CARD15 allele frequency differences in New Zealand Maori: ancestry specific susceptibility to Crohn's disease in New Zealand?

The discovery in 2001 that three single nucleotide polymorphisms (SNPs) in the *CARD15* gene are associated with Crohn's disease is one of the most important advances in inflammatory bowel disease (IBD) research in recent years.[1 2] This finding has led to further insights into disease pathogenesis,[3] and subsequent genotype-phenotype studies have suggested that these SNPs are associated with an increased risk of terminal ileal and complicated disease behaviour.[4] Interestingly, alleles of these *CARD15* SNPs are known to vary significantly among ethnic subgroups,[5] which may have important implications for the ethnic specific risk of Crohn's disease. In this letter, we report *CARD15* allele frequencies for the New Zealand (NZ) Maori population and discuss these in terms of varying susceptibility of Crohn's disease in this indigenous population.

The Maori population represents the final link in a long chain of island hopping voyages beginning in Southeast Asia and stretching across the South Pacific to NZ. This unique population originated from restricted groups of common ancestors who arrived in NZ from Eastern Polynesia between 800 and 1000AD. Prior to colonisation approximately 200 years ago, the Maori population had been geographically separated from Europeans for at least 10 000 years (or 40 000 generations). This separation, coupled with genetic founder effects in the Maori population, has led to significant differences in allele frequencies between Caucasians and a reduction in genetic diversity. Recent widespread intermarriage has led to genetic admixture, with the modern Maori gene pool comprised of 20–40% ''European'' genes (unpublished findings).

Incidence rates for IBD have increased rapidly in NZ over the past 50 years, as observed in many Western populations. However, it has long been recognised that the disease is uncommon in NZ Maori.[6–8] We hypothesised that NZ Maori have a lower frequency of *CARD15* mutations than NZ Caucasians, and reasoned that this may be a factor in the different incidence and prevalence rates of CD between the two ancestral groups.

In this study, 90 Maori of varying self reported ancestry fractions, and 201 Caucasians were genotyped for three polymorphisms of the *CARD15* gene associated with CD, and a background variant (P268S) found in association with the other polymorphisms, using a previously published ARMS assay.[9] Ethics approval was obtained from the Canterbury and Central Regional Ethics Committees and all volunteers gave written informed consent. Table 1 shows the allele frequency for these SNPs in Maori (divided into ancestral subgroups) and Caucasians. Clear differences in allele frequencies between NZ Maori and Caucasian groups were observed. In particular, decreasing CARD15 (P268S) allele frequency showed a linear correlation with increasing Maori ancestry ($\chi^2 = 5.7$, $p = 0.016$).

These data suggest that a low frequency of *CARD15* polymorphisms may contribute to the low incidence and prevalence of Crohn's disease in NZ Maori. To begin addressing the hypothesis that Maori are genetically protected from Crohn's disease, it will be important to first obtain accurate ancestral information from patients with Maori ancestry using a panel of ancestry informative DNA markers. This information will also provide data to control for ancestry as a potential confounder in case control association studies involving this subgroup. Finally, the hypothesised correlation between genotype and disease variation in NZ Maori suggests that this ethnic group may be a useful candidate population for future admixture mapping studies aimed at uncovering novel IBD susceptibility genes.[10]

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Table 1 *CARD15* allele frequencies among New Zealand ancestral groups

CARD15 variant	Allele frequency (%) Caucasian (n = 201)	Admixed Maori (n = 37)	Non-admixed Maori (n = 53)
P268S*	23.4	16.2	12.3
R702W	3.0	1.4	0.9
G908R	1.2	1.4	0.9
1007fs	1.0	1.0	0.0

*P268S (background) variant + R702W, G908R, or 1007fs.
Test for linear trend (p = 0.016).

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Risk of lymphoma: inflammatory bowel disease and immunomodulators

We read with great interest the meta-analysis by Kandiel *et al* (*Gut* 2005;**54**:1121–5), the purpose of which was to provide a more precise estimate of the relative risk of lymphoma among inflammatory bowel disease (IBD) patients treated with azathioprine or 6-mercaptopurine (6-MP). Based on the six studies included in their meta-analysis, Kandiel *et al* determined that the risk of lymphoma among IBD patients who did not receive immunomodulators was similar to that of the general population while the lymphoma risk among IBD patients treated with azathioprine/6-MP was increased approximately fourfold. It is reassuring that the largest study included in their meta-analysis, which utilised the UK General Practice Research Database, failed to show a significantly higher risk of lymphoma among 16 996 IBD patients, regardless of whether or not patients received azathioprine/6-MP.[1] While several population based and hospital based studies have similarly failed to identify a significantly increased risk of lymphoma in IBD patients who never received immunomodulators,[2] it is worth noting that two studies have recently reported an increased lymphoma risk in IBD patients independent of immunomodulator or biological therapy.

In 2000, an Italian study of 920 IBD patients reported a ninefold increased risk of Hodgkin's disease among ulcerative colitis patients but not among Crohn's disease