

A Mini-review of the Genomes and Allergens of Mites and Ticks

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Abstract

Mites and ticks are associated with many human diseases including allergic diseases and scabies. With the recent advances in the high throughput DNA sequencing technology, many mitochondrial nuclear genomes of these species have been sequenced and the resulting genomic resources will certainly provide novel insights for the future investigation of the functionally important proteins and peptides in these species. In this mini-review, the current situation of mite and tick genomes is described and the future perspectives for the application of the genomic resources are discussed, especially including the novel identification and structural analysis of allergens.

Key words

Mites and ticks, allergic disease, genome, transcriptome, identification of allergen, DNA sequencing

Introduction

Mites and ticks are small organisms that are associated with many human diseases including the devastating allergic diseases and scabies. Therefore, it is not surprising that the allergens and pathogenic microbes carried by mites and ticks have been extensively investigated in the last few decades. With the recent advances in the high throughput DNA sequencing technology, the mitochondrial and as well as draft genomes of these species are reporting at an unprecedented pace. The resulting genomic resources will certainly provide novel insights for the future investigation of the functionally important proteins and peptides in these group of disease-related organisms. In this mini-review, an update of the current situation of genomic research in mites and ticks will be outlined. To highlight the contribution of such resources, some examples of clinically relevant applications would be also provided.

Mite Genomes

In 2011, the genome sizes of 134 arthropods species were predicted using the traditional flow cytometry approach. Among them, there are two mites (Trombidiformes: *Tetranychus urticae*, genome size=90.7 Mb; Oribatida: *Archegozetes longisetosus*, genome size=150 Mb) and their genomes are nearly the smallest in all the analyzed arthropods [1]. As shown in **Table 1**, most of the mites have the genome sizes of less than 200 Mbp except the *Tropilaelaps mercedesae*, *Dermanyssus gallinae*, *Varroa destructor* and *Varroa jacobsoni*, which belong to Mesotigmata. [2-13] (**Table 1**). To unveil the phylogenetic relationship of mite and tick genomes, data were downloaded from the National Center for Biotechnology Information and analyzed bioinformatics tools. As shown in **Figure 1**, there are significant clusters of domestic, soil, plant and insect mites but livestock mites tend to scatter among different clusters.

As a shortcut for the species characterization, the mitochondrial genomes of many tick and mite species were first reported [14-27] (**Table 2**). Most of them have the sizes of 13-14 kbp, although the sizes of mitochondrial genomes of *Phytoseiutus persimilis* and *Varroa destructor* are exceeding 16 kbp. This is in with the much bigger genome sizes of these two species. Such mitochondrial genomes could be employed for studying their evolutionary origins as well as the mode of adaption in their hosts.

One of the earliest complete genome sequenced using the next generation sequencing was that from the spider mite *Tetranychus (T.) urticae*, an agricultural pest with a wide host plant range and extensive pesticide resistance [6]. This genome has unique changes in the hormonal environment and the organization of the Hox complex, as well as evolutionary innovation of silk production. Moreover, in this study genes potentially related to polyphagy and detoxification were identified. The resources accumulated will be very useful for the future establishment of this spider mite as a model for studying interactions between mites and plants [28]. Subsequent investigation of the *T. urticae*'s genome led to the identification of an expansion of ABC (ATP-binding cassette) gene superfamily, which might be associated with the broad plant host range and high levels of pesticide resistance in *T. urticae* [29]. Surprisingly, a diverse family of UDP-glycosyltransferase genes in the *T. urticae* genome was found to have a bacterial origin [30]. This is an interesting finding in mite evolution because this family of genes play an important role in the detoxification of xenobiotics and in the regulation of endobiotics. Later, a massive incorporation of microbial genes into the genome of *T. urticae* was reported [31], highlighting

the importance of horizontal gene transfer in mite evolution and a significant and underestimated impact on the metabolic repertoire of plant-feeding spider mites.

Besides the pests of plants, house dust mites related to human allergic diseases were also a hot topic in mite genome research. The first genome reported was from *Dermatophagoides (D.) farinae* [32], resulting in a 53.5-Mb *D. farinae* draft genome with 516 nuclear genome scaffolds and a 14.3-kb mitochondrial genome. Altogether, 16,376 gene models were obtained, including 9,142 that were supported by RNA sequencing results. The full gene structures of 20 canonical allergens and 7 non-canonical allergen homologues were produced. This work was described as the cornerstone work guiding the future dust mite research to the omics era [33] and was also honored as one of the major advances in mechanisms of allergic diseases in 2015 [34]. This study not only generated a dust mite genome but also pioneered the combination of genome information with mass spectrometry and immunoblotting in the identification of novel allergens. The identities of protein spots bound by IgE from patient sera could be easily elucidated using the proteome database predicted from the genome and transcriptome information. This strategy had been found to be very efficient and was subsequently used in many other allergen-related genome studies. The capability of this approach was well demonstrated by the fact that many novel allergens in *D. farinae* have been cloned and characterized in the last few years, including Der f 27 [35], Der f 28 [36], Der f 29 [37], Der f 29b [38] and Der f 33 [39]. Subsequently, the genomes of *D. pteronyssinus* [2, 40-41] and *Euroglyphus maynei* [3] were finished with similar strategies, although the genome finished by Liu et al. is the most high quality one in term of completeness and accuracy because of the use of a hybrid approach combining the advantages of Illumina, Ion torrent and Pacific Bioscience DNA sequencing platforms.

Another important human pathogen is the ectoparasitic mite *Sarcoptes scabiei*, which causes significant morbidity in humans and other mammals worldwide by scabies [42]. The genome of this mite is relatively small [4], which is only around 56 kbp in size, and genes potentially coding for antigen-production proteins, immune modulating proteins and pathways and proteins responsible for acaricide resistance were identified. The number of protein coding genes predicted is only a little bit more than ten thousand and thus smaller than expected. This phenomenon could be related to the stringent criteria incorporated for genome annotation.

Another group of mite genomes that have been widely investigated is the agriculture-related mites. They include the false spider mite *Brevipalpus yothersi* [43], which is a vector of several plant viruses, some of which cause diseases in economically important crops [44]; the poultry red mite *Dermanyssus gallinae* [10], which is a major health and welfare concerns for the egg-producing industry worldwide [45]; the sheep scab mite *Psoroptes ovis* [5], which can cause sheep scab and is characterized by pruritus and skin irritation; the phytoseiid predatory mite *Metaseiulus occidentalis* [9], which is employed for the biological control of mites that feed on crops including spider mites [46]; the honey bee ectoparasitic mite *Tropilaelaps mercedesae* [8], which is prevalent in most Asian countries [47]. Although the genome sizes of the chigger mites *Leptotrombidium pallidum* and *Leptotrombidium scutellare*, which is known to transmit *Orientia tsutsugamushi* that causes scrub typhus, had been estimated [48], the genomes of these two species are still unavailable.

Mite allergens

There are 10 species of mites that are reported to cause human allergic diseases, in which *D. farinae* and *D. pteronyssinus* are the most investigated mites (**Table 3**). According to the habitat of house dust or storage food, these mites are categorized into house dust mites and storage mites. *D. farinae*, *D. pteronyssinus*, *D. microceras* and *E. maynei* are classical as house dust mites, while the other 6 species are storage mites, in which *B. tropicalis* is now considered as a house dust mite [49-54].

According to the WHO/IUIS allergen nomenclature, totally 39 groups of mite allergens have been identified [2, 32, 40-41, 55-57] (**Table 3**). For example, in *D. farinae*, 34 groups of allergens have been reported, although the existence of Der f 12, Der f 17 and Der f 19 had been confirmed [32]. In recent years, researchers have recognized that mite genomes are important resources for identifying novel allergens. The *D. farinae* genome, the first house dust mite genome sequenced, was published in 2015, in which the novel group 24 allergen, UQCRB-like protein homologue, was identified [32]. In 2017, the draft genome of *E. maynei* also elucidated more than 30 different groups of allergens [3]. Moreover, three genome assemblies of *D. pteronyssinus* were published in the last three years, in which many more novel groups or isoforms of allergens were identified [2, 40-41]. As to other mites, especially storage mites, the lack of genome assembly impedes the identification of novel allergens, resulting in much fewer identified allergens than house dust mites. With more genome assemblies of mites published in the future, we believe a more complete spectrum of mite allergens will be established.

Besides the identification of novel allergens, protein structure also provides much necessary information of allergens, like IgE-binding epitopes [58-77]. So far, only three mites (*D. farinae*,

D. pteronyssinus and *B. tropicalis*) have published structure of allergen proteins and many of them belong to the major allergen groups, e.g. groups 1, 2, 5 and 23. The structural analysis of recombinant allergen proteins and their complex with antibody fragments paves the way to analyse allergens at the more precise level of IgE-binding epitopes [58-59, 62-66, 68-72, 74-75, 77]. Although the same group of allergens among different mite species share high identities, the cross-reactivity of these allergens is very common, resulting in difficulties on clinical diagnosis [78-84]. Structural comparison of allergens among mites can explain the structural basis of the limited cross-reactivity, which may in turn facilitate the precision diagnosis of allergy [58, 61-63, 67, 73].

Tick Genomes

Ticks are external parasites that live by feeding on the blood of animals and constitute Acari subclass along with mites. Tick-borne diseases are common among humans and animals, in which ticks transmit infectious pathogens or toxins [85]. Many genomic studies conducted in the last decade have broaden our knowledge on tick-host-pathogen interactions [86].

As a typical example, *Ixodes scapularis* (black-legged tick) is a common livestock tick which transmits a wide range of human and animal pathogens and distributes among North America. The *Ixodes scapularis* Genome Project was initiated in 2007 and the genome of *Ixodes scapularis*, which is the first assembled tick genome, was obtained by Sanger sequencing in 2008, [87]. The assembled *Ixodes scapularis* genome provides genomic information of tick immune responses and facilitate the understanding of the molecular basis of tick-borne pathogen persistence and the development of novel interventions against the relevant infections [88].

With the advancement of DNA sequencing technology, a more completed 2.1 Gbp *Ixodes scapularis* genome was assembled in 2016, in which 20,486 protein-coding genes were annotated and expansion of gene families associated with tick–host interactions were observed [89]. In 2018, the J. Craig Venter Institute assembled an even better *Ixodes scapularis* genome (cell line ISE6) of approximately 2.1 Gbp genome size with a BUSCO completeness of 93.7% [12]. As we seen, the genome sizes of ticks are many times bigger than mite genomes (**Table 1**). It is also not surprising the gene numbers of ticks are much more than that of mites because of the differences in habitats and diets.

The genome of another tick in the *Ixodes* genus, *Ixodes ricinus* (castor bean tick), was assembled in 2016 with a low sequence coverage of 6.0X. The assembled sequence is approximately 515 Mbp in size and therefore significantly smaller than that of *Ixodes scapularis* (**Table 1**) [13]. The underlying reason for the genome reduction in this species remains to be investigated. Based on this *Ixodes ricinus* genome, an in-depth multi-omics study on the tick midgut metabolism was conducted to analyze the interaction between the pathogen and the host [90].

The cattle tick *Rhipicephalus microplus* is another common tick that transmits livestock diseases (especially bovine diseases) and distributes in tropical and subtropical countries [11]. In 2010, partial genome of *Rhipicephalus microplus* was sequenced by the 454 FLX pyrosequencing approach [91]. Recently, the genome of *Rhipicephalus microplus* was assembled in 2017 by the hybrid strategy involving the Pacific Bioscience and Illumina DNA sequencing platforms [11]. In the *Rhipicephalus microplus* genome, 2.0 Gbp draft sequences were assembled with 24,758

protein-coding genes annotated (**Table 1**) and 191 miRNA families identified [11]. Additionally, it was identified that several highly divergent esterases shared sequence similarity to acetylcholinesterase and a novel cytochrome P450 CYP41 homolog showed similar protein folding to the known CYP41 proteins [11].

Tick-induced allergies includes mammalian meat allergy and tick anaphylaxis [92-95]. Mammalian meat allergy is a type of food allergy, which is also called as alpha-gal syndrome. Mammalian meat allergy occurs after tick bites and the responsible allergen for the allergic reaction is α -gal (galactose- α -1,3-galactose), which is widespread in mammalian meat [96-99]. It is generally believe that tick anaphylaxis is a classical allergic reaction induced by some proteins in the tick saliva [100-103]. Although ticks are closely related with allergic diseases, only one tick allergen Arg r 1 from the European pigeon tick *Argas reflexus* causing anaphylactic reaction after tick bites was reported [104]. More efforts should be put on the identification of ticks allergens in the future.

Conclusion

Genome is one of the most important biological information to comprehensively understand and research a species. Although many mites and ticks (especially house dust mites and storage mites) are common allergen sources, the first house dust mite genome, the draft genome of *D. farinae* was published in 2015. Until now, more than 20 species of mites and ticks have published genome (**Table 1**), which greatly expand our knowledge on these small organisms. With the genome as dataset, much more complete profile of allergens (include 39 allergen groups) has

been identified in allergic mites (**Table 3**), which may facilitate clinical diagnosis and therapy to the associated allergic diseases, while few allergens of ticks have been identified.

Future perspectives

Although we have only mentioned the mite and tick genomes in the above paragraphs, transcriptomes of these species were generally generated at the same time to facilitate genome annotation. Such transcriptomic information, together with the predicted promoter / enhancer sequences of the genomes, should be very helpful for the future analysis of the regulation of genes that are crucial for the pathological roles of mites and ticks. Furthermore, the relative amounts of each proteins in mite and tick species can be estimated by the relative proportion of the corresponding transcripts in the transcriptomes. Long read sequencing techniques will also enable the accurate detection of the post-transcriptional alternative splicing and then could shed light on the existence and relative abundance of protein isoforms of functional important proteins. At the protein level, the nearly completed proteomes projected from the genomes and transcription will greatly expand the scope of study in these species, e.g. the non-allergens proteins that are similar to human proteins and therefore cross react and disrupt the human immune responses.

As time passes by, it can be envisaged that the number of genomes and transcriptomes available for mite and tick species will continue to grow with the further advance in the genomic technology. Further exploration into the interaction of multiple levels of omics, including but not limited to genomics, epigenomics, proteomics and metagenomics, in mites and ticks will be our

future goal in the pursue of combating diseases caused by these enemies of human health and food sources.

Table 1. The genome information of mites and ticks.

* Genome completeness was evaluated by BUSCO (version 3.0.2) with dataset arthropoda_odb9.

Not applicable.

Species	Genome size (bp)	Gene number	Completeness *	Reference
Mites				
<i>Dermatophagoides farinae</i>	63,746,680	18,087	91.3%	N. A. #
<i>Dermatophagoides pteronyssinus</i>	66,623,663	16,805	89.0%	[2]
<i>Euroglyphus maynei</i>	43,437,841	15,257	65.0%	[3]
<i>Blomia tropicalis</i>	62,729,071	12,427	91.3%	N. A.
<i>Tyrophagus putrescentiae</i>	97,387,900	21,050	91.5%	N. A.
<i>Sarcoptes scabiei</i>	56,262,437	10,473	86.5%	[4]
<i>Psoroptes ovis</i>	63,214,126	12,041	90.6%	[5]
<i>Tetranychus urticae</i>	90,828,597	15,684	92.7%	[6]
<i>Brevipalpus yothersi</i>	71,162,551	N. A.	89.6%	N. A.
<i>Dinotrombium tinctorium</i>	180,399,227	19,024	94.1%	[7]
<i>Leptotrombidium deliense</i>	117,319,042	14,667	87.6%	[7]
<i>Achipteria coleoptrata</i>	88,443,889	N. A.	83.6%	N. A.
<i>Hypochthonius rufulus</i>	172,365,132	N. A.	89.6%	N. A.
<i>Steganacarus magnus</i>	113,565,242	N. A.	86.5%	N. A.
<i>Platynothrus peltifer</i>	100,532,934	N. A.	75.0%	N. A.
<i>Tropilaelaps mercedesae</i>	352,534,912	14,342	89.6%	[8]
<i>Galendromus occidentalis</i>	151,724,311	18,338	95.5%	[9]
<i>Dermanyssus gallinae</i>	959,010,206	14,608	91.0%	[10]
<i>Varroa destructor</i>	368,942,295	30,221	93.4%	N. A.
<i>Varroa jacobsoni</i>	365,585,945	26,214	93.2%	N. A.
Ticks				
<i>Rhipicephalus microplus</i>	2,008,371,944	24,758	52.0%	[11]
<i>Ixodes scapularis</i>	2,126,657,207	20,486	93.7%	[12]
<i>Ixodes ricinus</i>	514,506,549	N. A.	23.2%	[13]

Table 2. Mitochondrial genomes of mites and ticks.

Species	Common name	Genome size (bp)	References
Mites			
<i>Dermatophagoides pteronyssinus</i>	House dust mite	14,203	[14]
<i>Sarcoptes scabiei</i>	Itch mite	13,837	[15]
<i>Panonychus citri</i>	citrus red mite	13,077	[16]
<i>Tyrophagus longior</i>	Storage mite pest	13,271	[17]
<i>Metaseiulus occidentalis</i>	Predatory mite	14,695	[18]
<i>Phytoseiutus persimilis</i>	Predatory mite	16,199	[19]
<i>Aleuroglyphus ovatus</i>	Brown leg mite	14,328	[20]
<i>Psoroptes cuniculi</i>	Scab mite	14,247	[21]
<i>Steganacarus magnus</i>	Sexual oribatid mite	13,818	[22]
<i>Paraleius leontonychus</i>	Oribatid mite	14,186	[23]
<i>Varroa destructor</i>	Honeybee ectoparasite mite	16,477	[24]
Ticks			
<i>Amblyomma americanum</i>	Lone star tick	14,709	[25]
<i>Rhipicephalus microplus</i>	Cattle tick	14,864 -14,948	[26]
<i>Rhipicephalus sanguineus</i>	Brown Dog Tick	14,714	[27]

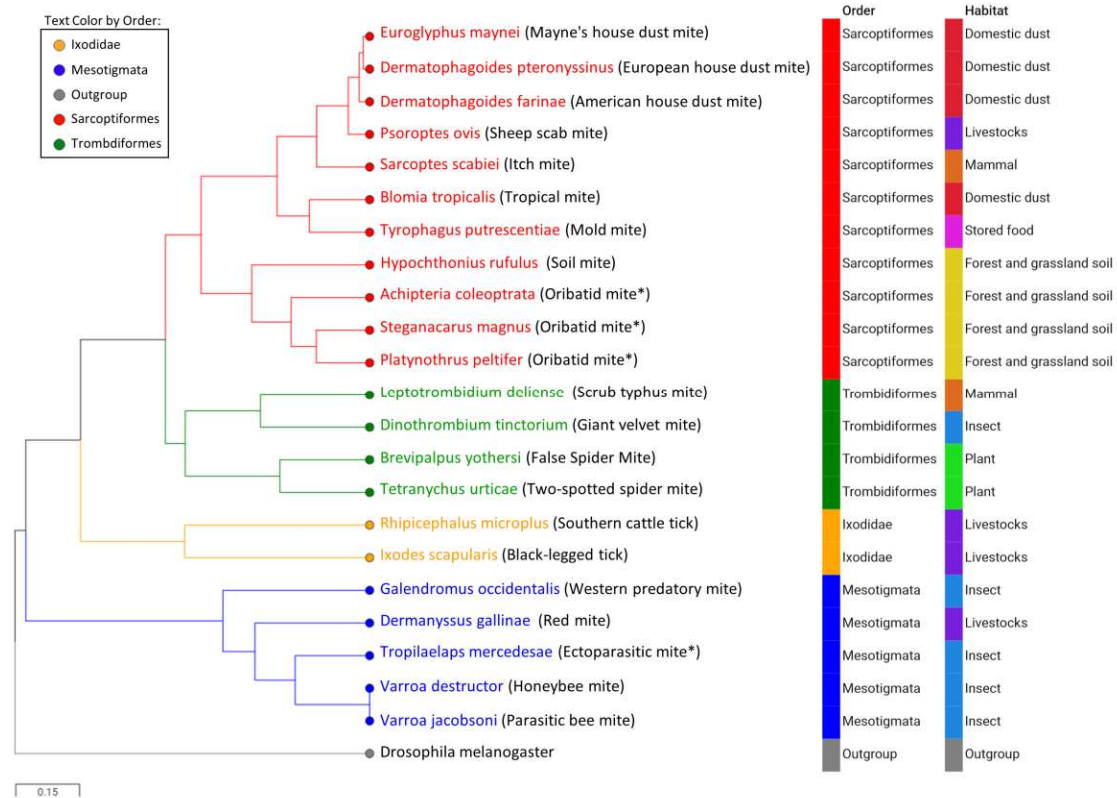
Table 3. Identified mite allergens.

Group ID	Df*	Dp*	Dm*	Em*	As*	Tp*	Bt*	Gd*	Ld*	Ca*
1	√ [#] [58, 61]	√ [58-59, 61-62, 66]					√ [67]			
2	√ [64-65, 73]	√ [63, 68]								
3										
4										
5		√ [69]					√ [70-71]			
6										
7	√ [74]									
8		√					√			
9										
10										
11										
12							√			
13	√ [60]									
14										
15										
16										
17										
18										
19							√			
20										
21	√ [72]						√ [75]			
22										
23	√	√ [77]								
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* Df: *Dermatophagoides farinae*; Dp: *Dermatophagoides pteronyssinus*; Dm: *Dermatophagoides microceras*; Em: *Euroglyphus maynei*; As: *Acarus siro*; Tp: *Tyrophagus putrescentiae*; Bt: *Blomia tropicalis*; Gd: *Glycyphagus domesticus*; Ld: *Lepidoglyphus destructor*; Ca: *Chortoglyphus arcuatus*.

Tick (√) means having published protein structure. The background of light grey means the allergen group has been published in the WHO/IUIS allergen nomenclature database.

Figure 1. The phylogeny tree of mites and ticks. The genomes of mites and ticks were download from NCBI database. The overlapped single complete BUSCOs (v3.0.2, with dataset arthropoda_odb9) were multi-aligned by MAFFT (v7.407), and the alignment result was used to build this phylogeny tree by MEGA (v7.0.26) program, with *Drosophila melanogaster* genome (Release 6, GCF_000001215.4) as outgroup. The tree was plotted using an online tool Microreact (<https://microreact.org/upload>). The texts inside blankets indicate the common name of the mites. (*= Not a specific common name).



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Conflict of interest

The authors declare that they have no relevant conflicts of interest.