



BRIEF COMMUNICATION

A polymorphic microsatellite marker in the human p55 TNF receptor, CD120a

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We provide characterization of a highly polymorphic dinucleotide repeat in the human TNF-receptor 1 gene (TNFR1, TNFRp55, CD120a). We have observed 11 alleles at this locus in individuals from the West of Scotland. In a panel of healthy, unrelated individuals from the West of Scotland ($n = 143$), the overall heterozygosity was 68%, indicating the potential usefulness of these markers in immunogenetic studies. *Genes and Immunity* (2000) 1, 228–230.

Keywords: Microsatellite; TNF; TNF-R1; CD120a; polymorphism

Tumor necrosis factor- α (TNF) is recognized to be a pivotal molecule in the inflammatory response. The wide range of TNF activities is mediated by the presence of two distinct types of TNF receptors, termed TNF-R1(p55, CD120a) (reviewed in Wallach *et al*¹) and TNF-R2(p75,CD120b). While TNF-R1(p55) has a wide expression, that of TNF-R2(p75) is largely restricted to lymphoid cells. In addition to their collaboration in signalling TNF effects, these two molecules also transduce lymphotoxin- α signals.^{2,3}

One of the most widely-studied aspects of TNF-R1(p55) function is as a primary mediator of TNF-induced cell-death,⁴ contributing through its own 'death domain'.⁵ Signalling through TNF-R1(p55) also results in events associated with activation of both NF κ B-dependent and NF κ B-independent gene transcription.⁶

While differences in levels of TNF production may contribute to inflammatory disorders (eg, rheumatoid arthritis (RA)), anomalous, and potentially pathogenic, signalling in the TNF system could equally originate from disease-associated changes in the TNF receptor side of the system. It was reported that serum levels of soluble TNF receptors vary amongst healthy individuals and that

these variations are stable,⁷ suggesting that intra-individual variation may have a genetic basis, at least in part. Also, since these sTNFR levels may have an inhibitory effect on TNF function, genetic variation in TNF receptor levels may impact on disease susceptibility. Many recent studies have measured the levels of soluble TNF receptor proteins in disease, particularly autoimmune disease. In RA studies have shown that the soluble forms of both receptors are found at elevated levels in the serum and synovial fluid,⁸ especially in severe disease.⁹ Parallel studies have revealed the same elevated levels in patients with systemic lupus erythematosus (SLE). Both receptor forms are elevated in SLE¹⁰ and these elevated levels of TNF-R1(p55) and TNF-R2(p75) correlated with stage and degree of disease activity in SLE patients.¹¹ Also, many animal models of human disease have been linked directly to regions syntenic with 12p13, wherein lies the TNF-R1(p55) gene, including experimental autoimmune encephalitis and insulin-dependent diabetes mellitus (reviewed in Becker *et al*¹²). We therefore believed that it would be important to define genetic markers within these genes. Recent reports have described polymorphic elements within the TNF-R2(p75) gene;^{13,14} here we describe a highly informative marker in the TNF-R1(p55) gene.

A genomic segment from intron 1 of the human TNF-R1(p55) gene¹⁵ was isolated and characterized, revealing a potentially polymorphic imperfect dinucleotide sequence (GT)₁₇(GA)₁₀, as shown in Figure 1. Primers were designed to amplify this sequence and PCR reactions were carried out as described in the legend to Figure 2. This element was indeed polymorphic and results from a typical gel are shown in Figure 2a; allele bands were contained within the size range 140–150 base pairs. We then examined the distribution of TNF-R1(p55) alleles in 143 unrelated individuals from the West of Scot-

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typed to provide universally-available standards: DUCAF (ASHI9019/CEPHws28), TNF-R1(p55) 4/7; QBL (ASHI9020/CEPHws71), 4/6; JESTHOM (ASHI9004/CEPHws09), 4/5; HOM-2 (ASHI9005/CEPHws17), 6/7. Although a thorough examination was not made, alleles appeared to be inherited Mendelianly.

Recently, a genomic sequence which contains the TNF-R1(p55) microsatellite was deposited in Genbank, accession number AC006057 (PAC RPCI1-96H9). This sequence shows a repeat region comprising (GT)₁₇(GA)₁₂ (Figure 1b) rather than the (GT)₁₇(GA)₁₀ present in our sequence. At this time we cannot say whether the (GT) element is more stable than the (GA) element in this complex repeat.

The role of TNF in inflammatory disease will continue to be important in a wide range of disorders and genetic markers such as that described here will greatly aid understanding of the role its receptors play and the definition of the 12p13 region generally. Indeed, while this manuscript was in preparation, McDermott *et al*¹⁶ utilized this marker in their definition of the TNF-R1(p55) gene as the gene responsible for Familial Hibernian Fever.

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