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## Introduction

Bovine tuberculosis (bTB) caused by *Mycobacterium bovis*, is a zoonotic disease which affects cattle worldwide. Diagnosis and control is based on the single intradermal comparative tuberculin test (SICTT), supported by active abattoir surveillance. Despite many years of active testing, and slaughter of test positive cattle, bTB remains endemic in both the UK and Ireland indicating a need to investigate alternative strategies. One approach, which could prove beneficial synergistically with current eradication measures, would be genetic selection for increased resistance to bTB in cattle. Exploitable genetic variation exists for resistance to bTB; the heritability on the liability scale has been estimated 0.18 in Republic of Ireland and Great Britain Holstein-Friesian (HF) dairy cows (Allen et al., 2010; Bermingham et al., 2011). However, genetic markers associated with resistance would greatly facilitate selection. The aim of this study was therefore to undertake a genome-wide association study to identify loci that are associated with resistance to bTB in HF dairy cattle.

**Material and methods**

Blood samples from cases were sampled at slaughter. Cases were defined as cattle with a positive reaction to the tuberculin skin test and a confirmed bTB lesion. Blood samples were collected from age matched controls traced to a subset of high prevalence case herds.

Controls were defined as animals which were contemporaneous to cases from high prevalence herds and

exhibited multiple negative tuberculin skin tests. In total, 3,715 blood samples were collected from 464 NI dairy herds between 2008 and 2009. DNA was extracted and quantified, and 1,324 female cattle (679 cases, 677 controls) were genotyped at 777,962 SNPs. Only SNPs with a minor allele frequency >1% were retained. Following quality control, 1156 cattle (594 cases, 562 controls), and 617,610 SNPs remained for inclusion in the analysis. Mixed model association analyses, using the genomic relationship matrix to remove population sub-structure, were fitted using GenABEL. Genome and chromosome-wide significance thresholds were estimated empirically. The heritability of resistance to bTB was estimated using ASReml. The odds ratios (OR) of significant bTB-associated risk alleles were estimated in the GLM package in R.

**Results**

The heritability of bTB resistance was estimated at 0.21 (standard error 0.06). The number and magnitude of associations between SNPs and resistance to bTB exceeded expectation under the null hypothesis of no association (Figure 1 The signal of association across the 29 bovine autosomal chromosomes reached chromosome wise significance at the 5% level for three SNPs, and 10% level for two SNPs. The minor alleles at three of these SNPs reduced risk (OR <0.65 [95% confidence interval {CI} 0.39-0.81]) and two increased

risk (OF >1.50 [95% CI 01.15-2.42]) of bTB, and together these SNPs explained 4.3% of the additive genetic variance in resistance to bTB in the NI HF dairy cattle population sample investigated in this study.

**Conclusion**

Resistance to bTB is a moderately polygenic trait, with the five most significant SNPs associated with bTB in this study explaining 4.3% of genetic variance. These results need to be replicated across different cattle populations, phenotype definitions and *M. bovis* strain environments to provide robust evidence for association with resistance to bTB.

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**Legend**

Fig.1

The Q-Q plot showing observed p-value for associations between genotyped SNPs and resistance to bovine tuberculosis (dots), compared to p-values expected under the null hypothesis of no association (diagonal line).