

Supplementary Table 1: Common genetic variants in pathways related to cytokine signaling and/or EBV control and the putative polymorphic effect on risk of AIDS-lymphoma.

Gene	Protein function related to AIDS-related NHL	dbSNP	SNP ^{ref} (alias)	Reported SNP allelic difference ^{ref}
<i>IL10</i>	Immunomodulatory cytokine produced by, among others, B cells(1), with pleiotropic cellular actions including	rs1800896	-1082A>G(6)	Genotypes IL10 592 CC is associated with higher IL10 serum level in HIV-seropositive men and increased risk of AIDS-related NHL as compared to all other genotypes(7).
	- enhancing B cell viability, particularly with IL4 co-stimulation(2) and lymphoma growth at the auto/para-crine level(3) - inducing differentiation of CD40-stimulated B cells(4) and apoptosis of <i>S. aureus</i> -activated B cells(5).	rs1800871	-819C>T(6)	
		rs1800872	-592C>A(6)	IL -1082 GG is associated with higher plasma IL10 in healthy individuals as compared to all other genotypes(8). Haplotypes <i>Cytokine transcription, production or blood levels by haplotypes (cell type or blood levels, stimulus or population):</i> a) GCC haplotype > ACC and ATA (PBMC, <i>E. coli</i> LPS) (6) (GCC>ATA; U937 monocyte cell line, luciferase assay)(9) (GCC>ATA; whole blood, <i>S. marcescens</i> LPS)(9) (plasma IL10, Sjorgen Syndrome, a B-cell hyperactivity syndrome)(10) b) ATA > GCC and/or ACC: (plasma IL10, neonates)(11) (IL10 mRNA in PBMCs, <i>S. pneumoniae</i>)(12) (Ala/Gln) in 3'UTR
<i>IL10RA</i>	- mediates the actions of IL10(13) - inhibits the synthesis of proinflammatory cytokines	rs9610	A3524G	
<i>CXCL12</i>	- regulate normal B-lymphocyte maturation and proliferation - expressed by malignant B cells derived from primary central nervous system lymphomas (CNS)(14).	rs1801157	3'UTR-801G-A (SDF1-3'A)	No detectable effect on mRNA transcript and protein(15) No allelic variation in gene expression in EBV-transformed lymphoblastoid cell lines(16) <i>SDF1-3'A</i> is associated with AIDS-related NHL(17)
<i>IL13</i>	- induces immunoglobulin E (IgE), the stimulus for allergic symptoms, in B cells (18) possibly through its receptor, IL4 receptor- α (IL4R). - influences growth of non-Hodgkin's B-lymphoma cells in vitro(19). - anti-inflammatory - suppresses IL1, IL6, and IL8 production	rs1800925	-1055C>T(20, 21) (-1069) (-1112)	1055T: increased IL13 production & increased recruitment of binding protein to the genomic region and allergic asthma(20)
<i>IL4</i>	- induce IgE, the stimulus for allergic symptoms, in B cells (18) possibly through its receptor, IL4R. - increases survival growth of non-Hodgkin's B-lymphoma cells in vitro(22). - regulates antibody production - attenuates inflammatory response	rs2243250	-584C>T (23) (590 from ATG codon)(24)	Allele 584T: Higher <i>IL4</i> transcriptional activity(26)
		rs2070874	(-524 from exon1)(25) Ex1 C-168T (-33)(24) (Q576R)(27)	In complete LD with rs2243250
<i>IL4R</i>	- receptor for IL4 and IL13 - regulates IgE production, chemo-kine and mucus production, allergic inflammation.	rs1801275	Q551R(28)	nonsynonymous (Gln/Arg) coding exon is associated with atopy and allergy(27) total IgE concentrations(29)

(continued)

Gene	Protein function related to AIDS-related NHL	dbSNP	SNP ^{ref} (alias)	Reported SNP allelic difference ^{ref}
<i>CCL5</i>	- upregulation relate to allergic inflammation and atopic diseases (30) and other cancers, i.e., breast and ovarian cancers(31).	rs2280788	-28C>G(32)	Allele 28G: higher <i>CCL5</i> transcription(32)
	- cd4 Tcell depletion in HIV	rs2107538	-403G>A(32)	Allele 403A: higher <i>CCL5</i> transcription and associated with atopic dermatitis(33)
<i>BCL6</i>	- a proto-oncogene identified from chromosomal breakpoints in the diffuse large B-cell subtypes of NHL in immunocompetent persons(34-36)	rs1056932	N387N	As compared to the TT homozygotes, carriers of the CC genotype were associated with increased NHL risk(40).
	- frequently translocated in lymphomas, regulates germinal center B cell differentiation and inflammation including T-helper type 2 cytokines in mast cells(37).		(Ex6-195C>T)(40)	
	- <i>BCL6</i> somatic mutations are associated with diffuse large-cell subtype of AIDS-NHL(38, 39).	rs3774306		IVS7-643G>A

rs, reference SNP ID

REFERENCES (note that SNP chromosomal location follows the reference)

- Howard, M., O'Garra, A., Ishida, H., de Waal Malefyt, R., and de Vries, J. Biological properties of interleukin 10. *J Clin Immunol*, **12**: 239–47, 1992.
- Rousset, F., Garcia, E., Defrance, T., Peronne, C., Vezzio, N., Hsu, D. H., Kastelein, R., Moore, K. W., and Banchereau, J. Interleukin 10 is a potent growth and differentiation factor for activated human B lymphocytes. *Proc Natl Acad Sci U S A*, **89**: 1890–3, 1992.
- Voorzanger, N., Touitou, R., Garcia, E., Delecluse, H. J., Rousset, F., Joab, I., Favrot, M. C., and Blay, J. Y. Interleukin (IL)-10 and IL-6 are produced in vivo by non-Hodgkin's lymphoma cells and act as cooperative growth factors. *Cancer Res*, **56**: 5499–505, 1996.
- Burdin, N., Van Kooten, C., Galibert, L., Abrams, J. S., Wijdenes, J., Banchereau, J., and Rousset, F. Endogenous IL-6 and IL-10 contribute to the differentiation of CD40-activated human B lymphocytes. *J Immunol*, **154**: 2533–44, 1995.
- Itoh, K., and Hirohata, S. The role of IL-10 in human B cell activation, proliferation, and differentiation. *J Immunol*, **154**: 4341–50, 1995.
- Turner, D. M., Williams, D. M., Sankaran, D., Lazarus, M., Sinnott, P. J., and Hutchinson, I. V. An investigation of polymorphism in the interleukin-10 gene promoter. *Eur J Immunogenet*, **24**: 1–8, 1997.
- Breen, E. C., Boscardin, W. J., Detels, R., Jacobson, L. P., Smith, M. W., O'Brien, S. J., Chmiel, J. S., Rinaldo, C. R., Lai, S., and Martinez-Maza, O. Non-Hodgkin's B cell lymphoma in persons with acquired immunodeficiency syndrome is associated with increased serum levels of IL10, or the IL10 promoter -592 C/C genotype. *Clin Immunol*, **109**: 119–29, 2003.
- Marka, M., Bessenyei, B., Zeher, M., and Semsei, I. IL-10 promoter -1082 polymorphism is associated with elevated IL-10 levels in control subjects but does not explain elevated plasma IL-10 observed in Sjogren's syndrome in a Hungarian cohort. *Scand J Immunol*, **62**: 474–80, 2005.
- Crawley, E., Kay, R., Sillibourne, J., Patel, P., Hutchinson, I., and Woo, P. Polymorphic haplotypes of the interleukin-10 5' flanking region determine variable interleukin-10 transcription and are associated with particular phenotypes of juvenile rheumatoid arthritis. *Arthritis Rheum*, **42**: 1101–8, 1999.
- Hukkanen, J., Pertovaara, M., Anttonen, J., Lahdepojha, N., Pasternack, A., and Hurme, M. Genetic association between interleukin-10 promoter region polymorphisms and primary Sjogren's syndrome. *Arthritis Rheum*, **44**: 176–9, 2001.
- Helminen, M. E., Kilpinen, S., Virta, M., and Hurme, M. Susceptibility to primary Epstein-Barr virus infection is associated with interleukin-10 gene promoter polymorphism. *J Infect Dis*, **184**: 777–80, 2001.

12. Temple, S. E., Lim, E., Cheong, K. Y., Almeida, C. A., Price, P., Ardlie, K. G., and Waterer, G. W. Alleles carried at positions -819 and -592 of the IL10 promoter affect transcription following stimulation of peripheral blood cells with *Streptococcus pneumoniae*. *Immunogenetics*, **55**: 629–32, 2003.
13. De Waal Malefyt, R., Yssel, H., Roncarolo, M.-G., Spits, H., and de Vries, J. E. Interleukin-10. *Current Opinion in Immunology*, **4**: 314–320, 1992.
14. Smith, J. R., Falkenhagen, K. M., Coupland, S. E., Chippis, T. J., Rosenbaum, J. T., and Braziel, R. M. Malignant B cells from patients with primary central nervous system lymphoma express stromal cell-derived factor-1. *Am J Clin Pathol*, **127**: 633–41, 2007.
15. Arya, S. K., Ginsberg, C. C., Davis-Warren, A., and D’Costa, J. In vitro phenotype of SDF1 gene mutant that delays the onset of human immunodeficiency virus disease in vivo. *J Hum Virol*, **2**: 133–8, 1999.
16. Kimura, R., Nishioka, T., and Ishida, T. The SDF1-G801A polymorphism is not associated with SDF1 gene expression in Epstein-Barr virus-transformed lymphoblastoid cells. *Genes Immun*, **4**: 356–61, 2003.
17. Rabkin, C. S., Yang, Q., Goedert, J. J., Nguyen, G., Mitsuya, H., and Sei, S. Chemokine and chemokine receptor gene variants and risk of non-Hodgkin’s lymphoma in human immunodeficiency virus-1-infected individuals. *Blood*, **93**: 1838–42, 1999.
18. Hilton, D. J., Zhang, J. G., Metcalf, D., Alexander, W. S., Nicola, N. A., and Willson, T. A. Cloning and characterization of a binding subunit of the interleukin 13 receptor that is also a component of the interleukin 4 receptor. *Proc Natl Acad Sci U S A*, **93**: 497–501, 1996.
19. Bonnefoix, T., Gressin, R., Jacrot, M., Perron, P., Swiercz, P., Chaffanjon, P., and Sotto, J. J. Growth modulation of freshly isolated non-Hodgkin’s B-lymphoma cells induced by various cytokines and all-trans-retinoic-acid. *Leuk Lymphoma*, **25**: 169–78, 1997.
20. van der Pouw Kraan, T. C., van Veen, A., Boeije, L. C., van Tuyl, S. A., de Groot, E. R., Stapel, S. O., Bakker, A., Verweij, C. L., Aarden, L. A., and van der Zee, J. S. An IL-13 promoter polymorphism associated with increased risk of allergic asthma. *Genes Immun*, **1**: 61–5, 1999.
21. Laundy, G. J., Spink, C. F., Keen, L. J., Wood, N. A., and Bidwell, J. L. A novel polymorphism in the human interleukin-13 (IL-13) promoter. *Eur J Immunogenet*, **27**: 53–4, 2000.
22. Billard, C., Caput, D., Vita, N., Ferrara, P., Orrico, M., Gaulard, P., Boumsell, L., Bensussan, A., and Faracet, J. P. Interleukin-13 responsiveness and interleukin-13 receptor expression in non-Hodgkin’s lymphoma and reactive lymph node B cells. Modulation by CD40 activation. *Eur Cytokine Netw*, **8**: 19–27, 1997.
23. Rosenwasser, L. J., Klemm, D. J., Dresback, J. K., Inamura, H., Mascali, J. J., Klinnert, M., and Borish, L. Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. *Clin Exp Allergy* **25 Suppl 2**, pp. 74–8; discussion 95–6, 1995.
24. Suzuki, I., Yamaguchi, E., Hizawa, N., Itoh, A., and Kawakami, Y. A new polymorphism in the 5' flanking region of the human interleukin (IL)-4 gene. *Immunogenetics*, **49**: 738–9, 1999.
25. Borish, L., Mascali, J. J., Klinnert, M., Leppert, M., and Rosenwasser, L. J. SSC polymorphisms in interleukin genes. *Hum Mol Genet*, **3**: 1710, 1994.
26. Song, Z., Casolaro, V., Chen, R., Georas, S. N., Monos, D., and Ono, S. J. Polymorphic nucleotides within the human IL-4 promoter that mediate over-expression of the gene. *J Immunol*, **156**: 424–9, 1996.
27. Hershey, G. K., Friedrich, M. F., Esswein, L. A., Thomas, M. L., and Chatila, T. A. The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med*, **337**: 1720–5, 1997.
28. Bugawan, T. L., Mirel, D. B., Valdes, A. M., Panelo, A., Pozzilli, P., and Erlich, H. A. Association and interaction of the IL4R, IL4, and IL13 loci with type 1 diabetes among Filipinos. *Am J Hum Genet*, **72**: 1505–14, 2003.
29. Kruse, S., Japha, T., Tedner, M., Sparholt, S. H., Forster, J., Kuehr, J., and Deichmann, K. A. The polymorphisms S503P and Q576R in the interleukin-4 receptor alpha gene are associated with atopy and influence the signal transduction. *Immunology*, **96**: 365–71, 1999.
30. Taguchi, M., Sampath, D., Koga, T., Castro, M., Look, D. C., Nakajima, S., and Holtzman, M. J. Patterns for RANTES secretion and intercellular adhesion molecule 1 expression mediate transepithelial T cell traffic based on analyses in vitro and in vivo. *J Exp Med*, **187**: 1927–40, 1998.
31. Ben-Baruch, A. The multifaceted roles of chemokines in malignancy. *Cancer Metastasis Rev*, **25**: 357–71, 2006.
32. Liu, H., Chao, D., Nakayama, E. E., Taguchi, H., Goto, M., Xin, X., Takamatsu, J. K., Saito, H., Ishikawa, Y., Akaza, T., Juji, T., Takebe, Y., Ohishi, T., Fukutake, K., Maruyama, Y., Yashiki, S., Sonoda, S., Nakamura, T., Nagai, Y., Iwamoto, A., and Shioda, T. Polymorphism in RANTES chemokine promoter affects HIV-1 disease progression. *Proc Natl Acad Sci U S A*, **96**: 4581–5, 1999.
33. Nickel, R. G., Casolaro, V., Wahn, U., Beyer, K., Barnes, K. C., Plunkett, B. S., Freidhoff, L. R., Sengler, C., Plitt, J. R., Schleimer, R. P., Caraballo, L., Naidu, R. P., Levett, P. N., Beaty, T. H., and Huang, S. K. Atopic dermatitis is associated with a functional mutation in the promoter of the C-C chemokine RANTES. *J Immunol*, **164**: 1612–6, 2000.
34. Kerckaert, J. P., Deweindt, C., Tilly, H., Quief, S., Lecocq, G., and Bastard, C. LAZ3, a novel zinc-finger encoding gene, is disrupted by recurring chromosome 3q27 translocations in human lymphomas. *Nat Genet*, **5**: 66–70, 1993.

35. Ye, B. H., Rao, P. H., Chaganti, R. S., and Dalla-Favera, R. Cloning of bcl-6, the locus involved in chromosome translocations affecting band 3q27 in B-cell lymphoma. *Cancer Res*, **53**: 2732–5, 1993.
36. Miki, T., Kawamata, N., Arai, A., Ohashi, K., Nakamura, Y., Kato, A., Hirosawa, S., and Aoki, N. Molecular cloning of the breakpoint for 3q27 translocation in B-cell lymphomas and leukemias. *Blood*, **83**: 217–22, 1994.
37. Ohtsuka, Y., Arima, M., Fujimura, L., Li, H., Sakamoto, A., Okamoto, Y., and Tokuhisa, T. Bcl6 regulates Th2 type cytokine productions by mast cells activated by FcepsilonRI/IgE cross-linking. *Mol Immunol*, **42**: 1453–9, 2005.
38. Ballerini, P., Gaidano, G., Gong, J. Z., Tassi, V., Saglio, G., Knowles, D. M., and Dalla-Favera, R. Multiple genetic lesions in acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma. *Blood*, **81**: 166–76, 1993.
39. Gaidano, G., Lo Coco, F., Ye, B. H., Shibata, D., Levine, A. M., Knowles, D. M., and Dalla-Favera, R. Rearrangements of the BCL-6 gene in acquired immunodeficiency syndrome-associated non-Hodgkin's lymphoma: association with diffuse large-cell subtype. *Blood*, **84**: 397–402, 1994.
40. Zhang, Y., Lan, Q., Rothman, N., Zhu, Y., Zahm, S. H., Wang, S. S., Holford, T. R., Leaderer, B., Boyle, P., Zhang, B., Zou, K., Chanock, S., and Zheng, T. A putative exonic splicing polymorphism in the BCL6 gene and the risk of non-Hodgkin lymphoma. *J Natl Cancer Inst*, **97**: 1616–8, 2005.