| | | | |
|---|---|---|---|
| *PREP129* | NM_004049 | BCL2-related protein A1 (BCL2A1) | s/d |
| *PREP130* | NM_021642 | Fc fragment of IgG, low affinity IIa, receptor for (CD32) (FCGR2A) | s |
| *PREP131* | NM_002965 | S100 calcium binding protein A9 (calgranulin B) (S100A9) | s/d |
| *PREP132* | NM_024298 | leukocyte receptor cluster (LRC) member 4 (LENG4) | s |
| *PREP133* | NM_002468 | myeloid differentiation primary response gene (88) (MYD88) | s |
| *PREP134* | NM_016612 | solute carrier family 25, member 37 (SLC25A37) | s |
| *PREP135* | NM_021149 | coactosin-like 1 (Dictyostelium) (COTL1) | s |
| *PREP136* | NM_000239 | lysozyme (renal amyloidosis) (LYZ) | s/d |
| *PREP137* | NM_002117 | major histocompatibility complex, class I, C (HLA-C) | s |
| *PREP138* | NM_003848 | succinate-CoA ligase, GDP-forming, beta subunit (SUCLG2) | s |
| *PREP139* | NM_004707 | APG12 autophagy 12-like (S. cerevisiae) (APG12L) | s |
| *PREP140* | NM_004355 | CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated) (CD74) | s |
| *PREP141* | NM_032955 | allograft inflammatory factor 1 (AIF1) | s |
| *PREP142* | NM_016337 | Enah/Vasp-like (EVL) | s |
| *PREP143* | NM_003794 | sorting nexin 4 (SNX4) | s |
| *PREP144* | NM_000994 | ribosomal protein L32 (RPL32) | s |
| *PREP145* | HSU40369 | spermidine/spermine N1-acetyltransferase (SSAT) | s |
| *PREP146* | NM_000982 | ribosomal protein L21 (RPL21) | s |
| *PREP147* | NM_001003 | ribosomal protein, large, P1 (RPLP1) | s |
| *PREP148* | NM_002029 | formyl peptide receptor 1 (FPR1) | s |
| *PREP149* | NM_000995 | ribosomal protein L34 (RPL34) | s |
| *PREP150* | NM_183057 | vacuolar protein sorting 28 (yeast) (VPS28) | s |
| *PREP151* | NM_014248 | ring-box 1 (RBX1) | s |
| *PREP152* | NM_000873 | intercellular adhesion molecule 2 (ICAM2) | s |
| *PREP153* | NM_000952 | platelet-activating factor receptor (PTAFR) | s |
| *PREP154* | NM_000569 | Fc fragment of IgG, low affinity IIIa, receptor (CD16a) (FCGR3A) | s/d |
| *PREP155* | NM_004047 | ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b (ATP6V0B) | s |
| *PREP156* | NM_007074 | coronin, actin binding protein, 1A (CORO1A) | s |
| *PREP157* | NM_139286 | CDC26, subunit of anaphase promoting complex (CDC26) | s |
| *PREP158* | BC016148 | integral membrane protein 2B (ITM2B) | s |
| *PREP159* | NM_004417 | dual specificity phosphatase 1 (DUSP1) | s |
| *PREP160* | NM_004665 | vanin 2 (VNN2) | s |
| *PREP161* | NM_006163 | nuclear factor (erythroid-derived 2), 45kDa (NFE2) | s/d |
| *PREP162* | NM_002964 | S100 calcium binding protein A8 (calgranulin A) (S100A8) | s/d |
| *PREP163* | NM_005534 | interferon gamma receptor 2 (interferon gamma transducer 1) (IFNGR2) | s |
| *PREP164* | NM_001706 | B-cell CLL/lymphoma 6 (zinc finger protein 51) (BCL6) | s |
| *PREP165* | NM_177924 | N-acylsphingosine amidohydrolase (acid ceramidase) 1(ASAH1) | s |
| *PREP166* | NM_003733 | 2'-5'oligoadenylate synthetase-like (OASL) | s |
| *PREP167* | NM_002961 | S100 calcium binding protein A4 (calcium protein,calvasculin, metastasin, murine placental homolog) (S100A4) | s |
| *PREP168* | NM_004106 | Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide (FCER1G) | s |
| *PREP169* | NM_001778 | CD48 antigen (B-cell membrane protein) (CD48) | s/d |
| *PREP170* | NM_001629 | arachidonate 5-lipoxygenase-activating protein (ALOX5AP) | s/d |
| *PREP171* | NM_001865 | cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2) | s |
| *PREP172* | NM_030808 | nudE nuclear distribution gene E homolog like 1 (A. nidulans) (NDEL1) | s |
| *PREP173* | NM_004582 | Rab geranylgeranyltransferase, beta subunit (RABGGTB) | s |
| *PREP174* | NM_031950 | Ksp37 protein (KSP37) | s/d |
| *PREP175* | NM_005127 | C-type (calcium dependent, carbohydrate-recognition domain) lectin, superfamily member 2 (activation-induced) (CLECSF2) | s |
| *PREP176* | NM_002123 | major histocompatibility complex, class II, DQ beta 1 (HLA-DQB1) | s/d |
| *PREP177* | NM_001967 | eukaryotic translation initiation factor 4A, isoform 2(EIF4A2) | s |
| *PREP178* | NM_004309 | Rho GDP dissociation inhibitor (GDI) alpha (ARHGDIA) | s |
| *PREP179* | NM_002341 | lymphotoxin beta (TNF superfamily, member 3) (LTB) | s |
| *PREP180* | NM_005737 | ADP-ribosylation factor-like 4C (ARL4C) | s |
| *PREP181* | NM_014153 | zinc finger CCCH-type containing 7A (ZC3H7A) | s |
| *PREP182* | NM_002124 | major histocompatibility complex, class II, DR beta 1 (HLA-DRB1) | s |
| *PREP183* | NM_002831 | protein tyrosine phosphatase, non-receptor type 6 (PTPN6) | s |
| *PREP184* | NM_002801 | proteasome (prosome, macropain) subunit, beta type, 10 (PSMB10) | s |
| *PREP185* | NM_007161 | leukocyte specific transcript 1 (LST1) | s/d |
| *PREP186* | NM_000962 | prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) (PTGS1) | s |
| *PREP187* | NM_012198 | grancalcin, EF-hand calcium binding protein (GCA) | s/d |
| *PREP188* | NM_000478 | alkaline phosphatase, liver/bone/kidney (ALPL) | s |
| *PREP189* | NM_001547 | interferon-induced protein with tetratricopeptide repeats 2 (IFIT2) | s/d |
| *PREP190* | NM_006743 | RNA binding motif (RNP1, RRM) protein 3 (RBM3) | s |
| *PREP191* | NM_001909 | cathepsin D (lysosomal aspartyl protease) (CTSD) | s |
| *PREP192* | NM_006763 | BTG family, member 2 (BTG2) | s |
| *PREP193* | NM_006561 | CUG triplet repeat, RNA binding protein 2 (CUGBP2) | s |
| *PREP194* | NM_016270 | Kruppel-like factor 2 (lung) (KLF2) | s |

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|---|---|---|---|
| *PREP195* | NM_000211 | integrin, beta 2 (antigen CD18 (p95), lymphocyte function-associated antigen 1; macrophage antigen 1 (mac-1) beta subunit) (ITGB2) | s/d |
| *PREP196* | NM_020820 | phosphatidylinositol 3,4,5-trisphosphate-dependent RAC exchanger 1 (PREX1) | s/d |
| *PREP197* | NM_005082 | tripartite motif-containing 25 (TRIM25) | s |
| *PREP198* | BC028068 | Janus kinase 3 (a protein tyrosine kinase, leukocyte) | s/d |
| *PREP199* | AB023211 | peptidyl arginine deiminase, type II (PADI2) | s |
| *PREP200* | AB032952 | solute carrier family 45, member 4 (SLC45A4) | s |
| *PREP201* | NM_000629 | interferon (alpha, beta and omega) receptor 1 (IFNAR1) | s |
| *PREP202* | NM_002086 | growth factor receptor-bound protein 2 (GRB2) | s |
| *PREP203* | NM_017853 | thioredoxin-like 4B (TXNL4B) | s |
| *PREP204* | NM_000978 | ribosomal protein L23 (RPL23) | s |
| *PREP205* | NM_004079 | cathepsin S (CTSS) | s |
| *PREP206* | NM_004718 | cytochrome c oxidase subunit VIIa polypeptide 2 like (COX7A2L), nuclear gene encoding mitochondrial protein | s |
| *PREP207* | NM_170662 | Cas-Br-M (murine) ecotropic retroviral transforming sequence b (CBLB) | s |
| *PREP208* | NM_005217 | defensin, alpha 3, neutrophil-specific (DEFA3) | d |
| *PREP209* | NM_006144 | granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3) (GZMA) | d |
| *PREP210* | NM_021935 | prokineticin 2 (PROK2) | d |
| *PREP211* | NM_020980 | aquaporin 9 (AQP9) | d |
| *PREP212* | NM_001008 | ribosomal protein S4, Y-linked (RPS4Y) | d |
| *PREP213* | NM_002838 | protein tyrosine phosphatase, receptor type, C (PTPRC), transcript variant 1 | d |
| *PREP214* | NM_130782 | regulator of G-protein signalling 18 (RGS18) | d |
| *PREP215* | NR_001435 | major histocompatibility complex, class II, DP beta 2 (pseudogene) (HLA-DPB2) on chromosome 6 | d |
| *PREP216* | NM_000433 | neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2) (NCF2) | d |
| *PREP217* | NM_001781 | CD69 antigen (CD69) | d |
| *PREP218* | NM_025228 | TRAF3-interacting Jun N-terminal kinase (JNK)-activating modulator (T3JAM) | d |
| *PREP219* | NM_000584 | interleukin 8 (IL8) | d |
| *PREP220* | NM_016619 | placenta-specific 8 (PLAC8) | d |
| *PREP221* | NM_003761 | vesicle-associated membrane protein 8 (endobrevin) (VAMP8) | d |
| *PREP222* | NM_000560 | CD53 antigen (CD53) | d |
| *PREP223* | NM_018326 | immunity associated protein 4 (HIMAP4) | d |
| *PREP224* | NM_004345 | cathelicidin antimicrobial peptide (CAMP) | d |
| *PREP225* | NM_001465 | FYN binding protein (FYB-120/130) (FYB) | d |
| *PREP226* | NM_006504 | protein tyrosine phosphatase, receptor type, E (PTPRE), transcript variant 1 | d |
| *PREP227* | NM_004633 | interleukin 1 receptor, type II (IL1R2), transcript variant 1 | d |
| *PREP228* | NM_052942 | guanylate binding protein 5 (GBP5) | d |
| *PREP229* | NM_001767 | CD2 antigen (p50), sheep red blood cell receptor (CD2) | d |
| *PREP230* | NM_006864 | leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 3 (LILRB3) | d |
| *PREP231* | NM_152680 | transmembrane protein 154 (TMEM154) | d |
| *PREP232* | NM_153236 | immune associated nucleotide (hIAN7) | d |
| *PREP233* | NM_005980 | S100 calcium binding protein P (S100P) | d |
| *PREP234* | NM_005248 | Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR) | d |
| *PREP235* | NM_005335 | hematopoietic cell-specific Lyn substrate 1 (HCLS1) | d |
| *PREP236* | NM_002258 | killer cell lectin-like receptor subfamily B, member 1 (KLRB1) | d |
| *PREP237* | NM_001828 | Charcot-Leyden crystal protein (CLC) | d |
| *PREP238* | NM_182790 | pre-B-cell colony enhancing factor 1 (PBEF1), transcript variant 2 | d |
| *PREP239* | NM_033423 | granzyme H (cathepsin G-like 2, protein h-CCPX) (GZMH) | d |
| *PREP240* | NM_001175 | Rho GDP dissociation inhibitor (GDI) beta (ARHGDIB) | d |
| *PREP241* | NM_005621 | S100 calcium binding protein A12 (calgranulin C) (S100A12) | d |
| *PREP242* | NM_002349 | lymphocyte antigen 75 (LY75) | d |
| *PREP243* | NM_000442 | platelet/endothelial cell adhesion molecule (CD31 antigen) (PECAM1) | d |
| *PREP244* | NM_013322 | sorting nexin 10 (SNX10) | d |
| *PREP245* | BC036402 | MAX dimerization protein 1 (MXD1) | d |
| *PREP246* | NM_006433 | granulysin (GNLY), transcript variant NKG5 | d |
| *PREP247* | AL834529 | Leucine-rich repeat kinase 2 (LRRK2) | d |
| *PREP248* | NM_002970 | spermidine/spermine N1-acetyltransferase (SAT) | d |
| *PREP249* | NM_002118 | major histocompatibility complex, class II, DM beta (HLA-DMB) | d |
| *PREP250* | NM_021966 | T-cell leukemia/lymphoma 1A (TCL1A) | d |
| *PREP251* | BC001699 | F11 receptor (F11R) | d |
| *PREP252* | NM_021983 | major histocompatibility complex, class II, DR beta 4 (HLA-DRB4) | d |
| *PREP253* | NM_002664 | pleckstrin (PLEK) | d |
| *PREP254* | NM_032489 | acrosin binding protein (ACRBP) | d |
| *PREP255* | NM_005252 | v-fos FBJ murine osteosarcoma viral oncogene homolog (FOS) | d |

| | | | |
|---|---|---|---|
| *PREP256* | NM_003264 | toll-like receptor 2 (TLR2) | d |
| *PREP257* | NM_002984 | chemokine (C-C motif) ligand 4 (CCL4) | d |
| *PREP258* | NM_005428 | vav 1 oncogene (VAV1) | d |
| *PREP259* | AK090478 | transmembrane channel-like 8 (TMC8) | d |
| *PREP260* | NM_018837 | sulfatase 2 (SULF2), transcript variant 1 | d |
| *PREP261* | NM_145699 | apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A (APOBEC3A) | d |
| *PREP262* | NM_003726 | src family associated phosphoprotein 1 (SCAP1) | d |
| *PREP263* | AK130644 | solute carrier organic anion transporter family, member 3A1 (SLCO3A1) | d |
| *PREP264* | NM_052960 | retinol binding protein 7, cellular (RBP7) | d |
| *PREP265* | NM_000507 | fructose-1,6-bisphosphatase 1 (FBP1) | d |
| *PREP266* | NM_032463 | Williams-Beuren syndrome chromosome region 5 (WBSCR5), transcript variant 2 | d |
| *PREP267* | AK090431 | NOD3 protein (NOD3) | d |
| *PREP268* | NM_002017 | Friend leukemia virus integration 1 (FLI1) | d |
| *PREP269* | NM_005825 | RAS guanyl releasing protein 2 (calcium and DAG-regulated) (RASGRP2), transcript variant 1 | d |
| *PREP270* | NM_005874 | leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 2 (LILRB2) | d |
| *PREP271* | NM_004288 | pleckstrin homology, Sec7 and coiled-coil domains, binding protein (PSCDBP) | d |
| *PREP272* | NM_144649 | transmembrane protein 71 (TMEM71) | d |
| *PREP273* | AF307332 | meningioma-expressed antigen 5s splice variant mRNA, complete cds | d |
| *PREP274* | NM_015714 | putative lymphocyte G0/G1 switch gene (G0S2) | d |
| *PREP275* | NM_178129 | purinergic receptor P2Y, G-protein coupled, 8 (P2RY8) | d |
| *PREP276* | NM_016610 | toll-like receptor 8 (TLR8), transcript variant 1 | d |
| *PREP277* | NM_145256 | leucine rich repeat containing 25 (LRRC25) | d |
| *PREP278* | NM_003853 | interleukin 18 receptor accessory protein (IL18RAP) | d |
| *PREP279* | NM_001548 | interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) | d |
| *PREP280* | NM_021995 | urotensin 2 (UTS2), transcript variant 1 | d |
| *PREP281* | NM_000081 | Chediak-Higashi syndrome 1 (CHS1) | d |
| *PREP282* | NM_002260 | killer cell lectin-like receptor subfamily C, member 2 (KLRC2) | d |
| *PREP283* | NM_172345 | sperm associated antigen 9 (SPAG9), transcript variant 2 | d |
| *PREP284* | NM_002155 | heat shock 70kDa protein 6 (HSP70B') (HSPA6) | d |
| *PREP285* | NM_006417 | interferon-induced protein 44 (IFI44) | d |
| *PREP286* | NM_006762 | lysosomal-associated multispanning membrane protein-5 (LAPTM5) | d |
| *PREP287* | NM_015184 | phospholipase C-like 2 (PLCL2) | d |
| *PREP288* | NM_013385 | pleckstrin homology, Sec7 and coiled-coil domains 4 (PSCD4) | d |
| *PREP289* | NM_139018 | NK inhibitory receptor precursor (NKIR) | d |
| *PREP290* | NM_002125 | major histocompatibility complex, class II, DR beta 5 (HLA-DRB5) | d |

**Table S4.** Grouping of *PREP* genes.

1) Major histocompatibility complex genes

| *PREP#* | Group Name | Sequence description | |
|---|---|---|---|
| *PREP33* | | MHC class I | HLA-A |
| *PREP36* | | MHC class I | HLA-B |
| *PREP46* | | MHC class II | HLA-DPB1 |
| *PREP48* | | MHC class I | HLA-E |
| *PREP137* | | MHC class I | HLA-C |
| *PREP176* | | MHC class II | HLA-DQB1 |
| *PREP182* | | MHC class II | HLA-DRB1 |
| *PREP215* | | MHC class II | HLA-DPB2 |
| *PREP249* | | MHC class II | HLA-DMB |
| *PREP252* | | MHC class II | HLA-DRB4 |
| *PREP290* | | MHC class II | HLA-DRB5 |

2) CD antigen genes

| *PREP#* | Sequence description |
|---|---|
| *PREP119* | CD52 antigen (CAMPATH-1 antigen) (CD52) |
| *PREP130* | CD32 antigen (Fc fragment of IgG, low affinity IIa) |
| *PREP140* | CD74 antigen |
| *PREP154* | CD16a (Fc fragment of IgG, low affinity IIIa, receptor) |
| *PREP169* | CD48 antigen (B-cell membrane protein) (CD48) |
| *PREP222* | CD53 antigen (CD53) |
| *PREP229* | CD2 antigen |
| *PREP243* | CD31 antigen (PECAM1) |

3) Ribosomal protein (RP) genes

| *PREP#* | Group Name | Sequence description | |
|---|---|---|---|
| *PREP116* | | Ribosomal protein L | RPL39 |
| *PREP125* | | Ribosomal protein L | RPL26 |
| *PREP144* | | Ribosomal protein L | RPL32 |
| *PREP146* | | Ribosomal protein L | RPL21 |
| *PREP147* | | Ribosomal protein L | RPLP1 |
| *PREP149* | | Ribosomal protein L | RPL34 |
| *PREP204* | | Ribosomal protein L | RPL23 |
| *PREP212* | | Ribosomal protein S | RPS4Y (Y-linked) |

4) Interferon (IFN) related genes

| *PREP#* | Group Name | Sequence description | |
|---|---|---|---|
| *PREP75* | | IFN gamma inducible | IFI30 |
| *PREP106* | | IFN stimulated | ISG20 |
| *PREP163* | | IFN gamma receptor | IFNGR2 |
| *PREP189* | | IFN induced | IFIT2 |
| *PREP201* | | IFN alfa receptor | IFNAR1 |
| *PREP279* | | IFN induced | IFIT1 |
| *PREP285* | | IFN induced | IFI44 |

interferon, gamma-inducible protein 30 (IFI30)
interferon gamma receptor 2 (IFNGR2)
interferon-induced protein with tetratricopeptide repeats 1 (IFIT1)

interferon-induced protein 44 (IFI44)

5) S100 calcium binding protein related genes

| *PREP#* | Sequence description |
|---|---|
| *PREP117* | calgizzarin (S100A11) |
| *PREP131* | calgranulin B (S100A9) |
| *PREP162* | calgranulin A (S100A8) |
| *PREP167* | calvasculin homolog (S100A4) |
| *PREP241* | calgranulin C (S100A12) |
| *PREP295* | S100 calcium binding protein P (S100P) |

6) Oncogene related genes

| *PREP#* | Sequence description |
|---|---|
| *PREP45* | v-ets erythroblastosis virus E26 oncogene homolog 1 (ETS1) |
| *PREP101* | c-src tyrosine kinase (CSK) |
| *PREP110* | v-yes-1 Yamaguchi sarcoma viral related oncogene homolog (LYN) |
| *PREP234* | Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR) |
| *PREP255* | v-fos FBJ murine osteosarcoma oncogene homolog (FOS) |
| *PREP292* | vav 1 oncogene (VAV1) |

7) Interleukine (IL) related genes

| *PREP#* | Group Name | Sequence description | |
|---|---|---|---|
| *PREP86* | | interleukin receptor | IL8RA |
| *PREP112* | | interleukin receptor | IL10RB |
| *PREP219* | | interleukin | IL8 |
| *PREP227* | | interleukin receptor | IL1R2 |
| *PREP278* | | interleukin receptor | IL18RAP |

interleukin 1 receptor, type II (IL1R2)
interleukin 8 receptor, alpha (IL8RA)
interleukin 10 receptor, beta (IL10RB)
interleukin 18 receptor accessory protein (IL18RAP)

8) Platelet related genes

| *PREP#* | Sequence description |
|---|---|
| *PREP113* | platelet factor 4 (chemokine (C-X-C motif) ligand 4) (PF4) |
| *PREP128* | pro-platelet basic protein (PPBP) |
| *PREP153* | platelet-activating factor receptor (PTAFR) |
| *PREP215* | platelet factor 4 variant 1 (PF4V1) |
| *PREP243* | platelet/endothelial cell adhesion molecule (CD31 antigen) |

9) Signal transduction related genes

| *PREP#* | Sequence description |
|---|---|
| *PREP79* | Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6 (ARHGEF6) |
| *PREP81* | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta (IKBKB) |
| *PREP84* | regulator of G-protein signalling 2, 24kDa (RGS2) |
| *PREP100* | rho family, small GTP binding protein Rac2 (RAC2) |
| *PREP103* | ras homolog gene family, member F (in filopodia) (ARHF) |

| | |
|---|---|
| *PREP109* | IQ motif containing GTPase activating protein 1 (IQGAP1) |
| *PREP173* | Rab geranylgeranyltransferase, beta subunit (RABGGTB) |
| *PREP178* | Rho GDP dissociation inhibitor (GDI) alpha (ARHGDIA) |
| *PREP183* | protein tyrosine phosphatase, non-receptor type 6 (PTPN6) |

10) Other immunity related genes

| *PREP#* | Sequence description |
|---|---|
| *PREP66* | lymphocyte adaptor protein (LNK) |
| *PREP69* | T-cell receptor germline gamma-chain (TCRGC1) |
| *PREP70* | lymphocyte cytosolic protein 1 (L-plastin) (LCP1) |
| *PREP78* | colony stimulating factor 3 receptor (granulocyte) (CSF3R) |
| *PREP81* | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta (IKBKB) |
| *PREP88* | defensin, alpha 1 (DEFA1) |
| *PREP89* | selectin L (lymphocyte adhesion molecule 1) (SELL) |
| *PREP90* | granzyme B |
| *PREP93* | hemoglobin, alpha 2 (HBA2) |
| *PREP102* | hemoglobin, beta (HBB) |
| *PREP104* | complement factor D (adipsin) (CFD) |
| *PREP113* | platelet factor 4 (chemokine (C-X-C motif) ligand 4) (PF4) |
| *PREP127* | natural killer-tumor recognition sequence (NKTR) |
| *PREP132* | leukocyte receptor cluster (LRC) member 4 (LENG4) *PREP164* B-cell CLL/lymphoma 6 (BCL6) |
| *PREP168* | Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide (FCER1G) |
| *PREP179* | lymphotoxin beta (TNF superfamily, member 3) (LTB) |
| *PREP185* | leukocyte specific transcript 1 (LST1) |
| *PREP208* | defensin, alpha 3, neutrophil-specific (DEFA3) |
| *PREP209* | granzyme A |
| *PREP223* | immunity associated protein 4 (HIMAP4) |
| *PREP230* | leukocyte immunoglobulin-like receptor |
| *PREP232* | immune associated nucleotide (hIAN7) |
| *PREP235* | hematopoietic cell-specific Lyn substrate 1 (HCLS1) |
| *PREP236* | killer cell lectin-like receptor subfamily B (KLRB1) |
| *PREP238* | pre-B-cell colony enhancing factor 1 (PBEF1) |
| *PREP239* | granzyme H |
| *PREP242* | lymphocyte antigen 75 (LY75) |
| *PREP250* | T-cell leukemia/lymphoma 1A (TCL1A) |
| *PREP256* | toll-like receptor 2 (TLR2) |
| *PREP257* | chemokine (C-C motif) ligand 4 (CCL4) |
| *PREP270* | leukocyte immunoglobulin-like receptor, subfamily B (LILRB2) |
| *PREP274* | putative lymphocyte G0/G1 switch gene (G0S2) |
| *PREP276* | toll-like receptor 8 (TLR8) |
| *PREP282* | killer cell lectin-like receptor subfamily C, member 2 (KLRC2) |

特集　血管炎の診療に役立つ新たな知見

# ANCA関連血管炎に関する疫学*

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**Key Words**：ANCA-associated vasculitis, epidemiology, microscopic polyangiitis

## 抗好中球細胞質抗体(ANCA)関連血管炎の疫学に関する特殊性

関節リウマチ(RA)，全身性エリテマトーデス(SLE)など代表的なリウマチ・膠原病疾患に関して，日本と諸外国との報告と比較すると，同じ分類基準を参考に診断され，細かな程度の差異はあれ，ほぼ同じ範疇の疾患(または疾患群)を対象に分類，診断，治療，研究されてきたと考えられる．これに比べ，ANCA関連血管炎や高安動脈炎・側頭動脈炎などの血管炎に関しては，日本と欧米間に疫学上大きな差異が認められる[1)~5)]．人種(遺伝因子)の差異なのか，環境因子の相違なのか，興味ある問題である．

## ANCA関連血管炎の疫学上の疑問点

海外の論文を読んで気がつくことは，欧米ではウェゲナー肉芽腫症(WG)が多いが，本邦で多く経験するのは，myeloperoxidase(MPO)に対するMPO-ANCAが陽性になる急速進行性糸球体腎炎(RPGN)の病態を伴う腎に限局したANCA関連腎血管炎(RLV：renal limited vasculitis)，または，腎障害および肺胞・腸管出血などの全身の血管炎を伴う顕微鏡的多発血管炎(MPA：microscopic polyangiitis)である．日本でWGの症例を経験することは多くはない．つまり，日本では，MPAがWGよりもより多い．また，検出される抗体は，MPAでは80~90%の症例でMPO-ANCAが陽性であるが，欧米の報告では50~70%に過ぎない．MPA症例のPR-3 ANCA陽性率は日本では7~20%であるが，欧米では，29~50%にPR-3 ANCAが検出される(表1)．

## 疑問点を解くためのアプローチ

2003年の国際血管炎・ANCAワークショップにおいて，著者らは，上述の疑問点を欧州血管炎研究グループ(EUVAS)のメンバーに相談した．

表1　欧米と日本でのANCAの種類・陽性率の差異

| | RPGN | | MPA | |
|---|---|---|---|---|
| | Japan | US & Euro | Japan | US & Euro |
| MPO-ANCA | ~90% | | 79~93% | 50~72% |
| PR-3 ANCA | ~10% | 30~62% | 7~21% | 28~50% |

J Am Soc Nephrol 1996；7：23~32, J Am Soc Nephrol 1998；9：842~52, Kidney Int 2000；57：2195~206, Kidney Int 1998；53：743~53.

* Epidemiology of ANCA-associated vasculitis in Japan.

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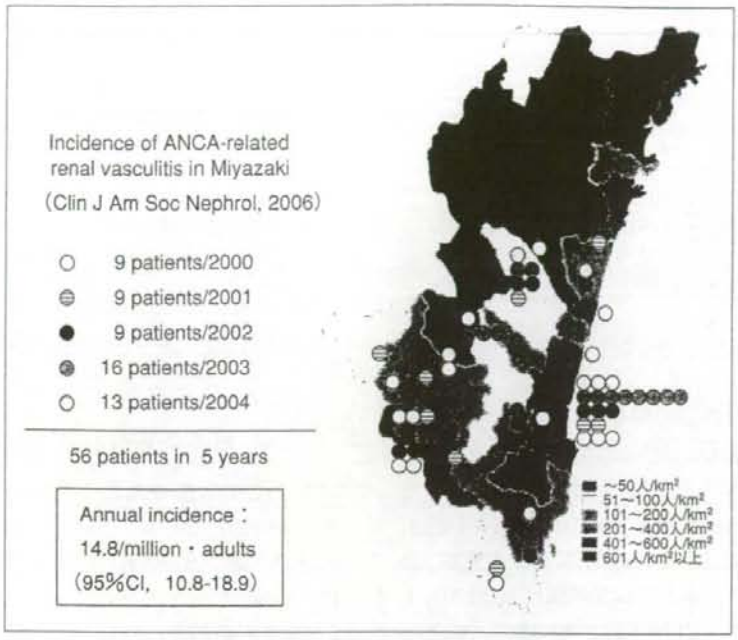


図1　宮崎県のANCA関連腎血管炎の発症率
（藤元昭一先生，布井博幸先生による）

表2　宮崎県と英国(Norwich)のANCA関連腎血管炎の比較(その1)

| | Japan | UK |
|---|---|---|
| male：female | 24：32 | 16：14 |
| mean age(yr) | 70.4 | 64.8 |
| Incidence(/million) | | |
| total | 14.8(10.8-18.9) | 13.9(9.48-19.8) |
| MPA | 14.8(10.8-18.9) | 5.8(3.1-10.0) |
| WG | 0 | 6.3(3.4-10.6) |
| CSS | 0 | 1.4(0.3-3.9) |

その結果，欧州と日本の概念や診断を，互いに理解・協調して問題点を解決する基本方針のもとに，同じ研究方法を用い，日・欧間の相違を解明し，血管炎の臨床・病態・治療に役立たせることを目標に国際協力研究が開始された．また，2001年ヒューマンサイエンス財団から「抗好中球細胞質抗体(ANCA)関連血管炎の本邦・欧州間での臨床疫学調査および診断薬と治療法開発に関する研究」(主任研究者　橋本博史)(2004～2006年)の研究助成を得て，研究班が発足された．

## 日本のANCA関連血管炎の発症率

これまで，厚生労働省血管炎研究班において発表されてきた各疾患の頻度は，同疫学班と共同に行った全国疫学調査結果である．その方法は全国の大きな病床数を有する施設を対象に，血管炎診療に関連ある多数の診療科に依頼したアンケートの集計に基づく．ただし，高安動脈炎は，臨床個人調査票をもとにした数字である．これらは研究班が作成した診断を目的にした「診断基準」に基づいて診断・報告される．1997年の全国疫学調査では，1年間に受診した患者の全国の総数であり，人口100万人あたり，MPA 15.0, WG 2.0, Churg-Strauss syndrome(CSS) 0.8であった[6]．この数字は厳密には異なるが有病率に近い数字であり，方法はa nationwide, retrospective, hospital-based surveyである．これに対して，英国の血管炎の疫学研究者は，住民の移動が非常に少ない地域を対象に，疾患の発症が必ず把握できる医療システムが確立されている地域(条件)で，前向き調査を行うこと(a prospective, population-based survey)が重要であると提唱した．「抗好中球細胞質抗体(ANCA)関連血管炎の本邦・欧州間での臨床疫学調査および診断薬と治療法開発に関する研究」の研究班は，英国の主要研究者とともに，2005年宮崎，沖縄，2006年仙台，盛岡，2007年旭川を訪問し，

表3 宮崎県と英国(Norwich)のANCA関連腎血管炎の比較(その2)

| | Japan | UK |
|---|---|---|
| ENT | 1(1.8%) | 19(63.3%)* |
| Respiratory | 19(33.9%) | 18(60.0%)* |
| Nervous | 3(5.4%) | 10(33.3%)* |
| GIT | 2(3.6%) | 3(10.0%) |
| pANCA/MPO | 51(91.1%) | 15(50.0%)* |
| cANCA/PR3 | 0(0.0%) | 11(36.7%)* |
| Negative ANCA | 5(8.9%) | 4(13.3%) |

* $P<0.001$, $X^2$ test
(藤元先生，布井先生，Drs. Watts RA, Scott DGによる)

拠点病院や関連病院の腎臓医，リウマチ医，呼吸器科医，病理医など多くの関係者からANCA関連血管炎の臨床現場を視察・調査を行った．

宮崎県のretrospective, population-based studyでは，5年間に56名の「ANCA関連腎血管炎」の症例が検出され，成人では1年間に人口100万人あたり14.8名(95%CI 10.8-18.9)の発症率であり，英国Norwichの成人での発症率13.9/100万人/年と大差はなかった(図1，表2)．すなわち，ANCA関連血管炎の発症率は，日本も英国もほぼ同等であることが初めて明らかになった[7]．

## ANCA関連腎血管炎の日英間の臨床の相違

宮崎県のretrospective調査(ANCA関連腎血管炎)の研究結果と同じ診断基準で，同じ5年間に英国Norwichで行ったprospective studyの調査結果を比較・検討した．宮崎では全例がMPAであったが，NorwichではWG, MPA, CSS(それぞれ，6.3, 5.8, 1.4人/100万人)が含まれ，両地域のANCA関連腎血管炎の疾患の頻度の差異が認められた．また，宮崎とNorwichのANCA関連腎血管炎患者のANCAの種類は，MPO-ANCAがそれぞれ91.1% vs. 50.0%，PR-3 ANCAは0% vs. 36.7%と明らかな差異が認められた．英国のANCA関連腎血管炎ではWGの症例が含まれることが理解された．とくに臨床症状の差異において，ENT所見が，日本では1例に対して，英国では19症例に検出された[8](表3)．日本でのANCA関連血管炎の現状を広く伝えるため，英文論文において報告することが重要である[9]．

表4 WGにおける腎合併症の頻度

1. 厚生労働省難治性血管炎研究班(39～63%)
   1988年63%(146症例)，発症時3.5%
   1998年39%(26症例)，発症時14.3%
2. 耳鼻咽喉科の報告(12～40%)
   2002年北大40%(15症例)
   2004年旭川医大12%(16症例)
3. 外国(全経過中)(77%)
   1992年Hoffman 77%(158症例)(初発時15%)
   2000年Gross 77%(70症例)
4. 順天堂大学膠原病内科の結果
   2006年45%(20症例)(1992年からの症例)

## 日本のWGと外国のWG

表1, 2で理解されたことは，外国のWGは腎症が多いことである．これまでの厚生労働省の研究班の2回の報告のWGにおける腎合併症の頻度は，39%，63%であった．また，北海道の耳鼻科2施設からの報告は12%，40%であり，欧米の報告77%(ドイツ)，77%(米)と比べ少ない傾向があった(表4)．上記研究班では，旭川医大の耳鼻科(原淵保明教授)のWGの約30症例の検討を行い，旭川医大の症例では，腎症が少ないこと，PR3-ANCAの陽性率が少ないこと，または陽性であっても抗体価が低い傾向があることが指摘された．この結果，日本では，腎合併症のないlocalized WGが比較的多いことが予想された．わが国では，WGが少なく，理解が少ないため，肺や鼻に肉芽腫病変があっても，MPO-ANCA陽性である理由から，WGであるべき診断がMPAになってしまうことが英国研究者から指摘された．

## 緯度の違いによるMPA, WGの発症率の差異

欧州では，北にWGが，南にMPAが多いことが報告されている(図2，表5)．この理由のひとつに緯度(latitude)による要因が考えられている[10]．3年間での，沖縄，宮崎，仙台，盛岡，旭川の施設を視察した結果，沖縄・宮崎や本州にはWGが非常に少なく，旭川ではWGが比較的多い傾向にあった．実際，北海道の緯度がスペインに相当するため，日本ではWGが少ないことが理解できる．今後のpopulation-based, prospective studyの研究結果を待つ必要がある．

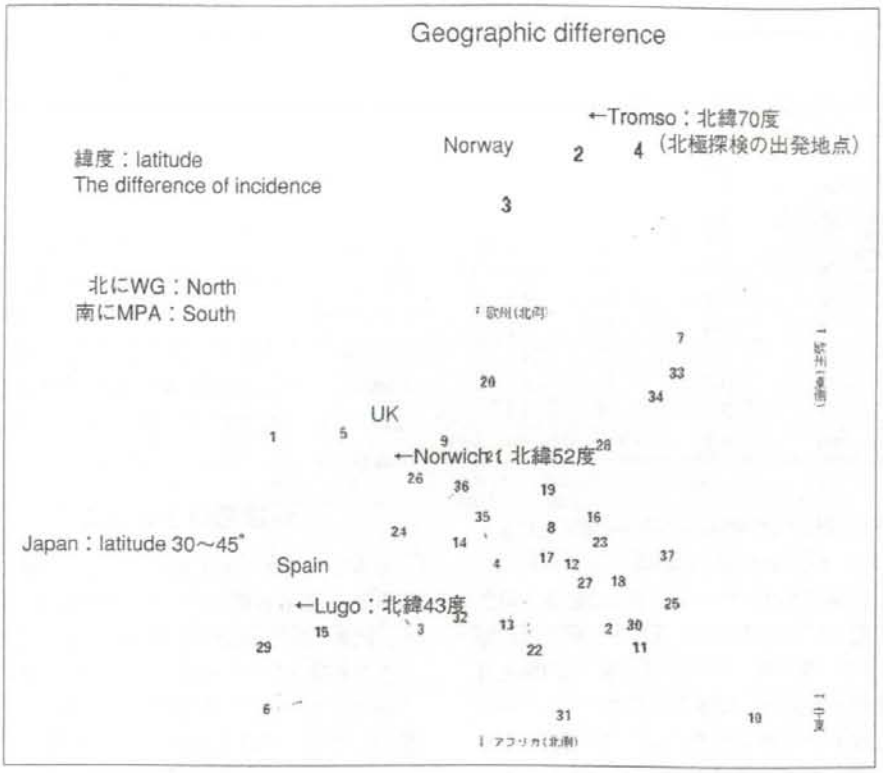


図2　緯度によるANCA関連血管炎の頻度の差異

表5　緯度によるANCA関連血管炎の発症頻度の差異

| | Tromso | Norwich | Lugo | Japan |
|---|---|---|---|---|
| Latitude | 70°N | 52°N | 43°N | 30～45° |
| WG | 10.5 | 10.6 | 4.9 | 2.0 |
| CSS | 0.5 | 3.1 | 0.9 | 0.8 |
| MPA | 2.7 | 8.4 | 11.6 | 15.0 |
| Total（Figure indicates/million） | 13.7 | 18.9 | 18.3 | 18.6 |

日本の数値は年間の受給者数.

厚生労働省の特定疾患受給者の調査(1997年度, 2005年度)では，WGの受給者数と人口比は，北海道に多く(それぞれ，46人，64人；8.1人/100万人，11.4人/100万人)，沖縄県(3人，6人；2.3人/100万人，4.4人/100万人)には少なかったが，人口比では他の地域で高い県も存在した(表6)．沖縄県でのこれまでの調査では，ANCA関連腎炎20/100万人，WG 1/100万人と報告され，本邦においても，南にMPA,北にWGが多い傾向が推定された．また，欧米の報告のように受給者数は増加している(図3)．ANCA関連疾患は比較的高齢者に起こり，多くの合併症を有し，QOLの低下，医療経済の負担の増加など，今後，社会的な問題にかかわることが予想される．このため，早期診断，ガンマグロブリン大量療法[11)12)]のような合併症発症の少ない治療が必要になってくる．

## ANCA関連血管炎の病因

疾患の病因は遺伝因子と環境因子に大きく分けられる．MPAに関して欧米では明らかな関連遺伝因子は報告されていない．わが国では土屋らの多くの報告で，*HLA-DRB1*0901*遺伝子がわが国のMPA症例に優位に検出される[13)]．有村らがそれ以前にHLA-DR9との相関を別個に報告し，*HLA-*

表6 1997年度と2005年度の北海道，東北，宮崎，沖縄，全国のウェゲナー肉芽腫症受給者数と人口比

| 県 | 1997年度 | | 2005年度 | |
|---|---|---|---|---|
| | 受給者数 | 人口100万対 | 受給者数 | 人口100万対 |
| 北海道 | 46 | 8.1 | 64 | 11.4 |
| 青森 | 5 | 3.4 | 9 | 6.3 |
| 岩手 | 7 | 4.9 | 10 | 7.2 |
| 宮城 | 10 | 4.3 | 20 | 8.5 |
| 秋田 | 5 | 4.2 | 15 | 13.1 |
| 山形 | 7 | 5.6 | 10 | 8.2 |
| 福島 | 15 | 7 | 30 | 14.3 |
| 宮崎 | 12 | 10.2 | 10 | 8.7 |
| 沖縄 | 3 | 2.3 | 6 | 4.4 |
| 全国 | 720 | 5.7 | 1,135 | 8.9 |

*DRB1*0901*遺伝子は根拠のある事実と考えられる．人種上の単一性がわが国での利点と考えられる．

一方の環境因子はシリカなど多くの物質を対象に疫学研究が行われている．注目する報告は1995年(平成7年)の阪神・淡路大震災後にMPA患者が多く発症した武曾・猪原らの報告である[14][15]．崩壊したビルや家屋の粉塵によって，MPAが誘発された可能性が考えられる．2001年のアメリカ同時多発テロの後，MPAの発症がどうであったか？2~3のアメリカの研究者に聞いてみたが明らかではなかった．

## ANCA測定試薬の違いによる影響の有無

MPO-ANCAとともに，PR-3 ANCAについても検討し，日欧において使用されているそれぞれ4種類の試薬について，わが国の患者血清を使用し，感度・特異度および試薬間の相関性を検討した．いずれの試薬も感度・特異度に優れ，日欧で使用している試薬間の相関性が確認された(図4)．このため，測定試薬キットに起因する欧州と本邦でのMPO-ANCAおよびPR-3 ANCAにおいても陽性率の差異はないことが明らかになった[16]．

## 今後期待されること

日本の血管炎はANCA関連血管炎に限らず，大型血管炎(高安動脈炎，巨細胞性動脈炎)に関しても，欧米の疫学・臨床・関連遺伝子など，多くの・大きな相違が認められる．このため日本では欧米で決められた基準や概念が当てはまらないことも多い．今回，EUVASのメンバーと国際共同研究を行ったことで，欧米の研究者に日本のANCA関連血管炎の現状が多少なりとも理解されたと考えられた[8][17]．現在，欧州と米国のリウマチ学会が共同で新しい血管炎の定義・分類基準・診断基準の作成のための会議が行われている．

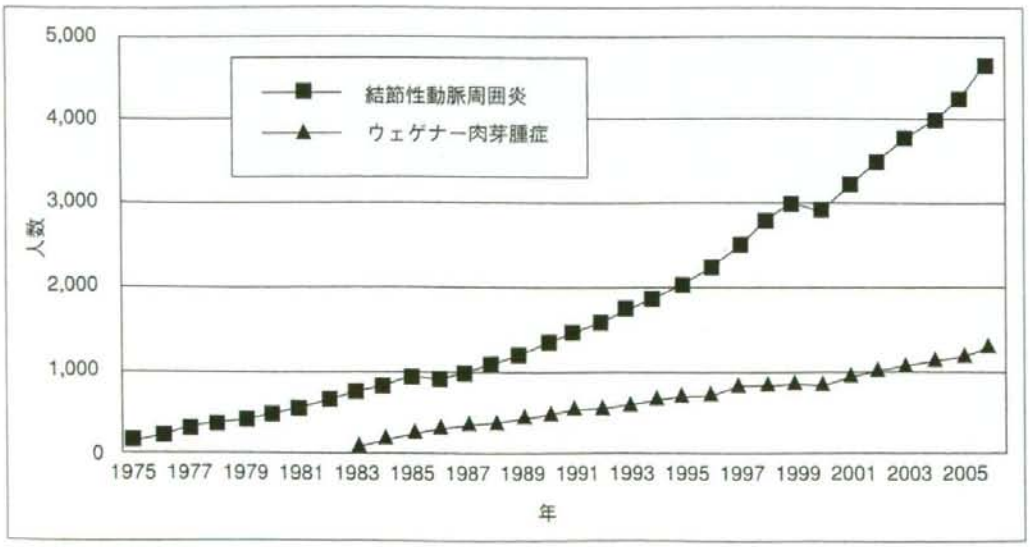


図3 結節性動脈周囲炎，ウェゲナー肉芽腫症の受給者数の推移

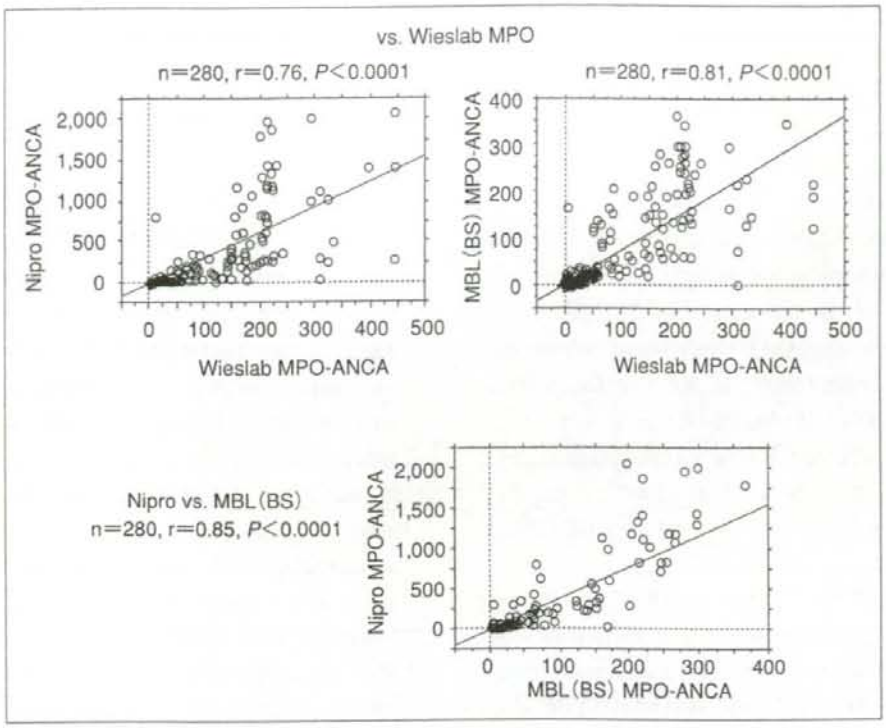


図4　日本と欧州におけるMPO-ANCA測定試薬間の相関性の検討

血管炎は稀な疾患であるため，疫学・病理・臨床(診断・評価法)・治療法の確立など血管炎研究に関して，EUVASの方法のように，日本の研究者による総合的・有機的なネットワークが確立され，欧米との国際共同研究を推進できるシステムづくりが必要と考えられる．

謝辞：「抗好中球細胞質抗体(ANCA)関連血管炎の本邦・欧州間での臨床疫学調査および診断薬と治療法開発に関する研究」(2003～2006)の分担研究者，研究協力者および訪問の際に歓待して頂いた臨床・研究施設の諸先生および本研究を推進・発展，全国視察に参加されたDrs. David Jayne, David Scott, Richard Watts (英国)，Franco Ferrario(イタリア)，Niels Rasmussen (デンマーク)，Ulrich Specks(米国)に深謝致します．

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# Valvular injury in a patient with PR3-ANCA-associated glomerulonephritis

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## SUMMARY

**Background** An 11-year-old boy who had hematuria at a routine health check-up was later diagnosed with proteinase 3 (PR3) antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. Despite treatment with corticosteroids and immunosuppressants, he went on to develop end-stage renal disease. The patient received a renal transplant at the age of 16 years, but relapse of PR3-ANCA-related nephritis to the graft occurred three times. Each relapse was successfully treated with corticosteroids and immunosuppressants. An echocardiogram at the age of 19 years revealed moderate-to-severe aortic regurgitation. The patient died of pneumonia when he was 24 years old. Autopsy revealed a perforation in the noncoronary cusp of the aortic valve and recurrence of crescentic glomerulonephritis in the transplanted kidney.

**Investigations** Physical examinations, urine and blood analyses, renal biopsies, echocardiograms and autopsy.

**Diagnosis** PR3-ANCA-associated glomerulonephritis, recurrence of crescentic glomerulonephritis to the graft, aortic regurgitation and perforation in the noncoronary cusp of the aortic valve.

**Management** Immunosuppressants and corticosteroids.


**KEYWORDS antineutrophil cytoplasmic antibody, endocarditis, glomerulonephritis, proteinase 3, vasculitis**

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**Received** 3 March 2008 **Accepted** 1 August 2008 **Published online** 2 September 2008
www.nature.com/clinicalpractice
doi:10.1038/ncpneph0943

## THE CASE

An 11-year-old boy was found to have hematuria at a routine health check-up. Over the next few weeks, the patient started to suffer from arthralgia, fever, purpura on both legs, and urticaria on the backs of his hands, elbows, feet, knees and thighs (Table 1). Rapid deterioration of his renal function occurred (serum creatinine level was 79.6 μmol/l at initial presentation and had increased to 495 μmol/l 1 month later). Two months after the initial presentation, a renal biopsy revealed crescentic glomerulonephritis. The patient was treated with intravenous steroids and plasma exchange.

When he was 13 years old, the patient was found to have a high serum titer of proteinase 3 (PR3) antineutrophil cytoplasmic antibodies (ANCAs; 24 EU/ml); no myeloperoxidase (MPO)-ANCAs were detected. The patient was diagnosed with PR3-ANCA-associated glomerulonephritis. His renal function improved after treatment with corticosteroids and immunosuppressants (a total of 4 g of cyclophosphamide over 3 months), but it deteriorated with the tapering of the immunosuppressive drugs. The patient was started on continuous ambulatory peritoneal dialysis because of uremia 9 months after the diagnosis of PR3-ANCA-associated glomerulonephritis.

At the age of 15 years, an echocardiogram revealed normal valvular function. When he was 16 years old, the patient received a renal transplant from his father. Graft function was good for 2 years.

Two years after transplantation, the patient was admitted to hospital with a serum creatinine level of 265 μmol/l, and he was treated with ciclosporin, mizoribine and glucocorticoids. The patient's PR3-ANCA titer was 12 EU/ml and a relapse of PR3-ANCA-associated glomerulonephritis was strongly suspected.[1] A renal biopsy of the graft at this time revealed no signs of chronic rejection, but immunofluorescence histochemistry revealed the presence of glomerular crescents with fibrinogen deposition

**Table 1** Summary of events for the main patient presented.

| Events | Patient's age (years) | Serum creatinine level (μmol/l) | ANCA (EU/ml) | Urine dipstick test | Blood pressure (mmHg) | Physical examination | Medications and procedures |
|---|---|---|---|---|---|---|---|
| Initial presentation | 11 | 79.6 | NA | Urinary occult blood (+), urinary protein (+) | NA | Arthralgia, fever, purpura on both legs, and urticaria on the backs of the hands, elbows, feet, knees and thighs | None |
| Deterioration in renal function; renal biopsy | 12 | 495 | NA | NA | NA | NA | Intravenous steroids, plasma exchange |
| Diagnosis of PR3-ANCA-associated glomerulonephritis; uraemia | 13 | 1,432 | 24 | NA | NA | NA | Cyclophosphamide, steroids, CAPD |
| Echocardiography | 15 | 1,335 | NA | NA | NA | NA | Echocardiography |
| Renal transplantation | 16 | 1,432 | NA | NA | 127/90 | No heart murmur | Renal transplantation |
| Relapse and biopsy of the graft | 18 | 265 | 12 | Urinary occult blood (+), urinary protein (+) | 104/58 | Systolic murmur | Gusperimus hydrochloride 300 mg/day, intravenous steroids, ciclosporin 200 mg/day, mizoribine 250 mg/day, oral steroids 5 mg/day |
| Echocardiography | 19 | 97 | <10 | NA | 120/58 | NA | Echocardiography |
| Relapse | 21 | 186 | 14.8 | Urinary occult blood (+), urinary protein (+) | 120/74 | Fever and systolic murmur | Antibiotics, intravenous steroids, two 3-day courses of 1 g/day methylprednisolone, ciclosporin 125 mg/day, mizoribine 250 mg/day; later, prednisolone 15–20 mg every other day |
| Relapse | 23 | 1,432 | 11.7 | Urinary occult blood (+), urinary protein (+) | 132/68 | Fever and systolic murmur | Two pulses of intravenous cyclophosphamide, temporary hemodialysis, ciclosporin 125 mg/day, mycophenolate mofetil 1 g/day, prednisolone 30 mg/day |
| Pneumonia and death | 24 | 159 | NA | NA | 118/42 | NA | Ciclosporin 125 mg/day, mycophenolate mofetil 1 g/day, methylprednisolone 12.5 mg/day, antibiotics |

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CAPD, continuous ambulatory peritoneal dialysis; NA, not available; PR3, proteinase 3.

(crescentic glomerulonephritis). Serum levels of complement components C3 and C4 were within normal ranges. The patient was treated with gusperimus hydrochloride, intravenous steroids, ciclosporin, mizoribine and oral steroids (5 mg/day). An echocardiogram at the age of 19 years revealed a systolic heart murmur caused by moderate-to-severe aortic regurgitation in the region of the tip of the noncoronary cusp.

At the age of 21 years, the patient presented to hospital with macroscopic hematuria and fever (38 °C). His systolic murmur was still present. Repeated blood cultures were negative and antibiotics were ineffective at resolving the patient's fever. A relapse of PR3-ANCA-associated glomerulonephritis was diagnosed, and the patient was given two 3-day courses of 1 g/day methylprednisolone together with mizoribine and ciclosporin; later, prednisolone 15–20 mg every other day was prescribed. High-dose corticosteroid pulse therapy improved the patient's general condition. His serum creatinine level decreased to a normal level and the PR3-ANCAs disappeared.

At the age of 23 years, the patient presented with a fever of 38 °C. He had an increased serum C-reactive protein level of 12.7 mg/dl and a PR3-ANCA titer of 11.7 EU/ml. A transthoracic echocardiogram showed severe aortic

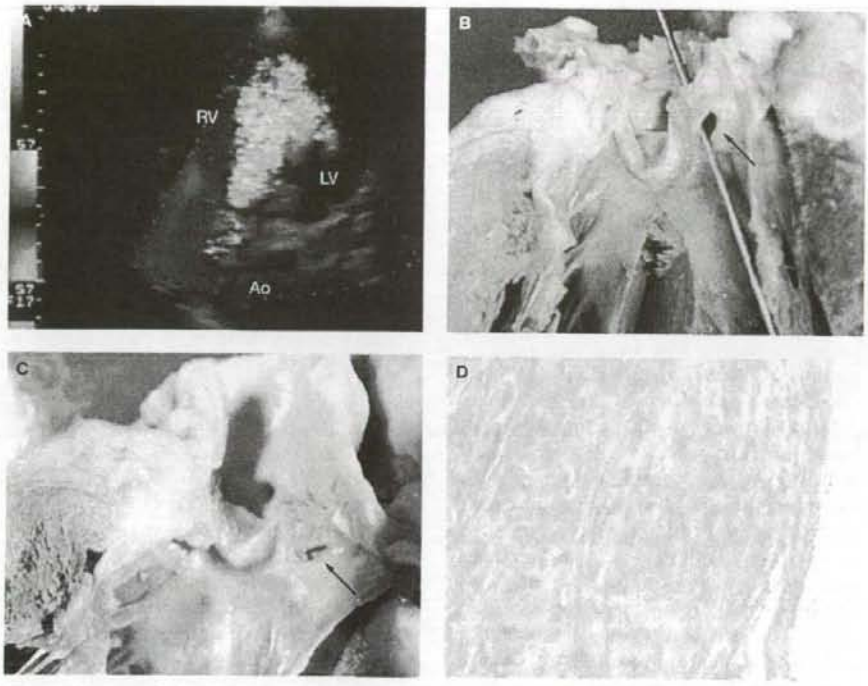


**Figure 1** Images of the aortic valve in the main patient presented. (**A**) Transthoracic echocardiogram 1 year before death showing severe aortic regurgitation. (**B**) Macroscopic view of the aortic valve at autopsy. A perforation in the noncoronary cusp of the aortic valve (arrow) was visualized with a Sonde enteroscope (original magnification ×1). (**C**) Another macroscopic view of the aortic valve at autopsy. The hole in the noncoronary cusp of the aortic valve is indicated by an arrow (original magnification ×1). (**D**) Histology of the resected aortic valve showing fibrosis and scarring (hematoxylin and eosin stain; original magnification ×400). Abbreviations: Ao, aorta; LV, left ventricle; RV, right ventricle.

regurgitation (Figure 1A). Repeated blood cultures were negative, and the patient was treated with immunosuppressants and corticosteroids as well as temporary hemodialysis; this treatment resulted in remission (serum creatinine level 106 μmol/l and a negative PR3-ANCA titer).

The patient started to suffer from respiratory distress due to pneumonia at the age of 24 years. Despite treatment with antibiotics, ciclosporin, mycophenolate mofetil and prednisolone, he died 3 days after hospital admission for pneumonia.

An autopsy revealed a perforation (2 cm in diameter) in the noncoronary cusp of the aortic valve (Figure 1B,C). Histologic analysis revealed moderate calcification, fibrosis and scarring in the aortic valve (Figure 1D). Arteriolosclerosis was prominent in the transplanted kidney, and approximately 20% of the glomeruli in that kidney showed global sclerosis. Segmental sclerosis and fibrous crescents were observed in the remaining glomeruli in the transplanted kidney, which led to a final diagnosis of recurrence of crescentic glomerulonephritis in the transplanted kidney. Since endocardium is one component of cardiac valves, the valvular injury that occurred in the patient presented here can be considered to be a type of noninfective endocarditis.

A further case of the presence of valvular injury and noninfective endocarditis in a patient with PR3-ANCA-associated glomerulonephritis is presented in Box 1 and Figure 2.

## DISCUSSION OF DIAGNOSIS

This report describes two cases of valvular injury associated with noninfective endocarditis in patients with PR3-ANCA-associated

glomerulonephritis. In patients with glomerulonephritis, valvular injury and a strongly positive PR3-ANCA test, two categories of disease should be considered in the differential diagnosis (Table 2).[2] The first category—noninfective endocarditis and/or valvular injury associated with PR3-ANCA glomerulonephritis—is characterized by vasculitis and a strongly positive PR3-ANCA test that is followed by valvular or endocardial disease. The second disease category—infective endocarditis evoking ANCAs—involves infective endocarditis accompanied by valvular disease, which is followed by a gradually increasing positive ANCA test. The differential diagnosis is crucial because the two disease categories require different treatments.

The first disease category, noninfective endocarditis associated with PR3-ANCA glomerulonephritis, consists of several autoimmune or autoimmune-related diseases that can cause valvular disease, including ANCA-associated small-vessel vasculitides such as Wegener's granulomatosis, Churg–Strauss syndrome (CSS) and microscopic polyangiitis. ANCA-associated small-vessel vasculitis affects small vessels such as those in the lung, kidneys and skin. Cardiac involvement—such as myocarditis, endocarditis, valvulitis and pericarditis—was believed to be rare in Wegener's granulomatosis, but it may be more common than originally thought. Estimates of the incidence of cardiac involvement in cases of Wegener's granulomatosis range from 6% to 44%.[3] ANCAs are found in some patients with CSS, a very rare autoimmune disease that has clinical manifestations including asthma, eosinophilia and glomerulonephritis. MPO-ANCAs are the most common ANCA type in CSS, but some patients are positive for PR3-ANCAs. Cardiac diseases such as pericarditis, myocarditis and coronary artery disease are the most common cause of death in patients with CSS. Few cases of endocarditis in patients with CSS have been reported so far.[4]

The second category of disease that should be considered involves infective endocarditis complicated by emerging ANCAs. Nine individuals with infective endocarditis associated with ANCA-associated glomerulonephritis have been described in the literature, seven of whom were positive for PR3-ANCAs[5–10] and two of whom were positive for MPO-ANCAs.[11,12] If an endothelial injury occurs, exogenous microorganisms in the circulation might attach to the injured site, and this attachment might be enough to induce infective endocarditis. An alternative hypothesis is that PR3-ANCAs associated with subacute bacterial endocarditis might be the result of polyclonal B-cell activation. Chronic vascular injury by a bacterial antigen might activate endothelial cells, induce the expression of cytoplasmic enzymes by polymorphonuclear cells and result in the production of ANCAs.[5,9] The etiologies of ANCA-associated diseases are currently unclear, but possibilities other than infection that are currently under investigation include silica exposure, certain medications and genetic factors.[13]

A review of the literature reveals reports of 15 patients with PR3-ANCA-associated glomerulonephritis who developed noninfective endocarditis with valvular disease.[2,14–24] To the best of our knowledge, there are no reported cases of patients with MPO-ANCA-associated glomerulonephritis who developed endocarditis. Some cases of valvular disease preceded by a high PR3-ANCA titer have been diagnosed as infective endocarditis without confirmation of the presence of a microorganism infection. Blood-culture-negative infective endocarditis has been reported to occur in approximately 20% of patients with infective endocarditis.[25] In patients with blood-culture-negative infective endocarditis, it could be speculated that the bacterial infection might not cause the endocarditis or the valvular injury, but that the ANCA-related

**Box 1** Endocardial injury in a second patient with proteinase 3 (PR3) antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis.

A 67-year-old man with stage 1b gastric cancer and impaired renal function (serum creatinine level 256 μmol/l) was diagnosed with PR3-ANCA-associated glomerulonephritis. Despite treatment with plasma exchange and oral corticosteroids, the patient's PR3-ANCA titer remained positive, fluctuating between approximately 40 EU/ml and 200 EU/ml. After distal gastrectomy for his gastric cancer, the patient's PR3-ANCA titer ranged from 16 EU/ml to 46 EU/ml over 9 months of treatment with 10 mg/day of oral corticosteroids. Eight months after distal gastrectomy, the patient developed what was initially thought to be blood-culture-negative infective endocarditis. Antibiotics were administered, but the patient was eventually diagnosed with noninfective endocarditis. Repeated echocardiograms demonstrated severe aortic and mitral regurgitation, and mobile vegetation on the left coronary cusp of the aortic valve and on both leaflets of the mitral valve (Figure 2A,B). One month later, the patient underwent aortic and mitral valve replacement. Vegetations were attached to the left ventricle side of all three aortic valve cusps (Figure 2C). A large vegetation was present on the anterior mitral leaflet, and a perforation was present in the center of the anterior mitral leaflet. Pathological examination of the resected aortic valve revealed increased fibrous tissue and inflammatory cell infiltration, dominated by neutrophils (Figure 2D).

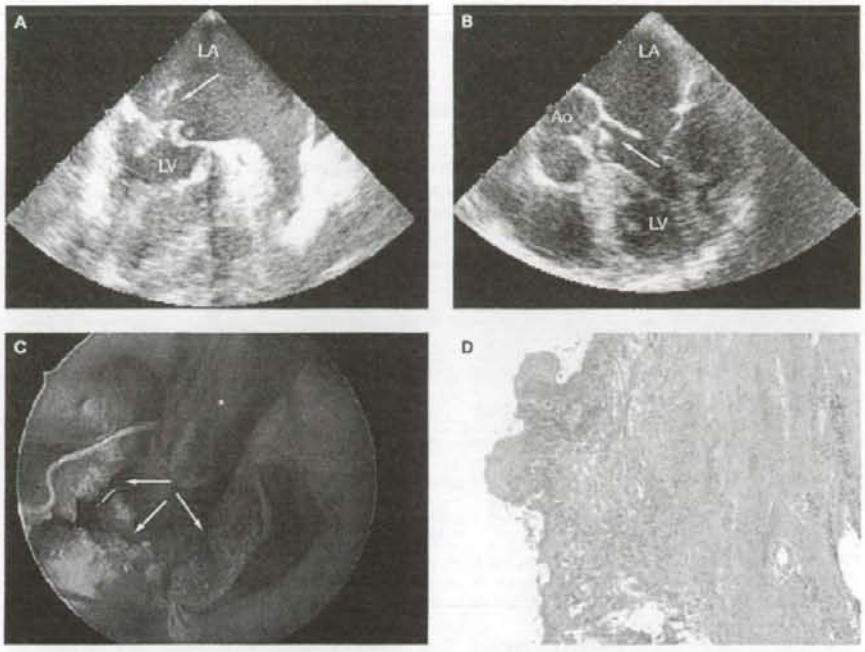


**Figure 2** Images of the cardiac valves in a second patient with PR3-ANCA-associated glomerulonephritis (see Box 1). (**A**) Transesophageal echocardiogram of the mitral valve. The arrow indicates vegetation attached to mitral valve. (**B**) Transesophageal echocardiogram of the mitral and aortic valves. The arrow indicates vegetation attached to the aortic valve. (**C**) Endoscopic view of the aortic valve during surgery showing vegetation (arrows) attached to the aortic valve. The asterisk indicates a suction instrument. (**D**) Histology of the resected aortic valve. Inflammatory cell infiltration can be seen in the perivascular area, consistent with a diagnosis of vasculitis (hematoxylin and eosin stain; original maginification ×400). Abbreviations: ANCA, antineutrophil cytoplasmic antibody; Ao, aorta; LA, left atrium; LV, left ventricle; PR3, proteinase 3.

vasculitis might be primarily responsible for the damage. An alternative explanation is that the jet stream of blood created by the valvular disease damages the endocardium of the heart; such damage might be augmented by detrimental effects of PR3-ANCAs.

In the main case presented here, the injury to the aortic valve occurred in the noncoronary cusp. Of the three aortic cusps, the noncoronary cusp might be the most susceptible to damage. The endocardium is one component of cardiac valves, which are located in a hypovascular area. Whether or not the affected site in vasculitis extends to this hypovascular area is unclear. It might, therefore, be unreasonable to suggest that vasculitis occurs at cardiac valves, but it is difficult to explain the presence of valvular disease in rheumatic fever or Kawasaki disease if the hypovascular area is not thought to be the target site of vasculitis. A recent paper reported that the hypovascularity of cardiac valves is abrogated in a number of valvular heart diseases, including infective endocarditis, rheumatic heart disease and atherosclerosis.[26] If we consider the hemodynamics of the heart, blood is pumped from the left-sided heart chambers at a higher pressure than is blood from the right-sided chambers, and, therefore, the valvular surfaces and the surrounding endocardium in the left side of the heart are more likely to become damaged than those on the right. If the surface of either the aortic or the mitral valve is injured, the site needs to be repaired. *In vitro* experiments have shown that the expression of cell surface adhesion molecules such as CD14 and CD18 on monocytes is upregulated

**Table 2** Differences between noninfective endocarditis associated with PR3-ANCA glomerulonephritis and infective endocarditis evoking ANCAs.

| | Noninfective endocarditis associated with PR3-ANCA glomerulonephritis | Infective endocarditis evoking ANCAs |
|---|---|---|
| Clinical findings | | |
| Heart sounds | Aortic valve stenosis or aortic valve stenosis and regurgitation | Mitral valve stenosis or aortic valve stenosis |
| Fever | High fever | High fever |
| Cutaneous symptoms | Splinter hemorrhages | Splinter hemorrhages, Osler's nodes |
| General condition | Malaise, weight loss | Malaise, weight loss |
| Hematuria | Common | Common |
| Renal insufficiency | Common | <15% of cases |
| Anemia | Common | 70–90% of cases |
| Presence of PR3-ANCA in the literature | 15 out of 15 reported cases | 7 out of 9 reported cases |
| Presence of MPO-ANCA in the literature | 0 out of 15 reported cases | 2 out of 9 reported cases |
| Bacterial culture | Negative | Positive |
| Pathological features of cardiac involvement | Mainly affects the aortic valve<br>Increased fibrous tissue and inflammatory cell infiltration | Aortic valve is more commonly affected than the mitral valve<br>Verrucous vegetations from bacteria or thrombi |
| Treatment | Corticosteroids and immunosuppressants; valve-replacement surgery is sometimes required | Penicillin G and aminoglycosides<br>Surgery to repair or replace damaged valves, remove vegetations, or drain abscesses |

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

in the presence of ANCA.[27] Monocytes in the peripheral blood or valves of patients who are ANCA-positive might, therefore, play a role in valvular destruction via CD14-related and CD18-related mechanisms.

## TREATMENT AND MANAGEMENT

The presenting symptoms of noninfective endocarditis associated with PR3-ANCA glomerulonephritis and those of infective endocarditis are similar: fever, malaise, weight loss, elevated C-reactive protein level and leukocytosis. Treatment of noninfective endocarditis associated with PR3-ANCA glomerulonephritis involves immunosuppression with corticosteroids and other immunosuppressants, whereas treatment of infective endocarditis requires antibiotics and valve-replacement surgery. Leaving infective endocarditis untreated (without antibiotics) is always fatal; however, blood culture tests are negative in some patients with this disease. Clearly, differentiation between the two diseases is very important.

In the main case presented here, PR3-ANCA-associated glomerulonephritis was severe and persistent even after renal transplantation. Such long-lasting positivity for PR3-ANCAs might be a risk factor for endocardial or valvular injury. The patient was treated with corticosteroids and immunosuppressants to treat the PR3-ANCA-associated nephritis, and his cardiac valves were monitored with echocardiography. Much earlier monitoring of the patient's cardiac valves and total elimination of PR3-ANCAs should have been the priority of treatment rather than just suppression of the PR3-ANCAs to a low positive titer. Maintenance drug therapy with corticosteroids and immunosuppressants may be necessary for patients even after the elimination of PR3-ANCAs. In addition, valvular repair surgery at an early stage would have been a useful approach. This surgery should be considered not only in patients with infective endocarditis (who must also receive antibiotics), but also in those with noninfective endocarditis who have massive valvular damage.

**Acknowledgments**
This paper was supported in part by a Health and Labor Science Research Grant from the Japanese Ministry of Health, Labor and Welfare.

**Competing interests**
The authors declared no competing interests.

## CONCLUSIONS

In conclusion, a diagnosis of endocarditis should be considered in patients with PR3-ANCA-associated glomerulonephritis who develop a heart murmur. Careful auscultation and echocardiography are helpful for diagnosing endocarditis in such patients and should be performed routinely.

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