

REVIEW ARTICLE

Host Genetic Determinants of Resistance to Bovine Babesiosis and Its Tick Vector: Implications for Sustainable Disease Control

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Abstract

Bovine babesiosis, caused primarily by the tick-borne apicomplexans *Babesia bovis* and *Babesia bigemina*, remains one of the most economically important haemoparasitic diseases affecting cattle in tropical and subtropical regions. Conventional control strategies, including acaricides, chemotherapy, and live blood-derived vaccines, are limited by resistance, chemical residues, cold-chain requirements, and incomplete strain protection, prompting interest in host genetic resistance as a sustainable complement. Indicine (*Bos indicus*) cattle, and some taurine breeds, exhibit heritable variation in resistance to both *Babesia* infection and its *Rhipicephalus* tick vector. This review integrates current knowledge of the immunological basis of resistance with advances in quantitative and functional genomics and their applications in breeding. We examine disease pathobiology, innate and adaptive immune mechanisms, breed-associated and within-breed variation, and the genetic architecture of resistance revealed through heritability estimates, bovine leukocyte antigen and immune-related genes, quantitative trait loci, genome-wide association studies, and selection signatures. Throughout, we distinguish direct evidence (*Babesia* infection measured) from indirect evidence (tick burden, general immune response, or tropical adaptation). We conclude that resistance is polygenic and environmentally influenced. Direct genomic evidence for *Babesia* resistance remains limited; most mapped loci derive from tick-count phenotypes.

Keywords: Bovine babesiosis, *Babesia bovis*, Genomic selection, Host genetic resistance, *Rhipicephalus microplus*, Sustainable disease control

INTRODUCTION

Bovine babesiosis is a tick-borne haemoprotozoan disease of cattle caused principally by the intraerythrocytic apicomplexan parasites *Babesia bovis* and *Babesia bigemina*, with *Babesia divergens* important in parts of Europe^[1]. Transmission depends on ixodid ticks, mainly *Rhipicephalus* (*Boophilus*) species, which acquire the parasite during feeding and pass it transovarially to the next generation^[2]. Several agents of the disease, and *B. divergens* in particular, also infect humans, which gives the problem a zoonotic dimension^[3].

The scale of the burden is large. Roughly 80% of the world's cattle are raised in regions at risk of tick-borne disease^[4], and a systematic meta-analysis placed the pooled global

prevalence of bovine babesiosis at 29%, highest in South America and lowest in Asia, with wide regional variation^[5]. In endemic countries the disease causes mortality, abortion, lost milk and weight gain, and the recurring cost of treatment and tick control, with smallholders absorbing a disproportionate share of these losses^[6]. Regional surveys, including work across Punjab in Pakistan and molecular characterization of piroplasms in cattle from Azad Kashmir, continue to record high *Babesia*/piroplasm prevalence in cattle and to expose gaps in diagnosis and control in South Asian systems^[7-9].

Current control rests on three pillars, each now under strain: acaricides, chemotherapy, and live blood-derived vaccines. Host genetic resistance has therefore emerged as a promising complement to these conventional control measures.



The central argument of this review is that heritable host resistance to *Babesia* and to its tick vector is real, measurable, and potentially exploitable, and that it should be treated as a complementary pillar of control rather than a curiosity. Here, tick resistance means a lower tick burden, measured as tick count, and *Babesia* resistance means a lower *Babesia* infection level, usually measured by quantitative polymerase chain reaction (qPCR); these two terms are used throughout. We distinguish resistance, which reduces tick or pathogen burden, from tolerance, which reduces disease impact at a given burden; studies scored on clinical outcome may capture both. Indicine (*Bos indicus*) cattle are markedly more resistant than taurine (*Bos taurus*) animals under controlled challenge ^[10], and variation persists within breeds, which is what makes selection feasible. What this review adds beyond existing accounts is an explicit integration of three literatures usually read separately: the immunology that defines the biological substrate of resistance, the quantitative and functional genomics that map and explain it, and the breeding and One Health strategies that translate it into the field.

We therefore summarize the disease and the limits of current control; describe the immune pathways on which resistance loci act; review the empirical evidence for breed-associated and within-breed resistance; synthesize the genetic architecture from heritability through genome-wide association and selection signatures; examine functional-genomic mechanisms and parasite and vector genetic variation; and assess how this knowledge can be deployed sustainably, before setting out the main knowledge gaps.

LITERATURE SEARCH STRATEGY

This article is a narrative review, and the literature was assembled through a structured but non-exhaustive search. PubMed, Web of Science, Scopus and Google Scholar were searched from database inception until the final search on 5 June 2026. Search strings combined terms for the disease and its agents (“bovine babesiosis”, “*Babesia bovis*”, “*Babesia bigemina*”, “tick-borne disease”, “*Rhipicephalus microplus*”) with terms for host genetics and control (“host genetic resistance”, “breed resistance”, “*Bos indicus*”, “heritability”, “quantitative trait loci”, “genome-wide association”, “selection signature”, “genomic selection”, “BoLA” (bovine leukocyte antigen), “transcriptome”, “vaccine”), using Boolean operators and truncation where the database permitted. The reference lists of retrieved reviews and primary papers were screened by hand, and a small number of further records were identified in this way. In total, approximately 1500 records were retrieved and 600 were screened by title and abstract.

Titles and abstracts were screened against three questions: whether host genotype influences *Babesia* infection or

tick burden in cattle, which genomic regions or immune pathways underlie that variation, and how the resulting knowledge can be applied in breeding and integrated control. Full texts were retained when they reported original phenotypic, genetic, genomic or functional data in cattle, or when they offered an authoritative synthesis of such data. Records were excluded when they concerned babesiosis in non-bovine hosts without comparative relevance, when they reported diagnosis or prevalence with no bearing on host variation or control, or when they duplicated data reported more fully elsewhere. Work published in the last ten years was prioritized, although older studies were kept where they remain the primary source for a finding, as with the controlled breed-challenge experiments of the 1990s and the earliest quantitative trait locus scans. Because the body of direct *Babesia*-resistance genomics is small, every study of that type that was identified has been retained, whereas the much larger tick-resistance literature was sampled for representative and methodologically strong reports. Sixty-six sources are cited in the final review.

BOVINE BABESIOSIS: ETIOLOGY, BURDEN, AND THE LIMITS OF CURRENT CONTROL

Causative Agents, Vectors, and Transmission

B. bovis and *B. bigemina* differ in biology and virulence. *B. bovis* is the more pathogenic, producing infected erythrocytes that sequester in the microvasculature and cause cerebral and respiratory disease, whereas *B. bigemina* typically causes a more acute but less neurovirulent haemolytic syndrome ^[1]. Both are transmitted by *Rhipicephalus* ticks with transovarial passage, a feature that sustains parasite populations independently of continuous cattle-to-cattle spread ^[2]. Vector competence is specific: the invasive Asian longhorned tick *Haemaphysalis longicornis*, despite acquiring *B. bovis* deoxyribonucleic acid (DNA), failed to transmit the parasite transstadially or transovarially, which constrains predictions of geographic spread ^[11]. The diversity of co-circulating haemoparasites is often underestimated, and molecular surveys in endemic regions frequently detect mixed piroplasm and *Anaplasma* communities that complicate diagnosis and control ^[12,13]. Recent South Asian work identifying cattle piroplasms in Azad Kashmir and cytochrome-b based *Theileria annulata* lineages in Pakistani bovines reinforces that *Babesia* control often occurs within a broader tick-borne-pathogen landscape ^[9,14].

Epidemiology, Economic Impact, and Endemic Stability

Whether babesiosis causes heavy losses in a given herd depends less on the presence of the parasite than on

the balance between infection pressure and the age structure of susceptibility, summarized in the concept of endemic stability. Where transmission is high and calves are infected while still protected by innate age-related resistance, clinical disease is rare; where transmission is unstable, naive adults are exposed and outbreaks follow [2,6]. This conditions every control decision, since measures that reduce tick contact can destabilize a previously stable system. The burden itself is unevenly distributed: pooled prevalence varies widely by region and host species, exceeding one-tenth of animals in parts of East Asia and reaching high levels in water buffaloes, which act as additional reservoirs [15,16], while Indonesian work on *Babesia naoakii* shows that ruminant babesiosis outside the classical *B. bovis* and *B. bigemina* framework can be clinically and epidemiologically important in Asian production systems [17,18]. Climate change adds further uncertainty, with distribution models projecting expansion of *R. microplus* into higher latitudes and altitudes under warming scenarios [19].

Current Control Tools and Their Limitations

The mechanisms, strengths, limitations, and sustainability profiles of the main control tools are compared in [Table 1](#). Two points deserve emphasis here. First, acaricide resistance in *R. microplus* is now widespread and multi-class, arising through target-site mutations and metabolic

detoxification, and molecular markers that reliably predict field resistance remain elusive, since several historically reported resistance mutations occur in both resistant and susceptible isolates [20,21]. Second, vaccine development has been difficult. Live attenuated blood vaccines protect but carry contamination and cold-chain risks [22], while rationally designed subunit and viral-vectored candidates have induced strong T helper 1 responses yet failed to elicit the neutralizing antibodies needed for protection on challenge [23]. Anti-tick vaccines that target parasite-independent tick antigens offer a complementary route but have shown variable, often incomplete, efficacy [24]. Plant-derived acaricides remain a secondary but active line of research, with recent studies/reviews testing essential oils and *Moringa oleifera* extracts against livestock ticks, including *R. microplus* [25,26]. Taken together, these limits, rather than any single failure, make a complementary host-encoded contribution attractive ([Fig. 1](#)).

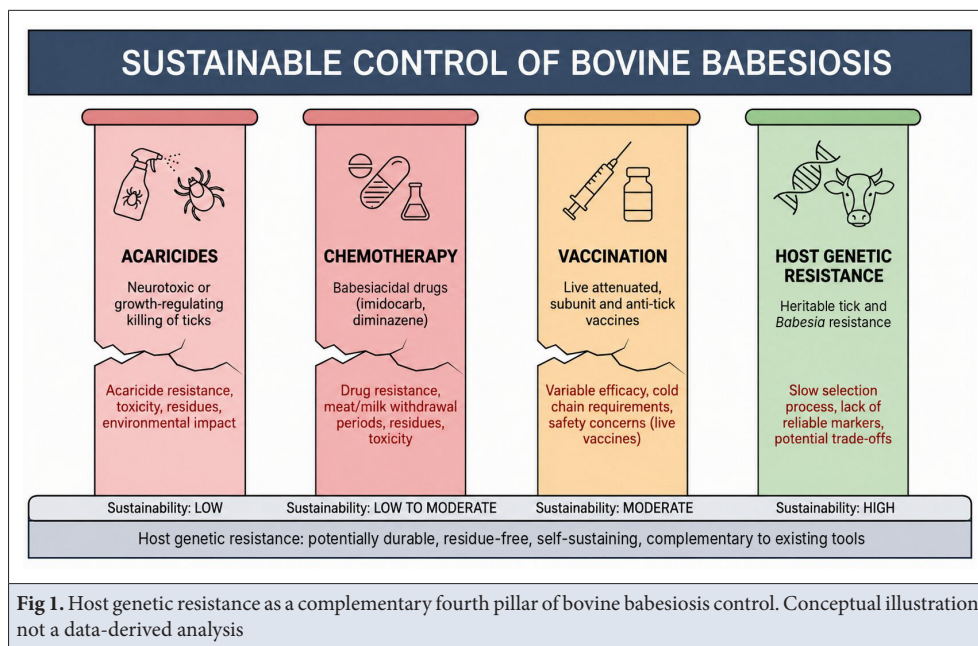
Zoonotic Dimensions and the One Health frame

Beyond the direct losses noted above, economic weight accumulates through the chronic carrier state, which sustains transmission while depressing performance below the threshold at which owners typically seek treatment [2]. The disease also constrains the use of high-producing taurine genetics in the tropics, because the productivity gain of taurine breeds is offset by their

Table 1. Principal tools for controlling bovine babesiosis and its tick vector, compared by mechanism, strengths, limitations, and sustainability

Control Approach	Mechanism/Basis	Key Strengths	Principal Limitations	Sustainability	References
Chemical acaricides	Neurotoxic or growth-regulating killing of ticks	Rapid knockdown; cheap; widely available	Multi-class resistance; milk and meat residues; environmental cost; can destabilize endemic stability	Low	[6,20,21]
Chemotherapy (imidocarb, diminazene)	Babesiocidal drugs	Effective acute treatment; can clear carrier state	Narrow arsenal; residue and withdrawal limits; emerging insensitivity; no new classes	Low to moderate	[27]
Live attenuated/blood-derived vaccines	Pre-immunization with attenuated parasites	Strong, durable protection; field-proven	Cold-chain dependence; contamination and reversion risk; batch variability	Moderate	[22,27]
Subunit/viral-vectored vaccines	Recombinant parasite antigens (e.g., MSA-2c, RAP-1)	Defined; safe; scalable	Incomplete strain coverage; weak neutralizing antibody; no licensed product	Moderate (developmental)	[23,28]
Anti-tick vaccines	Immunization against tick antigens (Bm86, serpins, FER2/TPM)	Reduce tick fitness; benign; slow acaricide resistance	Variable, often incomplete efficacy; antigen and strain dependence; multi-dose	Moderate to high	[24,29,30]
Botanical/biological control	Plant extracts; entomopathogens	Low residue; locally sourced	Early stage; variable potency; limited field validation	Moderate	[25,26,31]
Host genetic resistance (this review)	Heritable tick resistance and <i>Babesia</i> resistance	Potentially durable; self-sustaining; no residues; additive to other tools	Slow to deploy; phenotyping-limited; possible productivity trade-offs	High	[32,33]

Sustainability ratings are qualitative author judgments based on the cited evidence, considering durability of effect, risk of resistance, residues, environmental impact and need for repeated inputs or a cold chain. MSA-2c, merozoite surface antigen 2c; RAP-1, rhoptry-associated protein 1; FER2, ferritin 2; TPM, tropomyosin



susceptibility to tick fever, which is the central tension that genetic improvement of resistance sets out to resolve [34]. A zoonotic dimension compounds the animal-health burden, since several *Babesia* species infect humans, splenectomized and immunocompromised people are at particular risk of severe disease, and the absence of a licensed human vaccine leaves control dependent on managing infection in animal reservoirs and limiting tick contact [3]. These features place bovine babesiosis within a One Health frame, in which animal genetics, human health, and tick ecology cannot be addressed in isolation.

PATHOBIOLOGY AND THE HOST IMMUNE RESPONSE AS THE SUBSTRATE FOR GENETIC VARIATION

Resistance loci do not act in a vacuum; they exert their effects through defined immune and physiological pathways, so the biology on which they operate is the necessary starting point.

Infection Biology and Pathogenesis

After tick inoculation, *Babesia* merozoites invade erythrocytes, replicate, and lyse the host cell, producing the haemolytic anaemia, haemoglobinuria, and fever that define acute disease [1]. The distinctive virulence of *B. bovis* follows from cytoadhesion: parasite proteins exported to the erythrocyte surface mediate binding to vascular endothelium, sequestering infected cells in the brain and other organs and producing the neurological and respiratory signs of cerebral babesiosis [35]. The variant

erythrocyte surface antigen 1 family, encoded by the *ves* multigene family, drives both this sequestration and antigenic variation, and recent transcriptomic work identifies *ves1α* expression as the principal determinant of cytoadhesion strength [35]. The accompanying inflammatory response is double-edged, controlling parasite replication while also contributing to the pathology of severe disease [36].

Innate Immunity

Control of acute infection is heavily spleen-dependent, with splenic macrophages activated to produce nitric oxide, reactive oxygen species, and inflammatory cytokines that limit parasitaemia [1]. The well-documented age-related resistance of calves, which underlies endemic stability, is largely innate and spleen-associated rather than antibody-mediated [2]. Differences between resistant and susceptible animals are detectable at these innate nodes: in cattle of differing indicine ancestry, animals with a *Bos indicus* maternal lineage mounted an earlier and more connected innate response to tick infestation, with greater monocyte and natural killer (NK) cell involvement, than animals of taurine lineage [37].

Adaptive Immunity

Protective adaptive immunity is dominated by CD4+ T helper 1 responses, in which interferon gamma (IFN-γ) primes macrophages, supported by antibodies that opsonize parasites and parasite antigens displayed on the erythrocyte surface [27]. Persistently infected animals develop concomitant immunity that limits disease on re-exposure, and antigen presentation by major histocompatibility complex (MHC) molecules restricts which T-cell epitopes are recognized, linking the adaptive

response directly to host genotype^[38]. The failure of a multi-antigen subunit vaccine to protect despite strong T helper 1 induction indicates that cellular responses alone are insufficient and that antibody quality matters^[23].

The relative contributions of the innate and adaptive arms are not fixed across the course of infection. Survival of the acute phase depends on rapid innate control before adaptive immunity matures, which is why the spleen and macrophage activation are decisive in naive animals, whereas durable protection in recovered animals rests on memory T cells and antibody^[1,27]. This temporal structure has a practical corollary that recurs later in this review: interventions that accelerate or broaden innate responsiveness, such as trained-immunity strategies, act on the same early window in which genetically resistant animals already hold an advantage^[39]. It also explains why animals of different genetic background diverge most clearly during early infection, when innate differences are expressed before the adaptive response converges^[37]. For genetic dissection the implication is concrete: a resistance phenotype measured at a single time point can misrepresent an animal's true standing, so the timing of sampling matters as much as the trait that is scored.

From Immune Phenotype to Genetic Variation

The nodes above, that is, MHC-restricted antigen presentation, cytokine signaling, and macrophage effector function, vary between animals and between breeds, and that variation is heritable. Expression of chemokine and Toll-like receptor genes during natural infection differs with genetic group and tracks with *Babesia* infection level^[36]. This provides the mechanistic rationale for the genetic dissection that follows, on the working assumption that at least some of the loci mapped in later sections correspond to heritable variation in these immune

pathways. The assumption is reasonable but largely untested, since few mapped loci have yet been connected experimentally to a specific immune function. The major pathobiological and immunogenetic control points linking infection biology to host resistance are shown in Fig. 2.

THE PHENOMENON OF BREED-ASSOCIATED RESISTANCE

The clearest evidence that host genetics shapes outcome comes from breed comparisons.

Bos indicus versus *Bos taurus*

Under controlled challenge with virulent *B. bovis*, pure *Bos indicus* cattle are markedly more resistant than *Bos taurus* cattle, with crossbreds intermediate^[10]. Natural-infection studies in dairy and beef systems also show wide variation in *Babesia* infection levels among taurine and high-taurine animals^[36,40].

The Crossbreeding Gradient: How Much Zebu is Enough?

The protection conferred by indicine ancestry is dose-dependent, and recent evidence sharpens an important caveat: a small proportion of zebu background in crossbred calves was not sufficient to measurably improve resistance to natural *Babesia* infection, with high-taurine composites carrying higher parasite DNA loads than purebred taurine animals^[34]. This argues against assuming that any indicine admixture yields useful protection and has direct consequences for crossbreeding design.

Within-breed Phenotypic Variation

Resistance is not purely a between-breed phenomenon. Resistant, intermediate, and susceptible phenotypes

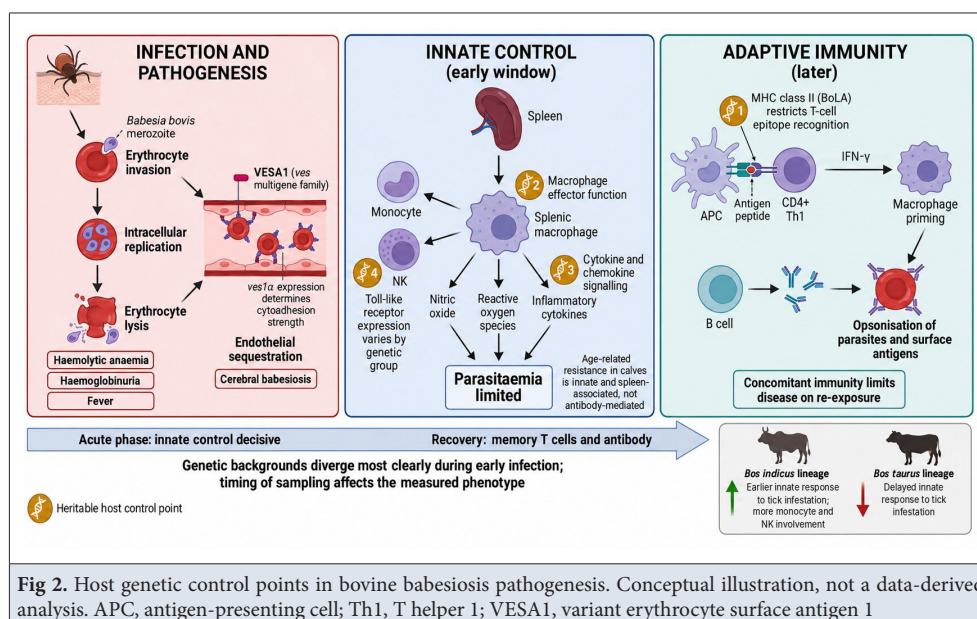


Fig 2. Host genetic control points in bovine babesiosis pathogenesis. Conceptual illustration, not a data-derived analysis. APC, antigen-presenting cell; Th1, T helper 1; VESA1, variant erythrocyte surface antigen 1

segregate within taurine and within zebu populations, and individual animals differ consistently over time in both tick burden and *Babesia* infection level, which is precisely the variation that selection can exploit ^[41,42]. In a tropically adapted taurine breed, resistance also tracked with coat and hair characteristics and varied with age, indicating that several heritable traits contribute to the resistant phenotype ^[42].

Disentangling Tick Resistance from *Babesia* Resistance

A point that is often blurred deserves emphasis: tick resistance and *Babesia* resistance are correlated but genetically distinct traits. Repeatability analyses show that an animal's tick count and its *Babesia* infection level are only weakly to moderately correlated, so an animal resistant to ticks is not automatically resistant to the parasite ^[41]. This distinction is consequential for the genetics that follows, because most mapping studies have measured tick count as a proxy and comparatively few have phenotyped *Babesia* infection directly.

This distinction also determines how the evidence in the sections that follow should be weighted, and it is worth setting out the grading applied from this point onward. Direct evidence comes from studies in which *Babesia* infection or clinical babesiosis was itself phenotyped and related to host breed or genotype. This category is small, and most of what exists has already been introduced: controlled challenge of indicine and taurine cattle with virulent *B. bovis* ^[10], comparison of natural infection across crossbred and purebred animals ^[34], differences in immune-gene expression and *Babesia* infection level between genetic groups under natural challenge ^[36], and repeatability estimates for infection level in dairy and beef herds ^[40,41]. The sections that follow add only a small number of quantitative-genetic and genomic studies that phenotyped *Babesia* infection directly.

Indirect evidence through the vector comes from the much larger body of work in which tick count or tick resistance was the measured phenotype ^[41,42], and it bears on *Babesia* only insofar as reducing tick burden reduces exposure, which the weak correlation between tick count and *Babesia* infection level shows to be a partial relationship ^[41]. Almost all of the mapping, association and prediction studies reviewed in the next section fall into this category.

Functional support comes from transcriptomic and immunological studies that separate resistant from susceptible animals but did not phenotype *Babesia* infection ^[4,37]. General adaptation evidence comes from selection scans in tropically adapted breeds, reviewed below, in which immune-related sweeps are recovered alongside heat tolerance and other adaptive traits and

cannot be assigned to babesiosis specifically. Where the sections that follow rest on the second, third or fourth of these categories, this is stated rather than left implied.

HOST GENETIC ARCHITECTURE OF SUSCEPTIBILITY AND RESISTANCE

The heart of the question is which genes and loci underlie resistance, how much of the variation they explain, and how repeatable the signals are across populations.

Heritability and Genetic Parameters

Resistance traits are heritable but only modestly so, which sets realistic expectations for selection. The pattern is informative rather than incidental. Heritability for tick count is low to moderate and highly variable across breeds and seasons, whereas heritability for *Babesia* infection level is consistently lower still, and the genetic correlation between the two traits is weak ^[33,43]. Two consequences follow. Direct selection on *Babesia* resistance will be slower than on tick resistance, and gains in one cannot be assumed to carry over to the other. Encouragingly, genetic correlations between resistance and production traits are generally weak rather than strongly antagonistic, which keeps combined improvement feasible ^[44].

Candidate Genes and Immunogenetics

The bovine MHC, the BoLA region, recurs as a candidate across mapping studies, which is consistent with its role in antigen presentation and T-cell epitope restriction. This recurrence comes largely from tick-resistance mapping, however, and the MHC is a gene-dense, highly polymorphic region that is recovered frequently in genome scans for many traits, so its repeated appearance is suggestive rather than confirmatory. Specific BoLA-DRB3 alleles associate with susceptibility or resistance to other bovine pathogens, such as bovine leukemia virus ^[45], and, more directly for this review, particular BoLA-DRB3 alleles were associated with reduced risk of *B. bigemina* infection while others were linked to increased susceptibility to *B. bovis* in Colombian Creole cattle ^[46]. Beyond the MHC, candidate windows from genome-wide studies repeatedly implicate immune and inflammatory genes, including cytokine and effector loci, which is broadly consistent with the immune pathways described earlier. The mapped windows are wide and gene-rich, so the genes named within them remain candidates awaiting functional confirmation rather than established effectors ^[33,47]. The Colombian Creole study is one of very few published associations between a defined host locus and *Babesia* infection status in cattle. It was observational and based on small samples from three breeds, so the alleles it identifies are best treated as leads for replication rather than as validated markers. The wider BoLA-DRB3 literature concerns other pathogens

and supports the general expectation that the region is relevant to infectious-disease outcome, not the specific claim that particular alleles govern babesiosis^[45].

Quantitative Trait Loci Mapping

Linkage mapping in indicine by taurine crosses established that resistance is polygenic. A genome-wide scan in a *Bos taurus* by *Bos indicus* population identified several quantitative trait loci (QTL) for tick resistance, including a strong signal on the chromosome that carries the MHC, with other loci detected only in one season^[48]. That seasonal pattern is not noise: reaction-norm analyses formally demonstrate single nucleotide polymorphism (SNP) by environment interaction, such that the genetic control of tick resistance depends on the level of tick challenge, with different loci relevant at different infestation pressures^[47]. This environment dependence helps explain why signals are not always reproducible across studies conducted under different exposure.

Genome-wide Association Studies and Genomic Regions

Higher-resolution association studies have refined these signals. For tick resistance, genome-wide association studies (GWAS) in indigenous and composite breeds have identified significant regions and candidate genes and have supported low-density tag-SNP panels for prediction^[49,50]. For *Babesia* infection level specifically, a dedicated genomic study in Hereford and Braford cattle identified top SNPs distributed across several chromosomes that overlapped immune-function candidate genes, and reported that infection level and tick count, though related, mapped partly to different regions, which reinforces the genetic distinction between *Babesia* resistance and tick resistance^[33].

Selection Signatures in Indigenous and Zebu Breeds

Natural selection has left detectable footprints on resistance-related loci in tropically adapted cattle, providing an independent line of evidence. Genome scans in indicine and African breeds repeatedly recover selective sweeps spanning immune-response and heat-tolerance genes, including, in Indian and Chinese zebu, loci with direct roles in tick resistance and immune function, and, in African dryland zebu, gene-rich immune sweeps shared across breeds^[51-54].

That immunity and adaptation genes are recurrent targets of selection is consistent with the resistance phenotypes of these breeds, but the inference is indirect in a way that matters. These scans were run on breed samples rather than on animals phenotyped for *Babesia* infection, and the swept regions recovered usually span heat tolerance, tick resistance and general immune function together, so they cannot be attributed to babesiosis resistance specifically.

Selection signatures are therefore best read as evidence that tropical adaptation has a genomic basis which includes immunity, and as a source of candidate regions for testing, rather than as evidence of *Babesia* resistance.

Non-additive Variation and the Limits of Additive Models

Most heritability estimates and genomic predictions for resistance assume an additive model, in which marker effects sum independently. This is a useful approximation but an incomplete one. Dominance and epistasis are plausible for immune traits, whose products act within regulatory networks rather than in isolation, and kernel-based machine-learning methods that explicitly compare additive, dominance, and epistatic models can both improve prediction and indicate which inheritance mode best fits a given trait^[55]. The stakes are practical: if non-additive variance is substantial, additive breeding values will systematically misrank the resistance of specific crosses, and the error will be largest precisely where it matters most, in the composite and crossbred animals that dominate tropical production^[32]. The recurrent appearance of regulatory rather than protein-coding candidates, including a regulatory locus prioritized from Braford skin, is consistent with an architecture in which network context modifies the effect of individual variants^[4]. How much of the resistance variance is non-additive is therefore not a statistical nicety but a direct determinant of how accurately a breeding program can rank candidate animals.

Synthesis of the Architecture

The genetic-parameter estimates discussed above are collated in [Table 2](#), and the mapped genomic regions, candidate genes and selection signatures, classified by category of evidence, are summarized in [Table 3](#). Three conclusions follow. First, resistance is polygenic, built from many loci of small effect rather than a few major genes, which is why marker panels rather than single markers are needed for prediction. Second, tick and *Babesia* resistance share part of their architecture but are not identical, and the evidence base is lopsided, because the great majority of mapped loci come from tick-count phenotypes while direct *Babesia*-infection genomics remains thin^[33,43]. The asymmetry is made explicit in the evidence column of [Table 3](#), where a single entry of nine rests on a phenotype in which *Babesia* infection itself was measured.

Third, the MHC and core immune pathways recur as themes across linkage, association, and selection-signature studies. This recurrence is biologically plausible, but the regions concerned are gene-dense and highly polymorphic and are frequently recovered in scans for unrelated traits, and the studies differ in breed, phenotype and design. The pattern is best treated as a convergence

Table 2. Representative heritability and genetic-parameter estimates for tick resistance and *Babesia*/hemoparasite infection in cattle

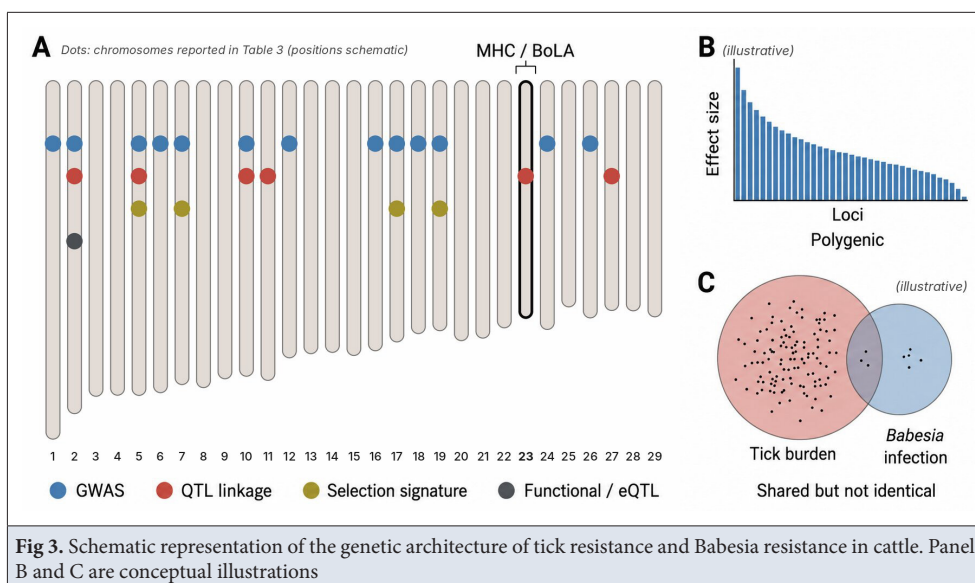
Trait	Breed/Population	Estimate	Method	Reference
Tick count (<i>R. microplus</i>)	Nellore (<i>B. indicus</i>), Brazil	$h^2 = 0.06-0.30$ (age-specific)	Bayesian random regression	[44]
Tick count (multiple ixodid species)	Nguni (indigenous), South Africa	$h^2 = 0.02-0.17$	GWAS; animal and sire models	[49]
Tick count (monthly, by location)	Nguni (indigenous), South Africa	$h^2 = 0.00-0.89$ (month/site-specific)	Bivariate sire models	[56]
Tick count (<i>R. microplus</i>)	Angus (<i>B. taurus</i>), Brazil	$h^2 = 0.16$; repeatability 0.21	Bayesian multi-trait	[43]
<i>B. bovis</i> infection level	Angus (<i>B. taurus</i>), Brazil	$h^2 = 0.03$; repeatability 0.07	Bayesian multi-trait	[43]
<i>B. bovis</i> infection level	Hereford and Braford, Brazil	$h^2 = 0.10$; genetic corr. with tick count 0.15	Single-step GBLUP, bivariate	[33]
Tick resistance (multi-breed)	7 breeds (Brazil, Australia, South Africa)	$h^2 = 0.05-0.42$; genetic corr. -0.01 to 0.87	Multi-breed genomic prediction	[32]
Tick count and <i>Babesia</i> infection level (repeatability)	Holstein and Canchim, Brazil	Low to moderate; weak tick- <i>Babesia</i> correlation	qPCR; mixed models	[40,41]

Ranges are not single population estimates; they span estimates that vary with age, month, anatomical location, tick species, breed or environment within the cited study. h^2 , heritability; GBLUP, genomic best linear unbiased prediction; qPCR, quantitative polymerase chain reaction

Table 3. Mapped genomic regions, candidate genes, and selection signatures for tick resistance and *Babesia* resistance in cattle, classified by category of evidence. Evidence categories: Direct, *Babesia* infection measured; Indirect, tick count measured; Functional support, expression data only; General adaptation, selection scans not specific to babesiosis

Population/Breed	Trait Phenotyped	Evidence Category	Chromosome/Region	Candidate Genes or Pathways (Not Functionally Validated)	Method	Reference
Hereford and Braford, Brazil	<i>B. bovis</i> infection level and tick count	Direct (infection level); indirect (tick count)	Top SNPs on BTA 1, 2, 5, 6, 12, 16, 17, 18, 24, 26	Immune-pathway candidate genes	Single-step GBLUP GWAS	[33]
Gyr x Holstein F2 (<i>B. indicus</i> x <i>B. taurus</i>)	Tick count	Indirect, through tick resistance	6 QTL; season-specific (BTA 2, 10 dry; BTA 5, 11, 27 rainy); BTA 23 in both seasons	MHC region (BTA 23)	Genome-wide microsatellite linkage scan	[48]
Nguni (indigenous), South Africa	Tick count (mainly <i>Amblyomma hebraeum</i>)	Indirect, through tick resistance	Genome-wide significant on BTA 7, 10, 19	Immune-region candidates	GWAS and regional heritability mapping	[49]
Hereford and Braford, Brazil	Tick count, across challenge levels	Indirect, through tick resistance	Multiple chromosomes; SNP by environment	Immune, inflammation and tissue-repair genes	GWAS with reaction norms	[47]
Hereford and Braford, Brazil	Tick count (prediction)	Indirect, through tick resistance	58 tag SNPs (genome-wide)	Low-density predictive panel	Bayesian tag-SNP selection	[50]
Braford, Brazil	Tick count, with skin transcriptome	Functional support	cis-eQTL; <i>PADI4</i> locus	WNT/ β -catenin, NF- κ B, JAK/STAT; <i>PADI4</i>	GWAS, RNA-seq and eQTL integration	[4,57]
Sahiwal (<i>B. indicus</i>), India	Tropical adaptation (no infection or tick phenotype)	General adaptation	BTA 17 (<i>IL2</i>) among 146 swept regions	<i>IL2</i> , <i>IFNL3</i> , <i>IRF8</i> , <i>BLK</i>	Selection signatures (ddRAD)	[51]
Dehong humped (<i>B. indicus</i>), China	Heat tolerance and disease resistance (no infection or tick phenotype)	General adaptation	Multiple selective sweeps	<i>LIPH</i> , <i>TP63</i> , <i>CBFA2T3</i> (immunity)	F_{ST} , XP-EHH, XP-CLR	[52]
African / Sudanese zebu	Dryland adaptation (no infection or tick phenotype)	General adaptation	Gene-rich sweeps on BTA 5, 7, 19	Immune-response genes	F_{ST} and haplotype sweep scans	[53]

Evidence categories follow the grading defined in the subsection "Disentangling tick resistance from *Babesia* resistance". Direct: *Babesia* infection itself measured and related to host genotype. Indirect: tick count was the measured phenotype. Functional support: expression data without a *Babesia* phenotype. General adaptation: selection scans in tropically adapted breeds, not attributable to babesiosis specifically. One of nine entries rests on a direct *Babesia* phenotype. BTA, *Bos taurus* autosome; ddRAD, double-digest restriction site-associated DNA sequencing; F_{ST} , fixation index; GBLUP, genomic best linear unbiased prediction; XP-CLR, cross-population composite likelihood ratio; XP-EHH, cross-population extended haplotype homozygosity



worth pursuing rather than as independent confirmation. The weakest part of the evidence is reproducibility across populations and environments, a problem that SNP by environment interaction shows is partly real biology rather than statistical noise [47]. The combined evidence from QTL mapping, GWAS, selection signatures and functional genomics is summarized in Fig. 3. The distinction between tick resistance and *Babesia* resistance that runs through this evidence is illustrated in Fig. 4.

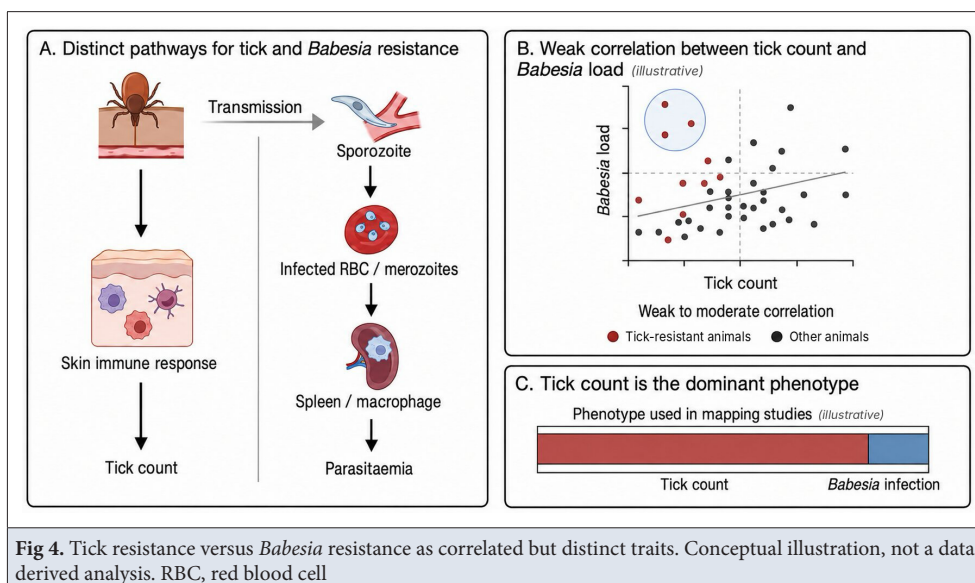
FUNCTIONAL GENOMICS AND MOLECULAR MECHANISMS

Association identifies where in the genome resistance lives; functional genomics asks what actually differs between resistant and susceptible animals. One qualification governs this entire section. The transcriptomic and

systems-biology work available in cattle was carried out on animals classified by tick burden rather than by *Babesia* infection, so the pathways described below are established for tick resistance and remain candidates, not demonstrated mechanisms, for *Babesia* resistance.

Host Transcriptomics

Transcriptomic profiling can distinguish resistant from susceptible animals, although the evidence in cattle rests on a small number of studies in a narrow range of breeds. In Braford cattle, ribonucleic acid sequencing (RNA-seq) of skin from artificially infested resistant and susceptible hosts identified differentially expressed genes consistent with specific anti-tick mechanisms, with resistant animals showing distinctive skin-remodeling and leukocyte-recruitment signatures [57]. The phenotype in that study was tick burden, and the contrasting groups came from



a single composite breed, so the signatures describe anti-tick responses in that population and have not been tested against *Babesia* infection.

Implicated Pathways

A recurring set of pathways is reported, though the independence of these reports is limited. Resistance-associated transcriptional programs have implicated the Wingless/integrated (WNT)/ β -catenin pathway, nuclear factor kappa B (NF- κ B), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling, together with proteolysis and tissue-repair processes, with WNT supported both by expression data and by a parallel association signal^[57]. A systems-biology synthesis of Braford resistance reported compatible modules and prioritized peptidyl arginine deiminase type IV (*PADI4*) as a candidate at a regulatory locus^[4]. Two qualifications follow. First, both analyses concern Braford cattle phenotyped for tick burden, so the agreement between them reflects a shared population and phenotype rather than independent replication across breeds or against *Babesia* infection. Second, WNT, NF- κ B and JAK/STAT are pleiotropic pathways recovered across a wide range of inflammatory and tissue-remodeling contexts, so their appearance here is compatible with a role in resistance without establishing one. These pathways are best regarded as prioritized hypotheses for functional testing.

Integrative and Systems Biology

The current frontier is integrating association with functional data to move from correlation toward causation. Combining GWAS with expression data to identify expression quantitative trait loci (eQTL) can prioritize causal candidates, and machine-learning approaches are increasingly used to annotate regulatory variants, including cross-species prediction of enhancers in cattle from better-annotated genomes^[58]. These methods are promising but still limited by small, tissue-restricted datasets, and few causal variants for resistance have been confirmed.

Parasite and Vector Genetics as Effect Modifiers

Resistance is one corner of a three-way interaction. Parasite and tick genetics modify it. *B. bovis* populations are genetically diverse and geographically sub-structured, which shapes immunity and the portability of antigen-based markers and vaccines across regions^[59]. Comparative genomics of *Babesia* species shows extensive variation in the multigene families that encode surface and virulence proteins, the same families that drive antigenic variation and cytoadhesion^[60]. On the vector side, *B. bovis* infection itself alters gene expression in *Rhipicephalus microplus* larvae, and reference transcriptomes spanning

the parasite's vertebrate and invertebrate stages are now available to dissect this host-vector-parasite interaction^[61,62]. The practical implication is that a marker or antigen validated against one parasite or tick population may not transfer to another, a caveat that applies equally to host-side markers selected in one environment.

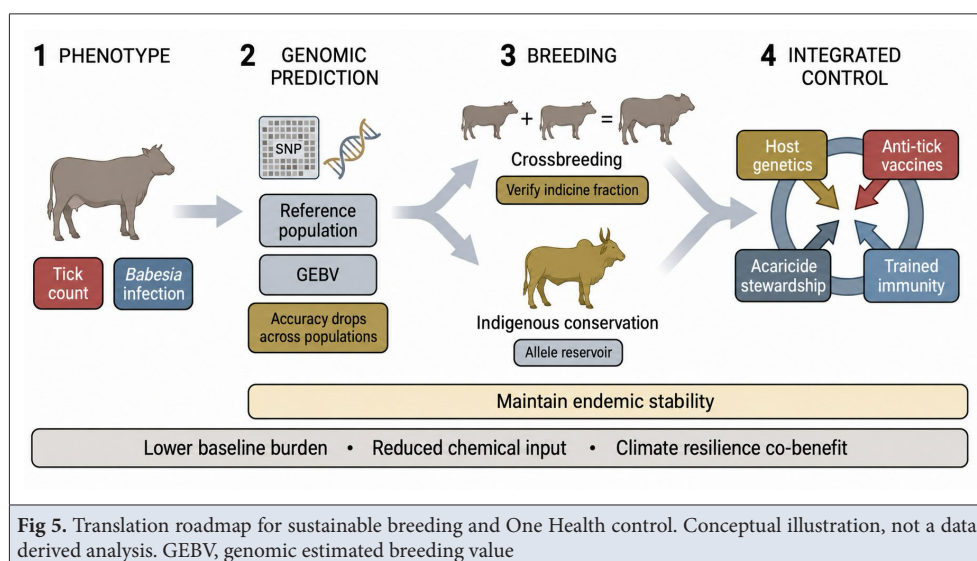
Two operational lessons follow from treating resistance as one vertex of a host-parasite-vector triad. First, the genetic diversity and geographic sub-structuring of *B. bovis* mean that immunity selected or acquired against one parasite population may be only partial against another, so resistance phenotypes and any antigen-based companion tools should be validated in the target epidemiological setting rather than assumed to transfer^[59,60]. Second, because the parasite reprograms gene expression in the tick and depends on tick physiology for transmission, vector competence is itself a variable that interacts with host resistance, and the stage-resolved reference data now available make it feasible to ask which host responses actually disrupt transmission rather than merely lowering parasitaemia^[61,62]. Separating resistance that reduces an individual animal's burden from resistance that reduces onward transmission is an underexplored distinction, and it bears directly on whether genetic selection can shift herd-level infection pressure and therefore on how selection interacts with endemic stability.

TRANSLATING HOST GENETICS INTO SUSTAINABLE DISEASE CONTROL

The implications half of the title concerns how this knowledge becomes durable, field-deployable control. A practical roadmap for translating resistance phenotypes and genomic data into breeding and integrated One Health control is shown in [Fig. 5](#).

Marker-Assisted and Genomic Selection

Genomic estimated breeding values for tick resistance can be computed with useful accuracy, and tag-SNP panels selected by Bayesian methods predict tick resistance in Hereford and Braford cattle at densities low enough to be economical^[50]. The same genomic framework extends to *Babesia* infection level, where infection and tick-count traits can be evaluated jointly^[33]. A central practical question is portability: multi-breed and multi-country genomic prediction of tick resistance is feasible, but accuracy depends strongly on the size and composition of the reference population and degrades when training and target populations differ in linkage-disequilibrium phase^[32]. The clearest near-term gains are therefore within-population, with cross-population prediction still requiring larger and more diverse reference cohorts.



Breeding Strategy and Indigenous-Breed Conservation

Two complementary strategies follow. Crossbreeding can capture indicine resistance while retaining taurine productivity, but the evidence that a small zebu fraction is insufficient^[34] means crossbreeding programs must target and verify a meaningful indicine contribution rather than assume it. In parallel, locally adapted indigenous breeds are reservoirs of resistance alleles shaped by generations of natural selection, and characterizing and conserving them is a genetic-resource priority, as selection-signature studies in Indian, Chinese, and African zebu suggest, although these signatures reflect general adaptation, not confirmed *Babesia* resistance^[51-53]. Conservation here is not only cultural but functional, protecting alleles that breeding programs may later need.

Integration within One Health and Integrated Pest Management

Host genetics is a complement to, not a replacement for, other tools, and its value is greatest inside an integrated framework. Trained-immunity approaches, including bacillus Calmette-Guérin (BCG)-based strategies, are being explored to broaden protection against babesiosis^[39], and next-generation anti-tick vaccines, such as multi-antigen cocktails that reduce tick fitness, can be layered with genetic selection and rational acaricide stewardship^[29]. For the reason set out above in the discussion of endemic stability, these elements must be coordinated rather than applied piecemeal^[6]. Genetic resistance is attractive within this framework because it is potentially durable and leaves no residues, addressing the failure modes of acaricides and drugs set out in *Table 1*.

Trade-offs and Sustainability

Selecting for resistance is not cost-free, and honest accounting matters. Resistance must be balanced against

growth, milk, and fertility, although the generally weak genetic correlations between resistance and production traits suggest the trade-offs are manageable rather than prohibitive^[44]. Resistance traits also intersect with climate resilience, since many of the same indigenous breeds combine disease resistance with heat tolerance in selection-signature scans, which reflect general adaptation, not confirmed *Babesia* resistance^[54].

For smallholder and tropical producers, who bear the heaviest burden and have the least access to acaricides and cold-chain vaccines, a self-sustaining genetic contribution is especially valuable, and regional framing for South Asian and Pakistani systems should weigh this equity dimension explicitly^[7,8,63].

The genomic resources needed to act on this are also expanding. Whole-genome analyses of indigenous African cattle recover candidate regions putatively linked to adaptation to ticks and vector-borne infection^[64], and comparable characterization of indigenous and composite breeds in southern Africa shows that locally adapted populations retain distinctive diversity that crossbreeding can erode if it is not documented first^[65]. Both point to the same practical conclusion for tropical smallholder systems, which is that the raw genetic material for a durable contribution may already exist in the breeds these producers keep, and that the priority is to characterize and use it rather than to displace it. The realistic position is that genetics lowers the baseline burden and the intensity of chemical control needed, rather than eliminating the need for other tools.

CHALLENGES, KNOWLEDGE GAPS, AND FUTURE DIRECTIONS

An honest appraisal of the field identifies several bottlenecks and a concrete agenda. The first is phenotyping. Resistance

is defined inconsistently across studies as clinical outcome, *Babesia* infection level, or tick count, and these are not interchangeable. Tick counts are laborious and noisy, and infection levels require quantitative molecular assays, so scalable, objective, standardized phenotypes are the rate-limiting step for everything downstream.

Progress here is partly a matter of technology. Quantitative molecular assays already allow *Babesia* infection level to be measured objectively rather than scored by eye, and high-throughput sequencing can resolve the full community of co-infecting haemoparasites in a single sample, which would let resistance be phenotyped against a defined parasite background rather than a presumed one.

Pairing such assays with routine regional surveillance, including in under-sampled South Asian systems, would generate the large, consistently phenotyped cohorts that genomic prediction requires while simultaneously informing control. Molecular screening of ticks also continues to reveal pathogens not previously reported in particular vectors and regions ^[66].

The second is population structure. Reference populations are small and region-specific, and markers transfer poorly across breeds and environments because linkage-disequilibrium phase differs and because, as SNP by environment analyses show, the underlying genetic control is itself environment-conditional. Larger multi-breed, multi-environment cohorts are needed before prediction can be portable.

The third, and most specific to this review, is the scarcity of direct *Babesia*-resistance genomics. Most inference is borrowed from tick-resistance studies, yet tick and *Babesia* resistance are genetically distinct, and dedicated cohorts phenotyped for *Babesia* infection remain few. Closing this gap is the single most valuable empirical step the field could take.

The fourth is functional validation. Candidate genes are abundant but confirmed causal variants are almost absent. Gene-editing tools now make validation tractable: clustered regularly interspaced short palindromic repeats (CRISPR)-based editing has been used to interrogate immune-gene function in bovine cells, and Cas9-expressing cattle have been generated, providing a route from candidate gene to experimental test in the target species. The limiting factors are efficiency, cost, and the regulatory and welfare questions that editing raises.

Emerging analytical tools may help but should be appraised soberly. Machine-learning methods for genomic prediction can model non-additive effects and generate hypotheses about inheritance mechanisms, while regulatory-variant annotation, single-cell immunogenomics, long-read reference genomes, and multi-omics integration each

address part of the causation problem. None is a shortcut around the need for large, well-phenotyped cohorts.

CONCLUSION

The host genome is a promising complementary pillar of bovine babesiosis control. Indicine cattle resist *Babesia* better than taurine cattle under controlled challenge, and potentially exploitable variation persists within breeds. Resistance is polygenic, but direct *Babesia* genomic evidence remains limited, and selection signatures reflect general tropical adaptation, not confirmed *Babesia*-resistance loci. Candidate pathways such as WNT, NF- κ B and JAK/STAT, identified in tick-resistance studies, await functional validation.

Genetics is complementary to vaccines and vector management, not a substitute for them, and its place is inside a coordinated One Health framework that also manages endemic stability. Three conditions will determine whether this potential is realized: scalable and standardized phenotyping, larger multi-breed and multi-environment reference cohorts, and experimental confirmation of causal variants. If these are met, genetics-informed breeding could help lower the babesiosis burden and the intensity of chemical control required, with the greatest benefit for the resource-limited tropical producers who currently bear the heaviest cost.

DECLARATIONS

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