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REVIEW

Cytokine gene polymorphism in human disease: on-line databases, Supplement 1

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Introduction

Genes and Immunity has previously published a systematic review of cytokine gene polymorphism in human disease.[1] The purpose of the present supplement is to update the entries for cytokine gene polymorphisms, *in vitro* expression studies, and *in vivo* disease association studies. Tabulated data from the original review and this supplement are reproduced in tandem as on-line databases, available in the public domain on the *Genes and Immunity* application web site, http://www.pam.bris.ac.uk/services/GAI/cytokine4.htm. The web site version of the databases contains a complete, amalgamated version of the tabulated data from the original review and the present supplement. This supplement contains only information on new or amended entries.

The web pages have been completely revised and contain the following new features:

- A permanent navigation bar providing instant access to all pages.
- Reference links: clicking on individual references now displays full details of authors, Journal and, where issued by MEDLINE, the abstract from the manuscript (Figure 1).
- Nucleotide sequence alignment links: clicking on relevant buttons in the 'Gene' column on the 'List of Polymorphisms' page will display a preview of downloadable MACAW files, enable downloading of the MACAW raw data files, or display an ASCII (DOS) annotated text version of the MACAW file (Figure 2). For details on using MACAW alignment files, see Bidwell *et al*[2], visit the web site, http://www.pam.bris.ac.uk/services/cytokine2.htm, and see the 'File Downloads' page, http://www.pam.bris.ac.uk/services/GAI/cytokine4.htm
- Updated cytokine web links.

We are aware that certain entries are absent from the present version of the Tables. Since we use Medline as a primary data source, it is not possible to include entries which have not yet appeared on Medline. Further, we have set a requirement to issue our interpreted conclusions from each manuscript. Where these manuscripts are difficult to obtain there will be an inevitable time lag between appearance on Medline and entry into the Tables. Nevertheless, to assist in dissemination of awareness about such manuscripts, we have included as many as possible in the 'Stop Press' page on the new web site. As more complete information comes to hand, these entries will be transferred to the main Tables.

Because of the rapidly growing number of entries in the 'disease association' Tables, these have been divided into two pages on the web site, those associated with TNFα and/or LTα polymorphisms, and others.

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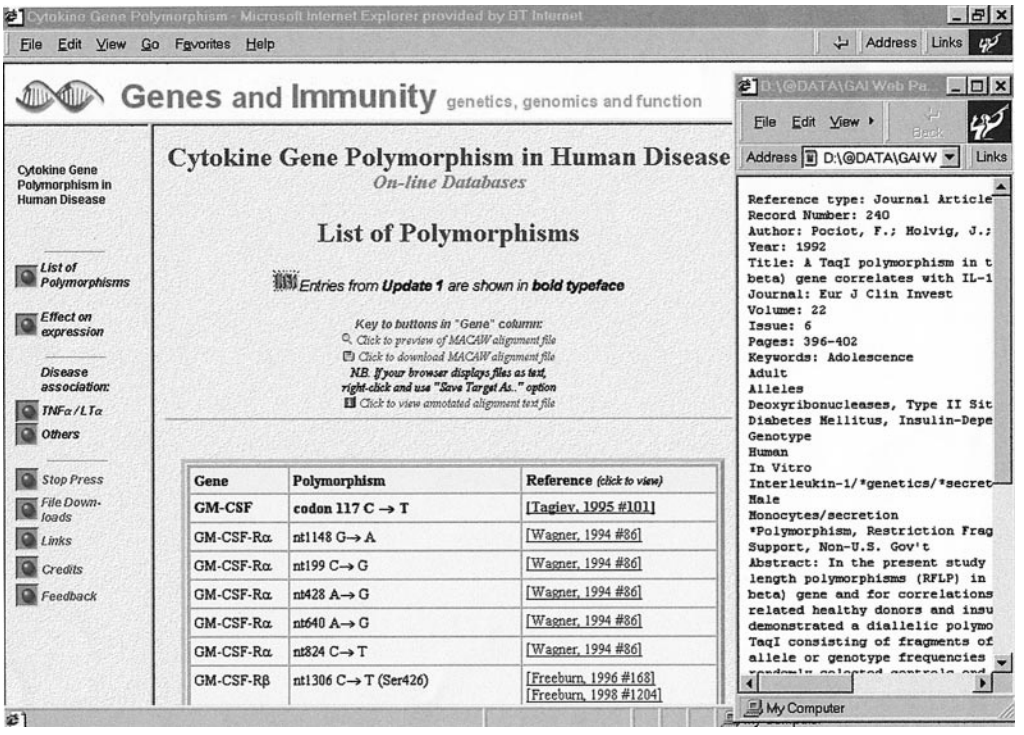

Figure 1 Screenshot from 'List of Polymorphisms' page on the Cytokine Gene Polymorphism in Human Disease web site, showing example of a window obtained following clicking on an individual reference link.

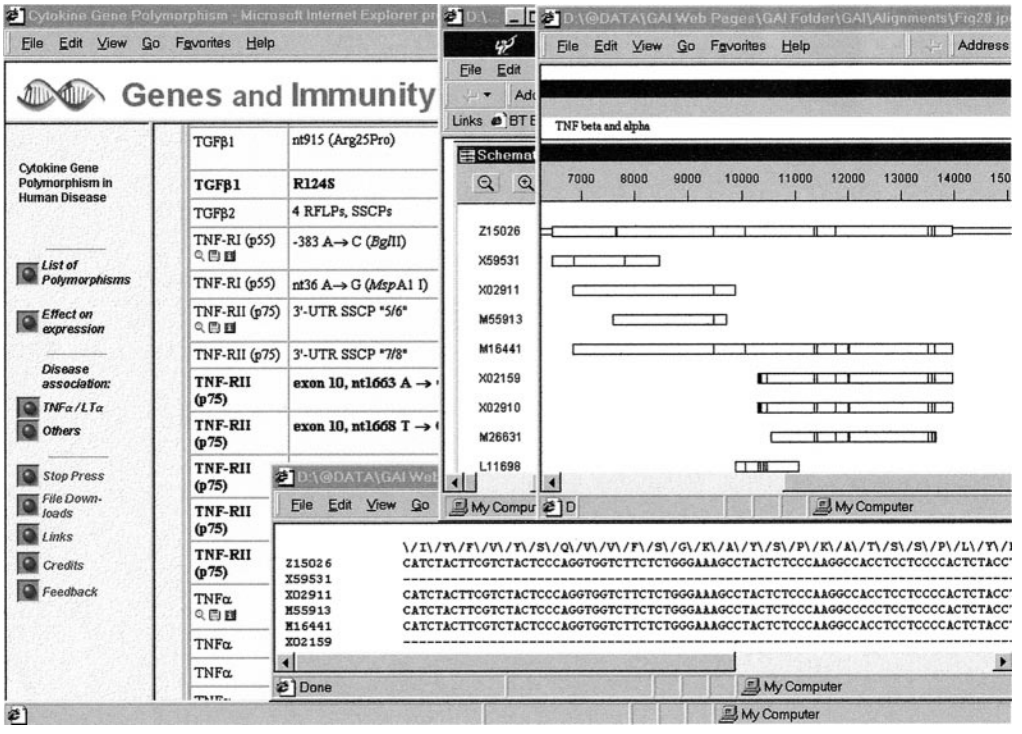

Figure 2 Screenshot from 'List of Polymorphisms' page on the Cytokine Gene Polymorphism in Human Disease web site, showing an example of a MACAW nucleotide sequence alignment window and its associated annotated text file window, obtained following clicking on relevant buttons beneath the gene name.

Table 1 List of human cytokine gene polymorphisms. Revisions to previous entries are shown in bold typeface. Entries for the *IFNA* gene family have been expanded for this supplement

Gene	*Polymorphism*	*Reference*
GM-CSF	codon 117 C → T	3
IFNα (*IFNA10*)	nt1265 A → C	4
IFNα (*IFNA10*)	nt991 (60*) T → A Cys20Stop (*Sau*3AI)	4; 5
IFNα (*IFNA17*)	nt1101 (170*) A → C	4, unconfirmed 5
IFNα (*IFNA17*)	nt1453 C → T	4
IFNα (*IFNA17*)	nt1482 (551*) T → G Ile 184Arg (*SSp* I RFLP)	4; 5
IFNα (*IFNA17*)	nt171insA (*Nla* III RFLP)	5
IFNα (*IFNA2*)	nt1068 G → A	4, unconfirmed 5
IFNα (*IFNA2*)	nt1101 G → A	4, unconfirmed 5
IFNβ	nt153 C → T	5
IFNγ	–333 C → T	6
IL-12 (p35)	–916 C → T	7
IL-12 (p40)	–1287 G → T	7
IL-13	–1055 C → T	8; 9
IL-13	additional Gln residue, position 98	10
IL-13Rα	+1050 C → T	11
IL-1Ra	nt1731 G → A	12
IL-1Ra	nt1821 G → A	12
IL-1Ra	nt1868 A → G	12
IL-1Ra	nt1887 G → C	12
IL-1Ra	nt1934 T → C	12
IL-1β	nt3263 C → T	12
IL-2	exon 1 nt742 T → G	13
IL-4	+33 C → T	14
IL-4	–34 C → T	15
IL-4	–524 C → T	16
IL-4	intron 2 dinucleotide repeat	17
IL-4Rα	nt1124 A → C (**E375A**)	18; 19
IL-4Rα	nt1216 T → C (**C406R**)	18; 19
IL-4Rα	nt148 A → G (**I50V**)	18; 19
IL-4Rα	nt1682 T → C (S478P) (previously S503P)	18–20
IL-4Rα	nt1902 G → A (**R551Q**) (previously R576Q)	19; 21
IL-4Rα	nt2281 T → C (**S761P**)	18; 19
IL-6	–572 G → C	22
IL-6	–597 G → A	22
RANTES	–28 C → G	23
RANTES	–403 A → G	24
TGF-β1	R124S	25
TNF-RII (p75)	exon 10, nt1663 A → G	26
TNF-RII (p75)	exon 10, nt1668 T → G	26
TNF-RII (p75)	exon 10, nt1690 C → T	26
TNF-RII (p75)	exon 6, M196R	27
TNF-RII (p75)	exon 6, nt676 C → T	26

Table 2 *In vitro* expression studies

Gene	*Polymorphism and allele (or haplotype)*	*Expression*	*Reference*
IFNγ (CA)n intron 1	all alleles	no effect	28
IFNγ (CA)n intron 1	allele 2	increased	29
IL-10	–1082A, –819T, –592A haplotype	decreased	30
IL-10	–1082G, –819C, –592C haplotype	increased	30; 31
IL-13	–1055 T	increased	8
IL-1Ra	intron 2 86bp VNTR (allele 2)	decreased	32
IL-6	3′ (AT)-rich minisatellite (790, 792, 808 and 820bp alleles)	increased	33
IL-6	–597A, –572G, $-373A_8/T_{12}$, –174G haplotype	decreased	22
IL-6	–597G, –572G, $-373A_9/T_{11}$, –174G haplotype	increased	22
TNFα microsatellite	A*13*	decreased	34
TNFα microsatellite	*a2* and *a9*	increased	34
TNFα	–308 (TNF2)	increased	35; 36; 37
TNFα	–308 (TNF2)	no effect	38
TNFα	–863 A	decreased (31%)	39

Table 3 *In vivo* disease association studies

Cytokine and polymorphism	*Disease*	*Association*	*Reference*
IFNα (GT)n allele 02	Multiple sclerosis	yes (protection)	5
IFNα (GT)n allele 07	Multiple sclerosis	yes (susceptibility)	5
IFNα (*IFNA10)* nt991 (60*) T → A Cys20Stop (*Sau*3A I)	Multiple sclerosis	no	5
IFNα (*IFNA17*) nt1482 (551*) T → G Ile184Arg (*Ssp* I RFLP)	Multiple sclerosis	no	5
IFNα (*IFNA17*) nt171insA (*Nla* III RFLP)	Multiple sclerosis	yes (susceptibility)	5
IFNβ nt153 C → T	Multiple sclerosis	no	5
IFNγ (CA)n Intron 1	Lung allograft fibrosis	yes	40
IFNγ (CA)n Intron 1	Multiple sclerosis	no (Europeans)	41
IFNγ –333 C → T	Multiple sclerosis	no	6
IFNγ-R1 (Val14Met)	SLE	yes	42
IFNγ-R1 Met14/Val14 genotype and IFNγ-R2 Gln64/Gln64 genotype	Systemic lupus erythematosus	yes (development)	43
IL-10 –1082	Psoriasis	no	44
IL-10 –1082	Rheumatoid arthritis	no	45
IL-10 –1082	Type I autoimmune hepatitis	no	46; 47
IL-10 –1082 A	Epstein–Barr virus infection	yes (susceptibility)	48
IL-10 –1082 G	Inflammatory bowel disease	yes (decreased frequency)	49
IL-10 –1082 G	Ulcerative colitis	yes (decreased frequency)	49
IL-10 –1082, –819, –592 haplotypes	Multiple sclerosis	no	50; 31
IL-10 –1082A, –819T, –592A haplotype	Juvenile rheumatoid arthritis	yes (involvement of >4 joints)	51
IL-10 –1082A, –819T, –592A haplotype	Response of chronic hepatitis C to IFNα therapy	yes (improved response)	52
IL-10 –592	Type I autoimmune hepatitis	no	46; 47
IL-10 –819	Type I autoimmune hepatitis	no	46; 47
IL-10*G* microsatellite (alleles 12–15)	HLA-identical bone marrow transplantation	yes (increased Graft-versus-Host disease)	53
IL-13 –1055 C → T	asthma	yes	8
IL-1Ra intron 2 86bp VNTR	Corneal melting in systemic vasculitis	no	54
IL-1Ra intron 2 86bp VNTR (A1/A2 genotype)	Perinuclear ANCA ulcerative colitis	yes	55
IL-1Ra intron 2 86bp VNTR	Rheumatoid arthritis	no	45
IL-1Ra intron 2 86bp VNTR	Type I autoimmune hepatitis	no	46; 47
IL-1Ra intron 2 86bp VNTR (A1 allele)	Multiple sclerosis	yes	56
IL-1Ra intron 2 86bp VNTR (A1A1/A3 alleles)	Osteoporosis	yes	12
IL-1Ra intron 2 86bp VNTR (A2 allele)	Ischaemic heart disease	no	57
IL-1Ra intron 2 86bp VNTR (A2 allele)	Multivessel coronary disease	no	58
IL-1Ra intron 2 86bp VNTR (A2 allele)	Severe sepsis	yes	59
IL-1Ra intron 2 86bp VNTR (A2 allele)	Single-vessel coronary disease	yes	58
IL-1Ra intron 2 86bp VNTR (A2 allele)	Systemic lupus erythematosus	yes (in LD with HLA DR17, DQ2)	60
IL-1Ra intron 2 86bp VNTR (A2 allele)	Tuberculin (Mantoux) reactivity	yes (reduced)	61
IL-1Ra intron 2 86bp VNTR (A2 allele)	Ulcerative colitis	no (Spaniards)	62
IL-1Ra intron2 86bp VNTR (A2 allele)	Ulcerative colitis	yes	32
IL-1Ra intron 2 86bp VNTR (A2 allele)	*Ureaplasma urealyticum* vaginal colonization	yes (negative association)	63
IL-1Ra intron 2 86bp VNTR (A2 allele)	Vulvar vestibulitis	yes	64
IL-1Ra intron 2 86bp VNTR (A2 allele) and IL-1β +3953 (allele 2)	Multiple sclerosis	yes (progression)	65
IL-1Ra intron 2 86bp VNTR A2(–)/IL-1β +3953 A1(+)	Tuberculous pleurisy	yes	61
IL-1α (CA)n intron 5	Juvenile chronic arthritis	no	66
IL-1α – 889	Juvenile chronic arthritis	no	66
IL-1α –889	Single and multivessel coronary disease	no	58
IL-1β +3953 (nt5887) C → T (*Taq*I)	Adult periodontitis	yes	67
IL-1β +3953 (nt5887) C → T (*Taq*I)	Alopecia areata	yes (in combination with KM loci)	68
IL-1β +3953 (nt5887) C → T (*Taq*I)	Severe sepsis	no	59
IL-1β +3953 (nt5887) C → T (*Taq*I)	Single and multivessel coronary disease	no	58

Continued

Table 3 *Continued*

Cytokine and polymorphism	*Disease*	*Association*	*Reference*
IL-1β +3953 (nt5887) C → T (*Taq*I)	Type I autoimmune hepatitis	no	46; 47
IL-1β +3953 (nt5887) C → T (*Taq*I)	Wegener's granulomatosis	no	69
IL-1β +3953 (nt5887) C → T (*Taq*I): T allele	Rheumatoid arthritis	yes (predictive of erosive disease)	45
IL-1β –511	Rheumatoid arthritis	no	45
IL-1β –511	Single and multivessel coronary disease	no	58
IL-1β –511 G → A (*Ava*I) and +3953 (nt5887) C → T (*Taq*I)	Inflammatory bowel disease	yes	70
IL-1β –511 (Allele 1), IL-1α –889 (allele 2), IL-1Ra intron 2 86bp VNTR (allele 1) haplotype	Schizophrenia	yes	71
IL-4 –590	Rheumatoid arthritis	no	45
IL-4 – 590 C → T (*Bsm*FI)	IgE levels	no	72
IL-4 intron 2 dinucleotide repeat	IgE levels	no	72
IL-4 intron 2 dinucleotide repeat	Minimal change nephropathy	no	73
IL-4 Intron 3, 70bp VNTR (RP1 allele)	Rheumatoid arthritis	yes	45
IL-4Rα nt148 A → G (I50V)	Atopy/asthma	no	74
IL-4Rα nt1902 G → A (R551Q, previously R576Q)	Atopic disease/asthma	no (Japanese)	75
IL-4α nt1682 T → C (S478P) (previously S503P)	Atopy/asthma	yes	20
IL-4Rα nt1902 G → A (R551Q) (previously R576Q)	Atopy/asthma	yes	20; 76
IL-4Rα nt1902 G → A (R551Q, previously R576Q)	Minimal change nephropathy	no	73
IL-6 (CA)n repeat (allele 1)	Female menopause	yes (bone mineral density)	77
IL-6 –174 G → C (*Nla*III)	Alzheimer's disease	no	78
IL-6 –174 G → C (*Nla*III)	Myasthenia gravis	no	79
IL-6 –174 G → C (*Nla*III)	Systemic lupus erythematosus	no	33
IL-6 –174 G → C (*Nla*III) G allele	Lipid abnormalities	yes	80
IL-6 3′ (AT)-rich minisatellite	Myasthenia gravis	no	79
IL-6 3′ (AT)-rich minisatellite (⩽792bp allele)	Systemic lupus erythematosus	yes (susceptibility: Caucasians and African-Americans)	33
IL-6 3′ (AT)-rich minisatellite (796bp and 828bp alleles)	Systemic lupus erythematosus	yes (protection: Caucasians)	33
IL-6 3′ (AT)-rich minisatellite (808bp and 820bp alleles)	Systemic lupus erythematosus	yes (susceptibility: Caucasians)	33
IL-6 3′ (AT)-rich minisatellite (828bp allele)	Systemic lupus erythematosus	yes (protection: African-Americans)	33
IL-6 3′ (AT)-rich minisatellite and IL-6 –174 G → C (*Nla*III) haplotype	Alzheimer's disease	yes	78
LTα (TNFβ) *Asp* HI	Cardiac transplant rejection	no	81
LTα (TNFβ) intron 1 *Nco*I RFLP (2/2 genotype)	Atopic asthma	yes (females)	82
LTα (TNFβ) intron 1 *Nco*I RFLP	Bronchial hyperreactivity in asthma	no	83
LTα (TNFβ) intron 1 *Nco*I RFLP	Cardiac transplant rejection	no	81
LTα (TNFβ) intron 1 *Nco*I RFLP	Pancreatic cancer	no	84
LTα (TNFβ) intron 1 *Nco*I RFLP	Primary sclerosing cholangitis	no	85
LTα (TNFβ) intron 1 *Nco*I RFLP	Sarcoidosis	no	86
LTα (TNFβ) intron 1 *Nco*I RFLP	Severe posttraumatic sepsis	yes	87
LTα (TNFβ) intron 1 *Nco*I RFLP	Severe sepsis	yes (non-survival)	59
LTα (TNFβ) intron 1 *Nco*I RFLP	Systemic scleroderma	yes	88
LTα (TNFβ) intron 1 *Nco*I RFLP	Wegener's granulomatosis	no	69
LTα (TNFβ) intron 1 *Nco*I RFLP (Allele 1)	Myasthenia gravis (early onset)	yes	89
TGFβ1 –509	Plasma levels of TGFβ1	yes	90
TGFβ1 –800	Plasma levels of TGFβ1	yes	90
TGFβ1 nt915 (Arg25Pro)	Hypertension	yes	91
TNF*a* microsatellite	Cardiac transplant rejection	no	81
TNF*a* microsatellite	Multiple sclerosis	yes (118bp allele)	92
TNF*a1* and *a7* microsatellite	Basal cell carcinoma	yes	93
TNF*a10* microsatellite	*Helicobacter pylori*-associated duodenal ulcers	yes (males: negative association)	94
TNF*a10b4* microsatellite	Multiple sclerosis	yes	95
TNF*a11b4* microsatellite	Multiple sclerosis	yes	95
TNF*a11* microsatellite	Rheumatoid arthritis (severity)	yes (in LD with HLA-DRB1)	96
TNF*a1b5* microsatellite	Multiple sclerosis	yes	95
TNF*a2b4d5* microsatellite	Basal cell carcinoma	yes	93

Continued

Table 3 *Continued*

Cytokine and polymorphism	*Disease*	*Association*	*Reference*
TNF*a6* microsatellite	*Helicobacter pylori*-associated gastric ulcers	yes (females: negative association)	94
TNF*a9* microsatellite	Insulin-dependent diabetes mellitus (early onset)	yes	34
TNF*a6* microsatellite	Rheumatoid arthritis	yes (with HLA-DRB1 shared epitope)	97
TNF*c* microsatellite	Rheumatoid arthritis	yes	98
TNF*d* microsatellite	Multiple sclerosis	no	92
TNF*d3d3* microsatellite	HLA-identical bone marrow transplantation	yes (early mortality)	53
TNF*d4 and d6* microsatellite	Basal cell carcinoma	yes	93
TNF-RII (p75) exon 6, M196	Systemic lupus erythematosus	no	99
TNF-RII 196R	SLE (Japanese)	yes	27
TNFα –1031	HTLV-1 uveitis	yes	100
TNFα –1031	Kawasaki disease	no	101
TNFα –1031 (C allele)	Crohn's disease	yes	102
TNFα –1031 (C allele)	Systemic juvenile chronic arthritis	yes	103
TNFα –1031C, –863A haplotype	Insulin-dependent diabetes mellitus	no	104
TNFα –238	Cardiac transplant rejection	no	81
TNFα –238	Kawasaki disease	no	101
TNFα –238	Primary sclerosing cholangitis	No	85
TNFα –238	Psoriasis	yes (males)	44
TNFα –238	Type I autoimmune hepatitis	no	46; 47
TNFα –238 (A allele)	ankylosing spondylitis	yes (via LD with HLA-B27)	105
TNFα –308	Atopic asthma	no	82
TNFα –308	Body fat content	yes (AA genotype)	106
TNFα –308	Bronchial hyperreactivity in asthma	yes, via LD with HLA?	83
TNFα –308	Cardiac transplant rejection	no	81
TNFα –308	Chronic lymphocytic leukaemia	no	107
TNFα –308	Chronic obstructive pulmonary disease	no	108
TNFα –308	Corneal melting in systemic vasculitis	no	54
TNFα –308	Hepatitis C-related liver failure	yes (TNF2)	109
TNFα –308	Hodgkin's disease	no	107
TNFα –308	Idiopathic dilated cardiomyopathy	no (TNF2)	110
TNFα –308	Infant malarial infection and morbidity	no	111
TNFα –308	Kawasaki disease	no	101
TNFα –308	Pancreatic cancer	no	84
TNFα –308	Polycystic ovaries	no	112
TNFα –308	Primary sclerosing cholangitis	yes (in LD with HLA-B8)	85
TNFα –308	Sarcoidosis	no	86
TNFα –308	Septic shock	yes	113
TNFα –308	System lupus erythematosus	yes (TNF2+ genotypes independent of DR3)	114
TNFα –308	Type 1 autoimmune hepatitis	yes, via LD with HLA?	46; 47
TNFα –308 (TNF1)	Adult periodontitis	yes (advanced disease)	67
TNFα –308 (TNF1)	Ankylosing spondylitis	yes	115
TNFα –308 (TNF1)	*Helicobacter pylori*-associated duodenal ulcers	yes (females) (increased risk)	94
TNFα –308 (TNF1/1)	Primary biliary cirrhosis	yes (late stage disease)	116
TNFα –308 (TNF2)	Asthma	yes	117
TNFα –308 (TNF2)	Cardiac sarcoidosis	yes	118
TNFα –308 (TNF2)	Crohn's disease (steroid-dependent)	yes	119
TNFα –308 (TNF2)	Excessive fat accumulation (females)	yes (TNF2 homozygotes)	120
TNFα –308 (TNF2)	Meliodosis	yes	121
TNFα –308 (TNF2)	Multiple sclerosis	no	37
TNFα –308 (TNF2)	Myasthenia gravis	yes (in LD with HLA?)	35
TNFα –308 (TNF2)	Myasthenia gravis (early onset)		89
TNFα –308 (TNF2)	Primary biliary cirrhosis	yes (negative association)	122
TNFα –308 (TNF2)	Primary biliary cirrhosis	yes	123

Continued

Table 3 *Continued*

Cytokine and polymorphism	*Disease*	*Association*	*Reference*
TNFα –308 (TNF2)	Pulmonary sarcoidosis (Lofgren)	yes (in LD with HLA?)	124
TNFα –308 (TNF2)	Spontaneous preterm birth	yes	125
TNFα –308 (TNF2)	Ulcerative colitis	yes	126
TNFα –376 G → A	Ankylosing spondylitis	no	105
TNFα –376 G → A	Cardiac transplant rejection	no	81
TNFα –376 G → A	Multiple sclerosis	yes (HLA-independent)	127
TNFα –850	Narcolepsy	no	128
TNFα –857	Kawasaki disease	no	101
TNFα –857	Narcolepsy	yes	129
TNFα –857 (T allele)	Crohn's disease	yes	102
TNFα –857 (T allele)	Insulin-dependent diabetes mellitus	no	104
TNFα –857 (T allele)	Narcolepsy	yes	130
TNFα –857 (T allele)	Rheumatoid arthritis	yes	131
TNFα –857 (T allele)	Systemic juvenile chronic arthritis	yes	103
TNFα –863	HTLV-1 uveitis	yes	100
TNFα –863	Kawasaki disease	no	101
TNFα –863 (A allele)	Crohn's disease	yes	102
TNFα –863 (A allele)	Systemic juvenile chronic arthritis	yes	103

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