

Genetic influence on peripheral blood T lymphocyte levels

MA Hall¹, KR Ahmadi², P Norman³, H Snieder², AJ MacGregor², RW Vaughan³, TD Spector² and JS Lanchbury¹

¹Molecular Immunogenetics Unit, Department of Rheumatology, Division of Medicine, 5th Floor Thomas Guy House, Guy's, King's and St Thomas' Hospitals School of Medicine, King's College, Guy's Hospital Campus, London SE1 9RT, UK; ²Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, London SE1, UK; ³South Thames Tissue Typing, 3rd Floor, New Guy's House, Guy's Hospital, London SE1 9RT, UK

T lymphocytes are a major component of the adaptive immune system. CD4 positive T cell subpopulations regulate B cell and macrophage effector function while CD8 positive T cells are largely responsible for anti-viral cytotoxic activity. The degree of natural variation in the levels and ratios of the various T cell subpopulations is a possible risk factor for the development of autoimmune disease, infectious disease and cancer. There is some evidence from studies of inbred strains of mice and humans which suggests that variation in T cell subpopulations is genetically influenced. However, family studies alone cannot distinguish between common environmental and shared genetic influences and provide less robust estimates of the heritability than twin studies. To comprehensively examine genetic influences on a selection of important T cell phenotypes, we investigated variation in levels of total lymphocytes, CD3⁺, CD4⁺, CD8⁺, CD3⁺CD4⁺, CD3⁺CD8⁺ lymphocytes and in CD4:CD8 ratio as a proportion of lymphocytes and of T cells using the classical twin model approach. Healthy female twin pairs were sampled from the St. Thomas' UK Adult Twin Registry. A maximum of 103 monozygotic (MZ) and 186 dizygotic (DZ) twins aged 18–80 years participated in the study. Whole blood samples were analysed for T cell subsets by flow cytometry. The relative genetic contribution to these phenotypes was estimated using a variance components model-fitting approach. Heritability estimates were calculated of 65% for CD4:CD8 T cell and lymphocyte ratios, around 50% for absolute lymphocyte, CD3⁺ and CD4⁺ counts, and 56% for CD8⁺ numbers. Unique (rather than shared) familial environment explains the remainder of the variance. Genetic factors have a major influence on the variation in peripheral T cell subset numbers. Polymorphism dictating such variation should be taken into account when assessing risk factors for T cell immune-mediated disease with a genetic background. *Genes and Immunity* (2000) 1, 423–427.

Keywords: T cells; genetics; immune system; heritability

Introduction

The human immune response is a key physiological system upon which mammalian survival depends and would be expected to be a crucial target for the action of natural selection. T cells are a fundamental component of the adaptive arm of this response and are involved in defence against pathogens including bacteria, viruses, fungi, protozoa, and multicellular parasites.¹ CD4 positive T cell subpopulations regulate B cell and macrophage effector function while CD8 positive T cells are responsible for anti-viral cytotoxic and some immunoreg-

ulatory activities. Studies of the impact of genetic variation on the functioning of the immune system have up to now largely concentrated on qualitative issues of response and non-response. Experimental manipulation of the murine genome using 'knock out' and transgenic technologies has enabled insight to be gained in systems which are driven to phenotypic extremes. The effects of CD4 and CD8 phenotypes are examples of the former^{2,3} while useful insights into T cell development have been gained from rearranged T cell receptor transgenics as examples of the latter.⁴

In contrast, the existence of genetically determined natural variation in levels of T cell subpopulations in mice and humans has received little attention. Studies in mice first showed that T cell subset representation was strain dependent and therefore under genetic control.⁵ Amadori *et al*⁶ more recently studied the genetics of CD4 and CD8 T cell ratios in healthy human nuclear families and concluded that CD4:CD8 T cell ratio was under genetic control. The degree of natural variation in the levels and ratios of the various T cell subpopulations may contribute to part of the genetic risk for the development of autoimmune disease, infectious disease and cancer. To explore this hypothesis we have measured a number of

Correspondence: Dr MA Hall, Molecular Immunogenetics Unit, Department of Rheumatology, Division of Medicine, 5th Floor Thomas Guy House, Guy's, King's and St Thomas' Hospitals Schools of Medicine, King's College, Guy's Hospital Campus, London SE1 9RT, UK. E-mail: margaret.a.hall@kcl.ac.uk

We are grateful to the Special Trustees of St Thomas' Hospital and Gemini Genomics Limited for support in initiating this research. The Twin Research Unit also receives support from the Arthritis Research Campaign, the Wellcome Trust and the Chronic Disease Research Foundation. The experiments described in this paper comply with the laws of the United Kingdom.

Received and revised 17 June 2000; accepted 21 June 2000