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Lack of association between KIR and HLA-C type and susceptibility to idiopathic bronchiectasis

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Summary
Introduction: Idiopathic bronchiectasis is a poorly defined disease characterised by persistent inflammation, infection and progressive lung damage. Natural killer (NK) cells provide a major defense against infection, through the interaction of their surface receptors, including the activating and inhibitory killer immunoglobulin-like receptors (KIR), and human leukocyte antigens (HLA) class I molecules. Homozygosity for HLA-C has been shown in a single study to confer increased genetic susceptibility to idiopathic bronchiectasis. We aimed to assess whether the KIR and HLA repertoire, alone or in combination, may influence the risk of developing idiopathic bronchiectasis, in an independent replication study.
Methods: In this prospective, observational, case-control association study, 79 idiopathic bronchiectasis patients diagnosed following extensive aetiological investigation were compared with 98 anonymous, healthy, age, sex and ethnically-matched controls attending blood donor

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sessions in the same geographical location. DNA extraction was performed according to standardised techniques. Determination of presence or absence of KIR genes was performed by a sequence specific oligonucleotide probe method. Allele frequencies for the proposed KIR, HLA-B and HLA-C risk alleles both individually and in combinations were compared.
Results: We found no significant differences in allele frequency between the idiopathic bronchiectasis and control samples, whether considering HLA-C group homozygosity alone or in combination with the KIR type.
Discussion: Our results do not show an association between HLA-C and KIR and therefore do not confirm previous positive findings. This may be explained by the lower frequency of HLA-C1 group homozygosity in the control population of the previous study (27.2%), compared to 42.3% in our study, which is consistent with the genetic profiling of control groups across the UK. The previous positive association study may therefore have been driven by an anomalous control group. Further larger prospective multicentre replication studies are needed to determine if an association exists.

At a glance commentary

A single centre study was reported in 2006 that linked HLA-C and killer cell immunoglobulin-like receptor (KIR) gene type with predisposition to the development of idiopathic bronchiectasis. This finding has subsequently been cited in numerous reviews of the immunology of bronchiectasis. However, replication studies to confirm or refute this finding have not been performed. Confirmation of this association in a second independent study population would potentially lead to a significant contribution to understanding the pathogenesis of idiopathic bronchiectasis. We have, therefore, conducted a study interrogating the same candidate gene polymorphisms in a population of rigorously phenotyped idiopathic bronchiectasis patients compared with age, gender, ethnicity and geographically-matched controls. Our study was of near identical size to the original work, employing similar well-tested technology. No associations between HLA-C type and idiopathic bronchiectasis were demonstrated, whether considering HLA-C group homozygosity alone or in combination with the KIR type, hence our results did not confirm the previous study findings. The main difference in the two studies appeared to be in the frequency of the control populations. 42% had HLA-C1 group homozygosity in our study, a finding consistent with genetic profiling of control groups across the UK. This compared to 27% in the previous study. Our findings raise the possibility that the previous positive association study may have been driven by an anomalous control group population or may represent geographical differences in the UK. We conclude that further larger multicentre replication studies are needed to confirm or refute that an association exists.

Introduction

Bronchiectasis encompasses a large group of conditions that share pathological dilatation of the bronchi as a consequence of repeated, vicious cycles of infection and inflammation [1]. There is growing awareness of the importance of phenotyping bronchiectasis patients in order to identify modifiable risk factors and to engage these patients in holistic disease management programs [2]. Up to 50% of patients, however, have no defined aetiology for their bronchiectasis and are deemed idiopathic [1,2]. Although evidence clearly indicates a dysregulated immune response in the pathogenesis of bronchiectasis, the pathophysiology of idiopathic bronchiectasis remains poorly elucidated, often resulting in a palliative, untargeted approach to treatment. Previous immunogenetic studies of idiopathic bronchiectasis have demonstrated defects in both innate and adaptive immunity [3—5]. Such patients appear to have shared clinical and radiological features, suggesting a potential interplay between immunogenetic susceptibility, immune dysregulation and chronic bacterial infection [6].

Natural killer (NK) cells are a potent, rapid part of innate immunity to infection and a link to priming of adaptive immunity [7]. NK cells play an important role in the normal functioning of lung host defence through the interaction of their receptors, Killer cell Immunoglobulin-like Receptors (KIR's), with major histocompatibility complex (MHC) class I molecules on target cells [8]. KIR's are cell surface receptors that are polymorphic in both structure and function, with both activating and inhibitory receptor types being expressed on an NK cell [8,9]. KIRs exhibit substantial diversity at both the allelic and haplotypic levels resulting in significant variation in susceptibility to pathogens and disease.

The KIR proteins are members of the immunoglobulin (Ig) superfamily of receptors. Their nomenclature is based on their structure, where the number of Ig-like