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Olfactory gene profiling in ticks: A scoping review with a functional perspective

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ABSTRACT

Olfaction is important in ticks' host-seeking and mating behaviors, as it enables them to detect volatile chemical compounds. This scoping review aims to systematically map and synthesize the existing literature on olfactory gene families in ticks and to examine the application of functional genomics or behavioral approaches. We conducted a thorough search in five databases for publications up to 19 September 2025. This scoping review was implemented according to the Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. A total of 15 studies were included in this review, and 12 tick species were reported. Among these, *Haemaphysalis longicornis* and *Ixodes scapularis* had the most olfactory genes identified. Ten related olfactory gene families were identified in the 12 tick species. Among these, Niemann–Pick type C2 protein families were the most frequent across tick species ($n = 11$), followed by gustatory receptor and ionotropic receptor families ($n = 7$). Additionally, the studies reviewed found differences in gene family distributions among tick species. Molecular methods were used to identify olfactory genes, with most studies reporting RNA sequencing and reverse transcription quantitative PCR. A small number of studies used functional validation techniques such as RNA interference, ligand-binding assays, molecular docking, electroantennography, or Y-tube olfactometer assay. This scoping review highlights significant progress in the molecular understanding of tick olfaction. It emphasizes the importance of advancing this knowledge to improve comprehension of molecular tick olfactory and enable the development of targeted, olfaction-driven tick control and tick-borne disease prevention strategies.

Introduction

Ticks are obligatory hematophagous ectoparasites of terrestrial vertebrates and are among the most important arthropod vectors of disease worldwide. They carry and transmit numerous pathogens, including viruses, bacteria, and protozoa, posing serious threats to human and veterinary health (Dantas-Torres et al., 2012; Eisen & Eisen, 2018; Estrada-Peña et al., 2008; Luciano et al., 2025; Mans et al., 2016; Rochlin & Toledo, 2020; Zhao et al., 2021). Their success as ectoparasites depends on their ability to locate and recognize hosts using chemosensory, vibration, heat, and humidity (Faraone, 2022; Gebremedhin et al., 2023).

Olfaction plays a particularly critical role in host-seeking and mating behaviors, enabling ticks to detect volatile organic compounds through the Haller's organ, a unique sensory structure located on the forelegs (Carr et al., 2017; Gebremedhin et al., 2023; Renthal et al., 2017). Understanding the molecular mechanisms underlying tick olfaction is important for creating novel, environmentally friendly vector control techniques, such as olfactory-based repellents and molecular interference technologies (Esteve-Gassent et al., 2016; Pérez de León et al., 2014) .

In insects, chemosensory systems have been well characterized through decades of molecular research. Several major gene and protein families, odorant receptors (ORs), gustatory receptors (GRs), ionotropic receptors (IRs), odorant-binding proteins (OBPs), chemosensory proteins (CSPs), and Niemann–Pick type C2 (NPC2) proteins, play essential

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roles in odor detection (Missbach et al., 2014; Pelosi et al., 2018, 2006). Comparative genomics has revealed that IRs and NPC2s are conserved across tick species (Jia et al., 2020).

In ticks, the study of olfactory molecular biology is relatively recent but advancing rapidly. The *Ixodes scapularis* genome (Gulia-Nuss et al., 2016) and subsequent foreleg transcriptome analyses identified multiple candidate IRs, GRs, and OBP-like genes potentially expressed in chemosensory tissues (Josek et al., 2018) . Proteomic studies of *Ixodes ricinus* have further characterized olfactory proteins, including OBP-like and CSP families (Iovinella et al., 2016). Recent transcriptomic and functional studies have uncovered NPC2 (Liang et al., 2023), microplusin-like (ML) proteins (Gebremedhin et al., 2024), G-protein-coupled receptors (GPCRs) (Guerrero et al., 2016; Munoz et al., 2017), and transient receptor potential (TRP) channels (Carr et al., 2017; Kuang et al., 2025) involved in tick olfaction.

Despite these advances, key knowledge gaps remain. Unlike insects, ticks lack the canonical odorant receptor (OR) gene family, indicating that chemosensory detection in ticks may have evolved through distinct molecular mechanisms (Carr et al., 2017; Gulia-Nuss et al., 2016). Moreover, while transcriptomic and genomic data have greatly expanded gene discovery, functional validation remains scarce. Only a limited number of studies have employed RNA interference (RNAi), fluorescence binding assays, or molecular docking to verify ligand–receptor interactions and olfactory function (Gebremedhin et al., 2024; Iovinella et al., 2016; Kuang et al., 2025; Liang et al., 2023; Liu et al., 2025). Furthermore, comprehensive cross-species analyses integrating multi-omics datasets (transcriptomics, proteomics, genomics, etc.) remain limited. The lack of experimental models, standardized functional assays, and comparative frameworks continues to constrain molecular understanding of tick olfaction. Addressing these challenges requires a systematic synthesis of existing molecular evidence.

This study aims to systematically map and synthesize the existing literature on olfactory gene families in ticks and to examine the application of functional genomics or behavioral approaches to the identification and characterization of tick olfactory genes. By integrating available evidence, this scoping review identifies molecular advances, highlights methodological and taxonomic gaps, and outlines future research priorities for elucidating the molecular basis of olfaction in ticks.

Materials and methods

Search strategy and selection criteria

The key question we sought to answer through this scoping review was "What is the current evidence on olfactory gene families in ticks, and how have functional genomics or behavioral approaches been applied to their characterization?" The Systematic Reviews and Meta-Analyses extension for Scoping Reviews (the PRISMA-ScR) guidelines for conducting a scoping review were followed (Moher et al., 2009). We performed a literature search across PubMed, Web of Science, Scopus, Embase, and ScienceDirect databases for publications up to 19 September 2025. The following search terms were utilized: "Tick", "Ixodidae", "Argasidae", "Acari", "olfactory", "gene", "genome" "protein", "odorant binding protein", "odorant receptor", "gustatory receptor", "ionotropic receptor", "chemosensory protein", "Niemann–Pick type C2 protein", "G protein-coupled receptor", "microplusin-like protein", "transcriptome", "proteome", "functional", "RNA interference", "RNAi", "CRISPR", "gene editing", "dock", "bind". When appropriate, Boolean operators such as "AND"/"OR" and the wildcard "*" were used within and between search terms. Backward and forward reverse citations were used to further expand the search scope. Two independent evaluators evaluated all records. If there was any disagreement amongst assessors, a third assessor was consulted. Potential articles were selected by removing duplicates and screening titles and abstracts. The selected studies were downloaded to allow full-text review for eligibility. EndNote v21 was used to store and manage full-text articles.

Inclusion and exclusion criteria

Appropriate inclusion and exclusion criteria were used in this study to guarantee the quality and relevance of the evaluated literature. Studies were considered eligible when they met the following eligibility criteria: (i) studies published in English; (ii) studies published in peer-reviewed journals; (iii) full text availability; (iv) studies that reported molecular or genomic identification of olfactory genes in ticks. The exclusion criteria were as follows: (i) review studies, (ii) duplication, and (iii) studies that did not meet the inclusion criteria.

Data extraction and data analysis

The detailed characteristics of each study that met the inclusion criteria were extracted using a pre-designed Excel data collection form. Information was recorded as follows: tick species, gene or protein family, gene or protein identified name, sample tissue type, molecular method used, genomic functional validation method, behavioral functional validation method, and study references. We used simple descriptive methods to characterize the data and summarize them in tables and figures, as needed for clarity.

Results

Characteristics of the studies included in the scoping review

The literature search yielded 882 studies across five databases, and 15 met the inclusion criteria (Fig. 1). The characteristics of the studies on olfactory genes in ticks are summarized in Supplementary Table 1. These included the tick species, gene or protein family, gene or protein identified name, sample tissue type, molecular method used for gene or protein identification, genomic functional validation method, behavioral functional validation method, and study references.

Species representation

Molecular evidence varied considerably among tick taxa. *H. longicornis* contributed to the most identified olfactory gene families, with $n = 5$ studies, followed by *I. scapularis* with $n = 3$ studies. While *Rhipicephalus microplus* and *Dermacentor variabilis* had $n = 2$ studies, *I. ricinus, Ixodes persulcatus, Rhipicephalus linnaei, Rhipicephalus australis, Rhipicephalus sanguineus, Amblyomma americanum, Hyalomma asiaticum, Dermacentor silvarum*, and *Dermacentor variabilis* yielded fewer studies, $n = 1$ (Fig. 2).

Gene family distribution across tick species

Ten principal olfactory-related gene or protein families were identified: ionotropic receptors (IRs), gustatory receptors (GRs), odorant binding proteins (OBP), odorant binding protein-like (OBPL), chemosensory proteins (CSPs), Niemann–Pick type C2 proteins (NPC2), microplusin-like (ML) proteins, G-protein-coupled receptors (GPCRs), transient receptor potential (TRP) channels, and lipocalins (Supplementary Table 1). Among these, NPC2 was the most reported in $n = 11$ tick species, followed by IR and GR families, $n = 7$. ML protein and GPCR families were moderately represented, $n = 6$ and $n = 4$ species, respectively. In contrast, OBP, TRP, and lipocalin families occurred in fewer tick species $n = 2$, and CSP was reported in one tick species (Fig. 3).

The studies included in this scoping review reported variation in gene family distribution across tick species. NPC2s, IRs, GRs, and ML protein families were widely present across most tick species. In contrast, OBPs, lipocalins, TPR, and CSP were less widespread across species (Fig. 4).

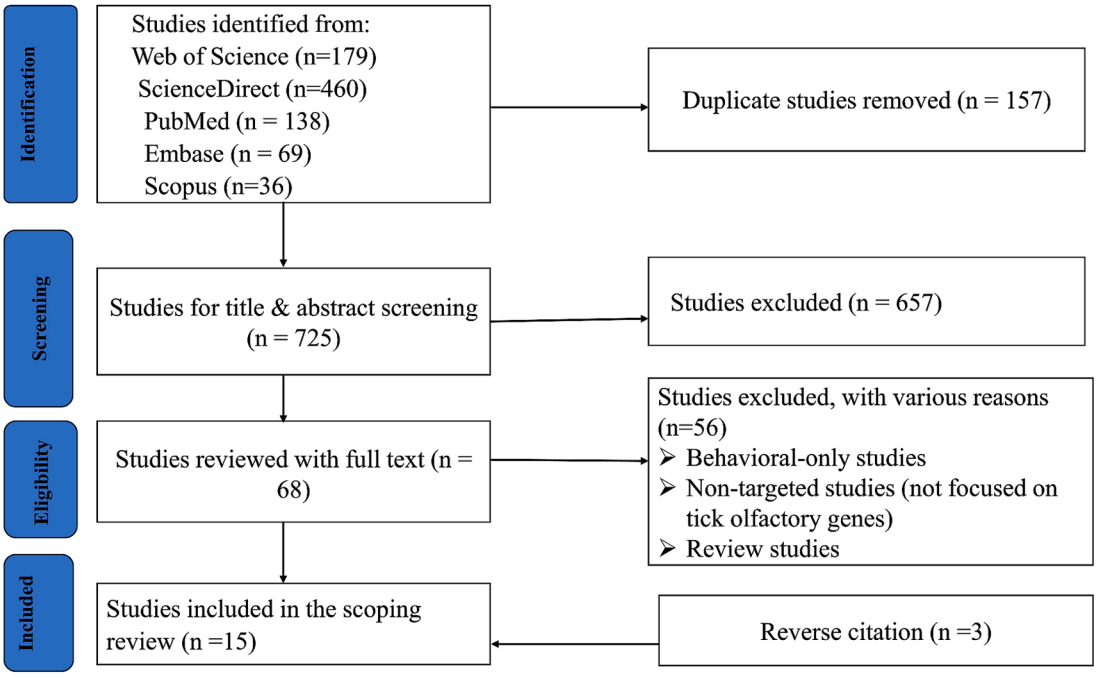

Fig. 1. PRISMA-Scr flow diagram of literature search and study selection.

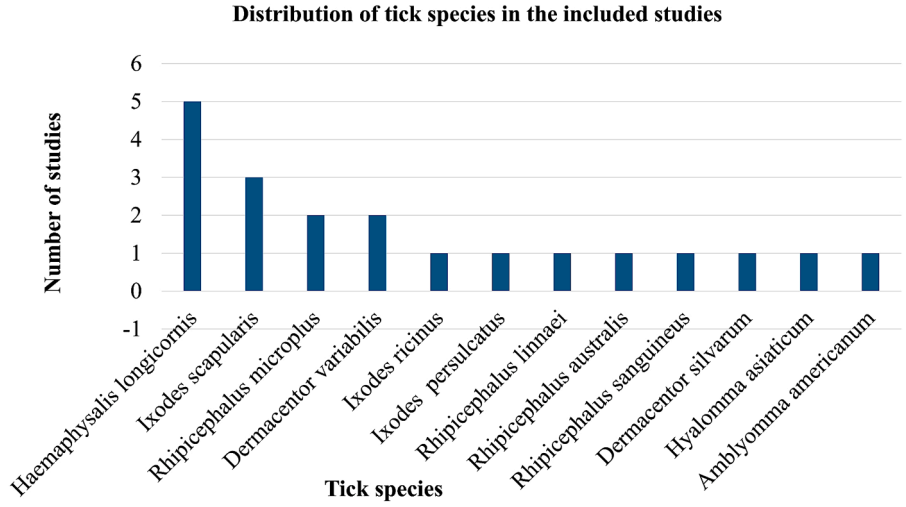

Fig. 2. Frequency of tick species that documented the presence of olfactory genes.

Tissue-specific distribution of the reported olfactory gene in ticks

Olfactory genes were identified across 13 distinct tissue types in the included studies. Among these, the forelegs were the most frequently reported tissues, accounting for 22.9 % of all included studies. This was followed by hindlegs, fore tarsi, and palps, which showed constantly moderate frequencies across studies, 11.4 % each. Other tissue samples, including legs (general), synganglion, whole body, midgut, ovaries, and salivary glands, were less frequently reported, 5.7 %. In contrast, the fat bodies, mouth, and capitulum exhibited the lowest frequency, 2.9 % (Fig. 5).

Molecular and genomic approaches for gene identification and functional characterization

Most studies utilized RNA sequencing (RNA-seq) and reverse transcription quantitative PCR (RT-qPCR) to identify and quantify gene expression in olfactory tissues (Fig. 6). Several investigations complemented these methods with proteomic assays (mass spectrometry, Western blotting) or in silico sequence annotation.

Genomics functional validation remains limited: only a small number of studies have performed RNA interference (RNAi) or ligand-binding assays to verify gene activity (Fig. 7). Experimental confirmation was used in some included studies for NPC2, ML, and TRP families. In contrast, the IR, GPCR, and GR families were primarily characterized through comparative genomics, expression profiling, or bioinformatic predictions, without direct functional evidence (Supplementary Table 1).

Behavioral validation of tick olfactory function

Only a limited number of studies incorporated behavioral or electrophysiological validation of olfactory gene function. Among the included studies, there are three that employed behavior-related

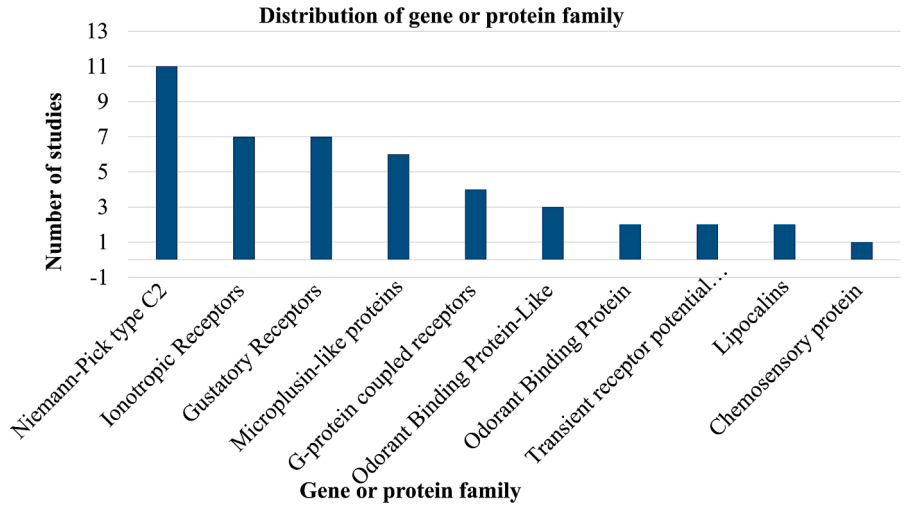

Fig. 3. Frequency of genes or protein families documented in different tick species from the included studies.

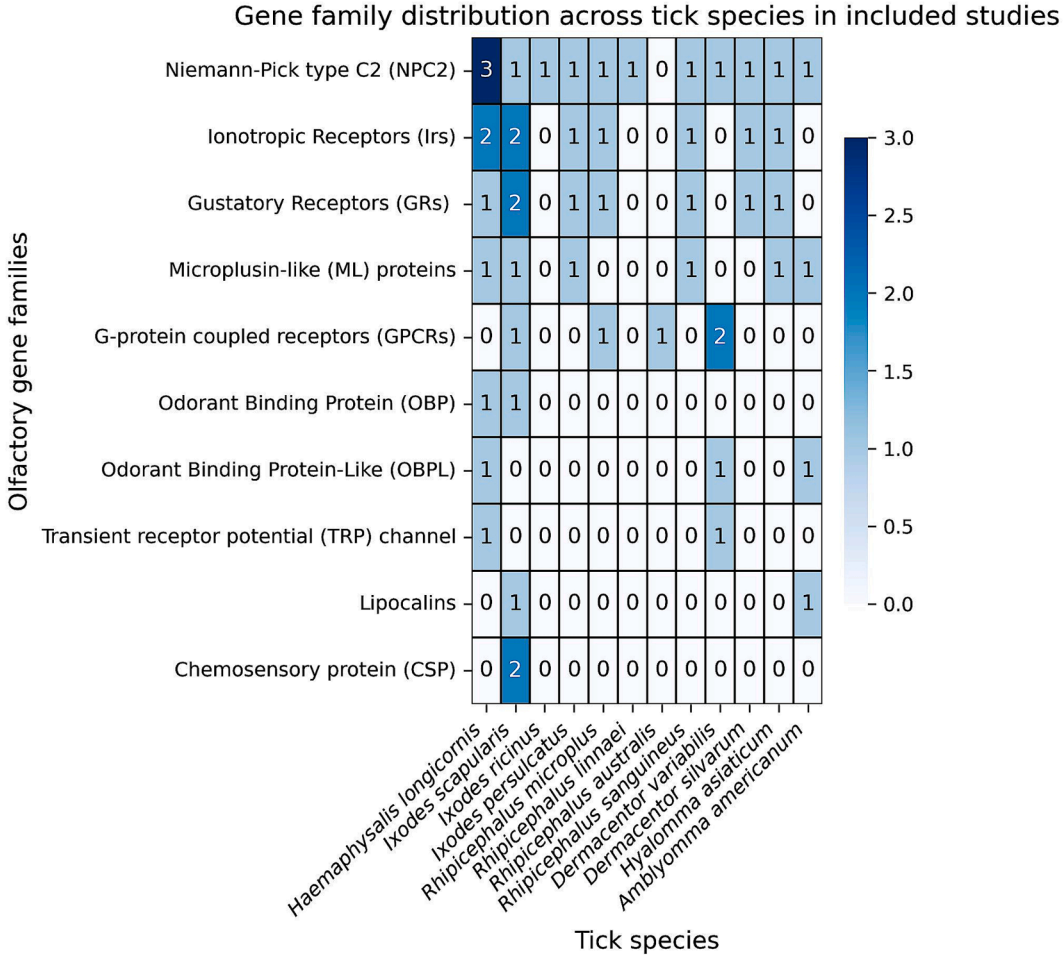

Fig. 4. Heatmap showing the distribution of olfactory-related gene families across tick species in the included studies.

validation approaches. One study combined electroantennography with a Y-tube olfactometer assay, while one study used electroantennography alone, and another relied exclusively on a Y-tube olfactometer assay (Fig. 8).

Discussion

This scoping review integrates molecular evidence on olfactory gene families in ticks and examines the extent to which functional genomics or behavioral methods have been used to characterize them. The findings confirm that ticks possess a complex chemosensory repertoire composed of several genes and protein families. However, despite

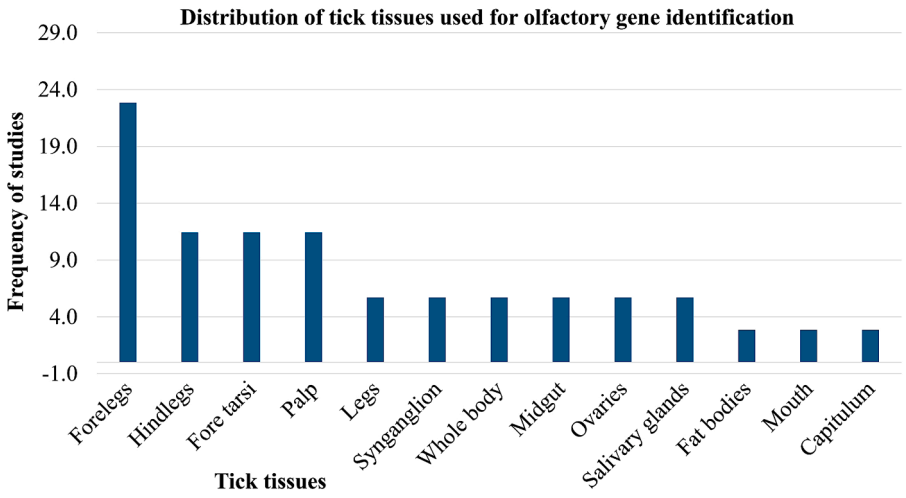

Fig. 5. Frequency of tick tissues used as samples for olfactory gene identification in the included studies.

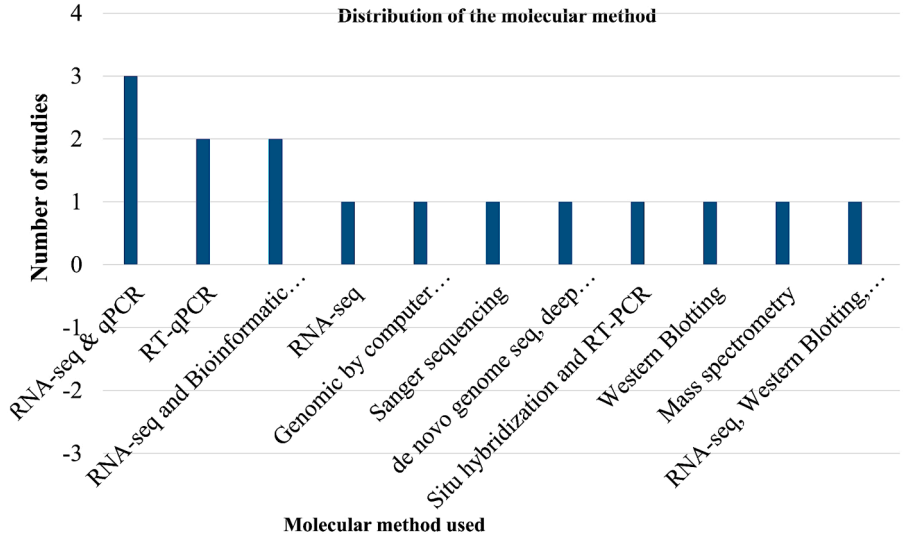

Fig. 6. Frequency of molecular methods used for olfactory gene identification in ticks.

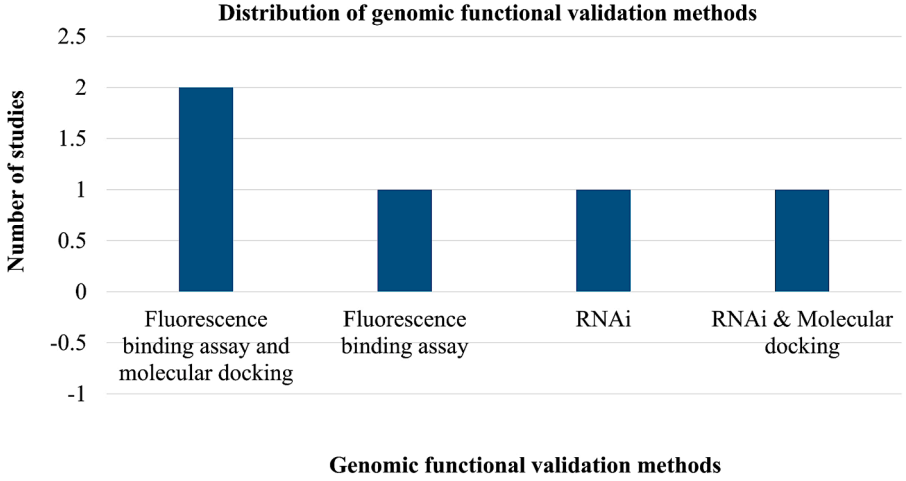

Fig. 7. Frequency of genomic functional validation methods used in included studies.

advances in gene discovery, functional and mechanistic understanding remains limited, with only a few studies providing experimental evidence of olfactory gene activity.

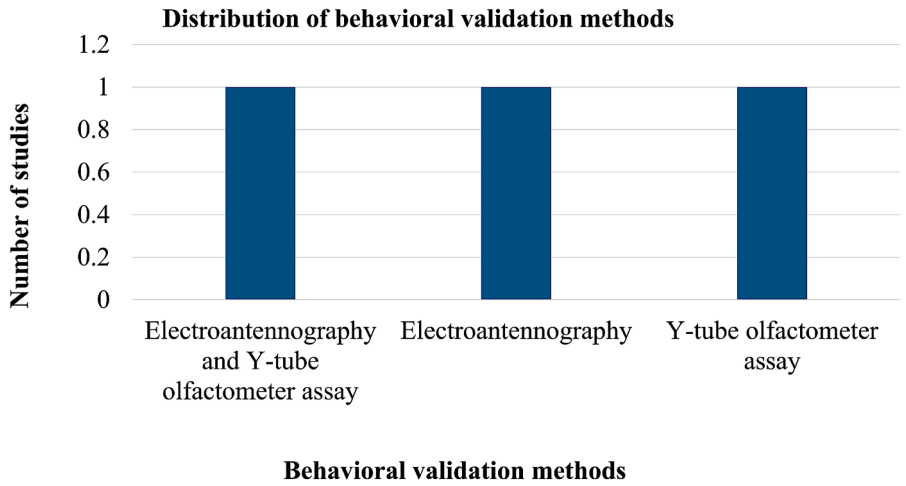

Fig. 8. Frequency of behavioral functional validation methods used in included studies.

Species representation

Species-level variation also emerges as an essential theme. *H. longicornis* had the most identified olfactory genes, followed by *I. scapularis*. These ticks are characterized by their generalist host-seeking behavior, their significance for public health, and the growing availability of genomic studies (Cui et al., 2022; Eisen & Eisen, 2018; Gulia-Nuss et al., 2016; Iovinella et al., 2016; Josek et al., 2018; Walker, 2003; Zhao et al., 2021). Conversely, *Rh. microplus, D. variabilis, I. ricinus, I. persulcatus, Rh. linnaei, Rh. australis, Rh. sanguineus, A. americanum, Hy. asiaticum, D. silvarum*, and *D. variabilis* have fewer studies. This can be explained by the fact that genome studies of some of these species are only now available or not available yet, and olfactory molecular-level studies are scarce, in addition to their specialized host associations, despite their veterinary and public health importance (Gebremedhin et al., 2023; Jia et al., 2020; Luciano et al., 2025; Walker, 2003). These differences emphasize the need for comparative multi-species analyses integrating behavioral assays, electrophysiology, and gene expression.

Gene family distribution across tick species

The identification of diverse gene families across the included studies in this scoping review, such as ionotropic receptors (IRs), gustatory receptors (GRs), odorant-binding protein-like (OBPL), chemosensory proteins (CSPs), Niemann–Pick type C2 (NPC2), microplusin-like (ML), G-protein-coupled receptors (GPCRs), transient receptor potential (TRP) channels, and lipocalins, suggests substantial evolutionary plasticity in tick olfaction (Carr et al., 2017; Gulia-Nuss et al., 2016; Josek et al., 2018).

The NPC2 family was the most reported in 11 tick species, followed by the IR and GR families found in 7 tick species. Additionally, the heatmap analysis of the included studies indicates that NPC2, IR, GR, and ML protein families are widely distributed across tick species, suggesting that they may play an important role in tick chemical communication (Croset et al., 2010; Gebremedhin et al., 2023; Jia et al., 2020). IRs, which are evolutionarily close to synaptic ionotropic glutamate receptors, have diversified across arthropods to mediate chemical and thermal sensitivity (Missbach et al., 2014; Renthal et al., 2017). Their presence in multiple tick species supports an ancient chemosensory origin predating insect divergence (Vieira & Rozas, 2011).

Similarly, NPC2 and ML proteins, lipid-binding carriers located in the sensillar lymph, likely substitute for insect OBPs by facilitating the transport of hydrophobic odorants (Liang et al., 2023; Pelosi et al., 2018). The predominance of these families in transcriptomic and proteomic datasets underscores their potential role in mediating ligand uptake within the Haller's organ. Comparative genomics further suggests lineage-specific expansions of IR and NPC2 genes in *H. longicornis, D. silvarum, I. persulcatus, Rh. sanguineus, Rh. microplus*, and *Hy. asiaticum*, which may contribute to species-specific host preferences and ecological adaptation (Cui et al., 2022; Gebremedhin et al., 2024; Jia et al., 2020).

The large-scale comparative analyses of six tick species conducted by Jia et al. to elucidate their genetic diversity and vector capacity reported the presence of the GR family in all six tick species (Jia et al., 2020). However, the study by Josek et al. found that the expression level of this gene family in ticks' forelegs was low, and its chemosensory role remains to be determined (Josek et al., 2018).

In this review, OBPs/OBPL and CSP gene families were detected in a limited number of tick species (OBPs or OBPL in 5 tick species, and the CSP family in 1 tick species). These genes have been shown to play key roles in host odor detection in other arthropods, particularly insects, as discussed by Pelosi et al. (Pelosi et al., 2018). However, their limited occurrence in ticks suggests that ticks may rely on alternative molecular pathways, such as IRs and NPC2s, for olfactory signaling, highlighting differences in chemosensory systems across different arthropod lineages. A comparative genomics study across arthropods, focusing on the origin and evolutionary history of the chemosensory system, reported low expression of the CSP and OBP families in the *I. scapularis* tick (Vieira & Rozas, 2011), suggesting that these genes may not be involved in chemical communication in ticks.

The presence of ML protein, TRP channel, lipocalin, and GPCR families across tick species indicates that these families may contribute to tick chemosensory processes. ML proteins were detected in six species, GPCRs in four tick species, TRP channels, and the lipocalins in two tick species. A study in *H. longicornis* reported that the ML proteins are involved in the detection of volatile chemical compounds essential for host location (Gebremedhin et al., 2024). ML proteins were detected in the foreleg transcriptome and hypothesized that these proteins could function as insect odorant-binding proteins, potentially involved in odorant transport to sensory neurons or in modulating neuronal responses(Josek et al., 2018). TRP channels are ubiquitous in arthropods and perform crucial roles in a variety of sensory processes (Fowler & Montell, 2013). The TRP channel acts as a chemosensory receptor for repellents, mediating avoidance behavior in ticks (Kuang et al., 2025). Vertebrate odorant-binding proteins belong to the lipocalin family, which has been linked to chemical signal reception in insects (Tsuchihara et al., 2000). The lipocalin protein family was identified as a potential olfactory-binding protein in ticks (Renthal et al., 2017). The GPCR family is found in insects and plays diverse biological roles (Nässel & Winther, 2010). They may also be involved in various functions in ticks, including olfaction, although their olfaction role remains to be

determined (Guerrero et al., 2016; Gulia-Nuss et al., 2016; Munoz et al., 2017). The study by Carr et al. suggests that this protein family may represent a novel type seven-transmembrane receptor (Carr et al., 2017).

Tissue-specific distribution of the reported olfactory gene in ticks

The tissue-specific distribution of reported olfactory genes in the included studies in this scoping review reveals anatomical bias toward sensory-associated appendages, particularly the forelegs. The predominance of olfactory genes in the forelegs (22.9 %) is biologically consistent with the presence of Haller's organ, a specialized sensory structure unique to ticks and located on the tarsi of the first pair of legs. Haller's organ is widely recognized as the principal site for the detection of host-derived volatile organic compounds and plays a central role in host-seeking and mating behaviors (Carr et al., 2017; Gebremedhin et al., 2023; Josek et al., 2018; Renthal et al., 2017).

The moderate but consistent frequencies observed in the hindlegs, fore tarsi, and palps (11.4 % each) further suggest that chemosensory perception in ticks is not restricted to a single appendage. These structures are known to possess diverse sensory sensilla and have been implicated in contact chemoreception and environmental signal detection, potentially contributing to complementary or redundant olfactory functions (Carr et al., 2017; Gebremedhin et al., 2023). Electrophysiological and behavioral studies further support the involvement of tick appendages in volatile detection, reinforcing the biological relevance of these findings (Mandal et al., 2025).

Molecular and genomic approaches for gene identification and functional characterization

Despite significant progress in gene discovery through transcriptomic analysis, functional validation remains scarce. Most studies used RNA sequencing (RNA-seq) and reverse transcription quantitative PCR (RT-qPCR) to identify and quantify gene expression in olfactory tissues. These techniques were supplemented by several investigations using proteomic assays (mass spectrometry, Western blotting) or in silico sequence annotation. Genomic functional validation remains scarce, as few studies have used ligand-binding or RNA interference (RNAi) to confirm the functions of olfactory genes. Experimental approaches such as RNA interference (RNAi) have been successfully applied to a few olfactory genes, particularly ML protein and HL-TRP channels, demonstrating their involvement in host-odor detection and behavioral modulation (Gebremedhin et al., 2024; Kuang et al., 2025).

Molecular docking and fluorescence binding assays have provided additional evidence of ligand affinity in NPC2 and OBP-like proteins, suggesting specific interactions with host-derived compounds and repellents (Iovinella et al., 2016; Liang et al., 2023; Liu et al., 2025). Nevertheless, these validations remain limited to a small subset of species. To date, no studies have applied CRISPR/Cas-mediated gene editing to directly assess olfactory gene function in ticks, although this method has proven highly informative in insect olfaction (Dong et al., 2021; Fan et al., 2022; Shankar et al., 2025). These methodological constraints reflect broader challenges in tick genomics, including the large genome size and the difficulty of maintaining laboratory colonies for experimental manipulation (Mans et al., 2016).

Behavioral validation of tick olfactory function

This scoping review indicates that behavioral and electrophysiological validation approaches remain underrepresented in tick olfactory research. Despite the essential role of olfaction in host-seeking and environmental sensing, only a small number of studies employed behavior-related validation experiments such as electroantennography or a Y-tube olfactometer. For example, electrophysiological recordings combined with Y-tube olfactometer assays have been used to link volatile detection by sensory organs with behavioral attraction or avoidance in ticks (Faraone et al., 2020; Kuang et al., 2025). Electrophysiological methods provide direct evidence of sensory responsiveness to odorant stimuli, while Y-tube olfactometer assays enable behavioral-level assessment of attraction or repellency. These approaches have been successfully applied to evaluate tick responses to host-related and environmental odor cues (Carnohan et al., 2017; Faraone et al., 2020; Ferreira et al., 2020).

Limitations of the current review

This scoping review has several limitations. First, the available literature is heavily biased toward a small number of tick species with available genomic resources, which may limit generalizability across tick taxa. Second, most studies rely on gene identification, while functional and behavioral characterization remain scarce. Third, heterogeneity in experimental designs, tissues analyzed, and annotation pipelines may affect data consistency across studies. Finally, the absence of standardized functional genomics approaches in ticks constrains the mechanistic interpretation of chemosensory gene function.

Future directions

Future studies should prioritize expanding the number of tick species investigated. Strengthening functional validation using RNAi, CRISPR/Cas systems, electroantennography, or Y-tube olfactometer assays to elucidate the role of candidate gene families. Immunolocalization and single-sensillum recording techniques should be incorporated to spatially map chemosensory proteins and establish direct functional links between receptor activity and odorant responsiveness at the sensillum level. Integrating ligand-binding assays, molecular docking, multi-omics approaches, and machine-learning-based odorant prediction models will be essential for revealing regulatory networks linking olfactory genes to physiological and behavioral outcomes and for translating these findings into practical tick control strategies within a One Health framework. Future studies should also conduct evolutionary analyses of chemosensory-related genes to elucidate their diversification, conservation, and adaptive significance in tick olfaction.

Conclusions

This scoping review reveals substantial progress in identifying olfactory-related gene families in ticks, including IRs, GRs, NPC2, ML, and GPCRs, highlighting the complexity of the tick chemosensory system. However, functional validation remains limited, which constrains mechanistic understanding of chemosensory signaling mechanisms. Expanding functional genomics, behavioral assays, and comparative multi-omics studies will be essential to establish causal links between chemosensory genes and host-seeking behavior. Advancing molecular knowledge of tick olfaction will enable the development of targeted, olfaction-based control strategies and support One Health approaches to tick-borne disease prevention.

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Data availability statement

We have shared supplementary files.

Generative AI statement

The authors declare that the GPT-5 model (OpenAI) was employed to assist in improving academic writing style, language clarity, and grammar, and to refine sentence structure and flow in parts of the manuscript. All AI-generated content was critically evaluated, edited, and verified by the authors. The authors take full responsibility for the content of the manuscript. Generative AI was not used for data analysis, data interpretation, figure generation, or scientific decision-making.

Ethics statement

Not applicable.

CRediT authorship contribution statement

Afito Luciano: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuxin Huo:** Writing – review & editing, Methodology. **Jiani Li:** Writing – review & editing, Visualization. **Yuting Ma:** Visualization, Data curation. **Sha Tan:** Writing – review & editing. **Jie Yang:** Visualization, Validation. **Haojia Guo:** Validation, Resources. **Bing Zhang:** Visualization, Validation. **Fanming Meng:** Writing – original draft, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.vas.2026.100615.

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