYP8B1	Class 5	Homo sapiens sterol 12-alpha hydroxylase CYP8B1 (Cyp8b1) mRNA,partial cds	Structure and chromosomal assignment of the sterol 12-alpha-hydroxylase gene (CYP8B1) in human and mouse: Eukaryotic cytochrome P-450 gene devoid of introns	P450	AF090318
<431>CYP17	Class 5	Human cytochrome P450c17 (steroid 17-alpha-hydroxylase/17,20 lyase) mRNA, complete cds.	cytochrome; cytochrome P450; cytochrome P450 C17; steroid 17-alpha-hydroxylase lyase	glucocorticoids (Cortisol)	M14564
<1257>IL12B	Class 5	Human natural killer cell stimulatory factor (NKSF) mRNA, complete cds, clone p40	cytokine; natural killer cell stimulatory factor	Cytokine, Signal	M65290
<713>ABL2	Class 5	Human tyrosine kinase arg gene mRNA	The complete coding sequence of arg defines the Abelson subfamily of cytoplasmic tyrosine kinases	oncogene	M35296
<303>EGFR	Class 5	Human mRNA for precursor of epidermal growth factor receptor	Human epidermal growth factor receptor cDNA sequence and aberrant expression of the amplified gene in A431 epidermoid	oncogene, Signal	X00588

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			carcinoma cells		
<930>SCYB14	Class 5	Homo sapiens CXC chemokine BRAK mRNA, Small inducible cytokine subfamily B (Cys-X-Cys), member 14	Cloning of BRAK, a novel divergent CXC chemokine preferentially expressed in normal versus malignant cells	Cytokine	AF073957
<956>TIMP3	Class 5	Human tissue inhibitor of metalloproteinase-3 precursor (TIMP-3) mRNA, complete cds	metalloproteinase inhibitor, extracellular matrix, collagenase	Signal	U02571
<90>CYP2E	Class 5	Human cytochrome P-450j mRNA, complete cds	cytochrome P450j	P450	J02625
<305>MIG	Class 5	H. sapiens Humig mRNA	chemokine; cytokine; Humig gene; secreted protein	Cytokine	X72755
<669>CYP4F2	Class 5	Human cytochrome P450 4F2 (CYP4F2) mRNA, complete cds	The human liver CYP4F2 cDNA sequence and expression in Baculovirus-infected insect cells	P450	U02388
<861>GJB1	Class 5	gap junction protein, beta 1, 32kD (connexin 32, Charcot-Marie-Tooth neuropathy, X-linked)	Cloning and characterization of human and rat liver cDNAs coding for a gap junction protein	Gap-junciton	X04325
<1007>GNG3	Class 5	Homo sapiens guanine nucleotide binding protein (G protein), gamma 3 (GNG3), mRNA	FLI_CDNA	Signal	NM_012202
<1063>CYP2A6	Class 5	Human cytochrome P450IIA3 (CYP2A3) mRNA, complete cds	coumarin 7-hydroxylase; cytochrome P450; cytochrome P450 IIA3	P450	M33318
<25>IGF2	Class 5	Human insulin-like growth factor II mRNA, complete cds	insulin-like growth factor II	GF	J03242
<349>NOVA1	Class 5	Human onconeural ventral antigen-1 (Nova-1) mRNA, complete cds	Brain; Motor Neuron; Paraneoplastic Antigen; RNA-Binding Protein; Breast Cancer	oncogene	U04840
<981>THY1	Class 5	Homo sapiens Thy-1 cell surface antigen (THY1), mRNA	The human Thy-1 gene: structure and chromosomal location	Signal	NM_006288
<1113>SCYA1	Class 5	Human secreted protein (I-309) mRNA; Small inducible cytokine A1 (I-309, homologous to mouse Tca-3)	A novel polypeptide secreted by activated human T lymphocytes	Cytokine	M57502
<1115>NFKB2	Class 5	H. sapiens mRNA for NF-kB subunit (p49/p100)	Cloning of an NF-kappa B subunit which stimulates HIV transcription in synergy with p65	Signal	X61498
<572>SCYA18	Class 5	Homo sapiens mRNA for alternative activated macrophage specific CC chemokine 1; Small inducible cytokine subfamily A (Cys-Cys), member 18, pulmonary and activation-regulated	Alternative macrophage activation-associated CC-chemokine-1, a novel structural homologue of macrophage inflammatory protein-1 alpha with a Th2-associated expression pattern	Cytokine	Y13710
<427>CDC25A	Class	Human cdc25A mRNA,	B-type cyclin; mitotic cyclin; tyrosine	CellCycle	M81933

	5	complete cds	phosphatase		
<15>TERF1	Class 5	Homo sapiens telomeric repeat binding factor (NIMA-interacting) 1	A mammalian factor that binds telomeric TTAGGG repeats in vitro	oncogene	NM_003218
<726>CES1	Class 5	Human carboxylesterase mRNA	carboxylesterase; glycosylation-dependent	esterase	L07765
<1431>SLC6A2	Class 5	Homo sapiens solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2 (SLC6A2)	Expression cloning of a cocaine- and antidepressant-sensitive human noradrenaline transporter	norepinephrine	NM_001043
<1415>AVP	Class 5	Human vasopressin mRNA; Arginine vasopressin (neurophysin II, antidiuretic hormone, diabetes insipidus, neurohypophyseal)	The neurohypophyseal hormones vasopressin and oxytocin. Precursor structure, synthesis and regulation	vasopressin	M25647
<1126>POLR2J	Class 5	polymerase (RNA) II (DNA directed) polypeptide J (13.3kD)	Cloning of a novel human RNA polymerase II subunit downregulated by doxorubicin: new potential mechanisms of drug related toxicity	polymerase	L37127
<324>GRO2	Class 5	Human mRNA for macrophage inflammatory protein-2alpha (MIP2alpha,; GRO2 oncogene	macrophage inflammatory protein	Cytokine	X53799
<323>GRO1	Class 5	Human mRNA for melanoma growth stimulatory activity (MGSA), groucho	Molecular characterization and chromosomal mapping of melanoma growth stimulatory activity, a growth factor structurally related to beta-thromboglobulin	Signal, TF	X12510

The 286 genes differentially expressed between 72 untreated MS patients and 22 CN subjects are listed. The hierarchical clustering analysis categorized 281 of them into five distinct classes numbered #1 to #5 as shown in Fig 1. The remaining five genes, including TOP1, CHST4, SLC35A1, ST1B2, and TAF2H, were unable to be categorized into any classes. All the class #5 genes were upregulated in MS, whereas the genes of classes #1 to #4 were downregulated in MS when compared with CN. The table includes their gene number on the array, symbol, class, name, keyword, category, and GenBank accession number.

Supplementary Table 2 Online.

Clinical Characteristics of IFN β -Treated and Untreated MS Patients

	Total	IFN β -treated patients	IFN β -untreated patients
The number of the patients	72	46	26
Age of the patients (average, SD)	36.1 \pm 10.3	33.2 \pm 7.6	38.2 \pm 11.9
Male to female ratio of the patients	17 to 55	8 to 38	9 to 17
RRMS to SPMS ratio of the patients	65 to 7	39 to 7	26 to 0
CMS to non-CMS ratio of the patients	57 to 15	39 to 7	18 to 8
Disease duration (year; average, SD)	7.7 \pm 5.4	8.5 \pm 5.9	6.3 \pm 4.2
Dropout during a 2 year followup period (n)	9	7	2
Increase in EDSS score during a 2 year followup period (average, SD)	0.3 \pm 1.0	0.5 \pm 1.2	0.0 \pm 0.3
Increase in the number of relapse during a 2 year followup period (average, SD)	-1.1 \pm 1.4	-1.5 \pm 1.3	-0.6 \pm 1.2
Increase in the day of IVMP treatment during a 2 year followup period (average, SD)	-4.2 \pm 4.7	-5.5 \pm 5.1	-2.8 \pm 2.8
Increase in the day of hospitalization during a 2 year followup period (average, SD)	-32.5 \pm 45.7	-44.4 \pm 49.2	-13.2 \pm 29.0
Increase in the number of lesions on T2-weighted MRI during a 2 year followup period (average, SD)	0.9 \pm 7.7	1.7 \pm 9.7	-0.4 \pm 1.8

Seventy two MS patients were divided into IFN β -treated group (n = 46) and untreated group (n = 26) by the patient's own determination upon enrollment. No statistically significant differences were observed between both groups in the increase of EDSS score, the number of relapse, the day of IVMP treatment, the day of hospitalization, and the number of MRI lesions during a 2 year followup period compared with those during 2 years before enrollment. Abbreviations: RRMS, relapsing-remitting MS; SP, secondary progressive MS; CMS, conventional form of MS; EDSS, Expanded Disability Status Scale; IVMP, intravenous methylprednisolone pulse.

II. 分 担 研 究 報 告

厚生労働科学研究費補助金(難治性疾患の画期的診断・治療法に関する研究事業)
分担研究報告書

末梢血 T 細胞の DNA microarray 解析による
多発性硬化症の病型分類とインターフェロンベータ治療反応性

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研究要旨 多発性硬化症(multiple sclerosis; MS)では何らかの遺伝的素因を有する個体において、脳炎惹起性自己抗原に分子相同性を示す外来抗原を認識して活性化した自己反応性 CD4⁺ Th1 T 細胞が誘導される。MS は臨床経過から relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), 病巣分布から conventional (CMS), opticospinal (OSMS), 治療反応性から interferon-beta (IFN β) responder, nonresponder に分類され、病理学的に T 細胞浸潤、抗体・補体沈着、oligodendrocyte apoptosis, axonal degeneration など多様な所見を呈する。このように多彩な MS の免疫病態の全てを Th1 bias に基づき説明するのは困難であり、non-Th1/Th2 遺伝子群の発現制御異常が MS 病態を修飾している可能性がある。本研究では MS 多様性(variability, heterogeneity)の分子遺伝学的基盤を解明するため、MS 患者末梢血 T 細胞の遺伝子発現プロファイルを DNA microarray を用いて包括的・網羅的・系統的に解析した。その結果、DNA microarray による T 細胞の遺伝子発現パターンは多様な病態を呈する MS を A, B, C, D の 4 群に分類し、それぞれの群は疾患活動性・病巣分布・IFN β 治療反応性との密接な関連を認めた。

A. 研究目的

多発性硬化症(multiple sclerosis; MS)では何らかの遺伝的素因を有する個体において、脳炎惹起性自己抗原に分子相同性を示す外来抗原を認識して活性化した自己反応性 CD4⁺ Th1 T 細胞が誘導される。MS は臨床経過から relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), 病巣分布から conventional (CMS), opticospinal (OSMS), 治療反応性から interferon-beta (IFN β) responder,

nonresponder に分類され、病理学的に T 細胞浸潤、抗体・補体沈着、oligodendrocyte apoptosis, axonal degeneration など多様な所見を呈する。このように多彩な MS の病態の全てを Th1 bias に基づき説明するのは困難であり、non-Th1/Th2 遺伝子群の発現制御異常が MS 病態を修飾している可能性がある。本研究では MS 多様性 (variability or heterogeneity)の分子遺伝学的基盤を解明するため、MS 患者末梢血 T リンパ球の遺伝子発現プロファイルを DNA microarray を

用いて包括的・網羅的・系統的に解析した。

B. 研究方法

1) 対象：Informed consent を取得した IFN β 未治療 clinically active MS 72 名(65 RRMS, 7 SPMS; 55 women, 17 men; the mean age 36.1 \pm 10.3)と健常者 22 名 (healthy controls; CN, 16 women, 6 men; the mean age 38.6 \pm 12.3)。

2) RNA の精製と DNA microarray 解析：末梢血リンパ球より、autoMACS で CD3 $^+$ T 細胞を精製、RNA を抽出・増幅して cDNA 作成時に Cy5 で標識した。別の健常者 3 名の pooled cDNA を Cy3 で標識し universal reference とし、1,258 cDNA microarray (Hitachi Life Science)上で競合的 hybridization を行い蛍光強度を測定、global normalization 後に Bayesian t test により MS versus CN で有意な発現差異を認めた遺伝子群を同定した。これを識別遺伝子(discriminator genes)として GeneSpring を用いて standard x standard algorithm に従い、階層クラスター解析(hierarchical clustering analysis; HCA)と主成分解析(principal component analysis; PCA)を行った。

3) IFN β responder の評価：上記 MS 患者 72 名中 46 名は初回採血後に 2 年間の IFN β 1b 治療を開始し、治療導入 3 ヶ月後と 6 ヶ月後に採血した。残りの 26 名は本人の希望に従い IFN β 治療を行わずに 2 年間追跡した。IFN β 治療導入前後 2 年間の 6 項目：再発回数・ステロイドパルス日数・入院日数・Expanded Disability Status Scale (EDSS) score・MRI 病巣数・患者満足度を 3 ランクに分けて点数化し、合計点が+6 から+3 を responder, -1 から-6 を nonresponder, 中

間を undetermined と定義した。

C. 研究結果

IFN β 未治療 MS 72 名と CN 22 名の CD3 $^+$ T 細胞間で発現差異を呈した 286 遺伝子 (discriminator genes)を指標とする階層クラスター解析で、MS は CN から独立した A, B, C, D 4 群(MS subgroups)に分類され、286 遺伝子は 1-5 群(class #1-#5)に分類された(図 1)。一方 CD3 $^-$ non-T 細胞の遺伝子発現に関するクラスター解析では明確な subgroup 化は認めなかった。MS の A, B, C, D 4 群分類の妥当性は主成分解析で確認された。MS では class #1-#4 に属する 203 遺伝子の発現が低下しており、class #5 に属する 78 遺伝子が発現上昇していた。MS subgroups のうち A 群が最も CN に近い遺伝子発現プロフィールを呈していた。D 群が最も EDSS score が高値で、C 群には大脳限局病変を示す患者 (cerebrum only)が集積していた。また B 群では CCL3, CXCL9 など chemokine 遺伝子が集積している class #5 遺伝子の発現レベルが最も高く、再発回数・入院日数・ステロイドパルス日数から見て、最も活動性が高い患者が集積していた。また IFN β responder は A 群 57.1%, B 群 57.1%, C 群 18.2%, D 群 0%であり、A, B 群に集積していた。IFN β responder では治療 3-6 ヶ月の時点で IFN 応答遺伝子群(IFN-responsive genes, IRGs: ISG15, IFI27, MCP-1, TNFRp75)の高発現が保持されていたが(persistent induction)、nonresponder では治療 3 ヶ月の時点で IRG 発現レベルが上昇していたが、治療 6 ヶ月には低下し seesaw pattern を呈した(図 2)。

D. 考察

遺伝子アレイ(DNA microarray, gene chip)は臨床所見や画像所見のみでは鑑別困難な疾患の補助診断のツールとして、また腫瘍の悪性度や予後の予測、種々の疾患の薬物反応性の予測、治療効果の判定、副作用の予測など、幅広い臨床応用が可能である。本研究では DNA microarray を用いて、IFN β 未治療 MS 72 名と CN 22 名から分離した CD3⁺ T 細胞の遺伝子発現プロフィールを比較解析した。両群間で 286 遺伝子の有意な発現差異を認め、昨年 top 30 遺伝子は apoptosis 制御遺伝子群であることを報告した (a counterbalance between proapoptotic and antiapoptotic genes)。本年度は MS versus CN の T 細胞で発現差異を認めた 286 遺伝子を指標とするクラスター解析で、MS が 4 群に分類され、各々の subgroup は疾患活動性・病巣分布・IFN β 治療反応性と密接な関連を認めることを報告した。本研究の結果は MS 発症における自己反応性 CD4⁺ T 細胞および CD8⁺ T 細胞の中心的な役割を支持する。

E. 結論

DNA microarray による T 細胞の遺伝子発現プロフィール解析は、多様な病態を呈する MS を 4 群に分類し、それぞれの群は疾患活動性・病巣分布・IFN β 治療反応性との密接な関連を認めた。

F. 健康危険情報

なし。

G. 研究発表

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H. 知的所有権の取得状況

1. 特許取得
 - 1) 多発性硬化症に対するインターフェロン・ベータ薬物治療の有効性予測法(特開 2004-28926)
 - 2) 多発性硬化症特異的遺伝子発現プロフィールの解析(出願中)
2. 実用新案登録

なし
3. その他

なし

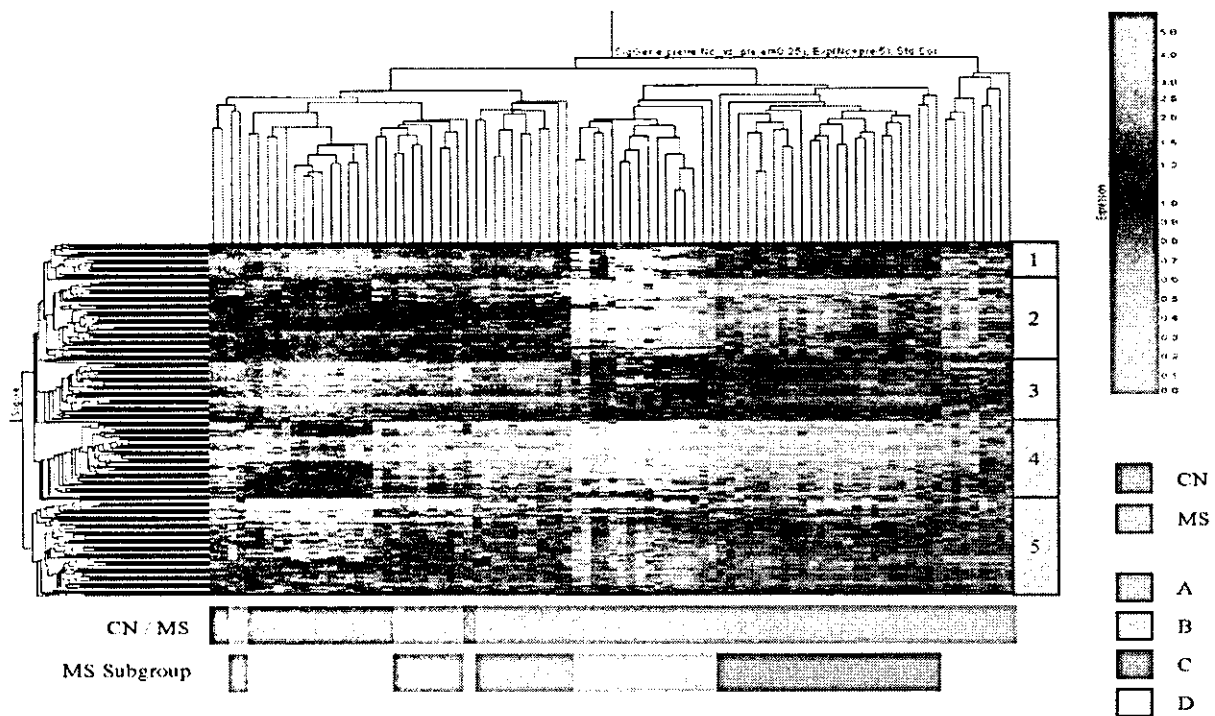


Fig. 1. Hierarchical clustering analysis of 286 genes differentially expressed between 72 untreated MS patients and 22 control subjects.

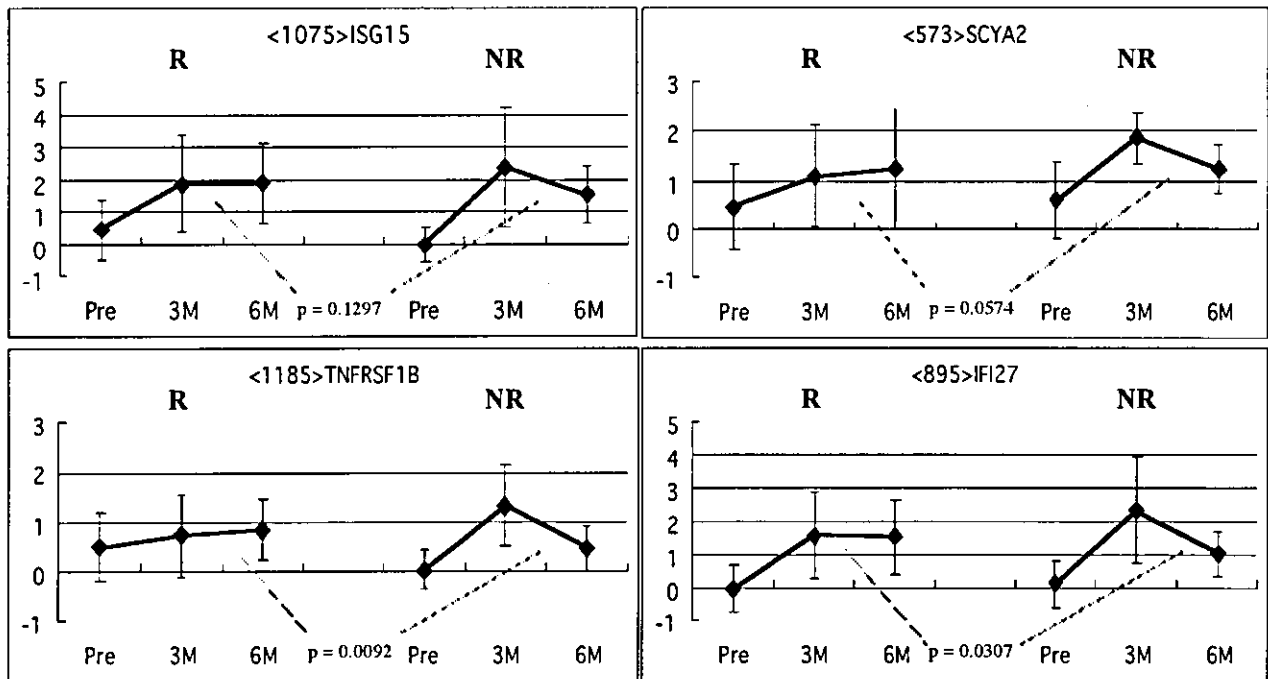


Fig. 2. The temporal profile of induction of IFN-responsive genes in IFN β responders (R) and nonresponders (NR) during IFN β treatment.

「対照疾患のマイクロアレイ解析」に関する研究

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研究要旨

多発性硬化症に対するインターフェロン療法の効果の発現及びその持続性に関する要因などの解析に関する研究を行うにあたって、多発性硬化症では T 細胞の遺伝子プロファイルが健常人とは異なることが明らかとなってきた。そこで、この遺伝子プロファイルが疾患特異的で診断的に有効かどうかを検討するため、Th 1 優位な臓器特異的自己免疫疾患である関節リウマチの末梢血における遺伝子プロファイルを検討した。RA では末梢血全体の解析で健常人と異なる遺伝子は、多発性硬化症とは異なる遺伝子プロファイルであり、多発性硬化症でみられた特徴的な遺伝子プロファイルは、疾患特異的であることが示唆された。

A. 研究目的

これまで多発性硬化症患者のタイプ I インターフェロンに対するレスポンスの予測に有効なマイクロアレイの研究を行う過程で、末梢血のリンパ球は多発性硬化症では健常人と比較して異なる遺伝子発現パターンをとることがわかってきた。そこで、これらの変化が他の自己免疫疾患でもみられるかどうかを検討し、診断に役立つカスタムアレイの開発を目的とした。

B. 研究方法

対照として、早期診断が治療に重要な、早期関節リウマチ(RA)を選択した。RA に対しては、近年続々と新規治療薬が開発・発売され、早期から積

極的に抗リウマチ薬を使用することによって軟骨・骨破壊が予防するという治療法が推称されるようになった。現在、早期 RA の診断に関しては、熟練したリウマチ専門医の臨床診断が最も信頼性が高く、リウマチ因子や炎症反応等の比較的非特異的な検査を補助的に用いているのが現状である。そこで、リウマチを専門としない一般医師が専門医に紹介するかどうかの判断材料として使用するのに適当な診断試薬が発達すると、より効率的に早期診断が可能になると考えられる。初診時に RA が強く疑われ、初診時から 6 ヶ月後に RA の診断が確定した患者さんの初診時の末梢血リンパ球の遺伝子プロファイルを、変形性関節症と診断された症例、健常人と比較し、発現に優位に差がある遺伝子を抽出する。これらの解析で、発現に優位に差がある遺伝子のみを測定できるチップを作製