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Host genetic resistance to mycobacterial infections in bovines

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Abstract
Bovine Tuberculosis and Paratuberculosis of mycobacterial etiology cause severe economic losses to dairy sector and also carry with them the associated risk of public health burden. In absence of cost effective treatment regimens or efficient vaccines for these mycobacterial infections, it is often very difficult to control/manage these at the dairy farms. Control is primarily restricted to culling of cattle that react positively to the single intradermal comparative cervical tuberculin test. Further, reservoirs of TB in wildlife populations have been linked to the persistence or increase of the incidence of bovine TB in some countries. Breeding for increased host resistance to infection is alternative or complementary strategy as changes are permanent. Genetic variation in susceptibility to tuberculosis has been observed in cattle. The present review highlights the underlying host genetic variation in resistance/susceptibility to mycobacterial infections and results of several genetic association studies carried out across the world.

Keywords: Genetic marker, resistance, mycobacteria, bovines

Introduction
Bovine Tuberculosis (bTB) and Bovine paratuberculosis (PTB) are two important mycobacterial infections that cause severe monetary losses to the dairy sector besides posing an enormous public health threat. BTB caused by Mycobacterium bovis, is a chronic respiratory disease characterised by granulomas in affected tissues with substantial animal health and welfare consequences, as well as a serious economic impact. On a global scale, this zoonotic pathogen is estimated to cause 10-15% of human TB cases in the developing world [25]. It is considered to be the fourth most significant livestock disease in terms of impact on human health and economics in developing countries, including risks to other livestock and wildlife [28]. Additionally, there is evidence that subclinical bTB has a negative impact on productivity in dairy cows, increasing the costs incurred by the dairy industry [9]. As many parts of the world have no active surveillance programmes and limited epidemiological studies, the prevalence and impact of bTB worldwide is likely to be underestimated [20]. It can be transmitted to humans via droplet infection or by food intake of unpasteurized milk. Bovine tuberculosis is also transmittable back from humans to cattle. The impact of bovine tuberculosis infection is manifold, with losses incurred by depopulation of herds, social problems from removal of cattle from small holdings and also the economic consequences resulting from herd restrictions, disruptions to trade and reduced agricultural productivity, particularly in the developing world. In India and many other countries though bovine tuberculosis is known to be reported in cattle, control policies have not been enforced effectively due to cost implications, lack of capacity and infrastructure limitations. Further the human population has a greater vulnerability due to population pressure, poverty and reduced access to health care. *Mycobacterium avium* sub species *paratuberculosis* (MAP) is a facultative intracellular pathogen that causes Johne's disease (JD), a chronic granulomatous inflammation of the intestine characterized by persistent diarrhea, progressive wasting, and finally death. Loss due to reduced milk yields alone in case of *Mycobacterium avium* subspecies paratuberculosis (MAP) infected cows were reported to be Rs 54,442.5 /cow/lactation in India [32]. Paratuberculosis is now-a- days viewed as one of the most important and wide spread bacterial disease of ruminants. Cattle less than 6 months of age are most susceptible and it was estimated that approximately one-third of calves may develop infection with a single exposure. In India, paratuberculosis is in endemic form [38] and it has zoonotic potential.

High prevalence of paratuberculosis was reported in domestic livestock using indigenous, sensitive and MAP specific test in north India. Sero-prevalence of bovines PTB was 29.0% (28.6% in buffalo and 29.8% in cattle) in north India [36]. In Uttar Pradesh and Punjab, seroprevalence of bovine PTB was 32.9% (31.9% in buffalo and 37.6% in cattle) and 25% (23.3% in buffalo and 26.9% in cattle), respectively [23]. Generally treatment for bovine tuberculosis and paratuberculosis is not recommended in animals since there is no cost effective treatment for bovine tuberculosis.

Host genetic variation in susceptibility to mycobacterial infections

In absence of strong treatment/ vaccination regimens, alternative or complementary control strategies are required and breeding for increased host resistance to infection or disease is one such approach. Host genetic variation in disease resistance invariably exists, due in large part to the variability in host immune responses to infection [8]. Therefore, in principle, it may be possible to improve genetic resistance. An alternate strategy that can be applied to combat mycobacterial infections is to identify cattle which are comparatively resistant/ tolerant to the tuberculosis and delineate the inherent genetic differences in immune response at molecular level. Genetic variation in susceptibility to tuberculosis has been observed in cattle. Higher resistance to bovine tuberculosis has been reported among *Bos indicus than Bos Taurus* [1]. Also, certain pedigree lines of cattle show greater and lesser susceptibility to the disease [29]. Estimates of the heritability of response to M. bovis PPD (purified protein derivative) in Irish herds were up 0.2769, while heritability of TB susceptibility in British herds was estimated as 0.18 ± 0.0410 [5, 10].Susceptibility to MAP infection is heritable with heritability estimates ranging from 0.06 to 0.102[19]. These studies provided evidence for the existence of important genetic variation in susceptibility to paratuberculosis.

Genes involved in recognition of components of *Mycobacterium bovis* and subsequent activation of both innate and adaptive immune response have been investigated as potential strong candidates for genetic basis of resistance. In the SP110 nuclear body protein (SP110) gene polymorphism has been reported to be associated with tuberculosis [37]. However [3] reported that in SNPs rs41256732 and rs134537150 of SP110 and SNPs rs137338039 and s208436798 of DC-SIGN gene, the genotype as well as allele had non-significant effect on occurrence of bovine tuberculosis. At rs109915208 locus the genotypic as well as allelic frequencies were differing significantly in case–control animals where the odds ratio (OR) of 'CC' verses 'CT' genotype and the OR of 'C' verses 'T' allele were approaching towards infinity, suggesting that animals having 'CT' genotype and 'T' allele were less susceptible for tuberculin reaction as compared to their contemporary genotype/allele [2]. In TLR2 gene, two of SNPs under study (rs55617172 and rs68268253) revealed polymorphism while in the case of TLR4 gene all four SNPs under investigation (rs8193041, rs207836014, rs8193060, and rs8193069) were found to be polymorphic in case-control population. SNP locus rs55617172 in TLR2 gene was found significantly (p<0.01) associated with susceptibility/resistance to TB in cattle [6]. Chauhan *et al* [14] reported that expression of candidate gene CXCR3 was significantly upregulated (5.22 fold) in PBMCs of *M. bovis* infected cattle vis a vis healthy controls. In TLR9 gene, SNP loci rs210982793 and rs207807011 were significantly associated with susceptibility to bovine tuberculosis in the case control population. At SNP locus rs210982793, probability values showed that the genotype (P = 0.01) as well as allele (P <0.01) had significant effect on occurrence of bovine tuberculosis. The odds of CC and CT genotypes verses TT were close to zero, revealing that TT genotypes were relatively more resistant to bTB in comparison to other two genotypes. The OR of A verse G was 0.27 revealing lower susceptibility of A allele with bTB in comparison to G allele at TLR9-A1433G locus. The OR of AG versus GG was 0.19 which suggested that AG genotype were less susceptible to tuberculosis as compared to GG. Both these SNPs loci were non-synonymous, thus suggestive of their functional role in the immune response against bovine tuberculosis [7].In an investigation on association between polymorphisms in TLR2 of Chinese Holstein cattle and susceptibility to bovine tuberculosis, the allele and genotype distributions of A631G (rs95214857) and T1707C (rs1388116488) were not different between case and control groups, indicated that these SNPs were not associated with susceptibility to BTB. Using microarray analysis, Shukla *et al.* [35] identified TLR2, CD80, NFKB1, IL8, CXCL6 and ADORA3 as putative candidate genes based on differential gene expression in *Mycobacterium bovis* challenged monocyte-derived macrophages of cattle. In study aimed to investigate the effect of four SNPs (G1793A, C1859A, A1980G, G1934A) in toll-like receptor 6 (TLR6) on bovine tuberculosis (bTB) resistance in Chinese Holstein cattle in a case-control study. Genotype frequencies of C1859A and A1980G site differed significantly between bTB-infected and non-infected cows. Relative risk of tuberculosis incidence result showed that genotypes of AA or CA had greater relative risk than those with genotype CC at C1859A site between bTB-infected and non-infected animals. Genotypes of GG or GA had greater relative risk than those with genotype AA at A1980G site. No significant association can be inferred from G1793A and G1934A polymorphism site. Significantly increased BTB susceptibility was evident in T allele carriers of -5C/T, G allele carriers of 613G/A and TG haplotype carriers of both SNPs in the CD14 gene in Chinese Holstein cows [41]. These results suggested that -5C/T and 613G/A are risk factors for BTB in Chinese Holstein cattle and might be used as candidate genetic markers in breeding cows with natural resistance to BTB [41]. Case-control association testing and statistical analysis identified six SNPs associated with susceptibility to BTB in Chinese Holstein cows. The frequency of genotypes C/T, A/G, A/G, A/G, C/T, and A/G in E4 (-37), 208, 1644, 1648, 1799, and E10 (+107), respectively, was significantly higher in cases than in controls, and also the alleles C, A, A, G, T, and A, respectively, were associated with a greater relative risk in cases than in controls. The distribution of two haplotypes, TGGACA and CAGACA, was significantly different between cases and controls. Overall, this case-control study suggested that E4 (-37)(C/T), 208(A/G), 1644(A/G), 1648(A/G), 1799(C/T), and E10 (+107)(A/G) in the CARD15 gene were significantly associated with susceptibility to BTB in Chinese Holstein cows and that haplotypes TGGACA and CAGACA could be used as genetic markers in marker-assisted breeding programs for breeding cows with high resistance to BTB[40].

Reports are available about association study of bovine paratuberculosis with candidate gene polymorphism [21, 22, 27, 30, 33, 34]. SNP N23 of Nramp1 (located in the BTA2 and comprises 15 exons) was genetically associated (P=0.0478)

with resistance to the paratuberculosis infection [33]. Koets *et al.* [21] reported that the TLR2-1903 T/C SNP was significantly associated with resistance to MAP where cows with CT and CC genotypes were at 1.7 (95% CI: 1.2, 2.8) times the odds of being MAP infected compared to cows with the TT genotype. Pant *et al.* [27] reported 22 SNPs on 7 different chromosomes significantly associated with the disease trait using this genome-wide threshold. Pinedo *et al.* [30] characterize the distribution of polymorphisms in the bovine CARD15 gene and test their association with paratuberculosis infection in cattle. Pinedo *et al.* [30] reported a significant association between infection status and BoIFNGSNP12781 and SLC11A1-275–279-281 microsatellites. Verschoor *et al.* [39] that SNPs in IL10RA are associated with MAP infection status in dairy cattle. Pant *et al*. (2011) reported four SNPs in IFNGR2, IL12RB1, IL12RB2, and IL23R were found to be associated with the MAP infection status of the resource population. In a case: control association study conducted in cattle using 20 SNPs selected from the cattle QTL database on the basis of the potential role in mycobacterium susceptibility, SNP (rs41945014) was significantly associated with MAP and revealed that ODDs of GG and GT genotypes verses TT genotype were 1.22 and 3.37 respectively. The proportion of GG and GT genotypes were significantly higher in bovine paratuberculosis positive animals suggested that selection against these 2 genotypes may confer resistance against bovine paratuberculosis [42]. Chauhan *et al.* [15] reported differential expression of candidate genes of Toll like Receptors and Interleukins family namely TLR2, IFN-ã, IL2, IL8 and TNF in *Mycobacterium avium* sub sp. Paratuberculosis infected cattle. Kumar *et al*. [22] reported that SNP rs110480812 in SP110 gene, two genotypes observed i.e. CT and TT were not significantly different ($p>0.05$) between case and control cattle. The ODDs of CT genotype verses TT genotype was 2.98 (0.74-11.94; 95 % CI). Neither alleles nor genotypes showed significant association with occurrence of paratuberculosis in the analyzed cattle population. As a criterion of innate immunity development, Chaudhary *et al.* [11] reported that levels of IgG in buffalo colostrums (before first milking) estimated by Indirect ELISA ranged from 11.22 to 185.1 mg/ml and mean IgG concentration in colostrum was 51.71 ± 5.99 mg/ml. In beta 2 micro globulin (β2M), a structural gene which acts as an integral component of FcRn (neonatal Fc receptor) heterodimer for its cell surface expression, two insertions and one deletion of nucleotides in the intronic and exonic regions of β2M gene in buffalo were observed in comparison to β2M gene of cattle[11]. The least square analysis of variance revealed a non-significant effect of dam β2M haplotype on IgG concentrations in colostrums [13]. Similar non-significant association between β2M haplotypes in buffalo calves with serum IgG concentration was also observed by [11]. Chauhan *et al.* [16] reported differential expression profile of innate immune response genes including TLR2, NFKB1, TNF, IFNG, IL2, CXCR3, PRKCB1, RPS6KB2, STK17B and EEF1. Mishra *et al.* [26] identified single nucleotide polymorphisms in 5' upstream region of bovine TLR4 gene affecting expression profile and transcription factor binding sites. These findings in different genes offer essential evidence that can be useful in future research exploring its role in immunity and these genes/SNPs can be used as a marker for selection for disease resistance in bovines.

Raphaka *et al.* [31] quantified the impact of genetic selection for bTB resistance on cattle-to-cattle disease transmission dynamics and prevalence by developing a stochastic genetic epidemiological model. The model was used to implement genetic selection in a simulated cattle population. The model considered various levels of selection intensity over 20 generations assuming genetic heterogeneity in host resistance to infection. Our model attempted to represent the dairy cattle population structure and current bTB control strategies in the UK, and was informed by genetic and epidemiological parameters inferred from data collected from UK bTB infected dairy herds. The risk of a bTB breakdown was modeled as the percentage of herds where initially infected cows (index cases) generated secondary cases by infecting herd-mates. The model predicted that this risk would be reduced by half after 4, 6, 9, and 15 generations for selection intensities corresponding to genetic selection of the 10, 25, 50, and 70% most resistant sires, respectively. In herds undergoing bTB breakdowns, genetic selection reduced the severity of breakdowns over generations by reducing both the percentage of secondary cases and the duration over which new secondary cases were detected. Selection of the 10, 25, 50, and 70% most resistant sires reduced the percentage of secondary cases to <1% in 4, 5, 7, and 11 generations, respectively. Similarly, the proportion of long breakdowns (breakdowns in which secondary cases were detected for more than 365 days) was reduced by half in 2, 2, 3, and 4 generations, respectively. Collectively, results suggest that genetic selection could be a viable tool that can complement existing management and surveillance methods to control and ultimately eradicate bTB.

Conclusion

The existing control strategies have proven insufficient to eradicate the disease. This may be partially attributed to the low sensitivity of the skin test, potentially leading to undetected infected animals that contribute to the recurrence of breakdowns [17]. Another contributing factor is the existence of wildlife reservoirs of M. bovis (for example, the Eurasian badger in the UK) [18]. The problem persists even in developed countries like UK and there is no clear evidence for a decline despite the UK government spending over £175 million annually in the control of the disease [24]. Thus, genetic selection for increased resistance of cattle may provide a potential complementary strategy. Importance of considering genetic selection as an additional control tool can complement existing strategies. Bearing in mind that genetic selection is important, especially with the view of accelerating the control and eradication of bTB, future research should consider additional genetic selection strategies such as selection for resistant dams and selection for reduced individual animal infectivity for mycobacterial infections.

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